STUDIES CONCERNING THE SYNTHESIS OF CYCLIC NITRO KETONES

by

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PREFACE

In the Introduction to this thesis, some general remarks on the significance of the chemistry of aliphatic nitro compounds will be followed by a brief review of some synthetic methods available in the field. The specific problems that were studied will then be outlined in the context of investigations performed earlier in this laboratory and elsewhere. The research carried out and the results obtained will be described in the chapter entitled "Discussion", which will precede the recording of the experiments in the "Experimental" section. A Summary, including Claims to Original Research, will conclude the thesis.

ACKNOWLEDGMENTS

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INTRODUCTION

In the early development of organic chemistry, the importance attached to aliphatic nitro compounds was small in comparison to that of their aromatic counterparts. Doubtless this was due in part to the fact that the latter were easily accessible by the nitration of aromatic hydrocarbons and their derivatives, while no equally convenient route to the former existed. Moreover, the great utility of aromatic nitro compounds as intermediates, especially in the dyestuff industry whose rapid expansion in the second half of the nineteenth century dominated the interests of organic chemists, apparently contributed to a measure of neglect suffered by the chemistry of aliphatic nitro derivatives. The foundations in this field nevertheless were laid by early investigators such as V. Meyer, A.R. Hantzsch, J.A. Wislicenus, L. Henry and J.U. Nef. However, it was not until the advent in the 1940's of the vapor phase nitration of paraffins (H. B. Hass) that nitroalkanes, nitroalkenes, and many types of their derivatives began to enjoy extensive use in the laboratory as well as in industry.

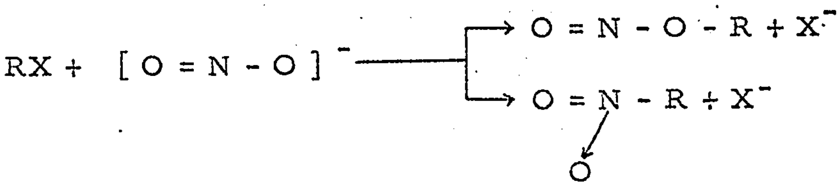
The nitro group, because of its activating and directing effects and its convertibility into other nitrogenous functions, endows compounds with great versatility for synthetic purposes. Suitably substituted aliphatic nitro compounds undergo, for example, aldol-type condensations, Mannich reactions, Michael additions and Diels-Alder reactions (1, 2, 3, 4). Many of them show promise as bacteriostatic and fungicidal agents as well as pesticides and insecticides (5), and the discovery during the past fifteen years of a considerable number of natural products containing an aliphatic nitro group has further stimulated interest in the field (6).

Since this thesis deals with certain synthetic problems in the realm of the chemistry of the aliphatic nitro group, it is deemed appropriate to give, as an introduction, a brief review of some of the more important syntheses that are available in this area.

1. Methods for introducing a Nitro Group into Aliphatic Compounds

(a) The Victor Meyer Reaction

The nucleophilic displacement by nitrite ion of halogen in alkyl halides was discovered by Victor Meyer (7) and has since been widely used in the laboratory. Silver nitrite and ether solutions of alkyl bromides or iodides are most frequently employed. Because of the ambident character of the nitrite ion, mixtures of nitroalkane and alkyl nitrite usually result, and the separation of such mixtures may present considerable difficulties.



$$RX + [O=N-O]^- \longrightarrow \begin{cases} O=N-O-R + X^- \\ O=\underset{\downarrow \atop O}{N}-R + X^- \end{cases}$$

With primary alkyl halides the formation of nitroalkanes is usually favored over that of the nitrite esters, whereas with secondary halides the reverse is true. Tertiary halides tend to give olefins along with nitrite esters, and tertiary nitroalkanes are not obtained.

The Victor Meyer reaction was considerably improved by Kornblum who introduced the use of sodium nitrite in dimethylformamide or dimethylsulfoxide as solvents (8). The reaction is faster under these conditions and good yields of nitroalkanes are obtained, although competing nitrite formation is also observed.

Another side reaction is nitrosation of the nitroalkanes produced, to give nitrolic acids or pseudonitroles according to the following equation (9):

$$RR'CHNO_2 + RR'CHONO \xrightarrow{NaNO_2} RR'C(NO)NO_2 + RR'CHOH$$

(R = alkyl, R' = alkyl or hydrogen)

The nitrosation is slower than the nitroalkane formation and can be minimized by prompt work-up. The addition of a scavenger such as phloroglucinol or resorcinol has also proved useful to forestall undesirable effects of nitrite esters. Kornblum and co-workers have also shown that sulfonate esters can be used, instead of alkyl halides, for displacement reactions with sodium nitrite. Furthermore, they have applied the reaction to α-halo esters and thus elaborated the only convenient, general route to α-nitro esters.

(b) Oxidation of Tertiary Carbinamines

Whereas tertiary nitro compounds cannot be generally obtained by the Victor Meyer reaction, they are accessible through permanganate oxidation of tertiary carbinamines (10).

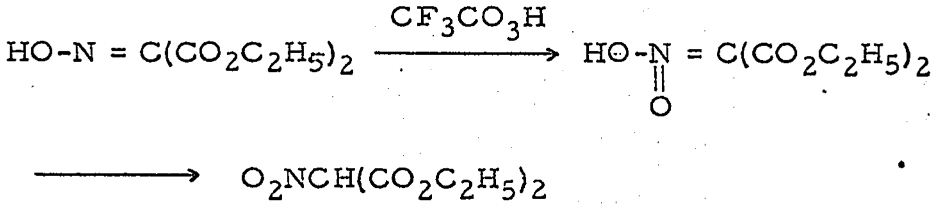
$$RR'R''CNH_2 \xrightarrow{KMnO_4} RR'R''CNO_2$$

Peracetic acid can also be used to oxidize the aliphatic amines to the nitro stage, but the permanganate method has been reported to be more convenient (11).

(c) Oxidation of Oximes

There are two principal methods for oxidizing oximes to nitro compounds.

One method, developed by Emmons and Pagano, can be applied to oximes that possess an ester function in alpha position to the oxime group. The oxidant is peroxytrifluoroacetic acid in a solvent such as chloroform or acetonitrile and in the presence of sodium bicarbonate or disodium hydrogen phosphate (12). The first product is the aci-form of the nitro compound which is then isomerized to the nitro form, e.g.

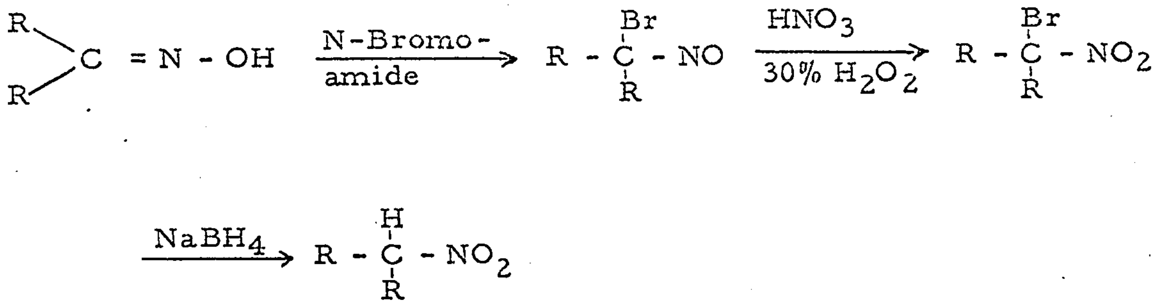


$$HO\text{-}N = C(CO_2C_2H_5)_2 \xrightarrow{CF_3CO_3H} HO\text{-}\underset{\underset{O}{\|}}{N} = C(CO_2C_2H_5)_2$$

$$\longrightarrow O_2NCH(CO_2C_2H_5)_2$$

The method is simple but has the disadvantage of being rather sensitive to steric hindrance.

The other method, which was developed by Iffland, is a more complicated, three-step procedure but is suitable for oxidizing sterically hindered oximes (13, 14, 15). The oxime is first treated with either N-bromosuccinimide or N-bromoacetamide and the resulting bromo nitroso compound is oxidized to the bromo nitro compound by a mixture of nitric acid and 30% hydrogen peroxide. The bromo nitro compound is then debrominated with sodium borohydride.



$$R_2C{=}N{-}OH \xrightarrow[\text{amide}]{\text{N-Bromo-}} R-\overset{Br}{\underset{R}{C}}-NO \xrightarrow[30\%\ H_2O_2]{HNO_3} R-\overset{Br}{\underset{R}{C}}-NO_2$$

$$\xrightarrow{NaBH_4} R-\overset{H}{\underset{R}{C}}-NO_2$$

The procedure can be used for the synthesis of secondary nitroalkanes including nitrocycloalkanes; it fails, however, with aldoximes and aromatic ketoximes.

(d) Nitration by Alkyl Nitrate

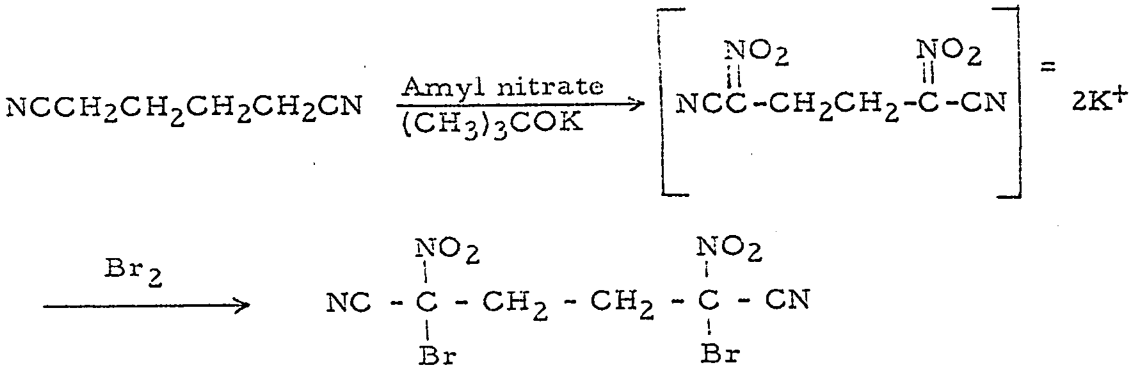
The nitration of reactive methylene compounds such as arylacetonitriles, arylacetic esters or fluorene by ethyl nitrate in the presence of potassium ethoxide was carried out by Wislicenus and his co-workers (16, 17, 18). The reaction involves, in essence, a nucleophilic displacement in the alkyl nitrate by the anion which is being nitrated:

$$AH + RO^- \longrightarrow A^- + ROH$$

$$A^- + RONO_2 \longrightarrow ANO_2 + RO^-$$

(A = reactive methylene residue)

In the alkaline reaction medium, the primary or secondary nitro compounds formed exist as alkali nitronates. Acidification leads to the free nitro compounds but may be accompanied by extensive decomposition to aldehydes or ketones, since nitro derivatives of reactive methylene compounds are particularly labile. Bromination at the nitronate stage, a virtually quantitative reaction, has been employed as a device of estimating the yields in the nitration, e.g.



$$\mathrm{NCCH_2CH_2CH_2CH_2CN} \xrightarrow[\mathrm{(CH_3)_3COK}]{\text{Amyl nitrate}} \left[\mathrm{NC\overset{\overset{NO_2}{\|}}{C}-CH_2CH_2-\overset{\overset{NO_2}{\|}}{C}-CN} \right]^{=} 2K^{+}$$

$$\xrightarrow{\mathrm{Br_2}} \mathrm{NC-\underset{\underset{Br}{|}}{\overset{\overset{NO_2}{|}}{C}}-CH_2-CH_2-\underset{\underset{Br}{|}}{\overset{\overset{NO_2}{|}}{C}}-CN}$$

The nitration with alkyl nitrate has been used for the synthesis of cyclic nitro ketones. Wieland and co-workers, nitrated cyclopentanone and obtained 2, 5-dinitrocyclopentanone*. Cyclohexanone gave the dipotassium salt of dinitrocyclohexanone and only a small yield of mononitrocyclohexanone (19).

Very recently, the mononitration of several cyclic ketones has been successfully carried out by Feuer and Pivawer, who used equivalent amounts of ketone and amyl nitrate and a 50% excess of sublimed potassium t-butoxide in tetrahydrofuran. The reaction mixtures were acidified with glacial acetic acid prior to work-up (21). However, the nitration was found to lead not only to cyclic α-nitro ketones but also to open-chain ω-nitro esters.

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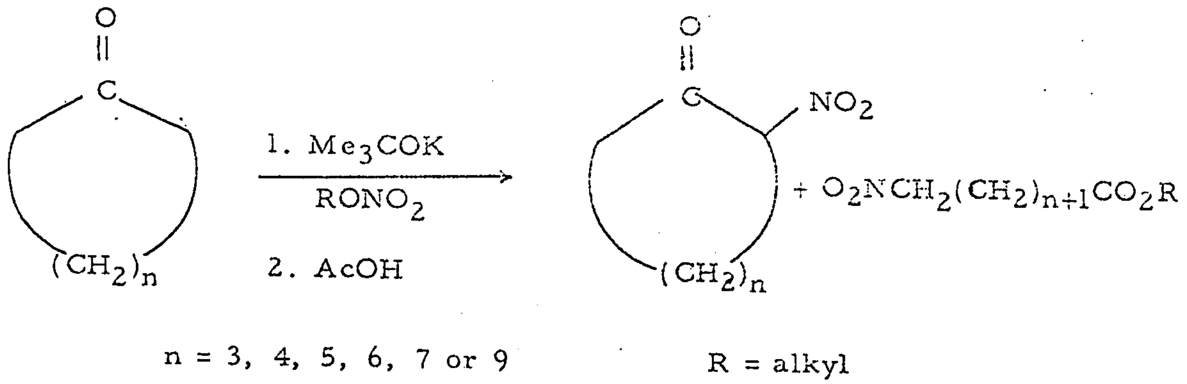
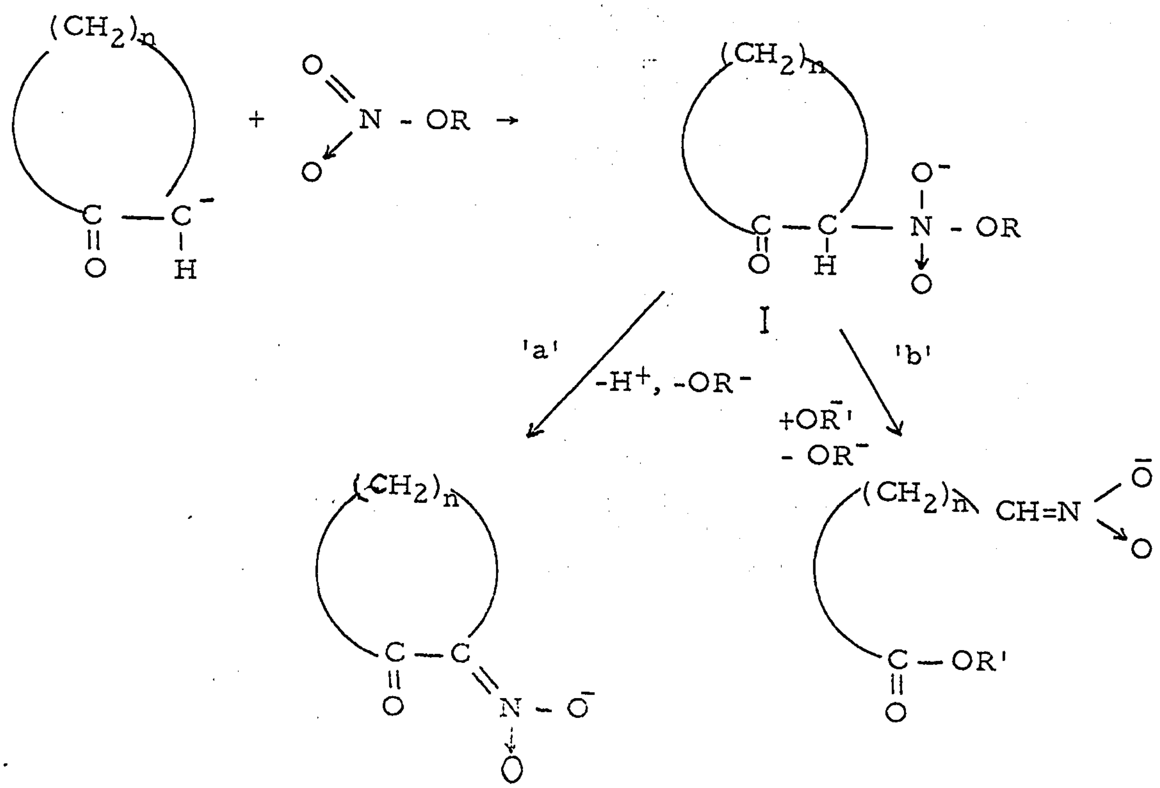
* 2, 5-Dinitrocyclopentanone is reported to be stable only at dry-ice temperature (20).



The ring opening was found to occur during the nitration step. Feuer and Pivawer proposed a mechanism that assumes the formation of an intermediate (I) which may have some stability at - 50°, the temperature at which the nitration is carried out.



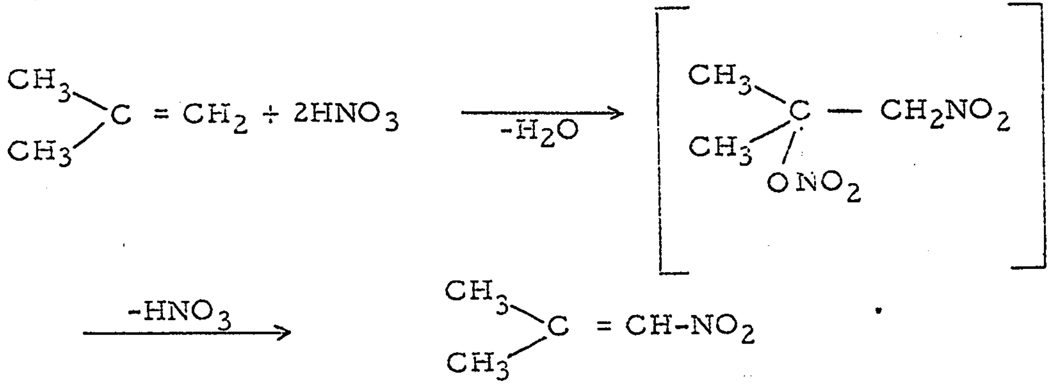
This intermediate may give the nitro ketone salt by abstraction of the α-hydrogen and expulsion of alkoxide ion (route 'a'). Alternatively, it may incur alkoxide attack at the carbonyl group leading to cleavage of the carbon-carbon bond and elimination of the alkoxyl group from the nitrogen atom (route 'b'). In cases where the intermediate (I) possesses an α-alkyl group instead of a α-hydrogen atom (i.e., when a tertiary nitro ketone should be formed), the reactinn cannot proceed to a nitronate along route 'a' and consequently gives rise to a high yield of cleavage product (route 'b'). That the cleavage occurs by direct alkoxide attack was supported by the finding that 2-bromo-2-nitrocyclooctanone on treatment with a mixture of potassium t-butoxide and absolute ethanol, gave ethyl 8-bromo-8-nitro-octanoate.

The mononitration of aryl alkyl ketones such as α-tetralone and propiophenone proceeds more slowly than that of other ketones; α-tetralone was the only ketone that did not undergo the cleavage reaction.

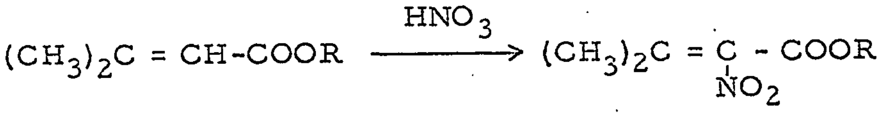
(e) Nitration of Alkenes

Several methods are available for introducing nitro groups into alkenes. Nitric acid, nitrogen tetroxide, nitryl chloride, or acetyl nitrate may be used for this purpose. In most of these nitrations one obtains saturated nitro compounds, but nitroolefins are sometimes formed as secondary products or may be made by subsequent conversions of the nitroalkane derivatives (see Section 2, d).

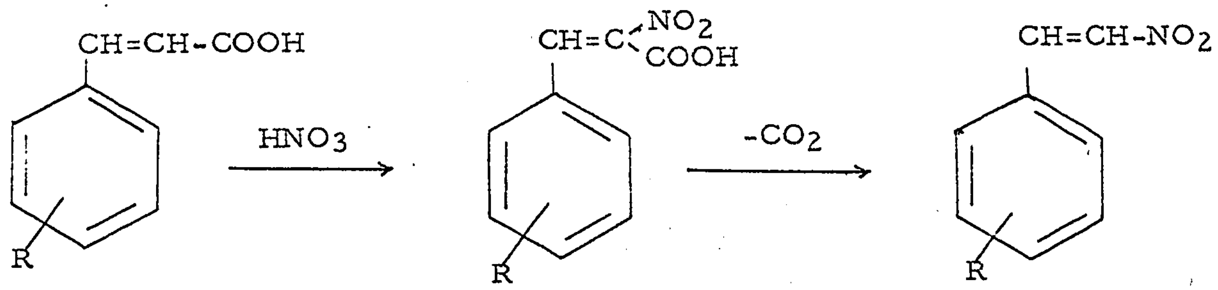
Nitric acid reacts with isobutylene to give 1-nitro-isobutylene (22), presumably as a result of the addition of dinitrogen pentoxide with subsequent elimination of nitric acid from intermediate nitro nitrate ester:

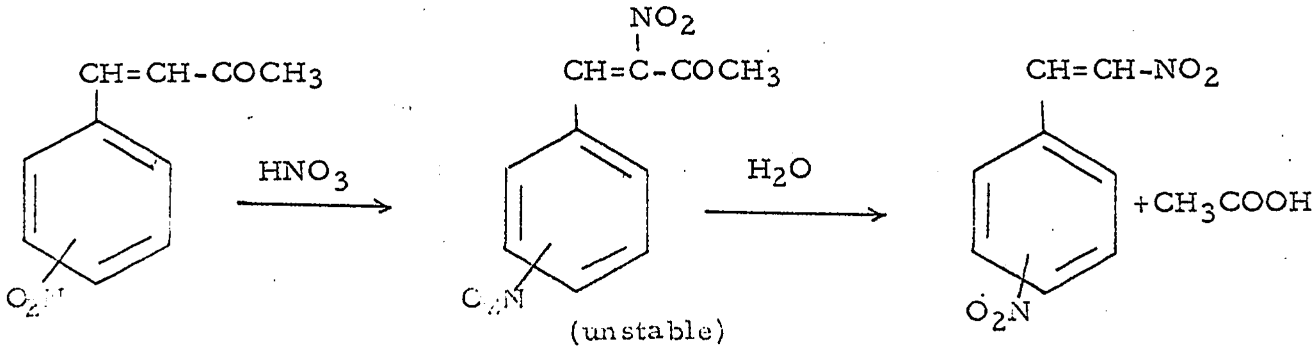


The procedure has also been applied to unsaturated acids and alkyl arylidene ketones (23, 24).

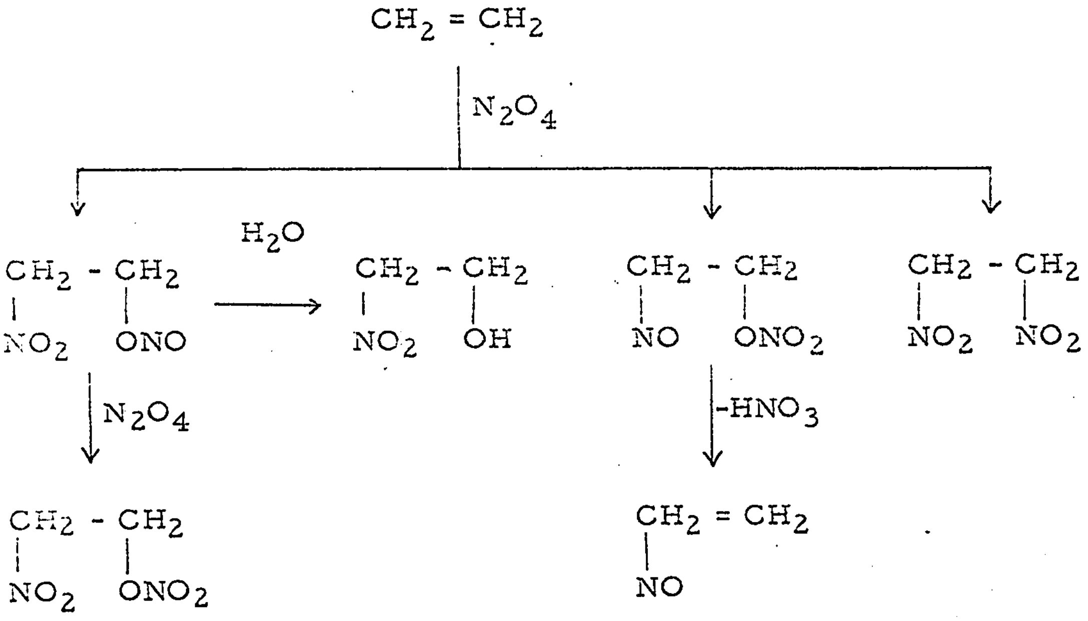


$$(CH_3)_2C = CH\text{-}COOR \xrightarrow{HNO_3} (CH_3)_2C = \underset{NO_2}{C} - COOR$$





The addition of dinitrogen tetroxide to ethylenic compounds results in the formation of various nitrogenous products as shown in the following scheme (25, 26).



The β-nitroalkyl nitrites arising from unsymmetrically substituted olefins always bear the nitro group on the more hydrogenated and the nitrite group on the less hydrogenated carbon atom.

Nitryl chloride reacts at 0° with olefins to give β-nitroalkyl chlorides (27) -

$$R\text{-}CH = CH_2 + NO_2Cl \longrightarrow RCHCl - CH_2NO_2$$

In monosubstituted ethylene derivatives the nitro group becomes attached to the terminal carbon of the double bond, whatever the nature of the substituent. Thus propylene, methyl acrylate and vinyl bromide all give primary nitro compounds (28, 29).

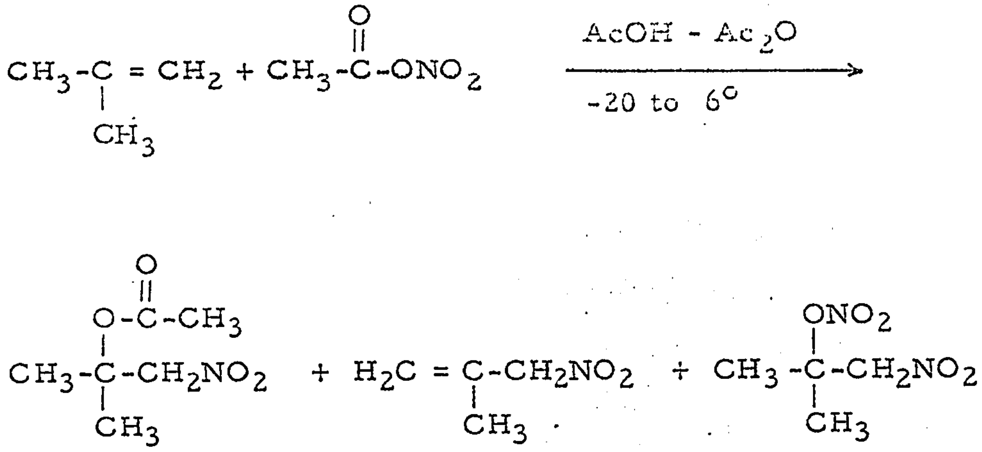
$$CH_2 = CH\text{-}CH_3 \xrightarrow{NO_2Cl} O_2N\text{-}CH_2\text{-}CHCl\text{-}CH_3$$

$$CH_2 = CH\text{-}CO_2CH_3 \xrightarrow{NO_2Cl} O_2N\text{-}CH_2\text{-}CHCl\text{-}CO_2CH_3$$

$$CH_2 = CH\text{-}Br \xrightarrow{NO_2Cl} O_2N\text{-}CH_2\text{-}CHClBr$$

On the basis of this, the authors suggested that the addition reaction of nitryl chloride involves a radical mechanism.

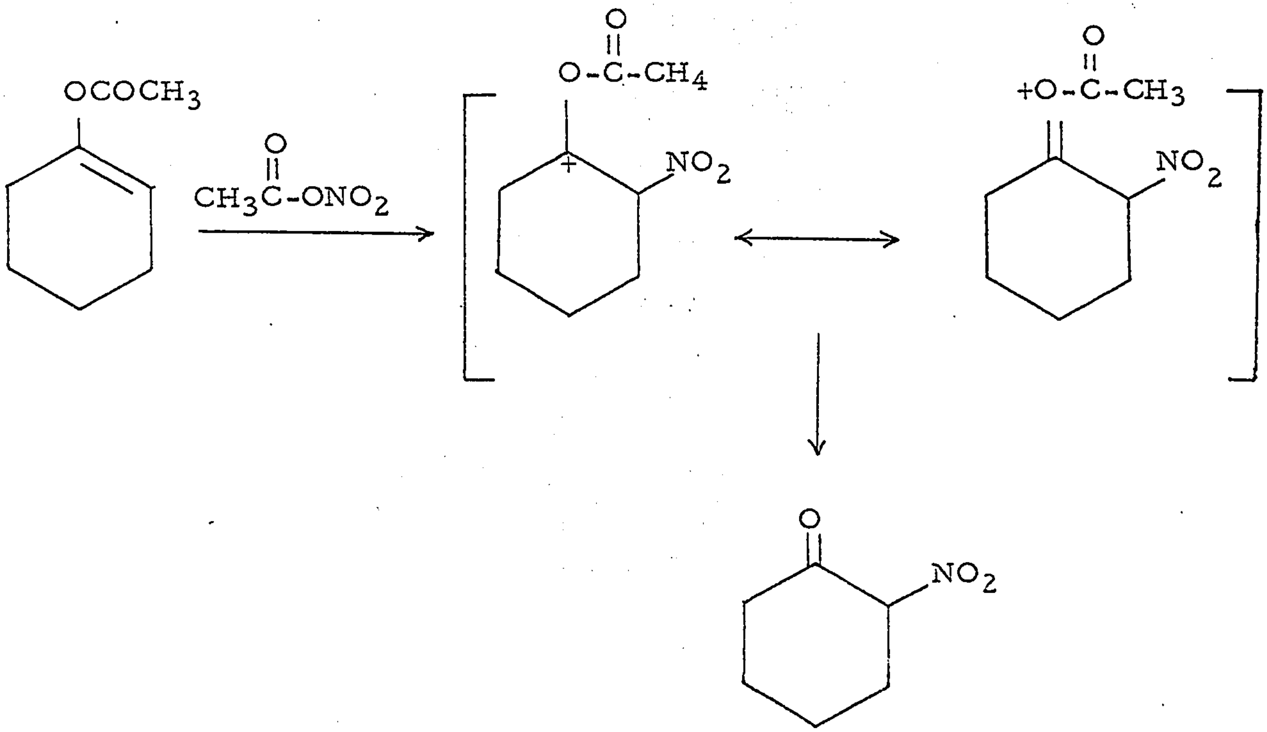
The nitration of alkenes with acetyl nitrate has been studied by Bordwell and Garbisch (30, 31, 32, 33). The reaction yields β-nitroalkyl acetates, β-nitroalkyl nitrates, and α-nitroalkenes:



$$CH_3\text{-}\underset{CH_3}{\underset{|}{C}}=CH_2 + CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}ONO_2 \xrightarrow[-20\text{ to }6^\circ]{AcOH - Ac_2O}$$

$$CH_3\text{-}\overset{O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3}{\overset{|}{\underset{\underset{CH_3}{|}}{C}}}\text{-}CH_2NO_2 + H_2C=\underset{CH_3}{\underset{|}{C}}\text{-}CH_2NO_2 + CH_3\text{-}\overset{ONO_2}{\overset{|}{\underset{\underset{CH_3}{|}}{C}}}\text{-}CH_2NO_2$$

1-Acetoxycyclohexene was nitrated with acetyl nitrate to give a 40% yield of 2-nitrocyclohexanone (34).



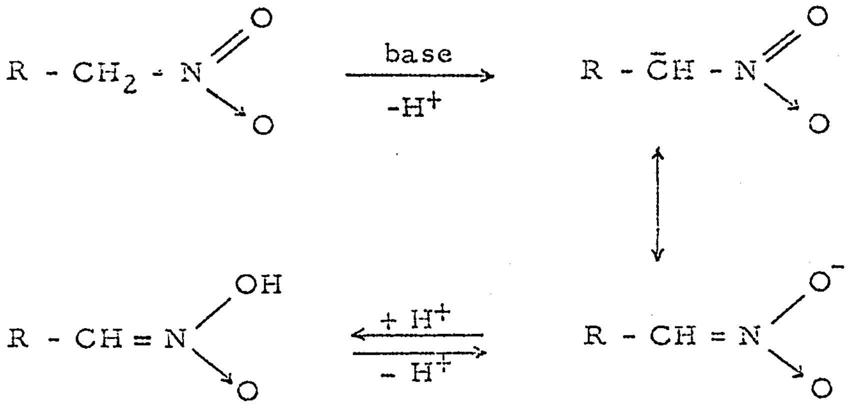
(f) Vapor Phase Nitration of Alkanes

Although not a convenient laboratory method, the vapor phase nitration of alkanes, which was developed by Hass (35), has become the best industrial source of lower nitroalkanes which are nowadays produced in large quantities for use as solvents and reagents. The procedure involves the rapid bubbling of the hydrocarbon vapor through a hot concentrated nitric acid (temperature 108°C) and the vapors are passed through a reactor maintained at 420°C. Nitration as well as chain fragmentation occurs, and from medium sized hydrocarbons one obtains mixtures of nitromethane, nitroethane, 1- and 2-nitropropane and some higher homologs.

2. Some Reactions of Aliphatic Nitro Compounds

(a) Salt Formation and Nitro-aci-nitro Tautomerism

In nitroalkanes the nitro group exerts a powerful activating effect on α-hydrogen atoms. Primary and secondary nitroalkanes therefore have acidic properties and readily form alkali salts known as aci-nitro salts or nitronates. The resonance-stabilized anion of such a salt gives, upon cautious acidification, an unstable nitronic acid which tautomerizes to the nitroalkane.



Recent studies by Russian (36) and American workers (37) have afforded new insights into the mechanism of this long-known reaction.

(b) <u>The Nef Reaction</u>

When acidification of an alkali nitronate is carried out with strong mineral acid in excess, hydrolysis to a carbonyl compound may occur. This is known as the Nef reaction (38).

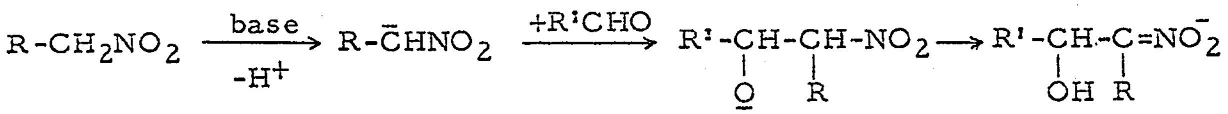
$$2R-CH = NO_2Na + 2H_2SO_4 \longrightarrow 2R-CHO + 2NaHSO_4 + N_2O + H_2O$$

$$2R_2C = NO_2Na + 2H_2SO_4 \longrightarrow 2R_2CO + 2NaHSO_4 + N_2O + H_2O$$

Kornblum has pointed out that this reaction can sometimes be brought about with weak acids such as acetic acid or even carbon dioxide (39). On the other hand, certain alicyclic nitro compounds, e.g. nitroinositols, have been found to resist the Nef reaction (40). An alternative way to convert nitroalkanes into carbonyl compounds is their oxidation with permanganate at a slightly alkaline pH (41).

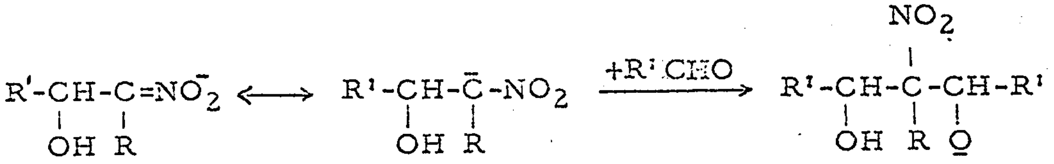
(c) The Henry Reaction

The most versatile method of synthesizing β-nitroalcohols is the aldol-type addition of nitroalkanes to aldehydes, which was discovered by L. Henry (42). The reaction is base-catalyzed and proceeds via the nitronate anion.



$$R\text{-}CH_2NO_2 \xrightarrow[-H^+]{base} R\text{-}\bar{C}HNO_2 \xrightarrow{+R'CHO} R'\text{-}\underset{\underline{O}}{CH}\text{-}\underset{R}{CH}\text{-}NO_2 \longrightarrow R'\text{-}\underset{OH}{CH}\text{-}\underset{R}{C}{=}NO_2^-$$

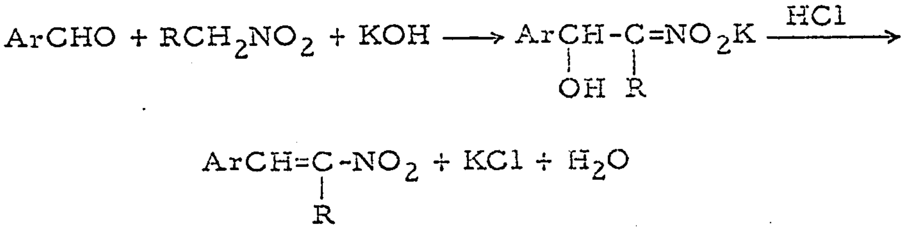
With excess aldehyde, a second addition can take place, and in the case of nitromethane and formaldehyde the tris-methylol derivative can be obtained.



$$R'\text{-}\underset{OH}{CH}\text{-}\underset{R}{C}{=}NO_2^- \longleftrightarrow R'\text{-}\underset{OH}{CH}\text{-}\underset{R}{\bar{C}}\text{-}NO_2 \xrightarrow{+R'CHO} R'\text{-}\underset{OH}{CH}\text{-}\underset{R}{\overset{NO_2}{C}}\text{-}\underset{\underline{O}}{CH}\text{-}R'$$

$$CH_3NO_2 + 3HCHO \longrightarrow O_2NC(CH_2OH)_3$$

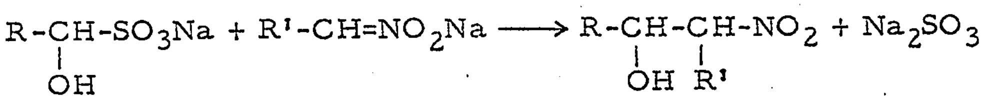
The isolation of the nitroalcohols formed necessitates acidification of the alkaline reaction mixtures. With reaction products possessing a primary or a secondary nitro group, this involves a risk of losses due to Nef reaction, but it can usually be accomplished by choosing mild conditions. Another complication is occasionally encountered, namely a dehydration to α-nitroalkenes, which may take place when β-nitroalcohols are liberated from alkaline solution. Although in alkyl-substituted β-nitroalcohols this is rarely of significance, α-aryl β-nitroalcohols tend to lose water spontaneously and thus, to yield β-nitrostyrene derivatives:



$$\mathrm{ArCHO + RCH_2NO_2 + KOH \longrightarrow Ar\underset{OH}{CH}\text{-}\underset{R}{C}{=}NO_2K \xrightarrow{HCl} ArCH{=}\underset{R}{C}\text{-}NO_2 + KCl + H_2O}$$

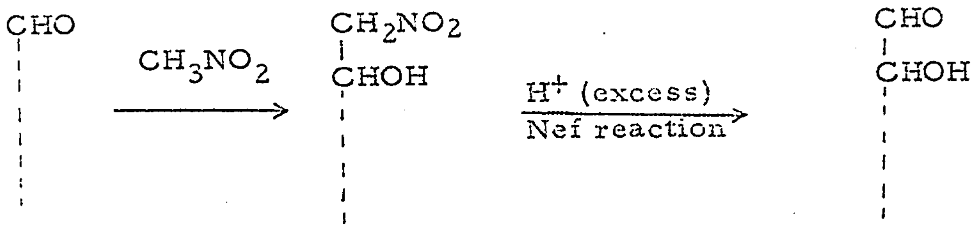
β-Nitrostyrenes are also obtained by the condensation of aromatic aldehydes with nitroalkanes in the presence of zinc chloride (43, 44), amines (45), or ammonium acetate in glacial acetic acid (46).

A useful modification of the Henry reaction was devised by Kamlet (47) who employed the aldehyde component as its bisulfite adduct and the nitroalkane as its sodium salt so that excess alkali was avoided and the product was obtained without need of acidification.



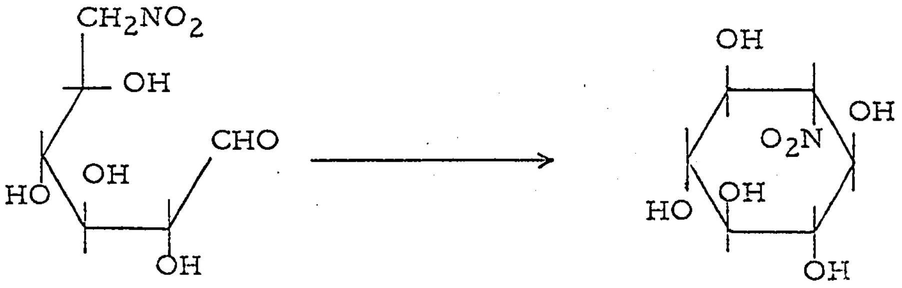
$$\mathrm{R\text{-}\underset{OH}{CH}\text{-}SO_3Na + R'\text{-}CH{=}NO_2Na \longrightarrow R\text{-}\underset{OH}{CH}\text{-}\underset{R'}{CH}\text{-}NO_2 + Na_2SO_3}$$

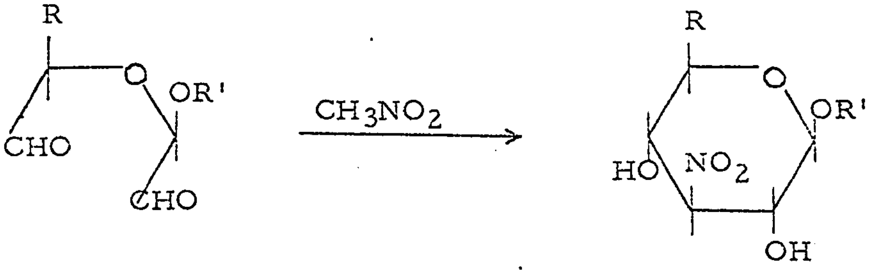
One area in which the Henry reaction has been used extensively in recent years is the chemistry of carbohydrates. Numerous aldoses have been converted to 1-nitro-1-deoxy-alditols which, in turn, have been converted to sugars by Nef reaction in a sequence affording a convenient lengthening of the carbon chain (48).



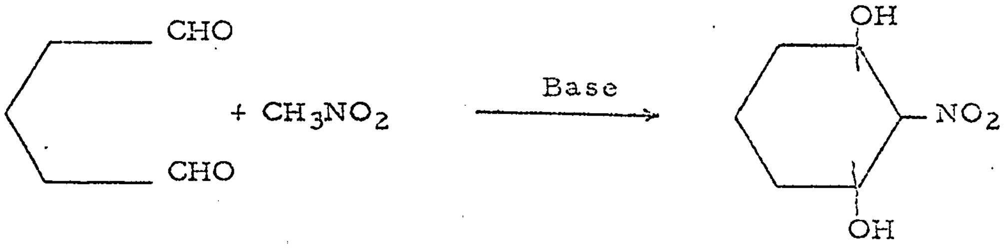
$$\begin{array}{c}\mathrm{CHO}\\ \vdots\end{array} \xrightarrow{\mathrm{CH_3NO_2}} \begin{array}{c}\mathrm{CH_2NO_2}\\ |\\ \mathrm{CHOH}\\ \vdots\end{array} \xrightarrow[\text{Nef reaction}]{\mathrm{H^+}\ \text{(excess)}} \begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{CHOH}\\ \vdots\end{array}$$

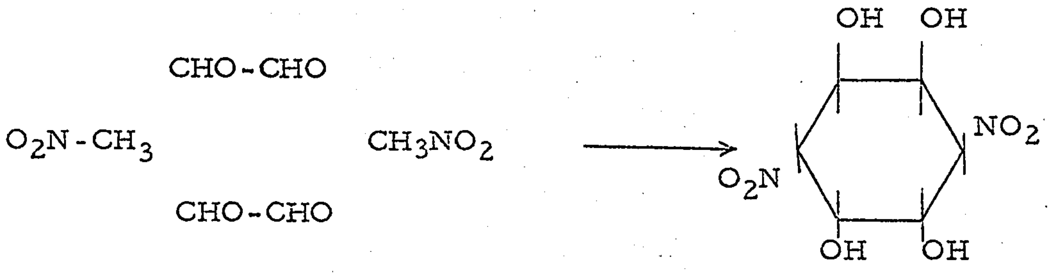
Cyclization of 6-nitro-6-deoxy-hexoses led to nitrodeoxyinositols (49), and the reaction between nitromethane and "sugar dialdehydes" was used widely to introduce nitrogen into pyranose rings (50, 51, 52).





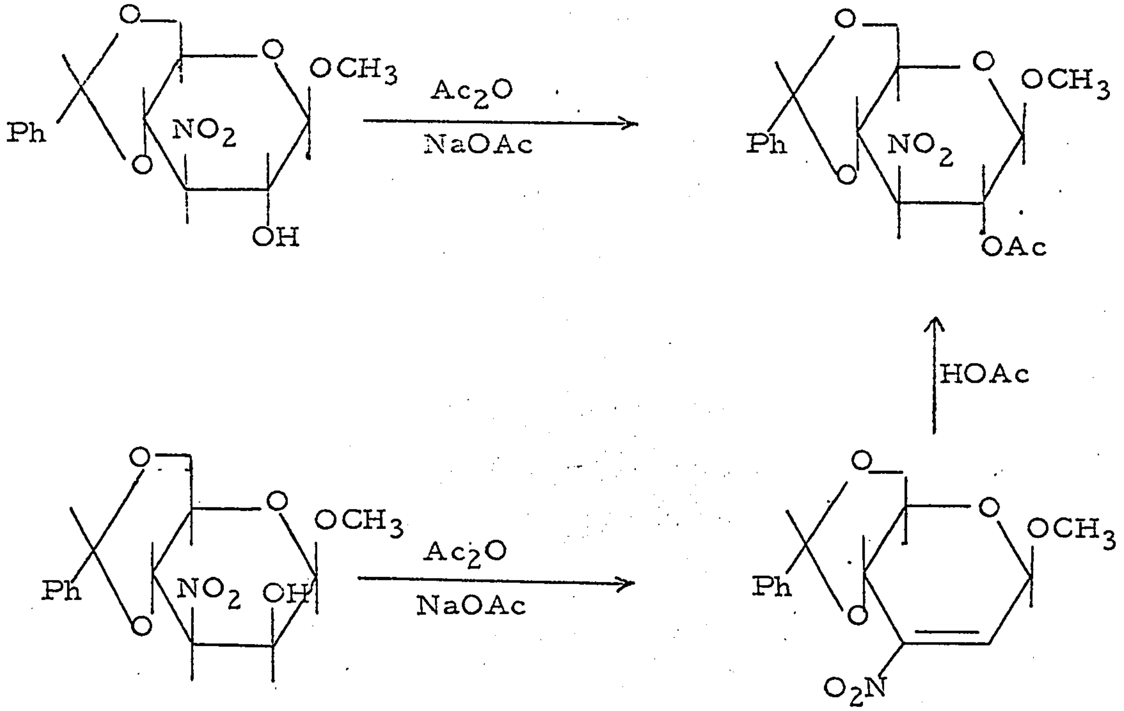
The cyclization of glutaric dialdehyde with nitromethane led to 1, 3-dihydroxy-2-nitrocyclohexane (53, 54), and glyoxal gave 1, 4-dinitro-2, 3, 5, 6-tetrahydroxycyclohexane (55).

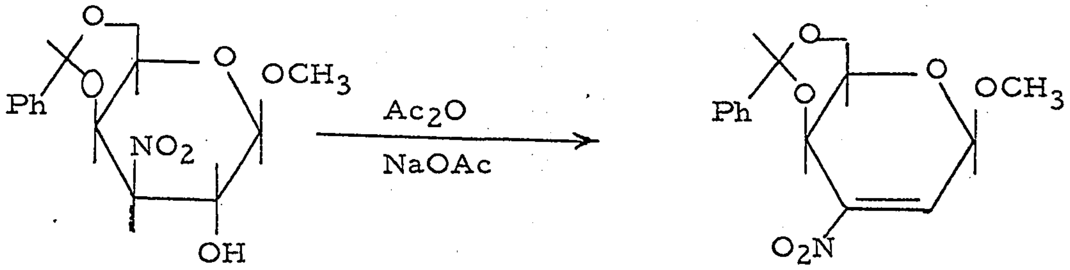




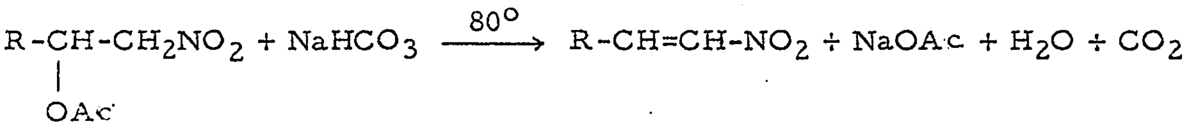
(d) The Synthesis of Nitroalkenes

As has been mentioned in the preceding section, some β-nitroalcohols, especially those carrying an aromatic substituent, dehydrate easily or even spontaneously to α-nitroalkenes. In other cases the use of a dehydrating agent such as zinc chloride (56), phthalic anhydride (57) or acetic anhydride (57) is required. The result of attempted dehydration may depend on the stereochemistry of the nitroalcohol. The action of acetic anhydride and sodium acetate upon the three stereoisomeric methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-hexopyranosides of <u>gluco</u>, <u>manno</u> and <u>galacto</u> configuration is an interesting case in point. The <u>gluco</u> isomer gives its 2-O-acetate without apparent dehydration; the <u>manno</u> isomer, however, also gives the <u>gluco</u> 2-O-acetate instead of the expected <u>manno</u> 2-O-acetate and it has been shown that the latter results from acetoxylation of intermediate nitroolefin ; the <u>galacto</u> isomer, finally, is dehydrated to the nitroolefin and no 2-O-acetate is obtained (58).





The most commonly used route to α-nitroolefins is the dehydroacetylation of β-nitroalkyl acetates with solid sodium bicarbonate or potassium carbonate in an inert solvent. (Schmidt-Rutz reaction) (59).



$$R\text{-}\underset{\displaystyle OAc}{\underset{|}{CH}}\text{-}CH_2NO_2 + NaHCO_3 \xrightarrow{80^{\circ}} R\text{-}CH{=}CH\text{-}NO_2 + NaOAc + H_2O + CO_2$$

The reaction can be performed in a continuous process by passing vapours of the nitro ester over hot catalysts such as alkaline earth salts (60). The acetic acid which is liberated acts, if allowed to remain in the reaction mixture, as an inhibitor of polymerization of the nitroalkene produced.

Related possibilities of preparing α-nitroalkenes are the dehydrohalogenation of β-nitroalkyl halides, performed by pyrolysis or by the action of basic reagants such as pyridine, aliphatic amines and sodium acetate (61, 62, 63), and the alkaline elimination of nitrous acid from β-nitroalkyl nitrites (25).

(e) Mannich Reactions

Mannich bases derived from formaldehyde and secondary aliphatic amines react with nitroalkanes to give β-nitroamines:

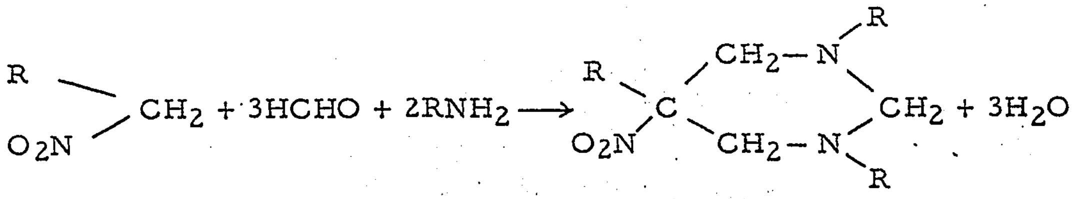
$$R_2NH + HCHO \longrightarrow R_2N\text{-}CH_2OH$$

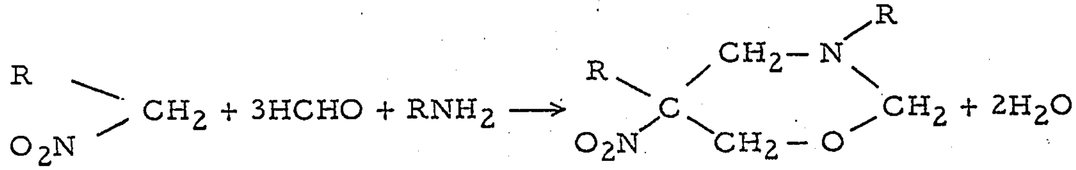
$$R_2N\text{-}CH_2OH + R'CH_2NO_2 \longrightarrow R_2N\text{-}CH_2\text{-}CHR'NO_2 + H_2O$$

The same nitroamine is obtained in the reaction between the secondary amine and the methylol derivative (i. e. the product of Henry addition of formaldehyde) of the nitroalkanes.

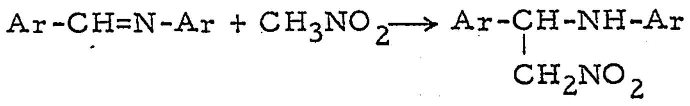
$$R_2NH + HOCH_2\text{-}CHR'NO_2 \longrightarrow R_2N\text{-}CH_2\text{-}CHR'NO_2 + H_2O$$

Primary aliphatic amines and ammonia undergo analogous condensations, which have found extensive applications in the synthesis of hexahydropyrimidine and oxazoline systems (64).



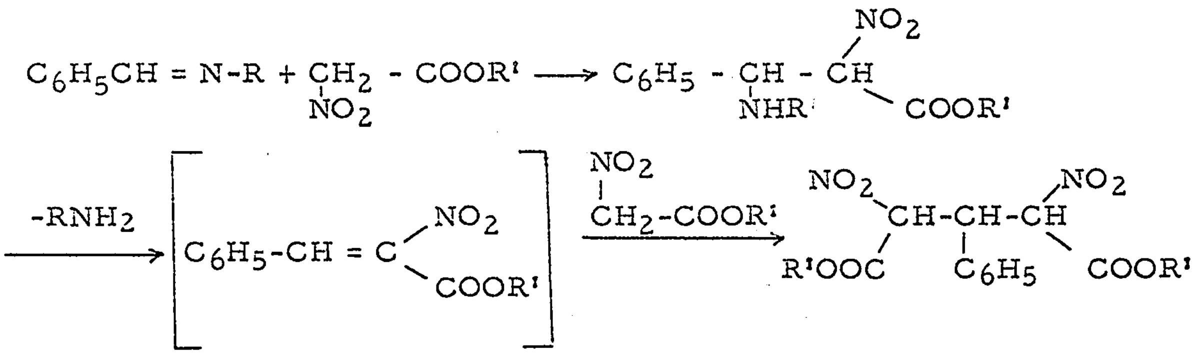


Azomethines (Schiff bases) add nitroalkanes to give β-nitroamines, too.



$$Ar\text{-}CH{=}N\text{-}Ar + CH_3NO_2 \longrightarrow Ar\text{-}\underset{\displaystyle CH_2NO_2}{\underset{|}{C}}H\text{-}NH\text{-}Ar$$

The β-nitroamines, when heated or acted upon by mineral acid, eliminate a molecule of amine and yield α-nitroolefins (65-69). Some β-nitroamines are so unstable that spontaneous decomposition occurs. For example, the reaction of benzalamine with ethyl nitroacetate proceeds as follows (70):



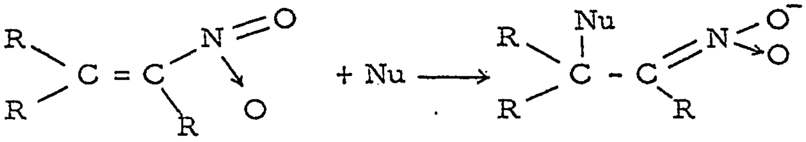
$$C_6H_5CH = N\text{-}R + \underset{NO_2}{CH_2} - COOR' \longrightarrow C_6H_5 - \underset{NHR}{CH} - CH(NO_2)COOR'$$

$$\xrightarrow{-RNH_2} \left[C_6H_5\text{-}CH = C(NO_2)COOR' \right] \xrightarrow{\overset{NO_2}{CH_2}\text{-}COOR'} (R'OOC)(NO_2)CH\text{-}\underset{C_6H_5}{CH}\text{-}CH(NO_2)(COOR')$$

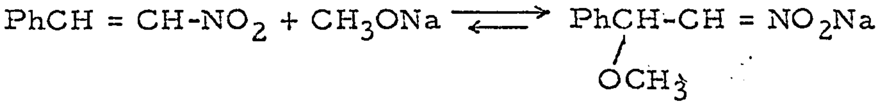
The initial addition product spontaneously loses amine which catalyzes the addition of a second molecule of ethyl nitroacetate to the intermediate α-nitrocinnamic ester, the end product being diethyl 2, 4-dinitro-3-phenyl glutarate. If, however, the reaction is carried out in the presence of acetic anhydride, the catalytic activity of the amine is relinquished by acetylation, and the reaction stops at the stage of the nitrocinnamate. An analogous reaction has been described using nitroacetone in place of ethyl nitroacetate (70).

(f) Additions to the Carbon-carbon Double Bond in Nitroalkenes

Because of the strong electron-withdrawing effect of the nitro group, electrophilic additions to the carbon-carbon double bond in nitroalkenes occur more slowly than in ordinary alkenes. Nevertheless, chlorination or bromination is possible, and leads to dihalonitroalkenes (71, 71a). Conversely, nucleophilic additions take place with great ease and are of considerable importance for various synthetic purposes. Nucleophiles such as amines, alcohols, thioalcohols, and reactive methylene and methine compounds readily add to the ethylenic double bond in the presence of a basic catalyst.

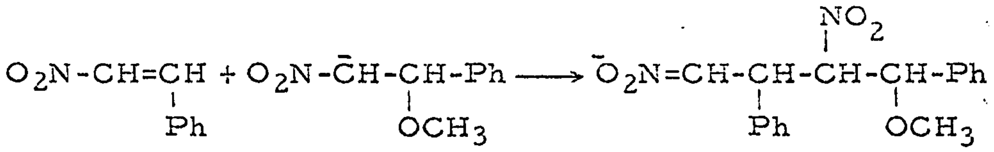


For example, β-nitrostyrene adds sodium methoxide instantaneously at room temperature:



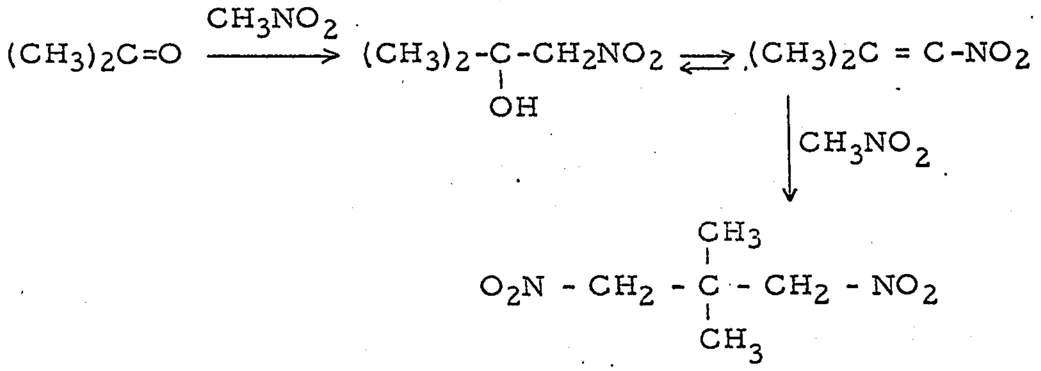
$$\mathrm{PhCH = CH\text{-}NO_2 + CH_3ONa \rightleftharpoons \underset{\displaystyle OCH_3}{PhCH}\text{-}CH = NO_2Na}$$

Some of the original olefin remains in the equilibrium, from where it is removed by another nucleophilic addition reaction, namely with the anion of the methoxy adduct, so that a dimeric product finally results (72):



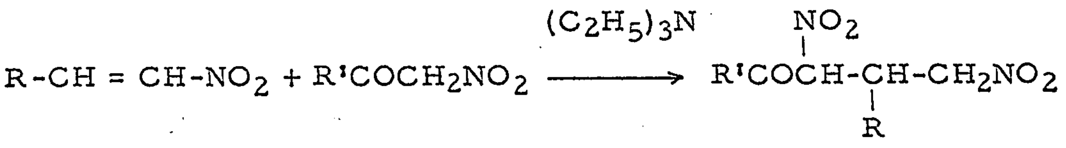
$$O_2N\text{-}CH\text{=}\underset{Ph}{CH} + O_2N\text{-}\bar{C}H\text{-}\underset{OCH_3}{CH}\text{-}Ph \longrightarrow \bar{O}_2N\text{=}CH\text{-}\underset{Ph}{CH}\text{-}\overset{NO_2}{CH}\text{-}\underset{OCH_3}{CH}\text{-}Ph$$

This example illustrates two very common reactions of nitroalkenes; first, the formation of β-nitroalkyl ether structures, and secondly the formation of 1, 3-dinitroalkanes by Michael-type additions (73, 74). Another example is the production of 1, 3-dinitro-2, 2-dimethylpropane from acetone and nitromethane (75). Henry addition leads to nitro-t-butanol which loses a molecule of water to give 1-nitro-2-methylpropene. This intermediate then adds nitromethane (which is present in excess) to furnish the dinitro compound:



$$(CH_3)_2C\text{=}O \xrightarrow{CH_3NO_2} (CH_3)_2\text{-}\underset{OH}{C}\text{-}CH_2NO_2 \rightleftarrows (CH_3)_2C = C\text{-}NO_2 \xrightarrow{CH_3NO_2} O_2N - CH_2 - \overset{CH_3}{\underset{CH_3}{C}} - CH_2 - NO_2$$

Similarly the reactive methylene compound, nitroacetone, adds to nitroalkenes to give α,γ -dinitroketones (76).



$$R\text{-}CH = CH\text{-}NO_2 + R'COCH_2NO_2 \xrightarrow{(C_2H_5)_3N} R'COCH\text{-}\underset{R}{\overset{NO_2}{C}}H\text{-}CH_2NO_2$$

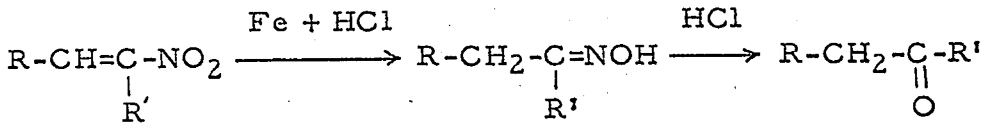
Another well-known consequence of the reactivity of α-nitroalkenes is that they can act as dienophiles in Diels-Alder reactions.

(g) Reduction of Aliphatic Nitro Compounds

Nitroalkanes are easily reduced either catalytically or chemically to the amine stage and the reduction cannot usually be arrested at the intermediate nitroso and hydroxylamino stages. On the other hand, the reduction of nitroalkenes may lead to different products depending upon the structure of the nitroalkene and the reaction conditions. Reduction of nitroolefins with aluminum amalgam in ether or zinc dust in acetic acid gives the oxime which can be further reduced to amine by sodium amalgam (78, 79).

$$R\text{-}CH{=}CH\text{-}NO_2 \xrightarrow[Zn+AcOH]{Al\text{-}Hg} R\text{-}CH_2\text{-}CH{=}NOH \xrightarrow{Na\text{-}Hg} R\text{-}CH_2\text{-}CH_2\text{-}NH_2$$

Nitroolefins are converted by iron and hydrochloric acid into ketoximes and ketones, depending on their structure. The reaction can be controlled to yield almost exclusively ketone when sufficient hydrochloric acid is employed, and almost exclusively ketoxime when a minimal quantity of acid is present (1, 44, 80).



$$R\text{-}CH{=}\underset{\underset{R'}{|}}{C}\text{-}NO_2 \xrightarrow{Fe + HCl} R\text{-}CH_2\text{-}\underset{\underset{R'}{|}}{C}{=}NOH \xrightarrow{HCl} R\text{-}CH_2\text{-}\underset{\underset{O}{\|}}{C}\text{-}R'$$

R = alkyl, aryl, heteryl; R' - alkyl.

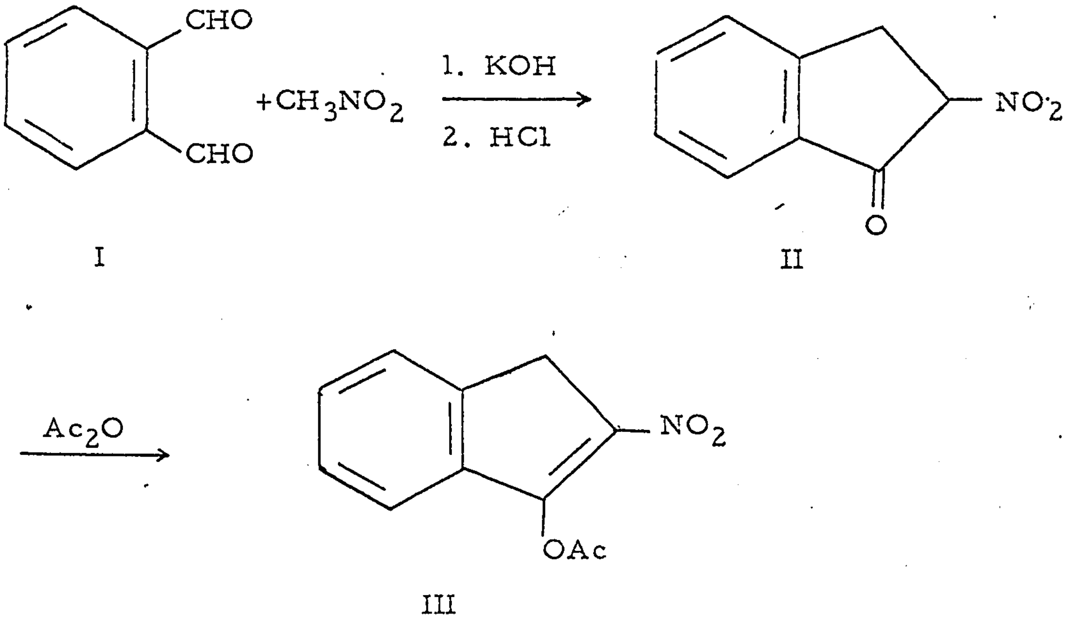
Hydrogenation by lithium aluminium hydride, lithium borohydride or sodium borohydride can lead to different types of compounds. For instance, with lithium aluminum hydride, nitroolefins give amines at 35°, oximes at 0° and nitroparaffins at -40 to -70° (81, 82, 83).

Nitroolefins are converted into nitroparaffins by palladium black or platinum oxide (84, 85). However, the product is an amine when hydrogenation is carried out in the presence of platinum oxide under a pressure of 2-3 atmospheres (86).

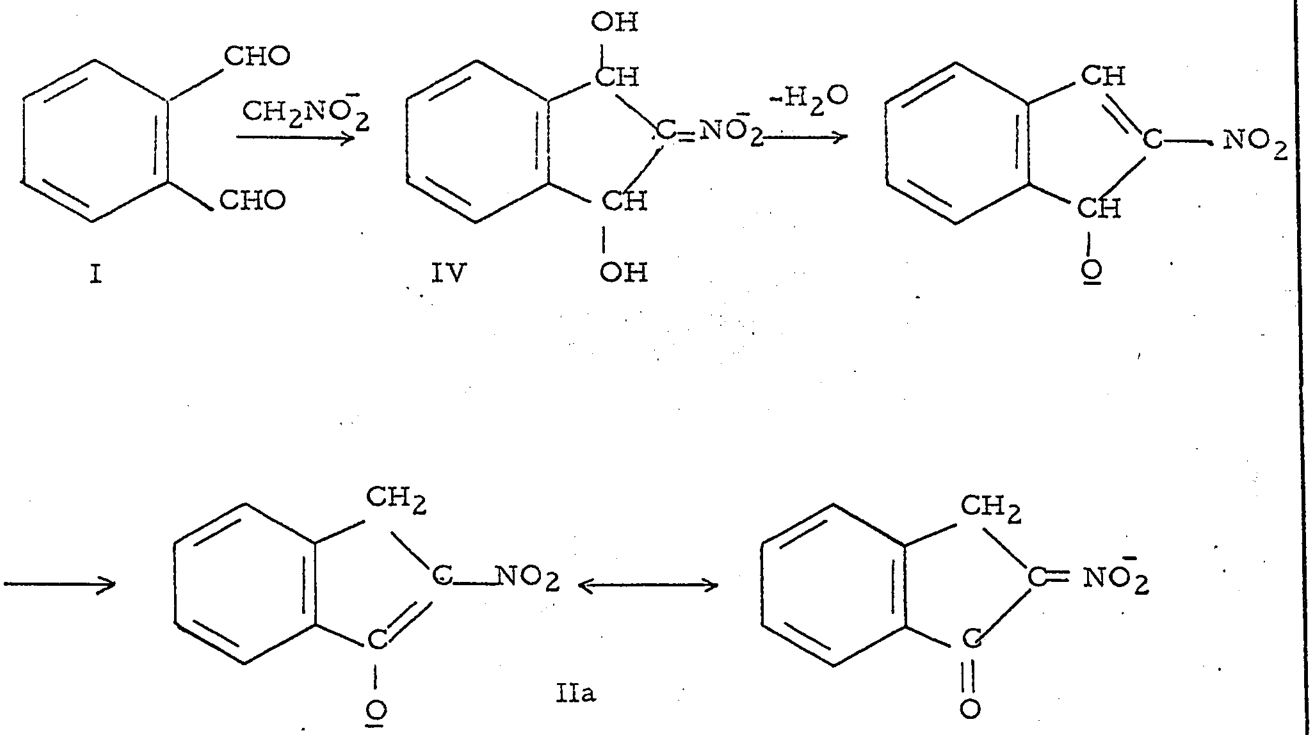
$$R - CH = CH - NO_2 \xrightarrow{Pd/C} R - CH_2 - CH_2 - NO_2$$

The Subject of the Present Study in the Context of Previous Investigations

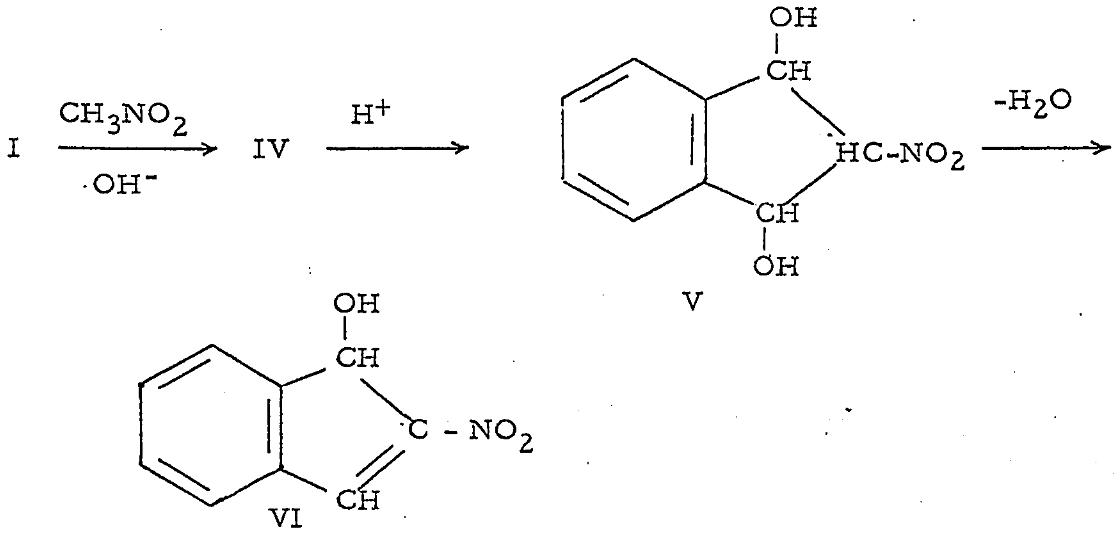
In 1910, Thiele and Weitz carried out a nitromethane condensation of o-phthaladehyde (I) in the presence of alcoholic potassium hydroxide (87). They observed the precipitation of a salt which was acidified, without prior isolation, to give a yellow crystalline compound. Acetylation of the compound furnished a monoacetyl derivative. The authors assigned the structure of 2-nitroindanone (II) to the condensation product and believed the acetate to be 3-acetoxy-2-nitroindene (III), that is, the enol acetate of II.



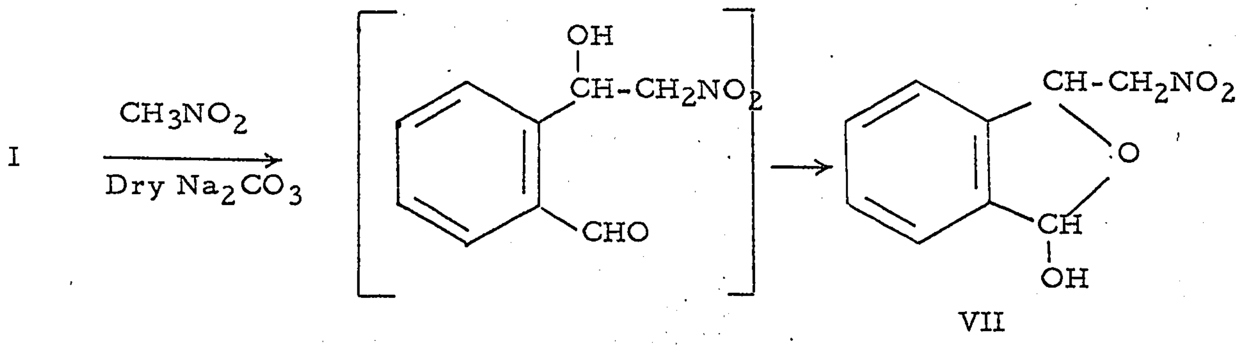
No explanation for the seemingly abnormal course of this nitromethane condensation was offered until, in 1959, Campbell and Pitzer (88) proposed a mechanism according to which the initial reaction product, correctly surmised to be the salt IV, would lose a molecule of water and then undergo a hydranion shift to give the salt (IIa) of 2-nitroindanone. However, it was found in 1963 by Achmatowicz (89)



and independently by Lichtenthaler (90) that the product claimed by the earlier authors to be 2-nitroindanone (or tautomeric 3-hydroxy-2-nitroindene) actually is an isomer, namely 1-hydroxy-2-nitroindene (VI). It was demonstrated in a detailed study by Baer and Achmatowicz (91) that the reaction proceeds in an expected manner via the salt IV and the colorless diol V (which were both isolated):

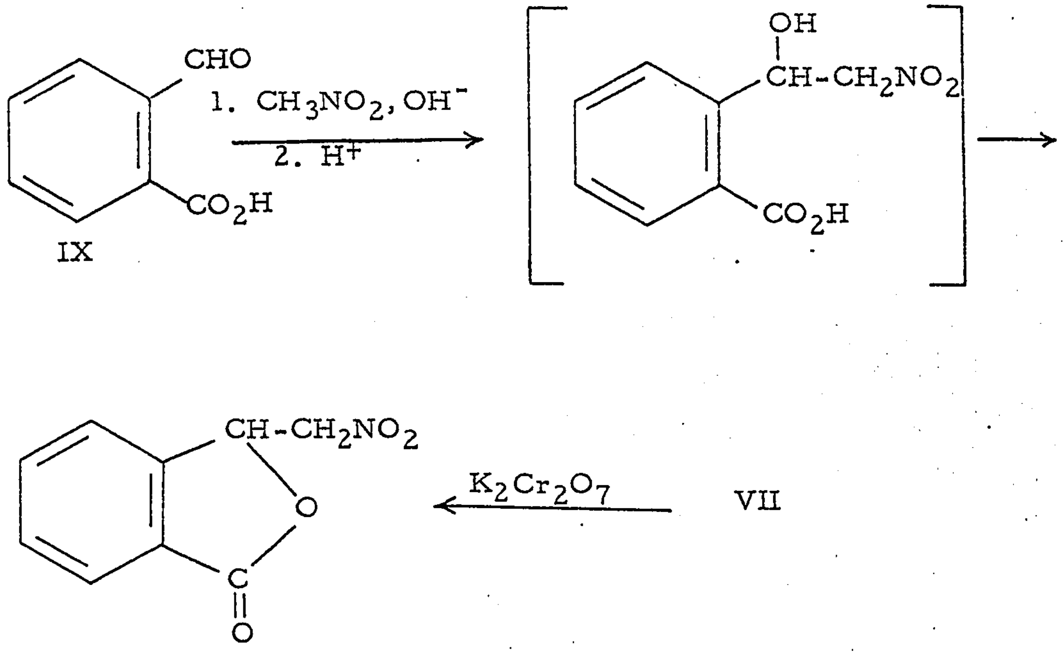


It was shown, furthermore, that condensation of I with nitromethane under aprotic conditions leads to the lactol VII of 2-(1-hydroxy-2-nitroethyl)benzaldehyde (91).



2-Nitroindanone was not encountered in these studies nor has it, apparently, been described elsewhere. Therefore, one of the projects for the present thesis was to attempt its synthesis.

In order to set forth more detailed objectives of this thesis it is necessary, first, to describe additional results that arose from the work just mentioned. Potassium dichromate oxidation of the lactol VII had given 3-phthalidylnitromethane (VIII) (91). This compound was well documented in the literature (92, 93, 94) and had been previously obtained by condensation of nitromethane with o-phthaladehydic acid (IX).

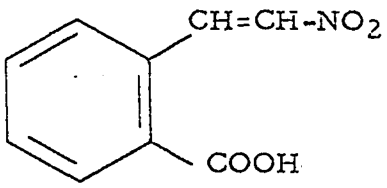


IX

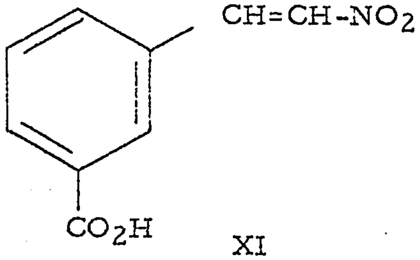
VII

VIII

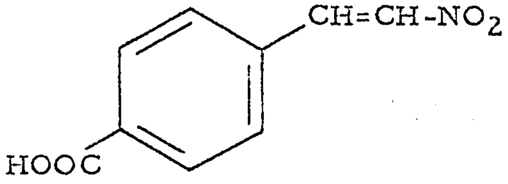
Evidently unaware of the previous work and without reference to it, Japanese workers (95) carried out the same nitromethane condensation of IX and reported the product to be 2-(2-nitrovinyl)benzoic acid (X), obviously in analogy to the formation (96) of the isomeric 3- and 4-(2-nitrovinyl)benzoic acids (XI, XII) from m- and p-phthaladehydic acids, respectively.



X

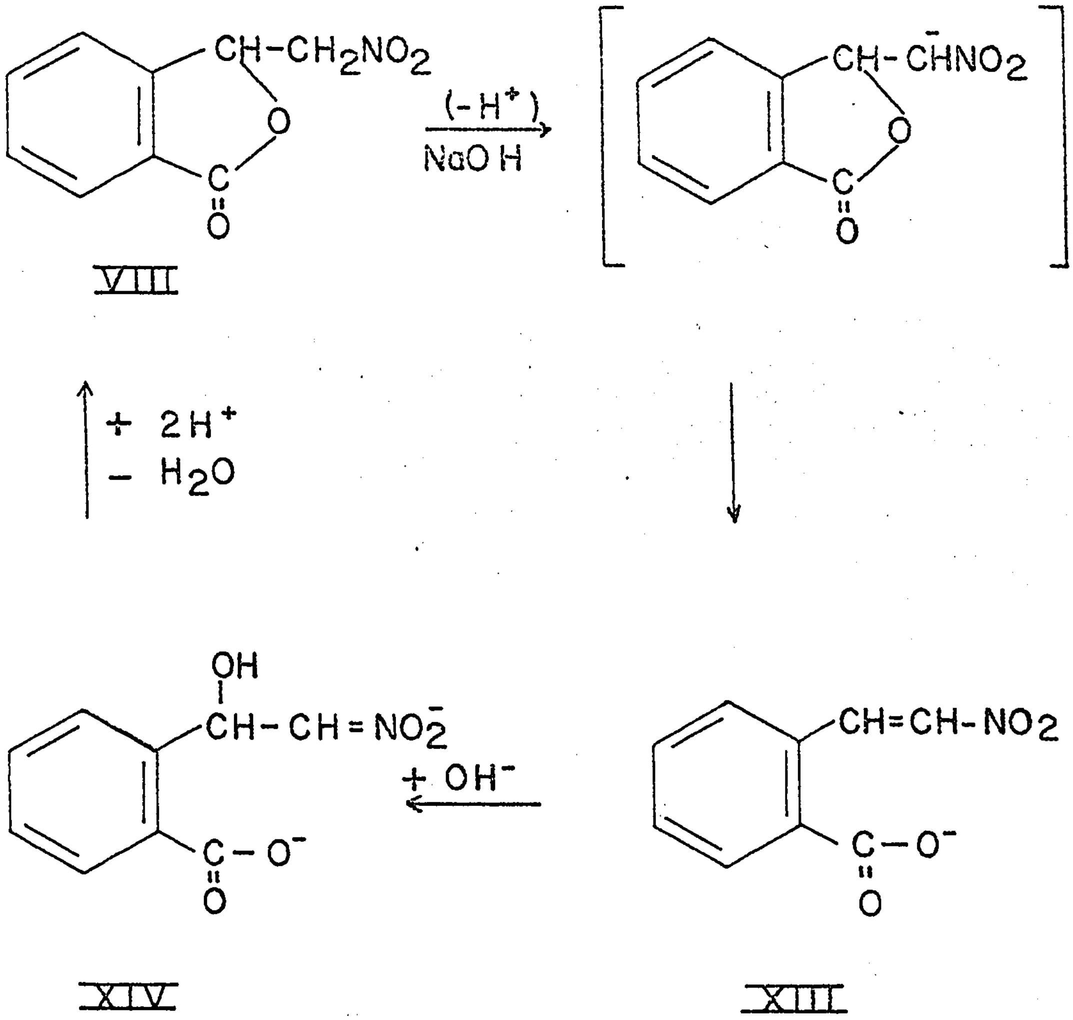


XI

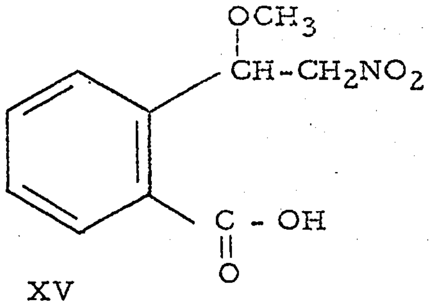


XII

Prompted by this report, Baer and Kienzle (97) investigated a possible occurrence of X under certain conditions although there was no doubt that the isolated reaction product was 3-phthalidylnitromethane (VIII). They established that action of aqueous alkali upon VIII causes lactone opening by β-elimination and momentarily regenerates the 2-(2-nitrovinyl)benzoate ion (XIII), which is then rapidly attacked by hydroxide ion to give the stable dianion XIV. Acidification of the alkaline solution to pH 5 or below results in a complete regeneration of VIII, even if this is done while intermediate XIII is still existing. Only when a fresh solution that contains XIII is at once buffered to pH 6, an appreciable part of the material - about 10% - retains the nitrovinyl structure in an equilibrium with predominant VIII. Isolation of free 2-(2-nitrovinyl)benzoic acid (X) could not be achieved.


CH-CH2NO2
O
C
O
VIII
(-H+)
NaOH
CH-CHNO2
O
C
O
+ 2H+
- H2O
OH
CH-CH=NO2-
+ OH-
C-O-
O
XIV
CH=CH-NO2
C-O-
O
XIII

Similar experiments using sodium methoxide in methanol instead of aqueous alkali resulted in methoxylation of the intermediate XIII, and acidification afforded the free 2-(1-methoxy-2-nitroethyl)benzoic acid (XV).

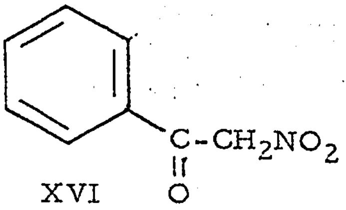


XV

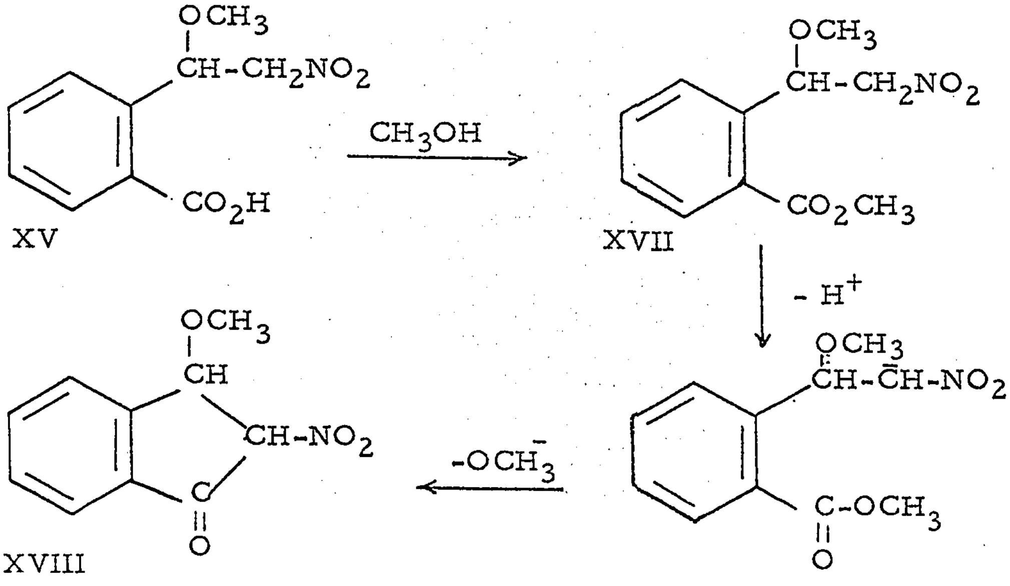
At the outset of the present work, the observation was made that addition of sodium methoxide to a methanolic solution of this acid (XV), which had been stored for a day, caused the appearance of an ultraviolet absorption peak at 370 mμ. This absorption could hardly be due to the generation of a nitrostyrene structure, since the nitrostyrene chromophore is known to absorb in the region of 311 mμ (96, 98). It was therefore decided to investigate the phenomenon and to see what consequences it might have from a viewpoint of preparative chemistry.

RESULTS AND DISCUSSION

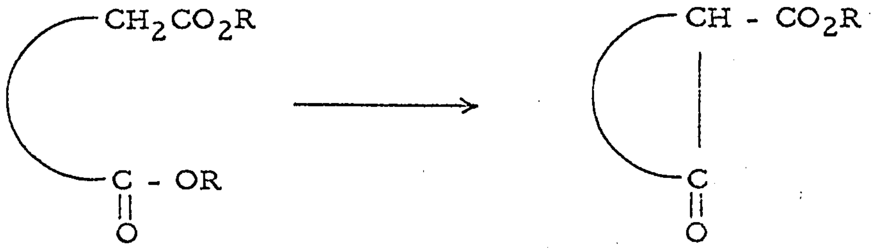
The observation, mentioned at the end of the Introduction, that addition of sodium methoxide to a methanolic solution of 2-(1-methoxy-2-nitroethyl)-benzoic acid (XV) caused appearance of an ultraviolet absorption peak at 370 mμ, drew attention to the possibility that a structure similar to ω-nitroacetophenone (XVI) might have been generated. ω-Nitroacetophenone is reported (88) to absorb at 352 mμ in alkaline solution. As a working hypothesis it was therefore considered that the acid XV had become esterified and that the ester XVII had cyclized to give a nitro ketone (XVIII).



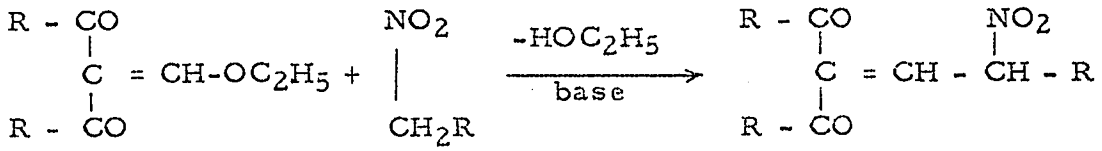
XVI



Such a reaction would be analogous to a Dieckmann condensation. Dieckmann condensations are cyclizations of dicarboxylic esters in which a reactive methylene group in alpha position of one ester function attacks the second ester function.



However, no instances appeared to have been reported in the literature of similar cyclizations involving a methylene function activated by a nitro instead of an ester group. The closest analogy that could be found is a condensation, described by Dornow and Lüpfert (99), of nitroalkanes with ethoxymethylène derivatives of β-dicarbonyl compounds.



$$\begin{array}{l} R-CO \\ \quad | \\ \quad C = CH-OC_2H_5 \\ \quad | \\ R-CO \end{array} + \begin{array}{c} NO_2 \\ | \\ CH_2R \end{array} \xrightarrow[\text{base}]{-HOC_2H_5} \begin{array}{l} R-CO \qquad\quad NO_2 \\ \quad | \qquad\qquad\quad | \\ \quad C = CH - CH - R \\ \quad | \\ R-CO \end{array}$$

The authors employed the ethoxymethylene derivatives of acetylacetone, benzoylacetone, ethyl acetoacetate and ethyl oxaloacetate which they regarded as vinylogous esters, and they pointed out the similarity of this reaction to the Claisen ester condensation.

In order to establish whether derivatives of 2-nitroindanone such as XVIII can in fact be synthesized by a Dieckmann-type condensation as proposed above, the ester XVII, methyl 2-(1-methoxy-2-nitroethyl)benzoate, was prepared by esterification of the acid (XV) with diazomethane. The ester was obtained as a colorless, crystalline compound (m.p. 98°) exhibiting infrared bands at 1720 cm^{-1} (ester carbonyl stretching vibration) and 1560 cm^{-1} (nitroalkane stretching vibration).. In neutral methanolic solution, no long wave-length absorption in the ultraviolet region was seen.

The nuclear magnetic resonance spectrum taken in deuterochloroform showed an intensity ratio of 4:3:3 for the signals attributable to the aromatic protons (multiplet at 2.22τ) and the two methyl groups (singlets at 6.67τ and 6.72 τ). Owing to magnetic non-equivalence of the two nitromethyl protons, the three remaining protons gave three quartets that were observed at 4.26 τ (the tertiary proton) and at 5.30 τ and 5.42 τ (the nitromethyl protons).

Treatment of the ester with sodium methoxide in methanol at room temperature caused, within a few minutes, high-intensity absorption with a maximum near 370 mμ. Following deionization with a cation exchange resin a crystalline substance, m.p. 164°, was isolated. The product, however, did not prove to be 3-methoxy-2-nitroindanone (XVIII). Its methoxyl content was found to be 9.2%, and a molecular weight determination* gave a value of 380, whereas the values calculated for XVIII are 15% and 207, respectively. A nuclear magnetic resonance spectrum taken in deuterochloroform revealed an intensity ratio of 8:3 for the signals attributable to the aromatic protons (multiplet centered at 2.28 τ) and to the methoxyl protons (singlet at 6.69 τ). On the basis of these data it was felt that a dimerization might have occurred, possibly according to the following scheme:

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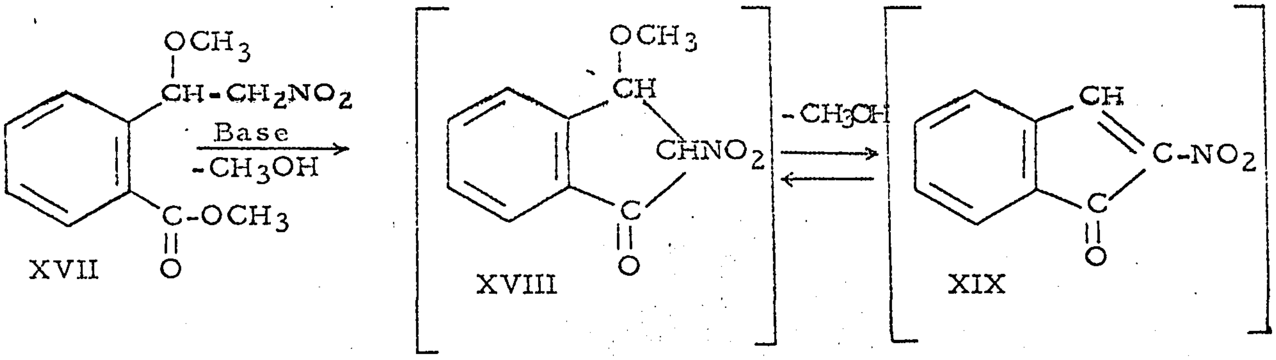
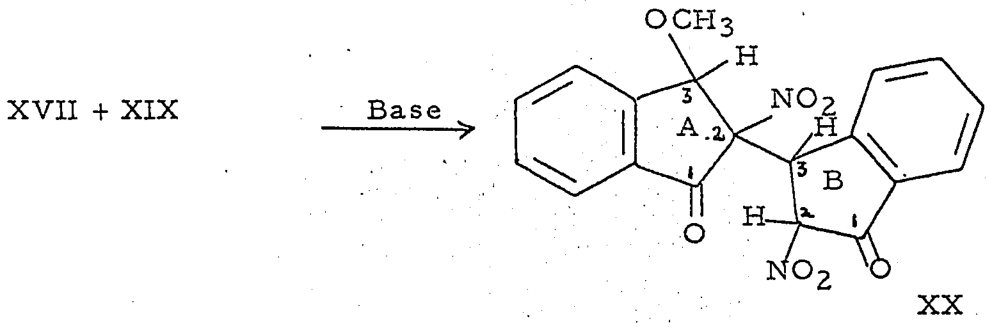
* The author is indebted to Dr. R.K. Hulyalkar, National Research Council, Ottawa, for having done this determination by osmometry in acetone solution.





The elemental analyses of the reaction product agreed with its formulation as 3-methoxy-2-nitro-2-(2-nitroindanone-3-yl)-indanone (XX). The n.m.r. spectrum exhibited, in addition to the signals for the aromatic and methoxyl protons mentioned above, signals for three more protons as required by structure XX. They appeared at 4.52 τ(singlet, 1 H) and 4.43 τ(singlet, 2 H). The protons at C-3 in ring A and C-2 in ring B can reasonably be expected to resonate in this region(21.). The signal for the proton at C-3 in ring B

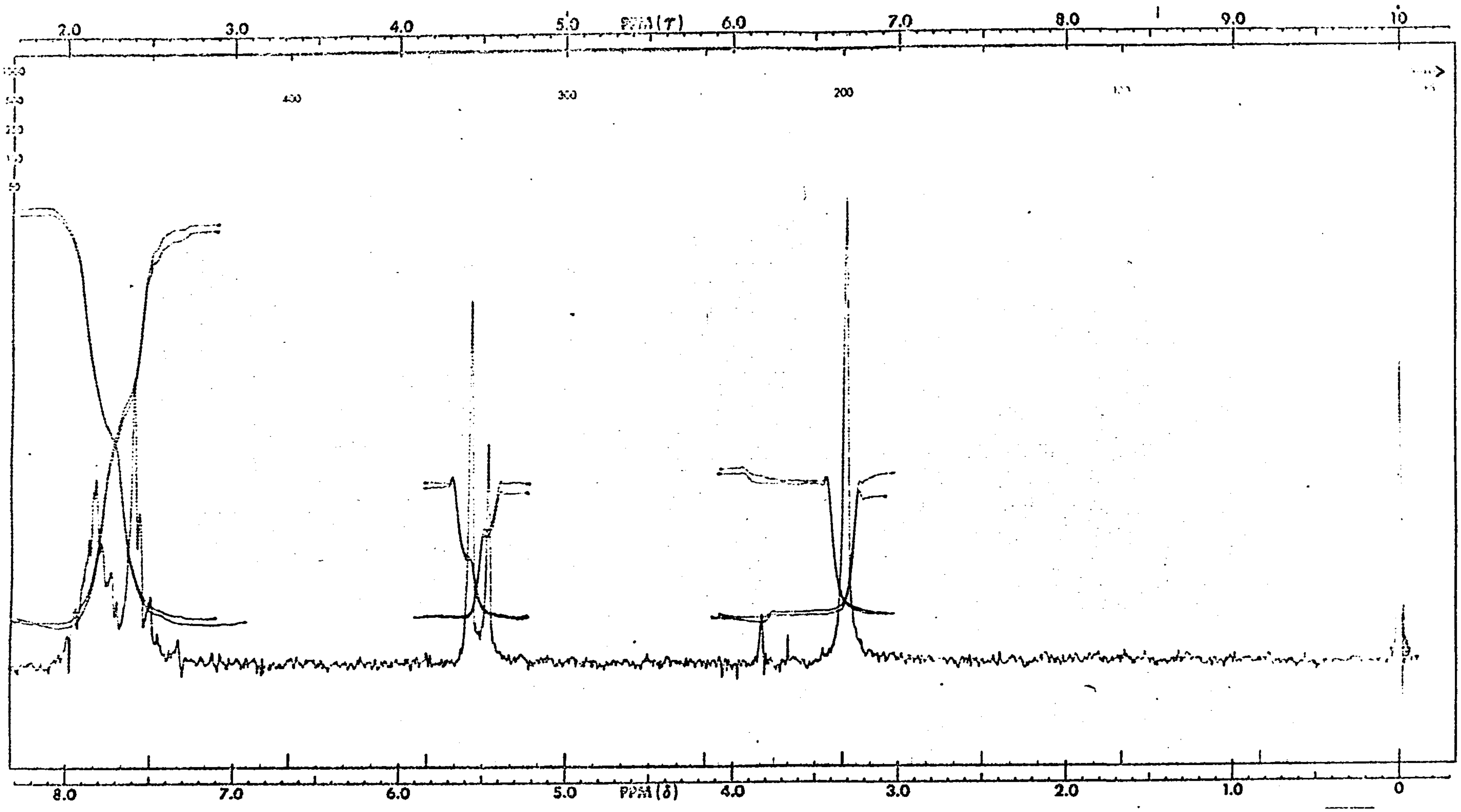
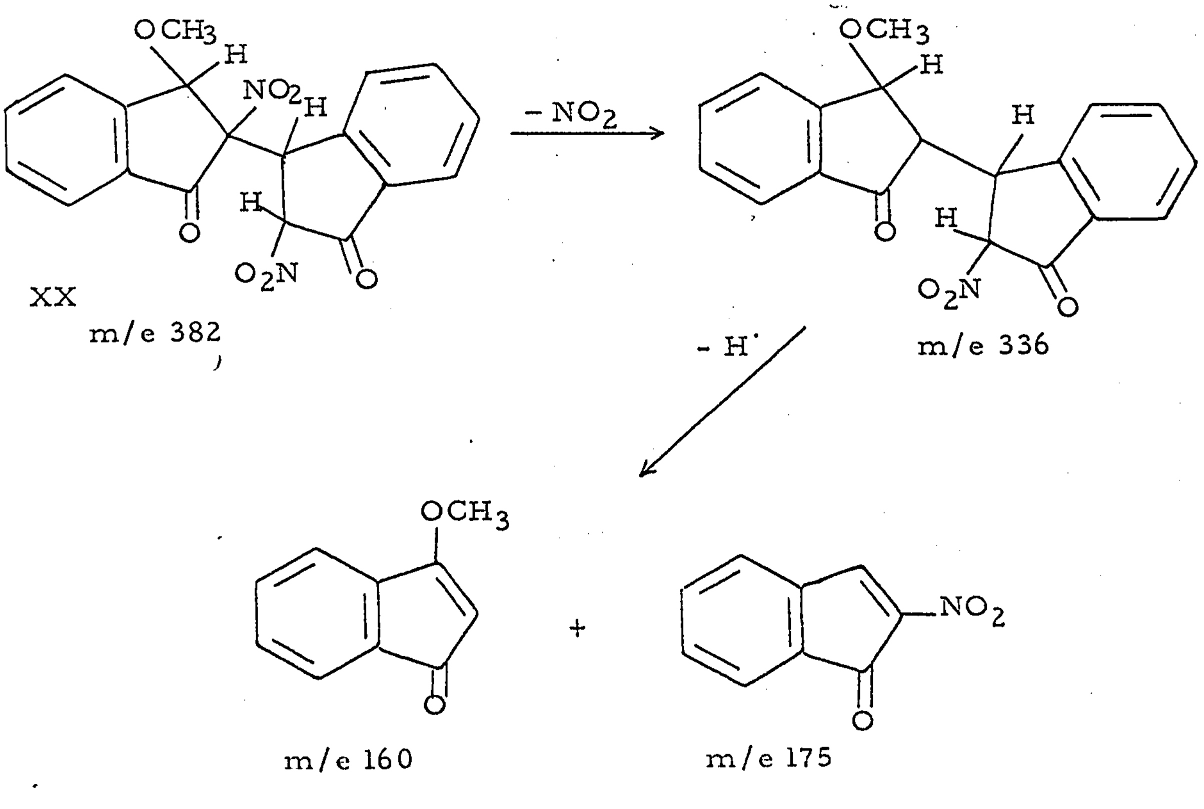


Fig. 1. N.M.R. Spectrum of 3-methoxy-2-nitro-2-(2-nitroindanone-3-yl)-indanone (XX) in deuterochloroform.

might have been thought to occur at higher field and to be split by vicinal coupling. Apparently it has been shifted downfield, possibly through the influence of the two neighboring nitro groups, so as to coincide in a fortuitous way with the signal of the neighboring proton; no coupling would then be observable.

The mass spectrum of XX did not show the molecular ion peak expected to occur at 382 m/e, but an intense peak at 336 m/e corresponding to the loss of a nitro group (46 mass units) was observed. Though few data only are available on the mass spectrometry of aliphatic nitro compounds, the facile cleavage of nitro groups in nitroalkanes is well known (100). Further fragmentation of XX resulted in a complex spectrum that was difficult to interpret in detail. There were, however, two intense peaks at 175 and 160 m/e, which may have been caused by a cleavage of the fragment of 336 mass units with a loss of one hydrogen atom.



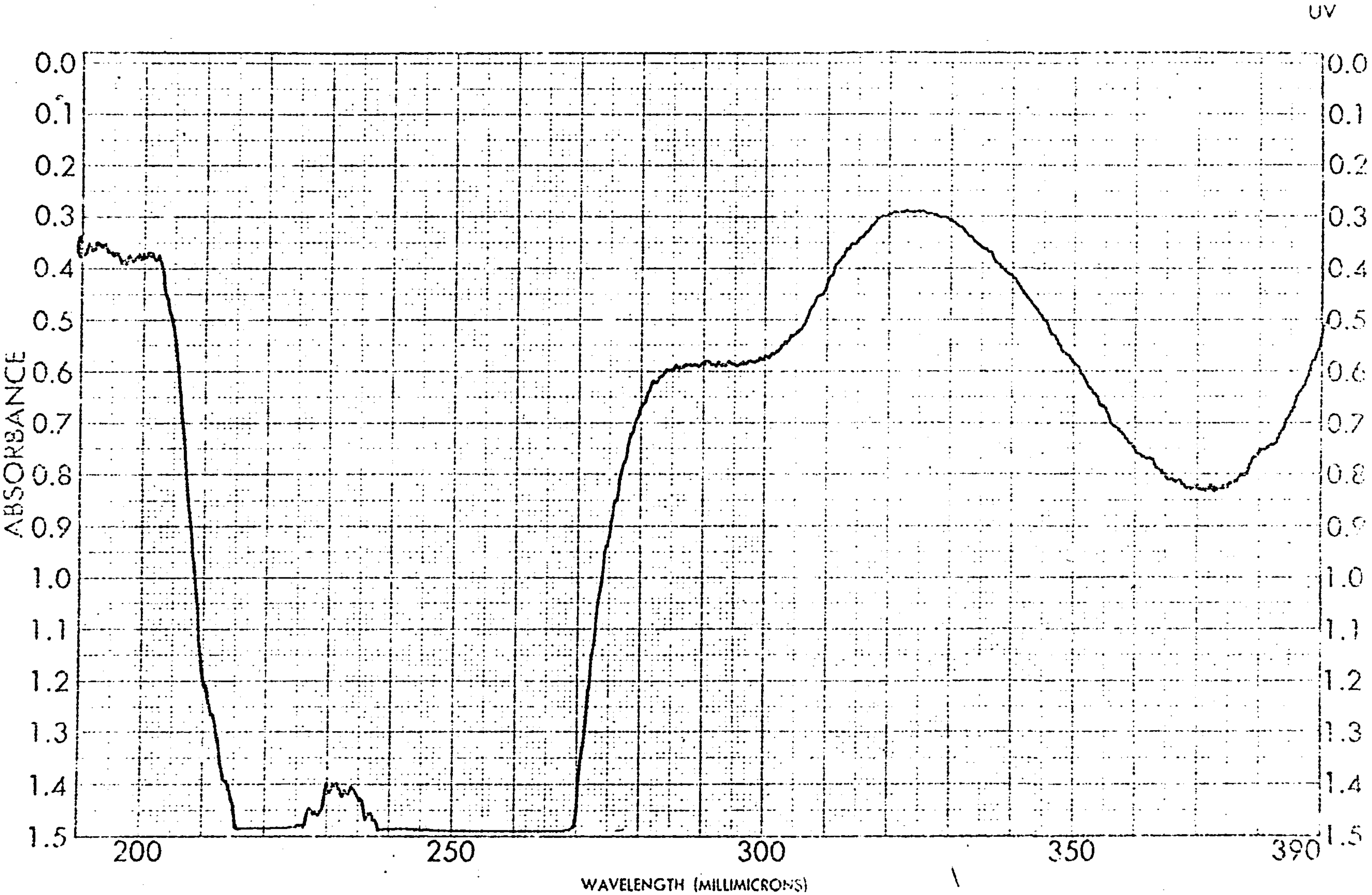
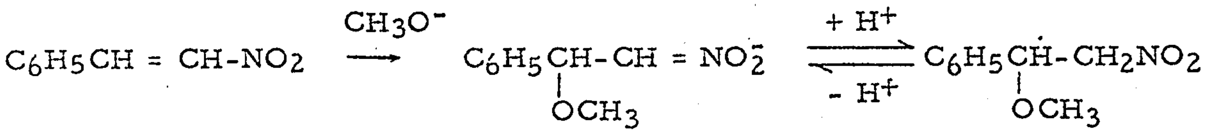
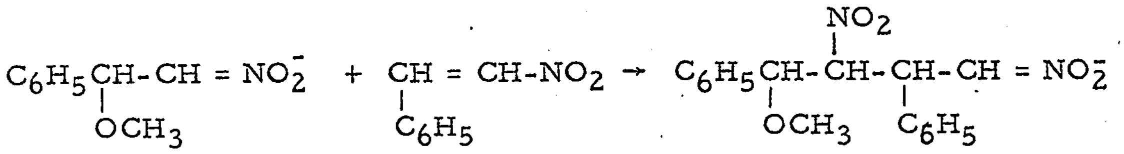


Fig. 2. U.V. Spectrum of 3-methoxy-2-nitro-2-(2-nitroindanone-3-yl)-indanone (XX); 10^{-4}M solution in methanol.

The reaction sequence leading to XX would imply, first, the formation of monomeric nitro ketone XVIII. Elimination of a molecule of methanol from part of XVIII would give the intermediate nitroolefin XIX, and subsequent Michael addition of surviving XVIII to XIX would then lead to the dinitro diketone XX. In support of such a sequence reference is made to the analogous reaction of 1-phenyl-1-methoxy-2-nitroethane which was discussed on page 25.

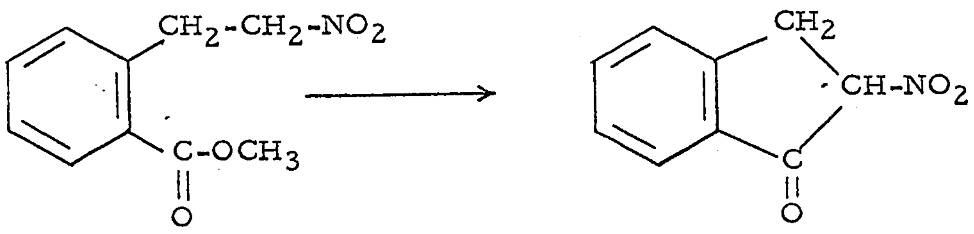


$$C_6H_5CH = CH\text{-}NO_2 \xrightarrow{CH_3O^-} C_6H_5\underset{\underset{\displaystyle OCH_3}{|}}{CH}\text{-}CH = NO_2^- \underset{-\,H^+}{\overset{+\,H^+}{\rightleftharpoons}} C_6H_5\underset{\underset{\displaystyle OCH_3}{|}}{CH}\text{-}CH_2NO_2$$



$$C_6H_5\underset{\underset{\displaystyle OCH_3}{|}}{CH}\text{-}CH = NO_2^- + \underset{\underset{\displaystyle C_6H_5}{|}}{CH} = CH\text{-}NO_2 \rightarrow C_6H_5\underset{\underset{\displaystyle OCH_3}{|}}{CH}\text{-}\overset{\overset{\displaystyle NO_2}{|}}{CH}\text{-}\underset{\underset{\displaystyle C_6H_5}{|}}{CH}\text{-}CH = NO_2^-$$

In view of these results it was reasoned that unsubstituted methyl 2-(2-nitroethyl)benzoate (XXI) - as opposed to its methoxy derivative XVII - should be capable of cyclization to the simple nitro ketone, 2-nitroindanone (II), without a subsequent complication such as arose in the case of XVII owing to a partial β-elimination of the ether function and an ensuing Michael addition (XVIII → XIX → XX).



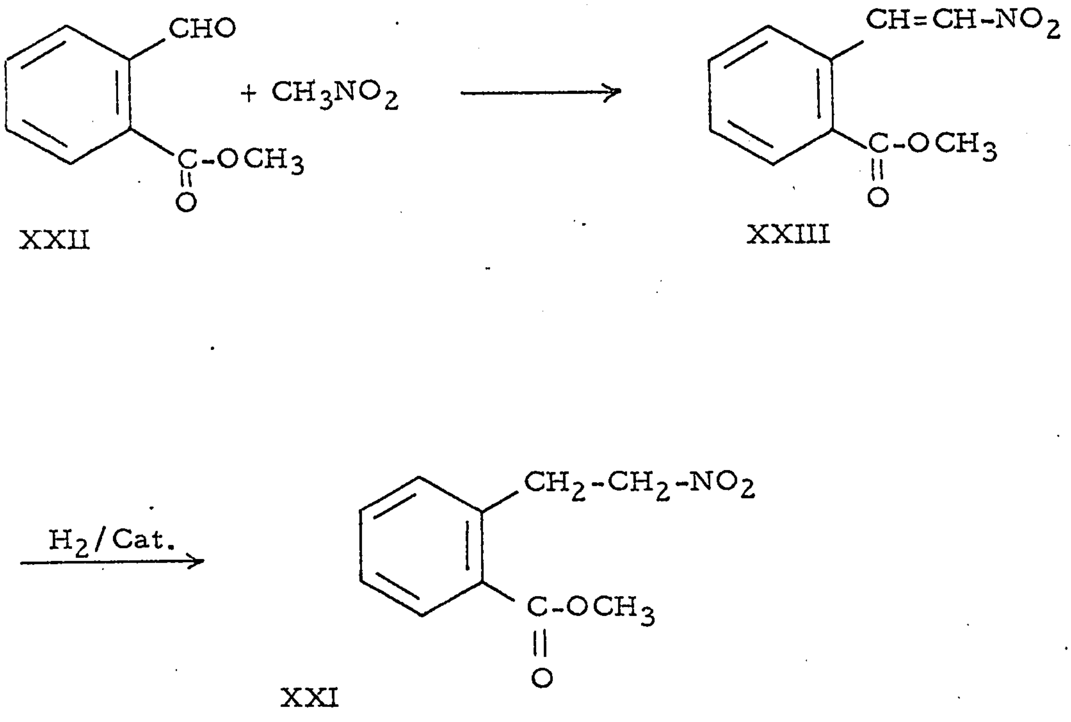
XXI

II

Methyl 2-(2-nitroethyl)benzoate (XXI) could thus be the key to one of the main objectives of this thesis, the synthesis of 2-nitroindanone. The ester XXI has not been reported in the literature, and considerable efforts were therefore expended in its preparation.

Two synthetic routes for the preparation of the ester XXI were attempted. One was to be the condensation of nitromethane with methyl o-phthalaldehydate (XXII) to give methyl 2-(2-nitrovinyl)-benzoate which, on selective reduction, should lead directly to XXI (route A).

Route A



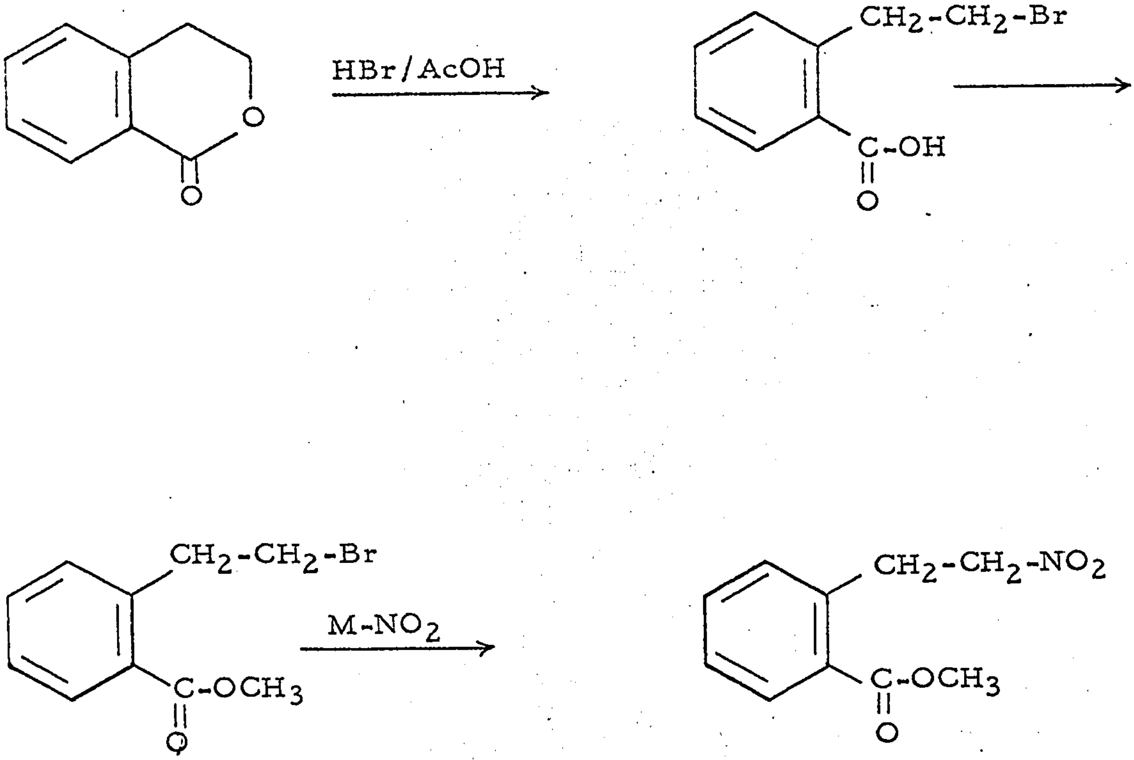
XXII

XXIII

XXI

The second procedure involved the cleavage of isochromanone to 2-(2-bromoethyl)-benzoic acid with hydrogen bromide, followed by esterification and treatment of the bromo ester with a nitrite (route B).

Route B



XXI

Route A

Although β-nitrostyrene (2-nitrovinylbenzene) is readily prepared by condensation of nitromethane and benzaldehyde, its o-carboxy derivative [2-(2-nitrovinyl)benzoic acid, X] cannot be obtained in an analogous fashion from o-phthaladehydic acid (IX), because lactonization to 3-phthalidylnitromethane (VIII) takes place as outlined on page 31. It was thought, however, that the methyl ester (XXII) of o-phthaladehydic acid might undergo nitromethane condensation affording the nitrovinyl compound XXIII without complication, provided that the ester group could be retained by choosing suitable reaction conditions.

Preparation of methyl o-phthalaldehydate (XXII)

The normal methyl ester of o-phthalaldehydic acid has been obtained by treatment of the silver salt of the acid with methyl iodide (101) and by Rosenmund reduction of o-carbomethoxybenzoyl chloride (102). No details were given for the former method, whereas the latter procedure was reported to give the ester in an 80% yield. Other methods of esterification yield the pseudo-ester, 3-methoxyphthalide (101). Since the Rosenmund approach appeared to be laborious, the choice fell on the silver salt method, which proved to be satisfactory, furnishing XXII in a yield of 78%. The ester had b.p. 136-138°/13 mm. in agreement with the literature (101, 102). The infrared spectrum, which had not been previously recorded, showed strong bands at 1695 and 1720 cm^{-1} as expected for the aromatic aldehyde and ester carbonyl groups, respectively. There was, however, an additional weak band at 1770 cm^{-1} which was probably due to the presence of a small amount of pseudo-ester, 3-methoxyphthalide. (The corresponding ethyl derivative, 3-ethoxyphthalide, showed carbonyl absorption at 1775 cm^{-1} (103)).

Reactions of Methyl o-Phalaldehydate with Nitro-methane

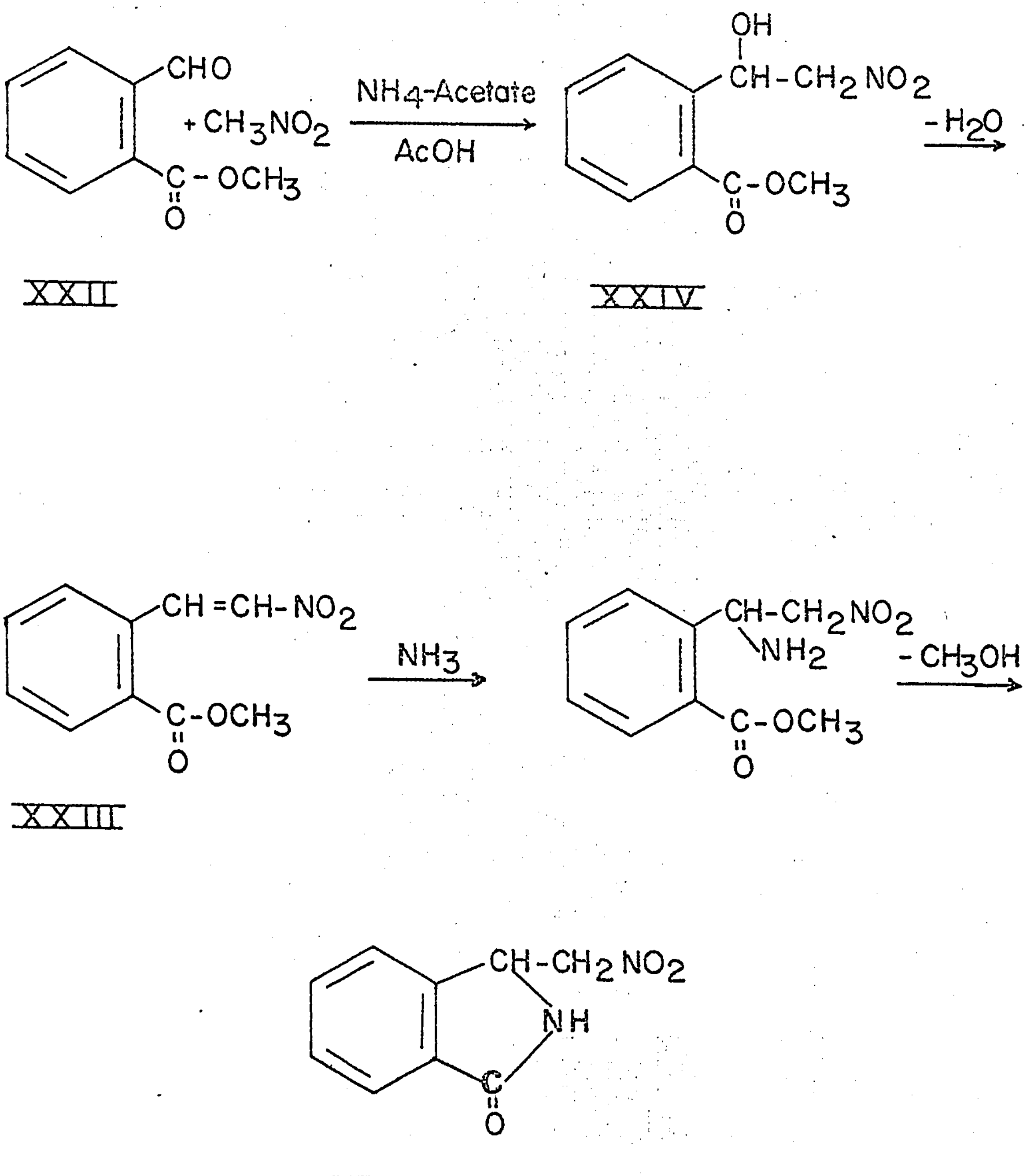
Reactions of nitromethane with methyl o-phthalaldehydate (XXII) were carried out in the presence of the following agents:

a) Ammonium acetate and acetic acid;
b) Sodium acetate and acetic acid;
c) Trimethylamine in methanol;
d) Dimethylamine in methanol;
e) Piperidine;
f) Pyridine;
g) Sodium bicarbonate;
h) Sodium methoxide;
i) Benzyltrimethylammonium hydroxide ('Triton B').

However, methyl 2-(2-nitrovinyl)benzoate could not be isolated in any of these reactions, although several products were obtained whose formation was explicable on the basis of its presence as an intermediate.

(a) Ammonium Acetate and Acetic Acid - Customarily the condensation of nitroalkanes with benzaldehyde and its substitution products is performed with catalysis by alkalies or amines. However, C.B. Gairaud and G.R. Lappin (46) have reported that in certain cases ammonium acetate in glacial acetic acid is a more satisfactory agent. The condensation of methyl o-phthalaldehydate with nitromethane was therefore investigated, using those authors' method. The reaction mixture did not develop any ultraviolet absorption in the 300-390 mμ region, which would have been indicative of the formation of a nitrovinyl grouping. A colorless product of m.p. 193° was isolated in low yield. Its elemental analysis indicated an empirical formula $C_9H_8N_2O_3$. Methoxyl was absent and the oxygen to nitrogen ratio allowed for the presence of only one nitro group, and it had to be considered possible that amine nitrogen had entered the molecule. The infrared spectrum in Nujol exhibited bands at 3225 cm^{-1}, 1720 cm^{-1} and 1550 cm^{-1}. The absorption at 1550 cm^{-1} was assigned to a nitro group, whereas the bands at 3225 and 1720 cm^{-1} pointed to the presence of a five-membered lactam, (dilute solution in chloroform exhibited the carbonyl band at 1710 cm^{-1}, in fair agreement with the reported value of 1700 cm^{-1} for the carbonyl absorption in phthalimidine [104]). On the basis of these data, it was concluded that the product was 2-(1-amino-2-nitroethyl)benzoic acid lactam (XXV, 3-nitromethylphthalimidine).

The lactam XXV may arise by the following mechanistic pathway:



XXII

XXIV

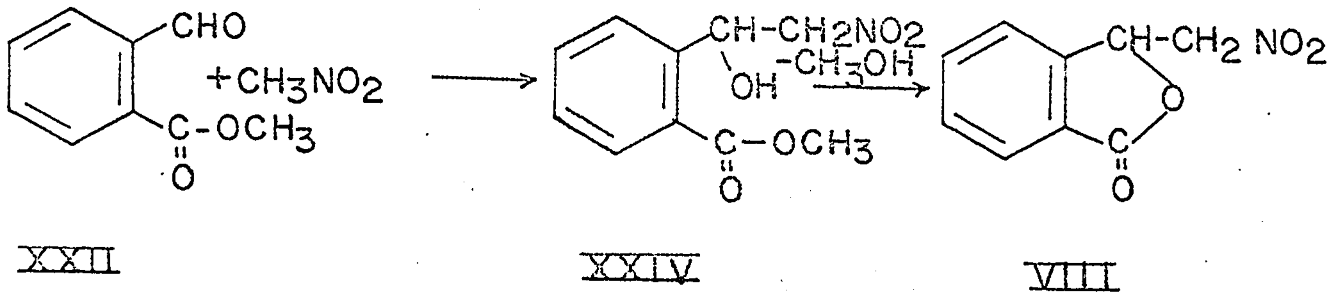
XXIII

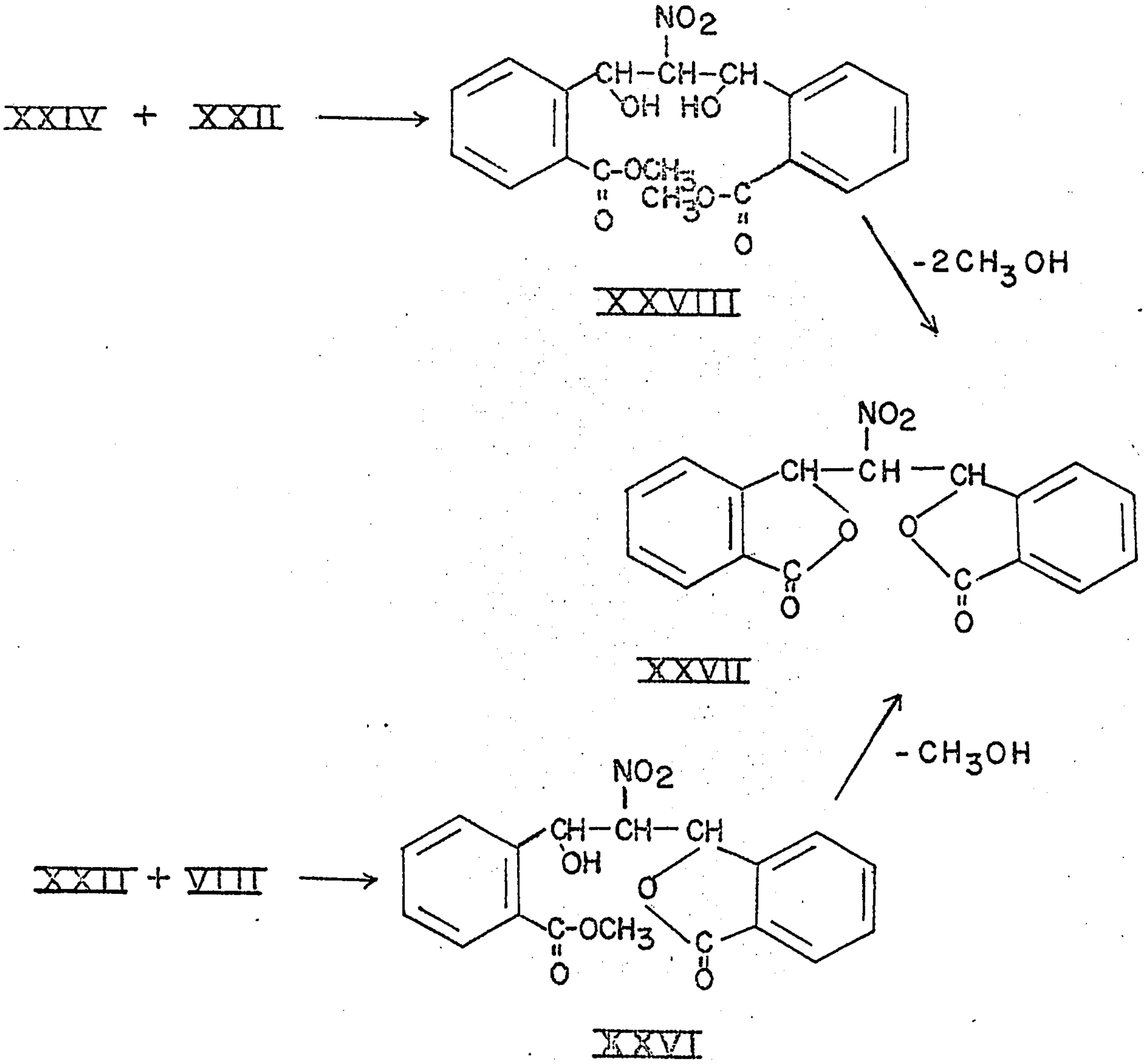
XXV

The formation of XXV can be rationalized as follows: nitromethane addition to the aldehydo ester (XXII) gives a nitrohydroxy ester XXIV which loses a water molecule to form the desired nitrovinyl derivative (XXIII). The latter, however, reacts further by adding ammonia that originates from the ammonium acetate, and the resulting nitroamino ester undergoes internal aminolysis leading to the lactam (XXV).

(b) Sodium Acetate and Acetic Acid - In view of the undesired introduction of ammonia in the preceding experiment, a similar reaction was carried out with sodium acetate in place of ammonium acetate. No methyl 2-(2-nitrovinyl)-benzoate could be isolated, but a new compound was obtained in very poor yield. It proved to be identical with the product that arose, in higher yield, in a similar reaction using trimethylamine as a catalyst, and its structure (XXVII) will be discussed in the next paragraph.

(c) Trimethylamine - Methyl o-phthalaldehydate (XXII) and nitromethane were allowed to react in methanolic solution in the presence of almost one mole of trimethylamine. Upon work-up, 73% of the starting ester was recovered but, in addition, a new crystalline compound was isolated in a yield of 20%. The purified product melted at 230°. It did not contain any methoxyl. Elemental analysis indicated an empirical formula $C_{17}H_{11}NO_6$, in accordance with which the mass spectrum showed a parent peak at m/e 325. The infrared spectrum exhibited bands attributable to the nitro group (1560 cm^{-1}) and the carbonyl group (1760 cm^{-1}). The ultraviolet spectrum in methanol solution exhibited maxima at 276 and 283 mμ, the absorption curve being nearly identical with that of known (97) 3-phthalidylnitromethane (VIII). On the basis of these data it was concluded that the reaction product was 3,3'-diphthalidylnitromethane (XXVII). It is presumed that XXVII arose by the following sequence of reactions:


CHO
+ CH3NO2
C-OCH3
O
XXII
CH-CH2NO2
OH
-CH3OH
C-OCH3
O
XXIV
CH-CH2 NO2
O
C
O
VIII


XXIV + XXII
NO2
CH-CH-CH
OH HO
C-OCH3
CH3O-C
O
O
XXVIII
-2CH3OH
NO2
CH—CH—CH
O
O
C
C
O
O
XXVII
- CH3OH
XXII + VIII
NO2
CH—CH—CH
OH
O
C-OCH3
C
O
O
XXVI

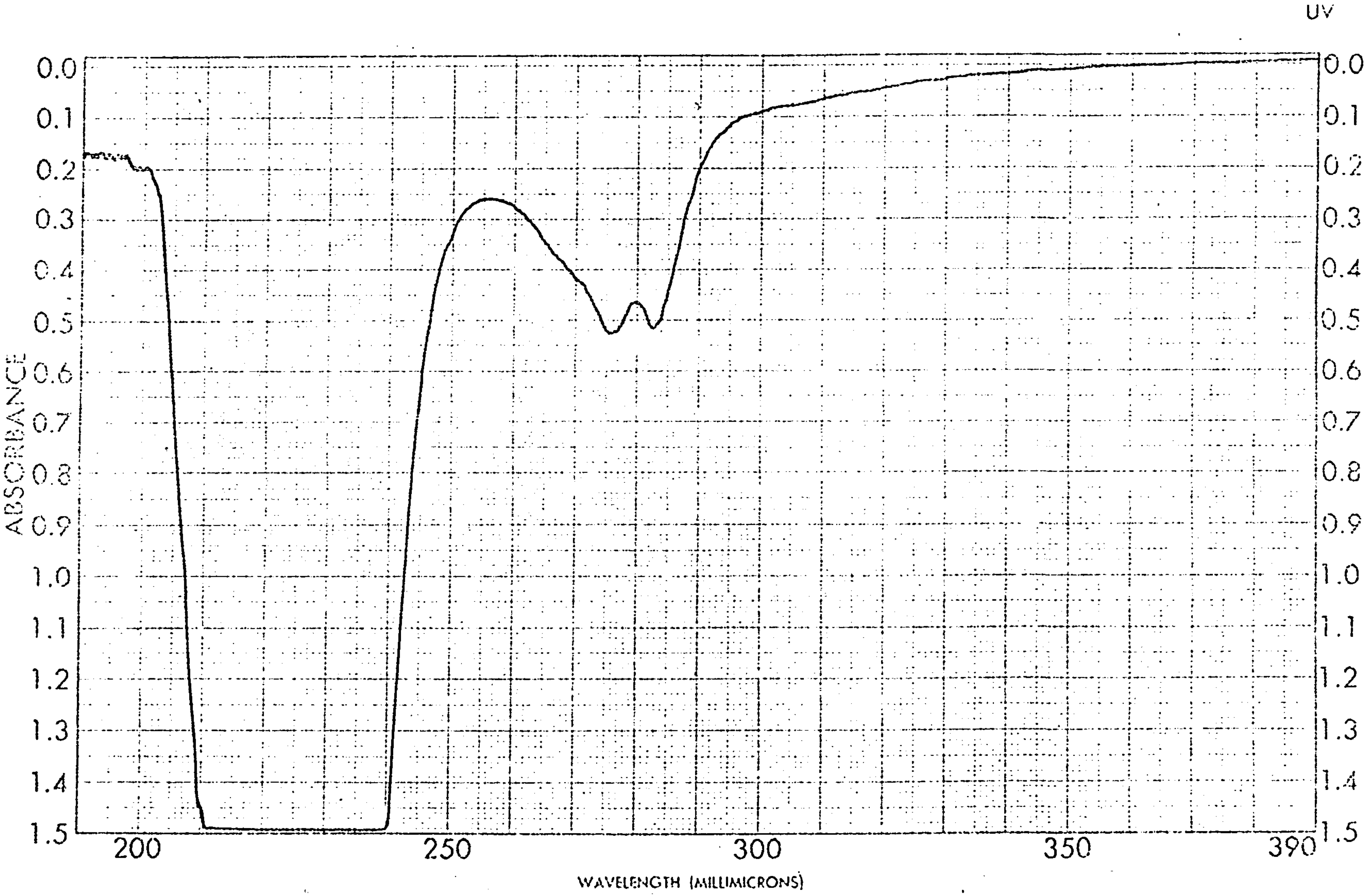


Fig. 3. U.V. Spectrum of 3, 3'-diphthalidylnitromethane (XXVII); 10^{-4}M solution in methanol.

Again, the first step is formation of the nitrohydroxy ester XXIV. Internal transesterification of XXIV leads to the lactone, 3-phthalidylnitromethane (VIII), which then adds a second molecule of XXII giving the intermediate XXVI, and a second lactonization produces the final product, XXVII. Alternatively, the reaction could well proceed from XXIV via the dihydroxy diester intermediate XXVIII.

(d) Dimethylamine - Catalysis by dimethylamine of the reaction between methyl o-phthalaldehydate (XXII) and nitromethane led to the isolation of a small amount of 3-phthalidylnitromethane (VIII). Its origin can be explained by the scheme described in the preceding section 'c'. The reaction mother liquor showed an ultraviolet absorption peak at 370 mμ, in contrast to the experiments reported under a, b and c. A yellow solid mass was isolated by thin layer chromatography, and although it did exhibit the peak mentioned, proper characterization could not be accomplished.

(e) Pyridine - The use of pyridine as a condensing agent was unsuccessful, and starting material was recovered.

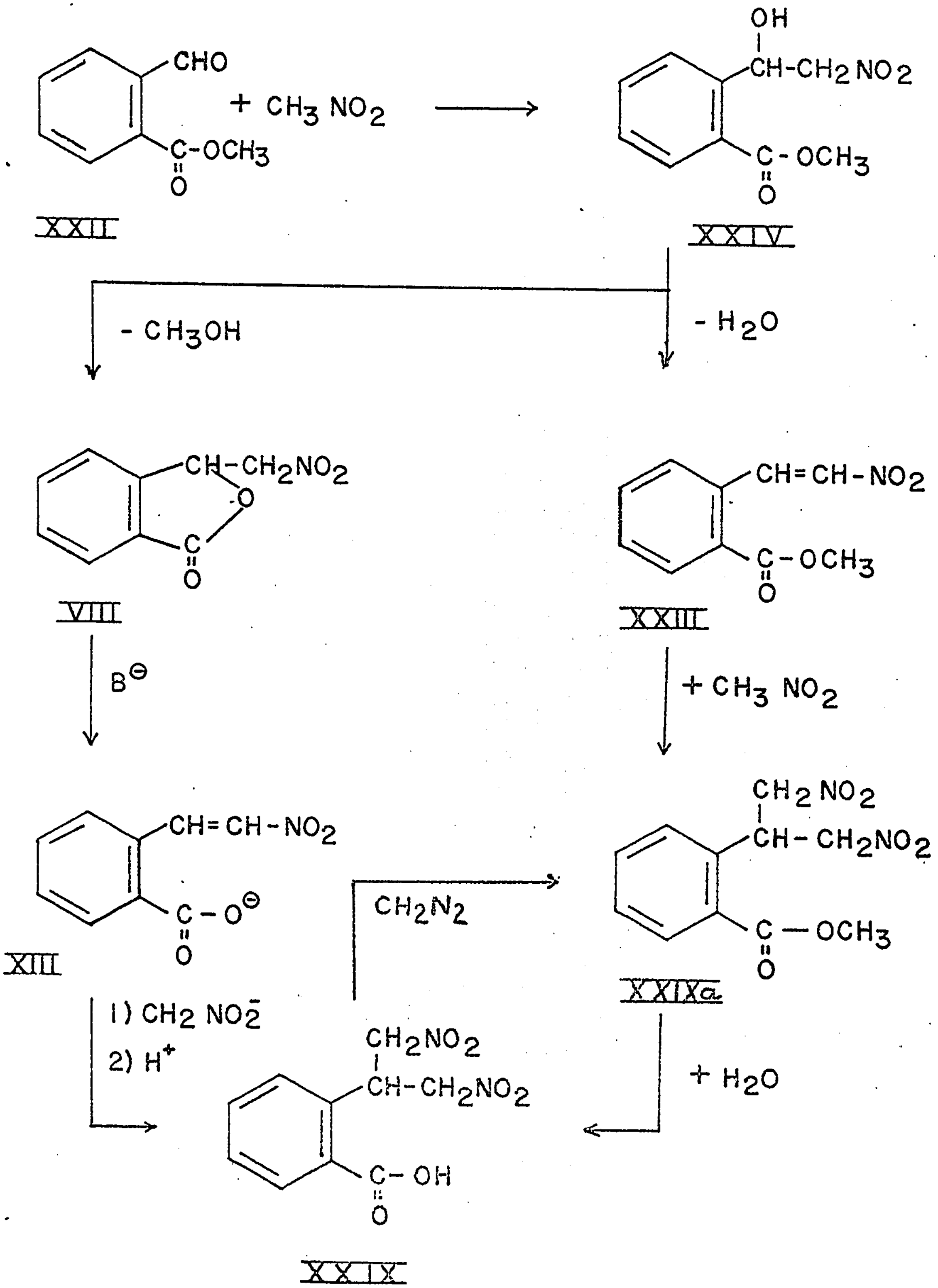
(f) Piperidine - This base likewise failed to catalyse the reaction.

(g) Sodium bicarbonate - The nitromethane condensation of XXII was attempted in anhydrous benzene in the presence of sodium bicarbonate, but no reaction took place.

(h) Sodium methoxide - Methyl o-phthalaldehydate (XXII) and nitromethane were allowed to react with sodium methoxide in methanolic solution at -5°. Upon deionization with a cation exchange resin, an amorphous product was obtained which failed to crystallise. Its infrared spectrum exhibited a nitro band at 1550 cm^{-1} but the ultraviolet spectrum did not reveal the presence of a chromophore attributable to a nitrostyrene moiety. Possibly the material was of a polymeric nature; it was not investigated further.

A modification of the procedure just described is the method of Kamlet (47) in which sodium methanenitronate is prepared by the interaction of nitromethane and sodium methoxide, and the solid nitronate is added in an equimolar amount to the bisulfite addition compound of the aldehyde. The method was tried with the aldehydo ester XXII, but no pure reaction product could be isolated, and no evidence for the formation of a nitrostyrene derivative was obtained.

(i) Benzyltrimethylammonium hydroxide ('Triton B') - The condensation of nitromethane with methyl o-phthalaldehydate (XXII) was carried out at 0 to -3° in the presence of benzyltrimethylammonium hydroxide (40% solution in methanol, commercially known as 'Triton B'). After neutralisation with hydrochloric acid, the reaction mixture yielded a colorless, crystalline solid of m.p. 139°. Elemental analysis corroborated by mass spectrometry (p. 79) indicated an empirical formula $C_{10}H_{10}N_2O_6$. The infrared spectrum in nujol showed absorption maxima at 1680, 1560 and 1550 cm^{-1} (shoulder) as well as a broad band at 3300-3000 cm^{-1}. The maxima at 1560 and 1550 cm^{-1} could be regarded as asymmetric nitroalkane stretching vibrations. The appearance of a shoulder (the band as a doublet) possibly (but not necessarily) meant that two non-conjugated nitro groups were present in different structural environments. The absorption at 1680 cm^{-1} should be due to the carbonyl stretching vibration of an aromatic carboxylic acid rather than an aromatic ester, since aromatic carboxylic acids and their esters are reported to absorb at 1700-1680 cm^{-1} and 1730-1717 cm^{-1} respectively. This suggested the loss of the ester group under the reaction conditions. The broad band at 3300-3000 cm^{-1} indicated the presence of hydrogen-bonded hydroxyl. The nuclear magnetic resonance spectrum in deuterochloroform confirmed the loss of the ester group by not revealing any absorption for methoxyl protons, although we could not observe a signal for the carboxylic proton. Lack of the ester grouping and the presence of six oxygen and two nitrogen atoms suggested that two molecules of nitromethane had condensed with one molecule of methyl o-phthalaldehydate. Based on the above data, we propose the structure XXIX, 2-(1,3-dinitro-2-propyl)-benzoic acid for the product which probably arises through a nitroolefin intermediate. Two alternate pathways can be envisaged, in both of which the first step would be the formation of the hydroxynitroester XXIV.


CHO
C-OCH3
O
+ CH3 NO2
XXII
OH
CH-CH2 NO2
C-OCH3
O
XXIV
- CH3OH
- H2O
CH-CH2NO2
O
C
O
VIII
CH=CH-NO2
C-OCH3
O
XXIII
B⊖
+ CH3 NO2
CH=CH-NO2
C-O⊖
O
XIII
CH2N2
CH2 NO2
CH-CH2NO2
C-OCH3
O
XXIXa
1) CH2 NO2⁻
2) H⁺
+ H2O
CH2NO2
CH-CH2NO2
C-OH
O
XXIX

The hydroxynitro ester XXIV, by internal transesterification, forms the lactone VIII which undergoes base-catalyzed β-elimination to yield the nitroolefin XII (97). The latter reacts with nitromethane to form XXIX (Michael addition). In the second pathway, a nitroolefinic ester (XXIII) may be initially formed and then undergo Michael addition of nitromethane and subsequent hydrolysis, to give XXIX.

The n.m.r. spectrum of XXIX in deuterated acetone showed an intensity ratio of 4:4 for the signals attributed to the aromatic protons (multiplets at 2.51 τ and 3.1 τ) and the nitromethyl protons (doublet at 5.5 τ). There is also a multiplet at 5.2 τ, with an intensity equalling one proton, which is ascribed to the tertiary proton.

As a confirmation of structure XXIX, the acid on treatment with diazomethane gave the methyl ester, XXIXa, m.p. 90° in 71.5% yield. Elemental analysis and the mass spectrum (p.82) were in agreement with the molecular formula $C_{11}H_{12}N_2O_6$. The ester showed absorption at 1720 cm^{-1} (aromatic ester carbonyl) and 1570 and 1560 cm^{-1} (shoulder) for the two nitro groups. The nuclear magnetic resonance spectrum taken in deuterochloroform revealed an intensity ratio of 4:3 for the signals attributed to the aromatic protons (multiplet at 1.9 τ and 2.6 τ) and the methoxyl protons (singlet at 6.1 τ). A doublet at 5.08 τ corresponded to the nitromethyl protons and the tertiary proton signal was at 4.88 τ (multiplet).

Route B

Synthesis of 2-(2-bromoethyl)benzoic acid (XXX)

Isochromanone was obtained by the oxidation of isochroman with selenium dioxide according to the method of J. Cologne and P. Boisde (105).

P. Maitte (106) has reported that isochromanone can be converted directly into 2-(2-bromoethyl)benzoic acid, in quantitative yield, by treatment with a saturated solution of hydrogen bromide in acetic acid in a sealed tube at 150°. However, full details of the reaction conditions have not been described. When the preparation was attempted using a commercial 30% solution of hydrogen bromide in acetic acid and allowing reaction times from one to six hours, the bromo acid was produced in extremely poor yields. A good yield (75.5%) of crystalline bromo acid (XXX) (m.p. 93°) was finally obtained by the use of a hydrogen bromide-acetic acid reagent that had been saturated at 0° with hydrogen bromide gas.

Methyl 2-(2-bromoethyl)benzoate (XXXI)

2-(2-Bromoethyl)benzoic acid (XXX) was esterified with diazomethane. The crude reaction product was a liquid whose methoxyl content of 12.5% (calculated, 13.3%) indicated that esterification had been accomplished. However, purification by vacuum distillation proved to be precarious in that the ester tended to suffer an unexpected change. In early experiments, distillation was carried out at an oil-bath temperature of 140-160° and a liquid boiling at 108-110°/0.8 mm. was collected. Since, after one such distillation, the infrared spectrum seemed reasonable for a sufficiently pure ester, the material was used in the next synthetic step which, however, revealed a considerable contamination by isochromanone (see p.62). An analytical sample was distilled thrice, whereby the ester, instead of being purified, was almost completely converted into isochromanone*. Later it was found that the crude ester may be distilled without apparent ill effect from a short-neck bulb at 0.3 mm and a bath temperature of 95-110°. The product so purified gave an infrared spectrum quite different from that of isochromanone, especially in the region from 1400 cm^{-1} to 650 cm^{-1}. The nuclear magnetic resonance spectrum in carbon tetrachloride showed an intensity ratio of 4:3 for the signals assigned to the aromatic protons (two multiplets centred at 2.0 and 2.66 τ) and to the methoxyl protons (singlet at 6.15 τ). In addition to these signals, the spectrum showed a symmetrical multiplet centred at 6.46 τ with a total intensity corresponding to four protons. It must be due to the bromoethyl group.

It is not known by what mechanism the bromo ester is converted into isochromanone at higher temperatures. One might speculate that departure of a bromide ion is aided by the formation of a resonance-stabilized oxonium ion (XXXII) and that the latter subsequently releases a methyl ion, thus giving rise to isochromanone and methyl bromide as illustrated.

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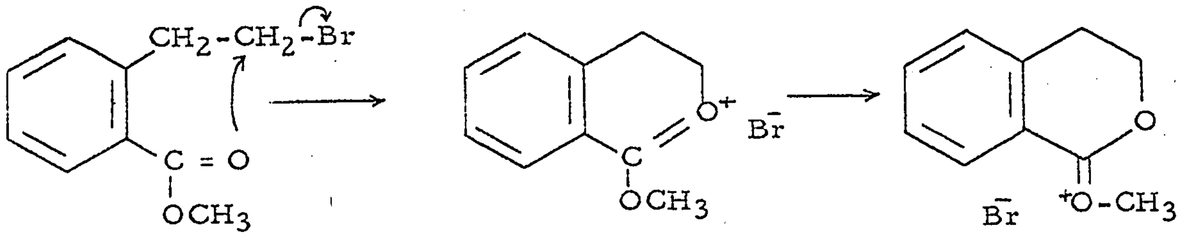
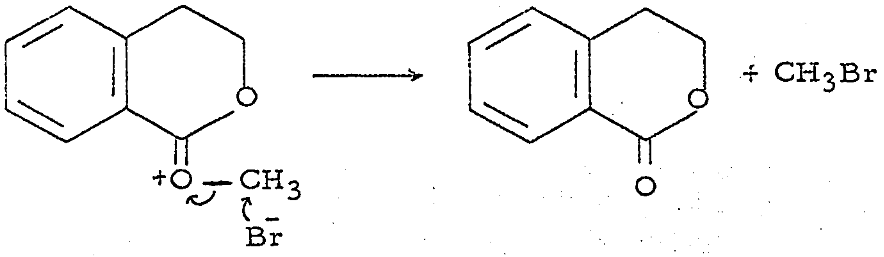
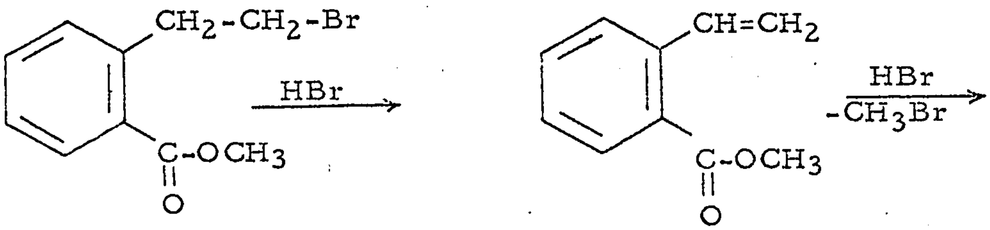
* This was ascertained by microanalysis and by the infrared and n.m.r. spectra which proved the identity of the product (see Experimental).



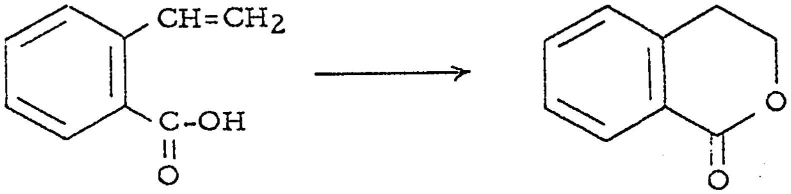
XXXI XXXII



Alternatively, one might assume an elimination of hydrogen bromide. Hydrogen bromide is known to be capable of cleaving carboxylic esters to give carboxylic acid and methyl bromide. The 2-vinylbenzoic acid (XXXIII) so produced might then cyclize to isochromanone.



XXXI



XXXIII

Methyl 2-(2-nitroethyl)benzoate (XXXIV)

A preparation of methyl 2-(2-bromoethyl)-benzoate that had been distilled once at a bath temperature of 140-160° and presumably contained a considerable amount of isochromanone (p.58) was allowed to react with sodium nitrite in dimethylsulfoxide* according to Kornblum (8). A colorless liquid boiling at 112-117°/0.5 mm was isolated. The product showed infrared absorption at 1720 cm^{-1} for aromatic ester carbonyl and 1550 cm^{-1} for the nitro group. Its nuclear magnetic resonance spectrum was complex, but it did reveal the presence of

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* The use of dimethylformamide was unsuccessful.

isochromanone. Isochromanone has a characteristic, easily recognizable A_2X_2 spectrum which consists, in the aliphatic proton region, of two symmetrical triplets with spacings of 6 cps. at 5.58 τ and 7.00 τ. A partial separation of isochromanone by thin layer chromatography confirmed the impure nature of the nitro ester. Since complete separation, either by fractional distillation or by chromatography, could not be effected, the crude mixture itself was used for a subsequent cyclisation reaction. The success of that reaction (p.65) confirmed the presence of at least some XXXIV.

When pure XXXI (p. 59) was treated with sodium nitrite in dimethylsulfoxide, XXXIV was obtained as a colorless, crystalline solid of m.p. 55-56°. It showed infrared bands at 1720 cm^{-1} for the aromatic ester carbonyl and at 1550 cm^{-1} for the nitro group.

An attempt to carry out a displacement reaction on 2-(2-bromoethyl)benzoic acid (XXX) itself rather than its methyl ester led to the isolation of isochromanone as the only product.

Phenyl 2-(2-bromoethyl)benzoate (XXXV)

Since in the earlier stages of this investigation the purification of the methyl ester of 2-(2-bromoethyl)benzoic acid (XXXI) was attended with the undesirable formation of isochromanone, the synthesis of the phenyl ester was undertaken. 2-(2-Bromoethyl)-benzoic acid (XXX) was converted into the acid chloride by refluxing with thionyl chloride and the acid chloride, on treatment with phenol in the presence of pyridine, gave phenyl 2-(2-bromoethyl)benzoate (XXXV), m.p. 84°, in a yield of 60% (yield based on the starting acid). The ester gave a correct elemental analysis and showed infrared absorption at 1730 cm^{-1} (aromatic ester carbonyl).

Phenyl 2-(2-nitroethyl)benzoate (XXXVI)

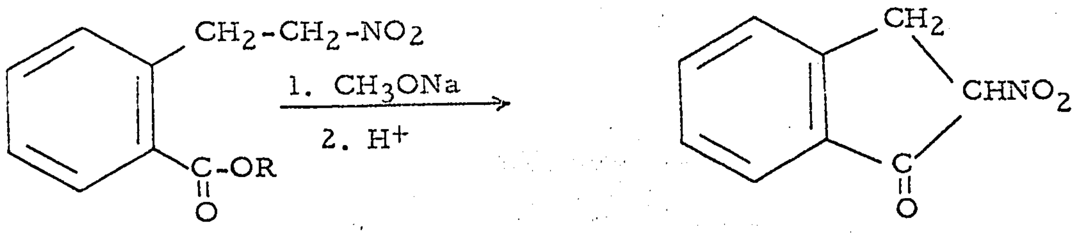
The reaction of sodium nitrite with (XXXV) in dimethylsulfoxide for four hours at room temperature gave a colorless crystalline product with a sharp melting point of 71°. The product showed infrared absorptions at 1730 cm^{-1} for the aromatic ester carbonyl and at 1550 cm^{-1} for the nitro group. The elemental analysis, however, suggested that the product was a mixture of the starting bromo ester and the nitro ester, apparently in a ratio of 1:1, since the carbon content was half-way between those calculated for the bromo and nitro esters and the nitrogen content was one-half of the expected. Separation by thin-layer chromatography on silica gel resulted in the isolation of pure phenyl 2-(2-nitroethyl)benzoate (XXXVI), m.p. 81°, which showed satisfactory analytical values.

It seemed an obvious way to attempt a complete conversion of the bromo into the nitro ester by prolonging the reaction time. However, a reaction time of 24 hours gave a brown oil from which no pure product could be isolated, although the expected infrared bands were observed.

2-Nitroindanone by Ester Cyclization

It has been shown on page 37 that the action of sodium methoxide upon methyl 2-(1-methoxy-2-nitroethyl)benzoate (XVII) leads to a product (XX) whose formation was explained by assuming an intermediate generation of 3-methoxy-2-nitroindanone (XVIII). With methyl 2-(2-nitroethyl)benzoate (XXXIV), phenyl 2-(2-nitroethyl)benzoate (XXXVI) and methyl 2-(1,3-dinitro-2-propyl)benzoate (XXIXa) at hand, our attention was now redirected towards this cyclization.

Treatment of crystalline methyl ester of 2-(2-nitroethyl)-benzoic acid (XXXIV) in methanolic solution with sodium methoxide at room temperature, followed by deionization, afforded crystalline 2-nitroindanone (II) in a 62% yield. The identity of the product was established by comparison with a specimen synthesized in an independent way as outlined on page 73.



XXXIV R = CH_3

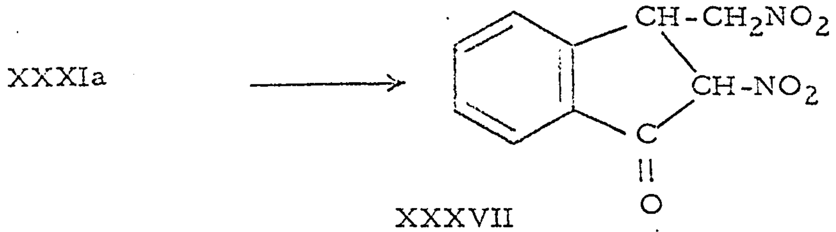
XXXVI R = C_6H_5

II

When the impure methyl ester [that contained isochromanone (cf. p. 62)] was used, 2-nitroindanone was also isolated in crystalline form although, naturally, in a poor yield (cf. Experimental).

Since only a small, analytical sample of pure phenyl 2-(2-nitroethyl)benzoate (XXXVI) had been isolated by thin-layer chromatography, the crude product which appeared to be an addition compound between the phenyl nitro ester and its precursor (XXXV) was employed for cyclization. Treatment with methanolic sodium methoxide at room temperature , followed by deionization, gave 2-nitroindanone (II).

The reaction of methyl 2-(1, 3-dinitro-2-propyl)benzoate (XXIXa) with methanolic sodium methoxide was carried out at ice-bath temperature, and a product melting at 118-119° which was presumed to be 3-nitromethyl-2-nitroindanone (XXXVII) was isolated in 43% yield. The structure was assigned on the basis of elemental analysis and spectroscopic evidence. The product exhibited infrared bands at 1725 and 1550 cm^{-1} in line with the presence of a cyclic, five-membered α, β-unsaturated ketone moiety and the nitroalkane groups. It exhibited an ultraviolet maximum at 370 mμ (ε, 8400), at the same wavelength as 2-nitrotetralone (21). The n.m.r. spectrum taken in deuterated dimethylsulfoxide showed a multiplet centred at 2.19 τ for the aromatic protons, a doublet at 3.9 τ (splitting, 4 c.p.s.), and several poorly resolved signals in the region of 4.3 - 5.3 τ .



XXXVII

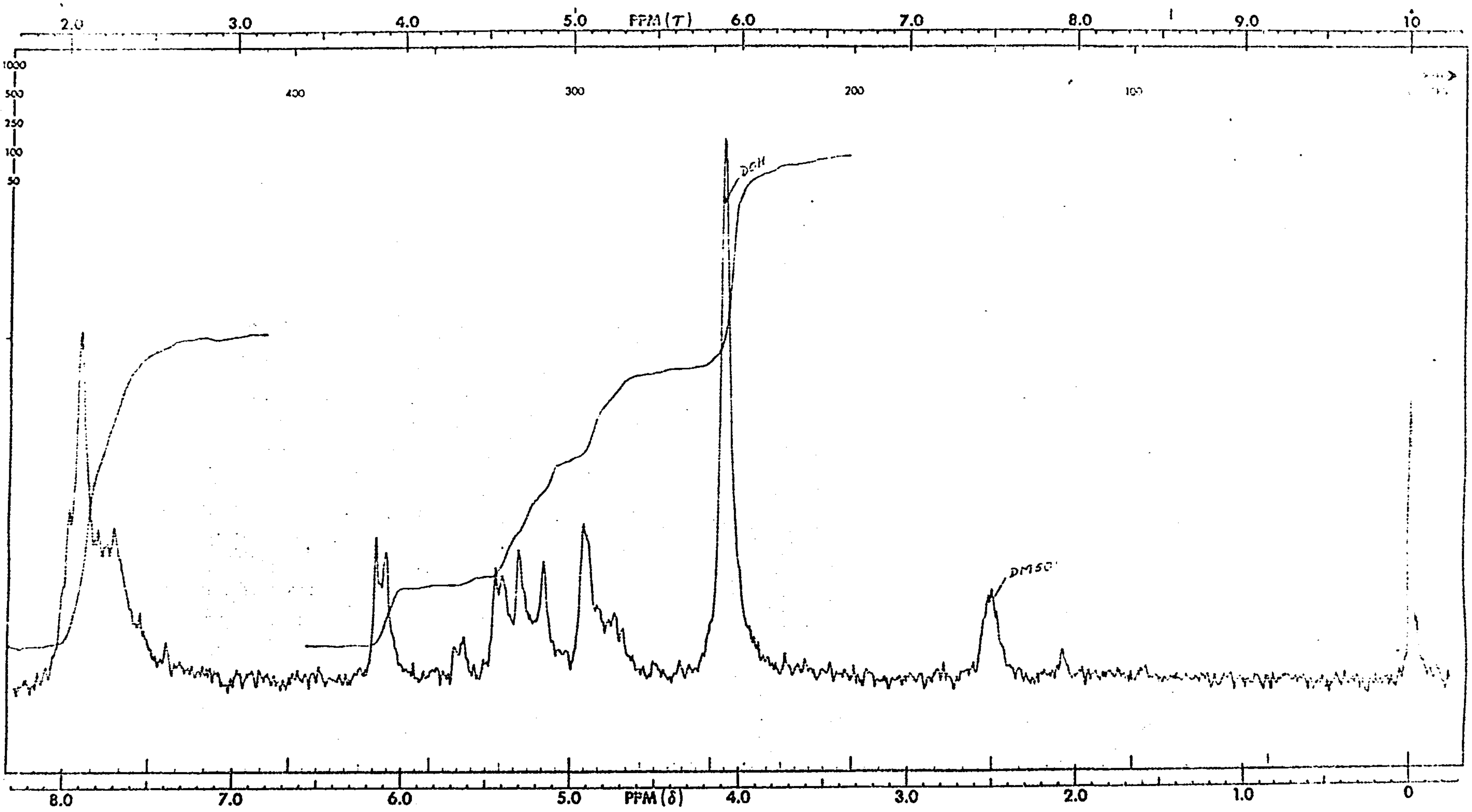


Fig. 4. N.M.R. Spectrum of 3-nitromethyl-2-nitroindanone (XXXVII) in deuterated dimethylsulfoxide.

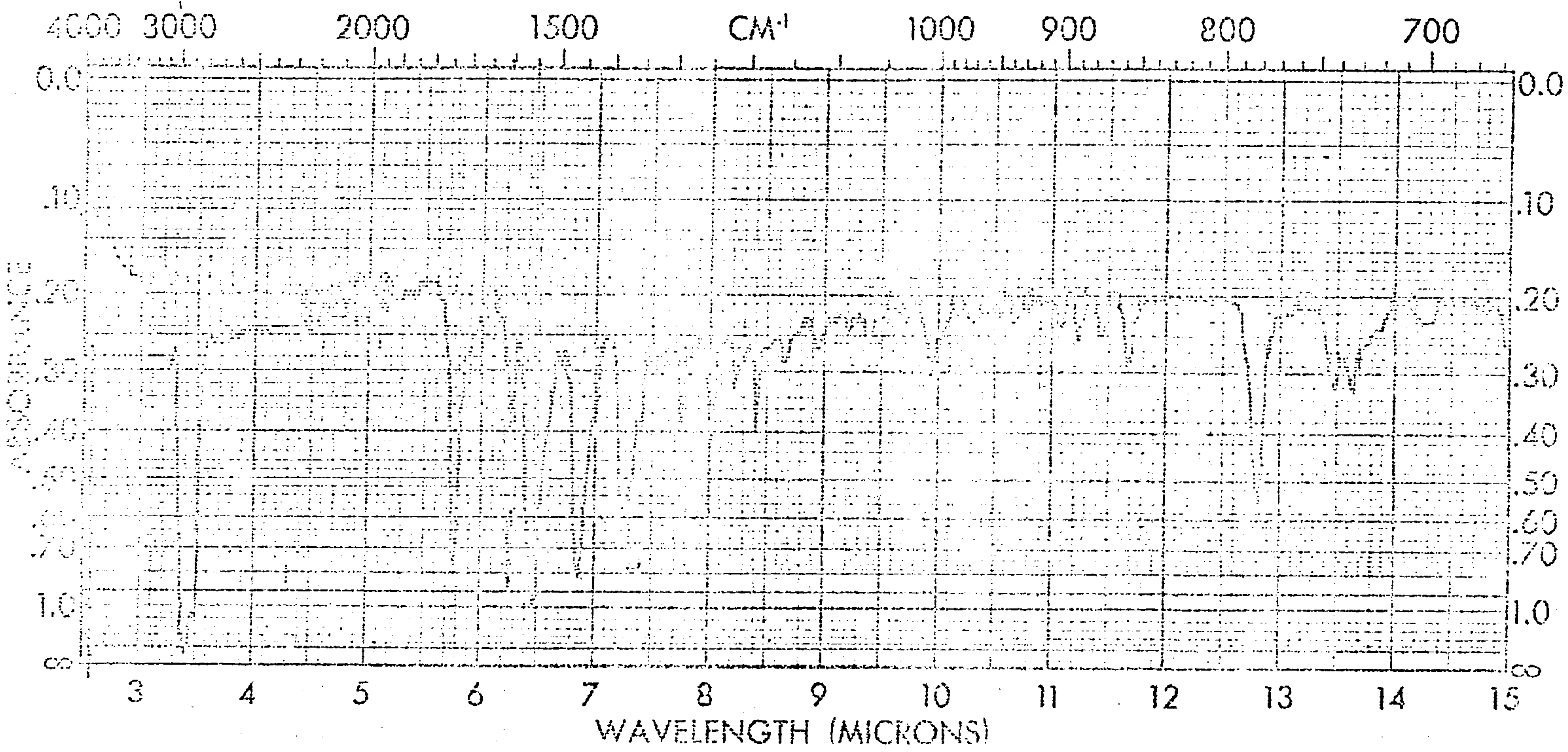
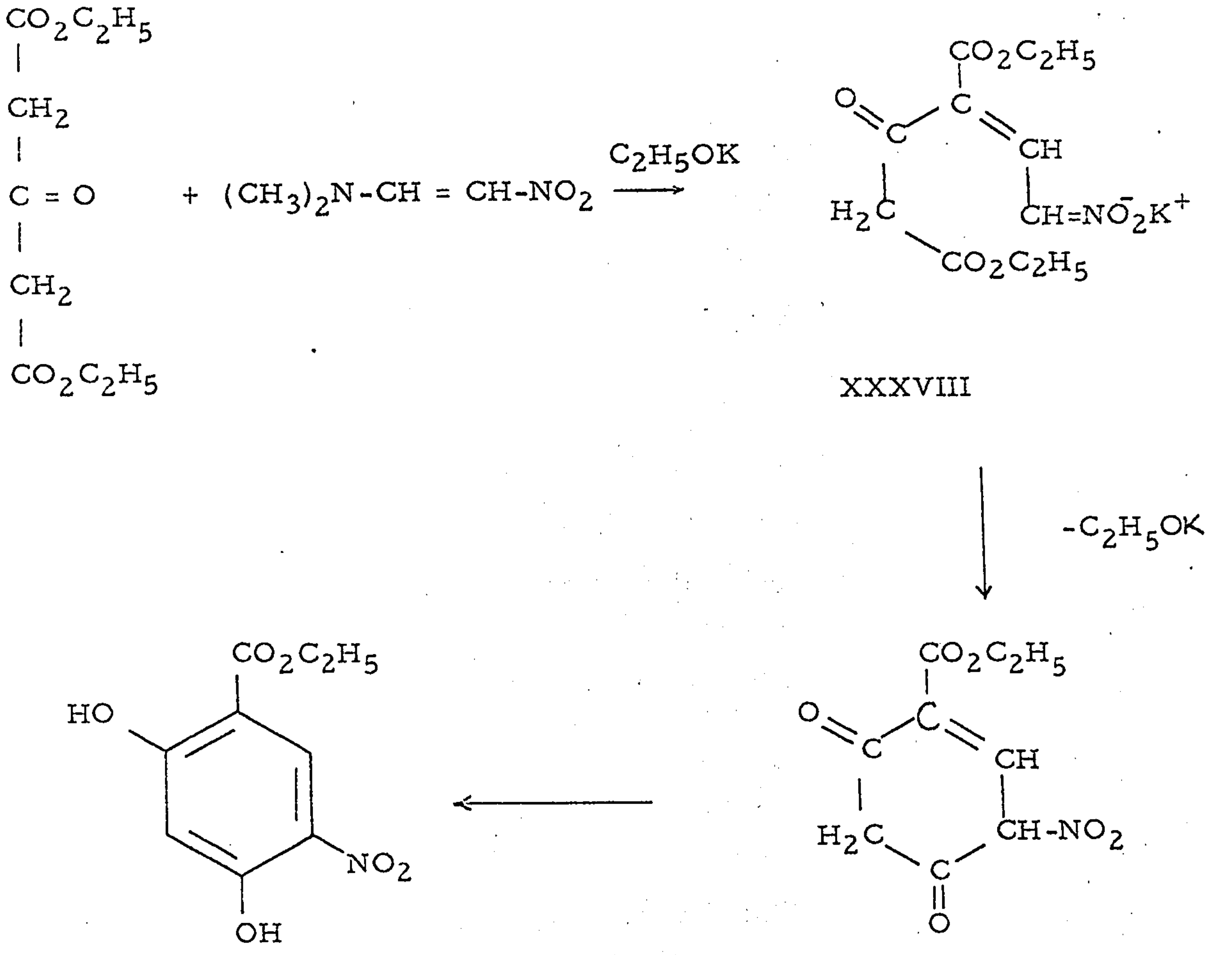


Fig. 5. I.R. Spectrum of 3-nitromethyl-2-nitroindanone in nujol.

The doublet at 3.9 τ must be due to H_2. Its intensity, if the aromatic proton signal is taken to represent four hydrogens, corresponded to 0.75 proton only. Possibly, this low value can be explained by a partial enolization, as has been done (21) for other cyclic nitroketones. The group of signals at higher field corresponded in intensity to slightly less than three protons. No resonance attributable to a methyl ester group was present.

The success of these reactions demonstrated that suitably constituted nitro esters can in fact be cyclized to α-nitro ketones in a Dieckmann-type reaction, in accordance with the proposition outlined on page 35. After this possibility had been established in principle, work by Severin and Adhikary (107) dealing with a related reaction came to the author's attention. These workers showed that certain ω-nitro esters obtained by the condensation of 1-nitro-2-dimethylaminoethylene with compounds of the type XCH_2Y containing activated methyl or methylene groups also undergo cyclization reactions. For instance, when ethyl acetonedicarboxylate was reacted with 1-nitro-2-dimethylaminoethylene in the presence of potassium ethoxide, the product was ethyl 2,4-dihydroxy-5-nitrobenzoate. The authors postulated a reaction sequence proceeding via the intermediate XXXVIIIwhich has a reactive nitronate group at one end of the chain and a carboethoxy group at the other end. This aci-nitrointermediate cyclises to give a nitro diketone which tautomerizes to the final product.



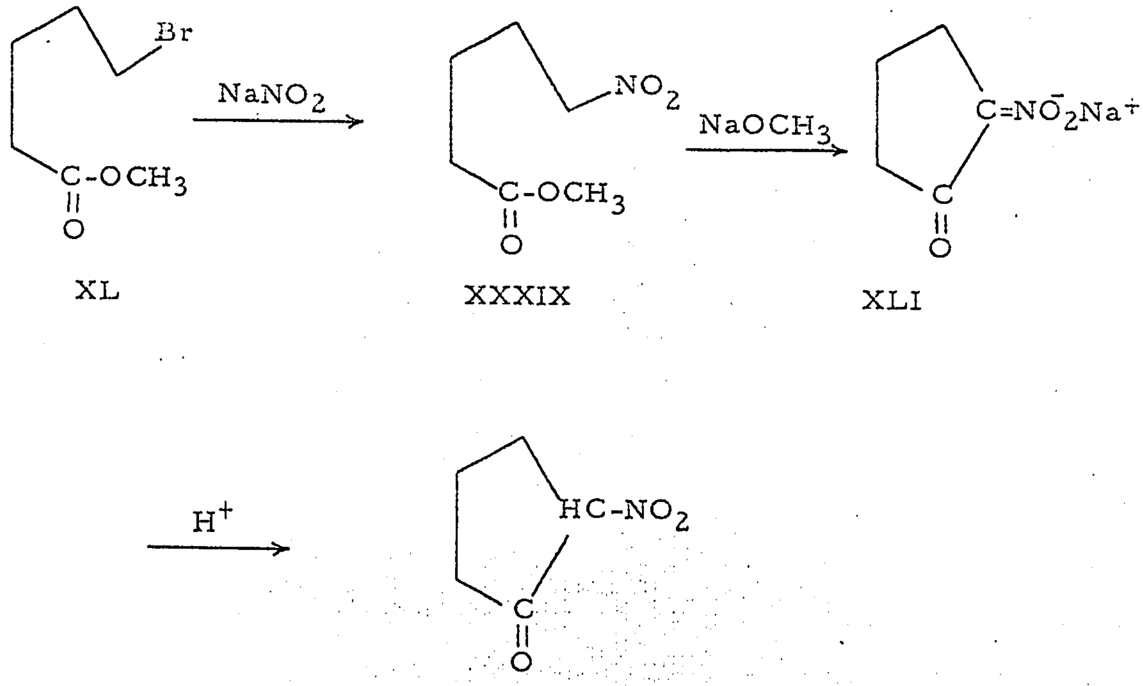
XXXVIII

These results and our own appear to be in harmony, although for the former reaction the aromatization of the system certainly provided a major driving force which is absent in our case.

Preliminary Studies concerning the Synthesis of 2-Nitrocyclopentanone

It appeared interesting to investigate whether the new synthesis of cyclic α-nitro ketones can be applied to purely aliphatic systems. An application to the synthesis of 2-nitrocyclohexanone might perhaps have had the greatest chance of success, that ketone being fairly stable and well-documented in the literature (19, 34, 21). However, it was more stimulating to try the synthesis of 2-nitrocyclopentanone for which no satisfactory method exists up to date. Feuer and Pivawer (21) have nitrated cyclopentanone with amyl nitrate in tetrahydrofuran, but upon work-up, during which they added glacial acetic acid and ethanol at 0°, they obtained amyl and ethyl 5-nitropentanoate (cf. Introduction, page 8). It was concluded that 2-nitrocyclopentanone is an extremely unstable substance prone to undergoing ring cleavage.

It was proposed to prepare methyl 5-nitropentanoate (XXXIX) from the corresponding commercially available bromo ester (XL) and to attempt its cyclization to 2-nitrocyclopentanone.



XL XXXIX XLI

Treatment of methyl 5-bromopentanoate with sodium nitrite in a mixture of dimethylsulfoxide and dimethylformamide gave a colorless liquid which exhibited infrared absorption at 1730 cm^{-1} for the ester carbonyl and at 1550 cm^{-1} for the nitro group. The elementary analysis, however, suggested that the product may have been contaminated with some methyl 4-pentenoate, since the carbon percentage was too high and the nitrogen content too low. Attempts to fractionate the mixture were unsuccessful.

Assuming that the mixture, nevertheless, contained the desired nitro ester, XXXIX, it was treated with sodium methoxide in methanol, whereupon an absorption maximum at 345 mμ developed. This may be taken as evidence for the formation of the ketone nitronate, XLI, as Feuer and Pivawer (21) have reported similar values for the potassium salts of several homologous α-nitro ketones. However, deionization resulted in the formation of the starting material as judged from the infrared spectrum.

2-Nitroindanone by Oxidation of 2-Oximinoindanone

The following three alternative syntheses of 2-nitroindanone were attempted:

1) Conversion of 2-bromoindanone into 2-nitroindanone;
2) Nitration of indanone;
3) Oxidation of 2-oximinoindanone.

Whereas the first two projects failed, the third succeeded.

Although sodium nitrite in dimethylsulfoxide or dimethylformamide has been widely used as a reagent for the conversion of secondary halides into nitro derivatives (8), its reaction with 2-bromoindanone did not afford the desired product. Brown syrups were obtained which failed to show any nitro group frequencies in their infrared spectra.

Attention was then focused on the direct nitration of indanone. For similar purposes acetyl nitrate in glacial acetic acid (34) and alkyl nitrates in the presence of alkoxides (21, 25) have previously been employed. In fact, Campbell and Pitzer (88) tried to nitrate indanone itself under a variety of conditions but failed. We used acetyl nitrate in glacial acetic acid, n-butyl nitrate and potassium t-butoxide in tetrahydrofuran, as well as 2-octyl nitrate and sodium methoxide in ether, but in all of these cases no identifiable products could be isolated.

After these failures it was thought worthwhile to attempt the oxidation of 2-oximinoindanone. This compound is available by nitrosation of indanone (108). Oxidation of oximes to nitro compounds has been performed previously with manganese dioxide (109), and peroxytrifluoroacetic acid (12). In the present case, the first oxidant did not yield the expected product. The use of peroxytrifluoroacetic acid finally brought success, despite a discouraging report by Campbell and Pitzer (88), who have been unable to oxidize 2-oximinoindanone with this reagent. These authors conducted their oxidation in boiling acetonitrile, which procedure had been recommended (12) for other oximes. Presumably, their negative result was due to instability of the oxidation product under the reaction conditions. In this connection, the great reactivity towards acid of 2-nitrocyclopentanone may be recalled. It was therefore decided to carry out the oxidation at room temperature, but for a longer period of time. It was found that, after eight hours, 2-nitroindanone (II) could be isolated in a yield of 18%. The product formed

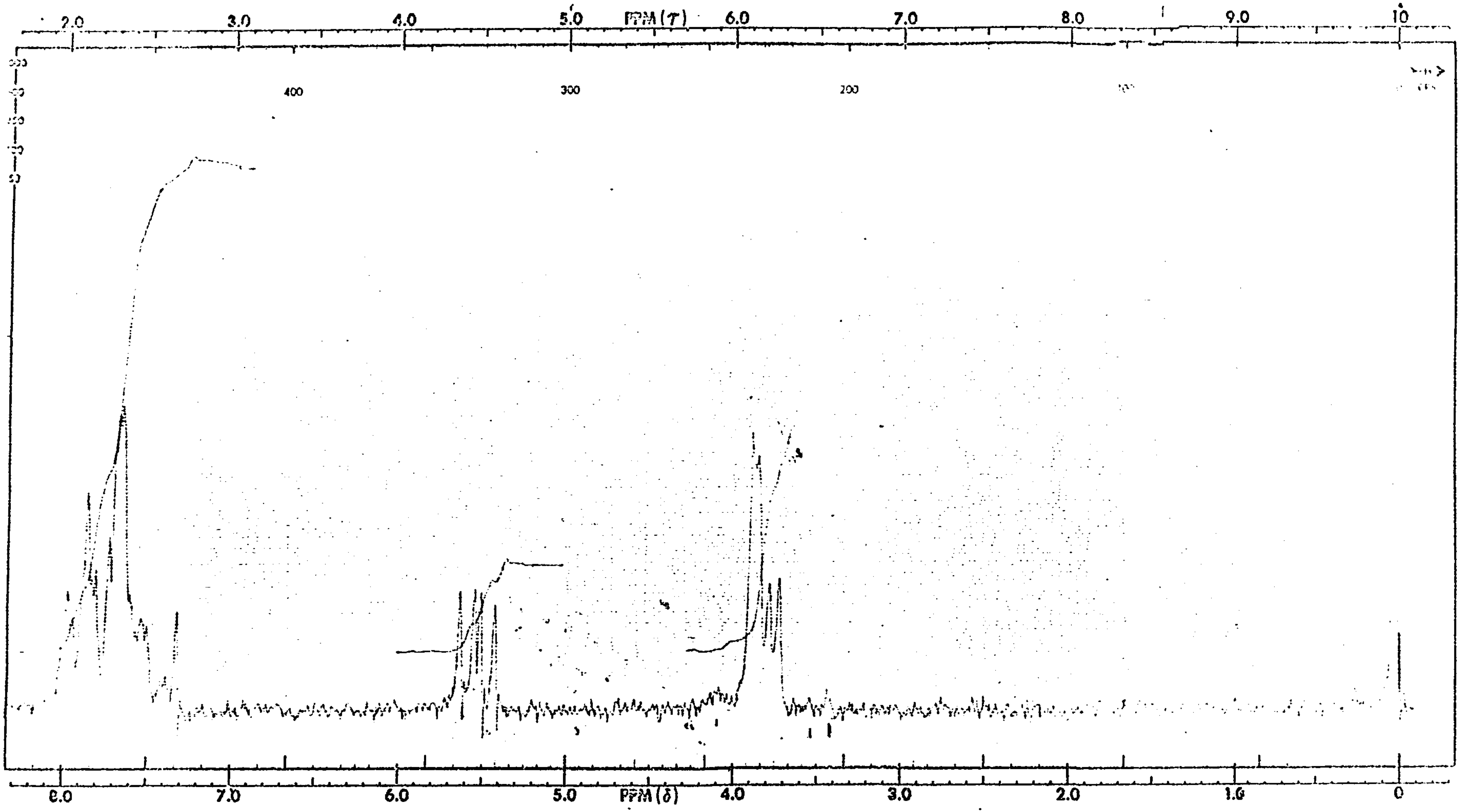


Fig. 6. N.M.R. Spectrum of 2-nitroindanone (II) in deuterochloroform.

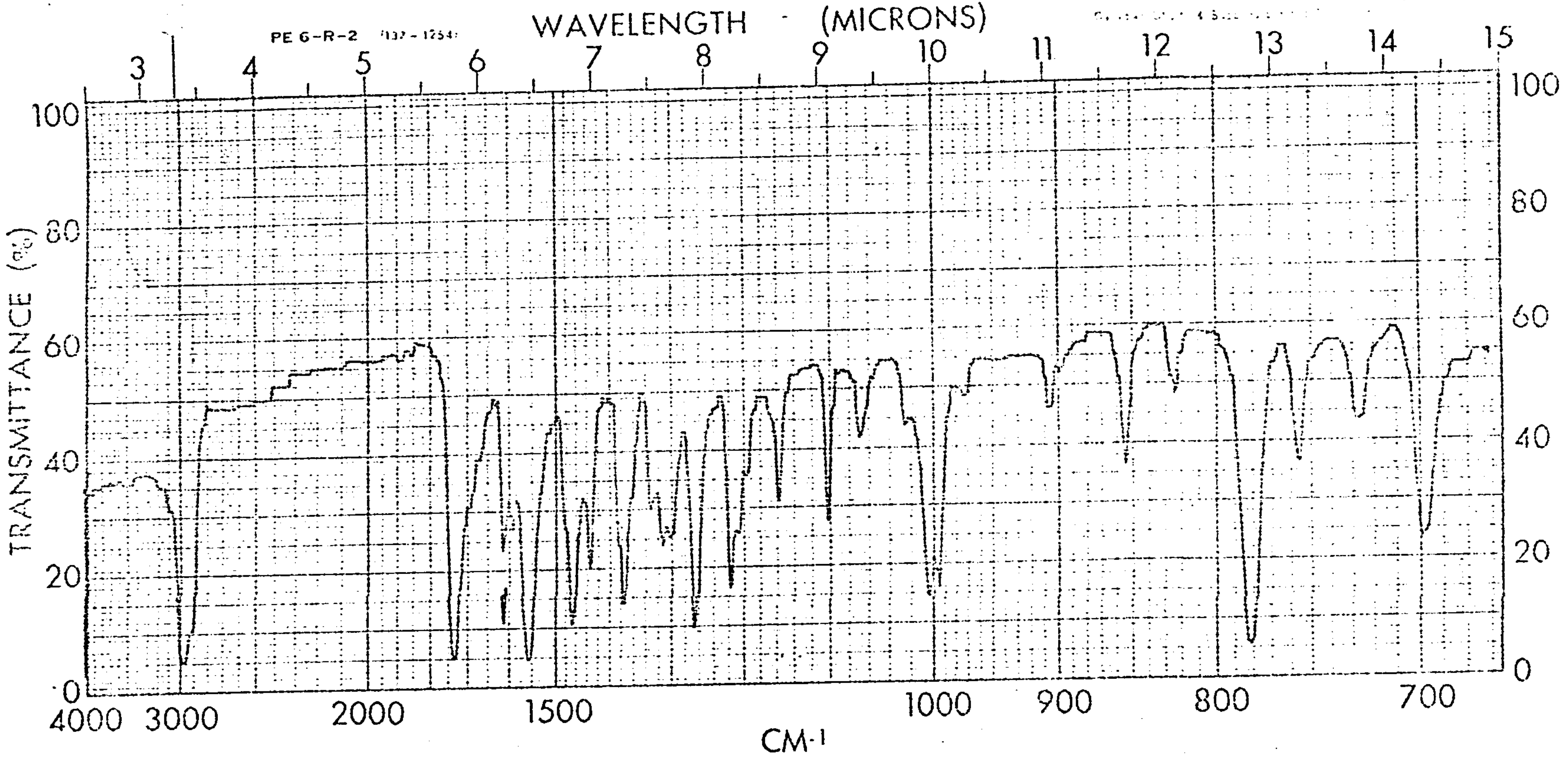


Fig. 7. I.R. Spectrum of 2-nitroindanone (II) in nujol.

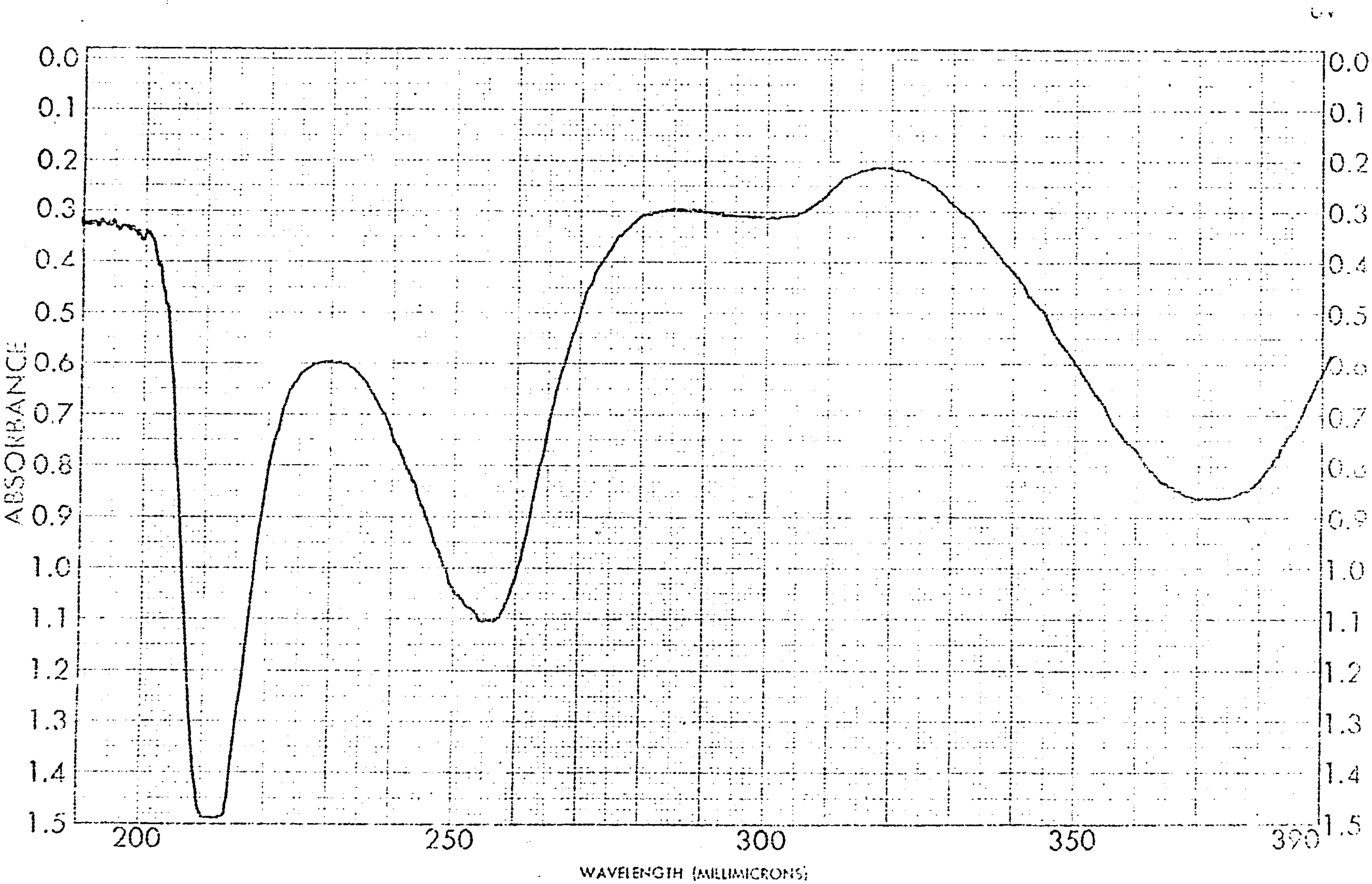


Fig. 8. U.V. Spectrum of 2-nitroindanone (II); 10^{-4}M solution in methanol.

colorless plates of m.p. 81°, showed infrared absorption at 1740 cm^{-1} for the carbonyl group and at 1550 cm^{-1} for the nitro group, and gave an ultraviolet absorption maximum at 373 mμ (ε = 8600 in methanol). Elemental analysis and mass spectrum were in agreement with the expected composition, $C_9H_7NO_3$. A nuclear magnetic resonance spectrum taken in deuterochloroform revealed an intensity ratio of 4:2 for the signal assigned to the aromatic protons (multiplet centred at 2.32 τ) and that of the benzylic protons (quartet at 6.2 τ). A quartet at 4.49 τ corresponded to the proton on the carbon bearing the nitro group. Its intensity was, however, 25% less than calculated for one proton. This can be explained by a partial enolization of the tertiary proton. In fact, the signal largely disappeared when the solution was shaken briefly with deuterium oxide.

Mass Spectral Studies of the Nitro Compounds

Mass spectra of compounds II, XXIX, XXIXa and XXXVII were taken as a matter of general interest. The fragmentation patterns were examined in order to see whether they could be rationalized in terms of the proposed structures. Unfortunately, no useful metastable peaks were found that would have established definitively some of the fragmentation reactions. It is, therefore, admitted that the reaction schemes given in the following charts have to be tentative. With this understanding, however, reasonable assumptions can be made that explain most of the more significant peaks. Those peaks in the spectra which relate to specific structures in the reaction schemes have been marked by their m/e figures. The peaks not so marked are not discussed. In the reproduction of the spectra, peaks of an intensity smaller than 5% of the base peak are omitted. No attempts were made to discuss the low-molecular fragments below approximately 100 mass units.

The fragments that give rise to spectral lines are ions or radical ions. Since the locations of their charges and unpaired electrons are in most instances difficult to pinpoint (if indeed they are fixed), they are not indicated in the charts. The device of enclosing the structures in brackets and denoting ionic and radical states without reference to specific atoms has been omitted for simplicity.

Mass spectrum of 2-(1, 3-dinitro-2-propyl)benzoic acid (XXIX) (Fig. 9 and Chart 1)

2-(1, 3-Dinitro-2-propyl)benzoic acid (XXIX) does not give the molecular ion peak in the mass spectrum. The highest peak, which is of very weak intensity, is observed at 208 m/e (a). This corresponds to a loss of 46 mass units (NO_2). Cyclisation of a with elimination of water leads to the fragment b (m/e 190), which, after loss of a hydrogen atom, rearranges to c (m/e 189). The latter can lose nitric oxide to give d (m/e 159), which breaks down further into e (m/e 131), and f (m/e 103)by a twofold loss of carbon monoxide.

The fragment b also gives rise to a species g (m/e 173) by the loss of hydroxyl.

The intense peak at m/e 161 (i) is derived by the loss of nitrous acid from fragment a. Decarboxylation of fragment i and then loss of a molecule of hydrogen leads to the fragment k (m/e 115) which may in an alternate way arise by dehydration of i followed by loss of carbon monoxide.

The fragment e (m/e 131) may also be arrived at through intermediate i by loss of methylene and oxygen.

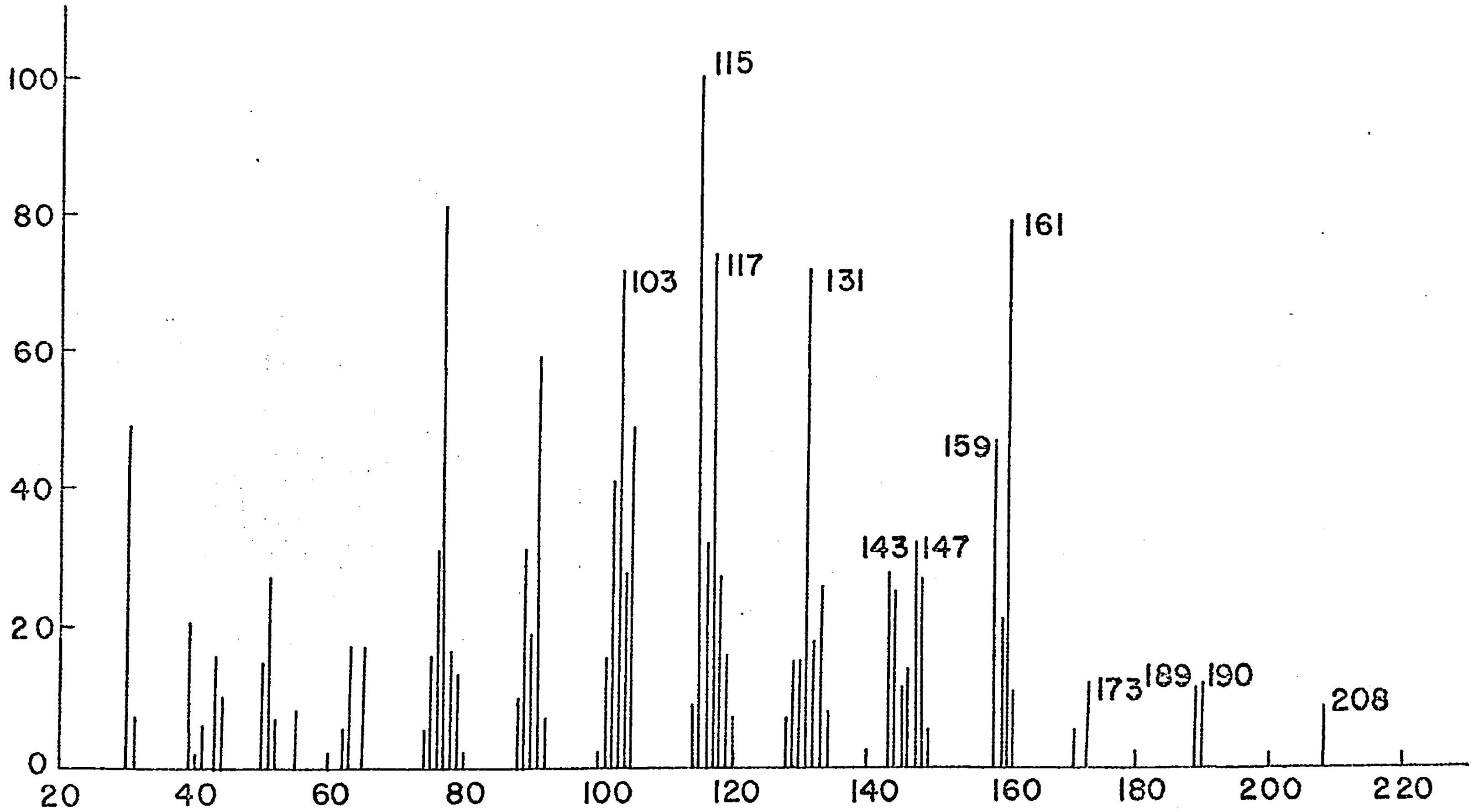


Fig. 9. Mass spectrum of 2-(1,3-dinitro-2-propyl)benzoic acid (XXIX).

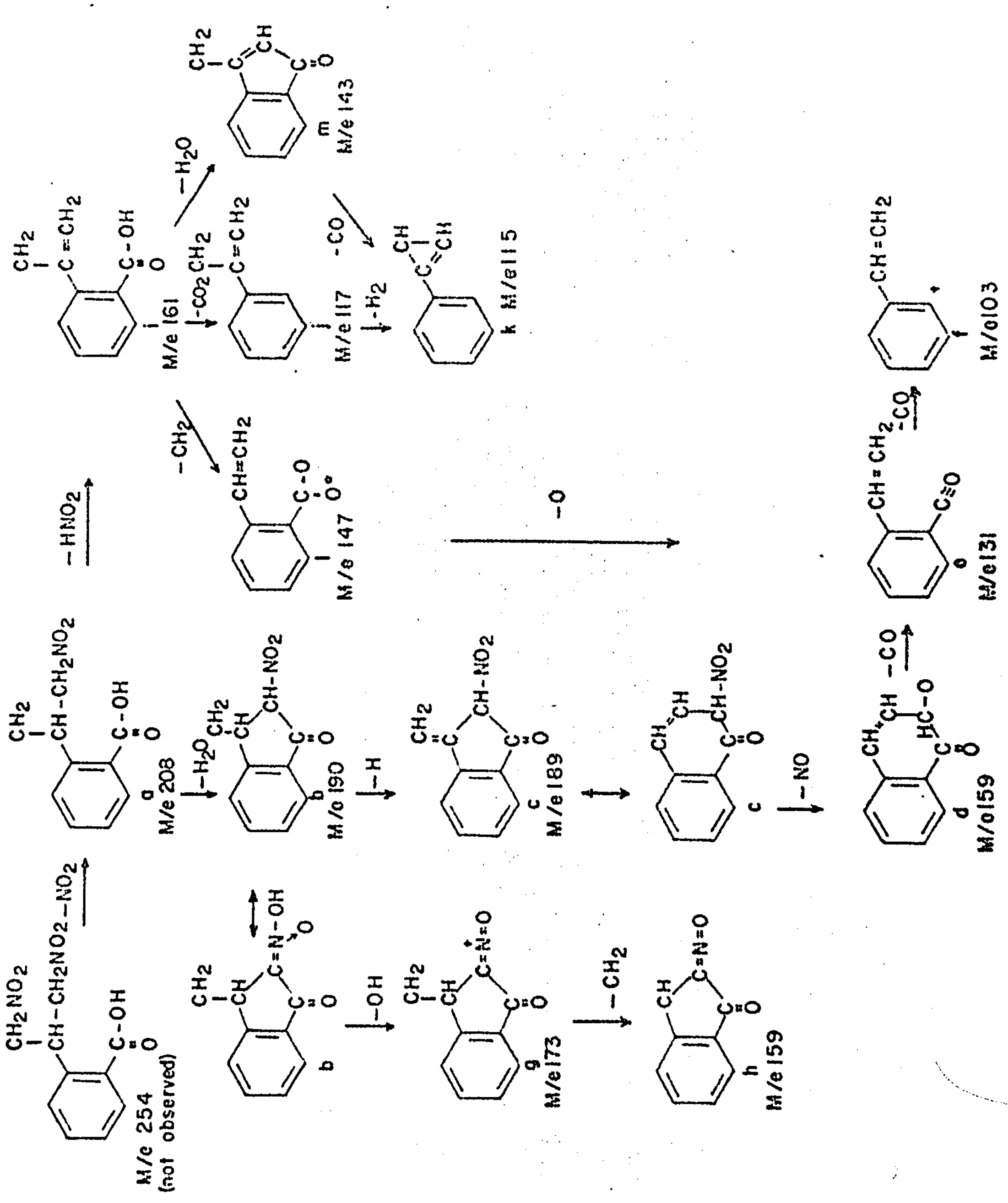


Chart 1. Fragmentation pattern of 2-(1, 3-dinitro-2-propyl)benzoic acid (XXIX)

Mass spectrum of methyl 2-(1, 3-dinitro-2-propyl)benzoate (XXIXa)

(Fig. 10 and Chart 2).

The molecular ion peak expected at 268 m/e (a) is not observed. Instead, the ester exhibits a peak at 237 m/e (b) of medium intensity, corresponding to the loss of the methoxyl group. The fragment b eliminates nitrous acid to give an intense peak at 190 m/e (c). The ester molecule, in an alternate degradation, loses a nitro group to give a peak of strong intensity at 222 m/e (d). The species d may further fragment to f (175 m/e), or e (176 m/e) by the loss of nitrous acid, or a nitro group, respectively. The absence of the peak at 173 m/e suggests that the decomposition should not occur via the cyclic species as in fragment b in the acid.

The intermediate f further breaks down to give a peak at 161 m/e.

The fragments n (m/e 144) and m, (m/e 143) are also derived from the intermediate f. The rest of the pattern is similar to that described for the acid.

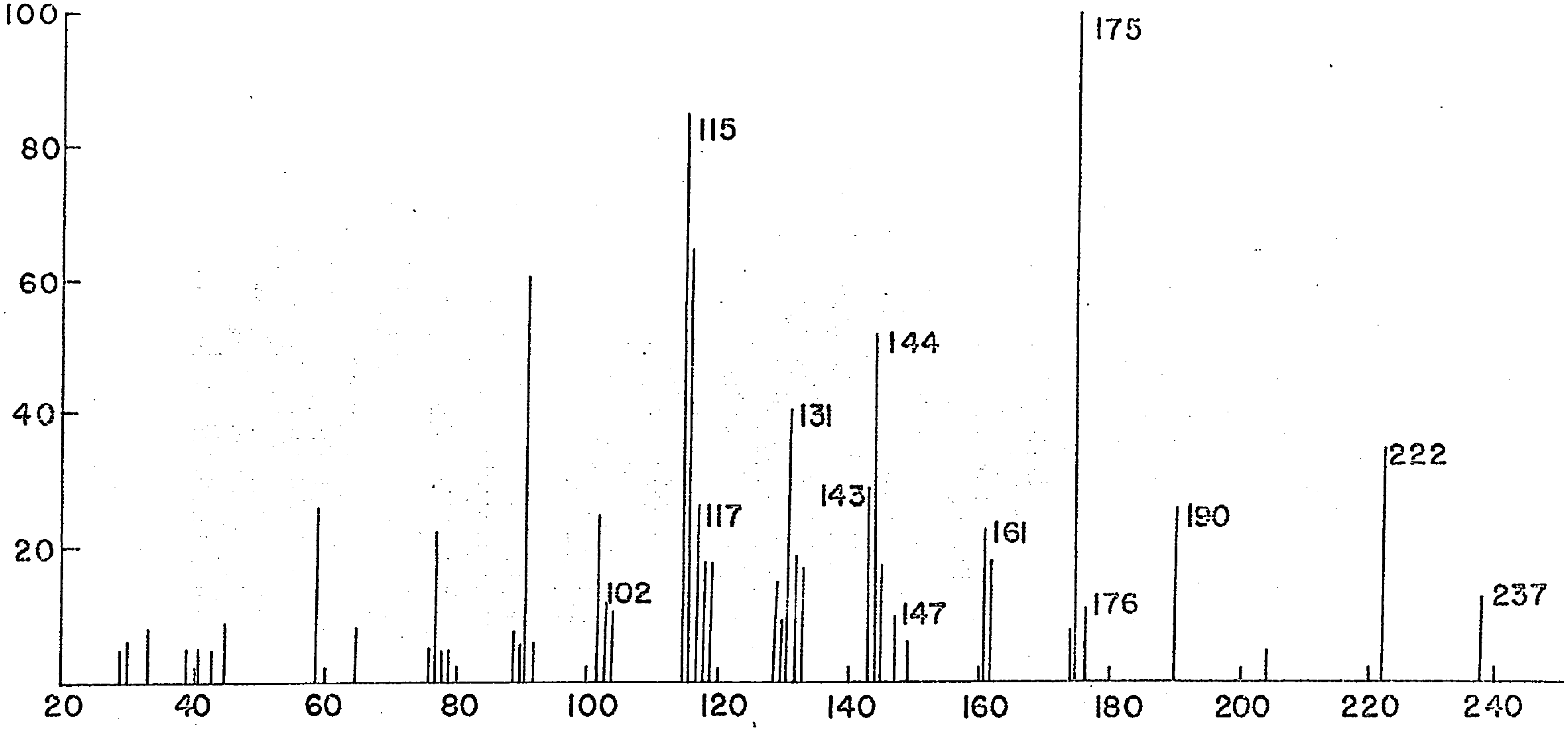


Fig. 10. Mass spectrum of methyl 2-(1, 3-dinitro-2-propyl)benzoate (XXIXa)

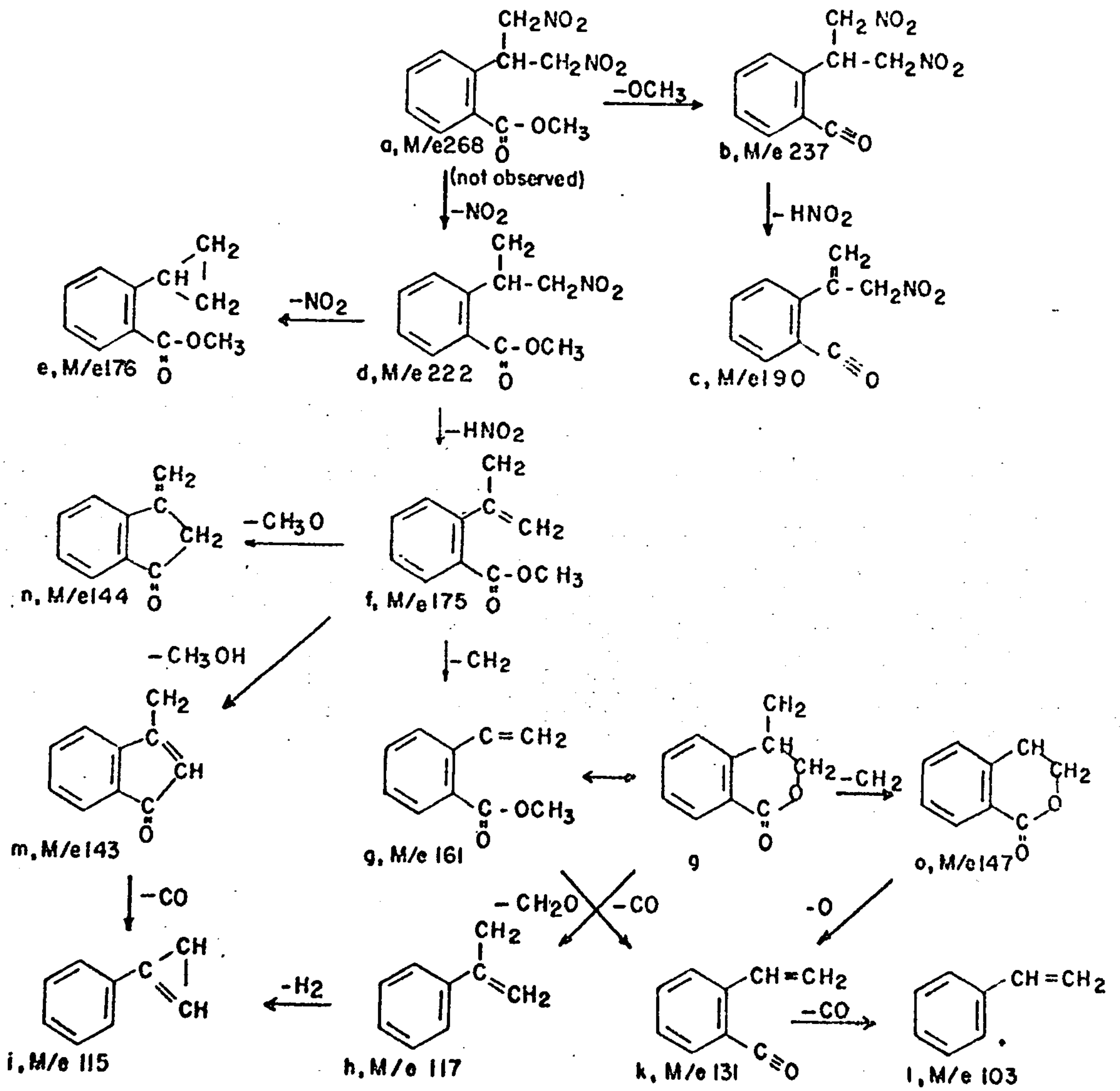


Chart 2. Fragmentation pattern of methyl 2-(1,3-dinitro-2-propyl)benzoate (XXIXa)

Mass spectrum of 3-nitromethyl-2-nitroindanone (XXXVII)

(Fig. 11 and Chart 3)

In contrast to the two preceding compounds, 3-nitromethyl-2-nitroindanone shows the molecular ion peak, which occurs with weak intensity at 236 m/e (a). In that regard the compound behaves in the same manner as 2-nitroindanone. Fragmentation appears to occur along three different routes. Loss of oxygen from the molecular ion leads to a fragment b (m/e 220) which then eliminates nitric oxide to give c (m/e 190). The fragment b also eliminates nitrous acid to give the species d (m/e 173) of very strong intensity. Decomposition of the molecular ion a by way of losing a nitro group or nitrous acid results in the formation of c (m/e 190) or f (m/e 189), respectively. The intermediate f can lose nitric oxide to give the fragment g (m/e 159) which further breaks down into the species i (m/e 131).

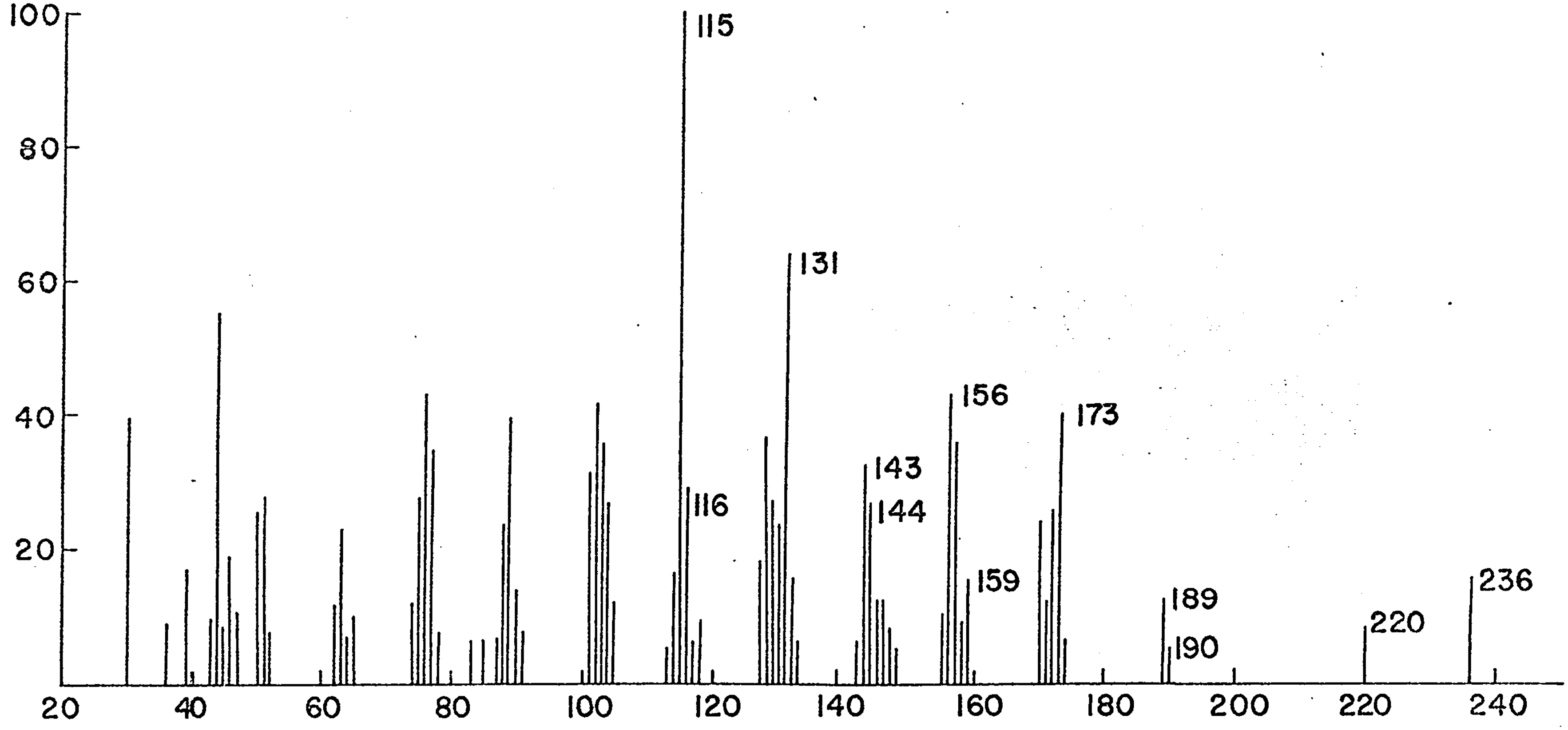


Fig.,11. Mass spectrum of 3-nitromethyl-2-nitroindanone (XXXVII).
(Molecular ion peak at m/e 237 increased by a factor of 10).

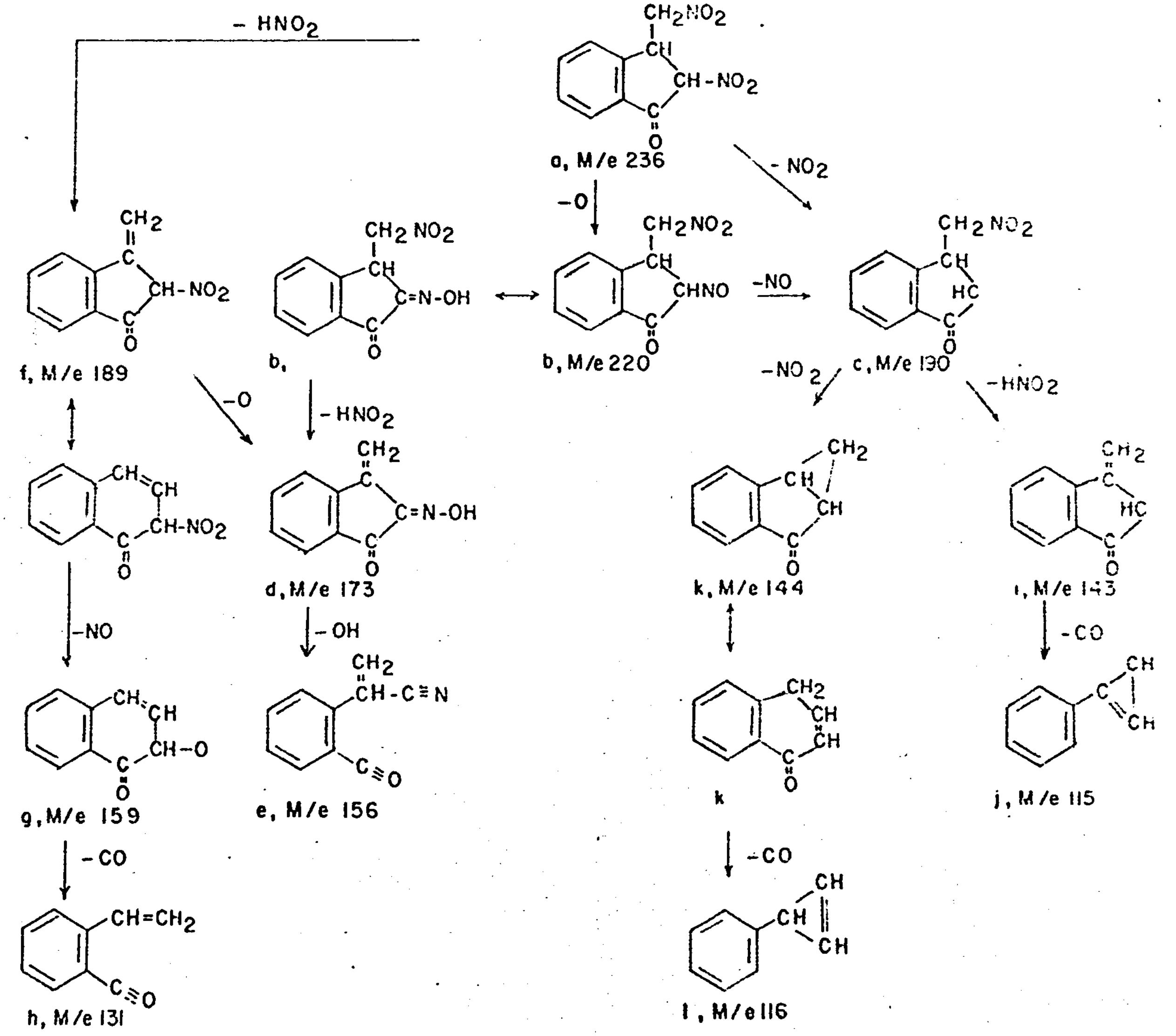


Chart 3. Fragmentation pattern of 3-nitromethyl-2-nitroindanone (XXXVII)

Mass spectrum of 2-nitroindanone (II)

(Fig. 12 and Chart 4)

The mass spectrum of II exhibits the molecular ion peak a at 177 m/e. Fragmentation appears to occur by three different routes as shown in the chart. Loss of oxygen leads to b (161 m/e) which, after isomerizing to the oxime, undergoes α-cleavage to form the fragment c, m/e 144. The latter loses carbon monoxide to give the ion d (m/e 116). The fragment e (131 m/e) seems to be derived either directly from the molecular ion a by the loss of the nitro group, or from the intermediate b. It loses either acetylene or carbon monoxide to give g (m/e 103) or f (m/e 105). The molecular ion is also found to form a fragment of 130 m/e (h) by the loss of nitrous acid. Fragment h decomposes to i (m/e 104).

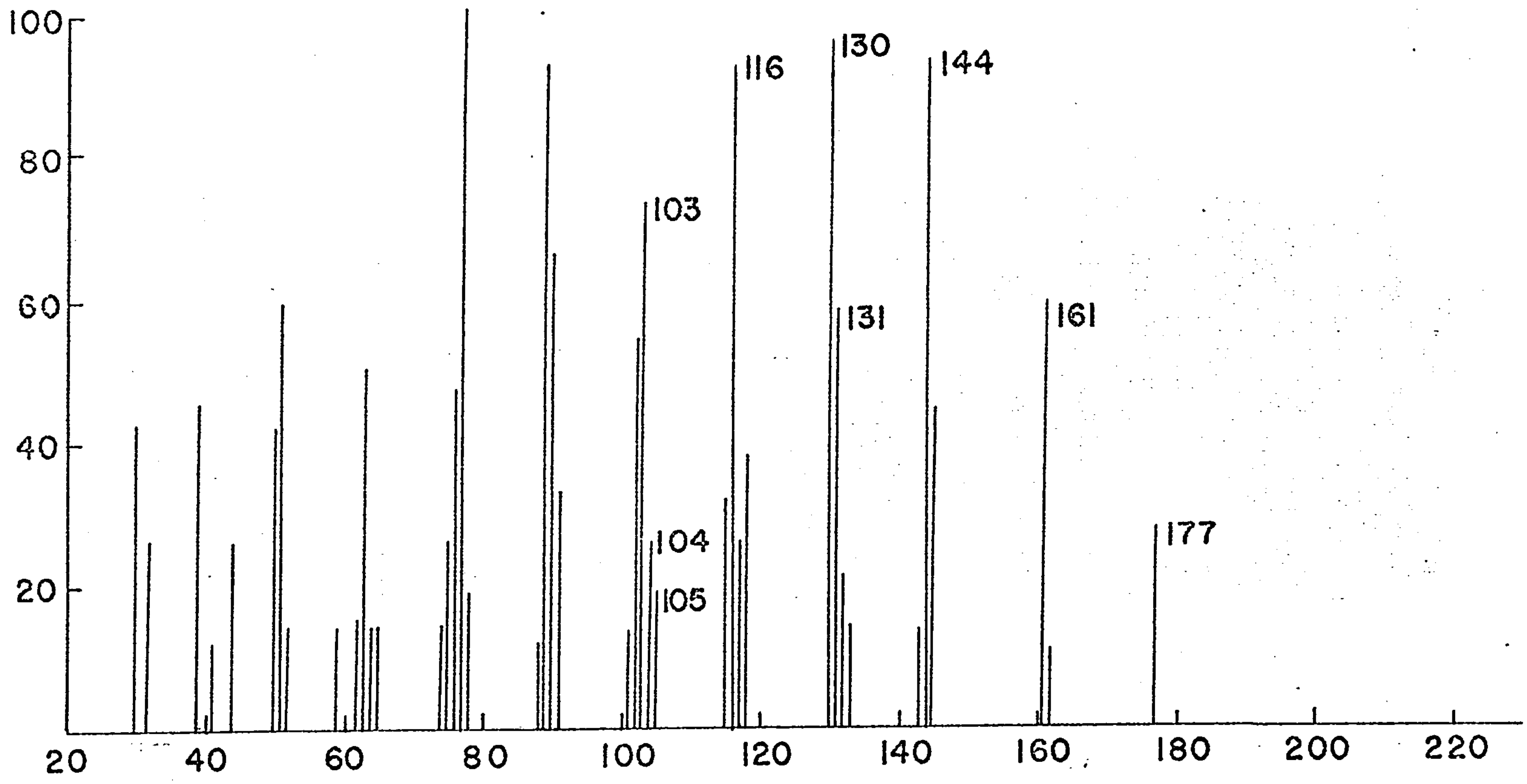


Fig. 12. Mass spectrum of 2-nitroindanone (II).

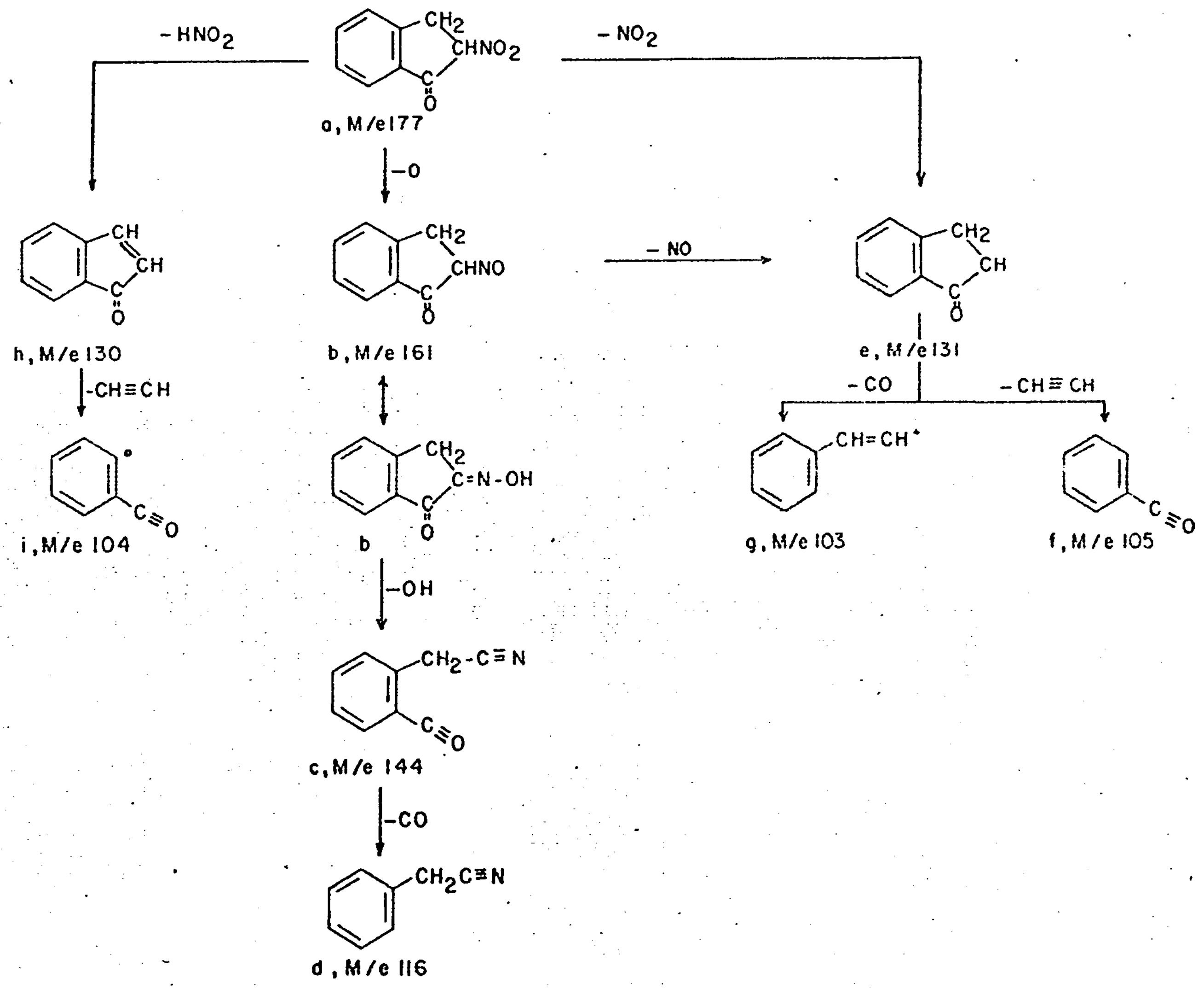
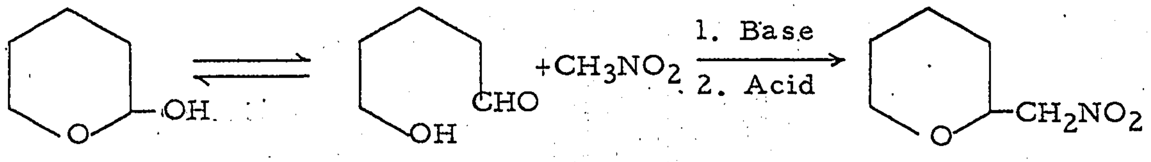


Chart 4. Fragmentation pattern of 2-nitroindanone (II).

ADDENDUM

Investigation concerning the Reaction of Nitromethane with 5-Hydroxypentanal

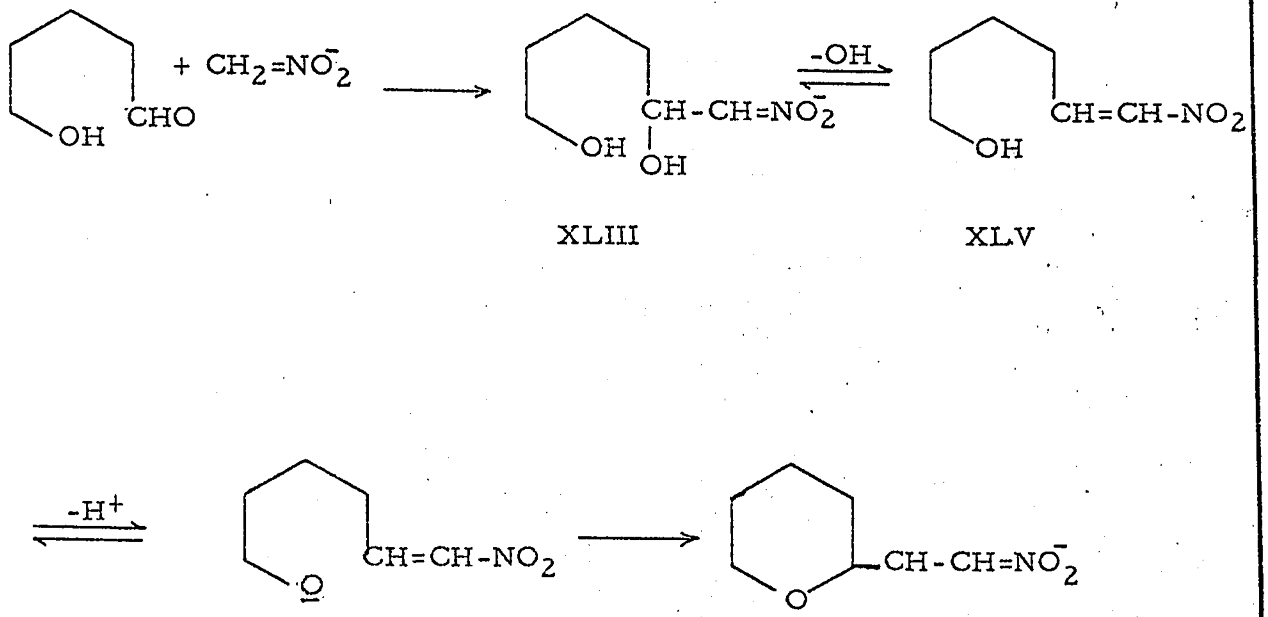
J. Cologne and P. Corbet reported the synthesis of 2-nitromethyltetrahydropyran (110) by base-catalysed condensation of nitromethane with 5-hydroxypentanal, the latter having been obtained by acid hydrolysis of dihydropyran. The nitro compound was isolated by steam distillation of the acidified reaction mixture.



XLII

The authors did not comment on the mechanism of formation of the ether (XLII). One may envision formation of XLII at three stages of the operation:

a. In the alkaline medium of the nitromethane condensation according to the following scheme:

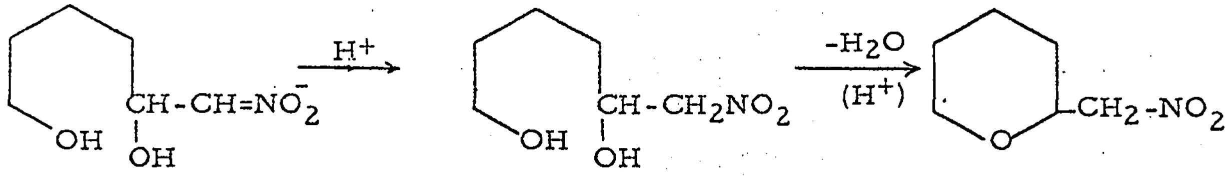


XLIII

XLV

XLII (as nitronate)

b. Immediately upon acidification of the normal nitromethane condensation product, the 2,6-dihydroxyhexanenitronate (XLIII), if the liberated 2,6-dihydroxy-1-nitrohexane (XLIV) were capable of rapid, acid-catalysed internal etherification in the cold:



XLIII XLIV XLII

c. During the steam distillation of the acidified reaction medium.

A study of this reaction was of interest because it represents a model for the internal anhydride formation observed in certain 1-deoxy-1-nitro-hexitols. Such nitro sugar polyols on week-long standing in alkaline medium form cyclic anhydrides, but careful acidification after a relatively short exposure to alkali regenerates the open-chain nitropolyols. The latter are fairly stable in neutral and weakly acidic aqueous media in the cold, but are cyclized to 2,6-anhydrides at reflux temperatures (111, 112, 113). For a future determination of the effect that varying numbers and sites of hydroxyl substituents may have on such carbohydrate reactions, the above model reaction will have to be studied in detail. For the present thesis, only a preliminary investigation was undertaken to establish the existence of XLIV in the acidified nitromethane condensation mixture and to confirm the conversion of XLIV into XLII at elevated temperature. In addition, the synthesis of the nitroolefinic alcohol XLV was attempted.

Equimolar quantities of 5-hydroxypentanal and nitromethane were condensed in the presence of aqueous sodium hydroxide at 0^{o}. After a reaction time of four hours, the solution was neutralized either by the addition of hydrochloric acid or by cation-exchange. A brown syrup was isolated; it was readily soluble in water, and its infrared spectrum indicated the presence of hydroxyl (3350 cm^{-1}, broad band) and nitro groups (1550 cm^{-1}). These properties suggested the syrup to consist largely of XLIV, rather than XLII (which is water-insoluble). When the product was distilled in vacuo at $115\text{-}117^{0}/21$ mm., XLII was obtained as a colorless liquid, identified by its boiling point, refractive index and absence of an OH-band in its infrared spectrum.

Since the purification of the presumed dihydroxy compound XLIV proved difficult, the crude material was acetylated with acetic anhydride in the presence of boron trifluoride-ethereate. Unfortunately, the acetylated product did not crystallise either, but the success of the acetylation was corroborated by the absence of hydroxyl absorption and the presence of the expected carbonyl (1735 cm^{-1}) and nitroalkane (1555 cm^{-1}) bands in the infrared.

Presuming the acetylated material to represent the diacetate of XLIV, its dehydroacetylation to the acetate of XLV was attempted. Pyrolysis in the presence of sodium acetate (114, 115, 116) led to polymeric material, but refluxing in benzene solution in the presence of sodium bicarbonate (59), did seem to produce nitroolefin, as evidenced by a gradual diminution of the nitroalkane peak (1555 cm^{-1}) with concomitant appearance of peaks at 1648 cm^{-1} (C = C) and 1525 cm^{-1} (nitroalkene). However, the nitroalkane band did not disappear completely, and as the reaction continued it grew in intensity again and, at the same time, the new peaks attributed to nitroolefin diminished. This tends to indicate that the nitroolefin produced is rather unstable and suffers changes under the condition of its formation, perhaps in the nature of polymerizations or Michael additions.

EXPERIMENTAL

Methyl 2-(1-methoxy-2-nitroethyl)benzoate (XVII)

2-(1-Methoxy-2-nitroethyl)benzoic acid (0.8 g., 3.5 m mole) is dissolved in ether (75 ml), and a solution of diazomethane in ether is added until the yellow color persists. After being kept in the refrigerator for one hour, the solution is evaporated to dryness and the solid residue obtained is crystallized from methanol. The yield of the methyl ester, m.p. 98° (colorless plates), is 0.602 g. (71%).

Analysis:

$C_{11}H_{13}NO_5$ (mol. wt. 239.23)

Calculated: C, 55.24; H, 5.48; N, 5.85.

Found: C, 55.31; H, 5.46; N, 5.98.

The ester exhibits infrared bands at 1720 cm^{-1} (aromatic ester carbonyl) and 1560 cm^{-1} (nitroalkane).

Cyclisation of methyl 2-(1-methoxy-2-nitroethyl)benzoate in the presence of sodium methoxide. 3-Methoxy-2-nitro-2-(2-nitroindanone-3-yl)-indanone (XX)

Methyl 2-(1-methoxy-2-nitroethyl)benzoate (1.195 g., 5 m mole) is dissolved in methanol (100 ml) and a solution of sodium methoxide (0.444 g., 7.5 m mole) in methanol (10 ml) is added over a period of half an hour. The solution is allowed to stand at room temperature for eight hours and is then deionised with ion-exchange resin, Rexyn 50 (H^+). Evaporation of the solvent leaves a solid which, on crystallisation from methanol, gives colorless prisms of m.p. 164° (0.475 g.).

Analysis:

$C_{19}H_{14}N_2O_7$ (mol. wt. 382.3)

Calculated: C, 59.69; H, 3.66; N, 7.3; OCH_3, 8.0.

Found: C, 59.56; H, 3.97; N, 7.5; OCH_3, 9.20.

The product shows absorption in the infrared at 1750 cm^{-1} (CO) and 1550 cm^{-1} (nitro groups), and it has an absorption maximum at 372 mμ (ε = 8300 in methanol) in the ultraviolet spectrum.

The mass spectrum does not show the molecular ion peak; an intense peak at 336 m/e corresponding to the loss of one nitro group is observed.

Methyl o-phthalaldehydate (XXII)

o-Phthalaldehydic acid (15.0 g., 0.1 mole) is dissolved in water (100 ml) by warming. The solution is cooled to room temperature and a solution of potassium carbonate (6.91 g., 0.05 mole) in water (15 ml) is added gradually. The filtered solution is heated to about 70° and a hot solution of silver nitrate (17.88 g., 0.105 mole) in water (25 ml) is added all at once, with vigorous stirring, whereby the white silver salt of o-phthalaldehydic acid precipitates. The beaker is covered to prevent exposure to light, and the mixture is allowed to cool. The precipitate is filtered, washed with water and then alcohol and dried at 80-90°. The dry silver salt is boiled under reflux with ether (200 ml) and methyl iodide (21.4 g., 0.177 mole) for two hours. After cooling, the silver iodide is filtered off and washed thoroughly with ether, and the ether solution is dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gives a pale yellow liquid which is distilled at 13 mm. o-Phthalaldehydic acid methyl ester boiling at 136-138° is collected in a yield of 12.9 g. (78.6%). [Boiling points reported in the literature: 136-138° (13 mm), 146-147° (17 mm) (101, 102)]. The infrared spectrum exhibits strong absorption bands at 1695 cm^{-1} (aromatic CHO), 1720 cm^{-1} (aromatic ester) and a weak band at 1770 cm^{-1} (α, β-unsaturated γ-lactone due to the presence of a small amount of γ-ester).

Reaction of nitromethane with methyl o-phthalaldehydate in the presence of ammonium acetate and acetic acid. 2-(1-Amino-2-nitroethyl)benzoic acid lactam (XXV)

A mixture of methyl o-phthalaldehydate (0.75 g), nitromethane (0.75 ml), ammonium acetate (0.3 g) and acetic acid (3 ml) is refluxed for two hours. The pale yellow solution is cooled and then poured over crushed ice. The aqueous mixture is extracted with chloroform (25 ml). The chloroform extract is washed twice with water and dried over anhydrous sodium sulfate. The solvent is evaporated to give a semi-solid product. Upon trituration with ethyl acetate (2 ml) a crude product (0.102 g) of m.p. 175-185° is isolated. Recrystallisation from ethyl acetate gives colorless needles (78 mg) of the lactam, melting at 193°.

Analysis:

$C_9H_8N_2O_3$ (mol. wt. 192.1)

Calculated: C, 56.25; H, 4.16; N, 14.57.

Found: C, 56.22; H, 3.94; N, 14.82.

Characteristic infrared bands in nujol are at 3255 cm^{-1} (N-H), 1720 cm^{-1} (amide-I) and 1550 (NO_2). (A dilute solution in chloroform exhibited the carbonyl band at 1710 cm^{-1}).

Reaction of nitromethane with methyl o-phthalaldehydate in the presence of sodium acetate and acetic acid.
3, 3'-Diphthalidylnitromethane (XXVII)

Methyl o-phthalaldehydate (0.75 g), nitromethane (0.75 ml), sodium acetate (0.3 g) and acetic acid (3 ml) are refluxed for two hours. Removal of the solvent by evaporation in vacuo gives a yellow solid which is partially dissolved in dry benzene. The filtered benzene solution is concentrated and a few drops of petroleum ether (b.p. 30-60°) are added. On allowing the solution to stand for a few hours, colorless crystals (75 mg, m.p. 175-190°) are deposited. Recrystallisation from acetonitrile raised the melting point to 226°. The infrared and ultraviolet spectra of the compound are identical with those of the product obtained in the next experiment.

Reaction of nitromethane with methyl o-phthalaldehydate in the presence of trimethylamine.
3, 3'-Diphthalidylnitromethane (XXVII)

A solution of methyl o-phthalaldehydate (4.92 g, 0.03 mole) and nitromethane (2.8 g, 0.046 mole) in methanol (50 ml) is cooled in an ice water bath, and a 5% solution of trimethylamine in methanol (30 ml) is added dropwise with stirring in the course of 30 minutes. The mixture is then stirred for five hours at room temperature, cooled again to 0° and neutralised with cold N hydrochloric acid to about pH 4. Most of the methanol is removed by evaporation, and the remaining, largely aqueous solution, is extracted with ether (100 ml). The ether solution is washed twice with water, dried over anhydrous sodium sulfate and evaporated to leave a yellow oil which on distillation at 20 mm gives 3.6 g of unreacted starting ester, b.p. 150-151°. The residue in the distilling flask is treated with benzene (2 ml) and a few drops of petroleum ether (b.p. 30-60°) which causes colorless crystals (250 mg) of m.p. 175-185° to be deposited within a few hours. Recrystallisation from acetonitrile gives 125 mg of colorless prisms melting at 230°.

Analysis:

$C_{17}H_{11}NO_6$ (mol. wt. 325.2)

Calculated: C, 62.77; H, 3.38; N, 4.3

Found: C, 62.88; H, 3.28; N, 4.41.

The mass spectrum shows a molecular ion peak at m/e 325. The product exhibits infrared absorption at 1760 cm^{-1} (α,β-unsaturated γ-lactone) and 1560 cm^{-1} (nitroalkane), and in methanol solution it shows ultraviolet maxima at 276 mμ ($\varepsilon = 5300$) and at 283 mμ ($\varepsilon = 5200$).

Attempted condensations of nitromethane with methyl o-phthalaldehydate in the presence of various other catalysts.

Dimethylamine: Methyl o-phthalaldehydate (0.4 g, 2.4 m mole) and nitromethane (0.22 g, 3.6 m mole) are dissolved in methanol (5 ml), and dimethylamine (2.5 ml of a 5% solution in methanol) is added slowly with stirring. The mixture is stirred at room temperature for seven hours. On evaporating the solvent and the dimethylamine, a syrup is obtained which exhibits ultraviolet absorption with a maximum at 370 mμ. The syrup is dissolved in benzene (2 ml) and the solution is stored at room temperature. A yellow solid is deposited and is isolated; it melted at 120-125°. Its ultraviolet and infrared spectra are identical with those of 3-phthalidylnitromethane. The filtrate from this material contains the species absorbing in the 370 mμ region. In an attempt to isolate this compound, its solution was evaporated to a syrup which was chromatographed on a thin layer plate of silica gel with a solvent mixture of n-heptane and methyl ethyl ketone in a ratio of 1:4 (v/v). The forerun did not show any absorption in the 300-390 mμ region. The slowest-moving band gave a small amount of a yellow solid that did show the 370 mμ absorption. However, the material, which decomposed on heating above 250°, was not obtained in crystalline form and could not be properly characterized.

In a repetition of the experiment, a shorter reaction time (3.5 hrs.) was employed. The syrupy reaction product, which again exhibited ultraviolet absorption at 370 mμ, was subjected to vacuum distillation at 0.5 mm. At an oil-bath temperature of 120-150° a white sublimate appeared which was identified as 3-phthalidylnitromethane, (m.p. 125°, λ_{max} 276, 283 mμ). The species which absorbs at 370 mμ could not be distilled and apparently decomposed.

<u>Piperidine</u>: Methyl-o-phthalaldehydate (0.164 g, 1 m mole), nitromethane (0.075 g, 1.2 m mole) are dissolved in benzene (10 ml), and piperidine (0.085 g., 1 m mole) is added dropwise with stirring. The mixture is stirred at room temperature for 22 hours and then acidified by shaking with N hydrochloric acid. The benzene layer is separated, dried over anhydrous sodium sulfate and evaporated to give a yellow syrup that shows no absorption in the 300-390 mμ region. On distilling the syrup at 18 mm, the starting ester (0.1 g) is recovered. The dark brown distillation residue was not investigated further.

<u>Pyridine</u>: A mixture of methyl o-phthalaldehydate (0.4 g, 2.4 m mole) and nitromethane (0.15 g, 2.4 m mole) is cooled to 0-5° and pyridine (0.15 ml) is added dropwise with stirring. The mixture is allowed to come to room temperature and stirring is

continued for six hours. The solution is then cooled in ice water, acidified with cold N hydrochloric acid, and extracted with ether (25 ml). The ether extract is washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, a pale yellow liquid is obtained whose infrared spectrum shows no absorption for the nitro group and is identical with that of the starting ester.

Sodium methoxide: Methyl o-phthalaldehydate (0.82 g, 5 m mole) and nitromethane (0.35 g, 5.7 m mole) are dissolved in methanol (10 ml) and cooled to -5°. An ice-cold solution of sodium methoxide (0.64 g, 11 m mole) in methanol (5 ml) is added dropwise with stirring in the course of 90 minutes. The mixture is stirred in the ice-bath for another hour and is then deionized by the addition of a cooled slurry of ion-exchange resin, Rexyn 101 (H^+). The solution is filtered, and the filtrate, after removal of the methanol, leaves a yellow solid residue. The infrared spectrum shows absorption for the nitro group at 1550 cm^{-1} but no absorption in the ultraviolet range of 300-390 mμ is observed. Purification by crystallisation from various solvents could not be effected. The product is probably a polymer.

In a modification (47) of this procedure, nitromethane (0.183 g., 3 m mole) is added slowly to a well-stirred solution of sodium methoxide (0.170 g., 0.31 m mole) in methanol (1.7 ml). The precipitated sodium methane-nitronate is dissolved by the addition of excess methanol (3.3 ml). A mixture of methyl o-phthalaldehydate (0.541 g., 3.3 m mole) and sodium bisulfite (0.378 g., 3.6 m mole) in water (5 ml) is added gradually, with stirring, over a period of thirty minutes, and stirring is then continued for twenty four hours. The reaction mixture is then poured over ice and extracted with ether (50 ml.). The ether extract is washed twice with water (20 ml), dried over anhydrous sodium sulfate and evaporated to yield a syrup whose infrared spectrum shows a very weak absorption for the nitro group. No absorption is observed in the 300-390 mμ range in the ultraviolet.

Sodium bicarbonate: Methyl o-phthalaldehydate (0.8 g., 4.8 m mole), nitromethane (0.35 g., 5.7 m mole), sodium bicarbonate (0.4 g., 4.7 m mole) and dry benzene (25 ml) are stirred together for eight hours at room temperature. The mixture is filtered and the filtrate, on evaporation of the solvent, gives a liquid whose infrared spectrum is identical with that of the starting ester.

Reaction of nitromethane with methyl o-phthalaldehydate in the presence of benzyltrimethylammonium hydroxide ('Triton B'). 2-(1, 3-Dinitro-2-propyl)benzoic acid (XXIX)

A solution of methyl o-phthalaldehydate (2.46 g, 0.015 mole) in nitromethane (12.5 g, 0.2 mole) is added dropwise during a period of two hours to a stirred mixture of nitromethane (18.3 g, 0.3 mole) and Triton B (6 ml of 40% methanolic solution, technical grade) which is kept at 0 to -3°. When the addition is complete the mixture is stirred for another fifteen minutes and is then neutralised with cold N hydrochloric acid. The reaction mixture is extracted with ether (100 ml), and the ether extract is washed with water and dried over anhydrous sodium sulfate. By evaporating the ether and nitromethane under reduced pressure, a pale yellow semi-solid is obtained. The product is triturated with benzene (5 ml) and a solid (2.15 g) of m.p. 125-127° is isolated. After two crystallisations from benzene the colorless needles show m.p. 138-139° (1 g.). Another crop of crystals (0.245 g) melting at 132-134° is obtained from the mother liquor.

Analysis:

$C_{10}H_{10}N_2O_6$ (mol. wt. 254.18).

Calculated: C, 47.22; H, 3.94; N, 11.03.

Found: C, 47.44; H, 4.09; N, 10.82.

The product exhibits absorption in the infrared spectrum at 1680 cm^{-1} (aromatic carboxyl), 1560 cm^{-1} (nitroalkane), 1550 cm^{-1} (NO_2; shoulder) and a broad band at 3300-3000 cm^{-1} (OH).

Methyl 2-(1, 3-dinitro-2-propyl)benzoate (XXIXa)

2-(1, 3-Dinitro-2-propyl)benzoic acid (0.610 g, 2.4 m mole) is dissolved in ether (50 ml) and a solution of diazomethane in ether is added until a yellow color persists. The solution is allowed to stand in the refrigerator for one hour. Evaporation of the excess diazomethane and ether under reduced pressure leaves a solid which crystallises from methanol in colorless plates (0. 460 g), m.p. 90°.

Analysis:

$C_{11}H_{12}N_2O_6$ (mol. wt. 268.2).

Calculated: C, 49.26; H, 4.51; N, 10.44.

Found: C, 49.49; H, 4.7; N, 10.50.

Infrared spectrum: 1720 cm^{-1} (ester CO), 1570 cm^{-1} (NO_2) and 1560 cm^{-1} (NO_2 ; shoulder).

Isochromanone

Isochromanone was prepared by the oxidation of isochroman with selenium dioxide according to the method of J. Cologne and P. Boisde (105).

2-(2-Bromoethyl)benzoic acid (XXX)

2-(2-Bromoethyl)benzoic acid was prepared by the method of P. Maitte (106), with minor modifications.

A 30% solution of hydrogen bromide in acetic acid, which is commercially available, is saturated at 0° with hydrogen bromide gas. Isochromanone (10 g) is heated with 40 ml of the saturated hydrogen bromide solution in a sealed tube at 150° for three hours. After the reaction the tube is allowed to cool to room temperature and then chilled in dry ice before opening. Acetic acid and hydrogen bromide are removed by vacuum distillation and the residue is crystallised from carbon tetrachloride. The yield of 2-(2-bromoethyl)benzoic acid (m.p. 93°) is 11.7 g [Literature - m.p. 93.5° (106)].

Methyl 2-(2-bromoethyl)benzoate (XXXI)

2-(2-Bromoethyl)benzoic acid (3 g, 13 m mole) is dissolved in ether (75 ml), and a solution of diazomethane in ether is added until a pale yellow color persists. The solution is kept in the refrigerator for one hour. Upon removal of the solvent, a pale yellow liquid is obtained which is distilled at 0.8 mm. The product (2.6 g) distills over at 108-110° (bath-temperature 140-160°). Its infrared spectrum exhibits absorption at 1725 cm^{-1} for the aromatic ester carbonyl. This material was used for the next synthetic step.

However, a sample which was distilled three times for analysis showed data which very nearly corresponded to those calculated for isochromanone.

Analysis:

$C_{10}H_{11}BrO_2$ (mol. wt. 243.1).

Calculated: C, 49.40; H, 4.55; Br, 32.87.

Found: C, 73.34; H, 5.90; Br, 0.42

Analysis for isochromanone:

C, 72.97; H, 5.40

The infrared spectrum of the analytical sample was identical with that of isochromanone.

When the crude ester, whose methoxyl content was 12.5% (calculated, 13.3%), was distilled from a short neck bulb at 0.3 mm and a bath temperature of 95-110°, the pure ester was obtained which had an infrared spectrum quite different from that of isochromanone, especially in the region from 1400 cm^{-1} to 750 cm^{-1}. The nuclear magnetic resonance spectrum did not show the signals attributed to the aliphatic protons in the isochromanone.

Reaction of sodium nitrite with impure methyl 2-(2-bromoethyl)benzoate in dimethylsulfoxide

Impure methyl 2-(2-bromoethyl)benzoate (distilled once at 0.8 mm) (2.2 g, 9 m mole) is stirred with sodium nitrite (1.1 g, 16 m mole), phloroglucinol (0.5 g) and dimethylsulfoxide (5 ml) at room temperature for eight hours. The solution is poured over crushed ice, and the mixture is extracted with ether (100 ml). The aqueous layer is extracted again with two 20 ml portions of ether. The combined ether extracts are washed with water, dried over anhydrous sodium sulfate and evaporated to leave a brown liquid which is distilled at 0.5 mm. A product (1 g.) with a boiling range of 112-117° is obtained, whose infrared spectrum showed bands at 1720 cm^{-1} (aromatic ester carbonyl) and 1550 cm^{-1} (nitroalkane).

Thin layer chromatography of the product on silica gel using a solvent mixture of chloroform, cyclohexane and acetone (5:3:0.5, v/v) shows two major spots very close to each other. Attempts to obtain a better separation by varying the solvent composition were unsuccessful. A preparative thin-layer separation using the above solvent system was then tried. The band containing the migrated substances was divided into a lower and an upper part which were individually eluted with chloroform. On evaporation, the eluate from the lower part left a small amount of a liquid whose infrared spectrum was completely identical with that of isochromanone. From the upper part a liquid was obtained whose infrared spectrum showed a nitro band at 1555 cm^{-1}. However, the liquid did not give a clear single spot on rechromatography and therefore appeared to be a mixture. The nitro compound contained in it was presumed to be methyl 2-(2-nitroethyl)benzoate.

Substitution of dimethylformamide for dimethylsulfoxide in the reaction just described did not lead to the desired conversion of the bromo into the nitro ester. Treatment of the bromo ester (0.243 g.) with silver nitrite (0.2 g) in ether (15 ml) for eight days at room temperature resulted in the recovery of the starting material only.

Methyl 2-(2-nitroethyl)benzoate (XXXIV)

Pure methyl 2-(2-bromoethyl)benzoate (0.71 g, 2.9 m mole) is stirred with sodium nitrite (0.350 g, 5.1 m mole) phloroglucinol (0.166 g) and dimethylsulfoxide (3 ml) at room temperature for eight hours. The solution is poured over crushed ice, and the precipitated solid material (0.375 g) is collected. The crude nitro ester melts at 45-48°. Crystallisation from methanol gives colorless rods, m.p. 55-56°. The product shows infrared absorption at 1720 cm^{-1} (aromatic ester carbonyl) and 1550 cm^{-1} (nitro group).

Analysis:

$C_{10}H_{11}NO_4$ (mol. wt. 209.18).

Calculated: C, 57.41; H, 5.29; N, 6.69.

Found: C, 57.19; H, 4.8; N, 6.3.

Reaction of sodium nitrite with 2-(2-bromoethyl)-benzoic acid

2-(2-Bromoethyl)benzoic acid (0.458 g, 2 m mole) is stirred with sodium nitrite (0.208 g, 3 m mole), urea (0.25 g) and dimethylsulfoxide (5 ml) for eight hours at room temperature. The mixture is poured over ice and immediately extracted with ether (50 ml). The ethereal layer is washed with water twice and then dried over anhydrous sodium sulfate. After removal of the solvent a brown liquid is obtained, whose infrared spectrum is completely identical with that of isochromanone.

Phenyl 2-(2-bromoethyl)benzoate (XXXV)

2-(2-Bromoethyl)benzoic acid (0.508 g) is refluxed with thionyl chloride (2ml) for one hour. The excess thionyl chloride is removed by distillation and the organic acid chloride is taken up in pyridine (5 ml). Phenol (0.209 g) is added, whereby heat is evolved and a crystalline substance (pyridinium salt) is deposited. The mixture is allowed to stand at room temperature for one to two hours and is then filtered. The filtrate, after removal of the pyridine in vacuo, leaves a solid which, on crystallisation from ethyl alcohol, gives colorless, hexagonal plates of the phenyl ester, m.p. 84°. The yield is 0.4 g.

Analysis:

$C_{15}H_{13}BrO_2$ (mol. wt. 305.18).

Calculated: C, 59.00; H, 4.29; Br, 26.17.

Found: C, 59.23; H, 4.16; Br, 26.06.

The infrared spectrum of the product exhibits absorption at 1730 cm^{-1} (ester CO).

Phenyl 2-(2-nitroethyl)benzoate (XXXVI)

Phenyl 2-(2-bromoethyl)benzoate (0.305 g) is stirred with sodium nitrite (0.11 g) and dimethylsulfoxide (5 ml) for four hours at room temperature. The mixture is poured over crushed ice, and the product is immediately extracted with ether (50 ml). The aqueous layer is extracted twice more with ether (20 ml). The combined ether extracts are washed twice with water, dried over anhydrous sodium sulfate and evaporated to give a colored solid (155 mg) which crystallises from ethyl alcohol as colorless prisms, m.p. 71°. The product exhibits infrared absorptions at 1730 cm^{-1} (ester CO) and 1550 cm^{-1} (nitroalkane).

Analysis:

For phenyl 2-(2-nitroethyl) benzoate - $C_{15}H_{13}NO_4$ (mol.wt. 271.26)

Calculated: C, 66.4; H, 4.83; N, 5.16.

Found: C, 63.35; H, 4.78; N, 2.47.

The analysis suggeste the product to be a mixture, the carbon value lying half-way between those calculated for the bromo and nitro esters, and the nitrogen content being about one-half of the expected.

Thin-layer chromatography of the product on silica gel with cyclohexane-chloroform (2:3, v/v) shows two major spots. A large scale separation of the mixture (0.250 g) was undertaken. The forerun is scraped off, extracted with chloroform and the solution filtered. Evaporation of the filtrate gives unreacted bromo ester (77 mg). The middle fraction, on similar work-up, gives the nitro ester (60 mg) which crystallises from methanol as colorless prisms of m.p. 81° and shows satisfactory analytical values.

Analysis:

Found: C, 66.20; H, 4.86; N, 5.33.

In a repetition of the experiment a longer reaction time of 24 hours was used. A brown oil was obtained, from which no pure product could be isolated, although it showed the same infrared bands as the above product.

Reaction of sodium methoxide with methyl 2-(2-nitroethyl)benzoate. 2-Nitroindanone (II)

Methyl 2-(2-nitroethyl)benzoate (50 mg) is dissolved in methanol (5 ml) and a solution of sodium methoxide (13 mg) in methanol (1 ml) is added. A yellow precipitate is formed after five minutes. The mixture is stirred for six hours at room temperature, cooled in ice-water and neutralised with cold N hydrochloric acid. The solution is evaporated to dryness and the residue is extracted with boiling petroleum ether (60-80°). On evaporation, a white substance (26 mg) is obtained, which, on recrystallisation from petroleum ether (60-80°) gives white plates, m.p. 80-81°. The infrared and ultraviolet spectra are identical with those of 2-nitroindanone prepared by an alternative method (see page 122).

Reaction of sodium methoxide with the mixture presumably containing methyl 2-(2-nitroethyl)benzoate

The reaction product (b.p.$_{0.5\ mm}$ 112-117°) described on page 110 (0.209 g) is dissolved in methanol (5ml) and a solution of sodium methoxide (0.054 g) in methanol (1 ml) is added. A yellow precipitate is formed after five minutes. The mixture is stirred for six hours at room temperature and the yellow solid (67 mg) is then collected. The solid is dissolved in methanol (20 ml) containing a few drops of water and the solution is cooled to 0°, acidified cautiously with cold N hydrochloric acid, and then evaporated to dryness. The residue is extracted with boiling petroleum ether (b.p. 60-80°). On evaporation, the extract yields a white substance (17 mg) which, on recrystallisation from petroleum ether, gives white plates (11 mg) of 2-nitroindanone, m.p. 80-81°. The infrared and ultraviolet spectra are identical with those of 2-nitroindanone prepared by an alternative method (see page122).

Reaction of sodium methoxide with the mixture of phenyl 2-(2-nitroethyl)benzoate and phenyl 2-(2-bromoethyl)benzoate

The mixture (90 mg., m.p. 71°) of the nitro and bromo esters described on page113 is dissolved in methanol (5 ml) and a solution of sodium methoxide (20 mg) in methanol (0.5 ml) is added. A yellow precipitate appears. After stirring of the reaction mixture for one hour at room temperature, it is cooled with ice and acidified with cold N hydrochloric acid. Evaporation to dryness affords a white residue which has a phenolic odour. The residue is extracted with boiling petroleum ether (b.p. 60-80°). The extract is concentrated and, on cooling, deposits crystals (13 mg) of 2-nitroindanone. The compound is identical with the specimen of 2-nitroindanone described on page 122with regard to its melting point (81°), infrared spectrum and ultraviolet spectrum.

3-Nitromethyl-2-nitroindanone (XXXVII)

To an ice-cooled solution of methyl 2-(1, 3-dinitro-2-propyl)benzoate (380 mg., 1.4 m mole) is added a solution of sodium methoxide (160 mg., 3 m mole) in methanol (3 ml) over a period of fifteen minutes. The mixture is stirred for one hour at 0° and is then acidified with cold N hydrochloric acid. The residue obtained, upon removal of the solvent in vacuo, is extracted with chloroform (50 ml). The chloroform extract is washed with water, dried over anhydrous sodium sulfate, concentrated to a small volume, and cooled in the refrigerator. Yellow crystals (135 mg) (43%) of m.p. 116-117° are deposited. Recrystallisation from chloroform gives bright yellow plates (75 mg) of m.p. 118-119°.

Analysis:

$C_{10}H_8N_2O_5$ (mol. wt. 236.2)

Calculated: C, 50.84; H, 3.41; N, 11.85.

Found: C, 50.90; H, 3.60; N, 11.98.

The product shows absorption in the infrared at 1725 cm^{-1} (carbonyl) and 1550 cm^{-1} (nitroalkane) and exhibits an ultraviolet maximum at 370 mμ ($\mathcal{E}$ = 8400) in methanolic solution.

Attempted preparation of methyl-5-nitrovalerate (XXXIX)

Methyl 5-bromovalerate (4.2 g, 2.1 m mole) is stirred with a mixture of sodium nitrite (2.8 g, 4 m mole), phloroglucinol (1.75 g), dimethylsulfoxide (28 ml) and dimethylformamide (7 ml) at room temperature for five hours. The brown solution is poured over crushed ice and the aqueous mixture is extracted with ether (100 ml). The ether layer is washed twice with two 30-ml portions of water, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gives a brown liquid which is distilled at 0.8 mm. A colorless liquid (1.5 g) is collected at 100 to 102°. The product exhibits infrared absorption at 1730 cm^{-1} (ester CO) and 1550 cm^{-1} (nitroalkane).

Analysis:

$C_6H_{11}NO_4$ (mol. wt. 161.2)

Calculated: C, 44.75; H, 7.32; N, 8.68.

Found: C, 47.77; H, 7.59; N, 7.92.

The high carbon and low nitrogen content suggests that a small amount of unsaturated ester, $CH_2 = CH\text{-}CH_2\text{-}CH_2\text{-}COOCH_3$, may be present in the product.

Reaction of sodium methoxide with impure methyl-5-nitrovalerate

The reaction product ($b_{0.8\ mm}$ 100-102°) from the preceding experiment (0.105 g.) is dissolved in methanol (2 ml) and a solution of sodium methoxide (0.035 g) in methanol (0.5 ml) is added. The solution is kept at room temperature for eight hours. The ultraviolet spectrum of the alkaline solution shows an absorption maximum at 345 mμ indicating the presence of sodium 2-ketocyclopentane nitronate. The alkaline solution is deionized with ion-exchange resin, Rexyn 101 (H^+). After filtration and evaporation of the solvent under reduced pressure, a colorless liquid is obtained. It has no absorption in the 300-390 mμ region and its infrared spectrum is completely identical with the starting material.

Attempted preparation of 2-nitro-1-indanone

(A) By conversion of 2-bromo-1-indanone to 2-nitro-1-indanone

2-Bromo-1-indanone (0.211 g), sodium nitrite (0.1 g) and urea (0.15 g) are stirred with dimethylformamide (5 ml) at room temperature. After half an hour a solid precipitates. The mixture is stirred for three more hours and then filtered. The solid product does not show any absorption for the nitro group in the infrared spectrum. The filtrate is poured over crushed ice and the mixture is extracted with ether (50 ml). The ether solution is washed twice with water and dried over anhydrous sodium sulfate. Removal of the solvent gives a thick syrup which does not exhibit any nitro group absorption in the infrared spectrum.

Repeating the experiment with dimethylsulfoxide as the solvent and with addition of phloroglucinol did not give the desired conversion.

(B) By nitration of 1-indanone - (1) with acetyl nitrate

Fuming nitric acid (0.5 ml) is added to a solution of 1-indanone (0.5 g) in glacial acetic acid (2 ml.). The temperature rises rapidly to 32° and is maintained at 32° by external cooling. After about five minutes the temperature begins to drop. The mixture is allowed to stand at room temperature for half an hour and is then poured over crushed ice. A semi-solid is formed, which is filtered and thoroughly dried. The infrared spectrum of the product does not show any absorption for the nitro group.

(2) with butyl nitrate in the presence of potassium t-butoxide

A solution of 1-indanone (0.132 g) in tetrahydrofuran (3 ml) is added dropwise, over a period of thirty minutes, to a solution of potassium t-butoxide (0.180 g) in tetrahydrofuran (5 ml) which is maintained at -30°. A solution of butyl nitrate in tetrahydrofuran (3.5 ml) is then added dropwise in half an hour, the temperature being maintained at -30°. After the addition is completed, the reaction mixture is allowed to warm up to 25°, and is then filtered. The filtrate is cooled and acidified with cold N hydrochloric acid. Removal of the solvent in vacuo affords a residue which is extracted with ether. The ether extract is dried and evaporated to give a black solid, which does not show any nitro group absorption in the infrared.

In a similar run, with the acidification effected by ion-exchange resin, Rexyn 101 (H^+), a syrup is obtained whose infrared spectrum shows a very weak absorption for the nitro group. However, no ultraviolet absorption in the 350-390 mμ region is observed.

Nitration of 1-indanone with dl-2-octyl nitrate in ether in the presence of sodium methoxide at room temperature was also unsuccessful.

(C) Oxidation of 2-oximino-1-indanone by manganese dioxide

A mixture of 2-oximino-1-indanone (0.32 g), manganese dioxide (0.1 g) and acetic acid (20 ml) is stirred for twenty-four hours at room temperature. The solution is filtered and the filtrate is diluted with water. The organic material is extracted with ether, and the ether solution dried over anhydrous sodium sulfate. Evaporation of the dry ether solution gives a brown oil which does not show any nitro group in the infrared spectrum.

(D) Oxidation of 2-oximino-1-indanone with peroxytrifluoroacetic acid. 2-Nitroindanone (II)

Trifluoroacetic anhydride (0.504 g, 2.4 m mole) is added in one portion to a stirred, ice-cooled solution of 98% hydrogen peroxide (0.068 g, 2 m mole) in acetonitrile (5 ml.). The solution is allowed to come to room temperature and is then added dropwise, with stirring, to a solution of 2-oximino-1-indanone (0.161 g., 1 m mole), urea (0.15 g) and acetonitrile (15 ml) during a period of one hour. After eight hours the mixture is poured over crushed ice and extracted with ether. Evaporation of the dried (sodium sulfate) ether solution leaves a brown residue which is extracted with boiling petroleum ether (b.p. 60-80°). The petroleum ether is evaporated, leaving a pale yellow solid (71 mg.). Recrystallisation from petroleum ether gives 2-nitroindanone (32 mg) as colorless plates of m.p. 81°.

Analysis:

$C_9H_7NO_3$ (mol. wt. 177.1).

Calculated: C, 61.01; H, 3.95; N, 7.91.

Found: C, 61.15; H, 3.99; N, 7.81.

The product shows absorption in the infrared spectrum at 1550 cm^{-1} (NO_2 group)and 1740 cm^{-1} (carbonyl absorption) and it has an absorption maximum in the ultraviolet at 373 mμ (ε = 8600 in methanol).

Condensation of 5-hydroxypentanal with nitromethane in the presence of sodium hydroxide. 2-Nitromethyltetrahydropyran

Nitromethane (0.33 g, 5.4 m mole) is added to a solution of 5-hydroxypentanal (0.51 g, 5 m mole) in methanol (5 ml) and the mixture is cooled in ice-water. A solution of sodium hydroxide (0.2 g, 5 m mole) in methanol (3.5 ml) containing a few drops of water is added, with stirring, over a period of half an hour. The reaction mixture is stirred for four hours, allowing the temperature to rise to 25°. Removal of the solvent under reduced pressure gives a pale yellow solid, the nitronate, (0.9 g).

An ice-cold solution of the nitronate (0.45 g) in methanol (5 ml) is deionized with ion-exchange resin, Rexyn 101 (H^+). Evaporation of the solvent leaves a brown syrup (0.33 g) (A), whose infrared spectrum shows absorption at 3350 cm^{-1} (OH, broad band), and 1550 cm^{-1} (nitroalkane).

Alternatively, the nitronate (0.45 g) is dissolved in water (5 ml), the solution is cooled in ice and neutralised with cold N hydrochloric acid. The solvent is removed under reduced pressure, and the residue is extracted with ether. The ether extract is dried over anhydrous sodium sulfate. Evaporation leaves a brown syrup (0.3 g), whose infrared spectrum is identical with that obtained by the ion-exchange procedure.

The syrup (A) (2.2 g.) is distilled at 21 mm. A colorless liquid (1.3 g.) distills over at 115-117°, n_D^{25} 1.4600. It exhibits absorption at 1550 cm^{-1} (nitroalkane) in the infrared spectrum and is identical with 2-nitromethyl tetrahydropyran with regard to its boiling point and refractive index (110).

Acetylation of the syrupy product (A) from the preceding experiment

The syrupy product (A) (3 g.) from the preceding experiment is dissolved in acetic anhydride (7 g.) and a few drops of boron trifluoride ethereate is added. The solution, which becomes warm spontaneously, is allowed to stand for half an hour and is then poured over crushed ice. After the excess acetic anhydride is hydrolysed, the mixture is extracted with ether, the ether extract thoroughly washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gives a brown syrup, the diacetate (B) whose infrared spectrum shows absorption at 1735 cm^{-1} (acetoxy CO), at 1555 cm^{-1} (nitroalkane) and no absorption for the hydroxyl group.

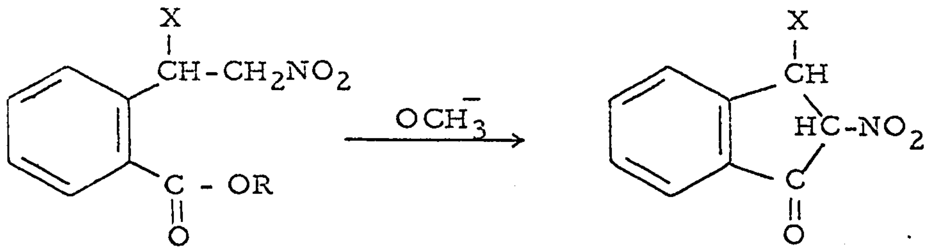
Reaction of sodium bicarbonate with the diacetate (B) in benzene (Schmidt-Rutz reaction)

A solution of the diacetate (B) (1 g) in dry benzene (10 ml) is refluxed, with magnetic stirring, in the presence of dry sodium bicarbonate (5 g). Small test samples are withdrawn occasionally, cleared from suspended bicarbonate, allowed to evaporate and inspected by infrared spectroscopy. A gradual decrease in the intensity of nitroalkane absorption at 1555 cm^{-1} and the appearance of an olefin peak at 1648 cm^{-1} and of a new nitro peak at 1525 cm^{-1} indicates the progress of the reaction. The completion of the reaction would be signified by the absence of the nitroalkane peak. In a trial experiment it was found that refluxing the mixture for forty-eight hours caused reappearance of the nitroalkane peak and a complete disappearance of the olefin and nitroalkene peaks that had been engendered initially. Hence, the reaction is carefully followed spectroscopically, and it is stopped when it is estimated that there is a maximum amount of nitroolefin present. The time varies from twelve hours to twenty hours, depending on the stirring efficiency and traces of moisture present. The bicarbonate is filtered off and thoroughly washed with dry benzene. Removal of benzene from the filtrate in vacuo gives the syrupy mixture (C) (0.75 g), presumably containing the nitroolefin. The infrared spectrum shows absorption at 1735 cm^{-1} (acetoxy CO), 1648 cm^{-1} (olefinic double bond), 1555 cm^{-1} (nitroalkane, weak) and 1525 cm^{-1} (nitroalkene, strong).

The product C is presumably a mixture of the diacetate B and the nitroolefin.

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

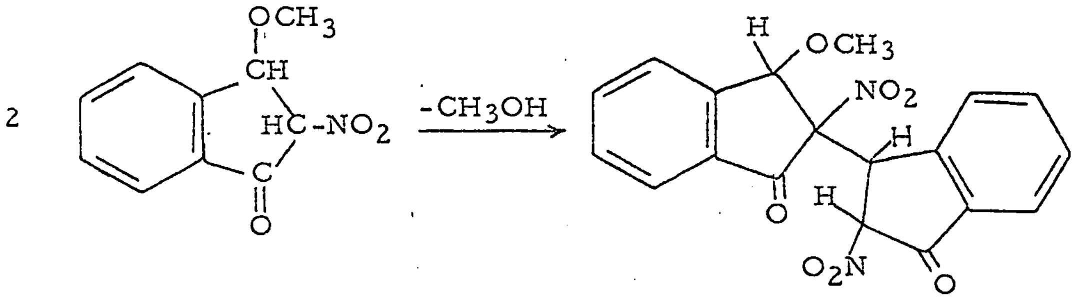
A novel reaction was discovered in which the methyl and phenyl esters of 2-(2-nitroethyl)benzoic acid undergo a base-catalyzed, Dieckmann-type cyclization furnishing hitherto unknown 2-nitroindanone:



R = CH_3 or C_6H_5 , X = H

R = CH_3 , X = CH_2NO_2 or OCH_3

Two new derivatives of 2-nitroindanone were obtained analogously. Thus the methyl ester of 2-(1,3-dinitro-2-propyl)benzoic acid gave 3-nitromethyl-2-nitroindanone. In the case of the methyl ester of 2-(1-methoxy-2-nitroethyl)benzoic acid the reaction proceeded in a more complicated manner, in that 3-methoxy-2-nitroindanone, presumed to be the primary product, reacted further to give 3-methoxy-2-nitro-2-(2-nitroindanone-3-yl)indanone:

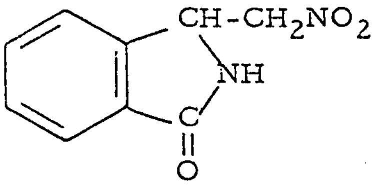


In preliminary investigation, methyl 5-nitropentanoate was treated with base, and spectroscopic evidence for cyclization to a nitroketone was found, although 2-nitrocyclopentanone could not be isolated.

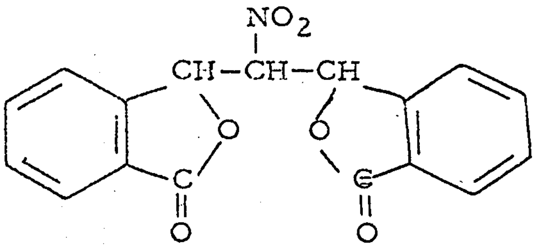
The esters required for these cyclizations had not been described previously. They were obtained as follows.

The methyl and phenyl 2-(2-nitroethyl)benzoates were made from the corresponding 2-bromoethyl esters by displacement with sodium nitrite in dimethylsulfoxide. Methyl 2-(1-methoxy-2-nitroethyl)benzoate was prepared from the known acid by treatment with diazomethane. 2-(1, 3-Dinitro-2-propyl)-benzoic acid arose when methyl o-phthalaldehydate was condensed with nitromethane in the presence of Triton B; the acid was then esterified with diazomethane.

The nitromethane condensation of methyl o-phthalaldehydate was studied using a large variety of catalysts, and in addition to the dinitro acid just mentioned, two other, new products were obtained. They were 2-(1-amino-2-nitroethyl)-benzoic acid lactam, which arose by catalysis with ammonium acetate-acetic acid, and 3, 3'-diphthalidylnitromethane, which arose by catalysis with trimethylamine or with sodium acetate-acetic acid.



2-(1-amino-2-nitroethyl)-
benzoic acid lactam



3, 3'-diphthalidylnitromethane.

Methyl 2-(2-nitrovinyl)benzoate could not be isolated in any of these reactions.

An independent synthesis of 2-nitroindanone was accomplished by oxidation of 2-oximinoindanone with peroxytrifluoroacetic acid.

A preliminary study was undertaken concerning the mechanism of the formation of 2-nitromethyltetrahydropyran from 5-hydroxypentanal and nitromethane.

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