



6-1949

A Study of Steric Inhibition of the Pfitzinger Reaction

Robert Earl Stobaugh
University of Tennessee, Knoxville

Follow this and additional works at: https://trace.tennessee.edu/utk_gradthes

 Part of the [Chemistry Commons](#)

Recommended Citation

Stobaugh, Robert Earl, "A Study of Steric Inhibition of the Pfitzinger Reaction. " Master's Thesis, University of Tennessee, 1949.
https://trace.tennessee.edu/utk_gradthes/4829

This Thesis is brought to you for free and open access by the Graduate School at TRACE: Tennessee Research and Creative Exchange. It has been accepted for inclusion in Masters Theses by an authorized administrator of TRACE: Tennessee Research and Creative Exchange. For more information, please contact trace@utk.edu.

To the Graduate Council:

I am submitting herewith a thesis written by Robert Earl Stobaugh entitled "A Study of Steric Inhibition of the Pfitzinger Reaction." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

George P. Mueller, Major Professor

We have read this thesis and recommend its acceptance:

Calvin Buehler, George K. Schweitzer

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

May 14, 1949

To the Committee on Graduate Study:

I am submitting to you a thesis written by Robert Earl Stobaugh entitled "A Study of Steric Inhibition of the Pfitzinger Reaction." I recommend that it be accepted for nine quarter hours of credit in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

George P. Mueller
Major Professor

We have read this thesis
and recommend its acceptance:

C. S. Neble

Geo. K. Schweitzer

Accepted for the Committee

E. A. Waters
Dean of the Graduate School

A STUDY OF STERIC INHIBITION
OF THE PFITZINGER REACTION

A THESIS

Submitted to
The Committee on Graduate Study
of
The University of Tennessee
in
Partial Fulfillment of the Requirements
for the degree of
Master of Science

by

Robert Earl Stobaugh

June 1949

ACKNOWLEDGMENT

I wish to express my appreciation for the help and encouragement of Dr. G. P. Mueller and Dr. L. K. Yourtee in the planning and carrying out of the work presented in this thesis.

Robert Stobaugh
Robert Stobaugh

TABLE OF CONTENTS

CHAPTER	PAGE
I. INTRODUCTION	1
II. HISTORICAL AND THEORETICAL	2
III. EXPERIMENTAL	11
The Synthesis of <u>n</u> -Caprophenone	11
<u>n</u> -Caproyl chloride	11
<u>n</u> -Caprophenone	11
The Synthesis of 4'-Methyl- desoxybenzoin	12
<u>p</u> -Xylyl chloride	12
<u>p</u> -Tolylacetonitrile	13
<u>p</u> -Tolylacetic acid	14
4'-Methyldesoxybenzoin	14
The Synthesis of 2',4'-Dimethyl- desoxybenzoin	16
2,4-Dimethylbenzyl chloride	16
2,4-Dimethylphenylacetonitrile	17
2',4'-Dimethyldesoxybenzoin	18
The Synthesis of 2',4',6'-Tri- methyldesoxybenzoin	19
Benzyl mesityl ketone	19
Mesityl phenyl diketone	20
2',4',6'-Trimethyldesoxybenzoin	20
The Synthesis of 2-Phenyl-3- <u>n</u> -butylcinchoninic acid	21

CHAPTER

PAGE

III. (continued)	
2-Phenyl-3- <u>n</u> -butylquinoline methiodide	22
The Synthesis of 2-Phenyl-3- p-tolylcinchoninic acid	23
2-Phenyl-3-p-tolylquinoline picrate	24
Attempted Preparation of 2-Phenyl- 3-p-tolylquinoline methiodide	24
The Synthesis of 2-Phenyl-3- (2,4-dimethylphenyl)cin- choninic acid	25
2-Phenyl-3-(2,4-dimethylphenyl)- quinoline picrate	26
Attempted Preparation of 2-Phenyl- 3-(2,4-dimethylphenyl)quinoline methiodide	27
Attempted Synthesis of 2-Phenyl- 3-mesitylcinchoninic acid	27
The Synthesis and Attempted Conden- sations of Potassium Isatate	29
The Synthesis of Isatic Acid	32
Attempted Esterification of Isatic Acid	33
IV. DISCUSSION OF RESULTS	34
V. SUMMARY	37
BIBLIOGRAPHY	38

CHAPTER I

INTRODUCTION

A survey of the Pfitzinger reaction reveals that little attention has been given to the steric factors likely to govern the course of the condensation; a major part of the research done has dealt with its value as a synthetic tool.

The primary purpose of this work was to add further information concerning steric inhibition in the Pfitzinger reaction; it was also hoped that the cinchoninic acids obtained might show physiological activity.

CHAPTER II

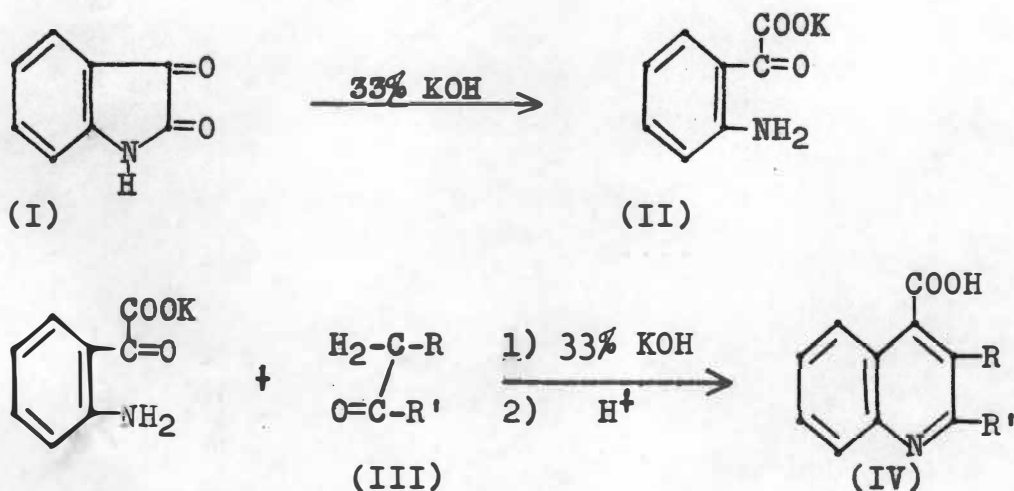
HISTORICAL AND THEORETICAL

Part 1

Although the condensation of isatin with ketones has frequently been used for the syntheses of quinoline derivatives, little work has been done on either the steric factors or the electronic effects involved in the reaction.

The first report of this condensation was by Pfitzinger,¹ who observed that isatin, in strongly alkaline solution, reacted with ketones bearing a methylene group adjacent to the carbonyl group. The product of this reaction was a quinoline-4-carboxylic acid.

Although the mechanism is unknown, the reaction may be represented by the following equations:



¹Pfitzinger, *J. prakt. chem.*, (2) 33, 100 (1886)

Isatin (I) is cleaved by strong base, generally 25-33% aqueous alcoholic potassium hydroxide, to a salt of isatic acid (II), which then condenses with a ketone of structure (III) to produce, after acidification, the cinchoninic acid (IV).

It is reasonable that the R and R' groups may exert a steric influence upon the condensation, in some cases hindering or completely preventing it.

Borsche and Rottsieper² could not bring isatin into reaction with menthone, pulegone, or camphor. These failures presumably were the result of steric effects in the ketone molecule, as, in each case, the carbon atoms adjacent to the reactive groups of the ketone are substituted with alkyl groups.

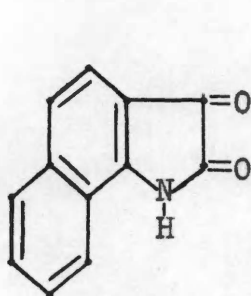
Buu-Hoi³ showed that isatin did not react with isopulegone, dihydroisopulegone, tetrahydrocarvone, norcamphor, or tropanone. These ketones also bear substituents near both the carbonyl and methylene groups which would be involved in the reaction. This also conforms with the inability, recorded by Borsche,⁴ of dehydrocholic acid and of dehydrodesoxycholic acid to react with more than one molecule of isatin.

²Borsche and Rottsieper, Ann. 377, 70 (1910)

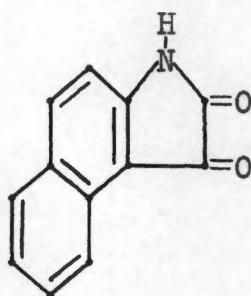
³Buu-Hoi, J. Chem. Soc. 1946, 795

⁴Borsche, Ber. 57, 1373 (1924)

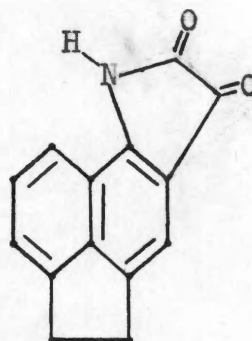
Buu-Hoi⁵ also observed that when the hindrance lies in the isatin molecule, the normal condensation again often does not take place. Likewise, it follows that if hindrance is present in both molecules, the reaction fails. Examples of the above are that cyclohexanone does not react with either 1- or 2-naphthisatin (V, VI),⁶ or with 1-acenaphthisatin (VII).⁷



(V)



(VI)



(VII)

Similarly, von Braun⁸ observed that tetrahydro-1-naphthisatin failed to react with 1-tetralone; this failure may be considered due to hindrance in both the isatin and ketone molecules.

In a study of ketones of the acetophenone series, $C_6H_5CO(CH_2)_nCH_3$, Buu-Hoi and Cagniant⁹ found that only those

⁵Buu-Hoi, J. Chem. Soc. 1946, 795

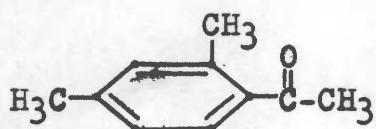
⁶Borsche and Wagner-Roemmich, Ann. 544, 287 (1940)

⁷Buu-Hoi, J. Chem. Soc. 1946, 795

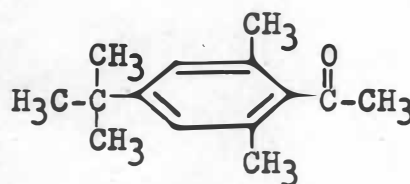
⁸von Braun, Ann. 451, 1 (1927)

⁹Buu-Hoi and Cagniant, Bull. soc. chim. 1946, 123

ketones in which n was not greater than two condensed with isatin. Substitution of the thiophene nucleus for the phenyl group had no effect on this transition point. The investigators ascribed the cessation of reaction to the increasing length of the alkyl chain present in the ketones. Ring substitution ortho to the carbonyl group did not impede the reaction, since both 2,4-dimethylacetophenone (VIII) and 2,6-dimethyl-4-tert-butylacetophenone (IX) condensed easily. However, the presence of one ortho methyl group was sufficient to block reaction with the naphthisatins.¹⁰



(VIII)

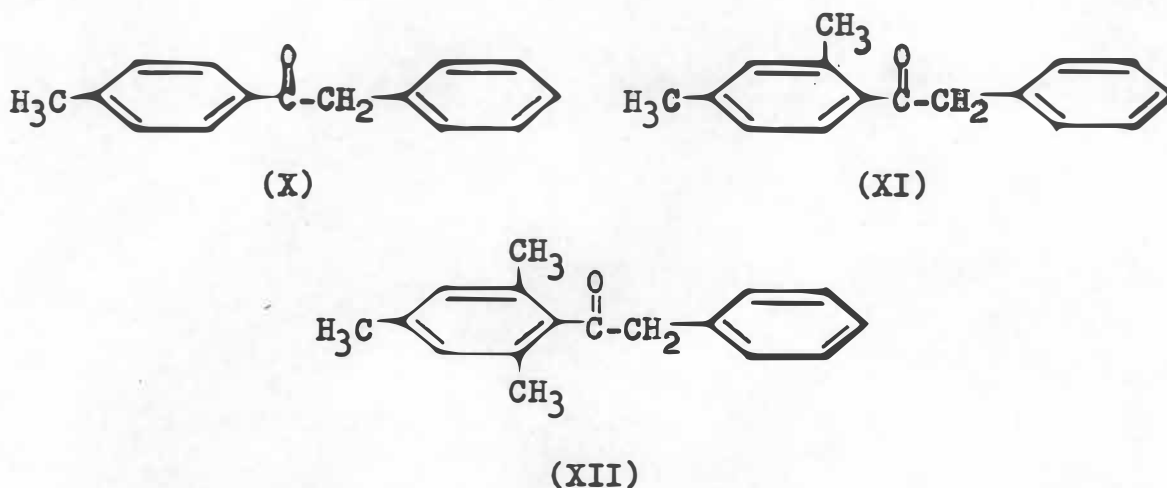


(IX)

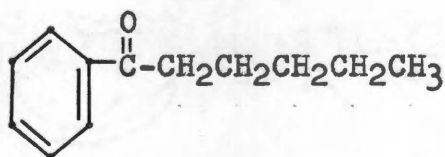
Investigations by Buu-Hoi and Royer¹¹ of the hindrance presented by various benzyl aryl ketones showed that 4-methyl-desoxybenzoin (X) condensed with isatin to give the corresponding cinchoninic acid in 62% yield, while 2,4-dimethyl-desoxybenzoin (XI) gave a low yield of the acid and 2,4,6-trimethyldesoxybenzoin (XII) failed to react.

¹⁰Buu-Hoi, J. Chem. Soc. 1946, 795

¹¹Buu-Hoi and Royer, Bull. soc. chim. 1946, 374



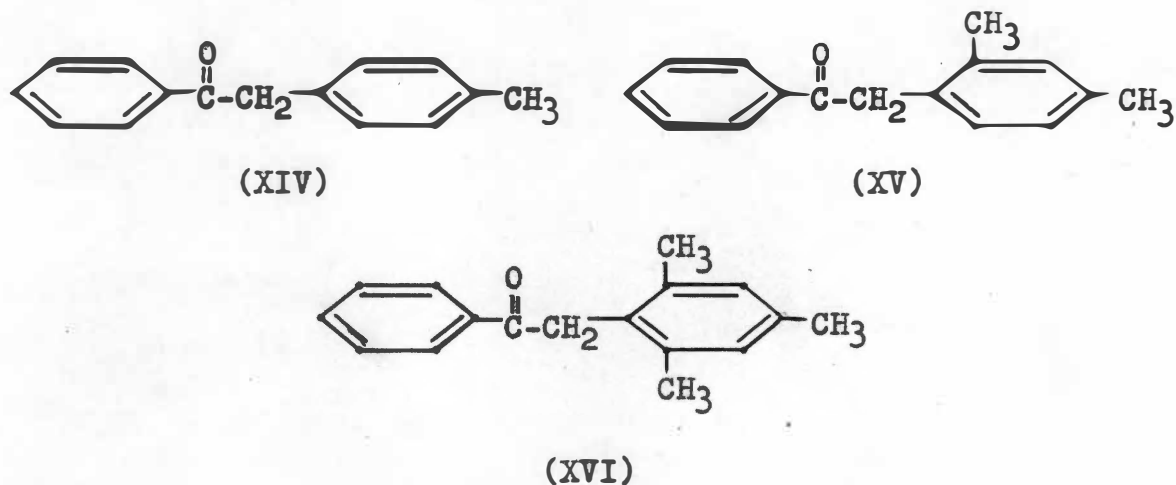
It was of interest to see what effect transposition of the methyl groups to the other ring of these ketones would have on their reactivity in the Pfitzinger condensation. In addition, it was planned to compare the effect of the methyl-substituted phenyl group with a straight-chain aliphatic group. n-Caprophenone (XIII) was used for this purpose, the n-butyl group replacing the substituted phenyl group. This ketone was reported by Buu-Hoi and Cagniant¹² as failing to react with isatin; however, the corresponding cinchoninic acid was obtained by the normal procedure.



(XIII)

¹²Buu-Hoi and Cagniant, Bull. soc. chim. 1946, 123

This work then involved the syntheses of cinchoninic acids from 4'-methyldesoxybenzoin (XIV), 2',4'-dimethyldesoxybenzoin (XV), and 2',4',6'-trimethyldesoxybenzoin (XVI), as well as from n-caprophenone.



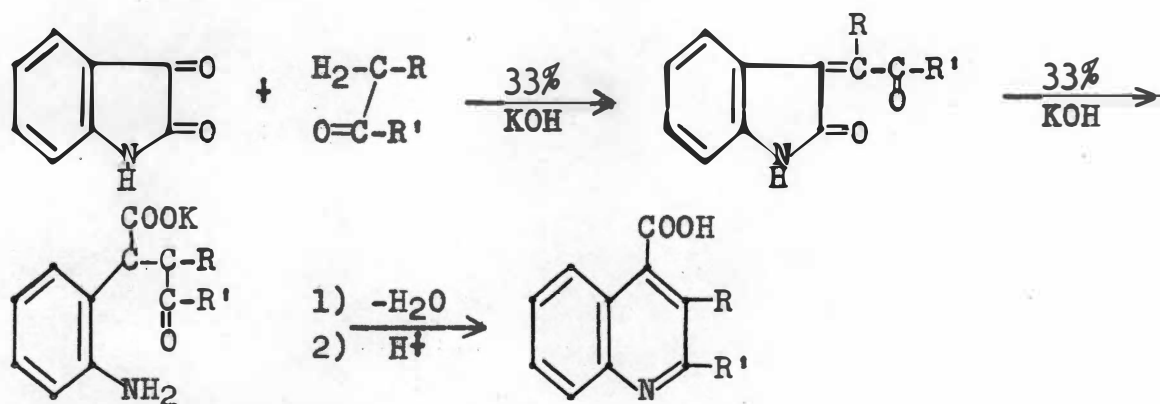
Three of the necessary ketones were synthesized by recorded methods while one, 2',4'-dimethyldesoxybenzoin, was made through a Grignard synthesis not previously reported. This ketone was obtained in 20-25% yield from the addition of 2,4-dimethylphenylacetonitrile to phenylmagnesiumbromide.

In the series of methyl desoxybenzoin it was expected that steric hindrance would progressively increase as the number of ortho methyl groups increased. Thus, the 4'-methyl ketone was not expected to show evidence of steric inhibition, while the 2',4',6'-trimethyl ketone should be highly hindered. The results obtained from Pfitzinger reactions with these ketones justified the foregoing speculations. In addition, as stated before, a cinchoninic acid was obtained from n-caprophenone.

This was not an entirely unexpected result, as the n-butyl group should present no unusually great hindrance. As predicted, the trimethyl desoxybenzoin did not react, even under very strenuous conditions.

Part 2

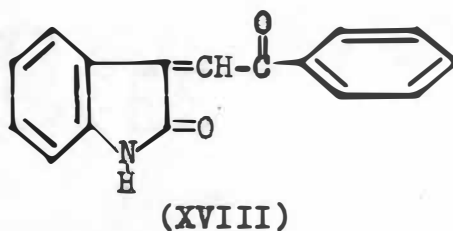
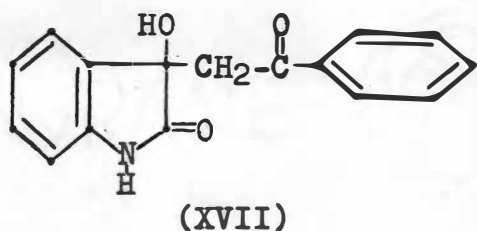
As it was noted in Part 1, the mechanism of the Pfitzinger reaction is unknown, and little research has been carried out on this important phase of the condensation. Borsche and Jacobs¹³ postulated the following mechanism based entirely on speculation:



As is shown, this involved a condensation of the ketonic methylene group with the 3-carbonyl group of isatin, cleavage of the ring, and subsequent ring closure.

¹³Borsche and Jacobs, Ber. 47, 354 (1914)

However, Lindwall and MacLennan¹⁴ condensed isatin with acetophenone in the presence of dimethylamine, piperidine, or dilute inorganic bases, to form 3-hydroxy-3-phenacyloxindole (XVII). This compound, when heated in alcohol with 33% aqueous potassium hydroxide, did not directly form 2-phenyleinchoninic acid. A reversal of the aldol-like condensation took place first, regenerating isatin and acetophenone, which then reacted normally under Pfitzinger conditions. The 3-hydroxy-3-phenacyloxindole was dehydrated with hydrochloric acid to 3-phenacylideneoxindole (XVIII), which was also heated with strong base and alcohol, but no cinchoninic acid was produced. These results tended to disprove the theory presented by Borsche and Jacobs.



Since no further work has been done toward presenting a mechanism for the reaction, it was of interest to attempt a formulation based on experimental evidence. As it is known that the heterocyclic ring of isatin undergoes cleavage very rapidly in the presence of strong base, the isatate salt may be an intermediate in the condensation. To test this

¹⁴Lindwall and MacLennan, *J. Am. Chem. Soc.* **54**, 4739 (1932)

hypothesis, potassium isatate was prepared and several attempts were made to condense it with acetophenone in various basic media. A substance which appeared to be an addition product of the two compounds was formed in the presence of dilute sodium hydroxide. However, its instability prevented satisfactory characterization.

Isatic acid was also prepared, and several trials were made to synthesize its methyl ester, with the aim, as before, of condensing it with acetophenone. These attempts were unsuccessful, and research concerning the mechanism of the Pfitzinger condensation was temporarily discontinued.

CHAPTER III

EXPERIMENTAL

The Synthesis of n-Caprophenone

n-Caproyl chloride¹

In a 500-ml. round-bottomed flask fitted with a rubber stopper holding a reflux condenser with an attached gas trap were placed 50 g. (0.43 moles) of n-caproic acid and 100 g. (0.84 moles) of thionyl chloride. After refluxing for one hour, the mixture was distilled at atmospheric pressure. The yield of n-caproyl chloride, b.p. 145-8°/745 mm., was 57 g. (98%).

n-Caprophenone²

In a one-liter, three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser, and a separatory funnel were placed 60.0 g. (0.44 moles) of anhydrous aluminum chloride and 175 ml. of anhydrous benzene. Calcium chloride tubes were attached to the tops of the condenser and the funnel. In the separatory funnel was placed 57.0 g. (0.42 moles) of n-caproyl chloride dissolved in 60 ml. of anhydrous

¹Gartenmeister, Ann. 233, 279 (1886)

²Tiffeneau and Levy, Compt. rend. 183, 969 (1926)

benzene. This solution was added dropwise to the stirred suspension of aluminum chloride. The addition required about thirty minutes. After refluxing for one hour, the mixture was cooled and hydrolyzed with ice and concentrated hydrochloric acid. The benzene layer was separated and the aqueous layer extracted twice with 100 ml. portions of benzene. The combined benzene layer and extracts were washed with 10% aqueous sodium carbonate solution, followed by water, and dried over sodium sulfate, and the benzene removed by distillation. Upon distillation of the residue, 59.6 g. (91.1%) of n-caprophenone, b.p. 122-4°/15 mm., was obtained. The melting point of the semicarbazone was 130-1°, which corresponds to the value given for this derivative.³

The Synthesis of 4'-Methyldesoxybenzoin

p-Xylyl chloride

Following the general procedure for chloromethylation as used by von Braun and Nelles,⁴ 400 g. (4.34 moles) of toluene, 450 g. (6.0 moles) of 40% formalin solution, 2.5 lb. of concentrated hydrochloric acid, and 125 g. of powdered zinc chloride were placed in a two-liter, three-necked, round-bottomed flask equipped with a gas inlet tube reaching almost

³Tiffeneau and Levy, Compt. rend. 183, 969 (1926)

⁴von Braun and Nelles, Ber. 67, 1094 (1934)

to the bottom, a mechanical stirrer, and a reflux condenser with an attached gas trap. The reaction mixture was heated to 65° on a water bath and kept at that temperature, within 5°, for four hours with stirring, while gaseous hydrogen chloride was passed in at the rate of 3-4 bubbles per second. At the end of this period, heating, stirring, and gas addition were stopped and the mixture was allowed to stand. After the lower layer was removed, the organic layer was washed successively with three 500-ml. portions of water, two 300-ml. portions of 10% aqueous sodium bicarbonate solution, and one 300-ml. portion of water. After drying over anhydrous calcium chloride, the solution was distilled in vacuo. The amount of unreacted toluene, b.p. 28-30°/12 mm., was 281 g.; the yield of p-xylyl chloride, b.p. 88-90°/7 mm., was 126.2 g. (70%).

p-Tolylacetonitrile

Following the procedure of Rupe and Wiederkehr⁵, 65 g. (1.3 moles) of sodium cyanide and 60 g. of water were placed in a one-liter, round-bottomed, three-necked flask fitted with a reflux condenser and a separatory funnel. After the cyanide had been dissolved by heating, 126.2 g. (0.9 moles) of p-xylyl chloride in 130 g. of absolute alcohol was added from the funnel over a period of thirty minutes. After refluxing for three hours, the mixture was cooled and filtered by suction.

⁵Rupe and Wiederkehr, Helv. Chim. Acta 7, 654 (1924)

After the water and alcohol were removed by distillation, the residual oil was distilled under reduced pressure; the yield of *p*-tolylacetonitrile, b.p. 124-6°/16 mm., was 88.7 g. (75%).

p-Tolylacetic acid

Following the procedure of Adams and Thal⁶ for the preparation of phenylacetic acid, 88.7 g. (0.68 moles) of *p*-tolylacetonitrile was added to a cooled mixture of 90 ml. of water, 90 ml. of glacial acetic acid, and 90 ml. of concentrated sulfuric acid. After an initially vigorous reaction, followed by refluxing for one hour, the mixture was poured into 300 ml. of water and crushed ice. Continued stirring caused solidification of the crude product. After melting, and washing this product twice with hot water, it was distilled under reduced pressure. The yield of *p*-tolylacetic acid, b.p. 161-3°/9 mm., m.p. 90-3°, was 60.7 g. (59.8%). This product was used in the following synthesis without further purification.

4'-Methyldesoxybenzoin

In a 250-ml., three-necked, round-bottomed flask fitted with a separatory funnel and a reflux condenser with an attached gas trap were placed 20.0 g. (0.2 moles) of *p*-tolylacetic acid and 13.6 g. (0.1 moles) of phosphorus trichloride. After

⁶Adams and Thal, "Organic Syntheses," Coll. Vol. I, 436 (1947)

heating on the steam bath for thirty minutes, 39 g. (0.5 moles) of benzene was added and the solution decanted from the phosphorus acid. The benzene solution of *p*-tolylacetyl chloride was allowed to drop slowly on to 30.7 g. (0.23 moles) of anhydrous aluminum chloride in a dry, 500-ml. flask fitted as described above. After the addition was complete and the vigorous reaction had subsided, the mixture was refluxed for one hour, cooled, and hydrolyzed with ice and concentrated hydrochloric acid. The benzene layer was separated and the aqueous layer extracted once with a mixture of 50 ml. of benzene and 50 ml. of ether. The combined solutions were washed once with 100 ml. of water and dried over sodium sulfate. After removal of the solvents, the residual oil was distilled in vacuo; 20.0 g. (73%) of 4'-methyldesoxybenzoin, b.p. 148-50°/3 mm., was obtained as a yellow oil which quickly solidified. After recrystallization from alcohol, the melting point of the ketone, 94-5°, and of the semicarbazone, 127-8°, agree with the reported values.⁷

In a previous attempt to prepare 4'-methyldesoxybenzoin, thionyl chloride was employed in the synthesis of *p*-tolylacetyl chloride. However, upon reaction of this compound with benzene in the presence of aluminum chloride, an odorous, violet liquid resulted. Although it solidified on cooling, it could not be

⁷Strassman, Ber. 22, 1230 (1889)

crystallized, nor could a derivative be made. The excess thionyl chloride in the reaction described above was removed by distillation with benzene; evidently small amounts remaining caused extensive side reactions with the result that little, or none of the desired ketone was obtained.

The Synthesis of 2',4'-Dimethyldesoxybenzoin

2,4-Dimethylbenzyl chloride⁸

In a five-liter, three-necked, round-bottomed flask fitted with a gas inlet reaching almost to the bottom, a mechanical stirrer, and a reflux condenser with an attached gas trap, were placed 500 g. (4.71 moles) of m-xylene, 500 g. (6.67 moles) of 40% formalin solution, and 6 lbs. of concentrated hydrochloric acid. The reaction mixture was heated to 65° on a water bath, and kept at that temperature for seven hours with stirring, while gaseous hydrogen chloride was passed in at the rate of 3 or 4 bubbles per second. At the end of this period, the reaction was set aside and allowed to cool overnight. After the lower aqueous layer was removed, the organic layer was washed successively with three 500-ml. portions of water, one 300-ml. portion of 10% sodium bicarbonate solution, and one 500-ml. portion of water, and dried over anhydrous calcium chloride. One-half of the dried mixture was

⁸von Braun and Nelles, Ber. 67, 1094 (1934)

filtered into a 500-ml. Claisen flask fitted with a Glas-Col heating mantle for removal of unreacted xylene. During the distillation, the entire amount of liquid polymerized to a clear yellow-green solid, with purple fluorescence. Preliminary to distillation of the remainder, the solution was again washed with two 300-ml. portions of water, one 300-ml. portion of 10% sodium bicarbonate solution, and one 300-ml. portion of water. After drying over potassium carbonate, the mixture was distilled under reduced pressure. The yield of 2,4-dimethylbenzyl chloride, b.p. 97-100°/12 mm., was 280 g. (38.5%).

2,4-Dimethylphenylacetonitrile⁹

In a one-liter, three-necked, round-bottomed flask fitted with a reflux condenser and a separatory funnel, were placed 130 g. (2.6 moles) of powdered sodium cyanide, and 130 ml. of water. This mixture was heated on the steam bath until the cyanide had completely dissolved. Then 280 g. (1.82 moles) of 2,4-dimethylbenzyl chloride in 280 g. of alcohol was added from the funnel over a period of one hour. After refluxing for three hours, the mixture was cooled and filtered by suction. The brown solution was returned to the flask and 400 ml. of alcohol and water were removed by distillation. The residual oil was distilled in vacuo; the yield

⁹Harispe, Ann. chim. 6, 247 (1936)

of 2,4-dimethylphenylacetonitrile, b.p. $111-3^{\circ}/2$ mm., was 205.7 g. (58.6%).

2',4'-Dimethyldesoxybenzoin

In a 500-ml., three-necked, round-bottomed flask, fitted with a mechanical stirrer, a separatory funnel, and a 60 cm. condenser were placed 2.9 g. (0.12 moles) of magnesium turnings, a small crystal of iodine, and 15 ml. of absolute ether. The stirrer was started and a solution of 18.8 g. (0.12 moles) of bromobenzene in 40 ml. of absolute ether was added dropwise over a period of thirty minutes. At the end of this addition, a solution of 13.1 g. (0.09 moles) of 2,4-dimethylphenylacetonitrile in 80 ml. of absolute ether was added slowly over a period of thirty minutes. The contents of the flask were then slowly poured, with vigorous stirring, into a mixture of 40 g. of concentrated sulfuric acid and one kg. of crushed ice. On separation and evaporation of the ether layer, a brown oil was obtained, which solidified on standing. After two crystallizations from alcohol, 4.8 g. (25%) of 2',4'-dimethyldesoxybenzoin was obtained in the form of fine, white needles, m.p. $106-7^{\circ}$; oxime, m.p. $113-4^{\circ}$, corresponding to the reported values.¹⁰

¹⁰cf. ref. 9

The preparation on a larger scale of 2',4'-dimethyl-desoxybenzoin from 166.9 g. (1.15 moles) of 2,4-dimethyl-phenylacetonitrile, 40.1 g. (1.65 moles) of magnesium, and 251.2 g. (1.60 moles) of bromobenzene yielded 57.9 g. (20.5%) of the desired product.

The Synthesis of 2',4',6'-Trimethyldesoxybenzoin

Benzyl mesityl ketone

Following the method of Klages and Lickroth,¹¹ 500 g. (3.64 moles) of phosphorus trichloride was added to 247.8 g. (1.82 moles) of phenylacetic acid in a three-liter, three-necked, round-bottomed flask fitted with a separatory funnel and a reflux condenser with an attached gas trap. After heating for two hours, 200 g. (1.66 moles) of mesitylene and 800 ml. of ligroin (b.p. 70-90°) were added and the solution decanted from the phosphorus acid. The mixture of phenylacetyl chloride, mesitylene, and ligroin was added slowly to 266.8 g. (2.0 moles) of aluminum chloride. After refluxing for four hours, the mixture was allowed to cool and was poured into 370 ml. of concentrated sulfuric acid and 2 kg. of crushed ice. The ligroin layer was separated and the aqueous layer extracted with two 100-ml. portions of ligroin. After removing the solvent, the residue was distilled under reduced pressure, giving 210.3 g.

¹¹Klages and Lickroth, Ber. 32, 1564 (1899)

(53.2%) of benzyl mesityl ketone, b.p. 177-90/10 mm., m.p. 29-31°. This product was used in the following preparation without further purification.

Mesityl phenyl diketone

According to the method of Weinstock and Fuson,¹² a mixture of 105.2 g. (0.44 moles) of benzyl mesityl ketone, 55.3 g. (0.50 moles) of selenium dioxide, 1000 ml. of dioxane, and 10 ml. of water was refluxed for five hours. After cooling, the mixture was filtered to remove the selenium, and the dioxane solution was concentrated by distillation. The diketone which precipitated was crystallized twice from chloroform. The yield of mesityl phenyl diketone, m.p. 136-7°, was 85.2 g. (76.7%). The melting point of the monoxime, after recrystallization from alcohol, was 154-5°, which is correct.¹²

2',4',6'-Trimethyldesoxybenzoin¹²

The reduction of mesityl phenyl diketone was carried out by refluxing a mixture of 5.0 g. (0.02 moles) of the diketone, 8.3 g. (0.07 moles) of granulated tin, 33 ml. of concentrated hydrochloric acid, and 100 ml. of alcohol for twenty-four hours. The product, which separated from the reaction mixture in white needles, was recrystallized from alcohol.

¹²Weinstock and Fuson, J. Am. Chem. Soc. 58, 1234 (1936)

The yield of 2',4',6'-trimethyldesoxybenzoin, m.p. 163-4°, was 3.6 g. (73.4%); phenylhydrazone, m.p. 104-50.¹³

The Synthesis of 2-Phenyl-3-n-butylcinchoninic Acid

In a 200-ml., round-bottomed flask equipped with a reflux condenser were placed 17.6 g. (0.10 moles) of n-caprophenone, 14.7 g. (0.10 moles) of isatin, 45.7 g. (0.29 moles) of 33% aqueous potassium hydroxide, and 90 ml. of alcohol. After refluxing for forty-eight hours, the alcohol was removed by distillation, the residue diluted with water, and extracted twice with 15 ml. of ether to remove any unreacted ketone. On evaporation of the ethereal solution, 2.1 g. of n-caprophenone were recovered. On acidification of the aqueous solution with 10% acetic acid, 13.7 g. of crude cinchoninic acid precipitated. After decolorization of a solution of this product in glacial acetic acid with activated charcoal and three recrystallizations from the same solvent, 4.5 g. (30%) of 2-phenyl-3-n-butylcinchoninic acid were obtained, m.p. 237-8° (dec.).

Anal. Calcd. for C₂₀H₁₉N₂O₂: C, 78.66; H, 6.27;
N, 4.59; N.E., 305.

Found: C, 78.42; H, 6.37; N, 4.62; N.E., 304.

Following a similar procedure, the mixture was refluxed for twenty-four hours, but no cinchoninic acid was produced.

¹³cf. ref. 12

Increasing the time of reflux to seventy-two hours did not raise the yield; however, none of the ketone was recovered.

2-Phenyl-3-n-butylquinoline Methiodide

The sodium salt of 2-phenyl-3-n-butylcinchoninic acid was prepared by dissolving 0.3 g. of the acid in 3 ml. of 10% aqueous sodium hydroxide. The salt crystallized in colorless needles after standing overnight. After filtering, washing with 1 ml. of water, and drying at 100° for one hour, the salt was mixed thoroughly with 1 g. of soda lime. On heating this mixture in a Hickman¹⁴ still for twenty minutes at a bath temperature of 280-300°, and a pressure of 1 mm., a yellow oil distilled into the receiver. This was dissolved in absolute ether, 1 ml. of methyl iodide added, and the solution heated slightly and allowed to stand overnight. The methiodide deposited in fine yellow needles which, after three recrystallizations from absolute alcohol diluted with absolute ether, melted at 204° (dec.).

Anal. Calcd. for C₂₀H₂₂NI: C, 59.56; H, 5.50; N, 3.47.
Found: C, 59.66; H, 5.57; N, 3.72.

¹⁴Hickman and Sanford, J. Phys. Chem. 34, 637 (1930)

The Synthesis of 2-Phenyl-3-p-tolylocinchoninic Acid

In a 200-ml., round-bottomed flask fitted with a reflux condenser were placed 6.3 g. (0.03 moles) of 4'-methyldesoxybenzoin, 5.2 g. (0.035 moles) of isatin, 16.8 g. (0.10 moles) of 33% aqueous potassium hydroxide, and 30 ml. of alcohol. After refluxing for forty-eight hours, the alcohol was removed and the residue diluted with water. Ethereal extraction afforded 4.8 g. of crude unreacted ketone, and upon acidification of the aqueous solution, 2.5 g. of coarse, brown material separated. This was dissolved in 10% aqueous sodium hydroxide, decolorized with charcoal, and re-acidified with 10% acetic acid. A cream colored flocculent product resulted. After three recrystallizations from glacial acetic acid, 1.2 g. (37%) of 2-phenyl-3-p-tolylocinchoninic acid was obtained, m.p. 271-2° (dec.).

Anal. Calcd. for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13;
N.E., 339.

Found: C, 81.18; H, 5.45; N, 4.09; N.E., 338.

By a similar procedure, refluxing was carried out for twenty-four hours with no yield of cinchoninic acid; a seventy-two hour reaction period did not result in increased yield of the acid.

2-Phenyl-3-p-tolylquinoline Picrate

On heating 0.3 g. of 2-phenyl-3-p-tolylcinchoninic acid for five minutes in the Hickman still, melting with immediate decarboxylation took place at a bath temperature of 320-40° under atmospheric pressure. The resulting viscous yellow quinoline was then distilled at a pressure of 1 mm. The oil was removed from the receiver by dissolving it in ether; the ether was evaporated and the residue then dissolved in 1 ml. of alcohol. This solution was added to 1 ml. of a saturated solution of picric acid in alcohol, the mixture was heated to boiling, and allowed to cool slowly. The picrate separated in yellow needles which, after three recrystallizations from alcohol, melted at 208-9°.

Anal. Calcd. for $C_{28}H_{20}N_4O_7$: C, 64.12; H, 3.84; N, 10.68.
Found: C, 63.82; H, 3.79; N, 10.77.

Attempted Preparation of 2-Phenyl-3-p-tolylquinoline Methiodide

The preparation of 2-phenyl-3-p-tolylquinoline was carried out as indicated above, by decarboxylation of the sodium salt of the cinchoninic acid. The yellow oil obtained was dissolved in absolute ether, 1 ml. of methyl iodide was added, the mixture heated slightly, and allowed to stand for three days. Since no product had separated, the solvents were evaporated and the viscous residue cooled. A solid material,

insoluble in ether, was thus obtained. Recrystallization of this substance was attempted from absolute alcohol and also from benzene, but in each case, the solution turned from yellow to violet on standing, and no methiodide could be isolated. The residue left on evaporating the solution could not be crystallized, and was not further investigated.

The Synthesis of

2-Phenyl-3-(2,4-dimethylphenyl)-cinchoninic Acid

In a 200-ml., round-bottomed flask fitted with a reflux condenser were placed 6.7 g. (0.03 moles) of 2',4'-dimethyl-desoxybenzoin, 5.2 g. (0.035 moles) of isatin, 16.8 g. (0.10 moles) of 33% aqueous potassium hydroxide, and 30 ml. of alcohol. After refluxing the mixture for forty-eight hours, the alcohol was partially removed by distillation and the residue diluted with water. The unreacted ketone which precipitated was collected; 3.1 g. of recovered material was obtained. Upon acidification of the filtrate with 10% acetic acid, 1.5 g. of crude product was obtained. After purification as before and recrystallization three times from glacial acetic acid, 0.7 g. (12%) of 2-phenyl-3-(2,4-dimethylphenyl)-cinchoninic acid, m.p. 282-3° (dec.), was obtained in white needles.

Anal. Calcd. for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42;
N, 3.96; N.E., 353.

Found: C, 80.65, 80.44; H, 5.49, 5.26;
N, 3.95; N.E., 352.

2-Phenyl-3-(2,4-dimethylphenyl)quinoline Picrate

Decarboxylation of 2-phenyl-3-(2,4-dimethylphenyl)-cinchoninic acid was accomplished by heating 0.3 g. of the acid in the Hickman still for five minutes at atmospheric pressure. As with the preceding acid, melting with immediate decarboxylation took place at a bath temperature of 320-40°.

The resulting quinoline was distilled under a pressure of 1 mm. This oil was removed from the receiver through solution in ether; the solvent was evaporated and the residue dissolved in 1 ml. of alcohol. This solution was added to 1 ml. of a saturated alcoholic solution of picric acid, the mixture heated to boiling, and allowed to cool slowly. The picrate separated in yellow needles; after three recrystallizations from alcohol, it melted at 203-4°.

Anal. Calcd. for $C_{29}H_{23}N_4O_7$: C, 64.68; H, 4.12;
N, 10.41.

Found: C, 64.37; H, 3.89; N, 10.34.

Attempted Preparation of
2-Phenyl-3-(2,4-dimethylphenyl)quinoline Methiodide

The preparation of 2-phenyl-3-(2,4-dimethylphenyl)-quinoline was carried out as indicated in the preceding section, and the crude methiodide was prepared by the same procedure as that used for the preparation of 2-phenyl-3-p-tolylquinoline methiodide. All attempts to recrystallize the material failed, a violet solution being obtained in each attempt. The residue left on evaporation of the solution was not further investigated.

Attempted Synthesis of
2-Phenyl-3-mesitylcinchoninic Acid

A mixture of 2.38 g. (0.01 moles) of 2',4',6'-trimethyldesoxybenzoin, 1.76 g. (0.012 moles) of isatin, 3.36 g. (0.03 moles) of 33% aqueous potassium hydroxide, and 20 ml. of alcohol was refluxed for forty-eight hours, removed, and allowed to cool. The precipitated ketone was collected and recrystallized from alcohol; 2.2 g. (92%) was recovered. No cinchoninic acid was obtained by acidification of the filtrate from the reaction mixture with 10% acetic acid.

By a like procedure, refluxing was maintained for ninety-six hours; no cinchoninic acid was formed, and the ketone was recovered in 90% yield.

Similarly, a mixture of 2.38 g. (0.01 moles) of the trimethyldesoxybenzoin, 1.76 g. (0.012 moles) of isatin, and 20.5 g. (0.03 moles) of 10% alcoholic sodium ethoxide was refluxed for forty-eight hours. Upon cooling, the unreacted ketone precipitated and was collected; after one recrystallization from alcohol, 2.2 g. (92%) was recovered. No cinchoninic acid resulted from acidification of the filtrate. Refluxing for ninety-six hours did not alter these results.

A third attempt involved the use of sodium amide as the basic condensing agent. This compound was prepared according to the method of Vaughn, Vogt, and Nieuwland¹⁵ from sodium and liquid ammonia. In a two-liter, round-bottomed flask fitted with a mechanical stirrer and packed in finely crushed dry ice contained in a Dewar flask, were placed 0.3 g. of finely powdered ferric nitrate, 500 ml. of liquid ammonia, and 1 g. of sodium. To this stirred mixture 25 g. of sodium in small pieces was added gradually; in twenty minutes the initial blue color was replaced with gray, indicating the end of the reaction. After evaporation of the excess ammonia, the sodium amide was obtained as a light gray powder; it was not exposed to air, but kept under anhydrous toluene.

A mixture of 2.38 g. (0.01 moles) of 2',4',6'-trimethyldesoxybenzoin, 1.76 g. (0.012 moles) of isatin, 1.2 g.

¹⁵Vaughn, Vogt, and Nieuwland, *J. Am. Chem. Soc.* **56**, 2120 (1934)

(0.03 moles) of sodium amide, and 20 ml. of anhydrous toluene was refluxed for five hours, and allowed to cool. The mixture was filtered, and the filtrate evaporated to dryness. After washing the residue with water to remove the isatin, 2.2 g. of crude ketone remained; after one recrystallization from alcohol, 2.1 g. (90%) of unreacted ketone was recovered. Upon decomposition with cold water of the black residue from filtration of the reaction mixture ammonia was evolved and no organic product resulted. In a similar procedure, refluxing was continued for ten hours, with the same results; 90% recovery of the ketone and no cinchoninic acid isolated.

Lastly, a mixture of 2.38 g. (0.01 moles) of the trimethyldesoxybenzoin, 1.76 g. (0.012 moles) of isatin, 3.36 g. (0.03 moles) of 33% aqueous potassium hydroxide, and 25 ml. of alcohol was placed in a steel bomb. The reaction mixture was kept at 200° under a pressure of 500 pounds for twenty-four hours. On cooling, the ketone precipitated; after recrystallization from alcohol, 2.1 g. (90%) was recovered. No cinchoninic acid nor any cleavage products could be found.

The Synthesis and Attempted Condensations of Potassium Isatate

In a 600-ml. beaker, cooled in an ice-salt bath, were placed 147.2 g. (1.0 moles) of isatin and 180 g. (1.08 moles) of 33% aqueous potassium hydroxide. Reaction took place

immediately, as evidenced by the heat evolved and dark color produced. After 80 ml. of water were removed by distillation, the mixture solidified into a mass of brown crystals. These were collected and washed with alcohol. The combined washings and filtrate were concentrated twice by distillation, the precipitated salt being removed after each concentration. After repeated washing with alcohol, 119 g. (59%) of cream-colored crystals of potassium isatate were obtained. Attempts at recrystallization failed, as the salt hydrolyzed appreciably in the presence of small amounts of water and was very insoluble in organic solvents.

The same procedure was followed in all of the attempted condensations; in a 100-ml., round-bottomed flask were placed 6.09 g. (0.03 moles) of potassium isatate, 3.60 g. (0.03 moles) of acetophenone, 6 drops of catalyst, 50 ml. of alcohol, and 5 ml. of water. In one case no catalyst was used, and in the others, these four were employed: piperidine, diethylamine, and aqueous sodium hydroxide, 5% and 10%.

The reaction mixture was allowed to stand for twenty-four hours, and then divided in half. The alcohol was removed from one half by distillation, and the residue extracted with ether to remove the unreacted ketone. The aqueous portion was then acidified with 5% acetic acid. The other half was refluxed for four hours and treated in the same manner.

Without a catalyst, and also with piperidine and diethylamine, 90 to 95% of the acetophenone was recovered from the ethereal extract. No product other than isatin resulted from acidification of the aqueous portion. With 5% and 10% aqueous sodium hydroxide, 70% of the acetophenone was recovered, and a yellow material precipitated from the acidified solution. This product was purified by dissolving it in 5% aqueous sodium hydroxide, decolorizing with charcoal, and acidifying with 5% hydrochloric acid. The resulting white powder, m.p. 177-8° (dec.) could not be recrystallized, due to its instability.

The solubility of the compound in 5% aqueous sodium bicarbonate indicated that it was a carboxylic acid; a neutral equivalent of 379 was found. Both concentrated hydrochloric acid and 33% aqueous potassium hydroxide decomposed the substance, with the formation of isatin. The action of the former was very rapid, while that of the base was much slower.

On standing, or heating, the material became yellow with a noticeable odor of acetophenone. This yellow decomposition product was isolated by trituration of the substance with water and evaporation of the aqueous solution. A small amount of red material was obtained, which, after recrystallization from alcohol, melted at 200°. A mixed melting point with a sample of isatin showed no depression.

The Synthesis of Isatic Acid

Following the method of Erdmann,¹⁶ a solution of 8.0 g. (0.036 moles) of lead oxide in 20% acetic acid was slowly added, with stirring, to a solution of 12.2 g. (0.06 moles) of potassium isatate in 250 ml. of water. The yellow precipitate of lead isatate was collected and washed with water to remove the acetic acid. The moist salt was then suspended in 300 ml. of water and hydrogen sulfide was passed into the mixture until the precipitation of lead sulfide ceased. The yellow-green solution resulting from removal of the sulfide slowly deposited small colorless crystals of isatic acid on cooling. These were collected, and the water removed from the filtrate by vacuum sublimation of ice from the frozen solution. The total amount of isatic acid obtained was 3.4 g. (34%), m.p. indeterminate, decomposition beginning at about 95°, with complete melting at 200°.

Anal. Calcd. for $C_8H_7NO_3$; C, 58.18; H, 4.27; N, 8.43;
N.E., 165.

Found: C, 55.53; H, 4.60; N, 8.80; N.E., 165.

There are indications that the data on elementary analysis are not reliable.

¹⁶Erdmann, J. prakt. chem. (1), 34, 13 (1841); cf. Chem. Zentr. 1841, 209.

Attempted Esterification of Isatic Acid

The formation of methyl isatate was attempted using dimethyl sulfate in alkaline solution, and also by use of silver isatate and methyl iodide. Both of these methods were carried out by standard procedures, and both resulted in the formation of a small amount of fine, red needles, which, after recrystallization from alcohol, melted from 133-4°. This product was identified as N-methylisatin by mixed melting point determination with a sample of the isatin prepared by the method of Heller¹⁷ from silver isatate and methyl iodide.

In a third attempt, diazomethane was prepared according to the method of Arndt¹⁸ by adding 4.5 g. (0.04 moles) of methylnitrosourea to a mixture of 10 ml. of 50% aqueous potassium hydroxide and 25 ml. of ether, cooled to 5°. The ethereal layer was decanted and dried for one hour over pellets of potassium hydroxide. This solution was added slowly to a suspension of 3.2 g. of isatic acid in 25 ml. of absolute ether. An immediate evolution of gas took place and a white material precipitated. Upon filtration, 3.4 g. of the substance was obtained. This material was quite inert to the action of bases and acids and was insoluble in water and in alcohol. It possessed a nauseating odor and was evidently not the desired ester.

¹⁷Heller, Ber. 40, 1299 (1907)

¹⁸Arndt, "Organic Syntheses," Coll. Vol. II, 166 (1947)

CHAPTER IV

DISCUSSION OF RESULTS

The preparation of 2',4'-dimethyldesoxybenzoin by the addition of 2,4-dimethylphenylacetonitrile to phenylmagnesium-bromide resulted in yields of 20.5-25% of pure product. The preponderance of tars formed contributed to the low yield obtained. The previous synthesis of this ketone involved the reaction between 2,4-dimethylphenylacetyl chloride and benzene in the presence of aluminum chloride.¹ However, as no yield was given, a comparison of the two methods cannot satisfactorily be made.

Tar formation was also encountered by Bary² in the preparation of desoxybenzoin by an analogous procedure. A yield of 10% was obtained and extensive polymerization of the phenylacetonitrile occurred. It is likely then, that a similar reaction took place in the preparation of 2',4'-dimethyldesoxybenzoin.

The yield of 37% of the cinchoninic acid obtained from condensation of 4'-methyldesoxybenzoin is somewhat lower than

¹Harispe, Ann. chim. 6, 247 (1936)

²Bary, Bull. soc. chim. Belg. 31, 402 (1923)

the yield of 62% reported by Buu-Hoi and Cagniant³ from the isomeric 4-methyldesoxybenzoin. Apparently the divergence is not due to a steric factor; it could perhaps result from electronic effects, about which no investigations have been made.

Buu-Hoi and Cagniant³ obtained a low yield of cinchoninic acid from 2,4-dimethyldesoxybenzoin, although the value was not given; the similarly low yield of 12% of the acid from 2',4'-dimethyldesoxybenzoin indicates that one ortho methyl group in either ring inhibits the condensation markedly. The carbonyl group and the methylene unit of the ketone are evidently affected sterically in about the same degree in this case.

The failure of 2',4',6'-trimethyldesoxybenzoin to undergo a Pfitzinger condensation shows the excessive hindrance presented by two ortho methyl groups. The hindered nature of the methylene group is also demonstrated by the unreactivity of the ketone toward sodium amide and strong base under pressure and heat. Both of these reagents would be expected to cause cleavage of the ketone. Buu-Hoi and Cagniant³ observed that 2,4,6-trimethyldesoxybenzoin did not react with isatin; this again indicates that the methyl groups exert similar steric effects upon both the carbonyl and methylene units of the ketone.

³Buu-Hoi and Cagniant, Bull. soc. chim. 1946, 123

Although it has been stated⁴ that n-caprophenone does not enter into the Pfitzinger condensation within forty-eight hours, it was found to do so in 30% yield.

The results obtained in this work show clearly the expected increase in steric inhibition presented by an increasing number of methyl groups ortho to the methylene unit of the ketone involved in the Pfitzinger reaction. In addition, it has been shown that the n-butyl group does not exert unusual hindrance upon the methylene group.

⁴cf. ref. 3

CHAPTER V

SUMMARY

Contrary to experience elsewhere, 2-phenyl-3-n-butylcinchoninic acid has been obtained from *n*-caprophenone through a Pfitzinger condensation. Similarly, the corresponding cinchoninic acids have been obtained from 4'-methyldesoxybenzoin and 2',4'-dimethyldesoxybenzoin. A condensation could not be effected with 2',4',6'-trimethyldesoxybenzoin.

The results obtained indicate that neither the n-butyl nor the *p*-tolyl group exerts a large amount of hindrance in the reaction. However, one ortho methyl group hinders the reaction greatly, and two such groups prevent it completely.

The synthesis, in a new way, of 2',4'-dimethyldesoxybenzoin, a previously known ketone, has been accomplished through reaction of phenylmagnesiumbromide with 2,4-dimethylphenylacetonitrile.

In the course of this work, new compounds prepared and characterized were 2-phenyl-3-n-butylcinchoninic acid, 2-phenyl-3-n-butylquinoline methiodide, 2-phenyl-3-*p*-tolylcinchoninic acid, 2-phenyl-3-*p*-tolylquinoline picrate, 2-phenyl-3-(2,4-dimethylphenyl)cinchoninic acid, and 2-phenyl-3-(2,4-dimethylphenyl)quinoline picrate.

BIBLIOGRAPHY

BIBLIOGRAPHY

- Adams, R., and Thal, A. F., "Organic Syntheses", John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. I, 2nd ed., 1947, p. 436.
- Arndt, F., "Organic Syntheses", John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. II, 2nd ed., 1947, p. 166.
- Bary, L., "L'Action des Composes Organomagnesiennes sur les Nitriles. L'Action de la Phenylmagnesienne Bromure", Bull. soc. chim. Belg. 31, 402 (1923).
- Borsche, W., "Uber die Kondensation einiger Ketonsauren der Cholsaure-Gruppe mit Aromatischen Aldehyden und mit Isatin", Ber. 57, 1373 (1924).
- Borsche, W., and Jacobs, W., "Untersuchungen uber Isatin und Verwandte Verbindungen", Ber. 47, 354 (1914).
- Borsche, W., and Rottsieper, H., "Uber Tricyclische Chinoline", Ann. 377, 70 (1910).
- Borsche, W., and Wagner-Roemmich, M., "Ringschlussversuche mit 3-Phenyl- und 3-Benzyl-7,8-benzocinchoninsauren", Ann. 544, 287 (1940).
- von Braun, J., "Uber das Tetrophan und seine Derivate", Ann. 451, 1 (1927).
- von Braun, J., and Nelles, J., "Bequeme Synthese von Durol und Pentamethyl-Benzol aus Roh-Xylol", Ber. 67, 1094 (1934).
- Buu-Hoi, N. P., "The Effect of Steric Hindrance on the Course of Pfitzinger Reactions", J. Chem. Soc. 1946, 795.
- Buu-Hoi, N. P., and Cagniant, P., "L'Empechement Sterique en la Reaction de Pfitzinger. I. L'Action de l'Isatine sur les Cetones Arylalkyles", Bull. soc. chim. 1946, 123.
- Buu-Hoi, N. P., and Royer, R., "L'Empechement Sterique en la Reaction de Pfitzinger. III. La Condensation de l'Isatine avec les Cetones Benzylaryles", Bull. soc. chim. 1946, 374.
- Erdmann, O., "Weitere Untersuchungen uber den Indig", J. prakt. chem. (1), 34, 13 (1841); Chem. Zentr. 1841, 709.

- Gartenmeister, R., "Über die Siedepunkte und Spezifischen Volumina Normaler Fettsaureester", Ann. 233, 279 (1886).
- Harispe, J., "Contribution a L'Etude de L'Acide Dimethyl-2,4-Phenylacetique et de ses Derives", Ann. chim. 6, 247 (1936).
- Heller, G., "Über die Farbenerscheinung der alkalischen Isatinlösung", Ber. 40, 1299 (1907).
- Hickman, K., and Sanford, C., "The Purification, Properties, and Uses of Certain High-Boiling Organic Liquids", J. Phys. Chem. 34, 637 (1930).
- Klages, A., and Lickroth, G., "Das Verhalten des Ketonrestes und der Carboxylgruppe", Ber. 32, 1564 (1899).
- Lindwall, H., and MacLennan, J., "A Condensation of Acetophenone with Isatin by the Knoevenagel Method", J. Am. Chem. Soc. 54, 4739 (1932).
- Pfizzinger, W., "Chinolinederivate aus Isatinsäure", J. prakt. chem. (2), 33, 100 (1886).
- Rupe, H., and Wiederkehr, F., "Die Constitution des Curcumons aus dem Curcuma-ol", Helv. Chim. Acta 7, 604 (1924).
- Strassman, H., "Vergleichung Zweier Isomerer Methyldeoxybenzoine", Ber. 22, 1230 (1889).
- Tiffeneau, M., and Levy, J., "La Formation des Acylophenones sans Rearrangement", Compt. rend. 183, 969 (1926).
- Vaughn, T. H., Vogt, R., and Nieuwland, J., "A Rapid Catalytic Preparation of Sodamide in Liquid Ammonia and Some of its Uses in the Preparation of Acetylenic Materials", J. Am. Chem. Soc. 56, 2120 (1934).
- Weinstock, H. H., and Fuson, R. C., "Mesityl Phenyl Diketone", J. Am. Chem. Soc. 58, 1234 (1936).