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A Synthetic Approach to Novel Heterocyclic Herbicides

Paul Antony Pathadan

A SYNTHETIC APPROACH TO NOVEL HETEROCYCLIC HERBICIDES

by

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A SYNTHETIC APPROACH TO NOVEL HETEROCYCLIC HERBICIDES

Paul Antony Pathadan, M.A.

Western Michigan University, 1988

The purpose of this research study was to prepare novel heterocyclic herbicides. The first phase of the project was to synthesize 1-(nitromethyl)-4-phthalazone.

In the second phase 1-(nitromethyl)-4-phthalazone was treated with 1,3-propane-dithio-di-p-toluene sulfonate in presence of sodium hydride to get the target compound 4-(1'-nitro-1,3-dithiane)phthalazone.

It is believed that this compound might block the electron transport system of aerobic cells[1]. So further investigation of this compound may lead to novel herbicides.

ACKNOWLEDGEMENTS

I am deeply indebted to my research advisor, Dr. Robert E. Harmon, for his support, encouragement, and guidance during the course of this project. I am also grateful to Dr. Lindsley J. Foote and Dr. Donald C. Berndt for their help.

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Paul Antony Pathadan

Order Number 1333166

A synthetic approach to novel heterocyclic herbicides

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CHAPTER I

INTRODUCTION

The purpose of this research project was to synthesize 4-(1'-nitro-1,3-dithiane) phthalazone. It is believed that this novel compound possesses herbicidal properties. It might block the electron transport system of aerobic cells[1]. All the enzymatic steps in the metabolism of carbohydrates, fats and amino acids in aerobic cells converge into the electron transport and oxidative phosphorylation. In this step electrons flow from organic substrates to oxygen, generating energy for the conversion of ADP to ATP. This conversion of ADP to ATP and back is carried out several thousand times each day[2]. So blocking the electron transport system is fatal to the living cells.

The synthesis consisted of two phases. The first phase was to synthesize 1-(nitromethyl)-4-phthalazone from dimethyl phthalate. In the second phase 1-(nitromethyl)-4-phthalazone was treated with 1,3-propane-dithio-di-*p*-toluene sulfonate to get the target compound. The scheme is illustrated in Figure 6. Two other novel compounds similar to the target compound were also synthesized. Their synthesis is outlined in Figure 7 and 8 respectively.

CHAPTER II

HISTORICAL

Disodium cromoglycate (Figure 1) has been shown to be effective in the treatment of bronchial asthma. The anti-allergic potential of a variety of substituted chromones related to disodium cromoglycate has been tested by their relative activities in a passive cutaneous anaphylaxis (PCA) reaction in the rat[3]. A later finding that 2-nitro-indan-1,3-dione (Figure 2) was also active in the PCA test led to the synthesis of a variety of substituted 2-nitro-indan-1,3-diones.

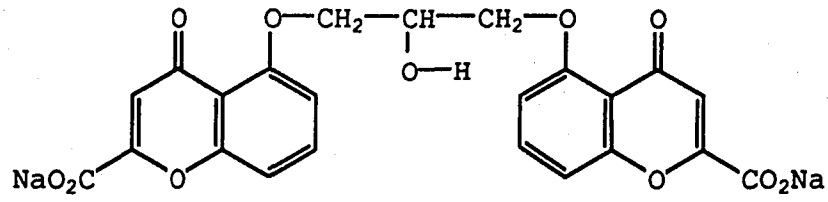


Figure 1. Disodium Cromoglycate

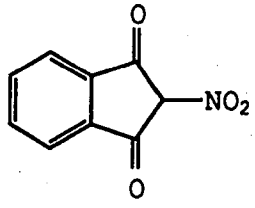


Figure 2. 2-Nitroindan-1,3-dione

Vanag and Matskanova (1956)[5] have investigated the reaction between 2-nitroindan-1,3-dione with hydrazine. This reaction in alcohol proceeds through the cleavage of the five-membered ring in 2-nitroindan-1,3-dione forming ω-nitro-acetophenone-o-carboxylic acid hydrazone (Figure 3) as an intermediate.

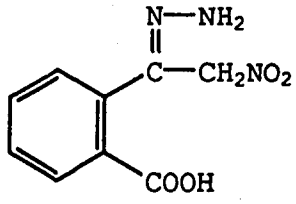


Figure 3. ω-Nitroacetophenone-o-carboxylic Acid Hydrazone

When the intermediate formed above is heated under reflux, it rearranges and eliminates a molecule of water to give 1-(nitromethyl)-4-phthalazone (Figure 4).

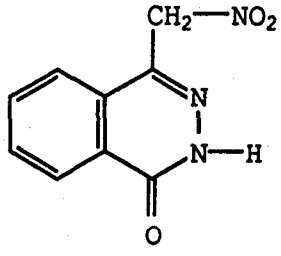


Figure 4. 1-(Nitromethyl)-4-phthalazone

Phthalazones in general, have been referred to in the literature under different names including 1-(2H)-phthalazinone and 1-hydroxy phthalazine.

Phthalazones can exist in two forms namely the lactams and lactims (Figure 5).

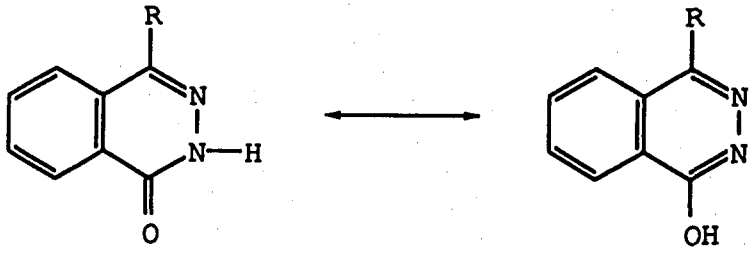


Figure 5. Lactam and Lactim

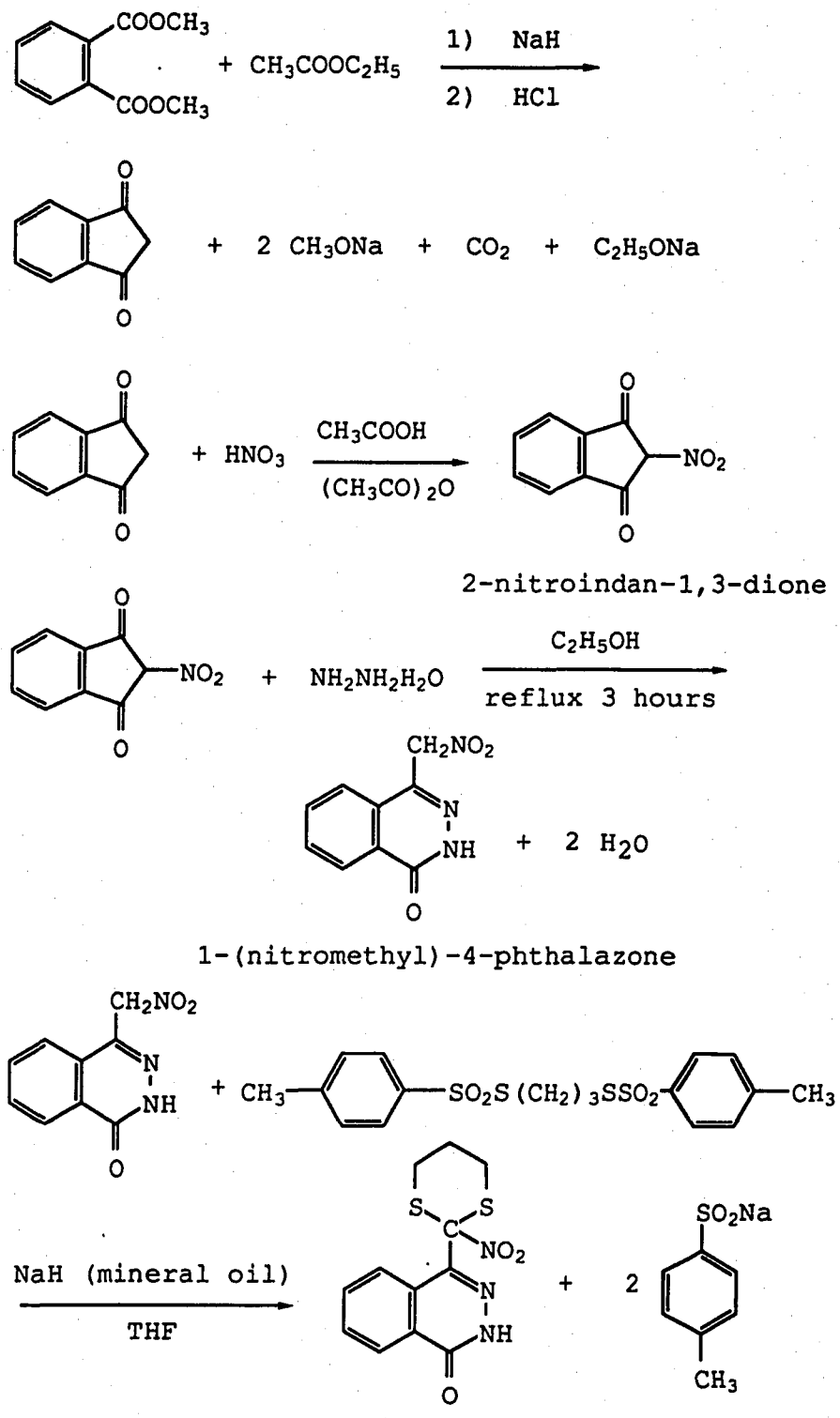


Figure 6. Scheme I

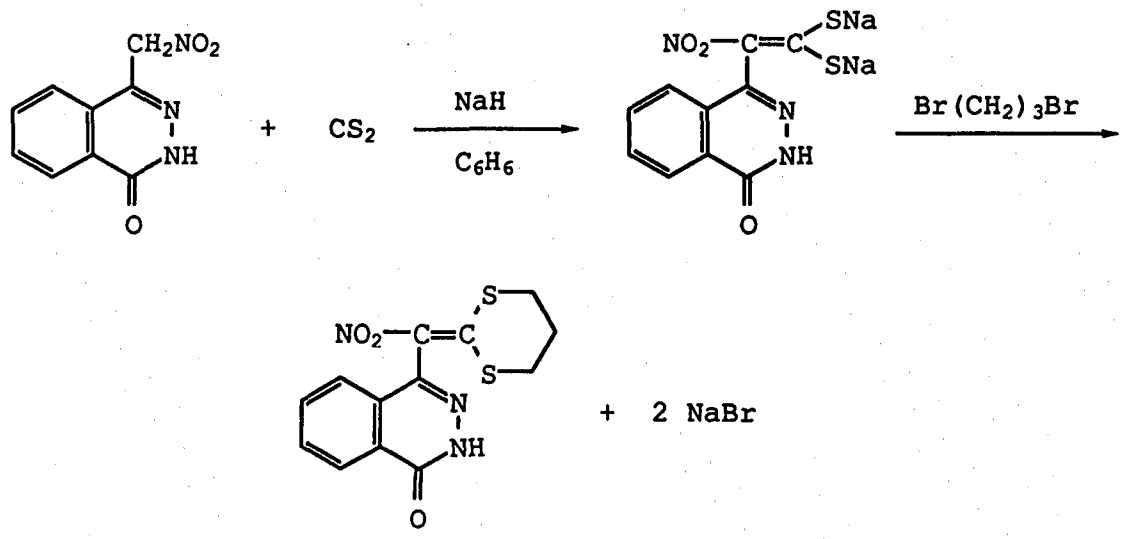


Figure 7. Scheme II

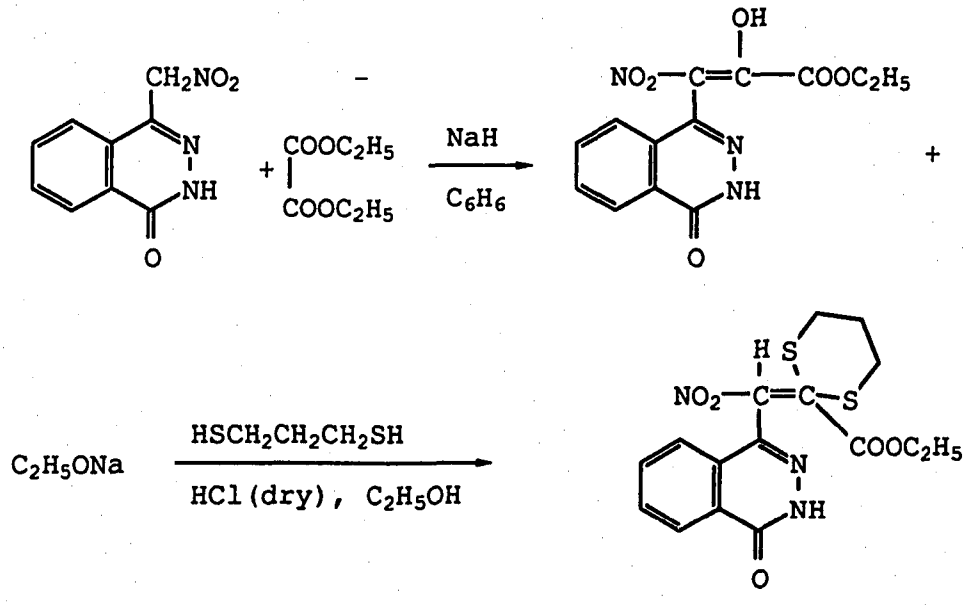


Figure 8. Scheme III

CHAPTER III

EXPERIMENTAL

The compounds synthesized during this project were identified by IR, NMR, UV and elemental analysis. The IR spectra were obtained using a Beckman Acculab Spectrophotometer. NMR spectra were obtained using an IBM--NR/200 AF NMR and UV using an HP 8451 Diode Array UV/VIS Spectrophotometer. Microanalyses were carried out by Midwest Microlab, Indianapolis, Indiana. Melting points were determined with a Thomas-Hoover Uni-Melt capillary melting point apparatus and are uncorrected. TLC was done to establish the purity of the compounds prepared.

Preparations

Indan-1,3-dione

This compound was synthesized by a procedure by Smith, et al (1973)[3].

The apparatus consisted of a 1000 ml 3-necked round bottom flask fitted with a condenser, mechanical stirrer and a cylindrical separatory funnel.

A 50% suspension of sodium hydride in mineral oil weighing 42.1 g was placed in the flask and a solution of 132.7 g of dimethyl phthalate (0.68 mole) in 181.8 g of

ethyl acetate (2.07 mole) was added to it slowly with stirring, from the funnel. The mixture was refluxed at 100°C for 4 hours on a heating mantle. After the solution was cooled, the yellow solid was filtered and washed well with a 1:1 mixture of ethyl alcohol and diethyl ether. The yellow solid was treated with 10% hydrochloric acid at 80°C for 7 minutes to get indan-1,3-dione as a buff colored solid. The crude product was filtered, dried over P_2O_5 and recrystallized from benzene to get a yield of 19.4 g (19.4%). IR (mineral oil): C=O 1695 cm^{-1}. MP 129-130°C (lit.[3] 129°C). Elemental analysis: found C 73.79, H 4.01. Calculated C 73.97, H 4.11.

2-Nitroindan-1,3-dione

This compound was prepared by nitrating indan-1,3-dione by a procedure by Fieser (1968)[4].

Seventy-five ml of acetic acid was mixed with 50 ml of acetic anhydride. 25 ml of concentrated nitric acid was added to the above mixture in 1 ml portions. After each addition the temperature was allowed to go up to 60°C. When the addition was complete the mixture was cooled to 35°C and poured on to 17.5 g(0.12 mole) of indan-1,3-dione in an Erlenmeyer flask, provided with a thermometer. The temperature dropped to 27°C and then it began to rise.

The temperature was carefully kept between 33-35°C for 20 minutes by occasional dips in an ice-bath. Then the product was cooled to 5°C, filtered and washed with ether. The yellow crystalline solid weighed 17.5 g (76.4%). IR (KBr): C=O 1660 cm-1, nitro 1550 cm^{-1} and 1380 cm^{-1}. MP 113-114°C (lit.[3] 113°C). Elemental analysis for 2-nitro-indan-1,3-dione dihydrate: found C 47.79, H 3.03, N 5.99. Calculated C 47.76, H 3.08, N 6.17.

1-(Nitromethyl)-4-phthalazone

This compound was prepared by a procedure by Vanag and Matskanova (1956)[5].

A solution of 11.4 g of 2-nitroindan-1,3-dione (0.05 mole) in 300 ml of ethyl alcohol was placed in a 500 ml 3-necked flask fitted with a reflux condenser and a mechanical stirrer. Then, 7.5 ml of hydrazine hydrate (0.15 mole) was added to it in drops with vigorous shaking. The yellow precipitate along with the mother liquor was heated under reflux for three hours in an oil bath at 120°C. The solution was then cooled and the precipitate was recrystallized from hot alcohol using formic acid to get white slender crystals. The crystallized product weighed 7.8 g (63.8%). IR (KBr): N-H 3160 cm^{-1} (stretch) 1650 cm^{-1} (bend), C=O 1660 cm^{-1}, nitro 1540 cm^{-1} and 1370 cm^{-1}.

MP 214-215°C (lit.[5] 215°C). Elemental analysis: found C 52.74, H 3.38, N 20.33. Calculated C 52.68, H 3.42, N 20.49.

1,3-Propane-dithio-di-p-toluene sulfonate

This compound was prepared by the procedure by Kodak, Soc. anon. (1961)[6]

A solution of 22.6 g (0.1 mole) of potassium thiotosylate in 100 ml of ethanol was prepared and 10 g of 1,3-dibromopropane (0.05 mole) was added to it. The reaction mixture was refluxed for five hours. The precipitated potassium bromide was removed by filtration. The filtrate was concentrated by boiling off ethanol and finally distilled under reduced pressure to get the product in the form of a jelly. It was dissolved in ethyl acetate and ethanol was added in drops until a white turbidity was obtained. It was corked and refrigerated for 2-3 hours to yield 5.3 g (25.7%) of white crystals. MP 65-67°C (lit.[6] 65-67°C). IR (mineral oil) S=O 1150 cm^{-1}.

4-(1'-Nitro-1,3-dithiane)phthalazone

This compound was prepared by the extension of a procedure by Woodward, Patchett, Darton, Ives and Kelly (1957)[7].

A solution of 0.936 g of 1-(nitromethyl)-4-phthalazone (0.0046 mole) in dry THF was added to a suspension of 0.4 g of a 60% suspension of sodium hydride in mineral oil. This was followed by the addition of 1.90 g of 1,3-propane-dithio-di-p-toluene sulfonate (0.0046 mole) and the reaction mixture was refluxed for two days. The precipitated product was filtered and washed with THF. The crude product was crystallized from water by the addition of acetic acid. The product weighed 0.80 g (56.70%). MP 155-156°C. IR (KBr): N-H 3100 cm^{-1}, C=O 1650 cm^{-1}, nitro 1540 cm^{-1} and 1380 cm^{-1}, dithiane 870 cm^{-1} (lit.[9] 880-900 cm^{-1}). NMR (DMSO): 7.4 ppm (d, 2H), 7.2 ppm (d, 2H), 2.5 ppm (s, 1H), 2.2 ppm (t, 4H) and a quintet at 1.6 ppm (2H). The integration was in the ratio 4:1:4:2 which was consistent with the structure. Elemental analysis: found C 46.48, H 3.52, N 13.40. Calculated C 46.60, H 3.56, N 13.60.

4-(1'-Nitro-2'-1,3-dithiane-1'-ene)phthalazone

This compound was prepared by a procedure similar to that by Chauhan and Junjappa (1976)[8].

To a suspension of 0.26 g of a 60% suspension of sodium hydride in dry benzene was added a solution of 1 g of 1-(nitromethyl)-4-phthalazone (0.005 mole) and 0.38 g of carbon disulfide (0.005 mole) in DMF. The mixture was

stirred for two hours followed by the addition of 0.51 ml of 1,3-dibromopropane (0.005 mole) in portions with cooling. The reaction mixture was allowed to stand at room temperature for two hours and then refluxed for four hours. The mixture was poured on to crushed ice and the benzene layer was separated. The aqueous layer was extracted with benzene and the combined organic extracts were washed with water and dried with anhydrous sodium sulfate. The solvent was removed and the crude sample purified by column chromatography to get the pure product. MP 210-211°C. IR (mineral oil): N-H 3180 cm^{-1}, C=O (ethyl acetate) 1750 cm^{-1}, C=O 1650 cm^{-1}, nitro 1560 cm^{-1} and 1380 cm^{-1}, dithiane 900 cm^{-1} (lit.[9] 880-900 cm^{-1}). NMR was taken after drying the sample completely. NMR (DMSO): 8.7 ppm (d, 2H), 8.3 ppm (d, 2H), 4.6 ppm (s, 1H), a quintet at 3.2 ppm (2H) and 2.1 ppm (t, 4H). The integration was in the ratio 4:1:2:4 which was consistent with the structure. Elemental analysis: found C 48.6, H 4.2, N 11.08. Calculated C 49.20, H 4.10, N 11.50.

Ethyl 3-nitro-3,4'-phthalazonyl-2-(1,3-dithiane) pyruvate

This compound was prepared in two steps. The first step was to prepare ethyl 3-nitro-3,4'-phthalazonyl pyruvate.

To a suspension of 0.5 g of sodium hydride in dry benzene was added 0.5 g of 1-(nitromethyl)-4-phthalazone (0.0024 mole), followed by 0.3 ml of diethyl oxalate (0.0024 mole). The reaction mixture was stirred at room temperature for two days and acidified with glacial acetic acid dropwise. The product was formed as a white precipitate which was collected, dried and used for the second step. IR (KBr): O-H (enol) 3600 cm^{-1}, N-H 3120 cm^{-1}, C=O (ester) 1713 cm^{-1}, C=O 1650 cm^{-1}, nitro 1540 cm^{-1} and 1380 cm^{-1}.

The conversion of ethyl 3-nitro-3,4'-phthalazonyl pyruvate to ethyl 3-nitro-3,4'-phthalazonyl-2-(1,3-dithiane) pyruvate was done by a procedure by Seebach and Corey (1975)[9].

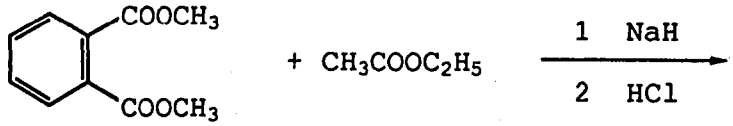
A solution of ethyl 3-nitro-3,4'-phthalazonyl pyruvate was prepared by dissolving 0.5 g (0.0016 mole) of it in absolute ethyl alcohol and 0.16 ml of 1,3-propane dithiol (0.0016 mole) was added. The reaction mixture was cooled in an ice bath and dry hydrogen chloride gas was bubbled through the reaction mixture for five minutes. It was stirred at room temperature for fifteen hours and the solvent was removed. The crude product was crystallized to get 0.23 g (36%) of a compound. MP 120-121°C. IR (KBr): N-H 3120 cm^{-1}, C=O (ester) 1720 cm^{-1}, C=O 1650 cm^{-1},

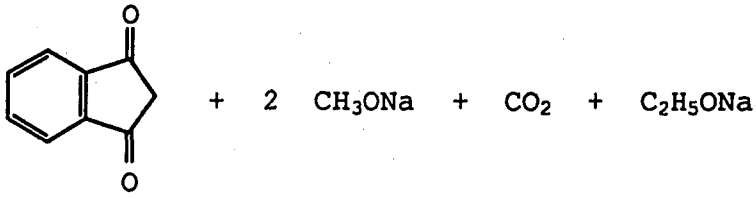
nitro 1550 cm^{-1} and 1380 cm^{-1}, dithiane 900 cm^{-1} (lit.[9] 880-900 cm^{-1}). NMR (CH_3OH): 8.2 ppm (d, 2H), a quartet at 3.8 ppm (2H), 2.4 ppm (s, 1H), 1.4 ppm (s, 1H) and 0.8 ppm (t, 3H). The integration was in the ratio 4:4:2:2:1:1:3 which was consistent with the structure. TLC indicated only one compound but the elemental analysis was not within an acceptable range. Analysis: found C 39.36, H 4.12. Calculated C 48.60, H 4.30.

CHAPTER IV

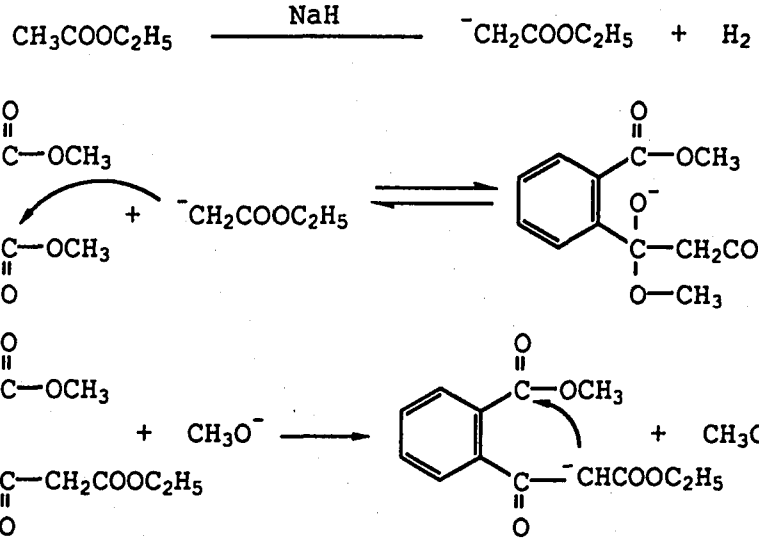
RESULTS AND DISCUSSION

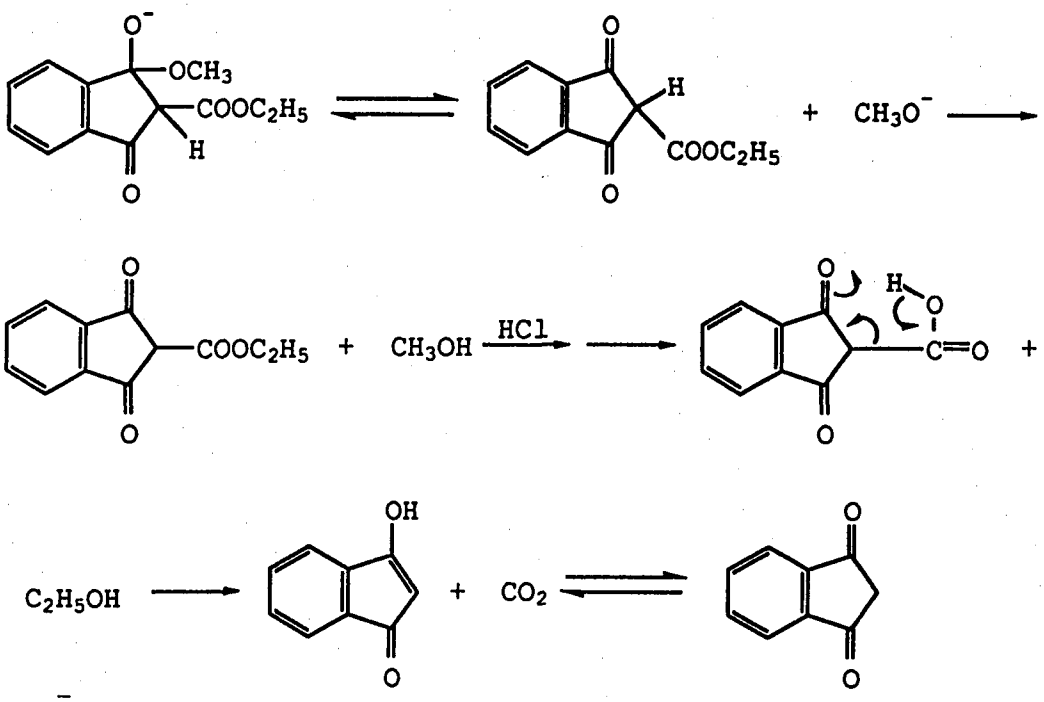
This research project could be summarized by the following equations.





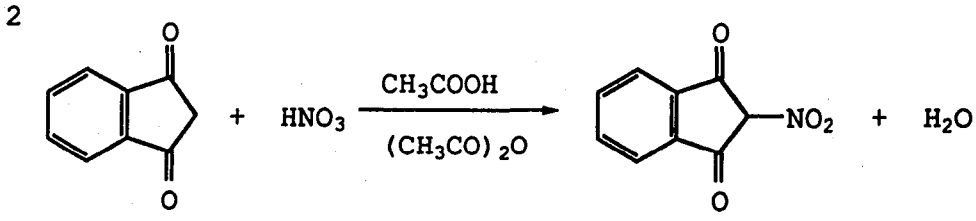
This reaction could be explained by the following mechanism[3].





Indan-1,3-dione

The above reaction provided a good method for the preparation of indan-1,3-dione. It failed only when the phthalate had substituants in both 3 and 6 positions[3].

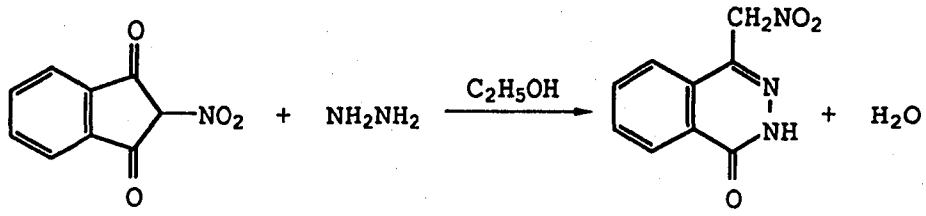


2-Nitroindan-1,3-dione

Ordinary nitrating agents like concentrated nitric acid or nitric acid and sulfuric acid failed to nitrate indan-1,3-

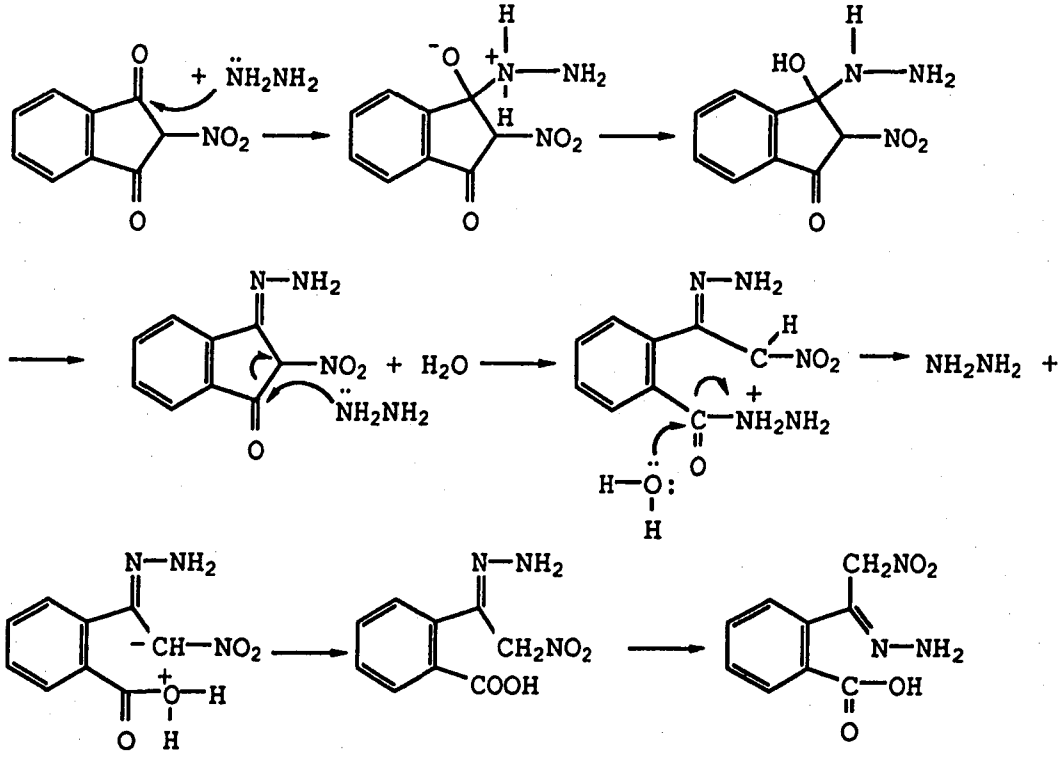
dione. This author tried these methods without success. The only one that was successful was nitric acid mixed with glacial acetic acid and acetic anhydride.

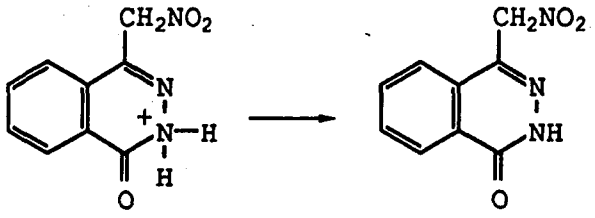
3



1-(Nitromethyl)-4-phthalazone

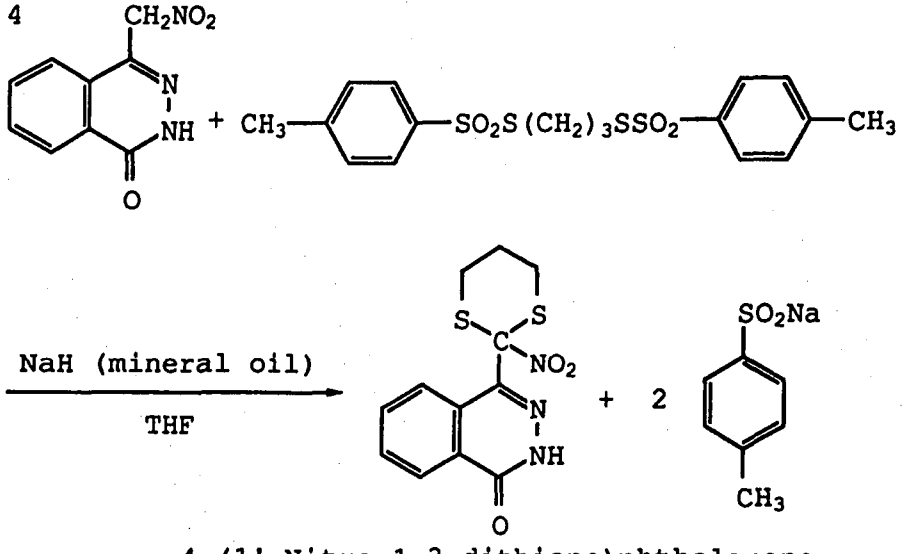
Vanag and Matskanova (1956)[5] proposed the following mechanism for the above reaction.





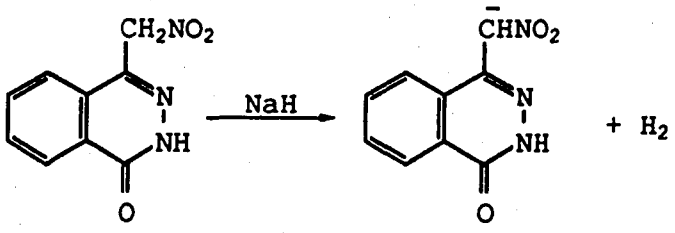
1-(Nitromethyl)-4-phthalazone

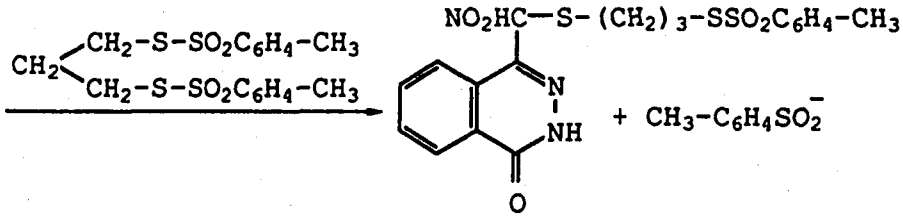
In this reaction, 2-nitroindan-1,3-dione reacted with a molecule of hydrazine, which under the influence of excess hydrazine, acting as a base, cleaved its five membered ring which resulted in the formation of ω-nitroacetophenone-ο-carboxylic acid hydrazone; the latter cleaved a molecule of water and cyclized to the 1-(nitromethyl)-4-phthalazone. The best yield was obtained when 2-nitroindan-1,3-dione and hydrazine were in the molar ratio 1:2.5[5].

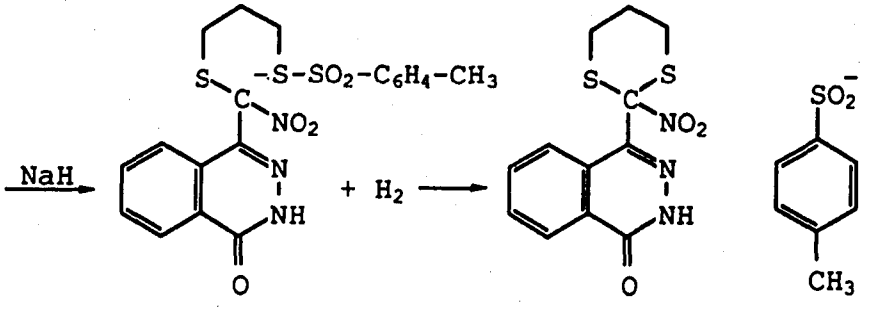


4-(1'-Nitro-1,3-dithiane)phthalazone

The following mechanism is suggested for the above reaction.







The success of this reaction depended on the acidic nature of the protons on the nitromethyl group. The nitro group made it more acidic than hydrocarbons.

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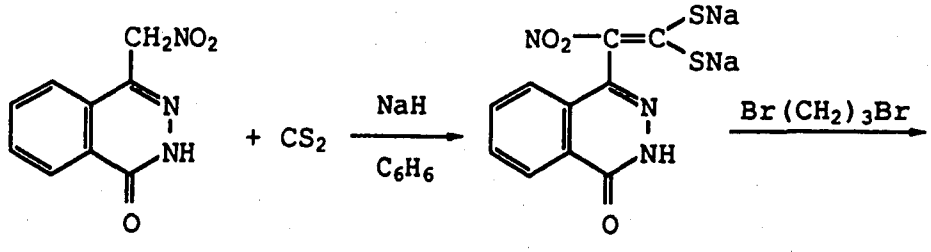
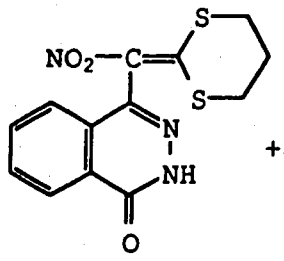
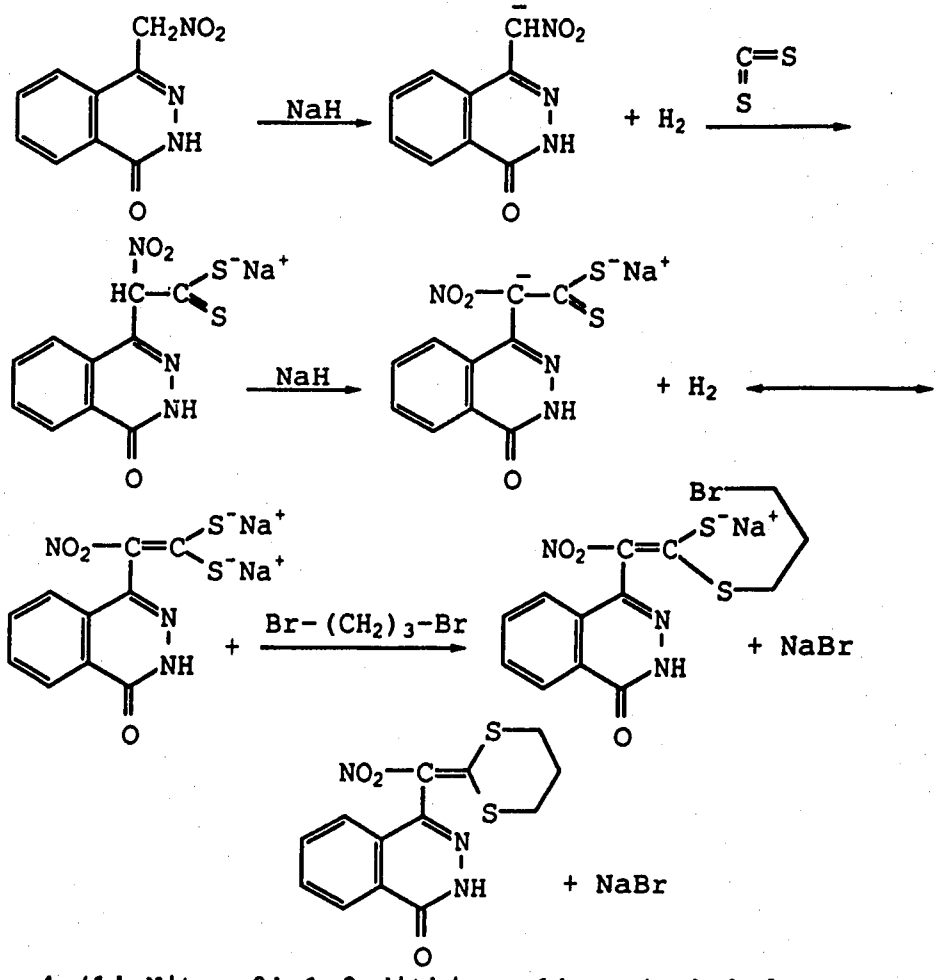




+ 2 NaBr

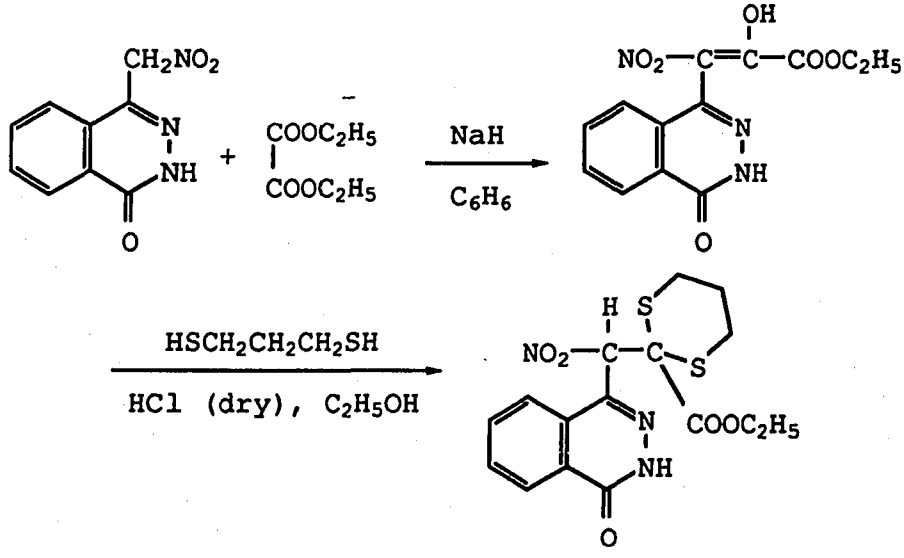
The following mechanism could be suggested for this reaction.



4-(1'-Nitro-2'-1,3-dithiane-1'-ene) phthalazone

The crude product was purified by column chromatography using hexane and ethyl acetate (1:5). Most of the product was not recovered and so the yield of the purified sample was only 3.1%. If it is assumed that a molecule of ethyl acetate (solvent) is associated with two molecules of the compound, the observed results of elemental analysis agrees with the calculated values. The presence of ethyl acetate was supported by the IR. Since the NMR was taken after drying the sample completely, the ethyl acetate was not seen in the NMR spectrum.

6



Recrystallization of the crude product gave a compound. TLC indicated one compound. But the structure of the compound could not be substantiated by elemental analysis. so

the identity of this compound was not established. Further chromatographic work might enable to purify and identify the compound.

The keto-enol tautomerism of ethyl 3-nitro-3,4'-phthalazonyl pyruvate was studied spectroscopically. A solution of the compound was prepared by dissolving 0.1 g (0.00033 mole) of it in DMSO and diluting to 1000 mL to get a concentration of 0.00033 M. Another solution was prepared by dissolving 0.1 g (0.00033 moles) in ethanol and diluting to 2000 mL to get a concentration of 0.00016 M. The absorption maxima of the solutions were measured using a HP 8451 Diode Array UV/VIS spectrophotometer (see Table 1).

It was observed that the λ_{max} were shifted to longer wave lengths in DMSO. This could be explained as follows. Of the two forms, the enol form was favored in DMSO, as it was stabilized by intramolecular hydrogen bonding.

Such a stabilization is not possible in ethanol. The enolization resulted in some compounds lower energy π^* states. So the transition required lower energy and hence the shift to longer wave length[13].

Table 1

Absorption Maxima

Solvent	λ_{max} (nm)	Concentration	A	ε_{max}
DMSO	212	0.00033 M	0.087	263.6
DMSO	260	0.00033 M	0.810	2455
DMSO	296	0.00033 M	1.03	3121
Ethanol	210	0.00016 M	1.60	10,000
Ethanol	254	0.00016 M	0.32	2,000
Ethanol	288	0.00016 M	0.29	1813

Table 2

Absorption Maxima

Solvent	λ_{max} (nm)	Concentration	A	ε_{max}
DMSO	222	0.00034 M	0.028	82.4
DMSO	250	0.00034 M	0.24	706.0
DMSO	262	0.00034 M	1.30	3824.0
Ethanol	222	0.000034 M	1.01	29701
Ethanol	252	0.000034 M	0.66	19412
Ethanol	260	0.000034 M	0.54	15882

A similar study was done with indan-1,3-dione. A solution of indan-1,3-dione was prepared by dissolving 0.1 g (0.00068 moles) of the compound in DMSO and diluting the solution to 2000 mL to get a concentration of 0.00034 M. Another solution was prepared by dissolving 0.1 g (0.00068 moles) of indan-1,3-dione in 1000 mL of ethanol, followed by a twenty-fold dilution to get a concentration of 0.000034 M. The absorption maxima of both the solutions were measured (see Table 2). A significant shift in λ_{max} was not observed in the case of indan-1,3-dione because an intra-molecular hydrogen bonding was not possible in this case.

This project was a success as the target compound (Scheme 1) was synthesized. Three other novel compounds were also synthesized. The yield could have been improved by working with larger quantities of chemicals because when smaller amounts were used, the loses in transferring and recrystallization were magnified.

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