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DERIVATIVES OF PYRIDO[2,3-d]PYRIDAZINE

by

Eugene Walter Alpern

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the
University of Michigan
1960

Doctoral Committee:

Professor Frederick F. Blicke, Chairman
Professor Adam A. Christman
Professor Albert M. Mattocks
Assistant Professor Ara G. Paul
Professor Wyman R. Vaughan

To My Wife

and Parents

ACKNOWLEDGEMENTS

The author wishes to express his appreciation to Professor F. F. Blicke who suggested this problem and supervised the investigation.

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Eugene W. Alpern

TABLE OF CONTENTS

	Page
GENERAL INTRODUCTION	1
Reaction of Amines and of Hydrazines with Cyclic Anhydrides	15
Cleavage of the Nitrogen-Nitrogen Bond	19
DISCUSSION OF THIS INVESTIGATION	22
Condensation of Quinolinic Anhydride with Hydrazine, Formylhydrazine and Acetylhydrazine and Reactions of the Condensation Products	23
Condensation of Quinolinic Anhydride with N,N'-Dimethylhydrazine and with N,N'-Dibenzylhydrazine	38
Condensation of Quinolinic Anhydride with Methylhydrazine and Reactions of the Condensation Products.	41
Condensation of Quinolinic Anhydride with Phenylhydrazine, Benzylamine, Benzylhydrazine, N-Benzyl-N'-phenylhydrazine and with Methylamine; Reactions of 6,7-Dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione	49
The Attempted Preparation of 3-Formylpicolinic Acid	55
EXPERIMENTAL PART	60
Quinolinic Anhydride	60
6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione	60
5-Acetoxy-7-acetylpyrido[2,3-d]pyridazin-8(7H)-one	60
7-Acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione	61
Acetylhydrazine	61
N-Acetyl-N'-(3-carboxypicolinoyl)hydrazine	61
6-Acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione	62

Page

Formylhydrazine 62

N-Formyl-N'-(3-carboxypicolinoyl)hydrazine . . 62

6,7-Dihydro-6-formylpyrido[2,3-d]pyridazine-5,8-dione 62

5-Chloropyrido[2,3-d]pyridazin-8(7H)-one . . 63

5,8-Dichloropyrido[2,3-d]pyridazine . . . 63

1,2,3,4,6,7-Hexahydropyrido[2,3-d]pyridazine-5,8-dione 64

6,7-Dihydro-6,7-dimethylpyrido[2,3-d]pyridazine-5,8-dione 64

6,7-Dimethyl-1,2,3,4,6,7-hexahydropyrido-[2,3-d]pyridazine-5,8-dione 65

Dimethyl quinolinate 65

2,3-Bis(N-methylcarbamoyl)pyridine . . . 65

6,7-Dibenzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione 65

6,7-Dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione 66

5-Chloro-7-methylpyrido[2,3-d]pyridazin-8(7H)-one 66

1,2,3,4,6,7-Hexahydro-7-methylpyrido[2,3-d]-pyridazine-5,8-dione 66

5-Methoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one 67

5-Acetoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one 67

1,2,3,4,6,7-Hexahydro-7-methylpyrido[2,3-d]-pyridazin-8(7H)-one 68

6-Benzoyl-7-methyl-5,6,7,8-tetrahydropyrido-[2,3-d]pyridazine 68

6,7-Dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione 69

8-Methoxy-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one Hydrochloride 69

Page

8-Acetoxy-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one 70

2-(N-Benzylcarbamoyl)nicotinic acid . . . 70

Benzylhydrazine 70

7-Benzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione 71

N-Benzyl-N'-phenylhydrazine 71

7-Benzyl-6,7-dihydro-6-phenylpyrido[2,3-d]-pyridazine-5,8-dione 72

2-(N-Methylcarbamoyl)nicotinic acid . . . 72

N-Methylquinolinimide 72

Ethyl 2-methylnicotinate 73

3-Hydroxymethyl-2-methylpyridine 73

2-Methyl-3-pyridinecarboxaldehyde. . . . 74

2-(2-Methyl-3-pyridyl)-1,3-dioxolane . . . 75

2-Methylnicotinic acid from 2-(2-methyl-3-pyridyl)-1,3-dioxolane 75

2-Methylnicotinic acid from 2-methyl-nicotinaldehyde 76

2-Methylnicotinic acid from 2-(2-methyl-3-pyridyl)-1,3-dioxolane 76

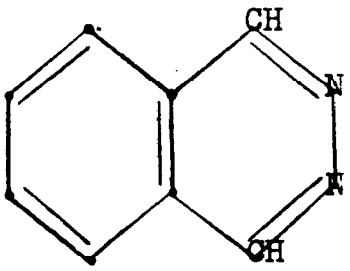
SUMMARY 77

BIBLIOGRAPHY 80

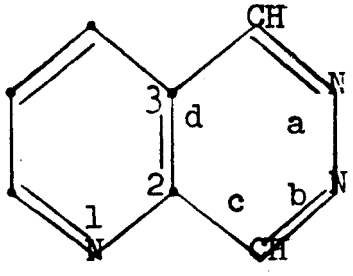
GENERAL INTRODUCTION

Prior to the synthesis of phthalazine itself in 1893, a number of derivatives of this parent compound had been prepared. Additional derivatives were described in the literature from time to time. Special interest in these derivatives was aroused by the discovery of the luminescence of 5-aminophthalazine-1,4-dione.(1) During the intensive search for antimalarials during World War II, a number of phthalazine derivatives were prepared and tested. Phthalazine derivatives have also been examined for activity in tuberculosis. As far as we are aware, the only phthalazine derivative which ever found extensive clinical use is 1-hydrazinophthalazine (Apresoline); this substance is an antihypertensive agent.

The object of this investigation was the preparation of a series of derivatives of pyrido[2,3-d]pyridazine(I)--a parent compound which consists of a phthalazine structure in which the benzene ring has been replaced by pyridine.



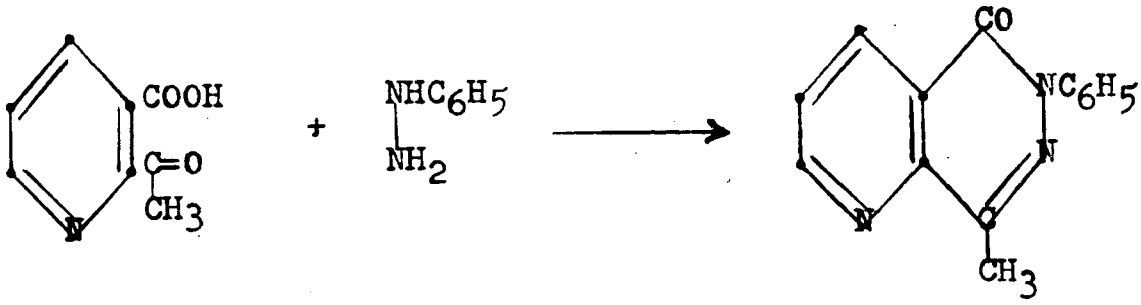
Phthalazine
(Benzo[d]pyridazine)



Pyrido[2,3-d]pyridazine(I)

The parent compound (I) has not been synthesized; however,

eighteen derivatives have been described in the literature. The first derivative, prepared in 1893, was 8-methyl-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one (II) (hydrazon-anhydride of 2-acetylnicotinic acid).(2) It was obtained by the interaction of 2-acetylnicotinic acid with phenyl-hydrazine. The other derivatives that have been described



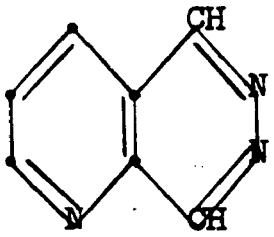
II

are mentioned below. In order to tabulate the derivatives in a simple manner, some of them are listed as carbonyl derivatives of di- or tetrahydropyrido[2,3-d]pyridazine (III, IV, V and VI).

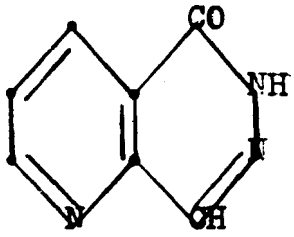
	Ref.
Pyrido[2,3-d]pyridazine (I)	
8-Chloro-5-phenyl-	a,b,c
3-Cyano-5,8-dihydroxy-2-methyl-	d
3-Cyano-2,5-dimethyl-8-hydroxy-	d
5,8-Diacetyl-	e
8-Hydrazino-5-phenyl-	a,b,c
Pyrido[2,3-d]pyridazin-5(6H)-one (III)	
8-Acetic acid, ethyl ester-6-p-nitrophenyl-	g
8-Methyl-6-p-nitrophenyl	h
Pyrido[2,3-d]pyridazin-8(7H)-one (IV)	i
5-Phenyl-	a,b,c
7-Phenyl-	i
6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione (V)	e
3-Bromo-2-hydroxy-	j
3-Chloro-2-hydroxy-	j
2-Hydroxy-	j
2-Hydroxy-3-iodo-	j

Ref.

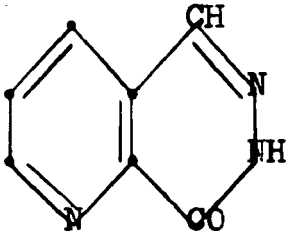
7,8-Dihydro-7,8-triazolopyrido[2,3-d]-pyridazine (VI)
4-Hydrazino- k



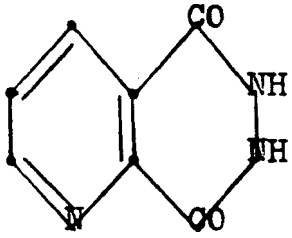
Pyrido[2,3-d]pyridazine (I)



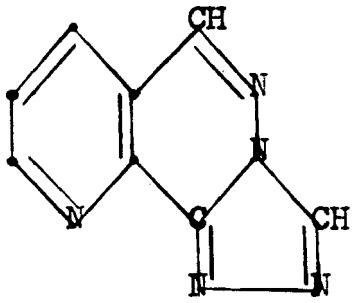
Pyrido[2,3-d]pyrid-azin-5(6H)-one (III)



Pyrido[2,3-d]pyridazin-8(7H)-one (IV)



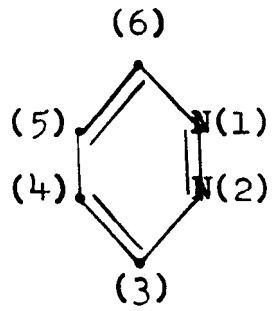
6,7-Dihydropyrido[2,3-d]-pyridazine-5,8-dione (V)



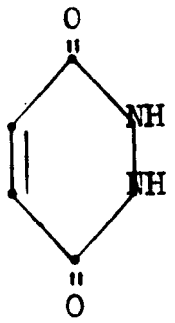
7,8-Dihydro-7,8-triazolo-pyrido[2,3-d]pyridazine (VI)

(a) J. Druey and R. H. Ringier, Helv. Chim. Acta, 34, 195 (1951)
(b) British Patent 629,177 (1949); C. A., 44, 4517 (1950)
(c) U. S. Patent 2,484,029 (1949); C. A., 44, 4046 (1950)
(d) R. G. Jones, J. Am. Chem. Soc., 78, 159 (1956)
(e) G. Gheorghiu, Bull. soc. chim. France, 47, 630 (1930)
(f) German Patent 947,971 (1956); C. A., 53, 2263 (1959)
(g) E. Ochiai, K. Miyaki, and S. Sato, Ber., 70, 2018 (1937)
(h) J. P. Wibaut and H. Boer, Rec. trav. Chim., 74, 241 (1955)
(i) F. Bottari and S. Carboni, Gazz. chim. ital., 86, 990 (1956)
(j) K. Gleu and K. Wackernagel, J. prakt. Chem., [2] 148, 72 (1937)
(k) German Patent 951,993 (1956); C. A., 53, 5298 (1959)

There is considerable diversity with respect to the naming of diketo compounds which contain the pyridazine, phthalazine or the pyrido[2,3-d]pyridazine ring systems.



Pyridazine

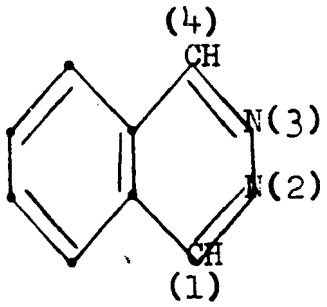


Maleic hydrazide

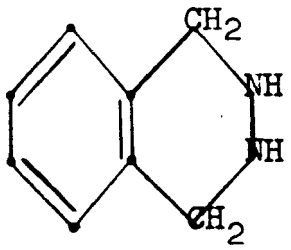
Maleic Hydrazide

(a) 1,2-Dihydropyridazine-3,6-dione
(b) 3,6-Diketo-1,2,3,6-tetrahydropyridazine

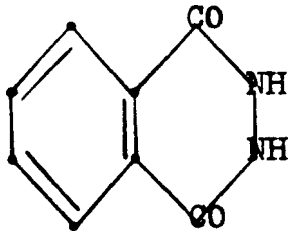
Name (a) is in accordance with the "extra hydrogen" nomenclature (3), and name (b) is one found in Heterocyclic Compounds, edited by R. C. Elderfield.(4)



Phthalazine
Benzo[d]pyridazine



1,2,3,4-Tetrahydrophthalazine



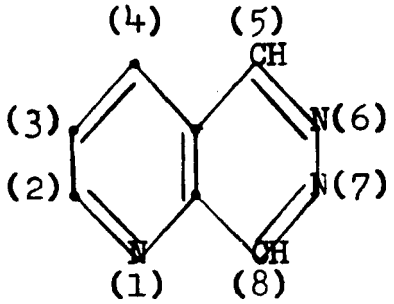
Phthalhydrazide

Phthalhydrazide

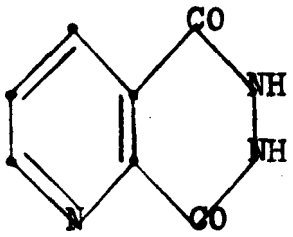
(c) 1,4-Diketo-1,2,3,4-tetrahydrophthalazine
(d) 1,2,3,4-Tetrahydrophthalazine-1,4-dione ("Beilstein")
(e) 2,3-Dihydro-1,4-phthalazinedione
(f) 1,4-Phthalazinedione

The first two names, (c) and (d), listed above are obvious and correct names for phthalhydrazide. The third name (e)

represents the use of "extra hydrogen" nomenclature (3), and the fourth name is one found in Dictionary of Organic Compounds.(5)



Pyrido[2,3-d]pyridazine



Quinolylhydrazide

Quinolylhydrazide

(g) Pyridine-2,3-dicarboxylic acid hydrazide (6)
(h) Quinolinic acid hydrazide (7)
(i) 6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione (Chemical Abstracts)

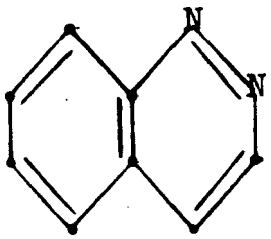
The name, quinolylhydrazide, was used by Gheorghiu.(8) The other names (g,h and i) have appeared in the literature.

In addition to the names listed above for compounds which contain the pyrido[2,3-d]pyridazine ring structure, other derivatives of this ring system which are named in accordance with a different system of nomenclature for the parent compound, e.g., 8-azaphthalazine (9), and 2,3,5-triazanaphthalene (10) are mentioned in the literature.

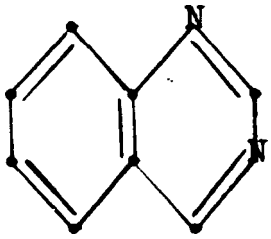
In this dissertation, the "extra hydrogen" nomenclature, as is illustrated by examples a, e and i, will be used in most instances to name compounds which contain a carbonyl group and the pyridazine ring system.

It is of interest to note the total number of parent compounds (benzodiazines) which are isomeric with phthalazine, and also the parent compounds (pyridodiazines) which

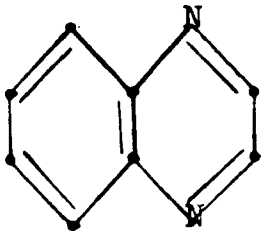
are isomeric with pyrido[2,3-d]pyridazine. There are four possible structural isomeric benzodiazines: cinnoline, quinazoline, quinoxaline, and phthalazine.



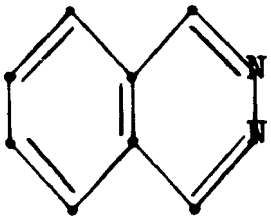
Cinnoline



Quinazoline



Quinoxaline



Phthalazine

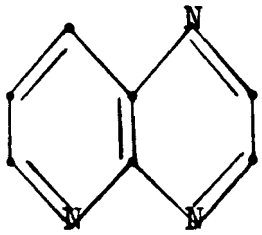
Many derivatives of these four parent compounds, cinnoline (11,12), quinazoline (13), quinoxaline (14,15) and phthalazine (4,16,17), have been reported in the literature. Some cinnoline derivatives have been examined for their trypanocidal and antimalarial activity.

Quinazoline derivatives have been studied more than the others with respect to physiological activity. The quinazoline nucleus has been found in some alkaloids.(13) Derivatives of quinazoline have been tested for their antibacterial, anticonvulsant and antimalarial activity, and a number of quinazolylsulfanilamides have been prepared (13). However, all of these compounds either were inactive or had only slight activity.

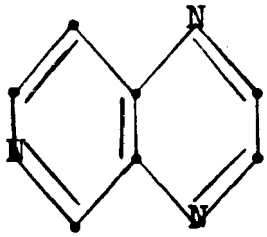
Quinoxaline derivatives have been tested for anti-

bacterial and antimalarial action.(15) Sulfaquinoxaline has found use in veterinary medicine.(18) The physiological activity of phthalazine derivatives has been described earlier in this dissertation.

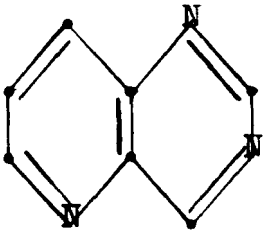
There are twelve isomeric pyridodiazines. The formulas for the eight of these which are known, either in the form of the parent compounds and/or in the form of derivatives of the parent compounds, are shown below.



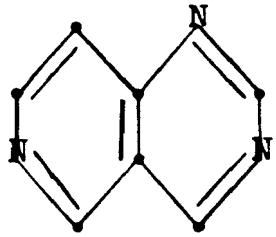
Pyrido[2,3-b]pyrazine



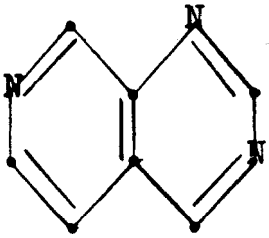
Pyrido[3,4-b]pyrazine



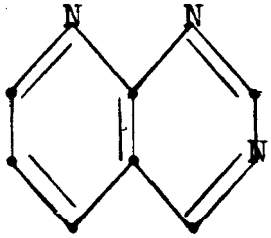
Pyrido[3,2-d]pyrimidine



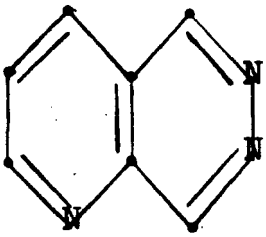
Pyrido[4,3-d]pyrimidine



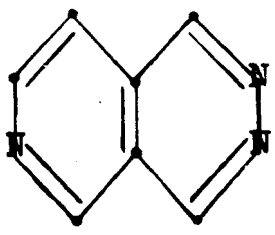
Pyrido[3,4-d]pyrimidine



Pyrido[2,3-d]pyrimidine

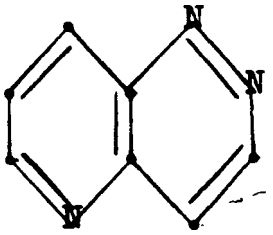


Pyrido[2,3-d]pyridazine

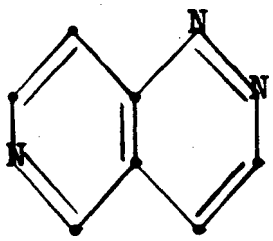


Pyrido[3,4-d]pyridazine

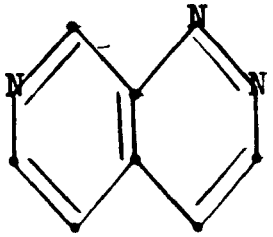
The following four formulas represent pyridodiazines which are unknown with respect to both the parent compounds and derivatives.



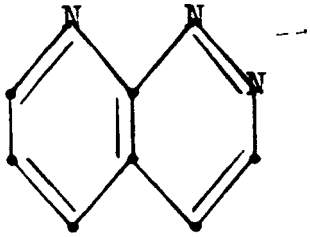
Pyrido[3,2-c]pyridazine



Pyrido[4,3-c]pyridazine



Pyrido[3,4-c]pyridazine



Pyrido[2,3-c]pyridazine

Comparatively few derivatives of pyridodiazines have been prepared. Only pyrido[2,3-d]pyridazine derivatives have shown any physiological activity; they have been patented as parasiticides, antiseptics, bacteriostatics, and bactericides.(19) 8-Hydrazino-5-phenylpyrido[2,3-d]pyridazine and 5,8-dihydrazinopyrido[2,3-d]pyridazine have been tested for antihypertensive activity; only the latter was active.(20)

Since this investigation is concerned with derivatives of pyridazine (1,2-diazine), this discussion will be limited to pyridazine, phthalazine (benzo[d]pyridazine), pyrido[2,3-d]-pyridazine and some of their derivatives.

Pyridazine is a liquid with a high boiling point, 208°, and a pyridine-like odor.(21) It is unstable to heat and

darkens in air. It is very soluble in water, benzene, dioxane and alcohol; less soluble in ether; and almost insoluble in cyclohexane. With strong acids pyridazine reacts as a monoacidic base. The pyridazine nucleus is known to be extremely resistant to electrophilic substitution.

Phthalazine was first prepared in 1893 from the reaction of α,α,α',α'-tetrachloro-o-xylene with hydrazine.(16) It exists in pale-yellow flat needles with a quinoline-like odor, m.p. 90-91° (b.p. 175°/17 mm.). Phthalazine is very soluble in water (it does not give an alkaline reaction), alcohols, benzene and ethyl acetate. It is slightly soluble in ether and insoluble in petroleum ether. It acts as a monoacidic base to form salts, e.g., hydrochloride and picrate.

When phthalazine was reduced with zinc and concentrated hydrochloric acid, the nitrogen-nitrogen bond was cleaved and o-aminomethylbenzylamine was obtained; 7% sodium amalgam reduced phthalazine to 1,2,3,4-tetrahydrophthalazine.(22,23) Alkaline potassium permanganate oxidized phthalazine to pyridazine-4,5-dicarboxylic acid.(24)

As already mentioned, pyrido[2,3-d]pyridazine has not been synthesized. A possible method of preparing it might be by the use of a process similar to that employed for the preparation of phthalazine. This last mentioned compound has been obtained by interaction of phthalaldehyde and hydrazine. Hence, it might be expected that pyrido[2,3-d]pyridazine would be formed by interaction of pyridine-2,3-dicarboxaldehyde with hydrazine. However, the dicarboxaldehyde, which was

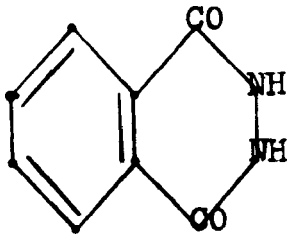
undoubtedly formed in the ozonolysis of quinoline, could not be isolated in the pure state, but it was obtained in the form of the bis p-nitrophenylhydrazone and the dioxime of quinolinic acid imide.(25)

A procedure for the preparation of pyridine-2,3-dicarboxaldehyde is needed. The methods generally used to obtain aldehydes give low yields when applied to the synthesis of pyridine aldehydes.(26,27) The Rosenmund reduction of acyl chlorides fails in the case of unsubstituted pyridine acid chlorides, but is successful with substituted compounds, e.g., 4,6-dichloropicolinoyl chloride.(28,29) Pyridine aldehydes have been obtained from the selenium dioxide oxidation of picoline (30-32), and by the McFadyen-Stevens procedure (31, 33-35) in low yields.

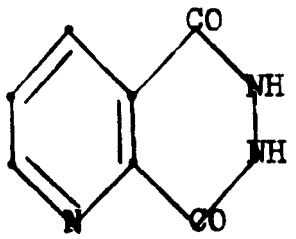
An improvement in the yields of pyridine aldehydes was described by Micovic and Mihailovic.(27) They reduced the ester of the corresponding pyridinecarboxylic acid to the alcohol with lithium aluminum hydride. The alcohol was oxidized by lead tetraacetate in benzene to the pyridinecarboxaldehyde in high yields. The preparation of the pyridine-2,3-dicarboxaldehyde required for the preparation of pyrido-[2,3-d]pyridazine might be obtained by this method.

It is of interest to compare the general properties of phthalazine with those of pyrido[2,3-d]pyridazine. Since this can be done only by comparison of the properties of known compounds, 2,3-dihydrophthalazine-1,4-dione (VII) (36) and 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (V) (8) were selected for this purpose. In this comparison, many similarities

are found. 2,3-Dihydrophthalazine-1,4-dione (VII) and



2,3-Dihydrophthalazine-1,4-dione (VII)

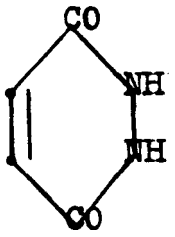


6,7-Dihydropyrido[2,3-d]-pyridazine-5,8-dione (V)

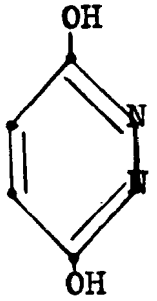
6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (V) react as monoacids and form monopotassium salts. Both are stable to heat and sublime without decomposition; they are not changed by heating with hydrochloric acid, acetic acid or potassium hydroxide solution. Neither compound reacts with benzaldehyde on short heating, but 2,3-dihydrophthalazine-1,4-dione (VII) will react when heated with benzaldehyde for a long time. Upon treatment with nitric acid, VII gives predominately 6-nitro-2,3-dihydrophthalazine-1,4-dione (37), while V yields quinolinic acid (8).

1,2-Dihydropyridazine-3,6-dione and its 1-substituted derivatives are considered to be aromatic compounds.(38) Pyridazine is resonance stabilized, with a resonance energy of 22 kcal./mole (39), which is lower than that of pyridine (37 kcal./mole). Based on its structure, 1,2-dihydropyridazine-3,6-dione may exist either as a cyclic diamide (VIII) or as a dihydroxy aromatic compound (IX). To differentiate between these two possibilities, its chemical reactivity was studied. A characteristic reaction of aromatic compounds is the preference to undergo substitution rather than

addition reactions.



Cyclic Diamide (VIII)



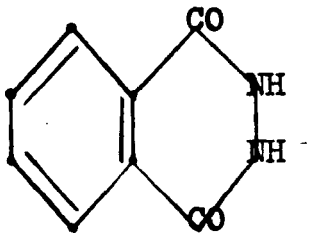
Dihydroxy- (IX)

1,2-Dihydropyridazine-3,6-dione

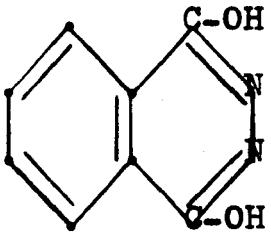
Upon reaction of 1,2-dihydropyridazine-3,6-dione or 1-substituted-1,2-dihydropyridazine-3,6-dione with diazomethane (40), the O-methyl derivative was formed, while with catalytic hydrogenation or bromination, no reaction was observed.(41) However, in 1,2-disubstituted-1,2-dihydropyridazine-3,6-dione, different reactions were noticed. Catalytic hydrogenation caused reduction of the double bond.(41) When 1,2-disubstituted-1,2-dihydropyridazine-3,6-dione was brominated, the 4,5-dibromo compound was produced.(41) Thus, it was determined that 1,2-dihydropyridazine-3,6-dione and 1-substituted-1,2-dihydropyridazine-3,6-dione undergo reactions that are characteristic of aromatic compounds, while 1,2-disubstituted-1,2-dihydropyridazine-3,6-dione reacts similarly to non-aromatic olefinic compounds.

Three tautomeric forms of 2,3-dihydrophthalazine-1,4-dione have been postulated. It was originally believed (36,41) that 2,3-dihydrophthalazine-1,4-dione existed in the dioxo form. Rowe and Peters (43) studied the reactions of 2,3-dihydrophthalazine-1,4-dione and proposed that it assumed

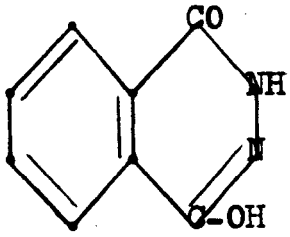
different tautomeric forms depending on the pH of the



Dioxo-



Dihydroxy-



Hydroxy-oxo-

solution: in alkali solution it probably existed as 1-hydroxyphthalazin-4(3H)-one, while in acid or neutral solution 1,4-dihydroxyphthalazine presumably was present.

Arndt (44) reacted diazomethane with cyclic amides and with hydrazides to determine the tautomeric forms of these compounds. Reaction of diazomethane with lactams (cyclic amides) gave N-methyl derivatives, but with lactims (enol form of cyclic amides) the O-methyl ethers were obtained. In this manner Arndt was able to show that the lactim form (-N=C(R)-OH) is not found in open chain compounds and rarely in cyclic compounds. It is found only when the amide group is part of an aromatic system. He postulated a zwitter-ion (R-NH=C-R') as an intermediate.

(+) O (-)

The reaction of diazomethane with cyclic hydrazides has been reported.(40) 1-Phenyl-1,2,4,5-tetrahydropyrid-

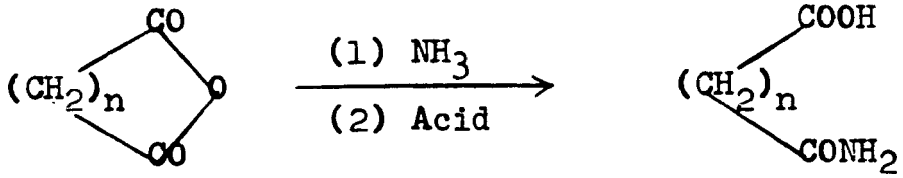
azine-3,6-dione reacted with diazomethane to produce 1-methyl-2-phenyl-1,2,4,5-tetrahydropyridazine-3,6-dione. N-Methylation is characteristic of the reaction of lactams with diazomethane. With 1,2-dihydropyridazine-3,6-dione or 2,3-dihydrophthalazine-1,4-dione, the product was the O-methyl derivative. Upon further reaction with diazomethane, the O,N-dimethyl compound was produced. O-Methylation occurs in amide groups that are part of an aromatic system. As the O,N-dimethyl compound was formed, the parent compound must exist in the hydroxy-oxo form.

Recently the tautomerism of 1,2-dihydropyridazine-3,6-dione and 2,3-dihydrophthalazine-1,4-dione has been studied with the aid of infrared spectra. Sheinker and coworkers (45-47) determined that these compounds must exist in the hydroxy-oxo form. Elvidge and Redman (48) have also concluded from a study of the infrared spectra of 2,3-dihydrophthalazine-1,4-dione and its O- and N-methyl derivatives that the correct structure would be represented by the hydroxy-oxo form.

Miller and White (49) compared the ultraviolet spectrum of 1,2-dihydropyridazine-3,6-dione with the spectra of its derivatives of known structure, and concluded that it must exist in the form of 6-hydroxypyridazin-3(2H)-one.

Reaction of Amines and of Hydrazines with Cyclic Anhydrides

Many reactions have been recorded in the literature concerning the acylation of amines with anhydrides of monocarboxylic acids, but there have been relatively few reactions reported in which the anhydride of a dicarboxylic acid has been used as the acylating agent. With anhydrides, such as acetic anhydride, amides were obtained, but in the case of dicarboxylic acid anhydrides, amic acids were the products.



Dicarboxylic acid anhydride

Amic acid

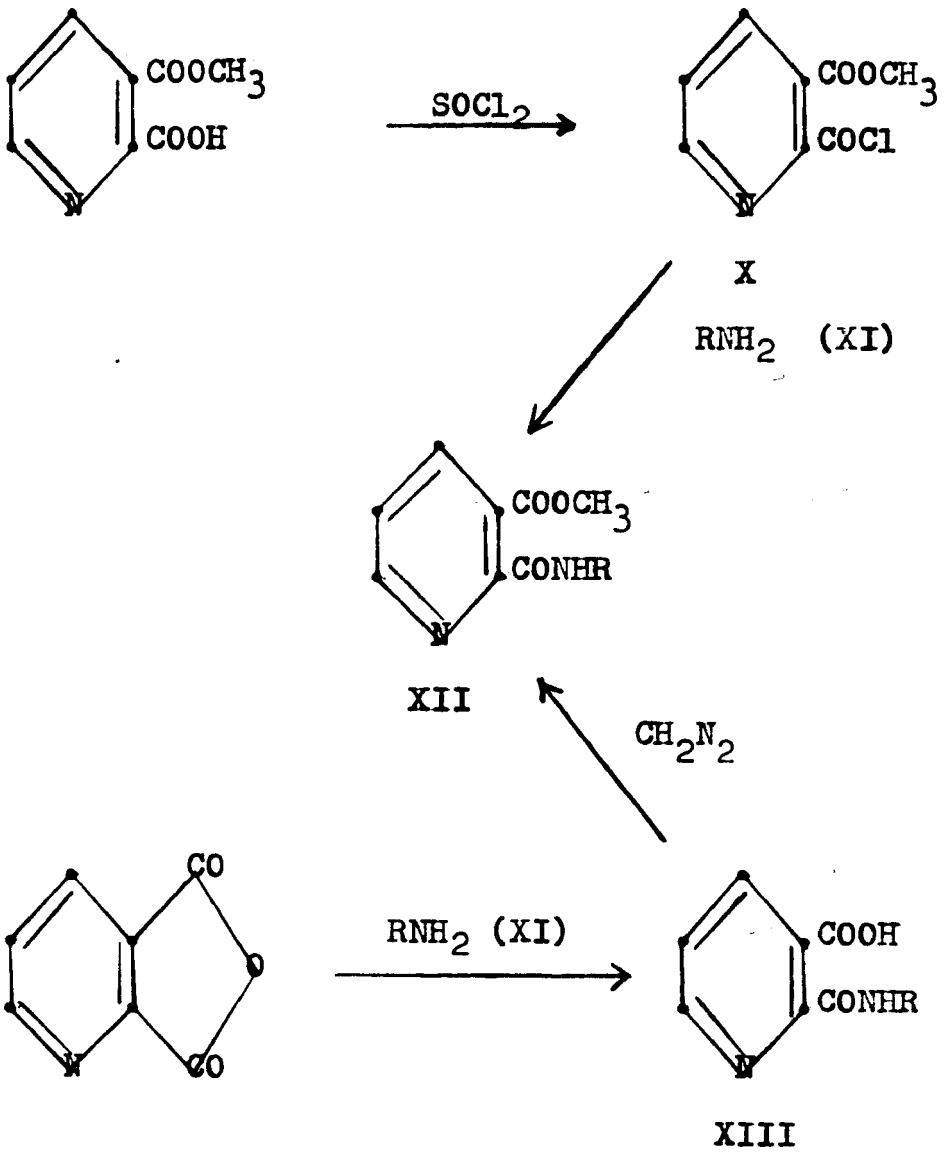
Typical examples of the formation of amic acids are the reactions of amines with succinic anhydride (50-52), maleic anhydride (51,53), phthalic anhydride (51,54-57) and quinolinic anhydride (58-61). In the case of succinic, maleic and phthalic anhydrides, only one product can be obtained, because the anhydrides are symmetrical. In the case of quinolinic anhydride, however, the two carbonyl groups are not equivalent, thus, two isomeric amic acids could be formed.

Just as there are many reactions which demonstrate the similarity between nitrobenzene and pyridine (62,63), the reactions of 3-nitrophthalic anhydride seem to be analogous to those of quinolinic anhydride. In both anhydrides, the carbonyl groups are in the 2 and 3 position relative to the nitro group and the pyridine nitrogen, respectively.

3-Nitrophthalic anhydride reacted with ammonia and with amines to form only 3-nitrophthalamic acids (2-carbamoyl-3-nitrobenzoic acids).(52,64,65) The position of the amide group was determined by reacting the nitrophthalamic acid with hypochlorite. The product obtained was 2-amino-3-nitrobenzoic acid.

In the reaction of ammonia with quinolinic anhydride, only the 2-amic acid (2-carbamoylnicotinic acid) was isolated. Thus, in both 3-nitrophthalamic and quinolin-2-amic acids, the amide group is adjacent to the nitro group or the ring nitrogen, respectively. The position of the amide group in quinolin-2-amic acid was determined by converting it into 2-aminonicotinic acid by the use of the Hoffmann rearrangement.(58) S. Fallab and H. Erlenmeyer (66) also proved the structure of the product from the reaction of quinolinic anhydride with ammonia. They converted the quinolinamic acid obtained into 2-aminonicotinic acid, then decarboxylated this acid into 2-aminopyridine.

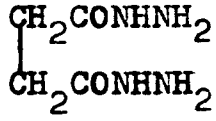
In order to establish that amines react similarly to ammonia with quinolinic anhydride, certain methyl 2-(N-substituted carbamoyl)nicotinates (XII) were prepared.(61) Methyl 2-carboxynicotinate (67) was treated with thionyl chloride to form 3-carbomethoxypicolinic acid chloride (X), which, when reacted with an amine (XI), gave methyl 2-(N-substituted carbamoyl)nicotinate (XII). This compound was found to be identical with the one obtained by treatment of the product (XIII), formed from the reaction of quinolinic anhydride with the amine (XI), with diazomethane.



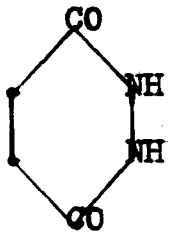
Feuer, et al. (68,69) studied the reactions of hydrazine with succinic and maleic anhydride and determined that the differences between the two series of reactions can be attributed to the facile ring closures which occur in the maleic acid series.

When hydrazine was reacted with succinic anhydride, the products which were obtained depended on the number of molar equivalents of hydrazine used. The final product of these reactions was succindihydrazide. In no case was cyclic

succinhydrazide produced by the reaction of succinic anhydride or ester with hydrazine. Feuer, et al., were able to synthesize cyclic succinhydrazide only by the reduction of the double bond in maleic hydrazide.



Succindihydrazide



Cyclic succinhydrazide

With maleic anhydride and hydrazine, products could be isolated which were similar to those found in the case of succinic anhydride. When these products were heated, maleic hydrazide was obtained. This ease of ring closure in the maleic acid series is greatly enhanced due to the lower energy of the cyclized, aromatic structure.(70)

The reactions of substituted hydrazines with acylating agents have been studied only to a limited extent. It is known that phenylhydrazine reacts with acids, esters or anhydrides to give β-acylphenylhydrazides. T. Ohta (71) reacted phthalic anhydride with β-formylphenylhydrazine and obtained a mixture of α- and β-phthalylphenylhydrazines, N-anilinophthalimide and 2-phenylphthalhydrazide. When he replaced the β-formylphenylhydrazine with β-acetylphenylhydrazine or β-benzoylphenylhydrazine, the only product that he obtained was phthalic acid mono β-acyl-α-phenylhydrazide.

Only recently has there been any mention of the acylation of methylhydrazine in the literature. It was reported

(72) that methylhydrazine reacts with methyl isonicotinate to give N-isonicotinoyl-N'-methylhydrazine, although no proof of this structure was given. The only extensive investigation of the acylation of methylhydrazine is that by Hinman and Fulton.(73) They studied the acylation of methylhydrazine with the methyl esters of acetic, propionic, isobutyric and benzoic acids, and acetic, propionic and benzoic anhydrides. Their conclusions were (a) the reaction of an anhydride and methylhydrazine yields mainly the N-acyl-N-methylhydrazine, and (b) the reaction of an ester and methylhydrazine gives predominately the N-acyl-N'-methylhydrazine, together with a small amount of the N-acyl-N-methylhydrazine.

Recently, isonicotinoyl chloride was reacted with isopropylhydrazine to yield 83% of N-isonicotinoyl-N'-isopropylhydrazine.(74) In this case, the acyl chloride reacted in the same manner as an ester with a substituted hydrazine to form the N-acyl-N'-alkylhydrazine.

Cleavage of the Nitrogen-Nitrogen Bond

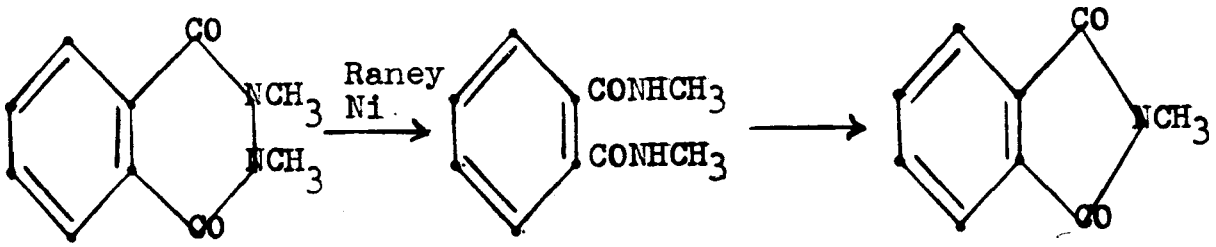
The nitrogen-nitrogen bond in hydrazines was found to be cleaved by Raney nickel (75,76), platinum oxide and hydrogen (77), and lithium aluminum hydride (78,79). C. Ainsworth reported (80) that Raney nickel had been found to cleave acylhydrazines into amides and amines. As an example, nicotinic

$$RCONHNH_2 \xrightarrow{\text{Raney nickel}} RCONH_2 + NH_3$$

acid hydrazide was converted in good yield to nicotinamide. In a later paper (81), he reported the hydrogenolysis of

N,N'-dibenzoylhydrazine, which yielded benzamide. However, when this hydrogenolysis was applied to maleic hydrazide and phthalhydrazide, only starting material was obtained. His procedure was to reflux for 2 to 3 hours a mixture of 2 g. of the compound and 10 g. of Raney nickel in 50 ml. of 95% ethanol.

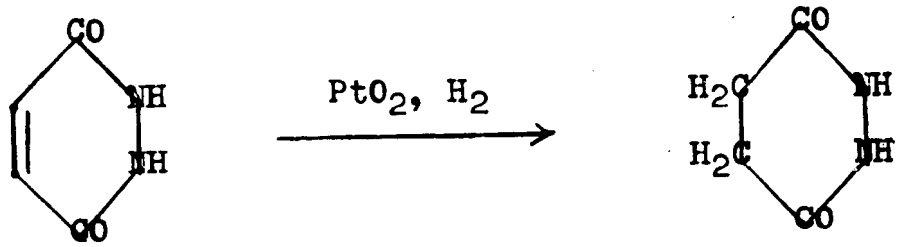
Hinman (82) reported the hydrogenolysis of other acylhydrazines. He found that N,N'-diacylhydrazines are cleaved in approximately 50-60% yield. N-Alkyl-N,N'-diacylhydrazines are cleaved in 12-30% yields, while N,N'-dialkyl-N,N'-diacylhydrazines do not cleave. In the hydrogenolysis of 2,3-dihydro-2,3-dimethylphthalazine-1,4-dione, he obtained N-methylphthalimide. This is probably formed by the cleavage of the bond between the two nitrogen atoms to form N,N'-dimethylphthalamide, followed by a ring closure to the imide.

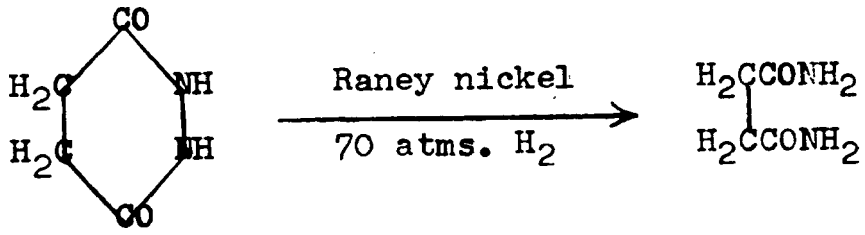


N,N'-Dimethylphthalamide has been shown to form N-methylphthalimide with ease.(83) Hinman was unable to cleave the hydrazine bond in phthalhydrazide.

Previously, H. Feuer, et al.(68), reported the hydrogenation of maleic hydrazide with Adams catalyst or with aluminum amalgam to form cyclic succinhydrazide. Treatment of cyclic succinhydrazide with Raney nickel catalyst and hydrogen at 70 atmospheres pressure gave succinamide (60%), in which the

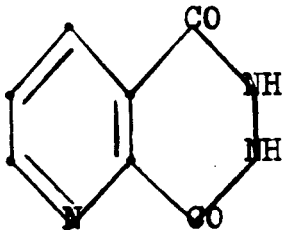
nitrogen-nitrogen bond must have been cleaved.



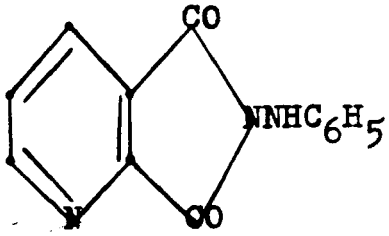


DISCUSSION OF THIS INVESTIGATION

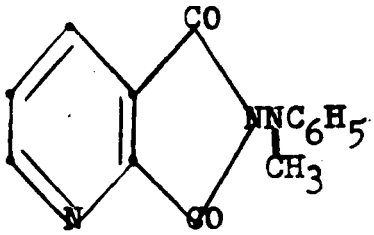
Prior to this investigation, as far as we are aware, quinolinic anhydride has been condensed only with the following hydrazines: hydrazine, phenylhydrazine, and N-methyl-N-phenylhydrazine. Based on the work of Gheorghiu (8), the bicyclic product obtained from the use of hydrazine was 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione. When phenylhydrazine was employed, a product was formed which was assumed to be N-anilinoquinolinimide (84), but no proof of structure was given. From N-methyl-N-phenylhydrazine the bicyclic product obtained was stated to be N-(N-methylanilino)quinolinimide.(85)



6,7-Dihydropyrido-[2,3-d]pyridazine-5,8-dione



N-Anilino-quinolinimide



N-(N-methylanilino)-quinolinimide

During this investigation, quinolinic anhydride was condensed with hydrazine and with eight substituted hydrazines to produce 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione or derivatives of this substance in which substituents occupy the 6-, 7-, or 6,7-positions.

Reasons for the assumption that the condensation products which we obtained contained the pyrido[2,3-d]pyridazine instead of the quinolinimide ring structure, and evidence for the position (6 or 7) of a substituent in the pyrido[2,3-d]pyridazine

will be discussed later.

A number of reactions were carried out with the pyrido-[2,3-d]pyridazines which have been prepared.

Finally, the new compounds, N-methylquinolinimide and eight 2,3-disubstituted pyridines, were synthesized.

The condensations which were carried out with the use of quinolinic anhydride are outlined in Reaction Scheme I (p. 24).

In each instance, a mixture of molecular equivalent amounts of the anhydride, the hydrazine and acetic acid, toluene or xylene was refluxed. The yield of condensation product varied from 19.7 to 87%.

Condensation of Quinolinic Anhydride with Hydrazine, Formylhydrazine and Acetylhydrazine and Reactions of the Condensation Products.

All of the products which are formulated in Reaction Scheme II (p. 25) are listed below.

Quinolinic anhydride* (I)
6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione* (II)
5-Acetoxy-7-acetylpyrido[2,3-d]pyridazin-8(7H)-one (III)
7-Acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (IV)
N-Acetyl-N'-(3-carboxypicolinoyl)hydrazine (V)
6-Acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (VI)
N-Formyl-N'-(3-carboxypicolinoyl)hydrazine (VII)
6-Formyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (VIII)
5-Chloropyrido[2,3-d]pyridazin-8(7H)-one (IX)
1,2,3,4,6,7-Hexahydropyrido[2,3-d]pyridazine-5,8-dione (X)

The first reported synthesis of 6,7-dihydropyrido[2,3-d]-pyridazine-5,8-dione (II), described by Gheorghiu, is the reaction between quinolinic anhydride (I) and hydrazine.(8) It was realized by Gheorghiu that one or more of the isomeric

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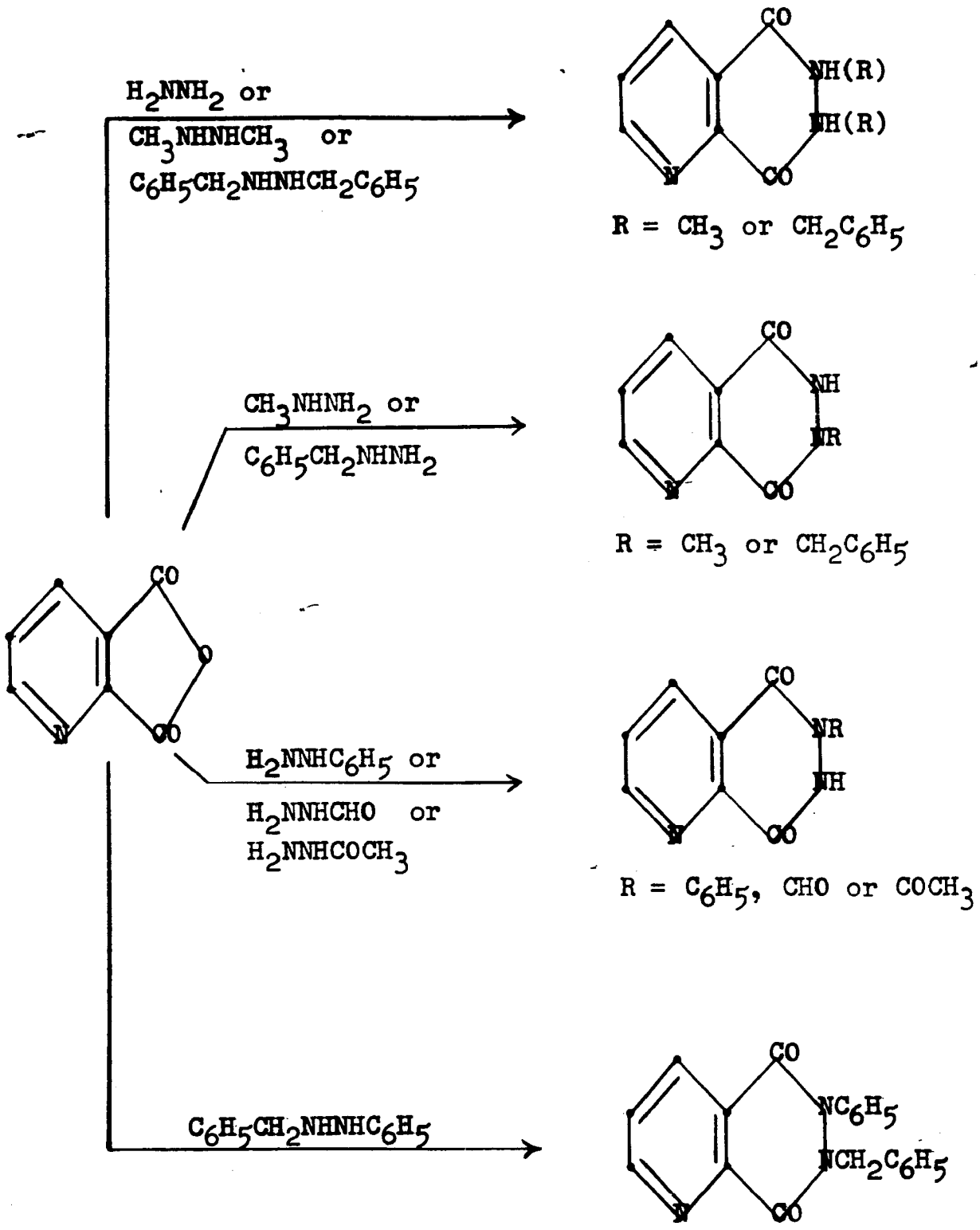
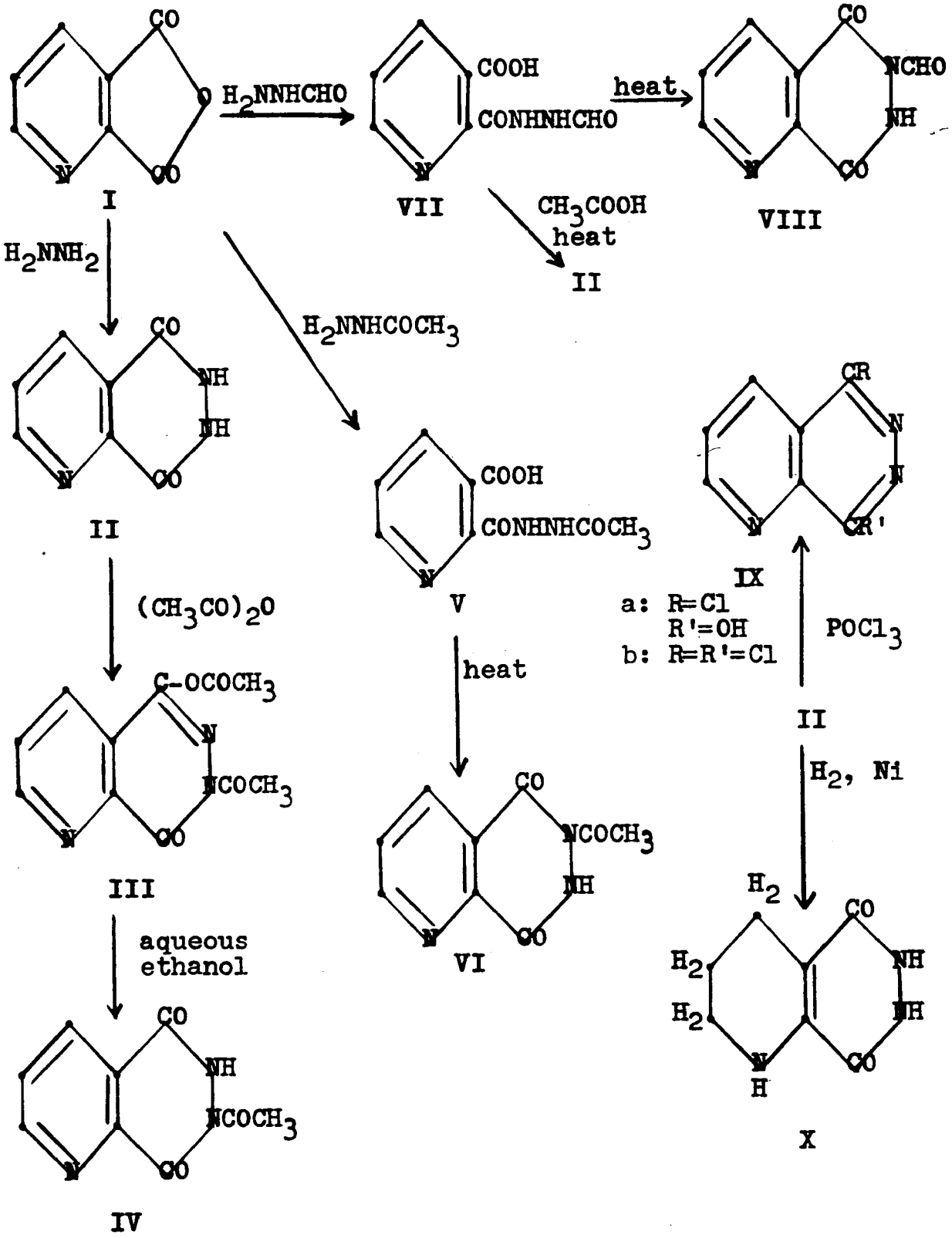
* Known compound

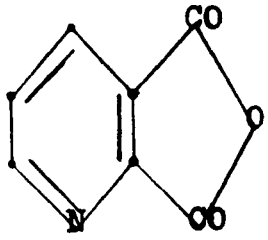
REACTION SCHEME I



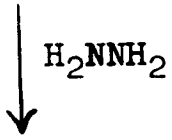
REACTION SCHEME II

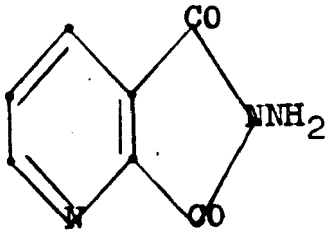


compounds (A, B, C, D) formulated below might have been obtained. However, only one product was isolated. The manner in which this product was shown to possess structure D is described below.

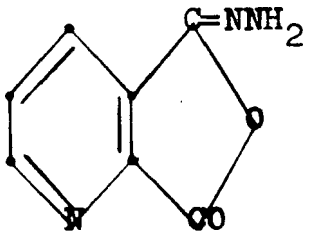


Quinolinic anhydride

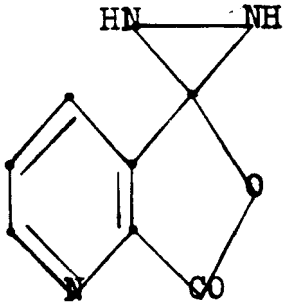




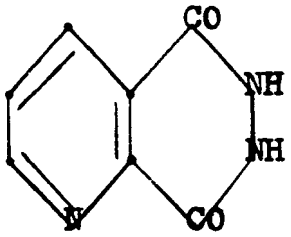
A



B



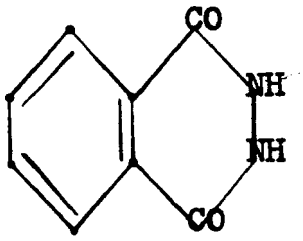
C



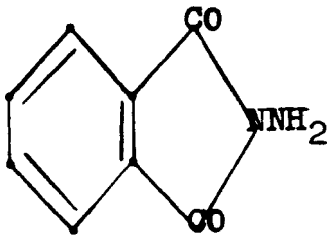
D (II)

The reactions used by Gheorghiu to establish D as the structure of his compound were of the same nature as those employed previously by Foersterling (36) to determine the structure of the product obtained from phthalic anhydride

and hydrazine. Any one of four structural isomers is possible from the reaction of phthalic anhydride with hydrazine. These four isomers are similar to A, B, C and D, except that the pyridine ring is replaced by a benzene ring. Foersterling was able to eliminate all structures except E, which is the benzene analog of D. This was accomplished by a study of the chemical reactions of his product.



E



F

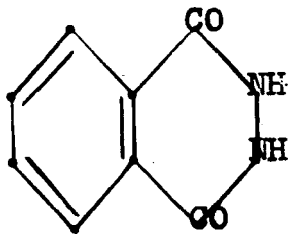
Although the compound obtained by Foersterling was shown to have structure E, other chemists (36,86,87) claimed that they synthesized the benzene analog of A or B. These reports were later disproved (42,88,89); these compounds were shown to be either 2,3-dihydrophthalazine-1,4-dione (E) or mixtures containing it. In 1937, Drew and Hatt (90) reported the synthesis of N-aminophthalimide (F) from phthalimide and hydrazine. The determining factor in obtaining F was the extent to which the reaction mixture was heated. If heated for a very short time, N-aminophthalimide (F) could be obtained; however, by heating for a longer time, only 2,3-dihydrophthalazine-1,4-dione (E) was isolated. At its melting point, N-aminophthalimide (F) was transformed into 2,3-dihydrophthalazine-1,4-dione (E). N-Aminophthalimide reacted with acetone and benzaldehyde to give condensation products.

In order to establish the structure of the compound obtained from the reaction of quinolinic anhydride with hydrazine, Gheorghiu allowed it to react with the same reagents that Foersterling had used previously to prove the structure of 2,3-dihydrophthalazine-1,4-dione. For example, formulas A and B were eliminated because the compound did not react with benzaldehyde to form an azomethine, nor did the compound hydrolyze in the presence of dilute acids. Formula C was discarded as a possibility since the compound was not oxidized by mercuric oxide to yield an azo compound, and because the compound was stable to heat. Therefore, he concluded that the product which he isolated possessed structure D.

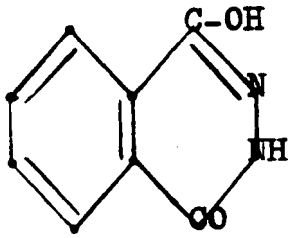
Gheorghiu reacted II (D) with acetic anhydride and obtained a compound, m.p. 144-147°; the analytical data corresponded to that calculated for a diacetyl derivative of II. He reported that this diacetyl compound was "rather stable" with regard to hydrolysis. This compound was formulated as 5,8-diacetoxypyrido[2,3-d]pyridazine.

The reaction of 2,3-dihydrophthalazine-1,4-dione (E) with acetic anhydride has been studied by Foersterling (36), Radulescu and Georgescu (42), Rowe and Peters (43) and Drew and Hatt (90); all of these investigators isolated a diacetyl derivative. Foersterling claimed that his product was 2,3-diacetylphthalhydrazide. Radulescu and Georgescu claimed that they isolated two diacetyl derivatives of E; one was stated to be the 1,3-diacetyl derivative, the other the 1,4-diacetyl derivative. According to Radulescu and Georgescu,

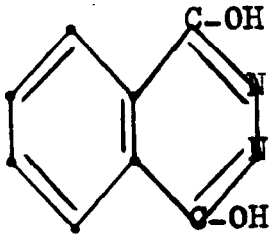
the 1,4-diacetyl derivative was more stable to hydrolysis than the 1,3 isomer.



Phthalhydrazide
2,3-Dihydrophthal-
azine-1,4-dione

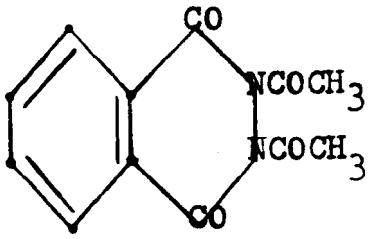


4-Hydroxyphthal-
azin-1(2H)-one

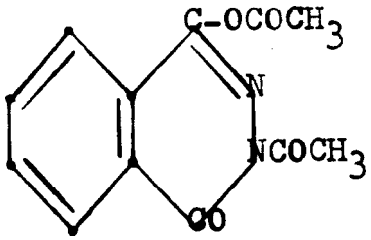


1,4-Dihydroxy-
phthalazine

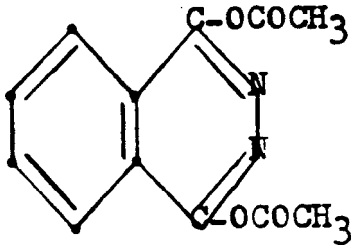
$(CH_3CO)_2O$



2,3-Diacetyl-
phthalhydrazide
2,3-Diacetyl-2,3-
dihydrophthalazine-
1,4-dione



4-Acetoxy-2-acetyl-
phthalazin-1(2H)-one
(1,3-Diacetyl
derivative)



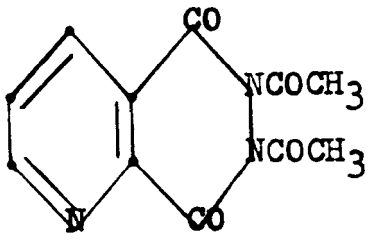
1,4-Diacetoxy-
phthalazine

When Rowe and Peters attempted to repeat the work of Radulescu and Georgescu, they were able to obtain only a single product which they claimed was the 1,4 derivative. According to Drew and Hatt, only one derivative was found in the reaction under discussion, and this substance was proved to be a 1,3-diacetyl derivative (4-acetoxy-2-acetyl-phthalazin-1(2H)-one).

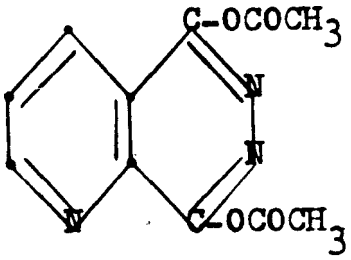
During this investigation, acetic anhydride was allowed to react with 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (II)

whereupon a diacetyl compound (Z), m.p. 142.5-145.5°, was formed. When this compound was recrystallized from aqueous alcohol, a monoacetyl derivative was obtained.

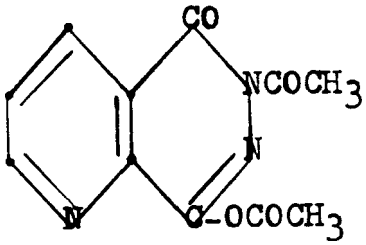
There are four possible diacetyl derivatives which might be formed from II: 6,7-diacetyl-6,7-dihydropyrido-[2,3-d]pyridazine-5,8-dione (G), 5,8-diacetoxypyrido[2,3-d]-pyridazine (H), 8-acetoxy-6-acetylpyrido[2,3-d]pyridazin-5(6H)-one (J), or 5-acetoxy-7-acetylpyrido[2,3-d]pyridazin-8(7H)-one (K).



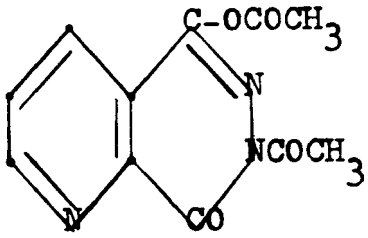
G



H



J

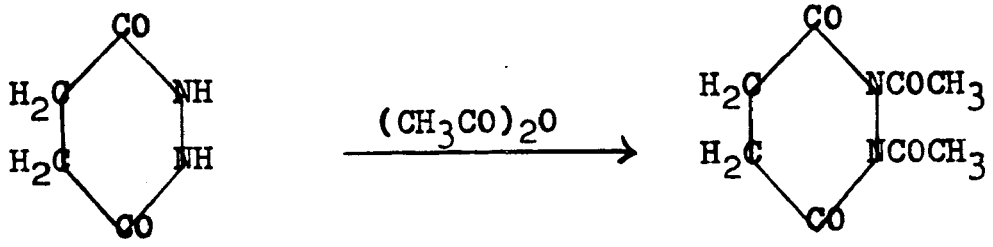


K

The reasons that can be given for the removal of G from the list of possible structures are as follows: Both of the acetyl groups in G are N-acetyl groups. The hydrolysis of compounds which contain N-acetyl groups, i.e., amides, requires rather drastic conditions, such as heating with an excess of aqueous alkali hydroxide or aqueous mineral acids. However, it was found that one of the acetyl groups in compound Z

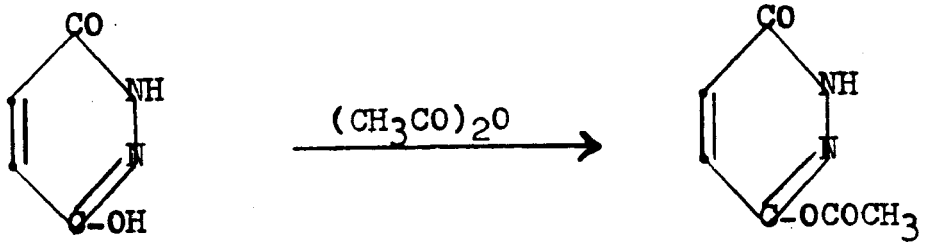
was hydrolyzed by aqueous alcohol. Since amides are not hydrolyzed under these conditions, it is suggested that one of the acetyl radicals is not an N-acetyl group.

In the reaction of acetic anhydride with cyclic succinhydrazide (1,2,4,5-tetrahydropyridazine-3,6-dione) and with 6-hydroxypyridazin-3(2H)-one (1,2-dihydropyridazine-3,6-dione) or its 4,5-disubstituted derivatives, different types of products have been obtained. Acetic anhydride reacts with cyclic succinhydrazide to form the N,N'-diacetyl compound.(68) With 6-hydroxypyridazin-3(2H)-one, acetic anhydride yields a monoacetyl compound, the O-acetyl derivative.(38) This



Cyclic succinhydrazide

N,N'-Diacetyl cyclic succinhydrazide



6-Hydroxypyridazin-3(2H)-one

6-Acetoxypyridazin-3(2H)-one

difference between the reaction of acetic anhydride with cyclic succinhydrazide and with 6-hydroxypyridazin-3(2H)-one, N-acetyl or O-acetyl formation, is due to the nature of the ring structure. Cyclic succinhydrazide can be represented as a cyclic diamide, while 6-hydroxypyridazin-3(2H)-one has

an aromatic structure.(70)

To produce G by the reaction of acetic anhydride on II, the aromatic characteristics of the pyridazine ring would have to be destroyed; G could be formed only if compound II acted as a cyclic diamide (similar to cyclic succinhydrazide). Since II is not a cyclic diamide, the diacetyl compound obtained during this investigation should not be formulated as a 6,7-diacetyl compound (G).

If compound Z were 5,8-diacetoxypyrido[2,3-d]pyridazine (H), there should not be a great difference in the extent of hydrolysis of the acetyl groups. It has been reported that O-acyl derivatives of pyridazines hydrolyze very readily.(43,91) Since both acetyl groups in H are O-acyl groups, they should hydrolyze quite readily. It has been stated above that one acetyl group of compound Z does not undergo facile hydrolysis; therefore, compound Z is believed not to be 5,8-diacetoxypyrido[2,3-d]pyridazine (H).

Additional support for these arguments has been found in the study of the infrared spectrum of compound Z. Three carbonyl absorptions are found, at 1698, 1740, and 1760 $cm.^{-1}$. The carbonyl group of the lactam accounts for the absorption at 1740 $cm.^{-1}$. The band at 1760 $cm.^{-1}$ is due to the vinyl ester group (92), $-C{=}C-O-COCH_3$ (or $-N{=}C-O-COCH_3$ in the case under discussion), while the absorption at 1698 $cm.^{-1}$ can be due only to an amide, in our case, $-NCOCH_3$. Thus, the infrared absorption spectrum demonstrates that both an O- and an N-acyl group are present. Of the four original possibilities for the diacetyl compound, two now remain, since

only 8-acetoxy-6-acetylpyrido[2,3-d]pyridazin-5(6H)-one (J) and 5-acetoxy-7-acetylpyrido[2,3-d]pyridazin-8(7H)-one (K) contain both an O- and an N-acyl group.

Since O-acyl derivatives of pyridazines hydrolyze very readily, partial hydrolysis of J should yield 6-acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione, and of K should give 7-acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione. 6-Acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (VI) was prepared by an unequivocal synthesis (Reaction Scheme II, I⟶V⟶VI, p. 25): N-acetyl-N'-(3-carboxypicolinoyl)hydrazine (V) was prepared by the reaction of acetylhydrazine on quinolinic anhydride at room temperature.* Compound V was cyclized by heating it in xylene whereupon VI was obtained. A mixed melting point determination of IV and VI gave a definite depression. Therefore, compound IV is 7-acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione and compound Z is actually 5-acetoxy-7-acetylpyrido[2,3-d]pyridazin-8(7H)-one (K) (compound III in Reaction Scheme II, p. 25).

We believe that the compound (m.p. 144-147°) which was named 5,8-diacetoxypyrido[2,3-d]pyridazine by Gheorghiu, and which has been mentioned on page 28, is the same as compound Z which we found to melt at 142.5-145.5°.

During this investigation, 6,7-dihydro-6-formylpyrido-[2,3-d]pyridazine-5,8-dione (VIII, Reaction Scheme II, p.25) was synthesized in a manner similar to that used for the synthesis of 6-acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione. Formylhydrazine was reacted with quinolinic anhydride

* It is known that amines react with quinolinic anhydride to form the quinolin-2-amic acids (See pages 15-19).

to give N-formyl-N'-(3-carboxypicolinoyl)hydrazine (VII) which, when heated in toluene, gave two cyclic products: a compound (33%) which, when analyzed, supplied data which corresponded to that calculated for 6,7-dihydro-6-formyl-pyrido[2,3-d]pyridazine-5,8-dione (VIII) and a compound which was shown to be identical with II by a mixed melting point determination. Compound II was produced exclusively when VII was heated in acetic acid. In order to obtain II from VII, the formyl group must have been removed by hydrolysis. A similar hydrolysis has been described by Ohta (71), when he reacted β-formylphenylhydrazine with phthalic anhydride.

The reaction of compound II with phosphorus oxychloride gave, depending on the hydrolytic procedure, two different products. When the reaction mixture was poured into a slowly stirred ice-water mixture, a product, m.p. 280.5-282°, was obtained; from the analysis of this product, it was learned that only one -C(=O)-NH- portion of II was converted into -C(Cl)=N-. Although the position of the chlorine atom has not been determined, the compound has been represented by IXa.

When the reaction mixture was added to a rapidly stirred ice-water mixture, a different compound, m.p. 164-166°, was isolated. This compound was determined from the analytical data to be 5,8-dichloropyrido[2,3-d]pyridazine (IXb). Compound IXb could not be hydrolyzed in a slightly ammoniacal solution, in a slightly acidic solution or in 2N hydrochloric acid.

The 1,4-dichloro compound in the phthalazine series, which corresponds to 5,8-dichloropyrido[2,3-d]pyridazine,

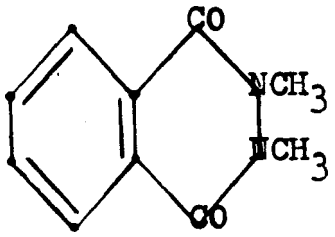
has been produced by the reaction of 2,3-dihydrophthalazine-1,4-dione with phosphorus pentachloride at 150° for 4 hours (90); with a mixture of phosphorus pentachloride and phosphorus oxychloride, 4-chlorophthalazin-1(2H)-one (1-chloro-4-hydroxyphthalazine) was obtained.(42) 1,4-Dichlorophthalazine is unstable and may be converted readily into 4-chlorophthalazin-1(2H)-one by heating it with phthalic acid, without the use of a solvent or in nitrobenzene (90), or by hydrolysis in 2N hydrochloric acid (93). While one of the chlorine atoms in 1,4-dichlorophthalazine is very reactive, the chlorine atom in 4-chlorophthalazin-1(2H)-one is fairly unreactive. One of the chlorine atoms in 3,6-dichloropyridazine (94) and in 1-substituted-4,7-dichloroimidazo[4,5-d]pyridazine (95) was found to be very reactive, while the second chlorine atom was not very active.

Castle and Seese (96) reported the preparation of 4,7-dichloroimidazo[4,5-d]pyridazine in low yield by treatment of the corresponding 4,7-dihydroxy compound with phosphorus oxychloride in dimethylaniline. According to them, attempts to form the dichloro compound under a variety of other chlorinating conditions were unsuccessful.

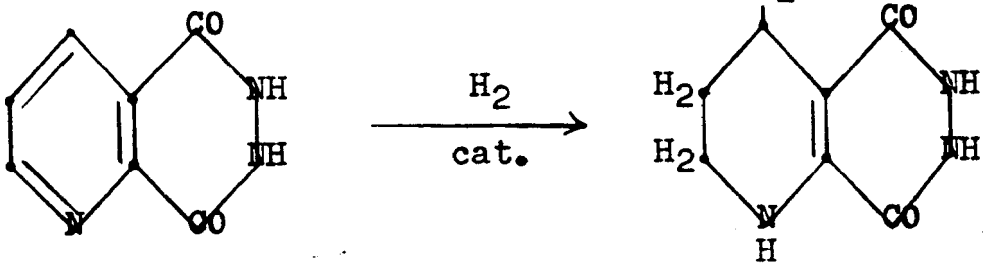
Carbon (95) attempted to convert 4,7-dihydroxyimidazo-[4,5-d]pyridazine into 4,7-dichloroimidazo[4,5-d]pyridazine without success, but he found that when the imino hydrogen was replaced by either a methyl, phenyl, or benzyl group, a high yield of the corresponding dichloro compound could be obtained. 1-Benzyl-4,7-dichloroimidazo[4,5-d]pyridazine, upon

hydrolysis, gave 1-benzyl-7-chloroimidazo[4,5-d]pyridazin-4(5H)-one.(95)

Since Raney nickel has been found to cleave the nitrogen-nitrogen bond in 2,3-dihydro-2,3-dimethylphthalazine-1,4-dione (82), it was of interest to determine if a similar reaction would occur in the case of 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (II). Compound II was refluxed in ethanol with nickel catalyst*, but only starting material could be isolated.



2,3-Dihydro-2,3-dimethyl-phthalazine-1,4-dione



II

$C_7H_5N_3O_2$
Calcd: C, 51.54; H, 3.09
m.p. 311°

X

$C_7H_9N_3O_2$
Calcd.: C, 50.29; H, 5.43
Found : C, 50.39; H, 5.46
m.p. 288-290.5°

In order to ascertain whether or not the failure of the cleavage was due to a lack of available hydrogen absorbed on the surface of the nickel catalyst*, compound II was shaken with the catalyst in a Parr apparatus under a hydrogen pressure

* Sponge Nickel Catalyst was obtained from the Davison Chemical Co., Division of W. R. Grace & Co., Cincinnati, Ohio.

of 62 p.s.i. A product was obtained which was assumed to be X; the analytical data supported this assumption. A mixture of II and X melted between 250-268°.

Compound X represents the absorption of two molecular equivalents of hydrogen by II. The calculated amount of hydrogen required for the formation of X is 10.8 p.s.i. (2 molecular equivalents); the amount absorbed was found to be 9 p.s.i.

In view of the information mentioned below, it seems probable that the compound possessed the structure which has been assigned to it. A cleavage of the N-N bond in II would require only one molecular equivalent of hydrogen. The fact that II reacted with two molecular equivalents of hydrogen could mean (a) that cleavage of the N-N bond and hydrogenation of one double bond in the pyridine ring had taken place or (b) that two double bonds in the pyridine ring had been hydrogenated. In the event that reactions (a) had taken place, a dihydropyridine would have been formed. Although pyridine and pyridine derivatives can be converted into dihydro derivatives (97), no examples have been found in which hydrogenation, with the use of Raney nickel, has resulted in the formation of a dihydro compound (98); in the presence of this catalyst hydrogenation has been found to yield tetrahydro* or hexahydro derivatives. It seems that if we had obtained a dihydropyridine from II, hydrogenation should have proceeded further. Since reactions (a) seemed improbable, it is

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* Hydrogenation of quinoline, in the presence of Raney nickel, yielded 1,2,3,4-tetrahydroquinoline.(99)

believed that reactions (b) may have taken place.

Compound II was also hydrogenated, in the presence of Raney nickel, under 3000 p.s.i. at 200° in an attempt to completely hydrogenate the pyridine ring; in this event, it would be expected that cleavage of the N-N bond would also take place. However, from this reaction only compound X could be isolated.

Condensation of Quinolinic Anhydride with N,N'-Dimethylhydrazine and with N,N'-Dibenzylhydrazine.

All of the products which are formulated in Reaction Scheme III (p. 39) are listed below.

Quinolinic anhydride* (I)
6,7-Dihydro-6,7-dimethylpyrido[2,3-d]pyridazine-5,8-dione (XI)
6,7-Dimethyl-1,2,3,4,6,7-hexahydropyrido[2,3-d]-pyridazine-5,8-dione (XII)
Dimethyl quinolinate* (XIII)
2,3-Bis(N-methylcarbamoyl)pyridine (XIV)
6,7-Dibenzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (XV)

Quinolinic anhydride reacted with N,N'-dimethylhydrazine to give a compound which, when analyzed, yielded data which corresponded to that calculated for 6,7-dihydro-6,7-dimethylpyrido[2,3-d]pyridazine-5,8-dione. (XI). Compound XI was refluxed in ethanol with Raney nickel W-2, a procedure used by Hinman (82) to cleave the N-N bond in 2,3-dihydro-2,3-dimethylphthalazine-1,4-dione. An analysis of the product (XII) obtained indicated that compound XI had reacted with two molecular equivalents of hydrogen.

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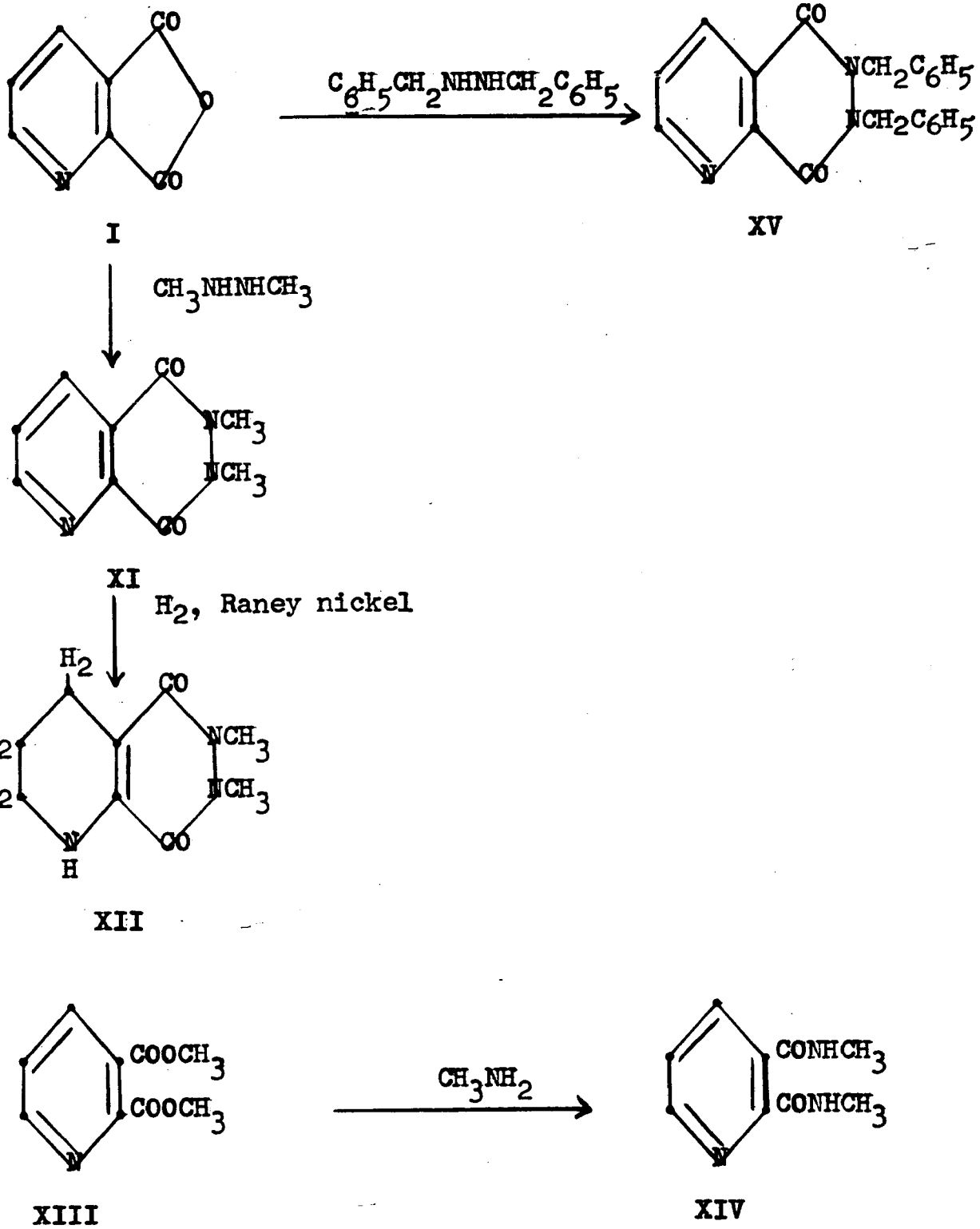
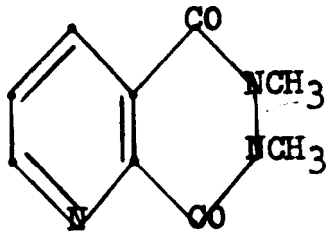
* Known compound

REACTION SCHEME III





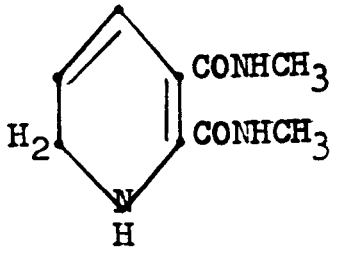
$\xrightarrow[\text{Raney nickel}\\ \text{W-2}]{2\ H_2}$ XII

XI

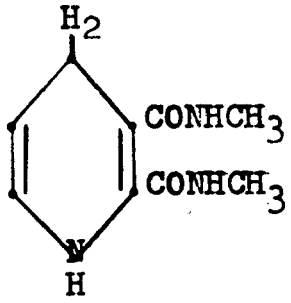
$C_9H_9N_3O_2$
Calcd.: C, 56.54; H, 4.75

$C_9H_{13}N_3O_2$
Calcd.: C, 55.37; H, 6.71
Found : C, 55.41; H, 6.43

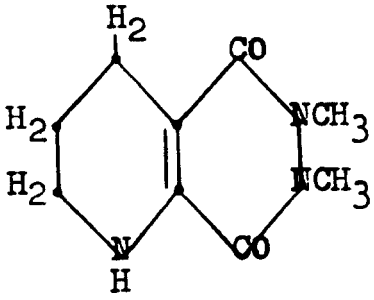
Possible Formulas for Compound XII:



XIIa

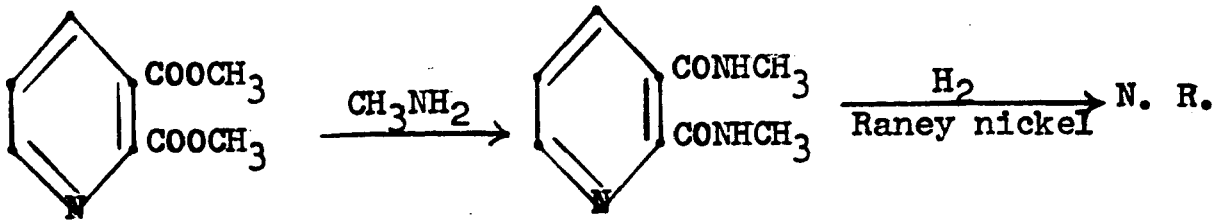


XIIb



XIIc

If XI had reacted with just one molecular equivalent of hydrogen with the rupture of the N-N bond, XIV would have been formed. Compound XIV was synthesized from dimethyl quinolinate (XIII) and methylamine and then refluxed in ethanol with Raney nickel W-2; it was also subjected to hydrogenation with the use of Raney nickel W-2 and hydrogen in a Parr hydrogenation apparatus. Compound XIV was



XIII XIV

recovered unchanged in both instances. In view of this fact, it seems that the hydrogenation of XI to XII does not proceed through the intermediate formation of XIV and consequently the product obtained by interaction of XI with two molecular equivalents of hydrogen was not formed by further reaction of XIV with hydrogen to yield a product such as XIIa or XIIb.

A probable formula for XII seems to be that represented by structure XIIc.

Quinolinic anhydride (I) was condensed with N,N'-dibenzylhydrazine with the formation of 6,7-dibenzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (XV). No reactions were carried out with the use of this compound.

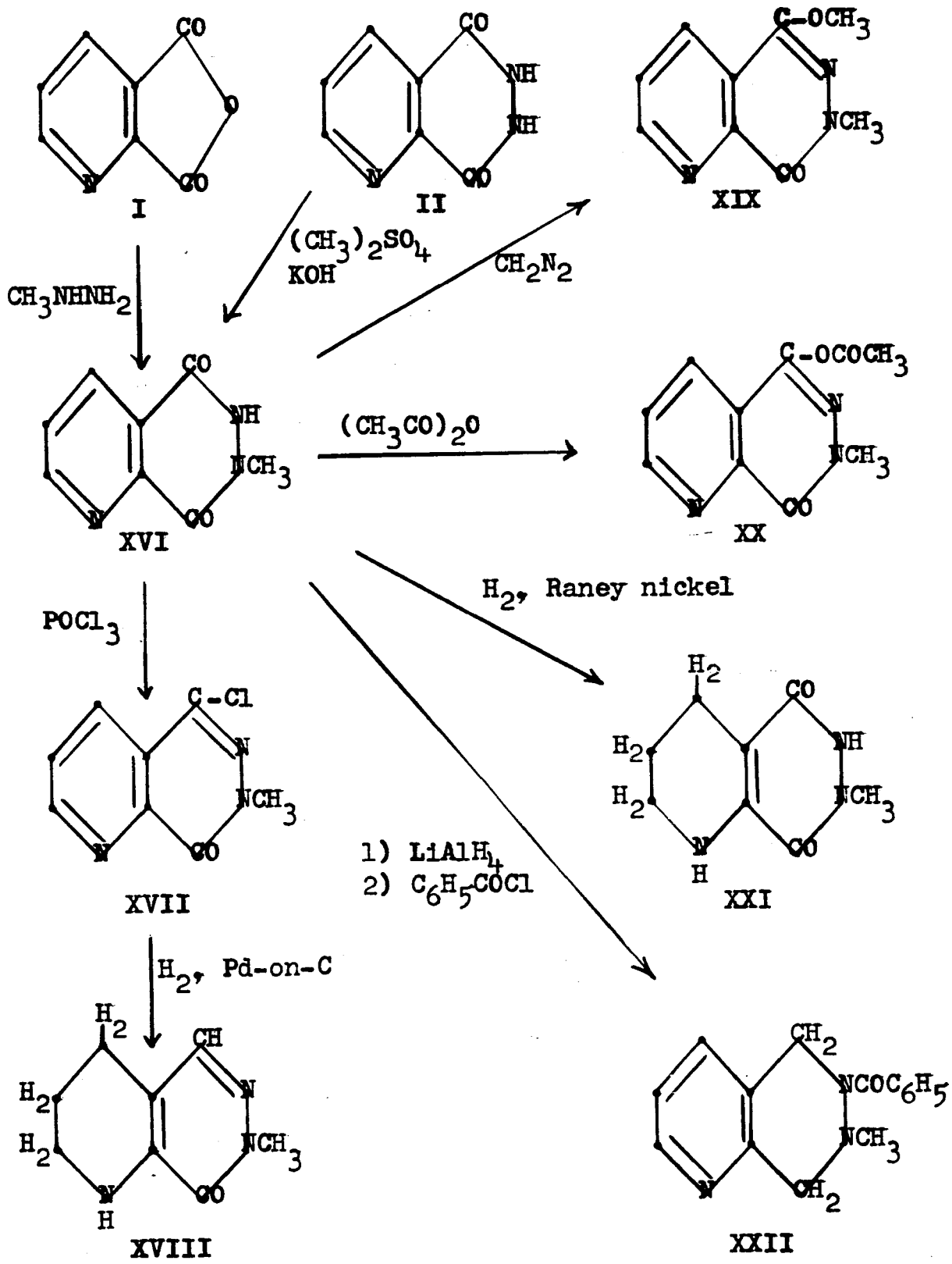
Condensation of Quinolinic Anhydride with Methylhydrazine and Reactions of the Condensation Product.

All of the products which are formulated in Reaction Scheme IV (p. 42) are listed below.

Quinolinic anhydride* (I)
6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione (II)
6,7-Dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (XVI)
5-Chloro-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XVII)
7-Methyl-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-8(7H)-one (XVIII)
5-Methoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XIX)

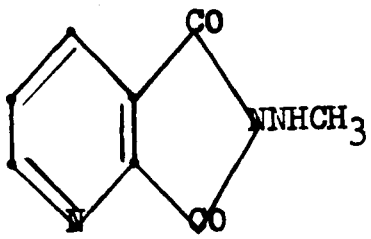
* Known compound

REACTION SCHEME IV

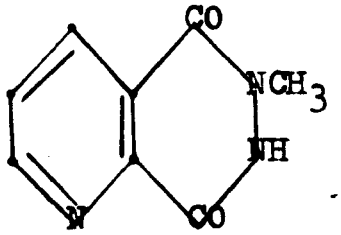


5-Acetoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XX)
7-Methyl-1,2,3,4,6,7-hexahydropyrido[2,3-d]pyridazine-5,8-dione (XXI)
6-Benzoyl-7-methyl-5,6,7,8-tetrahydropyrido[2,3-d]-pyridazine (XXII)

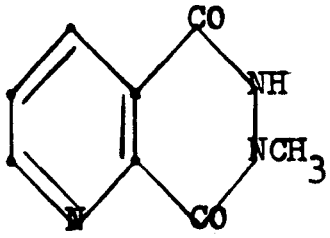
The reaction of quinolinic anhydride (I) with methylhydrazine in refluxing acetic acid gave a product (XVI) which could be N-methylaminoquinolinimide (M), 6,7-dihydro-6-methylpyrido[2,3-d]pyridazine-5,8-dione (N) or 6,7-dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (O). When I and methylhydrazine were reacted at room temperature in benzene, a crude product (m.p. 135-145°) was obtained which, when recrystallized, gave XVI. Compound XVI did not seem to be M since it could not be hydrolyzed by alkali. Reaction of



M



N

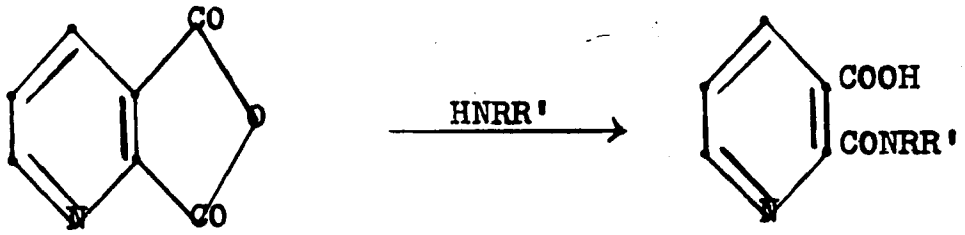


O
(XVI)

XVI with phosphorus oxychloride yielded a substance which, based on analysis, was a monochloro derivative of either N or O.

If the N-N bonds in compounds N and O could have been cleaved by hydrogenation, 3-(N-methylcarbamoyl)picolinamide would have been obtained from N, and 2-(N-methylcarbamoyl)-nicotinamide from O. Attempts to cleave the N-N bond of XVI were unsuccessful.

It has been proven that quinolinic anhydride reacts with ammonia to form a product of type P (R and R' = H).(58)

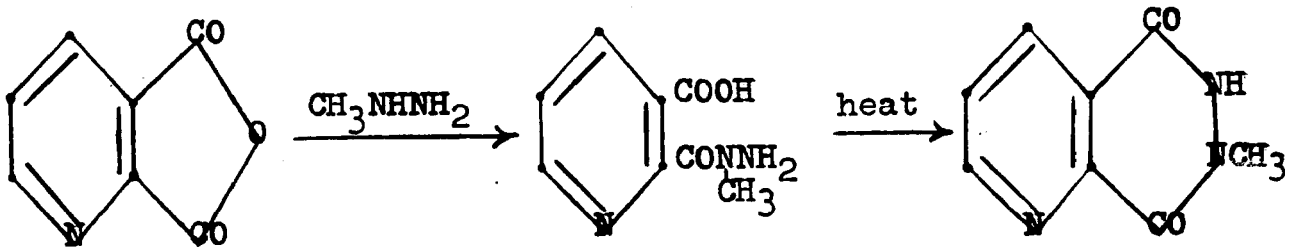


P

Quinolinic anhydride reacted with hydrazine to form a product which was not isolated; it was postulated that the product possessed structure P (R = H, R' = NH_2).(7)

Interaction of quinolinic anhydride with phenylhydrazine produced a substance which was isolated but its structure was not established; it was assumed to be P (R = H, R' = NHC_6H_5). (85)

As previously stated, when I and methylhydrazine reacted at room temperature in benzene, the crude product which was obtained melted between 135-145° and gave XVI (m.p. 289°) upon recrystallization. Because of the large difference in melting points before and after recrystallization, it is believed that the crude product cyclized to form XVI when recrystallized. If the information which has been presented on pages 15-19 is valid for this reaction, the initial product



XVI

would be N-methyl-N-(3-carbamoylpicolinoyl)hydrazine (P, R = CH_3, R' = NH_2) and the cyclized product (XVI) would have to be O. In view of the probable formation of XVI from the intermediate N-methyl-N-(3-carboxypicolinoyl)hydrazine, it is assumed that compound XVI is probably 6,7-dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione.

6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione (II) was methylated by the use of potassium hydroxide and dimethyl sulfate. A mixed melting point determination proved that the product was identical to XVI.

In reviewing the literature, it was found that 1,2-dihydropyridazine-3,6-dione and its substituted derivatives can be alkylated to give O- or N- alkyl or O,N-dialkyl compounds. Arndt (40) reported the preparation of 3-methoxypyridazin-6(1H)-one from the reaction of diazomethane with 1,2-dihydropyridazine-3,6-dione. Further reaction with diazomethane gave 3-methoxy-1-methylpyridazin-6(1H)-one.

1,2-Dihydro-1-methylpyridazine-3,6-dione was obtained from the reaction of dimethyl sulfate and sodium hydroxide with 1,2-dihydropyridazine-3,6-dione; further reaction with dimethyl sulfate and sodium hydroxide gave 3-methoxy-1-methylpyridazin-6(1H)-one and 1,2-dihydro-1,2-dimethylpyridazine-3,6-dione.(41)

2,3-Dihydrophthalazine-1,4-dione has been alkylated by the use of dimethyl sulfate and potassium hydroxide (43); the products obtained were 2,3-dihydro-2-methylphthalazine-1,4-dione and 4-methoxy-2-methylphthalazin-1(2H)-one. Other examples of alkylation of 2,3-dihydrophthalazine-1,4-dione

have been reported in the literature.(19,100) The preparation of 2,3-dihydro-2,3-dimethylphthalazine-1,4-dione by the methylation of 2,3-dihydrophthalazine-1,4-dione or 2,3-dihydro-2-methylphthalazine-1,4-dione has not been reported. However, 2,3-dihydro-2,3-dimethylphthalazine-1,4-dione has been prepared from the reaction of phthalic anhydride with N,N'-dimethylhydrazine.(101)

Compound XVI, when treated with phosphorus oxychloride, yielded a compound which, when analyzed, supplied data which corresponded to that calculated for 5-chloro-7-methylpyrido-[2,3-d]pyridazin-8(7H)-one (XVII).

In an attempt to prepare 7-methylpyrido[2,3-d]pyridazin-8(7H)-one by removal of the chlorine atom by catalytic hydrogenolysis of 5-chloro-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XVII) with 5% palladium-on-carbon, we obtained a product which was analyzed. The analytical data indicated that not only had a chlorine atom been removed but that two molecular equivalents of hydrogen had been absorbed. It is believed that the two molecular equivalents had reacted in such a manner as to form 7-methyl-1,2,3,4-tetrahydropyrido[2,3-d]-pyridazin-8(7H)-one (XVIII).

It has been reported that a chlorine atom, attached to either a benzene or a pyridine ring, may be removed by hydrogenation with 10% palladium-on-charcoal without reduction of the ring.(102) A chlorine atom, attached to a pyridazine ring, may be removed easily by hydrogenation.(95,103-105) The two chlorine atoms in 3,6-dichloropyridazine have been eliminated by hydrogenation with the use of a 5% palladium-

on-charcoal catalyst.(103) Hydrogenation of 3-chloro-1-phenylpyridazin-6(1H)-one in the presence of palladium-on-charcoal (10%) gave 1-phenylpyridazin-6(1H)-one (104); 3-chloro-4-dimethylamino-1-phenylpyridazin-6(1H)-one yielded 4-dimethylamino-1-phenylpyridazin-6(1H)-one (105). The chlorine atoms in 1-benzyl-4,7-dichloroimidazo[4,5-d]pyridazine and 4-amino-7-chloro-1-methylimidazo[4,5-d]pyridazine have been removed by catalytic hydrogenation.(95)

Reaction of XVI with diazomethane gave a compound; the analytical data corresponded to that calculated for 5-methoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XIX). When compound XVI was reacted with acetic anhydride the structure of the product, based on analytical data, was 5-acetoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XX).

Compound XVI was hydrogenated catalytically using either nickel catalyst* or platinum dioxide to form compound XXI. Compound XXI was also formed when XVI and Raney nickel W-2 catalyst were heated in refluxing ethanol. The analytical data indicated that XVI had absorbed two molecular equivalents of hydrogen. It is believed that the hydrogen reacted with XVI to form 1,2,3,4,6,7-hexahydro-7-methylpyrido[2,3-d]-pyridazine-5,8-dione (XXI). Reasons for this assumption have been given in the discussion on the following compounds: 1,2,3,4,6,7-hexahydropyrido[2,3-d]pyridazine-5,8-dione (X) and 6,7-dimethyl-1,2,3,4,6,7-hexahydropyrido[2,3-d]pyridazine-5,8-dione (XII). Compound XXI does not form a hydro-

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* Sponge Nickel Catalyst was obtained from the Davison Chemical Co., Division of W. R. Grace & Co., Cincinnati, Ohio

chloride salt, but it does dissolve in aqueous ammonia and can be precipitated by neutralization with sulfur dioxide.

Reduction of compound XVI with lithium aluminum hydride yielded a substance in 24% yield which oxidized rapidly in air to a highly colored oil. This oil was treated with benzoyl chloride and a compound was obtained which, when analyzed, gave analytical data which corresponded to that calculated for 6-benzoyl-7-methyl-5,6,7,8-tetrahydropyrido-[2,3-d]pyridazine (XXII).

A related compound, 4,5-dihydro-6-methylpyridazin-3(2H)-one, was reduced by lithium aluminum hydride; 3-methyl-1,4,5,6-tetrahydropyridazine was obtained in 17% yield.(106)

The low yield obtained from the reduction of compound XVI may possibly be attributed to the presence of the pyridine ring and to the enolic character of cyclic hydrazides. Reduction of N-substituted phthalimides by lithium aluminum hydride resulted in excellent yields.(54) However, in the reduction of N-substituted quinolinimide, the yields were lower.(54) Barnes and Godfrey (107) were unable to reduce N-benzhydryl-quinolinimide with lithium aluminum hydride. In order to obtain the desired 2-benzhydryl-4-azaisoindoline, they first reduced N-benzhydrylquinolinimide with tin and hydrochloric acid in glacial acetic acid in order to obtain 1-keto-2-benzhydryl-4-azaisoindoline. This compound was easily reduced with lithium aluminum hydride to 2-benzhydryl-4-azaisoindoline.

It has been reported (106) that when hydantoins, uracils, and barbiturates were treated with lithium aluminum hydride in attempts to reduce all of the carbonyl groups in these

compounds, (a) reduction did not take place at all, (b) only some of the carbonyl groups were reduced or (c) reduction of all of the carbonyl groups took place but only in low yield.

Hinman (108) found that he was unable to reduce N,N'-dibenzoylhydrazine, N,N'-diformylhydrazine or N-benzoyl-N',N'-dimethylhydrazine with lithium aluminum hydride. However, reduction could be effected, in low yields, after partial alkylation of these compounds, and in high yields after these compounds had been completely alkylated.

Hinman (109), who studied the reduction of hydrazides with lithium aluminum hydride, concluded that if reduction takes place at all, the yield of the reduction product will be low if a NH group is present in the molecule; in such instances, he assumed that $-\overset{(+)\,OAlH_3}{C}=N-$ will be formed and this group will not undergo further reaction. This structure resembles the enolate ion, which has been reported to resist attack by lithium aluminum hydride.

Condensation of Quinolinic Anhydride with Phenylhydrazine, Benzylamine, Benzylhydrazine, N-Benzyl-N'-phenylhydrazine, and with Methylamine; Reactions of 6,7-Dihydro-6-phenylpyrido[2,3-d]-pyridazine-5,8-dione.

All of the products which are formulated in Reaction Scheme V (p. 50) are listed below.

Quinolinic anhydride* (I)
6,7-Dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione (XXIII)

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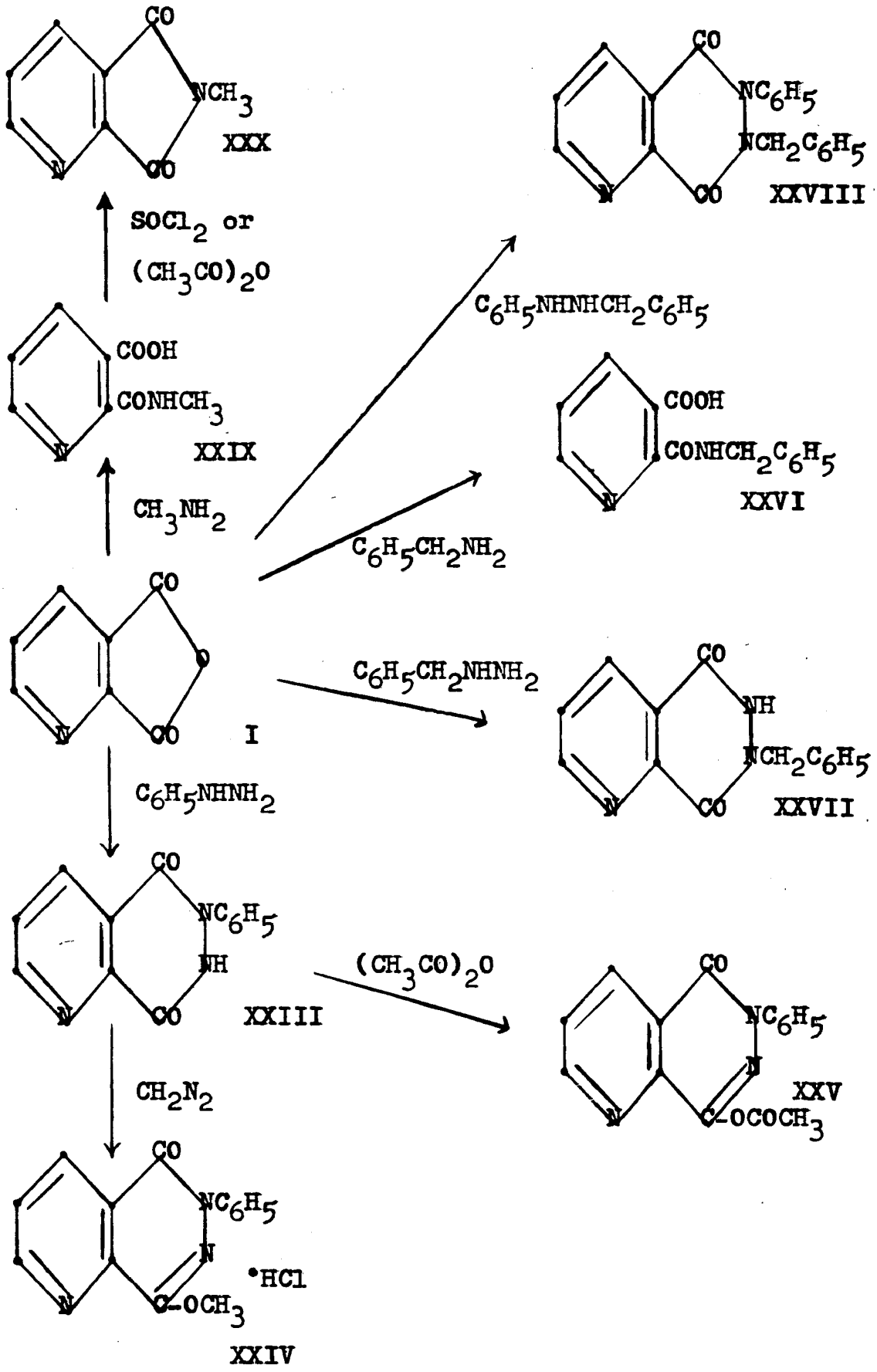
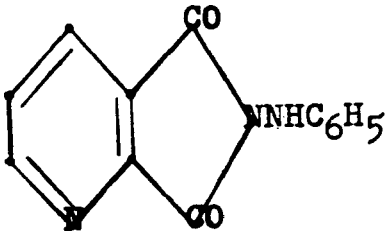
* Known compound

REACTION SCHEME V

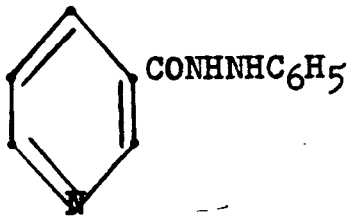


8-Methoxy-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one hydrochloride (XXIV)
8-Acetoxy-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one (XXV)
N-Benzyl-N'-(3-carboxypicolinoyl)hydrazine (XXVI)
7-Benzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (XXVII)
7-Benzyl-6,7-dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione (XXVIII)
N-Methyl-N'-(3-carboxypicolinoyl)hydrazine (XXIX)
N-Methylquinolinimide (XXX)

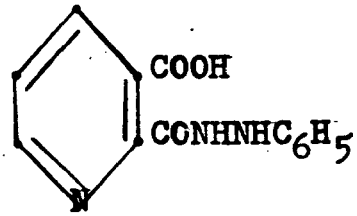
The reaction of quinolinic acid or anhydride with phenylhydrazine has been studied only superficially. Ghosh (84) heated phenylhydrazine and quinolinic acid and obtained a compound which melted at 237-238°. He claimed that the structure of this compound was that of N-anilinoquinolinimide. When Sen-Gupta and Sircar (85) heated quinolinic acid and phenylhydrazine at 200-230°, N-phenyl-N'-nicotinoylhydrazine, m.p. 185° was obtained.



N-Anilinoquinolinimide



N-Phenyl-N'-nicotinoylhydrazine



N-Phenyl-N'-(3-carboxypicolinoyl)-hydrazine

From quinolinic anhydride and phenylhydrazine in benzene at room temperature, a compound, m.p. 146°, was isolated by Sen-Gupta and Sircar.(85) This compound was represented as N-phenyl-N'-(3-carboxypicolinoyl)hydrazine.

In this laboratory, quinolinic anhydride and phenylhydrazine were refluxed in acetic acid and a product (Q), m.p. 234-234.5°, was obtained which, based on analytical data,

must have been N-anilinoquinolinimide, 6,7-dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione or 6,7-dihydro-7-phenylpyrido[2,3-d]pyridazine-5,8-dione. The first mentioned compound may be differentiated from the two other products by its ease of hydrolysis. N-Anilinoquinolinimide would be expected to hydrolyze without difficulty with base to an N-anilinoquinolinamic acid. Both 6,7-dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione and 6,7-dihydro-7-phenylpyrido[2,3-d]pyridazine-5,8-dione would be expected to form only the salt.

Attempted basic hydrolysis of Q, followed by neutralization, gave only starting material. Therefore, it is believed that Q is not N-anilinoquinolinimide, but one of the pyridazine compounds. We believe that the compound, m.p. 237-238°, obtained by Ghosh (84), which was reported to be N-anilinoquinolinimide, is probably one of the pyridazine compounds. To the best of our knowledge, no N-aminoquinolinimide or N-monosubstitutedaminoquinolinimide has ever been isolated.

It is of interest to review the reaction of phenylhydrazine with phthalic anhydride. Hötte (110) treated a benzene solution of phthalic anhydride with phenylhydrazine and obtained an N-phenyl-o-carboxybenzhydrazide. To prove that the phenyl group was attached to the β-nitrogen rather than the α-nitrogen, he partially hydrolyzed N-anilinophthalimide with base and obtained N-anilinophthalamic acid. He proved that this acid is the same as the one obtained directly from phthalic anhydride and phenylhydrazine. From this example and others (111), it has been shown that acylation of phenylhydrazine takes place on the β-nitrogen.

Both phthalic anhydride and quinolinic anhydride would be expected to give analogous products when treated with phenylhydrazine. Thus, in the case of quinolinic anhydride, the expected product, the one prepared by Sen-Gupta and Sircar (85), would be N-phenyl-N'-(3-carboxypicolinoyl)-hydrazine. Cyclization of N-phenyl-N'-(3-carboxypicolinoyl)-hydrazine should give 6,7-dihydro-6-phenylpyrido[2,3-d]-pyridazine-5,8-dione; the formula for this compound will be that represented by XXIII.

Diazomethane reacted with XXIII to give an oil. Treatment of this oil with ethereal hydrogen chloride gave a product which, based on analytical data, was found to fit that calculated for 8-methoxy-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one hydrochloride (XXIV).

When XXIII was acylated with acetic anhydride, a substance was obtained. This compound was analyzed and the analytical data was found to fit that calculated for 8-acetoxy-6,7-dihydro-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one (XXV). Compound XXV was recrystallized from aqueous alcohol to give XXIII. Only starting material was obtained from the reaction of XXIII with phosphorus oxychloride.

Compound I reacted with benzylamine to yield a product which, based on analytical data, is believed to be 2-(N-benzylcarbamoyl)nicotinic acid (XXVI). The assumption of the structure of this product receives support from the behavior of I with ammonia and with amines (see p. 15-19); in these instances the structures of the reaction products have been proven.

Quinolinic anhydride (I) reacted with benzylhydrazine to form a product to which structure XXVII (7-benzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione) was assigned. When the literature concerning benzylhydrazine was reviewed, no mention of its acylation by an anhydride could be found. It has been reported (112) that benzylhydrazine and isocyanates react to form the 2-benzylsemicarbazides. When N-benzyl-N'-phenylhydrazine was acylated, the N-acyl-N-benzyl-N'-phenylhydrazine was obtained.(113) From this information, acylation of benzylhydrazine by quinolinic anhydride might be expected to produce N-benzyl-N-(3-carboxypicolinoyl)-hydrazine as the initial product, followed by cyclization to 7-benzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (XXVII) under the reaction conditions employed.

Compound I was refluxed in acetic acid with N-benzyl-N'-phenylhydrazine. A compound was obtained which, when analyzed, supplied data which corresponded to that calculated for 7-benzyl-6,7-dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione (XXVIII). Since N-benzyl-N'-phenylhydrazine is known to react with acetic anhydride to yield N-acetyl-N-benzyl-N'-phenylhydrazine (113), the product from the reaction of quinolinic anhydride with N-benzyl-N'-phenylhydrazine would be expected to form XXVIII.

When I was reacted with methylamine, XXIX was isolated. Since compound XXIX was formed in a similar manner to that used for the preparation of 2-(N-benzylcarbamoyl)nicotinic acid (XXVI), it is undoubtedly 2-(N-methylcarbamoyl)nicotinic acid. When XXIX was reacted with thionyl chloride, a new

compound was obtained. Based on the analytical data, this compound is N-methylquinolinimide (XXX). A similar reaction occurred when N-alkylphthalamic acids reacted with thionyl chloride; the corresponding N-alkylphthalimides were obtained. (114) Compound XXX was also produced from the interaction of XXIX with acetic anhydride.

The Attempted Preparation of 3-Formylpicolinic Acid

All of the products which are formulated in Reaction Scheme VI (p. 56) are listed below.

Ethyl 2-methylnicotinate* (XXXI)
3-Hydroxymethyl-2-methylpyridine (XXXII)
2-Methylnicotinaldehyde* (XXXIII)
2-(2-Methyl-3-pyridyl)-1,3-dioxolane (XXXIV)
2-Methylnicotinic acid* (XXXV)

3-Formylpicolinic acid was desired for use in a structure proof of the pyrido[2,3-d]pyridazines which we had prepared. 3-Formylpicolinic acid had been synthesized from 8-quinolinol (115,116); however, this work could not be repeated in this laboratory. An attempt was made to synthesize 3-formylpicolinic acid by the use of the following products: XXXI ⟶ XXXII ⟶ XXXIII ⟶ XXXIV ⟶ XXXVI ⟶ XXXVII.

Ethyl 2-methylnicotinate (XXXI) had been made by reaction of ethyl β-aminocrotonate with acrolein (117), with β-ethoxyacrolein-diethyl acetal (118), or with propargyl aldehyde (119). It had also been prepared by treatment of ethyl 4-hydroxy-2-methylnicotinate with phosphorus pentachloride to yield

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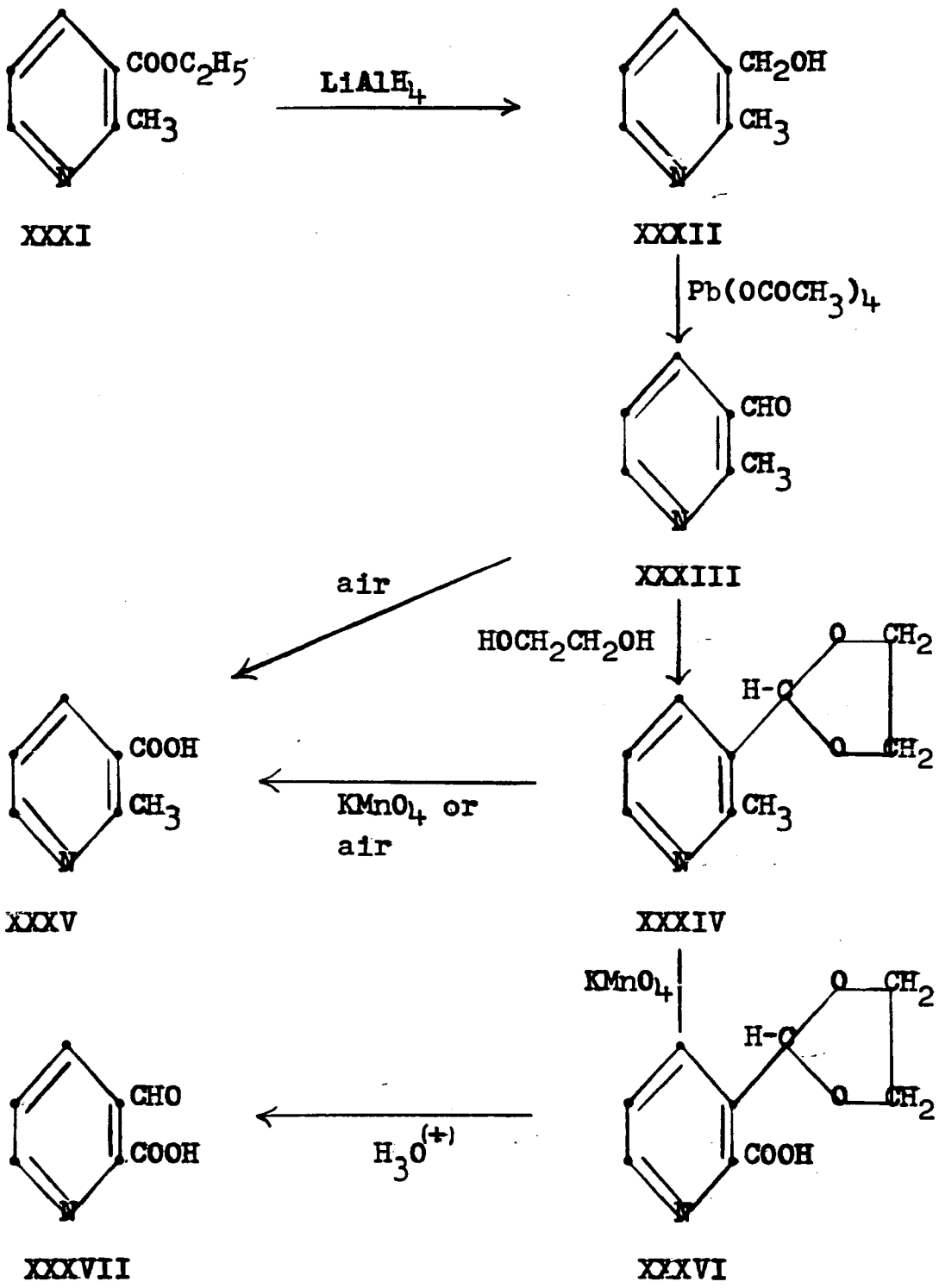
* Known compound

REACTION SCHEME VI



ethyl 4-chloro-2-methylnicotinate and reduction of this chloro compound to ethyl 2-methylnicotinate. (120)

In this laboratory a low yield of ethyl 2-methylnicotinate (XXXI) was obtained from the interaction of ethyl β-aminocrotonate and acrolein; however, the desired product was prepared in 66.5% yield by reaction of ethyl β-aminocrotonate with propargyl aldehyde.

When XXXI was reduced with lithium aluminum hydride, 3-hydroxymethyl-2-methylpyridine (XXXII) was formed. An example of the lithium aluminum hydride reduction of a pyridinecarboxylic acid ester to the corresponding hydroxymethylpyridine is the reduction of ethyl nicotinate to yield 3-hydroxymethylpyridine.(121) Other pyridinecarboxylic acid esters have been reduced in this manner.(122,123)

Compound XXXII was then oxidized by lead tetraacetate (26) in benzene to 2-methylnicotinaldehyde (XXXIII) in 62.5% yield. 2-Methylnicotinaldehyde had been prepared in 16% yield from XXXI by a different method (33); by our method XXXIII was obtained in 44% yield from XXXI.

Oxidation of 2-methylnicotinaldehyde (XXXIII) would result in 2-methylnicotinic acid or in quinolinic acid. Conversion of the carboxaldehyde radical into an acetal should prevent its oxidation to a carboxyl group. According to Royals (124):

> "Acetals are perfectly unreactive toward basic reagents. This fact is of practical usefulness when it is desired to protect the aldehyde function from the action of basic reagents or oxidizing agents."

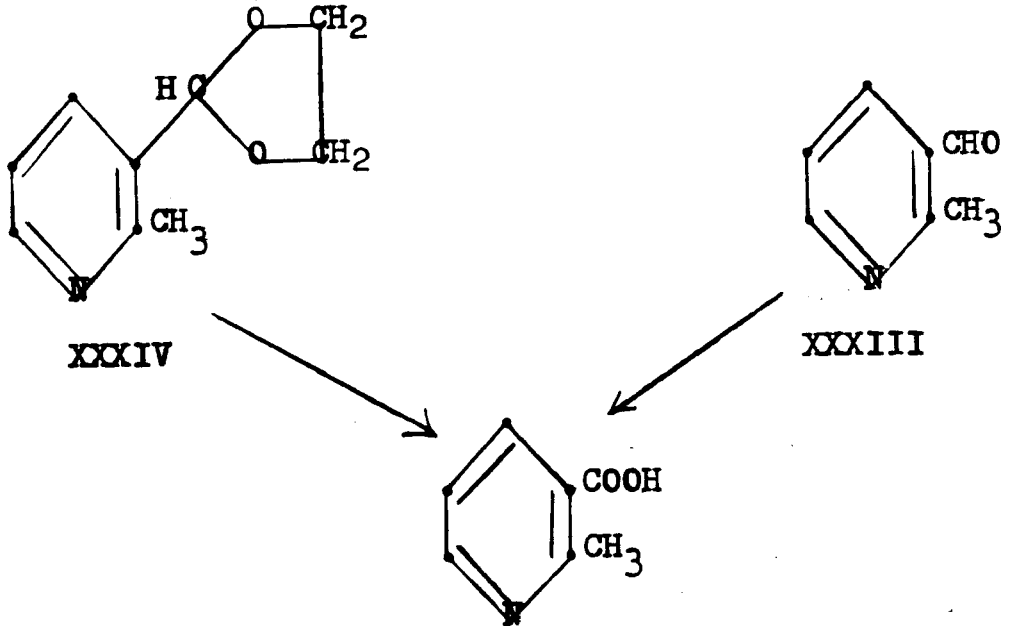
In Migrdichian's Organic Synthesis (125) we find the statement:

"Acetals are resistant to the action of many reducing and oxidizing agents. Among oxidizing agents only ozone seems to attack acetals, ..."

We therefore planned to prepare the acetal of XXXIII, submit the compound to oxidation under basic conditions whereby the methyl group would be oxidized to a carboxyl group and then, after removal of the acetal group by hydrolysis, 3-formylpicolinic acid should be obtained.

Reaction of XXXIII with ethylene glycol under conditions suitable for acetal formation (126) gave a 41.5% yield of 2-(2-methyl-3-pyridyl)-1,3-dioxolane (XXXIV).

When XXXIV was oxidized with a limited amount of basic permanganate solution and then neutralized, a compound was isolated which melted at 223-225°. It was shown by a mixed melting point determination that this compound was 2-methyl-



XXXIV XXXIII

XXXV

nicotinic acid (XXXV), rather than the desired 2-(2-carboxy-3-pyridyl)-1,3-dioxolane. Both XXXIII and XXXIV were found to oxidize in the presence of air to XXXV. Therefore, 3-formylpicolinic acid cannot be prepared in the manner herein presented, due to the ease of oxidation of the acetal of 2-methylnicotinaldehyde (XXXIV).

EXPERIMENTAL PART

Quinolinic anhydride (I).- This compound was prepared by the method described by Phillips (58) but a purer product was obtained when a slight modification was made. After removal of the acetic acid from the reaction mixture by distillation, the solution was cooled and the precipitated material was recrystallized from benzene.

6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione (II).- In order to obtain this substance, the procedure (8) published by Gheorghiu was employed with the following changes. A mixture of 14.9 g. (0.1 mole) of quinolinic anhydride, 5.0 g. (0.1 mole) of 85% hydrazine hydrate in water and 200 ml. of acetic acid was refluxed for 4 hours. The yield was 14.2 g. (87%).

5-Acetoxy-7-acetylpyrido[2,3-d]pyridazin-8(7H)-one (III).- 6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione (II) (16.3 g., 0.1 mole) and 61.0 g. (0.6 mole) of acetic anhydride were refluxed for 12 hours. The hot solution was filtered and the solvent was removed under reduced pressure on a steam bath until solid material started to precipitate. The solution was heated to dissolve the solid material, filtered and allowed to cool slowly. After filtration, the precipitate was washed with ether. The yield was 15.3 g. (62%); m.p. 142.5-145.5°.

Anal. Calcd. for $C_{11}H_9N_3O_4$: C, 53.44; H, 3.67. Found: C, 53.15; H, 3.45

7-Acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (IV).- Recrystallization of 5-acetoxy-7-acetylpyrido[2,3-d]pyridazin-8(7H)-one (III) from aqueous alcohol (50%) gave a quantitative yield of product, m.p. 209-211°.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.68; H, 3.44. Found: C, 52.65; H, 3.45.

Acetylhydrazine.- Ethyl acetate (52.8 g., 0.6 mole) was added, dropwise, to a refluxing solution of 35.3 g. (0.6 mole) of 85% hydrazine hydrate* in 50 ml. of ethanol. After addition was completed, the mixture was refluxed for 18 hours. The solution was cooled and dried over anhydrous potassium carbonate. The mixture was filtered, the solvent removed from the filtrate and the residue was distilled; the portion which distilled between 121-129°/15 mm. was collected. The yield was 25.6 g. (57.5%); m.p. 66-68° after recrystallization from ethanol. The melting point of acetylhydrazine has been reported to be 67°.(127)

N-Acetyl-N'-(3-carboxypicolinoyl)hydrazine (V).- Powdered acetylhydrazine (7.4 g., 0.1 mole) was added, in small portions, to a stirred suspension of 15 g. (0.1 mole) of quinolinic anhydride in 200 ml. of acetic acid. The mixture was stirred at room temperature for 4 hours and the precipitate was filtered; yield 15 g. (67.5%). The product was recrystallized from isopropyl alcohol; m.p. 162-163°.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06. Found: C, 48.70; H, 4.36.

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* Purchased from Matheson Coleman and Bell.

6-Acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (VI).- N-Acetyl-N'-(3-carboxypicolinoyl)hydrazine (V) (2.0 g., 0.09 mole) and 125 ml. of sodium-dried xylene were refluxed for 6 hours and the water which was evolved was collected in a Dean-Stark trap. The mixture was cooled; the precipitated product was filtered and recrystallized from ethanol. The yield was 1.1 g. (60%); m.p. 206-207°.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.68; H, 3.44. Found: C, 52.71; H, 3.47.

Formylhydrazine.- Formylhydrazine was prepared from ethyl formate and hydrazine hydrate in the same general manner as acetylhydrazine. The product was distilled and the portion which distilled between 120-130°/8 mm. was collected. The yield was 38%; m.p. 57-58° after recrystallization from ethanol. The melting point of formylhydrazine has been reported to be 54°.(128)

N-Formyl-N'-(3-carboxypicolinoyl)hydrazine (VII).- Powdered formylhydrazine (6.0 g., 0.1 mole) was added, in small portions, to a stirred suspension of 14.9 g. (0.1 mole) of quinolinic anhydride in 200 ml. of acetic acid. The mixture was stirred at room temperature for 2 hours, the precipitate was filtered and recrystallized from isopropyl alcohol-water; yield 11.5 g. (55%); m.p. 148-149°.

Anal. Calcd. for $C_8H_7N_3O_4$: C, 45.94; H, 3.37. Found: C, 46.23; H, 3.54.

6,7-Dihydro-6-formylpyrido[2,3-d]pyridazine-5,8-dione (VIII).- N-Formyl-N'-(3-carboxypicolinoyl)hydrazine (VII) (1.0 g., 0.005 mole) was refluxed with 45 ml. of sodium-dried

toluene and the water evolved was collected in a Dean-Stark trap. The solid material was filtered and recrystallized from ethanol; yield 300 mg. (33%); m.p. 171.5-172.5°.

Anal. Calcd. for $C_8H_5N_3O_3$: C, 50.26; H, 2.64; N, 21.99. Found: C, 50.31; H, 2.82; N, 22.17.

5-Chloropyrido[2,3-d]pyridazin-8(7H)-one (IXa).- Although the structure of this compound is not known, it has been given the above name.

6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione (II) (17.9 g., 0.1 mole) was refluxed for 8 hours with 200 ml. of phosphorus oxychloride. The excess phosphorus oxychloride was removed by distillation under reduced pressure and the residue was hydrolyzed with ice water. The solution was made slightly alkaline with ammonium hydroxide solution and then extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed from the filtrate. The residue was recrystallized from a small amount of chloroform; yield 1.1 g. (6%); m.p. 280.5-282°.

Anal. Calcd. for $C_7H_4ClN_3O$: C, 46.30; H, 2.22. Found: C, 46.13; H, 2.03.

5,8-Dichloropyrido[2,3-d]pyridazine (IXb).- A suspension of 2.0 g. (0.012 mole) of II and 10 ml. of phosphorus oxychloride was refluxed for 2 hours and the suspension was poured into a mixture of ice and water which was stirred rapidly. The mixture was made slightly alkaline with ammonium hydroxide solution and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate,

filtered, and the solvent was removed from the filtrate. The residue was recrystallized from chloroform-petroleum ether (90-100°); yield 0.9 g. (38%); m.p. 164-166°.

Anal. Calcd. for $C_7H_3Cl_2N_3$: C, 42.05; H, 1.51; N, 21.01. Found: C, 42.07; H, 1.41; N, 21.05.

1,2,3,4,6,7-Hexahydropyrido[2,3-d]pyridazine-5,8-dione (X).- 6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione (II) (10.0 g., 0.06 mole), 10 g. of nickel catalyst* and 150 ml. of ethanol were shaken under an initial pressure of 62 p.s.i. of hydrogen for 15 hours in a Parr hydrogenation apparatus. The suspension absorbed 1.67 molecular equivalents of hydrogen. The suspension was filtered, the solvent was removed from the filtrate and the residue was recrystallized from acetic acid; yield 3.7 g. (36%); m.p. 288-290.5°.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43. Found: C, 50.39; H, 5.46.

6,7-Dihydro-6,7-dimethylpyrido[2,3-d]pyridazine-5,8-dione (XI).- Quinolinic anhydride (16.7 g., 0.112 mole), 14.9 g. (0.112 mole) of N,N'-dimethylhydrazine dihydrochloride (108), 18.5 g. (0.224 mole) of sodium acetate and 200 ml. of acetic acid were refluxed and stirred for 10 hours. The hot suspension was filtered and the solvent removed from the filtrate. The residue was recrystallized from ethanol; yield 9.7 g. (45%); m.p. 235.5-237.5°.

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.75. Found: C, 56.62; H, 4.81.

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* Sponge Nickel Catalyst was obtained from the Davison Chemical Co., Division of W. R. Grace and Co., Cincinnati, Ohio

6,7-Dimethyl-1,2,3,4,6,7-hexahydropyrido[2,3-d]pyridazine-5,8-dione (XII).- 6,7-Dihydro-6,7-dimethylpyrido[2,3-d]-pyridazine-5,8-dione (XI) (1.5 g., 0.009 mole) and 20 g. of Raney nickel W-2 catalyst were refluxed in 200 ml. of ethanol for 11 hours. The hot suspension was filtered and the filtrate was evaporated to dryness. The residue was recrystallized twice from benzene-petroleum ether (90-100°), then from cyclohexane. The yield was 1 g. (58%); m.p. 170.5-171.5°.

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.41; H, 6.43; N, 21.56.

Dimethyl quinolinate (XIII).- Dimethyl quinolinate was prepared by the method described by Engler (129).

2,3-Bis(N-methylcarbamoyl)pyridine (XIV).- Dimethyl quinolinate (XIII) (5.0 g., 0.026 mole) and 200 ml. of an ice-cold saturated solution of methylamine in methanol were placed in a pressure bottle. After 48 hours the solution was evaporated to dryness and the residue was recrystallized from benzene to give 4 g. (84%) of product; m.p. 152-154°.

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.16; H, 5.63; N, 21.81.

6,7-Dibenzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (XV).- Quinolinic anhydride (14.9 g., 0.1 mole), 24.9 g. (0.1 mole) of N,N'-dibenzylhydrazine hydrochloride (130), 20 g. (0.244 mole) of sodium acetate and 250 ml. of acetic acid were refluxed for 12 hours. The suspension was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from ethanol-water; yield, 18.5 g. (54%); m.p. 191.5-192.5°.

Anal. Calcd. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99. Found: C, 73.59; H, 5.05.

6,7-Dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (XVI).- A mixture of 14.9 g. (0.1 mole) of quinolinic anhydride, 14.4 g. (0.1 mole) of methylhydrazine sulfate*, 17 g. (0.2 mole) of sodium acetate and 200 ml. of acetic acid was refluxed for 8 hours. The hot solution was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from water; yield 10 g. (56.5%); m.p. 288-289°.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98. Found: C, 54.11; H, 4.08.

5-Chloro-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XVII).- 6,7-Dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (XVI) (9 g., 0.051 mole) and 50 ml. of phosphorus oxychloride were refluxed for 3 hours. The excess phosphorus oxychloride was removed under reduced pressure. The residue was recrystallized from ethanol and then sublimed *in vacuo*. The yield was 4.3 g. (43%); m.p. 189.5-191.5°.

Anal. Calcd. for $C_8H_6ClN_3O$: C, 49.13; H, 3.09. Found: C, 49.11; H, 3.11.

1,2,3,4,6,7-Hexahydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (XVIII).- 6,7-Dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (XVI) (10.0 g., 0.056 mole), 10 g. of nickel catalyst** and 175 ml. of ethanol were shaken in a Parr

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* Obtained from Distillation Products Industries.

** Sponge Nickel Catalyst was obtained from the Davison Chemical Co., Division of W. R. Grace & Co., Cincinnati, Ohio.

hydrogenation apparatus under an initial pressure of 50 p.s.i. of hydrogen for 12 hours. The suspension absorbed 1.1 molecular equivalents of hydrogen. The suspension was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from ethanol; yield 4.6 g. (46%); m.p. 277.5-279.5°.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12. Found: C, 53.05; H, 6.09.

5-Methoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XIX).- Diazomethane (0.07 mole)* in ether solution was added to a suspension of 5.0 g. (0.03 mole) of 6,7-dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (XVI) in 300 ml. of ether. The suspension was kept cold in an ice bath for 4 hours. The ether was removed and the residue was recrystallized from ethanol; yield 3.7 g. (69%); m.p. 219.5-221.5°.

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.75. Found: C, 56.61; H, 4.82.

5-Acetoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XX).- 6,7-Dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (XVI) (17.7 g., 0.1 mole) and 50 ml. of acetic anhydride were refluxed for 4 hours and the cool solution was then concentrated. The product was recrystallized from acetic anhydride; yield 15 g. (69%); m.p. 172.5-175.5°.

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14. Found: C, 54.77; H, 3.99.

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* Prepared from Diazald according to the directions from the Aldrich Chemical Company, Milwaukee, Wisconsin.

1,2,3,4,6,7-Hexahydro-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XXI).- A suspension of 600 mg. (0.003 mole) of 5-chloro-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (XVII), 0.5 g. of 5% palladium-on-carbon catalyst* and 1 g. (0.013 mole) of sodium acetate in 100 ml. of absolute alcohol was hydrogenated under an initial pressure of 50 p.s.i. for 1 hour.

The suspension was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from benzene; yield 100 mg. (18%); m.p. 175-176°.

Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.16; H, 6.71. Found: C, 58.26; H, 6.72.

6-Benzoyl-7-methyl-5,6,7,8-tetrahydropyrido[2,3-d]-pyridazine (XXII).- To a stirred suspension of 5.2 g. (0.14 mole) of lithium aluminum hydride in 200 ml. of dry tetrahydrofuran there was added 10 g. (0.057 mole) of 6,7-dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (XVI). The suspension was stirred and refluxed for 22 hours. Water (15 ml.) was added, dropwise, and the suspension was stirred for an additional 4 hours. The suspension was filtered and the filtrate was dried over anhydrous magnesium sulfate. The solvent was removed and the residue was distilled; the portion which distilled between 84-86°/0.5 mm. was collected. The yield was 2 g. (24%).

The benzamide of this compound was prepared from 2 g. of this oil under Schotten-Baumann conditions. The yield of benzamide was 2 g. (59%); m.p. 80.5-82°. The overall yield

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* Obtained from Baker and Company, Inc., 113 Astor Street, Newark 5, New Jersey

based on 6,7-dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione was 14%.

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.97. Found: C, 71.18; H, 5.98.

6,7-Dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione (XXIII).- Quinolinic anhydride (15.0 g., 0.1 mole), 12.1 g. (0.11 mole) of phenylhydrazine* and 100 ml. of acetic acid were refluxed for 3 hours. The solution was cooled and evaporated to dryness. The residue was recrystallized from ethanol; yield 4.7 g. (19.7%); m.p. 234-234.5°.

Anal. Calcd. for $C_{13}H_9N_3O_2$: C, 65.26; H, 3.79. Found: C, 65.13; H, 3.84.

8-Methoxy-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one Hydrochloride (XXIV).- Diazomethane (0.07 mole)** in ether was added to an ice-cold suspension of 2.0 g. (0.008 mole) of 6,7-dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione (XXIII) in ether. This suspension was allowed to warm to room temperature. The solvent was removed and an oily residue remained. This oil was dissolved in anhydrous ether and and excess of ethereal hydrogen chloride was added. The precipitated hydrochloride was recrystallized from ethanol; yield 0.6 g. (25%); m.p. 205.5-206.5°.

Anal. Calcd. for $C_{14}H_{12}ClN_3O_2$: C, 58.04; H, 4.18. Found: C, 58.24; H, 4.30.

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* Purchased from Distillation Products Industries.

** Prepared from Diazald according to the directions from the Aldrich Chemical Company, Milwaukee, Wisconsin

8-Acetoxy-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one (XXV).- 6,7-Dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione (XXIII) (1 g., 0.004 mole), 10 ml. of acetic anhydride, and 10 ml. of acetic acid were refluxed for 3 hours. The hot solution was filtered, cooled, and ether was added to the filtrate until it became cloudy. The precipitate was filtered and dried to give 1.1 g. (93%) of product; m.p. 202.5-203.5°.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94. Found: C, 63.93; H, 3.80.

2-(N-Benzylcarbamoyl)-nicotinic acid (XXVI).- To a stirred solution of 27 g. (0.18 mole) of quinolinic anhydride in 350 ml. of butanone, cooled in ice, there was added, dropwise, a solution of 19.5 g. (0.18 mole) of benzylamine in 50 ml. of butanone. After the addition was completed, the suspension was stirred for an additional hour and then filtered. The solvent was removed from the filtrate and the oily residue was dissolved in a small amount of water with the aid of ammonium hydroxide solution, treated with charcoal and filtered; the filtrate was then acidified with sulfur dioxide. The precipitate was filtered and recrystallized from benzene to give 26.3 g. (55%) of product; m.p. 134.5-135.5°.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72. Found: C, 65.82; H, 4.81.

Benzylhydrazine.- This method is different from any of those described in the literature.

Benzyl chloride (126.6 g., 1.0 mole) was added, dropwise, over a period of 2 hours, to a stirred ice-cold suspension of

84 g. (1.0 mole) of sodium bicarbonate in 590 g. (10 moles) of 85% hydrazine hydrate in water. The suspension was stirred for an additional 2 hours, saturated with potassium carbonate, and then extracted with ether in a continuous liquid-liquid extractor.(131) The ether layer was dried over anhydrous magnesium sulfate, filtered and the ether was removed. The residue was distilled; b.p. 135°/29 mm; yield 56.5 g. (46%). Benzylhydrazine has been reported to distill at 135°/29 mm. (130)

7-Benzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (XXVII).- A mixture of 14.9 g. (0.1 mole) of quinolinic anhydride (I), 12.2 g. (0.1 mole) of benzylhydrazine and 150 ml. of acetic acid was refluxed for 2 hours. The solution was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from ethanol to give 20 g. (79%) of product; m.p. 246.5-248°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.22; H, 4.38; N, 16.82.

N-Benzyl-N'-phenylhydrazine.- To a suspension of 3.8 g. (0.1 mole) of lithium aluminum hydride in 250 ml. of anhydrous ether there was added, dropwise, a hot solution of 31.1 g. (0.16 mole) of benzaldehyde phenylhydrazone in a slight excess of benzene. The suspension was stirred and refluxed for 12 hours. Water (8 ml.) was added to hydrolyze the mixture and stirring was continued for an additional eight hours. The suspension was filtered and the filtrate was dried over sodium hydroxide pellets. The solvents were removed and the residue was distilled; the portion which distilled between 195-197°/15 mm.

was collected; m.p. 33-34°. The yield was 20.2 g. (64%). N-Benzyl-N'-phenylhydrazine has been reported to melt at 35°.(113)

7-Benzyl-6,7-dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione (XXVIII).- A mixture of 14.9 g. (0.1 mole) of quinolinic anhydride, 19.8 g. (0.1 mole) of N-benzyl-N'-phenylhydrazine and 100 ml. of acetic acid was refluxed for 6 hours. The solution was evaporated to dryness and the residue was recrystallized from ethanol; yield 14 g. (43%); m.p. 172°.

Anal. Calcd. For $C_{20}H_{15}N_3O_2$: C, 72.93; H, 4.59. Found: C, 72.83; H, 4.62.

2-(N-Methylcarbamoyl)nicotinic acid (XXIX).- Anhydrous methylamine was bubbled through an ice-cold solution of 27.0 g. (0.18 mole) of quinolinic anhydride in 350 ml. of butanone until material no longer precipitated. The precipitate was filtered, then dissolved in water with the aid of a small quantity of ammonium hydroxide. The solution was treated with charcoal and filtered; then it was acidified with sulfur dioxide. The precipitate was filtered and recrystallized from ethanol to give 13.2 g. (41%) of product, m.p. 154-155.5°.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48. Found: C, 53.38; H, 4.57.

N-Methylquinolinimide (XXX).- 2-(N-Methylcarbamoyl)-nicotinic acid (XXIX) (10 g., 0.056 mole) and 50 ml. of thionyl chloride were stirred and refluxed. Due to the formation of a ball of sticky material in the reaction flask, stirring was stopped but refluxing was continued for 4 hours.

The thionyl chloride was decanted and the residue was recrystallized from petroleum ether (90-100°); yield 3.9 g. (43%); m.p. 116.5-118.5°.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.25; H, 3.73. Found: C, 59.25; H, 3.87.

N-Methylquinolinimide was also prepared by stirring a mixture of 8.0 g. (0.045 mole) of 2-(N-methylcarbamoyl)nicotinic acid (XXIX) and 50 ml. of acetic anhydride on a steam-bath. The mixture was evaporated to dryness and the residue was recrystallized from petroleum ether (90-100°) to yield 7.0 g. (97%) of product; m.p. 116-118°.

Ethyl 2-methylnicotinate (XXXI).- In order to obtain this substance, the procedure (119) of Bohlmann and Rahtz was employed.

3-Hydroxymethyl-2-methylpyridine (XXXII).- A solution of 55.0 g. (0.33 mole) of ethyl 2-methylnicotinate (XXXI) in 100 ml. of anhydrous ether was added as rapidly as possible to a stirred and refluxing suspension of 15.6 g. (0.41 mole) of lithium aluminum hydride in 1400 ml. of anhydrous ether. The suspension was stirred and refluxed for 10 minutes after the addition of the ester was completed; then the heat was removed and 31 ml. of water were added, dropwise, to the stirred solution, followed by 26 ml. of a 10% solution of sodium hydroxide. The mixture was stirred for an additional 6 hours.

The ethereal mixture was filtered and the filtrate was dried over magnesium sulfate. After filtration, the solvent was removed from the filtrate and the residue was distilled;

the colorless liquid which distilled at 111°/1.2 mm. was collected; yield 27.7 g. (68%).

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37. Found: C, 67.99; H, 7.40.

The acid oxalate salt of 3-hydroxymethyl-2-methylpyridine was prepared and recrystallized from ethanol; m.p. 115-116°.

Anal. Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.80; H, 5.28; N, 6.69.

2-Methyl-3-pyridinecarboxaldehyde (XXXIII).- A mixture of 80.3 g. (0.18 mole) of lead tetraacetate (132) and 200 ml. of benzene was stirred and refluxed in a nitrogen atmosphere for 15 minutes. The heat was removed and 14.7 g. (0.12 mole) of 3-hydroxymethyl-2-methylpyridine, dissolved in 100 ml. of benzene, was added during a period of 10 minutes. After the addition was completed, the suspension was stirred and refluxed for 1.5 hours. The suspension was cooled, filtered and the precipitate was washed with benzene. The benzene filtrate was extracted with two 100 ml. portions of 10% sodium carbonate solution. The combined aqueous layers were extracted with five 50 ml. portions of chloroform. The benzene and chloroform solutions were combined and dried over anhydrous sodium carbonate, filtered, the solvent removed from the filtrate, and the residue was distilled; b.p. 100-110°/20 mm.; yield 9.0 g. (62.5%) The boiling point of 2-methyl-3-pyridinecarboxaldehyde has been reported to be 94°/12 mm.(33) The semicarbazone was prepared; it melted at 210° (reported m.p. 209° (33)).

2-(2-Methyl-3-pyridyl)-1,3-dioxolane (XXXIV).- A mixture of 8.0 g. (0.07 mole) of 2-methyl-3-pyridinecarboxaldehyde (XXXIII), 8.4 g. (0.14 mole) of ethylene glycol, 100 mg. of p-toluenesulfonic acid and 65 ml. of anhydrous benzene was stirred and refluxed for 48 hours; the water evolved was collected in a Dean-Stark trap. The mixture was extracted with two 25 ml. portions of 10% sodium carbonate solution. The aqueous solution was extracted with four 25 ml. portions of chloroform. The benzene and chloroform extracts were combined and dried over anhydrous sodium carbonate. The solvents were removed and the residue was distilled; two fractions were obtained. The first fraction, b.p. 105-113°/20 mm., was found to be 2-methyl-3-pyridinecarboxaldehyde; it was identified by its semicarbazone, m.p. 210° (reported m.p. 209° (33)). The yield was 3.0 g. (37.5%).

The second fraction, b.p. 138°/18 mm., was found to be the desired 2-(2-methyl-3-pyridyl)-1,3-dioxolane; yield 4.5 g. (41.5%).

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.63; H, 6.93; N, 8.20.

The following experiment represents only a preliminary one and was carried out only in a qualitative manner.

2-Methylnicotinic acid (XXXV) from 2-(2-methyl-3-pyridyl)-1,3-dioxolane (XXXIV).- A portion of XXXIV was dissolved in 10% sodium hydroxide solution and a saturated aqueous solution of potassium permanganate was added, dropwise, until the disappearance of the permanganate color was definitely slower than at the start of the oxidation. The suspension was

stirred for an additional hour, then neutralized, filtered, and the solvent removed from the filtrate. Recrystallization of the residue from ethanol yielded only 2-methylnicotinic acid, m.p. 223-225°.*

2-Methylnicotinic acid (XXXV) from 2-methylnicotinaldehyde (XXXIII).- A portion of XXXIII was allowed to remain exposed to air for 6 hours. The solid material which formed was filtered and recrystallized from ethanol to yield 2-methylnicotinic acid, m.p. 223-225°.*

2-Methylnicotinic acid (XXXV) from 2-(2-methyl-3-pyridyl)-1,3-dioxolane (XXXIV).- A portion of XXXIV was allowed to remain exposed to air for 8 hours. The solid material which formed was filtered and recrystallized from ethanol to yield 2-methylnicotinic acid, m.p. 222-224°.*

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* Baumgarten and Dornow prepared 2-methylnicotinic acid, m.p. 226-227°, from the basic hydrolysis of ethyl 2-methylnicotinate.(118)

SUMMARY

A series of 6,7-dihydropyrido[2,3-d]pyridazine-5,8-diones substituted in the 6, 7 or 6,7 positions were prepared by the reaction of quinolinic anhydride (I) with the following hydrazines: hydrazine, N,N'-dimethylhydrazine, N,N'-dibenzylhydrazine, methylhydrazine, phenylhydrazine, benzylhydrazine and N-benzyl-N'-phenylhydrazine. The condensation products obtained from these reactions were 6,7-dihydropyrido-[2,3-d]pyridazine-5,8-dione (II), 6,7-dihydro-6,7-dimethylpyrido[2,3-d]pyridazine-5,8-dione (III), 6,7-dibenzyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione and, presumably, 6,7-dihydro-7-methylpyrido[2,3-d]pyridazine-5,8-dione (IV) instead of the corresponding 6-methyl derivative, 6,7-dihydro-6-phenylpyrido[2,3-d]pyridazine-5,8-dione (V) instead of the corresponding 7-phenyl derivative, 7-benzyl-6,7-dihydropyrido-[2,3-d]pyridazine-5,8-dione instead of the corresponding 6-benzyl derivative, and 7-benzyl-6,7-dihydro-6-phenylpyrido-[2,3-d]pyridazine-5,8-dione instead of the corresponding 6-benzyl-7-phenyl derivative.

5-Acetoxy-7-acetylpyrido[2,3-d]pyridazin-8(7H)-one (VI) was prepared from the reaction of II with acetic anhydride. Under very mild hydrolytic conditions, VI lost one acetyl group with the formation of a product which was believed to be the N-acetyl derivative, 7-acetyl-6,7-dihydropyrido[2,3-d]-pyridazine-5,8-dione (VII). The only other N-acetyl derivative which could be formed would have been 6-acetyl-6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione (VIII). Compound VIII

was synthesized by reaction of I with acetylhydrazine to form N-acetyl-N'-(3-carboxypicolinoyl)hydrazine and subsequent cyclization of this product. The structure of VII was deduced from the fact that it was shown to be different from VIII by a mixed melting point determination.

Compound I reacted with formylhydrazine to give N-formyl-N'-(3-carboxypicolinoyl)hydrazine (IX); cyclization of IX formed 6,7-dihydro-6-formylpyrido[2,3-d]pyridazine-5,8-dione. Reaction of acetic anhydride with IV yielded 5-acetoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one and with V formed 8-acetoxy-6-phenylpyrido[2,3-d]pyridazin-5(6H)-one.

Diazomethane reacted with IV to give 5-methoxy-7-methylpyrido[2,3-d]pyridazin-8(7H)-one and with V to form 8-methoxy-6-phenylpyrido[2,3-d]pyridazine-5(6H)-one, isolated as the hydrochloride.

From the interaction of II and phosphorus oxychloride a product was obtained which, as indicated by analytical data, may be either 5-chloropyrido[2,3-d]pyridazin-8(7H)-one or 8-chloropyrido[2,3-d]pyridazin-5(6H)-one. From the reaction of II and phosphorus oxychloride, under slightly different conditions, the product obtained was 5,8-dichloropyrido[2,3-d]-pyridazine. Reaction of IV with phosphorus oxychloride gave 5-chloro-7-methylpyrido[2,3-d]pyridazin-8(7H)-one (X).

Catalytic hydrogenation of II, III and IV gave the corresponding 1,2,3,4-tetrahydro compounds. When X was hydrogenated, 7-methyl-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-8(7H)-one was obtained.

Reduction of IV with lithium aluminum hydride gave an oil which, when treated with benzoyl chloride, formed a product which was, presumably, 6-benzoyl-7-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyridazine.

Compound I reacted with benzylamine to yield 2-(N-benzylcarbamoyl)nicotinic acid. The reaction of I with methylamine gave 2-(N-methylcarbamoyl)nicotinic acid, which was cyclized to N-methylquinolinimide by the use of thionyl chloride or acetic anhydride.

An attempt was made to synthesize 3-formylpicolinic acid which was desired for a structure proof of the pyrido[2,3-d]-pyridazines. Ethyl 2-methylnicotinate (XI) was obtained from the reaction of ethyl β-aminocrotonate with propargyl aldehyde. Compound XI was reduced with lithium aluminum hydride to 3-hydroxymethyl-2-methylpyridine, which was oxidized by lead tetraacetate to 2-methylnicotinaldehyde (XII) in 62.5% yield. The acetal of XII was prepared by the use of ethylene glycol. This acetal was oxidized with basic permanganate with the result that 2-methylnicotinic acid was obtained, instead of the acetal of 3-formylpicolinic acid which could have been hydrolyzed to the desired 3-formylpicolinic acid.

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