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STUDIES ON THE PREPARATION OF
TETRASUBSTITUTED HYDRAZONES

A Thesis
Presented to
The Faculty of the School of Graduate Studies
Western Michigan University

In partial fulfillment
of the requirement for
the degree of Master of Arts
in Chemistry

by
William Kao
Kalamazoo, Michigan
August 1966

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INTRODUCTION

In a recent study of the ultraviolet spectra of substituted hydrazones, it was concluded that a steric effect existed in tetrasubstituted hydrazones that significantly hindered complete rotation about the nitrogen-nitrogen bond. Weber¹⁸ noted that di- and tri-substituted hydrazones exhibited similar spectra with three strong absorption bands at approximately 235, 300, and 340 mμ. In acid solutions, the spectra of these compounds showed a marked decrease in intensity of the long wavelength band. It has been postulated that this change was a consequence of the protonation of the non-bonding electron-pair on the amino nitrogen atom, and thus correlated the long wavelength band to a promotion of one of these electrons to a higher energy level.

Weber also noted that the spectra of tetrasubstituted hydrazones was similar to the spectra of the di- and tri-substituted hydrazones in acid media. Specifically, three absorption bands were observed with the long wavelength being the lowest in intensity. This similarity suggested that in these compounds, the non-bonding electron-pair on the amino nitrogen atom was likewise unavailable for the excitation to develop the long wavelength band.

The long wavelength band excitation was related to orbital overlap between the p atomic orbital of the

imino nitrogen atom and the p or sp^3 atomic orbital (depending upon the type of hybridization) of the amino nitrogen atom.

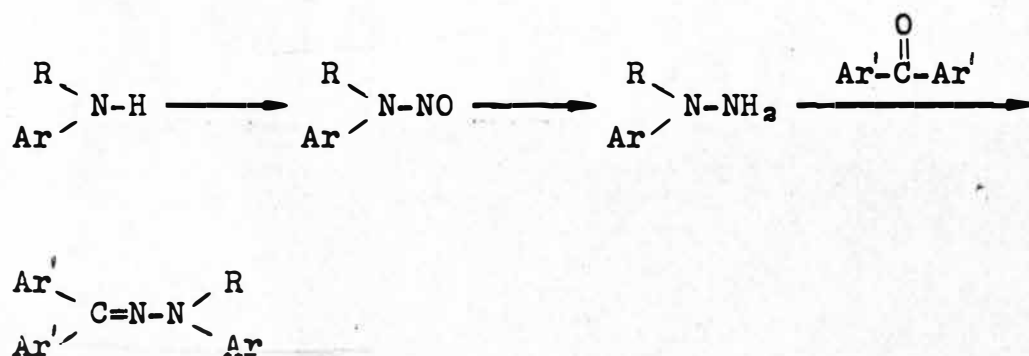
Fischer-Hirshfelder-Taylor molecular models of di- and trisubstituted hydrazones having at least one hydrogen atom on the amino nitrogen atom or the carbon atom (provided the hydrogen is syn to the nitrogen atom) suggested the possibility of rotation in excess of 180° about the nitrogen-nitrogen bond. However, with the tetrasubstituted hydrazones (or trisubstituted hydrazones with a hydrogen atom anti to the nitrogen atom), rotation less than 180° can only occur because of the steric interference between neighboring groups on the carbon and amino nitrogen atoms. The resulting conformations would consist of two dissymmetric collections. If the rotational energy barrier was sufficient, two enantiomeric configurational isomers might be isolated.

It has been the purpose of this research to prepare such a tetrasubstituted hydrazone and to attempt its resolution into enantiomers.

The simplest approach to resolution appeared to be column chromatography on an optically active substrate. However, after an early unsuccessful exploratory experiment applying this method, effort was concentrated on the preparation of a tetrasubstituted hydrazone with a suitable functional group to permit the formation of diastereoisomeric salts with an optically active acid or base.

The general preparation of a hydrazone by the condensation of a disubstituted hydrazine with a suitable ketone was anticipated to be useful. The disubstituted hydrazine could be prepared by the reduction of the corresponding nitroso compound which, in turn, could be synthesized from the related amine.

The following scheme illustrates the general synthetic route planned:



EXPERIMENTAL

In this experimental section all melting points are uncorrected and are expressed as degrees centigrades.

The infrared spectra were taken on a Perkin-Elmer Model 21 recording spectrophotometer and all NMR spectra were obtained from a Varian A-60 spectrometer.

The elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

Preparation of Benzophenone Methylphenylhydrazone.—

Successively, 30.5 g. (0.25 mole) of methylphenylhydrazine and 15 ml. of glacial acetic acid was added to a solution of 45.5 g. (0.25 mole) of benzophenone dissolved in 150 ml. of absolute ethanol. After the reaction mixture was refluxed for 2 hours and cooled, yellow crystals formed. This mixture was filtered and the solid recrystallized from 95% ethanol to give 58.3 g. (81%) of the hydrazone, m.p. 79-80° (lit.³ m.p. 81-82°).

Attempted Resolution of Benzophenone Methylphenylhydrazone with Dibenzoyltartaric Acid.— a. A 2.5×40.0 cm. chromatographic column was prepared by the introduction of a slurry of (-)-dibenzoyltartaric acid⁴ and cyclohexane into the chromatographic tube. After removing the excess liquid, a solution containing 2.0 g. of benzophenone methylphenyl-

hydrazone dissolved in 30 ml. of cyclohexane was poured onto the column. Additional cyclohexane was added to the column as eluent. Thirteen 25 ml. portions of eluent were collected. The solvent was removed by vacuum evaporation and the resulting solid was examined. The hydrazone was concentrated in fractions 4 through 11. The melting point of the hydrazone in all these fractions was 71-74°.

b. A second 2.5 x 40.0 cm. chromatographic column was prepared as described above using a slurry of (+)-tartaric acid in cyclohexane. Again, a 2.0 g. sample of benzophenone methylphenylhydrazone dissolved in 30 ml. of cyclohexane was added to the column and developed with additional cyclohexane. The eluent was collected in fifteen 25 ml. portions. After removing the cyclohexane by vacuum evaporation, the hydrazone was found in fractions 2 through 15. The melting point of the solid from all fractions was 75-78°. Saturated solutions of fractions 3, 4, 8, and 14 failed to exhibit optical activity ($l=1$ dm.).

Preparation of Methyl p-Methylaminobenzoate.— A solution composed of 45.3 g. (0.3 mole) of p-methylaminobenzoic acid (E.K.C. # 8122) in 150 ml. (3.6 moles) of methanol was stirred at reflux temperature. Hydrogen chloride was bubbled into the solution for a period of 2 hours. The resulting light-brown solution was cooled in an ice-water bath and made alkaline by the addition of 350 ml. of a 10% sodium

hydroxide solution. The precipitate that formed was collected and washed with 400 ml. of water. After drying, the crude product was recrystallized from petroleum ether (60-110°) to give 41.8 g. (85%) of white crystalline ester, m.p. 94-95° (lit.¹⁰ m.p. 95.5°).

Preparation of Methyl p-Methylnitrosaminobenzoate.— A solution of 38.0 g. (0.23 mole) of methyl p-methylamino-benzoate dissolved in 130 ml. of glacial acetic acid was added dropwise and with stirring to a solution containing 18.0 g. (0.26 g.f.wt.) of sodium nitrite dissolved in 45 ml. of water. A yellow slurry developed during the half-hour addition time. The nitroso compound was collected by filtration and washed with three 400 ml. portions of water. After drying, the product weighed 42.7 g. (96%), m.p. 113-115° (lit.¹⁰ m.p. 115.5°).

Preparation of N-Methyl-p-carbomethoxyphenylhydrazine.—

This reaction was carried out by the slow addition of 13.1 g. (0.2 g.at.wt.) of zinc dust to 9.7 g. (0.05 mole) of methyl p-methylnitrosaminobenzoate suspended in a mixture of 46 ml. of glacial acetic acid and 46 ml. of water. The reaction mixture was stirred and the temperature of the reaction was maintained at 25°. The zinc dust addition was completed in one hour and the stirring was continued for 2 hours. The reaction mixture was transferred to a beaker and mixed

with 40 ml. of a cold 50% sodium hydroxide solution. Several portions of benzene were used to extract the reduction product. The benzene extract was concentrated by vacuum evaporation to leave an oil which solidified on standing at room temperature. Two recrystallizations of the solid from petroleum ether (60-110°) gave 0.5 g. (5.1%) of the white crystalline product, m.p. 79-81°.

The nmr spectrum of the hydrazine showed proton resonances at 3.17, 3.58 (broad signal), 3.77, and doublets centered at 6.75 and 7.73 ppm. downfield from TMS. Integration of these peaks gave a proton ratio of 3 : 5 (composite of the 3.58 and 3.77 ppm. signals) : 2 : 2 respectively, corresponding to three protons of the carboxymethyl group, five protons of the N-methyl and N-amino groups, and four protons of the phenyl group. Removal of the 3.58 ppm. signal by deuterium exchange confirmed the assignment of this signal to the protons of the N-amino group.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.11; H, 6.70; N, 15.34.

Preparation of Acetone N-Methyl-p-carboxyphenylhydrazone.—

A 23.4 g. (0.12 mole) portion of methyl p-methylnitrosamino-benzoate was mixed with a solution containing 110 ml. (1.9 moles) of glacial acetic acid, 110 ml. of methanol, and 110 ml. of water. Reduction was effected by the slow

addition of 31.5 g. (0.48 g.at.wt.) of zinc dust. The reaction mixture was stirred overnight with the temperature maintained at 10-15°. The reaction mixture was filtered to remove the excess zinc and a solution of 210 g. of sodium hydroxide dissolved in one liter of water was slowly added to the filtrate. The temperature was maintained at 10-15° during this neutralization process. The alkaline solution was extracted with three 150 ml. portions of benzene. The benzene extract was dried over anhydrous sodium sulfate and the benzene was evaporated under reduced pressure. Only a trace quantity of the hydrazine product was obtained. The alkaline solution gave a positive test for hydrazine as determined by the reduction of silver ion in a 5% silver nitrate solution. This suggested that much of the reduced product was not extracted, possibly as a consequence of hydrolysis of the ester group to the free carboxylic acid. Accordingly, this alkaline solution was used as a source of the hydrazine in the preparation of acetone N-methyl-p-carboxyphenylhydrazone described below.

Seventy grams (1.2 moles) of acetone was added to the alkaline solution and the mixture was acidified with 346 g. (5.75 moles) of glacial acetic acid. The temperature of the solution was maintained at 15-20°. The acid solution was refluxed for 5 hours. During this time, a yellow coloration developed. The reaction mixture was extracted with five 250 ml. portions of benzene. The yellow benzene

solution was dried over anhydrous sodium sulfate and concentrated by vacuum evaporation. The residue was dissolved in hot benzene and reprecipitated with the addition of pentane to give the yellow crystalline hydrazone. The product weighed 3.7 g. (15% based on 0.12 mole of the nitroso compound), m.p. 188-190°.

A nmr spectrum of the hydrazone showed proton resonances at 1.94, 2.14, 3.06, 6.66(d), 7.92(d), and 11.26 ppm. downfield from TMS. By integration, the area ratio of these peaks was found to be 6(composite of the 1.94 and 2.14 ppm. signals) : 3 : 2 : 2 : 1 respectively. Downfield from TMS, these signals may be assigned to the six protons of the two C-methyl groups, the three N-methyl protons, the four protons of the phenyl group, and the carboxylic acid proton.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 64.25; H, 6.90; N, 13.65.

Attempted Preparation of Benzophenone N-Methyl-p-carboxy-phenylhydrazone.— The reaction mixture consisting of 3.1 g. (0.015 mole) of acetone N-methyl-p-carboxyphenylhydrazone, 2.8 g. (0.015 mole) of benzophenone, and 0.2 ml. of glacial acetic acid dissolved in 100 ml. of dioxane was prepared and refluxed for 2 hours. About one-half of the solvent was removed by distillation and the distillate was tested for acetone using 2,4-dinitrophenylhydrazine

reagent. The test was negative. Accordingly, 50 ml. of dioxane was returned to the reaction mixture and refluxed for 10 hours. The above procedure for detecting acetone was repeated with negative results. At the end of reflux for an additional day, the test remained negative. It was concluded that little if any ketone exchange occurred to form benzophenone N-methyl-p-carboxyphenylhydrazone.

Preparation of p-Methylnitrosaminobenzoic Acid.— Following the procedure described by Houben and Schottmiller⁸, a solution consisting of 39.6 g. (0.57 g.f.wt.) of sodium nitrite dissolved in 100 ml. of water was added to a stirred mixture containing 78.5 g. (0.52 mole) of p-methylaminobenzoic acid in 290 ml. of glacial acetic acid. The yellow slurry that developed was washed with water until the wash liquid was clear and neutral to litmus. The crude product was dissolved in hot tetrahydrofuran and reprecipitated with pentane to give 85 g. (91%) of yellow crystals, m.p. 213-215° (dec.). Literature⁸ m.p. 215-217° (dec.).

Attempted Reduction of p-Methylnitrosaminobenzoic Acid.— The following experiments were attempts in the preparation of acetone N-methyl-p-carboxyphenylhydrazone from the hydrazine obtained from the reduction of p-methylnitrosaminobenzoic acid. These procedures differed only in the reagents used for the reductions.

a.— Zinc dust and glacial acetic acid. Nine grams (0.05 mole) of p-methylnitrosaminobenzoic acid was dissolved in 100 ml. of glacial acetic acid and 9.8 g. (0.15 g.at.wt.) of zinc dust was slowly added. After the reaction mixture was stirred for 2 hours, the unreacted zinc was filtered from the solution and 40 ml. of acetone was added to the filtrate. The reaction mixture was refluxed for 2 hours, cooled, and extracted with several portions of benzene. The benzene solution was dried over anhydrous sodium sulfate and the benzene was concentrated by vacuum evaporation. The residue was dissolved in hot p-dioxane and reprecipitated with pentane to give 5.0 g. (67%) of a powder, m.p. 160-162°. Literature¹¹ value for p-methylaminobenzoic acid: 163°.

b.— Zinc dust and dilute acetic acid. The procedure and reactant quantities as described above were repeated with the exception that a 1 : 1 glacial acetic acid - water solution was used instead of the glacial acetic acid alone. This attempt produced only 4.9 g. (65%) of p-methylaminobenzoic acid, m.p. 159-162°.

c.— Zinc dust and dilute hydrochloric acid. A mixture of 4.5 g. (0.025 mole) of p-methylnitrosaminobenzoic acid, 13 ml. (0.125 mole) of concentrated hydrochloric acid and 50 ml. of water was prepared. In small portions, 4.8 g. (0.075 g.at.wt.) of zinc dust was added to the acid mixture and the mixture stirred for one hour. The

unreacted zinc was separated and 7.3 ml. (0.1 mole) of acetone was added. Attempted isolation of the hydrazone following the procedure outlined above gave 2.0 g. (53%) of p-methylaminobenzoic acid, m.p. 162°.

d.— Sodium and ethanol. In small portions, 11.5 g. (0.5 g.at.wt.) of sodium metal was slowly added to a cold stirred solution of 4.5 g. (0.025 mole) of p-methylnitrosaminobenzoic acid dissolved in 150 ml. of absolute ethanol. The reaction mixture was warmed to room temperature and stirred for 3 hours. A small sample of the reaction mixture was withdrawn and acidified with nitric acid. The addition of a 5% silver nitrate solution failed to indicate the presence of the hydrazine. The reaction mixture was stirred for an additional 10 hours at room temperature. The test for the hydrazine was repeated with a similar negative result.

e.— Hydrogen and platinum oxide. A 9.0 g. (0.05 mole) portion of p-methylnitrosaminobenzoic acid was dissolved in 150 ml. of p-dioxane. Platinum oxide (0.1 g.) was added and the reaction mixture was shaken with hydrogen at 60 psi. An absorption of 8 lbs. of hydrogen was required to complete the reduction. However, after 24 hours, no noticable decrease in the hydrogen pressure was observed. Hydrogenation was continued for three days without further change in the hydrogen pressure.

Attempted Reaction of p-Methylaminobenzoic Acid with Hydroxylamine-O-sulfonic Acid.— Three grams (0.02 mole) of p-methylaminobenzoic acid was dissolved in a solution prepared from 20.0 g. (0.5 g.f.wt.) of sodium hydroxide dissolved in 50 ml. of water and 70 ml. of ethanol. Under reflux condition, a solution of 23.0 g. (0.2 mole) of hydroxylamine-O-sulfonic acid dissolved in 40 ml. of water was slowly added. After completion of the addition, the mixture was stirred for 10 hours at reflux temperature. Following the addition of 40 ml. (0.7 mole) of glacial acetic acid and 40 ml. of acetone, the mixture was further refluxed for 3 hours, cooled, and extracted with five 75 ml. portions of benzene. The benzene solution was dried over anhydrous sodium sulfate and the benzene was evaporated. The residue was dissolved in hot p-dioxane and reprecipitated with pentane to give p-methylamino-benzoic acid, m.p. 160-162°.

Preparation of Ethyl p-Hydrazinobenzoate.— Hydrogen chloride was bubbled into a solution of 30.4 g. (0.2 mole) of p-hydrazinobenzoic acid dissolved in 150 ml. of absolute ethanol over a period of 4 hours. After cooling, the light-brown solid that precipitated was collected and washed with 400 ml. of a cold 10% sodium hydroxide solution. The solid was again collected by filtration and washed with water until free of base. After drying in air,

the crude product was dissolved in hot benzene and reprecipitated by the addition of pentane to yield 24.9 g. (69%) of ethyl p-hydrazinobenzoate, m.p. 115-117° (lit.⁶ m.p. 118°).

Preparation of Ethyl p-(β -Acetylhydrazino)-benzoate.—

The reaction mixture was prepared by dissolving 3.6 g. (0.02 mole) of ethyl p-hydrazinobenzoate in 40 ml. of a 1:1 pyridine - water solution. To this solution was added 2.3 g. (0.02 mole) of acetic anhydride. The reaction mixture was refluxed for one-half hour. The solution was reduced to one-third of its original volume by distillation of the solvent. The product crystallized upon the addition of 100 ml. of water. The ethyl p-(β -acetylhydrazino)-benzoate collected by filtration weighed 3.4 g. (79%), m.p. 150-151° (lit.⁷ m.p. 148-149°).

Attempted Methylation of Ethyl p-(β -Acetylhydrazino)-

benzoate.— The following experiments were attempted in the preparation of ethyl N-methyl-p-(β -acetylhydrazino)-benzoate employing different reagents:

a.— Methyl iodide in ethanol. A solution containing 1.1 g. (0.005 mole) of ethyl p-(β -acetylhydrazino)-benzoate dissolved in 20 ml. of absolute ethanol was heated to reflux temperature and 0.31 ml. (0.005 mole) of methyl iodide dissolved in 5 ml. of absolute ethanol

was added. Reflux was continued for 18 hours. After water was added, the reaction mixture was chilled in an ice bath. Collection of the crystals that formed provided 0.8 g. (73%) of a light-yellow solid, m.p. 148-150°. A mixed melting point with the starting hydrazide was undepressed.

b.— Methyl iodide and sodium hydroxide in ethanol. A solution of 0.24 g. (0.006 g.f.wt.) of sodium hydroxide dissolved in 2 ml. of water and 30 ml. of absolute ethanol was prepared. To this solution, there was added 1.1 g. (0.005 mole) of ethyl p-(β -acetylhydrazino)-benzoate and 0.38 ml. (0.006 mole) of methyl iodide. The reaction mixture was refluxed for 10 hours. The solution was cooled and the solvent was evaporated to leave an oil. This oil was washed with several portions of water. Upon standing, the oil solidified to give 0.6 g. (55%) of the hydrazide, m.p. 145-148°.

c.— Methyl iodide and sodium ethoxide. A reaction mixture was prepared by dissolving 0.15 g. (0.005 g.at.wt.) of sodium in 20 ml. of absolute ethanol followed by the addition of 1.1 g. (0.005 mole) of ethyl p-(β -acetylhydrazino)-benzoate and a solution of 1.1 g. (0.008 mole) of methyl iodide dissolved in 5 ml. of absolute ethanol. The reaction mixture was refluxed for 24 hours. The solvent was removed by evaporation to leave an oil residue. The oil was washed several times with water, dissolved in

hot benzene, and chilled. Crystals formed, which, when collected and dried, melted at 149-150°. The recovery of the starting material was 0.5 g. (45%).

d.— Methyl iodide and lithium aluminum hydride in tetrahydrofuran. A 5.1 g. (0.023 mole) sample of ethyl p-(β -acetylhydrazino)-benzoate was dissolved in 60 ml. of hot anhydrous tetrahydrofuran. A suspension of 0.88 g. (0.023 g.f.wt.) of lithium aluminum hydride in 100 ml. of anhydrous tetrahydrofuran was added to the hydrazide solution. After this mixture was refluxed and stirred for 10 hours, 15 ml. (0.24 mole) of methyl iodide was added. Heating at reflux temperature was continued for 10 hours. After cooling, sufficient ethanol was added to decompose any unchanged lithium aluminum hydride. The mixture was filtered and the filtrate was concentrated by vacuum evaporation to leave an oil. The nmr spectrum of this crude reaction product showed only one signal not present in the spectrum of the starting hydrazide. This proton resonance at 3.33 ppm. downfield from TMS was assignable to a N-methyl group. This oil failed to solidify with prolonged chilling. Attempted purification by vacuum distillation at 1 mm. pressure resulted in decomposition and no distillate below 200°.

Attempted Nitration of Benzophenone Methylphenylhydrazone.—

In an attempt to obtain benzophenone methyl-p-nitrophenyl-

hydrazone, a systematic study of the nitration of benzophenone methylphenylhydrazone was made. In these nitration reactions, 1 : 1.25 and 1 : 2.25 mole ratios of hydrazone to nitric acid were used. Nitric acid concentrations of 20%, 40%, and 70% were employed with each reaction ratio. Glacial acetic acid was used as the solvent. The reaction with each combination of reactants was examined at the following temperatures: 40°, 50°, 60°, and 70°. The following procedure is representative and describes one combination of the reaction conditions:

A solution composed of 0.57 g. (0.002 mole) of benzophenone methylphenylhydrazone dissolved in 5 ml. of glacial acetic acid was maintained at a temperature of 40°. To this mixture was added 0.29 ml. (0.0045 mole) of 70% nitric acid, causing the temperature of the reaction mixture to rise to 44°. The solution was cooled to 40° and maintained at this temperature for 15 minutes. During this time, a brown precipitate formed. This solid was filtered from the solution and washed with water until free of acid. This crude material was dissolved in hot benzene and reprecipitated with pentane, giving 0.1 g. (15%) of orange crystals, m.p. 173-175°.

Repetition of the reaction with variations in reaction conditions as previously outlined gave similar brown reaction product which, after purification, melted at 173-175°.

Hydrolysis of the Nitrated Hydrazone.— One gram (0.003 mole) of the nitrated hydrazone was dissolved in 10 ml. of glacial acetic acid and 5 ml. of water. After 1 ml. of concentrated hydrochloric acid was added, the reaction mixture was refluxed for 3 hours. After cooling, 100 ml. of water was added and the mixture was extracted with three portions of benzene. The benzene solution was washed with water until free of acid, dried over anhydrous sodium sulfate, and concentrated to give an orange oil. The infrared spectrum of this oil showed a strong carbonyl absorption band² at 1656 cm^{-1} and two strong nitro group absorption bands² at 1530 and 1338 cm^{-1}

From this infrared spectrum of the neutral hydrolysis product, it was concluded that nitration occurred on the ketone portion of the hydrazone rather than on the hydrazine portion as desired.

DISCUSSION OF RESULTS

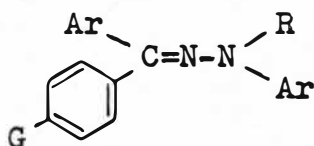
As indicated in the Introduction, there is reason to believe that suitably substituted tetrasubstituted hydrazones are dissymmetric as a consequence of restricted rotation about the nitrogen-nitrogen bond. Resolution and the isolation of an optically active enantiomer would constitute the most effective evidence for this steric effect and dissymmetry.

Of the several methods of effecting resolution of enantiomers, conversion to diastereoisomers is the most common procedure but highly empirical in the selection of optically active resolving agent, crystallization solvent, etc. For this reason, it was believed of value to try resolution by column chromatography with an optically active absorbant. While this technique is also empirical, its occasional success has been striking. Its principal advantage - simplicity - seemed to warrant its consideration.

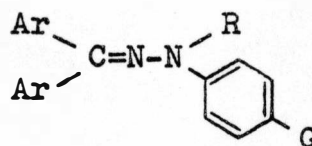
For this purpose, benzophenone methylphenylhydrazone was prepared and resolution chromatography was attempted over (-)-dibenzoyltartaric acid and (+)-tartaric acid as described in the Experimental Section. No optical activity was observed. The melting point of the hydrazone was unchanged. Most generally, the melting point of an enantiomer or a mixture rich in one enantiomer is markedly

different from the melting point of the racemic mixture.¹⁷ Although the reason for this failure is uncertain, it may be a consequence of either improper choice of optically active absorbant or the dissymmetric hydrazone is optically unstable at the experimental temperature, i.e. racemization is rapid.

Following this chromatographic resolution attempt, attention was turned to tetrasubstituted hydrazones carrying a suitable functional group to permit the formation of diastereoisomers. The following types were considered, where G represents the suitable functional group:



Type A

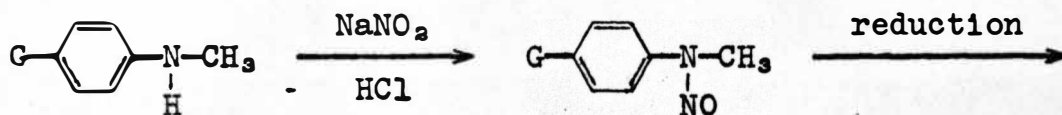


Type B

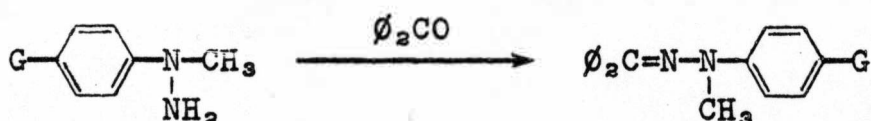
The formation of hydrazones of type A may lead to syn and anti geometric isomers, each of which is a potentially resolvable enantiomeric pair. Geometric isomerism is not possible with type B (Ar = Ar). Hence, due to the greater simplicity, effort was turned to the preparation of a hydrazone of type B.

As indicated in the Experimental Section, numerous attempts have been made to prepare a compound of type B. The first group of attempts were based upon the following

planned sequence of reactions:



G = COOH, COOCH₃



The nitrosation of p-methylaminobenzoic acid and methyl p-methylaminobenzoate proceeded without difficulty to produce products having properties corresponding to reported values for the expected nitroso compounds. The reduction step proved to be unexpectedly difficult and was never achieved on a sufficiently satisfactory scale to permit completion of the sequence. Various reduction attempts using zinc and acid (hydrochloric and acetic acids) produced detectable amounts of hydrazine but the principle product was the p-methylaminobenzoic acid derivative. This formation of the secondary amino group presumably is a result of the acid-promoted cleavage of the hydrazine. Precedent for this side reaction has been reported.¹⁴ However, this factor ordinarily has not been severe enough to reduce the yield of hydrazines to a negligible value and useful amounts of substituted hydrazines have been commonly prepared by this route. In one instance,

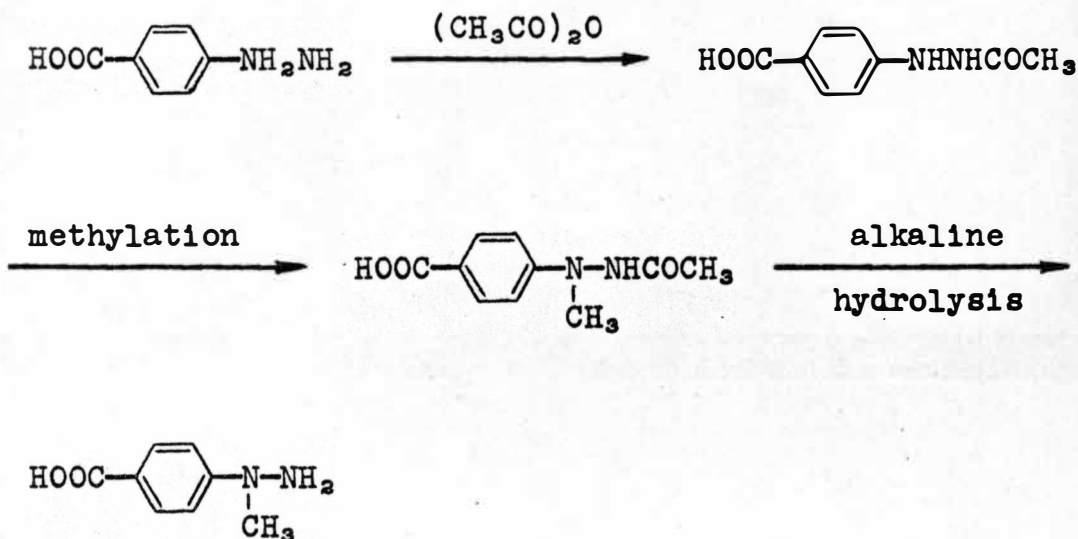
in this study, an isolable amount of acetone methyl p-carboxyphenylhydrazone was obtained and characterized. An attempt to prepare a larger amount of this hydrazone by conducting the reduction of the nitroso compound in a mixture rich in acetone also failed. This modification was an attempt to intercept the hydrazine cleavage reaction by the formation of the hydrazone.

The planned attempt to convert the acetone hydrazone derivative to the benzophenone derivative by acid-catalyzed exchange also was unsuccessful.

The less commonly employed catalytic hydrogenation¹² and sodium-alcohol¹⁸ reduction of the nitroso group failed to produced detectable reduction with the p-methylnitrosaminobenzoic acid.

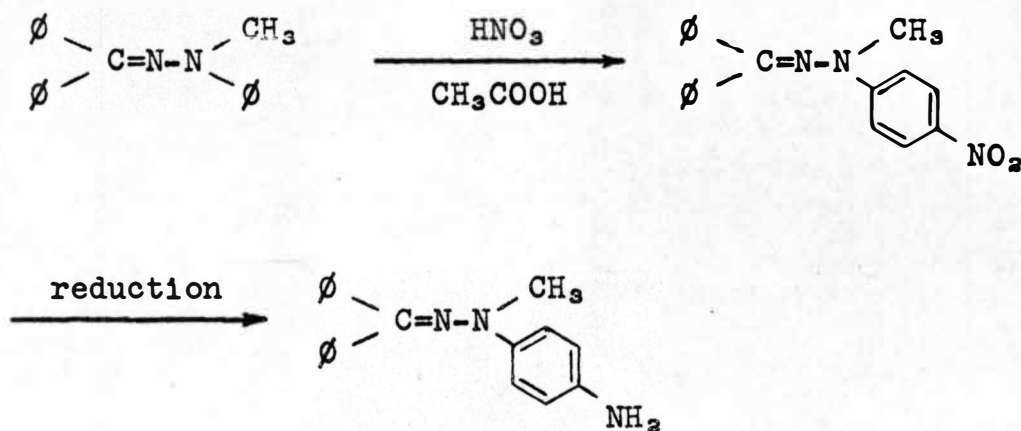
The formation of monosubstituted hydrazines has been accomplished often by the reaction of hydroxylamine-O-sulfonic acid with primary amines.⁵ Even though the reported yields of disubstituted hydrazines are low when secondary amines are employed, the reaction gave no detectable hydrazine when applied to p-methylaminobenzoic acid.

In view of the several failures to obtain the desired disubstituted hydrazine by the reduction of the nitrosamine, the following less frequently used type of sequence¹³ was considered and attempted:



After the preparation of the hydrazide, the usual methods of N-alkylation were used and resulted only in the recovery of unreacted starting material. The only indication of N-methylation developed from the treatment of methyl iodide with the hydrazide salt prepared by reacting the hydrazide with lithium aluminum hydride. In this case, proton resonance spectra of the crude reaction product provided a signal at 3.33 ppm. downfield from TMS and attributable to a N-methyl group. However, no pure product was isolable.

In view of the difficulty in preparing the desired hydrazine via the hydrazide, attention was turned to the preparation of a hydrazone with a p-amino group to serve as the "handle" in the resolution process. It was anticipated that such a hydrazone might readily be prepared in the following manner:

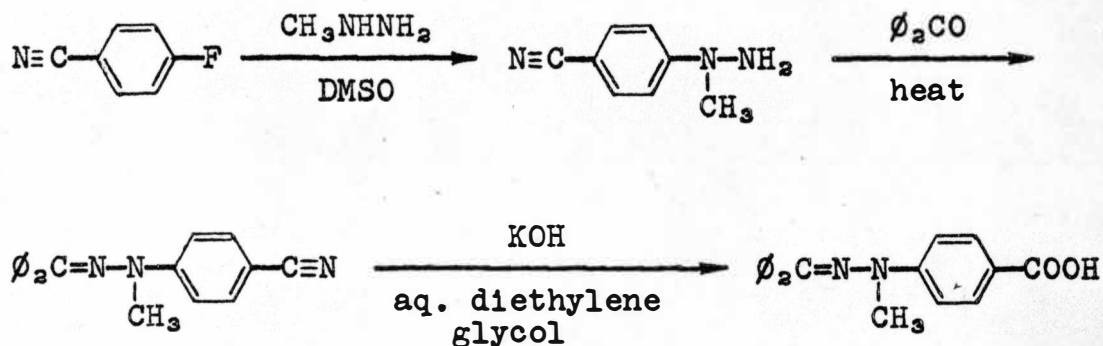


It was recognized that as a consequence of the weak basicity and susceptibility toward oxidation, the p-amino group may be less satisfactory than the carboxylic acid group in the resolution process. It was expected that nitration with nitric acid dissolved in a glacial acetic acid solution would effect substitution of a nitro group on the phenyl ring adjacent to the amino nitrogen atom. The activating effect of an amino group in an electrophilic aromatic substitution reaction is well established whereas the unsaturated group, >C=N- , like >C=O , is likely to be deactivating.

The nitro-substituted derivatives of benzophenone methylphenylhydrazone have not been reported. The product obtained in this nitration reaction was not fully characterized. However, acid-catalyzed hydrolysis yielded a neutral portion which, as indicated by the infrared spectrum, contained the nitro group. It was concluded that substitution occurred on the C-phenyl ring contrary to expectations.

Therefore, this reaction did not yield a useful product for this study.

Since the completion of the above attempts to prepare benzophenone N-methyl-p-carboxyphenylhydrazone, the compound has been obtained⁹ in reasonable yield by the following sequence:



This nucleophilic substitution on p-fluorocyanobenzene using methylhydrazine is an extension of the similar substitution reaction reported, using ammonia¹⁵ and amines.¹

It is anticipated that resolution of this compound or a similar derivative will be carried out.

SUMMARY

The potential dissymmetry of tetrasubstituted hydrazones has been considered. Two approaches to demonstrate this dissymmetry by attempted resolution of tetrasubstituted hydrazones have been made. Resolution of benzophenone methylphenylhydrazone chromatographically over (-)-dibenzoyl-tartaric acid and (+)-tartaric acid have been unsuccessful.

The failure to obtain a benzophenone methylphenylhydrazone derivative suitable for conversion to diastereoisomers prevented examination of this approach. This failure centered in the unsuccessful reduction of an alkylaryl nitrosamine to the alkylaryl hydrazine.

BIBLIOGRAPHY

1. H. Bader, A.R. Hansen, and F.J. McCarty, Abstracts of Papers presented at the 151st Meeting of the Am. Chem. Soc., March 1966, Org. Div., p. K, 125.
2. L.J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1958, pp. 132 and 300.
3. F. Bovini, Att. accad. Lincei, 22, II 460(1913).
4. C.L. Butler and L.H. Cretchen, J. Am. Chem. Soc., 55, 2605 (1933).
5. G. Gever and K. Hayes, J. Org. Chem., 14, 813 (1949).
6. G. Heller, J. prakt. Chem., [2] 111, 368 (1925).
7. G. Heller, J. prakt. Chem., [2] 111, 372 (1925).
8. J. Houben and A. Schottmiller, Ber., 42, 3741 (1909).
9. D.C. Iffland, unpublished work.
10. F. Klaus and O. Baudisch, Ber., 51, 1036 (1918).
11. F. Klaus and O. Baudisch, Ber., 51, 1043 (1918).
12. D.R. Levering and L.G. Maury, Brit. Pat. 797,483 (July 2, 1958).
13. V. Migrdichian, "Organic Synthesis," Vol. 2, Reinhold Publishing Corp., New York, N.Y., 1957, p. 1450.

14. P.A.S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W.A. Benjamin, Inc., New York, N.Y., 1966, p. 139.
15. H. Suhr, Z. Naturforsch., 19b (2), 171 (1964).
16. D.J. Weber, M.A. Thesis, Western Michigan University, 1962.
17. G.W. Wheland, "Advanced Organic Chemistry," 3rd ed., John Wiley & Sons, Inc., New York, N.Y., 1960, p. 222.
18. H. Zimmer, L.F. Audrieth, M. Zimmer, and R.V. Rowe, J. Am. Chem. Soc., 77, 790 (1955).

VITA

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