4-1988

Synthesis and Reactions of $_a$-Diketones and Preparation of Some New Benzimidazoles

Mohamad Reza Agharahimi

SYNTHESIS AND REACTIONS OF α-DIKETONES AND PREPARATION OF SOME NEW BENZIMIDAZOLES

by

Mohamad Reza Agharahimi

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Arts
Department of Chemistry

Western Michigan University
Kalamazoo, Michigan
April 1988

SYNTHESIS AND REACTIONS OF α-DIKETONES AND PREPARATION OF SOME NEW BENZIMIDAZOLES

Mohamad Reza Agharahimi, M.A.

Western Michigan University, 1988

This report will discuss the synthesis of 2,5-di-(*p*-chlorophenyl)-3,4-dioxo-adiponitrile and its reactions. This compound exists in the form of 4,4'-dichloropulvinic nitrile which is a precursor to 4,4'-dichlorovulpinic acid. These compounds have been shown to have antiinflammatory activity in rats.

The benzimidazole and pyridazine derivatives of 4,4'-dichloropulvinic nitrile and the benzimidazole derivative of 4,4'-dichlorovulpinic acid are another group of compounds that are also believed to have useful biological activities. The Pinner synthesis of imidates is used to make the intermediate to the benzimidazole derivative of 4,4'-dichloropulvinic nitrile.

This report will include the methodology of the reactions and the spectral data of these compounds.

ACKNOWLEDGMENTS

I would like to thank my research advisor Dr. Robert E. Harmon for his support and patience during the course of my research.

I would also like to express my appreciation to the member of my grduate committee Dr. Robert Anderson and Dr. William Kelly.

I would like to dedicate this thesis to my wife Ahdiyeh.

Mohamad Reza Agharahimi

INFORMATION TO USERS

This reproduction was made from a copy of a document sent to us for microfilming. While the most advanced technology has been used to photograph and reproduce this document, the quality of the reproduction is heavily dependent upon the quality of the material submitted.

The following explanation of techniques is provided to help clarify markings or notations which may appear on this reproduction.

1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting through an image and duplicating adjacent pages to assure complete continuity.

2. When an image on the film is obliterated with a round black mark, it is an indication of either blurred copy because of movement during exposure, duplicate copy, or copyrighted materials that should not have been filmed. For blurred pages, a good image of the page can be found in the adjacent frame. If copyrighted materials were deleted, a target note will appear listing the pages in the adjacent frame.

3. When a map, drawing or chart, etc., is part of the material being photographed, a definite method of "sectioning" the material has been followed. It is customary to begin filming at the upper left hand corner of a large sheet and to continue from left to right in equal sections with small overlaps. If necessary, sectioning is continued again—beginning below the first row and continuing on until complete.

4. For illustrations that cannot be satisfactorily reproduced by xerographic means, photographic prints can be purchased at additional cost and inserted into your xerographic copy. These prints are available upon request from the Dissertations Customer Services Department.

5. Some pages in any document may have indistinct print. In all cases the best available copy has been filmed.

University Microfilms International
300 N. Zeeb Road
Ann Arbor, MI 48106

Order Number 1333495

Synthesis and reactions of α-diketones and preparation of some new benzimidazoles

Agharahimi, Mohamad Reza, M.A.

Western Michigan University, 1988

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Vulpinic acid (Figure 1) is a yellow pigment which can be found in different kinds of *lichens*. The structure of this compound was first derived by Spiegel[1] and Karrer, Gehrciens and Heuss[2] and confirmed through synthesis by Volhard[3].

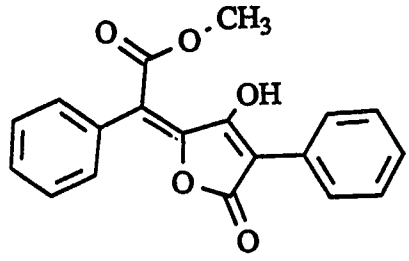


Figure 1. Vulpinic acid

The natural product vulpinic acid has remarkable resemblance to the compound 3-acyl-5-arylidene-4-hydroxy-2-oxo-2,5-dihydrothiophenes[4] (Figure 2) which is an immunosuppressive agent. Despite this resemblance, vulpinic acid showed no immunosuppressive activity but was found to be active in the adjuvant arthritis test in rats[5].

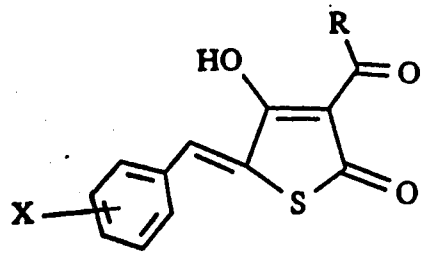


Figure 2. 3-Acyl-5-arylidene-4-hydroxy-2-oxo-2,5-dihydrothiophenes

Because of the interesting biological activity of vulpinic acid, some analogs of this compound were synthesized and are discussed in this report.

The first step of this project was to synthesize 4,4'-dichloropulvinic nitrile (Scheme I, 2) and subsequently synthesize 4,4'-dichlorovulpinic acid (Scheme I, 3). The reaction of 4,4'-dichlorovulpinic acid with o-phenylenediamine led to one of the target compounds benzimidazole (Scheme I, 4). In order to make the benzimidazole derivative of 4,4'-dichloropulvinic nitrile (Scheme II, 6) the Pinner synthesis was used to make its imidate derivative[13]. Then the imidate derivative of 4,4'-dichloropulvinic nitrile (Scheme II, 5) was reacted with o-phenylenediamine which gave the second target compound benzimidazole (Scheme II, 6). These new benzimidazoles are believed to have antiviral activities. The reaction between 4,4'-dichloropulvinic nitrile and hydrazine led to a new pyridazine compound (Scheme III, 7) which also has potential biological activity. The summary of the reactions are shown in Schemes I - III.

CHAPTER II

HISTORICAL

The antiinflammatory activity of the phenylacetic acids have been reported in the literature[6,7]. It is believed that the antiinflammatory activity of vulpinic acid is due to the transport of the phenylacetic acids to the receptor sites of the cells in the body. The lactone bond and the ester group of the vulpinic acid can be hydrolyzed and form a diketone with two phenylacetic acid residues on each side (Figure 3).

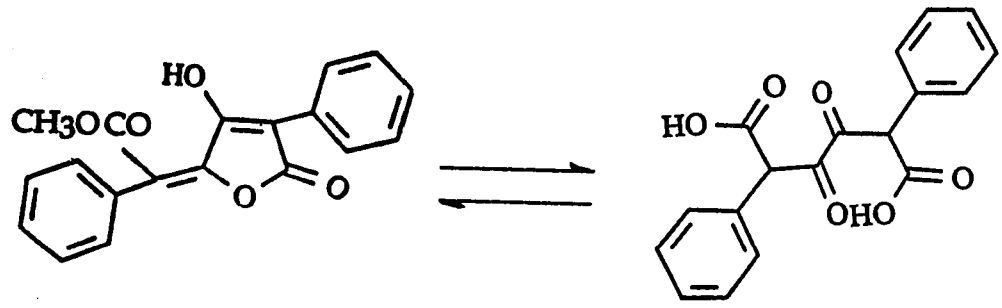
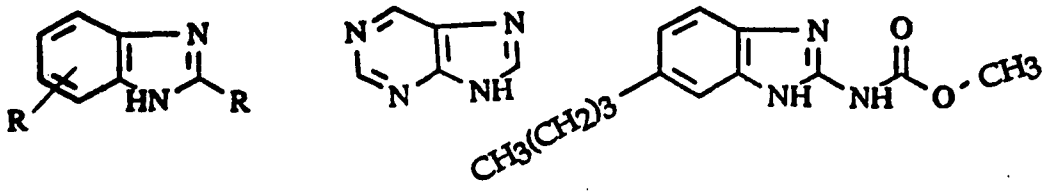


Figure 3. Hydrolysis of Vulpinic acid

Since as early as 1935, the use of purine derivatives have been under investigation as chemotherapeutic agents. In 1954 Bendich, Russell and Fox[8] reported the synthesis and antitumor activity of 6-chloropurine. The most natural occurrence of purine is in the nucleotides and nucleic acids which perform the most important functions in metabolism. Nucleic acids are found in all living cells and they direct the synthesis of proteins and are responsible for the transfer of genetic information.

Nucleotides are composed of either D-ribose or 2-deoxy-D-ribose linked at C5 oxygen to a phosphate unit and by the C1 to the nitrogen of either purine or pyrimidine base.

Benzimidazoles exhibit a great structural similarity with the purine as shown in Figure 4. When benzimidazoles are present in the host cell they behave analogously to purine bases. This replacement in the viral nucleic acid during replication leads to non-functional DNA.



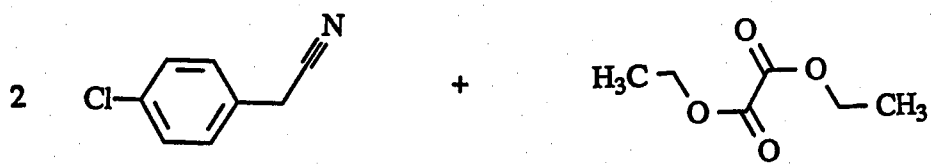
(a) (b) (c)

Figure 4. Benzimidazole (4a), Purine (4b), and Parbendazole (4c)

It is known that the replacement of hydrogen on the nitrogen atom would destroy the activity since the >N-H group of the imidazole group attaches itself to the ribose or deoxy-ribose of the nucleotide.

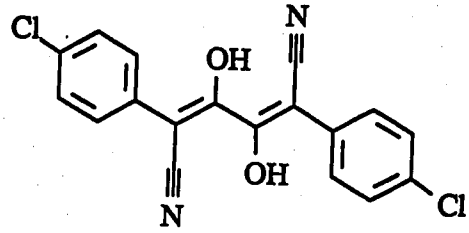
Benzimidazoles have been reported to have antitumor[9] and antithyroid[9] activity. These compounds also have been known to inhibit viral production in tissue cultures[9]. The activity of this compound depends on the location and the nature of the substituents. For example, Parbendazole[10] (Figure 4) was found to be an antitumor agent.

Scheme I

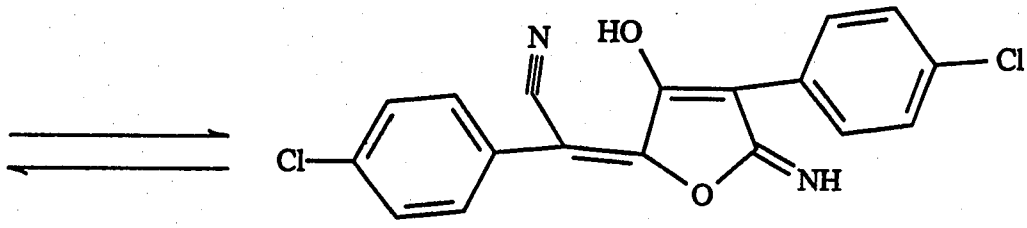


1) 2 M-$NaOC_2H_5$
C_2H_5OH

Reflux
2) 50% Acetic acid

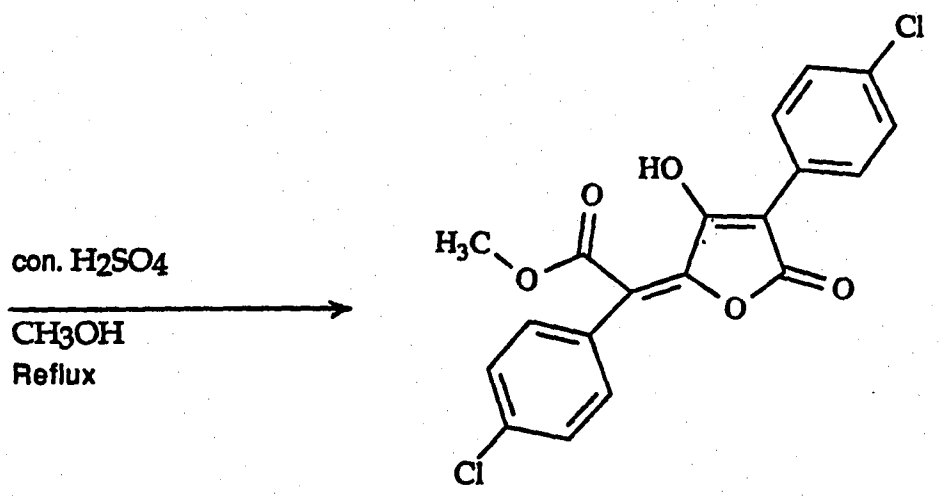


1

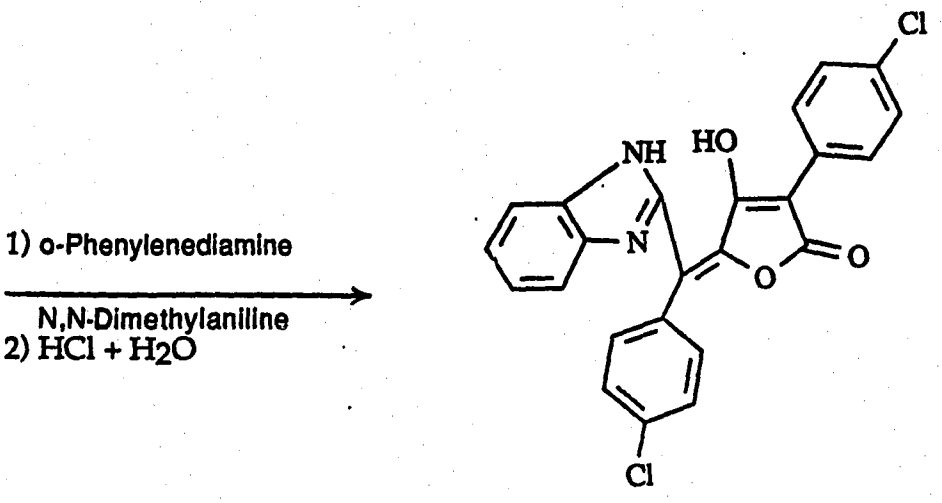


2

Scheme 1 --continued

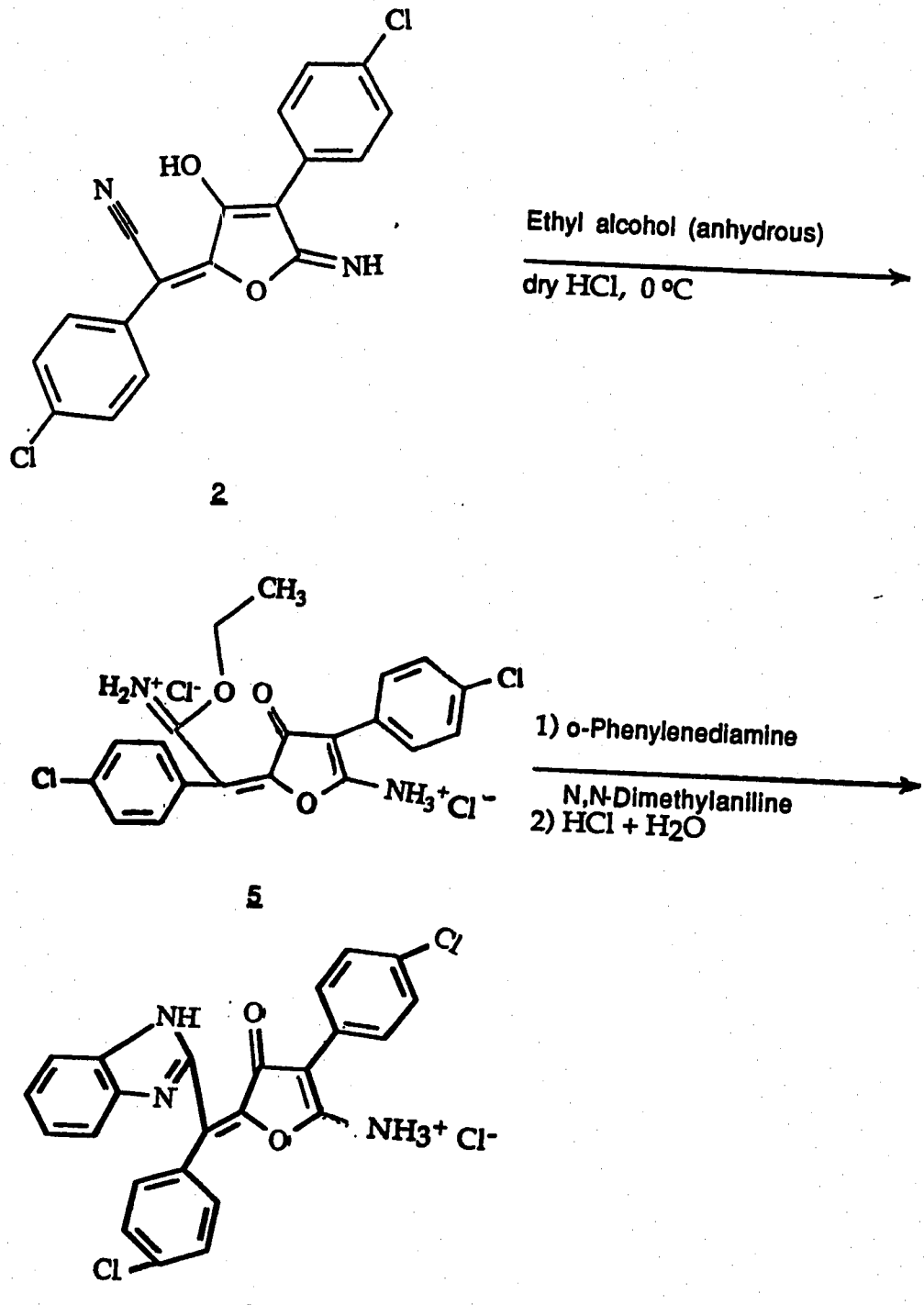


3

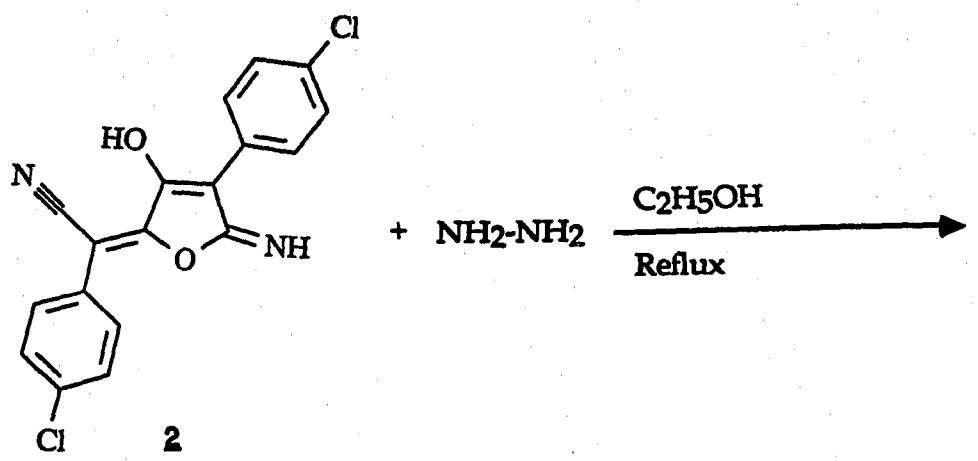


4

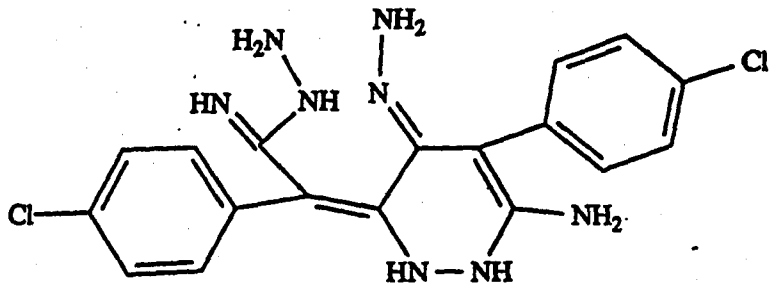
Scheme II



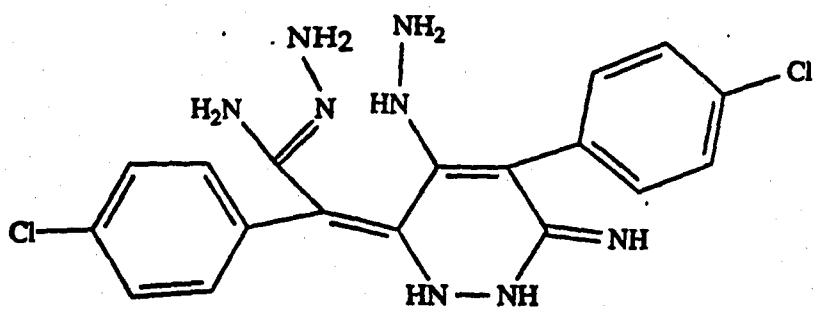
Scheme III



2



7



8

CHAPTER III

EXPERIMENTAL

The structures of these compounds was verified by using infrared spectroscopy, nuclear magnetic resonance spectroscopy, ultraviolet spectroscopy and microanalysis. The Beckman Acculab Spectrophotometer was used for IR spectra determination. The IBM-NR/200AF Spectrophotometer was used to determined NMR spectra. The UV spectra were obtained by using an HP 8452 Diode Array UV/VIS Spectrophotometer. Samples were sent to Midwest Microlab of Indianapolis for elemental analysis. Melting points were determined by using a Thomas Uni-melt Capillary Melting Point apparatus and are not corrected.

Procedures

4,4'-Dichloropulvinic nitrile (2)

This compound was prepared using the method by Foden, McCormick and O'Mant.[11]

Sodium 2.30 g (0.10 mol), was dissolved in 50 mL of absolute ethyl alcohol. The solution was cooled and 15.20 g (0.10 mol) of p-chlorobenzyl cyanide was added. Then 7.30 g (50 mmol) of diethyl oxalate was added and the mixture was refluxed at 60-70 °C for 1 hour. The cooled solution was diluted with 15 mL of distilled water and acidified with 50% acetic acid to PH 5. The mixture was again diluted with 80 mL of distilled water and the product was filtered. This compound was recrystallized from N,N-dimethylformamide and weighed 9.35 g

(53% theoretical), m.p. 275-284 °C (literature[11] 268-283 °C). IR (KBr) cm^{-1}: 3600-3800 (O-H), 3250 (N-H), 2250 (C≡N), Elemental analysis: found C 60.33, H 2.77, N 8.12, Cl 19.63; calculated C 60.53, H 2.82, N 7.84, Cl 19.85.

4,4'- Dichlorovulpinic acid (3)

To synthesize this compound a modification of a procedure used by Foden, McCormick and O'Mant[11] was employed. The refluxing time was increased from 17 to 24 hours.

To begin the procedure 5.0 g (14 mmol) of 4,4'-dichloropulvinic nitrile was dissolved in 30 mL of methyl alcohol. Then 10 mL of concentrated sulfuric acid was added drop by drop. The mixture was refluxed for 24 hours. After cooling the product was filtered. The bright yellow product was recrystallized from 1-butanol. Yield 3.75 g (92% theoretical), m.p. 183-185 °C (literature[11] 183-185 °C). IR (KBr) cm^{-1}: 3600-3750 (O-H stretch), 1775 (C=O lactone), 1680 (C=O ester). Elemental analysis: found C 58.33, H 3.12, Cl 17.83; calculated C 58.18, H 3.34, Cl 18.08.

2-(α-2-Benziminazolyl-4-chlorobenzylidene)-4-(*p*-chlorophenyl)-3-hydroxy-5-oxo-furan (4)

A modification of a procedure by Mittal and Seshadri[12] was used to prepare this compound.

The compound 4,4'-dichlorovulpinic acid 0.20 g (0.5 mmol), and o-phenylenediamine 0.14 g (1.3 mmol) were refluxed in 10 mL of N,N-dimethylaniline for 7 hours. In the original procedure the refluxing time was only 4 hours. After cooling the mixture was poured into 50 mL of dilute hydrochloric acid. The product was then filtered and washed with dilute acid. The brown product was

recrystallized from a mixture of ethyl acetate and hexane and weighed 0.10 g (48% theoretical). The melting point was 134-135 °C. IR (KBr) cm^{-1}: 3600-3850 (O-H stretch), 3400 (N-H), 1740 (C=O). Elemental analysis: found C 63.47, Cl 16.18, N 6.46, H 3.44; calculated C 64.16, Cl 15.78, N 6.24, H 3.14.

5-Amino-2-(4-chlorobenzylidene-α-ethylformimidate hydrochloride)-4-(*p*-chlorophenyl)-3-oxo-furan hydrochloride (5)

This compound was synthesized by using a procedure by McElvain and Stevens[13].

The compound 4,4'-dichloropulvinic nitrile 1.07 g (3.0 mmol) was dissolved in 40 mL of absolute ethyl alcohol in a 250 mL flask. Dry hydrogen chloride was bubbled into the solution for 3-4 minutes and the flask was stoppered and stored in the freezer for two days. The resulting solution was then diluted with anhydrous ethyl ether and filtered. The filtrate was left overnight to crystallize. The bright yellow product was recrystallized from a mixture of anhydrous ethyl alcohol and ethyl ether and stored in a dessicator over sodium hydroxide for 24 hours. The salt weighed 0.92 g (65% theoretical) and decomposed at 238-240 °C. IR (KBr) cm^{-1}: 3090-3260 (N-H stretch), 1760 (C=O). Elemental analysis: found C50.66, H 3.28, Cl 30.26; calculated C 50.46, H 3.81, Cl 29.78.

5-Amino-2-(α-2-benziminazolyl-4-chlorobenzylidene)-4-(*p*-chlorophenyl)-3-oxo-furan hydrochloride (6)

A modification of a procedure by Mittal and Seshadri[12] was used to prepare this compound.

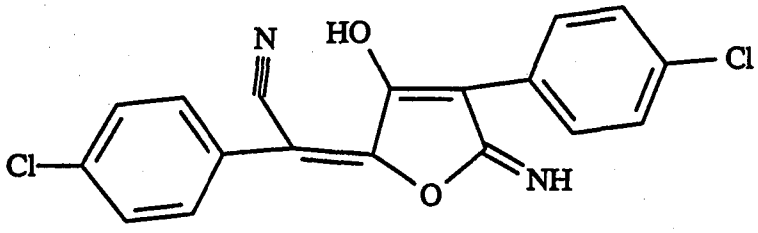
5-Amino-2-(4-chlorobenzylidene-α-ethylformimidate hydrochloride)-4-(*p*-chlorophenyl)-3-oxo-furan hydrochloride 0.11 g (0.25 mmol) was added to 0.027

g (0.25 mmol) of o-phenylenediamine in 15 mL of N,N-dimethyl aniline. The mixture was refluxed for 8 hours. In the original procedure the time of the reflux was only 4 hours. After cooling the solution was poured into 30 mL of dilute hydrochloric acid. The product was then filtered and washed with dilute acid and recrystallized from a mixture of ethyl acetate and hexane. Yield 0.077 g (65% theoretical), m.p. 205-206 °C. IR (KBr) cm^{-1}: 3200-3400 (N-H stretch), 1710 (C=O). Elemental analysis: found C 58.79, N 8.77 H 3.64; calculated C 59.46, N 8.67, H 3.34.

6-(*p*-Chloroarylidene-7-amidehydrazone)-4-(*p*-chlorophenyl)-5-hydrazone-3-pyridazine imide (8)

The compound 4,4'-dichloropulvinic nitrile 1.07 g (3.0 mmol) was added to 50 mL of ethyl alcohol. To this solution 0.22 mL (7.0 mmol) of hydrazine was added . The mixture was refluxed for 18 hours and then the volume reduced to 25 mL and the solution kept in the refrigerator to crystallize. The yellowish product was filtered and recrystallized from hexane. Yield 0.22 g (23% theoretical), m.p. 285-286 °C. IR (KBr) cm^{-1}: 3150-3400 (N-H stretch). Elemental analysis: found C 50.79, H 3.78, N 25.17, Cl 16.05; calculated C 51.80, H 4.35, N 26.86, Cl 16.99.

SPECTRAL DATA



2

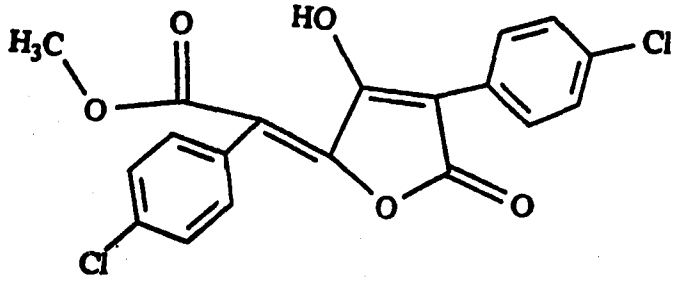
Table 1

NMR and UV Data for 4,4'-Dichloropulvinic nitrile

NMR (solvent D6 DMSO)			
Assignment	δ (ppm)	Multiplicity	Integration
Aromatic	7.32-7.98	Multiplet	7.35
N-H	3.38	Singlet	-
O-H	9.57	Singlet	1.00

UV (2.24 E-5 M DMSO		
λ_{max} (nm)	Absorbance	ε_{max}
276	0.0482	2153
322	0.02175	9711
434	0.0311	1189

SPECTRAL DATA (continued)



3

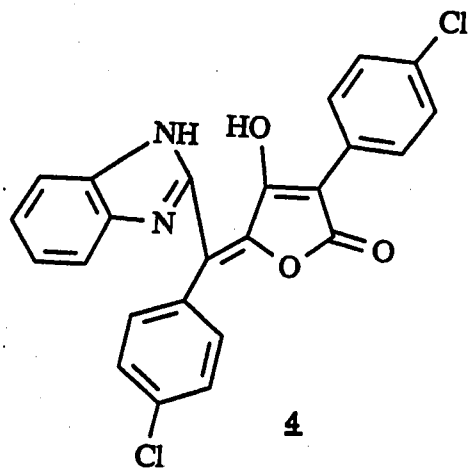
Table 2

NMR and UV Data for 4,4'-Dichlorovulpinic acid

NMR (solvent D6 Acetone)			
Assignment	δ (ppm)	Multiplicity	Integration
Aromatic	7.42-8.19	Multiplet	7.97
CH_3	3.97	Singlet	3.00
O-H	14.25	Singlet	-

UV (1.75 E-4 M $CHCl_3$)		
λ_{max} (nm)	Absorbance	ε_{max}
248	2.0864	11903
382	1.5753	8987

SPECTRAL DATA (continued)



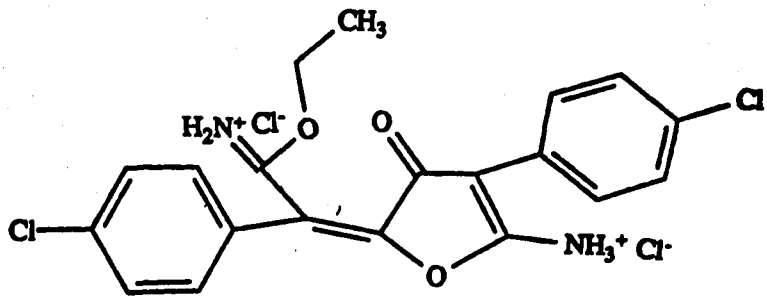
4

Table 3

NMR and UV Data for 2-(α-2-Benziminazolyl-4-chlorobenzylidene)-4-(*p*-chlorophenyl)-3-hydroxy-5-oxo-furan

NMR (solvent D6 Acetone)			
Assignment	δ (ppm)	Multiplicity	Intergration
Aromatic	7.22-8.23	Multiplet	11.55
N-H	3.14	Singlet	1.00
UV (1.11 E-4 M $CHCl_3$)			
λ_{max} (nm)	Absorbance		ε_{max}
250	1.9872		17857
364	1.1960		10748

SPECTRAL DATA (continued)



5

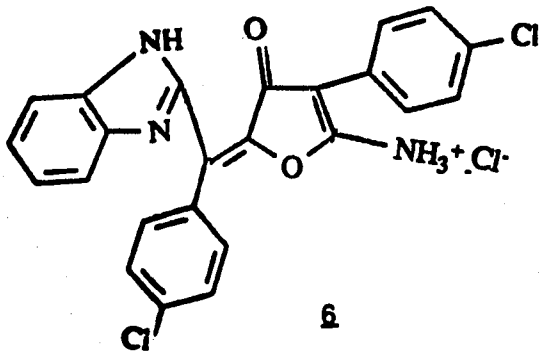
Table 4

NMR and UV Data for 5-Amino-2-(4-chlorobenzylidene-α-ethylformimidate hydrochloride)-4-(*p*-chlorophenyl)-3-oxo-furan hydrochloride

NMR (solvent D6 DMSO)			
Assignment	δ (ppm)	Multiplicity	Intergration
Aromatic	7.19-8.23	Multiplet	8.00
CH_3	1.24	Triplet	3.11
CH_2	4.23	Quartet	2.00

UV (1.68 E-5 M DMSO)		
λ_{max} (nm)	Absorbance	ε_{max}
308	0.1288	7669
392	0.0365	2173

SPECTRAL DATA (continued)



6

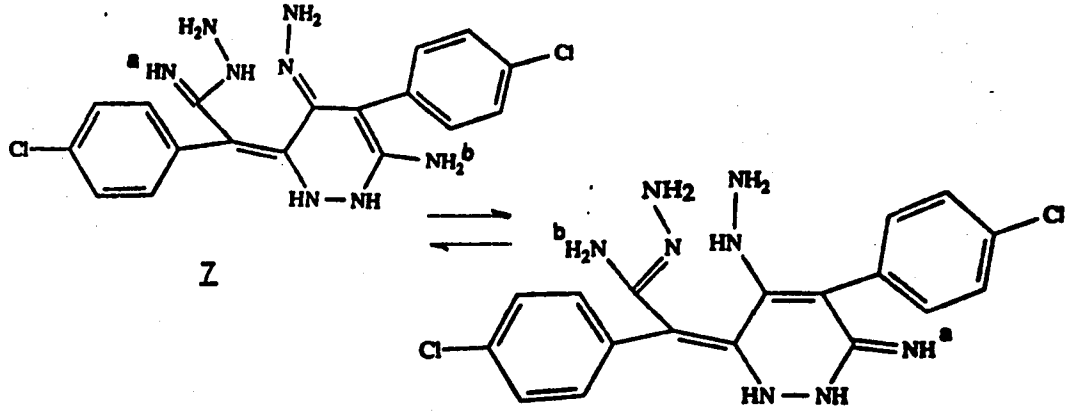
Table 5

NMR and UV Data for 5-Amino-2-(α-2-benziminazolyl-4-(chlorobenzylidene)-4-(*p*-chlorophenyl)-3-oxo-furan hydrochloride

NMR (solvent D6 Acetone)			
Assignment	δ (ppm)	Multiplicity	Integration
Aromatic	7.42-8.38	Multiplet	12.50
$^+NH_3$	3.11	Singlet	4.00
N-H	3.35	Singlet	4.00

UV (4.54 E-4 $CHCl_3$)		
λ_{max} (nm)	Absorbance	ε_{max}
252	0.8812	1942
368	0.7820	1723
398	0.8312	1832

SPECTRAL DATA (continued)



7

8

Table 6

NMR and UV Data for 6-(*p*-Chloroarylidene-7-amidehydrazone)-4-(*p*-chlorophenyl)-5-hydrazone-3-pyridazine imide

NMR (solvent D6 DMSO)			
Assignment	δ(ppm)	Multiplicity	Integration
Aromatic	7.00-7.35	Multiplet	12.18
$(NH)^a$	11.99	Singlet	1.00
$(NH_2)^b$	9.09	Singlet	2.18
NH and NH_2	4.37-5.05	3 Singlets	11.83

UV (3.83 E-4 M $CHCl_3$)		
λ_{max} (nm)	Absorbance	ε_{max}
244	1.2578	3284

CHAPTER IV

RESULTS AND DISCUSSION

The structural information of all the compounds prepared in this report were obtained using IR and NMR spectroscopy. Elemental analysis and UV/VIS spectroscopy were mainly used to complement this information.

The following represents the proposed mechanism of the main reactions:

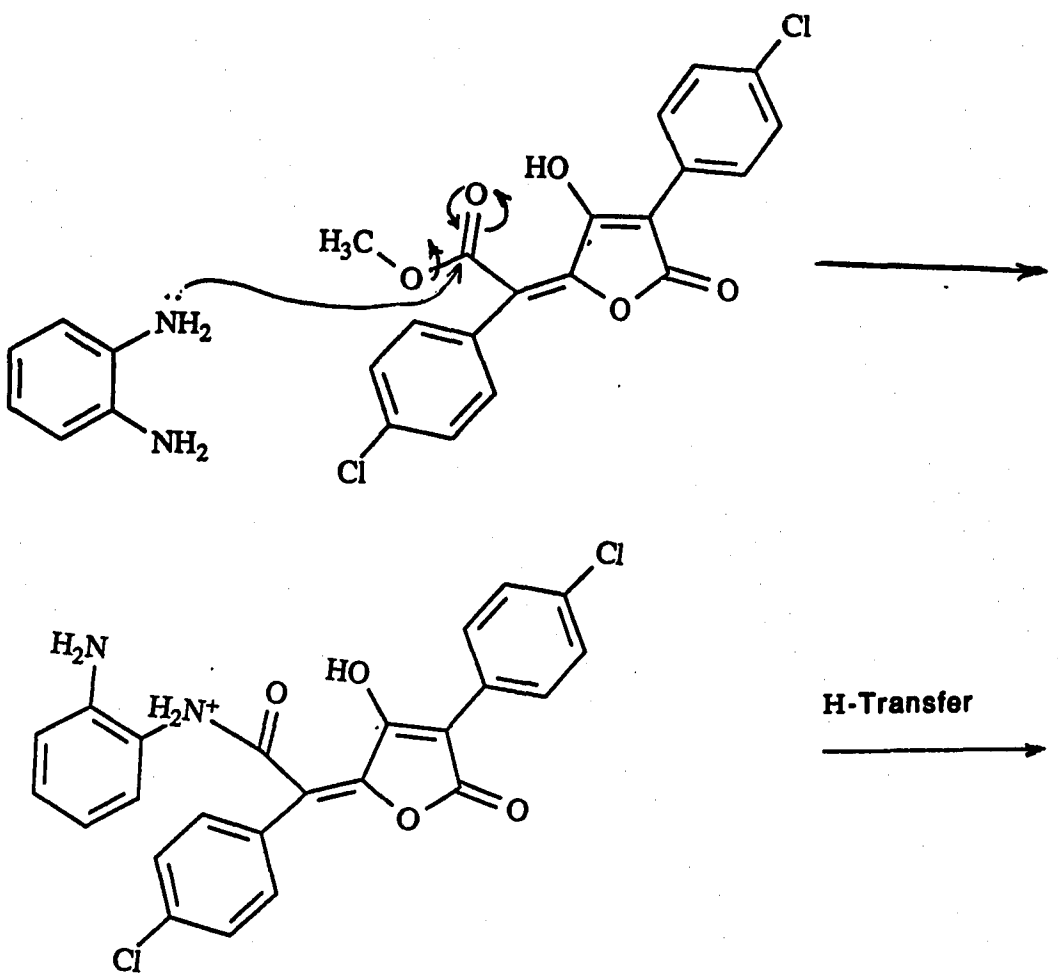
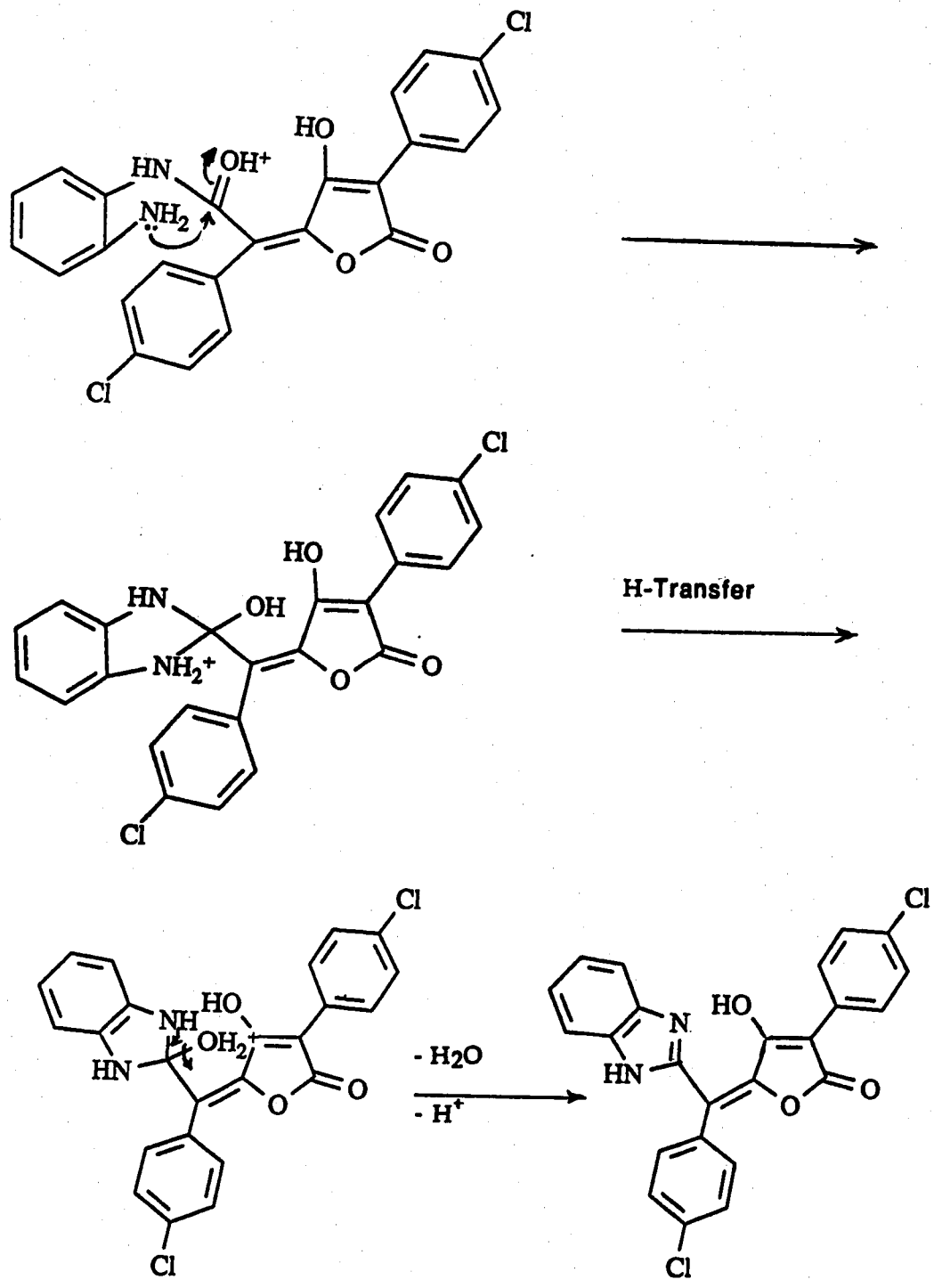


Figure 5. Mechanism for Preparation of 2-(α–2-Benziminazolyl-4-chloro-benzylidene)-4-(*p*-chlorophenyl)-3-hydroxy-5-oxo-furan

Figure 5 -- continued



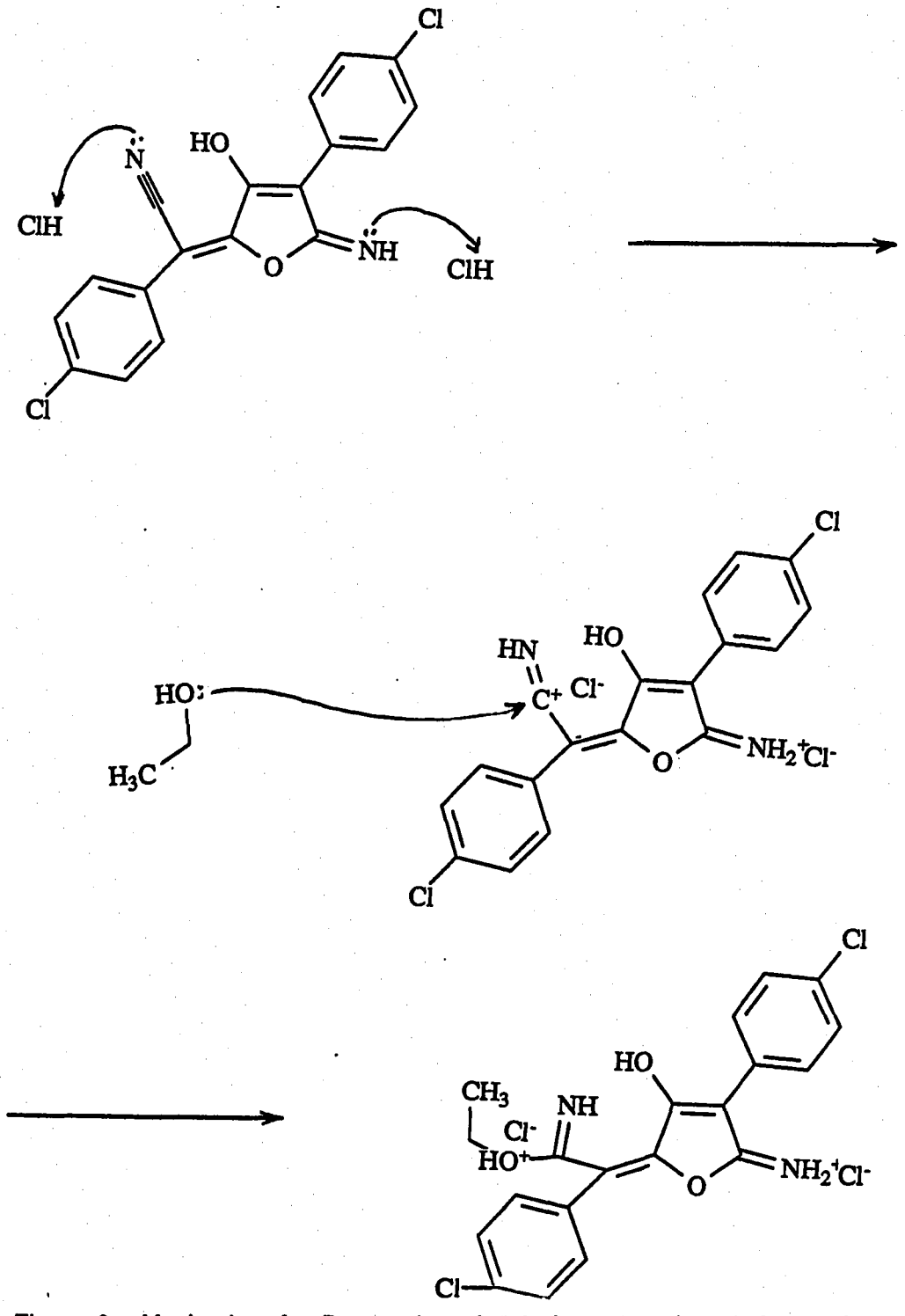
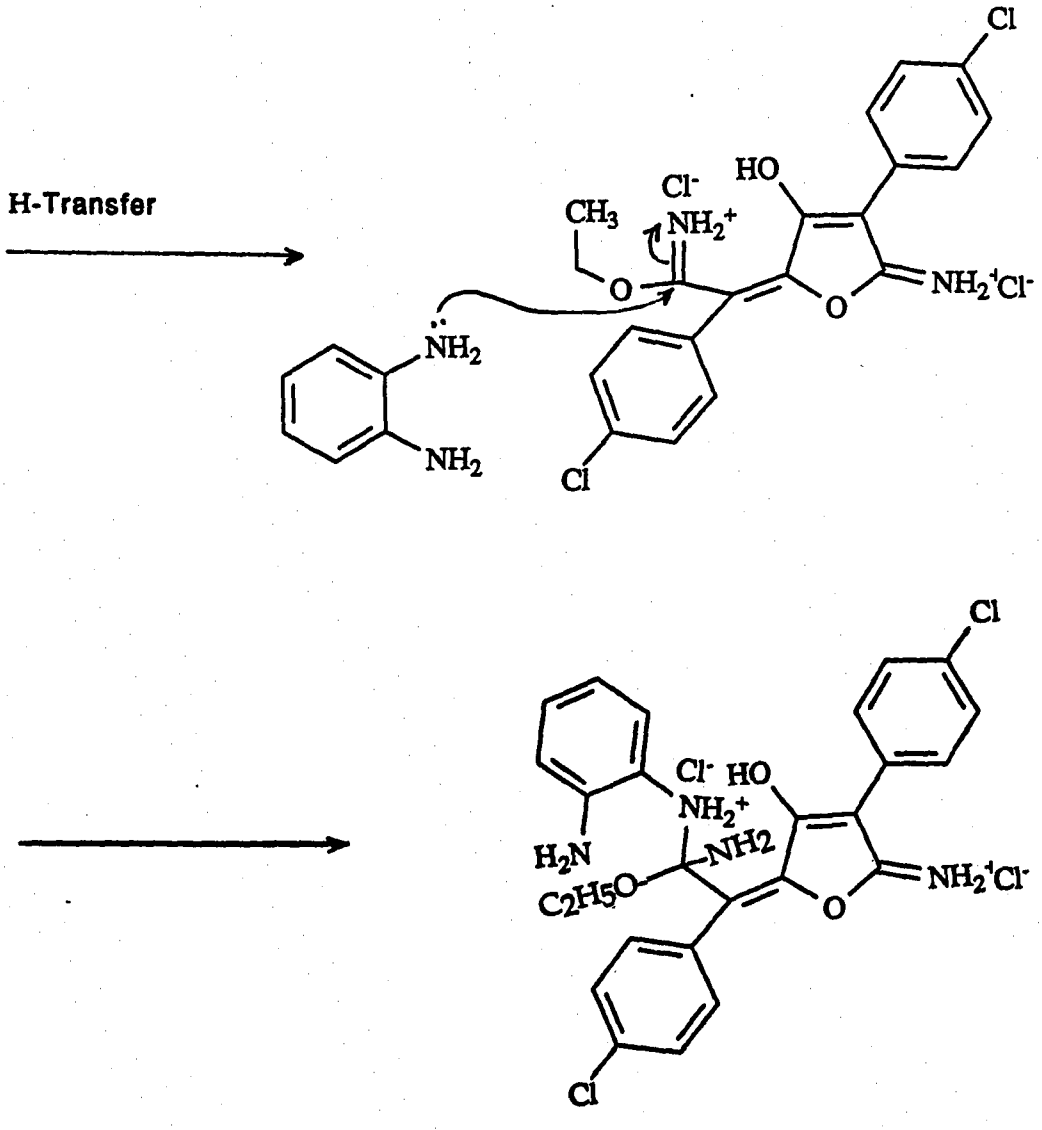


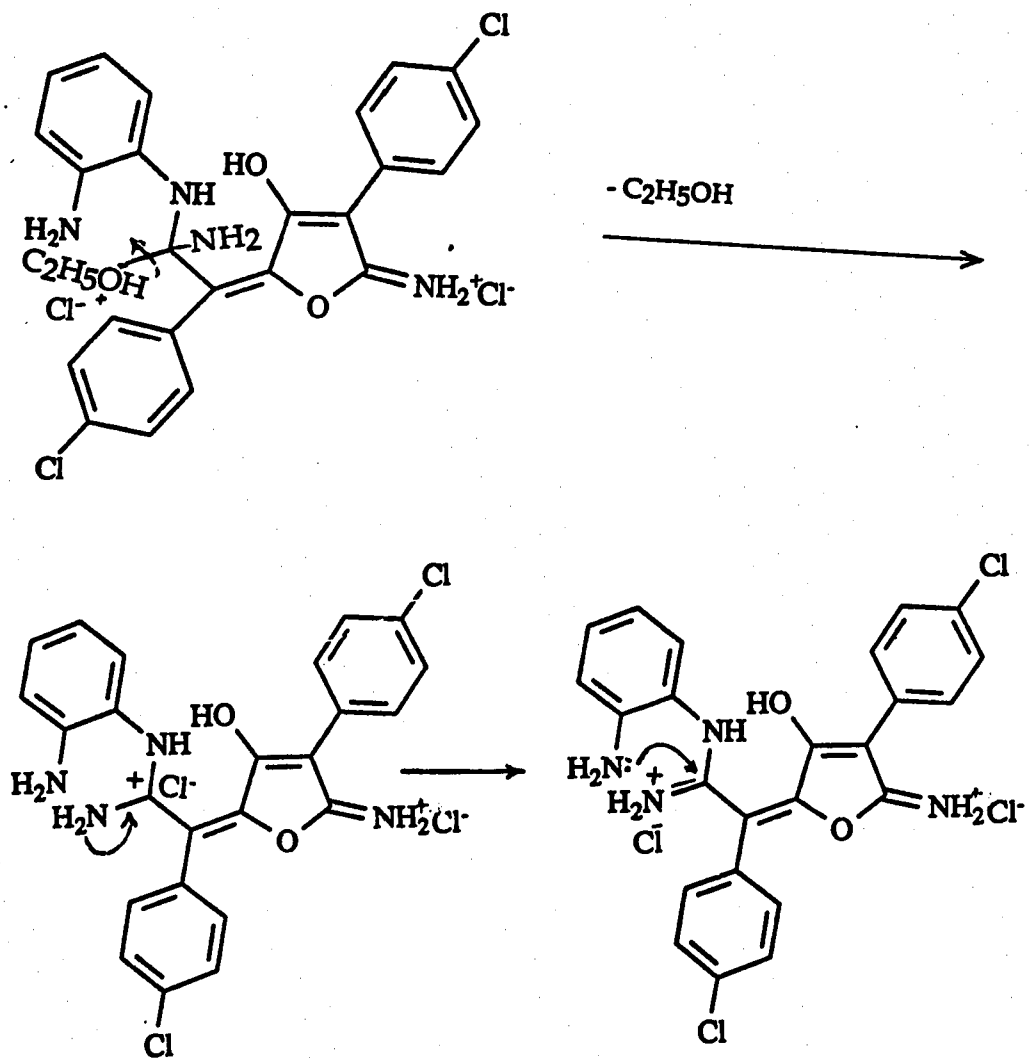
Figure 6. Mechanism for Preparation of 5-Amino-2-(α–2-benziminazolyl-4-chloro-benzylidene)-4-(*p*-chlorophenyl)-3-oxo-furan *h*ydrochloride

Figure 6 -- continued



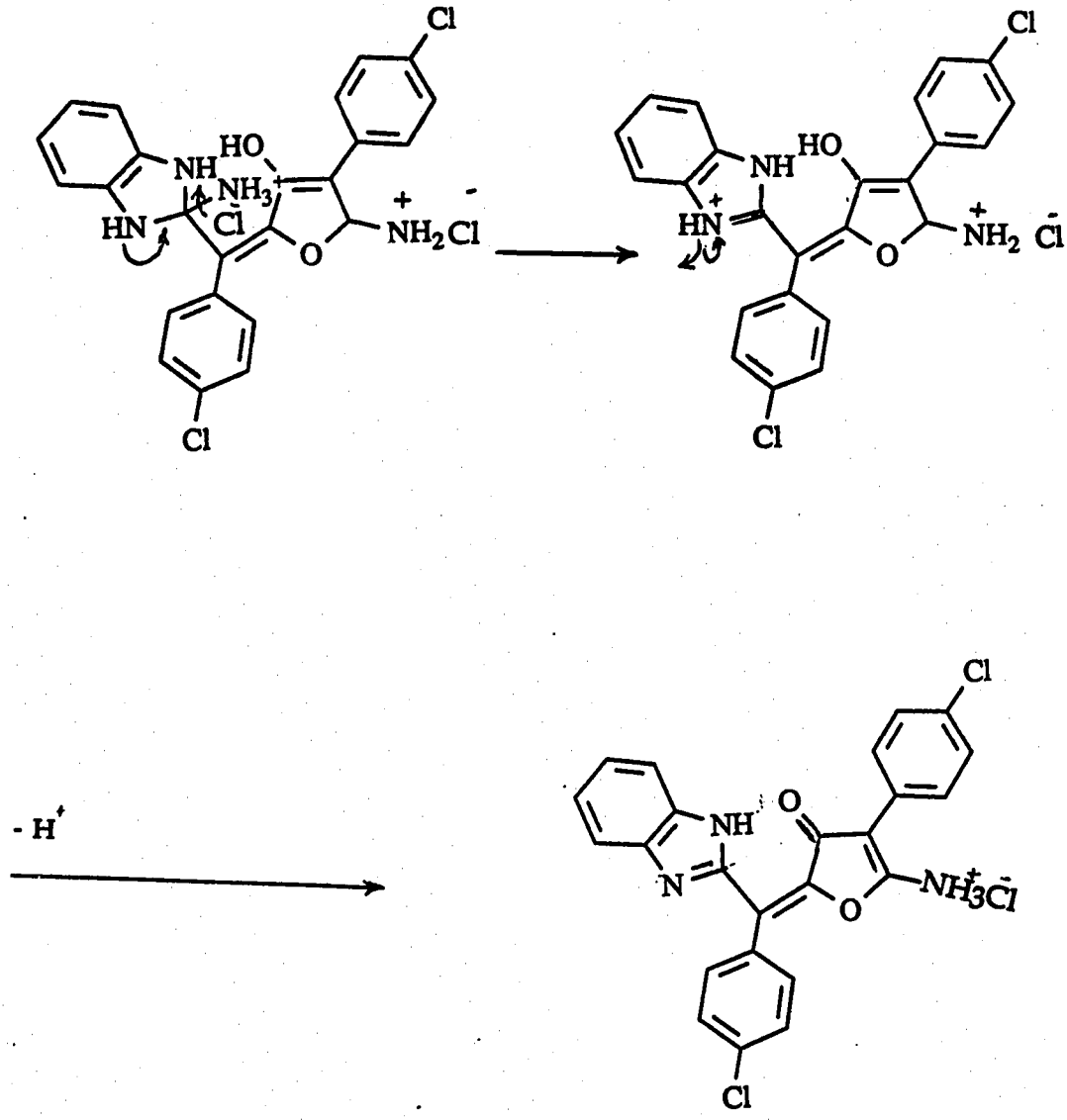
H-Transfer

Figure 6 -- continued



H-Transfer

Figure 6. -- continued



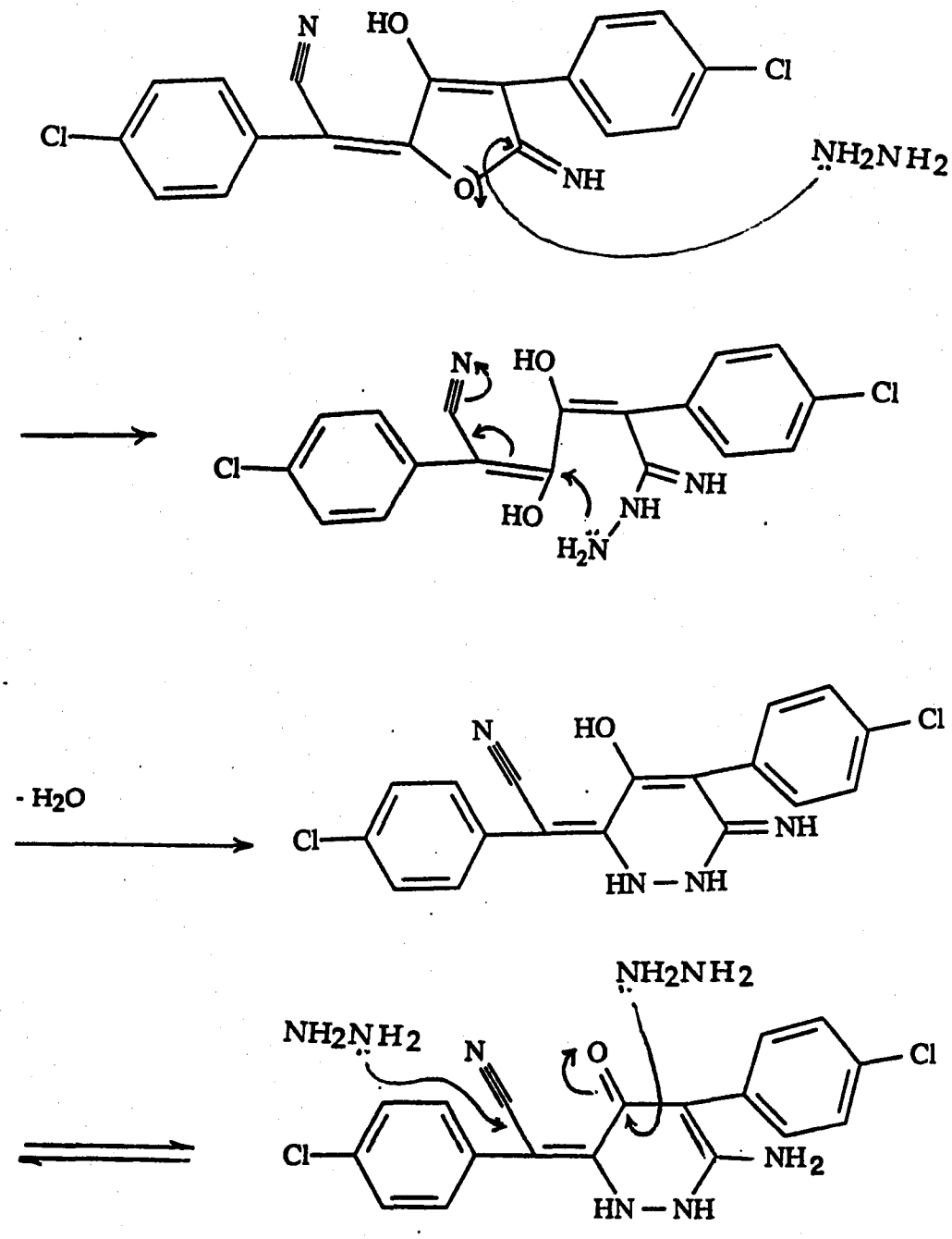
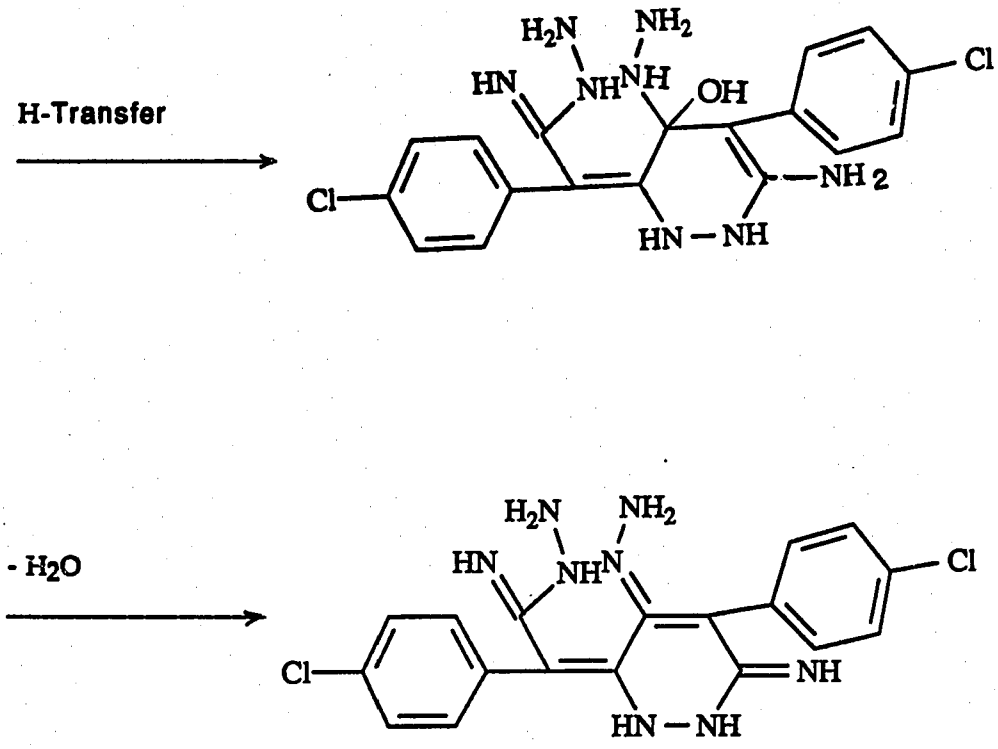


Figure 7. Mechanism for Preparation of 6-(*p*-Chloroarylidene-7-amidehydrazone)-4-(*p*-chlorophenyl)-5-hydrazone-3-pyridazine imide

Figure 7 -- continued



When *p*-chlorobenzyl cyanide reacts with diethyl oxalate the intermediate 2,5-di-(*p*-chlorophenyl)-3,4-dihydroxy adiponitrile is formed. This compound then participates in a ring closure between the enolic hydroxy and one of the cyano groups and exists in the form of 4,4'-dichloropulvinic nitrile. The IUPAC name of this compound is 4-(*p*-chlorophenyl)-2-(*α*-cyano-4-chlorobenzylidene)-3-hydroxy-5-imino-furan.

To prevent the opening of the lactone ring, 4,4'-dichloropulvinic nitrile was acid hydrolysed to form 4,4'-dichlorovulpinic acid. The IUPAC name of this compound is 2,5-di-(*p*-chlorophenyl)-3,4-dihydroxy-2,4-hexadienedioic acid, γ-lactone, methyl ester.

When 4,4'-dichloropulvinic nitrile was reacted with hydrazine, it was assumed the reaction occurs only at the carbon with the imino substituent. The IR spectra of the product showed no cyano peak due to the possible reaction with hydrazine. Because of the complexity of the structure of 6-(*p*-chloroarylidene-7-amidehydrazone)-4-(*p*-chlorophenyl)-5-hydrazone-3-pyridazine imide it is difficult to assign each individual NMR peak. The integration of the total NH and NH_2 peaks of NMR is consistant with that which is observed. The structure of this compound that is shown throughout this report is one of the possible isomeric forms of this compound and it may exist in other forms.

CHAPTER V

CONCLUSION

The synthesis of these compounds and assignment of their structures using different spectral methods proves that the project was a success. After analyzing the information gathered in this report, the compounds that were synthesized can help explore the unproven dimension of the chemical sciences. Combination of different substituents and study of their reaction and biological activities may prove interesting.

REFERENCES

1. Spiegel, A., Ann. 219 (1883) 1.

2. Karrer, P., Gehrckens, K. A., and Heuss, W., Helv. Chim. Acta. 9 (1926) 446.

3. Volhard, J., Ann. 282, (1894) 1.

4. O'Mant, D. M., J. Chem. Soc. 1501 (1968)

5. Newbould, B. B., Brit, J. Pharmacol. Chemother., 21, 127 (1963).

6. Chalmers, I. M., Ann. Rheum. Dis., 31, 110 (1972)

7. Nickander, R. C., Fed. Proc., Fed. Amer. Soc. Exp. Biol., 30, 2059 (1971)

8. Bendich, A., Russell, P. J., and Fox, J. J., J. Am. Chem. Soc., 76, 6073 (1954)

9. Preston, P. N., "Benzimidazoles and Congeneric Tricyclic Compounds", part 2; John Wiley and Sons: New York, NY, 1980, p. 531-541

10. Smith Kline & French Laboratories Brit. 1, 123, 317 (cl.c 07d), 14 Aug. 1968, US Appl. 23 Dec 1965-01 Jul. 1966; 12 pp; Chem. Abstr., vol 69 p. 9060

11. Foden, F. R., McCormick, J., and O'Mant, D. M., J. Med.Chem., 1975, vol. 18, no. 2

12. Mittal, O. P., and Seshadri, T. R., J. Chem. Soc., 1734 (1956)

13. McElvain, S. M., and Stevens, Calvin. L., J. Am. Chem. Soc., 69, 2663 (1947)