

Methodicum Chimicum

A Critical Survey of Proven Methods
and Their Application in Chemistry,
Natural Science, and Medicine

Editor-in-Chief

Friedhelm Korte

Volume 6

C-N Compounds

Volume 6

C-N Compounds

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Preface of the Series

The *METHODICUM CHIMICUM* is a short critical description of chemical methods applied in scientific research and practice. It is particularly aimed at chemists as well as scientists working in associated areas including medicine who make use of chemical methods to solve their 'interrelated' problems.

Considering the present development of science and the necessity for concise and unambiguous information, the series provides a guide to rapid and reliable detection of the method suitable for the solution of the problem concerned. Thus, particular emphasis is placed on the description of proved procedures whereby a complete and exhaustive compilation of all reported methods and also a detailed description of experimental techniques have been deliberately omitted. Newer methods as well as those which have not yet been reported in review articles are treated more extensively, whereas conventional methods are dealt with concisely. Biological procedures which, in specific cases, are more useful for characterizing substances than chemical or physical methods, will be discussed in the analytical volume. The interrelated methods and concepts which are constantly gaining importance will be fully discussed in the third 'Specific Part'.

The *METHODICUM CHIMICUM* is comprised of three parts. The first, the 'General Part' consists of Volumes 1, 2 and 3. Volume 1 (Analytical Methods) is concerned with chemical, physical, and biological analytical methods including those necessary for the elucidation of structures of compounds.

Volume 2 (Planning of Syntheses) contains a review on fundamentals, principles, and models with particular respect to the concepts and applications of theoretical chemistry essential to the practically working scientist.

Volume 3 (Types of Reactions) is designed to illustrate the scope and utility of proved working techniques and syntheses.

The second part (Vols. 4–8), which is particularly devoted to 'Systematic Syntheses', deals with proved methods for syntheses of specific compounds. These procedures are classified according to functional groups linked together in the last step of reaction.

Volume 4 (Syntheses of Skeletons) describes the construction of hydrocarbons and heterocyclic compounds.

Volume 5 the formation of C–O-bonds, Volume 6 the formation of C–N-bonds, Volume 7 the syntheses of compounds containing main group elements, and Volume 8 compounds containing transition metal elements.

The third 'Special Part' (Volume 9–11) is concerned with the chemical aspects connected with the formulation of a question or problem.

Volume 9 deals with nonmetallic synthetic fibers and synthetic materials as well as their additives, Volume 10 with synthetic compounds and Volume 11 with natural products and natural occurring compounds.

All Volumes should not contain more than 900 printed pages. They are intended to give the chemist and any person working in fields related to chemistry a sufficient answer to his problem. Selected review articles or important original works are cited for the sake of detailed information.

We wish to thank the Georg Thieme Verlag, Stuttgart, for making possible the realization of the basic concept of *METHODICUM CHIMICUM* and for the excellent presentation of the work.

Bonn, September 1974

Friedhelm Korte

Preface of Volume 6

Volume 6 of *Methodicum Chemicum* concerns itself with methods for the formation of carbon-nitrogen bonds. The material is arranged according to the resultant substance class; the suitable methods are described and their efficiency and limitations are compared.

The many new developments in the field of organic nitrogen chemistry have necessitated a selection which, in spite of all attempts at objectivity, may be influenced by the personal experiences and view-points of the individual authors. Heteroaromatic nitrogen compounds are described in Volume 4 of *Methodicum Chemicum*. In volume 6 only examples for the syntheses of heteroaromatic nitrogen compounds which make use of generally applicable methods for the formation of nitrogen-carbon bonds are included. It was not possible to avoid mentioning some methods for the preparation of organic nitrogen compounds which are based on the formation of nitrogen-nitrogen bonds or transformation of other organo-nitrogen compounds.

Possibilities for the further reactions as well as preparations have only been included when either the reaction products belong to a class of compounds which is not described elsewhere in M.C. or the products are so labile (even **explosive!**) that

they are not isolated during organic syntheses but are always reacted further *in situ*.

A reference work is only of use when the reader can find what he seeks rapidly. Thus, much effort has been made in the clear structure of the individual chapters, in the extensive lists of contents, in the many formula schemes, and also in the tabular surveys to ensure that the search is as easy as possible. Although well-proven methods are described more briefly than new developments, references to the original literature are always given. The literature has been covered up to 1971.

I would like to thank all contributors to this volume for their willing cooperation and the punctual submission of their manuscripts in spite of the short dead-lines and other duties. Dr. Simchen, Stuttgart, helped me especially by editing the extensive and relatively heterogeneous chapter on *N*-functional carboxylic acid derivatives. The editor-in-chief, Prof. Korte, Munich, arranged many important contacts and gave many valuable hints. The publishers are to be thank for the technical preparation of the volume and the understanding cooperation during its preparation.

July 1975

F. Zymalkowski

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1 Organic Nitro Compounds

Contributed by

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Tübingen

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1.1 Preparation of aromatic C-nitro compounds by substitution

A variety of factors influence the substitution of aromatic compounds by the nitro group. In addition to nitrating agent and temperature the reactivity of the compound concerned plays the decisive role.

As nitration is initiated by the nitronium cation NO_2^+ as the attacking group, aromatic compounds rich in π -electrons (aromatic compounds with electron-donating substituents or five-membered heteroaromatic compounds) may be described as readily nitratable. Aromatic compounds with few π -electrons (those with electron-withdrawing substituents or six-membered heteroaromatic compounds) are difficult to nitrate. (For details concerning the reactivity of aromatic and heteroaromatic compounds, see refs. ^{1, 168}).

The directing effect of already existing substituents on the aromatic compound on the direction of the substitution of an aromatic H-atom by the nitro group follow from the familiar empirically found rules for the electrophilic (secondary) substitution of aromatic systems^{1, 168}. Substituents of *first order* direct the nitro group predominantly into the *o*- and *p*-positions. These include those substituents which due to their (predominant) $-\text{M}$ and/or $+\text{I}$ effect increase the basicity (e.g., OH , NH_2 , NHR , NR_2 , O^- , Alkyl) and the halogens. Substituents of 'second order' direct the entering substituent mainly into the *m*-position. These are substituents which reduce the reactivity of the aromatic compound (e.g., CO-R , COOH , COOR , CN , NO_2 , NR_4^+), i.e., groups with a predominant $-\text{M}$ and/or $-\text{I}$ effect, except the halogens (cf. p. 4).

Promotion of nitration by the solvent diminishes in the order (*Houben-Weyl*, Vol. X/1, p. 472):

sulfuric acid > nitric acid > nitromethane > glacial acetic acid > 1,4-dioxane > water

The active agent during the nitration is the nitronium ion, NO_2^+ , which is formed from nitrating agents of the general formula X-NO_2 .

The readiness with which X^\oplus is split off leads to the following series having a progressively diminishing nitration action¹:

Nitronium ion	NO_2^+
Nitracidium ion	$\text{H}_2\text{O}^\oplus\text{-NO}_2$
Nitronium chloride	Cl-NO_2
Dinitrogen pentoxide	$\text{O}_3\text{N-NO}_2$
Acetyl nitrate	$\text{H}_3\text{C-CO-O-NO}_2$
Nitric acid	HO-NO_2
Ethyl nitrate	$\text{H}_3\text{C}_2\text{-O-NO}_2$

1.1.1 Replacement of hydrogen

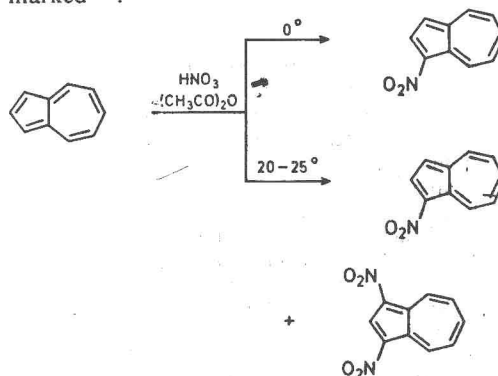
1.1.1.1 Readily nitrated aromatic compounds

Electrophilic aromatic substitutions, including replacement of a hydrogen atom by the nitro group, are facilitated by excess π -electrons. This simple empirical rule explains the behavior of many aromatic compounds during nitration that is described in what follows.

In biphenyl the participation of the second phenyl ring in the mesomerism of the first leads to enhanced electrophilic reactivity (relative to benzene). However, this applies only if there are no substituents in the *o*, *o'*-position which bring about a stronger rotation of the ring planes¹.

When nitrating acid or nitric acid (admixed with acetic anhydride or glacial acetic acid) act on naphthalene, predominantly *1-nitronaphthalene* (95% at 40–45°) together with 4–5% of the 2-isomer are formed^{2, 3}. The introduced nitro group deactivates (see p. 8) the aromatic compound, but this deactivation does not extend or extends only little to a fused ring, as is demonstrated by the relatively ready nitration of naphthalene to form *1,5*- and *1,8-dinitronaphthalene*⁴.

Azulene can likewise be nitrated under mild conditions (nitric acid-acetic anhydride mixtures). Here the influence of temperature is very marked^{5, 6}:



¹ W. Seidenfaden, D. Pawellek in *Houben-Weyl*, Methoden der organischen Chemie, Bd. X/1, p. 477, 488, Georg Thieme Verlag, Stuttgart 1971.

² H.E. Fierz-David, R. Sponagel, *Helv. Chim. Acta* 26, 98 (1943).

³ M.J.S. Dewar, T. Mole, *J. Chem. Soc. (London)* 1441 (1956);

A.A. Spryskow, I.K. Barvinskaja, *Zh. Org. Khim.* 4, 191 (1968); C.A. 68, 104298 (1968).

⁴ H.H. Hodgson, J. Walker, *J. Chem. Soc. (London)* 1346 (1933).

Monoalkylbenzenes, too, are much more reactive than benzene⁷ and can be nitrated under mild conditions. Table 1 shows the dependence on nitrating agent and temperature of the isomer ratio obtained in the case of toluene.

In principle the same mild conditions are used for nitrating higher alkylaromatic compounds, though the size of the alkyl group plays a part⁸. Thus, nitration of, for example, 1-phenyl- or 1-benzyladamantane⁹, cumene (>30° with acetyl nitrate¹⁰), and paracyclophanes^{11,12} yields practically only ring-nitrated derivatives.

Table 1. Nitration toluene with various nitrating agents (cf. *Houben-Weyl*, Vol. X/1, p. 516)

Nitrating agent	Temperature [°C]	<i>o</i> -Nitro-toluene %	<i>m</i> -Nitro-toluene %	<i>p</i> -Nitro-toluene %
85% Nitric acid	-30	55.6	2.7	41.7
	60	57.5	4.0	38.5
23.8% Nitric acid, 58.7% sulfuric acid, 17.5% water	50	62.2	4.3	33.5
5.4% Nitric acid, 71.4% sulfuric acid, 21.5% water	60	58.2	5.5	36.2
90% Nitric acid, Amberlite IR-120	50	41	—	45
90% Nitric acid, aromatic sulfonic acid	50	51.0	3.6	45.4

Mononitration of *dialkylated benzenes* with a mixed acid containing 10–20% water using approximately theoretical stoichiometric proportions also succeeds without difficulty. The entering nitro group seeks the proximity of the smaller alkyl group; the displacement of the alkyl group by the nitro group which occurs in certain polyalkylbenzenes can be suppressed by adopting suitable measures. Unless they are sterically hindered polyal-

kylated benzenes are likewise readily nitrated. Their reactivity is dependent on the number, nature, and position of the alkyl substituents, and these parameters also influence the possibility of side-reactions occurring. Nitration of 1,3-dialkyl-substituted benzene proceeds relatively readily and uniformly, and generally goes to the trinitro stage. Thus 1,3-dimethyl-2,4,6-trinitrobenzene is obtained from 1,3-xylene, while 1,3,5-trimethyl-2,4-dinitrobenzene is obtained in high yield during nitration of mesitylene in liquid hydrogen fluoride with sodium nitrate at 5° (see *Houben-Weyl*, Vol. X/1, pp. 528, 533, 825).

If the *alkylbenzenes* are *monohalogenated* on the nucleus then nitration can ensue under relatively mild conditions just as in the case of the unsubstituted alkylbenzenes. Polyhaloalkylbenzenes require more energetic conditions (see *Houben-Weyl*, Vol. X/1, p. 552).

The nature and position of a halogen atom on the ring can reduce the *m*-directing effect of a trifluoromethyl group strongly. A fluorine or chlorine atom in the *para*- or *meta* position with respect to the trihalomethyl group on the ring will determine where the nitro group enters.

3-Chlorotoluene is more readily and uniformly dinitrated than 2-chlorotoluene (see *Houben-Weyl*, Vol. X/1, p. 557).

A functional group in an alkyl substituent can influence the reaction in dependence on its nature and distance from the aromatic nucleus. As the

⁵ *Houben-Weyl*, Methoden der organischen Chemie, Bd. V/2, Herstellung carbocyclischer konjugierter π -Elektronensysteme, Georg Thieme Verlag, Stuttgart (in preparation).

⁶ A. G. Anderson, Jr., R. Scotoni, Jr., E. J. Cowles, J. Org. Chem. 22, 1193 (1957).

⁷ C. K. Ingold, F. R. Shaw, J. Chem. Soc. (London) 2918 (1927);

W. W. Jones, M. Russell, J. Chem. Soc. (London) 921 (1947);

⁸ C. K. Ingold, Structure and Mechanism in Organic Chemistry, p. 258, Cornell University Press, Ithaca 1953;

J. R. Knowles, R. O. C. Norman, G. K. Radda, J. Chem. Soc. (London) 4885 (1960);

H. C. Brown, W. H. Bonner, J. Amer. Chem. Soc. 76, 605 (1954);

K. Le Roi Nelson, H. C. Brown, J. Amer. Chem. Soc. 73, 5605, 5607 (1951).

⁹ H. Stetter, J. Weber, C. Wulff, Chem. Ber. 97, 3488 (1964);

F. N. Stepanov, E. I. Dikolenko, G. I. Danilenko, Zh. Org. Khim. 2, 640 (1966); Engl.: 640; C. A. 65, 8782h (1966).

¹⁰ G. Vavon, A. Callier, Bull. Soc. Chim. France [4] 41, 357 (1927);

L. Bert, P. C. Dorier, Bull. Soc. Chim. France [4] 41, 1170 (1927).

¹¹ D. J. Cram, R. A. Reeves, J. Amer. Chem. Soc. 80, 3094 (1958).

¹² D. J. Cram, R. H. Bauer, N. L. Allinger, R. A. Reeves, W. J. Wechter, E. Heilbronner, J. Amer. Chem. Soc. 81, 5977 (1959).

1.1 Preparation of aromatic C-nitro compounds by substitution

distance grows the effect diminishes and the resulting isomer ratio approaches that in the case of an alkylaromatic compound.

Table 2. Nitration of substituted alkyl aromatic compounds

Side-chain substituent	Nitrating agent	see <i>Houben-Weyl</i> , Vol. X/1, p. 516
Nitro group	conc. HNO ₃ , nitrating acid	536
Carbonyl group	HNO ₃	544
Carboxy group		545
Halogens	HNO ₃	537
Hydroxy and alkoxy groups	HNO ₃	542
Amino group	HNO ₃ or mixtures with H ₂ SO ₄ , CH ₃ COOH	549

Nitration of *halogenated aromatic compounds* proceeds diversely. Substituent halogens hinder nitration because their $-I$ effect reduces the overall basicity ($-I$ effect $>$ $-M$ effect in the ground state). In the positively charged δ -complex the $+M$ effect predominates, and so halogens are *o-p* directing¹⁶⁸ (for the *o-p* isomer distribution see *Houben-Weyl*, Vol. X/1, p. 500).

Dihalobenzenes can be nitrated approximately quantitatively (using calculated or slightly more mixed acid containing 5–10% water and slightly elevated temperature).

m-Dihalo derivatives are nitrated the most readily, *o*-compounds less so, *p*-compounds least readily. Nitration of 2,4-difluoro-1,3,5-trimethylbenzene with sodium nitrate in anhydrous hydrogen fluoride proceeds very smoothly¹⁷¹.

The $+M$ effect of the *hydroxy group* promotes aromatic nitration and directs the entering nitro group into the *o* and *p* positions. Nitration proceeds even in strongly diluted aqueous nitric acid if it contains nitrous acid; if not, an induction period is observed (formation of minor amounts of nitrous acid)¹³.

Nitration of phenols may ensue spontaneously and **violently**. It is therefore appropriate to stir well and to check the temperature constantly during addition of the nitrating agent. Nitrate ions cata-

lyze the further nitration beyond 2-nitrophenol¹⁴ to 2,4- and 2,6-dinitrophenol¹⁵. 80–90% nitric acid/glacial acetic acid or mixed acid with cooling is employed for nitrating nitrophenols themselves further. 2-Nitrophenol is nitrated to a mixture of 2,4- and 2,6-dinitrophenol, while with 3-nitrophenol the hydroxy group makes the nitro group enter the *o* or *p* position¹⁶. Nitrating phenol with a 50% excess of nitric acid invariably leads to some 2,4-dinitrophenol¹⁷.

Phenol may be nitrated also with tetranitromethane¹⁸ to give equal parts 2- and 4-nitro derivative; a similar result is obtained with dinitrogen tetroxide¹⁹. On passing nitrous gases into a solution of pyrogallol in ether one nitro group is introduced into the aromatic nucleus¹⁷². Nitration of phenol esters and ethers, too, proceeds smoothly (*Houben-Weyl*, Vol. X/1, p. 565).

Pyrocatechol and resorcinol (*o*- and *m*-dihydroxybenzenes) can be nitrated very readily. Depending on the reaction conditions used, nitric acid of varying concentration is employed²⁰.

¹⁴ F. W. Henle, Anleitung für das organisch-chemische Praktikum, p. 39, Akademische Verlagsgesellschaft, Leipzig 1927;

L. Gattermann, Die Praxis des organischen Chemikers, 41. Aufl., p. 214, Walter de Gruyter Verlag, Berlin 1962;

H. E. Fierz-David, L. Blangey, Grundlegende Operationen der Farbenchemie, 8. Aufl., p. 142, Springer Verlag, Wien 1952;

F. Arnall, J. Chem. Soc. (London) 125, 811 (1924);

Houben-Weyl, Methoden der organischen Chemie, Bd. VI/1c, Kap. Herstellung von Phenolen (in preparation);

K. Beaucourt, E. Hämmerle, J. Prakt. Chem. [2] 120, 185 (1928).

¹⁵ J. J. Rinkes, Rec. Trav. Chim. Pays-Bas 45, 846 (1926);

D. H. Olson, P. W. Storms, J. Org. Chem. 31, 1469 (1966).

¹⁶ A. F. Holleman, G. Wilhelmy, Rec. Trav. Chim. Pays-Bas 21, 436 (1902).

¹⁷ R. A. Slavinskaya, Zh. Obshch. Khim. 27, 1160 (1957); Engl.: 1243; C. A. 52, 2793 (1958).

¹⁸ S. Skraup, W. Beifuss, Ber. 60, 1074 (1927); K. Auwers, Ber. 35, 455 (1902).

¹⁹ P. Podkowka, A. Tarnawski, Monatsh. Chem. 90, 179 (1959);

P. F. Frankland, R. C. Farmer, J. Chem. Soc. (London) 79, 1356 (1901);

K. Auwers, Ber. 35, 456 (1902);

H. Wieland, Ber. 54, 1776 (1921);

L. B. Haines, H. Adkins, J. Amer. Chem. Soc. 47, 1419 (1925);

L. Monti, Gazz. Chim. Ital. 67, 628 (1937); Chem. Zentr. I, 3034 (1938);

P. P. Schorygin, A. V. Topchiev, Zh. Obshch. Khim. 8, 986 (1938); Chem. Zentr. I, 2174 (1939).

¹³ A. Klemenc, E. Ekl, Monatsh. Chem. 39, 641 (1918); S. Veibel, Ber. 63, 1577 (1930); S. Veibel, Z. Physik. Chem. (Leipzig) B 10, 22 (1930).

As it is readily oxidized to *p*-benzoquinone, hydroquinone can be nitrated only in the form of its *O*-derivatives. Under overenergetic conditions oxidation nonetheless occurs due to hydrolysis. In tri- and polyphenols nitration may be made difficult in dependence on the position of the hydroxy groups; this effect is alleviated by partial *O*-acylation. During dinitration of phloroglucinol partial oxidation occurs under the drastic conditions required (*Houben-Weyl*, Vol. X/1, p. 597ff.).

Aromatic compounds containing three and more hydroxy groups are nitrated with dilute nitric acid at room temperature only where quinone formation is excluded (e.g., phloroglucinol = 1,3,5-trihydroxybenzene). In other cases two hydroxy groups need to be protected.

3-Alkoxyphenols are readily nitrated under mild conditions, viz. glacial acetic acid as diluent and solvent, efficient cooling²¹. The nitro group enters mainly in the *o*-position to the free hydroxy group. Alkyl-*m*-methoxyphenols react very violently with nitric acid.

Benzoyl nitrate in carbon tetrachloride or acetonitrile likewise lends itself for nitrating phenols and their derivatives; solutions of metal nitrates²² in sulfuric acid, too, can be used for carrying out nitrations but offer no advantages.

During nitration of *halogenated phenols*²³, which ensues as readily as that of the halogenfree parent compounds, the directing effect of the halogen does not manifest itself. However, replacement of the *o*- or *p*-halogen by the nitro group can occur (more readily of Br than of Cl).

Alkylphenols are nitrated more readily than phenol, especially 3-alkylphenols. On the other hand, dinitration and formation of decomposition products are also favored, and occur even at -15° and using 65% nitric acid admixed with glacial acetic acid. Di- and polynitration of monoalkylphenols, above all of methylphenols, often proceed violently, so that it is appropriate to work in a solvent (e.g., glacial acetic acid, carbon tetrachloride,

chloroform) and to use moderately diluted nitric acid in order to restrain the reaction²⁴. 4-Cyclopentyl-, cyclohexyl-, and cyclooctylphenols²⁵, too, are readily dinitrated.

Dialkyl- and *polyalkylphenols* very readily react; not only nitration but side-reactions such as dinitration, resinification, etc., are facilitated as a result²⁶. These side-reactions are reduced by keeping the concentration of the nitric acid low and using moderately elevated temperature. Where di- or polynitration of dialkyl- or polyalkylphenols is desired it is possible to perform it under mild conditions²⁷.

On polynitrating polyalkylphenols with substituents in the *o*- and *p*-position a predominant simultaneous displacement of an alkyl substituent by the nitro group takes place²⁷.

In phenol ethers the substitution site is influenced as a function of the ether group. The ready nitration of this substance class often makes it difficult to arrest the reaction at the mononitro product stage²⁸.

Ring-halogenated alkylphenols also are readily nitrated²⁹. A free hydroxy group determines the site of entry of the nitro group. Nitration of aromatic *aldehydes* is promoted by the presence of a hydroxy group including in the form of its derivatives. The same is true also if the *hydroxy aldehyde* contains an additional chlorine atom on the ring (*Houben-Weyl*, Vol. X/1, p. 600).

²⁴ DDRP. 12398 (1956), Erf.: G. Fricke, R. Kaltofen; Chem. Zentr. 11434 (1957).

²⁵ A.R. Abdurasuleva, F.K. Shadieva, Zh. Obshch. Khim. 29, 4021 (1959); Engl.: 3980; C.A. 54, 20940e (1960);

A.R. Abdurasuleva, N.G. Korolnik, Zh. Obshch. Khim. 30, 1635 (1960); Engl.: 1633; C.A. 55, 1512i (1961);

Brit. P. 861 792 (1958), British Oxygen Co., Ltd., Inv.: W.O. Jones; C.A. 55, 18666c (1961).

²⁶ M.S. Carpenter, W.M. Easter, T.F. Wood, J. Org. Chem. 16, 586 (1951);

K. Ley, Eu. Müller, Chem. Ber. 89, 1402 (1956).

²⁷ W. Seidenfaden, D. Pawellek in *Houben-Weyl*, Methoden der organischen Chemie, Bd. X/1, p. 583, Georg Thieme Verlag, Stuttgart 1971.

²⁸ W. Seidenfaden, D. Pawellek in *Houben-Weyl*, Methoden der organischen Chemie, Bd. X/1, p. 584, 825, Georg Thieme Verlag, Stuttgart 1971.

²⁹ P.W. Robertson, J. Chem. Soc. (London) 93 T, 788 (1908); G.M. Robinson, J. Chem. Soc. (London) 109, 1078 (1912);

R. v. Walther, W. Zipper, J. Prakt. Chem. [2] 91, 364 (1915);

R. v. Walther, K. Demmelmeyer, J. Prakt. Chem. [2] 92, 107 (1915).

²⁰ W. Seidenfaden, D. Pawellek in *Houben-Weyl*, Methoden der organischen Chemie, Bd. X/1, p. 588, Georg Thieme Verlag, Stuttgart 1971.

²¹ H.H. Hodgson, H. Clay, J. Chem. Soc. (London) 2775 (1929);

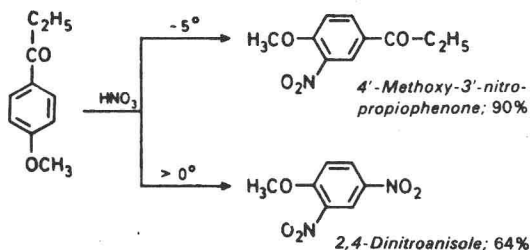
W. Seidenfaden, D. Pawellek in *Houben-Weyl*, Methoden der organischen Chemie, Bd. X/1, p. 592, Georg Thieme Verlag, Stuttgart 1971.

²² L. Spiegel, H. Haymann, Ber. 59, 202 (1926).

²³ W. Seidenfaden, D. Pawellek in *Houben-Weyl*, Methoden der organischen Chemie, Bd. X/1, p. 569, Georg Thieme Verlag, Stuttgart 1971.

Molten 1- and 2-naphthols react with liquid dinitrogen tetroxide with **explosive** violence. Solutions in ether afford 2,4-dinitro-1-naphthol (50%) and 1,6-dinitro-2-naphthol (81%) respectively³⁰. By contrast, the corresponding naphthol ethers furnish, for example, 1-methoxy-4-nitronaphthalene and 1-ethoxy-4-nitronaphthalene with liquid dinitrogen tetroxide at -10 to -20° .

Acyl groups make nitration difficult; the *meta*:*ortho* ratio is strongly dependent on temperature³¹. Ring-alkylated aromatic ketones are more readily nitrated than the unsubstituted parent compounds³², *p*-alkylated derivatives afford uniform products. Thus, nitration of 4-methylacetophenone gives 4-methyl-3-nitroacetophenone. C-acylphenols are readily nitrated, severe reaction conditions bring about the entry of several nitro groups or a replacement of the acyl group by the nitro group³³, e.g.:



Anthraquinone is difficult to nitrate (see p. 9)³⁴, ring-alkylated anthraquinones³⁵ and hydroxyanthraquinones³⁶ are nitrated much more readily. Because of the $-I/-M$ effect of the carboxy group nitration of aromatic carboxylic acids is made difficult. By contrast, alkylated aromatic carboxylic acids are dinitrated with excess nitric acid. Al-

kali metal nitrates produce substantially only mononitration³⁷.

Trinitromethane ($25^\circ/\text{pyridine}$) furnishes a good yield of 1-nitro-3-azulene-carboxylic acid from 3-azulene-carboxylic acid¹⁶⁴.

During nitration of hydroxybenzoic acids the inhibiting effect of the carboxy group is entirely eliminated. The resinification that arises on nitrating phenols occurs to only a small extent or not at all³⁸.

Introducing several nitro groups directly into hydroxybenzoic acids can be performed without difficulty³⁸.

Table 3 shows that the nitration of arylamines is dependent on many different factors.

Nitration of aminophenols is readily accomplished if the amino or amino and hydroxy groups are acylated, or the hydroxy is alkylated³⁹. Dinitration of *p*-aminophenols is achieved by using excess nitric acid. Both dinitration and polynitration are facilitated particularly where the two functional groups are in the *m*-position to each other. Nitration of carbonyl group containing aromatic amines takes place even under mild conditions³⁸.

Aromatic *N*-acyl and *N*-alkyl amino acids are readily nitrated⁴⁰; phenolic amino acids particularly so⁴¹.

Aromatic sulfonic acids, too, are easily nitrated if electron-donating substituents are present (Houben-Weyl, Vol. X/1, p. 635 ff.).

Azo compounds can be readily nitrated, and with the usual agents, to give preferentially *p*-substitution.

Aromatic compounds with substituents containing boron, silicon, or other heteroatoms can be fairly readily nitrated. Admittedly, a lesser or greater portion of the heteroatom may be split off (see p. 12)⁴².

Furan, as a π -electron-rich heterocycle, decomposes violently on nitration in bulk⁴³. Alkylated

³⁰ J. Schmidt, Ber. 33, 3244 (1900).

³¹ G.T. Morgan, J.E. Moss, J. Soc. Chem. Ind. 42, T 461 (1923); Chem. Zentr. I, 1028 (1924); G.T. Morgan, L.P. Walls, J. Soc. Chem. Ind. 49, T 15 (1930); Chem. Zentr. I, 1132 (1930); R.L. Jenkins, R. McCullough, C.F. Booth, Ind. Eng. Chem. 22, 31 (1930).

³² W. Seidenfaden, D. Pawellek in Houben-Weyl, Methoden der organischen Chemie, Bd. X/1, p. 610, Georg Thieme Verlag, Stuttgart 1971.

³³ L. Szekeres, G. Fodor, Acta Chem. Acad. Sci. Hung. 1, 391 (1951); Chem. Zentr. 4674 (1953).

³⁴ R.J. Gillespie, D.J. Millen, Quart. Rev. Chem. Soc. 2, 277 (1948).

³⁵ V.Y. Fain, V.L. Plakidin, Zh. Obshch. Khim. 31, 1588 (1961); Engl.: 1476; C.A. 55, 24699a (1961).

³⁶ DRP. 163 042, 170 728 (1904), Farb. Bayer; Fortschritte der Teerfabrikation und verwandter Industriezweige 8, 268, 250 (1905); Chem. Zentr. II, 1062 (1905).

³⁷ T.R. Govindachari, S. Rajappa, V. Sudarsanam, Indian J. Chem. 1, 247 (1963); D. Peltier, Bull. Soc. Sci. Bretagne 31, 7 (1956); C.A. 52, 9016h (1958); A. Giacalone, Gazz. Chim. Ital. 65, 840 (1935); Chem. Zentr. I, 3137 (1936); L. Vanscherpenzeel, Rec. Trav. Chim. Pays-Bas 20, 149 (1901); W. Findelee, Ber. 38, 3553 (1905); M. Kerfanto, D. Raphalen, Compt. Rend. 258, 6441 (1964).

³⁸ W. Seidenfaden, D. Pawellek in Houben-Weyl, Methoden der organischen Chemie, Bd. X/1, p. 629, 633, 679, Georg Thieme Verlag, Stuttgart 1971.

³⁹ W. Weigel, J. Prakt. Chem. [4] 4, 79 (1956).

Table 3. Nitration of arylamines (Houben-Weyl, Vol. X/1, p. 642 ff.)

H_2C_6-R R =	Experimental conditions	Orientation of the nitro group relative to
$-NH_2$	Dissolved in at least fivefold sulfuric acid, preferably below 0° , using nitric acid or nitrating acid	Predominantly in <i>m</i> -position
$-NH-Alkyl$		
$-N(Alkyl)_2$		
$-NH-Alkyl$	In acid solution with sodium nitrite or dinitrogen trioxide	<i>p</i> -Orientation; <i>o</i> -position if <i>p</i> -position is occupied
$-N(Alkyl)_2$	Nitrous acid or dinitrogen trioxide	<i>o</i> - and <i>p</i> -orientation
$-NH-CO-Alkyl$	With nitric acid	<i>o</i> - and <i>p</i> -orientation
$-NH-CO-Aryl$	With nitric acid-glacial acetic acid	
	With nitric acid-sulfuric acid	
	With nitric acid-acetic anhydride	
$\begin{array}{c} \text{Acyl} \\ \\ -N- \\ \\ \text{Alkyl} \end{array}$	With nitric acid	<i>o</i> - and <i>p</i> -positions preferred
	With nitric acid-glacial acetic acid	
	With nitric acid-sulfuric acid	
$-NH-SO_2-Aryl$	Preferably in aqueous medium or in organic solvents with dilute nitric acid	<i>p</i> -Position is unambiguously preferred; if it is occupied <i>o</i> -substitution
$-N^+(Alkyl)_3$	With usual nitrating agents	Predominantly <i>m</i> position

furans are generally nitrated in acetic anhydride with concentrated or fuming nitric acid^{43, 44}.

Unlike xanthone, 1-hydroxyxanthone can be reacted to form 1-hydroxy-2-nitroxanthone⁴⁵ under mild conditions.

With its aromatic character *thiophene* stands between benzene and furan and is therefore nitrated readily; thus benzo[b]thiophene gives 3-nitro-benzo[b]thiophene⁶² (50%). Selenophene behaves similarly⁴⁶.

Pyridine contains few π -electrons and hence is difficult to nitrate (see p. 9). By contrast, nitration in position 2 or 4 succeeds readily in *pyridine N-oxide*. This same technique is recommended for substituted pyridines; a strongly activating substituent makes the N-oxide detour unnecessary. Six-membered heteroaromatic compounds with two nitrogen atoms in the ring behave similarly⁴⁶.

The behavior of thiazole illustrates that an abundance of π -electrons is no unambiguous criterion of ready nitration (see p. 10).

Copper nitrate/acetic anhydride is a conservative nitrating agent used for substances which suffer substantial cleavage with conventional agents (Houben-Weyl, Vol. X/1, p. 768 ff.).

1.1.1.2 Reluctantly nitrated aromatic compounds

The following section discusses compounds with few π -electrons (aromatic compounds with electron-withdrawing substituents, six-membered heteroaromatic compounds) which make the attack by the nitronium cation difficult as a result of the slight basicity of the nucleus.

Nitro groups already present on the ring make an electrophilic secondary substitution difficult, including nitration. Thus, dinitration of benzene on reaction with nitrating acid takes place

⁴⁰ F.G. Mann, J.H. Turnbull, J. Chem. Soc. (London) 754 (1951);
H. Rupe, Ber. 30, 1097 (1897);
F. Reverdin, Ber. 40, 2444 (1907);
F. Reverdin, E. Deletra, Ber. 39, 972 (1906);
A. Einhorn, E. Uhfelder, Justus Liebigs Ann. Chem. 371, 176 (1909);
USP. 3 177 247 (1962), DuPont, Inv.: J.M. Ross;
C.A. 63, 545b (1965);
W. Theilacker, R. Hopp, Justus Liebigs Ann. Chem. 669, 85 (1963).

⁴¹ J.L. Simonsen, M.G. Rau, J. Chem. Soc. (London) 111, 220 (1917);
C.S. Gibson, J.L. Simonsen, M.G. Rau, J. Chem. Soc. (London) 111, 69 (1917).
⁴² R.T. Hawkins, W.J. Lennarz, H.R. Snyder, J. Amer. Chem. Soc. 82, 3053 (1960);
L.I. Zakharkin, V.I. Stanko, A.I. Klimova, Zh. Obshch. Khim. 35, 394 (1965); Engl.: 393; C.A. 62, 13165d (1965);
V.I. Stanko, A.V. Bobrov, Zh. Obshch. Khim. 35, 2003 (1965); Engl.: 1994; C.A. 64, 6674h (1966);
J.L. Speier, J. Amer. Chem. Soc. 75, 2930 (1953);
F.S. Kipping, N.W. Cusà, J. Chem. Soc. (London) 1088 (1935);
F.S. Kipping, J.C. Blackburn, J. Chem. Soc. (London) 2200 (1932);
E.A. Chernyshev, M.E. Dolgaya, A.D. Petrov, Izv. Akad. Nauk SSSR 1425 (1960); C.A. 55, 1424 (1961);
Fr. P. 1 205 994 (1958); US. P. 3 020 302 (1959), Union Carbide Corp., Erf.: D.L. Bailey, R.M. Pike Chem. Zentr. 6586 (1962); 21350 (1963);
Fr. P. 1 303 018 (1961), Union Carbide Corp., C.A. 58, 9137h (1963);
T. Hashimoto, J. Pharm. Soc. Jap. 80, 730 (1960); C.A. 54, 24480i (1960).

1.1 Preparation of aromatic C-nitro compounds by substitution

only a subordinate extent. By choosing more energetic nitration conditions, for instance, doubling of the sulfuric acid and a reaction temperature of just above 100°, dinitration of the benzene can be obtained in one step⁴⁷. Further nitration of *m*-dinitrobenzene to 1,3,5-trinitrobenzene (71%) succeeds by prolonged heating to 110° with a mixture of 60% oleum and anhydrous nitric acid⁴⁸.

The in part marked electronegateness of the halogens makes the nitration of *halogenated aromatic compounds* difficult by comparison to that of the unsubstituted parent compound (in the ground state $-I$ effect $> +M$ effect). Practically no difference is observed during nitration with acetyl nitrate.

However, as in the positively charged δ -complex the $+M$ effect of the halogens exceeds their $-I$ effect they direct the entering nitro group into the *o*- and *p*-positions.

Dinitration of halobenzenes can be achieved by more energetic conditions and the use of appropriate amounts of nitrating agent. Predominantly the 2,4-dinitro-1-halo compound and a little 2,6-dinitro-1-halo compound are obtained (Houben-Weyl, Vol. X/1, p. 504).

During nitration of halobenzenes with dinitrogen tetroxide the yield increases as the halogen concerned is found higher up in the periodic table⁴⁹.

The more drastic conditions required for mononitrating tri- and tetrahalobenzenes consist in using

either a large excess of concentrated nitric acid (up to 100%) or close to anhydrous nitrating acid with almost molar amounts of nitric acid at slightly elevated temperature. Dinitration of trifluorinated benzene also requires fuming nitric acid and sulfuric acid. A mixture of boron trifluoride and nitric acid is recommended for nitrating aromatic polyfluoro compounds¹⁶².

While monoalkyl aromatic compounds are readily nitrated the entering nitro group inhibits the further reaction. 2,4,5- and 2,3,4-trinitrotoluene do not afford the tetranitro compound even with oleum-containing nitric acid at 140°⁵⁰.

Free positions in alkylbenzenes with multiple halogen atoms on the ring are deactivated in dependence on the number and type of the halogen; nitration requires more energetic conditions⁵¹. Halogen atoms in the side-chain as well as on the ring are an additional hindrance.

5-Bromo-1,3-di-*tert*-butylbenzene is relatively resistant to attempted nitration; it requires 100% nitric acid in acetic acid/sulfuric acid and elevated temperature to give 6-bromo-2,4-di-*tert*-butyl-1-nitrobenzene. Twice as much acid and more drastic conditions afford 2-bromo-4,6-di-*tert*-butyl-1,3-dinitrobenzene⁵².

As a second order substituent the carbonyl function makes nitration more difficult because of its $-M$ effect and the nitro group is directed into the *m*-position. Although this general property presupposes drastic nitration conditions, aldehydes of the benzene series are nitrated with pure nitric acid or anhydrous nitrating acid at below 10° in order to avoid oxidation to carboxylic acid⁵³. Ring-halogenated aromatic aldehydes require at least the same strong nitrating agents (Houben-Weyl, Vol. X/1, p. 601).

⁴³ R. Marquis, Ann. Chim. (Paris) [8] 4, 196 (1905); Bull. Soc. Chim. France [3] 29, 276 (1903); J.J. Rinkes, Rec. Trav. Chim. Pays-Bas 49, 1118, 1169 (1930); 50, 590 (1931); B.T. Freure, J.R. Johnson, J. Amer. Chem. Soc. 53, 1142 (1931).

⁴⁴ H.B. Hill, G.R. White, Amer. Chem. J. 27, 193 (1902); K. Kawabe, T. Suzui, M. Iguchi, J. Pharm. Soc. Jap. 80, 62 (1960); C.A. 54, 12091f (1960); Fr. P. 1330332 (1962), Italfarmaco S.p.A.; C.A. 60, 2894e (1964); 59, 3895f (1963); Jap. P. 62: 15635, 10688, 10689 (1959), Inv.: R. Ueno; C.A. 59, 9986d (1963); USSR. P. 130045 (1959), Inv.: S. Hillers, K. Venters, N. Saldabols, R. Yu. Kalnberg; C.A. 55, 5530g (1961); K. Venters, S. Hillers, Dokl. Akad. Nauk SSSR 137, 83 (1961); C.A. 55, 19907b (1961); Y. Arata, T. Obashi, K. Aoki, M. Koseki, K. Sakai, J. Pharm. Soc. Jap. 76, 211 (1956); C.A. 59, 3895 (1963); K. Venters, S.P. Korshunov, L.I. Vereshchagin, R.L. Bol'shedvorskaya, D.O. Lolya, S. Hillers, Khim. Geterotsikl. Soedin. 616 (1965); C.A. 64, 5028d (1966).

⁴⁵ H. Haase, J. Prakt. Chem. [4] 20, 161 (1963).

⁴⁶ W. Seidenfaden, D. Pawellek in Houben-Weyl, Methoden der organischen Chemie, Bd. X/1, p. 704, 706, 732, Georg Thieme Verlag, Stuttgart 1971.

⁴⁷ H. Goldschmidt, Chemiker-Ztg. 37, 642 (1913).

⁴⁸ L. Desvergues, Chim. Ind. (Paris) 25, No. 3, 291 (1931);

L.G. Radcliffe, A.A. Pollitt, J. Soc. Chem. Ind. 40, 45 T (1921).

⁴⁹ A. Schaarschmidt, H. Balzerkiewicz, J. Gante, Ber. 58, 499 (1925).

⁵⁰ P. Debeule, Bull. Soc. Chim. Belg. 42, 27 (1933); Chem. Zentr. I, 2675 (1933).

⁵¹ W. Seidenfaden, D. Pawellek in Houben-Weyl, Methoden der organischen Chemie, Bd. X/1, p. 552, Georg Thieme Verlag, Stuttgart 1971.

⁵² W. Rundel, Chem. Ber. 96, 636 (1963).

⁵³ O. Bayer in Houben-Weyl, Methoden der organischen Chemie, Bd. VII/1, p. 406, Georg Thieme Verlag, Stuttgart 1954.

Anthraquinone is even more difficult to nitrate than benzoic acid or nitrobenzene⁵⁴ (it substitutes preferentially in the 1-position). Phenanthraquinone reacts more easily (*Houben-Weyl*, Vol. X/1, p. 614).

Although the nitration of aromatic carboxylic acids requires more drastic conditions, the use of excess nitrating agent at 185° leads to dinitration, e.g., formation of 3,5-dinitrobenzoic acid⁵⁵ from benzoic acid. Aromatic dicarboxylic acids require even more drastic conditions. Nitration of ring-halogenated benzoic acids ensues under approximately the same conditions as that of the non-halogenated parent compound. Di- and polynitration requires very energetic conditions which are avoided by using alkali metal nitrates (*Houben-Weyl*, Vol. X/1, p. 624).

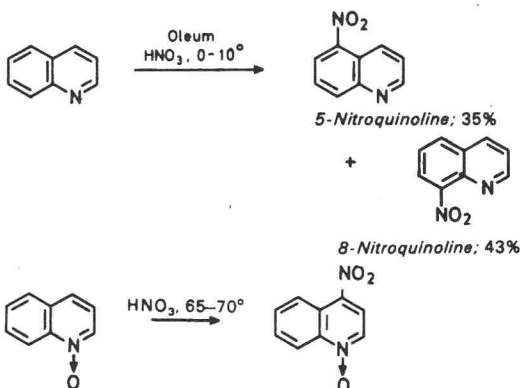
Phenolic monocarboxylic acids are readily nitrated; using energetic conditions leads to replacement of the carboxy group by nitro. The nitro group enters particularly easily into alkyl- or halogen-substituted hydroxybenzoic acids (*Houben-Weyl*, Vol. X/1, p. 629ff.).

Of *O*-heteroaromatic compounds xanthone is difficult to nitrate because of the deactivating effect of the carbonyl function.

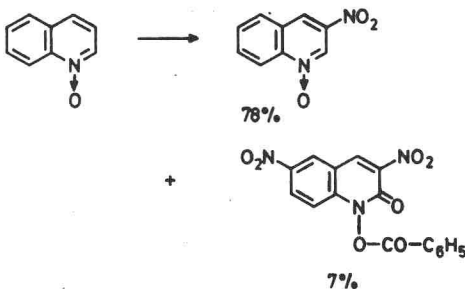
Six-membered heteroaromatic compounds containing nitrogen as the heteroatom contain few π -electrons. The consequent relatively low electron density of the C-2, C-4, and C-6 atoms makes electrophilic substitution difficult⁵⁶. Pyridine is comparable with dinitrobenzene in its behavior toward nitrating agents. Drastic methods such as the use of anhydrous mixed acid and temperatures as high as 300° are required to bring about reaction to 3-nitropyridine (5%)⁵⁷. A preliminary oxidation to pyridine *N*-oxide facilitates the nitration (see p. 8) and affords 2-nitropyridine *N*-oxide (8%) and 4-nitropyridine *N*-oxide (72%)⁶⁰. 2,2'-Bipyridyl is another compound that can be converted into 4,4'-dinitro-2,2'-bipyridyl via the *N*-oxide⁵⁸.

Quinoline is nitrated only on the nitrogenfree ring with nitric acid⁵⁹, the nitro group enters both rings

as a function of the temperature when quinoline *N*-oxide is used⁶⁰. At 65–70° 67% 4-nitroquinoline 1-oxide and at 0–10° 5- and 8-nitroquinoline 1-oxides are obtained.



With benzoyl nitrate partial oxidation occurs⁶¹



As has been shown, the substituent does not enter the heteroaromatic ring but the benzene ring during electrophilic substitution of condensed six-membered *N*-heteroaromatic compounds.

A lower π -electron density than benzene also characterizes heteroaromatic compounds with two nitrogen atoms. Attempts to nitrate pyrimidine, pyridazine, and pyrazine were therefore fruitless⁶³ and it required the presence of electron-donating substituents or the use of the *N*-oxides to bring about a satisfactory reaction (*Houben-Weyl*, Vol. X/1, p. 732ff.).

Oxadiazoles are among the heteroaromatic compounds with few π -electrons. Nonetheless, nitration of, e.g., 1,2,4-oxadiazoles, even when the 3- and 5-positions are free, does not take place. The same is true of the sydnone. As a result phenyl-

⁵⁴ R.J. Gillespie, D.J. Millen, *Quart. Rev. Chem. Soc.* 2, 277 (1948).

⁵⁵ DDRP. 34 329 (1961), Erf.: H. Cassebaum; C.A. 63, 13161g (1965).

⁵⁶ A. Albert, *Chemie der Heterocyclen*, p. 42, Verlag Chemie, Weinheim/Bergstr. 1962.

⁵⁷ F. Friedl, *Ber.* 45, 428 (1912); E. Ochai, K. Arima, M. Ishikawa, *J. Pharm. Soc. Jap.* 63, 79 (1943); C.A. 45, 5151 (1951).

⁵⁸ F.H. Case, *J. Org. Chem.* 27, 640 (1962); I. Murase, *J. Pharm. Soc. Jap.* 77, 682 (1956); C.A. 52, 9100 (1958).

⁵⁹ W. Seidenfaden, D. Pawellek in *Houben-Weyl, Methoden der organischen Chemie*, Bd. X/1, p. 720, Georg Thieme Verlag, Stuttgart 1971; Re the preparation of 4-nitroisoquinoline (13%) from isoquinoline/nitric acid/acetic anhydride (100°/1 hr.) s. J.W. Bunting, W.G. Meathrel, *Org. Prep. Proc. Int.* 4, 9 (1972).