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I hereby recommend that the thesis prepared under my supervision by Mr. William C. Francis entitled Indoles and Pyrimidines: Their Synthesis and Physiological Properties

be accepted as fulfilling this part of the requirements for the degree of Doctor of Philosophy

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INDOLES AND PYRIMIDINES: THEIR SYNTHESSES AND PHYSIOLOGICAL  
PROPERTIES

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1944

by

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## I. INTRODUCTION

The original object of this investigation was the synthesis of possible antimalarial drugs containing the indole nucleus and possessing a structure somewhat analogous to that of plasmochine.

This aim was subsequently dropped because of experimental difficulties and in its place a study of Mannich reaction products derived from indole, was substituted.

In addition to the above, we undertook the synthesis of 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane which could be obtained from 4,4'-diamidino-1,3-diphenoxypropane (Propamidine) and acetylacetone. The propamidine presented considerable difficulty in this reaction because of its insoluble nature, and hence we undertook to obtain 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane by preparing 2-(4'-hydroxyphenyl)-4,6-dimethylpyrimidine and allowing it to react, in the form of its sodium salt, with trimethylene bromide. Both methods of attack eventually met with success.

Since this latter procedure makes it possible to prepare numerous homologues, we began the synthesis of the isomeric 3,3'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane in an identical manner. The necessary pyrimidine was prepared from the known 3-nitrobenzamidine hydrochloride

and acetylacetone.

An interesting sidelight of this investigation was the fact that the 2-(3'-nitrophenyl)-4,6-dimethylpyrimidine thus obtained was identical (by mixed melting point) with the compound prepared by Japanese investigators who nitrated 2-phenyl-4,6-dimethylpyrimidine. These workers did not locate the position of the nitro group. This we tentatively suggest is in the 3 position of the phenyl ring.

## II. HISTORICAL

### A. Introduction

(1) Need for Antimalarial Research. - In the field of chemotherapy, the discovery of synthetic medicinals effective in the prevention and treatment of malaria is a problem whose importance can be scarcely over emphasized.

In World War II, many of the battle fronts are in tropical regions where the insect vectors of malaria are most prevalent, hence the problem of treatment and control assumes tremendous proportions. One military medical authority has said, "We have four enemies, Japan, Germany, Italy, - and malaria. There is only one that can lick us. That's malaria. We've got to get results."

The three drugs in general use - quinine, plasmochin, and atabrine - though satisfactory in the majority of cases, are still far from being perfect drugs. Thus, quinine, although relatively nontoxic in man, does at times, produce symptoms such as tinnitus, deafness with prolonged use, and, at times, even allergy. In spite of these undesirable features, many members of the medical profession still prefer to use quinine when they can get it. Its use in the present emergency is almost an impossibility, except in special cases, due to the fact that almost all of the quinine in the world today comes from the Dutch East Indies. This source has, of course, been cut off since all these lands are in the hands of the enemy.

Plasmochin, although possessing a relatively high therapeutic index when tested in birds, is considerably decreased in effectiveness when tested in man and an effective dose approaches almost the toxic level in many cases. It is definitely not a drug which may be used indiscriminantly by individuals not under medical supervision. Atabrine, although possessing a relatively high therapeutic index, when tested in man, possesses the undesirable feature of frequently turning the skin yellow (1).

#### B. Chemotherapy of Malaria

The earliest investigations on the use of the cinchonas against malaria were carried out on patients who were suffering with the disease. The Jesuits, on their arrival in Peru learned from native medicine men that malarial fever could be effectively treated by drinking an extract of the bark from the tree "quinaquina". It is from this aboriginal name of the tree that quinine takes its name. Cinchona, another alkaloid occurring in the bark of this tree, is supposed to have received its name in commemoration of the Countess of Chinchon who was treated for malaria with an extract of the bark.

When the study of chemotherapeutics began to expand it became apparent that a test animal would have to be found before any proper evaluation of possible antimalarials could be carried out.

(1) The Use of Birds as Test Animals. - A beginning

in this direction was made by Roehl (2) of I. G. Farben-industrie, when he introduced birds as test animals to guide the chemotherapeutic studies which eventually led to the discovery of Plasmochin. Roehl's lead was subsequently continued by Kikuth (3)(4) who studied a variety of strains of bird malaria and finally found the haemoproteus infection of the paddy bird to be a valuable tool for this purpose.

Similar studies were carried out by Fourneau and Bovet (5) in France. Collier and Krause (6) introduced the use of the Java sparrow in 1929 and James (7) in 1937 introduced the use of canaries infected by mosquito bite instead of the straight blood inoculation devised by Roehl. Magidson et al (8) in Russia used siskins for their tests and introduced the idea of injecting the drugs instead of feeding them.

(2) Other Test Methods. - In addition to the use of avian malaria as a test means, the use of Paramoecia has been suggested by Hegner, Shaw and Manwell (9). The use of Plasmodium knowlesi infections in monkeys dates from the year 1932, when Knowles and Das Gupta (10) described this malarial parasite. It has been found to be particularly valuable in the testing of the sulfanilamide drugs (11)(12)(13)(14) because of the close similarity of simian and human malaria.

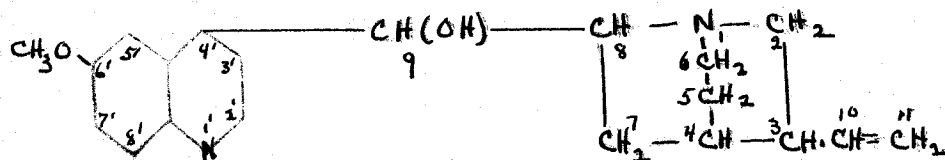
Recent attempts have been made by Hewitt (15) and Coggeshall (16)(14) to develop a method of testing anti-malarial drugs against parasites grown in vitro. Great

difficulty, however, has been experienced in trying to obtain good and prolonged propagation of the protozoa. The latter's method involves the determination of the inhibition of oxygen uptake of protozoa, by drugs added to the protozoa in a Warburg apparatus.

The interdependency of the two branches of chemotherapeutic research, namely, that which is concerned with the physiological aspects of testing various substances, and that which is concerned with the purely chemical aspect of synthesis of possible drugs, is close indeed. From the chemist's point of view it is relevant, therefore, that a discussion of the various drugs, naturally occurring and synthetic, their properties, and the pertinent facts of their history be briefly summarized.

### C. The Naturally Occurring and Chemically Modified Alkaloids.

(1) Quinine and Cinchonine. - The chemotherapeutic approach to malaria had its beginning in 1827 when Pelletier and Caventon received the ten-thousand franc prize from the French Institute of Science for isolating the active principles of cinchona bark. It was not until 1908, however, that the now accepted structure of quinine, I, was announced to the world of science by Rabe (17). Much research followed as



I

the result of attempts by many investigators to synthesize the cinchona alkaloids. Kaufmann's (18) publication on the synthesis of compounds related to quinine in 1913 and the synthesis of dihydroquinine by Rabe et al (19) in 1931 represent an exceptionally interesting phase of alkaloid chemistry.

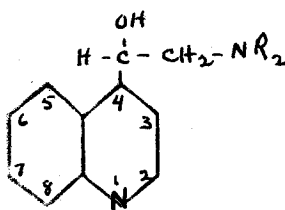
The following facts are brought out by a study of the structure of quinine and cinchonine. The formula of each is made up of a quinoline and a quinuclidine heterocycle joined together by a carbinol bridge in position 9. Quinine differs from cinchonine only in the presence of a methoxy group at position 6' of the quinoline portion of the molecule. Examination of the formula for quinine shows that positions 3, 4, 8, and 9 are centers of optical asymmetry. Hence the given formula might represent one of sixteen possible optical isomers. Fortunately, however, nature tends towards simplicity and while quinine  $(\alpha)_D = -158.2^\circ$  is isomeric with quinidine  $(\alpha)_D = 274.7^\circ$ , they both give the same ketone  $(\alpha)_D = 73.8^\circ$  on oxidation, thus showing that their primary difference is about  $C_9$ . The same holds true for cinchonine and cinchonidine (20).

(2) Chemical Manipulation. - Chemical alterations upon the quinine and cinchonine molecules shows that no alteration of the secondary hydroxy groups at  $C_9$  has yet been achieved without destroying the activity of the parent cinchona alkaloid (21)(22)(23)(24). The presence of the

vinyl group at position 3 in the quinuclidine heterocycle is of minor importance for its activity is increased somewhat by hydrogenation (25) and its activity remains even after addition of the elements of water (26), hydrogen halide, or halogen (26). Oxidation to the carboxylic acid, however, renders the molecule inactive (21)(27). More than likely, this is due to the altered physical properties rather than to its chemical structure for esterification will partially restore the original activity (21)(27)(28).

There is also no obvious relationship between optical activity and antimalarial action. Thus Buttle, Henry, and Trevan (29) have pointed out that epimerism at the C<sub>6</sub> atom reduces the quinine equivalent from 1 in quinine to 0.1 in epi-C<sub>6</sub>-quinine and from 0.5 in quinidine to 0.1 in epi-C<sub>6</sub>-quinidine. Similarly the l-bases, quinine and cinchonidine, are more active than the corresponding d-bases, quinidine and cinchonine. On the other hand the d-quinine-isomer, methyl-apoquinidine, is more active than either of its l-isomers, alpha- or beta-isoquinine.

King and Work (30), as the result of substituting the quinuclidine heterocycle by tertiary amine groups, have stated the requirements for activity of the quinine type compounds as "being a system in which a basic group approaching in size that of the quinuclidine radical is attached to the alpha carbon of a 4-quinolyl ethanol."

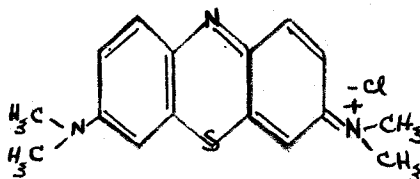


Other studies concerned with the location of the tertiary amine groups in positions other than 4 seems to indicate that only this position confers such activity to these groupings (31)(32).

#### D. Synthetic Antimalarials.

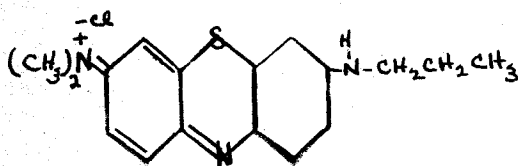
Since the difficulties are considerable in manipulating the various groupings in the quinine molecule, it was only natural that investigators were led eventually to try the substitution of similar groupings in other heterocyclic ring structures.

(1) Methylene Blue Derivatives. - The molecule of methylene blue, II, had been shown to exhibit some anti-

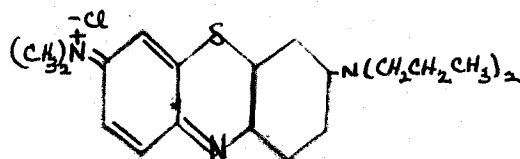


malarial action by Ehrlich and Guttman in 1891 (33). With this as their lead, Schulemann (34), Schönhöfer (35), and Winger (36) of the I. G. Farbenindustrie began their investigations by modifying the methylene blue molecule. Their first experiments were aimed at increasing the anti-malarial effect by introducing alkyl groups onto the aromatic

amino radical in place of the methyl groups already there. As a first trial, compounds, III and IV, were synthesized and when tested in canaries infected with malaria they showed a slight increase in activity over that of methylene blue (2). The therapeutic index of these compounds (the ratio between

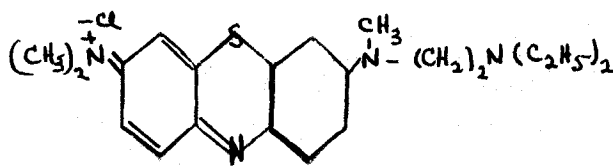


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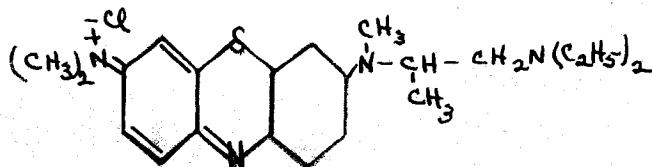


IV

the maximum tolerated dose and the minimum curative dose) was still quite low, scarcely exceeding 1:1. A far greater degree of success was achieved by the introduction of basic alkyl groups into the aromatic amino group of methylene blue. Compound, V, showed only a slight increase in activity over that of methylene blue, but did not show a decrease in toxicity, i. e., a therapeutic index of 2. Compound, VI, showed a marked increase in its effect, the therapeutic index being almost 8.

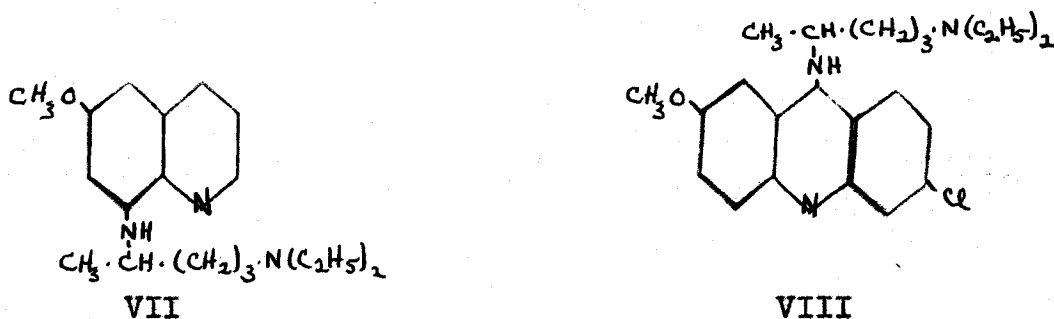


V



VI

These investigations, carried out with regard to the methylene blue molecule, showed that the introduction of an N-basic alkyl group enhanced the effect of methylene blue, and the nature and structure of the basic alkyl group. The experience thus gained was soon applied to other ring systems underlying dyes, such as, triphenylmethane, azines, oxazines and acridine and quinoline. This latter gave compounds possessing marked activity against the malarial parasite and lacking the character of a dye. The quinoline series led eventually to Plasmochin, VII, with an index of 30. Similar studies in the acridine series by Mietzsch and Mauss (37) yielded atabrine, VIII.

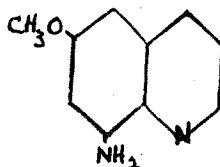


When atabrine was tested by Kikuth (3) it proved to be schizonticidal drug of considerably lower toxicity than Plasmochin.

(2) Quinoline Compounds other than the Quinine Type. -

The effect of adding similar dialkylamino alkylene amino groups to heterocyclic rings other than methylene blue and particularly to those nuclei which had been shown to have strong specific action against parasites in themselves,

subsequently led to experiments towards increasing the activity exhibited by 6-methoxy-8-aminoquinoline, IX, (38). Accordingly the formula of



IX

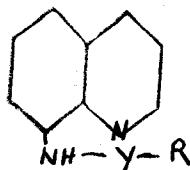
a large number of 6-alkoxy-8-dialkylamino alkalene amino quinolines were prepared and tested. Among those which showed promise was 6-methoxy-8-( $\alpha$ -methyl- $\delta$ -diethylaminobutyl-amino) quinoline (Plasmochin)(39). This, it turned out, exhibited the best relationship between activity and toxicity of all the quinoline compounds studied.

With the discovery of Plasmochin numerous investigators began a systematic study of the basic structure, 8-amino-quinoline with the following features in mind:

1. Variations in the length of the side chain.
2. Variations in the degree of branching of the side chain.
3. Alterations of the terminal basic group of the side chain.
4. The effect of different types of side chains.
5. Modifications of the alkoxy group in position 6.

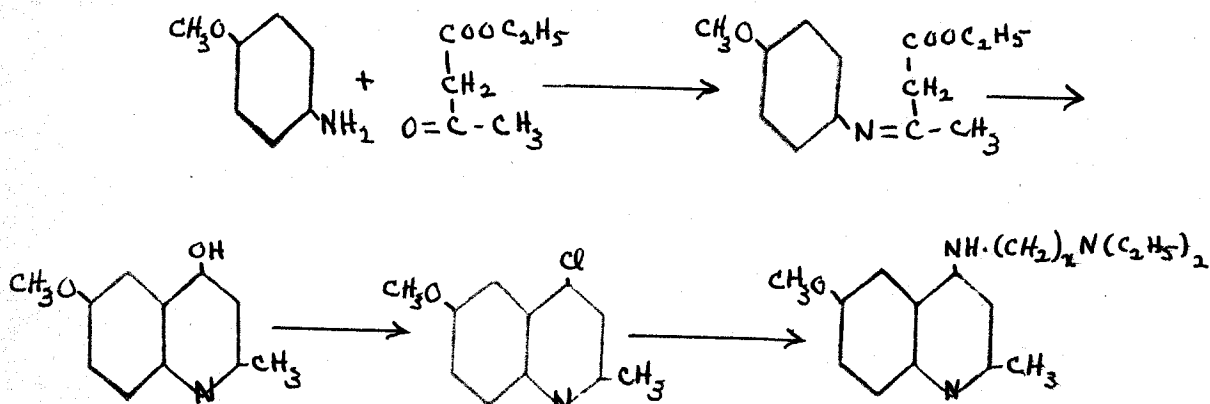
It is generally agreed, as the result of testing a large number of derivatives, that the fundamental structure which appears to be responsible for their antimalarial activity may be represented by the general formula,  $\text{Y}$ , in which Y represents a chain either of a hydrocarbon, ether, thioether, or

amino residue and where R is a basic radical. A methoxy group



in position 6 is desirable but not essential (40)(41).

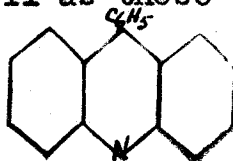
The second most important group of compounds in the quinoline series of the Plasmochin type is made up of the 6-methoxy-4-dialkylamino alkylene amino derivatives which may be synthesized by means of the Conrad-Limpach (42) condensation, as follows:



Since the synthesis of the corresponding compounds lacking the 2-methyl group requires considerable manipulation and because Krichevskii et al (43) reported the presence of this group destroyed the activity of the 4-isomers, little work has been done in this series. More recent work by Holcomb and Hamilton (44), however, has shown that these derivatives do possess appreciable activity. A recent patent issued to Winthrop Chemical Company (45) indicates that a

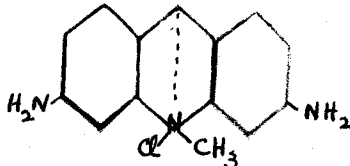
3-methyl group enhances the activity and that a 6-methyl group is not essential and may be replaced by a halogen in the 7- position.

(3) Acridine Compounds as Antimalarials. - The earliest reference to the use of acridine compounds against various types of infective organisms, including the malarial parasite, is the work of Mannaberg (46). His work was concerned with the testing of dyestuffs containing the phosphine nucleus, X. These tests as well as those of Kalberlah and Schlossberger



X

(47) with tryflavin, XI, were found to have no effect in



XI

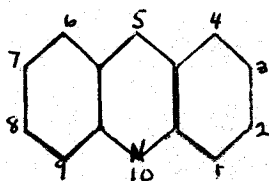
malaria. However, it must be realized that these studies were carried out prior to the development of the test method of Roehl (2) and only serve to illustrate the haphazard methods of characterization in use before the advent of the intensive researches undertaken by I. G. Farbenindustrie.

Investigations using the acridine nucleus in place of that of quinoline were begun at about the same time as the work with 8-amino quinoline derivatives. Thus, not long after 1926, when Plasmochin was placed at the disposal of the medical profession, Mauss and Mietzsch (48) obtained patents on

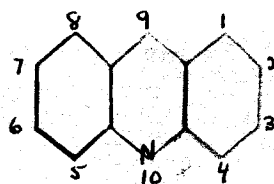
analogous compounds based on the nitrogen bearing nucleus of acridine. Among these was 3-chloro-7-methoxy-9-(1-methyl-4-diethylamino) butylamino acridine (Atabrine), the formula of which was not made known to the public until 1933 (49). This, when tested on Plasmodium praecox infections in siskins compared favorably with the action of quinine as a schizonticide. Also, like quinine, it was ineffective against the gametes in the peripheral blood (3)(50).

Subsequently other research workers throughout the world took up the hunt for compounds of a similar nature. Since very little has been published by the German investigators outside of the patent literature, it is necessary to turn to the Russian publications for definite information between therapeutic activity and chemical structure.

Before entering into such a discussion it should be noted that two general methods of numbering the acridine ring are in use. Both systems are used by various journals and it is usually necessary to check the starting materials and method of synthesis in order to be certain of the structure. System XII, was used by the French and by Chemical Abstracts prior to 1936. System XIII, has been used by the Germans, Russians and by Chemical Abstracts, subsequent to 1936.



XII



XIII

The relation between therapeutic activity and chemical structure of the 2, 6 and 8 substituted acridines can be best seen through an examination of the following:

- (a) Effect of variations in the dialkylamino alkylene amino group in position 9.
- (b) Effect of changing the group in position 2.
- (c) Effect of changing the group in position 6.

From the data of Magidson et al (51)(52)(53)(54), the conclusions which have been made with regard to the acridine type antimalarials may be summarized at this point.

(a) When the length of the dialkylamino alkylene amino side-chain is increased the activity rises until n is equal to four, whereupon a maximum is obtained. For a further increase in the length of the side-chain, activity abruptly decreases. The lower homologues are more active, but they are also more toxic. The C<sub>4</sub> compounds therefore represent an optimum on the basis of both activity and toxicity.

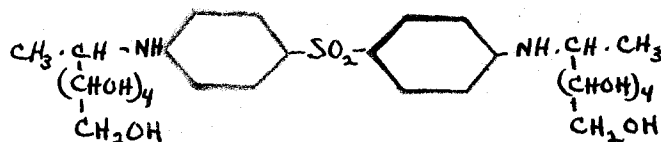
(b) The consideration of the butyl homologues, shows that unbranched isomers are more than twice as effective as branched isomers. However, the presence of an alpha-methyl group in an amyl side-chain more than doubles the therapeutic index.

(c) If the -OCH<sub>3</sub> group is replaced by the -CH<sub>3</sub> group in the 2-position, the index is lowered but not destroyed entirely. On the other hand, when the -SCH<sub>3</sub> group is used in place of the -OCH<sub>3</sub> group distherapeutic results are obtained.

(d) When a nitrile group is substituted for the chlorine atom in the 6-position, a compound of comparable activity is obtained. It is interesting to note that a nitro- group in position 7 seems capable of compensating the removal of the chlorine in position 6. All other substituents in position 6 give distherapeutic results.

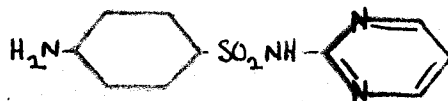
(4) Sulfanilamide Derivatives. - In 1935, Mietzsch and Mauss (55) obtained a patent in which they described some sulfanilamide substituted acridines, for use in combating blood parasites. However, the first reported test of a sulfanilamide compound against malaria appeared in 1937 (56). Since that time most of the better known sulfanilamide compounds have been tested by one of more different methods. An anomaly which appeared in this connection is that certain of these drugs give negative results in avian studies, but were found to give positive results in human malaria.

Thus, when "Promin", XIV, was used against Plasmodium



XIV

lophurae infections in chicks, Coggeshall (57) obtained negative results, however, when it was given to human paretics infected with induced benign tertian malaria, a reduction of fever was observed. As a consequence of this anomaly, Coggeshall undertook to investigate the use of drugs such as sulfadiazine, XV, 2-sulfanilamidopyrimidine, against human



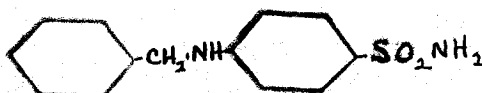
XV

malaria regardless of the fact that they might exhibit no activity either in bird malaria or in vitro.

The value of sulfanilamide in the treatment of malaria has been a much argued point, and many papers on both sides of the question appear in the literature. For a discussion of some of these the reader is referred to the paper by Sinton, Hutton and Shute (58).

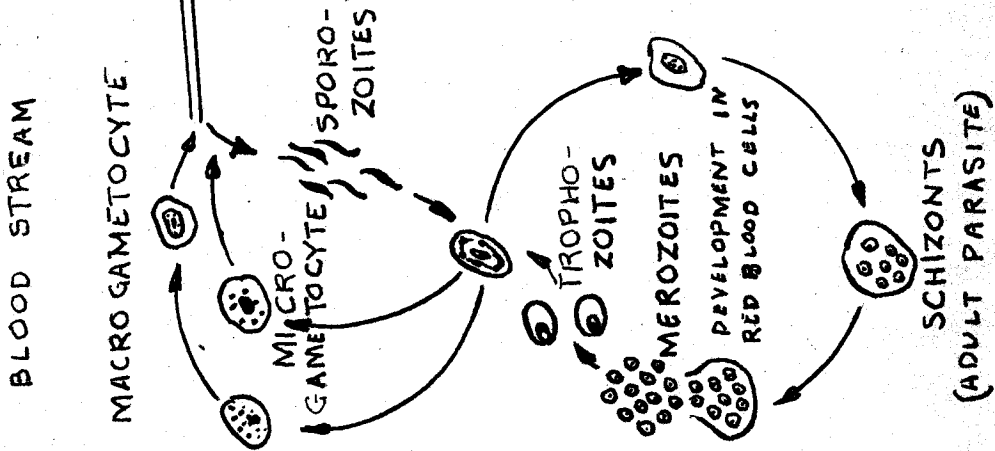
From the recent publications it seems quite certain that sulfanilamide itself is of no value in human malaria (59) (60)(61)(62) and has little or no effect on Plasmodium infections in birds (16)(63). It does, however, exert a definite effect on Plasmodium knowlesi infections in monkeys (11)(12) (13)(16). The positive action of some of the other sulfanilamide derivatives is a little more firmly established, and Walker and Van Dyke (64) have found the reactivity on Plasmodium lophurae in young ducks to be in the decreasing order, sulfathiazole, sulfadiazine, sulfanilamide. Sulfathiazole has also been shown to be active against Plasmodium vivax infections in human malaria (65), whereas sulfadiazine is effective against all forms of malaria in man (57).

An important aspect of the problem which needs more study before its value can be determined is the prophylactic action of the sulfanilamide derivatives. That such action of the sulfanilamide derivatives exists is well known. Thus, when Proseptazine (N<sup>+</sup>-Benzylsulfanilamide), XVI, was given to neuro-syphilitics

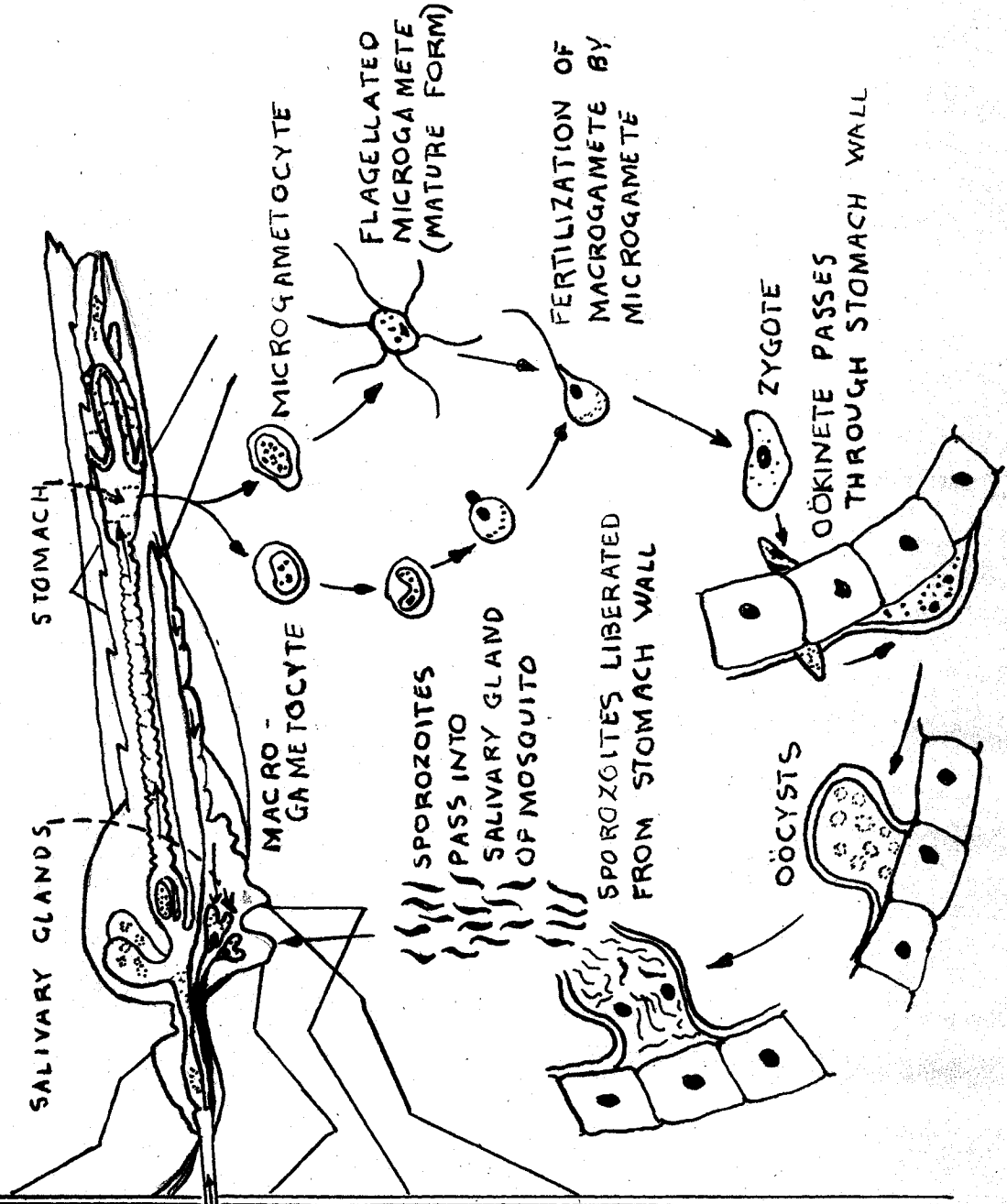


XVI

CYCLE IN MAN



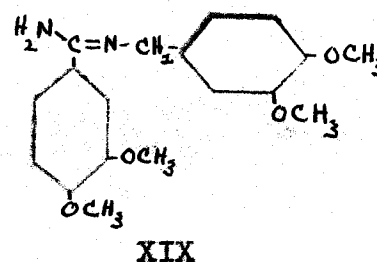
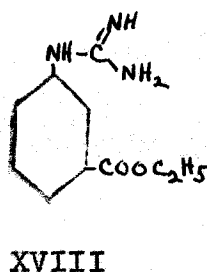
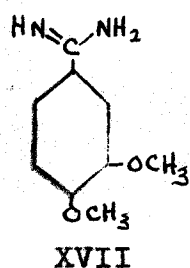
CYCLE IN MOSQUITO



prior to inoculation with Plasmodium falciparum, the patients failed to develop malaria. This prophylactic action was of short duration and, because of toxicity and dietary limitations, it is of little practical value (58). These same investigators stated that the drug is effective against the sporozoites in tertian malaria, but that it is without action on the trophozoites.

Of the many drugs tested this is the only reference mentioning a specific action upon the sporozoit stage in the development of the malarial parasite. Although seemingly insignificant, this prophylactic action indicates that the sporozoites themselves are attacked by Proseptazine, and hence there can be no possible development of merozoites and trophozoites and no malarial symptoms. The importance of this fact is readily understood when one considers the life cycle of the malarial parasite in both man and in the mosquito. The appended diagram (Fig. 1) issued by the Winthrop Chemical Company (66) illustrates this at a glance.

(5) Amidines as Antimalarials. - The use of amidino compounds as antimalarials was first investigated by Easson and Pyman (67) in 1931. In their work they tested three structurally unrelated amidino compounds, XVII, XVIII, XIX,



upon bird malaria without success.

King, Lourie and Yorke (68) in 1937 reexamined this use of the amidines basing their research on a postulate they had made from certain well founded considerations. Though this postulate was later shown to be false, their work was not without fruit. On that account it will be of value to review those considerations (69).

Boit, Boit, and Richard (70) in 1911 first noted the excessive amounts of glucose required in the metabolism of the trypanosomes. Subsequent work confirmed this original observation and the facts may be summarized herewith.

1. The presence of glucose is necessary for the existence of trypanosomes.
2. Trypanosomes consume relatively enormous quantities of glucose in their metabolism.
3. Laboratory animals experimentally infected with trypanosomes frequently exhibit during the course of the infection a certain degree of hypogluccemia. However, hypoglycemia is constantly present to a very marked degree in the agonal period of the disease or in the stage immediately preceeding it.
4. The mechanism whereby hypoglycemia is produced is still uncertain.

Anent this mechanism, Lourie and Yorke (71) checked the observation of Schern and Artagaveyta-Allende (72)

and showed that synthalin (decamethylene diguanidine dihydrochloride) has a definite action of Trypanosoma equinum and concluded that the effect must be due to its action in the removal of blood sugar, thereby producing hypoglycemia. The work of Lourie and Yorke done in vitro showed a powerful trypanocidal action, whereas in vivo the dosage necessary to obtain hypoglycemia caused severe injury to the liver. Moreover, they found that insulin, which causes hypoglycemia has no effect on the trypanosomes either in vitro or in vivo. They concluded, accordingly, that the action must be direct, and that their previous assumption that the effect was due to the removal of blood sugar was false.

Following up this lead, King, Lourie and Yorke (68) carried out tests with a series of guanigines, amidines, isothioureas and other similar compounds prepared in the laboratories of May and Baker (73)(47). From these studies it was found that symmetrical diamidine alkanes showed an even greater trypanocidal action than that of the corresponding guanidine derivatives, the most active being 1, 11-diamidinoundecane dihydrochloride,

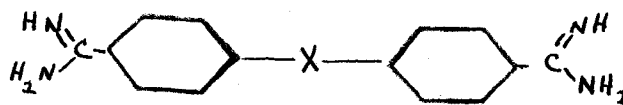


The discovery of the trypanocidal action of the diamidino compounds provided a new field of investigation, and its extension to the aromatic compounds was the work of Ashley et al (75). They undertook this in the hope that such compounds would more readily lend themselves to a study of

the effects of substitutions, and thus to products of increased trypanocidal action and of possible therapeutic application. Their studies were directed at a comparison of the following effects:

- (a) effect of nuclear substitution,
- (b) effect of increasing the length of the hydrocarbon chain,
- (c) effect of substituting hetero-atoms in the chain,
- (d) effect of partly oxidized linkages,
- (e) effect of unsaturated linkages,
- (f) effect of substitution in the amidine groups,
- (g) effect of the position of the amidine groups, symmetrical or otherwise.

The general inferences which they drew from the data available was that the most active trypanocidal compounds were of the type



where X is a simple alkane chain in which one or more of the  $-CH_2-$  groups are replaced by oxygen, or by an ethylenic linkage as in the stilbenes. No compounds were found possessing greater activity than Propamidine, Stilbamidine, and 4,4'-diamidino-1,5-diphenoxypentane.

In view of the analogous nature of the trypanosome and malaria metabolisms - both requiring large amounts of glucose (76)(77) - it was thought that the drugs which had been effective in the trypanosome infections might also be applicable in malaria.

a. Use of 1,11-Diamidinoundecane in Malaria. - Working with this idea in mind, Glyn-Hughes, Lourie and Yorke (78) used 1, 11-diamidinoundecane dihydrochloride on Plasmodium vivax infections in humans. They found that man can safely tolerate 50 milligrams per day intravenously or 100 milligrams per day orally, and that one-half of this dosage has a definite effect on vivax malaria. It is also effective against Plasmodium knowlesi in Macacus rhesus monkeys, however, it causes toxic side reactions in the liver (79).

Tests were then carried out using aromatic diamidines in the belief that a drug might be obtained having a higher therapeutic index than the aliphatic derivative previously studied.

b. Use of 4,4'-Diamidinostilbene in Malaria. - The action of Stilbamidine in malaria was investigated by Fulton (80). He found that when given intraperitoneally to canaries infected with Plasmodium relictum that the drug did not delay the appearance of parasites in the peripheral blood. Whereas, when used again simian malaria the drug was found to have a definite action. These observations were confirmed by Yorke (69), who found in addition that the 4,4'-diamidinostilbene

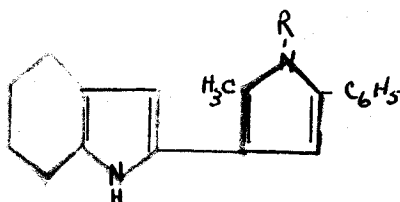
was also effective with Plasmodium vivax and Plasmodium falciperum in human malaria.

c. Use of 4,4'-Diamidino-1,5-diphenoxypentane in Malaria. - The other aromatic diamidine tested was 4,4'-diamidino-1,5-diphenoxypentane. Fulton(80) and Yorke (69) reported this compound to be effective against Plasmodium relictum in canaries, but that its therapeutic index was small. The drug was also active against Plasmodium knowlesi infections in monkeys.

### III. THEORETICAL

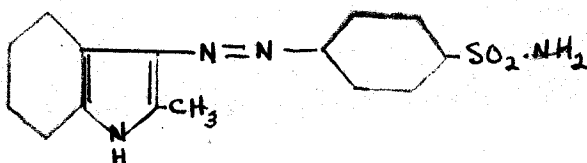
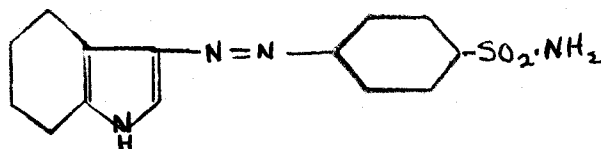
#### A. Indole Compounds.

Since indole derivatives analogous to plasmochin have not been reported, it should be of value to synthesize possible antimalarials using indole as a nucleus. Little work has been done in this series with the exception of the preparation of a few pyrrol indole compounds of the type, XX, where R is  $-C_6H_5$ ,  $-3-C_6H_4.CH_3$ ,  $-4-C_6H_4.CH_3$  and



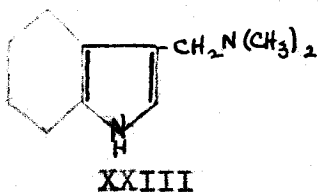
$-4-C_6H_4.OCH_3$  (81). These substances exhibited some anti-pyretic action and were toxic to paramecia, but they were not tested against the malarial parasite.

In addition to the above, the following azo-derivatives of indole, XXII, XXI, have been prepared and tested for sulfanilamide action.

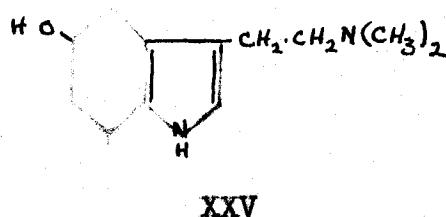
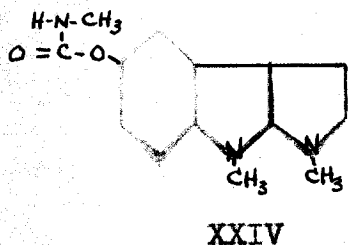


These were shown to exhibit considerable activity (82).

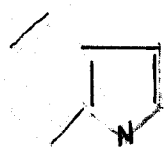
Besides these derivatives, which are purely synthetic, there are numerous naturally occurring substances containing the indole nucleus that possess physiological properties. A few of these are herewith cited. Gramine, XXIII, which is found in the germ of Swedish barley (83),



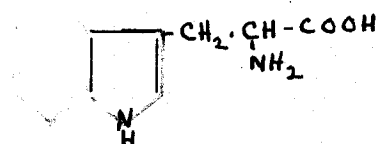
and certain alkaloids from both the plant and animal kingdoms, two examples of which are physostigmine, XXIV, found in the "Calabar or Ordeal Bean" from the West African coast (84), and Bufotenine, XXV, found in the glands of the toad



Bufo vulgaris (85). Besides these mention should be made of the auxins or plant growth hormones of the general type, XXVI, where n is an odd number, and the essential amino acid, l-tryptophane, XXVII.

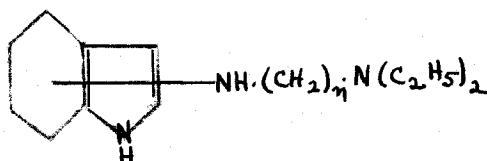


XXVI



XXVII

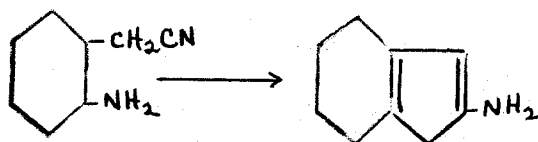
The structure of indole is somewhat similar to the quinoline nucleus, except that it lacks a  $C_4$  atom in the nitrogen heterocycle and that the nitrogen in position 1 is secondary rather than tertiary as in quinoline. Because of this similar nature, it would seem that compounds of type, XXVIII, might possess antimalarial activity. A possible method



XXVIII

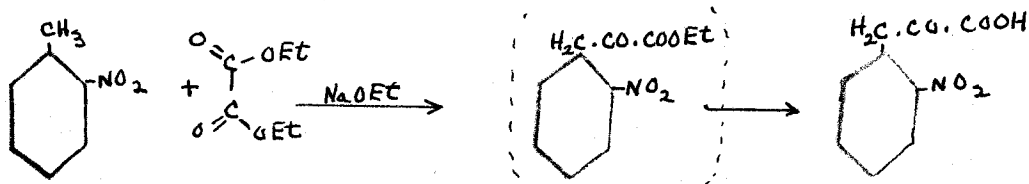
of synthesis of such compounds would be from the amino- or halogen-substituted indoles.

(1) Alpha-substituted indoles. - 2-Aminoindole has been prepared by Pschorr and Hoppe (86) by the action of sodium ethylate on 2-aminobenzylcyanide. To obtain the latter substance it was necessary to start with 2-nitrotoluene and

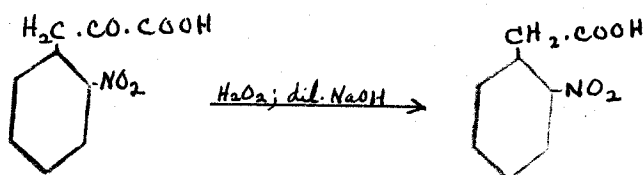


condense it with ethylalate in the presence of sodium

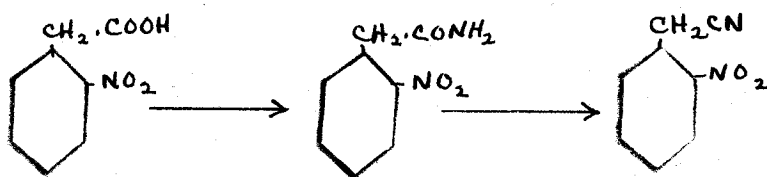
ethylate to give 2-nitrophenyl ethylpyruvate. This was followed by hydrolysis, yielding the corresponding 2-nitrophenylpyruvic acid.



The latter substance was next converted to 2-nitrophenylacetic acid by alkaline peroxide oxidation (87). Treatment of this acid with phosphorus pentachloride and ammonia gas gave

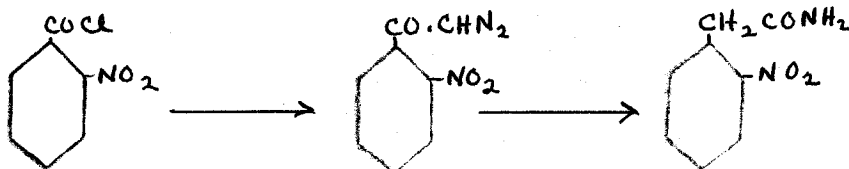


the amide. Dehydration of the amide gave the corresponding nitrile, which was reduced to the desired 2-aminobenzyleyanide with stannous chloride (86).

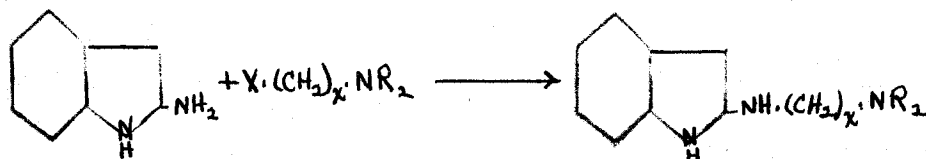


More recent work by Arndt and Eistert (88) affords the necessary 2-nitrophenylacetic acid in two steps. By the action of diazomethane on 2-nitrobenzoyl chloride the omega-diazo-2-nitroacetophenone is formed. Rearrangement of the latter compound was effected by means of ammonium hydroxide

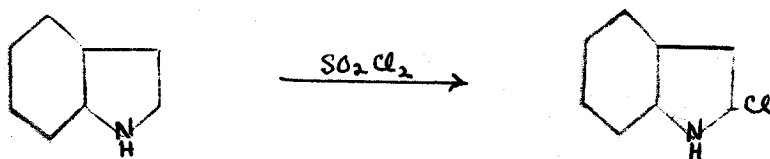
and freshly precipitated silver oxide to give 2-nitrobenzylamide.



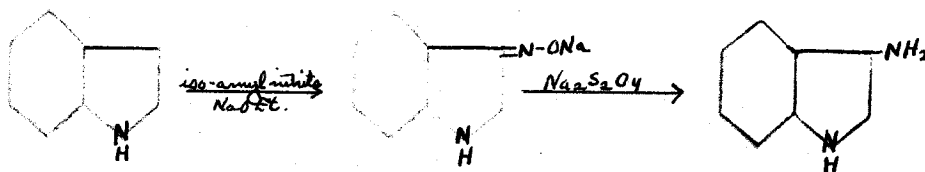
Once the desired 2-aminoindole is obtained, it should be possible to condense this with a suitable alpha, omega-substituted side-chain, as follows:



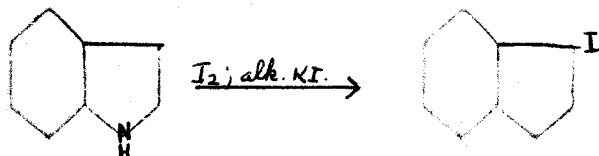
A more direct way of arriving at the corresponding 2-substituted amino alkylene dialkylamino indole would be from the known 2-chloroindole (89) and the corresponding alpha-amino, omega-dialkylamine. The chloroindole is prepared by the action of sulfuryl chloride on indole.



(2) Beta-substituted indoles. - 3-Aminoindole is also known, having been prepared by Madelung (90). When indole is treated with amyl nitrite in the presence of sodium ethylate, it reacts to give the sodium salt of 3-iso-nitrosoindole (indolonoxime). Reduction with sodium hydrosulfite then gives the desired 3-aminoindole.



The corresponding 3-indoindole (91)(92) is likewise known, being readily obtained when indole is dissolved in dilute alkali and then titrated with a solution of iodine in potassium iodide.

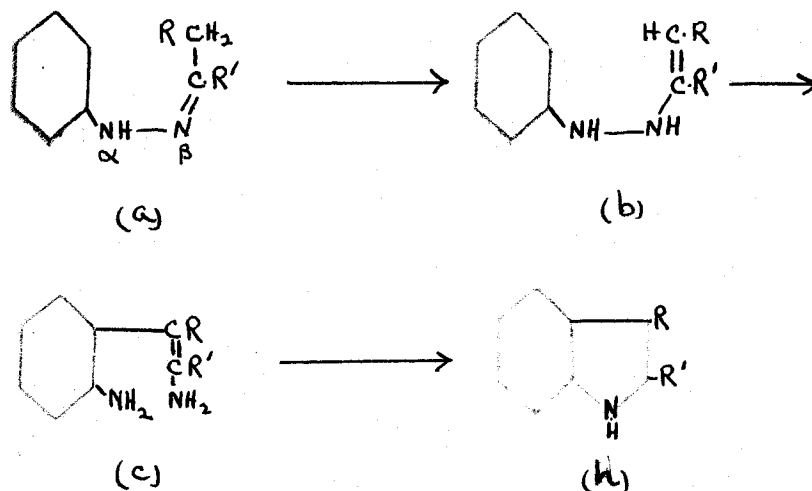


(3) Nuclear substituents in the benzene ring of indole. -

The methods for obtaining indole derivatives with substituents in the benzene nucleus usually require the total synthesis of the indole heterocycle. This may be done from suitably substituted ortho-toluidines (93)(94), or from the substituted phenylhydrazones by means of the Fischer indole rearrangement (95)(96). The latter method is particularly useful for preparing derivatives with substituents in positions 5 or 7.

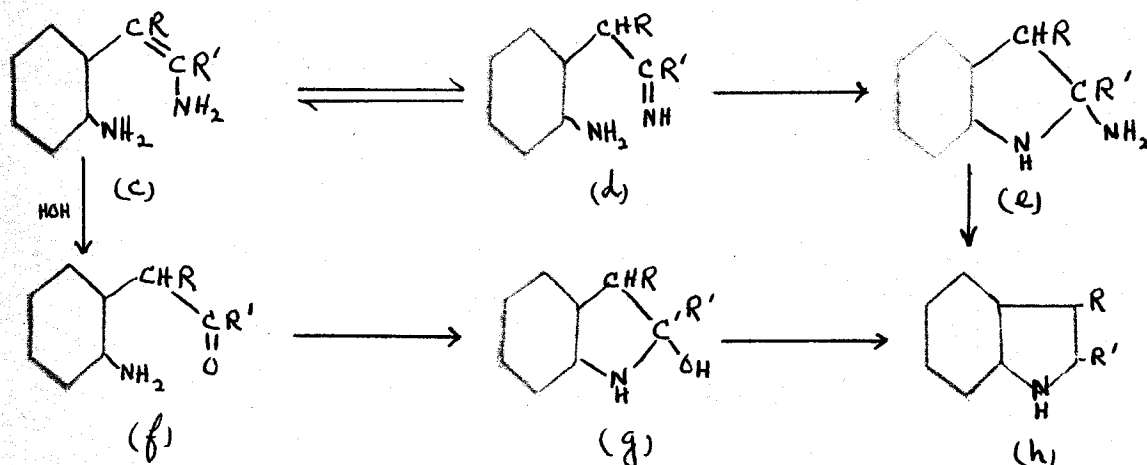
The Fischer synthesis, in general, may be described as the elimination of ammonia from the phenylhydrazones of most carbonyl compounds whose structures permit ring closures. The actual mechanism of this synthesis has been the subject of much speculation (97). Robinsons' (98) representation has been generally accepted as the most probable, and consists

of an ortho-benzidine type rearrangement prior to ring closure.



This mechanism was restudied in 1943 using  $N^{15}$  nitrogen as a tracer element. Working on the generally accepted idea that the nitrogen atom farthest removed from the aromatic ring is the one that is eliminated, Allen and Wilson (99) substituted heavy nitrogen on the benzene nucleus by treating benzoyl chloride with ammonium hydroxide containing  $N^{15}$ . The amide was converted to the amine by the Hoffmann hypobromite reaction. Diazotization and reduction of the latter yielded the corresponding hydrazine with the  $N^{15}$  nitrogen in the alpha-position and the ordinary nitrogen in the beta-position. After condensation of this with acetophenone, they then carried out the Fischer rearrangement, and obtained 2-phenyl-indole which still possessed the heavy nitrogen. This proved that the beta-nitrogen is the one which is lost.

These authors agree with Robinsons' formulation as far as the elimination of ammonia is concerned, but they prefer to think of this as the usual addition-elimination mechanism. The mechanism which they proposed is illustrated by the accompanying equations.



The imide (d) is a tautomeric form of (c), the  $\text{-NH}_2$  group of which can enter into a 1,2-addition reaction with the  $\text{C=N}$  to form (e), from which ammonia is eliminated. On the other hand, the imino group may be regarded as hydrolyzing to the corresponding carbonyl, as in (f), whereupon the 1,2-addition product may be represented as in (g).

The usefulness of the Fischer synthesis has been considerably increased by the technique which Japp and Klingemann (100)(101) employed for the preparation of otherwise unobtainable hydrazones. Their method consists in the addition of the desired diazonium salt to an alcoholic-alkali solution of the aldehyde or ketone. The product

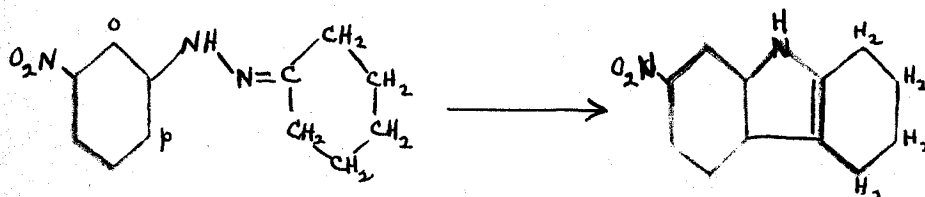
usually precipitates immediately or may be thrown out of solution by the addition of water.

Another feature of the Fischer rearrangement which should be mentioned is that it always leads to products containing substituents in the alpha- or beta-positions, or both. Thus, with hydrazones prepared from acetone, the corresponding alpha-methylindole is obtained; whereas with methyl-ethylketone the alpha, beta-substituted derivative results. The hydrazones obtainable from acetaldehyde should give the unsubstituted indoles, but this rearrangement has not been successful as yet (102)(103). To obtain such indole derivatives it is necessary to prepare the hydrazone of ethyl pyruvate, carry out the necessary rearrangement, and then decarboxylate. This last operation frequently gives unsatisfactory yields (104), though Shorygin and Polyakova (105) report that the decarboxylation of 2-carboxyindole to indole occurs in good yields.

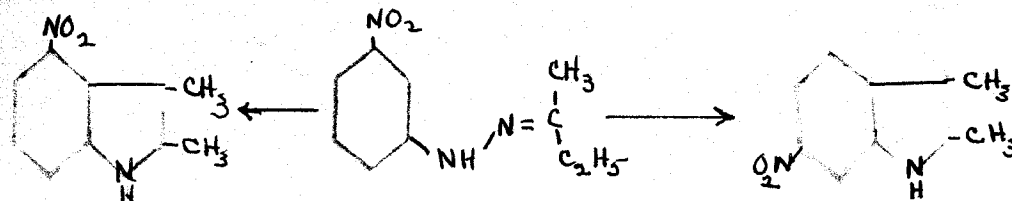
Indole compounds having amino alkylene dialkylamino groups in the benzene ring should lend themselves to synthesis from the corresponding amino derivatives that result when the nitro compounds are reduced by sodium hydrosulfite (106) or by stannous chloride in glacial acetic acid (107). Other methods lead to the reduction of the double bond in the 2,3-position to give the corresponding dihydroindoles. The ease of reduction varies depending on the substituent and its

position in the pyrrol half of the indole nucleus. The carboxylic acid derivatives are the most stable and the stability of the other derivatives decreases in the order 2,3-dimethyl-, 2-methyl-, and 1-methyl-indole (97).

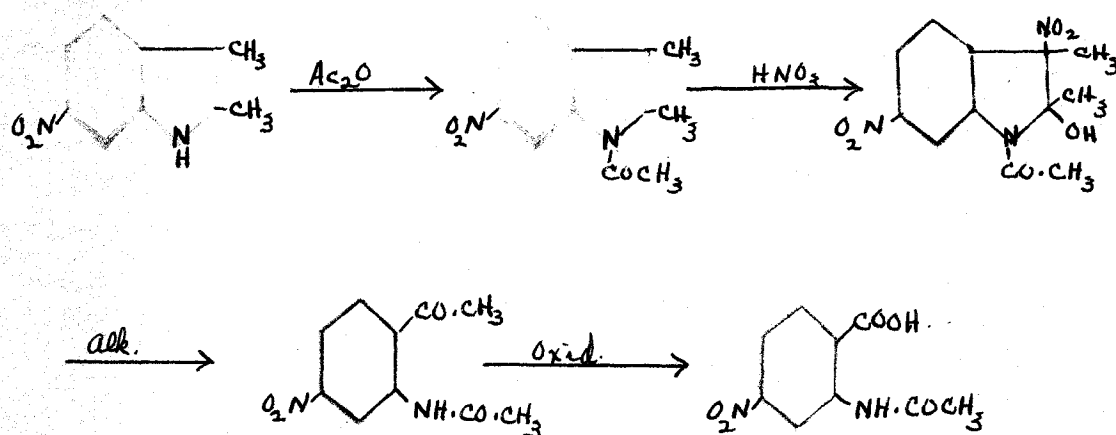
All of the mononitro-2,3-dimethylindoles have been prepared (106)(108) by the Fischer indole condensation. It must be realized, nevertheless, that to attain the 4 or 6 derivatives by this procedure the meta-substituted phenylhydrazone is required. A mixture usually results because the rearrangement can occur in two different ways yielding a mixture of the 4- and 6-substituted compounds. Exceptions to this have been reported. Borsche (109) found that the Fischer indole rearrangement with the 3-nitrophenylhydrazone of cyclohexanone only condensed in the position para to the nitro-group. On the other hand, Plant and Tomlinson (108)



have shown that the 4-nitrophenyl hydrazone of methylethyl ketone gives a mixture containing both the 4- and 6-nitro-2,3-dimethylindoles. The compound described by Bauer and



Strauss (106) as 6(4)-nitro-2,3-dimethylindole and which they report to melt at 126° can be made to melt at 130° by further recrystallization from aqueous alcohol. It is obviously 4-nitro-2,3-dimethylindole because it gives a depression of the melting point with 6-nitro-3,6-dimethyl-indole, melting point 142°. The structure of the latter substance was definitely proved by converting it to the known 2-acetylamino-4-nitrobenzoic acid by the following series of reactions (110).



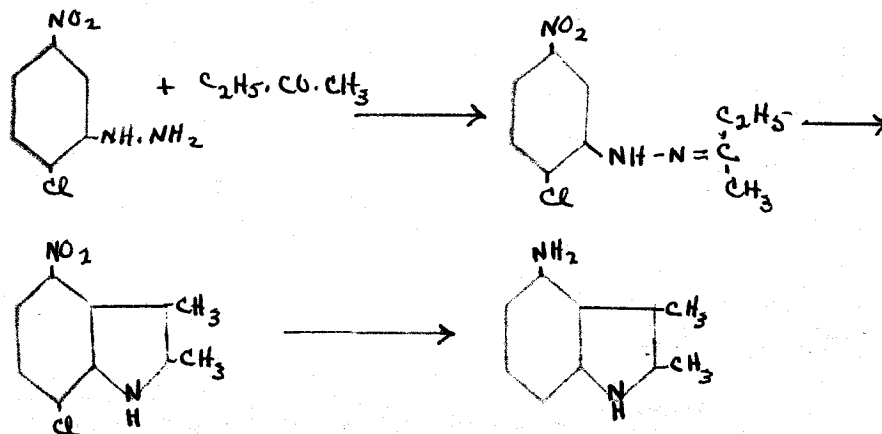
6-Nitro-2,3-dimethylindole, melting at 142°, may be prepared by the careful nitration of 1-acetyl-2,3-dimethylindole. Alkaline hydrolysis of this compound yields the 6-nitro-2,3-dimethylindole (108). When 2,3-dimethylindole is treated with potassium nitrate in concentrated sulfuric acid below  $-3^\circ\text{C.}$ , the 5-nitro-2,3-dimethylindole results. This was confirmed by a mixed melting point with the compound prepared from the 4-nitrophenylhydrazone of methylethyl ketone.

The nuclear amino derivatives which have been prepared are 6-aminoindole (107), 4-amino-2,3-dimethylindole (110) and 6-amino-2,3-dimethylindole (106).

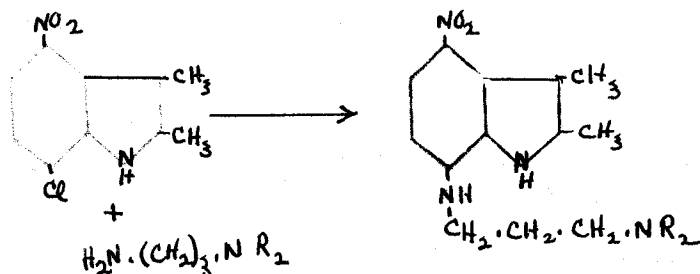
6-Aminoindole was obtained by the decarboxylation of 6-nitroindole-2-carboxylic acid followed by stannous chloride reduction of the corresponding nitro-compound in glacial acetic acid. Both the hydrochloride and the free base were too unstable to permit recrystallization.



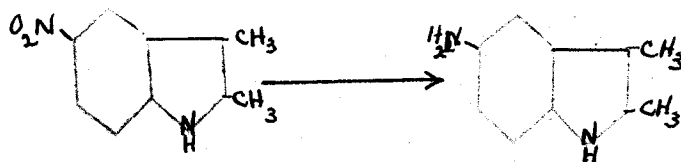
The method of obtaining the 4-amino-2,3-dimethylindole differs from the usual procedure in that the 2-chloro-5-nitrophenylhydrazone of methylethyl ketone was converted into the corresponding 4-nitro-7-chloro-2,3-dimethylindole. When this was reduced the simultaneous reduction of the nitro-group and loss of the chloro-substituent in position 7 occurred. In view of the lability of this chlorine it would



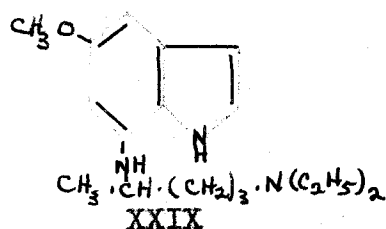
probably react with an amino alkylene dialkylamino compound to yield the 4-nitro-7-( $\alpha$ -aminoalkylene- $\omega$ -dialkylamino)-2,3-dimethylindole.



The remaining 5-amino-2,3-dimethylindole was obtained by the reduction of the corresponding nitro compound with sodium hydrosulfite.

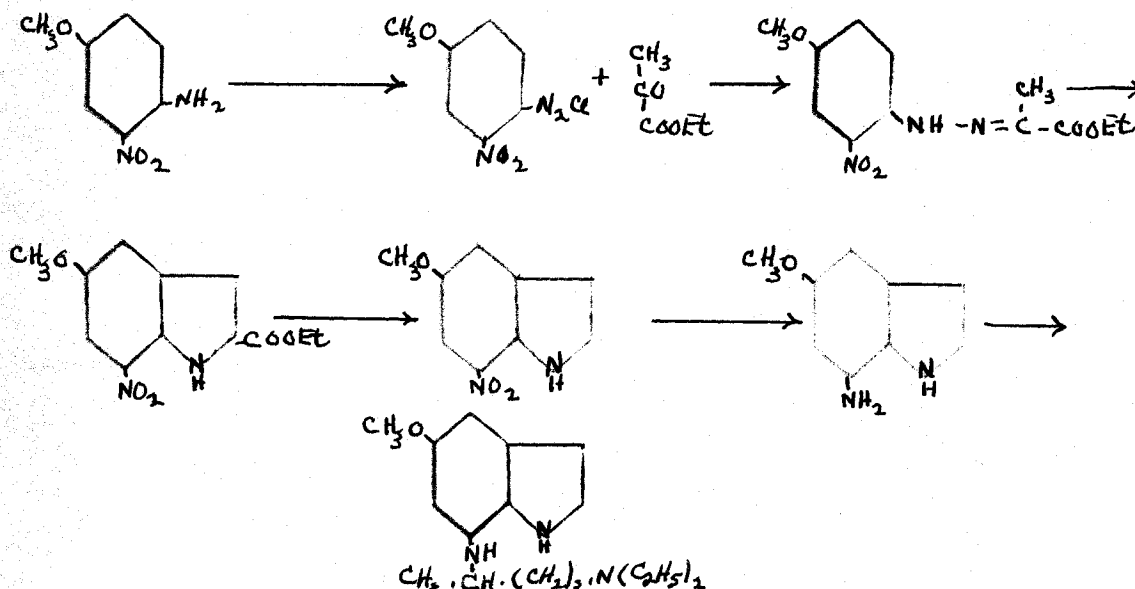


The analogue of plasmochin in the indole series would have the following structure, XXIX. This should be derivable

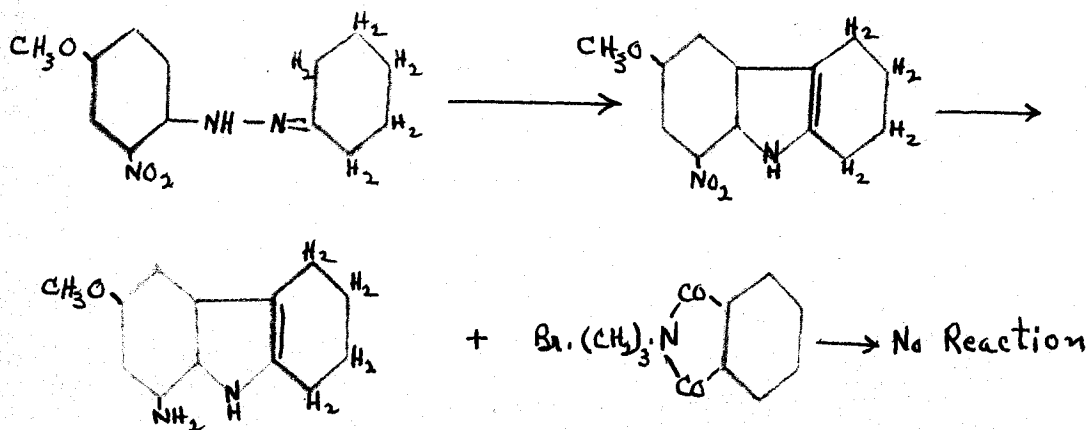


from the corresponding 5-methoxy-7-aminoindole. To obtain it by means of the Fischer indole synthesis would involve the preparation of 2-nitro-4-methoxyphenylhydrazone of ethylpyruvate, and its rearrangement to 5-methoxy-7-nitroindole-2-ethyl carboxylate. Hydrolysis and decarboxylation should

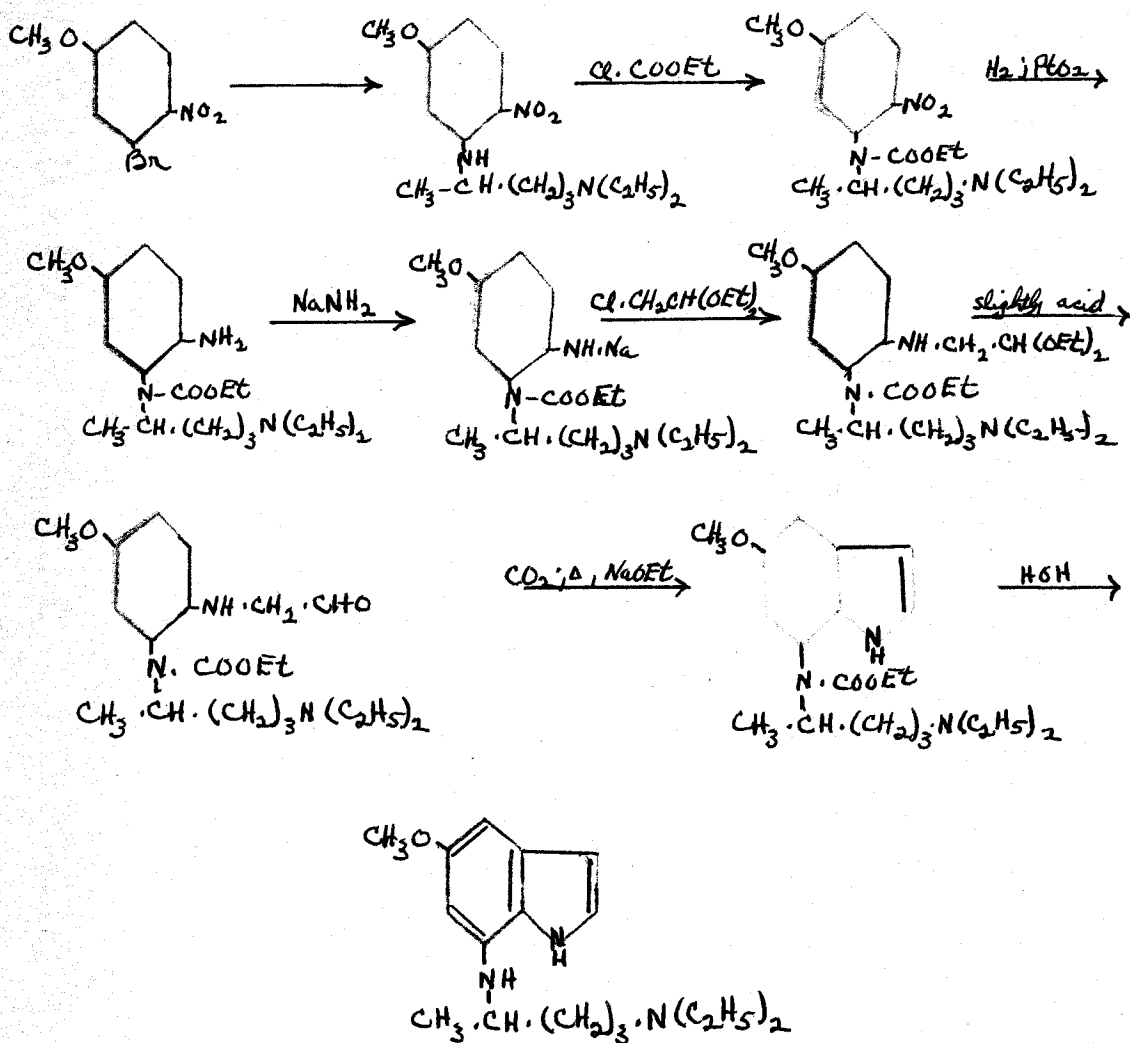
then give 5-methoxy-7-nitroindole, which could be reduced and condensed with 2-chloro-5-diethylaminopentane to give the plasmochin analogue.



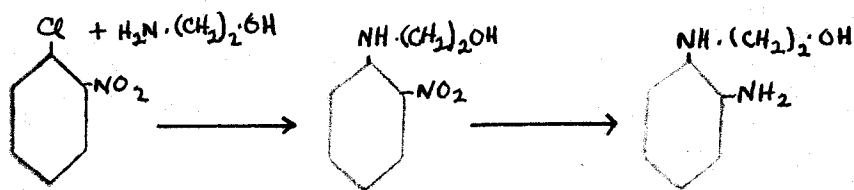
A procedure similar to this was attempted by Robinson and Tomlinson (111) with partial success. They prepared the 2-nitro-4-methoxyphenylhydrazone of cyclohexanone and rearranged it to the corresponding 8-nitro-6-methoxytetrahydrocarbazole which was then reduced to the amine with sodium hydrosulfite. This latter substance could not be made to react with phthaloyl- $\gamma$ -bromopropylimide.



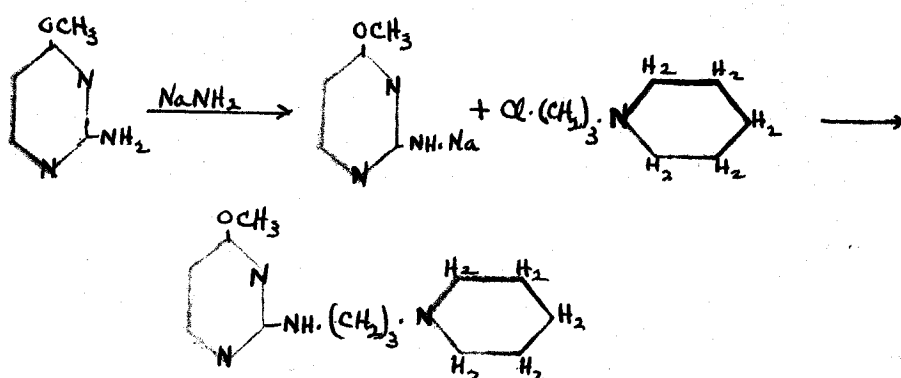
It is highly probable that this same difficulty would be encountered in trying to synthesize the plasmochin analogue. A way of circumventing this difficulty might be as follows:



Procedures quite similar to this have been used by Karrer et al (112)(113) in the iso-alloxazine series.



Adams and Whitmore (114) have recently developed a method of synthesis for amino-alkylamino-pyrimidines using sodamide.



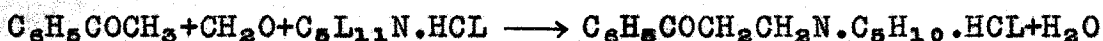
The remaining steps in the suggested procedure make use of standard reactions.

(4) Mannich Reaction products of indole. - The Mannich reaction is essentially a condensation between a compound containing active hydrogen, formaldehyde, and a suitable amine.

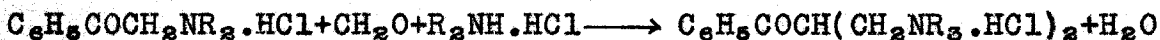


The essential feature of the reaction being the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. Thus, the product from the reaction of acetophenone, formaldehyde, and piperidine hydrochloride

is  $\beta$ -piperidinoethylphenyl ketone. (115).



Since the product obtained from a methyl ketone contains a reactive hydrogen, it is sometimes possible to carry the reaction one step further, yielding a compound with two basic groups. (116).



If the substance used in the condensation contains reactive hydrogen atoms on two or more different carbons, then substituted amino-methyl groups may appear at different points in the molecule (117). Only one product is obtained providing all the active hydrogens are replaced; however, mixtures result when only two or more stages occur.

Since the ortho- and para-hydrogens in phenols are sufficiently active, they enter into the Mannich reaction (117)(118)(119). Compounds having other substituents as well have been found to react. Examples of these are 4-acetaminophenol (118), ortho- and para-cresol (117), meta-cresol (119), 3,5-dimethylphenol (120), 2-methyl-4-ethylphenol (117), 2- and 4-methoxyphenol (121), beta-naphthol (121), and 8-hydroxyquinoline (118) have all been found to react with formaldehyde and dimethylamine or piperidine or morpholine.

Other substances which have been reported to undergo the Mannich reaction are quinaldine (122), cyclohexanone (123), 2-acetylthiophene, 2-acetyl-4-phenylthiozole and 2-acetylfuran (124).

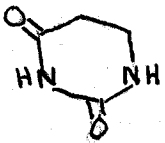
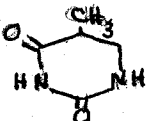
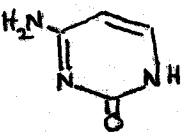
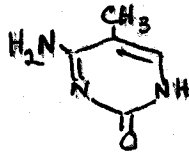
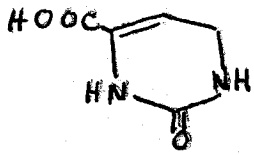
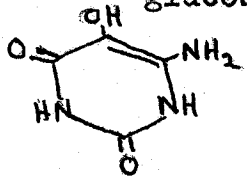
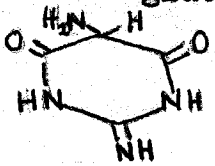
The first reported use of the Mannich reaction with indole is that of Heinrich Kühn and Otto Stein (125). In their paper they state that this reaction leads to good yields of gramine (3-dimethylaminomethylindole), 3-diethylaminomethylindole, melting at 165°, and 3-(N-piperidylmethyl)-indole. Two years later a German patent (126) was issued to Otto Stein and Heinrich Kuehn, presumably the same men, for 3-dialkylaminomethylindole derivatives to be used in the preparation of wetting agents. All of the above compounds are stated as having been prepared by carrying out the reaction in acid solution. In addition to these three compounds they also describe the 3-(N-morphoylmethyl)-indole. The point which should be noted, however, is that these investigators report the 3-diethylaminomethylindole compound to melt at 105° to 106°. This indicates that either the compound melting at 165° and that melting at the lower temperature are different substances or that a typographical error was made in the printing of a zero for a six or vice versa. A careful examination of Kühn and Stein's procedure indicates that an alkaline medium was probably used. Since this condition would tend to favor polymerization it is highly probable that the higher melting substance is such a product rather than the reported 3-diethylaminomethylindole.

#### B. Pyrimidine Compounds.

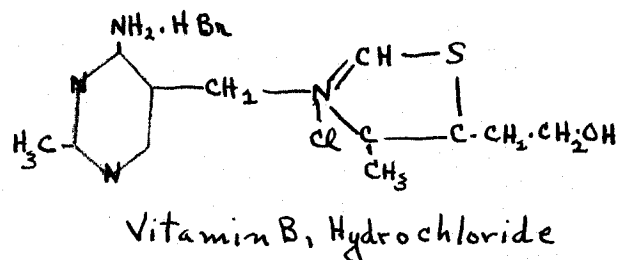
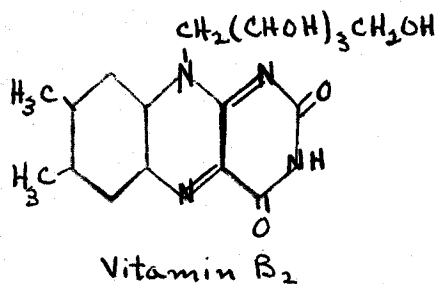
Representatives of the pyrimidine group have been

discovered in nature occurring as normal constituents of the nucleic acids. These derivatives are keto forms of pyrimidine and are classified as cyclic ureides containing  $\text{-CO-NH-}$  groupings. The derivatives thus found in nature are represented structurally in the following Table I (127).

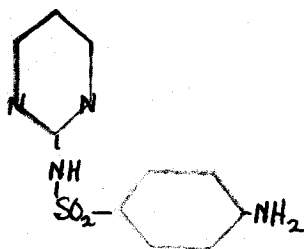
Table I. Natural Occurrence of Pyrimidines

Natural Source	Type of Pyrimidine	Name	Formula
Animal, plant, or bacterial nucleic acids	Dioxypyrimidines	Uracil	
		Thymine	
Animal, plant or bacterial nucleic acids.	Aminooxypyrimidines.	Cytosine	
		5-Methylcytosine	
Milk	Dioxypyrimidine-carboxylic acid.	Orotic acid	
Seeds of plants.	Trioxypyrimidineglucoside.	Convicine Isouramil	Isouramil+d-glucose 
Seeds of plants.	Diamino-dioxypyrimidineglucoside	Vicine Divicine	Divicine+d-glucose 

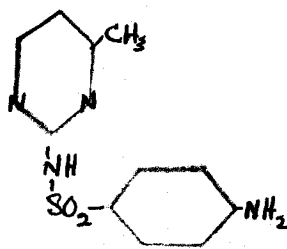
Recent investigations in vitamin chemistry has also established the existence of a pyrimidine cycle in vitamin B<sub>2</sub> (128)(129) (130)(131) as well as in vitamin B<sub>1</sub> (132)(133).



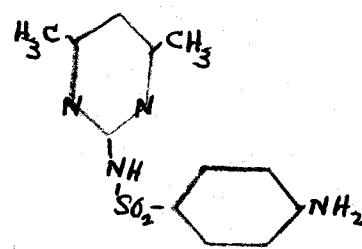
In recent years sulfa drugs containing the pyrimidine ring have appeared (134)(135). Sulfadiazine (2-sulfanilamidopyrimidine), XXX, sulfamethyldiazine (2-sulfanilamido-4-methylpyrimidine), XXXI, as well as sulfamerizine (2-sulfanilamido-4,6-dimethylpyrimidine), XXXII, are cited as examples.



XXX



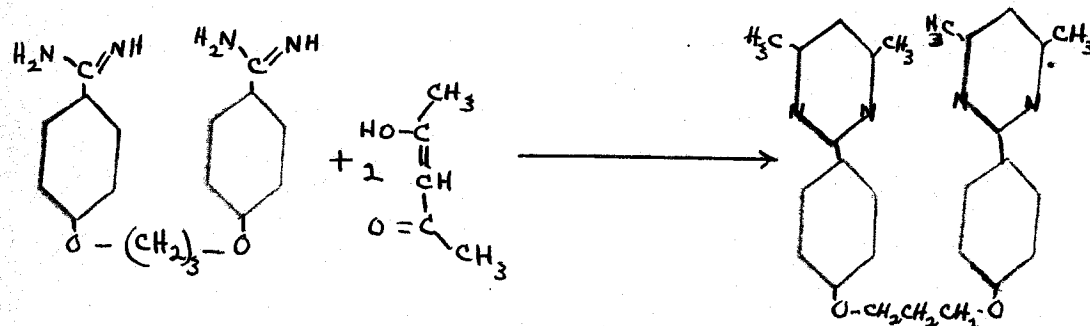
XXXI



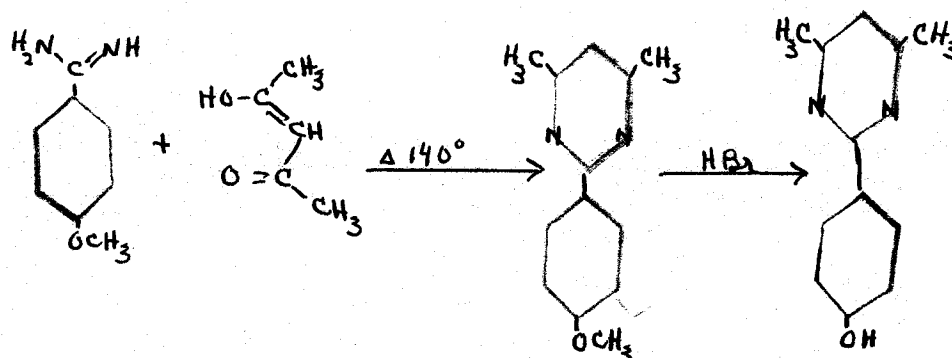
XXXII

These compounds have been found to be quite active (136).

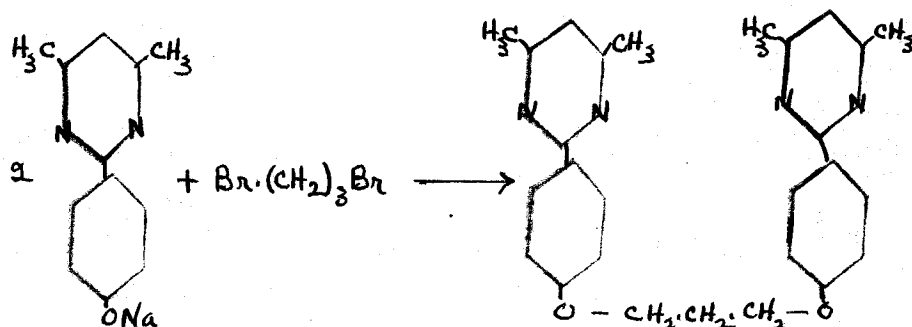
Since the aromatic diamidino compounds, such as propamidine and stilbamidine could be converted into the corresponding bis-dimethylpyrimidyl compounds by the action of acetylacetone, it would be of interest to try this. The action of acetylacetone on propamidine for example should proceed as follows to give 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane.



A method of preparing pyrimidines from acetylacetone has been described by Pinner (137). Using this procedure he was able to prepare the following substances, 2-phenyl-4,6-dimethylpyrimidine, 2-(4-methylphenyl)-4,6-dimethylpyrimidine, 2-benzyl-4,6-dimethylpyrimidine, 2-( $\beta$ -naphthyl)-4,6-dimethylpyrimidine and 2-( $\alpha$ -furyl)-4,6-dimethylpyrimidine. Gabriel and Colman (138) only obtained a complex of the type,  $C_6H_{10}N_2O + C_5H_6O_2$ , on reacting 4-methoxybenzamide with acetylacetone under these conditions. The desired 2-(4'-methoxyphenyl)-pyrimidine was obtained, however, by heating the above additional compound at about  $140^\circ$ . The product thus obtained was found to melt at  $96^\circ$  to  $97^\circ$ . It was also converted to the corresponding 2-(4'-hydroxyphenyl)-4,6-dimethylpyrimidine with constant boiling hydrobromic acid. The reactions used by these investigators were as follows:



An alternate synthesis of 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane might also proceed from the 2-(4'-nitrophenyl)-4,6-dimethylpyrimidine through the amino and hydroxy compound. Reaction of two moles of the sodium salt of 2-(4'-hydroxyphenyl)-4,6-dimethylpyrimidine with one mole of trimethylene bromide should give the desired compound. This method of attack would also offer an independent

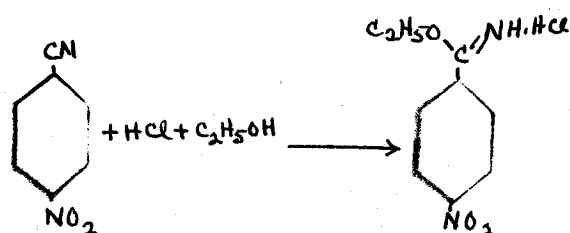


synthesis of Gabriel and Colman's hydroxyphenyldimethyl pyrimidine. Moreover, it would lead to two new compounds because the corresponding nitro and amino derivatives are at present unknown.

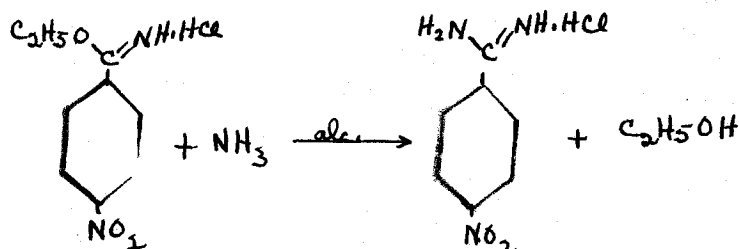
So far as we have been able to ascertain only one mononitro-2-phenyl-4,6-dimethylpyrimidine has been prepared. This was obtained by Ochiai *et al* (139). This was prepared by nitrating 2-phenyl-4,6-dimethylpyrimidine in the cold. They also reported converting it into the amino compound by catalytic reduction and this in turn into the corresponding hydroxy derivative by means of the Sandmeyer reaction. This latter substance was definitely shown to be different from Gabriel and Colman's compound by a mixed melting point.

The synthesis of the 2-(4'-nitrophenyl)-4,6-

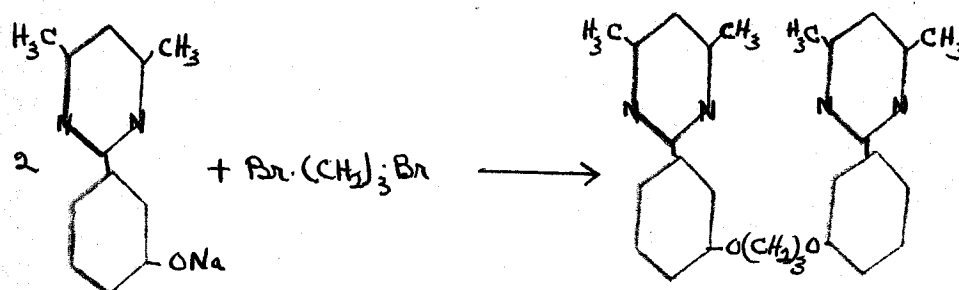
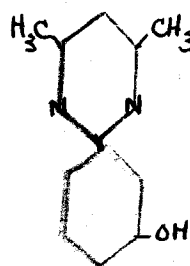
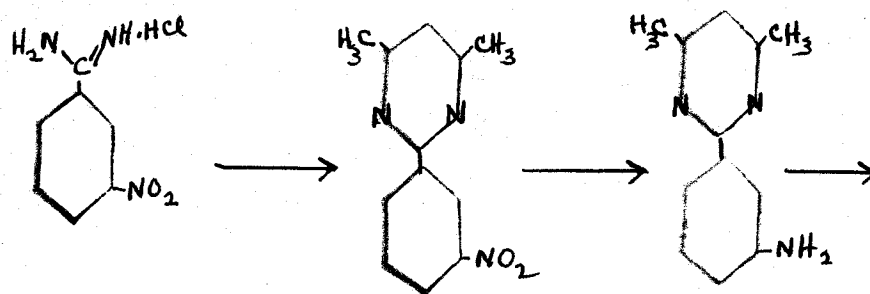
dimethylpyrimidine would involve the preparation of 4-nitrobenzamidine. The latter substance was reported by Pinner and Gradenwitz (140), who obtained it by converting 4-nitrobenzocarbonitrile into the corresponding 4-nitrobenzimidinoether hydrochloride by the action of anhydrous hydrogen chloride gas and alcohol.



Reaction of this with alcoholic ammonia transforms the imino ether into the corresponding 4-nitrobenzamidine hydrochloride.



The isomeric 3-nitrobenzamidine has also been prepared (141)(142), and it would be of interest to convert it into 2-(3'-nitrophenyl)-4,6-dimethylpyrimidine for comparison with the nitro compound obtained by Ochiai *et al.* In addition, its conversion into 3,3'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane, isomeric with 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane, should be possible.

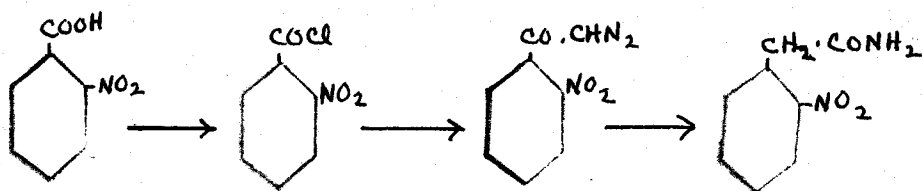


#### IV. DISCUSSION OF EXPERIMENTAL RESULTS

##### A. Synthesis of Indole Compounds and Intermediates.

The experimental work in the indole series may be regarded as exploratory in nature since no compounds analogous to plasmochin were synthesized. The research was begun with the object of systematically preparing aminoalkylamino derivatives of indole in which these substituents would be located in the alpha- and beta-positions of the pyrrol half of the indole molecule.

The synthesis of 2-aminoindole, as originally carried out, requires six separate operations (86). In an attempt to avoid some of these, we decided to start with 2-nitrobenzoic acid and prepare the necessary 2-nitrophenylacetamide by means of the Arndt-Eistert reaction. An inspection of the proposed procedure shows that three separate



steps are required:

1. The formation of the acid chloride.
2. Reaction of the acid chloride with diazomethane to yield the diazoketone.
3. Rearrangement of the diazoketone, with the loss of nitrogen, in the presence of freshly precipitated silver

oxide to give the amide when the medium is ammonical. From a first inspection of the proposed method, it would appear that no saving of time would result. It should be realized, however, that in the actual Arndt-Eistert procedure, the preparation of the diazoketone from the acid chloride and its conversion to the amide, can be carried out in one day. The actual number of steps are reduced since the diazoketone may be used immediately. The other step of course being the preparation and purification of the acid chloride.

(1) Synthesis of 2-nitrobenzoyl chloride. - The acid chloride of 2-nitrobenzoic acid was prepared by both the method of Claisen and Shadwell (143) from 2-nitrobenzoic acid and phosphorus pentachloride and by the method of Meyer (144) from 2-nitrobenzoic acid and thionyl chloride. The latter's method was found to be the most satisfactory. Real difficulty was experienced in attempting to purify the product by distillation at reduced pressure as recommended by Schroeter and Eisleb (145) because of rapid decomposition, often with explosive violence. Recrystallization at low temperatures was then attempted. This procedure was found to be satisfactory for the preparation of large quantities of the acid chloride. The product thus obtained possessed a light orange color rather than colorless as the crystals reported by Erdmann (146), melting at 20°, and by Movrojanis (147), melting at 24°-25°. Our product melted at 22°-25°.

It may have been possible to distill this purified material under reduced pressure without decomposition. No attempt was made to do this.

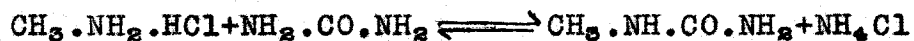
(2) N-Nitrosomethylurea. - The diazomethane, used in the Arndt-Eistert reaction was obtained from N-nitrosomethylurea.



This substance was prepared by the reaction of methylamine hydrochloride, potassium cyanate and sodium nitrite (148) and by the reaction of methylamine hydrochloride, urea and



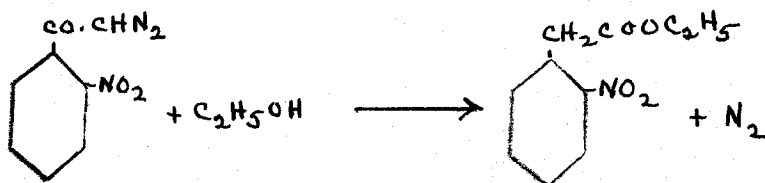
sodium nitrite (149). This last procedure is readily



carried out and represents a considerable improvement over the first, since less labor is involved. In carrying out the second stage of this operation, the addition of the Methylamine-urea-nitrous acid solution to the cold aqueous sulfuric acid, it was found best to have the inlet tube extending below the surface of the liquid. This avoids the loss of nitrous oxide liberated in the reaction.

(3) 2-Nitrophenylacetamide. - To prepare the desired 2-nitrophenylacetamide the preparation of Arndt and Eistert

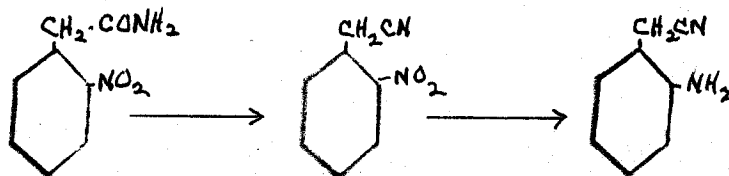
(88) was attempted. Instead of the expected amide, melting at 160°-161°, a compound melting at 70°-71° with decomposition was obtained. Extraction of this with dilute alkali, filtering and then acidifying gave a small amount of material which melted at 100°-108° with decomposition. Reissert and Scherk (150) reported that 2-nitrophenylacetic acid melted at 100°-110° with decomposition. The insoluble residue on recrystallization from 95 per cent alcohol melted at 69°-70°. Reissert and Scherk report the ethylester of 2-nitrophenylacetic acid melts at 69°. It is evident from this that the alcohol used in the procedure reacted with the diazoketone to give the corresponding ester.



To avoid this reaction we decided to use a procedure similar to that described by Burger and Avakian (151) for the preparation of para-homoanisamide. In this way we were able to obtain a 44 per cent yield of the crude amide, melting point 150°-160°. Recrystallization from 95 per cent alcohol caused it to melt at 160°-161°. This yield is about 10 per cent lower than that recorded by Apndt and Eistert (88), but we feel that our modification should give even better results providing the acid chloride and the dioxane were free of all impurities.

(4) 2-Nitrobenzylcyanide. - The conversion of the acid amide to 2-nitrobenzylcyanide was carried out using the directions of Pschor and Hoppe (86). Two methods may be used, (a) dehydration by heating with phosphorus pentoxide and distilling off the cyanide as it is formed, and (b) refluxing with thionylchloride in anhydrous benzene, and steam distilling the amorphous residue. Both methods were tried, the latter gave the most satisfactory yield. The product obtained by both methods melted at 85°-86°. Pschorr and Hoppe's product melted at 84°.

(5) 2-Aminobenzylcyanide. - The conversion of the cyanide to the 2-aminobenzylcyanide was also carried out using the above investigators procedure. The method was found to give the expected amine in good yield, but on trying to recrystallize this product it was changed into an insoluble blue substance. The investigation was not carried further because it was felt that the 2-aminoindole would be even more difficult to handle due to a tendency to undergo air oxidation. The reactions thus far carried out were as follows:



No attempt has been made as yet to prepare 2-chloroindole by the method of Mazzara and Borgo (89) from indole and

sulfuryl chloride.

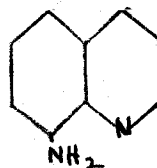
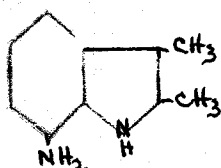
(6) 3-Iodoindole. - Attention was next turned to the preparation of 3-iodoindole by the procedure of Pauly and Gundermann (91). This gave an excellent product. It was not found to be too stable, for on allowing to remain in contact with air overnight it underwent decomposition. An attempt to react this with morpholine and  $\gamma$ -diethylamino-propylamine yielded tars from which nothing could be separated.

(7) 3-Aminoindole. - Since the 3-iodoindole was found to be unsatisfactory, we then attempted the preparation of 3-aminoindole by the method of Madelung (90). Indole was allowed to stand in contact with iso-amyl-nitrite and sodium ethylate for two days in the refrigerator. The amyl alcohol was extracted with ether and the aqueous layer treated with a 6 normal alkaline solution of sodium hydrosulfate until the color was discharged. The product, of which only a trace was obtained, was in the form of pale yellow plates. These plates melted at  $115^{\circ}$  with decomposition when rapidly heated. Madelung reported the compound to melt at  $117^{\circ}$  with decomposition upon heating rapidly. The above pale yellow plates probably represented a slightly impure form of 2-aminoindole. This procedure gave such unsatisfactory yields that any synthesis depending on its use would be impractical. No further attempts were made to increase the yields.

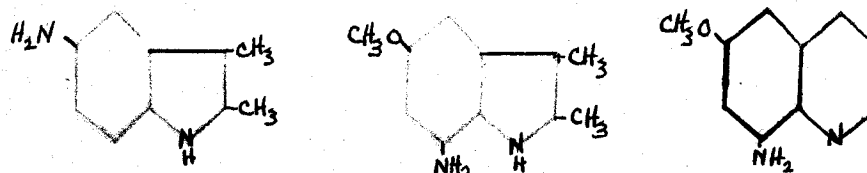
Instead of continuing investigations along these lines we began work with the object of synthesizing indole

compounds possessing aminodialkylamino side chains in the benzene half of the molecule. These derivatives it was thought, might be more stable providing the 2- or the 2,3-positions were occupied by methyl groups. These compounds can be obtained from either the 2-nitro- or 4-nitrophenylhydrazone of acetone or methylethyl ketone by means of the Fischer rearrangement. Reference to the literature showed that all the mononitro-2,3-dimethylindole compounds had been prepared (106) (108). Attention was therefore turned to these compounds.

The meta-nitrophenylhydrazone of methylethyl ketone gives a mixture when a Fischer rearrangement is carried out, therefore we decided to confine our attention to the corresponding ortho- and para-derivatives. Since the para-compound had been converted into the 5-amino-2,3-dimethylindole by Bauer and Strauss (106), it was felt that the corresponding ortho-nitrophenylhydrazone should also be capable of conversion to the corresponding 7-amino-2,3-dimethylindole using similar conditions. The reason for selecting this particular derivative, being that it was not yet known and that it ought to be more nearly like the corresponding 8-aminoquinoline analogue. This similarity is readily seen by a comparison of these two structures. In addition to this, the



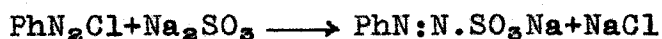
simultaneous preparation of the 5-amino-2,3-dimethylindole and 5-methoxy-7-amino-2,3-dimethyl indole was also planned. This last substance is the indole analogue of 6-methoxy-8-amino-quinoline, plasmochin base.



Because each of these substances required different intermediates they will be discussed in the order in which the substituents occur in the benzene half of the indole molecule rather than in the order which they were studied in the laboratory. Thus, the 5-amino-compound was not prepared, even though its preparation had already been described, because the 7-amino-2,3-dimethylindole was the first obtained in this investigation. Since it was found to be unstable, this line of study was dropped and the remaining time was given over to a study of the Mannich reaction products of indole and to the synthesis of 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane.

(8) 4-Nitrophenylhydrazine. - The starting point for the synthesis of 5-nitro-2,3-dimethylindole was 4-nitrophenylhydrazine. The most satisfactory methods for obtaining this substance are those published by Davies (152) and which depend on the use of sodium sulfite or of ammonium sulfite to bring about reduction of the diazotized 4-nitroaniline.

The usual course which the reaction takes consists in the formation of the appropriate diazosulfonate by the action of sodium sulfite on the diazonium chloride. This is then reduced with bisulfite or sulfur dioxide to the hydrazinesulfonic acid. Hydrolysis of this gives the corresponding hydrazine hydrochloride (153).



Reduction of diazotized 4-nitroaniline does not follow this course (152)(154). In this particular instance the diazonium chloride reacts with two moles of sodium sulfite and one mole of water to produce a diazodisulfonate compound in addition to sodium chloride and sodium hydroxide. It is not necessary in this instance to reduce the compound with sodium bisulfite or sulfur dioxide since the hydrazine hydrochloride is formed on hydrolysis of this addition product.



Although Davies designates the quantities to be used in the diazotization of 4-nitroaniline he does not specify the method. Para-nitroaniline tends to form

diazooxides and couples with itself when diazotized slowly. We therefore pasted the amine with the acid and then caused the free base to precipitate in a finely divided form by adding crushed ice and water all at once. Treated thus, the temperature of the mixture tends to drop to  $0^{\circ}$  to  $-3^{\circ}$  whereupon the calculated amount of sodium nitrite, in a small amount of water, was added. This procedure resulted in the formation of a nearly clear solution within about ten minutes providing good agitation was used. This was filtered and added to the cold sulfite solution in accordance with Davies' directions. The hydrazine was obtained in a yield which amounted to 67 per cent of the theoretical amount. It also melted sharply at  $158^{\circ}$  with decomposition. A sample on recrystallization from dilute alcohol formed light brown platelets which still melted at this temperature. Davies stated the compound melts at  $157^{\circ}$  (dec.).

(9) 4-Nitrophenylhydrazone of methylethyl ketone. -

The procedure of Bauer and Strauss (106) was followed in the preparation of 4-nitrophenylhydrazone of methylethyl ketone. According to the authors the yields were good. A yield of 70 per cent was obtained by us from two six gram runs. When the same mother liquor was used for two additional preparations the combined yields amounted to 86 per cent of the calculated amount. The crude product melted at  $124^{\circ}$ , but one recrystallization from dilute alcohol caused it to melt at  $126^{\circ}$ - $127^{\circ}$ . This is 2 degrees higher than that

reported by Bauer and Strauss.

(10) 5-Nitro-2,3-dimethylindole. - To rearrange the 4-nitrophenylhydrazone into the corresponding 5-nitro-2,3-dimethylindole we used the same author's directions. Using 5 grams of the finely powdered hydrazone and refluxing with concentrated hydrochloric acid on the water bath, a yield of 44 per cent of the theoretical amount was obtained. In another preparation approximately three times this amount of the hydrazone was transformed using the same period of heating. The yield was 60 per cent of the calculated amount, melting point 182°-184°. Recrystallization from dilute acetic acid gave tiny, brown crystals, melting at 186°. This is in agreement with Bauer and Strauss' value.

(11) 2-Nitrophenylhydrazine. - This was first prepared by Bischler's procedure which consisted in the formation of the tin double salt by allowing a strongly acid stannous chloride solution to run into the diazotized ortho-nitroaniline. The precipitated tin double salt was filtered, dissolved in hot water and hydrogen sulfide gas passed in to precipitate the tin as stannic sulfide which could be filtered off. The free base was then liberated by adding a saturated solution of sodium acetate to the mother liquor. Under these conditions a 42 per cent yield of the crude product resulted, melting at 83°-85°. Recrystallization from benzene raised its melting point to 90° which agreed with that reported by Bischler (155). The yields were too poor

and the labor involved too great to make this method of practical value.

A careful search through chemical abstracts brought to light the procedure of Müller, Montegel and Reichstein. (156). This they reported to give yields varying from 74 to 89 per cent of the theoretical amounts using a 0.35 mole quantity of ortho-nitroaniline. At no time, however, were we ever able to obtain yields as good as this. In one instance a crude yield amounting to 30 per cent of the theoretical resulted, and in another the yield of the pure product 43 per cent, melting at 92°-93°.

As far as we were able to determine no detail in the preparation had been overlooked. Two sources of trouble may have been due, however, either to an incomplete diazotization of the amine or incomplete hydrolysis of the hydrazinesulfonate. Incomplete diazotization may have occurred, since the process was carried out in the cold. Bogert and Hand have (157) pointed out that no external cooling is necessary in this diazotization and that cooling only retarded it. The other source of error is more positive, since we found the hydrazinesulfonate to be relatively insoluble in the hydrolytic medium and that prolonged boiling was necessary. This treatment, since concentrated hydrochloric acid was used, presented considerable trouble because of the evolution of hydrogen chloride gas during this digestion.

Hoping to find a better procedure, we sought for a quick method of diazotization for weakly basic substances similar to ortho-nitroaniline as well as a hydrazine sulfonate which should not be too resistant to hydrolysis.

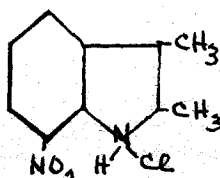
To bring about quick diazotization we found the inverted method devised by C. and H. Sunder (158) for para-nitroaniline to be quite satisfactory. It also possessed an advantage over the more common direct method in that it yields a more concentrated solution and can be carried out more quickly, since the amine is pasted with water and sodium nitrite instead of being dissolved in acid by heating. The acid requirement may also be cut down to 0.1 mole excess over the theoretical amount.

A satisfactory reducing agent was found in ammonium sulfite using the method of Davies (152) for para-nitroaniline. Since the diazosulfonate is more soluble than the para-isomer, it was necessary to make the reaction mixture strongly acid and to allow it to stand overnight before a precipitate was formed. By heating this with concentrated hydrochloric acid on the steam bath it was readily converted into the hydrazine hydrochloride. Strong cooling caused this to precipitate. By taking it up in hot water and adding a saturated solution of sodium acetate it was possible to obtain good yields of 2-nitrophenylhydrazine.

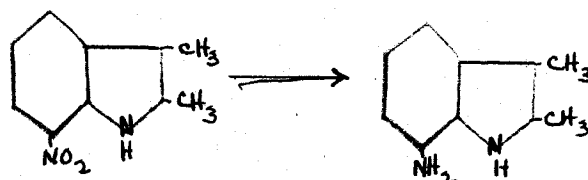
(12) 2-Nitrophenylhydrazone of methylethyl ketone. - This was prepared in the same way as for the para-isomer.

The yields were also quite good and the technique of reusing the mother liquor was found to equally satisfactory as in the previous case. It was not necessary to recrystallize the hydrazone since it melted at  $73^{\circ}$ . This is the same as that reported by Bauer and Strauss (106).

(13) 7-Nitro-2,3-dimethylindole. - This hydrazone was found to be somewhat more resistant to rearrangement than the para-isomer. However, by filtering off the nearly pure product, melting point  $158^{\circ}$ - $160^{\circ}$  (dec.), after cooling the reaction mixture and then diluting the mother liquor, it was possible to recover any unchanged hydrazone due to its insolubility. On allowing the above diluted mother liquor to stand overnight we obtained slightly more than a gram of reddish colored needles which melted at  $208^{\circ}$  (dec.). On the basis of a nitrogen analysis of this product it appears to be the hydrochloride of 7-nitro-2,3-dimethylindole, however, the analytical results are 0.4 per cent too high for the calculated value. To confirm this it would be necessary to have a chlorine analysis. If we assume the analytical data sufficient the formula could be represented by the following:



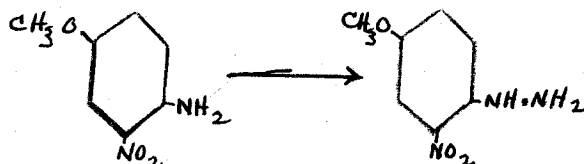
(14) 7-Amino-2,3-dimethylindole. - About 0.03 mole of 7-nitro-2,3-dimethylindole, melting at 158°-160°, was treated with a sodium hydrosulfite until approximately 0.3 mole excess had been added to the boiling mixture. The resulting pale yellow solution, after removal of about 150 ml. of solvent, yielded slightly over one gram of a product melting at 125°-127°. It was found to be extremely soluble in alcohol as well as in benzene. The latter was used as a solvent for recrystallization. The white crystalline product which separated out, melted at 129°-130°. A nitrogen analysis agreed closely with the calculated value for the desired amine. The product is not stable, for on standing several days in a tightly stoppered bottle, it turned black. The manner of synthesis is illustrated in the accompanying equation.



This represents, we believe, the first recorded synthesis of the particular amine. The one which is still unknown is 6-amino-2,3-dimethylindole.

(15) Attempted preparation of 2-nitro-4-methoxyphenylhydrazine. - The preparation of this compound has been reported by Robinson and Tomlinson (111). They reported that this compound was obtained by adding a cold diazotized

3-nitro-4-anisidine solution to a cold stannous chloride solution. Treatment of the precipitate, after redissolving in water, with excess sodium acetate yielded bright red plates which melted at  $127^{\circ}$ .

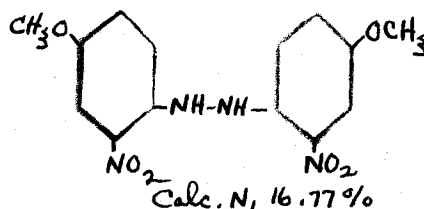
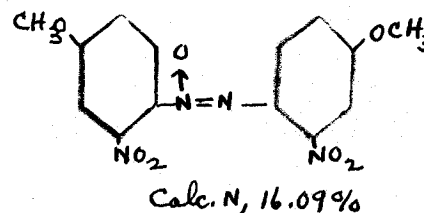
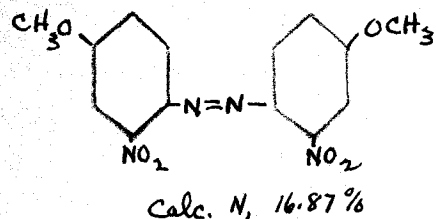


A repetition of their work yielded only a small amount of tiny red needles. The heavy precipitate which was formed appears to be composed for the most part of tin, since considerable ash remained as a residue on burning. The needles were also found to give a depression of the melting point with 3-nitro-4-anisidine.

In a second and much larger run we were able to obtain about 8 grams of bright red needles, melting at  $102^{\circ}$ - $103^{\circ}$ . This was raised to  $108^{\circ}$ - $109^{\circ}$  on recrystallization from dilute alcohol. The melting point was not raised any higher by an additional recrystallization. Analysis showed it to contain 16.4 per cent of nitrogen. It is definitely not the hydrazine since this must contain 23 per cent of nitrogen.

Assuming the presence of one nitrogen in the molecule it may be found by calculation that the formula weight is approximately 85 or some integral multiple of this value. By a process of trial and error and by speculating on the possible course of the reaction, the

following three formulas were found to fit the analytical data the closest.



From the amount of information available, however, it must be realized that these are theoretical possibilities and nothing more.

In another large run in which potassium sulfite was used we succeeded in obtaining some material possessing a red granular appearance and which melted at  $123^{\circ}$ - $127^{\circ}$ . Since this agreed fairly well with the reported value of Robinson and Tomlinson, we decided to try preparing the hydrazone of methyl ethyl ketone. To do this we poured over the above product a mixture of concentrated sulfuric acid and 95 per cent alcohol (1:5 by volume). A vigorous evolution of gas occurred. This did not seem too surprising since the product was crude and could have contained sodium carbonate. Dilution of this mixture after a few minutes with water caused crystallization. In this way we obtained tiny, pink needles melting at  $170^{\circ}$ - $172^{\circ}$  with decomposition. Recrystallization from alcohol raised the melting point to

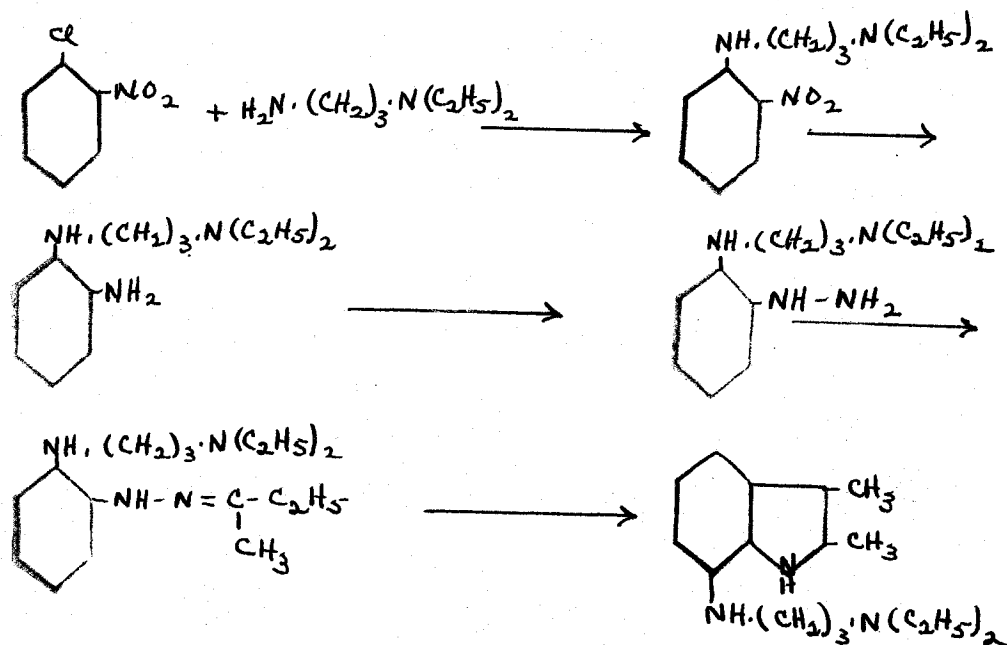
172°-173° (dec.). Analysis of this showed it to contain slightly more than 9 per cent of nitrogen. Calculation, as before, indicates the formula weight to be about 154 or an integral multiple of this. We are not prepared, as yet, to suggest a possible structure for this.

In a fourth trial we attempted the preparation by forming the diazo-sulfonate followed by reduction of this with sodium bisulfite. From this reaction we obtained a product which was soluble in hot water. When dried it was found to melt with decomposition at 119°-122°. Recrystallization from 95 per cent alcohol gave pink colored needles, melting at 168°-170° (dec.). Since these appeared to be identical with the previous product, melting point 172°-173°, a mixed melting point was taken. Instead of a depression the mixture was found to melt with decomposition at 170°-171°. It was assumed therefore that the two products were identical and that the material, melting point 168°-170° (dec.), was the less pure sample. Analysis for nitrogen agrees with this surmise, since it contains about 8.5 per cent nitrogen.

A last and final attempt was made to prepare this hydrazine by the ammonium sulfite process of Davies (152). In this instance the procedure seemed to proceed satisfactorily up to the hydrolytic stage. Here considerable decomposition and tar formation occurred. Filtering this off and adding a

saturated solution of sodium acetate to the filtrate, effected the precipitation of a small amount of brilliant, red, colored plates contaminated with some tarry material. These have not been sufficiently purified, as yet, to warrant any conclusions, but it should be noted that this is the only product thus far obtained which formed plates. If these should turn out to be identical with the material described by Robinson and Tomlinson, it may be possible to work out a suitable preparation based on the above procedure.

(16) N-( $\gamma$ -Diethylaminopropyl)-2-nitroaniline. - Towards the end of the above experimental work, it was decided that a new scheme for synthesizing the dialkylaminoalkylamine derivatives of indole would be necessary. With this object in mind the following series of reactions were outlined.



This problem was begun at about the time our attention was shifted to a study of the Mannich reaction products of indole and the synthesis of 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane. We only managed, therefore to carry out the first step in the series.

To accomplish this we adapted the procedure of Karrer and Naef (113) for the preparation of N-hydroxyethyl-2-nitroaniline to the above reaction between 2-nitrochlorobenzene and  $\gamma$ -diethylaminopropylamine in the presence of pyridine. The reaction mixture was steam distilled to remove the pyridine and any unreacted 2-nitrochlorobenzene. Since all three components of the mixture were volatile in steam, distillation was only continued until the odor of pyridine could no longer be detected. The filtrate was not discarded since it contained a fair quantity of the desired compound. Instead it was evaporated and steam distilled from an acid solution so as to remove any unchanged 2-chloro-nitroaniline. The reaction mixture remaining in the flask following the removal of pyridine was treated in the same way. Both acid fractions were then made alkaline with concentrated ammonium hydroxide and subjected to another steam distillation until all of the N-( $\gamma$ -diethylaminopropyl)-2-nitroaniline had come over. This was then extracted with ether and precipitated as the hydrochloride by passing in dry hydrogen chloride gas. The product thus obtained melted at 169°-174°. Recrystallization from a small volume of alcohol gave orange

needles, melting at  $183^{\circ}$ - $184^{\circ}$ . A nitrogen analysis indicated that the compound was combined with one molecule of hydrogen chloride. No chlorine analysis was carried out.

In place of the 2-chloronitrobenzene we also used 2-iodonitrobenzene and instead of steam distilling as in the previous case, we extracted the reaction mixture with ether. This was then washed in turn with sodium thiosulfate to remove free iodine, water, dilute ammonia and finally water again. The ethereal layer was dried over anhydrous sodium sulfate and the hydrochloride precipitated by passing in dry hydrogen chloride gas. The hydrochloride usually precipitated as a red colored oil, but solidified on chilling in an ice-bath. The product obtained by this procedure melted at  $172^{\circ}$ - $175^{\circ}$ . It contained an impurity which was difficult to remove, hence it required several recrystallizations before the melting point was raised to  $183^{\circ}$ - $184^{\circ}$ .

## B. Mannich Reaction Products of Indole.

The Mannich products derived by reacting indole, formaldehyde and a suitable amine together are somewhat similar to the dialkylaminoalkylamines. Their difference is that in one instance the amino group is attached directly to the nucleus and in the other, the amino group is separated from the nucleus by a methylene linkage.

It would seem likely, therefore, that compounds of this type might exhibit some antimalarial activity. The investigation of these substances was undertaken for this reason.

Since Kühn and Stein (125) had reported the synthesis of a number of such products in good yields, we decided to prepare these materials so that they might be included in a proposed series as well as to acquaint ourselves with the general applicability of Kühn and Stein's method of synthesis.

(1) 3-Dimethylaminomethylindole (Gramine). - Kühn and Stein's procedure calls for the use of an aqueous solution of dimethylamine, but since this was not available we decided to try the reaction with dimethylamine hydrochloride.

The hydrochloride and sodium acetate were dissolved in water and to this solution was added glacial acetic acid. The mixture was cooled and to it was added 40 per cent formalin. The resulting mixture, at 5°, was poured over the indole. The indole dissolved on shaking and the temperature rose to 30°-35°. The following day the clear solution was neutralized,

and the crude product which separated melted at 110°-112°. Recrystallization from dilute alcohol raised the melting point to 127°-129°. Two additional recrystallizations were required, however, before the product was obtained in the form of beautiful white plates melting at 134°. The main difficulty which we encountered was the removal of a red colored contaminant.

This preparation has been carried out recently using molar quantities by Snyder, Smith and Stewart (159). The yield was quite good and their crude product was reported to melt at 127°-128°. It would appear from this that a better product is obtained when the amine is used as a 35 per cent solution.

(2) 3-Diethylaminomethylindole. - Kühn and Stein reported that this compound was insoluble in acetone and that it melted at 165°. In several attempts to prepare it, however, we either got an unworkable gum or, when the conditions were acid, a product melting at 105°. A number of recrystallizations only raised the melting point to 107°-108°. This substance was also found to be fairly soluble in acetone.

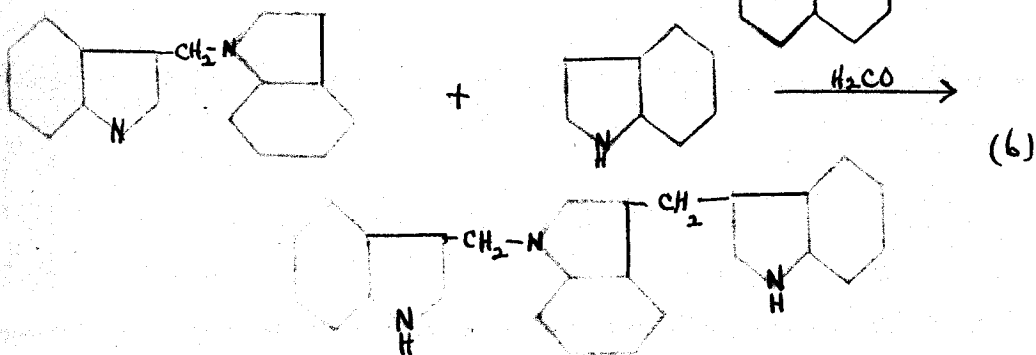
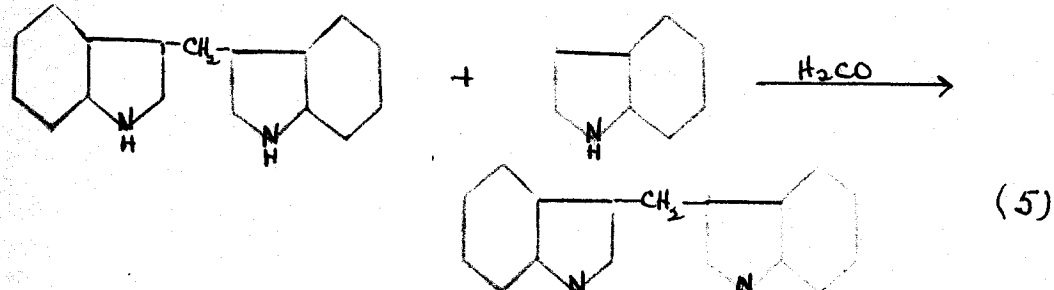
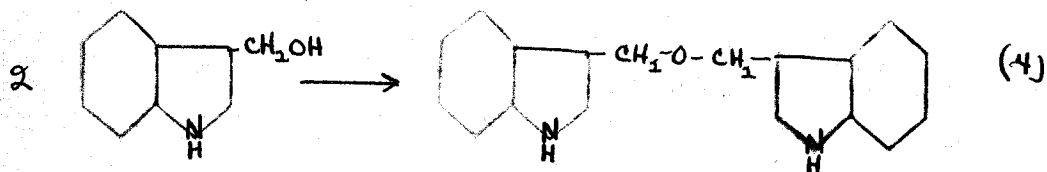
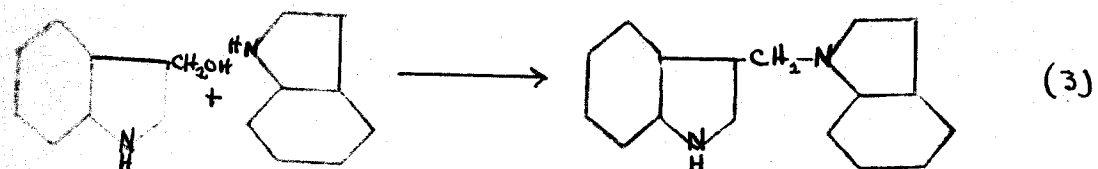
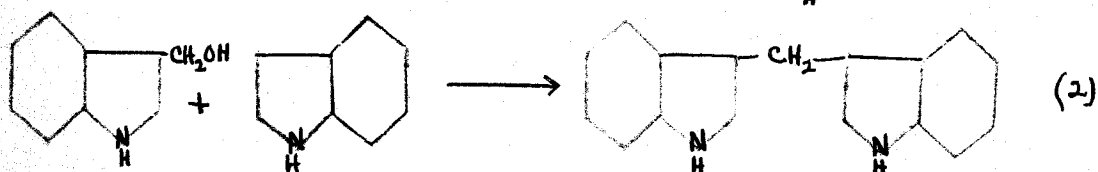
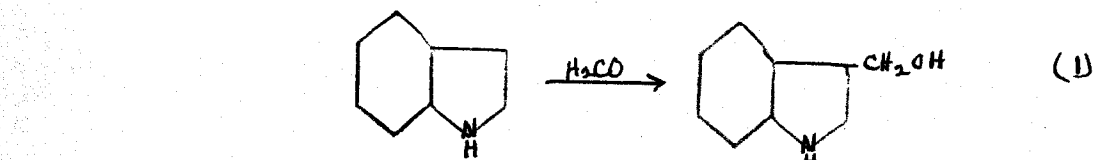
No explanation of the above results was thought of until a search through the patent literature was made. This revealed that a patent (126) had been issued to Otto Stein and Heinrich Kuehn for several 3-dialkylaminomethylindole derivatives. Among those listed was the 3-diethylaminomethylindole, and surprisingly enough it was reported to melt at

105°-106°. Rechecking the article by Kühn and Stein we noticed the slightly different spelling of Heinrich's last name. This suggested that the individuals to whom the patent was issued and the above investigators were one and the same persons.

At about this time, we repeated the preparation of the diethyl compound, but used less than the equivalent amount of sodium acetate. When the product was isolated, however, we were surprised to find it melted at 165° and that it possessed the properties designated by Kühn and Stein for their diethylaminomethylindole. This ruled out immediately the possibility that a typographical error had been made in printing a zero instead of a six or vice versa for the melting point. It was necessary, therefore, to decide which of the above reported values were in error. Since the patent had specified the necessity of carrying out the reaction under acid conditions, we examined the procedure of Kühn and Stein to see if such were the case. This was not found to be true, hence we concluded that patent description was the correct one. Analysis of the compound melting at 107°-108° and that melting at 165° for nitrogen showed the percentage composition to be 13.9 and 11.1 respectively. The calculated value for 3-diethylaminomethylindole is 13.87 per cent.

The substance with the lower nitrogen content must have a molecular weight of about one hundred or some integral multiple of this value. It is a well known fact that indole

tends to polymerize under alkaline conditions, therefore any of the following reactions may occur. The calculated per cent of nitrogen for the dimers from reactions 2 and 3



would be 11.48, whereas for the trimers from reactions 5 and 6, it is 11.2. The nitrogen content of the ether derivable from reaction 4 is 10.15 per cent. A tetramer would require 11.97 per cent nitrogen. From previous experience regarding the accuracy of the particular method of analysis which was used, it is highly probable that one or the other of the trimeric products is identical with the substance melting at 165°.

A substance has also been obtained from the reaction of a mole of indole and one half a mole of formaldehyde which melts at 162°-163°. The compound has not been completely purified as yet, hence it is not possible to say definitely that it is the same as the product melting at 165°. However, on the basis of appearance and the fact that a mixed melting point occurred at 160-162° it would seem to be the same material.

(3) 3-N-Piperidylmethylindole. - This substance has been prepared in poor yields using the procedure of Kühn and Stein as well as by allowing the reaction to take place at room temperature in 95 per cent alcohol. Both procedures gave products melting at 156°-157° after one recrystallization. Several recrystallizations were necessary to raise the melting point to 161°.

(4) 3-N-Morphoymethylindole. - This was prepared by allowing a mixture of indole, morpholine and formaldehyde in alcohol to stand at room temperature for a week. The

product was obtained as a sticky white precipitate by pouring the reaction mixture into cold water. By taking this up in ether and diluting with ligroin while cooling in an ice-salt bath, it was crystallized as a granular white product melting at  $118^{\circ}$ - $122^{\circ}$ . It still retained some sticky material. The product was obtained as white crystals, melting at  $123^{\circ}$ - $124^{\circ}$ , after a second recrystallization from ether-ligroin. Analysis showed it to have about 13 per cent nitrogen, whereas the calculated value is 12.96 per cent.

Its preparation has been reported by Otto Stein and Heinrich Kuehn (126). This was not known to us at the time we first prepared the compound. These investigators report it melts at  $124^{\circ}$ .

Using the same conditions which were found to be effective in the preparation of the morphoyl compound, we attempted to prepare similar reaction products from diethanolamine, dibutylamine, di-isobutylamine, di-2-ethylhexylamine, diphenylamine and 2-aminopyridine. In every instance a sticky, very dark colored resin resulted from which no crystalline products could be isolated.

It is evident from the above trials that these conditions permit polymerizations to occur. To avoid this it will be necessary to use an acid medium. The experimental procedure devised by Snyder, Smith and Stewart (159) should be suitable for this purpose.

### C. Pyrimidine Syntheses.

In the theoretical section of this paper it was pointed out that 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane might possess some antimalarial activity. We decided to synthesize it so that this could be determined. To do this we began work towards obtaining it from the reaction of 4,4'-diamidino-1,3-diphenoxypropane and acetylacetone. We also decided to synthesize it from 2-(4'-hydroxyphenyl)-4,6-dimethylpyrimidine and trimethylene bromide. Both procedures eventually yielded the expected compound. We also obtained a product from the reaction of acetylacetone with Propamidine which corresponds to 4-(2,3-dimethylpyrimidyl-2)-4'-N-(2-penteneoylamidino)-1,3-diphenoxypropane on the basis of a nitrogen analysis.

In addition to this work we started the synthesis of the isomeric 3,3'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane. Thus far we have succeeded in synthesizing 2-(3'-nitrophenyl)-4,6-dimethylpyrimidine. This has been reduced catalytically to the corresponding 2-(3'-aminophenyl)-4,6-dimethylpyrimidine and several attempts to prepare the phenol have been made, however, it has not, as yet, been completely purified.

We also prepared the mononitro derivative of 2-phenyl-4,6-dimethylpyrimidine by the method of Ochiai et al (139). A mixed melting point between this substance and the 2-(3'-nitrophenyl)-4,6-dimethylpyrimidine gave no

depression.

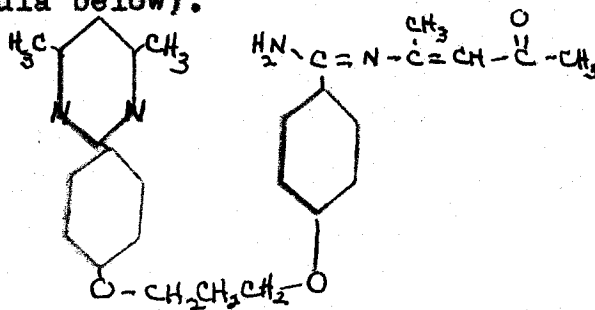
(1) 4,4'-Di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane. - By refluxing together an alcohol-water solution of the sodium salt of 2-(4'-hydroxyphenyl)-4,6-dimethylpyrimidine and trimethylene bromide we got a tan colored product which showed some softening at 180°-190° and which melted at 190°-200°. Recrystallization from dilute alcohol, it melted at 178°. A second recrystallization from hot dilute dioxane gave a finely crystalline, nearly colorless product, which melted at 183°-184°. The nitrogen analysis checked closely with the calculated value.

This same compound was also obtained when 4,4'-diamidino-1,3-diphenoxypropane was refluxed with a large excess of acetylacetone. It was necessary to decant the solvent from a rather large amount of insoluble material. The filtrate, on cooling, yielded small crystals of the desired pyrimidine, melting at 180°-182°. Recrystallized from dioxane it melted at 183°-184°. It was insoluble in water, alcohol, benzene, chloroform and carbon tetrachloride, but dissolved readily in concentrated hydrochloric acid on heating. On cooling beautiful needles were formed, which appeared to sinter at 190° and decreased in volume up to the melting point at 226°-227°. Analysis of the compound for nitrogen showed this element was present to the extent of 9.6 per cent. A formula which most nearly fits this value is  $C_{27}H_{27}N_4O_2 \cdot 4HCl \cdot 5H_2O$  and which contains 9.74 per cent

nitrogen. Without analyzing for chlorine it is not possible to say that this is the true formula, since there may be fewer molecules of hydrogen chloride and correspondingly more of water.

If the acetylacetone mother liquor is diluted with water it is possible to recover about 1.5 grams more of 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane, melting at 178°-180°.

The insoluble material, which was present to the greatest extent, was insoluble in all the solvents tried with the dipyrimidine derivative, with the exception of concentrated hydrochloric acid. The crude material was found to melt at 264°-265° with decomposition. Its melting point was raised to a constant value of 271° (dec.) by boiling with absolute alcohol. The substance, thus obtained, contained 12.36 per cent nitrogen which is in close agreement with the calculated value (12.23 per cent) for 4-(2,3-dimethylpyrimidyl-2)-4',-N-(2-penteneoylamidino)-1,3-diphenoxypropane (see formula below).



This compound yielded a white crystalline material after dissolving in concentrated hydrochloric acid and then

recrystallizing the resulting product from absolute alcohol. The product melted sharply at  $285^{\circ}$  and was found to possess about 13.7 per cent nitrogen. This indicates it must have at least a molecular weight of about a hundred or an integral multiple of this. Without further analytical data, no structure can be decided upon.

In the light of the above, it is possible to interpret some of the results which were gotten when Propamidine, as the highly insoluble free base and melting at  $193^{\circ}$ - $195^{\circ}$ , was treated with somewhat more than the theoretical amount of acetylacetone. A diluent such as anhydrous dioxane was used since no satisfactory solvent for the free base could be found. On heating such a mixture in an oil bath at  $140^{\circ}$ - $150^{\circ}$  and then filtering off the reaction mixture we were able to obtain a product which melted at  $257^{\circ}$ - $260^{\circ}$  with decomposition. Analysis of this showed it contained approximately 13 per cent nitrogen. Since this value was nearer to that of the diprimidine than to any other possible compounds, we thought it might be this substance in an impure form. This impurity we also thought must be the substance which underwent decomposition, since the pyrimidine itself should be relatively stable. However, because so little of this was available at the time we did not attempt its purification. It is evident now, that this must have been the pyrimidyl-penteneoylamidino compound in a less pure form.

Along with the above compound, we were able to

recover a product melting at 180°-185° by evaporating the solvent used in extracting the impurities from the higher melting substance. At the time, we thought this to be a less pure form of Propamide, however, it is more probable that this was the desired 4,4'-di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane contaminated with the higher melting substance.

An unsuccessful attempt was also made to prepare the desired compound by Pinner's procedure (137), but because of the very slight solubility of Propamide in the form of the free base it failed to react.

The 4,4'-diamidine-1,3-diphenoxypropane was prepared according to the directions of C. K. Banks of the Parke-Davis Company. Directions somewhat different from these have been published recently by Ashley *et al* (75).

In order to prepare 2(4'-hydroxyphenyl)-4,6-dimethylpyrimidine we had to prepare 4-nitrobenzotrile and then convert it into 4-nitroethoxycarbaminobenzene hydrochloride and this in turn into the corresponding 4-nitrobenzamide. Reaction of the latter substance with acetylacetone yielded the corresponding 2(4'-nitrophenyl)-4,6-dimethylpyrimidine. Catalytic reduction of this gave the corresponding 2(4'-aminophenyl)-4,6-dimethylpyrimidine which was converted into the desired hydroxy compound.

(2) 4-Nitrocyanobenzene. - This was prepared from both 4-nitroaniline and 4-nitrobenzamide. An unsuccessful

attempt was also made to obtain it from 4-nitrobromobenzene and cuprous cyanide by following the directions of Newman (160) for preparing 1-cyanonaphthalene. Only a trace of the cyano-compound was obtained from the dark brown reaction mixture by extraction with boiling carbon tetrachloride. The insoluble material was probably 4,4'-dinitrodiphenyl, however, this was not determined. It is quite possible that the reaction will go in the desired direction if a lower temperature were used. The cuprous cyanide used was prepared according to the method of Barber (161).

An 81 per cent yield of 4-nitrocyanobenzene was gotten by refluxing an anhydrous benzene suspension of 4-nitrobenzamide with thionyl chloride until no more hydrogen chloride gas was evolved. The desired nitrile crystallized in part from solution and that remaining in solution could be precipitated by the addition of ligroin. No recrystallization was necessary since the product was quite pure, melting at 146°-148°. This method was not used except for one preparation since there was little 4-nitrobenzoic acid on hand from which to prepare the necessary amide.

Practically all of the 4-nitrocyanobenzene used was prepared from 4-nitroaniline by the Sandmeyer procedure (162)(163)(164)(165). The careful procedure of Bogert et al (163)(164)(165) was found to give yields of about 60 per cent of the theoretical amount, but required considerable time to carry out the diazotization of the 4-nitroaniline. The

procedure was improved considerably by using a more concentrated solution and by carrying out the diazotization by adding the theoretical amount of sodium nitrite solution all at once. The use of crushed ice internally also prevented any rise in temperature of the reaction mixture and made for better agitation. Less than half an hour was necessary to obtain complete diazotization of half a mole, however, we preferred to allow an hour for this. The resulting solution was filtered and allowed to drop slowly into a well stirred cuprous cyanide-potassium cyanide solution. It was also quite important for the temperature to be maintained between 90° and 100°C. during this addition. We also preferred to use the method of steam distillation for removing the nitrile rather than extract it with boiling carbon tetrachloride. The product as thus obtained was always quite pure, melting at 146°-147°, and did not require further purification.

(3) 4-Nitroethoxycarbiminobenzene hydrochloride. -

This was prepared by the method of Pinner and Gradenwitz (140). We found it convenient to carry out the reaction in a three-necked flask arranged with an efficient mechanical, mercury sealed stirrer, a calcium chloride drying tube and a gas inlet tube. The 4-nitrocyanobenzene was dissolved in anhydrous nitrobenzene with about a half mole excess of anhydrous alcohol and cooled in an ice-bath. Stirring was begun and anhydrous hydrogen chloride allowed to pass in until the

solution was saturated. The flask was then tightly stoppered and allowed to stand for a week or better. Usually by the next day crystals had begun to form. These were quite pure, and, if desired in this form, could be removed by suction filtration, washed with anhydrous ether and placed in a vacuum dessicator over potassium hydroxide pellets. The crystals thus obtained melted at 198°-200° and represented a yield of about 56 per cent of the theoretical amount. A further quantity of the same material was retained in solution in the mother liquor. This could be precipitated from solution, however, by the addition of anhydrous ether. This product usually possessed a pink color and melted at 194°-197°. The pink coloration apparently did not matter since the melting point range was near that of the pure product. This usually represented about 31 per cent of the theoretical amount. It was usually preferable, however, to collect the entire yield at one time by adding the ether before filtering off the crystalline product.

If the imino ether is desired pure the anhydrous alcohol used should be dehydrated with magnesium ethylate, however, if one is more concerned with getting the corresponding amidine, the alcohol can be dehydrated with magnesium methylate.

(4) 4-Nitrobenzamidine. - This was likewise prepared according to the directions of Pinner and Gradenwitz (140). A few modifications were made however, which are worth men-

tioning. Instead of using an alcoholic ammonia solution of known strength and using only the theoretical quantity, we preferred to use a large excess. Since the free base is only slightly soluble it tends to crystallize out of solution as it is formed under these conditions. The pure product is then obtained pure, melting point  $214^{\circ}$ - $215^{\circ}$ , simply by filtering off the ammonium chloride-benzamidine mixture and treating with a little warm 6 normal sodium hydroxide. When washed free of the alkali and any undecomposed ammonium chloride on a Büchner funnel, it may be stored in a desiccator over calcium chloride or dried in an oven at  $100^{\circ}$ , whence it is ready for use. The substitution of the ethoxy group in the imino ether by the  $-NH_2$  group occurs best by heating the reaction mixture in a pressure bottle in a constant temperature water bath at  $60^{\circ}$ - $70^{\circ}$  for six to eight hours.

(5) 2-(4'-Nitrophenyl)-4,6-dimethylpyrimidine. - In so far as we know this particular compound has not been previously prepared. It could not be made by reacting 4-nitrobenzamidine with acetylacetone using the directions of Pinner (137) due to the insolubility of this substance. We therefore suspended the amidine in a large excess of acetylacetone and allowed the mixture to reflux together until everything had dissolved. This usually required about ten to twelve hours. On allowing to cool the product separated as a solid crystalline mass of long needles. Since the mother liquor had become a very dark red color, these crystals were contaminated with the same

material, however, careful washing with alcohol removed most of this. To completely purify the product it is necessary to recrystallize from 95 per cent alcohol. The product crystallizes in exceptionally long, silky, white needles, melting at 172°-173°. A nitrogen analysis agreed closely with the calculated value.

A moderate amount of the product remains in solution in the mother liquor. To recover it, the excess solvent can be distilled off or it can be precipitated from solution by pouring the mother liquor into water. A yield of 69 per cent of the theoretical amount based on the purified product may be obtained.

(6) 2-(4'-Aminophenyl)-4,6-dimethylpyrimidine. - This is likewise a new compound. It was prepared by catalytic reduction of the corresponding nitro compound using 95 per cent alcohol as the solvent and platinum oxide catalyst. The hydrogen is absorbed within the space of fifteen minutes to a half hour if 0.2 grams of the catalyst is used per each 0.1 mole of the nitro derivative. Some of the amino compound crystallizes from solution on cooling, however, it is best to heat the reaction mixture on a water bath until solution occurs and then filter while hot to remove the catalyst. On cooling some of the amine separates as white crystals, melting point 163°-165°. Dilution or evaporation of the mother liquor may be used for recovering that which remains in solution. This is usually found to possess a light brown color,

however, it does not seem to interfere in the Sandmeyer reaction. The purest sample we have obtained melted at 165°. It was analyzed for nitrogen and agreed closely with the calculated value.

(7) 2-(4'-Hydroxyphenyl)-4,6-dimethylpyrimidine. -

This compound has been reported previously by Gabriel and Colman (138), however, they prepared it by hydrolysis of 2-(4'-methoxyphenyl)-pyrimidine with constant boiling hydrobromic acid.

This is the first time that it has been prepared from the amino compound by the Sandmeyer reaction, and serves, therefore, as a further confirmation of the structure already assigned to the hydroxy derivative.

The best way in which to carry out the diazotization was to dissolve the amine in a mixture of water and concentrated sulfuric acid. On cooling, ice was added, and then the required amount of sodium nitrite in a little water was introduced all at once. Rapid stirring while keeping cold in an ice-bath caused the diazonium salt to separate as a white viscous mass. Continued stirring for about ten minutes produced a smooth slurry. This was then added dropwise to a boiling dilute sulfuric acid solution. The resulting dark red solution was cooled and neutralized with sodium hydroxide, whereupon the compound precipitated from solution. The crude product possessed a light tan color and melted at 170°-173°. It is best to give this product a preliminary

purification by boiling an alkaline solution of it with Darco before trying to recrystallize from carbon tetrachloride or dilute alcohol. The product thus obtained melted at 176°-178°, whereas Gabriel and Colman report their product melts at 178°-179°. After several recrystallizations from approximately 40 per cent alcohol we got a white crystalline product which melted at 180°-181°. Its nitrogen analysis agrees closely with the calculated value.

A similar procedure was used to synthesize the isomeric 2-(3'-nitrophenyl)-4,6-dimethylpyrimidine. The principle difference being in the preparation of the 3-nitrobenzotrile.

In addition to this synthesis we prepared the mononitro derivative of Ochiai et al (139) by nitrating 2-phenyl-4,6-dimethylpyrimidine in the cold with a fuming nitric-sulfuric acid mixture. The corresponding 2-phenyl-4,6-dimethylpyrimidine being obtained from benzamide hydrochloride according to the directions of Pinner (137).

(8) 3-Nitrocyanobenzene. - This was prepared using the excellent directions of Bogert and Beans (166). The nitration is carried out by making a solution of potassium nitrate in concentrated sulfuric acid, cooling to 10° and allowing the benzonitrile to drop in at such a rate that the temperature does not rise above 20°. The temperature was easily maintained at 15° by using an ice-salt cooling bath. The product

is then poured with stirring into a mixture of ice and water and filtered. After washing free of color with dilute ammonium hydroxide, it may be recrystallized from 6 normal acetic acid. An 80 per cent yield of long, slender, silky needles, melting at 117°-118° was obtained.

(9) 3-Nitroethoxycarbiminobenzene hydrochloride. -

This compound has been previously reported by Lossen and Neubert (141) and by Pinner (142). Essentially the method of Lossen and Neubert was used, otherwise this preparation did not differ from that of the isomeric 4-nitroethoxycarbiminobenzene hydrochloride. The product was collected by the addition of anhydrous ether to the nitrobenzene reaction mixture. A sample dried in vacuo over potassium hydroxide pellets melted at 137° with decomposition. The yield was 87 per cent of the theory.

(10) 3-Nitrobenzamidine hydrochloride. - This has also been previously prepared by Lossen and Neubert (141) and by Pinner (142). The method of preparation used by us did not differ from that used with the isomeric compound. It was isolated, however, by evaporating the solvent in vacuo. To the resulting residue was added concentrated hydrochloric acid and the stable chloride formed by this treatment dissolved by the addition of more water and heating. After purifying with Darco it was evaporated to dryness. Recrystallized from 95 per cent alcohol, it yielded finely crystalline, colorless needles which melted at 248°-249°.

The yield was 72 per cent of the theoretical based on the pure hydrochloride.

(11) 2-(3'-Nitrophenyl)-4,6-dimethylpyrimidine. - This substance has not been reported in so far as we have been able to ascertain. We have succeeded in making it by two different procedures. The first preparation was based on the method of Pinner (137) in which the hydrochloride in a 30 per cent potassium carbonate solution is treated with the calculated amount of acetylacetone. This causes the solution to turn yellow and after standing overnight the tiny, yellow leaflets, which form, may be collected. The crude product melted at 154°-156°. Recrystallized from dilute alcohol it melted at 157°-158°. This gave no depression of the melting point when mixed with the Japanese investigators compound. It was also found to contain the correct amount of nitrogen by analysis.

The same compound was obtained in a 87 per cent yield by suspending the 3-nitrobenzamidinium hydrochloride in excess acetylacetone and then adding the calculated amount of sodium ethylate for liberation of the free base. The mixture was maintained under reflux until solution occurred. Dilution of the reaction mixture yielded a crude product which melted at 155°-157°. Recrystallized from an alcohol-acetone mixture it melted at 156°-157°.

(12) 2-(3-Aminophenyl)-4,6-dimethylpyrimidine. - This amino derivative was prepared in exactly the same way as that used for the para-compound. Evaporation of the solvent

in vacuo yielded the theoretical amount of a product melting at 88°-90°. By dissolving in ether and allowing the solvent to evaporate slowly we were able to get the product in the form of large transparent prisms which melted at 90°-91°. The picrate was prepared and appeared to melt at 199°, however, this is not too easy to distinguish because of its tendency to undergo shrinkage and become quite dark before liquifying. The amino compound possessed the theoretical amount of nitrogen, however, the picrate gave high results. This may be due to its not being completely free of excess picric acid. The compound appears to be identical with that reported by Ochiai et al (139).

(13) 2-Phenyl-4,6-dimethylpyrimidine. - This has been previously prepared by Pinner (137) from benzamidine hydrochloride in a 30 per cent potassium carbonate solution by the addition of the calculated amount of acetylacetone and allowing to stand. This procedure was followed; however, the yield of pure product was only 32 per cent of the theoretical. It melted sharply at 82°-83°.

It would probably be obtained in a more satisfactory yield by refluxing with acetylacetone and the calculated amount of sodium ethylate.

The benzamidine hydrochloride used in this preparation was obtained from benzamidine by the procedure of Ronzino and Ekeley (167).

(14) Mononitro-2-phenyl-4,6-dimethylpyrimidine. - This nitration was carried out, except for a slight change in conditions, in the manner described by Ochiai et al (139). The change mentioned was to allow stirring to take place without external cooling after all of the 2-phenyl-4,6-dimethylpyrimidine had been introduced. When the temperature rose to 15° the ice-salt bath was replaced and stirring allowed to take place for an hour in the cold. The crude product melted at 82°-110° and still contained considerable unchanged phenyl-dimethylpyrimidine. Fractional crystallization from an acetone-alcohol mixture yielded a product melting at 148°-152°. A second recrystallization from acetone alcohol caused it to melt at 157°-158°.

In a subsequent preparation the exact directions of Ochiai was followed, but none of the mononitro compound was produced. It is apparent that the best temperature for nitration is somewhere near 15° but definitely below room temperature.

## V. EXPERIMENTAL

### A. Indole Compounds and Their Intermediates.

Purification of 2-Nitrobenzoic acid. - One hundred grams of technical 2-nitrobenzoic acid was dissolved with refluxing in 150 ml. of distilled water. One gram of Darco charcoal was added and the resulting mixture refluxed for one-half hour, whence it was filtered through a previously heated hot-water funnel and the filtrate allowed to cool slowly over a period of several hours to permit crystallization to occur. The product was collected on a Büchner funnel, washed thoroughly with several portions of cold water, pressed as dry as possible and the product allowed to dry for one-half hour at 100°C. The product thus obtained weighed 90.7 grams and melted at 146°-148°C.

2-Nitrobenzoyl chloride (144)(145): One hundred grams of 2-nitrobenzoic acid (0.564 mole) and 206 ml. (326g; 2.82 moles) of thionylchloride were refluxed together on a water-bath until no more hydrogen chloride gas was evolved. The excess thionyl chloride was then distilled off, first under ordinary pressure and finally under reduced pressure (water-pump). To the dark colored viscous liquid which remained there was added twice its volume of anhydrous ether, with swirling until a solution was obtained. The solvent was then removed at reduced pressure and the process repeated so as to remove the last traces of thionyl chloride. The viscous product was taken up once again in ether, Darco added

and the resulting mixture allowed to reflux on a water-bath for 15 minutes, whereupon it was filtered through a fluted filter paper and the solvent removed at reduced pressure. The viscous residue was then dissolved in as small an amount of ether possible and the acid chloride caused to crystallize by the slow addition of petroleum ether while cooling in an ice-salt mixture and while stirring and scratching the walls of the beaker. As soon as crystals began to make their appearance, the addition of ligroin was discontinued until the crystals had a chance to form. Ligroin was then added rapidly with stirring until no more crystals were deposited. These crystals were collected on a cold Büchner funnel and washed several times with small portions of cold ligroin. The crystals were then quickly transferred to a vacuum dessicator containing paraffin wax and anhydrous calcium chloride and then stored in a refrigerator. The product thus obtained weighed 95 grams (97 per cent of the theoretical amount) of light orange colored needles, melting at 22°-25°. Erdmann's (146) product melted at 20° and that of Mavrojannis (147) at 24°-25°.

N-Nitrosomethylurea (148)(149):

a. Preparation from methylamine hydrochloride, potassium cyanate and sodium nitrite. - In 600 ml. of warm water contained in a 1.5-l. round-bottomed flask are dissolved 100 g. (1.48 moles) of methylamine hydrochloride and 150 g. (1.85 moles) of C. P. granular potassium cyanate. The

solution is boiled gently for ten minutes and then vigorously for five minutes. The hot solution is filtered and added to a solution of 100 g. (1.38 moles) of 95 per cent sodium nitrite in 200 ml. of water. The whole is cooled to  $-5^{\circ}$  and poured into a mixture of 600 g. of ice and 100 g. of concentrated sulfuric acid contained in a 3-l. beaker. The beaker is surrounded by an ice-salt mixture and the methylurea solution added at such a rate that the temperature does not rise above  $0^{\circ}$ . The addition requires about 45 minutes.

The nitrosomethylurea separates as a crystalline, foamy precipitate which is filtered at once with suction and well pressed on the filter. The crystals are stirred to a paste with cold water (about 30 ml.), sucked as dry as possible, and dried in a vacuum desiccator to constant weight. Yield 120-140 g. 84-98 per cent of theoretical amount.

b. Preparation from methylamine hydrochloride, urea and sodium nitrite. - One hundred grams (1.5 moles) of methylamine hydrochloride and 300 grams (3 moles) of urea were dissolved in 400 ml. of water and gently refluxed for two and three-quarters hours, and then more vigorously for one-quarter hour. To this there was then added 110 g. (1.06 moles) of sodium nitrite. The resulting solution was then cooled to  $-10^{\circ}$ . It was then allowed to run in, beneath the surface, of a well cooled mixture containing 110 g. of concentrated sulfuric acid and 600 g. of crushed ice. At the end of this addition the product is transferred to a Büchner

funnel and sucked as dry as possible. The product is then washed with 30 ml. of ice-cold water. Keep the product in a vacuum dessicator in the refrigerator.

2-Nitrophenylacetamide (88) (157):

a. Attempted preparation by the method of Arndt and Eistert (88). - A mixture of 500 ml. of ether and 75 ml. of 45 per cent aqueous potassium hydroxide was cooled to 5°. To this mixture there was added, with continuous cooling and efficient stirring, 35 g. (0.473 mole) of finely powdered N-nitrosomethylurea in small portions as rapidly as the crystals dissolve (this requires a few minutes). The deep yellow ethereal solution of diazomethane can be separated from the aqueous layer by decantation or by means of a separatory funnel. The solution, which contains approximately 9.6 g. (0.1 mole) of diazomethane, was dried for several hours (2 hr.) over pellets of pure potassium hydroxide.

To this solution in a liter three-necked flask arranged with a condenser, a dropping funnel and a mechanical stirrer there was added in a dropwise manner 18.6 g. (0.1 mole) of 2-nitrobenzoylchloride dissolved in about 10-20 ml. of anhydrous ether while the temperature is maintained at 0°-5°. After the addition stirring is continued at this temperature for one-half hour, and then at room temperature for one or two hours. omega-Diazo-2-nitroacetophenone was formed with the evolution of gas, and was immediately precipitated, in part, in crystalline form. It was then cooled vigorously

the ether was decanted off and the crystals were tibrated with small amounts of cold ether.

These crystals were then dissolved in 150 ml. of 95 per cent alcohol at 50°-60° with stirring. An equal volume of 2-normal ammonium hydroxide was added to decompose the diazoketone. To this reaction mixture there was then added 10 ml. of 10 per cent silver nitrate solution and the resulting mixture was maintained at a temperature of 70° until the evolution of gas had ceased (about 1-1/2 hrs.). The product was filtered through a sintered glass funnel with suction while still hot in order to remove the oxides of silver. The dark red colored solution was then cooled in an ice-salt mixture and diluted with cold water. A light tan colored product precipitated out of solution. This was collected on a sintered glass funnel and washed well with water and sucked as dry as possible. The yield of crude material after drying overnight was 6 g., melting point 71°-72°, the product appeared to boil in the capillary tube at about 110°.

Extraction of a portion of this with dilute alkali, filtering and then acidifying gave a small amount of material melting with decomposition at 100°-108°. Reissert and Scherk (150) reported that 2-nitrophenylacetic acid melted at 100°-110° with decomposition. The insoluble residue on recrystallization from 95 per cent alcohol melted at 69°-70°. Reissert and Scherk report the ethylester of 2-nitrophenylacetic acid

melts at 69°.

b. Preparation by the modified procedure of Burger and Avakian. (151). - The omega-diazo-2-nitroacetophenone was prepared in exactly the same way as described above. The ethereal solution was cooled vigorously, the ether decanted and the crystals triturated with a small amount of cold ether. The diazoketone was dissolved in 100 ml. of dioxane with slight warming and stirring on a water-bath at 60-70°. To this solution there was then added, in a dropwise manner, 150 ml. of concentrated ammonium hydroxide followed by 30 ml. of 10 per cent silver nitrate solution. This reaction mixture was then allowed to reflux until the evolution of gas had ceased (1-2 hrs.). The reaction mixture was filtered through a sintered glass funnel, while hot, in order that the silver oxides were removed. The filtrate was cooled vigorously until crystallization began to occur and then diluted with water to cause complete precipitation. The product was allowed to settle and was then collected on a sintered glass funnel. It was washed several times with small amounts of water, sucked as dry as possible, and transferred to a watch glass. After drying overnight a crude yield of 8 g. (44 per cent of the theoretical amount) of a product (melting point 150-160°) was obtained. Recrystallization from 95 per cent alcohol caused it to melt at 160-161°. This agrees with that reported by Arndt and Eistert (88).

2-Nitrobenzylcyanide (86):

a. Dehydration of 2-nitrophenylacetamide with thionyl chloride. - Twenty grams (0.11 mole) of 2-nitrophenylacetamide was refluxed for 20 minutes with 13 ml. of thionyl chloride on a water-bath in the absence of moisture. Fifty milliliters of anhydrous benzene is then added and the whole allowed to reflux for 5 hours. The amorphous residue was filtered off, steam distilled, and the residue dissolved in 20 ml. of alcohol. On cooling the 2-nitrobenzylcyanide came down as needles which melted at 84°. The purified product melted at 85-86° after recrystallization from 95 per cent alcohol. The yield of purified product was 13.3 g. (75 per cent of the theoretical amount).

b. Dehydration of 2-nitrophenylacetamide with phosphorus pentoxide. - Five and four-tenths grams (0.03 mole) of 2-nitrophenylacetamide and 11.4 g. (0.08 mole) of phosphorus pentoxide were heated together in a vacuum at a temperature of 215-220° by means of an oil-bath. By playing the flame of the burner around the neck of the flask it was possible to drive over the 2-nitrobenzylcyanide. A pressure within the flask was 8 mm. Recrystallization of this product from 95 per cent alcohol yielded 1.5 g. (30 per cent of the theoretical amount), melting at 85-86°.

2-Aminobenzylcyanide (86): A suspension of 16 g. (0.12 mole) of 2-nitrobenzylcyanide in 200 ml. of 95 per cent alcohol was cooled and a solution containing 20 g.

of tin dissolved in 90 ml. of concentrated hydrochloric acid was added with stirring and in small portions to the above suspension. This mixture was then warmed for a time at 30° until a test portion no longer gave rise to violet color of 2-nitrobenzylcyanide on the addition of a sodium hydroxide solution. About 50 ml. of the solution was distilled off in a vacuum, whence on cooling, there was isolated a precipitated tin double salt. This was dissolved in 280 ml. of cold water. The filtrate of the well cooled solution was then gradually decomposed by warming cautiously with 41 ml. of 30 per cent sodium hydroxide solution. The 2-aminobenzylcyanide precipitated at almost a quantitative yield within a short time as colorless, crystalline needles.

In an attempt to recrystallize this from alcohol it was changed over into an insoluble blue product.

3-Iodoindole (91): Eight grams (0.107 mole) of indole was dissolved with mechanical stirring in 12 l. of warm water previously heated to 70-80°. To the resulting clear solution there was then added 13 g. of potassium hydroxide. There was then added to this slightly alkaline solution an approximately one-tenth normal solution of iodine in potassium iodide solution, while stirring mechanically, until the solution had assumed a slightly yellowish tinge. This was due to the presence of a slight excess of iodine. The 3-iodoindole was filtered and washed well with water and sucked as dry as possible. The product melted at

73-75°. The yield was 9 g. (100 per cent of the theoretical amount.)

The product is not stable on too long exposure to the air. If it is allowed to stand in the air it is changed into a black sticky product which smells strongly of free iodine.

3-Aminoindole.(90): Thirty grams of absolute ethyl alcohol and 2.4 g. of clean sodium were allowed to react. To the resulting opalescent solution was then added 10 g. of indole and 10 g. of iso-amyl nitrite. The solution then changed from colorless to dark red on the addition of the amyl nitrite. The resulting mixture was placed in the refrigerator.

After standing two days, there was added to the cold reaction mixture 200 ml. of distilled water and the resulting solution was extracted several times with ether to remove the iso-amyl alcohol. To the resulting aqueous layer there was added, without heating, and while stirring mechanically, a strongly alkaline solution of sodium hydrosulfite (50 g. of sodium hydrosulfite plus 100 ml. of 6N sodium hydroxide plus 200 ml. of water). No change of color occurred even after all the sulfite solution had been added. It was then heated on the water-bath. The color was not discharged.

Since the above treatment had failed the hydrosulfite was then added in powdered form to the reaction mixture. After

a very large excess (approximately 10 times the designated amount) had been added the reaction mixture became pale yellow in color. This was not discharged on further addition of sodium hydrosulfite. The reaction mixture was then chilled in an ice-bath. Pale yellowish to silvery white needles came down along with considerable quantities of sodium sulfite. This mixture was refluxed with Darco and filtered hot. The pale yellow filtrate was placed in the refrigerator to aid crystallization. Only a small trace of pale yellow plates was obtained. On rapid heating they melted with decomposition at  $115^{\circ}$ . They probably represent the desired product in a slightly impure form. They were not further investigated because of the small quantity which was obtained.

4-Nitrophenylhydrazine (155): Thirteen and eight-tenth grams (0.1 mole) of 4-nitroaniline was mixed with 29 g. (25 ml.; 0.3 mole) of concentrated hydrochloric acid (sp. gr. 1.19) and then diluted with 42 ml. of water. To this mixture was then added 126 g. of finely crushed ice. There was then added, all at once, 7.0 g. (0.1 mole) of sodium nitrite dissolved in 20 ml. of water and the resulting mixture stirred by hand for about ten minutes, whereupon a clear solution resulted. This was filtered and allowed to run in, beneath the surface, of a sodium sulfite slurry made by partially dissolving 53 g. (0.42 mole) of anhydrous sodium sulfite in 125 ml. of water containing 5.5 g. (1.37 mole) of sodium

hydroxide and cooled in an ice-salt bath. The mixture was stirred mechanically during the addition, which should require about seven minutes. After keeping for a further period of seven minutes, the dark red solution was acidified with 98 ml. (1.19 mole) of concentrated hydrochloric acid (sp. gr. 1.19) and then heated in a water-bath at 55° for four minutes. This mixture was then allowed to stand overnight at room temperature. The orange colored precipitate was collected on a Büchner funnel, sucked as dry as possible and then digested with 28 ml. (0.33 mole) of concentrated hydrochloric acid (sp. gr. 1.19) in a 150-ml. beaker on the steam-bath for ten minutes. The product dissolved at first and then precipitated again on continued heating. The dark colored red mass was cooled, filtered with suction and redissolved in 50 ml. of hot water. A small amount of an insoluble brown product was removed by filtration and to the filtrate was added 25 ml. of a cold solution of sodium acetate (150 g. of sodium acetate trihydrate in 100 ml. water). The free base separated immediately, was cooled, filtered with suction, washed well with water and allowed to dry at about 50°. The orange colored product weighed 10.3 g. (67 per cent of the theoretical amount), and melted sharply with decomposition at 158°. It crystallized as light brown platelets from aqueous alcohol.

4-Nitrophenylhydrazone of methylethyl ketone (106):

Six grams (0.044 mole) of 4-nitrophenylhydrazine was dissolved in two liters of ice-cold 6N acetic acid (680 ml. of glacial acetic acid and 1320 ml. of water). To this there was added, slowly from a dropping funnel, 3.2 g. (0.044 mole; 4.0 ml.) of methylethyl ketone diluted with about 30 ml. of 45 per cent alcohol. Vigorous stirring was maintained throughout the dropwise addition of this solution to the hydrazine. Stirring was then continued for about twenty minutes after the hydrazone precipitated. The yellow crystalline hydrazone was collected on a Büchner funnel and washed well with water.

The filtrate was used again as the solvent in a second preparation. From this and the previous run, there was obtained 11.5 g. (72 per cent of the theoretical amount) of a product melting at 121-123°. One recrystallization of some of this material from dilute alcohol gave glistening, tiny, bronze colored needles which had a melting point 126-127°.

Two more additional runs were carried through using the same mother liquor. The combined yield was 14.0 g. (86 per cent of the theoretical amount) of a product melting at 114-122°. One recrystallization from dilute alcohol caused it to melt at 125°C.

5-Nitro-2,3-dimethylindole (106): Sixteen grams (0.077 mole) of the finely powdered 4-nitrophenylhydrazone of methylethyl ketone was covered with 160 ml. of concentrated hydrochloric acid and the mixture refluxed for one hour on a vigorously boiling water bath. On cooling we obtained 8.8 g.

(60 per cent of the theoretical amount) of 5-nitro-2,3-dimethylindole which melted at 182-184°. Recrystallization of a small sample from dilute acetic acid yielded tiny, brown crystals, melting point 186°.

2-Nitrophenylhydrazine (155)(156)(158)(152):

a. Reduction of diazotized 2-nitroaniline with stannous chloride (155). - Ten grams (0.072 mole) of 2-nitroaniline was dissolved in 100 ml. of concentrated hydrochloric acid by boiling. On cooling the hydrochloride precipitated from solution. This solution of the hydrochloride was diazotized below 0° with 5 g. (0.072 mole) of sodium nitrite dissolved in 30 ml. of water. The hydrochloride dissolved and a brown colored solution resulted. To this diazo solution there was added, slowly, and below the surface, 40 ml. of stannous chloride solution (made from 32 g. stannous chloride and 32 g. of concentrated hydrochloric acid). Throughout the addition the temperature was maintained below 0°. Each drop of stannous chloride brings fourth a yellow precipitate. At the end of the reduction, the thick, dark yellow paste was separated from the mother liquor with suction filtration, washed with a small amount of ice-cold water and pressed as dry as possible. After allowing to dry overnight, the tin double salt weighed 17.6 g.

This salt was dissolved in 100 ml. of distilled water by boiling. About 0.5 g. of a tarry product failed to dissolve, hence it was filtered, leaving a clear orange colored solution.

The tin double salt was decomposed by saturating the solution four times with hydrogen sulfide gas. The precipitated tin sulfide was removed most readily by centrifuging. When all of the tin had been removed, the solution containing the 2-nitrophenylhydrazine was treated with excess sodium acetate. The free base was collected and found to melt at 83-85°. Yield 3.5 g. (42 per cent of the theoretical). When recrystallized from benzene it melted at 90°.

b. Reduction of diazotized 2-nitroaniline with potassium sulfite. (156). - Fifty grams (0.37 mole) of 2-nitroaniline was stirred with 125 ml. of concentrated hydrochloric acid until the formation of the hydrochloride salt was complete. It was then cooled to -10° and diazotized with 30 g. (0.41 mole) of sodium nitrite in 50 ml. of water, filtered and neutralized with alkali to slight turbidity (approximately 15 ml. of a cold saturated potassium hydroxide solution). This solution was then added to a sulfite solution prepared by dissolving 50 g. (1.09 mole) of potassium hydroxide in 250 ml. of water, saturating with sulfur dioxide, adding 90 g. (0.25 mole) of anhydrous potassium carbonate and cooling to 0°. The temperature must not exceed 5°. The solution was then stirred for one hour, acidified with concentrated hydrochloric acid and allowed to stand overnight.

The potassium sulfite addition product was decomposed by refluxing for approximately three hours with 600 ml. of concentrated hydrochloric acid. The reaction mixture was allowed

to cool and the residue collected. This was dissolved in the least volume of boiling water possible and neutralized in turn with sodium carbonate and sodium acetate. The impure hydrazine was collected on a Büchner funnel and washed with water to remove inorganic salts. Similar treatment of the mother liquor gave a further quantity of the hydrazine. The combined products were recrystallized from benzene. The yield of the pure hydrazine was 22.7 g. (43 per cent of the theoretical amount). It melted at 92-93°.

c. Reduction of diazotized 2-nitroaniline with ammonium sulfite (158)(152). - Fifty milliliters of concentrated ammonium hydroxide (sp. gr. 0.880) and 50 g. of crushed ice was cooled in an ice-salt mixture and saturated with sulfur dioxide. The excess sulfurous acid was neutralized with concentrated ammonium hydroxide.

Diazotization. - Fourteen grams (0.1 mole) of 2-nitroaniline was pasted with 28 ml. of water and 7.5 g. (0.107 mole) of sodium nitrite to a smooth slurry and then poured onto a mixture containing 30 g. of ice and 29 g. (0.3 mole) of concentrated hydrochloric acid (sp. gr. 1.19). The resulting mixture was stirred by hand and filtered after ten minutes to remove any unchanged amine as well as impurities.

Sulfite addition reaction. - In the meantime 60 ml. of the above saturated ammonium sulfite solution was taken and to it was added 10 ml. of concentrated ammonium hydroxide. The resulting mixture was cooled in an ice-salt bath, thus

causing the ammonium sulfite to separate in the form of a this slurry. A separatory funnel was then arranged so that the tip extended beneath the surface of the alkaline ammonium sulfite mixture. The diazotized 2-nitroaniline was allowed to run in at a uniform rate. The resulting orange colored solution was stirred for an hour in the freezing mixture and then made strongly acid by the addition of concentrated hydrochloric acid. The reaction mixture was set aside for a day, whence the orange precipitate was collected on a Büchner funnel and pressed as dry as possible. This cake was then transferred to a 250-ml. beaker and mixed with 20 ml. of concentrated hydrochloric acid and digested on the steam bath until hydrolysis was complete. The thick paste formed on cooling was filtered with suction, redissolved in water and the free base liberated by the addition of 50 ml. of a saturated sodium acetate solution. The free base was precipitated as a red, semi-crystalline mass which was filtered with suction, washed thoroughly with water and allowed to air dry. The crude hydrazine thus obtained melted at 86-87° and weighed 11 g. (72 per cent of the theoretical amount). A sample recrystallized from benzene was found to melt at 90-91°.

2-Nitrophenylhydrazone of methylethyl ketone (106):

Three grams (0.02 mole) of 2-nitrophenylhydrazine was dissolved in 1 l. of ice-cold 6N acetic acid (340 ml. glacial

acetic acid and 660 ml. water). To this there was added slowly from a dropping funnel 1.6 g (0.02 mole) of methyl-ethyl ketone. Vigorous stirring was maintained throughout the addition. When all of the ketone had been added a period of fifteen minutes elapsed before any change was noticed. At the end of this time an orange colored precipitate began to form throughout the liquid. Stirring was continued during this time and then continued for ten minutes more before the hydrazone was collected on a Buchner funnel. The resulting orange powder, on drying, weighed 3.5 g. (85.4 per cent of the theoretical amount) melted at 65-70°. Recrystallized from dilute acetic acid it melted at 73°. Increased yields are obtained by using the mother liquor over again.

7-Nitro-2,3-dimethylindole (106): Twenty-four grams (0.12 mole) of 2-nitrophenylhydrazone of methylethyl ketone was covered with 240 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and refluxed for one hour on a vigorously boiling water-bath. From the chilled reaction mixture there was obtained 6 g. of nearly pure 7-nitro-2,3-dimethylindole, melting point 158-160° (dec.).

Dilution of the filtrate with water caused the precipitation of 5 g. of the unchanged hydrazone. This was returned to the flask and refluxed once again with 50 ml. of concentrated hydrochloric acid over an asbestos covered wire gauze for one hour. The chilled reaction mixture yielded 1.5 g. of the impure nitro-indole, melting at 140-145° (dec.).

Further dilution of the mother liquor failed to cause any unchanged hydrazone to precipitate. From these two separate runs a total yield of 7.5 g. (33 per cent of the theoretical amount).

The mother liquor from which the 6 g. of nearly pure product was obtained was diluted and allowed to stand overnight. From this diluted solution we obtained reddish colored needles which melted with decomposition at 208°.

This compound was analyzed for nitrogen by an adaptation of Winkler's modification of the Kjeldahl method (168) to a semi-micro scale.

One-tenth gram of the nitro-compound to be analyzed was wrapped in a filter paper and placed in a 50-ml. round-bottom, long-neck flask. To this was added 0.06 g. of copper sulfate ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ) as a catalyst, 0.4-0.6 g. of zinc dust as a reducing agent, 2.0 g. of potassium sulfate to raise the boiling point of the mixture, and 6 ml. of concentrated sulfuric acid. The flask was heated over a free flame, cautiously at first, and finally boiled vigorously until all coloration due to the organic matter disappeared. The contents were allowed to cool and then transferred to the distilling flask and diluted with 25 ml. of distilled water. A solution of 10 g. of sodium hydroxide in 20 ml. of distilled water was carefully added to the flask so as to form a layer below the surface of the acid. After careful mixing steam was passed

in to drive over the liberated ammonia. This was absorbed in 10 ml. of a 2 per cent boric acid solution containing 10-15 drops of the mixed indicator (169) made by mixing 10 ml. of a 0.1 per cent alcoholic bromocresol green solution with 2 ml. of a 0.1 per cent alcoholic methyl red solution. Direct titration of the ammonia was carried out using approximately 0.05 normal hydrochloric acid to the disappearance of the blue color and the appearance of the greenish yellow color. The percentage nitrogen was calculated directly, using the following equation:

$$\% \text{ Nitrogen} = \frac{N_{\text{HCl}} \cdot V_{\text{HCl}} \cdot e_{\text{N}}/1000 \cdot 100}{w}$$

Where  $N_{\text{HCl}}$  = Normality of hydrochloric acid  
 $V_{\text{HCl}}$  = Volume of hydrochloric acid used in ml.  
 $e_{\text{N}}/1000$  = Milliequivalent weight of nitrogen (0.014).  
 $w$  = Weight of sample in grams.

	I	II
Weight of Sample:	0.1055 g.	0.1063 g.
Volume of 0.04668 N HCl used:	20.71 ml.	20.79 ml.
Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{N}_2 \cdot \text{HCl}$ : $\text{N}_1$	12.39%	
Found: $\text{N}_1$	12.82%	12.78%

7-Amino-2,3-dimethylindole: Five and seven-tenths grams (0.029 mole) of 7-nitro-2,3-dimethylindole, melting point 158-160°, was partially dissolved in 150 ml. of warm 95 per cent alcohol by heating on the water bath, and then treated with 50 ml. of 2N sodium hydroxide. The colored al-

cohol solution yields a precipitate on the addition of the alkali. Four hundred milliliters of water was then added. To this mechanically stirred mixture there was added portion-wise 36.6 g. (0.174 mole) of sodium hydrosulfite ( $\text{Na}_2\text{S}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ ). After approximately four hours of heating, a nearly clear, dark brown solution had resulted. The hot reaction mixture was filtered with suction and allowed to stand overnight. At the end of this time a tiny amount of a finely crystalline product had separated. It was collected in a Gooch crucible and the mother liquor returned to the flask. Since it was still quite dark, it was subjected to reheating and the addition of more sodium hydrosulfite (18.3 g). The dark colored solution then became much lighter in color. This was boiled with Darco and filtered hot. The resulting pale yellow filtrate gave no precipitate on cooling. It was therefore, concentrated in vacuo until about 135 ml. of solvent had been removed. Vigorous cooling of this mixture yielded about 1.1 g. of a dirty grey precipitate which melted at 125-127°.

This substance was found to be extremely soluble in alcohol, and was not readily precipitated even on diluting greatly with water. It was obtained as a white, finely crystalline product by recrystallizing from a benzene-ligroin mixture and found to melt at 129-130°. It is sensitive to air oxidation, turning black after a few days, even when kept in a tightly stoppered bottle.

	I	II
Weight of Sample:	0.1333 g.	0.1052 g.
Volume of 0.04668 N HCl used:	38.50 ml.	28.04 ml.
Calcd. for $C_{10}H_{12}N_2$ : N, 17.5%		
Found: N,	17.4 %	17.42 %

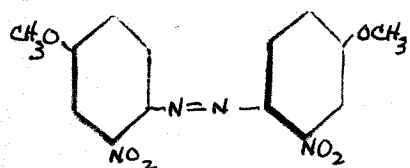
Attempted preparation of 2-nitro-5-methoxyphenylhydrazine (111):

a. Reduction of diazotized 3-nitro-4-anisidine with stannous chloride (111). - Fifty grams (0.3 mole) of 3-nitro-4-anisidine, 125 ml. of concentrated hydrochloric acid and 125 ml. of water were heated together until solution occurred. The dark red solution was then diazotized below  $0^{\circ}C$ . with 22 g. (0.31 mole) of sodium nitrite dissolved in 50 ml. of water. This cold diazo-solution was then added very slowly, with vigorous stirring to a cold solution,  $0^{\circ}-5^{\circ}$ , of stannous chloride (175 g. stannous chloride and 175 ml. of concentrated hydrochloric acid). On the addition of the diazo-solution to the stannous chloride mixture, a tarry product began to form. Addition was discontinued until the temperature had dropped below  $0^{\circ}C$ . Once more the addition was begun, but very cautiously so that the temperature did not rise above  $0^{\circ}C$ . The tarry product, however, continued to form along with the yellow flocculent precipitate of the tin double salt. Since the tarry product tended to clump together it was possible to lift it out of the reaction medium. When precipitation of the tin double salt was completed it was

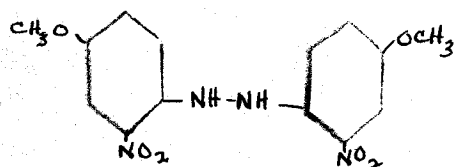
collected on a Buchner funnel, washed with a little cold water and then allowed to dry. The yield of the impure product smelled strongly of hydrogen chloride and had a thin coating of tar on its surface. The product was purified by dissolving in water, refluxing with Darco and filtered hot. A clear red filtrate was thus obtained. The addition of excess sodium acetate caused a precipitate to form. Since the precipitated product contained inorganic material (ignition residue) it was extracted with alcohol and the dissolved product precipitated by the addition of water. In this way 8 g. of a red colored product was obtained which melted at 102-103°. Recrystallized from dilute alcohol, it yielded beautiful red needles, melting at 108-109°. Further recrystallization failed to raise the melting point any higher.

	I	II
Weight of sample:	0.1236 g.	0.1033 g.
Volume of 0.0493 N HCl used:	29.4 ml.	24.6 ml.

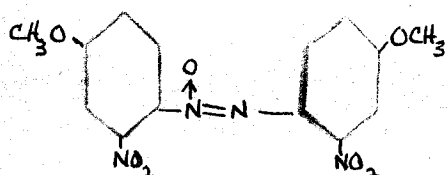
Calcd. for



N, 16.87%



N, 16.77%



N, 16.09%

	I	II
Found: N,	16.38%	16.44%

b. Reduction of diazotized 3-nitro-4-anisidine with potassium sulfite. - Sixty grams (0.326 mole) of 3-nitro-4-anisidine was stirred with 125 ml. of concentrated hydrochloric acid until the formation of the hydrochloride salt was complete, then cooled to  $-10^{\circ}$  by means of an ice-salt bath, and diazotized with 30 g. (0.43 mole) of sodium nitrite in 50 ml. of water, filtered and neutralized with a saturated potassium hydroxide solution, until slightly turbid. This solution was added to a sulfite solution prepared by dissolving 50 g. of potassium hydroxide in 250 ml. of water, saturating with sulfur dioxide, adding 90 g. of anhydrous potassium carbonate and cooling to  $0^{\circ}\text{C}.$ ; the temperature of the reaction mixture not being permitted to rise above  $0^{\circ}$ . The pasty mass which formed was then stirred for one hour, filtered with suction and air dried. The mother liquor was cautiously acidified and allowed to stand.

The residue obtained from the mother liquor was dissolved in a minimum of hot water, neutralized with sodium carbonate and finally with sodium acetate. A tar formed on the surface of the liquid during the neutralization process, consequently, Darco was added and the resulting mixture boiled for a few minutes longer before filtering. A pink granular product separated from solution. It exhibited only partial

melting at 117-120° since it was found to contain inorganic material by ashing.

The pasty reaction product, after air drying, was added in portions to a mixture containing 200 ml. of concentrated hydrochloric acid and 200 ml. of water. This was then heated on a steam-bath for approximately five minutes. Considerable tarry material formed on the surface of the liquid. This was skimmed off as the solution cooled. A product then separated on cooling. This was collected on a Buchner funnel, dissolved in the minimum amount of hot water and neutralized with sodium carbonate and sodium acetate and Darco was added to free the product from tar. Filtration of this hot mixture and cooling of the filtrate gave 3 grams of a red granular product, melting at 123-127°. This was found to be slightly more pure product than that melting at 117-120°.

Because of the closeness of this melting point to that reported for the 2-nitro-4-methoxyphenylhydrazine, we decided to try to make the phenylhydrazine of methylethyl ketone.

To do this we made up a mixture containing 12 ml. of concentrated sulfuric acid and 100 ml. of alcohol and poured it over the above product. After effervescence had ceased, we added 2.4 ml. of methylethyl ketone and after standing for several minutes, the reaction mixture was diluted with water, whereupon we obtained micro-crystalline,

pink needles which melted at 172-173° (dec.). Recrystallized from dilute alcohol they melted at 172-174° (dec.). Analysis showed this to be different from the expected hydrazine.

## I

Weight of substance: 0.1050 g.

Volume of 0.04668 N HCl used: 14.61 ml.

Calcd. for  $C_7H_9O_3N_3$ : N, 23.0%

Found : N, 9.09 %

c. Reduction of diazotized 3-nitro-4-anisidine with sodium sulfite. - To 168 g. of ice (126 g.) and water (42 g.) contained in a 2-l. beaker fitted with a mechanical stirrer, thermometer and a dropping funnel, there was added 2-nitro-4-anisidine (16.8 g.; 0.1 mole) and hydrochloric acid as a 31 per cent solution (19.4 ml. of concentrated hydrochloric acid and 3.8 ml. water). This was agitated and caused to cool to -5°C., whence the sodium nitrite, as a 30 per cent solution (6.9 g. sodium nitrite and 16 g. of water) was added slowly. The temperature was maintained at -5° until diazotization was completed. The excess mineral acid was neutralized to litmus with sodium carbonate (7 g.) and the temperature was maintained at -5° during this operation. The sodium sulfite was used as crystals and the temperature was kept below 0° until the coupling reaction was completed, as shown by a negative test for free diazo with alkaline beta-naphthol solution. The sodium bisulfite as a 30-35° solution was added (12.1 g. sodium bisulfite and 28 g. water) and heated

slowly (hot plate) to 90-95°C. This temperature was maintained until reduction was completed. The hydrochloric acid was 31 per cent (25.7 ml. hydrochloric acid and 5 ml. of water) was added to the above solution at 90°, slowly, until most of the sulfur dioxide has evolved. (Be careful of foaming). The remainder of the acid is added fast at 90°C. for 30 minutes.

No odor of sulfur dioxide was detected, therefore the mixture must have been sufficiently alkaline. No change in the appearance of the reaction mixture was noted and it still gave the  $\beta$ -naphthol reaction. The mixture was then heated slowly to 90-95°. When the temperature had risen to about 40°, whence a test portion no longer gave a color reaction, hence the bisulfite addition reaction must occur somewhere near this temperature. This still dark red colored mixture was then maintained at 90-95° for an hour. Darco was added to remove a slight amount of tarry material. To the filtrate at 90-95° was then added slowly the hydrochloric acid in order to convert the hydrazine sulfonate into the hydrazine hydrochloride. The evolution of sulfur dioxide appeared to be eliminated quite slowly, so the resulting reaction mixture was heated with stirring until half the original volume had evaporated. It was then removed from the hot plate in order to filter off a reddish brown product. When dry it weighed 9.0 g. and showed partial melting with decomposition at 115°. A small sample was asked and showed the presence of

inorganic material. This could be due to the presence of sodium bisulfite or the presence of unchanged hydrazine sulfonate. A sample portion was then digested with concentrated hydrochloric acid. Dilution of the resulting dark red solution caused the separation of an orange colored product which melted with decomposition at 122-125° (the hydrazine reported by Robinson and Tomlinson, melted 127°).

The above 9.0 g. of material was finely powdered and placed in a Soxhlet and extracted with 95 per cent alcohol. Evaporation of the solvent and boiling of the sticky residue with water and Darco and filtering hot caused the separation of a red product from the filtrate. It melted at 119-122° (dec.). Dissolving this in alcohol and purifying yielded pink colored needles, melting at 168-170° (dec.).

A mixed melting point between this and the product obtained from the potassium bisulfite reaction melted with decomposition at 170-171°. It is quite probable, therefore, that the products from these two reactions are identical. Since this is the lower melting compound it is probably less pure. Nitrogen would appear to confirm this.

	I	II
Weight of sample:	0.1071 g.	0.1030 g.
Volume of 0.04668 N HCl:	13.90 ml.	13.35 ml.
Found: N,	8.48 %	8.47 %

d. Reduction of diazotized 2-nitro-4-anisidine with ammonium sulfite. - Fifty milliliters of concentrated ammonium hydroxide and 50 grams of finely crushed ice was cooled in an ice-salt mixture and saturated with sulfur dioxide. It was neutralized with concentrated ammonium hydroxide.

Seventeen grams (0.1 mole) of 3-nitro-4-anisidine was pasted with 28 ml. of water and 7.5 g. (0.107 mole) of sodium nitrite to a smooth slurry and then poured onto 30 g. of ice and 29 g. (0.3 mole) of concentrated hydrochloric acid (sp. gr. 1.19). The resulting mixture was stirred and filtered after ten minutes.

Sixty milliliters of the previously prepared ammonium sulfite solution was taken and to it was added 10 ml. of concentrated ammonium hydroxide. This mixture was cooled in an ice-salt bath which caused the ammonium sulfite to separate in the form of a thin slurry. To this mixture there was then added the above diazo-solution. This was carried out by having the end of the separatory funnel dipping beneath the surface of the ammonium sulfite slurry. The rate of addition had to be slow enough to prevent bar formation. The resulting orange colored slurry was stirred for an hour in the cold. The precipitate was then collected on a Buchner funnel and transferred to a 250-ml. beaker. The addition of 20 ml. of concentrated hydrochloric acid caused vigorous effervescence and tar formation. In spite of this, the mixture was subjected

to a ten minute heating period in a water-bath at 55°. On cooling in an ice-salt mixture it quickly set to an orange colored paste. This was filtered and dissolved with heating in 50 ml. of water and the insoluble tar filtered off. On cooling the red colored filtrate and adding excess of cold sodium acetate we were able to obtain a small amount of brilliant, red colored plates which melted at about 120-125°. Since these are the only plates ever obtained by any of the procedures, they may well be the desired hydrazine.

N-(-Diethylaminopropyl)-2-nitroaniline: This compound was also obtained from 2-nitrochloro-benzene as well as from the iodo-derivative, however, the method of synthesis was the same in either case. For convenience and because more of the preparations were made with the iodo-derivative we include directions for its synthesis, but not that of the chloro-compound.

a. From 2-nitroiodobenzene. - A mixture of 50 g. (0.2 mole) of 2-nitroiodobenzene, 26 g. (0.2 mole) of -diethylaminopropylamine and 32 g. of anhydrous pyridine were heated together in an oil-bath at 100°-120° for six hours. The mixture was then concentrated to a viscous reddish brown semi-crystalline mass by aspirating dry air through the reaction mixture while it was being heated on a water-bath. Excess ammonium hydroxide was then added to liberate the free amine which formed a dark red oil. This was then extracted with ether and washed by shaking with dilute alkali and then

with water. The dark red ethereal solution was treated with dry hydrogen chloride gas. This treatment causes the amine hydrochloride to separate as a quickly solidifying, viscous, red oil. As thus obtained it is an orange-red solid. The ether was decanted and the orange residue taken up in the least volume of absolute alcohol and refluxed for ten to fifteen minutes with Darco and then filtered hot. On cooling, ether was added until insipient precipitation, whereupon it was stored in the refrigerator overnight. In this way it was possible to obtain orange needles which were still contaminated with a dark red sticky product, melting at 165-170°. The yield of the crude product was 14 g. (24.3 per cent of the theoretical amount).

To obtain a pure product it was usually necessary to decompose the hydrochloride with concentrated ammonium hydroxide, extract the oil with ether, and dry over anhydrous sodium sulfate. The hydrochloride was then precipitated by passing in dry hydrogen chloride gas and then recrystallized by dissolving in the least volume of absolute alcohol possible and allowing slow crystallization to take place in the refrigerator or in an ice-salt mixture. It was generally, more preferable, to reflux with Darco before allowing crystallization to take place. This procedure used one or more times gives micro-crystalline, orange colored needles melting at 183-184°.

	I	II	III
Weight of Sample:	0.0982 g.	0.0999 g.	0.1032 g.
Volume of 0.0493 N HCl			
used:	20.48 ml.	20.60 ml.	21.00 ml.
Calcd. for $C_{13}H_{21}O_2N_3HCl$ : N, 14.6%			
Found:	14.39%	14.23%	14.05%

B. Mannich Reaction Products of Indole.

3-Dimethylaminomethylindole (Gramine) (125) (159):

Four and one-tenth grams (0.05 mole) of dimethylamine hydrochloride, 4.1 g. (0.05 mole) of anhydrous sodium acetate were dissolved in 16 ml. of water and 7 g. of glacial acetic acid. This solution was cooled to 5° and to it was added 3.8 g. (about 4.0 ml.) of 47 per cent formalin previously cooled to 5°. The resulting cold mixture (Ca 3°C.) was poured over 5.8 g. (0.05 mole) of indole contained in a 150-ml. Erlenmeyer flask. The flask was stoppered and shaken vigorously until a clear solution was obtained (ca. 10 min.).

The temperature rose to 34°. The reaction mixture was then allowed to stand at room temperature for ten hours. It was then poured slowly and with stirring into 50 ml. of water containing 5.2 g. of sodium hydroxide. This was then allowed to stand in an ice-bath for two hours, whence it was filtered and washed well with water. The white product thus obtained melted at 110-112°. When dry it weighed 7.3 g. (84 per cent of the theoretical amount). Drying at 50°, however, caused the product to be covered with a reddish substance. This was removed in part by dissolving in alcohol and cautiously

precipitating with water. The product as thus obtained was not entirely freed of the reddish contaminant, however, it now melted at 127-129°. Recrystallized several times from hot acetone, after cleaning with Darco, yielded lustrous white scales melting at 134°.

3-Diethylaminomethylindole (125)(126):

a. Polymerization product from indole, diethylamine and formaldehyde. - Five and five-tenths grams (0.05 mole) of diethylamine hydrochloride and 4.0 g. (0.028 mole) of sodium acetate trihydrate were dissolved in 20 ml. of water. To this solution was then added 4.0 g. (1.5 g., 0.05 mole of  $H_2CO$ ) of an approximately 37 per cent formalin solution. This mixture was poured over 5.9 g. (0.05 mole) of indole. On allowing to stand, with occasional shaking, the indole dissolved and in its place there formed a clear yellow oil. This change took place in about ten to fifteen minutes. The reaction mixture was allowed to stand at room temperature for about thirty minutes, whence it was placed in the refrigerator until the oil solidified (ca. 20 hrs.). At the end of this time the mother liquor was decanted and discarded. The solid was taken up in 30 ml. of acetone and made to crystallize by the careful addition of ligroin while stirring in an ice-bath. The white product formed still retained a sticky contaminant and weighed 5.0 g., melting point 138-155°. A second treatment yielded 4.2 g. of a product melting at 144-150°. One recrystallization from dioxane caused it to melt at 165-166°

which agrees with that reported by Kuhn and Stein. The yield was 3.8 g. of pure product.

	I	II
Weight of Sample:	0.1058 g.=	0.1333 g.
Volume of 0.04668 N HCl:	17.80 ml.	22.80 ml.
Calcd. for $C_{26}H_{21}N_3$ :	N, 11.20%	
Found:	N, 11.00 %	11.18 %

b. Polymerization product from indole and formaldehyde. - In a 50-ml. Erlenmeyer flask was placed 5.8 g. (0.05 mole) of indole and 5 ml. of 95 per cent alcohol. After chilling in an ice-bath there was added 1.9 g. (0.025 mole) of cold 40 per cent formalin. The flask was stoppered and shaken until a clear yellow solution resulted. This was then allowed to stand at room temperature for several weeks. The solid reaction product which had separated was washed by decantation several times with alcohol. So far it has been made to melt at 162-163° by recrystallization from acetone. A mixed melting point with the previously described polymer, melting point 165°, gave a melting point of 160-162°. From this one may conclude that the substances are identical, however, we should like to get an analysis before deciding definitely.

	I	II
Weight of Sample:		
Volume of 0.04668 N HCl used:		
Calcd. for		
Found:		

c. Reaction product from indole, diethylamine and formaldehyde in acetic acid (126). - Four grams (0.055 mole) of diethylamine was dissolved in 4.0 g. of water to give a 50 per cent aqueous solution and then cooled to 5°. This solution was then added to 7.2 g. (ca. 8 ml.; 0.12 mole) of glacial acetic acid. This was then cooled to 5° and 4.0 g. (ca. 3.6 ml.; (0.05 mole) of H<sub>2</sub>CO) of approximately 37 per cent formalin was added. The resulting mixture was agitated mildly and poured slowly and with shaking into a flask containing 5.9 g. (0.05 mole) of indole. The flask was then shaken occasionally until the indole dissolved. By the time this had occurred the temperature had risen to 38°. This clear, pale yellow, solution was allowed to stand at room temperature for twenty-four hours. At the end of this time it was added slowly and with stirring to a cold solution of 5 g. (0.12 mole) of sodium hydroxide in 30 ml. of water. The resulting mixture was allowed to stand for an hour in an ice-bath. It was then filtered with suction, pressed dry and washed several times with three 10 ml. portions of water. When dry the product weighed 9.3 g. (92 per cent of the theoretical) and melted at 93-105°. Repeated recrystallizations from acetone yielded 2.0 g. of a constant melting product, melting point 107-108°.

	I	II
Weight of Sample:	0.1057 g.	0.1115 g.
Volume of 0.04668 N HCl:	22.50 ml.	23.83 ml.
Calcd. for $C_{15}H_{16}N_2$ : N, 13.87%		
Found : N,	13.91 %	13.97 %

3-N-Morphoylmethylindole (126): Eleven and Sevenths grams (0.1 mole) of indole was dissolved in 30 ml. of absolute alcohol. To this was added, in turn, and with stirring 9.6 g. (0.11 mole) of morpholine and 3.0 g. (0.1 mole) of formaldehyde (7.3 g. of 40% formalin). The flask was stoppered and allowed to stand at room temperature for a week. The still clear reaction mixture was then poured with stirring into about 500 ml. of water, whence a white sticky product precipitated. This was washed by decantation several times with ligroin, and then taken up in as small a volume of ether possible. The ethereal solution was cooled in an ice-salt bath, whence a granular white product came down. This was filtered with suction and washed several times with ligroin. In this condition it melted at 118-122° and weighed 13. g. (75.8 per cent of the theoretical amount). In this condition it still retained a sticky contaminant, however, on reflux with ligroin this may be removed. One recrystallization from ether-ligroin with chilling in an ice-bath yield white crystals melting at 123-124°. The amount of pure product was 8 grams.

	I	II
Weight of Sample:	0.1039 g.	0.0856 g.
Volume of 0.04668 N HCl used:	20.61 ml.	17.01 ml.
Calc. for $C_{13}H_{18}N_2$ : N, 12.96%		
Found : N,	12.99%	12.98%

C. Pyrimidine Syntheses.

4,4'-Di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxy-  
propane:

a. From 2-(4'-Hydroxyphenyl)-4,6-dimethylpyrimidine. -

Six grams (0.03 mole) of 2-(4'-hydroxyphenyl)-4,6-dimethylpyrimidine was dissolved in 25 ml. of water containing 1.2 g. (0.03 mole) of sodium hydroxide with slight heating. To the ruby red solution which resulted, there was added 3.0 g. (0.015 mole) of trimethylene bromide dissolved in 20 ml. of 95 per cent alcohol. This mixture was then allowed to reflux for forty-eight hours. After about twelve hours heating the solution had become amber colored and no further change was observed except the increase in the amount of insoluble reaction product. A portion of the solvent was removed in vacuo and the insoluble residue taken up in 6 normal hydrochloric acid. The resulting mixture was boiled with Darco, filtered and allowed to crystallize. A tan product weighing 1.5 g. and melting at 190-200° was obtained. This dissolved readily in hot alcohol. Dilution of the alcoholic solution yielded a light tan product, melting point 178°. Since the product was no longer soluble in alcohol it is apparent that it dissolved as the chloride, but was hydrolyzed by the hot aqueous alcohol to the free base which is not soluble in alcohol. It dissolved readily in dioxane and crystallized in the form of white micro-crystals, melting at 183-184°. The amount of pure product thus obtained was only 0.4 g.

	I	II
Weight of Substance:	0.1056 g.	0.1089 g.
Volume of 0.04668 N HCl used:	20.70 ml.	21.30 ml.
Calcd. for $C_{27}H_{28}O_2N_4$ :	N, 12.78%	
Found: N,	12.80 %	12.77 %

b. From 4-4'-Diamidino-1,3-diphenoxypropane. - Nine and four tenth grams (0.03 mole) of 4,4'-diamidino-1,3-diphenoxypropane was suspended in 50 ml. of acetylacetone and refluxed together for approximately seventy hours. The hot reaction mixture was filtered to remove the insoluble reaction product. The filtrate on cooling deposited tiny crystals, melting at 180-182°. They weighed about 5 g. A sample recrystallized from dioxane melted at 183-184° and gave no depression of the melting point with the compound prepared by reacting 2-(4'-hydroxyphenyl)-4,6-dimethylpyrimidine in the form of its sodium salt with trimethylene bromide. The yield of this product was about 45.4 per cent of the theoretical amount.

c. 4-(2-phenyl-4,6-dimethylpyrimidyl)-4'-(N-penteneoylamidino)-1,3-diphenoxypropane. - The insoluble product from the above reaction was obtained in greatest quantity. This substance melted at 264-265° with decomposition. Since it was insoluble in the usual organic solvents we boiled it with absolute alcohol to remove any soluble impurities. This treatment gave a white product which melted sharply at 271° with decomposition. A loss of 1.1 g. occurred by this

method of purification. The final yield of the pure product was 4.6 g. (34 per cent of the theoretical amount).

	I	II
Weight of Substance:	0.1057 g.	0.1008 g.
Volume of 0.04668 N HCl used:	19.90 ml.	19.15 ml.
Calcd for $C_{27}H_{30}O_3N_4$ : N, 12.23%		
Found: N,	12.30 %	12.42 %

A hydrochloride of 4,4'-Di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane is obtained by dissolving the free base in concentrated hydrochloric acid. The hydrochloride crystallizes out of solution in the form of long, silky white needles which melt at 226-227° and begin to sinter at 190°.

	I	II
Weight of Substance:	0.1101 g.	0.1030 g.
Volume of 0.04668 N HCl used:	16.22 ml.	15.10 ml.
Calcd. for $C_{27}H_{27}N_4O_2 \cdot 4HCl \cdot 5H_2O$ : N, 9.74%		
Found: N,	9.63%	9.58%

The pyrimidyl-penteneoylamidino compound also dissolves readily in hot concentrated hydrochloric acid. It crystallized on cooling as tiny white felt-like needles which after recrystallization from alcohol were found to melt at 283°. Some deep seated change must take place by this treatment, since an analysis for nitrogen gives too little information as to the possible structure of the hydrochloride. A

chloride analysis would be helpful in deciding this, however, this has not been carried out, as yet.

	I	II
Weight of Substance:	0.1077 g.	0.1035 g.
Volume of 0.04668 N HCl used:	22.61 ml.	21.80 ml.
Calcd. for		
Found: N,	13.72 %	13.77 %

From the above analytical data it is evident that the molecular weight is at least 100 or some integral multiple of this.

4,4'-Diamidino-1,3-diphenoxypropane: This was prepared according to the directions of C. K. Banks of the Parke-Davis Company.

4-Nitrocyanobenzene (162) (163) (164) (165):

a. Preparation of cuprous cyanide (161). - Copper sulfate (commercial crystalline; 1 kg.) was dissolved in water (3.2 l.) at 40-50°. Sodium bisulfite (commercial powder; 280 g.) was dissolved in water (800 ml.) at 50-60° and potassium cyanide (95 per cent) "grey single salt"; (280 g.) in water (800 ml.) at 50-60°. Each solution was filtered and, all being at 60°, the bisulfite solution was run with stirring during 1 to 2 minutes into the copper solution (acidified faintly to Congo-red), followed immediately by the cyanide solution. There is slight frothing and a little sulfur dioxide was evolved, but no appreciable amount of cyanogen or hydrogen cyanide. After about 10 minutes, the hot solution

was filtered, and the product washed thoroughly with boiling water, then with alcohol. It was dried at 100° to a fine powder; yield, almost quantitative.

b. Attempted preparation from 4-nitrobromobenzene. -

In a dry flask fitted with a ground-in condenser and protected from moisture were placed 21.2 g. (0.1 mole) of 4-nitrobromobenzene, 11.7 g. (0.13 mole) of cuprous cyanide, and 10 ml. of pyridine (dried over BaO). The mixture was heated at 195-200° for fifteen hours. On cooling the reaction mixture set to a hard black mass. This was shaken vigorously several times with dilute ammonia to dissolve out the copper salt. This treatment was only effective on the surface, since it could not penetrate the inside of the solid. It was then refluxed with carbon tetrachloride in an attempt to dissolve out any of the cyanonitro compound. Evaporation of the solvent yielded only a trace of the 4-nitrocyanobenzene, melting point 145-147°.

c. Preparation from 4-nitrobenzamide. - Sixteen and

six tenth grams (0.1 mole) of 4-nitrobenzamide (melting point 201-202°) was placed in round-bottom flask along with 13 ml. (0.18 mole) of thionyl chloride (sp. gr. ca. 1.638) and heated on a water-bath for thirty minutes. Fifty milliliters of anhydrous benzene was then added and heating continued for five hours. The top of the condenser was closed with a calcium chloride drying tube and the flask and a condenser were connected by means of a ground glass joint. The water-bath was replaced

by an asbestos centered wire gauze and heating continued. In all about 12 hours heating over an asbestos centered wire gauze was required before the reaction appeared to be ended. The contents of the flask were allowed to cool to room temperature. This caused the crystallization of the product in solution. The contents of the flask were then transferred to a beaker and diluted with ligroin. The precipitate was collected on a Buchner funnel and washed free of benzene and any unreacted thionyl chloride with ligroin. The product when dry weighed 12 g. and melted 146-148°C. The yield amounts to 81 per cent of the theoretical amount based on the amount of amide taken.

d. Preparation from 4-nitroaniline. - Sixty-nine grams (0.5 mole) of technical 4-nitroaniline was finely powdered and then mixed to a uniform paste with 87.5 ml. of concentrated hydrochloric acid (sp. gr. 1.187). This was then poured into a 2-gal. crock and diluted, all at once with 210 ml. of water while stirring. To the finely divided suspension of 4-nitroaniline was then added 630 g. of crushed ice. The temperature soon drops to -3° to -5° c. To this well agitated mixture was then added all at once 34.5 g. (0.5 mole) of U.S.P. sodium nitrite dissolved in 86 ml. of water. Stirring was then continued for approximately an hour. The nearly clear, pale yellow diazo solution was filtered with suction to remove any unreacted 4-nitroaniline (only trace) and other contaminants to which may be present.

While the diazotization is in progress the potassium copper cyanide solution may be prepared. To do this 125 g. ( mole) of crystallized copper sulfate is placed in a 5-liter, round-bottom flask, possessing a fairly long neck, along with 750 ml. of water. Then while stirring mechanically, the mixture is heated until a temperature of 90-100° is attained. To this hot solution was then added 140 g. (0.205 mole) of 95 per cent potassium cyanide dissolved in sufficient water (ca. 250-300 ml. H<sub>2</sub>O). This must of course be carried out in a hood to take care of the cyanogen which is evolved. When the mixture has attained a temperature of 90-100°, the diazonium solution is allowed to run in slowly. When this had all been added, heating and stirring was continued for several minutes. The reaction mixture was then allowed to cool.

The flask containing the reaction product was arranged for steam distillation. After 5 liters of distillate plus product had been collected, distillation was discontinued and the contents of the steam flask was decanted until only half of the original volume was present. This was then resubjected to a vigorous current of steam and another 5 liters of distillate was collected. The residue in the flask was discarded and the remaining portion distilled as in the previous cases. Thus in all, there was obtained approximately 15 liters of distillate. On cooling to room temperature, the 4-nitro-cyanobenzene was collected on a Buchner funnel and washed thoroughly with water. It was then dried in an oven. The

product thus obtained was quite pure; it melted sharply between 147-148°C. and weighed 44.5 g. (60 per cent of the theoretical amount).

4-Nitroethoxycarbiminobenzene hydrochloride (140):

Fourteen and eight tenth grams (0.1 mole) of 4-nitrocyano-benzene, 6.9 g. (0.15 mole) of 10 ml. of anhydrous alcohol and 250 ml. of dry benzene was placed in a three-necked flask arranged with a Herschberg, mercury sealed, stirrer, a gas inlet tube and a calcium chloride drying tube. The resulting clear yellow solution was cooled to 0-5° in an ice-bath and dry hydrogen chloride gas passed in until the liquid was saturated. The flask was then tightly stoppered and allowed to stand at room temperature for a week. The pale yellow, rather dense needles could be filtered if desired in a pure form, however, we preferred to collect all of the imine ether hydrochloride at one time, by precipitating that which remains in solution by the addition of anhydrous ether. This was then collected on a Buchner funnel and washed free of benzene with more ether. This product was then stored in a vacuum dessicator over potassium hydroxide pellets until desired. This treatment effectively removes excess hydrogen chloride. The product is generally obtained in a fairly pure form and need not be further purified for further use. The yield was 19.7 g. (87 per cent of the theoretical amount) of a product melting at 194-197°. If desired it may be recrystallized from absolute alcohol to give fairly dense, pale yellow needles with slow cooling or tiny, white

needles with more rapid cooling. The product so obtained usually melted at 198-200°.

When larger runs were carried out, we preferred to use nitrobenzene as the solvent instead of benzene as described above. The crude product is frequently pale pink in color, however, this need not be recrystallized before use. The contaminant also has little effect on the melting point. This pink color also faded out on storage in the vacuum desiccator.

4-Nitrobenzamidine (140): Eleven and five tenth grams (0.05 mole) of the 4-nitrobenzimidinoether hydrochloride and 75 ml. of an approximately 10 per cent anhydrous ammoniacal alcohol solution were placed together in a pressure bottle and well shaken. This was then heated continuously for from six to eight hours in a constant level water-bath maintained at a temperature of 60-70°. An insoluble, yellow, micro-crystalline product separates along with considerable quantities of ammonium chloride. At the end of the heating period, the contents of the flask are allowed to cool, the pressure bottle is opened (caution) and the product collected on a Buchner funnel. The product, containing ammonium chloride and some of the amidine hydrochloride is transferred to a beaker and warmed slightly with approximately 6N sodium hydrochloride. It is then filtered with suction and washed thoroughly with water, pressed dry, and stored in a desiccator over calcium chloride until desired or it may safely be dried

at 100° in an oven for one half hour. The yield was 8.8 g. (87 per cent of the theoretical amount) of a pure product melting at 215°.

2-(4'-Nitrophenyl)-4,6-dimethylpyrimidine: Fourteen and six tenth grams (0.09 mole) of 4-nitrobenzamidine was refluxed with 100 ml. of acetylacetone until a clear, red solution was produced. This required about twelve hours. The product may then be obtained by pouring the reaction mixture into water or, preferably, it may be distilled and the excess solvent collected. This can be used in subsequent preparations, if free from water. The product thus obtained possesses a brown to tan color, but compares closely favorably with the melting point of the pure product. It may, however, be obtained as long, silky, nearly colorless needles by recrystallizing from 95 per cent alcohol. It is necessary to reflux for about fifteen minutes with Darco to remove colored impurities. The needles thus obtained melted at 172-173° and weighed 14. g. (69 per cent of the theoretical amount).

	I	II
Weight of Sample:	0.1092 g.	0.1036 g.
Volume of 0.04668 N HCl used:	30.59 ml.	29.17 ml.
Calc. for $C_{12}H_{11}N_3O_2$ : N, 18.34%		
Found: N,	18.31 %	18.40 %

2-(4'-Aminophenyl)-4,6-dimethylpyrimidine: Eleven and five tenth grams (0.05 mole) of 2-(4'-nitrophenyl)-4,6-dimethylpyrimidine was suspended in 100 ml. of 95 per cent

alcohol and 0.1 g. of Adam's platinum oxide catalyst added. The bottle was evacuated and the product reduced by shaking in an atmosphere of hydrogen until no further absorption of gas occurs. A pale yellow solution, containing some of the white, crystalline amine is thus obtained. To separate it from the oxide catalyst it is best to dissolve this precipitate by heating the reaction mixture in a water bath until solution occurs. This is filtered hot and the filtrate allowed to cool, whereupon a white, granular product, melting at 163-165° is obtained. It weighed 5.6 g. Evaporation of the mother liquor to dryness on the steam cone yielded 4.3 g. of the amine, melting at 160-162°, in the form of a light brown powder. The total yield is almost equal to the theoretical amount. The best sample of the amine we were able to obtain melted at 165°.

	I	II
Weight of Sample:	0.1032 g.	0.0802 g.
Volume of 0.04668 N HCl used:	33.16 ml.	26.04 ml.
Calc. for $C_{12}H_{13}N_3$ : N, 21.10%		
Found: N,	21.0 %	21.21 %

2-(4'-Hydroxyphenyl)-4,6-dimethylpyrimidine: Ten grams (0.05 mole) of 2-(4'-aminophenyl)-4,6-dimethylpyrimidine was dissolved in a cold mixture of dilute sulfuric acid (15 ml. water and 11 ml. of concentrated sulfuric acid.). To the resulting red colored solution was then added 27 g. of crushed ice, and while stirring by hand there was added, all at once,

3.5 g. (0.05 mole) of sodium nitrite dissolved in 8 ml. of water. Some fumes were evolved, but if stirring is vigorous there is not much loss. The beaker containing the nitrite was rinsed with about 1 ml. of water and then added to the reaction mixture. Within the space of a few minutes the diazonium salt begins to come out of solution as a white precipitate and soon forms a heavy paste. Continued stirring for about 10 minutes renders this somewhat more fluid. This was then added dropwise, from a 10 ml. pipette possessing a wide tip, to a boiling (165°) mixture containing 25 ml. of water and 33 ml. of concentrated sulfuric acid. The diazonium salt was decomposed as rapidly as it came in contact with the boiling solution and gives a deep red colored solution. No tar formation occurred. The beaker containing the diazonium salt was rinsed carefully with cold water into the boiling acid so that none was lost. Heating was continued for a few minutes. The hot solution was then poured out into a liter beaker and cooled in an ice-bath. When cold, there was added to it, 500 g. of crushed ice and then with stirring a previously cooled solution containing 63 g. (1.58 mole) of sodium hydroxide dissolved in 500 ml. of water. A precipitate forms after a time, but dissolves again to give a clear red solution. The resulting alkaline was then neutralized by the dropwise addition of 6N sulfuric acid. This caused the product to separate in the form of a somewhat gelatinous precipitate which is best collected by filtering through a large

Buchner funnel. The resulting past was then suspended in water and refiltered, repeating the process until the filtrate no longer tested for acid. The wet cake was transferred to a watch-glass and dried in an oven at 100°. The dried crude product weighed 9.5 g. (95 per cent of the theoretical amount) and melted at 168-172°C. By dissolving this indilute sulfuric acid and boiling with Darco, it may be reobtained as above. The product was colorless, weighed 8.0 g. and melted at 170-172°. Coleman and Gabriel report it melted at 178-179°. Several recrystallizations from dilute 40 per cent alcohol finally yielded a snow-white, micro-crystalline product, melting at 180-181°.

	I	II
Weight of Compound:	0.1003 g.	0.1050 g.
Volume of 0.04668 N HCl used:	21.64 ml.	22.57 ml.
Calc. for $C_{12}H_{12}ON_2$ : N, 14%		
Found: N,	14.10 %	14.05%

3-Nitrocyanobenzene (166): To 110 g. (1.09 moles) of pulverized potassium nitrate, was added 300 ml. of concentrated sulfuric acid and the mass well mixed and cooled to 10°. To this mixture was then added, drop by drop, and with constant stirring, 100 g. (0.98 mole) of benzonitrile. During the addition of the nitrile the temperature must be watched carefully as it is essential that it should not rise above 20°. In order to maintain this condition an ice-salt bath was used. After a time the acid potassium sulfate began

to separate, forming a thick pasty mass which tends to retard stirring. The temperature must be watched at this stage since it tends to rise above 20°. The addition of the benzonitrile required two and a half hours. The mixture was then allowed to stand in the cold with stirring for an hour longer to insure a complete reaction. The thick, pasty mass was then added gradually, while stirring mechanically to approximately 2 liters of water containing ice. On coming in contact with the water the product solidified into a pale yellow mass which was broken up into smaller particles by vigorous stirring. It was filtered with suction and washed six times with dilute ammonium hydroxide to remove a yellow colored material. It was then recrystallized from 6N acetic acid. The product thus obtained melted at 117-118°, and weighed 130g. (80 per cent of the theoretical amount).

3-Nitrocarbiminobenzene hydrochloride (141): This was prepared in the same way as for the 4-nitrocarbiminobenzene hydrochloride. The product melted at 137° and was obtained in a yield of 60 g. (87 per cent of the theoretical amount), based 0.3 mole of 3-nitrobenzonitrile used. The solvent was nitrobenzene (200 ml.). A sample recrystallized from absolute alcohol still melted at 137° with decomposition.

3-Nitrobenzamidinium hydrochloride (141)(142): This was also prepared in the same way as for the corresponding 4-nitrobenzamidinium. The method of isolation differed. The reaction mixture from 11.5 g. (0.05 mole) of 3-nitrobenzimidino-

ether hydrochloride was filtered from the precipitated ammonium chloride and then evaporated in vacuo at room temperature. The orange colored residue was treated in turn with 10 mo. of concentrated hydrochloric acid so as to form the stable hydrochloride and then dissolved in water by heating. The solution was purified with Darco. To the filtrate on cooling, there was added 10 ml. of concentrated hydrochloric acid, whereupon we obtained 3.8 g. (dried weight) of the hydrochloride, melting point 248-249°. The mother liquor was concentrated to one quarter its original volume by heating on a hot plate. On cooling, obtained 3.0 g. (dried) of the same product, melting point 240-244°. Complete evaporation of the remaining mother liquor yielded 1.2 g. (melting point 220-230°). The combined yield was 8.0 g. (80 per cent of the theoretical).

It may be recrystallized from 95 per cent alcohol, whereupon a product melting at 248-249° is obtained. There is little loss in this purification process if only the required amount of alcohol is used.

2-(3'-Nitrophenyl)-4,6-dimethylpyrimidine:

a. Reaction between 3-nitrobenzamidine hydrochloride and acetylacetone in a 30 per cent aqueous potassium carbonate solution. - Twenty and two tenth grams (0.1 mole) of 3-nitrobenzamidine hydrochloride was dissolved in 100 ml. of cold distilled water and 28 g. (0.2 mole) of potassium carbonate dissolved in 100 ml. of water was added. To the

thoroughly mixed solution there was then added 10 g. (0.1 mole) of acetylacetone. On shaking, a clear yellow solution resulted and which began to deposit yellow scale-like crystals within a space of a few minutes. After allowing to stand at room temperature for two days, the product was collected. It weighed 12.5 g. and melted at 154-156°. The yield by this procedure was only 54 per cent of the theoretical amount. Several recrystallizations from acetone-alcohol caused it to melt at 157-158°. It gave no depression of the melting point with the mononitro-compound described by Ochiai et al (139).

b. Reaction between 3-nitrobenzamidinium hydrochloride, acetylacetone and sodium ethylate. - Ten and one tenth grams (0.105 mole) of 3-nitrobenzamidinium hydrochloride was suspended in 50 ml. of acetylacetone. To this was then added 3.4 g. (0.05 mole) of sodium ethylate. The pasty mixture was diluted with 50 ml. of anhydrous dioxane and then allowed to reflux for twenty-four hours. The insoluble sodium chloride was removed by filtering the hot reaction mixture with suction. The filtrate was diluted with water, whereupon the pyrimidine precipitated. Dried at 50° overnight, it weighed 10 g. (87 per cent of the theoretical amount) and melted at 155-157°. A sample recrystallized several times, finally melted at 157-158°. It gave no depression with Ochiai's product.

	I	II
Weight of Sample:	0.1085 g.	0.1063 g.
Volume of 0.04668 N HCl used:	30.73 ml.	39.77 ml.
Calc. for $C_{12}H_{11}N_3O_2$ : N, 18.34%		
Found: N,	18.50 %	18.30 %

2-(3'-Aminophenyl)-4,6-dimethylpyrimidine: Eight grams (0.035 mole) of 2-(3'-nitrophenyl)-4,6-dimethylpyrimidine 50 ml. of 95 per cent alcohol and 0.1 g. of Adam's platinum oxide catalyst were placed in a pressure bottle and shaken in a hydrogen atmosphere until no more absorption occurs. The solvent was evaporated on a steam cone. The resulting viscous brown residue was stirred with ligroin in an ice-salt bath until crystallization occurred. The yield was quantitative on a product melting at 88-90° (in agreement with Ochiai's value). The compound is very soluble in most organic solvents, hence to obtain it in well defined crystals it may be dissolved in ether and the solvent allowed to evaporate while being cooled in an ice-salt bath. The product thus obtained melted at 90-91°.

	I	II
Weight of Sample:	0.1135 g.	0.1002 g.
Volume of 0.04668 N HCl used:	36.90 ml.	32.22 ml.
Calc. for $C_{12}H_{13}N_3$ : N, 21.10%		
Found: N,	21.24 %	21.05 %

The picrate was also prepared and appeared to melt at 199-200°, however, this was difficult to see because it melted down to a black liquid and underwent decomposition.

Ochiai et al report it melts at 199°. The nitrogen analysis was too high, however, this could be accounted for by assuming the picrate was not completely free from excess picric acid.

2-Phenyl-4,6-dimethylpyrimidine (137): Sixty-three grams (0.35 mole) of benzamidine hydrochloride dihydrate was dissolved in 225 ml. of cold distilled water. To the resulting solution there was added with vigorous shaking, a previously cooled solution containing 111g. (0.8 mole) of anhydrous potassium carbonate dissolved in 400 ml. of water and to the resulting solution there was added 40 g. (0.4 mole) of acetylacetone. The resulting yellow solution was allowed to stand at room temperature for about four days. The white crystals of the tyramidine agreed in melting point (82-83°) with that reported by Pinner. The yield was only 18.3 g. (32 per cent of the theoretical amount).

Benzamidine hydrochloride (167) : This was prepared using the directions of A. R. Ronzio and J. B. Ekeley as published in "Organic Syntheses". The yield was 65 grams of a product melting at 73-80°.

Mononitro-2-phenyl-4,6-dimethylpyrimidine (139): Ten grams (0.054 mole) of 2-phenyl-4,6-dimethylpyrimidine was dissolved in 10 ml. of concentrated sulfuric acid. Cooling was necessary since considerable heat was evolved. This was then added slowly to a well cooled mixture containing 40 g. of fuming nitric acid. (sp. gr. 1.49) and 40 g. of concentrated sulfuric acid. The reaction mixture was not allowed to rise

more than 2-3° above 0°C. during the above addition (ice-salt bath). The resulting mixture was stirred for a few minutes in the cold. The ice-salt bath was then removed and stirring permitted at room temperature so as to cause small lumps of the pyrimidine to dissolve. In a space of 10 to 15 minutes the temperature of the reaction mixture rose to 15°C. The ice-salt bath was then replaced and stirring was maintained in the cold for about an hour. The reaction mixture was then poured slowly and with stirring onto 1500 grams of crushed ice. The acid mixture was then made alkaline by pouring in a sodium hydroxide solution containing 50 g. of sodium hydroxide in about 500 ml. of water. The mixture was then allowed to stand for about an hour to permit the nitro-compound to settle. It was then filtered with suction and washed free of alkali with copious quantities of water. The wet cake was broken up into small pieces and allowed to dry at about 30° overnight. Yield 8.6 g., melting point 82-110°. This was dissolved in an alcohol-acetone mixture, refluxed with Darco, filtered hot and allowed to cool slowly to room temperature. A product separated which melted at 148-152°. One additional recrystallization from hot acetone-alcohol caused it to melt at 156-157°. The yield of pure product was 2.5 g. This gave no depression of the melting point with 2-(3'-nitrophenyl)-4,6-dimethylpyrimidine.

The mother liquor from the first recrystallization yield 4.2 g. of the unchanged 2-phenyl-4,6-dimethylpyrimidine.

## VI. SUMMARY

1. No analogues of plasmochin in the indole series have been prepared.

2. The reported diazotization and reduction of 3-nitro-4-anisidine to the corresponding 2-nitro-4-methoxyphenylhydrazine has been attempted, but without success (111).

3. Several products from this reaction have been isolated and nitrogen analyses have been made. From these meager data we have suggested three possible structures for the compound melting at 108-109°.

4. A compound from this reaction and which was thought to be the desired hydrazine has been used in an attempt to prepare the corresponding phenylhydrazone of methylethyl ketone. The pink compound so obtained has been shown not to be the expected hydrazone, but no structure has, as yet, been assigned to it.

5. A compound which is apparently identical with this by a mixed melting point was also obtained by recrystallizing a reaction product somewhat similar to that described above, before its reaction with methylethyl ketone, from ethyl alcohol.

6. A compound corresponding to that of the hydrochloride of 7-nitro-2,3-dimethylindole has been isolated as one of the products from the Fischer rearrangement of the corresponding phenylhydrazone.

7. 7-Amino-2,3-dimethylindole has been obtained,

in poor yield, by reduction of the nitro-compound with sodium hydrosulfite.

8. A synthesis of N-( $\beta$ -diethylaminopropyl)-2-nitroaniline is given.

9. The product, melting at 165°, from the Mannich reaction between indole, diethylamine and formaldehyde and which was reported by Kühn and Stein (125) to be 3-diethylaminomethylindole has been shown to be a polymer.

10. The desired 3-diethylaminomethylindole has been prepared, using an acid medium, and found to agree with that reported by Heinrich Kuehn and Otto Stein (126).

11. 4,4'-Di-(4,6-dimethylpyrimidyl-2)-1,3-diphenoxypropane and its hydrochloride have been prepared from the reaction of 4,4'-diamidino-1,3-diphenoxypropane and acetylacetone and reaction of 2-(4'-hydroxyphenyl)-4,6-dimethylpyrimidine in the form of its sodium salt with trimethylene bromide.

12. A second product also formed from 4,4'-diamidino-1,3-diphenoxypropane and acetylacetone corresponds to that of 4-(4,6-dimethylpyrimidyl-2)-4'-N-(2-penteneoylamidino)-1,3-diphenoxypropane on the basis of a nitrogen analysis.

13. A product has been obtained from this latter substance by dissolving it in concentrated hydrochloric acid and recrystallizing the resulting product from alcohol. No structure has been suggested in view of the meager data available.

14. Two new compounds, 2-(4'-nitrophenyl)-4,6-dimethylphrimidine and 2-(4'-aminophenyl)-4,6-dimethylphrimidine, have been prepared.

15. The 2-(4'-hydroxyphenyl)-4,6-dimethylphrimidine derived from the corresponding amino-compound has been found to agree in its melting point with the compound prepared by the hydrolysis of 2-(4'-methoxyphenyl)-4,6-dimethylphrimidine (138).

16. The preparation of 2-(3'-nitrophenyl)-4,6-dimethylphrimidine and the corresponding 2-(3'-aminophenyl)-4,6-dimethylphrimidine is described.

17. The 2-(3'-nitrophenyl)-4,6-dimethylpyrimidine has been found to give no depression of the melting point with the nitro-2-phenyl-4,6-dimethylpyrimidine of Ochiai et al (139).

18. The 2-(3'-aminophenyl)-4,6-dimethylpyrimidine, in its crude form, agrees in its melting point with that of Ochiai et al, however, further recrystallization of this has given a somewhat higher melting point.

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