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Synthesis and Study of Novel Quinoxaline Di-N-oxide and 3-Acyl-2-Methylquinoxaline Di-N-oxides

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SYNTHESIS AND STUDY OF NOVEL QUINOXALINE DI-N-OXIDE AND 3-ACYL-2-METHYLQUINOXALINE DI-N-OXIDES

by

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Western Michigan University, 1988

This research project consists of two parts. The first involved the synthesis of a novel quninoxaline di-N-oxide via benzofuroxan. The second part was the use of this compound as a synthetic precursor.

It was assumed that 3,4-dimethylaniline would be successfully converted to 5,6-dimethylbenzofurazan 1-oxide (5,6-dimethylbenzofuroxan) through a sequence of reaction steps. Fortunately, this assumption was correct as the desired compound was produced. This compound was utilized in synthesizing the novel 3-acetyl-2,6,7-trimethylquinoxaline 1,4-dioxide. From the structure of this adduct, it is believed that it will take part in condensation reactions associated with methyl ketones without disrupting the quinoxaline di-N-oxide framework, and this is demonstrated by its reactions with a variety of aromatic aldehydes.

Some portions of 3-acetyl-2,6,7-trimethylquinoxaline 1,4-dioxide were reacted with aromatic aldehydes to produce 3-acyl-2,6,7-trimethylquinoxaline 1,4-dioxides which are novel. The reaction descriptions, spectra, and microanalyses will help to clarify these findings.

ACKNOWLEDGEMENTS

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CHAPTER I

INTRODUCTION

The goal of this research project has been to synthesize novel heterocyclic compounds of potential biological activity. The intent was to come up with some compounds that will retain the quinoxaline di-N-oxide structure and yet resemble the conventional or known chalcones. Literature data have shown that chalcones in general do show a variety of biological activities that range from bactericides,[1,2] fungicides,[1,2] parasiticides,[1,2] insecticides,[1,2] protozoacides,[3] to carcinoma inhibition,[4] and cell proliferation regulation.[5] Quinoxaline di-N-oxides, on the other hand, are very active against many microbes, and in some cases have been used as growth promoting agents for some livestocks.[6] The use of some di-N-oxide compounds in cancer therapy[7] has also been cited. Therefore, the incorporation of both of these structural features would probably lead to compounds whose properties and potential biological activities will very much exceed either of those inferred. This we hope will be the case.

The reaction pathways utilized in the syntheses of the target compounds, 3-acyl-2-methylquinoxaline di-N-oxides, will be discussed. Included in the discussion will be spectral information necessary for the identification and characterization of these compounds and their precursors.

At this point, anyone with access to any of these compounds should exercise caution until some measure of their toxicity or biological activities are determined and documented.

CHAPTER II

SYNTHETIC APPROACH TO DIMETHYLBENZOFURAZAN N-OXIDE

Experimental

The compounds synthesized during the preliminary course of this investigation were identified and characterized mainly by infrared spectroscopy. The IR spectra were recorded on a Beckman Acculab spectrometer. Melting points were determined on a Thomas Hoover Uni-melt melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab, Indianapolis, Indiana.

Preparations

3,4-Dimethylacetanilide

This compound was prepared by a modification of The Lumiere-Barbier Method.[8]

3,4-Dimethylaniline, 12.12 g (0.10 mol), was added to a solution of 10 mL of concentrated hydrochloric acid and 250 mL of distilled water in a 1-L flask. The solution was warmed to about 40 ^{o}C until all the solids dissolved. In the reference used, a higher temperature was needed to dissolve the aniline. Also, a small amount of decolorizing carbon was added to the colored aniline solution. This was not necessary in our case where the solution was not discolored. To this solution (aniline hydrochloride), 11.5 mL of acetic anhydride was added and the mixture shaken for 15 seconds. Immediately a solution of sodium acetate, previously prepared by dissolving 16.33 g of sodium acetate trihydrate in 50 mL of distilled

water, was added. The reaction mixture was sufficiently stirred while letting it cool in an ice-salt bath for five minutes. Shortly afterwards, crystals began to form as the stirring continued. The resulting white solid was filtered, washed with ice-cold distilled water and left to air dry. The product was sufficiently pure (sharp m.p.) that no recrystallization was necessary. The yield was 14.81 g (90.7%), m.p. 97-98 ^{o}C (lit. value not available). Infrared spectrum (KBr) cm^{-1}: 3280 (N-H), 1660 (C=O), and 1370-1390 (CH_3).

4,5-Dimethyl-2-nitroacetanilide

This compound was synthesized by a modification of the procedure of Adams, Johnson, and Wilcox.[9]

A mixture of 8.20 g (0.05 mol) of 3,4-dimethylacetanilide and 7.5 mL of glacial acetic acid in a 250 mL Erlenmeyer flask was warmed until the anilide dissolved. The resulting solution was cooled in an ice bath until crystals began to form. At this point, 10 mL of cold concentrated sulfuric acid was slowly added while stirring. Following the addition of the acid, the mixture was cooled to below 0 ^{o}C. Note: the solution may freeze if chilled for a long time, but this will not ruin the experiment as long as the nitration is slow.

While the solution was being cooled, a nitrating mixture composed of 3.5 mL of conc. nitric acid and 10 mL of cold conc. sulfuric acid was cooled to 5 ^{o}C and transferred to a clean dry separatory funnel. This nitrating mixture was only cooled to room temperature in the reference used. The cold anilide solution was then removed from the ice bath and the nitrating mixture slowly added while shaking. The reaction temperature was maintained between 15 and 20 ^{o}C at all times. This is another deviation from the reference where the reaction

temperature was maintained between 20 and 25 °C. Following the completion of the nitration, the solution was left to stand for 60 minutes at room temperature for the reaction to complete. After this time elapsed, the solution was poured while stirring into a 1-liter beaker containing about 100 g of ice-water slush. Immediately, orange-yellow crystals separated, which were filtered and washed with a large volume of ice-cold water. In the reference used, the product was pressed into a cake and transferred to a beaker of water, resuspended, refiltered, and washed with more cold water. The crude product was recrystallized from 95% ethanol-water mixture (2:1). The yield was 7.85 g (75.4%), m.p. 105-106.5 °C (lit. value not available). The IR (KBr) cm^{-1}: 3340 (N-H), 1660 (C=O), 1360 and 1570 (NO_2), 1400 (CH_3).

4,5-Dimethyl-2-nitroaniline hydrochloride

This compound was prepared by a modification of the procedure of Adams, Johnson and Wilcox.[9]

In a 250 mL round bottom flask equipped with a reflux condenser was put 9.60 g (0.046 mol) of 4,5-dimethyl-2-nitroacetanilide, 40 mL of distilled water, and 35 mL of concentrated hydrochloric acid. The reaction mixture was refluxed for 24 hours at 80 °C. A deviation from the reference where the hydrolysis of p-nitroacetanilide was completed in 30-40 minutes. At the end of this time, chunks of ice and about 25 mL of cold distilled water were added, and immediately the orange-red precipitate separated from the orange solution. Another deviation from the reference where concentrated aqueous ammonia was added to liberate the free nitroaniline from the nitroaniline hydrochloride. The product was filtered and washed with cold water. The dried product 7.69 g (42%), melted at 127-129 °C

(lit. value not available). IR (KBr) cm^{-1}: 3360 and 3480 (N-H stretches), 1370 and 1560 (NO_2), 1400 (CH_3).

2-Azido-4,5-dimethylnitrobenzene

This compound was synthesized by a modified method of Smith and Boyer.[10]

4,5-Dimethyl-2-nitroaniline hydrochloride, 5.64 g (0.034 mol) was placed in a 3-necked flask equipped with a stirrer, a thermometer, and a dropping funnel, and containing 15 mL of distilled water and 7.5 mL of conc. hydrochloric acid. The mixture was stirred while being cooled in an ice bath to 0-5 °C. The amine hydrochloride was diazotized by adding dropwise a solution of 2.45 g of sodium nitrite in 8 mL of distilled water for 1 hour. Stirring was continued for another 1 hour at this temperature range. The resulting yellow-green solution was filtered from muddy impurities into a 2-litre beaker in an ice bath. A longer reaction time was employed here than was done in the reference used, for the diazotization of *o*-nitroaniline. Other than that, the reference never mentioned the formation of any muddy impurities that was observed in this reaction. The filtrate was constantly stirred while a solution of 2.52 g (0.38 mol) of sodium azide in 8.5 mL of water was added. Instantly, the product began to form from a foamy solution that filled up the entire beaker. The stirring was continued for 5 minutes following the cessation of nitrogen evolution. The product was filtered, washed with cold water and left to air dry. The product was recrystallized from 95% ethanol. The yield was 5.64 g (56.2%), m.p. 101-103 °C (lit. value not available). IR (KBr) cm^{-1}: 2110 (N_3), 1350 and 1540 (NO_2), 1375-1390 (CH_3).

5,6-Dimethylbenzofurazan 1-oxide

This compound was prepared by a thermal decomposition of the *o*-nitrophenylazide.[11-14]

2-Azido-4,5-dimethylnitrobenzene, 3.53 g (0.0184 mol) and 10 mL of distilled toluene were put into a 50 mL round bottom flask equipped with a reflux condenser and refluxed for 3-5 hours at 110 ^{o}C. Nitrogen evolution was observed for the time indicated, and when it stopped (nitrogen evolution), the solution was cooled in an ice bath. Yellow-brown needles crystallized out of the solution. Following filtration, the mother liquor was concentrated to give more products of darker color. The combined products were recrystallized from a 95% ethanol-water mixture (2:1). The yield was 3.02 g (81.8%), m.p. 138-140 ^{o}C (new compound). IR (KBr) cm^{-1}: 1520 (N-O), 1620 (C=O), 1650 ($C=N^{+}$), 1385 (CH_3). The proton magnetic resonance (PMR) spectrum in $CDCl_3$ showed two singlets at 2.33 and 7.18 delta values (integration: 6.1:2) corresponding to the methyl and ring hydrogens respectively. The UV spectrum (0.001 g/100 mL chloroform) showed two absorption peaks at 242 and 358 nm wavelengths. Their corresponding molar absorptivities were 2700 and 4000 L/mol.cm respectively. Elemental analysis: calculated C 58.53, H 4.91, N 17.06; found C 58.21, H 4.47, N 16.93.

Benzofurazan1-oxide

A general and an established synthetic procedure of benzofurazan 1-oxide has been reported. The method often used was to treat *o*-nitroaniline with sodium hypochlorite in the presence of 95% ethanolic potassium hydroxide, a basic

catalyst.[11, 14-15] In our work, this compound was obtained from the Aldrich Chemical Company, Inc. and also synthesized at 80% yield with the substitution of commercial bleach (Clorox "sodium hypochlorite solution") for a freshly prepared sodium hypochlorite.

Discussion

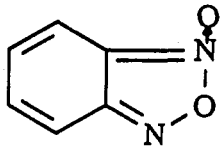
All the significant IR functional groups of the first four compounds synthesized during this early work are consistent with the expected vibrational frequencies. The IR spectra of both the dimethyl substituted and the unsubstituted benzofurazan 1-oxide are very diagnostic, yet it is difficult to assign the corresponding vibrational frequencies. There are four bands between 1450 and 1630 cm^{-1} which have been associated with the benzofuroxan ring.[13,16]

The need for the acetylation of the starting material, 3,4-dimethylaniline, was to protect the amine from being oxidized in the nitration step of our reaction sequence. Later, the amine was regenerated as a chloride salt for the subsequent steps. To regenerate the amine, the nitroacetanilide was hydrolyzed in an acidic solution. The choice for the acid hydrolysis was because the diazotization step had to be conducted in an acidic medium. Ordinarily, 30-40 minutes would suffice in such simple hydrolysis, but in our case, the maximum yield was obtained when refluxed for 24 hours. A significant factor that might have contributed to a low yield in the hydrolysis step was a lump of black tar that must have resulted from some kind of oxidation and or polymerization of the free amine. Every attempt made to eliminate this problem failed.

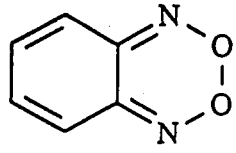
During the azidotization step, the reaction was conducted under the hood to avoid possible exposure to hydrazoic acid (NH_3) that could be formed.

The compound benzofurazan 1-oxide has been reported as early as the late 19th century, but the knowledge of its structure eluded chemists for quite some time. There was as much confusion as there were suggestions as to what the structure was.[14, 16-18] It was not until 1960 that the true structure was determined through NMR and X-ray crystallography.[11-12] Figure 1 shows a few of such early structures.

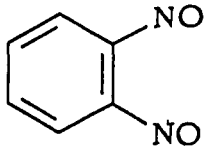
The target compound in this preliminary raections, 5,6-dimethylbenzofurazan 1-oxide, was obtained and proved to be correct. This early research project can be summarized by the following reactions (see Figure 2).



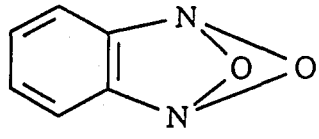
Accepted Structure



Peroxide Structure



Dinitroso Structure



Epoxide Structure

Figure 1. The Various Structures that were Proposed for Benzofurazan N-oxide

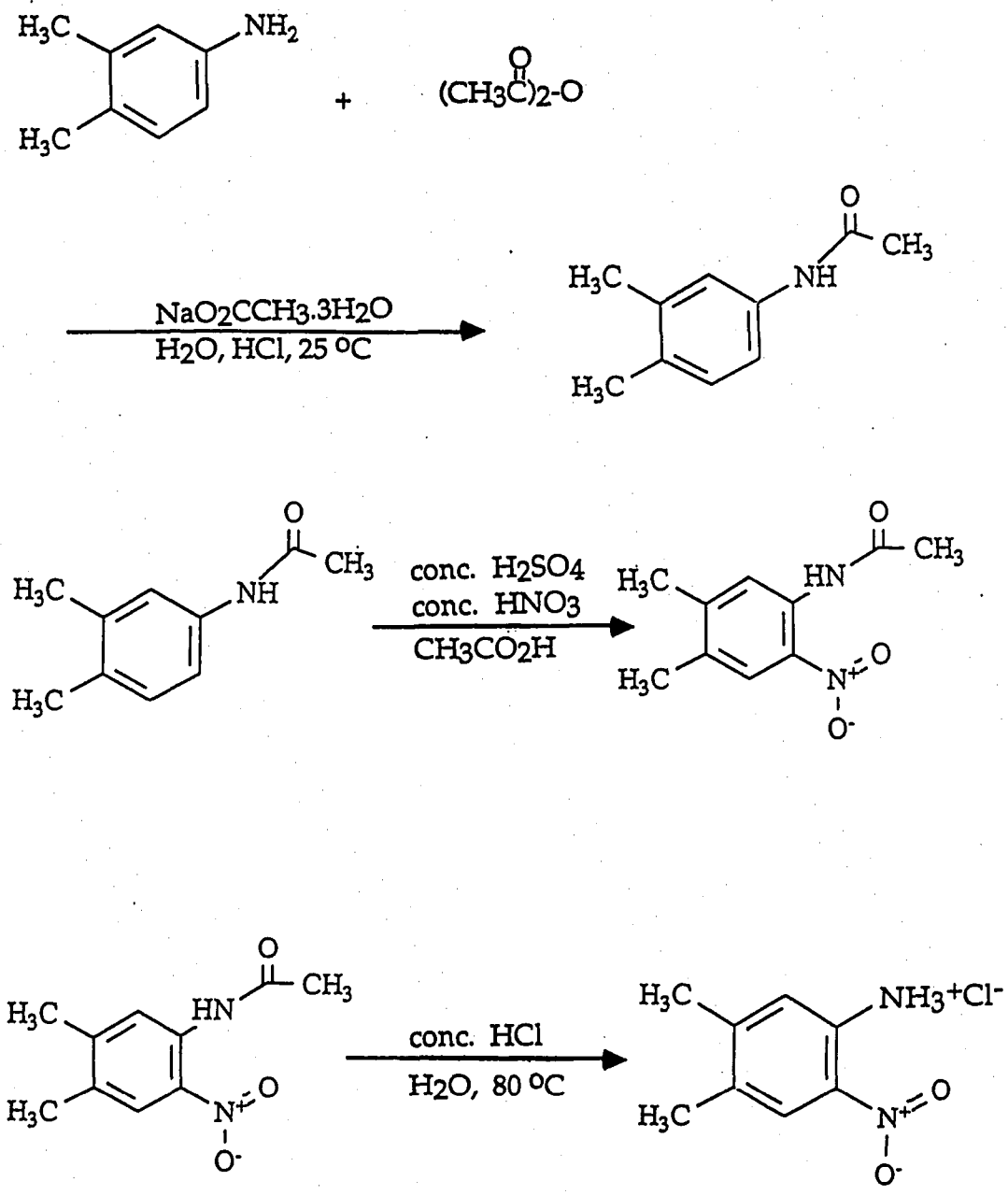


Figure 2. Reaction Sequence for the Formation of 5,6-Dimethylbenzofurazan 1-oxide

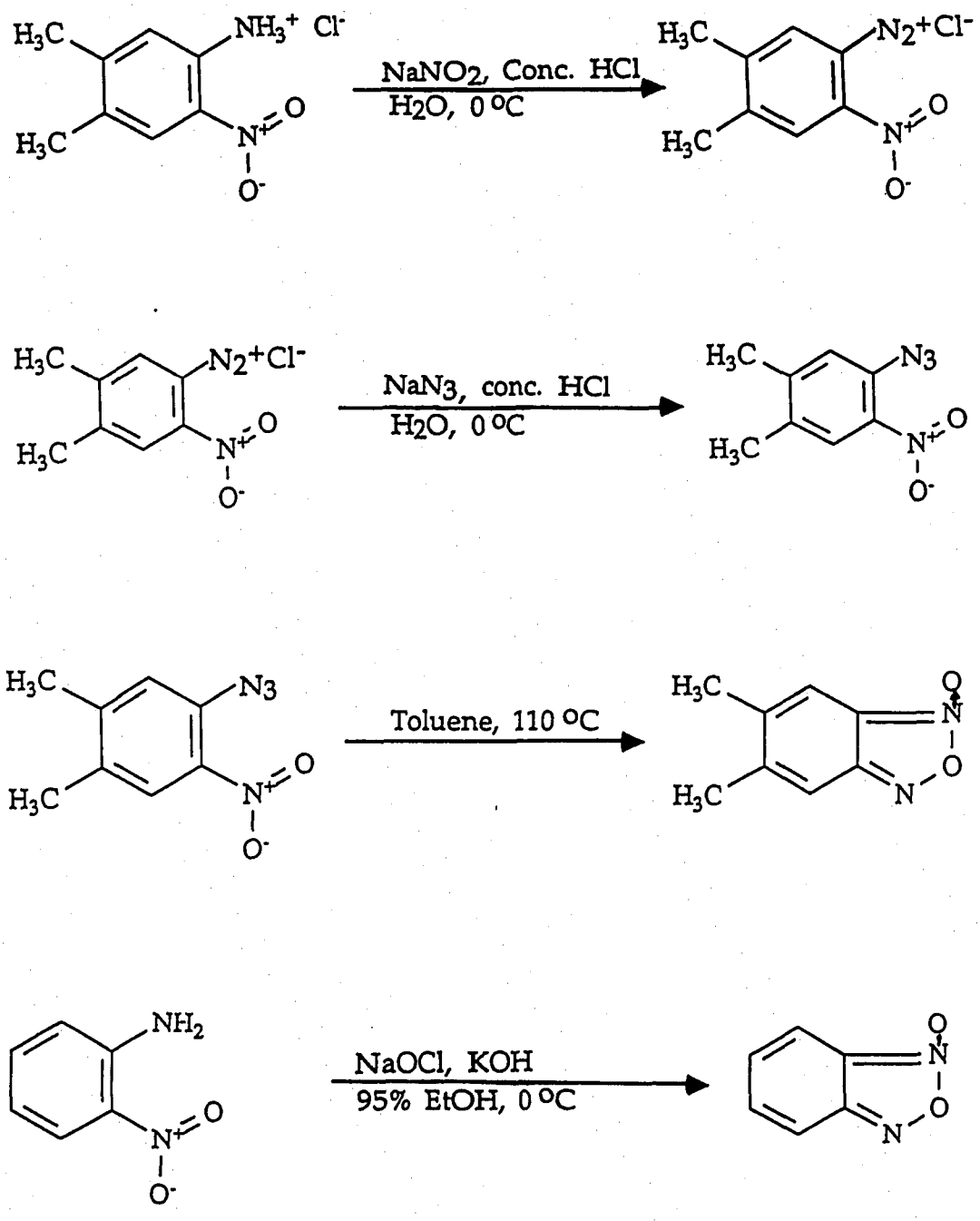


Figure 2. (continued)

CHAPTER III

SYNTHESES OF QUINOXALINE 1,4-DIOXIDES

Experimental

The compounds synthesized during the intermediate stage of this project were identified by infrared spectroscopy, nuclear magnetic resonance, UV spectroscopy and elemental analyeses. IR spectra were recorded on a Beckman Acculab spectrophotometer, and nmr spectra were obtained with an IBM-NR/200AF spectrometer using TMS as an internal standard. The UV spectra were run on a HP 8451 Diode Array UV/VIS spectrophotometer using chloroform as solvent and reference. Microanalyses were performed by Midwest Microlab, Indianapolis, Indiana. Melting points were determined on a Thomas Hoover Uni-melt melting apparatus and are uncorrected. Thin layer chromatography was performed to establish the purity of the compounds and each consisted of only one component. Each sample was dissolved in methylene chloride and eluted in a hexane/ethylacetate (1:5) solution.

Preparations

2,3-Cyclodecylquinoxaline 1,4-dioxide

In a 125 mL Erlenmeyer flask was placed 1.36 g (0.01 mol) of benzofurazan 1-oxide in 10 mL of methanol. Then 2.19 g (0.012 mol) of cyclododecanone and 5 mL of conc. ammonia solution were added and the mixture stirred in an ice-bath until the reaction cooled to room temperature. The reaction was further stirred for 24 hours at room temperature. The resulting solution was poured into a 150

mL beaker and the methanol was allowed to evaporate and yellow-brown crystals remained. This was recrystallized from methanol to give yellow products. The yield was 1.78 g (59.3%), m.p. 138-140 ^{o}C (new compound). The UV spectrum (0.001 g/100 mL chloroform): 242 nm (a_m 16246), 270 nm (a_m 42402), and 392 nm (a_m 15075). NMR ($CDCl_3$) ppm: 1.49-3.22 (-CH_2-, multiplet), 7.77-7.82 and 8.59-8.64 (ring hydrogens, two multiplets), integration: 20.2:2:2. IR (KBr) cm^{-1}: 2840-2950 (CH_2 aliphatic), 1340 (N-O). Elemental analysis: calculated C 71.79, H 8.05, N 9.33; found C 72.29, H8.40, N 9.60.

3-Acetyl-2-methylquinoxaline 1,4-oxide

This compound was synthesized by a modification of the procedure of Issidorides and Haddadin.[19]

A mixture of 5.44 g of (0.04 mol) of benzofurazan 1-oxide and 5.0 mL (0.05 mol) of acetylacetone were placed in a 250 mL round bottom flask containing 25 mL of triethylamine. The flask was set aside for 24 hours for the yellow product to form. A deviation from the reference used, here the solution was not heated before setting it aside. The solid was removed by filtration and recrystallized from methanol and air dried. The yield was 6.00 g (68.8%), m.p. 154-155 ^{o}C (lit. value 153-154 ^{o}C). UV (0.001 g/100 mL chloroform): 242 nm (a_m 7424), 266 nm (a_m 8079), 394 nm (a_m 4672), and two other small shoulders at 307 and 373 nm whose molar absorptivities were not determined. NMR ($CDCl_3$) ppm: 2.54 N=C-CH_3, singlet), 2.74 (acetyl CH_3, singlet), 7.85-7.96 and 8.53-8.69 (ring protons, two multiplets), integration: 6.2:2:2. IR (KBr) cm^{-1}: 1700 (C=O), 1410 (CH_3), and 1330 (N-O).

3-Acetyl-2,6,7-trimethylquinoxaline 1,4-dioxide

A modified procedure of Issidorides and Haddadin was used in the preparation of this compound.[19]

5,6-Dimethylbenzofurazan 1-oxide, 1.50 g (0.0096 mol) and acetylacetone 1.06 mL (0.0104 mol) were added to a 30 mL of diethylamine in a 250 mL round bottom flask. In the reference cited, triethylamine was the base used, but for this reaction, it did not seem to catalyze the reaction unless a longer reaction time (14 days) is allowed. The mixture was warmed for 2-5 minutes until all dissolved. The flask was stoppered and left undisturbed. Five minutes later, fine long yellow needles began to crystallize out of the solution. The product was filtered after 12 hours and washed with cold methanol, as opposed to 24 hours allowed for this reaction in the reference used. A second crop was filtered from the mother liquor after 24 hours, and the combined products were recrystallized from methanol. The yield 1.68 g (71.2%), m.p. 212-213 ^{o}C (new compound). UV (0.001 g/100 mL chloroform): 244 nm (a_m 20874), 268 nm (a_m 21601), 392 nm (a_m 9852), and two small shoulders at 307 and 374 nm whose molar absorptivities were not determined. The nmr ($CDCl_3$) ppm: 2.53 (CH_3 9H, singlet), 2.73 (acetyl CH_3, singlet), 8.28 and 8.36 (ring protons, two singlets), integration: 9.1:3:1:1. IR (KBr) cm^{-1}: 1700-1710 (C=O), 1330-1335 (N-O), and 1390-1420 (CH_3). Elemental analysis: calculated C 63.40, H 5.73, N 11.38; found C 63.33, H 5.85, N 11.11.

Discussion

The intermediate steps of our reaction project can be summed up by the following reactions in Figure 3.

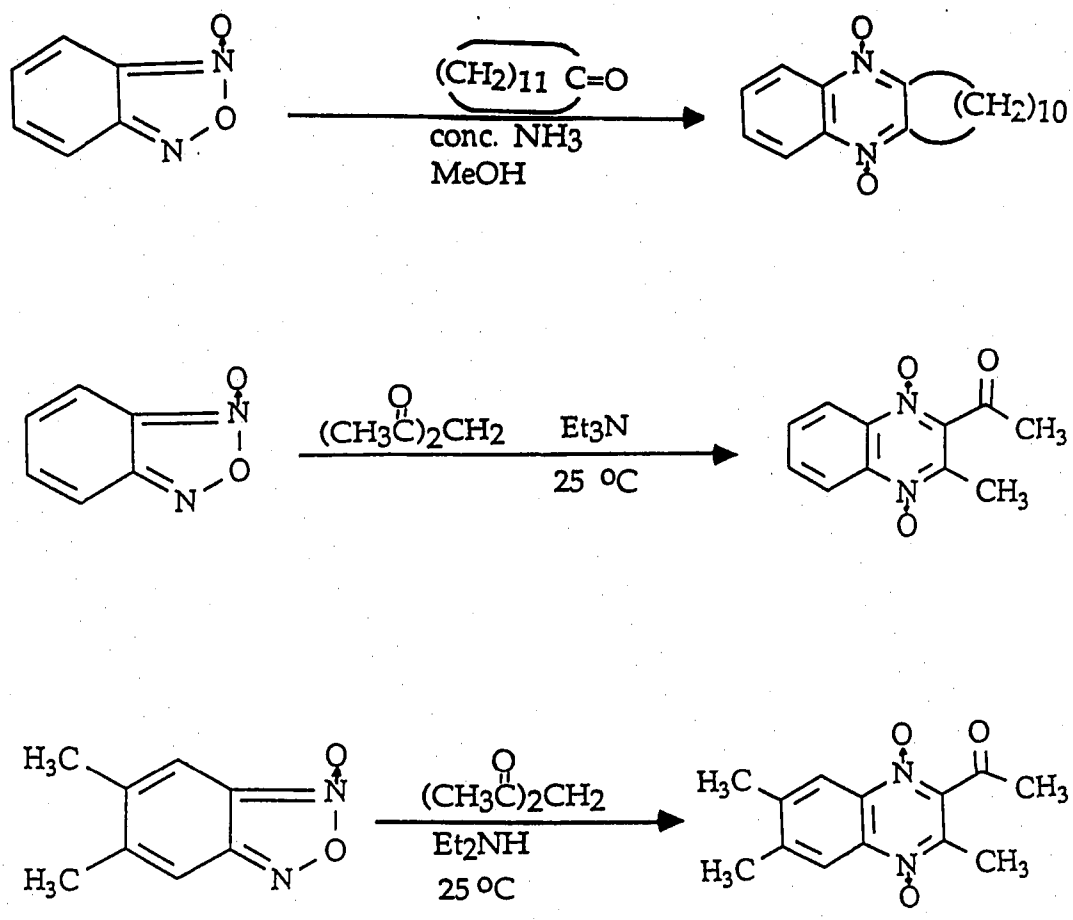


Figure 3. The Formation of 2,3-Disubstituted Quinoxalines

The mechanism for the formation of similar compounds has been proposed by Issidorides and Haddadin,[19-20] Ley and Seng,[21] and Ley, Seng, Eholzer, Nast, and Schubart,[22] therefore we decided not to include it in this paper. It should be mentioned that both of the 3-acetyl products have to be completely dried following recrystallization, and should be stored in a dark container that can block sunlight. As we found out, long exposure of the wet product does lead to the formation of another species, possibly benzoimidazolone[23] as detected by thin layer chromatography (TLC). This problem was not noticed with the 2,3-cyclodecyl product which does not have a carbonyl group.

CHAPTER IV

SYNTHESES OF 3-ACYL-2-METHYLQUINOXALINE 1,4-DIOXIDES

Experimental

The instruments used to obtain the various spectra and melting points were the same as those described in the experimental section of Chapter 3. Microanalyses were also carried out by Midwest Microlab, Indianapolis, Indiana.

Preparation

3-Acyl-2-methylquinoxaline 1,4-dioxides

In a 250 mL Erlenmeyer flask containing 20 mL of absolute ethanol and a stirring bar, 0.0020 mol of 3-acetyl-2-methylquinoxaline 1,4-oxide and 0.0021 mol of an aromatic aldehyde were placed. Then 0.020 g (0.0005 mol) of sodium hydroxide dissolved in about 10 mL of absolute ethanol was added and the flask tightly stoppered. The reaction was stirred at room temperature from 1 to 24 hours. The solid product was filtered and washed with 95% ethanol and left to air dry.

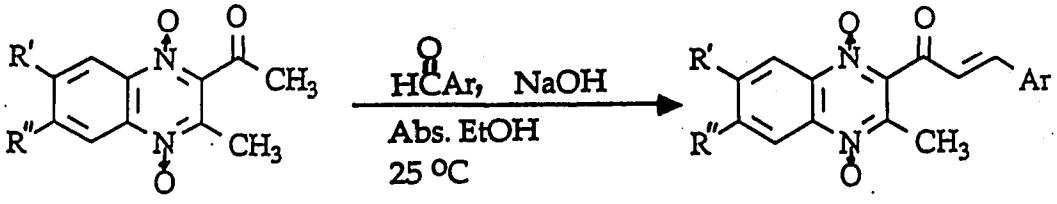
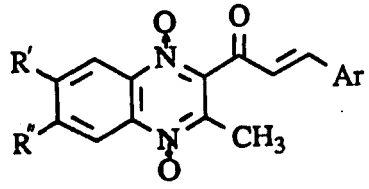


Figure 4. The Reaction of 3-Acetyl-2-methylquinoxaline 1,4-dioxide with aromatic aldehydes

Table 1

Reaction data for 3-Acyl-2-methylquinoxaline 1,4-dioxide



Compound No.	R'	R"	Ar	M.P. (°C)	Yield (%)	Analysis Calcd.	% Found
1	Hydrogen	Hydrogen	3,4-Methylene-dioxyphenyl	194-6	39.6	C: 65.14 H: 4.03 N: 8.00	65.47 4.18 8.22
2	Hydrogen	Hydrogen	4-Nitrophenyl	232-4	79.2	C: 61.54 H: 3.73 N: 11.96	61.32 4.02 12.07
3	Hydrogen	Hydrogen	Phenyl	193-5	45.9	C: 70.58 H: 4.61 N: 9.15	70.35 4.65 9.00
4	Hydrogen	Hydrogen	1-Naphthyl	180-2	56.1	C: 74.14 H: 4.53 N: 7.86	72.85 4.64 7.61
5	Hydrogen	Hydrogen	4-Chlorophenyl	201-3	65.6	C: 63.44 H: 3.84 N: 8.22 Cl: 10.40	63.56 3.85 8.21 10.38
6	Hydrogen	Hydrogen	2-Furyl	183-4	30.2	C: 64.86 H: 4.08 N: 9.46	64.91 4.21 10.18

Table 1--Continued

Compound No.	R'	R"	Ar	M.P. (°C)	Yield (%)	Analysis	Calcd.	Found
7	Hydrogen	Hydrogen	2-Chlorophenyl	180-1	70.5	C:	63.44	63.50
						H:	3.84	3.91
						N:	8.22	8.02
						Cl:	10.40	10.56
8	Hydrogen	Hydrogen	2-Nitrophenyl	192-4	60.3	C:	61.54	61.33
						H:	3.73	3.81
						N:	11.96	12.05
9	Hydrogen	Hydrogen	2-Styryl	171-3	31.8	C:	72.27	72.03
						H:	4.85	4.91
						N:	8.43	8.15
10	Methyl	Methyl	2-Chlorophenyl	207-9	77.3	C:	65.13	64.55
						H:	4.65	4.89
						N:	7.60	7.64
						Cl:	9.61	9.75
11	Methyl	Methyl	2-Nitrophenyl	224-5	60.9	C:	63.32	63.07
						H:	4.52	4.35
						N:	11.08	10.97
12	Methyl	Methyl	3,4-Methylene-dioxyphenyl	226-8	41.6	C:	66.66	66.46
						H:	4.79	4.78
						N:	7.41	7.37
13	Methyl	Methyl	4-Chlorophenyl	214-5	76.8	C:	65.13	65.17
						H:	4.65	4.86
						N:	7.60	7.56
						Cl:	9.61	9.69

Table 2

A List of Compounds 1 through 13 (see Table 1)

Compound No.	Full Names
1	2-Methyl-3-(3,4-methylenedioxy cinnamoyl) quinoxaline 1,4-dioxide
2	2-Methyl-3-(4-nitrocinnamoyl)quinoxaline 1,4-dioxide
3	2-Methyl-3-(cinnamoyl)quinoxaline 1,4-dioxide
4	2-Methyl-3-[3-(1-naphthyl)propenoyl]quinoxaline 1,4-dioxide
5	2-Methyl-3-(4-chlorocinnamoyl)quinoxaline 1,4-dioxide
6	2-Methyl-3-[3-(2-furyl)propenoyl]quinoxaline 1,4 dioxide
7	2-Methyl-3-(2-chlorocinnamoyl)quinoxaline 1,4-dioxide
8	2-Methyl-3-(2-nitrocinnamoyl)quinoxaline 1,4-dioxide
9	2-Methyl-3-(5-phenyl-2,4-pentadienoyl)quinoxaline 1,4-dioxide
10	2,6,7-Trimethyl-3-(2-chlorocinnamoyl)quinoxaline 1,4-dioxide
11	2,6,7-Trimethyl-3-(2-nitrocinnamoyl)quinoxaline 1,4-dioxide
12	2,6,7-Trimethyl-3-(3,4-methylenedioxy cinnamoyl)quinoxaline 1,4-dioxide
13	2,6,7-Trimethyl-3-(4-chlorocinnamoyl)quinoxaline 1,4-dioxide

Discussion and Spectral Data

IR

The tremendous information made available by the infrared spectra of these compounds played a significant part in their structural confirmations. High atmospheric humidity continuously clouded the KBr pellet and caused difficulty in obtaining clean spectra. All the samples were run in nujol. The IR and UV spectral data are presented in Table 3.

UV

As with the others, the UV spectra of these compounds were run in chloroform. These spectra were of immense help for a quick determination that the reaction products were different from the starting materials. All of these compounds do have similar spectral forms, but still hold their individualities. The molar absorptivities were also calculated for characterization purposes.

NMR

The nuclear magnetic resonance spectra of this set of compounds cannot go without comments. They also helped to confirm their structures. The entire class of these compounds were soluble enough in deuterated chloroform which was used as the solvent except for compound 2 which was only slightly soluble in chloroform and acetic acid, and insoluble in most solvents available for nmr spectra. To obtain its spectra, compound 2 required heating and concentrating in deuterated acetic acid because it was slow to dissolve. See Table 4 for nmr data.

Table 3

IR and UV Spectral Data

Compound No.	C=O	C=C	cm^{-1} N→O	NO_2	C-Cl
1	1660	1590-1610	1335	---	---
2	1680	1590-1610	1335	1340 and 1520	---
3	1660	1625	1335	---	---
4	1670	1610	1335	---	---
5	1680	1590-1610	1335	---	810
6	1625	1600	1335	---	---
7	1680	1610	1340	---	760
8	1680	1610	1335	1340 and 1520	---
9	1650	1610	1335	---	---
10	1680	1610	1330	---	750
11	1685	1610	1330	1350 and 1530	---
12	1660	1590	1335	---	---
13	1680	1610	1330	---	780

Compound No.	λmax (a_m)	λmax (a_m)	λmax (a_m)	λmax (a_m)	λmax (a_m)
1	242 (18947)	266 (18140)	314 (7965)	376 (22211)	--- ---

Table 3--Continued

Compound No.	λ_{max} (am)	λ_{max} (am)	λ_{max} (am)	λ_{max} (am)	λ_{max} (am)
2*	242 (7219)	268 (7228)	316 (9649)	374 (3368)	394 (2140)
3	242 (14110)	268 (15276)	314 (16288)	374 (8742)	394 (8098)
4	242 (35516)	268 (40000)	278 (29431)	--- ---	--- ---
5	242 (15154)	268 (12799)	324 (17986)	373 (9488)	394 (8191)
6	244 (11154)	328 (11479)	362 (23935)	373 (11036)	--- ---
7	242 (7812)	266 (7074)	316 (7074)	374 (4402)	395 (4198)
8	244 (22947)	268 (23053)	--- ---	376 (8632)	392 (7123)
9	244 (24319)	268 (21329)	358 (35216)	--- ---	--- ---
10	244 (23838)	270 (23284)	308 (11587)	374 (11550)	393 (8782)
11	244 (24205)	272 (23636)	--- ---	372 (8106)	393 (6364)
12	244 (9697)	272 (8409)	310 (3750)	372 (8826)	--- ---
13	244 (45351)	272 (44684)	322 (51513)	372 (26827)	393 (19852)

* Not completely soluble.

Table 4

NMR proton Resonances for Compounds 1 through 13

Compound No.	Assignment	Multiplicity	(PPM)	Integration
1	Methyl (3H)	Singlet	2.57	3
	Methylene (2H)	Singlet	6.04	2
	Aromatic/Vinyl (9H)	Mlutiplet	6.08-8.62	9.2
2	Methyl (3H)	Singlet	2.61	-
	Aromatic/Vinyl (10H)	Multiplet	7.34-8.72	-
3	Methyl (3H)	Singlet	2.58	3
	Aromatic/Vinyl (11H)	Multiplet	7.11-8.70	11
4	Methyl (3H)	Singlet	3.65	3
	Aromatic/Vinyl (13H)	Multiplet	7.25-8.88	13.5
5	Methyl (3H)	Singlet	2.58	3
	Aromatic/Vinyl (10H)	Multiplet	7.08-8.70	10.5
6	Methyl (3H)	Singlet	2.58	3
	Aromatic/Vinyl (9H)	Multiplet	6.54-8.67	9
7	Methyl (3H)	Singlet	2.64	3
	Aromatic/Vinyl (10H)	Multiplet	7.12-8.73	10.4
8	Methyl (3H)	Singlet	2.64	3
	Aromatic/Vinyl (10H)	Multiplet	7.01-8.70	10.3
9	Methyl (3H)	Singlet	2.56	3
	Aromatic/Vinyl (13H)	Multiplet	6.64-8.68	12.8
10	Methyl (9H)	3 Singlets	2.53-2.58	9.2
	Aromatic/Vinyl (8H)	Multiplet	7.12-8.42	8
11	Methyl (9H)	3 Singlets	2.52-2.61	9.1
	Aromatic/Vinyl (8H)	Multiplet	7.03-8.42	8
12	Methyl (9H)	2 Singlets	2.52-2.55	9.1
	Methylene (2H)	Singlet	6.04	2
	Aromatic/Vinyl (7H)	Multiplet	6.83-8.40	6.9

Table 4--Continued

Compound No.	Assignment	Multiplicity	(PPM)	Integration
13	Methyl (9H)	2 Singlets	2.52-2.55	9.2
	Aromatic/Vinyl (8H)	Multiplet	7.08-8.39	8

The reaction mechanism for the formation of the 3-acyl-2-methylquinoxaline 1,4-dioxides is analogous to the well known Claisen-Schmidt[24] reaction and as such will not be presented in this paper. The resulting double bond is conjugated with the carbonyl group, which introduces an extended overlapping p-orbitals, resulting in a resonance stabilized structure. The effect of this conjugation is more noticeable in the IR spectra than in the UV spectra. In the IR spectra , the carbonyl (C=O) absorption frequencies did shift to a longer wavelength as compared to that of the ketone that has no conjugation. Also noticeable from the IR is the effect of the electron withdrawing groups on the absorbing frequencies of the carbonyl group. The presence of a chloro or a nitro group on the aldehyde component did shift the C=O frequencies to a shorter wavelength relative to those compounds without such groups.

The reaction time required for the complete formation of compounds 1 through 9 (see Table 1) is somewhere between 18 to 24 hours. For compounds 10 through 13, this length of time resulted in the formation of a product different from either of the starting materials, and whose structure could not be determined from the spectral information and expected mechanism. A similar effect was noticed with some of the other compounds when the base concentration was much higher than indicated. In any case, the IR spectra showed no carbonyl peak among other things. It was through the aid of TLC that an adequate reaction time, 1-hour, was

established for compounds 10 through 13.

All of the reaction products but compound 2 were of high purity (by TLC) so that no recrystallization was necessary. Compound 2 was recrystallized from dimethylsulfoxide (DMSO) to give an orange-red product. Compound 6 and 9 are greenish-yellow in color, all the others are yellow of varying intensities. Melting points were sharp and clean. The overall yields of these compounds were probably higher than shown in Table 1 because a loss of very small amount of the products on filtration will affect the millimolar reaction ratios used. Had the reactions been conducted on a larger reaction ratios, such a loss will not lower the total yield significantly.

CHAPTER V

CONCLUSION

To conclude this effort, it should be pointed out that the use of 3-acetyl-2,6,7-trimethylquinoxaline 1,4-dioxide as a synthetic precursor is very promising. This compound can be condensed with a variety of carbonyl compounds and other reagents, thereby opening up avenues to a whole new class of compounds with potential biological activities. Reactions of 3-acetyl-2-methylquinoxaline 1,4-dioxide and 3-acetyl-2,6,7-trimethylquinoxaline 1,4-dioxide with aromatic ketones proved this point, though, the biological activities of the resulting products have not been tested.

The syntheses and structural evaluations of the target compounds made possible by the spectral information obtained have proved this project a successful one. Apart from the educational benefits of this research project, it has been an interesting and a memorable one.

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