

STUDIES OF SODIUM AZIDE WITH TETRAPHENYLCYCLOPENTADIENONES
AND VARIOUS ANALOGS

by

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(ABSTRACT)

The reaction of sodium azide with 2-p-chloro- and 2-p-methoxyphenyl-3,4,5-triphenyl-2,4-cyclopentadien-1-one was studied to determine if the substituent would have any appreciable effect on the product distribution of the corresponding 1,5,7,8-tetraphenyl-2,3,4-triazabicyclo[3.3.0]octa-2,7-dien-6-ones and the 3,4,5,6-tetraphenyl-2(1H)-pyridinones that were formed by an acid catalyzed rearrangement. It was found that the chloro substituent had no effect on the reaction. The methoxy substituent had a moderate effect in that the product arising from the stabilized intermediate cation was favored by a ratio of approximately 3 to 1.

The two simple linear analogs studied were 1,2,3,3-tetraphenyl-2-propen-1-one and 3,4,4-triphenyl-3-buten-2-one. These compounds did not react with azide, presumably due to charge delocalization. Also studied as a cyclic analog was 2,7-diphenyltropone which did not react due to the aromatic character of the tropone ring system. A reaction did occur with diphenylcyclopropenone to give an unidentified product. However, the reaction did not take place in the same fashion as for the tetracyclones.

DEDICATION

With appropriate apologies to all others, this work is lovingly
dedicated to

and

my sorely missed grandfathers, who thought that education was of more
than a little importance.

ACKNOWLEDGEMENTS

The author extends many thanks to Dr. O (Michael A. Ogliaruso - not to be confused with monoamine oxidase) for taking me from a world of blue solutions and placing me in one of sticky, yellow oils. His patience and direction has been greatly appreciated.

I would also like to thank Dr. Milos Hudlický for his assistance to a poor German scholar and for his many synthetic and technical suggestions.

Kilos of appreciation also go to Professor Harold McNair and his research group, particularly to

and . These guys really bent over to help with both projects, even when it wasn't convenient - and they still speak to me in public.

A hearty handshake must also be given to (alias Captain Carbon, a.k.a. "Clark Kent") and ("TPic") who unselfishly spent hours trying to beat reasonable NMR spectra out of my cursed compounds and for otherwise trying to do the impossible.

My hat goes off to all those of Davidson Hall (but especially to) from whom I pilfered chemicals, equipment, services, suggestions, and/or munchies.

As for those on the home front - what can I say? Mom, Dad, Mamaw and Papaw , Mamaw and Papaw , and Ma - I'll never be able to thank them all enough for the love, encouragement, and support (including financial) when things didn't look so good. Special thanks hafta go to my "little" brother who set me straight when I was thinking of dropping out of grad school with the now (in)famous comment:

"Now you talkin' 'bout a real ___-whippin' !"

Above all other mortals my deepest heartfelt love and appreciation goes to my wife . I feel that she has survived more than most graduate students' wives including my own frustration, confusion, aching body (from karate practise), bad jokes, chemically destroyed clothing, etc., etc. Without her I would never have survived. Perhaps one day all that she's gone through will have been worth it. I certainly hope so.

Last, but definitely not least, my humble thanks and praises go to God - who helped most of all and let me do it.

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INTRODUCTION

If one surveys the literature references for substituted 2(1H)-pyridinones, two points quickly become evident: (1) this class of compounds becomes more important every year with various members of this class being used as fungicides, herbicides, antihypertensives, dye-stuff intermediates, etc.¹, and (2) there is a conspicuous absence of tetraphenyl-2(1H)-pyridinones. To date there are only four published²⁻⁵ syntheses of tetraphenyl-2(1H)-pyridinone and none for aryl substituted tetraphenylpyridinones. The published syntheses all seem to suffer from multiple steps, exotic reagents, or poor yields.

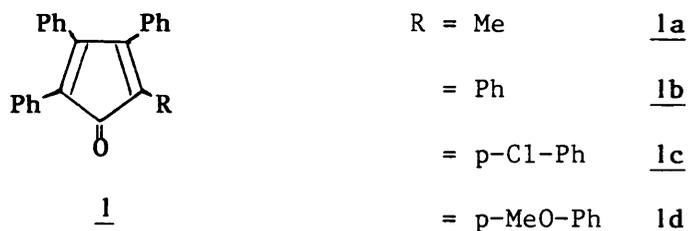
The discovery of a new route to this compound from tetracyclone and sodium azide by way of a triazabicyclo[3.3.0] intermediate⁶ offers the possibilities of synthesizing phenyl substituted tetraphenyl-2(1H)-pyridinones in good yield as well as similar smaller and larger ring systems, all from relatively convenient starting materials. The only limitation being the necessity of a phenyl ring alpha to the carbonyl.

The object of this research, then, is two-fold: (1) to determine a partial scope of the azide reaction with various unsaturated ketones, and (2) to determine if para-substitution on the alpha phenyl ring influences to any appreciable extent the distribution of isomeric products.

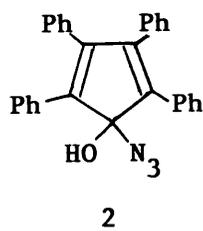
HISTORICAL

Since the discovery of the first organic azide in 1865⁷ and of azide rearrangements in 1890^{8,9} a large number of reactions and rearrangements have been found for this class of compounds. They react with electrophiles, nucleophiles, undergo 1,3-dipolar additions with olefins, decompose to generate nitrenes which can cyclize, dimerize, etc.¹⁰ It is therefore not surprising that there are still research interests in this versatile class of compounds even after 100 years.

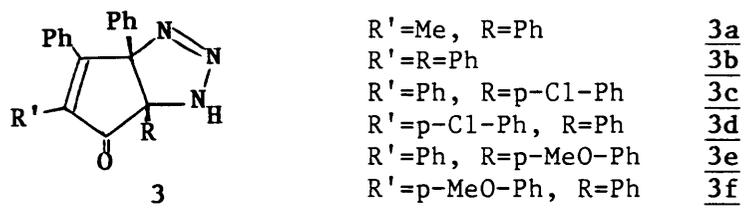
During an attempt to add azide to tetracyclone (2,3,4,5-tetraphenyl-



2,4-cyclopentadien-1-one, 1b) by a 1,2-addition, it was discovered that the expected tetraphenylazidoalcohol (2) was not the product isolated,



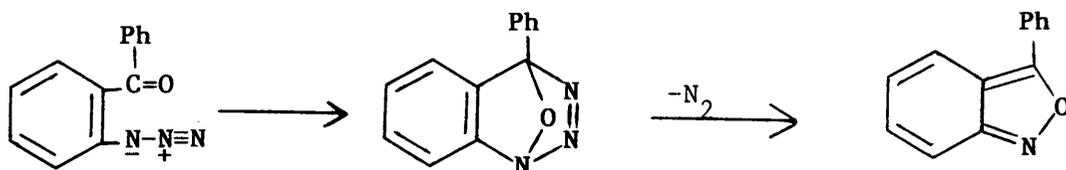
but a compound which was assigned structure 3b. The structure was later



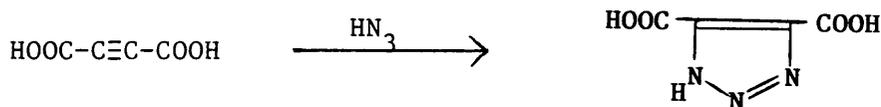
confirmed by X-ray crystallography.⁶ The triazabicyclo[3.3.0] compound probably arises from a 1,4-addition of azide and subsequent cyclization

as shown in Scheme I, though a 1,3-dipolar addition has not been ruled out as a mechanism.

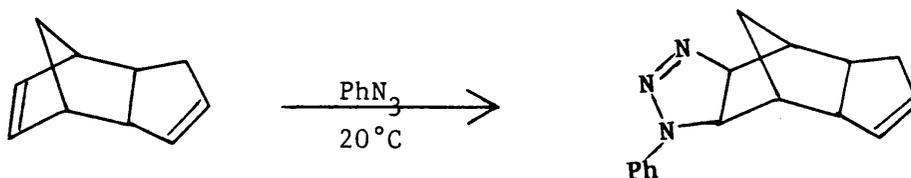
Cyclizations from azides can be found in the literature though they are usually seen with aromatic,¹¹



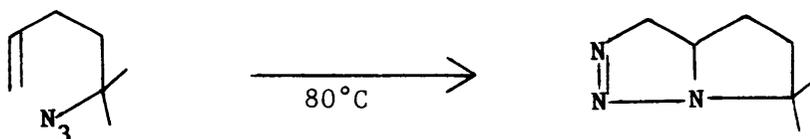
highly unsaturated,¹²



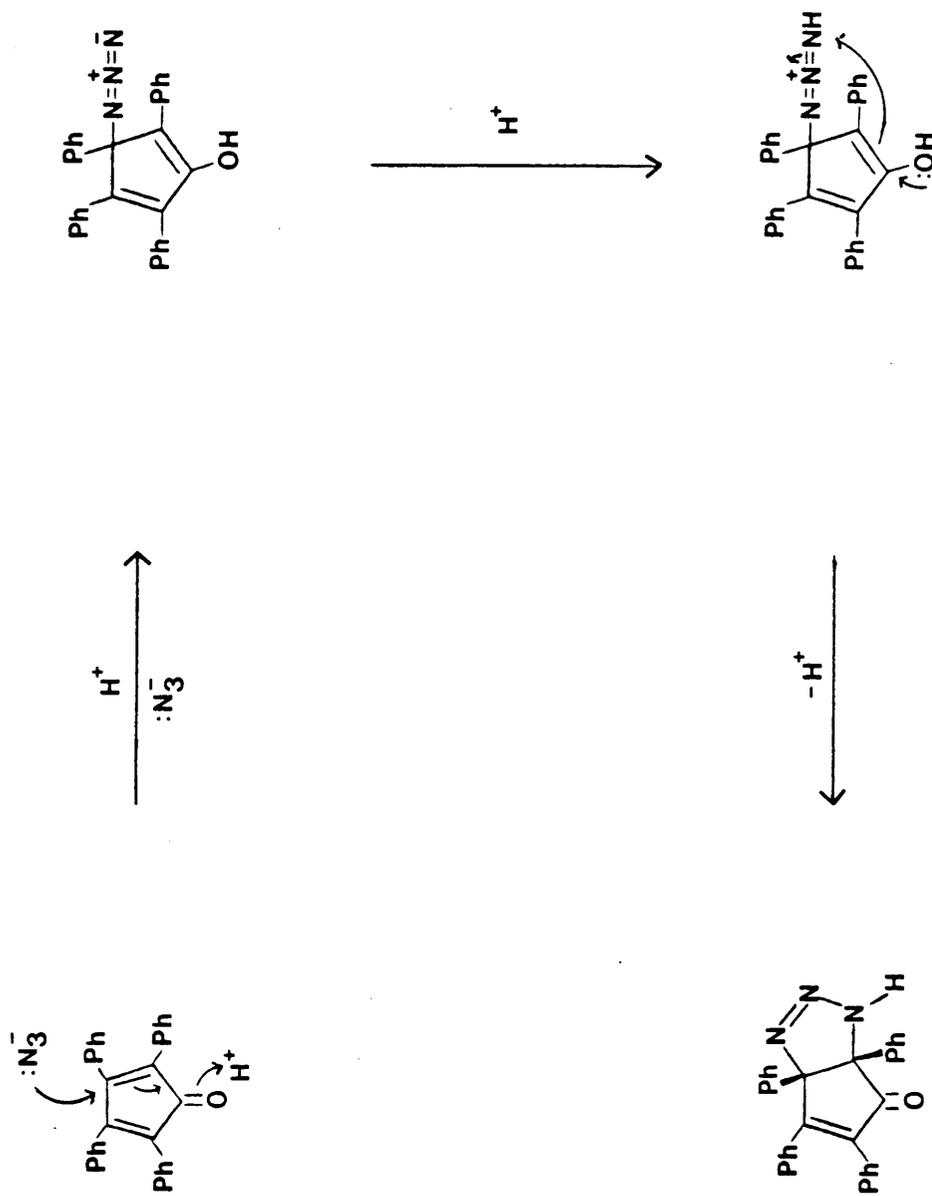
or strained systems,¹³



or as dipolar additions,¹⁴



and usually under different conditions than the reaction of interest.¹⁵



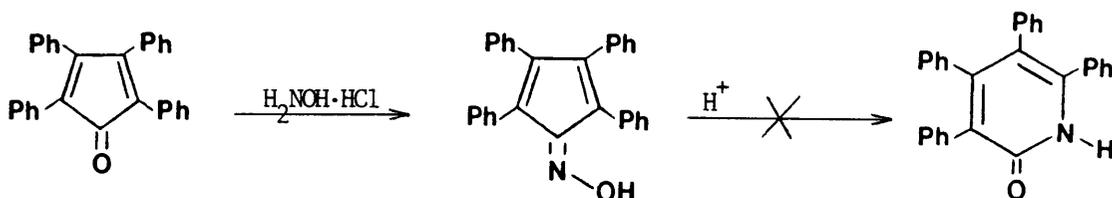
Scheme I

It was found that if 3b was warmed under acidic conditions, nitrogen gas evolved and 3,4,5,6-tetraphenyl-2(1H)-pyridinone (4b) could

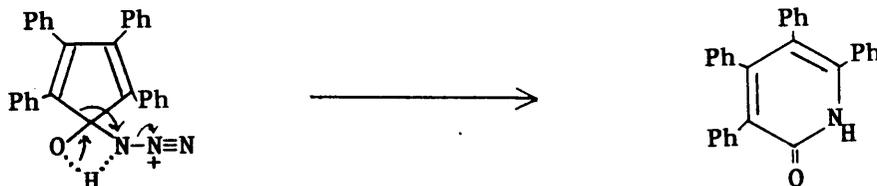


R=Me, R'=Ph	<u>4a</u>
R=R'=Ph	<u>4b</u>
R=Ph, R'=p-Cl-Ph	<u>4c</u>
R=p-Cl-Ph, R'=Ph	<u>4d</u>
R=Ph, R'=p-MeO-Ph	<u>4e</u>
R=p-MeO-Ph, R'=Ph	<u>4f</u>

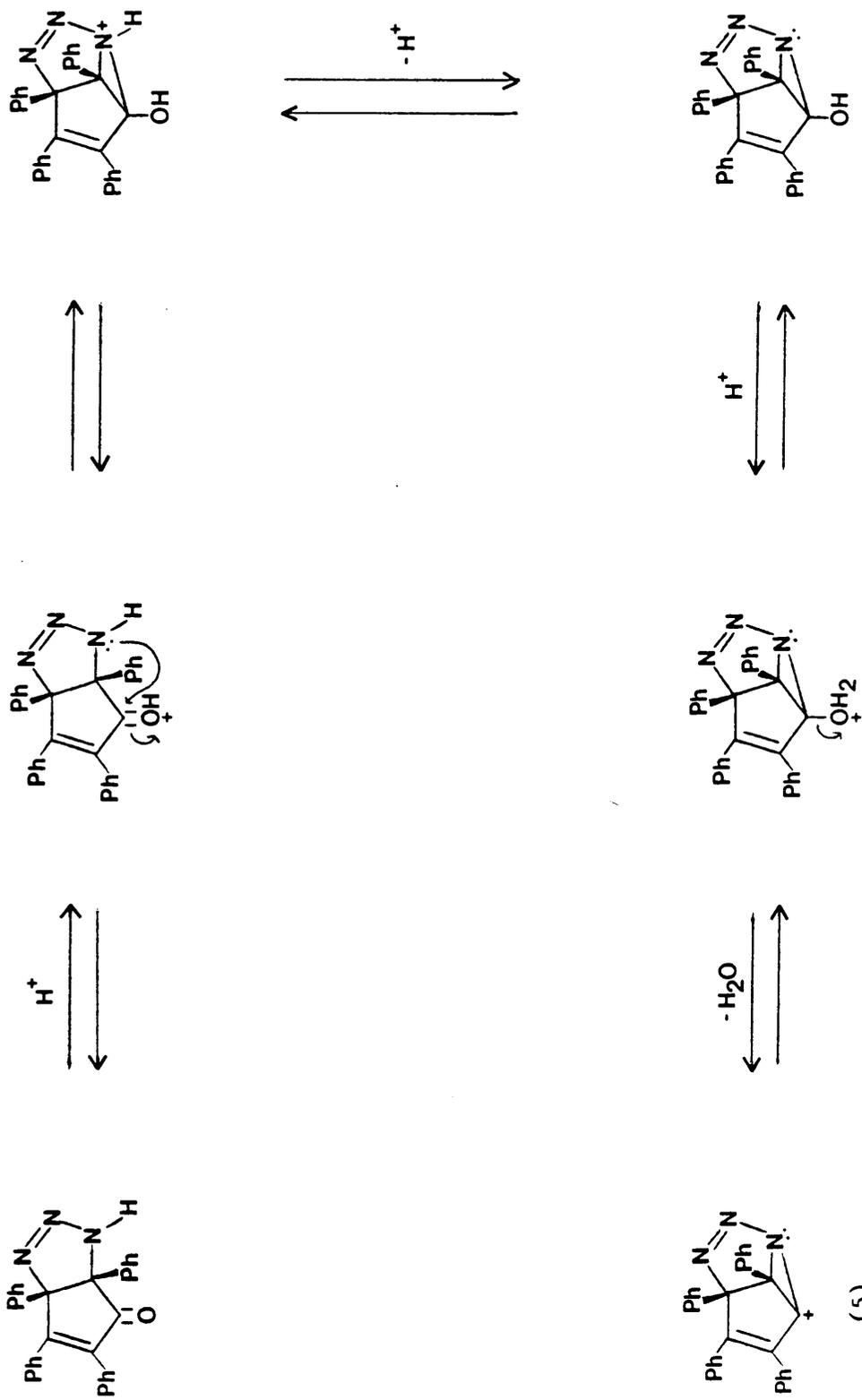
be isolated in 90% yield.⁶ Initially, the rearrangement was thought to be a classical Schmidt reaction,¹⁶ but preparation of the Beckman/Schmidt intermediate showed that this was not the case:¹⁷



The mechanism that has been postulated for the reaction is shown in Scheme II.¹⁷ It is interesting to note that the tetraphenylpyridinone (4b) could also be obtained from the azidoalcohol (2) by rearrangement:¹⁸

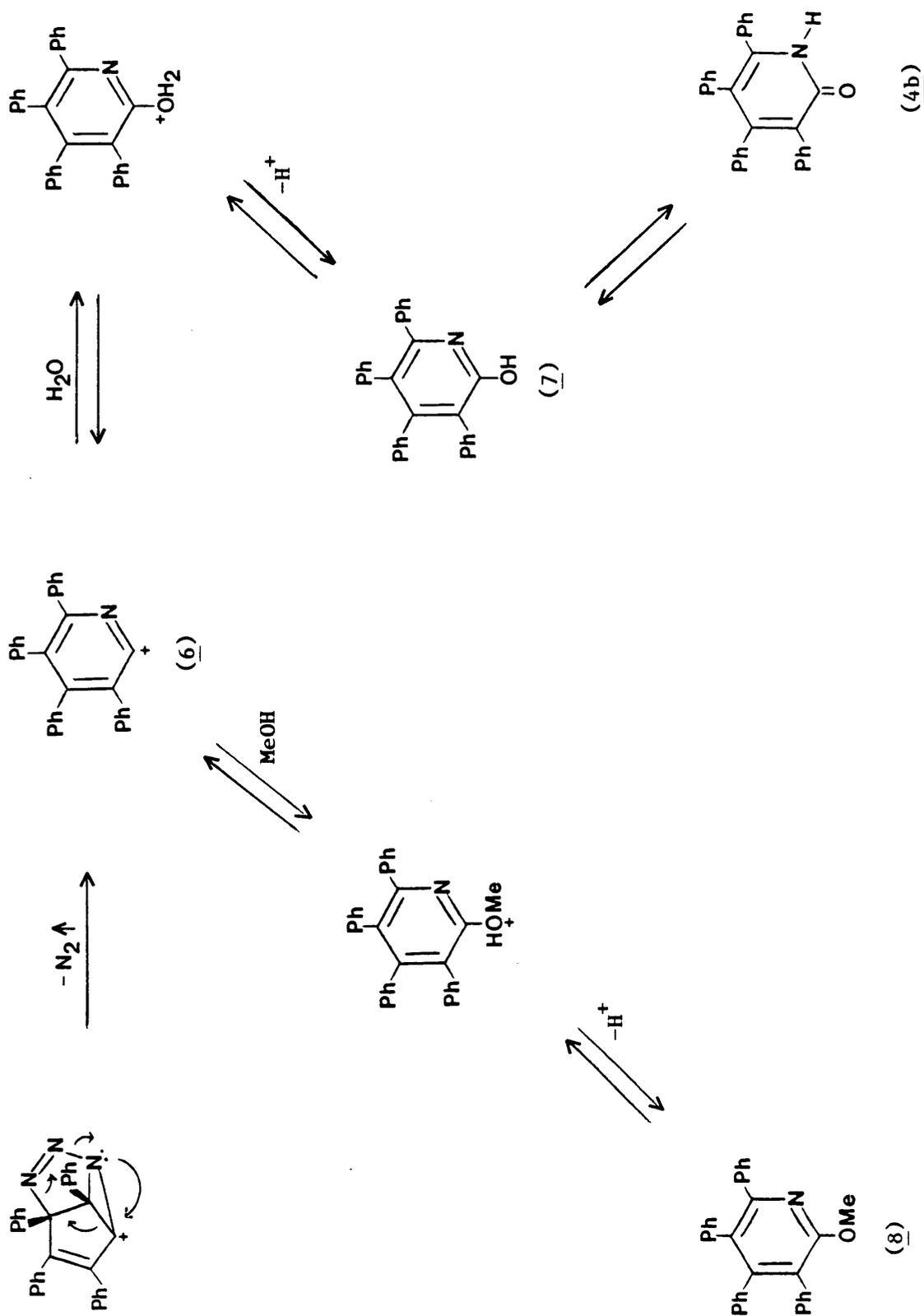


It was also shown that if an aliphatic group is in the 2-position (e.g. 1a), the addition occurs exclusively on the side with the phenyl ring, apparently due to the stabilization of the ion 5 (see Scheme II). If aliphatic groups occupy both the 2- and the 5-positions, the reaction becomes very messy and if any product can be isolated, the yield is quite low.¹⁷



SCHEME II

(5)

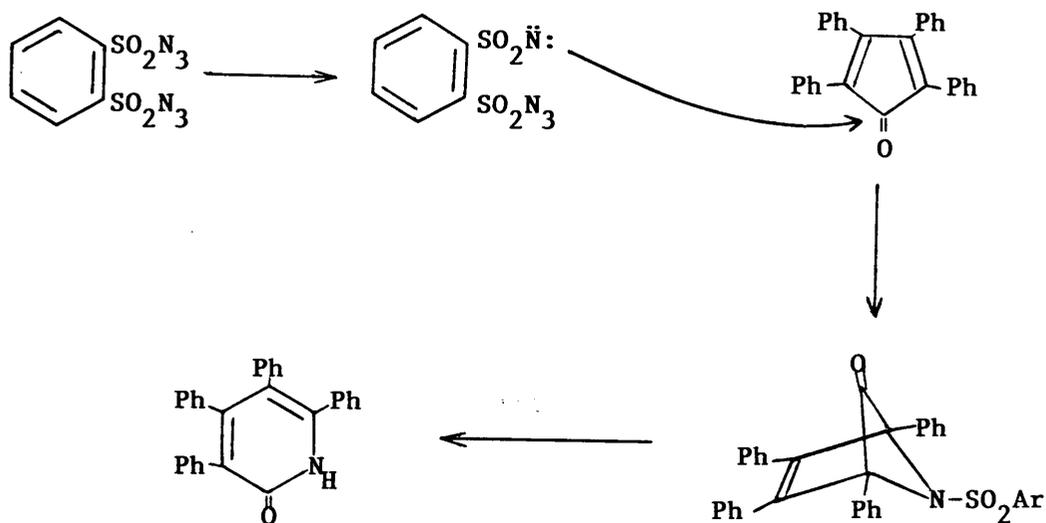


SCHEME II (con't)

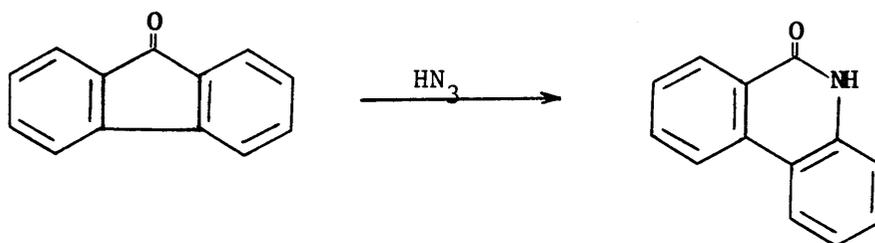
(8)

(4b)

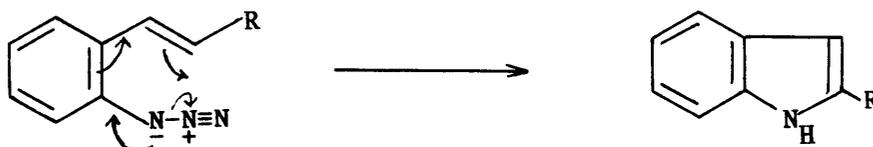
Many examples of nitrogen "insertion" reactions can be found in the literature. Most occur by a nitrene intermediate,⁴



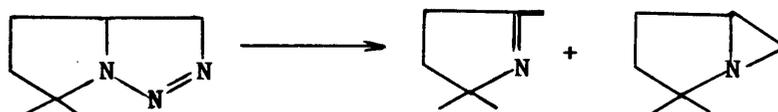
a Schmidt-type migration,¹⁹



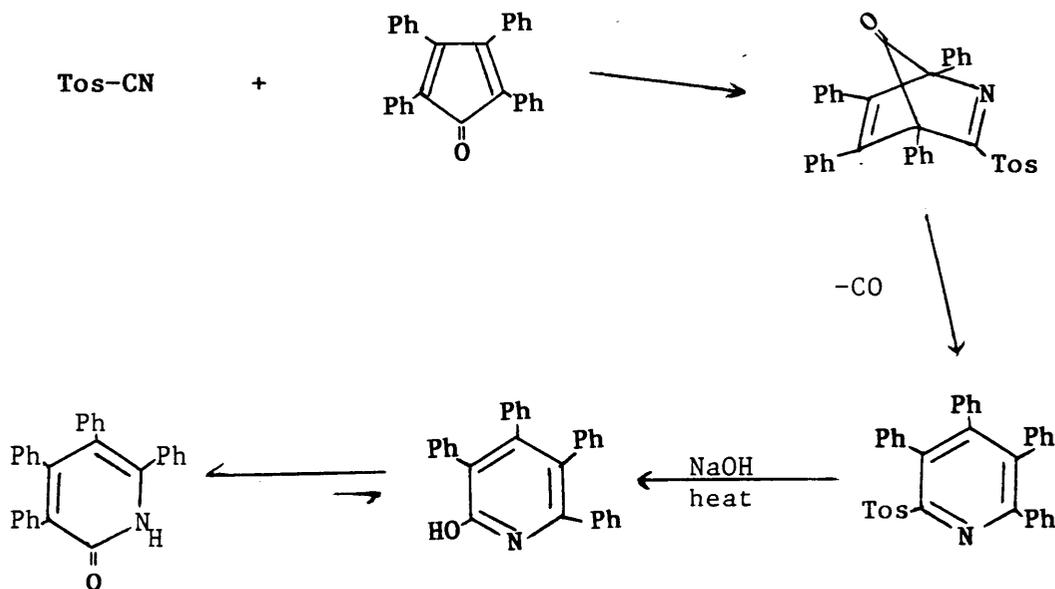
or a concerted rearrangement.²⁰



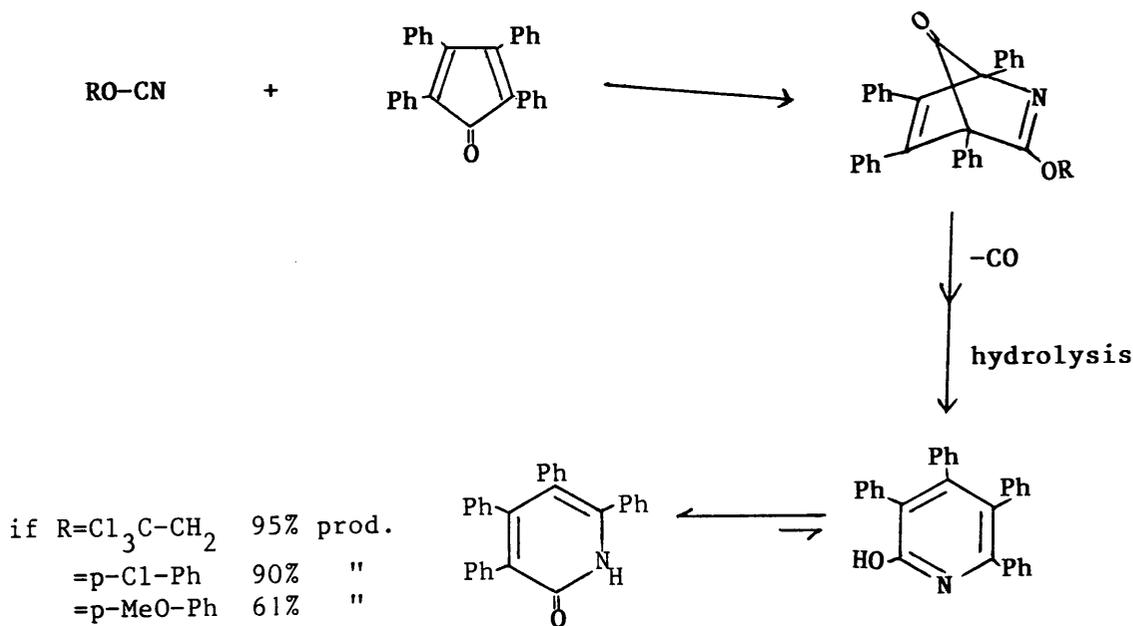
The rearrangement of the triazabicyclo[3.3.0] compounds (3) to 2(1H)-pyridinones (4) represents an unusual case in several respects. Similar cyclic systems are usually saturated and do not rearrange²¹⁻²⁴ though examples can be found:²⁵



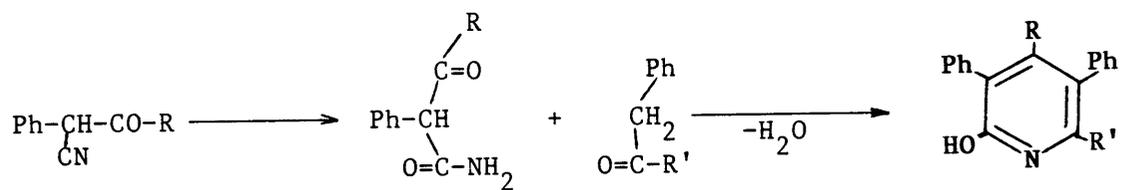
The rearrangements that could be found that involved a 3-membered ring did not proceed to insertion. The ring was either stable²⁶ (as in the above example) or it reopened.²⁷ Also, the production of tetraphenyl-2(1H)-pyridinone (4b) is unusual in itself, since only four other syntheses of this compound are known. One involves a singlet nitrene⁴ (see previous page), a second involves addition of tosyl cyanide,³



a third uses various cyanates,⁵



and the fourth involves the acid-catalyzed condensation of the desoxybenzoin with the amide, both of which come from the nitrile.²



30% yield from nitrile in $\text{HOAc/H}_2\text{SO}_4$

50% yield from nitrile + desoxybenzoin in H_2SO_4

General Experimental

All reagents were purchased from Aldrich, Fischer, J. T. Baker, or Eastman (ACS Reagent Grade or equivalent) and were used without purification.

Mass spectra were determined on either the Varian MAT-112 or the VG 7070E-HF GC-MS systems by the Biochemistry Department of VPI & SU.

Elemental analyses were performed by MultiChem Laboratories, Inc., of Lowell, Mass.

Gas chromatography was done on the Perkin Elmer Sigma 2000 and the Hewlett Packard 5890A using an OV-101 or similar column.

¹H-NMR spectra were determined on the Varian EM-390 (90 MHz) and the Bruker WP-270SY (270 MHz) spectrometers. ¹³C-NMR spectra were done on the Bruker NR-80 (80 MHz) and the Bruker WP-270SY (67.5 MHz) spectrometers. The Pseudo-INEPT and INEPT pulse sequences were done on the Bruker NR-80. The INADEQUATE-2D experiments were attempted on the Bruker WP-200. All NMR spectra were determined in CDCl₃ or DMSO-d₆ as saturated solutions except for the tetracyclones which were used at a concentration of 150 mg/mL. All values are ppm downfield from TMS.

IR spectra were determined on a Perkin Elmer 710B spectrophotometer as 40 mg/mL or saturated CHCl₃ solutions using a CHCl₃ blank in sodium chloride cells.

Melting points were determined on a Thomas-Hoover melting point apparatus or on a Thermolyne melting point stage and are uncorrected.

A Note on Azides

Due to the high toxicity (both chronic and acute) and explosive nature of certain inorganic and organic azides, the chemical and physical properties of these materials should be thoroughly investigated before beginning any experimentation with these compounds.^{27,28}

The Linear Ketones

1,2,3,3-Tetraphenyl-2-propen-1-one (9a)

A 250 mL 3-neck flask fitted with a reflux condenser, magnetic stirring bar, and addition funnel was immersed in a bath of ice water. The flask was charged with 50 mL of carbon disulfide, 25 mL of nitrobenzene (to prevent tar formation), and 1.26 g (9.45 mmol) of anhydrous aluminum chloride. Triphenylethylene (2.21 g, 8.62 mmol) was dissolved in 50 mL of carbon disulfide and placed in the funnel. This solution was added to the flask in 15 minutes with vigorous stirring. A solution of 1.00 mL (1.21 g, 8.62 mmol) of benzoyl chloride in 50 mL of carbon disulfide was then placed in the funnel and added to the flask over a period of 30 minutes. After the addition was completed, the reaction mixture was allowed to stir an additional 30 minutes at 0° C. The ice bath was then removed and stirring was continued at room temperature for three hours. At the end of this time the contents of the flask were carefully poured over a mixture of 300 g of ice and 100 mL of concentrated hydrochloric acid. This mixture was allowed to stir for at least one additional hour, the layers separated, and the organic layer

was washed with 50 mL of water, two 50 mL portions of 5% sodium bicarbonate, and finally with water until the wash tested pH 7. The organic layer was then dried with anhydrous magnesium sulfate, filtered, and the carbon disulfide stripped on the rotary evaporator. The nitrobenzene was removed by vacuum distillation (1.5 - 0.4 mm Hg). The very viscous oil in the distilling flask was allowed to cool and was then placed under vacuum (0.4 mm Hg) for 30 minutes. The oil would usually form a spongy mass which, along with the undried oil itself, refused to be recrystallized. Upon standing open to the atmosphere for a long period of time, the spongy mass dried sufficiently to be broken into a powder. The powder did not give a melting point, but softened and became an oil again when it was heated. The yield was approximately 79% as determined by gas chromatography. The compound could be purified on silica gel by elution with benzene.

Mass Spec.: Calculated for $C_{27}H_{20}O$: 360.47. Found: 360.
Other peaks at m/e 283, 255, 178, 77

^{13}C -NMR (ppm): 206.47 C=O
143.37 Beta
131.99 - 126.92 Aromatic (7 signals)
125.69 Alpha

1H -NMR (ppm): 6.57 - 7.90 Complex aromatic

IR(cm^{-1}): 3055, 1675, 1620, 1515, 1470, 1335, 1295.

Addition of Sodium Azide to 1,2,3,3-Tetraphenyl-2-propen-1-one

Procedure 1: A 100 mL 3-neck flask was placed in a heating mantle and fitted with a reflux condenser and magnetic stirring bar. A solution of 1.50 g (4.16 mmol) of the propenone (**9a**) in 50 mL of dimethylformamide was placed in the flask along with 2.70 g (41.6 mmol) of sodium azide.

The Variac was adjusted to 40 V and 0.45 mL of concentrated sulfuric acid was added. The mixture was stirred for 2, 24, or 72 hours at approximately 90°C. The flask was briefly cooled, 75 mL of benzene was added, and the organic layer was washed with three 40 mL portions of water, dried with anhydrous magnesium sulfate, filtered, and stripped on the Buchi evaporator. By IR analysis the resulting oil was indistinguishable from starting material. The oil was dissolved in 50 mL of benzene, approximately 1 mL of concentrated hydrochloric acid was added, and the mixture was refluxed for 2 hours. The flask was cooled in an ice bath and the contents transferred to a separatory funnel and washed twice with 35 mL of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to yield a yellow oil. The IR spectrum was essentially the same as that of the starting material except for the formation of a small amount of the haloketone (1740 cm^{-1}).

Procedure 2:^{29,30} The same apparatus was used as in procedure 1. Approximately 1.0 g of the propenone (9a) was dissolved in 60 mL of glacial acetic acid and 10 mL of benzene. A solution of 2.0 g (30.8 mmol) of sodium azide in 10 mL of water was added and the mixture was heated at 85°C for 24 hours. The flask was cooled briefly in an ice bath and the contents transferred to a separatory funnel containing 75 mL of water and 50 mL of benzene. The flask was rinsed with 25 mL each of water and benzene and the rinses added to the funnel. The mixture was shaken, separated, and the organic layer washed with 100 mL water, 100 mL of 5% sodium bicarbonate, and finally with two 100 mL portions of water. The benzene layer was dried with anhydrous magnesium sulfate,

filtered, and stripped to yield a brownish oil. The IR spectrum was taken and the remaining sample was dissolved in benzene and refluxed with 0.33 mL of concentrated hydrochloric acid for 2 hours. The flask was cooled and the solution was washed with 50 mL water, two 50 mL portions of 5% sodium bicarbonate, and finally with 50 mL of water. The benzene layer was dried with anhydrous magnesium sulfate, filtered, and stripped. The resulting yellow oil had an IR spectrum which was identical with the oil in procedure 1.

3,4,4-Triphenyl-3-buten-2-one (9b)

A 250 mL 3-neck flask was equipped with a reflux condenser, and addition funnel, and a magnetic stirring bar and was immersed in an ice bath. The flask was charged with 50 mL of carbon disulfide, 25 mL of nitrobenzene, and 2.07 g (15.5 mmol) of anhydrous aluminum chloride. A solution of 3.61 g (14.1 mmol) of triphenylethylene in 50 mL of carbon disulfide was placed in the funnel and added over a period of 30 minutes with vigorous stirring. The funnel was refilled with a mixture of 1.00 mL (1.10 g, 14.1 mmol) of acetyl chloride in 50 mL of carbon disulfide. This was slowly added to the stirred solution. After 30 minutes the addition was complete and the reaction mixture was allowed to stir at 0°C for 1 hour. The ice bath was then removed and stirring continued for 1 hour at room temperature. At the end of that time the contents of the flask were carefully poured over 300 g of ice in 100 mL of concentrated hydrochloric acid. This was allowed to stir at room temperature for at least 1 hour. The layers were separated and the organic layer was washed with 80 mL each of water, 5% sodium bicarbonate,

and finally water. It was dried with anhydrous magnesium sulfate, filtered, and stripped on the rotary evaporator. The nitrobenzene was removed by distillation in vacuo. The residue in the distillation flask gave a very viscous yellow oil (approximately 49% crude yield as determined by gas chromatography) upon cooling which could not be made to form crystals. It could be purified on silica gel by elution with toluene. If the oil was placed under vacuum (<1.0 mm Hg) for 30 minutes, a voluminous spongy mass formed which could be pulverized if left open to the atmosphere for several days. The solid did not melt, but softened and became an oil when it was heated.

Mass Spec.: Calculated for $C_{22}H_{18}O$: 298.40. Found: 298.
also 283 (64.9%)
 255 (17.6%)
 77 (2.14%)
 43 (12.2%)

^{13}C -NMR (ppm): 197.26 C=O
 145.18 Beta
 135.05 Alpha
 130.13 - 125.79 Aromatic (9 signals)
 26.16 Acetyl

1H -NMR (ppm): 2.47 3H Singlet
 6.93 - 7.40 complex aromatic with a singlet at 7.28
 and a doublet centered at 7.68.

IR(cm^{-1}): 3060, 1695, 1620, 1510, 1465, 1425, 1375, 1285, 1200,
 1090, 975, 925.

Addition of Sodium Azide to 3,4,4-Triphenyl-3-buten-2-one

In a 100 mL 3-neck flask equipped with a reflux condenser and magnetic stirring bar, 2.40 g (36.9 mmol) of sodium azide was added to a solution of 1.10 g (3.69 mmol) of the butenone (**9b**) in 50 mL of dimethylformamide. The Variac was adjusted to 40 V and 0.26 mL (4.91 mmol) of concentrated sulfuric acid was added to the mixture. The temperature

was maintained at approximately 90°C for 2, 24, or 72 hours after which the flask was cooled, 80 mL of benzene were added and the contents washed with three 50 mL portions of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and stripped to yield a brownish oil. The IR spectrum was taken at this point. The residue was dissolved in 50 mL of benzene and refluxed for 2 hours with approximately 1 mL of concentrated hydrochloric acid. The solution was cooled, washed with 50 mL of water, dried with anhydrous magnesium sulfate, filtered, and the benzene stripped on the rotary evaporator. The IR spectrum was taken of the residue. Neither spectrum showed any significant difference from starting material, except perhaps the formation of the chloroketone due to the acid treatment.

Diphenyltropone and Intermediates

1-Diethylamino-1,3-butadiene (16)

The procedure is essentially that of Hünig and Kahanek.³¹ Approximately 60 g of anhydrous calcium carbonate was placed in a 1 L 3-neck flask equipped with a magnetic stirring bar and dropping funnel. The flask was placed in an ice bath and 225 g (318 mL, 3.08 mol) of diethylamine was added with vigorous stirring. The funnel was charged with 124 mL (105 g, 1.50 mol) of crotonaldehyde which had been freshly distilled under nitrogen, and 150 mL of benzene. This solution was added to the flask over a period of $\frac{1}{2}$ hour after which the reaction mixture was stirred at 0°C for 2 hours. The ice bath was removed and stirring was continued at room temperature for 4 hours. The calcium carbonate

was then allowed to settle and the solution was decanted to a beaker. Any remaining product was collected by filtering the solid and washing it with hexane. After 0.9 g (4.3 mmol) of phenanthrenquinone was added to a 1 L round bottomed distilling flask, the volatiles were removed from the product by rotary evaporation of 500 mL portions from the previously mentioned flask at 60°C. The dark solution was vacuum distilled (9.0 - 0.45 mm Hg) over a 12 cm column packed with a copper sponge until no more liquid distilled. The final temperature was 85°C. The orange distillate was redistilled at 0.45 mm Hg from 51 - 56°C to yield the title compound as a yellow liquid. The product should be used immediately since it blackens upon extended exposure to light and air. Once the liquid has darkened, it can be redistilled to a useable form.

¹H-NMR(ppm): 1.12 6H triplet
3.04 4H quartet
4.37*, 4.48*, 4.58*, 4.77*, 4.87, 5.00*, 5.13 3H
6.00, 6.10*, 6.19*, 6.23, 6.30, 6.42 2H complex

* finely split doublet

IR(cm⁻¹): 3125, 3075, 3000, 2960, 1645, 1470, 1440, 1410, 1380,
1320, 1300, 1270, 1220, 1175, 1130, 1010, 865.

2,7-Diphenyl-2,4,6-cycloheptatrien-1-one (2,7-Diphenyltropone, 14)

The procedure is essentially that of Ciabattoni and Berchtold.³² A solution of 1.00 g (4.85 mmol) of diphenylcyclopropenone in 30 mL of anhydrous benzene was added to 1.29 g (10.3 mmol) of 1-diethylamino-1,3-butadiene (16) in 30 mL of anhydrous benzene in a 100 mL round-bottomed flask. The flask was surmounted by a reflux condenser and the mixture was refluxed for 7 hours. An ice bath was used to cool the flask before

the addition of 30 mL of ether. The combined solution was washed with 30 mL portions of 1N hydrochloric acid until the wash was essentially colorless. The organic layer was then washed with 30 mL of water and 10 mL of a saturated sodium chloride solution before being dried with anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was stripped on the rotary evaporator. A thin, dark oil resulted. The oil was covered with petroleum ether and allowed to stand overnight. In the morning dark crystals had formed. Recrystallization from hot absolute ethanol afforded 0.709 g (2.74 mmol, 57%) of yellow crystals [Lit. 68%]³², m.p., 131.5 - 133.0°C [Lit. 133°C].³²

¹H-NMR(ppm): 6.90 - 7.08

7.27 - 7.43

7.50 - 7.60

IR(cm⁻¹): 3110, 1640, 1600, 1510, 1460, 1380, 1290, 1245, 1100,³²
1050. Values correspond to those in the literature.

Addition of Sodium Azide to 2,7-Diphenyl-2,4,6-cycloheptatrien-1-one

A 50 mL round-bottomed flask was equipped with a magnetic stirring bar and reflux condenser after being charged with 0.251 g (0.972 mmol) of 2,7-diphenyltropone (14), 0.739 g (11.4 mmol) of sodium azide, 0.10 mL (1.88 mmol) of concentrated sulfuric acid, and 20 mL of dimethylformamide. The Variac was adjusted to 40 V and the solution was allowed to stir for 2, 24, or 72 hours at approximately 90°C. The flask was then cooled and 30 mL of benzene were added to the solution. The organic layer was washed with 30 mL of water, dried with anhydrous magnesium sulfate, filtered, and stripped on the rotary evaporator. The residue was placed under pump vacuum (0.4 mm Hg) for 30 minutes to remove the residual dimethylformamide. The dry solid was covered with

petroleum ether and allowed to stand overnight. The next day the petroleum ether was removed and the solid recrystallized from hot absolute ethanol. Since the IR spectra in all cases showed no difference from starting material, the benzene/hydrochloric acid reflux was not performed.

Substituted Tetracyclones and Intermediates

2-(p-Methoxyphenyl)-4-phenylacetoacetonitrile³³

A 250 mL 3-neck flask equipped with a reflux condenser, addition funnel, and magnetic stirring bar was charged with 50 mL of absolute ethanol. Freshly cut sodium (under toluene, 3.39 g, 0.147 mol) was added to the alcohol in small pieces. The mixture was warmed gently and stirred to effect complete formation of ethoxide. A solution of 10.00 mL (10.85 g, 73.72 mmol) of (4-methoxyphenyl)acetonitrile, 15.13 g (14.68 mL, 92.15 mmol) of ethyl phenylacetate and five mL of absolute alcohol was placed in the funnel and added to the flask over a period of 15 minutes. The solution was then refluxed for 3 hours, cooled in an ice bath, and added to 250 mL of ice-cold water in a separatory funnel. The mixture was extracted 3 times with 80 mL of ether. The ether was combined and extracted with 50 mL of 10% sodium bicarbonate. The sodium bicarbonate extract was combined with the original aqueous layer. The ether was discarded. The aqueous layer was acidified with 45 mL of 6N hydrochloric acid to a pH of approximately 3. The acid solution was extracted with two 80 mL portions of ether which were combined and washed with 50 mL of water, three 50 mL portions of 5% sodium

bicarbonate, and 50 mL of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and stripped to yield 13.5 g (50.9 mmol, 69%) of a white semi-solid.

Mass Spec.: Calculated for $C_{17}H_{15}NO_2$: 265.33. Found: 265.

1-(p-Methoxyphenyl)-3-phenylpropanone³³

The 13.5 g of the crude nitrile from the previous procedure was left in the 250 mL flask. Added to it was 140 mL of a 1:1 (v/v) solution of concentrated hydrochloric acid/glacial acetic acid. A magnetic stirring bar was placed in the flask, a reflux condenser was attached, and the solution was refluxed at approximately 105°C for 25 hours. The flask was cooled in an ice bath and the contents were transferred to a separatory funnel containing 100 mL of ice-cold water. The mixture was then extracted 3 times with 80 mL of ether. The extracts were combined and stirred overnight with 100 mL of a saturated sodium bicarbonate solution. The next morning the phases were separated and the aqueous layer was extracted with 50 mL of ether before being discarded. The ether layers were combined and 75 mL of 10% sodium hydroxide was carefully added to the separatory funnel. When the bubbling ceased, the layers were gently shaken together. Frequent venting of the funnel while maintaining a tight grip on the stopper was necessary. The organic layer was then washed with two 75 mL portions of water. The ether was dried with anhydrous magnesium sulfate, filtered, and stripped to yield 11.15 g of a golden oil. Vacuum distillation over a 10 cm Vigreux Bantamware column at 0.7 mm Hg (190 - 197°C) yielded 6.993 g (29.14 mmol, 39.5% from p-methoxyphenylacetonitrile) of

a pale yellow liquid.

¹H-NMR(ppm): 3.57 2H singlet (benzyl)
3.62 2H singlet (substituted benzyl)
3.68 3H singlet (methoxy)
6.72 - 7.47 9H complex aromatic with peaks at
6.72, 6.82, 6.95, 7.07, 7.13,
and 7.20.

2-(p-Chlorophenyl)-4-phenylacetoacetonitrile³³

A 250 mL 3-neck flask equipped with a reflux condenser, magnetic stirring bar, and addition funnel was charged with 30 mL of absolute ethanol. The stirrer was started and 2.9 g (0.13 g-atom) of freshly cut sodium was added to the alcohol in small pieces. When all the sodium had been added the mixture was gently warmed to effect a complete reaction. The heat was removed and a mixture of 9.46 g (9.18 mL, 62.6 mmol) of p-chlorophenylacetonitrile and 12.4 mL (12.8 g, 78.1 mmol) of ethyl phenylacetate was placed in the addition funnel. The addition to the slightly warm ethoxide took place over a period of approximately 30 minutes. Heat was then reapplied and the solution refluxed for 4 - 10 hours. The flask was cooled in an ice bath and 100 mL of ice-cold water was added. The solution was extracted with three 35 mL portions of benzene. The extracts were combined and washed with 30 mL of 10% sodium carbonate. The benzene was then discarded. The sodium carbonate wash was combined with the original aqueous layer and acidified with 6N hydrochloric acid to approximately pH 3. The white flocculant was filtered from solution and the aqueous layer discarded. The product was washed with benzene and then with ethanol to remove any water. The solid was allowed to dry in the fritted glass filter overnight to yield 8.1 g (30 mmol, 48%) of a product that melts at 125 - 127°C. The

ethanol and benzene washes were combined, washed with 100 mL of water, dried with anhydrous magnesium sulfate, filtered, and stripped to yield 6.6 g of a yellow-white solid. Recrystallization from 45 mL of boiling carbon tetrachloride yields 2.85 g (10.6 mmol, 17%) of additional nitrile.

¹H-NMR(ppm): 3.83 2H singlet (benzyl)
4.72 1H singlet [-CH(CN)-]
7.02 - 7.50 9H complex aromatic with signals at
7.12 Ph
7.27 ortho on subst. ring
7.35 para on subst. ring

IR(cm⁻¹): 3060, 2250, 1750, 1510, 1425, 1110, 1020.

1-(p-Chlorophenyl)-3-phenylpropanone³³

A 250 mL 3-neck flask was fitted with a reflux condenser and magnetic stirring bar. It was then charged with 6.90 g (25.6 mmol) of 2-(p-chlorophenyl)-4-phenylacetoacetonitrile, 50 mL of absolute ethanol, 31 mL of concentrated sulfuric acid, and 19 mL of water. The Variac was set at 90 V (115°C) and the mixture refluxed with stirring for 46 hours. The contents of the flask were then poured onto 50 g of ice. The flask was rinsed twice with 10 mL of ethanol and was added to the mixture. Ether was used in 40 mL portions to extract the solution 3 times. The extracts were combined and stirred overnight with 50 mL of a saturated sodium bicarbonate solution. In the morning the phases were separated and the aqueous layer was extracted with two 25 mL portions of ether. These extracts were combined with the original ether layer. The combined extracts were washed with 40 mL of 5% sodium bicarbonate and two 30 mL portions of water before being dried with anhydrous magnesium sulfate. The mixture was then filtered and stripped on the rotary

evaporator. The resulting oil was vacuum distilled at 0.5 mm Hg (175 - 178°C) over a 10 cm Vigreux column to yield 4.37 g (17.8 mmol, 70%) of a clear, almost colorless liquid.

¹H-NMR(ppm): 3.58 2H singlet (benzyl)
3.63 2H singlet (chlorobenzyl)
6.90 - 7.35 9H complex aromatic with signals at
6.90, 6.98, 7.13, and 7.22.

IR(cm⁻¹): 3075, 2950, 1730, 1620, 1510, 1475, 1425, 1345, 1200,
1105, 1030.

2-(p-Chlorophenyl)-3,4,5-triphenyl-2,4-cyclopentadien-1-one (1c)

A 250 mL flask equipped with a magnetic stirring bar and reflux condenser was charged with 4.37 g (17.9 mmol) of 1-(p-chlorophenyl)-3-phenylpropanone, 3.76 g (17.9 mmol) of benzil and 37 mL of 95% ethanol. The Variac was set at 70 V and the mixture was brought almost to reflux before adding a solution of 0.55 g (9.8 mmol) of solid potassium hydroxide dissolved in 4 mL of 95% ethanol through the condenser. The addition was done carefully due to frothing of the reaction mixture. A dark precipitate formed and approximately 10 mL of 95% ethanol was added, the Variac setting reduced to 40 V and heating continued for 20 minutes. The flask was cooled to 0°C in an ice bath and the product was filtered and washed 3 times with 5 mL of cold 95% ethanol. Drying in a vacuum dessicator yielded 6.15 g (14.7 mmol, 82%) of a very dark, brown-black lustery solid, m.p., 186.5 - 188.5°C. [Lit. 188.3 - 188.8°C]³⁴

IR(cm⁻¹): 3050, 1725, 1510, 1465, 1375, 1340, 1320, 1130, 1110, 1030.

¹H-NMR(ppm): 6.88 4H meta
6.93 4H ortho
7.17 5H 3-phenyl
7.22 10H 4- & 5-phenyl

<u>Mass Spec.:</u>	<u>m/e</u>	<u>% Base</u>	
	418	100	
	419	33.9	
	420	37.8	
	421	11.3	
	422	2.27	
also	390	32.6	loss of C=O
	212	52.2	-C(p-Cl-Ph)=C(Ph)-
	178	97.4	-C(Ph)=C(Ph)-

Calculated for C₂₉H₁₉ClO: 418.93.

2-(p-Methoxyphenyl)-3,4,5-triphenyl-2,4-cyclopentadien-1-one (1d)

A 100 mL 3-neck flask was equipped with a magnetic stirring bar and reflux condenser and was charged with 6.78 g (0.03 mol) of 1-(p-methoxyphenyl)-3-phenylpropanone, 5.92 g (0.03 mol) of benzil, and 45 mL of 95% ethanol. The mixture was heated to reflux and 0.80 g (14.3 mmol) of solid potassium hydroxide dissolved in 4.5 mL of 95% ethanol was added slowly through the condenser. The solution was allowed to reflux another 20 minutes before being cooled to 0°C in an ice bath. The product was filtered, washed with four 10 mL portions of cold 95% ethanol, and allowed to air dry to yield 11.11 g (26.8 mmol, 95%) of a dark, bluish-purple solid, m.p., 187 - 188°C. [Lit. 190.0 - 190.5°C]³⁴

IR(cm⁻¹): 3050, 1725, 1625, 1530, 1510, 1460, 1310, 1265, 1195, 1045.

¹H-NMR(ppm): 3.75 3H singlet (methoxy)
6.68 - 7.43 complex aromatic with signals at 6.68, 6.78, 6.93, 7.15, and 7.25.

Mass Spec.: Calculated for C₃₀H₂₂O₂: 414.52.

found:	<u>m/e</u>	<u>% Base</u>	
	414	100	
	415	32.4	
	416	5.78	
also	386	12.1	loss of C=O
	208	48.4	-C(Ph)=C(p-MeO-Ph)-
	178	7.81	-C(Ph)=C(Ph)-

$^{13}\text{C-NMR}(\text{ppm}):$	200.68	C=O
	158.94	methoxy substituted
	154.80	Beta
	152.54	
	124.81	Alpha
	123.16	
	113.55	ortho to methoxy
	55.03	methoxy

2,3,4,5-Tetraphenyl-2,4-cyclopentadien-1-one (tetracyclone, **1b**)

The unsubstituted tetracyclone was synthesized by the procedure of Johnson and Grummitt,³⁵ m.p., 218 - 220°C. [Lit. 218.5 - 220.0°C]³⁶

IR(cm^{-1}): 3050, 1725, 1620, 1510, 1460, 1375, 1340, 1325, 1130, 1110, 1090, 1045.

<u>$^{13}\text{C-NMR}(\text{ppm}):$</u>			<u>Lit.</u> ³⁷
	200.0	C=O	200.0
	154.4	Beta	154.6
	125.3	Alpha	125.1

Bicycloadducts of the Tetracyclones

1,5,7,8-Tetraphenyl-2,3,4-triazabicyclo[3.3.0]octa-2,7-dien-6-one (**3b**)

A 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged with 1.00 g (2.60 mmol) of tetracyclone (**1b**), 75 mL of dimethylformamide, and a ten molar excess (1.69 g, 26.0 mmol) of sodium azide. The Variac was adjusted to 40 V (approximately 90°C) and a twice molar excess (0.28 mL, 5.6 mmol) of concentrated sulfuric acid was added to the solution. The flask was topped by a reflux condenser and the mixture was allowed to stir until the solution had changed from dark purple to cloudy white or pale yellow (approximately 25 minutes from the addition of the acid). The heat was removed and the flask was cooled

briefly in an ice bath. After adding 60 mL of benzene, the contents of the flask were transferred to a separatory funnel containing 75 mL of water. The flask was rinsed with 10 mL each of water and benzene and these rinses were added to the funnel before the mixture was shaken together. The aqueous layer was discarded and the organic layer was dried with anhydrous magnesium sulfate, filtered, and stripped to yield a crude yellow-white solid. The solid was placed under pump vacuum to remove any residual dimethylformamide. The dry solid was dissolved in 60 to 80 mL of hot benzene. After the solution had cooled slightly, an equal volume of petroleum ether was dripped into the flask from a separatory funnel. The solution was stirred and allowed to stand until the flask was filled with fine white needles. These were filtered through a coarse fritted glass filter and dried to yield 0.970 g (2.27 mmol, 87%) of the title compound, m.p., 183 - 184°C (dec.).

IR(cm^{-1}): 3450(NH), 3050, 1730(C=O), 1620, 1510, 1470, 1360, 1180, 1110.

Mass Spec.: Calculated for $\text{C}_{29}\text{H}_{21}\text{N}_3\text{O}$: 427.53 (428).

Found:	<u>m/e</u>	<u>% Base</u>
(EI) 398		100
399		63.3
400		15.1
401		2.30
also 384		16.0
178		20.5
Found (FAB) 429		M+1

$^1\text{H-NMR}$ (ppm): 6.50 - 7.65 complex aromatic with signals at 6.87, 7.00, 7.13, 7.23, 7.33, 7.49, 7.53, 7.60.
8.83 NH

$^{13}\text{C-NMR}$ (ppm):	200.82	C=O
	166.51	C-8 (Beta)
	141.43	C-7 (Alpha)
	135.41	
	134.66	
	133.17	ipso
	131.19	
	97.75	C-5
	75.06	C-1

5-(p-Chlorophenyl)-1,7,8-triphenyl-2,3,4-triazabicyclo[3.3.0]octa-2,7-dien-6-one (3c) and 7-(p-Chlorophenyl)-1,5,8-triphenyl-2,3,4-triazabicyclo[3.3.0]octa-2,7-dien-6-one (3d)

The procedure was the same as for the tetraphenyl compound (3b) except with the following modifications:

Use 1.00 g (2.39 mmol) of 2-(p-chloro)tetracyclone (1c), 1.55g(23.9 mmol) of sodium azide, and 0.25 mL (4.78 mmol) of concentrated sulfuric acid. After the aqueous layer was discarded, the organic layer was washed with an additional 50 mL of water. Also, after the crude solid was removed from vacuum, 150 mL of hot benzene was used to dissolve the solid. The recrystallized product was air dried to yield 0.998 g (2.16 mmol, 91%) of a pale yellow solid, m.p., 187 - 188°C (dec.).

IR(cm^{-1}): 3450(NH), 3050, 1725(C=O), 1620, 1510, 1500, 1465, 1360, 1110.

Mass Spec.: Calculated for $\text{C}_{29}\text{H}_{20}\text{N}_3\text{OCl}$: 461.97 (462).

	<u>m/e</u>	<u>% Base</u>
found(EI):	432	100
	433	62.6
	434	45.6
	435	22.4
	436	5.10
	also	418
	265	8.37
	178	13.3
found(FAB):	461	incl. large cont. from glycerol

<u>Elem. Anal.:</u>	<u>Calcd.*</u>	<u>Found</u>
C:	75.39	75.63
H:	4.37	4.76
N:	9.10	9.07
Cl:	7.67	7.38

* as for Mass Spec.

¹H-NMR(ppm): 6.77 - 7.73 complex aromatic with finely split peaks at 6.95, 7.01, 7.04, 7.15, 7.35, and 7.57.
12.22 & 12.27 NH

¹³C-NMR(ppm): 200.3 C=O
166.5 C-8 (Beta)
141.4 C-7 (Alpha)
97.9 C-5
74.5 C-1

5-(p-Methoxyphenyl)-1,7,8-triphenyl-2,3,4-triazabicyclo[3.3.0]octa-2,7-dien-6-one (3e) and 7-(p-Methoxyphenyl)-1,5,8-triphenyl-2,3,4-triazabicyclo[3.3.0]octa-2,7-dien-6-one (3f)

The procedure was the same as for the 2-p-chlorophenyl compounds (3c and 3d) except with the following changes:

Use 1.00 g (2.41 mmol) of 2-(p-chloro)tetracyclone (1d), 1.57 g (24.1 mmol) of sodium azide, and 0.26 mL (4.81 mmol) of concentrated sulfuric acid. After the crude solid was removed from vacuum, 105 mL of hot benzene was used to dissolve the solid. The recrystallized product was dried to yield 0.891 g (1.95 mmol, 81%) of the yellow product, m.p., 174 - 175°C (dec.).

IR(cm⁻¹): 3450(NH), 3050, 1725(C=O), 1625, 1595, 1580, 1530, 1510, 1465, 1375*, 1360, 1330*, 1310, 1265, 1225, 1195, 1175, 1125, 1045.

* shoulder

Mass Spec.: Calculated for $C_{30}H_{23}N_3O_2$: 457.56.

found(EI):	m/e	% Base	
	428	100	
	429	61.0	
	430	15.2	
	431	2.80	
also	414	11.6	
	208	6.69	-C(Ph)=C(p-MeO-Ph)-
	178	4.55	-C(Ph)=C(Ph)-

<u>Elem. Anal.:</u>	<u>Calcd.*</u>	<u>Found</u>
C:	78.74	79.02
H:	5.08	5.46
N:	9.19	8.98

* as for mass spec.

<u>1H-NMR(ppm):</u>		
3.61 (31%)		Methoxy
3.79 (69%)		
6.53 - 7.61	finely split complex aromatic with signals at 6.57, 6.82, 6.86, 6.89, 7.00, 7.10, 7.13, 7.29, 7.34, 7.60.	
8.38 (minor)		NH
8.99		

<u>^{13}C-NMR(ppm):</u>		
202.84		C=O
166.90		C-8 (Beta)
141.44		C-7 (Alpha)
113.95		ortho to methoxy
113.31		C-5
74.48		C-1
55.10		OMe

The Pyridinones

3,4,5,6-Tetraphenyl-2(1H)-pyridinone (4b)³⁸

A 100 mL round-bottom flask was equipped with a magnetic stirring bar and was charged with 0.500 g (1.17 mmol) of the tetraphenylbicyclo adduct (3b) and 25 mL of glacial acetic acid. To this stirred solution, 0.10 mL (1.9 mmol) of concentrated sulfuric acid was added very cautiously. When the frothing subsided, the Variac was set at 60 V, a reflux condenser was placed on the flask and the solution was gently

refluxed for 30 minutes. The heat was removed and the flask was cooled briefly in an ice bath. The contents of the flask were transferred to a 250 mL Erlenmeyer flask, 100 mL of water were added, and the flask was immersed in an ice bath for approximately 10 minutes. The white precipitate was then filtered through a medium porosity fritted glass filter and was washed with copious amounts of water. The white solid was finally washed with two 10 mL portions of ice-cold 95% ethanol.

Drying yielded 0.397 g (0.994 mmol, 85%) of the title compound, m.p., 269 - 271°C. [Lit. 272 - 273°C,² 264 - 267°C,⁵ 262 - 267°C.³]

IR(cm⁻¹): 3420(NH), 3030, 1645(C=O), 1615, 1510, 1465, 1230, 1110.

Mass Spec.: Calculated for C₂₉H₂₁NO: 399.51.

found (EI)	<u>m/e</u>	<u>% Base</u>
	398	100
	399	84.9
	400	24.9
	401	4.63

<u>¹³C-NMR</u> (ppm):		
	163.0	C=O
	152.9	C-4 (Beta)
	143.5	C-6
	120.1	C-3 (Alpha)

<u>¹H-NMR</u> (ppm):		
	6.67 - 6.77	
	6.85 - 6.96	
	7.02 - 7.15	clusters of very close signals
	7.19 - 7.26	
	12.37	v. low, v. broad NH

3-(p-Chlorophenyl)-4,5,6-triphenyl-2(1H)-pyridinone (4d) and 6-(p-Chlorophenyl)-3,4,5-triphenyl-2(1H)-pyridinone (4c)

The procedure was exactly the same as for the tetraphenylpyridinone (4b). The amount of chloroadduct mixture (3c and 3d) used was 0.500 g (1.08 mmol). Drying yielded 0.423 g (0.974 mmol, 90%) of the white product, m.p., 315 - 321°C after slow recrystallization from dioxane.

IR(cm^{-1}): 3420(NH), 3030, 1640(C=O), 1615, 1510, 1465, 1420, 1350, 1310, 1230, 1110, 1030, 930, 850.

$^1\text{H-NMR}$ (ppm): 6.77 - 7.31 complex aromatic with signals at 6.82, 6.92, 7.09, 7.21, 7.26.
12.10 (DMSO- d_6)
12.97 (CDCl_3)⁶ low, broad, very labile NH

Mass Spec.: Calculated for $\text{C}_{29}\text{H}_{20}\text{NOCl}$: 433.95.

found(EI)	m/e	% Base
	432	100
	433	86.6
	434	55.1
	435	31.2
	436	7.84
	437	1.31

<u>Elem. Anal.</u> :	<u>Calcd.*</u>	<u>Found</u>
C:	80.26	80.54
H:	4.65	4.61
N:	3.23	3.03
Cl:	8.17	8.48

* as for mass spec.

<u>$^{13}\text{C-NMR}$</u> (ppm):	
163.9	C=O
163.3	
153.8	C-4 (Beta)
153.1	
143.9	C-6
142.5	
120.4	C-3 (Alpha)
120.3	

Due to the large number of aromatic signals and to the long relaxation time, an assignment could not be made for the chlorine-substituted carbon, even with the assistance of INEPT and Pseudo-INEPT experiments.³⁹

3-(p-Methoxyphenyl)-4,5,6-triphenyl-2(1H)-pyridinone (4f) and 6-(p-Methoxyphenyl)-3,4,5-triphenyl-2(1H)-pyridinone (4e)

The procedure was exactly the same as for the tetraphenylpyridinone (**4b**). The amount of methoxyadduct mixture (**3e,3f**) used was 0.500 g (1.09 mmol). Drying yielded 0.390 g (.907 mmol, 83%) of the yellow-white solid, m.p., 298 - 303°C after slow recrystallization from dioxane.

IR(cm^{-1}): 3425(NH), 3030, 2980, 2890, 1640(C=O), 1620, 1525, 1510, 1475, 1460, 1395, 1350, 1310, 1260(ArOMe), 1215(ArOMe), 1190, 1125, 1045, 845.

$^1\text{H-NMR}$ (ppm): 3.65 (70%)
 3.69 (30%) OMe
 6.65 - 7.40 complex aromatic
 7.20 meta to methoxy
 7.36 ortho to methoxy
 12.00 broad, low, very labile NH

$^{13}\text{C-NMR}$ (ppm): 163.0 C=O
 157.9 C-OMe
 152.5 C-4 (Beta)
 142.8 C-6
 129.4 meta to OMe
 129.2
 120.1 C-3 (Alpha)
 113.4 ortho to OMe
 112.7
 54.9 OMe

Mass Spec.: Calculated for $\text{C}_{30}\text{H}_{23}\text{NO}_2$: 429.54.

found (EI)	m/e	% Base
	428	95.6
	429	100
	430	28.1
	431	4.79
	432	2.55
	433	1.97
	434	1.29
	435	0.71

<u>Elem. Anal.</u> :	<u>Calcd.*</u>	<u>Found</u>
C:	83.88	83.61
H:	5.41	5.64
N:	3.26	2.89

*as for mass spec.

6-(p-Methoxyphenyl)-3,4,5-triphenyl-2(1H)-pyridinone (4e)⁴⁰

A 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged with 2.2139 g (10.0 mmol) of alpha-benzoylbenzylcyanide (25)⁴¹ and 4.5258 g (20.0 mmol) of p-methoxyphenyl benzyl ketone

(4-methoxydesoxybenzoin).⁴² The flask was immersed in an oil bath and 1.0 mL of concentrated sulfuric acid was added. The temperature was slowly increased to 80 - 90°C and maintained for 2 hours. The temperature was then increased to 100 - 110°C and held for another 2 hours. Finally, the temperature was increased to a constant 120 - 125°C for 1½ hours.

While still warm, approximately 35 mL of water was added to the flask and the tarry residue was stirred manually until the stirring bar was freed. Stirring was continued magnetically as a saturated sodium carbonate solution was added dropwise until no more frothing occurred. The mixture was then stirred until all of the tarry residue was suspended in the aqueous medium. Three 50 mL portions of benzene were used to extract simple organics from the aqueous product phase. Chloroform was used in 50 mL portions to extract the product from the aqueous phase. The suspension was extracted until the chloroform was only moderately colored. The extracts were combined and dried with anhydrous magnesium sulfate, filtered, and stripped on the rotary evaporator to yield a crude yellow solid. The solid was dissolved in a minimum amount of hot benzene and an equal volume of petroleum ether was added to the solution. After filtration, the pale yellow solid was again recrystallized by the same method to yield approximately 0.47 g (1.1 mmol, 11%) of the off-white product, m.p., 314 - 316°C.

The product was then used to spike a ¹H-NMR sample of a methoxy-pyridinone mixture as described in the "Results and Discussion" section.

Adducts of Diphenylcyclopropenone with Sodium Azide

A 25 mL round-bottomed flask was equipped with a magnetic stirring bar and charged with 0.500 g (2.42 mmol) of diphenylcyclopropenone and 1.567 g (24.2 mmol) of sodium azide. Approximately 5 seconds after the solvent had been added (15 mL of either DMF or DMSO) the solution changed from colorless to green. After 2 minutes of stirring at room temperature the solution had become opaque. Small gas bubbles, presumably nitrogen, were emitted as the solution stirred. The Variac was set at 40 V and 0.26 mL (4.8 mmol) of concentrated sulfuric acid was added to the solution which immediately turned red-orange. Heating was continued for approximately 20 minutes. The flask was cooled briefly, the contents were transferred to a separatory funnel with 30 mL each of benzene and water, and the mixture was shaken together. When the phases separated, the organic layer was collected, dried with anhydrous magnesium sulfate, filtered, and stripped to yield a dark oil. The oil was covered with petroleum ether and allowed to stand until it solidified. It was then recrystallized from absolute alcohol or from hot benzene and an equal volume of petroleum ether. The yield of the pale yellow solid was 0.1558 g (0.481 mmol, 19.8%) m.p., 296 - 298°C.

IR(cm^{-1}): 3560, 3440, 3060, 1660(C=O), 1620, 1580, 1510, 1460, 1430, 1330, 1140, 1025, 940.

^{13}C -NMR(ppm): 190.6* C=O
 162.4* Beta
 131.8
 131.1
 129.4
 128.7 - 126.6 complex: 127.6 max.
 119.1* Alpha

*Very weak: may not be a legitimate peak, but assigned as if so.

¹H-NMR(ppm): 6.60 - 7.73 complex aromatic with peaks at 6.98, 7.10, 7.19, 7.39.
 11.46 NH

<u>Elem. Anal.:</u>	<u>C</u>	<u>H</u>	<u>N</u>
	79.32	5.11	3.98
	79.47	5.19	4.00
	79.30	5.20	3.99

Yields a formula of $C_{23}H_{17}NO_2$; MW = 339.40.

<u>Mass Spec.:</u>	<u>m/e</u>	<u>% Base</u>	
<u>found (FAB)</u>	340	M+1	
	249	1.86	Compound <u>27</u>
	456	2.79	Compound <u>28</u>
<u>found (EI)</u>	398	100	
	399	84.0	
	400	22.6	
	401	3.71	
<u>also</u>	338	84.8	
	339	73.0	
	340	22.8	
	341	5.96	
	265	10.5	
	222	11.6	
	179	18.4	
	178	48.7	
	177	10.6	
	176	11.6	
	165	15.9	
	118	12.8	
	105	31.8	
	104	26.1	
	91	12.6	
	90	11.4	
	89	15.0	
	77	37.6	
	78	14.0	
	79	2.44	

As a second procedure, the diphenylcyclopropenone/sodium azide mixture was treated as before except it was not refluxed: it was merely stirred for varying periods (15 minutes to 10 hours). The yield was independent of the reaction time and solvent (dimethylformamide and

dimethylsulfoxide gave the same compound) and was approximately 11% (0.089 g, 0.265 mmol) in each case. The spectral properties were entirely different from the adduct of the reflux, m.p., 164 - 166°C.

IR(cm^{-1}): 3050, 1760 and 1720,⁴³ 1620, 1510, 1460, 1360, 1280, 1220, 1160, 900. A very small band also shows at 2285.

¹H-NMR(ppm): 1.53 broad (approx. 1H)
 4.23
 7.26, 7.33, 7.40 10H essentially close singlets

<u>Mass Spec.:</u>	<u>m/e</u>	<u>% Base</u>	
found (EI)	324	100	
	325	25.0	
	326	3.60	
also	268	11.8	neut. loss of 56
	178	51.6	loss of 90 ⁴⁴
	118	17.0	neut. loss of 60
	90	16.3	loss of CO

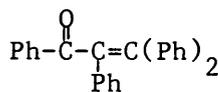
Elem. Anal. (avg.): C: 84.47%
 H: 5.04%
 N: 0.14% (essentially zero)

Yields a formula of $\text{C}_{22}\text{H}_{15}\text{O}_2$ assuming 10.49% oxygen.

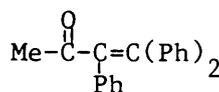
When the unheated adduct was refluxed in benzene for 2 hours with approximately 1 mL of concentrated hydrochloric acid, the IR spectrum changed below 1620 cm^{-1} to show absorptions at: 1600, 1510, 1470, 1345, 1320, 1295, 1160, 1020, 960, and 940 cm^{-1} . In the ¹H-NMR spectrum, the peaks at 1.53 and 4.23 ppm almost completely disappeared and a new peak appeared at 3.67 ppm. The melting point rose to 166 - 168°C. The EI mass spectrum gave the same base peak as for the unheated adduct.

RESULTS and DISCUSSION

The substituted propenone (9a) and butenone (9b) were synthesized by reacting the appropriate acid chloride with triphenylethylene in the

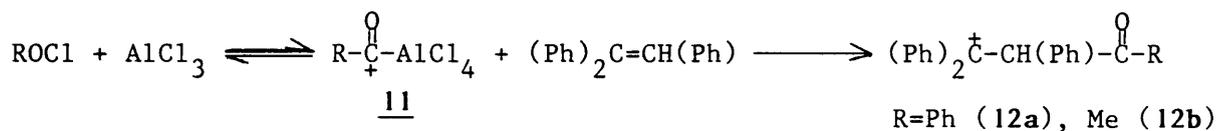


9a



9b

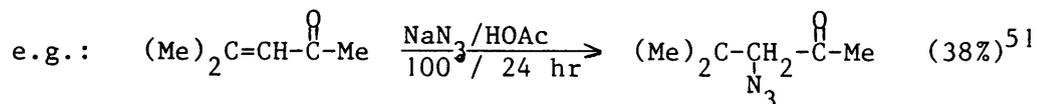
presence of aluminum chloride in a Friedel-Crafts type aliphatic acylation. The olefin acts as a nucleophile in the presence of the acetylium or benzoylium cation to form the carbonium ion (10a, 10b) according to Markownikov (inductive) effects.⁴⁵ The carbonium can either



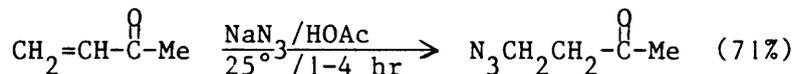
add chloride to form the beta-chloro ketone or may undergo proton elimination to yield the desired unsaturated ketone. The chloro ketone can be dehydrochlorinated by refluxing with a basic reagent such as dimethylaniline⁴⁶ or by stirring with concentrated hydrochloric acid and ice.^{47,48} It has been found in practice that the optimum conditions for the acid chloride/AlCl₃ complex (11) necessitate the ratio of moles AlCl₃ to moles of acid chloride being 1.1 : 1.⁴⁹ Keeping the reaction mixture above 0°C would cause less formation of halo ketone,⁵⁰ but would increase the probability of acylation of one or more of the aromatic rings.

When the attempt was made to add azide to the compounds, no addition occurred under the same conditions as for tetracyclone (1b) or under the conditions of the Michael addition/Schmidt reaction.⁵¹ The time frame

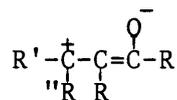
for the reaction varied from 2 to 72 hours. The total absence of a reaction was thought to be peculiar, especially in light of the fact that simple unsaturated ketones do add azide in a Michael reaction;²⁷



However, it was noticed that the simpler ketones undergo the reaction much more readily than do the more substituted ones:⁵²



A more intensive search of the literature showed that it is generally accepted that hydrazoic acid does not add to substrates that have a phenyl group in the beta position.⁵³ This can be explained if one considers the resonance form of the ketone, 13:

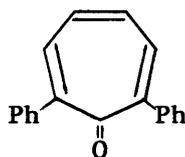


13

A phenyl group would stabilize the positive charge by delocalization. With two phenyl groups in the beta position, the charge is spread over so many carbon atoms that the molecule is unreactive toward the only moderately nucleophilic azide ion, i.e. the beta carbon is not electrophilic enough to react. The compound would be expected to be reactive toward electrophilic addition⁵⁴ and this is born out by the observed formation of the chloroketone when 9a and 9b are refluxed in benzene with concentrated hydrochloric acid.

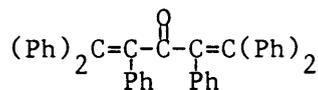
Since this type of delocalization was also present in tetracyclone (1b), why did it undergo the addition/cyclization while the linear ketones did not? What did tetracyclone have that the linear ketones did not have? The two properties of extra conjugation and ring strain immediately come to mind.

It was then decided that a 7-membered ring system should be studied. The ideal case would have been hexaphenyltropone. However, neither it nor the 2,3,6,7-tetraphenyltropone had been reported in the literature. The 2,7-diphenyltropone (14) had been reported and was studied in the reaction because of the stabilizing phenyl groups in the alpha positions and because of the "activating" ring strain of the 7-membered ring. If



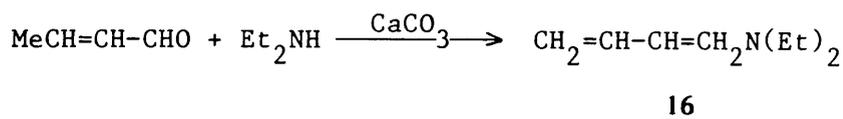
14

14 would give the desired reaction then a study of a compound such as 15⁵⁵ would determine if the reactivity were due to ring strain or due to conjugation.

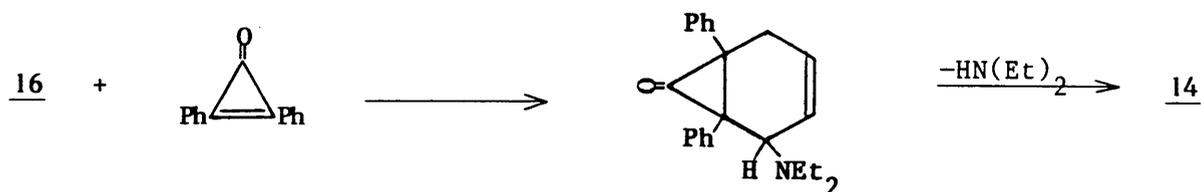


15⁵⁶

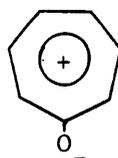
The diphenyltropone was synthesized by reacting diethylamine with crotonaldehyde to yield 1-diethylaminobutadiene (16). The activated



diene was then allowed to react in a Diels-Alder fashion with diphenylcyclopropenone⁵⁷ to yield 14.



When the tropone (14) was treated for 2, 24, or 72 hours under the conditions of the tetracyclone reaction, it was determined (by IR analysis) that no addition occurred. Further research into the literature indicated that tropones are characteristically unreactive toward almost all types of addition reactions.⁵⁸ Even the "addition" of Br₂ proceeds by a tetrabromo complex which eliminates hydrogen bromide and results in the regeneration of the cycloheptatriene system.⁵⁸ This would be expected of a compound with the substantial aromatic character of a tropone. The aromatic character results from a significant contribution to the real state of the molecule from its dipolar form (structure 17).⁵⁸⁻⁶⁰



17

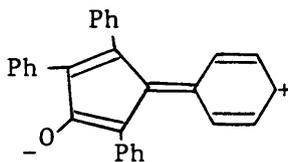
The 7-membered ring donates electrons to the carbonyl and stabilizes the system.⁶⁰ Addition to such a system would disrupt the aromatic character (and the lower ground state energy) of the structure. Therefore, as with true aromatic compounds, substitution is the reaction of choice. These factors outweigh any stabilization the intermediate might derive from the alpha phenyl groups or any activation of the molecule from ring strain.

In contrast, the strained 5-membered ring of tetracyclone requires electrons from the carbonyl which destabilizes the system.⁶⁰ There is no dipolar form such as 18 which contributes appreciably to the real



18

structure of the molecule. Even forms of tetracyclone like 19 contribute little due to steric hindrance to resonance.⁶¹ Spectroscopic studies

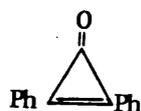


19

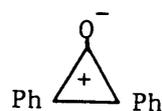
have shown that the carbonyl has a full double bond⁶¹ and this causes the ring to pucker. The phenyl groups are also crowded and are turned in a propeller-like fashion around the ring. These data also indicate that there is little chance of a resonant effect. It must therefore be

assumed that the reactivity of the tetracyclones is due to the strain in the 5-membered ring.

Because of the unreactive nature of the diphenyltroponone, it was decided to study another system with a high degree of charge separation, viz. diphenylcyclopropenone (20a).⁶² The high dipole moment (5.1 Debye)



20a



20b

indicates that the dipolar form (20b) is even more significant for this compound than for the tropones.⁶³ This, along with the fact that many of the physical and chemical properties (e.g. UV, IR, and ¹H-NMR spectra) suggest "Hückel aromaticity" ($4n + 2$ where $n=0$),⁶⁴ might lead one to believe that the molecule would be unreactive toward addition reactions. However, the ring system is highly strained and apparently is not completely delocalized.⁶⁴

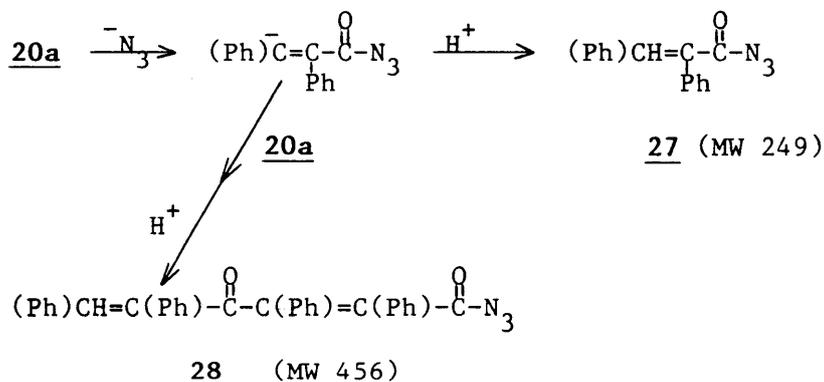
The latter notions seemed to be the deciding factors: diphenylcyclopropenone does react with sodium azide under the conditions of the tetracyclone reaction. In fact, it begins to react with azide when merely stirred together in dimethylformamide at room temperature within five seconds. Unfortunately, several products are obtained depending on the reaction temperature and all are poorly defined: melting points vary widely as do ¹H-NMR spectra (even sometimes from different runs that should give the same compound), and the elemental analyses usually do not agree with the mass spectra. Initially, it was thought that 20a was

reacting with the dimethylformamide⁶⁵ but it was shown that this was not the case.

If 20a is stirred from 15 minutes to 10 hours at room temperature with a ten molar excess of sodium azide and then quenched with concentrated sulfuric acid, a product is obtained in 11% yield that melts at 164 - 166°C (see experimental). The molecular weight (EI-MS) is 324 but elemental analysis shows that there is essentially no nitrogen in the molecule.

If the reaction is carried out at 80 - 90°C for 30 minutes, the product gives a pyridinone-like ¹H-NMR spectrum and melting point. Elemental analysis indicates a molecular formula of C₂₃H₁₇NO₂ (MW 339.4). The FAB mass spectrum is seemingly in agreement with this result. However, the EI mass spectrum indicates a molecular weight of 398.

It is obvious that none of the major products arise from a simple addition. The mass spectrum of the heated reaction shows impurities (less than 2% each) at m/e 249 and 456 which could result from a simple nucleophilic attack by azide (249) and from subsequent attack by the initial adduct ion on a second molecule of diphenylcyclopropenone:⁶⁶



Whatever the product is, it must be derived from the attack of the initial adduct on a second molecule of 20a followed by a complex rearrangement. The initial adduct could have any of the following forms:⁶⁶



Because a considerable number of possible structures exist for an intermediate, it would be prohibitive to work toward the true structure of the molecule mechanistically. Due to the limited availability and the hazardous nature of the starting material, however, this aspect of the study was not pursued further.

SUBSTITUTED TETRACYCLONES

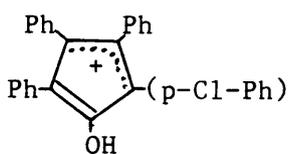
During the original studies¹⁷ of the addition of azide to cyclopentadienones it was soon discovered that if there were no phenyl groups in the alpha positions the reaction went poorly, the reaction mixture became difficult to handle, and if a product could be isolated, it was in a rather low yield.

The second part of this research was to establish if a para-substituent on the 2-phenyl moiety would direct the addition of azide to a particular side of the cyclopentadienone ring due to the establishment of an electronic system which was different from that of tetracyclone. The substituents chosen were chloro (for its electron

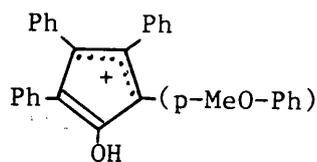
withdrawing effect) and methoxy (for its electron donating effect).

The 2-para-substituted tetracyclones were synthesized by condensing the appropriately substituted dibenzyl ketone with benzil (for details see the experimental section).

In the case of the 2-(p-chloro)tetracyclone (1c), it was reasoned that the electron withdrawing ability of the chlorine would destabilize the intermediate cation 21a. Attack would then have been preferred on the



21a



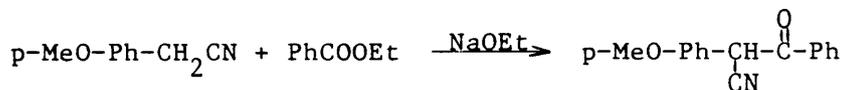
21b

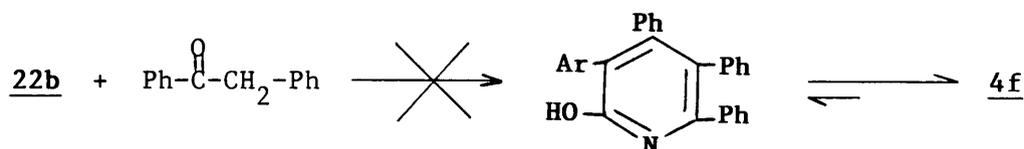
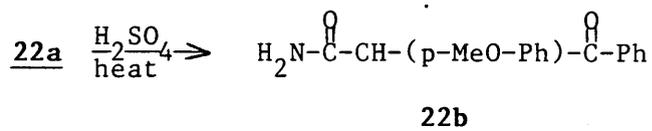
substituted side of the cyclopentadienone system, i.e., at the terminus of the more stable allylic system. However, the experimental evidence indicates that there was essentially no effect. A mixture was obtained which defied all attempts at separation. Because of the insoluble nature of the bicycloadducts, they were converted to the corresponding 2-pyridinones (4c,4d) for analysis. A good separation could not be obtained but reverse phase elution on a 10 micron LiChrosorb CN (250 X 4 mm ID) column with tetrahydrofuran/acetonitrile/water (5:1:4) and normal phase elution on a 5 micron LiChrosorb SI-60 column (250 X 4.6 mm ID) with chloroform indicated a mixture of approximately 50% of each isomer. Comparison of the carbonyl peak heights indicated a mixture of 52%/48%. Due to the insignificant difference, no attempt was made to assign the structure of the "major" component.

It seems that the electron donating (resonance) effect of the

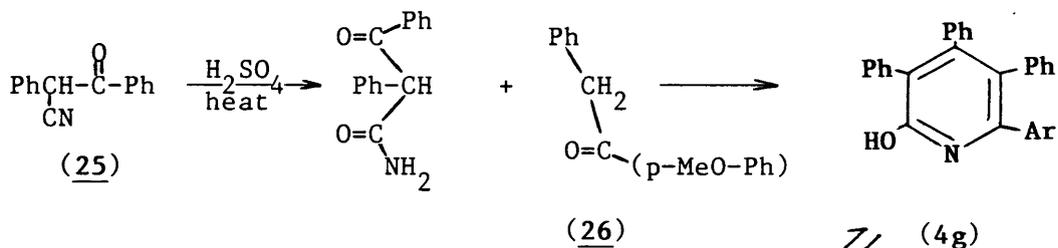
chlorine is almost evenly balanced by the electron withdrawing (inductive) effect, hence no selectivity to site substitution is seen.

In the case of the 2-(p-methoxy)tetracyclone (1d), it was reasoned that the electron donating nature of the methoxy group would stabilize the cation 21b and hence the addition of azide would be preferred on the unsubstituted side of the tetracyclone. Again, a mixture was obtained and converted to the corresponding 2-pyridinones (4e, 4f) for ease of analysis. Both of these mixtures also eluded separation. A good HPLC analysis could not be obtained⁶⁷ but normal phase elution on the LiChrosorb CN column with diethyl ether indicated a noticeable excess of one isomer. Comparison of the methoxy peak heights in the ¹H-NMR spectrum showed a 72% / 28% product distribution. Attempts at assigning either structure by ¹H/¹³C-NOE and ¹³C-INADEQUATE experiments failed due to sample and instrumental difficulties. The compounds have not been described in the literature so a specific synthesis for a single isomer is unknown. Two of the four known syntheses for tetraphenyl-2(1H)-pyridinone would also give a mixture of the same isomers.^{3,5} The third synthesis would not only have yielded a mixture, but utilized such exotic reagents and gave such poor yields as to preclude its use in any case.⁴ An attempt to synthesize the 3-(p-methoxyphenyl)triphenyl-2(1H)-pyridinone (4f) from desoxybenzoin and alpha-benzoyl-p-methoxybenzyl cyanide² yielded only starting material and tarry by-products:

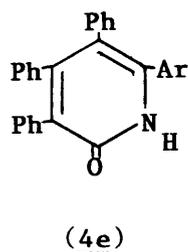




However, the synthesis was successful when alpha-benzoylbenzyl cyanide and p-methoxyphenyl benzyl ketone (4-methoxydesoxybenzoin) were used:



Ar = p-MeO-Ph

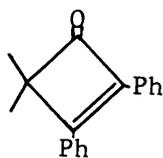


The product was used to spike the $^1\text{H-NMR}$ sample of the pyridinone mixture (4e and 4f) which had been obtained from the azide reaction. A 12% enhancement of the smaller, downfield peak confirmed that 4f was the major isomer, as was expected.

SUMMARY and CONCLUSIONS

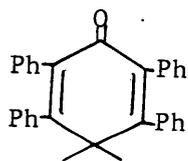
In conclusion, two points should be noted.

First, reactions of the type which yield tetraphenyl-2(1H)-pyridinone from tetracyclone and sodium azide seem to be limited to cases of strained, cyclic, unsaturated ketones which have an alpha phenyl group and no other stabilization for the cyclic ketone. None of the simple linear ketones reacted due to charge delocalization from the beta carbons into the phenyl rings. The 7-membered tropone system did not react due to the aromatic character of the ring system which comes from electron delocalization in the ring. The 3-membered ring system reacted, but not in the same fashion as did the tetracyclones. To complete the series, a 4-membered cyclic ketone such as 23⁶⁹ and a 6-membered ketone such as 24a or 24b should also be studied.

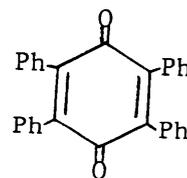


23

If 24b is studied, 15 or a similar compound should also be examined.



24a⁵⁵



24b⁷⁰

Second, para-substitution on the 2-phenyl moiety has little or no effect on the reaction in terms of the ratio of products obtained due to site selectivity of the azide ion. The 2-(p-chloro)tetracyclone (1c)

gives a 1:1 product ratio of the two possible isomers, i.e., the substituent causes no effect. This is due to the electron withdrawing properties (induction) being equal and opposite to the electron donating properties (resonance). The two phenomena cancel and the reaction occurs as if there is no substituent. The methoxy substituent has a moderate directing effect on site selectivity, so the product ratio of the two possible isomers from 2-(p-methoxy)tetracyclone (1d) is approximately 3:1 in favor of the isomer resulting from the most stable initial allylic cation, 21b.

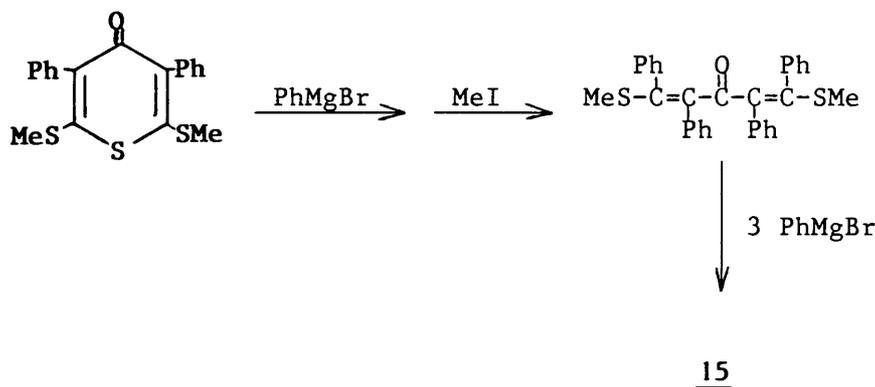
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Cyano column

ether

THF

methylene chloride

THF/water (9:1, 4:1, 7:3, 1:1)

THF/ACN/water (5:1:4, 4:1:5,
65:10:25)

SI-60 column

chloroform

chloroform/hexane (9:1, 4:1)

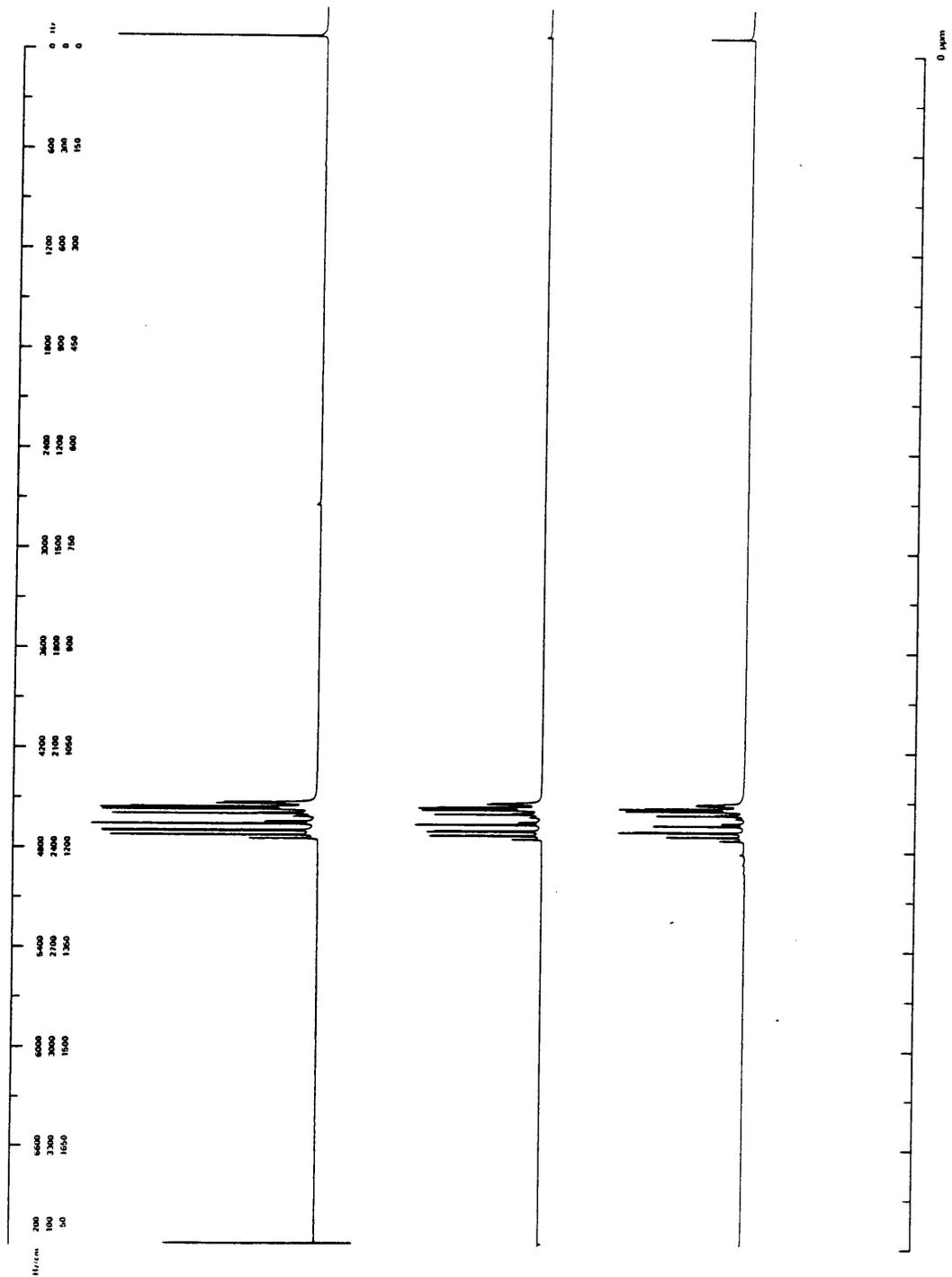
ether

benzene

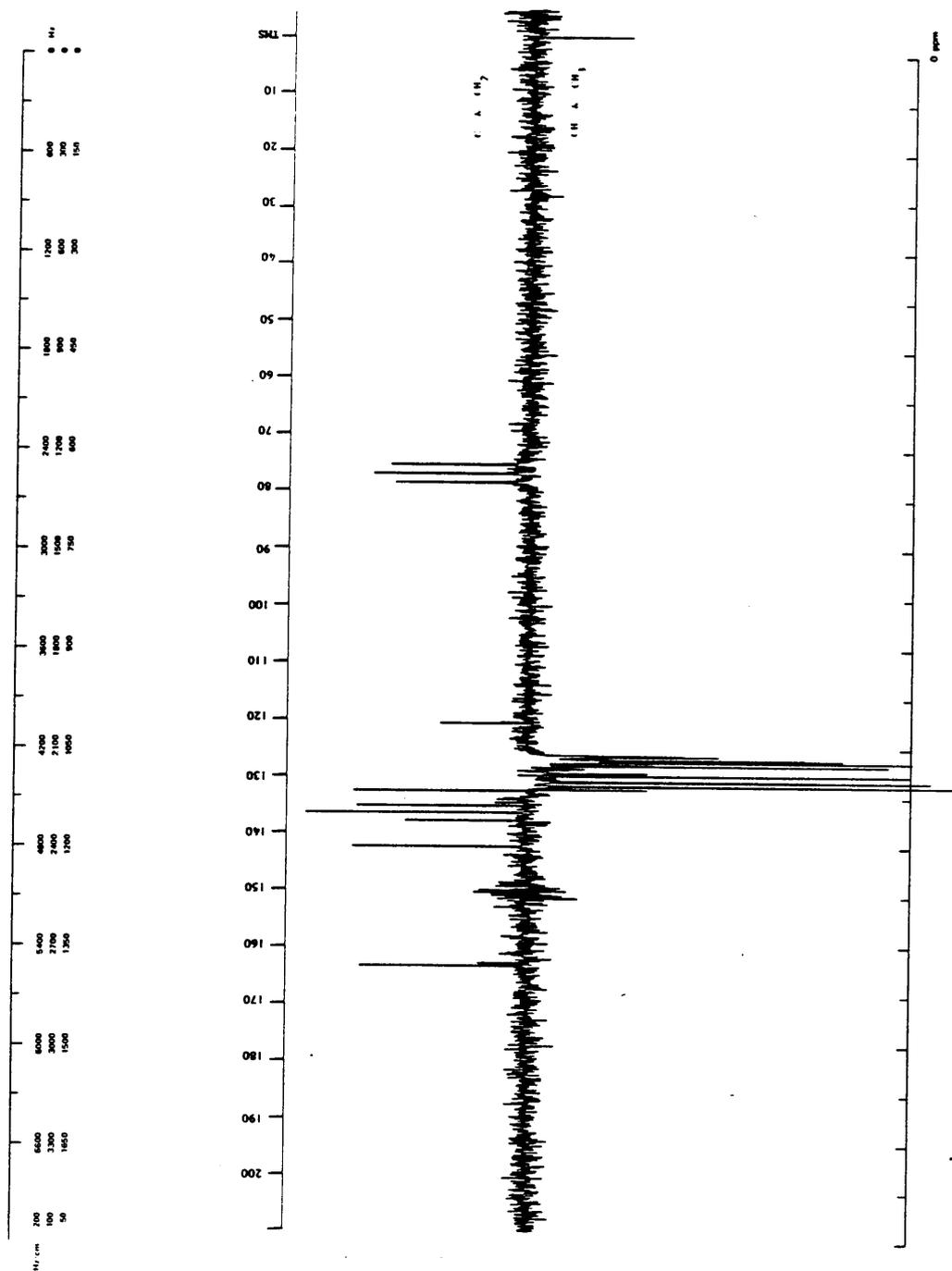
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APPENDIX A



^{13}C -INEPT spectrum of pyridinone mixture from 2-(p-chloro)tetracyclone



¹³C-Pseudo-INEPT spectrum of pyridinone mixture from 2-(p-chloro)-tetracyclone

APPENDIX B

Experiments with 3-(p-Chlorophenyl)tetracyclone

The title compound⁷¹ was reacted in the usual way with sodium azide in 70% yield of pale yellow needles, m.p., 179 - 181°C (dec.). Upon thermal decomposition, the compound did not become red-brown as did the 2-substituted tetracyclone adducts, but decomposed to a "chablis" colored liquid. The corresponding pyridinone had the same color in acetic acid solution.

For the pyridinone:

IR(cm⁻¹): 3425(NH), 1640(C=O).

¹³C-NMR(ppm):

163.09	C=O
152.87	
151.87	C-4 (Beta)
143.76	C-6
120.14	
119.12	C-3 (Alpha)

Peak intensities of the alpha and beta carbons indicate a product distribution of approximately 65% / 35%. Even in the 3-position, p-chloro substitution had essentially no effect on the reaction. The opposing inductive/resonant effects of chlorine are too closely matched in this reaction to direct the addition.

APPENDIX C

Experiments with 3-(p-Methoxyphenyl)tetracyclone

The title compound was prepared by condensing p-methoxybenzil with dibenzyl ketone by the procedure of Johnson and Grummitt³⁵ in 79% yield. The tetracyclone is "milk-chocolate" colored and melts at 196 - 198°C.

The ketone was treated in the usual way to form first the bicyclo-adduct and then the corresponding pyridinone.

For the pyridinone:

IR(cm^{-1}): 3660(str, sh), 3475, 3425, 1645(C=O).

¹³C-NMR(ppm):

162.79	C=O	
157.79	C-4 (Beta)	
157.64		
143.33	C-6	
143.19		
137.63	C-3 (Alpha)	
136.22		
112.74	ortho to MeO	
112.39		
57.47	(88%)	MeO
54.66	(12%)	

The peak intensities of the methoxy carbons indicate a product distribution of 88% / 12%. When the substituted phenyl is in the 3-position, its effect is apparently intensified somewhat by a weak conjugation effect.⁶¹ It is assumed that attack by azide would be preferred on the carbon bearing the substituted ring.

APPENDIX D

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