ANOMALOUS NITRATION REACTIONS

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I. INTRODUCTION

Nitration as presented in beginning textbooks of organic chemistry is an orthodox reaction characteristic of aromatic nuclei in which hydrogen is replaced by nitro groups in accordance with the rules of directive influence.

In the literature, however, there are numerous nitrations in which halogens, alkyl, alkoxyl, acyl, carboxyl, and sulfonic groups have been replaced by one or more nitro groups. In some cases, one hydrogen in an alkyl group is replaced by the nitrate radical. Some polysubstituted polyphenolic ethers are partially cleaved and oxidized by nitric acid to form substituted quinones. Occasionally, with compounds of suitable structure, cyclization takes place, along with nitration.

In general, abnormal reactions are more likely to be encountered in the nitration of polysubstituted benzene compounds—notably the polyalkylbenzenes and some of their derivatives—and polysubstituted phenolic compounds.

The formation of anomalous nitration products is influenced by such factors as the composition of the nitrating mixture,[1] the temperature of the reaction, and the number, orientation, structure, and types of groups attached to the nucleus.

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[1] Unless otherwise stated, the specifications of the acids referred to in the text are as follows: sulfuric acid, sp. gr. 1.84; nitric acid, sp. gr. 1.42; fuming nitric acid, sp. gr. 1.5.

II. MONOALKYLBENZENES

The monoalkylbenzenes yield the expected nitro compounds with the usual nitrating agents. Even *n*-octylbenzene forms *o*- and *p*-octylnitrobenzenes when nitrated at −5°C. (61). Electrolytic nitration of toluene with nitric acid in methyl alcohol solution (total acidity 30 per cent) yields some picric acid as a by-product of the reaction (3, 4).

III. DIALKYLBENZENES

The three dimethylbenzenes and the three diethylbenzenes form only the usual nitro compounds with the various nitrating agents, but with *p*-cymene and *p*-diisopropylbenzene anomalous reactions occur. There is no mention of abnormal reaction products from any *o*- or *m*-dialkylbenzenes or from the di-*n*-propylbenzenes.

The isopropyl group can be replaced with a nitro group or it can be oxidized to an acetyl group or to a carboxyl group, along with nuclear nitration. The nitration of *p*-cymene has been extensively studied in an effort to minimize side reactions and to improve the yield and purity of the 2-nitro- and 2,6-dinitro-*p*-cymenes[2] (1, 43).

Since the isopropyl group is easily oxidized, it is not surprising that methyl *p*-tolyl ketone, *p*-toluic acid, 2-nitro-*p*-toluic acid, and 2,6-dinitro-*p*-toluic acid have been reported as by-products of the nitration of *p*-cymene. *p*-Nitrotoluene and 2,4-dinitrotoluene are the principal impurities in the 2-nitro- and 2,6-dinitrocymene fractions, even when the nitration is carefully carried out at low temperatures (1, 43, 87).

The extent of the formation of oxidation or replacement products can be controlled somewhat by varying the composition of the nitrating mixture and the temperature of the reaction. As might be expected, higher temperature favor the formation of oxidation products. At temperatures of 0°C. to −10°C. the product is mainly mono- or dinitrocymene with varying amounts of *p*-nitrotoluene and 2,4-dinitrotoluene. Kobi and Doumani (43) report 90 per cent yields of mononitrocymene containing 8 per cent of *p*-nitrotoluene by carrying out the nitration at −10°C. with a mixture of glacial acetic acid, nitric acid, and sulfuric acid.

For the preparation of 2,6-dinitro-*p*-cymene, Wheeler and Harris (87) used a mixture of fuming nitric acid and sulfuric acid below 0°C. Their product contained 24 per cent of dinitrotoluene and 6 per cent of *p*-nitrotoluene. Alfthan (1) used this same nitrating mixture at 0°C. and reported some *p*-toluic acid and some methyl *p*-tolyl ketone as by-products.

To explain the formation of both the oxidation products and the replacement products, it might appear that the following series of reactions takes place during nitration:

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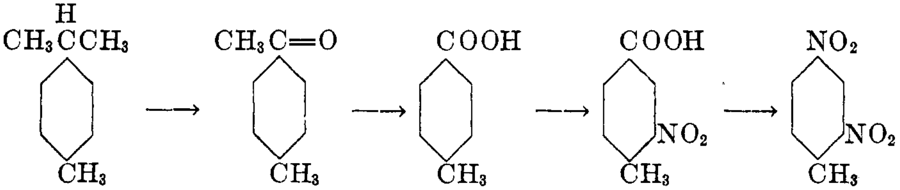
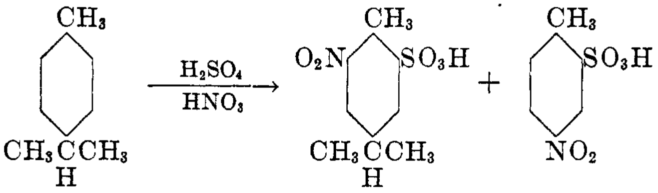
[2] Alfthan's paper (1) contains a survey of the literature on the nitration of *p*-cymene prior to 1920 and includes abstracts of work published in Scandinavian journals not readily available. The paper by Kobi and Doumani (43) also has a complete bibliography covering both early work and the period 1920-38.



If this mechanism is correct, either methyl *p*-tolyl ketone or *p*-toluic acid should yield some nitrotoluene or dinitrotoluene among its nitration products. Alfthan found that nitration of methyl *p*-tolyl ketone with fuming nitric acid and sulfuric acid at −10°C. yielded methyl 2-nitro-*p*-tolyl ketone, while at 60–70°C. the principal product was 2,6-dinitro-*p*-toluic acid. *p*-Toluic acid yielded either 2-nitro- or 2,6-dinitro-*p*-toluic acid but no nitrotoluenes, even under drastic conditions.

If *p*-cymene is first treated with sulfuric acid and then nitrated, the product is a mixture of the expected nitro compound and *p*-nitrotoluene-2-sulfonic acid (35):



2-Methyl-5-isopropylbenzenesulfonic acid and nitric acid also yield *p*-nitrotoluenesulfonic acid. The sulfonic group is not replaced.

Newton (47) has made a careful study of the nitration of the polyisopropylbenzenes and some of their derivatives. His nitrations were carried out with 96 per cent nitric acid in a mixture of acetic acid and acetic anhydride at 45–50°C. or with a mixture of 70 per cent nitric acid and 96 per cent sulfuric acid at 0–6°C.

In the nitration of 1,4-diisopropylbenzene, the effect of the composition of the nitrating mixture is striking, though the nitrations were carried out at different temperatures. The product from both nitrations was a mixture of the replacement product, 4-nitroisopropylbenzene, and the normal product, 2-nitro-1,4-diisopropylbenzene. With nitric acid, acetic acid, and acetic anhydride, the products were present in the mole ratio 1.44:1, while with nitric acid and sulfuric acid the ratio was 4.78:1.

Nitration of 1,4-diisopropylbenzene-2-sulfonyl chloride with a large excess of 96 per cent nitric acid at 0–5°C. yielded 4-nitroisopropylbenzene-2-sulfonyl chloride.

No abnormal products were reported from the nitration of 1,3-diisopropylbenzene or any of its derivatives.

Nitration of the chlorocymenes and the chlorocumenes has resulted in the replacement of the isopropyl group by a nitro group. Dinitro-2-chlorotoluene is an impurity in the preparation of 5,6-dinitro-2-chlorocymene with 25 per cent fuming sulfuric acid and fuming nitric acid at 0°C. as the nitrating agent (45).

The nitration of 2,5,6-trichloro-*p*-cymene with fuming nitric acid at 100°C. yields some 2,5,6-trichloro-3,4-dinitrotoluene (53). The 2,3,5,6-tetrachlorocymene yielded 2,3,5,6-tetrachloro-4-nitrotoluene under the same conditions or with a mixture of nitric and sulfuric acids. The isopropyl group is also replaced in pentachlorocumene, 2,4,5,6-tetrachlorocumene, and 2,4,5-trichlorocumene.

IV. TRIALKYLBENZENES

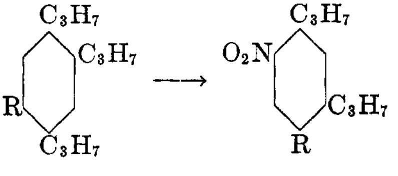
Only the usual nitration products have been reported from the trimethylbenzenes, the triethylbenzenes, and the triisopropylbenzenes, but with trialkylbenzenes containing tertiary radicals, replacement reactions occur. Unfortunately, the structures of some of the hydrocarbons were not definitely established and often neither the composition of the nitrating mixture nor the experimental conditions were recorded.

Isopropyl-4-*tert*-butyltoluene (prepared by the reaction of 4-*tert*-butyltoluene with isopropyl chloride and aluminum chloride or with isopropyl alcohol and sulfuric acid) loses an isopropyl group when nitrated with fuming nitric acid below 0°C., but isopropyl-3-*tert*-butyltoluene prepared in the same way from 3-*tert*-butyltoluene yields dinitroisopropyl-3-*tert*-butyltoluene (8, 9). Other isomeric isopropyl-*tert*-butyltoluenes yielded only normal nitration products. The replacement of the isopropyl group in the one isomer only is interesting, since Newton found no replacement products with either 1,2,4- or 1,3,5-triisopropylbenzene or with *m*-diisopropylbenzene. The hydrocarbon could have been predominantly 2-isopropyl-4-*tert*-butyltoluene, provided no rearrangement took place during alkylation.

Butyl-*m*-xylene (presumably 1,3-dimethyl-5-*tert*-butylbenzene) yields some trinitro-*m*-xylene, and *tert*-amyl-*m*-xylene yields a notable amount of trinitro-*m*-xylene (22). No experimental details are given, but it is likely that the nitrating agent was nitric acid at 70°C. or nitric acid and fuming sulfuric acid at 55°C., as described in earlier papers on the nitration of some *m*-dialkylbenzenes (21).

1,3-Dimethyl-5-(triethylmethyl)benzene yields only trinitro-*m*-xylene when nitrated with 94 per cent nitric acid and 15 per cent fuming sulfuric acid at 0–70°C. (10). It can be nitrated with absolute nitric acid in acetic anhydride at 10–80°C. to form trinitro-1,3-dimethyl-5-(triethylmethyl)benzene.

An isopropyl group is replaced during the nitration of some derivatives of 1,2,4-triisopropylbenzene (47) with either a large excess of 96 per cent nitric acid or 70 per cent nitric acid in sulfuric acid.



R = SO_2Cl, CN, or NH_2

There is a noticeable difference in the ease of nitration of some of the butyl-*m*-xylenes, due perhaps in part to the orientation of the radicals and in part to the structure of the butyl groups (48). 1,3-Dimethyl-5-*tert*-butylbenzene nitrates readily to yield the solid trinitro derivative, but the nitration product of 1,3-dimethyl-4-*n*-butyl- and 4-*sec*-butylbenzenes under the same conditions is an oil which deposits a few crystals of trinitro derivative only on long standing. The oils have not been investigated.

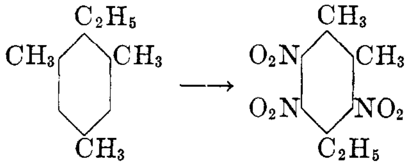
V. POLYALKYLBENZENES

Nitration of the alkylbenzenes above the trialkylbenzenes and some of their halogen derivatives can be carried out so as to yield normal nitration products in some cases, or abnormal products of two types: (*1*) those in which one or two alkyl groups have been replaced by nitro groups, or (*2*) those in which a hydrogen in one of the radicals has been replaced by $—ONO_2$ to form a benzyl nitrate.

The type of product formed by the nitration of these compounds depends upon their structure, the amount and composition of the nitrating agent, the time of reaction, and the temperature of the reaction. Nitration with fuming nitric acid alone at 0°C. to −11°C. favors the formation of nitrates, while a mixture of fuming nitric acid and sulfuric acid at 0–30°C. favors replacement products.

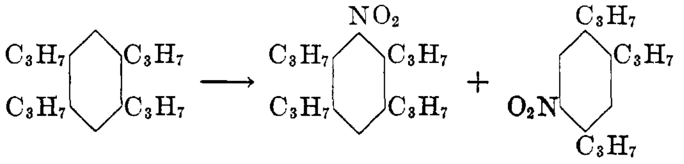
A. Replacement of alkyl groups

No irregularities have been reported among the nitration products of the three tetramethylbenzenes or the three tetraethylbenzes, but with ethylmesitylene apparently one methyl group is replaced and a methyl group migrates during nitration with fuming nitric acid and sulfuric acid (74):



Tohl and Tripke (83) reported 3,5-dinitroethylmesitylene from the reaction between this hydrocarbon and fuming nitric acid, but Smith and Kiess (74) established its identity as a trinitro compound and state that it is not trinitroethyl-*p*-xylene or trinitroethyl-*m*-xylene, but that it may be 3,5,6-trinitro-4-ethyl-*o*-xylene. These authors also report that vigorous nitration of the ethylpseudocumenes causes replacement of the ethyl group, with the formation of large amounts of trinitropseudocumene.

The effect of temperature on the yield of replacement product and normal product is striking in the nitration of 1,2,4,5-tetraisopropylbenzene with nitric acid and acetic anhydride (47). At 45°C. the yield of replacement product is 85 per cent, while at 80°C. it is the only product.

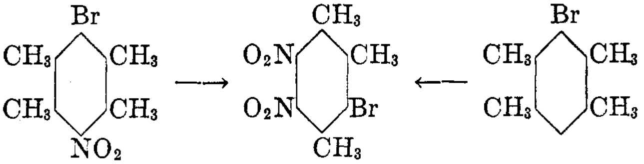


The most striking anomalous reactions occur when pentamethylbenzene, pentaethylbenzene, hexamethylbenzene, and hexaethylbenzene are nitrated. The pentamethylbenzene and hexamethylbenzene yield dinitroprehnitene (29, 72, 90), while pentaethylbenzene and hexaethylbenzene yield *p*-dinitrotetraethylbenzene (26, 40, 71). The nitrating agent can be either fuming nitric acid alone or fuming nitric acid and sulfuric acid in chloroform solution. Yields of the dinitro compounds are 22–75 per cent, with the best yields from the pentaalkylbenzenes.

Gottschalk (29) suggested that pentamethylbenzene first rearranged to prehnitene and hexamethylbenzene under the influence of the sulfuric acid, and that dinitroprehnitene was formed by nitration of the prehnitene. The principal objection to this mechanism is that pentamethylbenzene does not rearrange rapidly enough at the low temperatures and the short time for the nitration to yield an appreciable amount of prehnitene (72).

Smith and Harris (72) suggest that pentamethylbenzene may first be oxidized to prehnitenecarboxylic acid and that this acid reacts to form dinitroprehnitene with the loss of carbon dioxide. As they point out, however, prehnitenecarboxylic acid does not react with nitric acid at 0–5°C. but requires a temperature of 25°C.

One of the methyl groups in bromonitrodurene and in bromodurene is replaced by the action of fuming nitric acid to form 3-bromo-5,6-dinitropseudocumene (78):



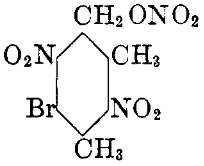
B. Nitrate formation

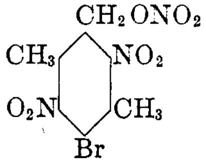
The possibility of the formation of nitrates during the nitration of polysubstituted benzenes was first recognized by Huender (38) in the course of an extensive study of nitrohalogenopseudocumenes. He found that 5-bromopseudocumene yielded the compound $C_9H_8O_7N_3Br$ (m. p. 150°C.) (I) when heated with a mixture of sulfuric acid and fuming nitric acid rather than 3,6-dinitro-5-bromopseudocumene, which was obtained when the nitration was carried out at ice-bath temperatures. Compound I could be obtained more readily by heating 3,6-dinitro-5-bromopseudocumene with the nitrating mixture. Huender heated I with ammonia and obtained the product $C_9H_7O_5N_2Br$ (m. p. 190–191°C.), which he did not identify. He prepared several other derivatives of I but did not identify any of them.

Since the analysis of I corresponded to $C_9H_8O_4N_2Br + NO_3$, or 3,6-dinitro-5-bromopseudocumene with one hydrogen replaced by $—NO_3$, Huender referred to it as a nitrate, though in conclusion he stated that it was either (*1*) a compound with the group $—CH_2NO_2$ in the side chain, (*2*) an addition product of 3,6-dinitro-5-bromopseudocumene and nitric acid, or (*3*) a nitrate.

He found that 3,6-dinitro-5-chloropseudocumene and 3,5-dinitro-6-bromopseudocumene also formed a nitrate, but that 5,6-dinitro-3-bromopseudocumene did not react with nitric acid.

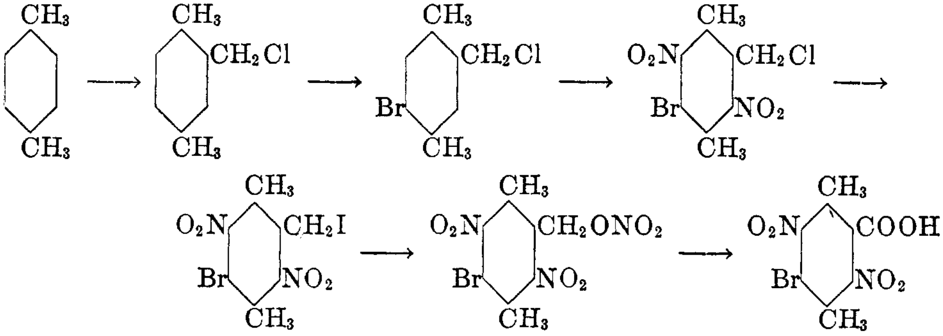
Nothing further was done with these compounds until 1937, when Rinkes (60) established the structure of Huender's nitrate (I) not only as a nitrate, but as a mixture of two isomeric nitrates (II and III):


II


III

He identified Huender's product from the nitrate and ammonia as an aldehyde and oxidized it to an acid which proved to be a mixture of isomeric acids. The acids were synthesized and a mixture of equal amounts of them melted at 229°C., as did the acid from Huender's nitrate.

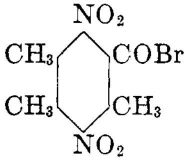
Rinkes synthesized the nitrate II by the following series of reactions:

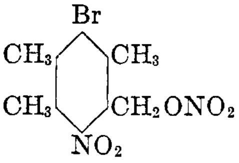

II

The nitrate III was synthesized in the same way from *m*-xylene. A mixture of equal amounts of the two nitrates melted at 153.5°C.

Shortly before Rinkes' work was published, Smith and coworkers had established that nitrates were formed by the action of fuming nitric acid on bromopentamethylbenzene (72) and bromodurene (78).

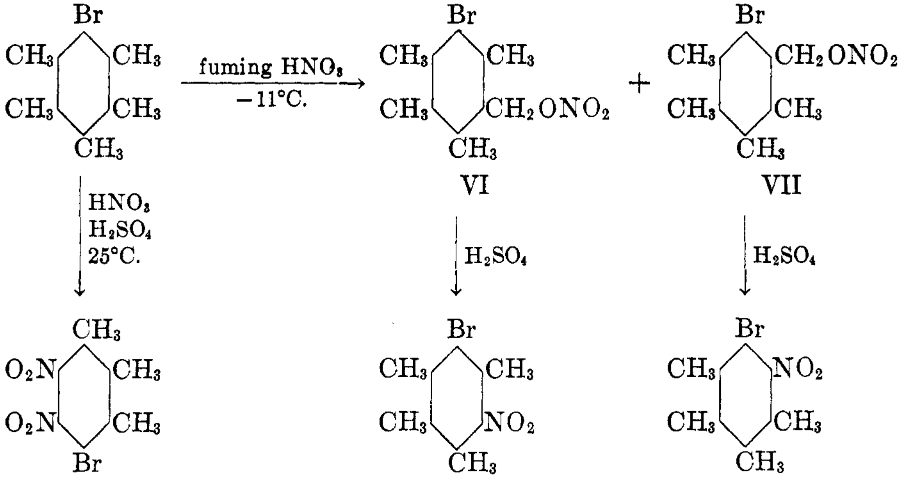
Smith and Tenenbaum (78) were using the directions of Willstatter and Kubli (90) for the preparation of dinitrodurylic acid bromide (IV) from bromodurene and fuming nitric acid at 0°C. They found that the compound definitely was not an acid bromide, and tentatively proposed the structure V for it.


IV


V

Smith, Taylor, and Webster (77) established the structure and identity of V as a nitrate by its reactions and by synthesis.

Smith and Horner (73) obtained a mixture of nitrates from bromopentamethylbenzene with fuming nitric acid, but with fuming nitric acid and sulfuric acid the product is 4-bromo-5,6-dinitrohemimellithene.



The structures of the nitrates were established by synthesis and by their reactions, as in previous work.

Since the group —CH_2ONO_2 in VI and VII can be replaced by a nitro group by the action of sulfuric acid at room temperature, Smith and Horner suggest that nitrates are intermediates in the replacement of methyl groups by nitro groups.

Smith and Guss (71) nitrated 3,6-dibromo-1,2,4,5-tetraethylbenzene by the same procedure as for the other halogenopolyalkylbenzenes and obtained a nitrate to which they assign tentatively the structure 3,6-dibromo-2,4,5-triethylbenzyl nitrate. If this is correct, then a methyl group has been removed from an ethyl group during nitration.

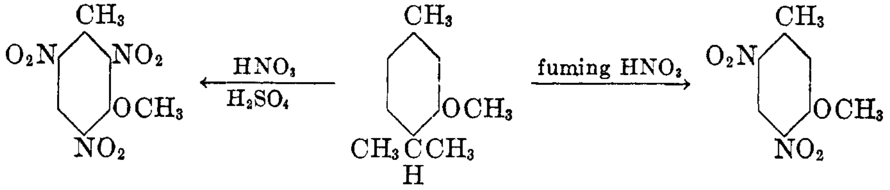
The conclusion of Smith and coworkers that the formation of nitrates is a general property of some of the highly alkylated benzenes and certain of their derivatives is amply justified. There must be some relationship between the orientation of the groups on the nucleus and nitrate formation, for not all of the isomeric bromopseudocumenes or bromotetraalkylbenzenes form nitrates.

VI. PHENOLS AND PHENOL ETHERS

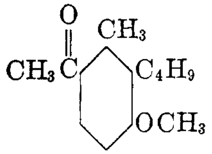
There are numerous examples of the replacement of halogens, alkyl, formyl, and acetyl groups by nitro groups during the nitration of polysubstituted phenol methyl ethers, along with demethylation and oxidation. Many of these anomalous reactions were encountered in the search for musk substitutes among the various polynitro compounds, while others were observed in connection with the preparation of nitro compounds for synthetic work or for purposes of identification.

The replacement of the isopropyl group of thymol by a nitro group (2) was observed in an attempt to prepare trinitrothymol by the nitration of 2,6-dinitrothymol with nitric acid and sulfuric acid. The product was always 2,4,6-trinitro-*m*-cresol.

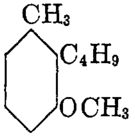
A careful study of the nitration of thymol and thymol ethers (28) proved that the isopropyl group is replaced by a nitro group even when the nitration is carried out with fuming nitric acid at low temperatures. The products were nitro-*m*-cresol ethers rather than trinitrothymol, as reported by early investigators.



Barbier (6) was interested in the synthetic musk problem and extended it to the nitration of *tert*-butylacetyl-*m*-cresol methyl ether. He prepared the ketone from *tert*-butyl-*m*-cresol methyl ether by the usual Friedel–Crafts procedure and used the structure I for it in his discussion,



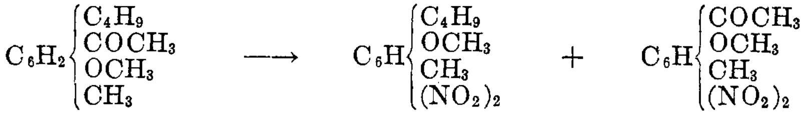
I



II

based on II as the structure for Baur's *tert*-butyl-*m*-cresol methyl ether, without proving any of the structures. As will be shown later, these structures and the structures Barbier assigned to compounds obtained from them are not correct.

The nitration of the ketone (I) with 92–95 per cent nitric acid at −10°C. yielded two dinitro compounds, expressed by Barbier as follows:



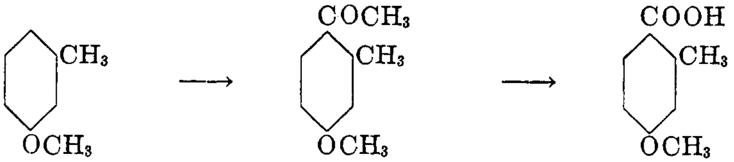
$$C_6H_2\begin{cases}C_4H_9\\COCH_3\\OCH_3\\CH_3\end{cases} \longrightarrow C_6H\begin{cases}C_4H_9\\OCH_3\\CH_3\\(NO_2)_2\end{cases} + C_6H\begin{cases}COCH_3\\OCH_3\\CH_3\\(NO_2)_2\end{cases}$$

I III IV

Musk ambrette

Compound III is identical with musk ambrette, obtained by Baur from the nitration of *tert*-butyl-*m*-cresol methyl ether.

Barbier prepared acetyl-*m*-cresol methyl ether (V) from *m*-cresol methyl ether, acetyl chloride, and aluminum chloride (6).

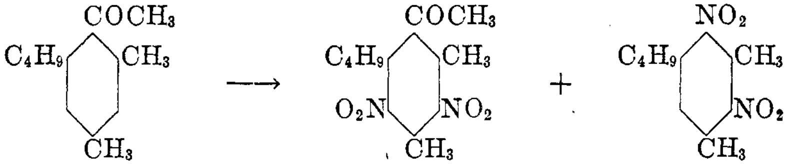


V

He states that the ketone should have the structure V, since it could be oxidized to a methylmethoxybenzoic acid melting at 176°C., the melting point of 2-methyl-4-methoxybenzoic acid described in the literature. Noller and Adams (49) accept this structure for their ketone, prepared from *m*-cresol methyl ether, acetic anhydride, and aluminum chloride. This structure still may be open to question however, since Thomas (80) states that with *m*-alkyl cresol ethers and acid chlorides the acyl group goes ortho to the ether linkage. According to Kranzlein (44), phenol ethers and acid chlorides follow the rule of ortho and para substitution. He cites as an example the reaction of *m*-cresol methyl ether with bromoisobutyryl bromide, which yields a mixture of *p*- and both *o*-bromoisobutyro-*m*-cresol methyl ethers. Nitration of V yielded a dinitro compound which was identical with IV.

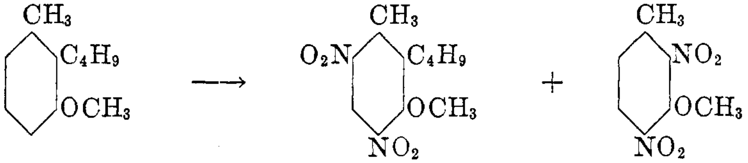
In a subsequent paper, Barbier lists his own and other examples in the literature in which various groups have been eliminated and replaced by a nitro group during nitration and makes the following generalization: When a highly substituted benzene nucleus is nitrated, the group meta to the first entering group is eliminated and is replaced by another nitro group (7).

This rule holds in the nitration of 6-*tert*-butyl-2,4-dimethylacetophenone (VI), from which Barbier obtained musk ketone (VII) and 2,4-dinitro-5-*tert*-butyl-*m*-xylene (VIII), the structures of which had been established by Baur (13).


VI VII VIII

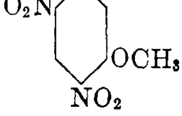
Its application to the nitration of acetylbutyl-*m*-cresol methyl ether (I) is uncertain, owing to the fact that the structure (II) which Barbier assigned to his starting material is not correct.

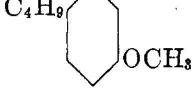
Barbier writes the nitration of *tert*-butyl-*m*-cresol methyl ether as follows (7):

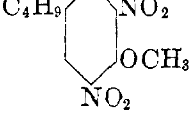

II IX X

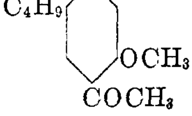
but structures IX and X cannot be correct, since II is wrong.

De Capeller (22) soon pointed out that X was 4,6-dinitro-*m*-cresol methyl ether (XI) rather than the 2,6-dinitro compound.


XI

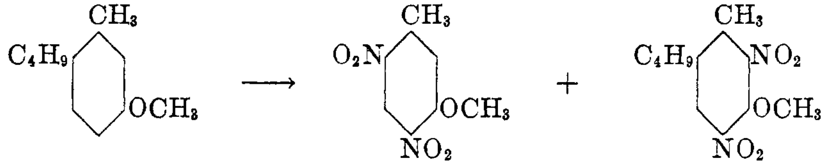

XII


XIII


XIV

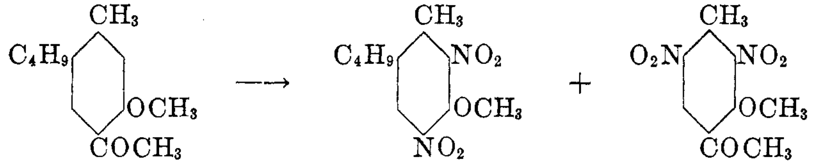
Darzens and Levy (20, 42) have established the structure of *tert*-butyl-*m*-cresol methyl ether as XII rather than II and musk ambrette as XIII, and assign XIV to the ketone I but without proof for the latter.

On this basis the nitration of XII can be written as follows:



XII XI XIII

This is in accordance with Barbier's rule. The nitration of XIV should then be written,



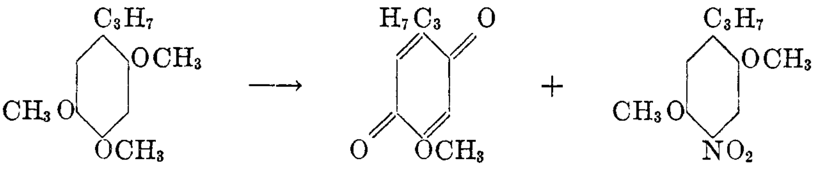
XIV XIII XV

but XV is a structural isomer of the dinitroacetyl-*m*-cresol methyl ether which Barbier obtained from the ketone V, the structure of which he and also Noller and Adams accepted as 2-methyl-4-methoxyacetophenone.

Barbier cites the formation of dinitroprehnitene from pentamethylbenzene as an exception to his rule. Another notable exception is the formation of *p*-dinitrotetraethylbenzene from pentaethylbenzene.

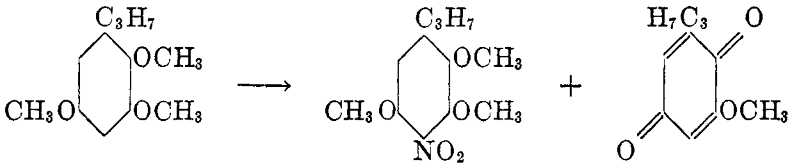
The isopropyl and *tert*-amyl radicals are replaced by nitro groups when isopropyl and *tert*-amyl-*m*-cresol methyl ethers are nitrated with nitric acid in glacial acetic acid (12).

Some interesting reactions take place during the nitration of polyphenolic ethers (81, 82, 86). When 1-*n*-propyl-2,4,5-trimethoxybenzene (XVI) reacts with fuming nitric acid at −18°C., the principal product is the quinone (XVII):



XVI XVII XVIII

and a small amount of the nitro compound (XVIII) in which one methoxyl has been replaced by a nitro group. If the reaction is carried out with 45 per cent nitric acid in glacial acetic acid at 50°C., the nitro compound (XVIII) is the main product and the quinone (XVII) is a by-product. If the isomeric 1-*n*-propyl-2,3,5-trimethoxybenzene is nitrated with 25 per cent nitric acid at 25°C., there is some demethylation and oxidation but no replacement of methoxyl groups (82).



XIX XX XXI

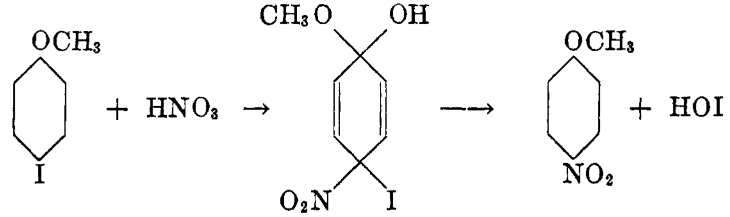
The ratio of XX to XXI is 2:1. The structures of the phenolic ethers, the nitro compounds, and the quinones were established by independent syntheses.

VII. HALOGENATED PHENOLS AND PHENOL ETHERS

The replacement of halogens by nitro groups in the halogenated phenols and phenol ethers is a common occurrence. The halogens are readily replaced when they are ortho or para to the hydroxyl or alkoxyl group, and in the order iodine, bromine, chlorine. A halogenated quinone is sometimes formed by either oxidative cleavage of the ether or oxidation of the phenol, and in some cases the halogen migrates to another position in the ring. Typical examples of these reactions are listed in table 1.

Robinson (65) suggested the following mechanism for the replacement reaction:

(1)

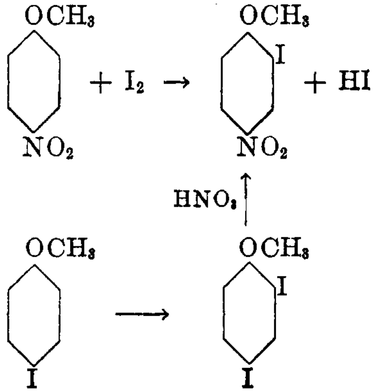


(2) $HOI \rightarrow I_2 + HOI_3$

(3) $HOI + HI \rightarrow I_2 + H_2O$

(4a)

(4b)



The iodine which separates during these nitrations will react either with *p*-nitroanisole according to equation 4a or with *p*-iodoanisole according to equation 4b.

TABLE 1

Nitration of phenols

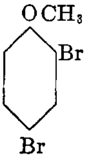
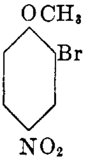
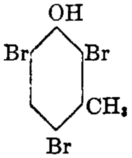
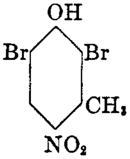
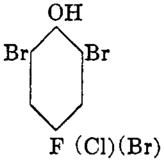
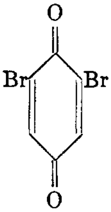
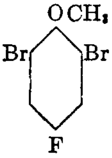
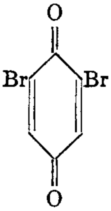
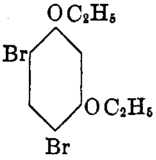
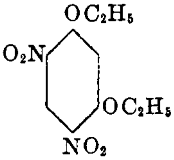
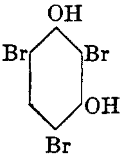
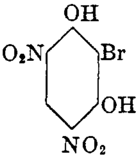
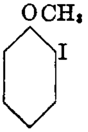
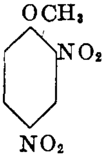
COMPOUND	REAGENT	PRODUCT	REFERENCES
	HNO_3		(15)
	HNO_3, CH_3COOH		(19, 54)
	HNO_3 (fuming)		(36)
	HNO_3 (fuming)		(36)
	HNO_3 (fuming)		(39)
	HNO_3 (fuming)		(39)
	HNO_3 (fuming)		(41)

TABLE 1—*Continued*

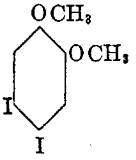
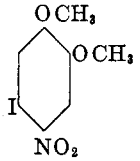
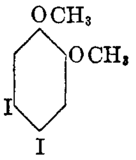
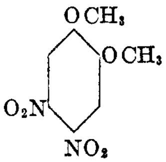
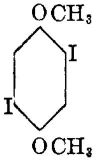
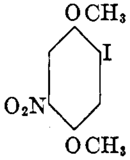
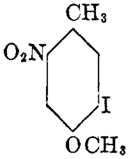
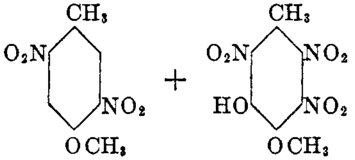
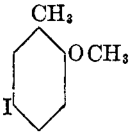
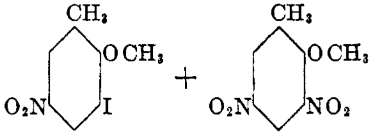
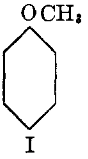
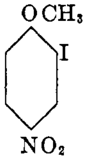
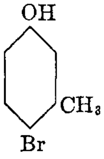
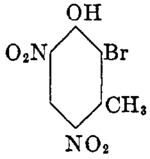
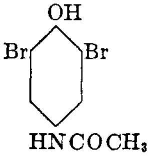
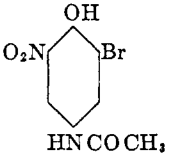
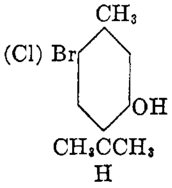
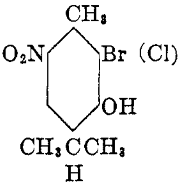
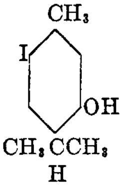
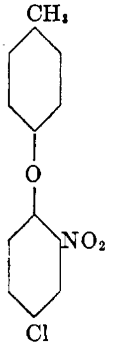
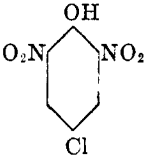
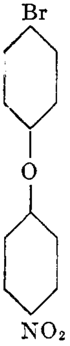
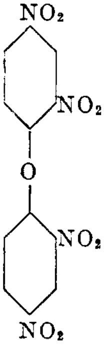
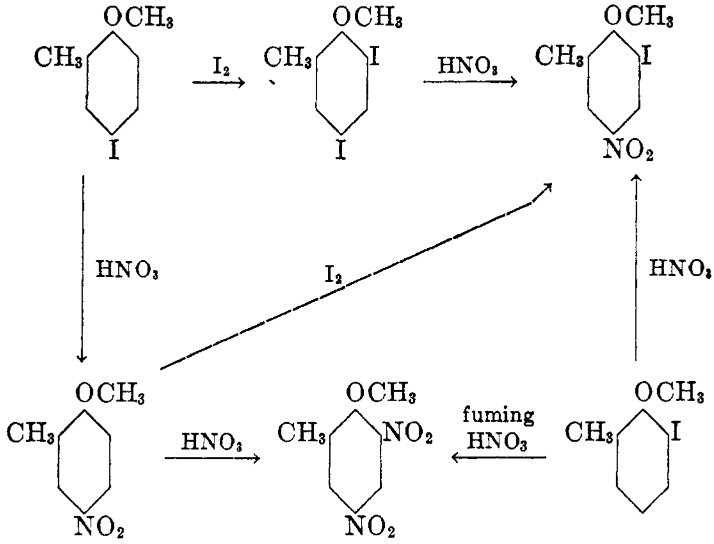
COMPOUND	REAGENT	PRODUCT	REFERENCES
	HNO_3, CH_3COOH		(65)
	HNO_3 (fuming)		
	$HNO_3 \cdot$ CH_3COOH		(65)
	HNO_3 (fuming)		(65)
	HNO_3		(65)
	HNO_3 (fuming)		(56)
	HNO_3		(68)
	HNO_3		(63)

TABLE 1—*Concluded*

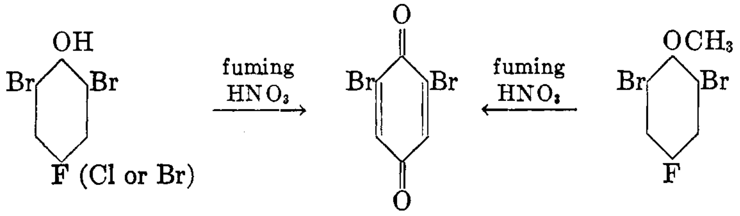
COMPOUND	REAGENT	PRODUCT	REFERENCES
	HNO_3, CH_3COOH		(64)
	HNO_3, CH_3COOH	Mixture of nitrothymols	(64)
	HNO_3(fuming)		(25)
	HNO_3		(55)

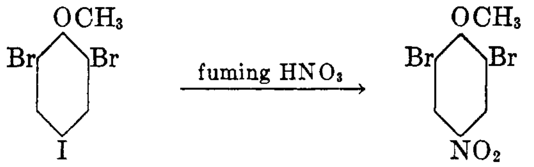
The concentration of the nitric acid appears to be rather critical for iodination to take place and, according to Robinson, the compound must have a strongly positive group, since otherwise the iodine will not be displaced.

The 5-iodo-*o*-tolylmethyl ether may react as follows:

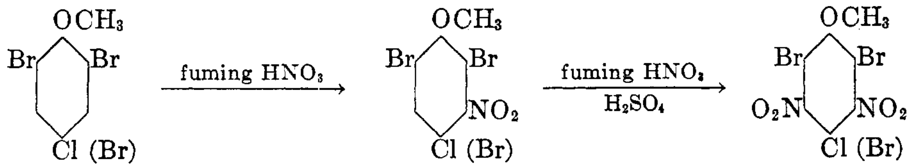


The 4-halogeno-2,6-dibromophenols and anisoles yield either halogenoquinones, normal nitration products, or, in the case of 4-iodo-2,6-dibromoanisole, a replacement product (36):





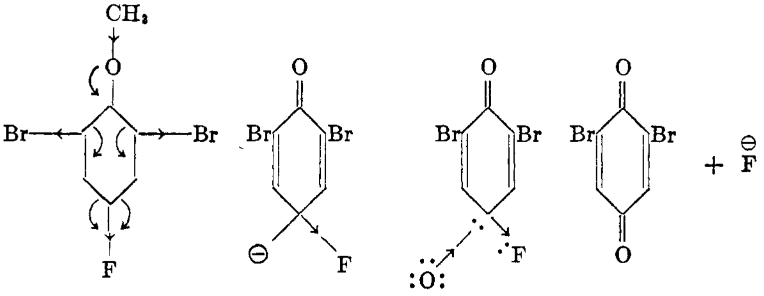
The 4-chloro- and 4-bromo-2,6-dibromoanisoles were nitrated in the 3-position. This mononitro compound on further nitration yielded a 3,5-dinitro compound:



Hodgson and Nixon (36) have explained the behavior of these compounds as follows:

> "The mechanism of reaction in the case of 4-fluoro-2:6-dibromoanisole can be regarded as a three-stage operation, *viz.*, the combined general effect . . . of the three halogens ren-

dering the methyl group sufficiently mobile (positive) for detachment and oxidation (I); rearrangement of the residue to the quinonoid form (II), facilitated by the same general effect; and subsequent attack by oxygen (III) with the separation of ionic fluorine (IV). The same mechanism will also apply to the phenols.



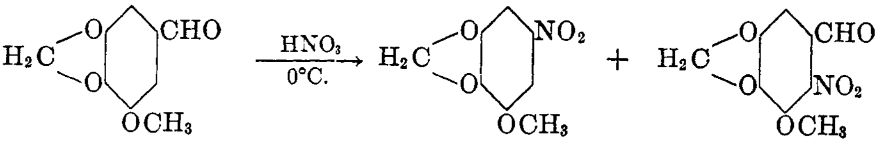
(I.) (II.) (III.) (IV.)

> "In the 4-chloro- and 4-bromo-2:6-dibromoanisoles, the combined general effect of the halogens is inadequate to produce the necessary reactivity (positivity) of the methyl group, and so normal nitration occurs. The above general effect is still further reduced in 4-iodo-2:6-dibromoanisole, and consequently the methyl group remains intact, but the electron-donating power of the iodine is now sufficient to enable kationoid attack by the nitric acid to take place at the 4-carbon atom with nitration and elimination of iodine. Fluorine exerts a far greater general effect than the other halogens. . . ."

VIII. PHENOLIC ALDEHYDES AND KETONES

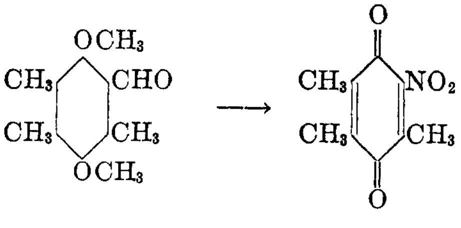
There are a few cases among the polyphenolic aldehydes and ketones in which a formyl or acyl group has been replaced by a nitro group.

An interesting example of this replacement is in the nitration of the methylenedioxybenzaldehydes (67):



Piperonal, vanillin, and anisaldehyde behave similarly (14, 23). The yield of replacement product is around 30 per cent.

The nitration of 2,5-dimethoxy-3,4,6-trimethylbenzaldehyde with nitric acid yields 3,4,6-trimethoxy-2-nitrobenzoquinone (70).



The acetyl group and the benzoyl group can be replaced by the action of nitric acid on highly substituted ketones of various types. Yields of replacement products are good in some cases. Examples are listed in table 2.

IX. AROMATIC ACIDS

Replacement products and occasionally cyclic compounds may be obtained from the nitration of aromatic acids, notably the phenolic acids and substituted acids, along with the expected nitro compounds.

A. Homologs of benzoic acid

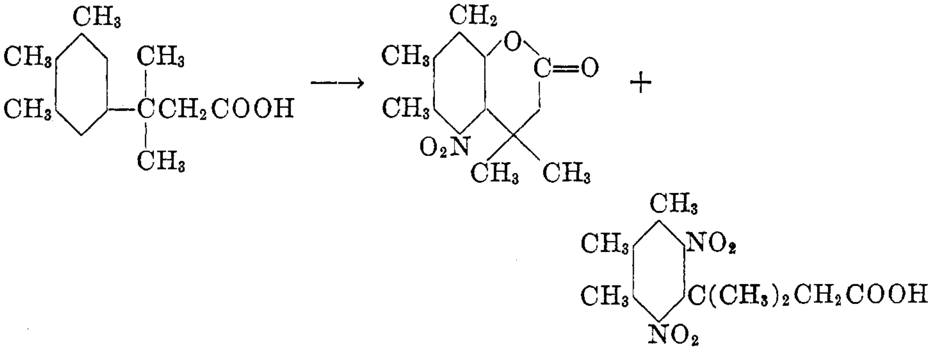
There are few abnormal products reported from the nitration of polyalkylbenzoic acids. The carboxyl group is not displaced to any extent in the polymethylbenzoic acids other than prehnitenecarboxylic acid, though Gissmann (27) remarks that durylic acid may give a small amount of nitrotrimethylbenzene when nitrated with strong nitric acid.

TABLE 2

Nitration of polysubstituted ketones

COMPOUND	REAGENT	PRODUCT	REFERENCES
2-Methyl-4,5-dimethoxyacetophenone	HNO_3, CH_3COOH	2-Nitro-4,5-dimethoxytoluene	(32)
3,4-Dimethoxyacetophenone	HNO_3, CH_3COOH	1,2-Dimethoxy-4,5-dinitrobenzene	(31)
2,6-Dibromo-4-aminobenzophenone	HNO_3	2,6-Dibromo-4-nitronitramine	(24)
2,6-Dibromo-4-aminoacetophenone	HNO_3	2,6-Dibromo-4-nitronitramine	(24)
3,4,5-Trimethoxyacetophenone	HNO_3	3,4,5-Trimethoxynitrobenzene	(31)

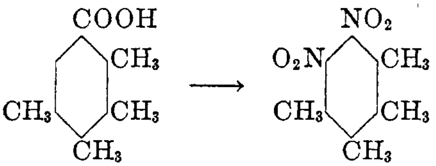
β-(3,4,5-Trimethylphenyl)isovaleric acid or its methyl ester reacts with fuming nitric acid and sulfuric acid at 10°C. to yield 4,4,6,7,8-pentamethyl-5-nitrohydrocoumarin, along with a compound whose composition agrees with that of 2,6-dinitro-β-(3,4,5-trimethylphenyl)isovaleric acid (75, 76).



Nitration of the ester with potassium nitrate and sulfuric acid also yielded the hydrocoumarin.

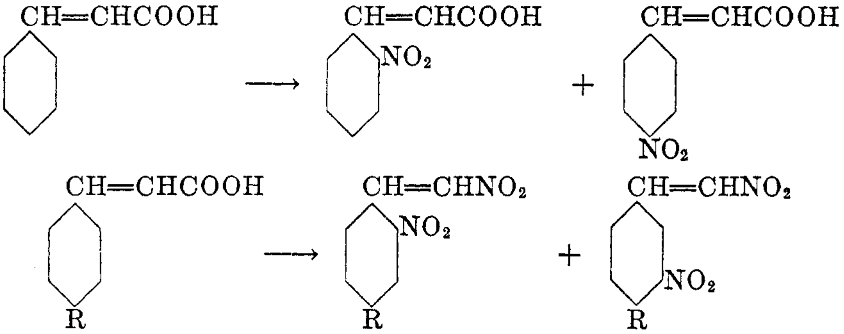
β-(3,5-Dimethylphenyl)isovaleric acid or its methyl ester yielded only the expected nuclear nitration products and no hydrocoumarin (76).

Dinitroprehnitene is formed quantitatively from prehnitenecarboxylic acid, fuming nitric acid, and sulfuric acid at 10°C. (5, 72).



B. Cinnamic acids

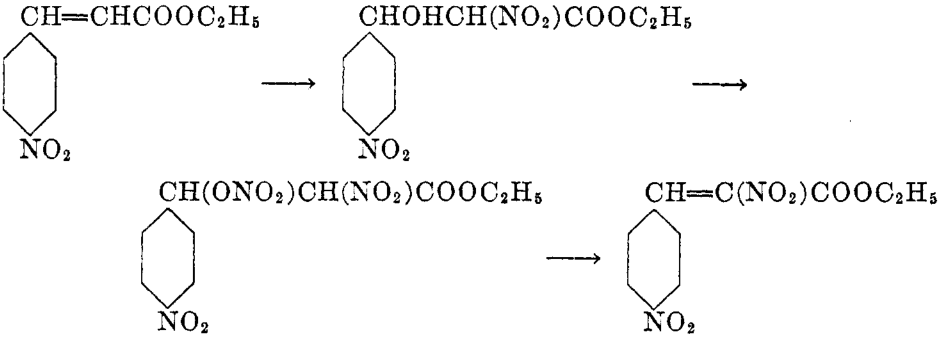
Cinnamic acid nitrates normally with nitric acid to yield a mixture of the *o*- and *p*-nitrocinnamic acids, but when absolute nitric acid (99.7 per cent HNO_3, sp. gr. 1.5204) is used at 0°C. the product is a mixture of β-2-dinitrostyrene and β-4-dinitrostyrene (84):



$R = NO_2, Cl, Br, NH_2, OCH_3$

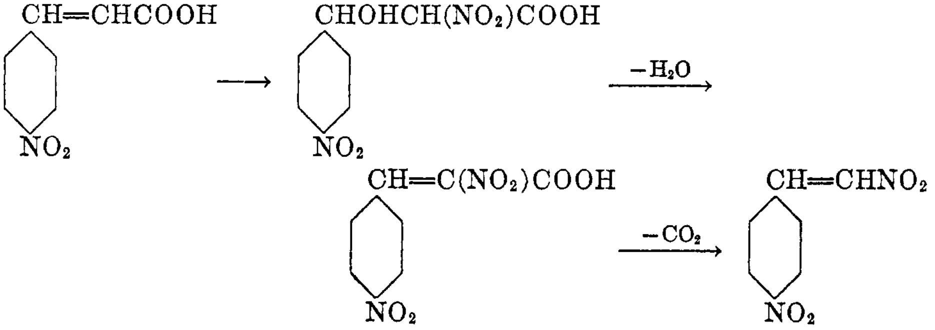
If there is a nitro group in the 2- or 3-position, there is no further nitration of the nucleus. Even β-chloro- and β-bromocinnamic acids yielded some β-chloro-(bromo)-β-*p*-dinitrostyrene (51). Yields of the β-nitrostyrenes were 50 to 75 per cent.

Nitration of ethyl *p*-nitrocinnamate with absolute nitric acid at 0°C. proceeds as follows (84):



I II

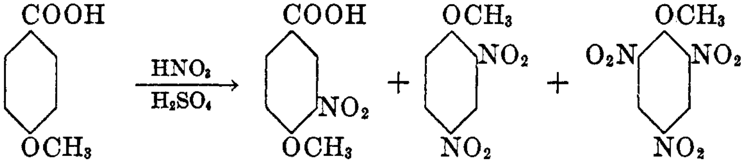
I and II were isolated and their structures established. Van der Lee suggests that the cinnamic acids react similarly:



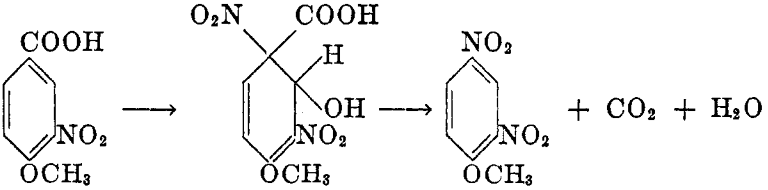
C. Phenolic acids

The replacement of the carboxyl group by a nitro group during the nitration of phenolic acids has been noted by many investigators (17, 23). In general, the carboxyl is more readily replaced when there are two or more hydroxyl groups or other ortho–para-directing groups on the nucleus, yet the nitration of 2,3,4-trimethoxybenzoic acid yields only the normal nitration product. The nitration of 3,4,5-trimethoxybenzoic acid leads to a mixture of the normal nitration product and 5-nitropyrogallol trimethyl ether, but if the nitration is carried out in the presence of a trace of hydrogen peroxide only the normal nitro compound is formed (30).

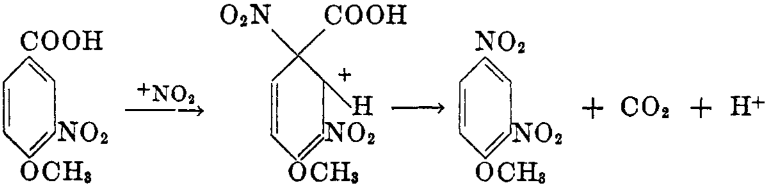
The nitration of anisic acid with sulfuric acid in absolute nitric acid yields three products (18, 23, 66):



Van der Lee (84) explained the replacement as follows:



The reaction can be explained on the basis of the cationoid mechanism of nitration (52):



Examples of the various types of replacement reactions are listed in table 3.

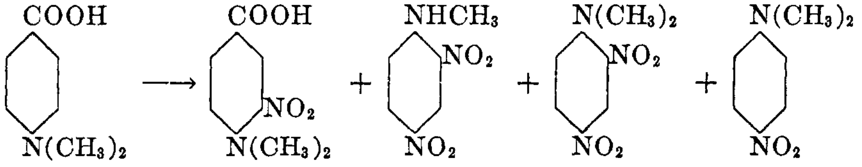
D. Aminobenzoic acids

The nitration of *p*-dimethylaminobenzoic acid can lead to a variety of products, depending on the composition of the nitrating agent and the temperature of the reaction. With a mixture of sulfuric acid and 60 per cent nitric acid at 5–10°C. the normal nitration product, 3-nitro-4-dimethylaminobenzoic acid, is obtained. At temperatures of 60–70°C. a complicated mixture of replacement products results (57, 58).

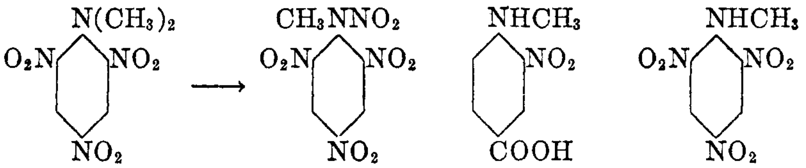
TABLE 3

Nitration of phenolic acids

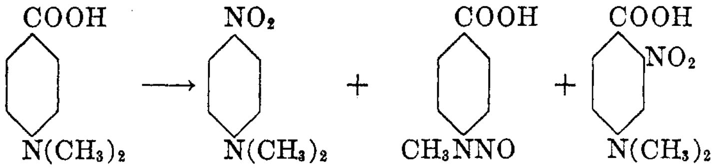
COMPOUND	REAGENT	PRODUCTS	REFERENCES
Salicylic acid	HNO_3 (fuming)	Picric acid	(18)
Anisic acid	HNO_3 (fuming)	Dinitroanisole; 3,5-dinitroanisic acid	(18)
	HNO_3, H_2SO_4	2,4-Dinitroanisole	(66)
	HNO_3, H_2SO_4	3,5-Dinitroanisic acid; 2,4,6-trinitroanisole	(23)
o-Nitrosalicylic acid	HNO_3 (fuming)	*o*-Dinitrophenol; dinitrosalicylic acid	(37)
3,5-Dibromosalicylic acid	HNO_3	6-Bromo-2,4-dinitrophenol	(62)
Dichlorosalicylic acid	HNO_3, CH_3COOH	Dichloronitrophenol	(69)
β-Resorcylic acid	HNO_3	Styphnic acid	(34)
Veratric acid	Hot HNO_3 (1.2)	4-Nitroveratrol	(46)
	HNO_3 (fuming)	3,4,6-Trinitroveratrol	
m-Hemipinic acid		Dinitroveratrol; trinitroveratrol	(33)
Hemipinic acid		Nitrodimethoxybenzoic acid	(88)



Prolonged action of large amounts of nitric acid results in a number of other substances (57):

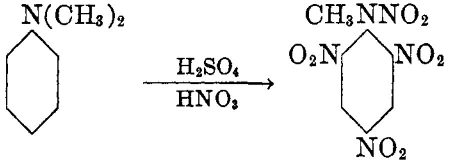


The ease with which the carboxyl group and a methyl group are displaced in *p*-dimethylaminobenzoic acid is illustrated by its reaction with sodium nitrite and hydrochloric acid. The principal products, formed in nearly equal amounts, are as follows (11):

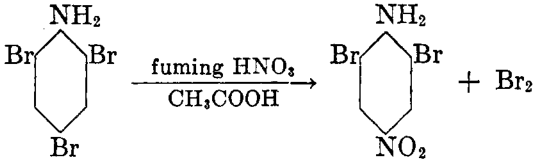


p-Diethylaminobenzoic acid yields corresponding compounds.

One methyl group in dimethylaniline is replaced by a nitro group when the amine is first dissolved in cold sulfuric acid and then nitrated with nitric acid at 40–55°C. (85).



When 2,4,6-tribromoaniline is nitrated with fuming nitric acid in glacial acetic acid, the bromine in the 4-position is replaced by a nitro group (50):



Similar results were obtained with 2-chloro-4,6-dibromo- and 2,6-dichloro-4-bromoanilines, but a chlorine in the 4-position is not replaced.

X. SULFONIC ACIDS

The nitration of sulfonic acids may lead either to normal nitration products or to the replacement by a nitro group of either the sulfonic group, a halogen, or an alkyl group. As might be expected, the products formed depend on the structure of the compound and the experimental conditions. The sulfonic group is readily replaced in the phenolsulfonic acids.

Since numerous examples of these reactions and an extensive bibliography are available in Suter's recent book on the organic sulfur compounds (79), it is not necessary to review them here.

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