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Investigations of the Knoevenagel Condensation of 4- Nitrohomophtalic Acid with Various Aldehydes.

Richard Allan Balding
Northern Michigan University

INVESTIGATIONS OF THE KNOEVENAGEL CONDENSATION OF 4-NITROHOMOPHTHALIC ACID WITH VARIOUS AROMATIC ALDEHYDES

by

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Submitted in Partial Fulfillment of the

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This thesis is recommended for approval by the student's thesis committee.

Chairman

Approved by Roland A Strobel, Dean of Graduate Studies.

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TABLE OF CONTENTS

PREFACE

ACKNOWLEDGEMENTS.....iii

LIST OF TABLES..... iv

ABSTRACT..... v

INTRODUCTION
1) Literature Review..... 1
2) Problem.....14

EXPERIMENTAL
1) Experimental Procedure.....15

RESULTS
1) List of Tables.....20

DISCUSSION
1) Previous Expectations.....24
2) Proof of Structures.....25

CONCLUSION.....27

REFERENCE.....29

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LIST OF TABLES

TABLE I	Condensation Products of 4-nitrohomophthalic Acid with Various Aldehydes
TABLE II	IR and NMR Data for Isocoumarin Products
TABLE III	Coupling Constants of Protons a, b and c
CHART 1	Possible Pathways for the Condensation of 4-nitrohomophthalic Acid with Aromatic Aldehydes

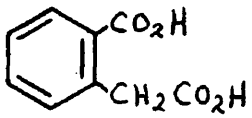
ABSTRACT

The Knoevenagel condensation of 4-nitrohomophthalic acid with various aldehydes was found to yield 3,4-dihydroisocoumarins as one of the types of products formed. The structure of the products, the subject of this study, was proven through elemental analysis, infra-red spectroscopy and nuclear magnetic resonance. One of the isocoumarins was hydrolyzed and dehydrated to a stilbene structure as further proof of the isocoumarin product.

INTRODUCTION

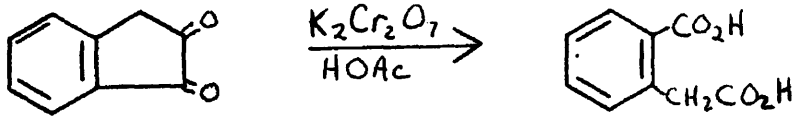
Preparation of Homophthalic Acid

Homophthalic acid (1) (also known as ∝- carboxy-o-toluic acid), its derivatives and reactions have long been sources of study, mostly by German scientists. Its main importance is as a starting material for the synthesis of multi-ring compounds and stilbene-2-carboxylic acids. In this study, the ring forming reaction leading to δ -lactones (isocoumarins) was investigated.



1

The preparation of homophthalic acid can be effected in many ways, a few of which are described in the succeeding discussion. Homophthalic acid is one of the products from acid catalyzed oxidation of 1,2-diketohydrindene (2) using potassium dichromate in acetic acid.[1]



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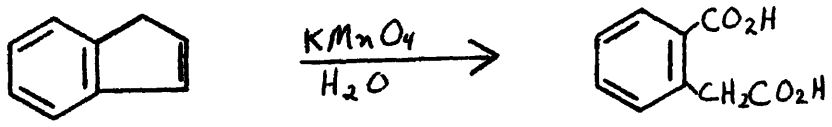
Both indene (3) and indane (4) in the presence of aqueous potassium permanganate have been oxidized to homophthalic acid.[2,3,4]



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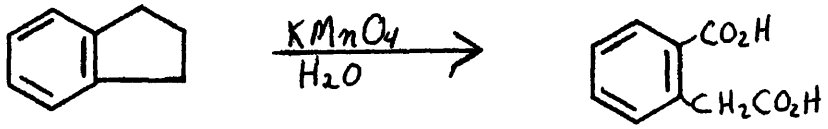

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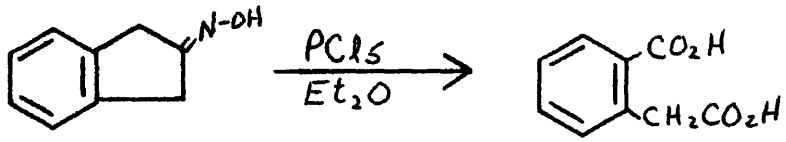
Treatment of 2-oximidohydrinden-1 (5) with phosphorous pentachloride in ether also gives the desired acid.[5]



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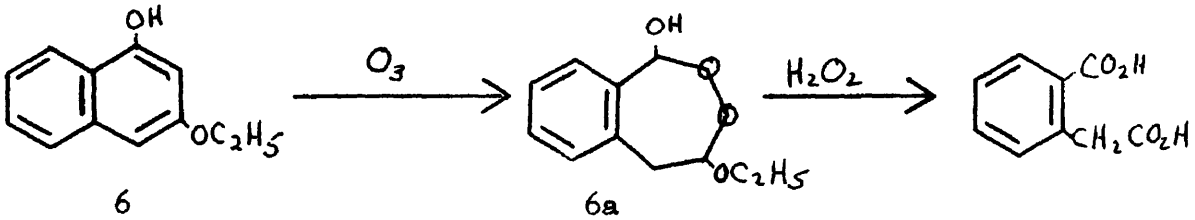
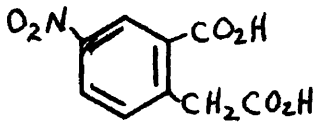
Another method, the reaction of 3-hydroxy-4,5-benzo-7-ethoxy-1,2-dioxacycloheptane (6a) with hydrogen peroxide can be used,[6] the reactant (6a) being obtained from ozonolysis of (6). This method, however, is limited in that the starting material is rather uncommon.



6 6a

Preparation of 4-Nitrohomophthalic Acid

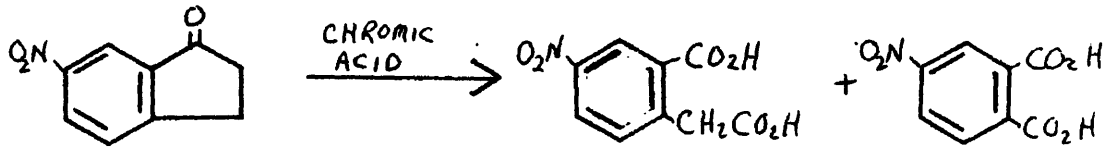
The common reactant in the condensations investigated in this study is 4-nitrohomophthalic acid (7).



7

Among methods of preparing 4-nitrohomophthalic acid is the direct nitration of homophthalic acid with fuming nitric acid.[7] The 4-nitro product was the isomer formed in greatest yield and was the only product which was isolated from the nitration. A somewhat simpler nitration has been reported by a team of German scientists,[8] wherein homophthalic acid was heated with potassium nitrate in sulfuric acid.

In some cases, the nitro group was already present in the precursor. For instance, oxidation of 6-nitrohydrindone (8) with chromic acid produces 4-nitrohomophthalic acid and 4-nitrophthalic acid, the 4-nitrohomophthalic acid being separated by precipitation.[7]



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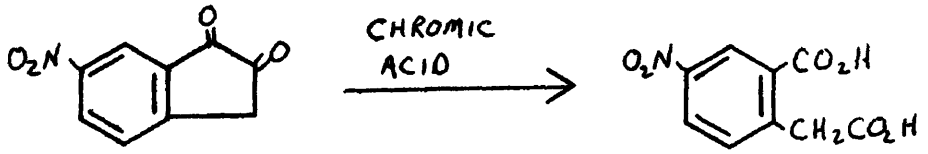
Another method entails the oxidation of 6-nitro-1,2-diketohydrindene (9) with a chromic acid solution.[7]



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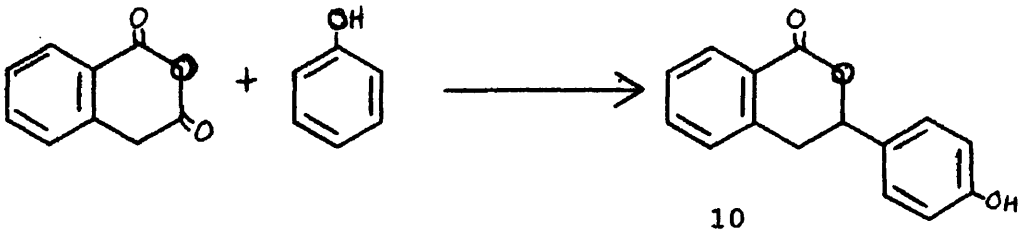
Reactions of Homophthalic Acid

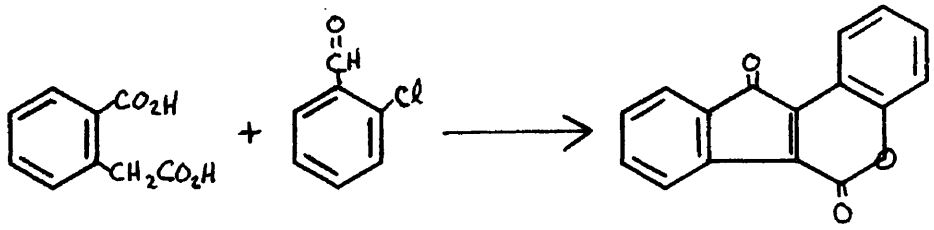
Homophthalic acid and its anhydride undergo various reactions pertinent to this investigation. In early studies, the anhydride was most frequently used, yielding the same or similar products to the acid. In some cases when the acid was used as starting material, the anhydride formed during the course of the reaction and the net result was the same as if the anhydride had been the starting material. A mixture of homophthalic anhydride and phenol in the presence of a dehydrating agent yields 3-(4-hydroxyphenyl)isocoumarin (10).[9]



10

The acid gives the same product and is easier to use and more readily reactive.[10]

Condensations similar to the type investigated in this paper have been reported. The condensation between homophthalic acid and o-chlorobenzaldehyde in the presence of piperidine has been shown to yield 2-(2-hydroxyphenyl)indenone-3-carboxylic acid lactone (11).[11]



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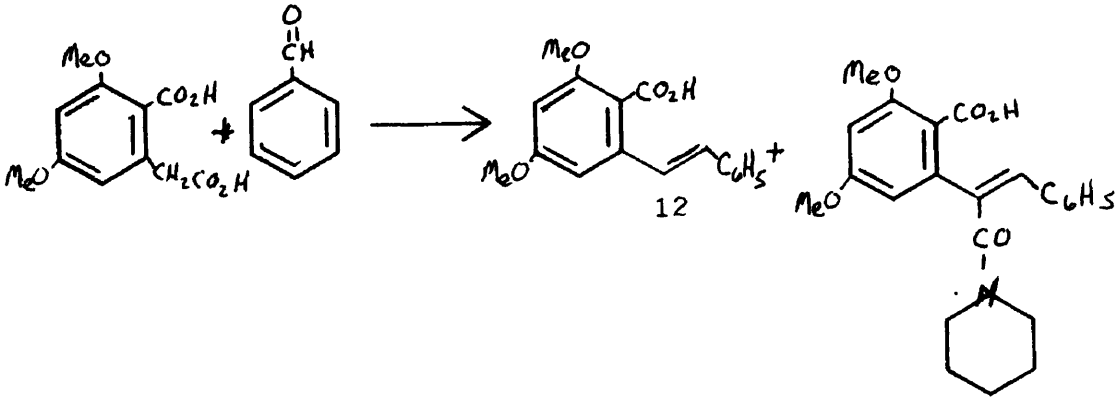
Benzaldehyde has been observed[12] to condense with 3,5-dimethoxyhomophthalic acid in a pyridine-piperidine mixture at 180° to yield mostly the Knoevenagel product (12) and minor amounts of another aldol product (13).



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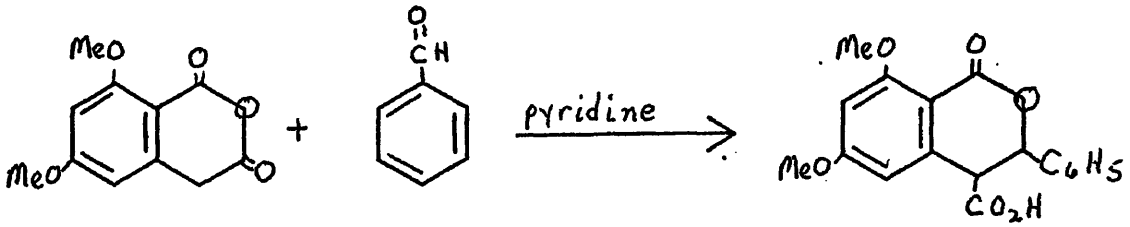
The anhydride of the 3,5-dimethoxyhomophthalic acid (14) can be condensed with benzaldehyde to yield a diastereoisomeric mixture of lactonic acid (15).



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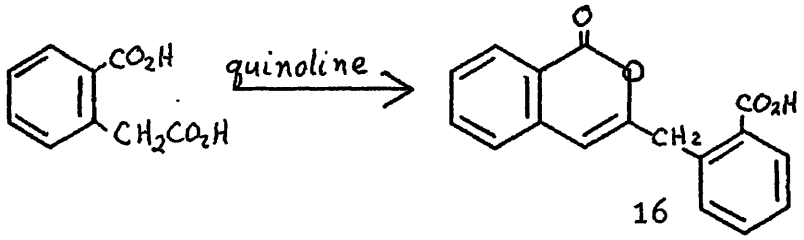
3-(2-Carboxybenzyl)isocoumarin (16) is the product of a reaction in which homophthalic acid and quinoline were refluxed for four hours[13].



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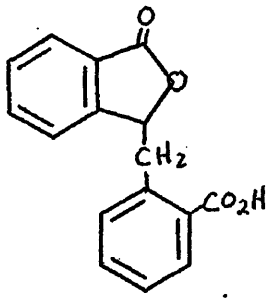
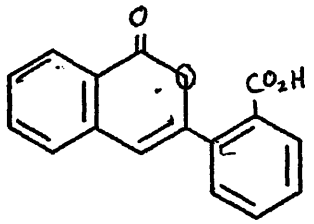
The self condensation of homophthalic anhydride in the presence of pyridine or piperidine also yields product (16).[14] Originally, it was thought that this reaction gave 3-(2-carboxybenzyl)phthalide (17).[15]



17

When sodium acetate is used as the base, a pair of

autocondensation products (18) and (19) are formed, (18) being the major product. Side products of this type could compete with condensations of aldehydes with homophthalic acid or the anhydride.



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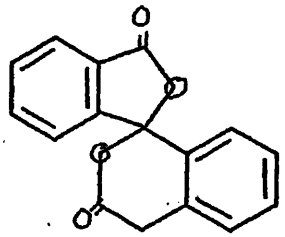

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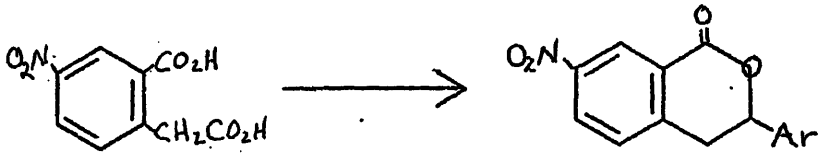
4-Nitrohomophthalic acid has been condensed with phenol, cresols and xylenols to yield 3-aryl-7-nitro-isocoumarins (20)[10] using either stannous chloride or polyphosphoric acid.



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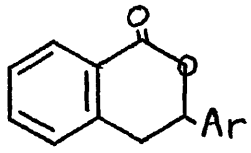
Preparation of Isocoumarins

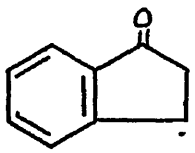
One of the purposes of this study was to develop a simpler method for preparing isocoumarins.



21

Isocoumarins of type (21) have been prepared by a large

variety of reactions, but all are rather tedius and usually require rarely available starting materials. One method involves the oxidation of indenes (3), indanones (22) or indones (23).



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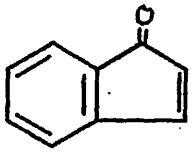

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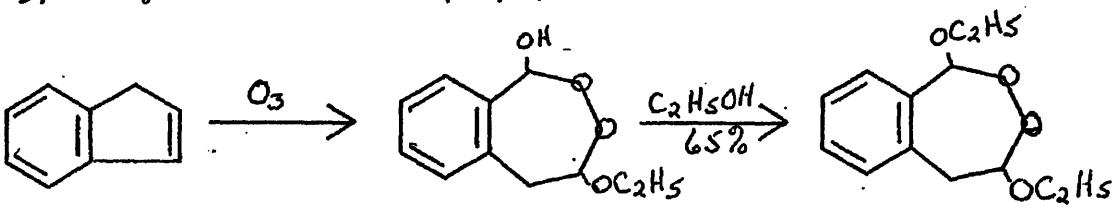
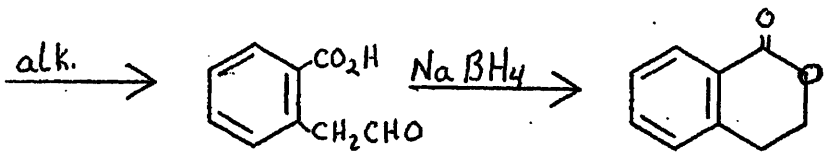
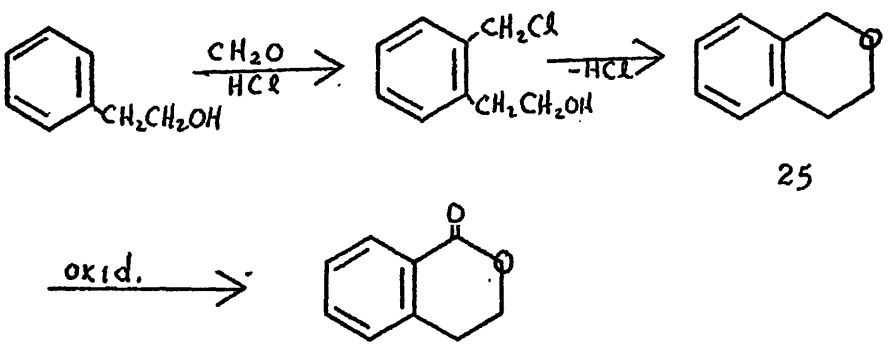
Ozonization of indene in 65% ethanol followed by sodium borohydride reduction and cyclization yields 3,4-dihydroisocoumarin (24)[6].





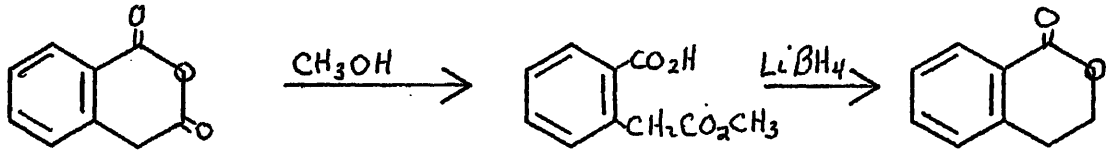
24

Oxidations of isochromans (25) furnishes a route to 3,4-dihydroisocoumarins. An example is the chloromethylation of 2-phenylethanol to 2-(2-chloromethylphenyl)ethanol and cyclization to isochroman (25).[16,17] Isochroman can be oxidized to the isocoumarin using chromic acid.

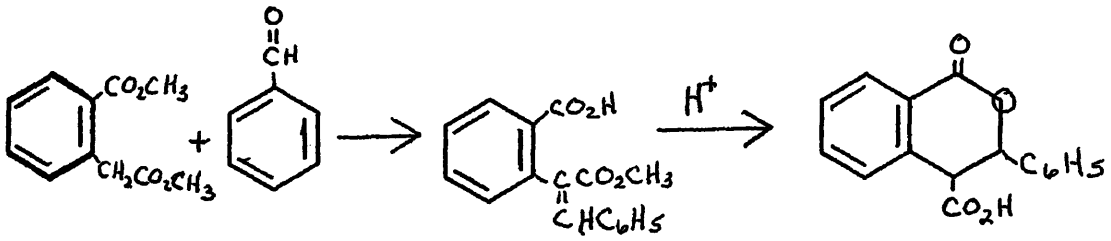


25

Reduction of 2-carboxyphenylacetates leads to isocoumarins. Homophthalic anhydride, upon methanolysis, yields methyl-2-carboxyphenylacetate (26), which yields 3,4-dihydroisocoumarin upon reduction with lithium borohydride.[18]

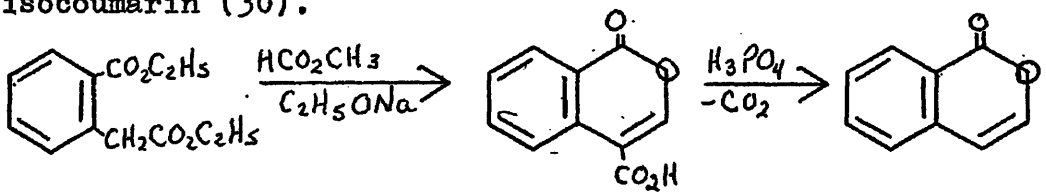


Condensations of many types have been used to prepare isocoumarins. Stobbe condensations between homophthalates and aldehydes or ketones have been reported.[19] Dimethyl homophthalate in the presence of sodium hydride in methanol reacts with benzaldehyde to give methyl α-benzylidene-α-(2-carboxyphenyl)acetate (27). In the presence of strong acids, the acetate is converted to 3-phenyl-3,4-dihydroisocoumarin-4-carboxylic acid (28).

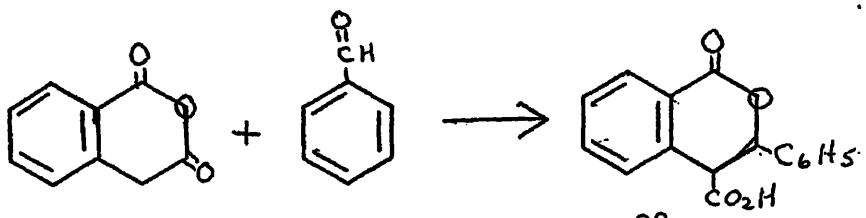


27 28

Claisen condensations of homophthalates with formates affords another preparation of isocoumarins. Diethyl homophthalate condenses with methyl formate in the presence of sodium ethoxide to yield isocoumarin-4-carboxylic acid (29), which can be decarboxylated to isocoumarin (30).[20]



The Perkin condensation of homophthalic anhydrides and aromatic aldehydes has been reported. In the presence of strong bases such as triphenylmethyl sodium, homophthalic anhydride reacts with benzaldehyde to produce 3-phenyl -3,4-dihydroisocoumarin-4-carboxylic acid (28).[21,22,23]



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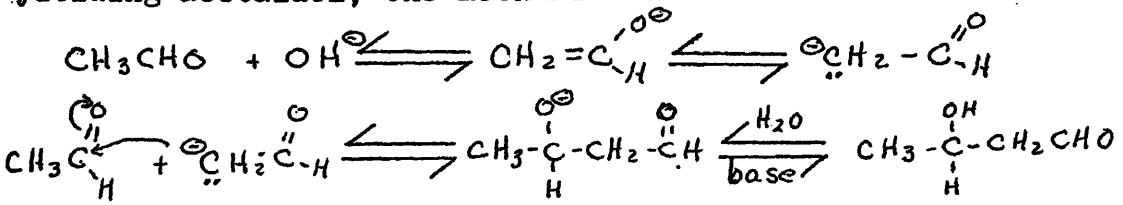
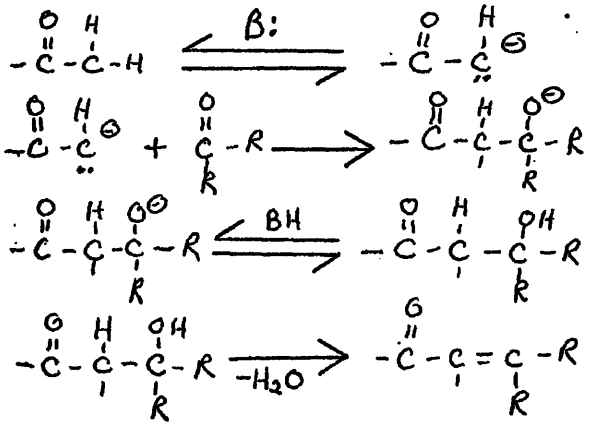
Aldol Condensations

Aldol condensations are acid or base catalyzed reactions between the enol of one carbonyl compound and

the carbonyl of the other substance, proceeding through a carbanion intermediate.[24] Originally, the name aldol derived from the self condensation of acetaldehyde yielding acetaldol, the mechanism of which is as follows.



In general, there are three basic steps to an aldol, each being reversible.[24] The first step is the formation of the carbanion through extraction of an active methylene proton by a suitable base (equation 1). The carbanion adds across the carbonyl double bond of the other reactant (equation 2) and finally, a proton is obtained from the solvent and the condensation is complete (equation 3). Most condensations, however, proceed one step further, eliminating water to form a double bond (equation 4).



equation 1

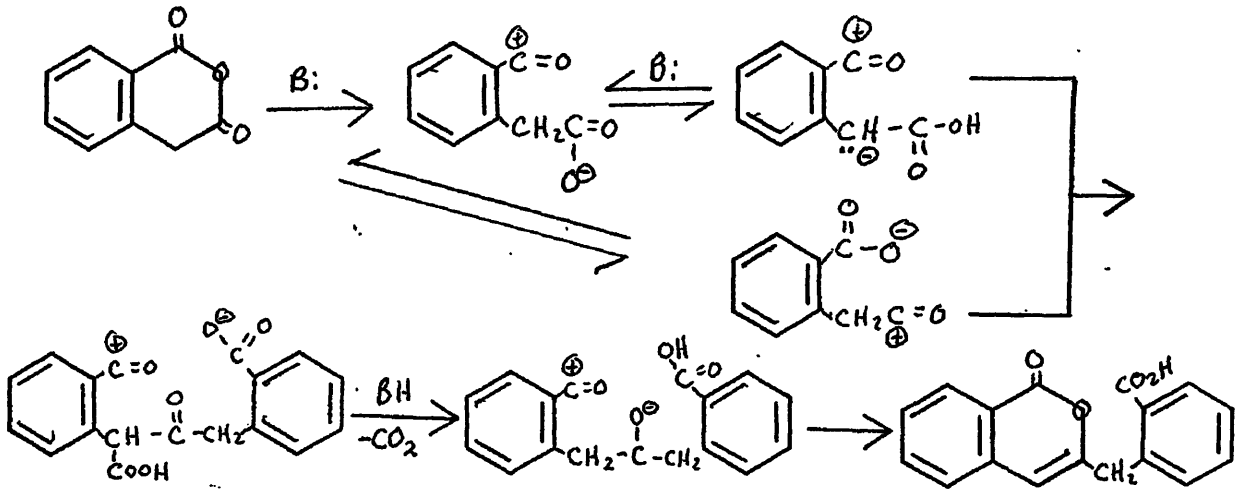
equation 2

equation 3

equation 4

Variations of this general mechanism have been proposed. Akmin and Molko, in attempting to explain the

product of the self-condensation of homophthalic anhydride proposed the following mechanism.[14]

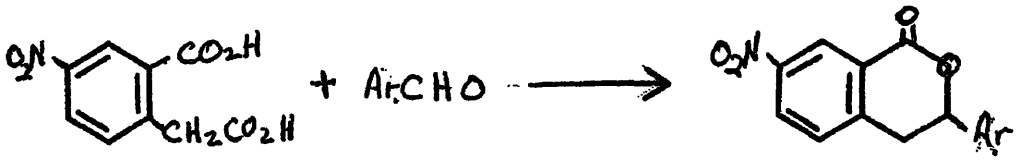


Knoevenagel Condensation

The Knoevenagel condensation is the reaction between an aldehyde or ketone and a compound containing an active methylene group. A catalytic amount of ammonia or a primary or secondary amine is necessary and sometimes a small amount of a carboxylic acid is added to the reaction mixture.[25] The usual product is the dehydrated form, the aldol addition compound being only seldom isolated. The self-condensation of homophthalic acid is of the Knoevenagel type, since the base is an amine.

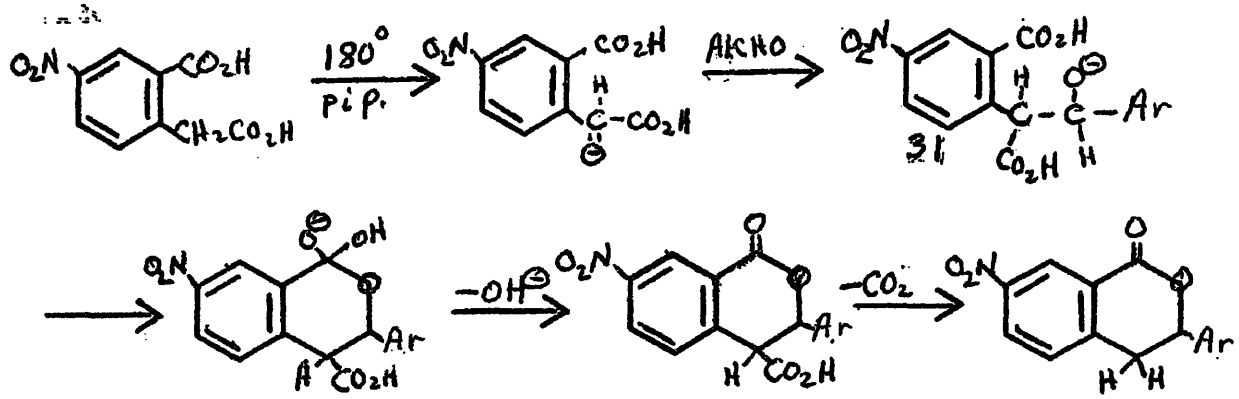
This Study

The reactions described in this investigation were of the Knoevenagel type. A series of aromatic aldehydes were condensed with 4-nitrohomophthalic acid, using piperidine as the amine catalyst.



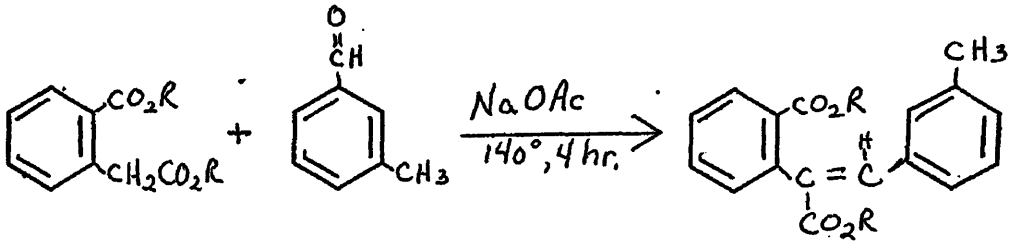
where Ar= 2-methylphenyl
3-methylphenyl
4-methylphenyl
4-isopropylphenyl
2-chlorophenyl
4-chlorophenyl
2,6-dichlorophenyl
2-methoxyphenyl
3,4-dimethoxyphenyl
3,4-methylenedioxyphenyl

The sequence of changes when 4-nitrohomophthalic acid is condensed with aromatic aldehydes in the presence of piperidine at 180-190° (Knoevenagel conditions) is somewhat complex since cyclization and/or decarboxylation can occur, leading to lactones, in addition to the usual Knoevenagel products.



It would seem possible that, if a low enough temperature was applied at a longer reaction time, a compound similar to (31) could be isolated. This has,

in fact, been accomplished for the reaction of homophthalic acid and 3-methylbenzaldehyde at 140° for four hours in the presence of sodium acetate.[26] The reported structure (32) corresponds to (31) if a dehydration and no cyclization took place.



32

This same reaction has been reported with other benzaldehydes including 3-chlorobenzaldehyde,[26] 3-methoxybenzaldehyde,[26] 3-nitrobenzaldehyde,[27] 3,4-dimethoxybenzaldehyde,[27] 3,4-methylenedioxybenzaldehyde,[27] 4-chlorobenzaldehyde,[28] and 4-methoxybenzaldehyde.[28] This kind of reaction is useful for preparing certain stilbene carboxylic acids of type (32).

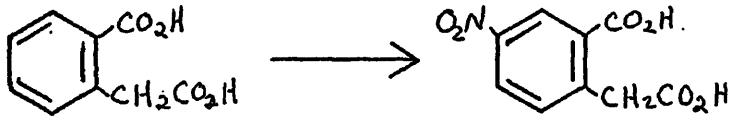
This investigation deals with the structure of certain products obtained from the condensation of 4-nitrohomophthalic acid with a series of aromatic aldehydes. The structure assigned to the products was based primarily on elemental analysis, nuclear magnetic resonance and infra-red spectrometry.

EXPERIMENTAL

Materials and Instruments

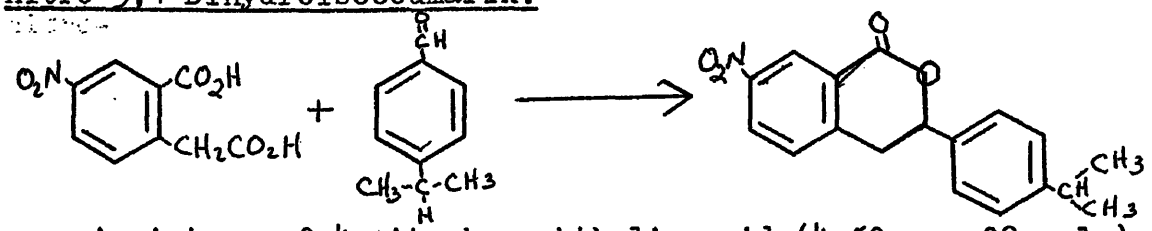
The chemicals used in this study were purchased from chemical supply houses and were all reagent grade except for certain organic compounds which were the best grade obtainable. The infra-red spectra were measured with a Perkin-Elmer Model 100 spectrophotometer as potassium bromide pellets. Nuclear magnetic resonance spectra were obtained on a Varian A-60A Analytical NMR Spectrometer. Elemental analyses were done by Huffman Laboratories, Inc., Wheatridge, Colorado. Melting points were determined with a Hershberg melting point apparatus and uncorrected.

Preparation of 4-Nitrohomophthalic Acid



Homophthalic acid (2g., 0.011 moles) was added slowly with stirring to yellow fuming nitric acid (16g, d 1.5) contained in a 500 ml round bottom flask at 10-15°. Following the addition the mixture was allowed to stand at room temperature for two hours. The deep brown solution was poured over a mixture of 50 grams of water and 50 grams of ice. The resulting yellow crystals were collected and recrystallized from 150 ml of water (yield, 40%, 0.98g. mp. 213-214°).

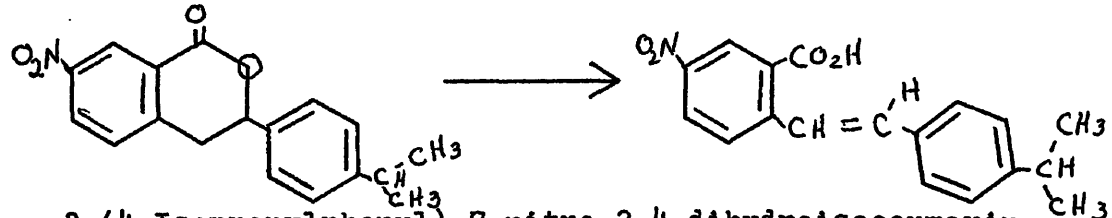
Condensation of 4-Nitrohomophthalic Acid with 4-Isopropylbenzaldehyde. Preparation of 3-(4-Isopropylphenyl)-7-nitro-3,4-Dihydroisocoumarin.



A mixture of 4-nitrohomophthalic acid (4.50g., .02 mole) 4-isopropylbenzaldehyde (4.44g., .02 mole) and piperidine (4 drops) contained in a 50ml round bottom flask was heated at 180° for one-half hour in a wax bath (Fisher Bath Wax B-219). The mixture was cooled to about 110°, then an equal volume of methanol was added with stirring. Yellow crystals separated and were collected and recrystallized from acetone/hexane (yield 38.5%, 2.30g., mp 149-150°).

Condensation of 4-nitrohomophthalic acid with 2-methylbenzaldehyde, 3-methylbenzaldehyde, 4-methylbenzaldehyde, 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 2,6-dichlorobenzaldehyde, 2-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, and 3,4-methylenedioxybenzaldehyde was performed in the same manner.

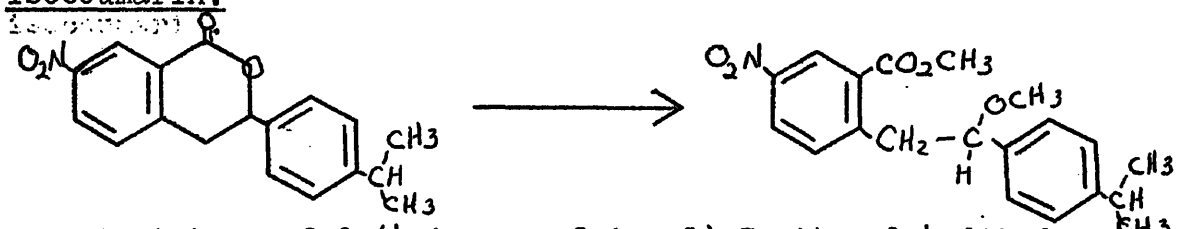
Preparation of 4-Nitro-4'-Isopropylstilbene-2-Carboxylic Acid.



3-(4-Isopropylphenyl)-7-nitro-3,4-dihydroisocoumarin (1.05 g., .0035 mole) was added to a solution of 25 ml of 80% ethanol and 0.18 g of potassium hydroxide and the

mixture was boiled until solution was complete (approximately 15 minutes). The solution was heated in a wax bath at 190° for 15 minutes after all the alcohol had evaporated. The residue was dissolved in 100 ml of water, acidified to Congo Red indicator, extracted with ether (100 ml) and the ether extract was dried and evaporated in vacuo. Yellow crystals were collected and dried over phosphorous pentoxide (yield 48.6%, .51 g., mp 219-220°). ir: 1690 cm^{-1}, 2500-3100 cm^{-1} (Carboxylic acid), 965 cm^{-1} (trans disubstituted double bond) nmr: 6.78, 2.79, 2.32, 2.07, 1.93, 1.58. Anal. Calcd for $C_{18}H_{17}O_4N$: C,69.44; H,5.50; O,20.56: N,4.50 Found: c,69.73; H,5.60; N,4.48.

Solvolysis of 3-(4-Isopropylphenyl)-7-Nitro-3,4-Dihydroisocoumarin.



A mixture of 3-(4-isopropylphenyl)-7-nitro-3,4-dihydroisocoumarin (2.0 g., .0064 moles), methanol (50 ml, anhydrous) and sulfuric acid (3 drops, concentrated) was refluxed for eight hours in a 100 ml round bottom flask. After cooling, 2 g. of solid sodium bicarbonate and 20 ml of 10% sodium bicarbonate solution were added to the reaction mixture. The solution was filtered to remove the precipitate and the filtrate was evaporated at reduced pressure. White crystals were collected and dried over phosphorous pentoxide (yield 48.4%, 1.07 g., mp 83-84°). ir: 1720 cm^{-1}

2800-3000 cm^{-1} nmr: 8.75,6.90,6.59,6.09,5.65,2.82,2.60 1.83,1.30. Anal. Calcd for $C_{20}H_{23}O_5N$: C,67.21; H,6.49; O,22.38; N,3.92 Found: C,69.11; H,5.37; N,4.38.

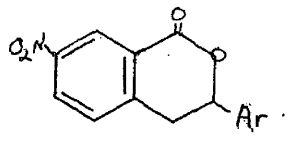
Solubility test of 3-(4-isopropylphenyl)-7-nitro-3,4-dihydroisocoumarin in sodium bicarbonate and sodium hydroxide.

3-(4-isopropylphenyl)-7-nitro-3,4-dihydroisocoumarin (approximately 0.1 g) was placed in two small test tubes, one containing 10 ml of 10% sodium bicarbonate solution and the other containing 10 ml of 10% sodium hydroxide solution. The tubes were heated to boiling, then allowed to cool. The tube containing the sodium hydroxide was acidified with dilute hydrochloric acid, the precipitate was collected and the melting point and a mixed melting point were taken (m.p. 149-150°, mixed m.p. 147-148°). The same tests were performed on products 36-45 (see Chart 1).

RESULTS

TABLE I.

Condensation Products of 4-Nitrohomophthalic Acid with Various Aldehydes

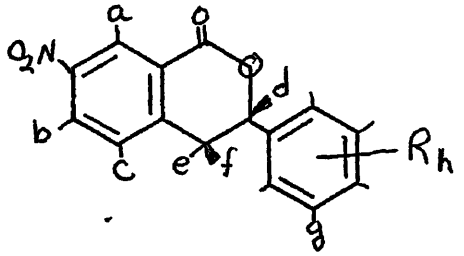


Ar	Empirical Formula	Yield (%)	Melting Point	Calculated C	Calculated H	Calculated N	Calculated Cl	Found* C	Found* H	Found* N	Found* Cl
2-methylphenyl	$C_{16}H_{13}NO_4$	29.0	171-172	67.84	4.63			67.97	4.78		
3-methylphenyl	$C_{16}H_{13}NO_4$	36.7	134-135	67.84	4.63			67.92	4.78		
4-methylphenyl	$C_{16}H_{13}NO_4$	76.1	177-178	67.84	4.63			67.79	4.46		
4-isopropylphenyl	$C_{18}H_{17}NO_4$	43.4	149-150	69.44	5.50			69.48	5.69		
2-chlorophenyl	$C_{15}H_{10}ClNO_4$	60.3	190-191	59.32	3.32			59.57	3.26		
4-chlorophenyl	$C_{15}H_{10}ClNO_4$	69.2	181-182	59.32	3.32			59.56	3.54		
2,6-dichlorophenyl	$C_{15}H_9Cl_2NO_4$	49.7	208-209	53.28	2.68	4.14	20.97	53.32	2.80	4.03	21.21
2-methoxyphenyl	$C_{16}H_{13}NO_6$	47.5	169-170	64.21	4.38			64.17	4.48		
3,4-dimethoxyphenyl	$C_{17}H_{15}NO_6$	25.5	173-174	62.00	4.59			62.20	4.75		
3,4-methylenedioxyphenyl	$C_{16}H_{11}NO_6$	56.3	179-180	61.34	3.54			61.48	3.64		

* All values agree within ± 0.4%

TABLE II

IR and NMR data for isocoumarin products

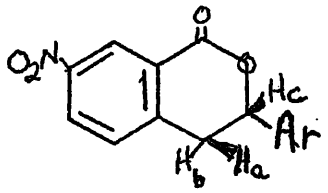


R	IR* cm^{-1}	NMR (τ) a	b	c	d	e	f	g	h
2-methyl	1730	--	2.60	1.65	4.60	6.65	6.70	2.72	7.66
3-methyl	1720	--	--	--	--	--	--	--	--
4-methyl	1715	1.08	2.55	1.65	4.40	6.63	6.68	2.70	7.63
4-isopropyl	1725	1.02	2.50	1.65	4.43	6.62	6.68	2.68	8.75
2-chloro	1720	--	--	--	--	--	--	--	--
4-chloro	1725	--	--	--	--	--	--	--	--
2,6-dichloro	1710	--	2.95	2.48	4.67	6.58	7.42	3.75	--
2-methoxy	1715	1.13	3.30	2.45	4.08	6.67	6.71	2.80	6.15
3,4-dimethoxy	1720	1.16	2.50	1.60	4.45	6.60	6.62	3.10	6.12
3,4-methylenedioxy	1715	--	2.77	1.65	4.50	6.61	6.65	3.15	4.08

*Lactone carbonyl peak

TABLE III

Coupling constants of protons a, b and c

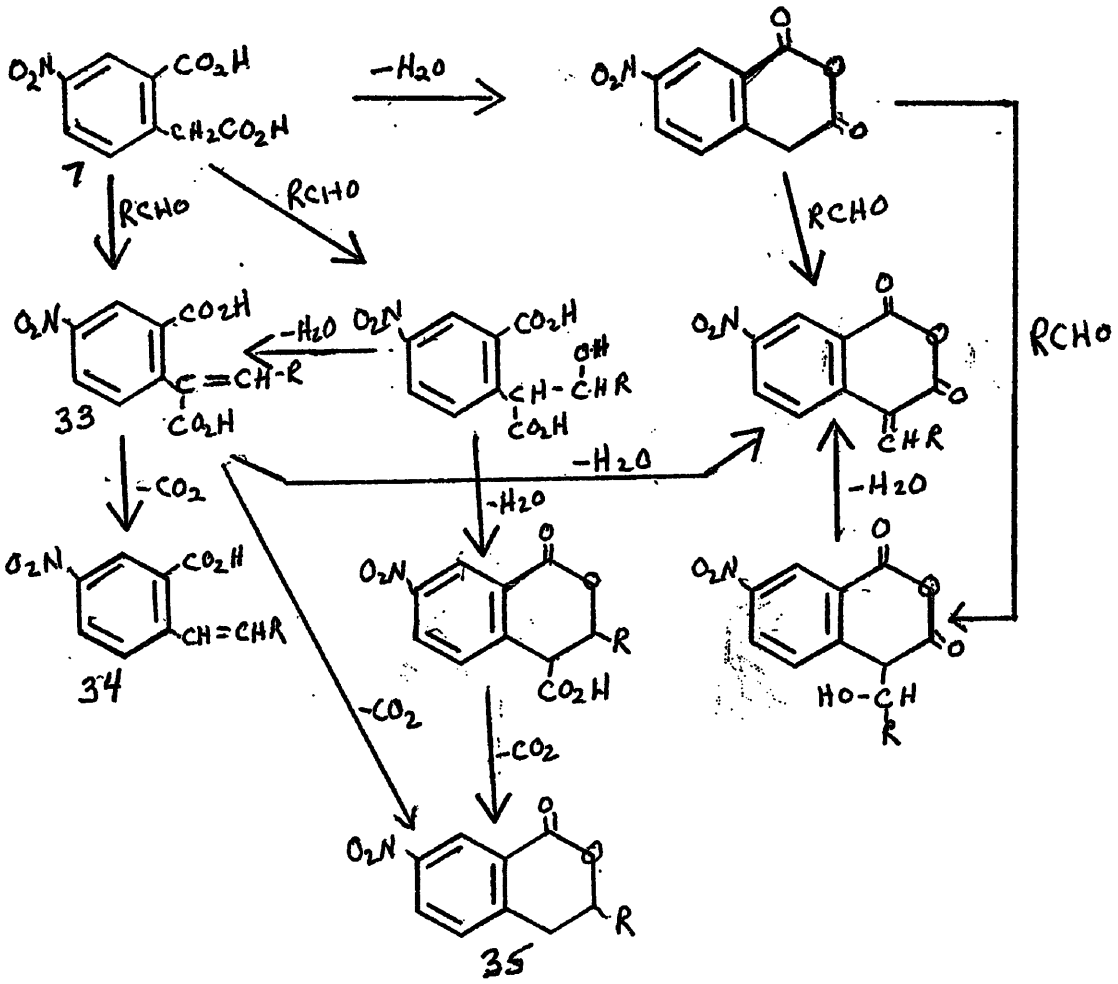


Ar	Coupling constants (Hz)
3-methylphenyl	J_{ab}=8.6, J_{bc}=5.9
4-methylphenyl	J_{ab}=8.9, J_{bc}=5.8
4-isopropylphenyl	J_{ab}=9.4, J_{bc}=6.0
2,6-dichlorophenyl	J_{ab}=8.5, J_{bc}=6.5, J_{ac}=1.8
2-methoxyphenyl	J_{ab}=8.5, J_{bc}=6.8
3,4-dimethoxyphenyl	J_{ab}=9.5, J_{bc}=5.3
3,4-methylenedioxyphenyl	J_{ab}=9.3, J_{bc}=5.5

NMR spectra could not be taken for R=3-methylphenyl, 2-chlorophenyl, or 4-chlorophenyl, due to the insolubility of these products in available NMR solvents.

CHART I

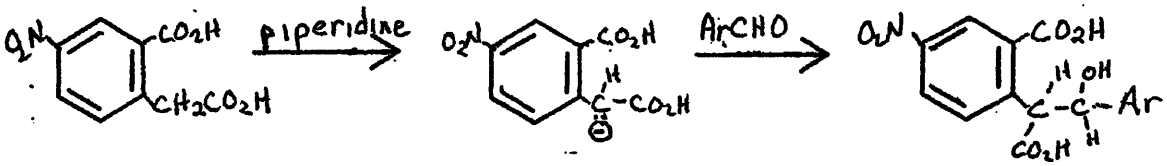
Possible pathways for the condensation of 4-nitrohomophthalic acid with aromatic aldehydes

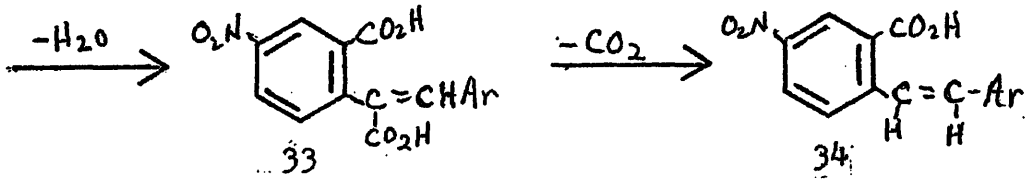


R=2-methylphenyl (36)
3-methylphenyl (37)
4-methylphenyl (38)
4-isopropylphenyl (39)
2-chlorophenyl (40)
4-chlorophenyl (41)
2,6-dichlorophenyl (42)
2-methoxyphenyl (43)
3,4-dimethoxyphenyl (44)
3,4-methylenedioxyphenyl (45)

DISCUSSION

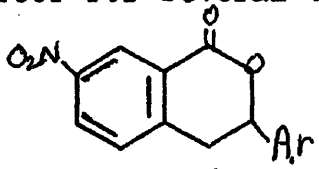
The purpose of this work was to determine the structure of the products from the Knoevenagel condensation between 4-nitrohomophthalic acid and various benzaldehydes. Originally, previous workers expected to obtain 4-nitrostilbene-2-carboxylic acids (33) and 4-nitro-α, 2'-dicarboxylic acids (34),[29] formed by the aldol-type condensation followed by a dehydration and decarboxylation.





33 34

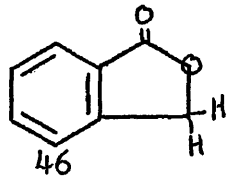
In some cases, the expected stilbenes were obtained. However, several aldehydes gave other substances as the major product, one of which was suspected of being an isocoumarin of structure (35). This study was directed at the structure proof for several type (35) compounds.



35

Elemental analysis of the major product from the condensation between 4-nitrohomophthalic acid and 4-isopropylbenzaldehyde satisfied the formula $C_{18}H_{17}NO_4$ and the infra-red spectrum showed a carbonyl absorption at 1735 cm;, the region assigned to a δ-lactone carbonyl. This evidence strongly suggested the lactone structure (39) in Chart 1. Lack of a peak in the infra-red for a carboxylic acid or alcohol eliminated (34) and the other structures on Chart 1 do not satisfy the elemental analysis for $C_{18}H_{17}NO_4$.

The NMR spectrum of the product showed the presence of methylenic protons, although shifted downfield more than expected. This shift seems to be due to the closed ring structure of the molecule, since a similar shift of 5.32 was found for the methylene protons in phthalide (46),[30] while a shift of 5.08 was found for the methylene protons in benzyl acetate.

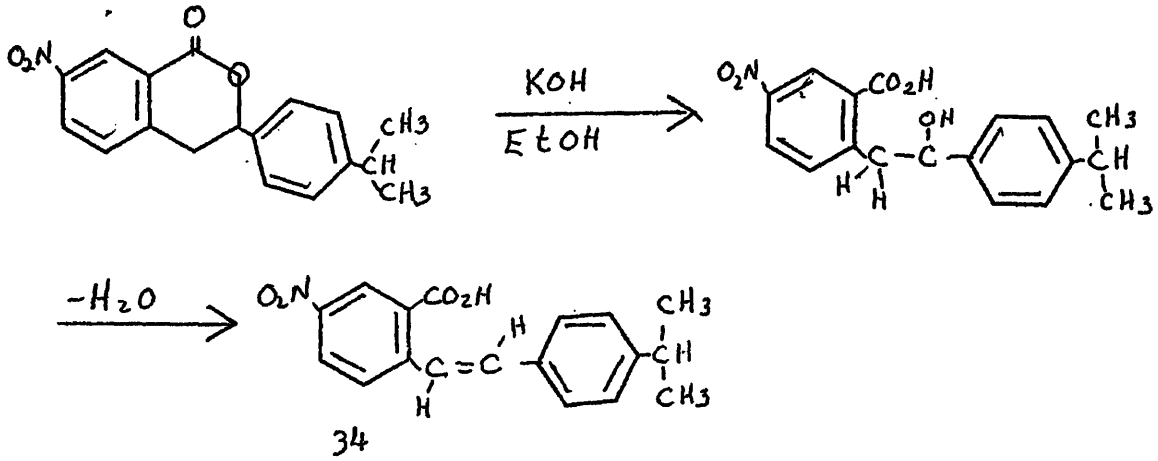


46

When the product was mixed with cold 10% sodium bicarbonate, no reaction occurred, but the compound dissolved in warm sodium hydroxide, a property of esters and lactones. The lactone was reisolated after acidification of the solution. Isocoumarins 36, 37, 38, 39, 40, 41, 42, 43, 44, and 45 (see Chart I) were identified by elemental

analysis, infra-red spectroscopy and nuclear magnetic resonance. All isocoumarins dissolved in sodium hydroxide and were reisolated upon acidification.

In order to find a possible way to prepare stilbenes and as further proof of structure (35), the product (39) was hydrolyzed to open the lactone ring, then dehydrated to the corresponding stilbene (34) where R=4-isopropyl-phenyl.



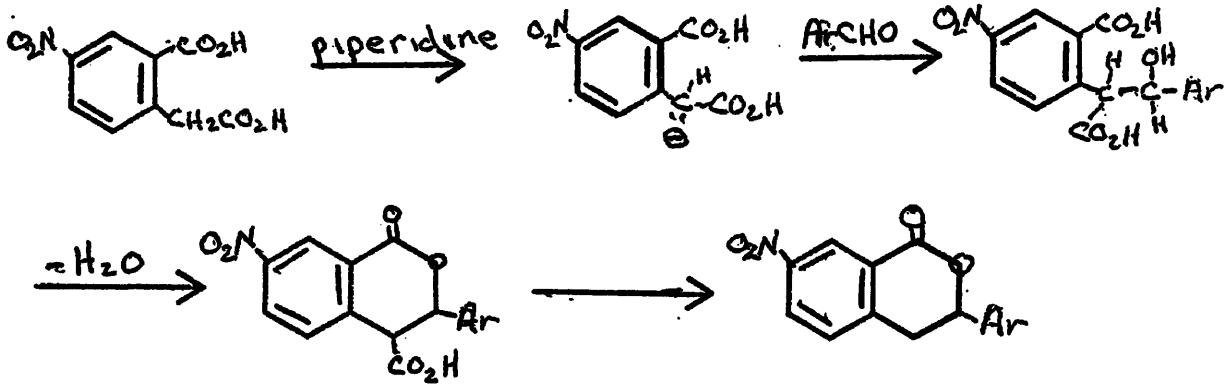
34

Elemental analysis, infra-red spectroscopy, and nuclear magnetic resonance confirmed the structure for (34).

The isocoumarin (39) was dissolved in anhydrons methanol containing a few drops of concentrated sulfuric acid and refluxed for eight hours. A product was isolated but not identified (see experimental section).

CONCLUSION

Certain aromatic aldehydes, under Knoevenagel conditions, have been found to form substituted 3,4-dihydroisocoumarins as the only isolated product when condensed with 4-nitrohomophthalic acid. The aldehydes which gave these types of products were 2-methylbenzaldehyde, 3-methylbenzaldehyde, 4-methylbenzaldehyde, 4-isopropylbenzaldehyde, 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 2,6-dichlorobenzaldehyde, 2-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, and 3,4-methylenedioxybenzaldehyde. The isocoumarins seem to be formed as follows:



This pathway is one of many which could be imagined for a reaction of this type (see Chart 1), but is the most logical choice, considering the products formed.

One of the previously expected initial products, a

stilbene, can be prepared from the isocoumarin through an opening of the lactone ring with potassium hydroxide followed by a decarboxylation at elevated temperatures (190°). In addition to providing further proof of the isocoumarin structure, the above procedure is a possible method for the synthesis of stilbenes.

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