Side-Reactions in Aromatic Nitration; Some Synthetic Aspects[1]

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Aromatic compounds undergo three different types of reaction with nitrating agents under ionic conditions; (a) replacement by a nitro group of an atom or a group from a ring position (ordinary nitration), (b) reaction on a substituent group, and (c) addition reaction followed by various transformations. The present survey is directed towards the latter two types of reaction which have been a subject of continuing interest in recent years.

Bei aromatischen Verbindungen sind mit nitrierenden Reagenzien unter ionischen Bedingungen 3 verschiedene Arten von Reaktionen möglich: (a) Substitution eines Atoms oder einer funktionellen Gruppe am Ring (normale Nitrierung), (b) Reaktion an Substituenten und (c) Addition mit nachfolgenden verschiedenartigen Umwandlungen. Die folgende Übersicht behandelt die letzten beiden Reaktionstypen, die besonders in den letzten Jahren großes Interesse fanden.

Nitration is one of the most basic reactions in organic chemistry and is widely used for the preparation of nitro compounds, which are among the most valuable intermediates in organic synthesis. The compound to be nitrated may be either aliphatic or aromatic, however, the reaction has more significance in aromatic chemistry. Aromatic nitration is the process in which the nitro group replaces an atom or group from a ring position of an aromatic compound. The reaction has already been dealt with by a number of excellent reviews and books[2]. In recent years, however, several new reactions have come to light in which the results deviated considerably from the ordinary concept of aromatic nitration. These include various substitutions on the alkyl side-chain of polyalkylbenzenes, nitrative coupling, oxidation to cyclic ketones, and nuclear acyloxylation. In spite of the mechanistic implications, these unusual reactions have so far been described only as a sub-topic and little information has appeared relative to their synthetic potential. This article is therefore intended to provide a basis for understanding this as yet poorly systematized area of aromatic nitrations[3]. A proper knowledge of these non-conventional processes may enable one to avoid the loss of material due to unexpected side reactions which often accompany ordinary nitration.

Although early works are included as far as they seem to be pertinent, the emphasis is not on an exhaustive coverage of the literature but on a survey of the broad spectrum of anomalous nitration so as to display its potential utility in organic synthesis. In most of the references cited herein, little or no effort seems to have been made to maximize the yields.

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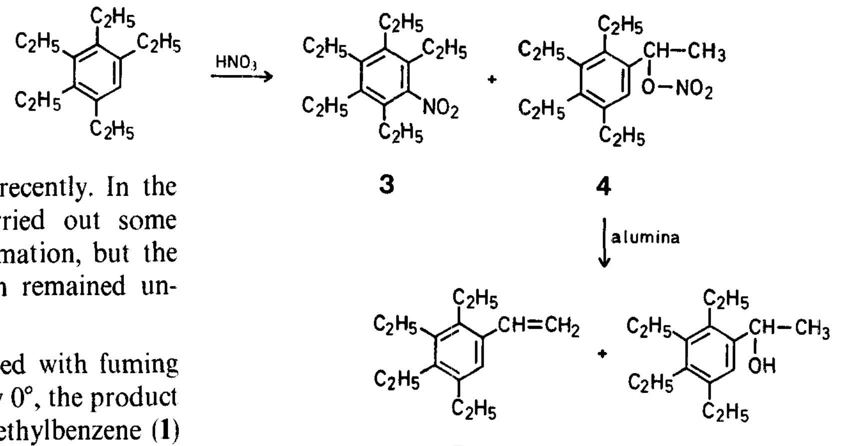
[1] Replacement by nitro group of *sec*- and *tert*-alkyl groups, halogens, acyl, carboxyl, and sulfonyl groups, which constitutes by far the most well documented non-conventional process in the aromatic nitration, is not considered in the present article. Also excluded are side-chain nitration of alkyl aromatics at high temperatures, nitration with nitrogen oxides, and introduction of nitro group *alpha* to a carbonyl function of alkyl aryl ketones.

[2] P. B. D. de la Mare, J. H. Ridd, *Aromatic Substitution, Nitration and Halogenation*, Butterworths, London, 1959.
R. O. C. Norman, R. Taylor, *Electrophilic Substitution in Benzenoid Compounds*, Elsevier, London, 1965.
J. G. Hoggett, R. B. Moodie, J. R. Penton, K. Schofield, *Nitration and Aromatic Reactivity*, University Press, Cambridge, 1971.
K. Schofield, S. R. Hartshorn, *Progress in Organic Chemistry*, Vol. 8, Butterworths, London, 1972, p. 278.
For nitration under radical conditions see, *inter alia*, A. I. Titov, *Tetrahedron* **19**, 557 (1963).
G. Sosnovsky, *Free Radical Reactions in Preparative Organic Chemistry*, G. Sosnovsky, Ed., MacMillan, New York, 1964, p. 213–282.

1. Side-Chain Nitrooxylation

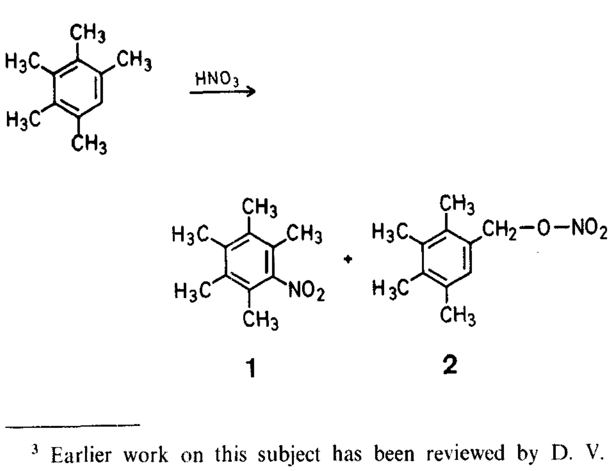
1.1. Polyalkylbenzenes

Although the first report of side-chain nitrooxylation of polyalkylbenzene derivatives appeared more than sixty years ago[4], this unique reaction had received only scattered attention until very recently. In the 1930's Smith[5,6,7] and Rinkes[8] carried out some pioneering work on the nitrate formation, but the character and scope of the reaction remained unclarified.



3 4 5 6

When pentamethylbenzene is nitrated with fuming nitric acid in dichloromethane below 0°, the product is mainly a mixture of nitropentamethylbenzene (**1**) and 2,3,4,5-tetramethylbenzyl nitrate (**2**)[9,10]. Other isomeric nitrates are not formed in any significant amount. 6-Nitro-2,3,4,5-tetramethylbenzyl nitrate, 2,3,4,5-tetramethylbenzaldehyde, 2,3,4,5-tetramethylbenzyl alcohol, and some polymethyldiphenylmethanes are among the minor products[10,11,12].

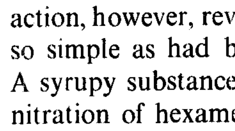


1 2

Pentaethylbenzene similarly reacts to give a mixture of nitropentaethylbenzene (**3**) and α-methyl-2,3,4,5-tetraethylbenzyl nitrate (**4**) along with some minor products of oxidation[9,10]. Repeated chromatography of the crude product on alumina converts nitrate **4** into 2,3,4,5-tetraethylstyrene (**5**) and α-methyl-2,3,4,5-tetraethylbenzyl alcohol (**6**).

Preferential attack occurs at the primary alkyl group adjacent to the unoccupied ring position. Thus, reaction of 1-methyl-2,3,4,5-tetraethylbenzene gives a comparable mixture of benzyl nitrate and α-methylbenzyl nitrate, while 3-methyl-1,2,4,5-tetraethylbenzene yields the secondary nitrate as the major product[10].

The side-chain nitrooxylation seems to be limited to methyl and ethyl groups. 3,6-Diisopropyl-1,2,4-trimethylbenzene undergoes extensive nitrodealkylation, and 2,5-diisopropyl-3,4-dimethylbenzyl nitrate (**7**) is the only side-chain substituted product identified[10].



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The nitration of pentamethylbenzene and hexamethylbenzene has been reported to give dinitrotetramethylbenzene[13]. A reinvestigation of the reaction, however, revealed that the products were not so simple as had been described in the literature. A syrupy substance formed in quantity during the nitration of hexamethylbenzene to 1,2-dinitrotetramethylbenzene has been found to consist of a mixture of pentamethylbenzyl nitrate (**8**) and 5,6-bis-[nitrooxymethyl]-1,2,3,4-tetramethylbenzene (**9**) as the main components, accompanied by nitropentamethylbenzene, 6-nitro-2,3,4,5-tetramethylbenzyl nitrate, pentamethylphenylnitromethane, pentamethylbenzaldehyde, and several other carbonyl compounds, nitrite esters, and aliphatic nitro compounds[14]. Side-

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[3] Earlier work on this subject has been reviewed by D. V. Nightingale, *Chem. Rev.* **40**, 117 (1947).
The original form of the present article appeared in 1972 in a research report of limited circulation; H. Suzuki, *Bull. Inst. Chem. Res., Kyoto Univ.* **50**, 407 (1972).

[4] A. Huender, *Recl. Trav. Chim. Pays Bas* **34**, 1 (1915).

[5] L. I. Smith, D. Tenenbaum, *J. Am. Chem. Soc.* **57**, 1293 (1935).

[6] L. I. Smith, F. L. Taylor, I. M. Webster, *J. Am. Chem. Soc.* **59**, 1082 (1937).

[7] L. I. Smith, J. W. Horner, *J. Am. Chem. Soc.* **62**, 1349 (1940).

[8] I. J. Rinkes, *Recl. Trav. Chim. Pays Bas* **57**, 1405 (1938).

[9] H. Suzuki, K. Nakamura, K. Maruyama, *Bull. Chem. Soc. Jpn.* **41**, 1487 (1968).

[10] H. Suzuki, K. Nakamura, *Bull. Chem. Soc. Jpn.* **43**, 473 (1970).

[11] E. Hunziker, J. R. Penton, H. Zollinger, *Helv. Chim. Acta* **54**, 2043 (1971).

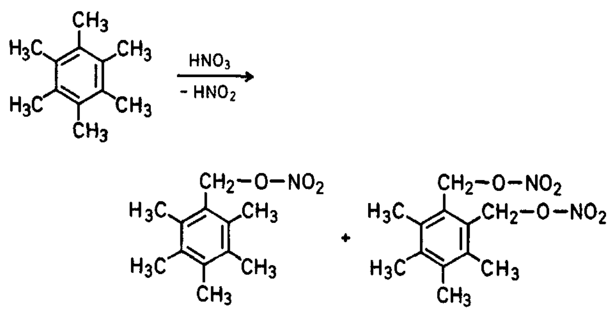
[12] E. Hunziker, P. C. Myhre, J. R. Penton, H. Zollinger, *Helv. Chim. Acta* **58**, 230 (1975).

[13] L. I. Smith, S. A. Harris, *J. Am. Chem. Soc.* **57**, 1289 (1935).

[14] H. Suzuki, *Bull. Chem. Soc. Jpn.* **43**, 879 (1970).

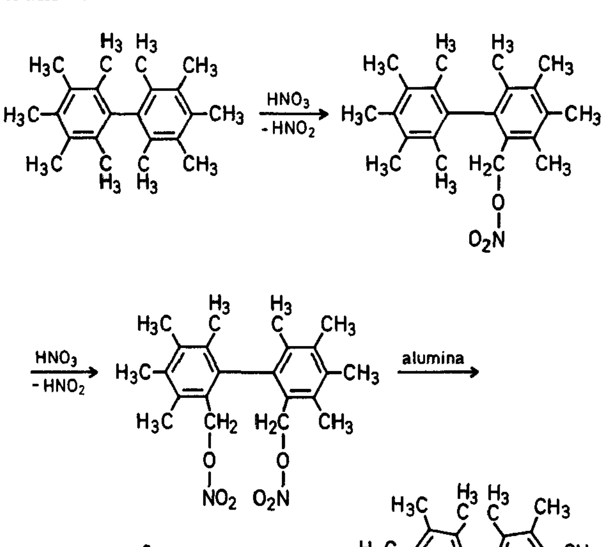
[15] H. Suzuki, *Nippon Kagaku Zasshi* **91**, 179 (1970); *C.A.* **73**, 14388 (1970).

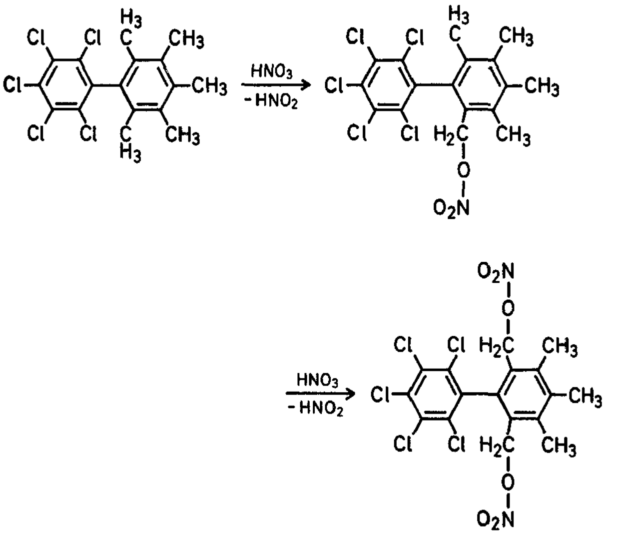
chain nitrooxylation of hexamethylbenzene thus provides a convenient preparative route to pentamethylbenzoic acid[15].



8 **9**

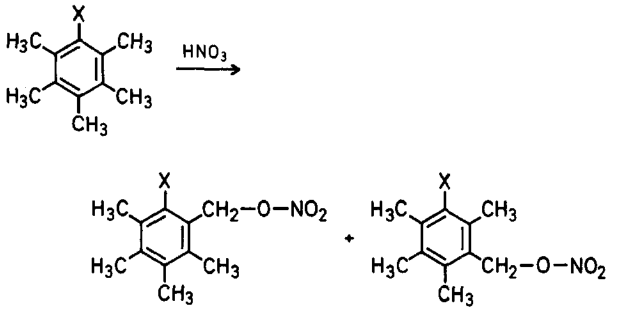
The high regiospecificity of the side-chain nitrooxylation reaction is best manifested in the nitration of decamethylbiphenyl and 2,3,4,5,6-pentamethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl. Exclusive *ortho* attack occurs on the alkyl side-chain and the crude product showed no peaks attributable to *meta* or *para* nitrooxymethyl groups in the ^{1}H-N.M.R. spectrum[16].





1.2. Halogen Derivatives of Polyalkylbenzenes

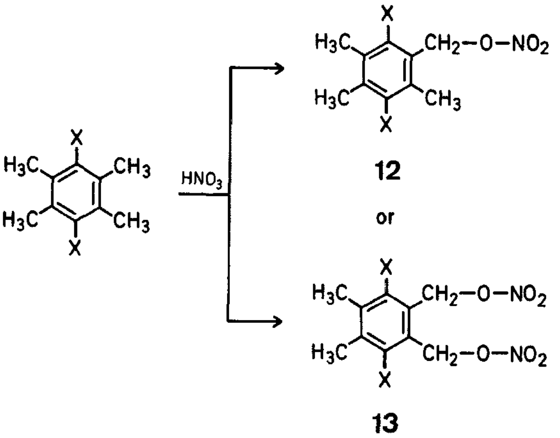
The action of the nitrating agent upon halopentamethylbenzenes leads to comparable amounts of 6-halo-2,3,4,5-tetramethylbenzyl nitrate (**10**) and 5-halo-2,3,4,6-tetramethylbenzyl nitrate (**11**). 4-Halo-2,3,5,6-tetramethylbenzyl nitrate is never formed in any significant amounts[7,17]. The amount of *meta* substitution relative to *ortho* increases from 42:58 (X=Cl) to 44:56 (X=Br) to 47:53 (X=J) as the atomic number of the halogen increases. The reaction of iodopentamethylbenzene is always accompanied by an extensive nitrodeiodination[17].



10 **11**

X = Cl, Br or J

The nitration of 3,6-dihalo-1,2,4,5-tetramethylbenzene with fuming nitric acid gives, depending on the reaction conditions, 3,6-dihalo-2,4,5-trimethylbenzyl nitrate (**12**) or 1,2-bis[nitrooxymethyl]-3,6-dihalo-4,5-dimethylbenzene (**13**)[18,19].



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or

13

4,6-Dihalo-1,2,3,5-tetramethylbenzene reacts with fuming nitric acid to give a mixture of 3,5-dihalo-2,4,6-trimethylbenzyl nitrate (**15**) and 2,6-dihalo-3,4,5-trimethylbenzyl nitrate (**14**), the latter being in somewhat greater amount.

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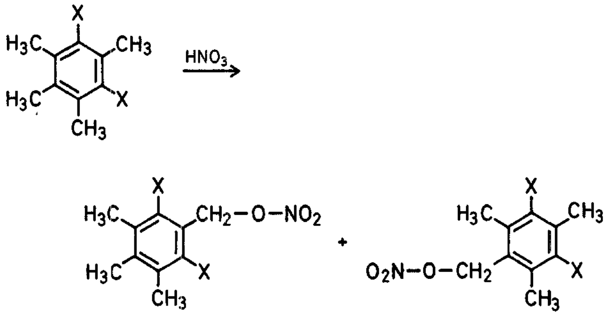
[16] H. Suzuki, O. Yagiu, T. Hanafusa, *Bull. Chem. Soc. Jpn.* **47**, 2260 (1974).

[17] H. Suzuki, *Bull. Chem. Soc. Jpn.* **43**, 481 (1970).

[18] K. Maruyama, K. Nakamura, H. Suzuki, *Nippon Kagaku Zasshi* **89**, 78 (1968); *C.A.* **69**, 26897 (1968).

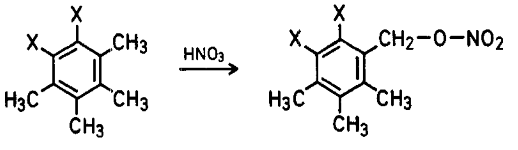
[19] H. Suzuki, K. Nakamura, M. Takeshima, *Bull. Chem. Soc. Jpn.* **44**, 2248 (1971).

[20] H. Suzuki, S. Maruyama, T. Hanafusa, *Bull. Chem. Soc. Jpn.* **47**, 876 (1974).



14 **15**

5,6-Dihalo-1,2,3,4-tetramethylbenzene reacts to give 5,6-dihalo-2,3,4-trimethylbenzyl nitrate (**16**)[19]. These reactions afford a convenient route to some precursors of various substituted benzylic compounds hitherto not easily obtained by ordinary methods.



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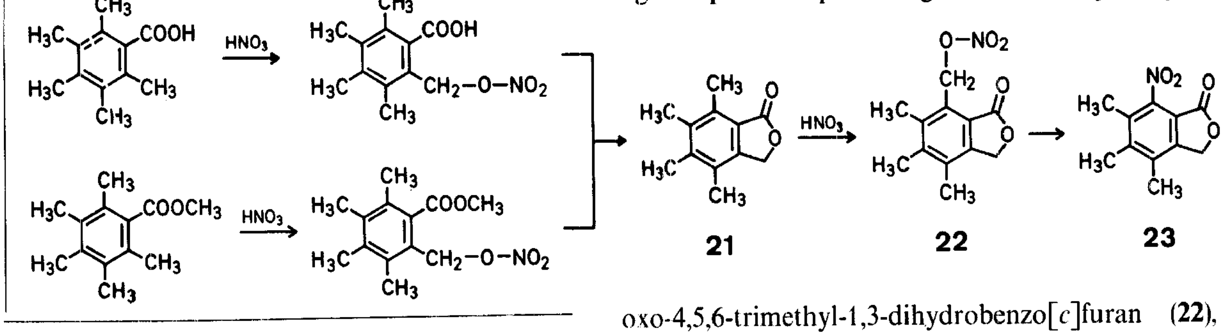
Of the three isomeric trichlorotrimethylbenzenes and tetrachloroxylenes, only 3,5,6-trichloro-1,2,4-trimethylbenzene and tetrachloro-*p*-xylene undergo side-chain nitrooxylation; the former reacts to give a mixture of two nitrates, **17** and **18**, and a nitroketone **19**[20], while the latter gives 4-methyl-2,3,5,6-tetrachlorobenzyl nitrate (**20**) in 82% yield[21].



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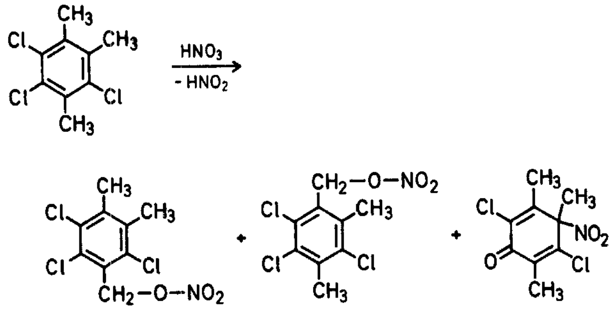
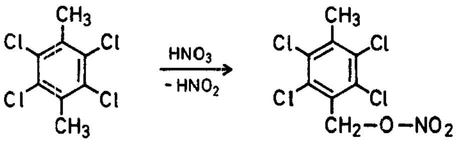


17 **18** **19**



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Preparation of 4-Methyl-2,3,5,6-tetrachlorobenzyl Nitrate (20)[21]:

A suspension of tetrachloro-*p*-xylene (0.51 g) in nitric acid (13 g; d = 1.5) is stirred at room temperature overnight. The dark mixture is poured into ice/water and the precipitated solid is filtered off, washed with aqueous sodium hydrogen carbonate, and dried. The crude product (0.64 g; m.p. 69–72°) is recrystallized from ethanol to give the nitrate as white leaflets; yield: 0.523 g (82%); m.p. 80–82°.

1.3. Carboxy, Cyano, and Nitro Derivatives of Polyalkylbenzenes

With strongly electron-withdrawing substituents such as nitro, cyano, carboxy, and methoxycarbonyl groups, substitution to give benzyl nitrates takes place almost exclusively at the *ortho*-position. Thus, nitropentamethylbenzene, on treatment with excess of fuming nitric acid, gives 6-nitro-2,3,4,5-tetramethylbenzyl nitrate together with only small amounts of 5-nitro-2,3,4,6-tetramethylbenzyl nitrate[22]. No 4-nitro-2,3,5,6-tetramethylbenzyl nitrate is detected.

Nitration of pentamethylbenzonitrile[23], pentamethylbenzoic acid and its methyl ester[22], and amide[24] similarly leads to the formation of the corresponding 6-nitrooxymethyl derivatives, all of which upon acid hydrolysis are converted to 1-oxo-4,5,6,7-tetramethyl-1,3-dihydrobenzo[*c*]furan (**21**). Action of the nitrating agent upon this product gives 7-nitrooxymethyl-1-oxo-4,5,6-trimethyl-1,3-dihydrobenzo[*c*]furan (**22**), which reacts further to give 7-nitro-1-oxo-4,5,6-trimethyl-1,3-dihydrobenzo[*c*]furan (**23**)[24].

Preparation of 1-Cyano-2-nitrooxymethyl-3,4,5,6-tetramethylbenzene[23]:

Fuming nitric acid (6.3 g; d = 1.5) is added dropwise to a strirred solution of pentamethylbenzonitrile (1.73 g) in dichloromethane (15 ml) at 0–5° over a period of 30 min. After the addition, the mixture is left to stand at room temperature for 5 h, and then diluted with water. The organic layer is taken up, thoroughly washed with water and dilute aqueous sodium hydrogen carbonate, and evaporated to give a light brown pasty cake (~2.3 g) which, on crystallization from a mixture of dichloromethane and light petroleum, gives the nitrate as colorless fine needles: yield: 1.98 g (85%); m.p. 85–86°.

On treatment with nitric acid at low temperatures, pentamethylbenzyl cyanide[23] and 4,6-bis[cyanomethyl]-1,2,3,5-tetramethylbenzene[25] give 6-nitrooxy-

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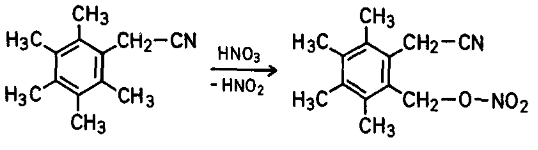
[21] H. Suzuki, K. Ishizaki, S. Maruyama, T. Hanafusa, *Bull. Chem. Soc. Jpn.* **48**, 2112 (1975).

[22] H. Suzuki, K. Nakamura, *Bull. Chem. Soc. Jpn.* **44**, 227 (1971).

[23] H. Suzuki, T. Hanafusa, *Bull. Chem. Soc. Jpn.* **46**, 3607 (1973).

[24] I. S. Isaev et al., *Zh. Org. Khim.* **7**, 2321 (1971); *C.A.* **76**, 59098 (1972).

methyl and 2-nitrooxymethyl derivatives (**24** and **25**, respectively) in 67–85% yields. These nitrates are readily hydrolyzed by dilute hydrochloric acid to give the corresponding 3-isochromanone derivatives in 47–75% yields.



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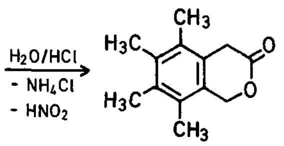

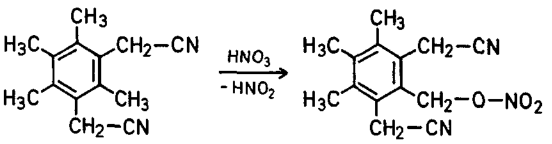

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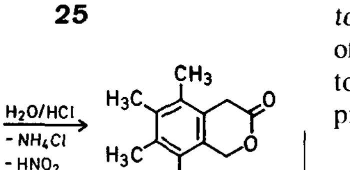
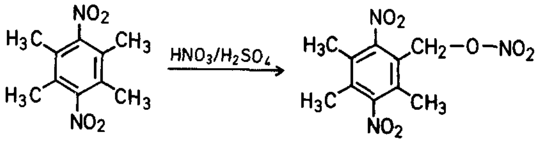


3,6-Dinitro-1,2,4,5-tetramethylbenzene is comparatively stable towards the action of fuming nitric acid, but, on heating with mixed acid at 40–50°, it is slowly converted into 3,6-dinitro-2,4,5-trimethylbenzyl nitrate (**26**), which is allowed to react further and produces 3,6-dinitro-2,4,5-trimethylbenzaldehyde (**27**)[28]. 4,6-Dinitro-1,2,3,5-tetramethylbenzene reacts similarly with mixed acid at room temperature, giving 2,6-dinitro-3,4,5-trimethylbenzyl nitrate (**28**) in 83% yield[28]. In some cases side-chain nitrooxylation seems to be rather sensitive to the nitrating agent used. Thus, the action of mixed acid upon 5,6-dinitro-1,2,3,4-tetramethylbenzene gives 5,6-dinitro-2,3,4-trimethylbenzyl nitrate (**29**) in 62% yield[28], while treatment with excess of fuming nitric acid results in an unsaturated cyclic ketone, **41**[26,27]. (See p. 229.)



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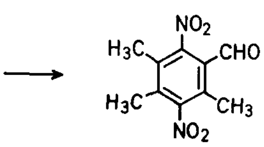

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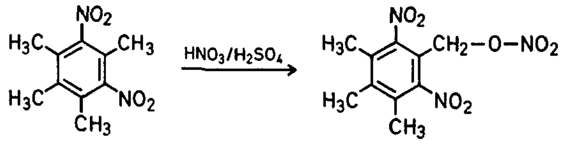

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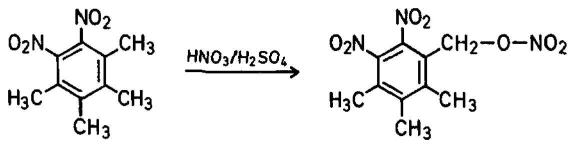

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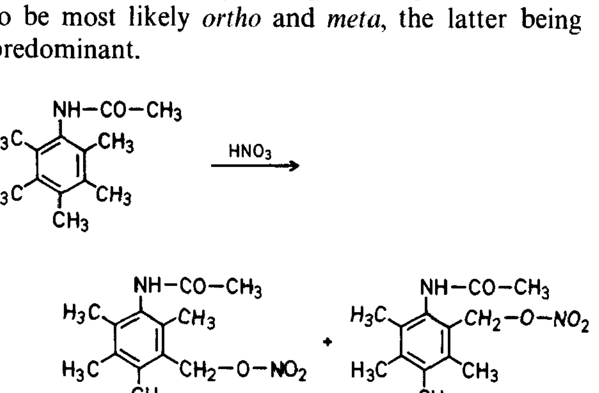
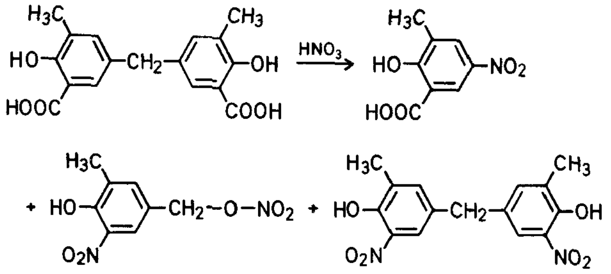
1.4. Polyalkylphenols, Polyalkylphenyl Ethers, and Polyalkylacetanilides

Under the conditions used for nitration, pentamethylphenol and methyl pentamethylphenyl ether give a cyclohexadienone, together with very small amounts of 3-substituted 2,4,5-trimethylbenzyl nitrate[22,30,31]. Under similar conditions, pentamethylacetanilide undergoes the side-chain nitrooxylation to give the two nitrates **30** and **31**[22]. The location of the nitrooxymethyl group in the product seems to be most likely *ortho* and *meta*, the latter being predominant.



major **30** minor **31**

Nitrative cleavage of hydroxydiphenylmethanes under controlled conditions provides a route to some hydroxybenzyl nitrates which are otherwise not readily accessible[32].



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[25] H. Suzuki, T. Hanafusa, *Bull. Chem. Soc. Jpn.* **47**, 2625 (1974).

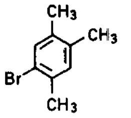
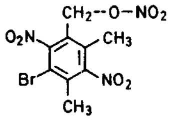
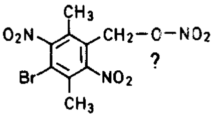
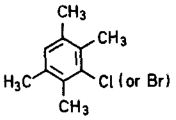
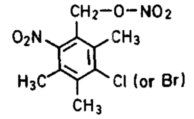
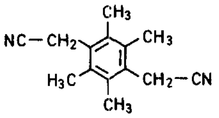
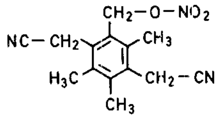
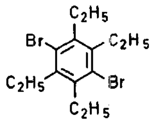
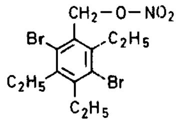
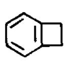
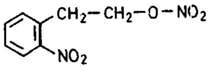
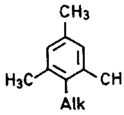
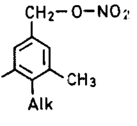
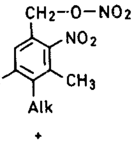
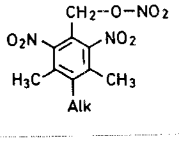
[26] H. Suzuki, K. Nakamura, *J. Chem. Soc. Chem. Commun.* **1972**, 340.

[27] H. Suzuki, K. Nakamura, *Bull. Chem. Soc. Jpn.* **45**, 2534 (1972).

[28] H. Suzuki, K. Nakamura, *Synthesis* **1972**, 606.

[29] K. Nakamura, *Bull. Chem. Soc. Jpn.* **44**, 133 (1971).

Table 1. Side-chain Nitrooxylation of Polyalkylbenzenes and Related Compounds

Compound	Nitrating agent and conditions	Product	Yield [%]	Reference
	HNO_3 / H_2SO_4		-	8
		+ 	-	
	HNO_3 (d = 1.52), 0-5°		-	5,6
	HNO_3 (d = 1.5) / CH_2Cl_2, -5° to 0°		-	25
	HNO_3 (d = 1.5)/H_2SO_4/ $CHCl_3$, -5° to -10°		-[a]	33
	HNO_3 (d = 1.5) / CH_3COOH 20-25°		16-20	34
	HNO_3 (d = 1.5) / $CHCl_3$, -5° to 0°		-	35
		+ 	-	
		+ 	-	

[a] A methyl group is removed during the reaction.

Table 1 contains some more examples of side-chain nitrooxylation.

The side-chain nitrooxylation of polyalkylbenzenes and their derivatives depends closely on the positional relationship of the alkyl groups in the nucleus and the preferential formation of *p*-alkylbenzyl nitrate is always observed.

The relative reactivity of substituted pentamethylbenzenes $C_6(CH_3)_5X$ for side-chain substitution decreases from 1 to 10^{-2} to 10^{-4} to 10^{-6} with the change of substituent groups from CH_3 to H to Br to NO_2 in accordance with the ionic character of the reaction. Added electrolytes have a profound influence on the reaction rates, but the ratio of products from side-chain nitrooxylation and nuclear nitration remains almost unchanged, indicating that both processes share a common intermediate[29].

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[30] A. N. Detsina, V. A. Koptyug, *Zh. Org. Khim.* **8**, 2215 (1972); *C.A.* **78**, 97236 (1973).

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[32] M. Shinoda, T. Asaoka, C. Shimasaki, H. Suzuki, *Nippon Kagaku Kaishi* **1974**, 2375; *C.A.* **82**, 97310 (1975).

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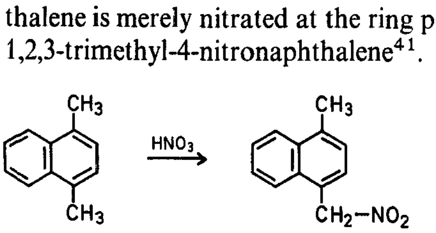
[37] R. Astolfi, E. Baciocchi, G. Illuminati, *Chem. Ind. (Rome)* **53**, 1153 (1971).

[38] K. Chiba, E. Sato, *Nippon Kagaku Kaishi* **1973**, 1249; *C.A* **79**, 52961 (1973).

2. Side-Chain Nitration

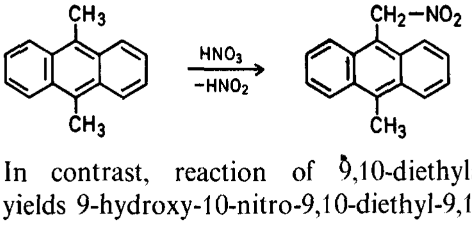
Side-chain nitration of polyalkylbenzenes was first reported by Willstätter and Kubli[36], who treated several polymethylbenzenes with benzoyl nitrate in carbon tetrachloride and obtained, besides the expected ring nitration product, some phenylnitromethane derivatives. The action of fuming nitric acid or acyl nitrate upon hexamethylbenzene also yields some phenylnitromethanes[14,37,38].

When 1,4-dimethylnaphthalene is treated with nitric acid in acetic anhydride[39,40], nitromethane[39], or dichloromethane[41] at low temperatures, the product is 1-methyl-4-nitromethylnaphthalene (**32**). Among the various polymethylnaphthalenes so far investigated, this anomaly seems to be encountered only with those systems in which both the 1- and the 4-positions are occupied by methyl groups. Thus, 1,2,4-trimethylnaphthalene readily undergoes side-chain nitration at the less hindered methyl group to give 3,4-dimethyl-1-nitromethylnaphthalene, and 1,2,3,4-tetramethylnaphthalene yields 2,3,4-trimethyl-1-nitromethylnaphthalene. In contrast, 1,2,3-trimethylnaphthalene is merely nitrated at the ring position to give 1,2,3-trimethyl-4-nitronaphthalene[41].

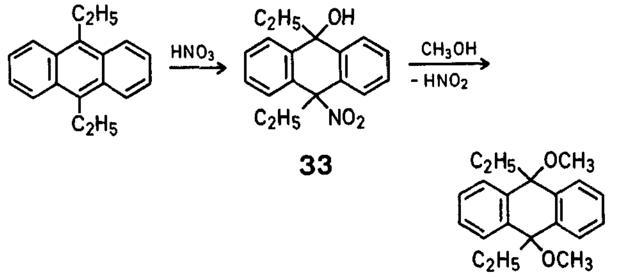


32

9-Methyl-[42], 9,10-dimethyl-[42], and 9-ethyl-10-methylanthracenes[43] all react to give the corresponding nitromethyl derivatives as the major product when treated with fuming nitric acid in dichloromethane at low temperatures. 9,10-Dimethyl- and 9-ethyl-10-methylphenanthrenes behave similarly[44].



In contrast, reaction of 9,10-diethylanthracene yields 9-hydroxy-10-nitro-9,10-diethyl-9,10-dihydroanthracene (**33**), which on refluxing in alcohol is readily converted into 9,10-dialkoxy-9,10-dihydroanthracene (**34**)[42]. Reaction of 9,10-diethylphenanthrene yields a mixture of products arising from side-chain nitration and side-chain nitrooxylation[44], while 9-methyl and 9-ethylphenanthrenes are simply nitrated at the 10-position[43].



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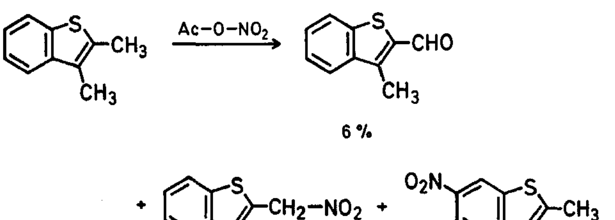
Side-chain nitration also occurs in the nitration of heterocyclic compounds; when treated with acetyl nitrate, 2,3-dimethylbenzo[*b*]thiophene undergoes nitration in the 2-methyl group[45].



Preparation of 3-Methyl-2-nitromethylbenzo[*b*]thiophene[45]:
A solution of 2,3-dimethylbenzo[*b*]thiophene (1.8 g) in acetic anhydride (5 ml) is added rapidly with stirring to a nitrating mixture of 70% nitric acid (0.7 ml) and acetic anhydride (5 ml) at −5°. After 20 min, the mixture is poured into ice/water, neutralized with sodium hydrogen carbonate, and extracted with ether. The yellow solid (1.8 g) obtained after removal of the solvent is chromatographed on silica gel, eluting with hexane and ether/hexane. There is obtained, in order of elution, 2,3-dimethyl-6-nitrobenzo[*b*]-thiophene (0.22 g; 9.6%), m.p. 124–125°; the nitromethyl compound (0.75 g; 32.6%), m.p. 103–104°; 3-methyl-2-benzo[*b*]thiophenecarboxaldehyde (0.12 g; 6.1%), m.p. 88–89°; and polymeric material (0.45 g).

The action of nitric acid upon styrene derivatives often leads to the displacement reaction on the vinyl side-chain, giving rise to β-nitrostyrenes. In some cases the products formed by addition of the nitrating agent to the unsaturated bond are isolated. These should rather be classified as aliphatic nitrations and will not be described further. Some examples are listed in Table 2.

The nitration and nitrooxylation on the alkyl side-chain may be explained by a process involving initial attack of the nitronium ion at the nuclear carbon atom bearing a methyl group which is *para* or *ortho* to another methyl group, followed by a proton release

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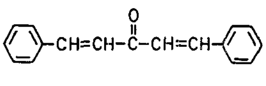
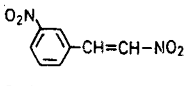
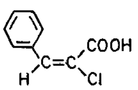
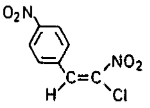
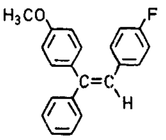
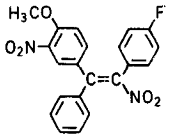
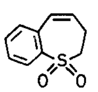
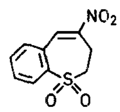
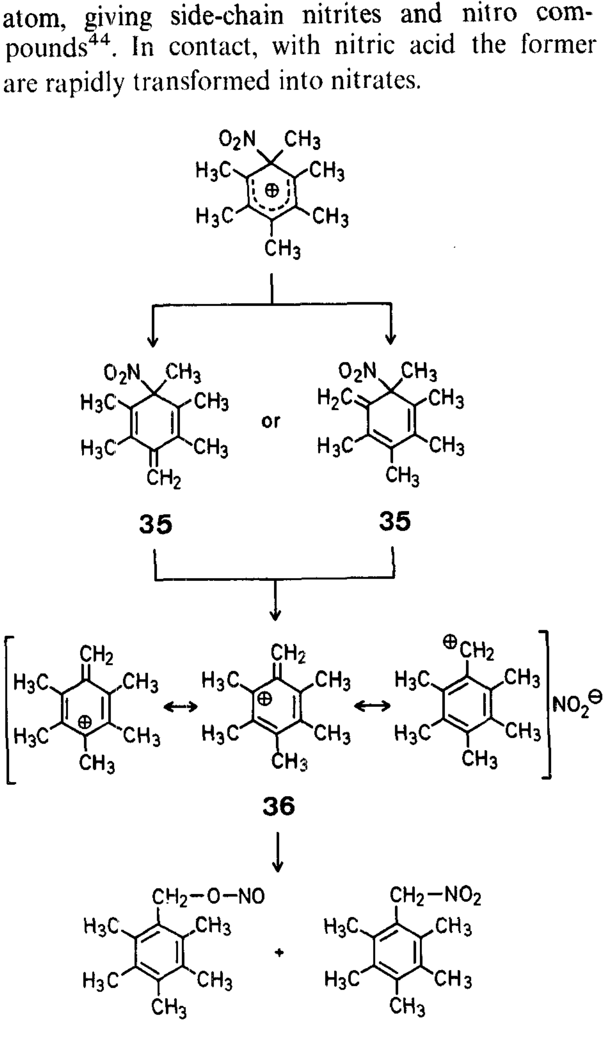
[49] V. J. Traynelis, R. F. Love, *J. Org. Chem.* **29**, 366 (1964).

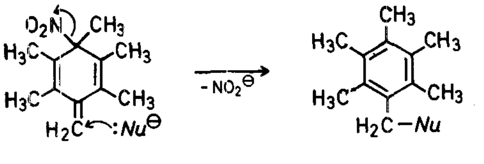
Table 2. Side-chain Nitration of Some Styrene Derivatives

Compound	Nitrating agent and conditions	Product	Yield [%]	Reference
	conc. HNO_3, 0°		60	46
	fuming HNO_3, 20-25°		—	47
	HNO_3 (d = 1.48)/AcOH		55	48
	HNO_3 (d = 1.5), 5-10°		64	49

from the latter group to give a nitromethylenecyclohexadiene **35**, which could collapse by heterolytic C—N bond fission to give an ion-pair **36**. The cationic portion of the ion-pair recombines with the ambident nitrite ion at a benzylic carbon atom either through the oxygen atom or through the nitrogen atom, giving side-chain nitrites and nitro compounds[44]. In contact, with nitric acid the former are rapidly transformed into nitrates.



An alternative possibility may involve a nucleophilic attack of nitrate or nitrite anions at the *exo*-methylene group of **35** with simultaneous loss of the nitro group as nitrite anion[29,50]. Mechanistic aspects of these non-conventional processes are dealt with in a recent review[51].



3. Acetoxylation, Acetamidation, and Alkoxylation on Alkyl Side-Chains

As would be anticipated from the pathways mentioned above, the intermediate nitromethylenecyclohexadiene (**35**) or benzyl cation-nitrite ion pair (**36**) may react with a nucleophile in the reaction medium. Thus, when polymethylbenzenes are nitrated with nitric acid/acetic anhydride, substantial amounts of polymethylbenzyl acetates are obtained[37,52]. These may also arise from the solvolysis of the initially formed benzyl esters, as well as from the decomposition of the addition products.

The use of acetonitrile as solvent leads to the formation of *N*-benzylacetamides[11,23,53]. The acetamidation is thought to be an ionic process in which the benzylic carbon atom of the cationic species attacks the nitrile nitrogen atom to form an iminocarbenium ion type intermediate that is in turn attacked by water, resulting in overall conversion to the amide.

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[50] A. Fischer, J. N. Ramsay, *Canad. J. Chem.* **52**, 3960 (1974).

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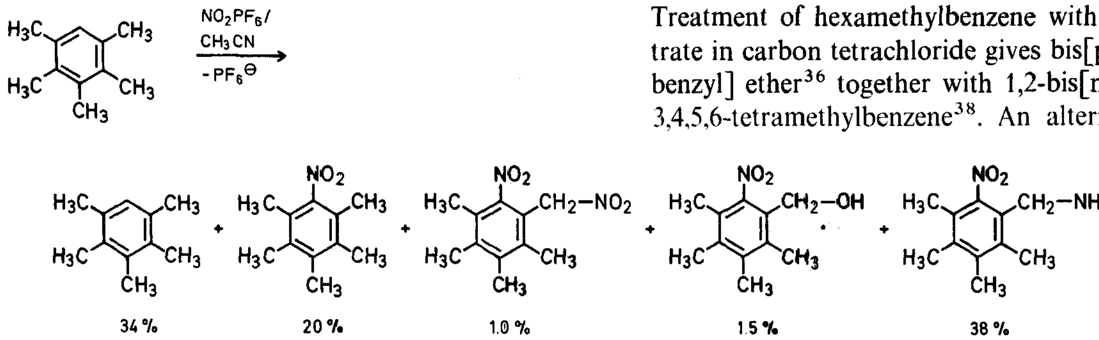
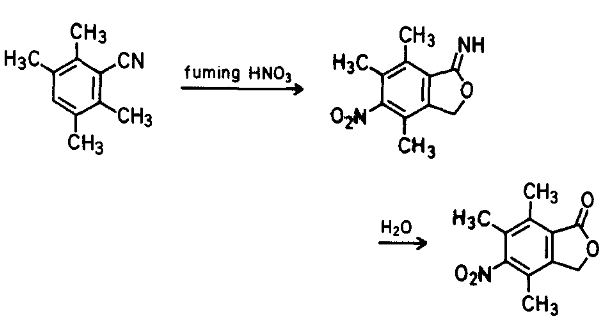


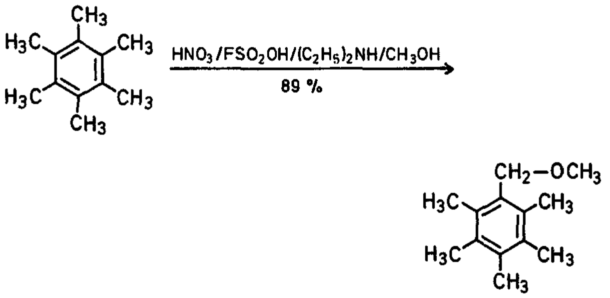
Preparation of N-(Pentamethylbenzyl)-acetamide[23]:

A mixture of hexamethylbenzene (4.1 g) and acetonitrile (30 ml) is cooled in an ice-bath and fuming nitric acid (8.4 g; d = 1.5) is added with vigorous stirring over a period of 30 min. After this the mixture is left to stand for several hours at room temperature, it is then poured into water, the precipitated solid is filtered off, washed with cold carbon tetrachloride, and crystallized from ethanol to give the amide as fine white needles, m.p. 229–231°. Yields based on unrecovered hydrocarbon range from 28 to 60%.

When a solution of tetramethylbenzonitrile or tetramethylbenzenedicarbonitrile in fuming nitric acid is allowed to stand at room temperature for several days and then poured into excess of water, phthalides slowly precipitate from the turbid aqueous solution[54]. If the aqueous solution is neutralized with sodium hydrogen carbonate immediately after quenching, an imino-ether is obtained[55].



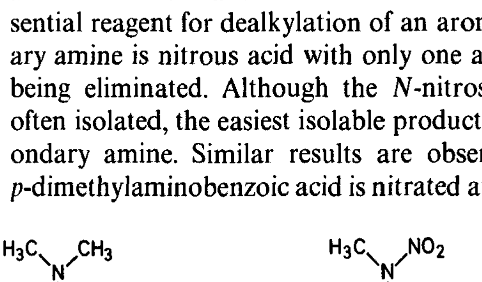
Quenching of the reaction mixture of hexamethylbenzene and fuming nitric acid in fluorosulfonic acid with methanol and diethylamine at −70° gives methyl pentamethylbenzyl ether in high yield[30].



Treatment of hexamethylbenzene with benzoyl nitrate in carbon tetrachloride gives bis[pentamethylbenzyl] ether[36] together with 1,2-bis[nitromethyl]-3,4,5,6-tetramethylbenzene[38]. An alternative direct route to symmetrical bis-benzyl ethers involves chromatography of the nitration product from polymethylbenzenes over activated alumina using light petroleum/benzene as eluent[19].

4. Displacement Reactions on the Lateral Nitrogen and Oxygen Atoms

When N,N-dimethylaniline is treated with mixed acid at 40–55°, one of the methyl groups in the dimethylamino function is replaced by a nitro group[56]. On the nitration routes are encountered various intermediates, which include 2,4-dinitro-N-methylaniline, and its N-nitroso and N-nitro derivatives[57]. The essential reagent for dealkylation of an aromatic tertiary amine is nitrous acid with only one alkyl group being eliminated. Although the N-nitrosoamine is often isolated, the easiest isolable product is the secondary amine. Similar results are observed when p-dimethylaminobenzoic acid is nitrated at 60–70°[58].



The nitration of anisole often leads to the formation of a mixture of nitroanisoles and nitrophenols in proportions which depend upon the experimental conditions; e.g., when anisole is nitrated with 40% nitric acid, the principal products are nitrophenols; with more concentrated nitric acid nitroanisoles are the main products[59].

The reaction has been assumed to involve the attack of a nitronium or nitrosonium ion at the oxygen atom to which the alkyl group is attached to form an oxonium ion, which then loses an alkylcarbenium ion after the usual heterolytic pattern of the onium ion decomposition[60].

Dealkylation and subsequent oxidation by nitric acid is the typical reaction of 1,4-dialkoxybenzenes having certain electron-releasing substituents in the 2- and 5-positions[61]. The behavior of diphenyl ethers on nitration is in many ways similar; when 4-chloro-2-nitrophenyl 4′-methylphenyl ether is allowed to dissolve in cold fuming nitric acid, the main product formed is 4-chloro-2,6-dinitrophenol[62].

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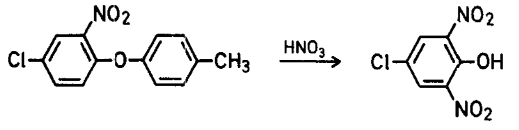
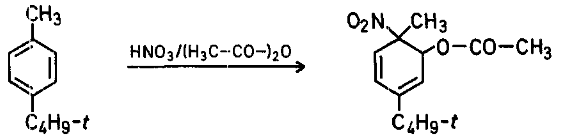


5. Formation of Addition Products

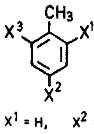
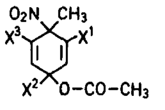
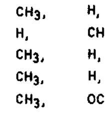
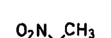
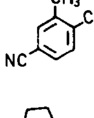
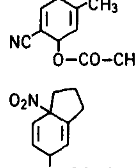
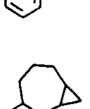
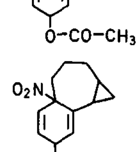
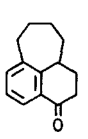
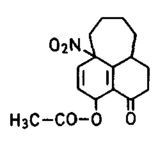
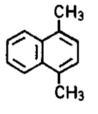
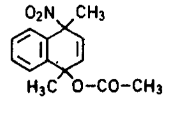
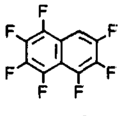
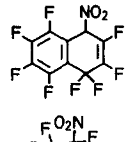
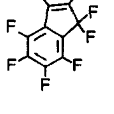
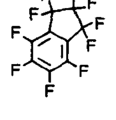
Since the ordinary nitration reaction proceeds through an intermediate of the carbenium type, this intermediate can give rise to products of addition by a process in which the nucleophile is captured. Thus, in acetic acid/acetic anhydride as solvent, moderately stable acetoxynitrocyclohexadienes are obtained in good yields from various polyalkylbenzenes (Table 3). These adducts occur as pairs of *cis*- and *trans*-isomers and, either on heating or in contact with acidic media, undergo a variety of rearomatization reactions leading to aryl acetates or nitroarenes[50,63,73].



Preparation of 2-Cyano-4,5-dimethyl-4-nitro-2,5-cyclohexadienyl Acetate[63]:

A solution of 3,4-dimethylbenzonitrile (15 g) in acetic anhydride (60 ml) is added to a mixture of pure nitric acid (23 ml) and acetic anhydride (50 ml) at 0°. The mixture is allowed to react at 15° for 24 h, then it is cooled in Dry Ice/acetone, ether is added, and ammonia is condensed into the solution. The cooling bath is removed, excess ammonia allowed to evaporate, the residue poured on to ice, and extracted with ether. The extract is thoroughly washed with water, dried over magnesium sulfate, and the ether evaporated at low temperature to give a dark red oil (yield: 23 g) whose N.M.R. spectrum indicated the composition: the starting material (41 %), diene (29 %), 5-, 2-, and 6-nitro-3,4-dimethylbenzonitriles (16, 8, and 5 %, respectively). Chromatography on alumina at 0° and elution with ether/pentane gives the unchanged nitrile in the 10% ether fraction, nitro compounds in the 20–40% frac-

Table 3. Addition Products Obtained in the Nitration of Alkylbenzenes and Related Compounds

Compound	Nitrating agent and conditions	Product	Yield [%]	References
	$HNO_3/(H_3C{-}CO{-})_2O$			
X^1 = H, X^2 = H, X^3 = H				64
CH_3, H, H				52, 65
H, CH_3, H				50
CH_3, H, CH_3				52
CH_3, H, Cl				67
CH_3, OCH_3, H				66
	$HNO_3/(H_3C{-}CO{-})_2O$, 0°		29	63
	$HNO_3/(H_3C{-}CO{-})_2O$, -30°		36-41	68
	$HNO_3/(H_3C{-}CO{-})_2O$		60	69
	$HNO_3/(H_3C{-}CO{-})_2O$, -50°		39	70
	$HNO_3/(H_3C{-}CO{-})_2O$, -40°		27	40
	HNO_3/HF, 20°			71
	HNO_3/HF, 15°		72	72

tions, and a diene in the 50% fraction. Recrystallization from carbon tetrachloride of the residue obtained after removal of the solvent from the 50% ether fraction gave the diene as white cubes; m.p. 87.5–88.5°.

6. Acetoxylation and Alkoxylation

When *o*-xylene is nitrated with nitric acid in acetic anhydride, the products are 4-acetoxy-*o*-xylene besides the expected 3- and 4-nitro-*o*-xylenes[74]. Other polymethylbenzenes behave similarly (Table 4).

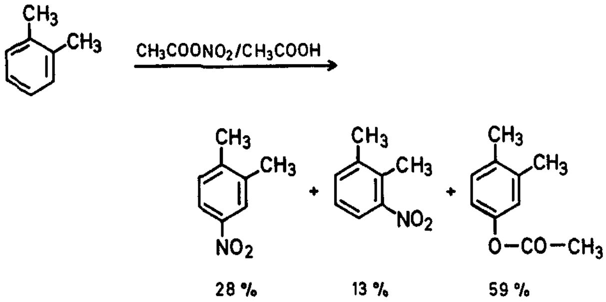
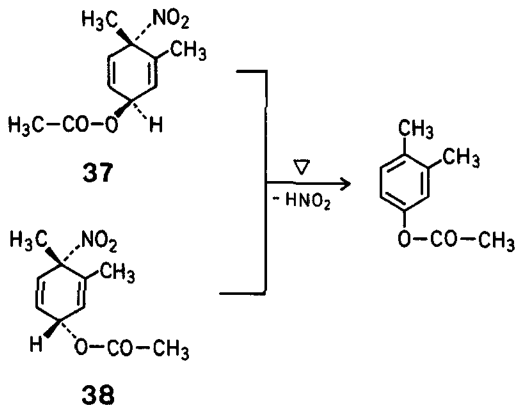


Table 4. Nitration and Acetoxylation of Some Methylbenzenes[a, 75, 76]

Compound	Nitro compounds [%][b]				Acetoxy compounds [%][b]		
	2-	3-	4-	5-	3-	4-	5-
toluene	58.2	2.8	35.9	—	—	3.1	—
o-xylene	—	13.5	28.0	—	—	58.6	—
m-xylene	14.7	—	84.7	—	—	0.7	—
hemimellitene	—	—	46.4	7.7	—	10.6	35.3
pseudocumene	—	10.0	—	49.5	10.3	—	25.6

[a] In nitric acid/acetic anhydride mixtures.
[b] Mol-% of total product.

The reaction was first suggested to involve the attack of protonated acetyl nitrate ($H_3CCOONO_2H^{\oplus}$)[74], but convincing evidence in support of an addition-elimination sequence has been presented[65, 76]; two adducts isolated from the reaction mixture, **37** and **38**, give the 4-acetoxy-*o*-xylene either on heating or on contact with aqueous acidic media.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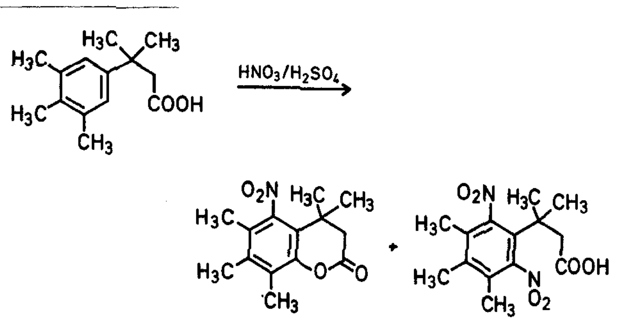
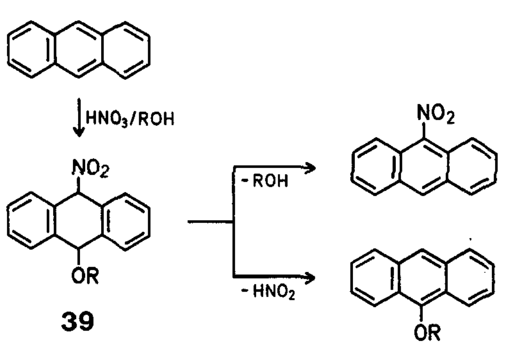
Upon treatment with mixed acid at 10°, β-(3,4,5-trimethylphenyl)-isovaleric acid or its methyl ester yields a cyclic compound, 4,4,6,7,8-pentamethyl-5-nitrohydrocoumarin, together with the expected dinitro derivative[77]. The reaction may follow a pathway similar to that shown above, but the situation is not clear as yet.



Polycylic aromatic hydrocarbons readily undergo addition reactions with electrophiles. Thus, when treated with nitric acid in the presence of an appropriate nucleophile (ROH), anthracene forms an isolable adduct **39** which, on heating, loses either nitrous acid or ROH to give products of substitution[78, 79]. Reaction of phenanthrene with absolute nitric acid at low temperature yields a coupling product, bis[9-nitro-10-phenanthryl] ether[80].


39

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[65] D. J. Blackstock et al., *J. Chem. Soc. Chem. Commun.* **1970**, 641.
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[71] O. I. Osina, V. D. Shteingarts, *Zh. Org. Khim.* **10**, 335 (1974); *C.A.* **80**, 120615 (1974).
[72] V. M. Karpov, V. E. Platonov, G. G. Yakobson, *Zh. Org. Khim.* **10**, 663 (1974); *C.A.* **80**, 133094 (1974).
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[74] A. Fischer, A. J. Read, J. Vaughan, *J. Chem. Soc.* **1964**, 3691.
[75] A. Fischer, J. Vaughan, G. J. Wright, *J. Chem. Soc. [B]* **1967**, 368.
[76] D. J. Blackstock, A. Fischer, G. J. Wright, *Aust. J. Chem.* **26**, 775 (1973).
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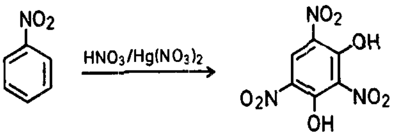
[78] E. de B. Barnett, J. W. Cook, M. A. Matthews, *J. Chem. Soc.* **123**, 1994 (1923).

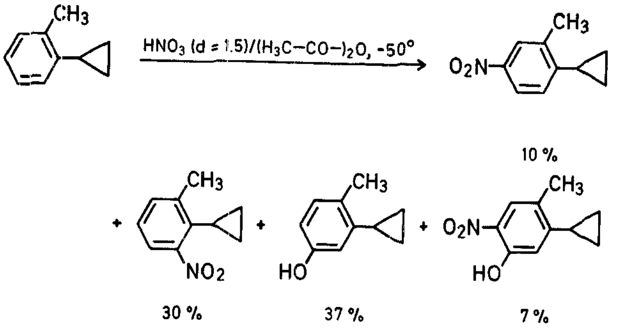
7. Oxynitration

When alkylbenzenes are nitrated with concentrated nitric acid or mixed acid and the aqueous ammonia washings of the crude product are treated with dilute acid, there are often obtained small amounts of nitrophenols in addition to the expected nitration products. The formation of phenolic substances is facilitated when some metal ion catalyst is added to the system. Thus, when benzene or its derivatives are nitrated in the presence of mercuric nitrate, polynitrohydroxy derivatives are obtained in fair to moderate yields (Table 5).



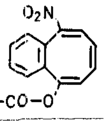
The reaction, usually called as oxynitration, is supposed to involve initial mercuration, followed by the displacement of the mercury by a nitroso group, and the reduction of the nitroso group to a diazonium ion. This decomposes to a phenol which is then nitrated[89]. A similar course is followed in the nitric acid oxidation of *o*-nitrotoluene to picric acid[90].

Nitration of *o*-cyclopropyltoluene in acetic anhydride leads to a mixture of nitro and hydroxyphenyl derivatives, the three-membered ring being retained. Under the same conditions the *p*-isomer gives products from opening of the cyclopropane ring[91].



Preparation of 3-Cyclopropyl-4-methylphenol[91]:
To a mixture of nitric acid (1.3 ml; d = 1.5) and acetic anhydride (4 ml), *o*-cyclopropyltoluene (1 g) is added at −50°. The reaction mixture is stirred at this temperature for 2 h and then added to hot water (80°). The products are extracted with ether, the extract is washed with water, saturated aqueous sodium carbonate, and again with water, and dried over magnesium sulfate. The solvent is removed, the residue is passed over alumina with light petroleum and a 10:1 mixture of ether and methanol as eluents. The following products are obtained: 2-cyclopropyl-5-nitrotoluene (10%), 2-cyclopropyl-3-nitrotoluene (30%), and 3-cyclopropyl-4-methylphenol (37%). From the soda washings 3-cyclopropyl-4-methyl-6-nitrophenol is obtained in 7% yield.

Table 5. Oxynitration of Aromatic Hydrocarbons and Related Compounds

Compound	Nitrating agent and conditions	Product	Yield [%]	Reference
benzene	50% $HNO_3/Hg(NO_3)_2$, 45–50°	2,4-dinitrophenol and picric acid	51% (9:1)	81
benzoic acid	HNO_3 (d = 1.35)/$Hg(NO_3)_2$, 105°, 20 h	3-hydroxy-2,4,6-trinitrobenzoic acid	—	82
o-xylene	HNO_3	2,3-dimethyl-4,6-dinitrophenol	—	83
acetoxymercuri-*p*-xylene	58% $HNO_3/Hg(NO_3)_2$, 2–4°	2,5-dimethyl-4,6-dinitrophenol	24	84
2-iodo-4-methyl-5-nitroanisole	HNO_3 (d = 1.5)	6-hydroxy-4-methyl-2,3,5-trinitroanisole	—	85
biphenyl	HNO_3 (d = 1.45), r.t.	4-hydroxy-3,4′,5-trinitrobiphenyl	22	86
quinoline	56% $HNO_3/Hg(NO_3)_2$	5-hydroxy-6,8-dinitroquinoline	—	86
quinoxaline	HNO_3 (d = 1.51)/$(F_3C—CO)_2O$, r.t., 88 h	x-hydroxy-y-nitroquinoxaline	28	87
biphenylene	$HNO_3/(H_3C—CO)_2O$	 O2N H3C–CO–O	40	88

Nitration of naphthalene gives rise to small amounts of 2,4-dinitro-1-naphthol, and the amount of this

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[79] J. W. Cook, *J. Chem. Soc.* **1926**, 2160.
[80] H. Wieland, F. Rahn, *Ber. Dtsch. Chem. Ges.* **54**, 1770 (1921).
[81] W. O. Teeters, M. B. Müller, *U.S. Patent* 2455322 (1948); *C.A.* **43**, 1805i (1949).
[82] R. Wolffenstein, J. Paar, *Ber. Dtsch. Chem. Ges.* **46**, 589 (1913).
[83] E. Nölting, B. Pick, *Ber. Dtsch. Chem. Ges.* **21**, 3158 (1888).
[84] P. I. Petrovich, *Zh. Obshch. Khim.* **29**, 2387 (1959); *C.A.* **54**, 9811 (1960).
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G. M. Bennett, J. F. Grove, *J. Chem. Soc.* **1945**, 378.
[87] M. J. S. Dewar, P. M. Maitlis, *J. Chem. Soc.* **1957**, 2518.
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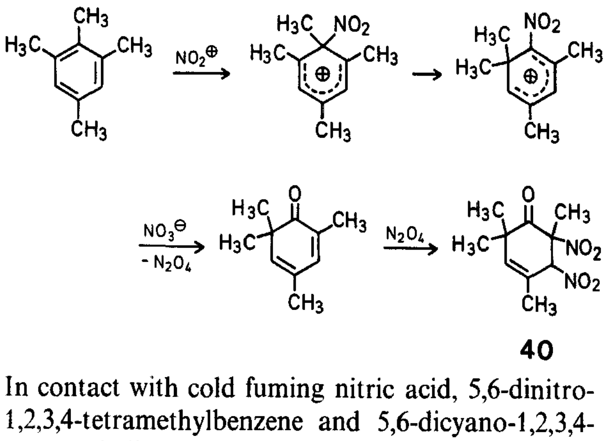
[89] F. H. Westheimer, E. Segel, R. Schramm, *J. Am. Chem. Soc.* **69**, 773 (1947).
M. Carmack et al., *J. Am. Chem. Soc.* **69**, 785 (1947).
[90] C. Håkanson, M. Nilsson, *Acta Chem. Scand.* **21**, 1978 (1967).
[91] Y. S. Shabarov, S. S. Mochalov, N. B. Matveeva, I. P. Stepanova, *Zh. Org. Khim.* **11**, 568 (1975); *C.A.* **82**, 155620 (1975).

by-product is increased by carrying out the reaction in the presence of nitrite ion[92]. An addition-elimination sequence is suggested to be involved in the reaction. The action of nitric acid upon 9-bromoanthracene affords nitroanthranol and 9-bromo-10-nitroanthracene, the former being predominant[93].

8. Formation of Carbonyl Compounds

8.1. Cyclohexanones and Cyclohexadienones

When 1,2,3,5-tetramethylbenzene is treated with excess nitric acid in dichloromethane below 0°, a small amount of unsaturated cyclic ketone **40** is obtained in addition to the normal ring substitution product[94]. 2-Ethyl-1,3,5-trimethylbenzene behaves similarly, giving 5,6-dinitro-2-ethyl-1-oxo-2,4,6-trimethylcyclohex-3-ene in 2–4% yield[94]. The formation of these ketones can be accounted for by an addition-elimination sequence involving 1,2-migration of alkyl groups.



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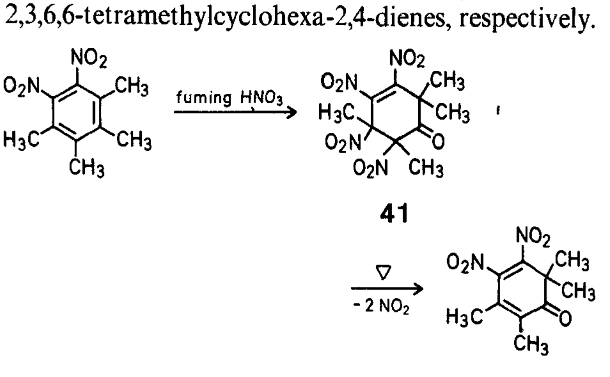
In contact with cold fuming nitric acid, 5,6-dinitro-1,2,3,4-tetramethylbenzene and 5,6-dicyano-1,2,3,4-tetramethylbenzene are converted to 1-oxo-2,3,6,6-tetramethyl-2,3,4,5-tetranitrocyclohex-4-ene (**41**)[27] and 4,5-dicyano-2,3-dinitro-1-oxo-2,3,6,6-tetramethylcyclohex-4-ene[55], respectively. These ketones are thermally unstable and on heating they lose nitrogen dioxide to form 4,5-dinitro- and 4,5-dicyano-1-oxo-2,3,6,6-tetramethylcyclohexa-2,4-dienes, respectively.



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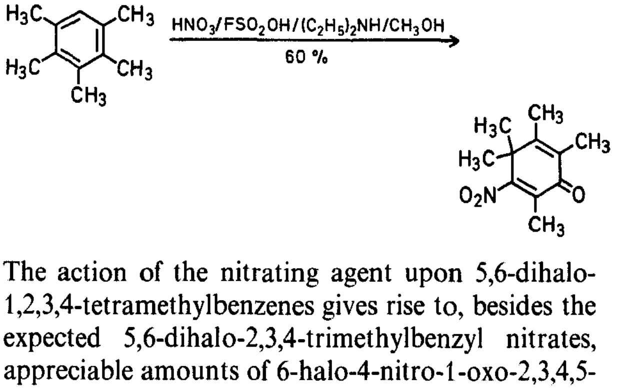
Preparation of 1-Oxo-2,3,6,6-tetramethyl-2,3,4,5-tetranitrocyclohex-4-ene (41)[27]:

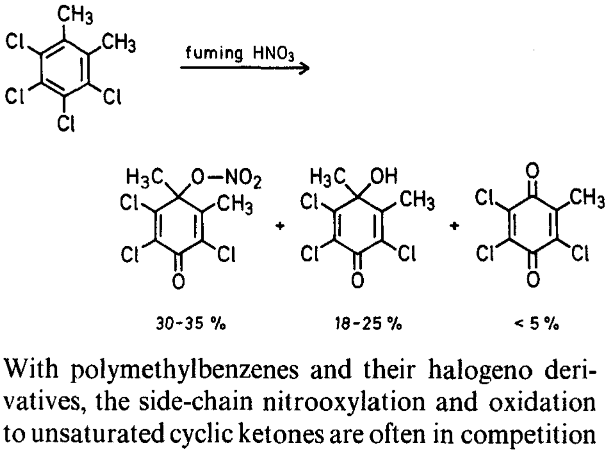
Dinitroprehnitene (7.5 g) is dissolved in cold fuming nitric acid (60 ml; d = 1.5) and the mixture allowed to stand at room temperature for several days, during the course of which the initial dark color fades to light yellow. On diluting with water, a pasty precipitate is obtained, which is thoroughly washed with water and dissolved in a minimum amount of dichloromethane. The solution is warmed at 35–40°, light petroleum (b.p. 40–50°) is added until the solution becomes slightly cloudy, and the solution left to stand under cover. The ketone soon begins to crystallize as pale yellow prisms; yield: 8.8–9.4 g (79–85%); m.p. 111–114° (complete decomp.).

By dissolving this ketone in hot carbon tetrachloride 4,5-dinitro-1-oxo-2,3,6,6-tetramethylcyclohexa-2,4-diene is obtained as bright yellow prisms, m.p. 94–96°.

An example of a multi-step methyl migration has been observed during the nitration of pentamethylbenzene with nitric acid in fluorosulfonic acid[95].



The action of the nitrating agent upon 5,6-dihalo-1,2,3,4-tetramethylbenzenes gives rise to, besides the expected 5,6-dihalo-2,3,4-trimethylbenzyl nitrates, appreciable amounts of 6-halo-4-nitro-1-oxo-2,3,4,5-tetramethylcyclohexa-2,5-dienes, which are converted to the corresponding 4-hydroxy derivatives during aqueous work-up[96]. Similar treatment of tetrachloro-*o*- and *m*-xylenes with fuming nitric acid gives 1,2-dimethyl-4-oxo-3,5,6-trichlorocyclohexa-2,5-dienyl nitrate and 1,3-dimethyl-4-oxo-2,5,6-trichlorocyclohexa-2,5-dienyl nitrate, respectively, as the major products[21,97].



With polymethylbenzenes and their halogeno derivatives, the side-chain nitrooxylation and oxidation to unsaturated cyclic ketones are often in competition and, when the substrate contains two methyl groups in a *para* relationship, preference for the side-chain

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[92] H. E. Fierz-David, R. Sponagel, *Helv. Chim. Acta* **26**, 98 (1943).

[93] E. de B. Barnett, J. W. Cook, *J. Chem. Soc.* **125**, 1084 (1924).

[94] These ketones were first formulated as 3-alkyl-2,4,6-trimethyl-5,6-dinitrocyclohex-3-enones (H. Suzuki, M. Sawaki, R. Sakimoto, *J. Chem. Soc. Chem. Commun.* **1971**, 1509; *Bull. Chem. Soc. Jpn.* **45**, 1834 (1972)), but later revised as 2-alkyl-2,4,6-trimethyl-5,6-dinitrocyclohex-3-enones on the chemical and spectral grounds (Unpublished work with Prof. S. Sternhell and co-workers).

[95] A. N. Detsina, V. I. Mamatyuk, V. A. Koptyug, *Izvest. Akad. Nauk SSSR, Ser. Khim.* **1973**, 2163; *C.A.* **80**, 26842 (1974).

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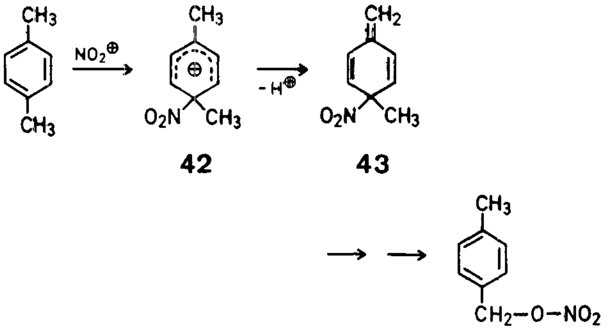
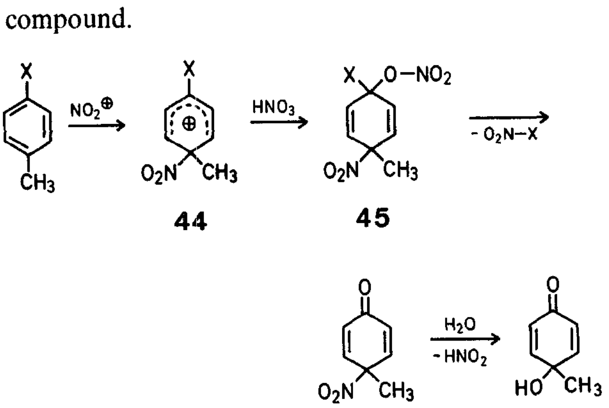
[97] H. Suzuki, K. Ishizaki, S. Maruyama, T. Hanafusa, *J. Chem. Soc. Chem. Commun.* **1975**, 51.

substitution dominates. The dichotomy of the reaction would presumably be determined by the structure of the most favored intermediate ion;

(a) If the ion has the structure **42** in which the nitro group is attached to the nuclear carbon atom bearing a methyl group which is *para* to another methyl group, proton release would occur from the latter group to give a nitrocyclohexadiene **43** which could be transformed into benzyl nitrate.

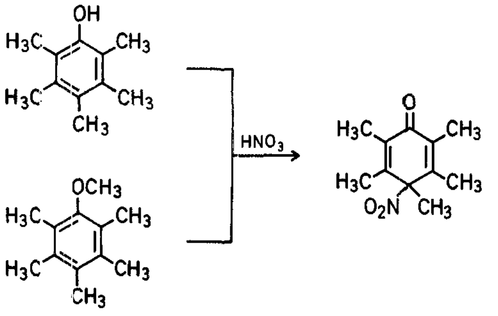


(b) If the ion has the structure **44** in which the nitro group is attached to the ring carbon atom bearing a methyl group which is *para* to a halogen atom, capture of the nitrate ion by the halogen-bearing carbon would occur to give an addition product **45**, which will then be converted to the unsaturated carbonyl compound.

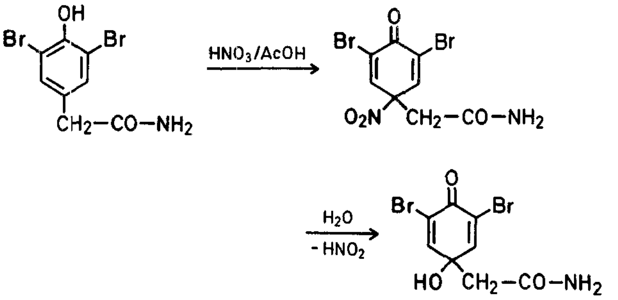


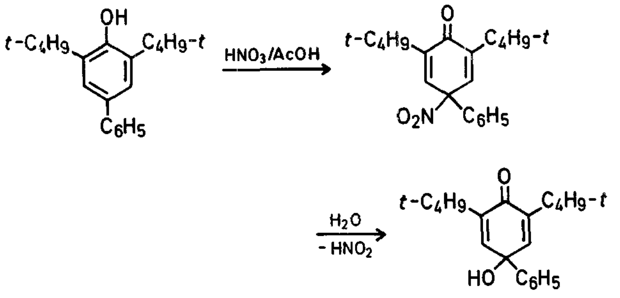
In accordance with the above guides (a) and (b), 3,5,6-trichloro-1,2,4-trimethylbenzene undergoes both side-chain nitrooxylation and nuclear oxidation to give two nitrates and an enone, while 2,4,6-trichloro-1,3,5-trimethylbenzene and 4,5,6-trichloro-1,2,3-trimethylbenzene yield only carbonyl compounds[20].

Nitration of phenols and phenolic ethers results in the formation of nitrocyclohexadienones (Table 6). Both pentamethylphenol and pentamethylanisole react actively with nitric acid to give an oily substance of almost identical composition, the main component of which is usually 4-nitro-1-oxo-2,3,4,5,6-pentamethylcyclohexa-2,5-diene[22, 30, 31].



As the nitro group on a doubly activated allylic position is subject to facile hydrolysis, 4-hydroxy-1-oxo-cyclohexa-2,5-dienes are often obtained as the major products from the nitration mixture[98, 99].





Treatment of pentachloro- or pentafluorophenols with excess of fuming nitric acid yields the corresponding pentahalo-4-(pentahalophenoxy)-cyclohexa-2,5-dienones[114], the formation of which is explained by the recombination of pentahalophenoxy radicals[100].

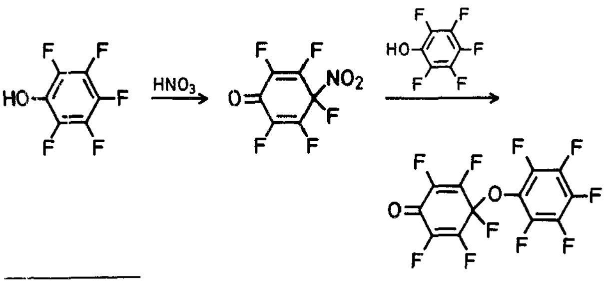


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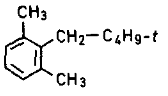
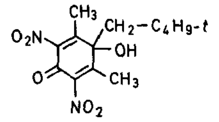
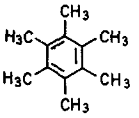
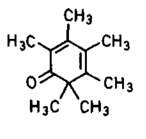
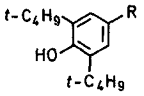
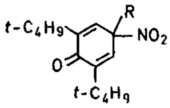
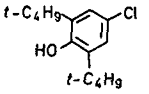
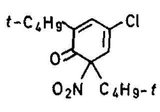
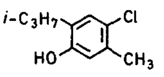
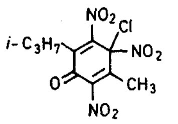
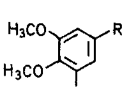
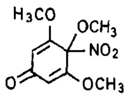
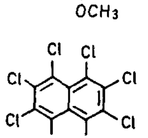
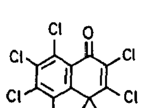
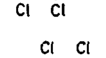
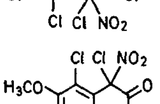
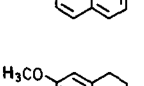
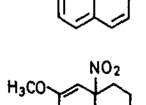
Table 6. Cyclohexenones and Cyclohexadienones Obtained in the Nitration of Polyalkylbenzenes and Related Compounds

Compound	Nitrating agent and conditions	Product	Yield [%]	Reference
	HNO_3(d = 1.4) / $(H_3C{-}CO{-})_2O$, r. t.		-	101
	HNO_3 / HSO_3F, -70°		63	30
	HNO_3 / CH_3COOH 0-5°		R = CN: 47 R = NO_2:52 R = CH_3:67 R = CHO:73	102
	HNO_3, 5°		62	102
	HNO_3 / $CHCl_3$, 20°		-	103
	HNO_3 /$(H_3C{-}CO)_2O$ -70°		R = AcO: 80 R = H_3CO: 51	104
	HNO_3 (d = 1.5), 0-3°		94	105
	HNO_3 / CH_3COOH		-	106
	HNO_3(d = 1.42) / CH_3COOH, 10°		-	107

8.2. Quinones

Formation of quinones during the nitration of phenols and phenolic ethers is quite common and has practical importance in organic synthesis. The reactions are usually performed under mild conditions and are very rapid. 1,2-Benzoquinones are less stable than are the corresponding 1,4-isomers and are rarely obtained. Oxidative demethylation leading to quinones is favored by the presence of electron-releasing groups in the 2- and 5-positions, although 2,6-disubstitution in a phenolic ether supresses the dealkylation to a significant extent. Tetra- and pentamethoxybenzenes usually undergo oxidative demethylation and hydrolysis concurrently, leading to the formation of mono- or dihydroxyquinones. The reaction has proved to be of considerable value in the determination of the structures of naturally occurring phenolic compounds[108].

The oxidation of phenols and phenolic ethers to quinones would involve the electrophilic attack by the nitronium ion at the site *para* to an oxygen atom, followed by removal of a cationic species from the oxygen and hydrolysis of the resulting cyclic dienone **46** to the quinone **47**. It is possible that reactions involving the nitrosonium ion, $NO^{\oplus}$, may also occur.

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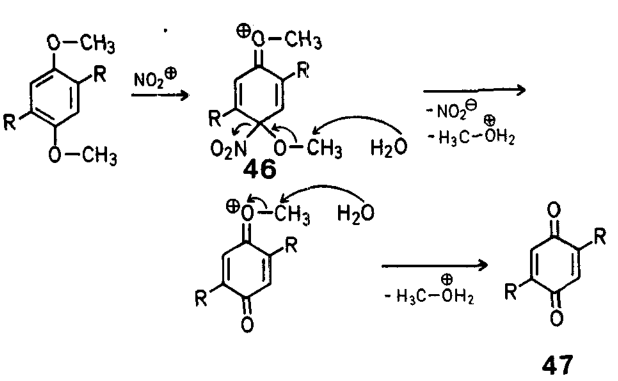
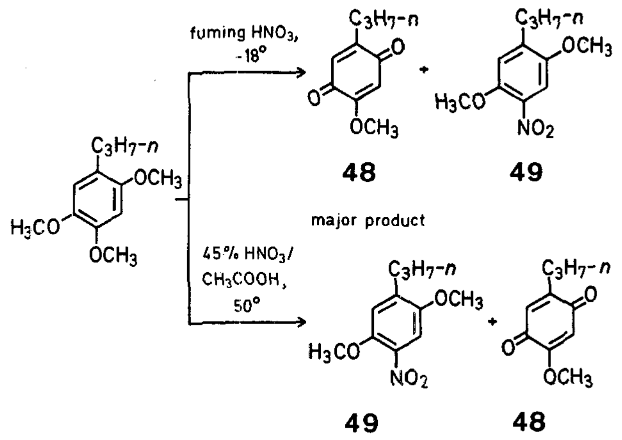
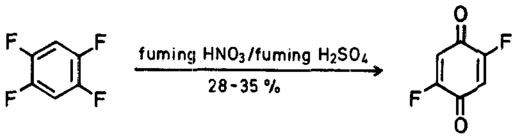




Nitration of polyhalobenzenes under forcing conditions often leads to the formation of quinones; all attempts to prepare a nitro derivative of 1,2,4,5-tetrafluorobenzene by nitration have failed[109].



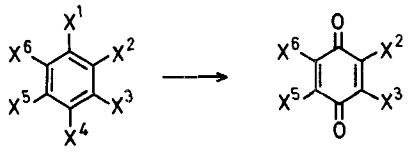
An interesting reaction is observed when 1-*n*-propyl-2,4,5-trimethoxybenzene is subjected to the nitration; with fuming nitric acid at −18°, it gives the quinone **48** as the major product, while with 45% nitric acid in acetic acid at 50°, **49** is predominant in the product mixture, the methoxy group having been displaced by a nitro group[110].

Preparation of Hexachloro-1,2-naphthoquinone[139]:

To a suspension of 3,4,5,6,7,8-hexachloro-2-naphthol (3.0 g) in glacial acetic acid (100 ml), a solution of nitric acid (2.0 ml) in acetic acid (5.0 ml) is added. The mixture is heated gently to dissolve the solid and is then set aside for 14 h. The solution is poured into ice/water (100 ml), and the yellow precipitate is filtered off and washed with water; yield: 2.8 g (90%); m.p. 145° (decomp.; from $CHCl_3$).

A compilation of various quinones and related compounds which have been obtained by the nitration of polyhalobenzenes, phenols, and phenolic ethers is presented in Table 7. In order to conserve space the tabulation is only representative.

Table 7. Quinones Obtained in the Nitration of Halobenzenes, Alkoxybenzenes, and Related Compounds



Halobenzenes and Alkoxybenzenes:

X^1	X^2	X^3	X^4	X^5	X^6	Nitrating agent and conditions	Yield [%]	References
F	F	F	F	F	F	HNO_3, 80°	30	111
F	Cl	F	Cl	F	Cl	HNO_3 (d = 1.51)	50	111
HO	Br	H	Br	H	Br	HNO_3 (d = 1.5), 0°	—	112
HO	J	H	F	H	J	HNO_3 (d = 1.5), 0°	—	112
HO	Cl	Cl	Cl	Cl	Cl	fuming HNO_3	17–40	113
HO	Cl	Cl	Cl	Cl	Cl	HNO_3/pentane	67[a]	114
H	NO_2	HO	OCH_3	H	CH_3	HNO_3/CH_3COOH	59	115
HO	CN	CN	HO	CH_3	H	HNO_3/ether	80	117
OCH_3	Cl	H	F	H	Cl	HNO_3 (d = 1.5), 0°	—	112
OCH_3	*t*-C_4H_9	H	H	CH_3	H	$HNO_3/(H_3CCO)_2O$, −20° to −15°	—	116
OCH_3	OCH_3	H	H	H	CH_3	HNO_3 (d = 1.4)/ CH_3COOH	—	118
OCH_3	OCH_3	H	Cl	Cl	H	HNO_3 (d = 1.45)/ $(H_3C{-}CO)_2O$, 0–2°	20	119
OCH_3	Cl	H	OCH_3	Cl	H	HNO_3 (d = 1.5)	—	120
OCH_3	Br	Br	OCH_3	H	Br	HNO_3 (d = 1.5)	—	121
OCH_3	2-Cl-C_6H_4	H	OCH_3	2-Cl-C_6H_4	H	HNO_3 (d = 1.4)	—	122
OCH_3	Br	Br	OCH_3	H	$H_3C{-}CO{-}NH{-}$	HNO_3/CH_3COOH	28[b]	123
OCH_3	CH_3	CH_3	OCH_3	CH_3	CHO	HNO_3 (d = 1.4)	—[c]	124
OCH_3	NH_2	H	OCH_3	CH_3	H	HNO_3 (d = 1.4)/ $(H_3C{-}CO)_2O$	78[d]	129

Table 7. (Continued)

X^1	X^2	X^3	X^4	X^5	X^6	Nitrating agent and conditions	Yield [%]	Ref-er-ences
H	OCH_3	H	OCH_3	H	OCH_3	HNO_3/ CH_3COOH or C_2H_5OH	19–80	132
OCH_3	OCH_3	H	OCH_3	n-C_3H_7	H	HNO_3	—	125
OCH_3	OCH_3	H	OCH_3	$(C_6H_5)_2C(CH_3)$—	H	HNO_3/CH_3COOH	—	126
OCH_3	OCH_3	H	OCH_3	cinnamoyl	OH	HNO_3/CH_3COOH	—	127
OCH_3	OCH_3	H	OCH_3	CHO	H	HNO_3/H_2SO_4 (as catalyst)	—^{e}	128
OCH_3	OCH_3	Br	OCH_3	H	Br	HNO_3 (d = 1.41)	84	130
OCH_3	OCH_3	Br	OCH_3	CH_3	Br	HNO_3 (d = 1.4), 50°	—	131
OC_2H_5	OC_2H_5	H	H	H	OC_2H_5	HNO_3/CH_3COOH or C_2H_5OH	43–59	133
$OCH_2C_6H_5$	$OCH_2C_6H_5$	H	H	H	$OCH_2C_6H_5$	HNO_3/CH_3COOH	45	134
$OCH_2C_6H_5$	$OCH_2C_6H_5$	H	H	H	OCH_3	HNO_3/ CH_3COOH, 40°	44	135
OCH_3	OCH_3	Br	OCH_3	H	OCH_3	35% HNO_3 C_2H_5OH, 35°	—	136
OCH_3	OCH_3	2-H_3C—$COOC_6H_4$	OCH_3	OCH_3	2-H_3C—$COOC_6H_4$	HNO_3 (d = 1.42)/ CH_3OH/H_2O	—	137

Related Compounds

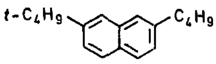
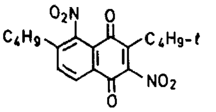
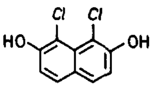
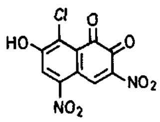
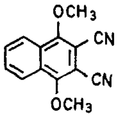
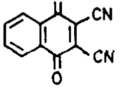
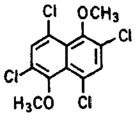
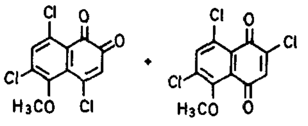
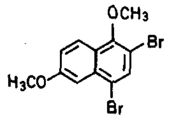
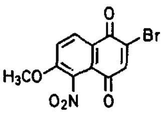
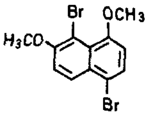
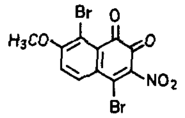
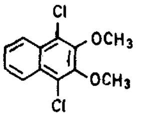
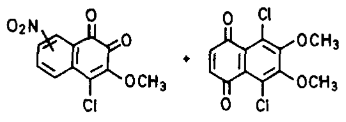
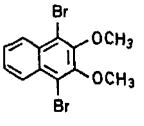
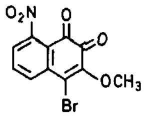
Substrate	Product	Nitrating agent and conditions	Yield [%]	Re-er-ences
		HNO_3/CH_3COOH	22	138
		HNO_3/CH_3COOH	—	106
		HNO_3	—	140
		HNO_3	—	142
		fuming HNO_3/ CH_3COOH	—	142
		HNO_3/CH_3COOH	—	142
		HNO_3	—	141
		HNO_3	—	142

Table 7. (Continued)

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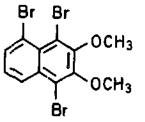
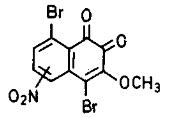
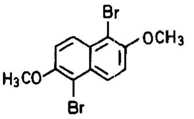
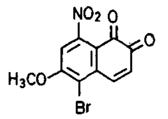
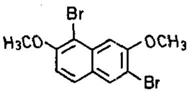
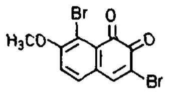
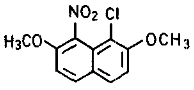
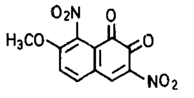
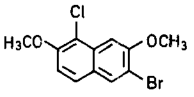
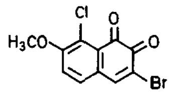
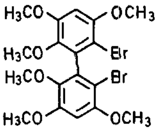
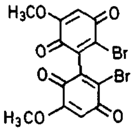
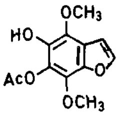
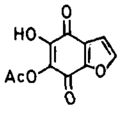
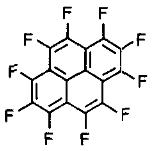
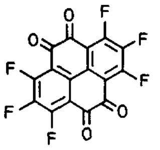
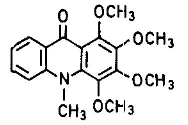
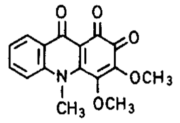
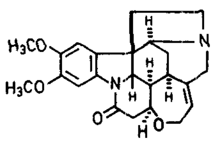
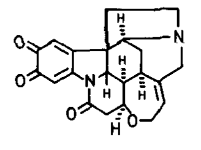
	→		HNO_3	—	142
	→		HNO_3(d=1.42)/ CH_3COOH,r.t.	—	143
	→		fuming HNO_3/ CH_3COOH	—	106
	→		fuming HNO_3	—	106
	→		HNO_3/CH_3COOH	—	106
	→		HNO_3	—	144
	→		HNO_3/ether	—	145
	→		HNO_3(d=1.51), 70°	52	146
	→		HNO_3	—[f]	147
 brucine	→		HNO_3, −5°	80	148

[a] Product is 3,4,5,6-tetrachloro-1,2-benzoquinone.

[b] Product is 6-acetamido-2,3-dibromo-5-nitro-1,4-benzoquinone.

[c] Product is 6-nitro-2,3,5-trimethyl-1,4-benzoquinone.

[d] Product is 2-acetamido-5-methyl-1,4-benzoquinone.

[e] Product is 2-diacetoxymethyl-5-methoxy-1,4-benzoquinone.

[f] 10-Methyl-2,3-dimethoxyacridone-1,4-quinone is also formed.

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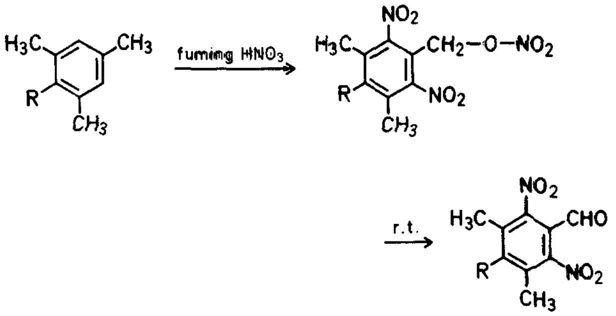
8.3. Benzaldehydes

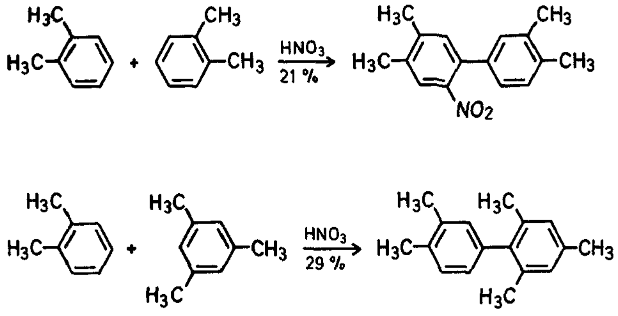
When the nitration of 2-alkyl-1,3,5-trimethylbenzene *is carried out by dissolving the hydrocarbon in a large* excess of cold fuming nitric acid, the major product is 4-alkyl-3,5-dimethyl-2,6-dinitrobenzyl nitrate soon after the reaction and 4-alkyl-3,5-dimethyl-2,6-dinitrobenzaldehyde when the mixture is left to stand at room temperature[35]. Preferential oxidation occurs at the non-vicinal methyl group.



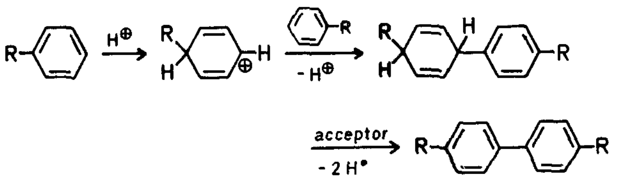
4,6-Dinitro-1,2,3,5-tetramethylbenzene readily reacts with fuming nitric acid at room temperature, giving 2,6-dinitro-3,4,5-trimethylbenzaldehyde in 77–84% yield[27]. Small amounts of 2,6-dinitro-3,4,5-trimethylbenzoic acid and 2,6-dinitro-3,4,5-trimethylphenylnitromethane are obtained as by-products. Dinitrotrimethylbenzaldehydes can also be prepared by heating the corresponding benzyl nitrates in wet dimethyl sulfoxide under gentle reflux[28].

9. *Nitrative Coupling*

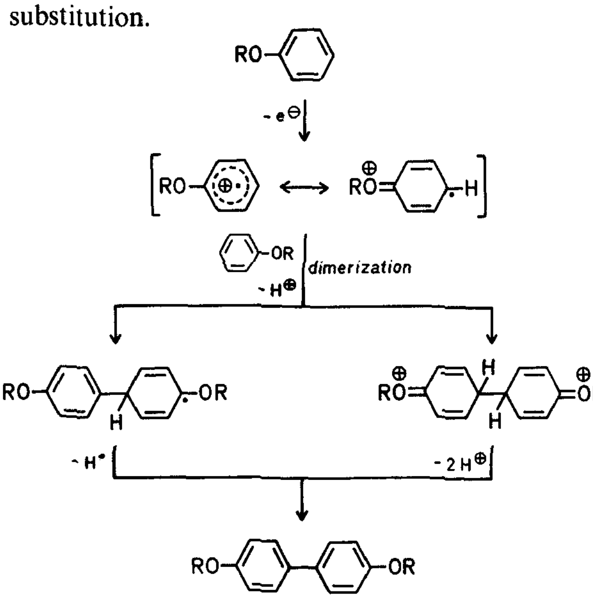
Nitration of alkyl homologs of benzene is often accompanied by coupling to give the nitrobiphenyls if the nitric acid is added to the hydrocarbon. This reaction was observed as early as in 1911[149], but its *synthetic value has received no attention until recently*. The reaction is quite sensitive to the structure of the hydrocarbon. Thus, *o*-xylene, *o*-ethyltoluene, 1,2,3- and 1,2,4-trimethylbenzenes give appreciable amounts of coupling, while toluene, *m*- and *p*-xylene, 1,3,5-trimethylbenzene, and 1,2,3,4-tetramethylbenzene form little or no coupling product[151]. When a mixture of *o*-xylene or 1,2,3-trimethylbenzene with more basic methylbenzenes are similarly treated, cross-coupled products are obtained in acceptable yields[152]. In these, the predominant path is coupling followed by nitration. Although the nitration mixtures contain many components such as the starting hydrocarbons, nitrated hydrocarbons and polyalkylbiphenyls, the last compounds are easily isolated by fractionation[152]. It appears possible to use this procedure as a preparative method for some polyalkylbiphenyls.



Two main types of mechanism have been suggested for these reactions; in the first, protonation of the aromatic molecule is followed by ordinary electrophilic substitution and subsequent dehydrogenation to the biphenyl.



The second mechanism involves the initial formation of a cation radical followed by dimerization or radical substitution.



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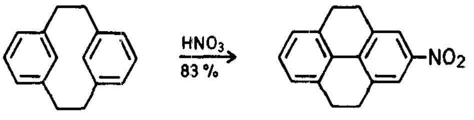
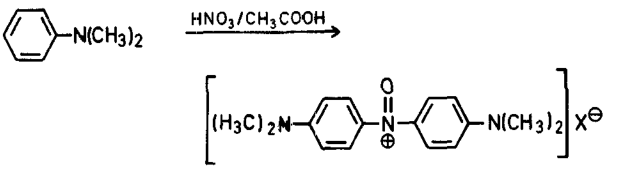
Nitration of [2,2]- and [3,2]metacyclophanes proceeds under mild conditions to give a product of a transannular cyclization; [2,2]metacyclophane is readily nitrated in acetic acid, giving 2-nitro-4,5,9,10-tetrahydropyrene in good yield[153,154].



During the nitration of dimethylaniline in acetic acid, there is formed a deep purple-colored substance containing the bis[4-*N*,*N*-dimethylaminophenyl]oxidoammonium ion (**50**). The proportions in which this cation is produced are quite large and are frequently in the range from 10 to 20% depending on the conditions[57]. It is highly probable that the unstable colored products which commonly appear during the nitration of aromatic compounds with nitric acid containing nitrous acid are derivatives of diphenylamine oxide.



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Action of the nitrating agent upon polyalkylbenzenes at low temperatures often forms some amounts of polyalkyldiphenylmethanes. Durene treated with mixed acid in nitromethane gives 2,2′,3,4′,5,5′,6-heptamethyldiphenylmethane in 5–12% yield, in addition to the expected mono- and dinitrodurene[53].

Pentamethylbenzene gives 2,2′,3,3′,4,4′,5,5′,6-nonamethyldiphenylmethane and 6-nitrooxymethyl-2,2′,3,3′,4,4′,5,5′-octamethyldiphenylmethane in low yields[10]. These diphenylmethanes are most likely to be formed by acid-catalyzed condensation of the initially formed benzylic esters with the parent hydrocarbon.

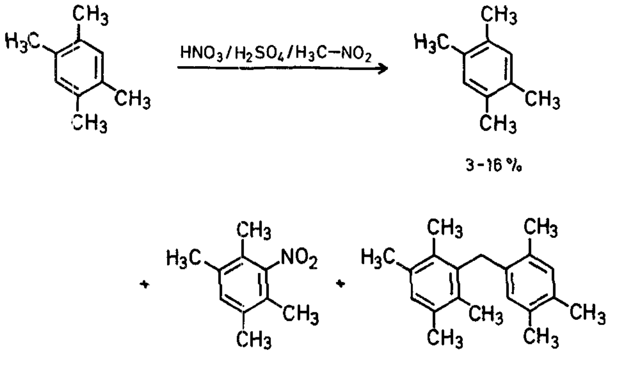
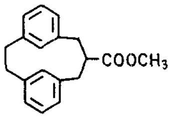
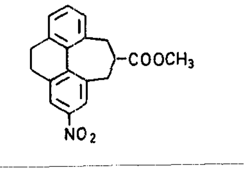


Table 8. Nitrative Coupling of Polyalkylbenzenes and Related Compounds

Compound	Nitrating agent and conditions	Product	Yield [%]	Reference
Homocoupling:				
1,2-diethylbenzene	HNO_3, −25° to −15°	nitrotetraethylbiphenyls	9	150
1-ethyl-2-methylbenzene	HNO_3, −3° to +7°	diethyldimethylnitrobiphenyls	12	150
1,2,3-trimethylbenzene	HNO_3, 1–9°	hexamethylnitrobiphenyls	15	150
1,2,4-trimethylbenzene	HNO_3, −17° to +15°	hexamethylnitrobiphenyls	4	150
		and pentamethyldiphenylmethanes	3	
N,*N*-dimethylaniline	20% HNO_3	4,4′-bis[dimethylamino]3,3′; 5,5′-tetranitrobiphenyl	—	155
1-methoxynaphthalene	NO_2/CCl_4, −20° to +14°	4,4′-dimethoxy-3,3′-dinitro-1,1′-binaphthyl	28	156
5,13-dimethyl-[2,2]metacyclophane	HNO_3/CH_3COOH, r.t.	2,7-dimethyl-4,5,9,10-tetrahydropyrene	20	153
		and 2,7-dimethyl-1-nitro-4,5,9,10-tetrahydropyrene	30	
	HNO_3/CH_3COOH, 30–35°		30–35	157
Cross-coupling with 1,2-dimethylbenzene:				
1,2,3-trimethylbenzene	HNO_3, −41° to −47°	polymethylbiphenyls	21[a]	152
1,3,5-trimethylbenzene	HNO_3, −38° to −42°	polymethylbiphenyls	30	152
1,2,3,4-tetramethylbenzene	HNO_3, −23° to −19°	polymethylbiphenyls	27	152
1,2,3,5-tetramethylbenzene	HNO_3, −36° to −40°	polymethylbiphenyls	25	152

[a] Averaged hydrocarbon conversion, 34–51%.

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See also: T. Sato, S. Akabori, S. Muto, K. Hata, *Tetrahedron* **24**, 5557 (1968).

10. Nitration with Rearrangement

When halogenated phenols and phenolic ethers are nitrated, it often occurs that a halogen atom *ortho* or *para* to a hydroxy or alkoxy group is replaced. The ease of replacement follows the order Cl < Br < J. In some cases the free halogen liberated in these displacements re-enters the aromatic ring, thus giving rise to an apparent substitution with rearrangement. The reaction is named after Reverdin, who discovered that the reaction of cold fuming nitric acid with *p*-iodoanisole gave 2-iodo-4-nitroanisole[158]. Some examples are listed in Table 9.

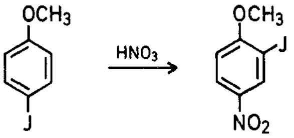
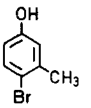
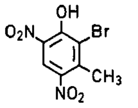
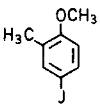
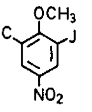
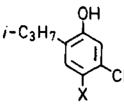
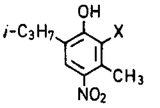
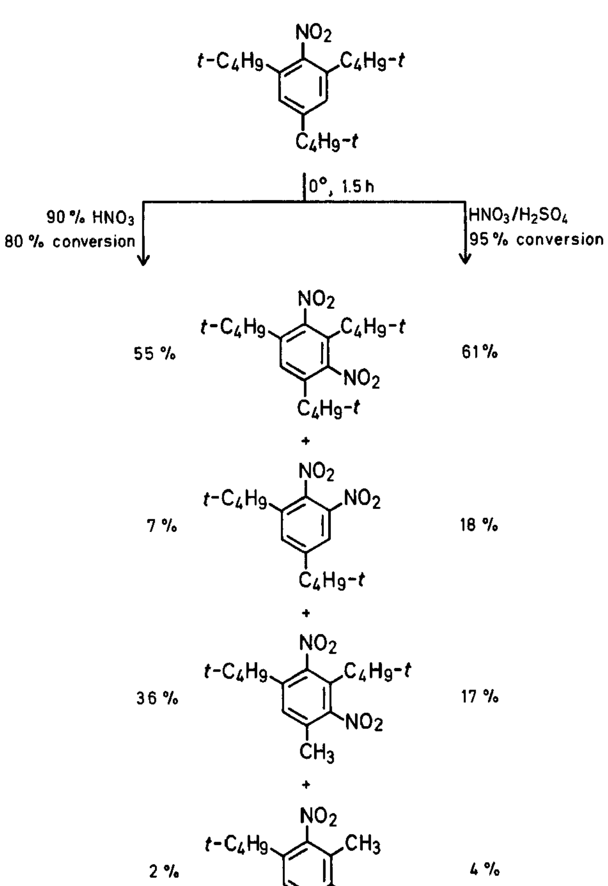


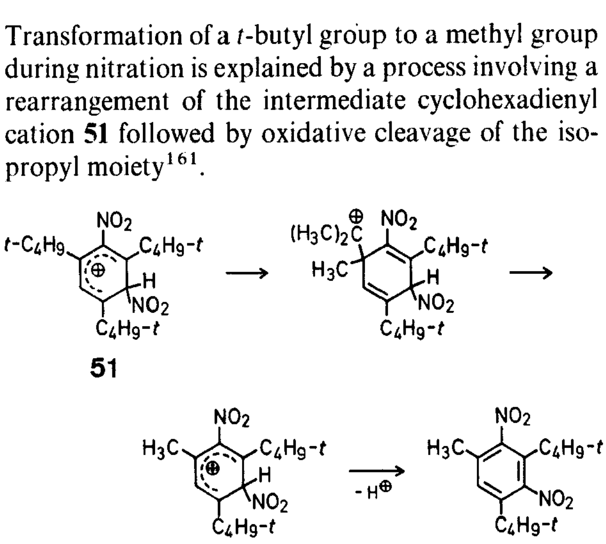
Table 9 Nitration of Halophenols and Haloanisoles

Compound	Nitrating agent	Product	Reference
	HNO_3		159
	HNO_3		85
 X = Cl, Br	HNO_3/AcOH		103

Nitration of polyalkylbenzenes has generally been recognized not to involve an alkyl rearrangement, and therefore, their polynitro derivatives have widely been used for the characterization of isomeric series of polyalkylbenzenes. An exception is seen when 2,4,6-tri-*t*-butylnitrobenzene is treated with the nitrating agent at 0°; migration of a methyl group from the side-chain to the nucleus occurs, giving four substitution products[160].



Transformation of a *t*-butyl group to a methyl group during nitration is explained by a process involving a rearrangement of the intermediate cyclohexadienyl cation **51** followed by oxidative cleavage of the isopropyl moiety[161].



11. Addenda

Since the original preparation of this manuscript, a few reports have appeared which provide further information on the chemistry of aromatic nitration. When 3,4-dimethylacylophenones are nitrated in acetic anhydride, a mixture of *cis*- and *trans*-2-acyl-4,5-dimethyl-4-nitro-2,5-cyclohexadienyl acetates is obtained as the main product, together with three isomeric dimethylnitroacylophenones[162]. Treatment of some dimethylpyrrole-2-carboxylates with nitric acid in acetic anhydride results in the formation of symmetrical pyrromethanes, one methyl group being removed during the reaction[163].

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See also: A. R. Butler, A. P. Sanderson, *J. Chem. Soc. Perkin Trans. 2* **1972,** 989.

[159] A. B. Sen, *Proc. Natl. Acad. Sci. India* **9,** 89 (1939); *C.A.* **35,** 1038 (1941).

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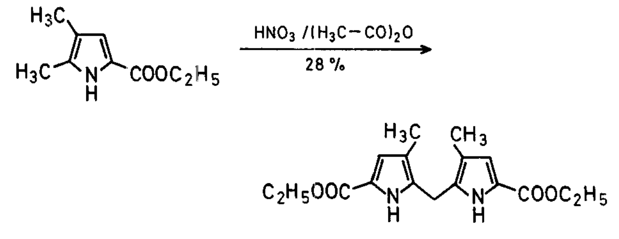
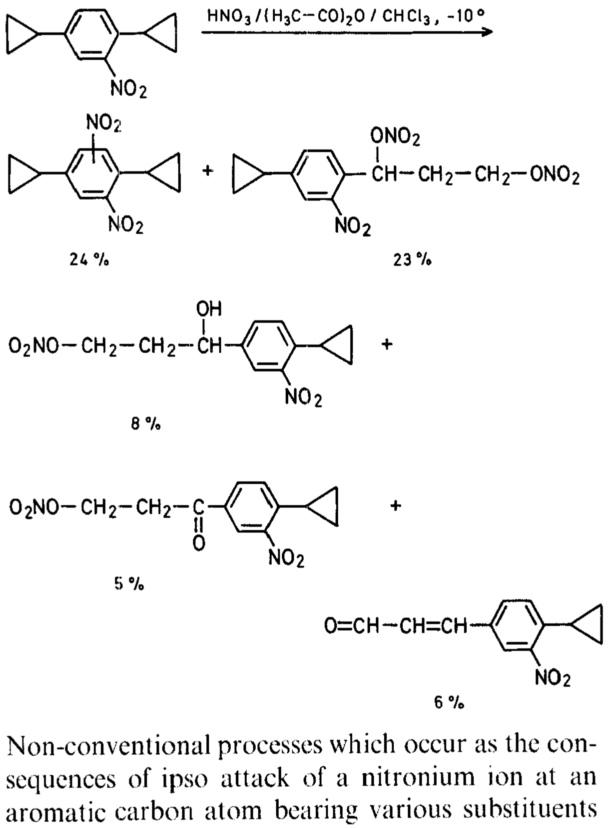
[162] A. Fischer, C. C. Greig, R. Röderer, *Canad. J. Chem.* **53,** 1570 (1975).

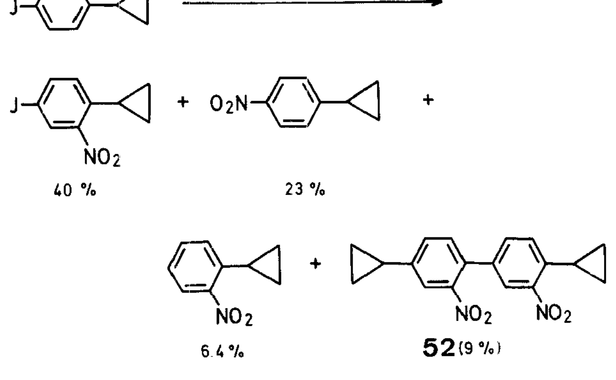
[163] M. M. King, R. H. Brown, *Tetrahedron Lett.* **1975,** 3995.



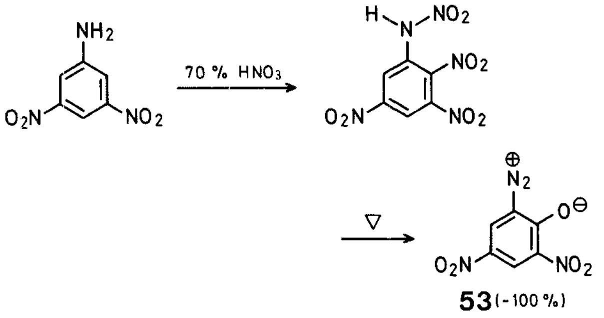
Nitration of 2-nitro-1,4-dicyclopropylbenzene with fuming nitric acid ($d = 1.5$) at low temperatures yields, besides the expected dinitro derivatives, several products arising from the opening of the three-membered ring[164].



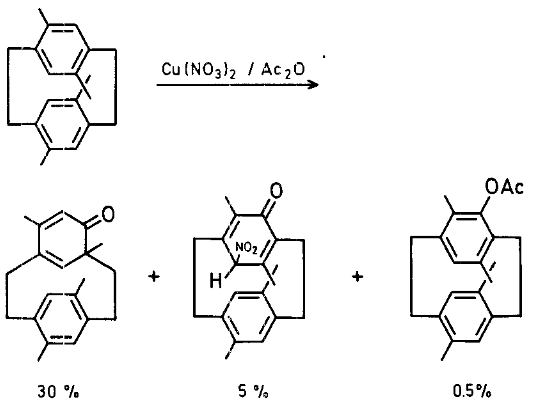
Non-conventional processes which occur as the consequences of ipso attack of a nitronium ion at an aromatic carbon atom bearing various substituents have been reviewed[165] and discussed[166]. Nitration of 1-phenyltetralin lignan, galbulin, with fuming nitric acid at ice/salt bath temperatures occurs with dealkylative ring opening, giving tetranitrodihydrogalbulinyl nitrate in high yields[167]. In the nitration of 4-iodophenylcyclopropane, 2,3′-dinitro-4,4′-dicyclopropylbiphenyl (**52**) is obtained in addition to the expected nitro compounds[168].



Nitration of 3,5-dinitroaniline with 70% nitric acid yields 2,3,5-trinitrophenylnitramine, which rearranges quantitatively on warming to give 4,6-dinitro-2-diazophenol (**53**) and nitric acid[169].



By treatment with copper(II) nitrate in acetic anhydride at −20°, some polymethyl[2,2]paracyclophanes undergo a facile oxidative nitration with alkyl rearrangement, giving a mixture of cyclohexadienones as the main product[170].



Nitration of *p*-cymene[171] and three isomeric tetramethylbenzenes[172] in acetic anhydride at temperatures below −45° has been reported to give a mixture of diastereoisomers of 1-acetoxy-4-nitro adducts in good yields. In some cases nitritonitro adducts are also formed[172]. Dissolution of methyl β-(2,6-dinitro-3,4,5-trimethylphenyl)-isovalerate in fuming nitric acid at 50°, followed by quenching with water affords a spiro-lactone, to which the structure 6,8,10-trinitro-1,1,7,8,9-pentamethyl-4-oxaspiro[4,5]deca-6,9-dien-3-one is assigned[173].

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