AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS[1]

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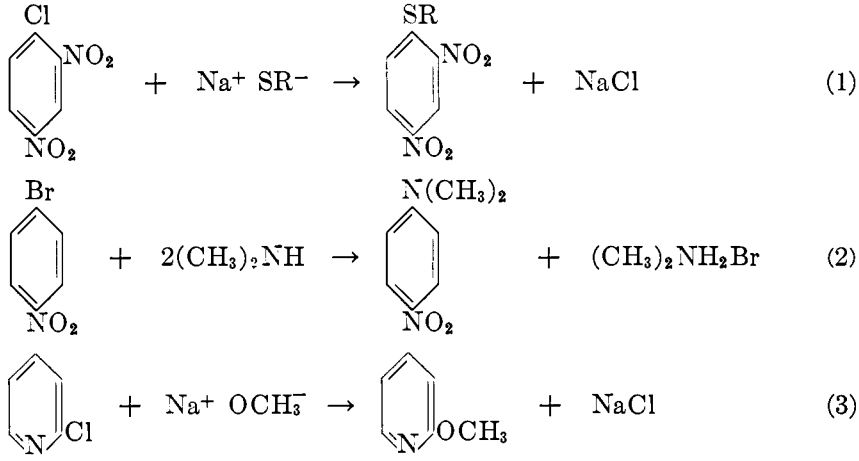
I. Introduction

In an aromatic substitution reaction[3] a bond is formed and a bond is broken. If both electrons for the new bond are furnished by the substitution reagent, the process is called "nucleophilic" substitution. Equations 1, 2, and 3 depict some familiar nucleophilic aromatic substitutions.



There are two other classes of aromatic substitution. If the substitution reagent furnishes one electron to the new bond, the process is a "free-radical" substitution. Free-radical aromatic substitutions are in general not very well understood; Waters (586) has reviewed them recently. If the substitution reagent furnishes zero electrons to the new bond, the substitution is termed "electrophilic." The best-known aromatic substitution reactions, such as nitration, halogenation, and the Friedel–Crafts reaction, are of the electrophilic type.

The emphasis in this review is on material of theoretical interest. The field comprises many reactions of preparative value, however, and while no particular attention is devoted herein to their preparative application, it is hoped and believed that much of the material in this article will be of assistance to the synthetic chemist. The literature coverage is not exhaustive, only a selection of the more important papers being referred to.

The vast field of aromatic nucleophilic substitution has received remarkably little attention during the development of theoretical organic chemistry in the last three decades. The reasons are various, but very important is the fact that

[3] The term "aromatic substitution" applies only to substitutions at carbon atoms which constitute part of an aromatic ring and specifically excludes substitution reactions occurring in side-chains of aromatic compounds.

its literature is poorly indexed and widely scattered throughout the world's principal chemical journals of the last eighty years. Furthermore, the field as a whole has not received the concentrated and sustained attention of a powerful research school.

As a result of this neglect, the strange situation has arisen of the term "aromatic substitution" having become identified in the minds of chemists solely with *electrophilic* aromatic substitution reactions. Substituents are classified as ortho–para directing or meta directing, and the qualification that they are so only for electrophilic substitutions is seldom stated. The nitro group, for instance, is called "meta directing," although it is specifically ortho–para directing *in nucleophilic substitutions*. One of the aims of this article is to raise the prestige of nucleophilic aromatic substitution closer to that enjoyed by its electrophilic counterpart.

One who has associated "aromatic substitution" exclusively with nitration, sulfonation, halogenation, and other electrophilic substitutions will have to make certain mental adjustments in order to be at ease with nucleophilic substitutions. The *first* adjustment arises from the circumstance that hydrogen is the group commonly replaced in electrophilic substitutions; in nucleophilic substitutions hydrogen is seldom replaced, the replaceable groups ordinarily being halogen atoms and other groups capable of reasonable stability as anions. *Secondly*, it is usually difficult to induce an aromatic nucleophilic substitution to occur unless there is, in addition to the replaceable group, some activating structure. This structure may be a substituent group (such as the nitro group), it may be a hetero nitrogen atom (as in pyridine), or it may be some other structural feature. And *thirdly*, since the commonly encountered compounds seldom possess more than one group replaceable in nucleophilic substitution, it is generally rather pointless to speak of the "directing" powers of substituents. If the group in question is sufficiently activated it will be replaced by an appropriate reagent, but if it is not sufficiently activated no reaction will occur. It is more profitable to speak of the "activating" powers of substituents; this terminology is followed in this article. Activation is, of course, dependent on the orientation of the activating structure to the replaceable group.

To make a sharp distinction between aromatic and unsaturated aliphatic compounds is difficult and arbitrary, for the borderline is indistinct. In this review, derivatives of fully aromatic hydrocarbons receive prime attention, followed by heterocycles of the pyridine series. Other cyclic types such as quinones and even open-chain aliphatic compounds are occasionally mentioned when their behavior is parallel to phenomena in properly aromatic substances.

Many of the facts and ideas expressed in this review are taken from earlier, though less extensive, general discussions of the field. Those of Kenner (320), Bennett (39), Bradley and Robinson (88), Waters (587), and Wheland (596b) have been particularly helpful. An effort has been made to acknowledge the original sources of generalizations and theories expressed in this review, but in some cases acknowledgement has been omitted because of oversight or unawareness or in the interest of clarity of style.

II. A Survey of Aromatic Nucleophilic Substitution Reactions

In the following survey, nucleophilic aromatic substitution reactions are divided into categories depending on the nature of the attacking reagent and of the group displaced. The main criteria for inclusion of reactions in this survey are (*a*) that the reagent appear to be nucleophilic and (*b*) that the reaction respond to activation such as that provided by an *o*- or *p*-nitro group. Abnormal and complicated reactions are omitted, as are cine-substitutions, nucleophilic replacements of hydrogen, and copper-catalyzed reactions, these in general being reserved for later sections.

A. REPLACEMENT OF HALOGEN

1. By halide ions

Exchange between aryl halides and halide ions does not occur as readily as many other typical nucleophilic substitutions. Activation by two nitro groups is necessary; thus from 1-chloro-2,4-dinitrobenzene and potassium fluoride in nitrobenzene at 200°C., 1-fluoro-2,4-dinitrobenzene was obtained in 30 per cent yield (227). Exchange with bromide or iodide ion may be effected by boiling the glycol solution of 1-chloro-2,4-dinitrobenzene with a bromide or iodide salt; in each case, there is an equilibrium which lies somewhat on the side of the chloro compound (40). Picryl chloride reacts with potassium iodide in alcohol at a lower temperature (255). Exchange of bromine between 1-bromo-2,4-dinitrobenzene and radioactive bromide ion has been observed (364); under the same conditions exchange of bromide ion with *n*-butyl bromide occurs twenty times more rapidly.

Exchange of halogen between ionic and aryl halides occurs much more rapidly when it is activated by the N_2^+ group of diazonium salts. In alcohol at room temterature, 2,6- and 2,4-dibromobenzenediazonium chlorides rearrange to form bromochlorobenzenediazonium bromides (241, 244). 2,4,6-Tribromobenzenediazonium chloride rearranges rapidly in alcohol at 5°C., but in water only at temperatures about 70°C. higher (244). Evidently the reverse reaction (replacement of chlorine by bromine) is not important. Halogen meta to the diazonium group is not replaced; 3,5-dibromobenzenediazonium chloride is stable (241).

The hetero nitrogen atom favors halogen exchange in the α- and γ-positions of pyridine and related heterocycles. Hydriodic acid replaces the chlorine of 4-chloropyridine by iodine (235); the reaction occurs more easily in 2,4-dichloropyridines containing a cyano group in the 3-position (101). From tetrachloropyrimidine, one or two chlorine atoms are replaced by sodium iodide in hot alcohol (167). 6-Chloronicotinic acid reacts with sodium iodide in boiling butanone as solvent (330). Halogen exchange was also observed during the attempted preparation of 6-bromonicotinic acid chloride, using thionyl or oxalyl chloride (90).

Chlorine replaces bromine in the reaction of 9-bromo-10-nitrophenanthrene with ammonium chloride at 320°C. (forming 9,10-dichlorophenanthrene), while *o*- (but not *m*- or *p*-) bromonitrobenzene, similarly treated, gives *o*-dichlorobenzene (515). All three bromonitrobenzenes give, with phosphorus pentachloride at 180°C., the corresponding dichlorobenzenes (516).

2. By cyanides

The condensation of aryl halides with cuprous cyanide is a standard method for the preparation of aromatic nitriles (431, 443b). Nickel cyanide reacts similarly, but alkali cyanides in aqueous or alcoholic solution show a marked preference for entry into unsubstituted positions rather than for displacement of halogen (*cf.* Section VI,C).

3. By thiocyanate or selenocyanate ions

Substitution of a thiocyano group in place of a halogen atom occurs in the rearrangement of *p*-halobenzenediazonium thiocyanates to *p*-thiocyanobenzenediazonium halides. From 2,4,6-tribromobenzenediazonium ion and excess thiocyanate in aqueous alcohol at 0°C., a 79 per cent yield of the 2,4,6-trithiocyano compound can be obtained (242, 261). Potassium thiocyanate in boiling alcohol displaces halogen from 1-chloro- or 1-bromo-2,4-dinitrobenzene (9, 116); the action of selenocyanate is similar (198). Cuprous thiocyanate and selenocyanate form the diaryl disulfide and diselenide, respectively, in reaction with the more feebly activated *o*-bromobenzoic acid, probably *via* *o*-thiocyano- and *o*-selenocyanobenzoic acids. Cuprous thiocyanate forms the corresponding nitriles from unactivated aryl bromides; the disulfides are also isolated (497).

4. By azide ions

A solution of sodium azide replaces the chlorine in picryl chloride or 1-chloro-2,4-dinitronaphthalene by the azido group (445).

5. By hydroxide ions or water

Hale and Britton (236) made an extensive study, leading to development of a commercial phenol synthesis, of the reactions of chloro- and bromobenzenes with alkalies. They have also reviewed critically earlier work on the subject. Bromobenzene with 2.5 moles of dilute caustic soda gives 89 per cent of phenol in 2.5 hr. at 236°C. Chlorobenzene with caustic soda in the same proportion gives 97 per cent of phenol in 30 min. at 370°C. Catalysis by cuprous oxide accelerates the reaction, chlorobenzene with catalysis furnishing 92 per cent of phenol in 1 hr. at 316°C. Diphenyl ether is a prominent by-product, and *o*- and *p*-hydroxybiphenyls as well as other bicyclic compounds are formed in smaller amounts. Caustic soda need not be used, hydrolysis by sodium carbonate, borax, sodium phenoxide, and other salts of weak acids and strong bases being surprisingly rapid; in these cases, the phenol produced may appear as such, rather than as sodium phenoxide, in the reaction mixture.

Reactions of chlorotoluenes with aqueous alkalies give cresols, but the positions taken by the hydroxy groups are sometimes not the same as those vacated by the chlorine atoms (*cf.* page 386).

The monohalobenzenes can be hydrolyzed by steam alone but high temperatures are necessary. The hydrolysis of chlorobenzene and bromobenzene at 500–550°C. is catalyzed by silica gel (115), but this catalyst is said to be ineffective

in the hydrolysis of fluorobenzene and iodobenzene (192). Copper and barium chlorides are also reported to catalyze the steam hydrolysis of chlorobenzene over silica gel (548).

As in other nucleophilic substitutions, nitro groups ortho or para to halogen increase its susceptibility to hydrolysis; thus, while chlorobenzene is best hydrolyzed above 300°C., 1-chloro-2,4-dinitrobenzene gives, in large-scale operation at 100°C., a 95 per cent yield of dinitrophenol (151). Sodium carbonate solution slowly hydrolyzes chlorobenzene at 300°C. (429), but its action on *o*- and *p*-chloronitrobenzenes is noticeable already at 130°C. (168).

Heterocyclic halides are often most readily hydrolyzed by aqueous acids. 4-Chloroquinoline, for instance, is hydrolyzed to 4-hydroxyquinoline by dilute acid at 120°C. (528); at the same temperature 2-chloroquinoline is hydrolyzed by water alone (195); the hydrolysis is evidently autocatalytic. 4-Chloroquinazoline is fairly stable to alcoholic alkali but is rapidly and autocatalytically hydrolyzed by neutral methanol (550). The mechanism and significance of this acid catalysis are considered in Section IV,D,7.

6. By alkoxide or phenoxide ions

From the reaction of alkali metal alkoxides with suitably activated aryl halides, aryl alkyl ethers result. Phenoxide ions, though less basic, can also replace halogen, forming diaryl ethers; for this reason, diphenyl ether is a by-product of the hydrolysis of chlorobenzene.

Aromatic halides without activating substitutents do not give ethers smoothly. At the high temperatures required for the reaction of unactivated halides, cleavage of ethers to phenols and reductive removal of halogen atoms seriously interfere. Thus, bromobenzene and methanolic sodium methoxide react incompletely at 220°C., forming anisole, phenol, and some benzene; from *s*-tribromobenzene, over 40 per cent of dibromophenol results (66). *p*-Dibromobenzene with sodium ethoxide solution gives phenetole, bromobenzene, and benzene (18). On the other hand, reactions of alcoholic alkoxides with *o*- and *p*-halonitrobenzenes give ethers in good yield even though water is present in the solvent. As reported in detail in Section VI,D, these reactions have been very carefully studied with the aim of minimizing reduction of the nitro group and the hydrolysis of ether to phenol. Ethers are formed with particular ease from nitrated fluorobenzenes (464); 2,4-dinitrophenyl ethers, readily formed from 1-fluoro-2,4-dinitrobenzene and alcohols containing triethylamine as a catalyst, have been recommended as derivatives of alcohols for identification purposes (594). Picryl chloride reacts even with neutral ethanol though not so fast as with sodium ethoxide (229).

The formation of substituted diphenyl ethers from substituted phenoxide ions and aryl halides (464, 568) is accelerated by nitro groups ortho or para to halogen but slowed down by nitro groups in the phenoxide ring (463).

Halogen in 2- or 4-halopyridines is quite susceptible to replacement by alkoxides (45b); halogen in the 3-position is less replaceable but clearly more so than in unsubstituted phenyl halides, as ether formation from 3-bromo- and 3,5-di-

bromopyridines illustrates (590). 2- and 4-Chloroquinolines condense readily with alkoxides to form ethers (195, 592).

7. By carboxylate ions

In one case an ester, 2,4-dinitrophenyl benzoate, was prepared by displacement of chlorine from 1-chloro-2,4-dinitrobenzene by potassium benzoate (344).

8. By sulfide or mercaptide ions

Displacement of halogen by inorganic sulfides or metal mercaptides resembles ether formation except that it usually occurs faster and with more serious complications, due to reductive side reactions. Aqueous-alcoholic sodium sulfide attacks activated chloronitrobenzenes, forming the corresponding thiophenoxide ions; a mixture is usually obtained, since the thiophenoxide ions so produced can on the one hand attack the chloro compound, giving symmetrical diaryl sulfides, and on the other hand undergo oxidation by the air to give the disulfide. Substitution is accompanied by reduction of nitro to azoxy or amino groups (273, 318). Replacement of halogen by xanthates (56, 459), thiourea (219, 468, 543), or thiocyanate (116, 497, 543) or thiosulfate ion (557) leads to intermediates which are easily decomposed to thiophenols, sulfides and/or disulfides; reduction of nitro groups appears not to be so serious. Conditions sometimes may be adjusted to give either thiophenols (459, 468) or symmetrical sulfides (219, 459) in favorable yields. Potassium hydrosulfide in water or alcohol converts chloropyrimidines into the corresponding thiols in yields which are satisfactory (103, 595).

Diaryl selenides may be prepared from 2,4-dinitrophenyl or picryl halides and selenosulfate salts, analogously to the formation of sulfides if thiosulfates are used (557).

Asymmetrical sulfides result when mercaptide ions react with a suitably activated aryl halide. For instance, nitroaryl methyl sulfides are generated by treating nitroaryl halides in alkaline alcoholic solution with methyl mercaptan (265). *o*- and *p*-Nitrothiophenoxide ions react readily with *p*-chloronitrobenzene and related halides (56, 272); this contrasts to the low activity of nitrophenoxide ions as nucleophilic reagents. 1-Chloro-2,4-dinitrobenzene, in alkaline solution, converts mercaptans and thiophenols into sulfide derivatives useful for identification purposes (81).

9. By sulfite or sulfinate ions

The action of alkali sulfites on aromatic halides can be used to prepare sulfonic acids. Even unactivated halides such as bromobenzene give this reaction if forcing conditions are used (copper sulfate catalysis at 200°C.). Nitro-activated halides react more readily but reduction of the nitro group also occurs (536a). In similar fashion, sulfones are produced by the action of arylsulfinate ions on chloronitrobenzenes (565) or 2-chloroquinolines (554). With very active aryl halides it is sometimes better to use the free sulfinic acids than their salts (371). Suter (536c) presents in tabular form a survey of sulfone preparation by these methods.

10. By arsenite ions

Potassium arsenite solution reacts with bromobenzene in the presence of copper catalyst to give benzenearsonic acid; a better yield (of *o*-arsonobenzoic acid) is obtained from *o*-bromobenzoic acid (496). However, similar treatment of *o*-chloronitrobenzene fails to give a product and with other nitro-activated halides the method also fails because of side reactions (239).

11. By ammonia or amines

Eight hours' treatment of chlorobenzene with aqueous ammonia at 300°C. gives a 30 per cent yield of aniline plus some phenol and diphenyl ether (429); the reaction can, however, be accomplished at 200°C. if catalysis by copper compounds is employed (462, 577). In liquid ammonia at −33°C., potassium amide quantitatively dehalogenates all the phenyl halides except fluorobenzene, forming aniline, diphenylamine, triphenylamine, and *p*-aminobiphenyl (50). Cine-substitution often occurs during this sort of reaction (Section X,B), and information on the amide-ion amination of several substituted halides is listed in table 56.

Ammonolysis of *o*- and *p*-chloronitrobenzenes, but not of the *m*-isomer, takes place uncatalyzed at 200°C. (578). In the presence of iodide ion, alcoholic ammonia acts fairly rapidly on the *o*- and *p*-isomers at 100°C. (605). 1-Chloro-2,4-dinitrobenzene reacts noticeably with alcoholic ammonia at 25°C.

Halogen alpha or gamma to the nitrogen atom of a pyridine or pyrimidine ring is readily replaced by ammonia, but copper catalysis is necessary in order to accomplish replacement of halogen beta to the hetero nitrogen (45, 259). Replacement of heterocyclic halogen atoms by amino groups may be effected at lower temperatures by the use of alkali amides in liquid ammonia (247).

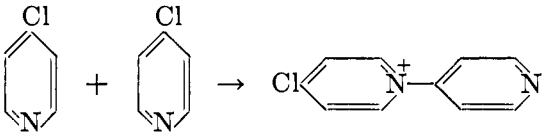
Most primary and secondary amines replace halogen more rapidly than does ammonia. Piperidine is especially reactive and has been used to measure the replaceability of halogen in different situations (94) and to form derivatives of activated aryl halides (359). Condensation of amines with 2,4-dinitrophenyl and picryl halides is used to prepare derivatives for identification purposes (454, 494). Because it reacts with amines at room temperature, 1-fluoro-2,4-dinitrobenzene is used as a "tagging agent" for free amino groups in proteins (510).

Anilines generally condense with aryl halides less readily than do aliphatic amines (Section VI). Condensation of aromatic amines with unactivated aryl halides in the presence of copper catalysts is a useful synthetic method, but such reactions are vanishingly slow without copper catalysis (Section XI,A,1). Diphenylamine and carbazole, representative diarylamines, give only molecular addition compounds with picryl chloride; steric effects may prevent displacement of the chlorine (589).

Chlorobenzene and bromobenzene are attacked by lithium dialkylamides in ether, forming dialkylanilines in fair yield (285), but they do not react with sodium amide in the same medium (50). In liquid ammonia, chlorobenzene and potassium anilide give diphenylamine; with potassium diphenylamide, triphenyl-

amine is formed. These reactions are catalyzed by the amide (NH_2^-) ion (608). Condensation of 2-chloroquinoline and 2-bromopyridine with the sodium, potassium, or magnesium derivatives of representative primary and secondary amines has been recorded (247).

Pyridine reacts readily with 1-chloro-2,4-dinitrobenzene (574) and with 1,3-dichloro-4,6-dinitrobenzene (614) to give arylpyridinium salts, and the polymerization of 4-chloropyridine is due to a similar reaction (equation 4) (598). Triethylamine is reported to give *o*-nitrophenyltriethylammonium bromide on



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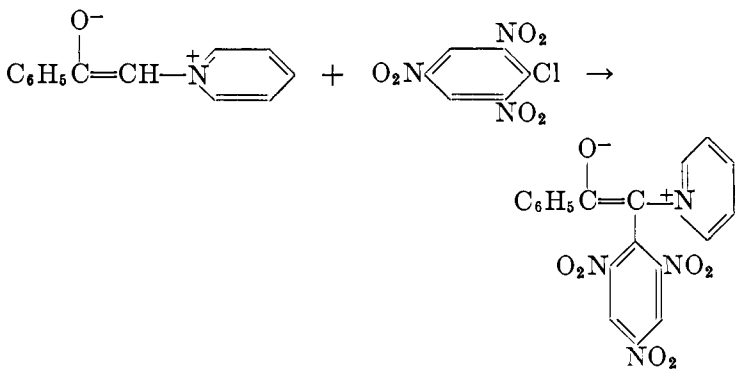
reaction with *o*-bromonitrobenzene (447), but Leymann (369) was unable to isolate a quaternary ammonium salt from the action of 1-chloro-2,4-dinitrobenzene on dimethylaniline, the product being the same as that obtained from 1-chloro-2,4-dinitrobenzene and methylaniline. Presumably a quaternary ammonium salt was first formed and then lost methyl chloride. Triethylamine in ethanol does not react with 1-chloro-2,4-dinitrobenzene to any considerable extent at 25°C. (92), and what reaction there is may not be quaternization (*cf.* page 344).

Hydrazine and its derivatives react with active aryl halides much as do amines (409), but sometimes condensation is followed by cyclization with an *o*-nitro group forming a vicinal-triazole ring (41).

12. By carbanions and organometallic compounds

The base-catalyzed condensation of suitably activated aryl halides with "active methylene" compounds finds occasional preparative use. 1-Bromo-2,4-dinitrobenzene, for instance, arylates malonic and acetoacetic esters; the normal product is a monoaryl derivative but some diarylation may occur (79, 250, 477). The condensation of cyanoacetic ester and 1-chloro-2,4-dinitrobenzene gives a 90 per cent yield of the expected product (174). Preparative use has also



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been made of the condensation of 2-bromopyridine with ethyl isobutyrate or α-methylbutyric ester (160). Similarly, 4,7-dichloroquinoline is alkylated at the 4-position by condensation with sodium phenylacetonitrile (140). In certain 1,1-diarylethylenes, the 2-carbon is sufficiently nucleophilic so that the compound may condense with picryl chloride and other very active aryl chlorides (602); the pyridinium enol-betaines behave similarly (equation 5) (341).

Chlorobenzene in liquid ammonia is able to phenylate the potassium derivatives of acetonitrile (46), picoline, quinaldine, *o*-tolunitrile (159), and triphenylmethane (608), provided excess potassium amide is supplied. Replacement of aromatic halogen by the organic radical of a Grignard reagent is uncommon but 2-*n*-butyl-3-methylpyridine has been formed from 2-bromo-3-methylpyridine by this method (411), and treatment of 2-chloroquinoline with phenylmagnesium bromide gives a 40 per cent yield of 2-phenylquinoline (247). The reaction of *n*-butyllithium with 2-bromopyridine gives not alkylation but rather halogen–metal interchange, forming 2-pyridyllithium and *n*-butyl bromide (1). However, *n*-butyllithium alkylates 2-chloroquinoline, forming 2-*n*-butylquinoline (616), although under some conditions 2-chloroquinoline is unaffected by *n*-butyllithium (216).

B. REPLACEMENT OF THE AZIDO GROUP

Though the process does not always go smoothly, hydrolysis by alcoholic alkali liberates azide ion from *p*-nitrophenyl azide, 2,4-dinitrophenyl azide (450), and 1-nitro-2-naphthyl azide and its 2,1- and 4,1-isomers (189). Picryl azide reacts with ammonia, amines, and hydrazines much as does picryl chloride (4). The replaceability of the azido group is greatest in picryl azide and less in the dinitro and mononitro compounds (403).

C. REPLACEMENT OF IODONIUM AND IODOXY GROUPS

The cleavage of diphenyliodonium chloride by certain thiols to yield their *S*-phenyl derivatives and iodobenzene (507) suggests a nucleophilic displacement of a novel type (equation 6). However, the action of the same iodonium compound on pyridine in alkaline solution to give 2-, 3-, and 4-phenylpyridines is believed

$$(C_6H_5)_2I^+ + RS^- \rightarrow RSC_6H_5 + C_6H_5I \qquad (6)$$

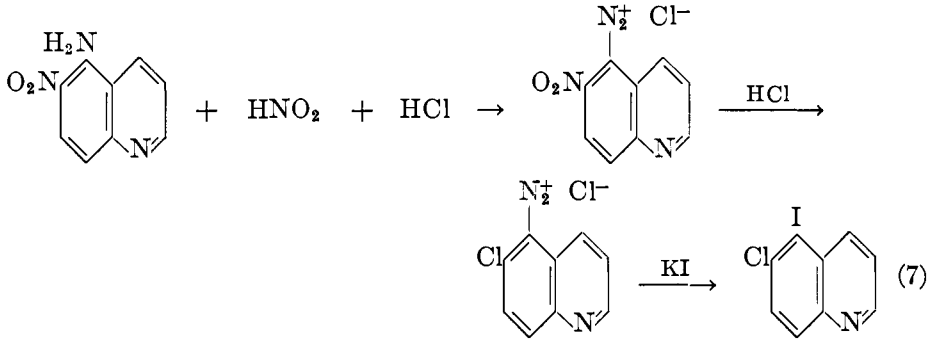
to occur *via* free phenyl radicals formed by dissociation of diphenyliodonium hydroxide (506).

p-Iodoxynitrobenzene in boiling sodium nitrite solution undergoes replacement of its iodoxy group by a nitro group; similar treatment of *p*-iodonitrobenzene or iodoxybenzene leads to no change. In boiling aqueous sodium azide, *p*-nitrophenyl azide is formed from *p*-iodoxynitrobenzene (575). These replacements occur with even greater ease in 1-iodoxy-2,4-dinitrobenzene (396). Aqueous alkali, however, replaces the iodoxy group by hydrogen and produces iodate ion (396, 575), perhaps *via* attack on the iodine atom, which competes with carbon as an electrophilic center.

D. REPLACEMENT OF THE NITRO GROUP

Replacement of a nitro group by chlorine upon treatment of bromonitrobenzenes with ammonium chloride or phosphorus pentachloride at rather high temperatures has been noted (Section II,A,1); thionyl chloride similarly affects nitrobenzene and *p*-chloronitrobenzene at about 190°C. (428). Hydrochloric acid (382) or chlorine (376) at 200°C. or above, acting on any of the three dinitrobenzenes, replaces at least one nitro group by a chlorine atom. One hesitates to classify these reactions as nucleophilic substitutions, since the characteristic distinction between reactive *o*- and *p*-dinitrobenzenes and unreactive nitrobenzene and *m*-dinitrobenzene is not shown.

Compounds with a nitro group ortho or para to a primary amino group sometimes suffer, during diazotization, replacement of a nitro group by halogen, though the exchange is not usually detected until a product of further reaction



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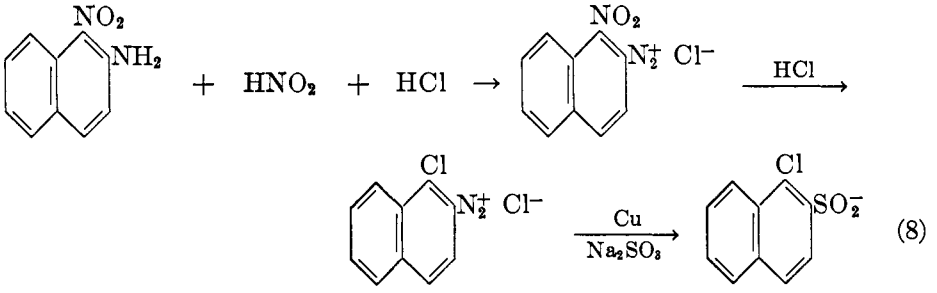

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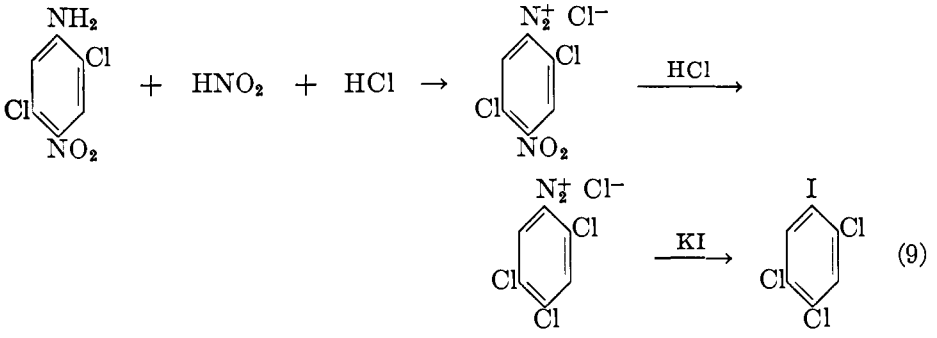

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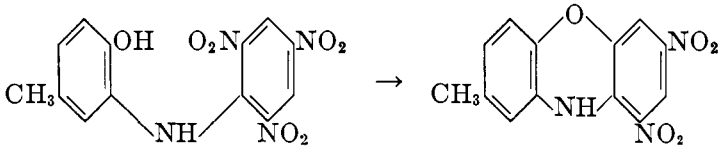
of the diazonium salt is isolated (as from a Sandmeyer reaction). This exchange is closely related to the exchange of halogens under similar conditions (Section II,A,1). Examples are the isolation of 6-chloro-5-iodoquinoline from the action of potassium iodide on the diazonium chloride from 5-amino-6-nitroquinoline (293) (equation 7), the conversion of 1-nitro-2-naphthylamine to 1-chloro-2-naphthalenesulfinic acid by diazotization and then a Gattermann reaction (579) (equation 8), and the conversion of 2,5-dichloro-4-nitroaniline to 2,4,5-trichloroiodobenzene by diazotization and potassium iodide treatment (154) (equation 9); in the latter two cases the expected nitro compounds were obtained when the diazotization was run in sulfuric rather than hydrochloric acid.

From similarly activated situations, the nitro group is more easily displaced by hydroxide or alkoxide ions than is chlorine; nitrite ion is liberated (*cf.* Section V,B). Straightforward hydrolysis or methanolysis of *o*- and *p*-dinitrobenzenes (534), *o*- and *p*-nitrobenzonitriles (465, 484), *s*-trinitrobenzene (469), and 1,2,4-trinitrobenzene (374) has been recorded, but ethoxide tends to reduce rather than replace the nitro group in *p*-nitrobenzonitrile (465).

Other nucleophilic reagents effect replacement of nitro groups much the same as replacement of halogen atoms. The 1-nitro group in 1,2,4-trinitrobenzene is replaced by alcoholic potassium thiocyanate or selenocyanate (116). Azide ion replaces a nitro group in reaction with 2,3,4-trinitrotoluene (91). Sodium benzenesulfinate replaces the 4-nitro group of 2,4-dinitrodiphenyl sulfone (388). Sodium sulfide acts on *o*-dinitrobenzene producing, according to the conditions, the *o*-nitrothiophenoxide ion or the symmetrical sulfide or disulfide, but *p*-dinitrobenzene suffers reduction (379). As an alternative route to symmetrical sulfides from polynitro compounds, the use of thiourea is possible (218). Methylthio (265) or arylthio (272) groups may also be introduced, giving asymmetrical sulfides. Sodium sulfite solution forms sulfonic acids from some nitro compounds (536a). Alcoholic ammonia at 100–110°C. quickly converts *o*-dinitrobenzene to *o*-nitroaniline (353); above 150°C. a nitro group of *p*-dinitrobenzene is replaced either by amino or by alkoxyl from the solvent, but *m*-dinitrobenzene is unaffected by methanolic ammonia even at 250°C. (377).

2-Mercapto- and 2-hydroxy-2′,4′,6′-trinitrodiphenylamines and related compounds are readily cyclized to, respectively, phenothiazines (599) and phenoxazines (equation 10) (486, 489, 562). The nitro groups displaced in these reactions are, it should be noted, situated meta to the activating nitro groups.



(10)

Few of these reactions in which nitro groups are displaced are of preparative value, because the compounds with mobile nitro groups are usually difficult to prepare.

E. REPLACEMENT OF SULFONATE AND OTHER ESTER GROUPS

p-Toluenesulfonyl esters of 2,4-dinitrophenol and similarly activated phenols are readily cleaved by aromatic amines, forming diarylamines (522, 561, 564). The *p*-toluenesulfonate group may also be replaced by reaction with pyridine, in which case pyridinium salts are obtained (73, 78), but two activating nitro groups are necessary for there is no reaction of pyridine with *p*-nitrophenyl *p*-toluenesulfonate. The reaction of 2,4-dinitrophenyl *p*-toluenesulfonate with sodium phenoxide gives not a diphenyl ether but rather phenyl *p*-toluenesulfonate as a result of the predominance of transesterification over nucleophilic displacement on aromatic carbon (73). Lithium chloride fails to react with esters of the 2,4-dinitrophenyl *p*-toluenesulfonate type, apparently because of the low nucleophilic reactivity of the chloride ion.

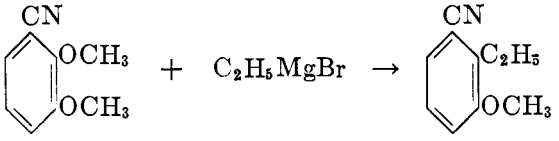
Triphenyl phosphate and potassium cyanide heated in a stream of hydrogen yield benzonitrile, exemplifying displacement of phosphate groups. Nitriles are obtained by the same method in yields up to 30 per cent from *o*- and *p*-cresyl and 1- and 2-naphthyl phosphates (251).

Intramolecular displacement of carboxylate groups is observed in the Smiles rearrangement of *p*-nitrophenyl salicylate to 2-carboxy-4′-nitrodiphenyl ether (Section VIII). Displacement at the carbonyl carbon, which ordinarily occurs more readily than at the aryl carbon atom of aryl carboxylates, is in this case not possible for steric reasons.

F. REPLACEMENT OF ALKOXY AND ARYLOXY GROUPS

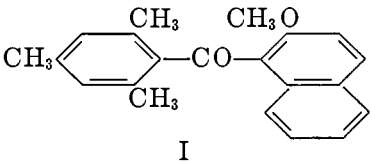
Several nucleophilic reagents have been found to effect replacement of suitably activated alkoxy or aryloxy groups. Ortho- and para-nitrated anisoles and phenetoles react with ammonia and amines to give the corresponding aniline derivatives, the reactions being more rapid the greater the number of activating nitro groups (505). Dinitrophenyl ethers react with hydroxylamine to form dinitrophenylhydroxylamines (75). The transetherification of 2,4-dinitrophenyl ethers under the influence of alkali alkoxides (452, 453) represents displacement of alkoxy or aryloxy groups by alkoxide ions. The formation of ethyl 2,4-dinitrophenylacetoacetate from 2,4-dinitrodiphenyl ether and sodioacetoacetic ester (74) is an example of displacement by a carbanion.

Alkoxy groups are also replaced by Grignard reagents in some cases; 2,3-dimethoxybenzonitrile and ethylmagnesium bromide form 60 per cent of 2-ethyl-3-methoxybenzonitrile (478, 479) (equation 11). Most other Grignard reagents react similarly, but the methyl Grignard reagent prefers to add to the cyano group, giving 2,3-dimethoxyacetophenone and some *o*-hydroxy ketone (3, 17). Attempts (201, 480) to extend this reaction to other methoxybenzonitriles have for the most part not been successful.

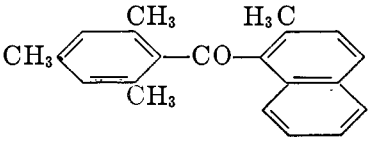


(11)

Similar replacement of methoxy groups is observed in the treatment of certain hindered aromatic ketones with Grignard reagents, as in the formation of mesityl 2-methyl-1-naphthyl ketone (II) from the action of methylmagnesium bromide on mesityl 2-methoxy-1-naphthyl ketone (I) (202). Other examples are described in the review of Gaertner (205).

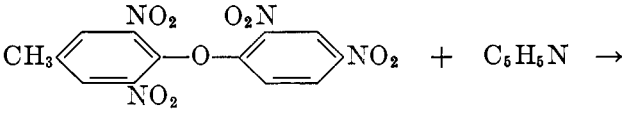


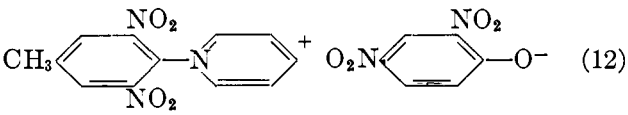
I + CH_3MgBr →



II

The cleavage of diphenyl ethers by nucleophilic reagents may occur on one side of the oxygen atom or the other depending on the electronic and steric characteristics of the two aryl groups. Turner and his colleagues (190, 232, 252, 358) investigated a number of such cleavages induced by piperidine and found that scission occurred next to the more greatly activated ring. Other similar cleavage reactions have been reviewed by Ungnade (568). Borrows, Clayton, Hems, and Long (73) recently investigated the cleavage by pyridine of a number of diphenyl ethers in which both rings were liberally provided with substituents which activate nucleophilic substitution. The direction of cleavage was sensitive in an apparently unpredictable way to moderate differences of substitution in the two rings; for example, 4-methyl-2,6,2′,4′-tetranitrodiphenyl ether was cleaved (equation 12) by displacement at the less activated carbon, while in other cases cleavage occurred next to the more activated carbon.





(12)

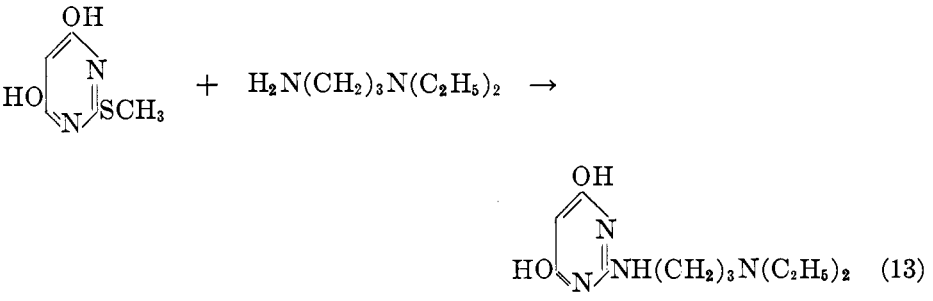
In alkyl aryl ethers there is also an opportunity for cleavage on either side of the oxygen atom. It is not entirely simple to generalize on the effect of substituents on the direction of cleavage. In anisole derivatives, the formation of *p*-nitroaniline from *p*-nitroanisole and ammonia (aqueous) at 200°C. (505) illustrates preferential substitution at a moderately activated aromatic carbon, while the formation of quaternary ammonium picrates, etc., by the action of tertiary

amines on 4-substituted-2,6-dinitroanisoles (256, 338) represents preference for attack on the methyl carbon rather than a highly activated aromatic carbon. The cleavage of *p*-chloroanisole by sodium methoxide to form *p*-chlorophenol (349) and of 2-ethoxyquinoline by thiophenol to form carbostyril (298) and ethyl phenyl sulfide are further examples of cleavage next to alkyl carbon; comparison of the latter with the reaction of 7-chloro-4-ethoxyquinoline and *p*-thiocresol to form 4,7-di(*p*-thiocresoxy)quinoline shows that these reactions are very close to a mechanistic balance point.

In the reverse Smiles rearrangement, intramolecular replacement of phenoxy groups by arylsulfinate ions occurs (Section VIII,F).

G. REPLACEMENT OF SULFHYDRYL, ALKYLTHIO, AND ARYLTHIO GROUPS

The condensation of 2,4-dithiolpyrimidine with ammonia and amines (502) is a convenient method for the synthesis of 4-amino-2-thiolpyrimidines. The reaction occurs with a wide variety of amines but is very sensitive to steric hindrance, failing completely if there is a substituent in the 5-position and a secondary amine is employed. The failure of the unhindered 2-thiol group to be replaced in the latter cases is noteworthy. Under rather different conditions replacement of a 2-thiol group (from 4,6-dihydroxy-2-thiolpyrimidine) was achieved; replacement of the methylthio group from the *S*-methyl ether of this compound has also been reported (equation 13) (326). Aminolysis of methylthio and ethylthio groups in the 2-position of related hydroxypyrimidines is a smooth

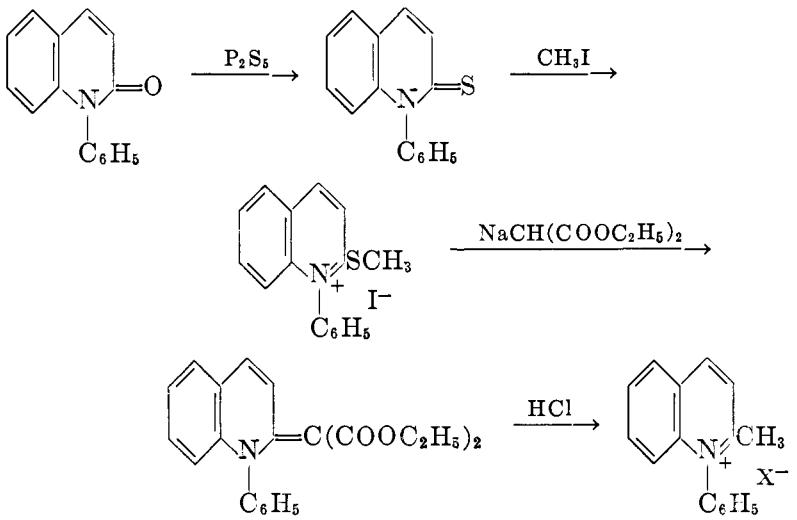


(13)

reaction used to prepare *N*-substituted aminohydroxypyrimidines (311). Alkylthio groups in the 4-position are also subject to this replacement (137). The methylthio group of 4-quinazolyl methyl sulfide is replaced by heating with a primary amine, but 4-quinazolinethiol gives the same product in better yield (363).

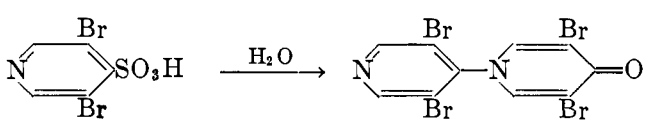
2-Pyrimidyl methyl sulfide is quantitatively hydrolyzed by boiling concentrated hydrochloric acid (415); an arylthio group in the 2-position may also be removed (175). 2-Thiouracils are quite stable to boiling aqueous alkali but the corresponding 2-methylthio compounds react to some extent, with liberation of methyl mercaptide ion (117).

The replaceability of alkylthio groups has recently been used to advantage in a synthesis of hitherto inaccessible *N*-arylquinolinium salts (96):



H. REPLACEMENT OF SULFO, SULFONYL, AND RELATED GROUPS

Benzenesulfonic acid, heated with fused alkali, sodium amide, or cyanides, gives, respectively, phenol, aniline, or benzonitrile. The formation of phenols and nitriles from sulfonic acids has been thoroughly reviewed by Suter (536b). These reactions respond to changes in activation in the fashion usual for nucleophilic substitutions. Alkaline hydrolysis of sulfo groups in the ortho or para position of phenol does not go well; in 2,4-dinitrobenzenesulfonic and anthraquinonesulfonic acids, on the other hand, a variety of displacements can be carried out which would fail on unactivated compounds. Thus ammonia, aqueous sulfide ion, methoxide, and thiophenoxide introduce amino, mercapto, methoxy, and thiophenoxy groups. Likewise, a sulfo group in the 2- or 4-position of pyridine is readily replaced by amines (405); with the 4-sulfo group there may be a combination of hydrolysis and self-condensation in aqueous solution (162):



Aminolysis and alcoholysis of methylsulfonyl groups in the 2-position of pyridine (188), benzothiazole, and related heterocycles (275) have been reported. A large number of replacements of arylsulfonyl groups by reagents such as the thiophenoxide ion, the methoxide ion, ammonia, piperidine, and sulfinate ions have been reported by Loudon and coworkers (371, 387, 388, 389, 392, 393, 394). Sulfonamide (SO_2NH_2) groups undergo analogous replacements but somewhat less readily (393).

In the Smiles rearrangement (Section VIII) suitably activated *o*-hydroxy- or *o*-aminodiphenyl sulfones rearrange to *o*-phenoxy- or *o*-anilinobenzenesulfinates. *o*-Acetamidodiphenyl sulfoxides also rearrange, as does 2-hydroxyethyl 2-nitrophenyl sulfoxide; these are apparently the only examples of the cleavage of sulfoxides by nucleophilic displacement at aromatic carbon.

I. REPLACEMENT OF THE ARSONO GROUP

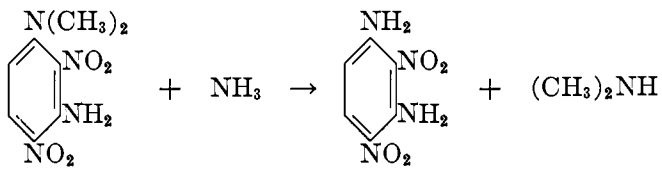
The hydrolysis of aromatic arsonic acids by alkali resembles that of the sulfonic acids. Benzenearsonic acid itself reacts with fused potassium hydroxide (347), while if a nitro group is in the ortho position the arsono group is readily displaced by boiling aqueous alkali (24).

J. REPLACEMENT OF AMINO GROUPS

Hot fused alkali forms *p*-phenolsulfonic acid from sulfanilic acid, replacing the amino and not the sulfo group (580). 2,4-Dinitroaniline (600), *p*-nitrosoaniline (185), and their *N*-alkyl or *N*,*N*-dialkyl derivatives (184, 370, 492, 493) when heated with alkali are hydrolyzed to the phenols and ammonia or an amine. Sodium bisulfite also effects the cleavage of *p*-nitrosodialkylanilines, and its use in the preparation of secondary amines has been recommended (446).

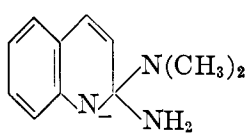
The amino group of 2-aminoquinoline may be hydrolyzed by heating with alkali or with acids (124).

Replacement of one sort of amino group by another has been observed on occasion. Ammonia converts 3-amino-2,4-dinitro-*N*,*N*-dimethylaniline (III) to 3-amino-2,4-dinitroaniline (IV), and replacement of dimethylamino by methylamino groups in the same series has also been described (495). Exchange of amino



III IV

groups in the 4-positions of quinoline (113) and quinazoline (135) induced by amine reagents is also known. Potassium amide in liquid ammonia replaces methylamino and dimethylamino groups in the 2-position of quinoline, and lithium methylamide converts 2-dimethylaminoquinoline to 2-methylaminoquinoline. The yellow color produced during these reactions has been ascribed to intermediate adducts such as V (398):



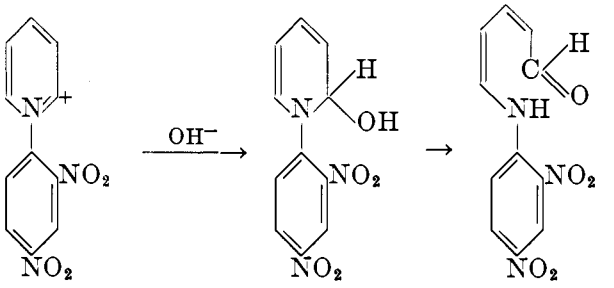
V

K. REPLACEMENT OF AMMONIO[4] GROUPS

Most aryltrimethylammonium compounds undergo demethylation when refluxed with sodium ethoxide in ethanol (576, 609), but when there is a nitro group para to the trimethylammonio group, trimethylamine is eliminated and a *p*-nitrophenetole is formed (609). Para to an aldehyde or ketone carbonyl group, a trimethylammonio group undergoes demethylation and replacement concurrently, giving a mixture of products (541).

The *N*-(2,4-dinitrophenyl)pyridinium ion, which may be formed by the action of pyridine on 1-chloro-2,4-dinitrobenzene, 2,4-dinitrophenyl *p*-toluenesulfonate, or 2,4,2′,4′-tetranitrodiphenyl ether, reacts with phenoxides to form 2,4-dinitrophenyl aryl ethers (73). A reaction of this sort constitutes an essential step in a recent synthesis of thyroxine in relatively high yield (72). Chloride ion may also effect replacement of ammonio groups; the action of hydrochloric acid on (6-methyl-2,4-dinitrophenyl)pyridinium *p*-toluenesulfonate gives 1-chloro-6-methyl-2,4-dinitrobenzene (78). Amines also displace ammonio groups; from *N*-(2,4-dinitrophenyl)pyridinium chloride and aniline, 2,4-dinitrodiphenylamine results (573), and *N*-(4-pyridyl)pyridinium chloride hydrochloride and aniline react similarly (331). *N*-(4-Pyridyl)pyridinium chloride hydrochloride is also cleaved by water alone, yielding 4-hydroxypyridine and pyridine. Analogously, water hydrolysis of *N*-(3-nitro-4-pyridyl)pyridinium chloride produces 4-hydroxy-3-nitropyridine (332).

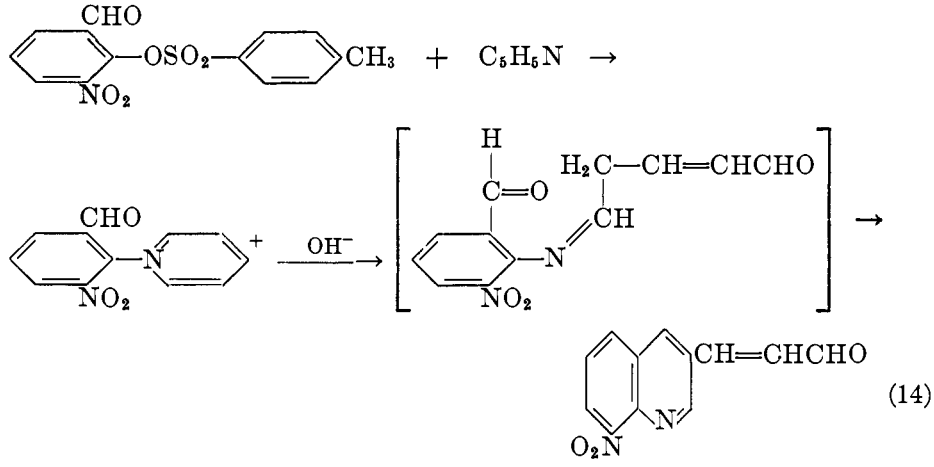
The action of hydroxides on some *N*-arylpyridinium salts causes cleavage of the pyridine ring rather than displacement of the pyridine moeity. This sort of reaction is favored, curiously, by the same groups which would be expected to facilitate displacement of the pyridine moeity intact. The best-known example is the action of hydroxide on *N*-(2,4-dinitrophenyl)pyridinium chloride (VI) to form a red substance which is presumably 5-(2,4-dinitrophenylamino)pentadienal (VIII) or a tautomer thereof (613). The reaction appears to involve initial formation of pseudo-base (VII), which then rearranges to the product obtained. This and related reactions have been discussed at length by Mosher (442b). They



VI VII VIII

[4] The term "ammonio group" is introduced here for the $-NH_3^+$ substituent group, for which no other satisfactory name exists. In a general sense, it applies also to $-NH_3^+$ groups substituted by alkyl or aryl groups.

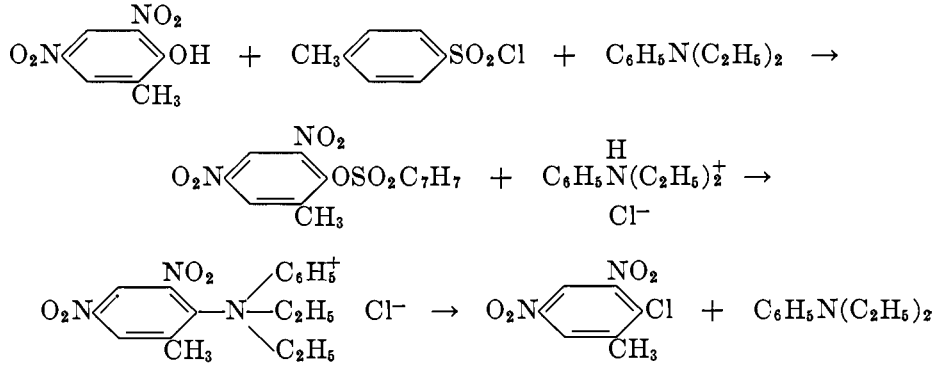
have recently been employed in a novel quinoline synthesis (2), as shown in equation 14.



(14)

L. REPLACEMENT OF THE HYDROXY GROUP

There are a number of reactions which, from consideration of the starting materials introduced and the products obtained, may be described as replacements of the hydroxy group, but which either certainly or probably occur *via* a sequence of reactions which involves conversion of the hydroxy group to some derivative prior to breaking of the carbon–oxygen bond. For example, treatment of 6-methyl-2,4-dinitrophenol with *p*-toluenesulfonyl chloride and diethylaniline results in the formation of 1-chloro-6-methyl-2,4-dinitrobenzene (564); on the basis of an experimental study, Borsche and Feske (78) formulated this reaction as follows:



Of these several reactions, tosylation of hydroxy groups is well known; replacement of the *p*-toluenesulfonate group by tertiary amines and displacement of ammonio groups by chlorine have been discussed above.

In parallel fashion it is possible to convert 2,6-dinitrophenol to 2,6-dinitrodiphenyl ether by treatment with phenol, *p*-toluenesulfonyl chloride, and pyridine (73). Each stage of the overall process has been run separately.

The action of phosphorus oxychloride on 4-hydroxy-3,5-dinitrobenzaldehyde, picric acid, and related polynitrophenols in the presence of diethylaniline produces high yields of compounds in which chlorine has taken the position formerly occupied by the hydroxy group (73). The same reagents also effect replacement of the hydroxy groups of 4-hydroxy- and 4,6-dihydroxypyrimidines by chlorine atoms (14). The intermediate stages in these reactions have not been isolated, but it is reasonable to assume that they go analogously to the reactions with *p*-toluenesulfonyl chloride in diethylaniline. The transformation of polynitrophenols to aryl chlorides under the influence of tertiary amines and phosgene (84, 246) is no doubt also of the same type.

Phosphorus pentachloride alone may be used to convert phenol to chlorobenzene in low yield; the triphenyl ester $(C_6H_5O)_3PCl_2$ is an intermediate (10). Phosphorus pentachloride and phosphorus oxychloride are commonly used for the preparation of heterocyclic chlorides from the corresponding hydroxy compounds.

Replacement of hydroxy by amino groups occurs in the Bucherer reaction; the reagent is an aqueous solution of bisulfite and ammonia or an amine, and the hydroxy groups of naphthols or resorcinol are most easily replaced. The Bucherer reaction occurs *via* the keto tautomers of the phenols (163), and is not to be classed as aromatic substitution.

The 4-hydroxy group in 2,4-dihydroxyquinoline may be replaced by amines; hydrochloric acid aids the reaction with aniline (138). Aminolysis of an *o*-nitrophenol has been reported, but the reaction is more difficult than that of the corresponding nitrophenyl alkyl ethers (540). Here again it might be argued that these direct replacements of hydroxy groups are in reality condensations of the keto tautomers of the phenols.

III. Mechanism

Nucleophilic substitution in aliphatic compounds may occur by two mechanisms, designated S_N1 and S_N2 (290). The S_N1 mechanism involves *slow* dissociation of the aliphatic compound into an alkyl cation and another fragment (usually an anion), followed by fast combination of the alkyl cation with whatever nucleophilic reagent is available. S_N1 substitution is favored by release of electrons in the aliphatic compound to the site of substitution. The S_N2 mechanism involves the rate-determining attack of the nucleophilic reagent on the aliphatic carbon atom with simultaneous departure of the displaced group. It is usually but not always favored by electron withdrawal from the site of substitution, the ambiguity resulting from the different electronic requirements for reagent approach and substituent expulsion.

There appears to be a parallel duality of mechanism in aromatic nucleophilic substitution.

A. UNIMOLECULAR AROMATIC NUCLEOPHILIC SUBSTITUTION

The aromatic S_N1 mechanism has been proposed for the decomposition of diazonium cations (152, 220, 585). Kinetic studies have shown that the reaction

$$ArN_2^+ \rightarrow Ar^+ + N_2 \qquad (15)$$

is first order in water solution (435). First-order kinetics is in agreement with the unimolecular mechanism but would also result from bimolecular attack of water molecules on diazonium cations. More persuasive for the unimolecular mechanism is the lack of dependence of rate on the identity or concentration of the anions accompanying the diazonium cations (108). Some anions become incorporated into the products of decomposition, chlorobenzene, for example, being formed along with phenol from benzenediazonium chloride; if this incorporation occurred *via* bimolecular displacement of N_2, the reactions would be more

TABLE 1

Effect of substituents on the rate of decomposition of benzenediazonium salts at 28.8°C.

SUBSTITUENT	RATE COEFFICIENT* (SEC.$^{-1}$ × 10^7)		
	Ortho	Meta	Para
—OH	6.8	9100	0.93
—OCH_3		3400	0.11
—C_6H_5	1100	1700	37
—CH_3	3700	3400	91
—H	740	740	740
—COOH	140	410	91
—SO_3^-	91	150	42
—Cl	0.14	31	1.4
—NO_2	0.37	0.69	3.1

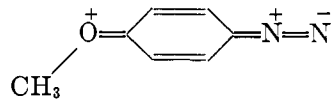
* Calculated from data in reference 134.

rapid with anions (such as chloride) of nucleophilic activity greater than that of water and also greater at higher concentrations of such anions.

The effects of substituents on the rate of decomposition are consistent with the unimolecular mechanism, providing two special assumptions are made. As expected for the unimolecular mechanism, the reaction is accelerated by electron-releasing meta-substituents (table 1) and retarded by electron-attracting meta-substituents. (Assignment of an overall electron-releasing effect to *m*-methoxy and hydroxy substituents is contrary to their observed effects on the dissociation constants of aromatic acids (158) and on the arylation velocities of anilines (table 34). Unimolecular decomposition of diazonium salts has, however, an electronic requirement which would be expected to call forth the $+T$ effects of these groups to a much greater extent.)

Electron-attracting para-substituents (NO_2, etc.) decelerate the reaction as one would expect, but so do electron-furnishing substituents! Professor E. D.

Hughes has suggested that the surprising deactivation by $+T$ substituents can be regarded as consistent with the S_N1 mechanism, because although these substituents facilitate attainment of an overall neutral charge in the $-N_2^+$ group, they do so by increasing the double-bond character and therefore the strength of the carbon–nitrogen bond which must be broken for dissociation to occur (*cf.* structure IX). (The influences of ortho-substituents are herein disregarded, because they are due in part to proximity effects of unknown magnitude.)



IX

In summary, the evidence supports a unimolecular mechanism for the decomposition of diazonium cations in dilute acid solution, but is not conclusive.

Hale and Britton (236) reported that the rate of alkaline hydrolysis of chlorobenzene (*cf.* page 278) was not greater at higher concentrations of sodium hydroxide, that hydrolysis by sodium carbonate was as rapid as by sodium hydroxide in equivalent concentration, and that satisfactory first-order rate coefficients were obtained. These data all indicate a unimolecular mechanism. Furthermore, the extraordinarily facile hydrolysis of *o*- and *p*-halophenols, exemplified by the 84 per cent yield of catechol from *o*-chlorophenol and alkali at 190°C. (67), is intelligible in terms of a unimolecular mechanism but contrary to experience with bimolecular aromatic nucleophilic substitutions. However, water and aqueous solutions of neutral salts appear to be ineffective in promoting these hydrolyses, and the heterogeneous conditions (including copper catalysis) may be responsible for the kinetics. Nevertheless, the unimolecular mechanism must be, from the above considerations, seriously considered for high-temperature nucleophilic substitution reactions of phenyl halides, either unsubstituted or provided with electron-furnishing substituents.

The aromatic S_N1 mechanism has been proposed for two other reactions (267, 395), but the supporting evidence is not compelling.

B. BIMOLECULAR AROMATIC NUCLEOPHILIC SUBSTITUTION

The vast majority of aromatic nucleophilic substitution reactions display kinetics and response to structural and environmental factors which indicate a bimolecular mechanism, according to criteria stated by Hughes (290). The evidence may be considered under three headings:

1. Second-order kinetics are regularly observed; reactions are first order with respect to the nucleophilic reagent and also with respect to the aromatic compound. Dozens of papers, most of which are referred to in the following sections, report satisfactory rate coefficients which have been obtained by application

of the usual second-order mathematical expression to experimental data. Lulofs' (397) investigation of the kinetics of the reaction of 1-chloro-2,4-dinitrobenzene with sodium alkoxides was particularly thorough, and is presented in part in table 2. The mild variation in rate coefficient accompanying a fivefold change in concentration is probably due to salt effects.

2. Substitutions occur more rapidly with stronger nucleophilic reagents. This is demonstrated in table 32 and elsewhere in Section VI. This criterion was employed by Graham, Hughes, and Ingold (229), who demonstrated that the quite rapid reaction of picryl chloride with neutral ethanol was not unimolecular because reaction was much faster when ethoxide ion was added.

3. Reactions are facilitated by substituents in the aromatic compound which withdraw electrons from the site of substitution. *A priori*, it cannot be predicted

TABLE 2

*Reaction of 1-chloro-2,4-dinitrobenzene with sodium ethoxide**

(Lulofs (397))

ORIGINAL CONCENTRATION = 0.058 *M*		ORIGINAL CONCENTRATION = 0.035 *M*		ORIGINAL CONCENTRATION = 0.012 *M*	
Time	Second-order rate coefficient	Time	Second-order rate coefficient	Time	Second-order rate coefficient
min.		*min.*		*min.*	
11.1	1.47	31.1	1.63	19.1	1.78
21.6	1.47	42.7	1.63	43.4	1.78
35.5	1.47	53.8	1.62	58.9	1.78
42.5	1.47	63.1	1.63	69.1	1.78
49.9	1.47			86.3	1.78
Mean.....	1.47	Mean.....	1.63	Mean.....	1.78

* Both reactants were in equal concentration in absolute ethanol. Temperature = 15°C. These runs represent about 70–75 per cent reaction.

whether bimolecular nucleophilic substitution will be assisted or hindered by electron recession from the site of substitution, but once activation by electron-withdrawing substituents is demonstrated, the process must be judged bimolecular because unimolecular substitution has a clear requirement of electron accession to the site of substitution.

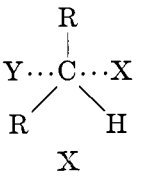
Hughes also cites salt and solvent effects as criteria which can be used to distinguish bimolecular from unimolecular substitution reactions. There is not enough information available concerning aromatic nucleophilic substitution to allow confident application of these criteria; such data as are at hand are discussed in Section VI,D.

This review is mainly concerned with the predominant bimolecular type of aromatic nucleophilic substitution and, unless it is stated to the contrary, the reader should assume that bimolecular substitutions are under discussion.

C. THE INTIMATE MECHANISM OF BIMOLECULAR AROMATIC SUBSTITUTION[5]

In this section, the reaction $ArX + Y \rightarrow ArY + X$ is considered.

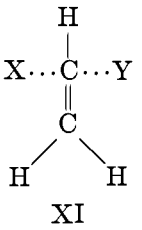
Let us first enquire to what extent the rather well understood (290) mecha nism of bimolecular substitution at saturated carbon atoms can be applied to the kinetically similar but very much slower substitutions in vinyl and phenyl halides. The aliphatic transition state is represented by structure X, in which the C···Y and C···X bonds are colinear and perpendicular to a plane in which lie the other three bonds shown. Formation of X involves, on the part of the



X

carbon atom, a change from tetrahedral sp^3 to planar trigonal sp^2 hybridization, the remaining p-orbital being used by means of its two lobes at their normal 180° angle to each other for the half-bonds to X and Y.

The analogous process in a vinyl halide would involve formation of transition state XI by transformation of the planar trigonal sp^2 hybridization of the carbon atom to linear sp hybridization. Of the remaining two p-orbitals, one would be



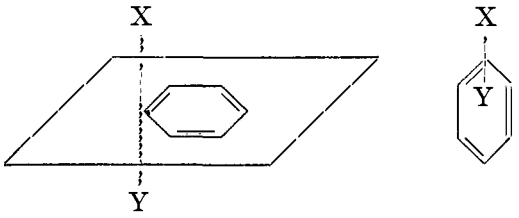
XI

used for the π-bond to the other carbon and the other for the half-bonds to X and Y. In XI, X and Y are necessarily in the same plane as the CH_2 group. All this seems reasonable, and makes it difficult to understand why vinyl halides are so resistant to nucleophilic substitution. The explanation may lie in some quantum-mechanical objection to structure XI which is not evident to the present authors. On the other hand, structure XI may be acceptable and the reason for its resistance to substitution may be embodied in one or more of the explanations which have already been advanced: a screening of the carbon atom from nucleophilic attack by its π-electrons (114), double-bondedness between carbon and halogen (arising from the resonance $CH_2{=}CHX \leftrightarrow CH_2^-{-}CH{=}X^+$) in-

[5] Part of the material in this section was presented at the 118th Meeting of the American Chemical Society, Chicago, Illinois, September 8, 1950. Criticism and discussion of some of this material by Dr. D. P. Craig is appreciated. *Note added in proof:* Gold (617) has recently offered a discussion of the transition states for bimolecular substitutions which, in part, resembles the argument in this section.

creasing the strength of a bond which must be broken for reaction to occur (290), or stabilization of the halide by this same resonance (596e).

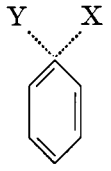
Although the preceding discussion is inconclusive as to the possibility of structure XI as a transition state for substitution in vinyl halides, there is no doubt that substitution in phenyl halides cannot proceed *via* any analogous transition state. Two possibilities, XII and XIII, in which (as in XI) the carbon atom has changed from planar trigonal sp^2 hybridization to linear sp hybridization, can be written. Each would require the carbon atom at which substitution occurs to be colinear with the two carbon atoms ortho to it, and this is an immediate objection to both. Further consideration shows that both are impossible, XII (in which the line X···C···Y is perpendicular to the plane of the ring) because



XII XIII

the perpendicular p-orbital is the one used for the π-bonds, and XIII (in which the line X···C···Y is in the plane of the ring) because Y and the benzene ring cannot occupy the same space (170).

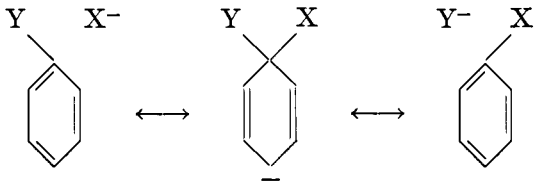
Suppose then that the carbon atom retains its sp^2 hybridization and half-bonds are formed to X and Y by means of the hybrid orbital ordinarily used for the C—X covalent bond. The transition state might then be written as XIV (in which the C···X and C···Y bonds supposedly form an angle of about 110° within a plane at right angles to the plane of the ring); such a transition state has been written in a tentative way many times. Since the available orbital



XIV

sticks straight out from the ring with its axis in the same plane, it is directed at neither X nor Y, and neither the C···X nor the C···Y bond has much reality (410). Furthermore, as Dr. D. P. Craig has pointed out (131), any bending of the orbital towards X or Y would cause it to partake of the nature of the vertically directed p-orbital, which is already used for π-bonds, and this would be a violation of the Pauli principle.

The same considerations also eliminate formulation (461, 596c) of the transition state for aromatic substitution as a resonance hybrid of structures XV. If XVb (and its sisters in which the negative charge is on the ortho carbon) were

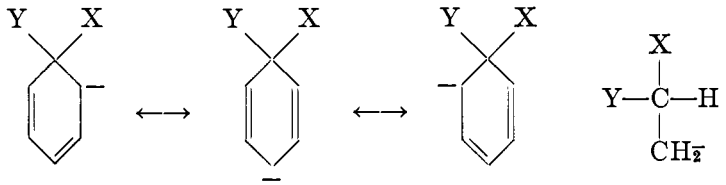


XVa XVb XVc

to participate in the proposed resonance, X and Y would have to occupy positions above and below the plane of the ring appropriate to a tetrahedral configuration of the carbon atom at the site of substitution. But XVa requires that Y lie in the plane of the ring, and XVc demands that X be in that plane. All three structures have different configurational requirements, and therefore they cannot resonate with one another. The argument is similar to that which eliminated XIV; indeed, XIV has sometimes been intended to represent the resonance discussed in this paragraph.

It thus appears that for aromatic substitution there is no acceptable transition-state model in which benzenoid resonance is maintained.

Let us then consider a transition state in which benzenoid resonance is lost, and in which the carbon atom assumes an sp^3 tetrahedral hybridization. Structures of type XVI have been proposed (291, 596c), and they are quantum-mechanically acceptable. The loss of benzenoid resonance has been cited (596e) as a factor unfavorable to XVI, but it is likely that the resonance energy of the pentadienate anion (XVIa ↔ XVIb ↔ XVIc) is nearly as great as the resonance

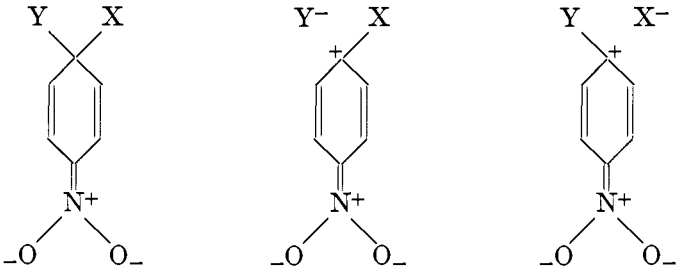


XVIa XVIb XVIc XVII

energy of benzene. A characteristic of XVI which, on the other hand, must very much increase its potential energy is that carbon is the seat of its negative charge. Carbon is also the seat of the negative charge in XVII, the corresponding stage in vinyl halide replacement by the same sort of mechanism, and indeed it may be this factor which is responsible for the similar inertness of phenyl and vinyl halides.

When there is sufficient activation, substances of type XVI can actually be isolated, as is reported in the following pages. Some of the isolable addition complexes are true intermediates in substitution reactions, and it is reasonable to believe that all the more activated substitutions proceed through intermediates of some stability. This belief has long been held for nitro-activated substitutions (52, 320, 367, 587). Acceptance of it is a fundamental assumption in the following argument.

By definition, a metastable intermediate is not a transition state. A reaction going through an intermediate has two transition states, one for its formation and one for its decomposition. In the case of the formation of XVIII, the intermediate for a *p*-nitro-activated substitution, the transition state must lie somewhere between the separate reactants and XVIII, and by the arguments in the preceding paragraphs must have sp^3 hybridization of the carbon atom at the site of substitution. These limitations leave something approximating structure XIX as the only possible formulation of the transition state. In XIX, X lies below the plane of the ring and Y above, and Y is separated from the carbon atom by a distance somewhat greater than the normal covalent bond length.



XVIII XIX XX

The attraction between Y and the carbon atom is probably mainly electrostatic in character. Transition state XX for decomposition of the intermediate is of the same type.

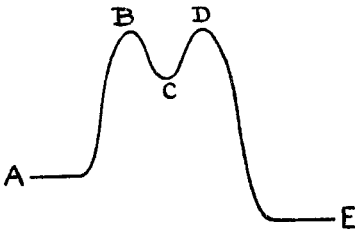


FIG. 1

The potential energy diagram for this reaction will have two "peaks," the heights of which will be determined by the potential energies of the transition states for formation and decomposition of the intermediate. Such a diagram is sketched in figure 1 for the special case that the potential energies of the two transition states are equal. In figure 1, the energy levels of the starting materials, of the transition state for formation of the intermediate, of the intermediate, of the transition state for decomposition, and of the products are represented by A, B, C, D, and E, respectively.

In general, the energies of the two transition states will not be equal; that is, the two "peaks" will be of unequal height. Now examination of XIX and XX reveals that the principal difference between the two transition states is that Y

appears as an anion in XIX whereas X is an anion in XX (for the common case in which both nucleophilic reagent and displaced group are anions). Thus the energies of XIX and XX should be governed very largely by the potential energies of Y^- and X^-, respectively.

If X^- has lower energy than Y^-, for example if $X^- = Cl^-$ and $Y^- = OCH_3^-$, the energy of transition state XX for decomposition of the intermediate is lower than the energy of XIX. In this case, the intermediate is able to pass over the second peak to form products more rapidly than to return over the first peak to regenerate starting materials. If the energy of the decomposition transition state is very much lower, formation of products becomes virtually the only path of reaction followed by the intermediate. The situation is then described by the following equations:

$$ArX + Y^- \xrightarrow{\text{slow}} ArXY^- \xrightarrow{\text{fast}} ArY + X^-$$

The rate of formation of products from starting materials is the rate of formation of the intermediate, and the rate of ejection of the displaced group has no effect on the overall rate of reaction. These, it should be remembered, are consequences of X^-, the displaced group, having much lower energy (that is, greater anionic stability) than Y^-, the reagent.

From similar reasoning, if X^-, the displaced group, has much greater energy (lesser anionic stability) than Y^-, the reagent, the situation is to be described by the equations:

$$ArX + Y^- \underset{\text{fast}}{\rightleftharpoons} ArXY^- \xrightarrow{\text{slow}} ArY + X^-$$

In this situation, the rate of formation of products from reactants is equal to the equilibrium concentration of the intermediate times the rate coefficient for decomposition of the intermediate. Since the position of an equilibrium is determined only by the energies of its initial and final states, in this case the rate of formation of products is independent of the rate of formation of the intermediate. An extreme example of this is displacement of hydrogen by hydroxide ion; here the rate of expulsion of X^- (hydride ion) from the intermediate is often so low that substitution can be completed only by the device of oxidizing the intermediate, as discussed in the following pages.

Between these two extremes there are cases in which the energies of X^- and Y^- are not very different, and therefore in which the energies of the two transition states have similar values. Such cases are described by the equations:

$$ArX + Y^- \underset{\text{slow}}{\rightleftharpoons} ArXY^- \underset{\text{slow}}{\rightleftharpoons} ArY + X^-$$

That is, the rate of formation of products from reactants is affected by both the rate of formation of the intermediate and the rate of its decomposition. The reversibility of such reactions is often experimentally verifiable.

The argument in the preceding paragraphs considers the potential energies of transition states XIX and XX as functions only of the stabilities of Y^- and X^-, respectively. This neglect of the effect of X on the stability of XIX, and of

Y on the stability of XX, is permissible as a first approximation because the effects would be mainly inductive effects operating along single covalent bonds and would probably have less influence on the energies of the transition states.

The foregoing picture of the mechanism of activated aromatic nucleophilic substitution reactions is theoretically reasonable and in accord with many experimental facts. Unfortunately, it does not seem possible at present to arrive at such definite conclusions about the mechanism of unactivated substitutions. If they go through an intermediate, it must have very low stability; on the other hand, structures such as XVI may be true transition states for unactivated substitutions.

Berliner, Quinn, and Edgerton (52) have recently offered a discussion of the mechanism of the reaction of piperidine with some naphthyl halides that is in some respects similar to the above. They visualize nitro-activated displacements as proceeding through intermediates similar to XVIII, but unactivated substitutions as "presumably S_N2 displacements with a transition state analogous to that for S_N2 displacements in aliphatic halides." They also consider the question of the relative rates of the formation and decomposition of the intermediate in activated substitutions, but do not arrive at definite conclusions as to which is more rapid in the reactions they studied.

Our conclusions may be summarized as follows:

(1) The transition state in aromatic nucleophilic substitution involves sp^3 (tetrahedral) hybridization of carbon, and does not possess benzenoid resonance.

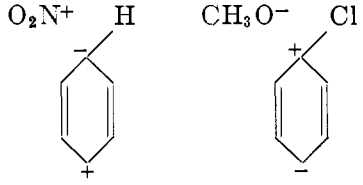
(2) The *more activated* substitutions proceed through an intermediate of some stability and the relative potential energies of the transition states for its formation and decomposition depend largely on the relative anionic stabilities of the entering and displaced groups. From this it follows that: (*a*) if the displaced group has much greater anionic stability than the entering group, the rate of formation of the intermediate is the rate of overall substitution; (*b*) if the entering group has much greater anionic stability than the displaced group, the rate of overall substitution is the equilibrium concentration of the intermediate times the rate constant for ejection of the displaced group from the intermediate, and the rate of formation of the intermediate has no effect on the overall rate of substitution.

(3) In *unactivated* substitutions, structures of type XVI might be either intermediates or proper transition states.

Although this discussion of the mechanism of aromatic substitution has been expressed in terms of nucleophilic substitution, its main conclusions are equally applicable to electrophilic substitution. The quantum-mechanical argument is directly applicable without change, while the discussion of the effect of the relative anionic stabilities of entering and displaced groups can be rephrased to apply to electrophilic substitution by substituting "cation" for "anion," etc. From experimental considerations, Melander (426) and Hughes, Ingold, and Reed (292) have concluded that the nitration of aromatic compounds by nitro-

nium ion involves slow formation of an adduct, followed by fast expulsion of hydrogen ion. Since the hydrogen ion (H^+) has much greater cationic stability than the nitronium ion, this is the result that the discussion of this section would predict.

The foregoing conclusions assist an understanding of the apparently greater susceptibility of unactivated aromatic compounds to electrophilic than to nucleophilic substitution. In the transition states for nitration of benzene and reaction of chlorobenzene with methoxide, represented in an approximate fashion by XXI and XXII, respectively, high potential energy is conferred by the presence of a



XXI XXII

positive charge on (ortho or para) carbon in XXI and a negative charge on carbon in XXII. (It is presumed that the positive and negative charges at the site of substitution are to a large extent offset by electrostatic interaction.) Since carbon is normally in a more stable condition when electron-poor than when electron-rich (467a), XXI should be more stable than XXII. The same effect is held responsible for the nucleophilic character of simple olefins (467a).

These phenomena have also been explained (114) as a consequence of π-electron shielding of unsaturated carbon atoms in the directions from which, for steric reasons, reagents would be most likely to approach; the π-electron cloud assists attack of electrophilic reagents and decreases susceptibility to nucleophilic attack. This is a further example of the concordance of explanations based, respectively, on thermodynamic and kinetic considerations.

It should be recognized that both these arguments are explanations of a phenomenon which, for the reasons given below, may present itself in practice in exaggerated form. The belief that aromatic compounds are inherently more vulnerable to electrophilic than to nucleophilic substitution is perhaps partly due to a chemical accident that a fair selection of very active electrophilic reagents (as used for bromination, nitration, sulfonation, etc.) are easily accessible from common materials, and that processes using them are of great utility, whereas very active nucleophilic reagents are less common and less useful. If comparison of the nitration of benzene with the reaction of chlorobenzene with potassium amide in liquid ammonia at −33°C. had been the only evidence available, a different impression might have been gained.

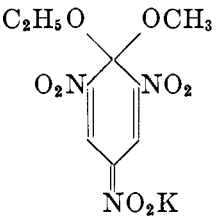
D. ISOLABLE ADDITION COMPLEXES

In the preceding discussion, considerable importance has been attached to the fact that in some cases substances analogous to the proposed intermediates can actually be isolated. These adducts are now presented. In accordance with

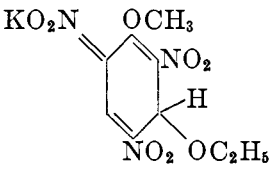
expectation, they are isolated only when neither the nucleophilic reagent nor the displaceable group has much potential anionic stability. Some of these addition complexes are true intermediates in displacement reactions which can be driven to completion; in other cases, the substitution has not been completed. They fall into three main groups: complexes formed between polynitro compounds and simple anions, adducts of organometallic to aromatic compounds, and pseudo-bases.

It must be recognized, as Morton (441) has emphasized, that the cationic part of the addition reagent may have an important influence on the formation of addition complexes, especially when it has rather strongly electrophilic properties (lithium and magnesium alkyls). Complex formation by the metal atom with the hetero nitrogen atom of pyridine must, for instance, appreciably activate attachment of an alkyl group to the 2-carbon (similar to protonation activation, Section IV,D,7). However, Morton's view that the addition reagents are therefore to be regarded as electrophilic seems extreme.

Polynitro compounds such as *s*-trinitrobenzene give with ordinary bases brightly colored solutions. From some such systems it has been possible to isolate the adducts responsible for the color. These include the adducts of *s*-trinitrobenzene with potassium methoxide (381) and potassium cyanide (243), of *s*-trinitrotoluene with potassium methoxide (243), of sodium 3,5-dinitro-*p*-anisate with sodium ethoxide (305), of the methyl, ethyl, propyl, isoamyl, and benzyl ethers of picric acid with the corresponding sodium alkoxides (301), and of 9-nitroanthracene with potassium methoxide (424). The constitution of these adducts was settled by Meisenheimer (424), who showed that the same adduct was obtained from 2,4,6-trinitroanisole and *ethanolic* potassium hydroxide as from 2,4,6-trinitrophenetole and *methanolic* potassium hydroxide. In each case, the adduct was decomposed by acids to give the same mixture of trinitroanisole and trinitrophenetole, the latter predominating. This shows that the adduct has structure XXIII (in which the position of potassium is assumed and there is presumably extensive resonance with the other nitro groups); the evidence



XXIII



XXIV

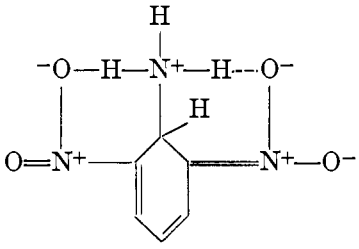
specifically excludes structures such as XXIV. Analogous results were obtained in an experiment with trinitrophenetole, potassium butoxide, etc.

Meisenheimer's adduct (XXIII) is a stable intermediate in a reversible substitution reaction between methoxide and trinitrophenetole on the one hand and ethoxide and trinitroanisole on the other (301). Addition of acid causes the equilibria to shift to both ends at once; that more trinitrophenetole is produced

indicates ejection of methoxide to be the faster process, as would be expected because methoxide is the more stable anion.

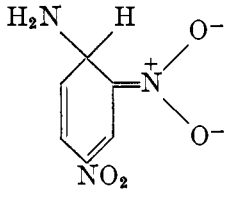
The adducts of *s*-trinitrobenzene are intermediates of the "second peak higher" variety, expulsion of hydride ion being energetically unfavorable. The best way to complete such a substitution is to add an oxidizing agent, which will effect the removal of hydrogen in some more stable form. For example, picric acid is produced by adding potassium ferricyanide to a boiling alkaline solution of *s*-trinitrobenzene (254). In like manner 2,4- and 2,6-dinitrophenols are produced from *m*-dinitrobenzene.

Aliphatic amines also form highly colored adducts with polynitro aromatic hydrocarbons. Ammonia and primary amines, though relatively weak bases, surpass secondary and tertiary amines and also alkoxides in their ability to form such complexes; this has been explained by Lewis and Seaborg (368) as a consequence of hydrogen-bonding to adjacent nitro groups (structure XXV).



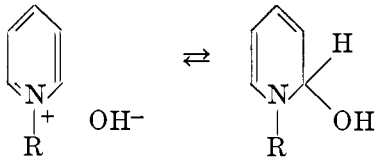
XXV

Solutions of *m*-dinitrobenzene in liquid ammonia are deep purple and good conductors of electricity; from a study of the products of electrolysis, Farr, Bard, and Wheland (177) concluded that the solution probably contains ammonium ion and the ion XXVI.



XXVI

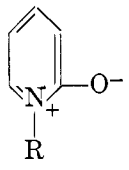
Quaternary ammonium hydroxides derived from pyridine, quinoline, isoquinoline, acridine, and related heterocycles exist in a tautomeric equilibrium.



(16)

N-Alkylpyridinium hydroxides are largely in the ionic form, but in some compounds the equilibrium is more on the side of the covalent form (the pseudo-base). All these bases, whether largely covalent or largely ionic, are converted by acids into proper salts. A more extensive discussion of them has been given by Bergstrom (45).

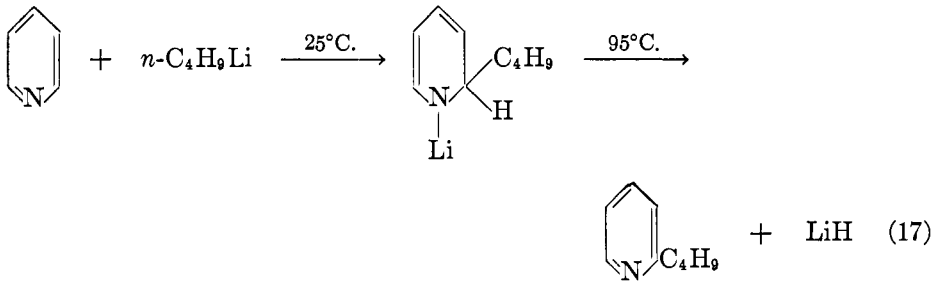
Pseudo-bases represent stable intermediates in substitutions in which the second peak is very high. Just as in the polynitrobenzene series, the substitution is difficult to complete unless an oxidizing agent is added; treatment of *N*-alkylpyridinium salts with alkaline ferricyanide is a useful method for the preparation of *N*-alkyl-α-pyridones (148). (This is better understood if attention is focused on the betaine resonance structure, XXVII, of *N*-alkyl-α-pyridones.) Again, as



XXVII

in the polynitrobenzene series, if the α-position is occupied by a group with potential anionic stability, substitution occurs forthwith and the intermediate cannot be isolated; thus, treatment of *N*-alkyl-2-chloropyridinium salts with hydroxides produces *N*-alkyl-α-pyridones directly.

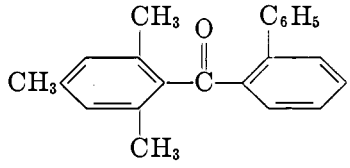
Very similar to the formation of pseudo-bases is the action of Grignard reagents on *N*-alkylquinolinium salts, which produces 1,2-dialkyl-1,2-dihydroquinolines (193, 194). Such additions also occur when the hetero ring lacks the special activation conferred by alkylation of the nitrogen atom. An early and beautiful example is the reaction of *n*-butyllithium with pyridine (610), shown in equation 17. The adduct could be crystallized and on hydrolysis gave 2-*n*-



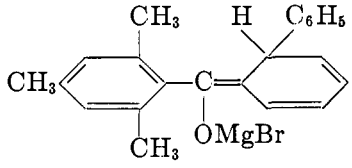
(17)

butyl-1,2-dihydropyridine. Substitution was completed by heating, which caused lithium hydride to precipitate. A similar adduct has been obtained from 2-phenylquinoline and *p*-tolyllithium (210); on hydrolysis it yields 2-phenyl-2-*p*-tolyl-1,2-dihydroquinoline. The same dihydroquinoline is obtained starting from 2-*p*-tolylquinoline and phenyllithium, and so its structure is established. This incipient substitution cannot be completed because of the difficulty of expelling an aryl anion.

Addition complexes of organometallic with aromatic compounds have also resulted from the action of Grignard reagents on hindered aromatic ketones. As applied in synthesis, these reactions usually appear to effect replacement of ring hydrogen by the alkyl or aryl group of the Grignard reagent. For example, phenylmagnesium bromide and benzoylmesitylene give 2-phenylbenzoylmesitylene (XXVIII) (199). Dihydro derivatives are sometimes formed as by-products (199, 200); these are the expected hydrolysis products of the 1,4-adduct (XXIX)



XXVIII



XXIX

which is believed to form initially. If the position ortho to the hindered carbonyl is occupied by a group of potential anionic stability (methoxy), the substitution is completed rapidly and high yields of the alkylation or arylation product are obtained (202). Further information on this and related reactions will be found in the review of Gaertner (205).

IV. The Influence of the Aromatic System in Which Substitution Occurs

The main chemical variables in aromatic nucleophilic substitution are the nucleophilic reagent, the group displaced, and the activation or deactivation provided by the structure of the aromatic compound. The last of these is now considered in detail.

A substituent is called activating or deactivating according as it produces, with respect to hydrogen, an increase or decrease in the rate of a reaction. In the case of heterocyclic compounds, a hetero atom is said to be activating if introduction of it into a ring in place of CH or CH=CH increases the rate of substitution.

A. ELECTRONIC ACTIVATION AND DEACTIVATION

1. General comparisons

It can be safely assumed that every substituent ortho to the site of a substitution has some steric effect on the rate of the process. Classification of all the activating effects discussed in this section as "electronic" is therefore not strictly correct. However, in most of the data considered herein the electronic effect of the group appears to be far more pronounced than the steric effect.

The more important activating groups are listed in table 3 in approximate order of decreasing activating power; the notes relate to the approximate effect of *one* activating group on the replaceability of a halogen atom ortho or para. Table 3 is based in part on the comparisons of rate coefficients shown in tables 4, 5, 6, and 7, and in part on qualitative observations which are discussed in the following sections.

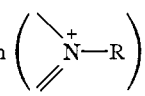
It is to be noted in table 4 that, although the relative activation by a group (on the scale $k_{NO_2} = 1000$) is not constant in the two series, the groups fall in the same general order of activating power. This shows that the activating effect of a secondary activating group (as in a 4-substituted-1-chloro-2-nitrobenzene) is similar to that of the group when it is the sole source of activation. Tables 5 and 6 are concerned with deactivating or slightly activating groups.

Other comparisons of activating groups in a single sort of reaction are more limited in scope and more qualitative in nature. They are listed in table 7.

The above activation sequences all apply to halogen displacement. Information on the activation of replacement of other groups is less abundant. However, in the Smiles rearrangement (Section VIII), which in its most familiar form in-

TABLE 3

Activating groups in order of decreasing activating power

Diazonium salt group ($-N_2^+$) Cationic carbon ($-CR_2^+$)	Activate halogen exchange at room temperature or below
Alkylated hetero nitrogen 	Activate replacement by strong nucleophilic reagents at room temperature
Nitroso group (NO) Nitro group (NO_2)	Activate reaction with strong nucleophilic reagents at *ca.* 80–100°C.
Hetero nitrogen atom 	
Methylsulfonyl (CH_3SO_2) Trimethylammonio ($(CH_3)_3N^+$) Trifluoromethyl (CF_3) Acyl groups (RCO) Cyano (CN) Carboxyl (COOH)	With nitro also present, activate reaction with strong nucleophilic reagents at room temperature
Ionized sulfo (SO_3^-) Halogens (Cl, Br, I) Carboxylate (COO^-) Phenyl	With nitro also present, activate reaction with strong nucleophilic reagents at *ca.* 40–60°C.

volves intramolecular displacement of a sulfonyl by a phenoxy group, the sequence of activating power $NO_2 > COC_6H_5 > COO^- > Cl > H$ has been found from a study of the rearrangement of LVI (206).

2. The activating effects of particular groups

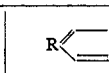
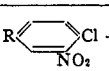
(a) Groups more strongly activating than the nitro group

The activating effect of the diazonium salt group (N_2^+), the strongest of the activating groups, is conspicuous for its nuisance importance. During the diazotization of anilines, a nitro, methoxy, or halogen group ortho or para to the amino group is sometimes replaced by hydroxy (owing to reaction with water) or by chlorine (if hydrochloric acid is used); the effect is pronounced if there is a second activating structure suitably oriented to the displaceable substituent. For

TABLE 4

Comparative activation in two reactions

(Bunnett and coworkers (105, 106))

GROUP R	 + PIPERIDINE AT 99°C.		 + $NaOCH_3$ at 25°C.	
	Rate coefficient		Rate coefficient	
	l. $mole^{-1}$ $min.^{-1}$	On scale $k_{NO_2} = 1000$	l. $mole^{-1}$ $min.^{-1}$	On scale $k_{NO_2} = 1000$
NO_2	387×10^{-6}	1000	150×10^{-2}*	1000
CH_3SO_2	21×10^{-6}	53	15.9×10^{-2}	106
$(CH_3)_3N^+$			5×10^{-2}§	33
CN	11.9×10^{-6}	31		
CH_3CO	5.2×10^{-6}	13	1.87×10^{-2}	12
Cl			0.010×10^{-2}†	0.07
H			0.0009×10^{-2}‡	0.006

* From table 49.
† From table 43.
‡ Calculated from data in table 43.
§ Approximate value.

TABLE 5

Reactions of 4-substituted-2-nitrobromobenzenes with excess piperidine

(Berliner and Monack (51))

GROUP IN 4-POSITION	RATE COEFFICIENT		*E*	LOG *PZ*
	25°C.	35°C.		
	min.$^{-1}$	*min.*$^{-1}$	*kcal.*	
Br	2.27×10^{-2}	4.23×10^{-2}	11.4	6.68
Cl	1.62×10^{-2}	3.07×10^{-2}	11.7	6.76
I	1.57×10^{-2}	3.11×10^{-2}	12.5	7.34
COOH	7.31×10^{-3}	1.44×10^{-2}	12.4	6.93
H	2.90×10^{-3}	5.63×10^{-3}	12.1	6.34
F	7.55×10^{-4}	1.56×10^{-3}	13.2	6.55
tert-C_4H_9	4.94×10^{-4}	9.99×10^{-4}	12.9	6.12
CH_3	4.23×10^{-4}	8.70×10^{-4}	13.2	6.27
OCH_3	5.22×10^{-5}	1.17×10^{-4}	14.7	6.52
OC_2H_5	4.37×10^{-5}	9.43×10^{-5}	14.0	6.44
$N(CH_3)_2$*	3.5×10^{-6}	7.5×10^{-6}	*	*
OH*	1.7×10^{-6}	4.4×10^{-6}	*	*
NH_2*	3.9×10^{-7}	8.0×10^{-7}	*	*

* These reactions occurred extremely slowly; the rate coefficients are not very accurate and do not justify calculation of Arrhenius parameters.

TABLE 6

Effects of chlorine, hydrogen, and methoxy on meta-substitutions

2,4-DINITRO-5-R-CHLOROBENZENE	REACTION WITH METHANOLIC METHOXIDE AT 0°C. RATE COEFFICIENT	REFERENCE
	l. mole^{-1} *min.*$^{-1}$	
R = Cl	0.60*	(282)
R = H	0.111	(283)
R = OCH_3	0.037	(386)

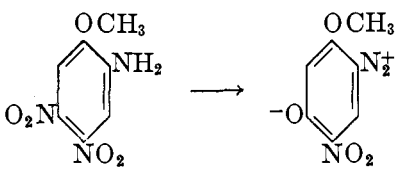
* Based on one chlorine atom.

TABLE 7

Comparative activation sequences

REACTION	SEQUENCE OF ACTIVATING POWER	REFERENCE
p-Substituted chlorobenzenes with:		
$NaOCH_3$ at 150°C	$NO_2 \gg Cl > H > NH_2 \sim CH_3 \sim O^-$	(342)
Aqueous-alcoholic KOH, temperatures up to 170°C	$NO_2 \gg SO_2^- > SO_3^- > COO^-$	(146)
Piperidine in boiling benzene	$NO_2 > CN > C_6H_5N{=}N- > H > NH_2$	(15)
p-Substituted bromobenzenes with $NaOCH_3$ at 150°C	$NO_2 \gg Br > H \sim NH_2 > OCH_3 \sim CH_3$	(342)
4-Substituted-2-nitrochlorobenzenes with boiling aqueous-alcoholic KOH	$NO_2 \gg SO_3^- > COO^- > H$	(146)
4-Substituted-2-nitrobromobenzenes with sodioacetoacetic ester	$CN > COCH_3 > COC_6H_5$	(79)
o-Substituted chlorobenzenes with $NaOCH_3$ at 150°C	$NO_2 > Cl > H > NH_2 > CH_3$	(342)
o-Substituted bromobenzenes with $NaOCH_3$ at 150°C	$OCH_3 > H > CH_3$	(342)
1-Substituted-2,5-dichlorobenzenes with $NaOCH_3$ at 183°C. (2-chlorine replaced)	$NO_2 > CN$ (at 100°C.) $> SO_3^- > COO^- > CH_2OH$	(132)
2-Substituted-4-nitrochlorobenzenes with:		
Aromatic amines	$NO_2 > COOH > CN$	(153)
$NaOCH_3$, $NaOC_2H_5$, and diethylamine	$NO_2 > CN > COO^-$	(153)
1,3-Disubstituted-4-chlorobenzenes with boiling aqueous alcoholic KOH	$SO_3^- > COO^-$	(146)
m-Substituted chlorobenzenes with $NaOCH_3$ at 150°C	$NO_2 > H > O^- > NH_2$	(342)
1-Substituted-3,4-dichlorobenzenes with $NaOCH_3$ at 183°C. (3-chlorine replaced)	$I > Br > Cl > CH_3 > O^-$	(339)

instance, diazotization of 6-methoxy-3,4-dinitroaniline in glacial acetic acid produces 6-methoxy-3-nitrobenzene-1,4-diazo oxide (427):

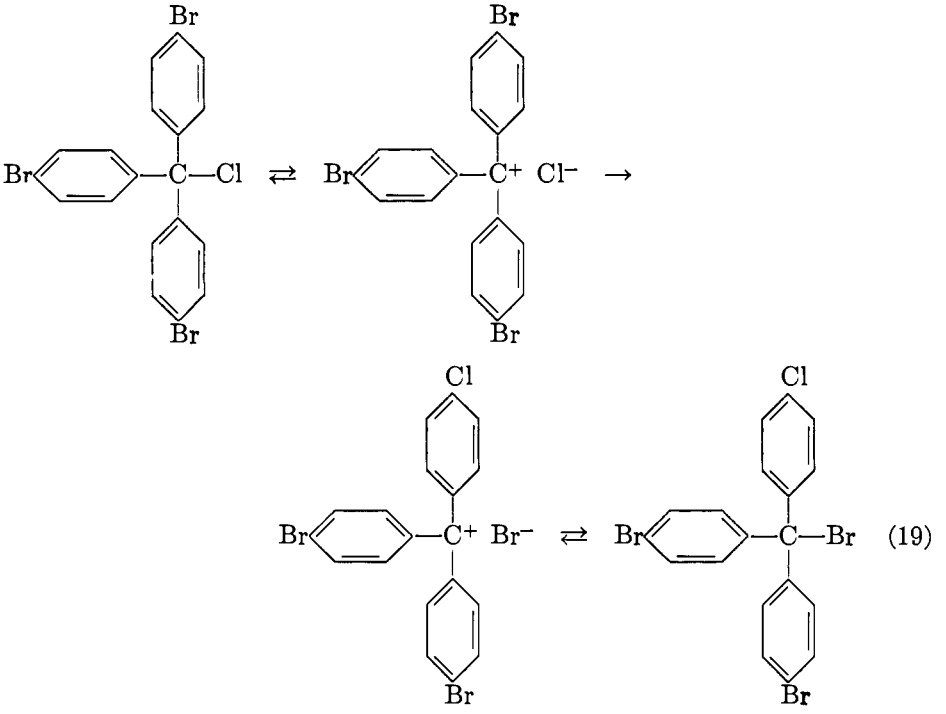


(18)

Other examples will be found on pages 277 and 285 and in a book by Saunders (512b).

Evidence for activation by the R_2C^+— grouping is the rearrangement under-

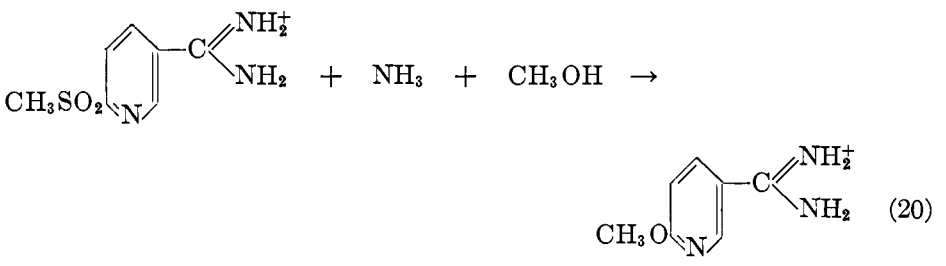
gone by *p*, *p'*, *p''*-tribromotriphenylmethyl chloride in liquid sulfur dioxide solution (226):



(19)

The conductivity of solutions of triphenylmethyl halides in sulfur dioxide shows that they ionize as indicated (225).

The reviewers encountered one instance, shown in equation 20, of apparent activation by the amidinium group (188). 2-Methylsulfonyl-5-nitropyridine also suffered replacement of its methylsulfonyl group under these



(20)

conditions, but an amino instead of a methoxy group was introduced.

The activating effect of the nitroso group is evident in the facile cleavage of *p*-nitrosodialkylanilines by alkali or bisulfite (446). Le Fevre (357) has shown that one nitroso group is superior to two nitro groups in promoting this reaction.

(b) The nitro group

The nitro group was the first recognized to activate aromatic nucleophilic substitutions. It continues to be the most prominent activating group because of the availability of nitro compounds *via* the nitration reaction and because it is the strongest activating group that is relatively stable under the basic conditions of common nucleophilic substitution reactions. Its activating effect is evident in most of the data presented in this review. There is considerable information about the activation pattern of the nitro group; this is now considered not only for its own interest but also because it may represent the activation pattern of other groups whose activating effect is due to similar electronic features.

The nitro group is conspicuously ortho-para activating; the meta position is also activated but meta-activation can seldom be detected because the nitro group itself reacts with many nucleophilic reagents. For example, *m*-chloronitrobenzene and methanolic sodium methoxide give *m,m'*-dichloroazoxybenzene (283). However, *m*-fluoronitrobenzene reacts with sodium methoxide to give *m*-nitroanisole (279), though this requires more vigorous conditions than the reaction of *p*-fluoronitrobenzene (276, 280). Again, the reaction of *s*-trinitrobenzene with sodium methoxide to give 3,5-dinitroanisole is a preparative method (469), although all other trinitrobenzenes react more rapidly (281).

Regarding the comparative activation of the ortho and para positions by the nitro group, no sweeping generalization can be made. The extensive pertinent data can, however, be arranged in categories, as follows: (*a*) from 2,4-dihalonitrobenzenes, the ortho halogen is preferentially displaced by all sorts of nucleophilic reagents (table 42); (*b*) *p*-halonitrobenzenes and *p*-dinitrobenzene react with alkoxides more rapidly than do their *o*-isomers (tables 43 and 52 and the following paragraph); and (*c*) *o*-halonitrobenzenes react more rapidly with amines (table 8) and with sodium thiophenoxide (83).

Rate constants for the reactions of *o*- and *p*-bromonitrobenzenes with sodium ethoxide at 50°C. are 0.00042 and 0.00080 l. mole^{-1} min.$^{-1}$, respectively (470). However, the order ortho > para was reported by Franzen and Bockhacker (191) for the same reaction in boiling ethanol. The kinetic evidence (table 43) that *p*-chloronitrobenzene reacts faster with alkoxides has been confirmed (kinetic studies) by Riklis (482, 483) and less rigorously by other workers (342).

The reader is referred to the tables in Section VII for additional information, both qualitative and quantitative, about the activating effect of the nitro group.

(c) Groups of intermediate activating power

Work in Schöpff's laboratory (183, 230, 231, 517, 518, 519, 520) about 1890 demonstrated qualitatively the activating effect of the carboxyl (COOH), carboxylate (COO^-), carboxylamido ($CONH_2$), carbethoxyl ($COOC_2H_5$), formyl, cyano, benzoyl, ionized sulfo (SO_3^-), and sulfonamido (SO_2NH_2) groups; each

when ortho or para to halogen in a halonitrobenzene increased the rate of condensation with aniline or ammonia. Condensation could also be promoted by two of these groups activating in concert, but higher temperatures were necessary than when nitro was one of the sources of activation.

Other qualitative information about the activation patterns of some of these groups is shown in table 9. Making the reasonable assumption that the chlorine atoms in these polychloro compounds activate each other in a reciprocally equivalent fashion, it is clear that formyl, carboxylate, and ionized sulfo groups are principally ortho-para activating.

TABLE 8

Reactions of amines with halonitrobenzenes

REACTION	REPLACEMENT OF HALOGEN UNDER STANDARD CONDITIONS		REFERENCE
	Ortho	Para	
	per cent	*per cent*	
Chloronitrobenzenes with:			
Diethylamine at 100°C.	10	3	(191)
Dipropylamine at 130°C.	13	1	(456)
Piperidine in boiling benzene	60*	2*	(94)
Bromonitrobenzenes† with:			
Diethylamine at 100°C.	18	4	(191)
Dipropylamine at 130°C.	20	1	(456)
Piperidine in boiling benzene	72*	4*	(94)
Iodonitrobenzenes with:			
Diethylamine at 100°C.	9	2	(191)
Dipropylamine at 130°C.	32	1	(456)
Piperidine in boiling benzene	30*	4*	(94)

* The order $o > p$ has also been found for the reactions with piperidine in alcohol at 100°C. (191). Still another source gives the order $o > p$ for the reaction of bromonitrobenzenes with piperidine (531), but the order $p > o$ (96 per cent and 53 per cent, respectively) has also been reported (111).

† The order $o > p$ has also been found for reactions of bromonitrobenzenes with diamylamine (447).

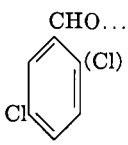
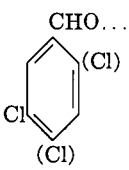
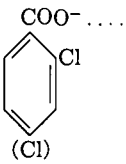
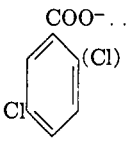
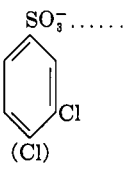
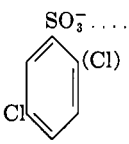
In table 5, the *p*-carboxylate (COO^-) group appears to be a weak activating group. Rouche (499) found that sodium 4-fluoro-3-nitrobenzoate reacted with methanolic sodium methoxide more than fifteen times as rapidly as did *o*-fluoronitrobenzene (the rate coefficients at 25°C. being 0.108 and 0.0070 l. $mole^{-1}$ $min.^{-1}$, respectively). Both sets of data, as well as qualitative observations summarized in table 7, indicate the activating effect of the carboxylate group to be of about the same order of magnitude as that of the chlorine atom.

A study of relative activation by the methylsulfonyl and nitro groups is summarized in table 10. The virtual absence of meta-activation by either group deserves notice.

Data on the activating effect of the trifluoromethyl group are shown in table 11. When nitro instead of trifluoromethyl is the source of activation, rate con-

TABLE 9

Activation patterns of some activating groups

COMPOUND*	REAGENTS EFFECTING SUBSTITUTION	COMPOUND*	REAGENTS EFFECTING SUBSTITUTION
	Sodium sulfite (207)		Sodium sulfite (207)
	Sodium methoxide (348)†		Sodium methoxide (132)
	Sodium methoxide (339)		Sodium methoxide (132)

* The atoms surrounded by parentheses are those replaced in the main reaction.
† The 2-chlorine is replaced to a lesser extent.

TABLE 10

Per cent replacement of chlorine in refluxing ethanolic sodium ethoxide in 2 hr.
(Todd and Shriner (549))

	ORTHO	META	PARA
Chlorophenyl methyl sulfone	2.5	0.07	1.5
Chloronitrobenzene	33	0.7	35

TABLE 11

Reactions of disubstituted benzenes with ethanolic sodium ethoxide at 150°C.
(Miller and Wrightson (433))

ACTIVATING GROUP	ORIENTATION	RATE COEFFICIENT WHEN GROUP DISPLACED IS		k_F/k_{Cl}
		Fluorine	Chlorine	
		l. mole^{-1} *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	
Trifluoromethyl	Para	0.27	0.00035	760
Chlorine	Para	0.00070	0.000008*	87
Trifluoromethyl	Meta	0.0065	0.000035	186
Chlorine	Meta	0.0033	0.000028*	118
Chlorine	Ortho	0.0048	0.000011*	436

* These are the reported rate coefficients divided by a statistical factor of 2.

stants of comparable magnitude are observed at 60°C. The superior mobility of fluorine as compared to chlorine evidenced in table 11 is discussed on page 333. The data also reveal a variation of the activating powers of the chlorine and trifluoromethyl groups, depending on the orientation and identity of the displaceable group. The value of the ratio k_{CF_3}/k_{Cl} is 390 for the displacement of *p*-fluorine, but only 44 for *p*-chlorine; for *m*-fluorine the ratio is 2.0, and for *m*-chlorine 1.25. Inasmuch as trifluoromethyl activates from the para position more strongly than from the meta, and chlorine is more strongly meta-activating, the difference in these ratios between the meta and para series is not surprising. The variation within each series shows, however, that trifluoromethyl is a stronger activating group when the displaceable group is fluorine, while the activating effect of chlorine is more pronounced when chlorine is displaced.

In reactions of some mono- and polytrifluoromethylchlorobenzenes with sodium alkoxides (417), there was displayed the following order of decreasing reactivity: 2,4,6-tri-CF_3 > 2,4-di-CF_3 > 2,6-di-CF_3 > 2,5-di-CF_3 > *p*-CF_3 > *o*-CF_3 > 3,5-di-CF_3 ~ *m*-CF_3.

Compounds with an arsono (—AsO_3H_2) group and a nitro group ortho and para to a halogen atom have several times been condensed with phenols or amines in synthetic work; alkoxy groups have also been replaced. Activation by the arsono group usually appears to be much weaker than by the nitro group. The media generally applied in these condensations are sufficiently alkaline to ionize the first but not the second hydrogen of the arsono group (524), and so activation must be ascribed to the grouping —AsO_3H^-. A detailed survey of these reactions has been given by Sweet, Calkins, and Banks (540).

An instance of activation by the phenyl group will be found in table 15.

(d) The halogens

The halogens have an activation pattern all their own; this is hardly surprising, in view of their unique influence on electrophilic substitution. They are activating, usually most so towards meta-substitution. This is illustrated by the data in table 11, and by the following rate coefficients for reactions (283) of, respectively, *o*-, *m*-, and *p*-dichlorobenzenes with sodium methoxide at 175–176°C.: 6.4×10^{-4}, 8.4×10^{-4}, and 1.9×10^{-4} l. mole^{-1} min.$^{-1}$ All these data concur in establishing the order of activating effect: $o \sim m > p$.

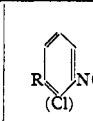
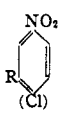
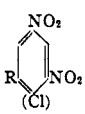
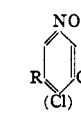
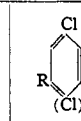
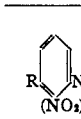
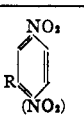
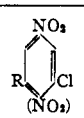
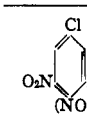
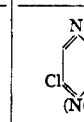
Additional information comes from table 12, in which is shown the effect on the reaction rate of introducing an additional chlorine atom into various positions of some chloronitrobenzenes. In this series *m*-chlorine, not ortho to a nitro group, has the most pronounced activating effect. *o*- and *p*-Chlorine have roughly equivalent effects. The activating effect of chlorine meta to the site of substitution is much lower if it is also ortho to an activating nitro group because of steric interference with the nitro group, as discussed on page 324. The overall activation pattern $m > o > p$ of chlorine for nucleophilic substitution is no doubt due to the same polarization of the ring which contributes to the *deactivation* pattern $m > o > p$ for electrophilic substitution.

In table 5, *p*-halogens stand in the order of activating power: Br > Cl > I > H > F. The deactivating influence of fluorine deserves notice.

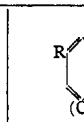
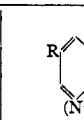
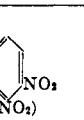
TABLE 12

The activating effect of chlorine (on reactions with sodium methoxide)*

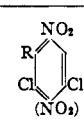
A. The effect of chlorine ortho to the site of substitution

					
Temperature	85°C.	85°C.	0°C.	25°C.	25°C.
k_H (R = H)	0.0062	0.0231	0.110	0.00055	0.000105
k_{Cl} (R = Cl)	0.030	0.29	0.409	0.00814	0.00083
k_{Cl}/k_H	4.8	12.5	3.7	14.8	8.0
					
Temperature	25°C.	25°C.	0°C.	0°C.	0°C.
k_H	0.0043†	0.0111†	0.0318	0.18†	0.346†
k_{Cl}	0.100	0.56	0.145	2.35	0.80
k_{Cl}/k_H	23	50	4.6	13	2.3

B. The effect of chlorine meta to the site of substitution but not ortho to a nitro group

				
Temperature	85°C.	25°C.	0°C.	0°C.
k_H	0.0062	0.0043†	0.00745	0.128
k_{Cl}	0.33	0.437	0.333	2.35
k_{Cl}/k_H	53	102	45	18.4

C. The effect of chlorine meta to the site of substitution and the sole substituent ortho to an activating nitro group

			
Temperature	0°C.	0°C.	0°C.
k_H	0.0318	0.145	0.110
k_{Cl}	0.346†	0.80	0.60‡
k_{Cl}/k_H	11	5.5	5.5

D. The effect of chlorine meta to the site of substitution and the second substituent ortho to an activating nitro group

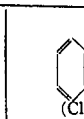
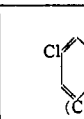
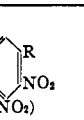
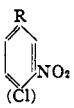
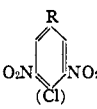
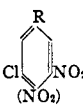
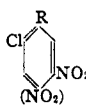
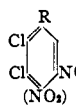
				
Temperature	85°C.	25°C.	0°C.	0°C.
k_H	0.0062	0.00050	0.00745	0.60‡
k_{Cl}	0.0012‡	0.000095‡	0.0131†	0.030‡
k_{Cl}/k_H	0.19	0.19	1.8	0.05

TABLE 12—*Concluded*

E. The effect of chlorine para to the site of substitution

					
Temperature	85°C.	0°C.	0°C.	0°C.	0°C.
k_H	0.0062	0.00289	0.00745	0.0331	0.333
k_{Cl}	0.065	0.025	0.128	0.18†	2.35
k_{Cl}/k_H	10.5	8.6	17.2	5.4	7.1

* All rate coefficients are taken from tables in Section VII.

† Based on one nitro group.

‡ Based on one chlorine atom.

k_H = rate coefficient when R = H; k_{Cl} = rate coefficient when R = Cl. The group in parentheses is displaced in the reaction.

(e) Deactivating groups

Table 5 contains the most extensive evidence about the relative effects of deactivating substituents. When para to the site of substitution, they stand in the following order of deactivating power: $NH_2 > OH > N(CH_3)_2 > OC_2H_5 > OCH_3 > CH_3 >$ *tert*-$C_4H_9 > F > H$, the amino group being the most deactivating. There are fewer data regarding effects on meta-substitution, but table 6 shows *m*-chlorine, *m*-hydrogen, and *m*-methoxy to stand in the same order as when they are in the para position. Qualitative observations about the effects of some deactivating groups are summarized in table 7.

Since activation is usually required to achieve substitution under convenient conditions, it is not surprising that in the reactions of tables 4, 5, and 6, as in most cases, the evidence for deactivation relates to the reduction in reaction rate caused by introduction of a deactivating group into a molecule well provided with activation.

In aromatic electrophilic substitution there are often several replaceable groups (hydrogen atoms) similarly activated by an activating group. From observation of the comparative ease with which the successive stages of substitution in such compounds can be realized, it is possible to draw valuable conclusions about the relative deactivating effects of groups. For example, from the fact that the reaction of phenol with one equivalent of bromine gives a monobromophenol and not polybromophenols, one can infer that bromine is more deactivating for electrophilic substitution than hydrogen. Opportunities for discerning the effects of groups on nucleophilic substitution by this method are more restricted, owing to the scarcity of substances with two or three identical replaceable groups similarly activated by a strong activating group. Cyanuric chloride is the most accessible of such substances; with amines in excess, it gives monosubstitution at 0°C., but a temperature of 25°C. is necessary for disubstitution, and trisubstitution is obtainable only at 120–140°C. (139). Thus amino groups must be, towards meta-substitution, less activating (more deactivating) than chlorine. The same conclusion is indicated by the requirement of progressively higher temperatures

to achieve the introduction of successive amino groups into 2,4,6-trichloropyrimidine by ammonia treatment (204).

The second stage in the amination of 2,6-dibromopyridine by alkylamines is more sluggish than in amination by ammonia (53), suggesting the following sequence of activating power: Br > NH_2 > NHR.

The successive steps of methoxylation of 2,4,6-tribromopyridine by methoxide (257) require progressively higher temperatures, but cyanuric chloride with one mole of sodium methoxide gives trimethoxytriazine (139).

TABLE 13

Deactivation by alkyl groups

(Bevan, Hughes, and Ingold (54))

CHLOROBENZENES	RATE COEFFICIENT*
	l. mole^{-1} *min.*$^{-1}$
2,6-Dinitro	0.882
2,6-Dinitro-4-*tert*-butyl	0.273
2,6-Dinitro-4-methyl	0.155

* For reaction with ethanolic sodium ethoxide at 50.00°C.

Such studies on polychloronitrobenzenes are less readily interpreted, because a group introduced ortho to the nitro group can influence the rate of the next step in substitution not only electronically but also by steric interference with

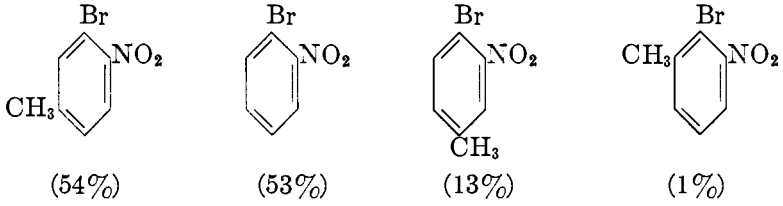


FIG. 2. Per cent removal of bromine in reaction with excess piperidine for 1 hr. at 45°C. (111).

the resonance of the nitro group (Section IV,B,2). It is conceivable that the product of replacement of chlorine by a small but electronically deactivating group might react in further substitution faster than the parent compound, because the small group would allow greater realization of the intrinsic activating effect of the nitro group. The second stage in the reaction of 2,4,6-trichloronitrobenzene with ammonia (281) occurs about as readily as the first, and this indeed may be such a case. It is also difficult to isolate the separate stages of reaction of 2,4,6-trichloronitrobenzene with sodium *p*-thiocresoxide (390), but here it is more likely that the electronic effects of the *p*-cresylthio group and of the chlorine atom are about equivalent. The reaction of 2,6-dichloro-1-nitrobenzene with sodium *p*-thiocresoxide may not be arrested at the monosubstitution

stage but its reactions with sodium methoxide, piperidine, and diethylamine occur stepwise (283, 390).

Regarding alkyl groups, table 13 confirms table 5 in establishing that methyl groups are more deactivating than *tert*-butyl groups. From figure 2, the deactivation pattern of methyl would seem to be $o\text{-}CH_3 > p\text{-}CH_3 > m\text{-}CH_3 \sim H$.

Information in preceding paragraphs indicates the methoxy group to be generally deactivating, and this is confirmed by other less systematic observations (142, 327, 420). However, replacement of one methoxy group in nitriles and hindered aromatic ketones by the organic moiety of a Grignard reagent is activated by another methoxy group ortho to the first. Gaertner (205) has suggested that coördination of the Grignard reagent with the activating methoxy group is the mechanism of activation. Such coördination would not only bring the reagent into position to effect substitution, but would also convert the methoxy oxygen to a positive pole which would activate for electronic reasons.

TABLE 14

Deactivation by hydroxy and amino groups*

(Clark and Ball (123))

COMPOUND	CONCENTRATION OF METHANOLIC $NaOCH_3$	CHLORINE REPLACEMENT†
	moles per liter	*per cent*
Chlorobenzene	2.0	4
	2.5	7
m-Chlorophenol	2.0	12
o- or *p*-Chlorophenol	2.0	0.0
2,5-Dichloroaniline	1.5	0.0

* Phenolic hydroxy groups are largely ionized under these conditions.

† Treatment for 50–60 hr. at 155°C.

The data in table 14 suggest that the hydroxy group, although ortho–para deactivating, is slightly activating towards meta-substitution. The amino group appears to deactivate all ring positions.

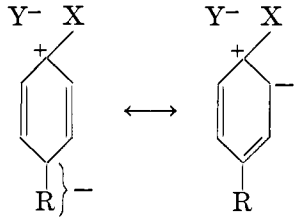
3. Transmission of activation through vinyl and phenyl groups

Table 15 shows that activation by a nitro group can be transmitted through a vinyl group with moderate loss of efficiency, but that its effect is not at all well transmitted through the biphenyl or the naphthalene two-ring systems.

4. Theoretical

In Section III, structure XXX was postulated to represent the transition state for formation of the intermediate in an activated substitution. The transition state for decomposition of the intermediate was assigned a similar sort of structure, which would be influenced by substituents in the ring in a similar

manner, and so it is not presently necessary to differentiate between them. For present purposes the important features of structure XXX are that the benzene



XXXa XXXb

resonance is replaced by pentadienate anion resonance and that there is a negative charge to be accommodated somewhere in the compound apart from the site of substitution.

TABLE 15

Transmission of activation through unsaturated systems

(Campbell and coworkers (111, 421))

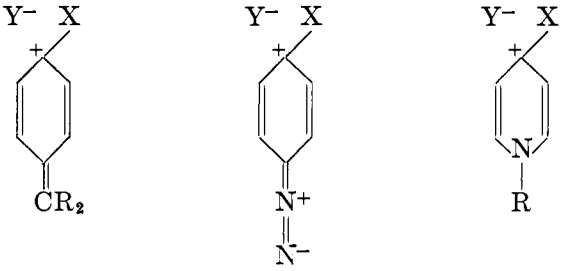
COMPOUND	REMOVAL OF BROMINE*	
	1 hr.	24 hr.
	per cent	*per cent*
o-Bromonitrobenzene	53	96
o-Bromo-ω-nitrostyrene		34
4-Bromo-3-nitrobiphenyl	78	98
2-Bromo-4′-nitrobiphenyl		0
p-Bromonitrobenzene	96	
4-Bromo-4′-nitrobiphenyl		.0
4-Bromo-2′-nitrobiphenyl		0
6-Bromo-2-nitronaphthalene		0
5,8-Dibromo-1-nitronaphthalene		0

* By excess piperidine at *ca.* 45°C.

Considering first the influence of the state of polarization of the aromatic molecule before substitution, to the extent that it is polarized similarly to structures XXX substitution will be aided, and to the extent that it is polarized in an opposite sense, substitution will be more difficult because the unfavorable polarization must be overcome before the necessary electrical orientation can be achieved. Polarization is the result of the operation of inductive ($\pm I$) and mesomeric ($\pm M$) effects of substituent groups; these effects have been discussed at length by Remick (467).

Substituent groups can further assist formation of the transition state if they are polarizable in a favorable sense, generally through their electromeric ($\pm E$) effects. In the case of aromatic nucleophilic substitution, the polarizability ($-E$) effect means its ability to accommodate the extra negative charge of structure XXX by becoming more negatively (or less positively) charged than it was in the normal state of the molecule.

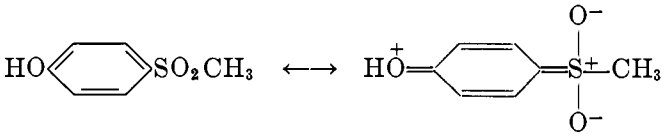
Inspection of table 3 shows that the most powerful activating structures (*a*) contain a positive pole and (*b*) can, by rearrangement of π-electrons, become neutral in the transition state; they have very strong $-E$ effects. The transition state structures are probably similar to XXXI, XXXII, and XXXIII. In this



XXXI XXXII XXXIII

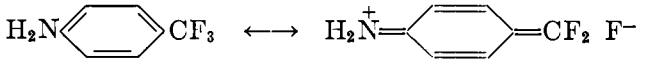
connection, it is significant that the trimethylammonio group ($-N(CH_3)_3^+$), which has a positive pole but *cannot* become neutral in the transition state by rearrangement of π-electrons (the covalency maximum of nitrogen is four), is not a particularly strong activating group. The trimethylammonio group exerts a strong inductive polarization, as shown by its strong deactivation of electrophilic substitution (69), but evidently its polarizability is very small. It contrasts with the nitro group, which is less deactivating for electrophilic substitution owing to less polarization ($-I$ and $-M$), but activates nucleophilic substitution very well because of its strong polarizability ($-E$) effect.

The mode of action of the other groups of intermediate activating power (acetyl, cyano, etc.) is undoubtedly a combination of $-I$, $-M$, and $-E$ effects. There has been some doubt about the mechanism of activation by sulfonyl (RSO_2) and trifluoromethyl groups, both of which according to older concepts were incapable of resonance with the ring. Spectroscopic studies (180) have produced evidence that the methylsulfonyl group has $-M$ and $-E$ effects; this requires that the sulfur atom be at least pentacovalent in certain structures (equation 21).



(21)

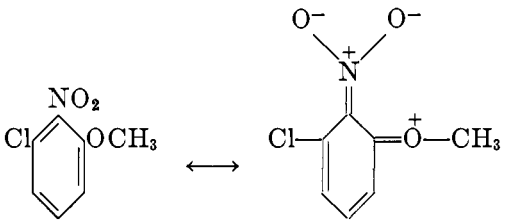
For the trifluoromethyl group, chemical, spectroscopic, and dipole moment evidence (488) indicates $-E$ and $-M$ effects in addition to the obvious $-I$ effect; a "no-bond" resonance was proposed (equation 22). It is difficult to believe that



(22)

negatively charged activating groups, such as carboxylate (COO^-), ionized sulfo (SO_3^-), and arsono (AsO_3H^-), have any $-I$ effect; activation by them must be assigned solely to resonance ($-E$ and $-M$) effects.

One can envisage two modes of operation of a deactivating group: "direct" deactivation of the site of substitution ($+I$ and $+M$ effects) and deactivation of the activating group. The former likely predominates when the deactivating group is ortho or para to the site of substitution, and the latter when the deactivating group is meta to the displaceable substituent (ortho or para to the activating group). The latter effect is illustrated by the resonance (equation 23) in 6-chloro-2-methoxy-1-nitrobenzene; the greater this resonance, the less will be the activating effect of the nitro group.



(23)

The fact that the 2-nitro group is preferentially replaced from 4-methyl- and 4-methoxy-1,2-dinitrobenzenes (table 45) shows that "direct" deactivation predominates over deactivation of the activating group when the two deactivating mechanisms can compete.

B. STERIC DEACTIVATION

1. Steric hindrance of reagent approach

Theoretical considerations, advanced in 1937 by Cowdrey, Hughes, Ingold, Masterman, and Scott (130) and considered from a somewhat different point of view in Section III,C of this review, indicate that a reagent entering into aromatic substitution should approach from a direction lateral to the plane of the ring. Accordingly, the approach of a small reagent should be but slightly disturbed by the bulk of large groups ortho to the site of substitution; facile substitution between two large groups is repeatedly observed in both nucleophilic and electrophilic aromatic substitution. This contrasts with the great sensitivity of reactions such as benzoic ester saponification and ketone oximation to the size of ortho substituents (312, 597).

Since steric hindrance of aromatic nucleophilic substitution by large ortho substituents is a minor effect, it is usually obscured by the electronic effects of those substituents. It is, for instance, usually impossible to tell to what extent the activating effect of *o*-nitro groups is diminished by their bulk, or how much of the deactivating effect of *o*-methyl groups is to be ascribed to their bulk. A study by Sandin and Liskear (table 16) demonstrates, however, deactivation by *o*-halogen substituents which, for their electronic influence alone, would be activating.

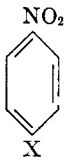
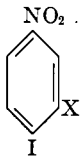
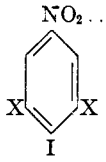
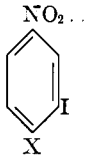
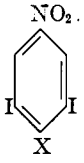
Considering the values in rows 1, 4, and 5 in any column, the introduction of one *o*-iodine atom increases the reaction rate, while a second *o*-iodine decreases it; the deactivation must be steric. Introduction of one *o*-chlorine or bromine (row 2) likewise increases the reaction rate, while the second *o*-chlorine or bromine

(row 3) causes little change; here the adverse steric and favorable electronic effects of the second *o*-halogen seem to balance each other. Assuming that the fivefold increase in reactivity caused by introduction of one iodine in the 2-position of 1-iodo-4-nitrobenzene had been repeated on introduction of iodine into

TABLE 16

Steric hindrance by bulky ortho substituents

(Sandin and Liskear (508))

COMPOUND	HALOGEN REMOVAL BY PIPERIDINE IN BOILING BENZENE FOR 8 HR.			ROW NO.
	X = Cl	X = Br	X = I	
	per cent	*per cent*	*per cent*	
	18	38	12	1
	74	77	55	2
	77	78	39	3
	51	91	55	4
	14	66	39	5

the 6-position, the bulk of the two *o*-iodines might be said very approximately to have decreased the reaction rate of 3,4,5-triiodo-1-nitrobenzene by a factor of six times. Though important, the effect is minute compared to the hindering effect of bulky ortho substituents on the reactions, say, of benzoic esters.

2. Steric interference with activating groups

Interference of bulky groups with the resonance of activating groups is often prominent, in contrast to their slight effect on reagent approach. In order for groups to exert $-M$ or $-E$ effects, they must participate in resonance structures in which they are double-bonded to the aromatic ring. These double-bonded structures often require that the group become coplanar with the benzene ring. If there are large substituents in ortho positions, there may be steric resistance to the activating groups becoming coplanar, and the $-M$, $-E$ effects may be diminished. There is good spectroscopic (179) and dipole moment (299, 313) evidence for the effect, and its chemical significance has been discussed by Wheland (596e).

The most obvious examples of its operation on aromatic nucleophilic substitution are contained in table 12, part D. Normally, introduction of a chlorine atom into an aromatic nucleus increases the rate of nucleophilic substitution, but if the chlorine is introduced ortho to an activating nitro group *which already has one o-chlorine substituent*, the result is a rate decrease. Part C of table 12 shows the effect of introducing a chlorine atom next to an activating nitro group which does *not* already have an ortho substituent. Here the chlorine causes a rate increase, but the increase is less than when chlorine is similarly introduced (meta to the site of substitution) but in such a way as to interfere not at all with resonance of the nitro group (part B, table 12).

Steric interference with the resonance of nitro groups is responsible for the displacement of the 1-nitro group from 2,6-disubstituted- and 2-substituted-1,4-dinitrobenzenes (table 50) and for displacement of the 2-nitro group from 3-substituted-1,2-dinitrobenzenes (table 45). In each of these cases, the nitro group which is displaced is both more hindered in the classical sense and less activated so far as the electronic effects of substituents other than nitro are concerned. The path actually followed in substitution must be ascribed to exertion of greater activation by the nitro group which is less hindered.

A study by Spitzer and Wheland (table 17) showed the effects of methyl groups on the reactions of *p*-cyano- and *p*-nitrobromobenzenes with piperidine. Introduction of two methyl groups ortho to bromine in each case decreased the reactivity of the aryl bromide one hundred-fold. Introduction of two methyl groups ortho to the activating groups decreased the reactivity of the nitro compound twenty-five-fold, but that of the cyano compound only about threefold. The greater effect of methyl groups ortho to a nitro group is ascribed to steric interference with its resonance; the cyano group, being linear, is not sensitive to such interference.

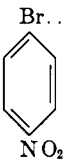
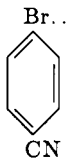
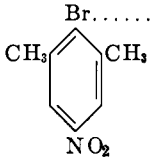
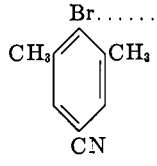
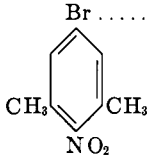
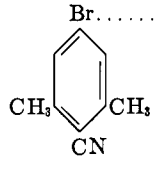
Still another example of the effect is displayed in table 18. Of any pair of isomeric halonitronaphthalenes, the 1-halo-2-nitro isomer reacts with piperidine about ten times faster than the 2-halo-1-nitro isomer. Since isomeric 1- and 2-halonaphthalenes react with piperidine at very similar rates (table 20), the rate differences in the present case must relate to the positioning of the nitro group. The carbon and hydrogen atoms in the 8-position of naphthalene are known from various studies to act as a bulky substituent ortho to the 1-position; thus the

nitro group in a 2-halo-1-nitronaphthalene has in effect two large ortho substituents, while that in a 1-halo-2-nitronaphthalene has but one. The nitro group

TABLE 17

Effects of methyl groups on reaction rates

(Spitzer and Wheland (531))

COMPOUND	PER CENT REACTION IN 8 HR.* AT *ca.* 80°C.	COMPOUND	PER CENT REACTION IN 8 HR.† AT *ca.* 136°C.
	54		13
	0.48		0.13
	2.		3.8

* With excess piperidine in boiling benzene.

† With excess piperidine in boiling ethylbenzene.

TABLE 18

Reactions of halonitronaphthalenes with piperidine (in excess)

(Berliner, Quinn, and Edgerton (52))

NAPHTHALENE	RATE COEFFICIENT		*E*	LOG *PZ*
	0°C.	25°C.		
	min.$^{-1}$	*min.*$^{-1}$	*kcal.*	
1-Iodo-2-nitro	0.18×10^{-2}	1.4×10^{-2}	13.5	8.06
2-Iodo-1-nitro	0.013×10^{-2}	0.13×10^{-2}	14.8	7.96
1-Bromo-2-nitro	1.8×10^{-2}	9.2×10^{-2}	10.4	6.59
2-Bromo-1-nitro	0.15×10^{-2}	1.0×10^{-2}	12.3	7.03
1-Chloro-2-nitro	1.4×10^{-2}	7.7×10^{-2}	10.9	6.88
2-Chloro-1-nitro	0.13×10^{-2}	0.78×10^{-2}	11.6	6.40

in the latter compound is more free to exert its activating effect, and the substance reacts faster.

A spectroscopic study (180) has shown that resonance of sulfonyl groups with the benzene ring is not susceptible to steric inhibition. Loudon and Shulman (394)

have observed that the activating effect of sulfonyl groups is not diminished by large ortho substituents, in harmony with the spectroscopic observation.

C. ACTIVATION IN NAPHTHALENE

In general, naphthyl halides are more susceptible to substitution than phenyl halides similarly provided with activating substituents. This, which might be described as the activating effect of a fused benzene ring, is demonstrated in

TABLE 19

Activation by a fused benzene ring

COMPOUND	RATE COEFFICIENT FOR REACTION AT 25°C.		
	With sodium methoxide (542)	With sodium ethoxide (542)	With aniline in alcohol (454)
	l. mole^{-1} *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$
1-Chloro-2,4-dinitrobenzene	1.50	4.96	0.0085
1-Chloro-2,4-dinitronaphthalene	20	44.2	1.31

TABLE 20

Reactions of phenyl and naphthyl halides with piperidine (in excess)

(Berliner, Quinn, and Edgerton (52))

	RATE COEFFICIENT AT 165°C. WHEN HALOGEN IS		
	Chlorine	Bromine	Iodine
	min.$^{-1}$	*min.*$^{-1}$	*min.*$^{-1}$
Halobenzenes	1.1×10^{-6}	8.7×10^{-6}	15.7×10^{-6}
1-Halonaphthalenes	2.5×10^{-6}	14×10^{-6}	28×10^{-6}
2-Halonaphthalenes	3.1×10^{-6}	25×10^{-6}	35×10^{-6}

	ARRHENIUS PARAMETERS WHEN HALOGEN IS			
	Bromine		Iodine	
	E	log *PZ*	*E*	log *PZ*
	kcal.		*kcal.*	
Halobenzenes			23.6	6.97
1-Halonaphthalenes	24.9	7.58	23.1	6.98
2-Halonaphthalenes	27.6	9.17	24.6	7.82

tables 19 and 20. In a number of other cases the effect has been observed more qualitatively (263, 406, 602).

The inherent susceptibilities of the α- and β-positions of naphthalene towards nucleophilic substitutions are not immediately apparent from available data. In reactions of naphthyl halides with piperidine (table 20) and in exchanges between naphthyl bromides and bromide ion (461), β-substitution is more rapid. However, 1-chloronaphthalene reacts more rapidly with potassium hydroxide at 320°C. than its 2-isomer (457), and 1-naphthalenesulfonic acids are more susceptible to alkaline hydrolysis (536b). Also, amination of naphthalene, naphthols, and naphthylamines by sodium amide occurs in the α-positions (503).

Further inspection of table 20 shows that, although β-naphthyl halides react

more rapidly with piperidine, their reactions have the higher activation energy. This, together with other data quoted above, permits the tentative generalization that energy factors favor α-substitution but that with some reagents entropy factors operate in the opposite direction sufficiently to make the β-isomers react faster. The proximity of the peri position would in every case introduce a special steric complication into α-substitution.

As in electrophilic substitution, a normally activating substituent in the 3-position of naphthalene confers little or no activation on substitution in the 2-position; 2-bromo-3-nitronaphthalene is unreactive to piperidine (421) under conditions which cause extensive reaction by *o*-bromonitrobenzene. The genesis of this effect has been discussed by Wheland (596d).

Activating or deactivating effects are not transmitted well from one ring to the other in naphthalene derivatives. For example, ammonia reacts readily with 1-chloro-4-nitronaphthalene, but not with its 1,5-isomer (119). Towards piperidine at 45°C., the bromine atoms of 6-bromo-2-nitronaphthalene and 5,8-dibromo-1-nitronaphthalene show no mobility (table 15). Also, alcoholic alkali expels azide ion from 2- and 4-nitro-1-naphthyl azides and from 1-nitro-2-naphthyl azide, but not from 5-nitro-1-naphthyl azide or 8-nitro-2-naphthyl

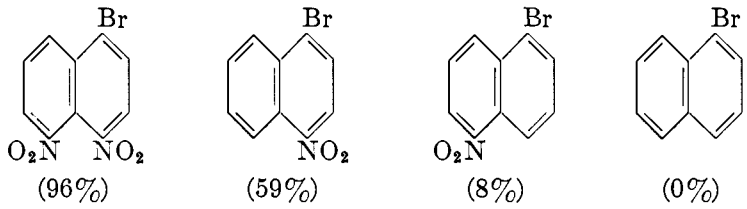


FIG. 3. Per cent halogen displacement in reaction with piperidine at 50–60°C. (504)

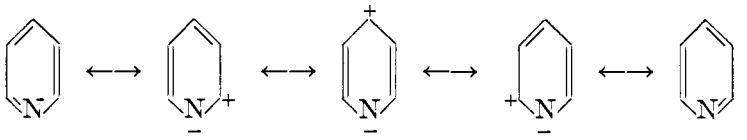
azide (173). On the other hand, mild internuclear activation is apparent in the yields of dicyanonaphthalenes which Bradbrook and Linstead (85) obtained by cyanide fusion of naphthalenedisulfonic acids. When a nitro group is already present in one ring, the activating effect of an added nitro group in the other ring may be noticed (542). A case of this is shown in figure 3.

Fused saturated rings, as in tetralin and hydrindene, are deactivating (421), as one would expect of alkyl groups.

D. ACTIVATION IN HETEROCYCLIC BASES

1. General

Positions α and γ to the nitrogen atom of pyridine are especially susceptible to nucleophilic attack. This and other chemical observations, together with physical data such as the dipole moments of pyridine derivatives (361), indicate for pyridine the resonance shown in equation 24.



(24)

Quantum-mechanical calculations (385, 458) furnish for pyridine, quinoline, quinazoline, and cinnoline the charge distributions shown in figure 4. Similar calculations were made for a host of other monoaza and diaza derivatives of naphthalene, phenanthrene, and anthracene (385). For substitutions at the 4-position, these values indicate the order of reactivity: quinazoline > cinnoline > quinoline > pyridine. This order was observed in the acid-catalyzed hydrolytic replacement of 4-situated chlorine, amino, and phenoxy groups by hydroxy groups (319), and in the condensation of 4-chloro derivatives with methoxide and phenoxide ions. A quantum-mechanical calculation of the order of activation energies for nucleophilic displacement of chlorine predicts the order of reactivity: 4-chloroquinazoline (XXXIV) > 4-chlorophthalazine (XXXV) ~ 4-chlorocinnoline (XXXVI) > 1-chloroisoquinoline ~ 4-chloroquinoline > 4-chloroisoquinoline > 4-chloronaphthalene (384), again in agreement with available experimental evidence.

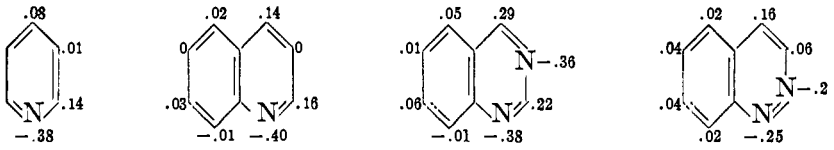
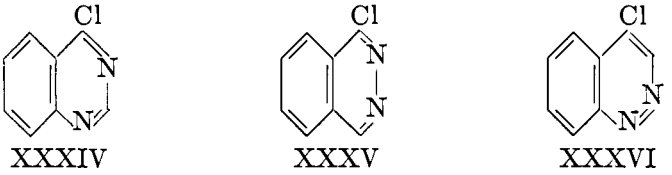


FIG. 4. Calculated charge distributions in heterocycles (385, 458)



XXXIV XXXV XXXVI

2. In pyridine

The hetero nitrogen atom of pyridine appears to be somewhat less strong than the nitro group as an activating structure. Mangini and Frenguelli (407) showed that condensations of 2-chloro-5-nitropyridine with several amines and alkoxides occurred only one-third to two-thirds as rapidly as reactions of these reagents with 1-chloro-2,4-dinitrobenzene. In preparative work a higher temperature is usually necessary, for example, to effect condensation of a reagent with 2-chloropyridine than with *o*-chloronitrobenzene.

The α- and γ-positions of pyridine seem to be about equally activated. Thus 4-bromopyridine polymerizes on storage while its 2-isomer is stable, but amination (by sodium amide) and alkylation (by lithium alkyls) occur preferentially in α-positions. Sodium methoxide initially displaces the 4-bromine atom from 2,4,6-tribromopyridine (257), but both chlorine atoms are replaced from 2,4-dichloropyridine by ammonia at similar rates (259).

The 3-position of pyridine is far less activated for nucleophilic substitution, but 3-bromopyridine is distinctly more reactive towards ammonia and amines than is bromobenzene (408). 3,5-Dibromopyridine reacts with alcoholic alkali

at 105°C. to give the bromoethoxy compound, which ammonia converts into 3-amino-5-ethoxypyridine (258); *m*-dibromobenzene could hardly be converted into *m*-phenetidine by this method.

Greater detail on nucleophilic displacements in pyridine derivatives will be found in reviews by Bergstrom (45) and Mosher (442a).

3. In quinoline and isoquinoline

The 2- and 4-positions in quinoline seem to be about equally activated for nucleophilic substitution. Condensations of 2,4-dichloroquinolines with alkoxides (102, 500) give mixtures of monoalkoxy derivatives, but acid hydrolysis of 2,4,7-trichloroquinoline (500) gives exclusively 4,7-dichlorocarbostyril. 4-Alkoxy-2-chloroquinolines are decidedly more susceptible to nucleophilic substitution than are 2-alkoxy-4-chloroquinolines (102).

Activating substituents in the benzenoid ring of quinoline can affect the rate of substitution reactions at the 4-position. 6- and 8-Nitro-4-chloroquinolines and 6- and 8-nitro-4-phenoxyquinolines undergo acid hydrolysis under conditions insufficient to hydrolyze the parent compounds lacking the nitro group (319). 4-Chloro-8-nitroquinoline is more reactive than most 4-chloroquinolines towards ammonia (phenol catalyzed) and condenses with water (acid catalyzed) more rapidly than does its 4-chloro-5-nitro isomer (228). The latter is reasonable because the 4- and 5-positions are related to each other similarly to meta-orientation, while the relationship of 4- and 8-positions resembles para-orientation.

In isoquinoline, by analogy with 2-nitronaphthalene, the 1-position is activated normally, all other positions being less affected. 1,3-Dichloroisoquinoline and 1,4-dichloro-3-phenylisoquinoline suffer replacement of the 1-chlorine with alkoxides and hydroxide (203).

Further information on nucleophilic substitution in quinoline and isoquinoline will be found in Bergstrom's review (45).

4. In quinazoline

Quinazolines containing a displaceable 4-substituent undergo acid hydrolysis with great ease (550), more rapidly than the 2-substituted isomers (350). When there are identical replaceable groups in both the 2- and the 4-positions, 4-substitution always occurs first (135, 350, 351). From 4-alkoxy-2-chloroquinazolines, primary aromatic amines (136) replace the 2-chlorine, while ammonia (607) replaces the 4-alkoxy group. If the 4-position carries a phenoxy, arylamino, or methylthio group, a primary amine will replace the 2-chlorine preferentially (135, 136).

5. In acridine

The 9-position of acridine is more activated than the 4-position of quinoline (511). Hydrogenation of one fused ring reduces the reactivity of 9-chlorine considerably (511). Table 21 shows moderate transmission of activation from one ring to another in the acridine system. The greater reactivity of 7-nitro- as compared to 6-nitro-2-ethoxy-9-chloroacridine is reasonable because the 7- and 9-

positions, like the para positions in benzene, are separated by an even number of carbon atoms, while the 6- and 9-positions are separated by an odd number of carbon atoms, thereby resembling meta-orientation.

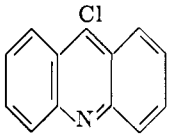
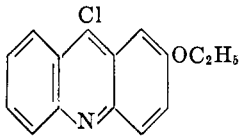
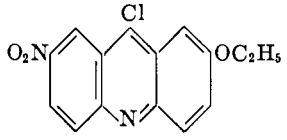
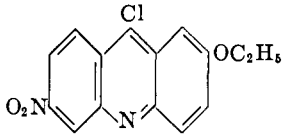
6. In other heterocyclic bases

One would expect that in other heterocyclic bases substitution would also be activated by a hetero nitrogen atom such as that in pyridine (but not by an NH group as in pyrrole). This is indeed the case. 2-Chlorobenzothiazole condenses

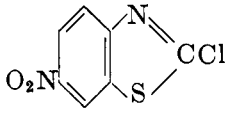
TABLE 21

Activation in acridine

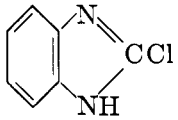
(Magidson and Grigorovski (401))

COMPOUND	FOR FIRST-ORDER SOLVOLYSIS RATE COEFFICIENT
	min.$^{-1}$
	28×10^{-3} (50% CH_3COOH at 60°C.)
	8.4×10^{-3} (50% CH_3COOH at 70°C.) 23.6×10^{-3} (100% CH_3COOH at 70°C.)
	62×10^{-3} (100% CH_3COOH at 80°C.)
	26×10^{-3} (100% CH_3COOH at 80°C.)

with nucleophilic reagents more readily than 2-chloroquinoline, and 2-chloro-6-nitrobenzothiazole (XXXVII) is even more reactive (127).



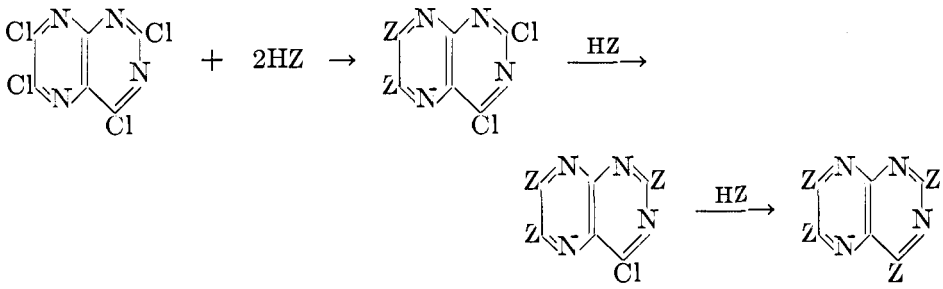
XXXVII



XXXVIII

2-Chlorobenzimidazole (XXXVIII) (346) and its 5-nitro derivative (309) condense normally with amines. The hetero nitrogen atoms also activate alpha

nucleophilic substitution in pyrazines (340), cinnolines (362), phthalazines (248, 570), quinoxalines (248, 535), and phenanthridine (545). In pteridine, which has the features of quinoxaline and quinazoline fused together, there is evidence for stepwise substitution proceeding as follows (109):



7. Acid catalysis of substitution in heterocyclic bases

Alkylation or acylation of the hetero nitrogen atom in a pyridine-type heterocycle greatly augments its activating power[5a]; examples, many of utility in synthetic work, will be found in Bergstrom's review (45). Protonation (conversion to ammonium ion by the action of acids) has the same effect, although it was only recently recognized (19). Condensation of halogenated pyrimidines, etc., with amines, a useful route to many compounds of pharmaceutical interest, often occurs slowly when run in a neutral or basic medium but rapidly when the medium is mildly acidic. There has been much use of this technique in synthesis (20, 21, 22, 29, 122).

The behavior of 4-chloroquinazoline (550) is a spectacular demonstration of the effect of protonation. The compound reacts spontaneously with absolute methanol at room temperature, yet it can be recrystallized from alcohol containing a trace of sodium hydroxide, and reacts but slowly with boiling aqueous or alcoholic alkali. Plainly, reaction with neutral methanol is autocatalytic, owing to the hydrogen chloride produced by the alcoholysis reaction, and this accounts for the instability of 4-chloroquinazoline in water or alcohols free from alkali. The instability of 4-alkoxyquinolines to acids (125) is another instance of the effect.

In application of the principle of protonation activation to the condensation of 9-alkoxyacridines (25) with amines it was found that reaction with primary amines went very well but that secondary amines would not condense. Morley and Simpson (440) showed that various primary amines reacted with 4-chloroquinazolines under acidic conditions only if the amines had pK_a values between about 1.0 and 5.2. They explained that more basic amines steal the activating proton from the hetero nitrogen atoms, while less basic amines are not sufficiently nucleophilic to attack the activated aromatic carbon atom. Since secondary amines are more basic than primary amines, their unreactivity is understandable; a steric factor may also be involved (*cf.* Section VI,B).

[5a] *Note added in proof:* The heterocyclic *N*-oxide function is also a strong activating group (618, 620, 621).

V. The Influence of the Group Displaced

The words "displaceability," "mobility," and "replaceability" are used interchangeably in the literature to indicate the susceptibility of groups to replacement in nucleophilic substitution reactions. The usage is continued in this section.

TABLE 22

Replaceable groups in approximate order of decreasing mobility

Fluorine
Nitro
Chlorine, bromine, iodine
Azido
Sulfonate groups (—OSO_2R)
Ammonio groups (—NR_3^+)
Phenoxy groups (—OAr)
Alkoxy groups (—OR)
Thioether groups (—SR and —SAr)
Sulfonyl groups (—SO_2R)
Amino groups

TABLE 23

Relative mobility of replaceable groups (except halogens)

SITUATION OF GROUP	NUCLEOPHILIC REAGENT	ORDER OF MOBILITY	REFERENCE
4-Position of quinoline, quinazoline, cinnoline	H_2O (acid catalysis)	Cl > —OC_6H_5 > —NH_2	(319)
4-Position of 1,3-dinitrobenzene	Aniline, or sodioacetoacetic ester	—OC_6H_5 > —OCH_3	(74)
In 1-halobenzene-3,5-disulfonates	60% KOH	Br > Cl > —SO_3^-	(537)
2-Position of nitrobenzene	ArO^-	—SO_2Ar > —SOAr	(366)
2-Position of 4-chloronitrobenzene	$NaOCH_3$	—NO_2 > —$SO_2C_6H_5$	(389)
9-Position of acridine	H_2O (acid catalysis)	—OR > —SR > —NHR	(125)
2-Position of nitrobenzene	Piperidine	—OC_6H_5 > —SC_6H_5	(358)

A. General Comparisons

Table 22 gives the more common replaceable substituents in approximate order of decreasing replaceability. For the most part, it is based upon observations (including those displayed in table 23) of the mobility of groups in rather strongly activated positions.

Although there is a relationship between the replaceability of substituents and their capacity for existence as stable anions, inspection of table 22 reveals that the relationship can only be valid in the most general way. Nitro and azido groups, for instance, have high mobility although, following liberation, they appear as anions of rather weak acids; sulfinic acids are stronger, yet sulfonyl

groups have comparatively low replaceability. On the other hand, within series of very similar groups, there may be close adherence to this relationship, the more replaceable groups being those which, following liberation, appear as anions of stronger acids. For example, mobility in a series of aryloxy groups was directly related to the dissociation constants of the related phenols (table 24). It is noteworthy that the *p*-nitrophenoxy group is, in this reaction, more mobile than chlorine (*cf.* table 49).

TABLE 24

Replaceability of aryloxy groups (in reaction with methanolic potassium hydroxide at 20°C.)

Reference	(453)	(95)
2,4-DINITROPHENYL ARYL ETHERS ARYL GROUP	RATE COEFFICIENT	K_a OF PHENOL FORMED
	l. mole^{-1} *min.*$^{-1}$	
p-Nitrophenyl	3.88	9.6×10^{-8}
p-Chlorophenyl	0.64	7.0×10^{-10}
β-Naphthyl	0.487	
α-Naphthyl	0.376	
Phenyl	0.283	1.3×10^{-10}
m-Tolyl	0.222	0.98×10^{-10}
p-Tolyl	0.170	0.67×10^{-10}
o-Tolyl	0.086	0.63×10^{-10}

TABLE 25

Relative mobility of halogens

REACTION	ORDER OF MOBILITY	REFERENCES
Monohalobenzenes with sodium methoxide at 165°C.	I > Br > Cl > F	(555)
Monohalobenzenes with piperidine at 210°C.	I > Br > Cl > F	(555)
Monohalobenzenes with potassium amide in liquid ammonia at −33°C.	Br > I > Cl ≫ F	(50)
m-Tolyl halides with potassium amide in liquid ammonia at −33°C.*	Br > I > Cl ≫ F	(48)
Acid-catalyzed hydrolysis of α-halopyridines and quinolines	F > Cl ~ Br	(90, 432)
Acid-catalyzed hydrolysis of 5-halo-6-methoxy-8-nitroquinolines (in course of Skraup reaction)	F > Cl	(166)
4-Nitrohalobenzenes with potassium alkoxides	F > Cl	(464)

* Apparently some cine-substitution occurs.

B. THE RELATIVE MOBILITIES OF THE HALOGENS AND THE NITRO GROUP

The many studies of the comparative displaceability of the halogens in various aromatic nucleophilic substitution reactions make it abundantly clear that the four halogens do not stand in any constant order of replaceability. In reactions of unsubstituted phenyl halides with sodium methoxide, piperidine, or potassium amide, fluorine is exceedingly resistant to displacement (table 25). On the other hand, as shown in tables 11, 25, 26, and 27, fluorine is by far the most easily replaced halogen when it is in an activated situation. A further example is the con-

version of *m*-fluoronitrobenzene to *m*-nitroanisole by sodium methoxide (279), whereas this reagent reduces *m*-chloronitrobenzene to *m*,*m*′-dichloroazoxybenzene (283). Also, fluorine is displaced from the 4-position of 4,4′-difluoro-2-nitrobiphenyl (513) and from slightly activated positions in other reactions (table 42).

There are also important variations in the mobilities of chlorine, bromine, and iodine, depending on the degree of activation and the nature of the nucleophilic reagent, though these variations are of a lesser magnitude than in the case of fluorine *vs.* the other halogens. As shown in tables 20 and 25, the order I > Br > Cl is displayed in reactions of unactivated aryl halides (phenyl and naphthyl halides) with piperidine and methoxide. From activated positions (tables 28 and 29), iodine is generally least rapidly replaced, while chlorine exceeds bromine

TABLE 26

Relative mobility of chlorine and fluorine

(Bevan, Hughes, and Ingold (54))

COMPOUND	RATE COEFFICIENT*
	l. mole^{-1} *min.*$^{-1}$
p-Fluoronitrobenzene	14.5×10^{-2}
p-Chloronitrobenzene	0.043×10^{-2}†

* For reaction with ethanolic sodium ethoxide at 39.95°C.

† Calculated from values at higher temperatures.

TABLE 27

Comparative replaceability of chlorine, fluorine, and the nitro group

COMPOUND	RATE COEFFICIENT*	REFERENCE
	l. mole^{-1} *min.*$^{-1}$	
o-Fluoronitrobenzene (F replaced)	0.0070	(499)
o-Dinitrobenzene	0.0042†	(534)
o-Chloronitrobenzene (Cl replaced)	0.000009‡	(283)

* For reaction with methanolic methoxide at 25°C.

† Per nitro group; the measured coefficient was 0.0085.

‡ Calculated from rates at higher temperatures.

in replaceability when the reagent is an alkoxide, ammonia, or methylamine, and bromine is more mobile than chlorine when the reagent is another amine, aliphatic or aromatic.

The relative mobilities of chlorine and bromine also show a variation with temperature, as shown in table 29 for the reactions of 2-halo-1,6,8-trinitronaphthalenes with sodium methoxide.

Table 27 indicates the fluorine atom and the nitro group to be about equally replaceable from activated positions. This indication of great mobility for the nitro group is corroborated by a number of qualitative observations (recorded in table 47), which show that nitro groups are sometimes displaced from situations which are only gently activated. The nitro group is regularly displaced in prefer-

ence to a similarly activated chlorine. Displacement of the nitro group instead of a chlorine atom from 2,3,5,6-tetrachloro-1-nitrobenzene (table 42) is a rather striking illustration of the mobility of the nitro group; in this case it is aided by the collective activating effects of a number of chlorine atoms and by the fact that the normal activating power of the nitro group, which would lead to displacement of chlorine, is severely decreased by the presence of substituents in both ortho positions (*cf.* page 324). Similar reasoning explains the displacement of nitro groups rather than bromine atoms in reactions of alkoxides with 1,3,5-tribromo-2,4,6-trinitrobenzene (306, 307).

TABLE 28

Relative mobility of chlorine, bromine, and iodine (from per cent of reaction under standard conditions)

REACTION	TEMPERATURE	PER CENT REACTION			ORDER OF REPLACEABILITY	REFERENCE
		Cl	Br	I		
	°C.					
Alcoholic ammonia with 1-halo-2,4-dinitrobenzenes	100	36.6	34.8	11.4	Cl > Br > I	(191)
Diethylamine with:						
o-Halonitrobenzenes	100	9.9	18.1	9.2	Br > Cl > I	(191)
p-Halonitrobenzenes	100	3.0	4.3	1.7	Br > Cl > I	(191)
Dipropylamine with:						
o-Halonitrobenzenes	130	13.1	19.9	32.1	I > Br > Cl	(456)
p-Halonitrobenzenes	130	0.8	1.4	1.2	Br ~ I > Cl	(456)
Piperidine in alcohol with:						
o-Halonitrobenzenes	100	43.8	62.8	29.6	Br > Cl > I	(191)
p-Halonitrobenzenes	100	10.5	14.3	2.3	Br > Cl > I	(191)
1-Halo-2,4-dinitrobenzenes	12	83.5	86.2	25.5	Br ~ Cl > I	(191)
Piperidine in benzene with:						
o-Halonitrobenzenes	Boil	59.9	71.8	29.5	Br > Cl > I	(94)
p-Halonitrobenzenes	Boil	1.7	3.9	3.7	Br ~ I > Cl	(94)
p-Halonitrobenzenes	Boil	18.5	37.7	11.8	Br > Cl > I	(508)
1-Halo-2,4-dinitrobenzenes	Boil	94.0	93.0	56.7	Cl ~ Br > I	(94)
1-Halo-2-iodo-4-nitrobenzenes	Boil	50.6	90.8	55.4	Br > I > Cl	(508)
1-Halo-2,6-diiodo-4-nitrobenzenes	Boil	14.3	66.1	38.6	Br > I > Cl	(508)
Aniline in alcohol with 1-halo-2,4-dinitrobenzenes	10	26.9	37.2	10.6	Br > Cl > I	(191)

C. DEPENDENCE OF MOBILITY ON THE NUCLEOPHILIC REAGENT

Loudon and coworkers (387, 388, 389, 392, 393, 394) studied the reactions of a number of isomeric or nearly isomeric chloronitrophenyl aryl sulfones with four principal reagents: sodium *p*-thiocresoxide, sodium methoxide, ammonia, and piperidine. (The departure from a strictly isomeric relationship arose from the aryl group being phenyl in some cases and *p*-tolyl in others.) A strong dependence of mobility on the nature of the reagent was obvious throughout the study, which was summarized by Loudon and Shulman (394) in a table, reproduced herein as table 30.

TABLE 29

Relative mobility of chlorine, bromine, and iodine (from kinetic data)

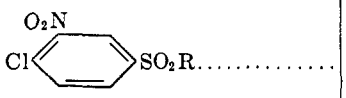
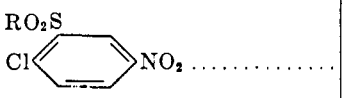
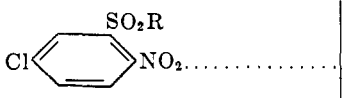
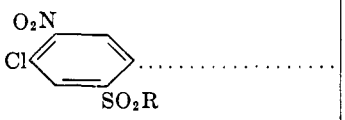
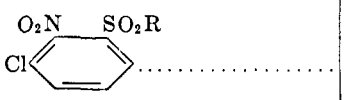
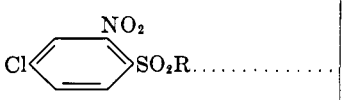
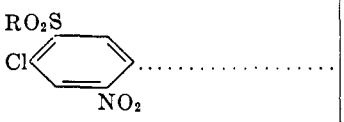
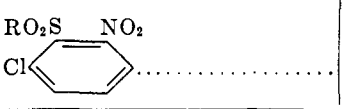
REACTION	TEMPERATURE	RATE COEFFICIENTS			k_{Cl}/k_{Br}	REFERENCE
		k_{Cl}	k_{Br}	k_I		
	°C.	*l. mole*$^{-1}$ *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$		
Sodium methoxide with:						
1-Halo-2,4-dinitrobenzenes	15	0.55	0.40		1.38	(397)
1-Halo-2,4-dinitrobenzenes	25	1.51	1.12		1.35	(416)
4-Cyano-1-halo-2-nitrobenzenes	25	0.0142	0.0102		1.39	(416)
2-Cyano-1-halo-4-nitrobenzenes	25	0.260	0.205		1.27	(31)
2-Halo-1,6,8-trinitronaphthalenes	0	2.2	1.2		1.8	(314)
	15	8.7	3.2		2.7	(314)
	25	37	10		3.7	(314)
Lithium chloride with 1-halo-2,4-dinitrobenzenes	175		3.7×10^{-2}	4.6×10^{-2}		(40)
Sodium ethoxide with 1-halo-2,4-dinitrobenzenes	15	1.63	1.02	0.228	1.60	(397)
Piperidine in benzene with *p*-halonitrobenzenes	99	6.8×10^{-5}	38.7×10^{-5}		0.18	(106)
1-Halo-2,4-dinitrobenzenes with:						
Ammonia	100	0.0384	0.0319		1.20	(65)
Methylamine	25	0.188	0.152		1.24	(65)
Heptylamine	25	0.0615	0.0608		1.01	(65)
Benzylamine	25	0.0271	0.0278		0.97	(65)
Hydrazine	25	0.358	0.371		0.96	(65)
Dimethylamine	25	2.09	2.10		1.00	(65)
Diethylamine	25	0.0108	0.0117		0.92	(65)
Piperidine	25	1.148	1.163		0.99	(65)
Aniline	50	0.0179	0.0271	0.0079	0.66	(470)
m-Toluidine	35	0.00975	0.01385		0.70	(525)
p-Toluidine	35	0.0213	0.0319		0.67	(525)
Methylaniline	50	0.00193	0.00573	0.00139	0.34	(470)
		min.$^{-1}$	*min.*$^{-1}$	*min.*$^{-1}$		
Piperidine with:						
Halobenzenes	165	0.11×10^{-5}	0.87×10^{-5}	1.57×10^{-5}	0.12	(52)
1-Halonaphthalenes	165	0.25×10^{-5}	1.43×10^{-5}	2.83×10^{-5}	0.17	(52)
2-Halonaphthalenes	165	0.31×10^{-5}	2.48×10^{-5}	3.52×10^{-5}	0.12	(52)
1-Halo-2-nitronaphthalenes	0	1.41×10^{-2}	1.83×10^{-2}	0.178×10^{-2}	0.77	(52)
2-Halo-1-nitronaphthalenes	0	1.31×10^{-3}	1.52×10^{-3}	0.13×10^{-3}	0.86	(52)

When the nitro and arylsulfonyl groups were situated ortho and para to the chlorine atom (rows 1 and 2), their activating effects were cumulative, resulting in exclusive replacement of the chlorine atom by all reagents. But when the

TABLE 30

Dependence of mobility on the reagent

(Loudon and Shulman (394))

COMPOUND*	SUBSTITUENT REPLACED† WHEN REAGENT IS			
	NaSR*	$NaOCH_3$	NH_3	Piperidine
	Cl	Cl	Cl	Cl
	Cl	Cl	Cl	Cl
	SO_2R	SO_2R	SO_2R	Cl
	Cl	NO_2	Cl (NO_2)	Cl
	NO_2 (Cl or SO_2R)	NO_2	NO_2	Cl
	SO_2R	NO_2	NO_2	Cl (NO_2)
	SO_2R	NO_2	‡	Cl
	SO_2R	NO_2 (Cl)	NO_2	Cl

* R is phenyl or *p*-tolyl.

† Groups in parentheses were replaced to a minor extent.

‡ NO_2 was replaced by methoxy from the methanolic solvent.

nitro and arylsulfonyl groups were ortho or para to each other, all three groups were in the position of being considerably activated for replacement by a nucleophilic reagent. In many cases each of the three could be selectively displaced by

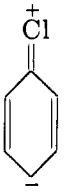
use of an appropriate reagent. Loudon and Shulman observed that in general mercaptide reagents preferred to displace substituents activated by nitro groups, piperidine favored replacement of chlorine, and nitro groups were particularly mobile in reactions with ammonia or sodium methoxide.

Loudon's researches (112, 284, 371) disclosed similar behavior in reactions of a number of related compounds.

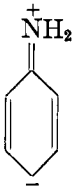
Chlorine in the 4-position of quinolines is surprisingly sluggish in reaction with ammonia or amines. Other groups ordinarily less mobile than chlorine are displaced from the 4-position at normal rates. In the preparation of 4-aminoquinolines, substances of considerable interest in pharmacology, it is therefore advantageous first to convert the 4-chloroquinoline to a 4-phenoxy or 4-sulfo derivative by reaction with phenol (164, 325, 466) or sodium sulfite (581), and then to condense with the amine. Usually both steps are performed in the same reaction mixture. The principle is similar to catalysis of condensations of alkyl chlorides by addition of alkali iodides. In this connection, iodide ion does not appear to catalyze the displacement of chlorine from aryl chlorides.[6] One would not expect catalysis by iodide ion, for it is not very active as a nucleophilic reagent towards aryl chlorides (40), and aryl iodides generally react more slowly than the corresponding chlorides.

D. THE EFFECT OF DOUBLE-BOND CHARACTER IN THE BOND TO THE DISPLACEABLE GROUP

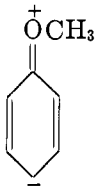
Several of the prominent displaceable groups are capable of entering into resonance with the aromatic ring, requiring double-bondedness in the bond which binds the group into the aromatic system. For example, structures XXXIX, XL, and XLI make a recognized contribution to resonance in chlorobenzene, aniline, and anisole, respectively. Dipole moments show that in the *p*-nitro de-



XXXIX



XL



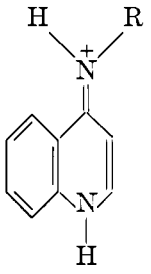
XLI

rivatives of these substances such structures are even more important (596a).

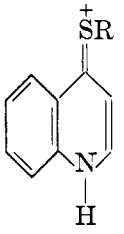
Various authors (16, 300, 461) have felt, from theoretical considerations, that such double-bondedness should decrease the replaceability of substituents, and Pullman, Rumpf, and Kieffer (461) have used this concept in explaining the

[6] However, Wohl (605) reported that sodium iodide catalyzed reactions of *o*- and *p*-chloronitrobenzenes with alcoholic ammonia, but was without effect on their reactions with sodium ethoxide. The mechanism of this catalysis is not evident, for nitro-activated aryl iodides generally react with amines more slowly than do the corresponding chlorides (tables 18 and 28).

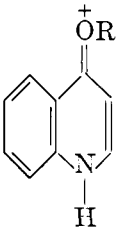
comparative activity, in exchanges with radioactive bromide ion, of some bromine derivatives of naphthalene and anthracene. Clinton and Suter (125) ascribed the order of mobility —OR > —SR > —NHR in the acid hydrolysis of 4-substituted quinolines and 9-substituted acridines to the comparative importance of structures XLII, XLIII, and XLIV. Clearly, structures with an



XLII



XLIII



XLIV

ammonium nitrogen should be more important than those with oxonium oxygen. Clinton and Suter also claimed spectroscopic evidence that structures (XLIII) with sulfonium sulfur are more important than those (XLIV) with oxonium oxygen; this proposition is difficult to accept, because it would predict greater activation of aromatic electrophilic substitution by —SR than by —OR groups. Evidence on this point is scanty; however, *p*-ethoxyphenyl methyl sulfide is brominated ortho to the ethoxy group (287), and furan is consistently more readily attacked by electrophilic reagents than is thiophene.

Indeed, it is reasonable to doubt whether double-bondedness to the displaceable group is unfavorable to its replacement. Of the *p*-halonitrobenzenes, *p*-fluoronitrobenzene probably has the greatest degree of double-bond character in its C—X bond, and yet it is the most susceptible to nucleophilic substitution.

VI. The Influence of the Nucleophilic Reagent

The commonly written chemical formula of a reagent is not a thoroughly adequate description of it. Properly, one should also specify the solvent and whatever other substances (salts, etc.) may be present. Solvation of the displaceable substituents and the activating groups of the aromatic compound, as well as of the nucleophilic reagent, usually has an important influence on both the energy and the entropy of activation. This important influence of the solvent complicates the comparison of reagents employed in different solvents.

Another sort of complication arises from actual chemical change by interaction with the solvent. An important case is the equilibrium (equation 25) in alcoholic hydroxide solutions which usually results in the introduction of an alkoxy rather than a hydroxy group.

$$OH^- + ROH \rightleftarrows RO^- + H_2O \qquad (25)$$

The possibility of these complications must be borne in mind in the following discussions.

A. GENERAL COMPARISONS

Information on the comparative activity of nucleophilic reagents in effecting aromatic substitution is not abundant. Except amongst reagents of very similar chemical character, there have been no experiments designed to afford a quantitative comparison of reagent powers. Therefore table 31, in which some of the

TABLE 31

Important nucleophilic reagents in approximate order of decreasing activity in aromatic substitution reactions

Amide ion Triphenylmethyl anion Phenylamide ion Sulfite ion Mercaptide ions	React with phenyl halides at low temperatures
Alkoxide ions Phenoxide ions Piperidine Hydroxide ion	React with 1-chloro-2,4-dinitrobenzene at room temperature
Aniline Ammonia Sulfinate ions	React with 1-chloro-2,4-dinitrobenzene at 100°C.
Halide ions Water	React with 1-chloro-2,4-dinitrobenzene at 170°C. or higher

TABLE 32

Comparative reactivity of 1-chloro-2,4-dinitrobenzene with various reagents

REAGENT	TEMPERATURE	RATE COEFFICIENT	REFERENCE
	°C.	$l.\ mole^{-1}\ min.^{-1}$	
Ethanolic sodium ethoxide	25	4.95	(542)
"Alcoholic" potassium hydroxide	25	4.40	(399)
Sodium sulfite in 50% ethanol	30	6.14	(532)
Methanolic sodium methoxide	25	1.50	(542)
Piperidine in ethanol	25	0.92	(92)
Ethanolic sodium phenoxide	25	0.900	(416)
Methanolic sodium phenoxide	25	0.429	(416)
Aniline in ethanol	25	0.0085	(454)
Ammonia in ethanol	100	0.038	(65)
Lithium iodide in ethylene glycol	175	0.010	(40)
Lithium bromide in ethylene glycol	175	0.0033	(40)

important reagents are listed in order of decreasing activity, is more of an approximation than the corresponding tables (3 and 22) in Sections IV and V.

Table 31 is based in part upon table 32, and in part upon qualitative observations, some of which are cited in following paragraphs. Simplicity of presentation in table 31 has been gained at the expense of ignoring the solvents in which the reagents occur, and the possibility that displacement of other groups may have

different reagent preferences. For example, piperidine in alcohol is nearly as active as methanolic methoxide in displacing chlorine from 1-chloro-2,4-dinitrobenzene (table 32), but piperidine in benzene is much less active than methanolic methoxide in reaction with moderately activated aryl bromides (106).

In a general fashion, the more basic reagents are the more active in effecting aromatic substitution. There are exceptions, of which the high activity of mercaptide ions may be mentioned, but the generalization is consistently borne out in comparisons of reagents of very similar chemical character. For instance, the activities of phenoxide and *m*- and *p*-cresoxide ions are in the same sequence as their basicities (table 33). (*o*-Cresoxide ion is out of order, apparently for steric reasons.) Also, the activities of *m*- and *p*-substituted anilines in reaction with 1-chloro-2,4-dinitrobenzene are directly related to their basic strengths (table 34). Indeed, this is one of the reaction types which Hammett (240) found to obey his famous relationship: $\log k - \log k_0 = \rho\sigma$. In table 34, *o*- and *N*-substituted anilines are out of the order of their basicities, probably for steric reasons.

Loudon and Robson (392) observed that a number of benzenesulfinate ions

TABLE 33

Reactions of 1-chloro-2,4-dinitrobenzene with sodium phenoxides in ethanol

REAGENT	RATE COEFFICIENT AT 25°C.	K_a OF PHENOL	REFERENCE
	l. mole^{-1} *min.*$^{-1}$		
Sodium phenoxide	0.900*	1.15×10^{-10}	(416)
Sodium *m*-cresoxide	0.97	0.98×10^{-10}	(454)
Sodium *o*-cresoxide	1.06	0.63×10^{-10}	(454)
Sodium *p*-cresoxide	1.98	0.67×10^{-10}	(454)

* In methanol k_{25} is 0.429 (416).

stood in the following order with regard to their rates of displacement of the 4-nitro group from 2,4-dinitrophenyl aryl sulfones: *p*-CH_3 > H > *p*-Cl > *m*-NO_2 > 2,5-dichloro. Dissociation constants for the corresponding sulfinic acids are not available, but are probably in this order, reversed.

Nucleophilic reactivity in the same order as basic strength is also shown in the reactions of several strongly basic anions with phenyl halides in liquid ammonia. Wright and Bergstrom (608) observed the order: NH_2^- > $(C_6H_5)_2CH^-$ ~ $(C_6H_5)_3C^-$ > $C_6H_5NH^-$ ~ $(C_6H_5)_2N^-$ > $C_6H_5O^-$. The intermediate members of this series required catalysis by amide ion in order to react; phenoxide ion was ineffective even with catalysis.

p-Toluenesulfinic acid is less active than its sodium salt in displacing nitro groups (371), probably because the acid furnishes a lower concentration of sulfinate ions.

B. AMINES

In reaction with 1-chloro-2,4-dinitrobenzene, the activities of a number of substituted anilines are parallel to their basicities (table 34), but the activities

of aliphatic amines towards the same aryl chloride (table 35) bear no particular relationship to their basic strengths. Brady and Cropper (92) pointed out that amines with a number of alkyl groups on or near their nitrogen atoms are in general less reactive than amines with less branching near the nucleophilic center.

TABLE 34

Reactions of primary aromatic amines with 2,4-dinitrohalobenzenes

AMINES	RATE COEFFICIENT (L. MOLE^{-1} MIN.$^{-1}$ × 10^3)						pK_a OF AMINE (IN H_2O)
	1-Chloro-2,4-dinitrobenzene				1-Bromo-2,4-dinitrobenzene		
Reference	(454)	(527)	(527)	(454)	(522)	(525)	(237)
Temperature	25°C.	35°C.	45°C.	100°C.	35°C.	45°C.	
Anilines:							
p-Ethoxy	85.7			2030			
p-Methyl	21.2‡	21.3‡	35.7	706	31.9	55.2	5.1
p-Methoxy	81.9‡	67.4‡	111.0	672			5.3
m-Methyl	10.9‡	9.75‡	17.7	425	13.8	25.2	4.7
Aniline	8.5‡	6.91‡	12.3	286	10.4	18.5	
m-Methoxy		5.00	8.31				4.2
o-Ethoxy				187			
β-Naphthylamine		2.73	5.03	182			
o-Methoxy		2.63	4.72	166			4.5
p-Phenyl				86			
p-Chloro*†		1.49	2.81	79			4.0
p-Bromo*		1.08	2.29				3.9
N-Methyl				33			4.8
o-Methyl		0.384	0.784	30			4.4
m-Bromo*		0.419	0.912				3.5
m-Chloro*†		0.44	0.86	29			3.5
α-Naphthylamine		0.2	0.363	21			4.0
o-Phenyl				10.4			
p-Acetyl				3.5			
m-Nitro				2.8			
o-Bromo		0.01§					2.6
o-Chloro†		0.01§		0.0			2.8
o-Nitro				0.0			0.1
p-Nitro				0.0			1.9

* Linke (369a) reported that *m*-haloanilines reacted faster than their *p*-isomers.

† Borodkin (71) reported the order of reactivity of chloroanilines, in reactions with dichloronitrobenzenes, to be $p > o > m$.

‡ In these cases, values at 25°C. and 35°C. (determined by different workers) do not have the usual relationship to each other.

§ Approximate value.

They observed that alkyl groups, in some configurations, would interfere with approach of the nitrogen atom to the aromatic carbon atom, whereas they would not affect the basicity of the amine. Their argument, that the intrinsic nucleophilic activity of the amines is modified by the steric effects of their alkyl groups, is convincing.

TABLE 35

Reactions of aliphatic primary and secondary amines with 1-halo-2,4-dinitrobenzenes in ethanol at 25°C.

AMINE	RATE COEFFICIENT (L. MOLE^{-1} MIN.$^{-1}$ × 10^2) FOR REACTION WITH			pK_a
	1-Chloro-2,4-dinitrobenzene		1-Bromo-2,4-dinitrobenzene	
Reference	(92)	(65)	(65)	(238)
Dimethylamine	213	209	210	10.7
Piperidine	92	115	116	11.1
Hydrazine		35.8	37.1	
Methylamine	19.0	18.8	15.2	10.6
n-Heptylamine	6.0	6.15	6.08	
Isohexylamine		6.07	5.87	
n-Amylamine		5.83	5.67	10.6
n-Butylamine	6.0	5.71	5.53	10.6
Isoamylamine		5.64	5.54	10.6
n-Propylamine	5.8	5.35	5.30	10.6
Ethylamine	5.5	5.18	4.96	10.7
Isobutylamine	4.1			10.4
Diethylamine	1.14	1.08	1.17	11.0
Di-*n*-butylamine	1.08			11.3
Diisoamylamine		0.99	1.13	11.0
Ethyl-*n*-propylamine	1.02			
Di-*n*-propylamine	0.96	0.96	1.06	10.9
Isopropylamine	0.60	0.67	0.64	10.6
sec-Butylamine	0.55	0.55	0.54	10.6
Diisobutylamine	0.35	0.40	0.42	10.8
α-Pipecoline	0.13			11.0
Ethylisopropylamine	0.1–0.02			
Ammonia	0.024			9.3
tert-Butylamine	0.023			10.4
Diisopropylamine	0.006–0.004			11.0
α,α-Lupetidine	0.006–0.004			
Tetrahydroquinoline	0.04–0.002			
Tetrahydroquinaldine	0.002–0.001			

TABLE 36

Some aliphatic amines in orders of decreasing activity

TOWARDS TRIMETHYLBORON	TOWARDS 1-CHLORO-2,4-DINITROBENZENE
Ethylamine	Dimethylamine
Methylamine	Methylamine
Dimethylamine	Ethylamine
Di-*n*-propylamine	Diethylamine
Isopropylamine	Di-*n*-propylamine
Trimethylamine	Isopropylamine
Diethylamine	Ammonia
Ammonia	Diisopropylamine
Diisopropylamine	Trimethylamine

Brown and coworkers (97, 98, 100) have demonstrated that the relative basic strengths of amines depend upon the acid (in the Lewis sense) which is used for reference. With a small reference acid, such as the proton, basicities are largely determined by the electronic influences of the alkyl groups upon the nitrogen atom, but with large reference acids both the electronic and the steric effects of the substituent alkyl groups are important. One might therefore expect that the order of basicities of a group of amines towards a large reference acid would be similar to the order of their reactivities towards an aryl halide. This is so, as shown in table 36, in further support of the suggestion of Brady and Cropper.

All the reactions in tables 34 and 35 were run in alcoholic solution. This introduces a kinetic complication which has not been entirely appreciated. In an alcoholic solution of an amine, equilibrium 26 exists,

$$RNH_2 + HOC_2H_5 \rightleftarrows RNH_3^+ + C_2H_5O^- \qquad (26)$$

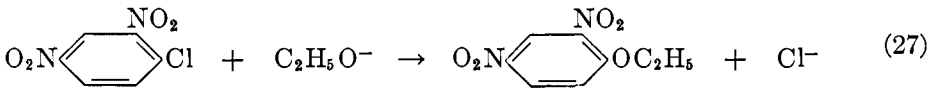
TABLE 37

Decline in calculated rate coefficient in reaction of ammonia with 1-chloro-2,4-dinitrobenzene (in ethanol)

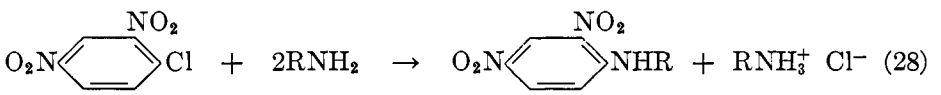
(Holleman, de Mooy, and ter Weel (283))

TIME	RATE COEFFICIENT AT 25°C.	TIME	RATE COEFFICIENT AT 25°C.
min.	*l. mole^{-1} min.$^{-1}$*	*min.*	*l. mole^{-1} min.$^{-1}$*
330	5.93×10^{-4}	10365	2.66×10^{-4}
1650	4.13×10^{-4}	16080	2.43×10^{-4}
4560	3.20×10^{-4}	24540	2.38×10^{-4}

and as a result two reactions (27 and 28) may occur with 1-chloro-2,4-dinitrobenzene or another suitable aromatic compound. That both reactions do on



(27)



(28)

occasion occur is shown by the isolation of both amino and alkoxy compounds from the action of alcoholic ammonia on *p*-dinitrobenzene (377), on 2-methylsulfonyl-5-nitropyridine (188), on chloronitrophenyl *p*-tolyl sulfones (392), and in other cases.

Now since the analytically determined extent of reaction represents the sum of the two processes, whether the appearance of chloride ion (92) or the disappearance of titratable amine (65) is followed, and since reaction 27 will damp out rapidly, because both it and reaction 28 cause the accumulation of RNH_3^+ ions which repress the formation of ethoxide in equilibrium 26, rate coefficients calculated from an expression appropriate for reaction 28 will fall off as the run progresses. This decline is apparent in the data of several workers; a case is given

in table 37. The values in table 35 for ammonia and less reactive amines are not constants but rather averages or extremes of a wandering coefficient. Indeed, it is possible that the recorded values for very weakly nucleophilic amines (such as α,α-lupetidine) apply entirely to the ether formation process; the point cannot be settled because analyses of the products were not performed.

A further complication arising from the same source is that rate coefficients calculated from an expression appropriate for reaction 28 and based upon determination of liberated halide ion will rise towards the end of the reaction if there was a considerable incursion of reaction 27 at an earlier stage. This phenomenon is negligible if a large excess of amine is used, but should become progressively more pronounced as the proportion of amine to 1-chloro-2,4-dinitrobenzene decreases. The overall effect of interference of reaction 27, an initial drop and then a rise in calculated rate coefficient, might appear to indicate the absence of a trend in rate values.

Relatively few complete descriptions of kinetic runs on reactions of alcoholic amines with aromatic compounds have been published. Runs with ammonia and other weakly nucleophilic amines always show a declining coefficient (92). Runs of diethylamine with some dichloronitrobenzenes show the declining coefficient, while runs with other isomers do not (283), and some authors (65) found a declining coefficient in the reaction of methylamine with 1-chloro-2,4-dinitrobenzene, while others (92) report a reasonably constant coefficient.

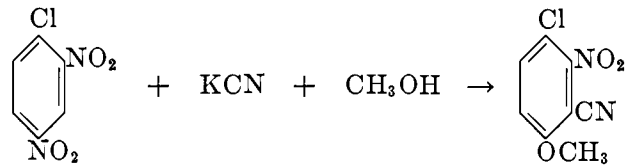
Energies of activation for reactions of diethylamine with dichloronitrobenzenes are not, because of these complications, very exact; their magnitude, however, is about 18 kcal. per mole (288), distinctly lower than the activation energies of about 23 kcal. per mole for reactions of dichloronitrobenzenes with methoxide (table 54). It is therefore to be expected that the phenomenon of the declining rate coefficient should be more pronounced at higher temperatures, and this has been observed (283). Also, the reaction of alcoholic ammonia with *p*-dinitrobenzene produces *p*-nitroaniline at low temperatures and *p*-nitrophenetole at elevated temperatures (377).

C. THE PECULIAR BEHAVIOR OF THE CYANIDE ION

In reactions with alkyl halides, acyl halides, and aldehydes, the cyanide ion behaves as a typical nucleophilic reagent. Similarly proper and normal are the reactions of aromatic sulfonic acids with fused sodium or potassium cyanide and also the reactions of aromatic halides with cuprous cyanide, all of which generally produce the expected nitriles. However, the cyanide ion in aqueous or alcoholic media shows the peculiar characteristic of forming addition complexes with suitably activated aromatic compounds with ease, but of hardly ever effecting the straightforward replacement of groups such as halogen or nitro, even from highly activated positions. The reader will find support for these statements in the book by Migrdichian (431) and in reviews by Mowry (443) and Bergstrom (45); we mention below only certain findings which especially demonstrate the odd character of the solvated cyanide ion.

The reluctance of cyanide ion in solution to displace halogen or nitro is shown

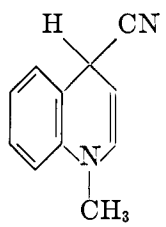
by the formation of *m*-bromobenzoic acid in reaction with *p*-nitrobromobenzene (*cf.* Section X,A), by the formation of 3-chloro-6-methoxy-2-nitrobenzonitrile in reaction with 1-chloro-2,4-dinitrobenzene in methanol (equation 29) (58, 260), and by the absence of nitrobenzonitriles or their hydrolysis products amongst the products of reaction of alcoholic potassium cyanide with *o*- or *p*-dinitrobenzene or 1,2,4-trinitrobenzene (374, 380).



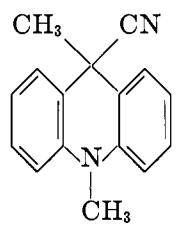
(29)

The two examples in which the solvated cyanide ion has effected replacement of halogen or nitro both refer to unusual structures; one is the formation of 2,5-dicyano-3,6-dihydroxyquinone from chloranil (472) and the other the replacement of the 6-nitro group from 2-methoxy-5,6-dinitrobenzonitrile (55, 378).

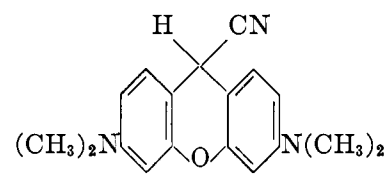
The numerous addition complexes formed by the solvated cyanide ion and aromatic compounds include XLV, XLVI, XLVII, XLVIII, and XLIX.



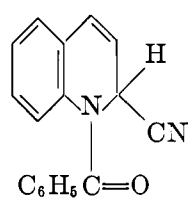
XLV



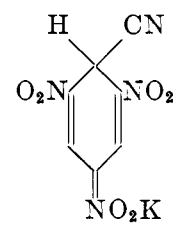
XLVI



XLVII



XLVIII



XLIX

These are formed by the action of cyanides on 1-methylquinolinium iodide (316), 9,10-dimethylacridinium chloride (315, 317), tetramethyldiaminoxanthylium chloride (165), a mixture of quinoline and benzoyl chloride (157), and *s*-trinitrobenzene (243, 424), respectively. There are also several reactions which, while not simple additions in an overall sense, presumably involve addition of cyanide to an unsubstituted aromatic position as an essential step. These include the carboxylation of pyrazines by ethanolic cyanide (340), and the formation of 2-methoxy-6-nitrobenzonitrile from *m*-dinitrobenzene in methanol (373, 380), of 5-cyano-6-methoxyquinoline from 6-nitroquinoline in methanol (293), of 1-

amino-4-cyano-2-naphthol from 1-nitroso-2-naphthol (89), and of purpuric acids from polynitrophenols (76), all under the action of an alkali cyanide. Bunnett, Cormack, and McKay (104) have given some consideration to the mechanisms of these reactions. The theoretical problem remains, however, largely unanswered.

D. EFFECTS OF CHANGES IN THE MEDIUM

A change in the environment may induce changes in the rate or even the course of an aromatic nucleophilic substitution reaction.

In the reactions of chloronitrobenzenes with sodium alkoxides, reduction of the nitro group can sometimes seriously interfere. The interference is observed with sodium methoxide (93) and is more serious with sodium ethoxide (463, 601), while some attempts (463) to prepare ethers with higher alkoxides have failed, owing to their reducing action. The reducing action of ethoxide is catalyzed by traces of aldehydes; in aldehyde-free alcohol reduction is largely eliminated (13). Reduction of the nitro group can also be minimized by use of lower temperatures, lower alkali concentrations (13), or a more aqueous medium (471, 601). For the industrial preparation of nitrophenetoles by this reaction, the addition

TABLE 38

Predicted effect of change to a more ionizing solvent on the rates of aliphatic S_N2 reactions

(Cooper, Dhar, Hughes, Ingold, MacNulty, and Woolf (128))

TYPE	REACTANTS	EFFECT OF ACTIVATION ON CHARGES	EFFECT OF IONIZING MEDIUM ON RATE
1	$Y^- + RX$	Dispersed	Small decrease
2	$Y + RX$	Increased	Large increase
3	$Y^- + RX^+$	Reduced	Large decrease
4	$Y + RX^+$	Dispersed	Small decrease

of manganese dioxide (155), cuprous oxide, lead dioxide (156), and sodium silicate (419) has been recommended.

Condensation of the phenylamide and diphenylamide ions with chlorobenzene in liquid ammonia will not occur unless the amide ion is also present (608). Similarly, the condensation of triphenylmethyl and benzhydryl anions with phenyl halides is rapid in the presence of amide ion but slow in its absence. No explanation for this catalytic activity of amide ion has been advanced. There is some indication that the solvated electron (in liquid ammonia) has the same catalytic effect.

In bimolecular *aliphatic* nucleophilic substitution, the effect on the reaction rate of a change to a more ionizing solvent depends on the charge types of both nucleophilic reagent and aliphatic compound, as shown in table 38. This table was derived from consideration of the charge magnitudes and distributions in the initial and transition states. Since the transition state for aromatic substitution is of a different nature, some caution must be exercised in applying the conclusions of table 38 to aromatic nucleophilic substitutions.

The condensation of phenoxide with 1-chloro-2,4-dinitrobenzene is an aromatic

reaction of Type 1 and, as predicted, its rate (table 32) is lower in methanol than in ethanol, methanol being a more ionizing solvent. Also, in the condensation of alkoxides with 1-halo-2,4-dinitrobenzenes, a smaller rate coefficient is observed at higher concentrations (table 39), the effect of greater ionic strength being similar to that of greater solvating power of the solvent (30). Lulofs (397) also found added sodium acetate and bromide to depress the rates of the reactions in table 39; the effect of bromide was more pronounced, especially in more aqueous media. Added sodium nitrite or acetate has no significant effect on the rate of reaction of *o*-dinitrobenzene with ethoxide in absolute ethanol (534).

The rates of condensation of alkoxides with suitable aromatic compounds also change when the medium is made more aqueous. Addition of water changes not only the composition of the solvent, but also that of the reagent itself through operation of equilibrium 25.

The equilibrium lies surprisingly far to the right; for example, the rate of condensation of *o*-dinitrobenzene with absolute ethanolic sodium *hydroxide* is not measurably different from its rate of condensation with ethanolic sodium

TABLE 39

Effect of concentration on reactions of 1-halo-2,4-dinitrobenzenes with sodium alkoxides (Lulofs (397))

REACTION	RATE COEFFICIENT AT 15°C. AS FUNCTION OF INITIAL CONCENTRATION (BOTH REACTANTS EQUAL)		
	0.012 *M*	0.035 *M*	0.058 *M*
	l. mole^{-1} *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$
1-Chloro-2,4-dinitrobenzene with methoxide.....	0.59	0.57	0.55
1-Chloro-2,4-dinitrobenzene with ethoxide.....	1.78	1.63	1.47
1-Bromo-2,4-dinitrobenzene with ethoxide.....	1.17	1.02	0.94

ethoxide (383). No sensible amount of *o*-nitrophenol is formed, and even in 50 per cent aqueous ethanol the product contains less than 5 per cent of *o*-nitrophenol. The proportion of *p*-nitrophenol resulting from the condensation of *p*-chloronitrobenzene with ethanolic potassium hydroxide increases with increasing temperature; at 60°C. 6 per cent of phenol and 92 per cent of ether are formed in a 95 per cent ethanolic solution 0.5 *M* in potassium hydroxide and 0.2 *M* in *p*-chloronitrobenzene (471).

The overall result of addition of water to condensations with methoxide is usually a rate increase, while added water usually retards condensations with ethoxide. Examples are summarized in table 40, and a more complete presentation of one pertinent study is presented in table 41.

The effect of water on the ethoxylation reactions is as expected, because water is a more powerful ionizing solvent than ethanol and because the higher the water concentration the less is the ethoxide concentration (equilibrium 25). Exaltation by water of the rate of methoxylation is entirely surprising and the present authors can offer no explanation of it.

The condensation of amines with 1-chloro-2,4-dinitrobenzene has the charge characteristics of a Type 2 reaction in the classification of table 38 and its rate should be greater in more ionizing media. Singh and Peacock (526) found that the reaction of aniline with 1-chloro-2,4-dinitrobenzene in ethanolic solution was retarded by added benzene, chlorobenzene, and nitrobenzene, and the rate coefficient was also decreased when excess aniline was used. Since these substances are all poorer ionizing solvents than ethanol, the prediction of table 38 is affirmed.

TABLE 40

Effect of more aqueous media on alkoxide condensations

AROMATIC COMPOUND	TEMPERATURE	EFFECT ON RATE OF REACTION WITH		REFERENCES
		Methanolic methoxide	Ethanolic ethoxide	
	°C.			
o-Dinitrobenzene	25	Rise	Drop	(383)
1-Chloro-2,4-dinitrobenzene	15	Rise*	Drop	(31, 397)
1-Bromo-2,4-dinitrobenzene	15		Drop	(397)
o-Chloronitrobenzene	80	Drop	Drop	(482, 483)
p-Chloronitrobenzene	80	No change	Drop	(482, 483)

* Maximum rate at *ca.* 24 per cent water, and then slight drop.

TABLE 41

Effect of water on the reactions of o-dinitrobenzene with sodium alkoxides

(Lobry de Bruyn and Steger (383))

WATER IN MEDIUM	RATE COEFFICIENT AT 25°C.	
	With ethanolic ethoxide	With methanolic methoxide
per cent by weight	*l. mole*$^{-1}$ *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$
0	0.0130	0.0084
2	0.0120	0.0086
4	0.0112	
6	0.0106	
8	0.0099	
10	0.0095	0.0091
20	0.0076	0.0098
30	0.0062	0.0104
40	0.0056	0.0112
50	0.0052	0.0124

However, cyclohexane, the least effective ionizing solvent added, had no effect whatsoever, and the retarding effect of dimethylaniline was much more pronounced than that of the others.

On the other hand, added triethylamine and excess methylamine elevate the (first-order) rate coefficient for the condensation of 1-chloro-2,4-dinitrobenzene with ethanolic methylamine (92). The elevation is proportional to the concentration of the excess amine.

VII. Nucleophilic Substitution in Some Polysubstituted Benzenes

In this section are presented in tabular form the results of several investigations of the courses and rates of reactions of some polysubstituted benzenes with typical nucleophilic reagents. The greater part of this work has been done by Dutch chemists, amongst whom the name of A. F. Holleman is most prominent. Most of the determinations of rate coefficients relate to reactions of polynitrochlorobenzenes and polychloronitrobenzenes with sodium methoxide, a strong nucleophilic reagent whose employment is exceptionally free from kinetic complications. Many of the results of this section have been referred to in earlier parts of this review; the reader's attention is particularly called to table 12.

Where rate coefficients at two or more temperatures are available, Arrhenius parameters have been calculated. These are presented with the rate data in most cases, and are assembled for comparison in table 54. Because many of them are based on insufficiently thorough data, their relative magnitudes are not discussed. It is, however, interesting to note that log PZ in reactions with alkoxides has a value of about 12, whereas when piperidine is the reagent, log PZ is about 7 (tables 5, 18, and 20), time being measured in minutes. Reactions of alkyl halides with amines also display remarkably low PZ values (434).

TABLE 42

*Substitution reactions in nitrobenzene derivatives**

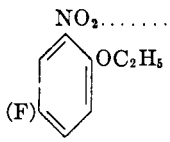
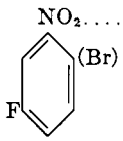
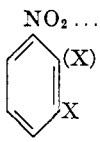
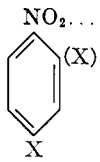
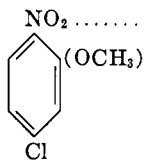
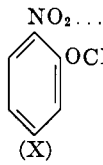
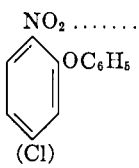
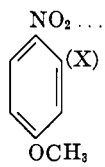
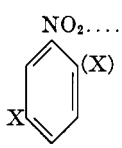
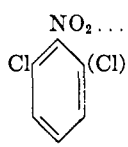
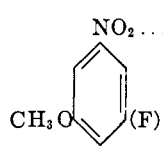
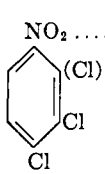
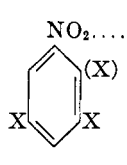
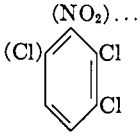
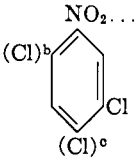
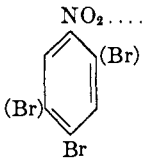
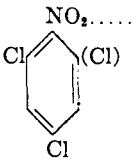
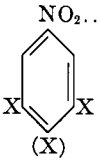
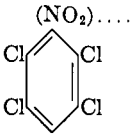
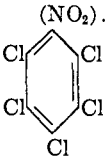
COMPOUND	REAGENTS EFFECTING SUBSTITUTION	COMPOUND	REAGENTS EFFECTING SUBSTITUTION
	NH_3 (538)		NaOH, $NaOCH_3$ (286)
	$NaOCH_3$, $(C_2H_5)_2NH$ (283); NH_3 (334)		$NaOCH_3$ (283, 539); alcoholic NaOH (32); NH_3 (333); $(C_2H_5)_2NH$ (283); $NaSCH_3$ (265)
	Alcoholic NH_3 (558)		$NaOCH_3$ (269); Na_2S_2 (264, 269); $NaSCH_3$ (265)
	Piperidine (358)		$NaOCH_3$ (269); $NaSCH_3$ (265); Na_2S_2 (264, 269)
	NH_3 (430); $NaOCH_3$, $(C_2H_5)_2NH$ (283); aqueous KOH, $NaOC_2H_5$ (538); alcoholic KOH (352); piperidine (359); K_2S (36); $NaSCH_3$ (265)		$NaOCH_3$, $(C_2H_5)_2NH$ (283)
	$NaOCH_3$ (283); alcoholic KOH (422); NH_3 (33); piperidine (359)		$NaOCH_3$ (149)
	$NaOCH_3$ (281); NH_3 (34)		$NaOCH_3$ (281); NH_3 (333)

TABLE 42—*Concluded*

COMPOUND	REAGENTS EFFECTING SUBSTITUTION	COMPOUND	REAGENTS EFFECTING SUBSTITUTION
	$NaOCH_3$ (281) (one group or the other replaced)		(b) NH_3 (35); piperidine (359) (c) $NaOCH_3$ (281)
	NH_3 (333)		$NaOCH_3$ (281)
	NaOH, $NaOCH_3$, $NaOC_2H_5$ (304); phenoxide (245); NH_3 (333); piperidine (508)		$NaOCH_3$ (43)
	$NaOCH_3$† (42)		

* In each formula the group replaced is enclosed within parentheses. X represents halogen when the same behavior has been observed with two or more different halogens, and R represents alkyl groups in the same way. "Alcoholic" indicates ethanolic solution.

† Pentachloroanisole has been identified in the mixture of products obtained.

TABLE 43

Reactions of chlorinated nitrobenzenes with methanolic sodium methoxide

(Holleman, de Mooy, and ter Weel (283))

COMPOUND*	RATE COEFFICIENT (L. MOLE^{-1} MIN.$^{-1}$)†			
	25°C.	50°C.	85°C.	110°C.
o-$ClC_6H_4NO_2$			0.0062	0.050
p-$ClC_6H_4NO_2$			0.0231‡	0.191‡
2,3-$Cl_2C_6H_3NO_2$			0.030	0.24
2,4-$Cl_2C_6H_3NO_2$	0.00050	0.0105	0.33	
2,5-$Cl_2C_6H_3NO_2$	0.000105	0.0020	0.065	0.55
2,6-$Cl_2C_6H_3NO_2$§			0.0023	0.022_3
3,**4**-$Cl_2C_6H_3NO_2$	0.00055	0.0100	0.29_0	

* The number in bold-face type indicates the position of the chlorine atom which is replaced.

† The last digit is, to judge from published data, subject to an uncertainty of 5 or less unless written as a subscript, in which case the uncertainty is between 5 and 10.

‡ Riklis (483) reported 0.063 at 100°C., lower than 0.084 as interpolated from these data.

§ Divide by 2 to get the rate coefficient per displaceable chlorine.

TABLE 44

Reactions of trichloronitrobenzenes with methanolic sodium methoxide

(Holleman and van Haeften (281))

COMPOUND*	RATE COEFFICIENT†		*E*	LOG *PZ*
	25°C.	35°C.		
	l. mole^{-1} *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	*kcal.*	
2,3,4-$Cl_3C_6H_2NO_2$	0.00191	0.0083	26.9‡	17.0‡
2,3,5-$Cl_3C_6H_2NO_2$	0.00084	0.00263	21.0	12.3
2,3,**6**-$Cl_3C_6H_2NO_2$	0.000047	0.000157	22.0	11.8
2,**4**,5-$Cl_3C_6H_2NO_2$	0.00729	0.0231	21.1	13.3
2,4,6-$Cl_3C_6H_2NO_2$§	0.000189	0.000725	$24._6$	14.4
3,**4**,5-$Cl_3C_6H_2NO_2$	0.00814	0.0246	20.2	12.7

* The number in bold-face type indicates the position of the chlorine atom which is replaced.

† The last digit is, to judge from published data, subject to an uncertainty of 5 or less unless written as a subscript, in which case the uncertainty is between 5 and 10.

‡ A gross experimental error is suspected.

§ Divide by 2 to get the rate coefficient per displaceable chlorine.

TABLE 45

*Substitution reactions in o-dinitrobenzene derivatives**

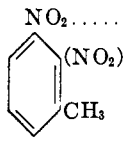
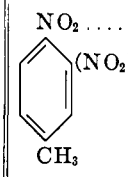
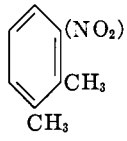
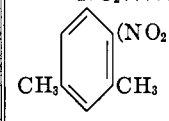
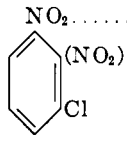
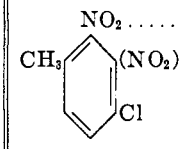
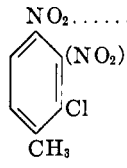
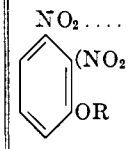
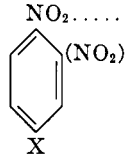
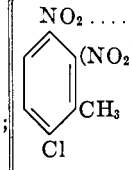
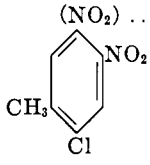
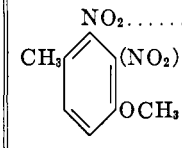
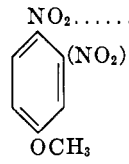
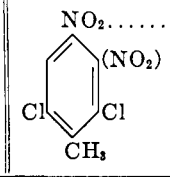
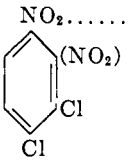
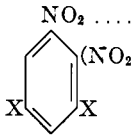
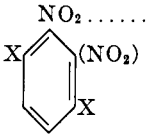
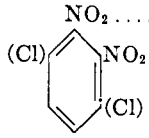
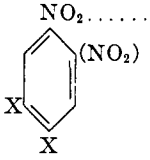
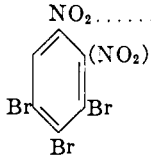
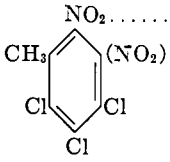
COMPOUND	REAGENTS EFFECTING SUBSTITUTION	COMPOUND	REAGENTS EFFECTING SUBSTITUTION
	$NaOCH_3$, methanolic NH_3 (321); aqueous NaOH, Na_2S (270)		Methanolic NH_3 (main reaction)† (321); hydrazine (404)
	Methanolic NH_3 (107)		NH_3 (main reaction)† (297)
	$NaOCH_3$, methanolic NH_3 (283)		Methanolic NH_3 (322)
	NH_3, $C_6H_5NH_2$ (438a)		NH_3, CH_3NH_2 (23, 63); $NaOCH_3$ (571)
	Aqueous NaOH (main reaction)† (354); $NaOCH_3$, $NaOC_2H_5$ (60, 283, 402); NH_3 (283, 591); KSH (37); $NaSCH_3$ (265); Na_2SO_3 (355)		NH_3 (438); CH_3NH_2, $C_6H_5NH_2$ (439)
	NH_3 (main reaction)† (437); CH_3NH_2, $C_6H_5NH_2$ (439)		$NaOCH_3$, NH_3 (main reaction)† (141)
	$NaOCH_3$ (571); NH_3 (23); RNH_2 (551)		NH_3 (145)

TABLE 45—*Concluded*

COMPOUND	REAGENTS EFFECTING SUBSTITUTION	COMPOUND	REAGENTS EFFECTING SUBSTITUTION
	$NaOCH_3$ (282)‡		KOH, NH_3 (64, 335); $NaOCH_3$ (282); Na_2S_2 (64)
	KOH, $NaOCH_3$, $NaOC_2H_5$ (282, 303); NH_3 (7, 400)		NH_3 (by-product) (400)
	$NaOCH_3$ (57, 282); NH_3 (57, 514); piperidine (359); Na_2S_2 (57)		NaOH, $NaOCH_3$, $NaOC_2H_5$, NH_3, $C_6H_5NH_2$ (304)
	NH_3 (521)		

* In each formula the group replaced is enclosed within parentheses. X represents halogen when the same behavior has been observed with two or more different halogens, and R represents alkyl groups in the same way.

† The other nitro group is replaced in a slower reaction to give an isomeric by-product.

‡ Nietzki (449) stated that alcoholic ammonia displaced chlorine from 3,4-dichloro-1,2-dinitrobenzene, but his compound (from the nitration of *o*-dichlorobenzene) was probably ,5-dichloro-1,3-dinitrobenzene; *cf.* reference 282.

TABLE 46

Reactions of chlorinated o-dinitrobenzenes with sodium methoxide

COMPOUND*	RATE COEFFICIENT†		*E*	LOG *PZ*	REFERENCE
	0°C.	25°C.			
	l. mole^{-1} *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	*kcal.*		
o-$C_6H_4(NO_2)_2$‡		0.0085	19.9¶	12.6¶	(534)
3-Cl-1,**2**-$C_6H_3(NO_2)_2$	0.0074_5	0.100	16.8	11.3	(283)
4-Cl-1,**2**-$C_6H_3(NO_2)_2$	0.0331	0.437	16.7	11.9	(283)
3,4-Cl_2-1,**2**-$C_6H_2(NO_2)_2$	0.333				(282)
3,5-Cl_2-1,**2**-$C_6H_2(NO_2)_2$	0.128				(282)
3,6-Cl_2-**1**,2-$C_6H_2(NO_2)_2$‡	0.0261				(282)
4,5-Cl_2-**1**,2-$C_6H_2(NO_2)_2$‡	0.36				(282)
3,4,5-Cl_3-1,**2**-$C_6H(NO_2)_2$	2.35				(289)
3,4,6-Cl_3-1,2-$C_6H(NO_2)_2$§	0.67_5				(289)

* The number in bold-face type indicates the position of the nitro group which is replaced.

† The last digit is, to judge from published data, subject to an uncertainty of 5 or less unless written as a subscript, in which case the uncertainty is between 5 and 10.

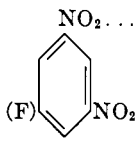
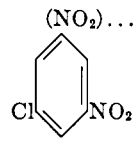
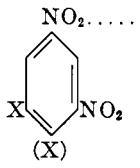
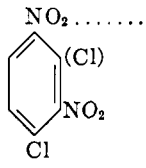
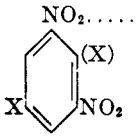
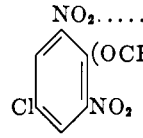
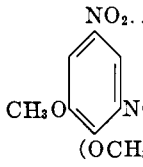
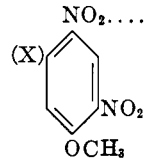
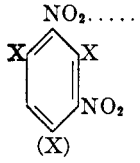
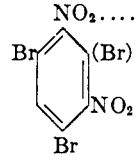
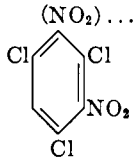
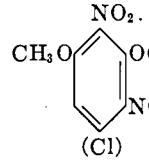
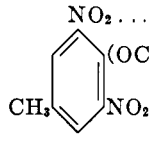
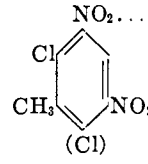
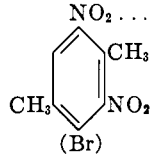
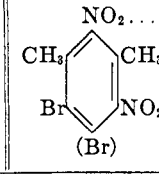
‡ Divide by 2 to get the rate constant per replaceable nitro group.

§ The 2-nitro group was displaced, but an unidentified chlorine atom was also replaced.

¶ Based on data in table 52.

TABLE 47

*Substitution reactions in m-dinitrobenzene derivatives**

COMPOUND	REAGENTS EFFECTING SUBSTITUTION	COMPOUND	REAGENTS EFFECTING SUBSTITUTION
	$NaOCH_3$, NH_3 (149)		$NaOCH_3$ (150)
	$NaOCH_3$ (282); NH_3 (509)		$NaOCH_3$ (572); NH_3†
	Aqueous Na_2CO_3 (169); $NaOCH_3$ (282); NH_3 (8, 400)		NH_3 (333)
	$NaOC_2H_5$ (63); CH_3NH_2 (59)		Aqueous-alcoholic NaOH, CH_3NH_2, $C_6H_5NH_2$, NH_3, Na_2S (60)
	$NaOC_6H_5$, piperidine (80); $NaOCH_3$ (289)		Aqueous Na_2CO_3 (308)
	$NaOCH_3$ (by-product) (481)		$C_6H_5NH_2$ (481)
	NH_3 (533)		Sodioacetoacetic ester (144)
	NH_3 (197); $C_6H_5NH_2$ (196)		CH_3NH_2 (61)

* In each formula the group replaced is enclosed within parentheses. X represents halogen when the same behavior has been observed with two or more different halogens, and R represents alkyl groups in the same way. "Alcoholic" refers to ethanol.

† Both chlorine atoms replaceable by ammonia (572).

TABLE 48

Reactions of chlorinated m-dinitrobenzenes with sodium methoxide

COMPOUND [a]	RATE COEFFICIENT (L. MOLE^{-1} MIN.$^{-1}$) [b]		E	LOG PZ	REFERENCE
	0°C.	25°C.			
			kcal.		
2-Cl-1,3-$C_6H_3(NO_2)_2$	0.00289	0.0460	17.9	11.8	(283)
4-Cl-1,3-$C_6H_3(NO_2)_2$ [c]	0.110	1.51	16.8 [g]	12.5	(283)
2,4-Cl_2-1,3-$C_6H_2(NO_2)_2$ [d]	0.021_3				(282)
2,5-Cl_2-1,3-$C_6H_2(NO_2)_2$	0.025				(282)
4,5-Cl_2-1,3-$C_6H_2(NO_2)_2$	0.41				(282)
4,6-Cl_2-1,3-$C_6H_2(NO_2)_2$ [e]	1.20				(282)
2,**4**,5-Cl_3-1,3-$C_6H(NO_2)_2$ [f]	0.32				(289)
2,**4**,6-Cl_3-1,3-$C_6H(NO_2)_2$ [e,h]	0.061				(289)
4,5,6-Cl_3-1,3-$C_6H(NO_2)_2$ [e]	3.3				(289)

[a] The number in bold-face type indicates the position of the chlorine atom which is replaced.

[b] The last digit is, to judge from published data, subject to an uncertainty of 5 or less unless written as a subscript, in which case the uncertainty is between 5 and 10.

[c] Fuller data on reactions of 1-chloro-2,4-dinitrobenzene with alkoxides are listed in table 49.

[d] The two chlorine atoms appear to be very similar in mobility, though it has been concluded that the 2-chlorine is displaced by methoxide (572).

[e] Divide by 2 to get the rate constant per displaceable chlorine.

[f] The chlorine atoms in positions 2 and 4 are very similar in mobility.

[g] Based on data in table 49.

[h] A nitro group is displaced in a side-reaction (481).

TABLE 49

Reactions of 1-halo-2,4-dinitrobenzenes with sodium alkoxides

HALOGEN	TEMPERATURE	RATE COEFFICIENT*† FOR REACTION WITH		REFERENCE
		Methoxide in methanol	Ethoxide in ethanol	
	°C.	*l. mole^{-1} min.$^{-1}$*	*l. mole^{-1} min.$^{-1}$*	
Chlorine	0	0.114	0.39	(542)
		0.111	0.36	(386)
		0.110		(283)
			0.41	(397)
	10		1.05	(386)
	15	0.61	1.81	(542)
		0.59	1.8	(386)
		0.57†	1.63†	(397)
	20		2.9	(386)
	25	1.50	4.9_5‡	(542)
		1.49	4.95‡	(386)
		1.51	2.98‡	(416)
		1.51		(283)
Bromine	0		0.22	(397)
	15	0.40_5	1.02†	(397)
	25	1.12	2.46	(416)
Iodine	15		0.228	(397)

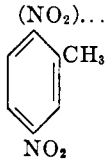
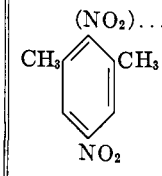
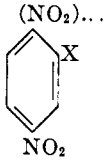
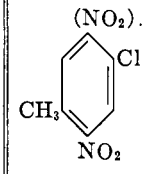
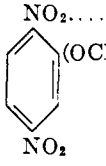
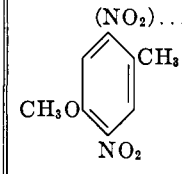
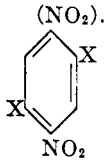
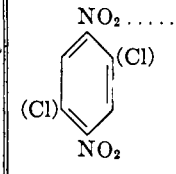
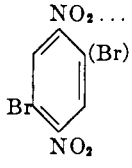
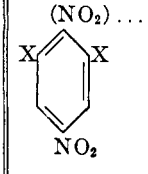
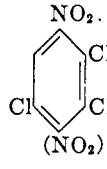
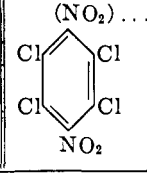
* The last digit is, to judge from published data, subject to an uncertainty of 5 or less unless written as a subscript, in which case the uncertainty is between 5 and 10.

† The rate coefficient is a function of concentration; *cf.* table 39.

‡ The higher value is corroborated by the rate coefficient, 4.4 l. mole^{-1} min.$^{-1}$, found for reaction with "alcoholic potassium hydroxide" (399).

TABLE 50

*Substitution reactions in p-dinitrobenzene derivatives**

COMPOUND	REAGENTS EFFECTING SUBSTITUTION	COMPOUND	REAGENTS EFFECTING SUBSTITUTION
	NH_3 (main reaction)† (321)		NH_3 (297)
	$NaOCH_3$ (283); NH_3‡ (283, 337)		$NaOCH_3$, NH_3 (323)
	NH_3 (253)		$NaOCH_3$ (main reaction)† (141)
	$NaOCH_3$ (282); $NaOC_2H_5$ (302); NH_3 (302, 400)		NH_3 (by-product) (400)
	$C_6H_5NH_2$ (302)		$NaOCH_3$ (282); NH_3 (336)
	$NaOCH_3$, NH_3 (289)		$NaOCH_3$ (42, 43)

* In each formula the group replaced is enclosed within parentheses. X represents halogen when the same behavior has been observed with two or more different halogens, and R represents alkyl groups in the same way.

† The other nitro group is replaced in a slower reaction to give an isomeric by-product.

‡ The other nitro group and the halogen atom are replaced in slower reactions to give by-products.

TABLE 51

Reactions of chlorinated p-dinitrobenzenes with sodium methoxide

COMPOUND*	RATE COEFFICIENT†		REFERENCE
	0°C.	25°C.	
	l. mole^{-1} *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	
p-$C_6H_4(NO_2)_2$‡		0.0222	(534)
2-Cl-**1**,4-$C_6H_3(NO_2)_2$§	0.0318	0.55_9	(283)
2,3-Cl_2-1,4-$C_6H_2(NO_2)_2$	Not available		
2,5-Cl_2-**1**,4-$C_6H_2(NO_2)_2$‡	0.691		(282)
2,6-Cl_2-**1**,4-$C_6H_2(NO_2)_2$	0.145		(282)
2,3,5-Cl_3-1,**4**-$C_6H(NO_2)_2$	0.80		(289)

* The number in bold-face type indicates the position of the nitro group which is replaced.

† The last digit is, to judge from published data, subject to an uncertainty of 5 or less unless written as a subscript, in which case the uncertainty is between 5 and 10.

‡ Divide by 2 to get the rate constant per displaceable nitro group.

§ From these data, E = 18.6 kcal. and log PZ = 13.4.

TABLE 52

Reactions of o- and p-dinitrobenzenes with sodium alkoxides

ISOMER	TEMPERATURE	RATE COEFFICIENT* FOR REACTION WITH		REFERENCE
		Methanolic methoxide	Ethanolic ethoxide	
	°C.	*l. mole*$^{-1}$ *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	
Ortho	25	0.0085	0.0130	(534)
	35	0.0244	0.039_2	(534)
	45	0.069_5	0.117	(534)
Para	25	0.0219		(455)
		0.0222	0.106	(534)
	35	0.072	0.354	(534)
	45	0.238	1.11	(534)

* The last digit is, to judge from published data, subject to an uncertainty of 5 or less unless written as a subscript, in which case the uncertainty is between 5 and 10. Each rate coefficient should be divided by 2 to get the rate coefficient per displaceable nitro group.

TABLE 53

Reactions of miscellaneous compounds with sodium alkoxides

COMPOUND	TEMPERATURE	RATE COEFFICIENT[a] FOR REACTION WITH		REFERENCE
		Methanolic methoxide	Ethanolic ethoxide	
	°C.	*l. mole*$^{-1}$ *min.*$^{-1}$	*l. mole*$^{-1}$ *min.*$^{-1}$	
1-Chloro-4-cyano-2-nitrobenzene[b,c]	25	0.0142[c]	0.0424[c]	(416)
1-Bromo-4-cyano-2-nitrobenzene[c]	25	0.0102[c]	0.0308[c]	(416)
1-Chloro-2-cyano-4-nitrobenzene[c]	25	0.260[c]	0.817[c]	(31)
		0.265[c]	1.07[c]	(31)
	35	0.824[c]	2.54[c]	(31)
1-Bromo-2-cyano-4-nitrobenzene[c]	25	0.20_5[c]	0.55_0[c]	(31)
	35	0.635[c]	1.67[c]	(31)
2,4-Dinitro-5-alkoxychlorobenzene[i]	0	0.037	0.112	(386)
	10	0.09_1	0.22	(386)
	15	0.200	0.47	(386)
	20	0.30	0.61	(386)
	25	0.47	1.10	(386)
4,5-Dimethoxy-1,2-dinitrobenzene[d]	35	0.0029		(455)
	45	0.0088		(455)
1-Chloro-2,4-dinitronaphthalene	15	8.4		(542)
	25	20.	$44._1$[e]	(542)
2-Chloro-1,6,8-trinitronaphthalene[f]	0	2.2	Rapid	(314)
	15	$8._7$		(314)
	25	37.		(314)
2-Bromo-1,6,8-trinitronaphthalene[f]	0	1.2		(314)
	15	3.2	5.7	(314)
	25	10.		(314)
1,3,5-Trinitrobenzene[g]	0	1.6		(281)
4-Chloro-1,2,3-trinitrobenzene[h]	0	10.7 (approx.)		(572)
5-Chloro-1,2,3-trinitrobenzene[h]	0	7.5 (approx.)		(572)

[a] The last digit is, to judge from published data, subject to an uncertainty of 5 or less unless written as a subscript, in which case the uncertainty is between 5 and 10.

[b] For reaction with sodium phenoxide in methanol $k_{25} = 0.0137$; in ethanol $k_{25} = 0.0297$ (416).

[c] Since nitriles in alcoholic alkoxides are in equilibrium with imino esters (413), these rate coefficients do not really represent the compounds introduced into the reactions.

[d] A nitro group is displaced; divide by 2 to get the rate coefficient per displaceable nitro group.

[e] For reaction with "alcoholic potassium hydroxide," $k_{25} = 32.6$ (399).

[f] The halogen atom is replaced.

[g] Divide by 3 to get the rate coefficient per displaceable nitro group; other trinitrobenzenes react too rapidly for convenient kinetic study.

[h] The 2-nitro group is displaced.

[i] Chlorine is displaced; the alkoxy group is methoxy in reaction with methoxide and ethoxy in reaction with ethoxide.

TABLE 54

Arrhenius parameters, assembled for comparison

Very few of these values can be regarded as properly established; most are based on rate coefficients at only two temperatures, and many of these rate coefficients are based on only a single determination

COMPOUND*	REACTION WITH METHANOLIC METHOXIDE		REACTION WITH ETHANOLIC ETHOXIDE		BASED ON DATA IN TABLE
	E	$\log_{10} PZ$	*E*	$\log_{10} PZ$	
	kcal.		*kcal.*		
o-Chloronitrobenzene	23.2	12.0			43
p-Chloronitrobenzene	23.0	12.5			43
o-Dinitrobenzene	19.9	12.6	20.8	13.3	52
p-Dinitrobenzene	22.5	14.8	22.2	15.3	52
2,3-Dichloro-1-nitrobenzene	22.6	12.3			43
2,4-Dichloro-1-nitrobenzene	23.3	13.8			43
2,5-Dichloro-1-nitrobenzene	23.0	12.8			43
2,6-Dichloro-1-nitrobenzene	25.0	12.6			43
3,**4**-Dichloro-1-nitrobenzene	22.2	13.0			43
3-Chloro-1,**2**-dinitrobenzene	16.8	11.3			46
4-Chloro-1,**2**-dinitrobenzene	16.7	11.9			46
2-Chloro-**1**,4-dinitrobenzene	18.6	13.4			51
2,3,4-Trichloro-1-nitrobenzene	26.9†	17.0†			44
2,3,5-Trichloro-1-nitrobenzene	21 0	12.3			44
2,3,**6**-Trichloro-1-nitrobenzene	22.0	11.8			44
2,**4**,5-Trichloro-1-nitrobenzene	21.1	13.3			44
2,4,6-Trichloro-1-nitrobenzene	24.6	14.4			44
3,**4**,5-Trichloro-1-nitrobenzene	20.2	12.7			44
1-Chloro-2,4-dinitrobenzene	17.0‡	12.7	16.5§	12.8	49
	16.8‡	12.5	13.4§	10.3	49
	16.7	12.5			49
1-Bromo-2,4-dinitrobenzene			15.1	11.5	49
1-Chloro-2.6-dinitrobenzene	17.9	11.8			48
1-Chloro-5-methoxy-2,4-dinitrobenzene	16.5	11.8			53
1-Chloro-5-ethoxy-2,4-dinitrobenzene			14.8	10.9	53
4,5-Dimethoxy-**1**,2-dinitrobenzene	22.0	13.3			53
1-Chloro-2-cyano-4-nitrobenzene	21.1	14.9	20.8	15.1	53
1-Bromo-2-cyano-4-nitrobenzene	20.7	14.5	20.3	14.6	53

* The position of the displaced substituent is in bold-face type.

† A gross experimental error is suspected.

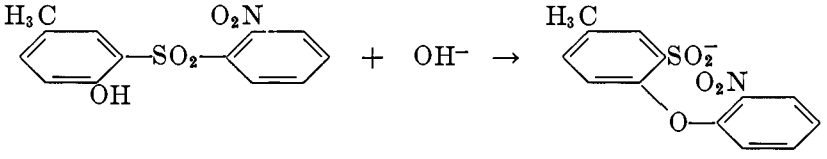
‡ Values calculated from three different sets of data.

§ Values calculated from two different sets of data.

VIII. The Smiles Rearrangement[7]

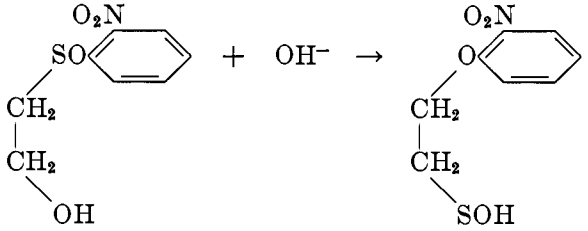
A group of reactions which are, in effect, intramolecular nucleophilic aromatic substitutions are collectively known as Smiles rearrangements, after Samuel Smiles who has largely developed this field.

A typical Smiles rearrangement is the transformation of 2-hydroxy-5-methyl-2′-nitrodiphenyl sulfone (L) into 4-methyl-2′-nitro-2-sulfinodiphenyl ether (LI) under the influence of a slight excess of aqueous sodium hydroxide at 50°C. (367).



L LI

Another example is the rearrangement of 2-hydroxyethyl 2-nitrophenyl sulfoxide (LII) into 2-(2-nitrophenoxy)ethanesulfenic acid (LIII) (324).

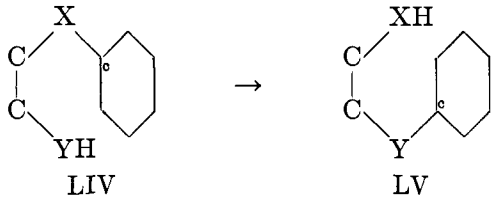


LII LIII

The Smiles rearrangement is one of the few aspects of the field of this review that has received a thorough, well-planned investigation, and the study has revealed several factors of general significance in nucleophilic aromatic substitution.

A. MECHANISM

A general representation of the Smiles rearrangement is the transformation of LIV into LV (171). Smiles's papers (reference 367 in particular) demonstrate



LIV LV

adequately that the mechanism of this rearrangement is firstly conversion of the —Y—H function to —Y⁻ by the action of sodium hydroxide or other strong base, followed by nucleophilic attack of the resulting —Y⁻ function on carbon c (in structure LIV) which displaces the —X⁻ function in its anionic condition. The carbon atoms joining X and Y may be saturated or in an aromatic ring (see the foregoing examples).

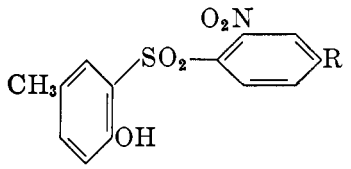
[7] This subject was more briefly reviewed in 1940 by Watson (588).

One would expect, knowing this mechanism, the following factors to influence the speed of rearrangement: (*a*) the activation present in the aromatic ring, (*b*) the replaceability of X, (*c*) the strength of $—Y^-$ as a nucleophilic reagent, and (*d*) the acidity of the —Y—H function, for in most cases —Y—H must be converted to the anionic $—Y^-$ form before reaction can occur. These several factors were recognized by Smiles (171), and he has provided evidence for the importance of all of them.

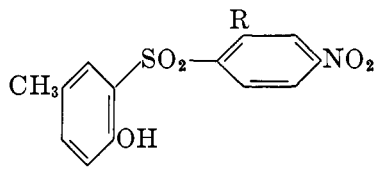
B. ACTIVATION

Very few Smiles rearrangements occur without some kind of activation in the aromatic ring of structure LIV. In most of the reported examples, the activating group has been an *o*- or *p*-nitro group, but activation by *p*-sulfonyl groups, though less strong, has also been observed (584). Remarkably, the first examples of the rearrangement encountered by Smiles were in naphthalene derivatives possessing no activating group whatsoever (582). In benzene derivatives, attempts to observe rearrangement activated solely by the *o*-carboxylate (COO^-), *m*-nitro (324), or *p*-methylthio (584) groups have been unsuccessful.

The most extensive study of the effect of activation on the Smiles rearrangement was made by Galbraith and Smiles (206), who determined by a rough colorimetric method the times necessary for complete rearrangement of a number of sulfones of the structural types LVI and LVII. Sulfones of structure LVI re-

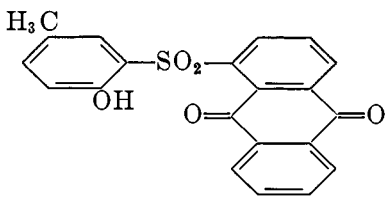


LVI



LVII

acted most rapidly when R was NO_2, showing the following order of reactivity with other groups: $NO_2 > C_6H_5CO > COO^- > Cl > H$. Similarly, sulfones of structure LVII varied in reactivity with the nature of group R as follows: $NO_2 > C_6H_5CO > COO^- > H$. The same study also showed that sulfone LVIII underwent rearrangement, although less rapidly than L or its *p*-nitro isomer. In this

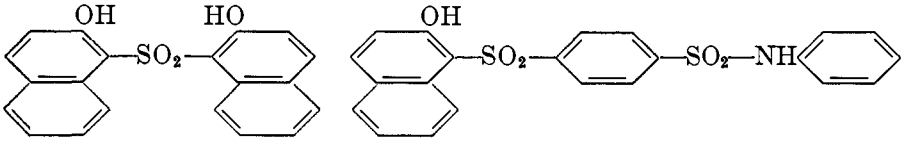


LVIII

connection, it is interesting to note that a lone *o*-nitro group is a stronger activator than a solitary *p*-nitro group (365).

Contrary to general experience with Smiles rearrangements, the rearrangements of sulfones LIX and LX are retarded by a large excess of alkali (583, 584). At high alkali concentrations the hydroxyl group is transformed to a greater extent into its ionized ($—O^-$) form, as is the sulfanilido group into its anionic

form ($—SO_2NC_6H_5^-$), and these negatively charged groups are less activating than their uncharged forms. In accordance with this explanation, the rate of re-



LIX LX

arrangement of the *N*-methyl derivative of LX was not depressed by high alkali concentration.

C. THE EFFECTS OF VARYING X AND/OR Y

Of the several factors governing the rate of Smiles rearrangements, activation of the carbon atom at which substitution occurs is the most easily isolated. Other influences, such as the nature of the group —Y—H and the bridge —X—, must be discussed with respect to each other, and also with respect to the sort of carbon chain which connects X and Y and, if the connection happens to be aromatic, the influence of substituents in that aromatic ring. Some of these interplaying influences are electronic, and others are steric.

The early exploratory work of Smiles's group showed that, in compounds provided with substantial activation, rearrangement would or would not occur depending on the nature of the groups X and Y. The early findings were summarized by Evans and Smiles (171) as follows:

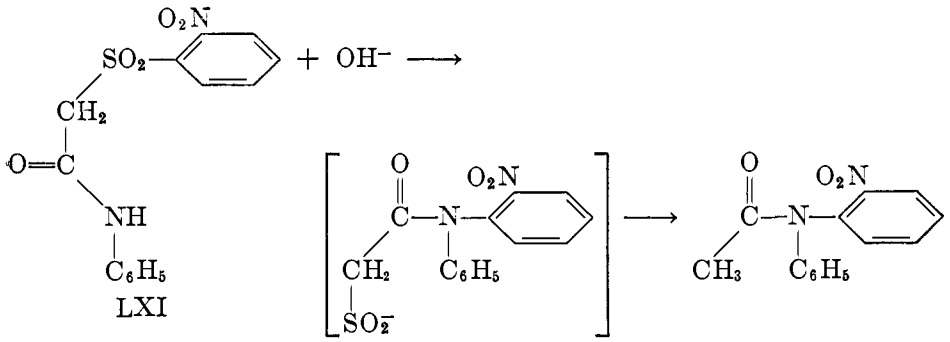
If YH is NHacyl,	X may be SO_2, SO, or S
If YH is OH (alkyl),	X may be SO_2 or SO but not S
If YH is NH_2 (aryl),	X may be SO_2 (SO?) but not S
If YH is OH (aryl),	X may be SO_2 but not SO or S
If YH is SH,	X may be O

This table shows that rearrangement occurs most generally with very easily replaceable X groups (e.g., SO_2) or with YH groups which, in their anionic ($—Y^-$) form, are very active nucleophilic reagents. The propensity to rearrange decreases as X becomes less readily replaceable or as $—Y^-$ becomes a weaker nucleophilic reagent.

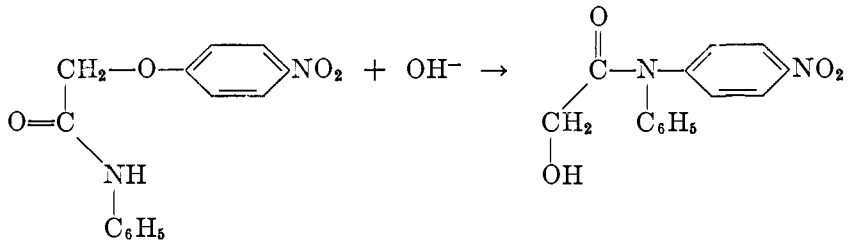
By including the findings of later papers (126, 172, 391, 485, 489, 552, 553) this table may be expanded to give the following résumé of the several sorts of Smiles rearrangement which have been observed:

If YH is NHacyl,	X may be SO_2, SO, S, or O
If YH is $CONH_2$,	X may be SO_2, S, or O
If YH is SO_2NH_2,	X may be O
If YH is OH (alkyl),	X may be SO_2 or SO but not S
If YH is NH_2 (aryl),	X may be SO_2 or O, but not S or NH
If YH is OH (aryl),	X may be SO_2, —COO—, $—SO_2O—$, or O, but not SO or S
If YH is SH,	X may be O
If YH is SO_2H,	X may be O

In addition, sulfone LXI (172) and ether LXIII (553), in which X and Y are connected by a saturated carbon chain containing a carbonyl function, have been found to rearrange, forming, respectively, LXII and LXIV.

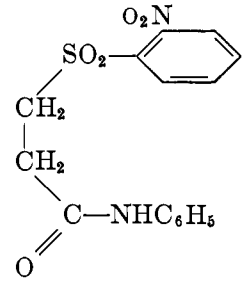


LXI LXII

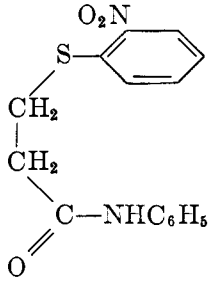


LXIII LXIV

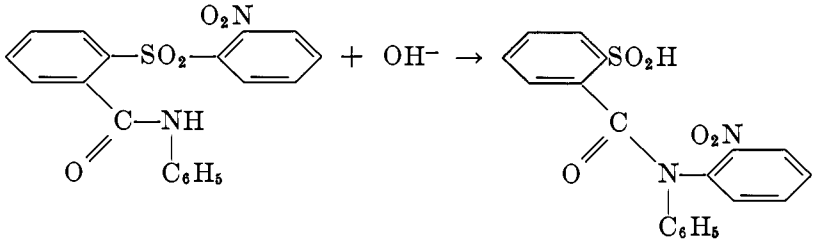
The failure of sulfone LXV and sulfide LXVI to rearrange contrasts with the facile rearrangement of their analogs LXVII and LXIX, in which X and Y are connected by aromatic rather than aliphatic carbon atoms; the latter two yield, respectively, LXVIII and LXX (172).



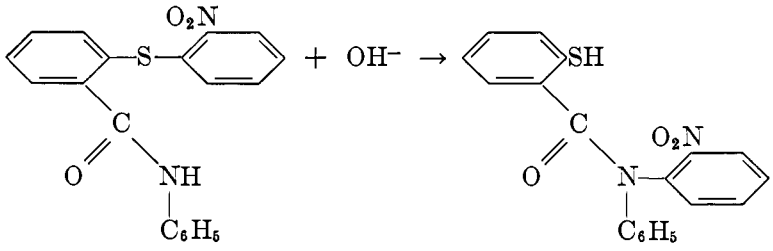
LXV



LXVI



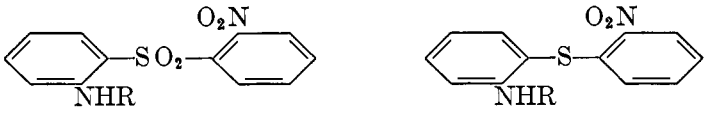
LXVII LXVIII



LXIX LXX

The failure of LXV and LXVI to rearrange was attributed partly to their possessing steric characteristics less favorable for rearrangement, and partly to their propensity, as β-substituted propionic acid derivatives, to undergo α,β-elimination in alkaline media. In cases such as these, in which other reactions compete with rearrangement, strong arguments cannot be built about the failure of a substance to rearrange.

There are some interesting variations in the capacity to rearrange of substances in which YH is an amino or a substituted amino group, depending on the substitution of the amino group. According to the mechanism proposed by Smiles for the rearrangement, the first step is conversion of —YH, by the base employed, to its anionic form (—Y^-); this is then followed by attack of —Y^- on the aromatic carbon atom. Since the nucleophilic activity of reagents is closely related to their basicity (Section VI), those substituents which operate to increase the acidity of the amino group at the same time decrease the nucleophilic activity of the amide ion. Thus one might expect that two classes of substituents would sharply decrease the capacity of a compound to rearrange: those which decreased the acidity of the amino group so much that the anion —Y^- could not be formed with the base employed, and those which increased the acidity of the amino group so much that the anion formed had but weak nucleophilic activity. The operation of both these effects is demonstrated in Smiles's papers.



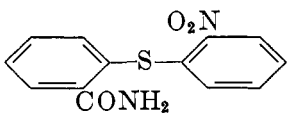
LXXI LXXII

In the case of sulfones of structure LXXI, it was necessary to use concentrated alkali to make the *N*-methyl derivative rearrange. The substances in which R was H or acetyl rearranged rapidly under usual conditions (1 *M* sodium hydroxide at 100°C. for 30 min.), but under these conditions rearrangement of the *N*-benzenesulfonyl derivative was incomplete (171). In this series of compounds of increasing acidity, maximum reactivity appears in the substances in which R is H or acetyl.

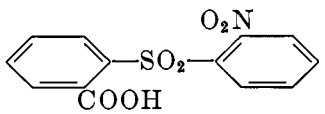
Sulfides of structure LXXII, in which R was H or CH_3, did not rearrange under conditions which were sufficient for good rearrangement of the compound in which R was acetyl. Under these same conditions, the sulfide in which R was *o*-nitrobenzoyl rearranged incompletely, and from the analogs in which R was

picryl or benzenesulfonyl, only the sodium salts of the starting materials could be isolated. The methylamino and free amino sulfides represent the situation of YH being insufficiently acidic to form an effective concentration of $—Y^-$ with the alkali used, while the picryl and benzenesulfonyl derivatives represent YH so acidic that the anions have low nucleophilic reactivity.

From the experiments described in the preceding two paragraphs, it appears that maximum reactivity is encountered, amongst compounds in which YH is of the NHR type, when R is an acyl group with electronic characteristics about like those of the acetyl group. (This conclusion, it should be remembered, is derived from experiments in dilute alkali solution; a different point of maximum reactivity would be expected if a more strongly basic medium were employed.) Another demonstration of the beneficial effect of acylating an amino group is the facile rearrangement of LXXIII, compared with the inertness of LXXII (R = H) (172).



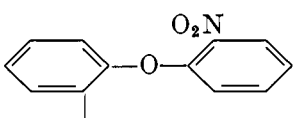
LXXIII



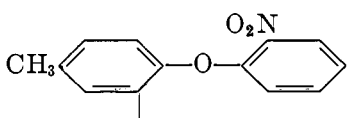
LXXIV

Acylation does not, however, assist rearrangement of compounds in which YH is OH. Thus LXXIV, in which YH is COOH, fails to rearrange, although derivatives of 2-hydroxy-2′-nitrodiphenyl sulfone rearrange readily. The $—COO^-$ anion is too stable.

The acidity of an amino group can also be increased by arylation; it was found that conversion of 2-(2-nitrophenoxy)benzamide (LXXV) into its *N*-phenyl derivative increased the rate of its rearrangement (553). However, the *N*-phenylsulfonamide LXXVI was incapable of rearrangement, whereas its parent (lacking the phenyl group) rearranged with ease. In the latter instance phenylation



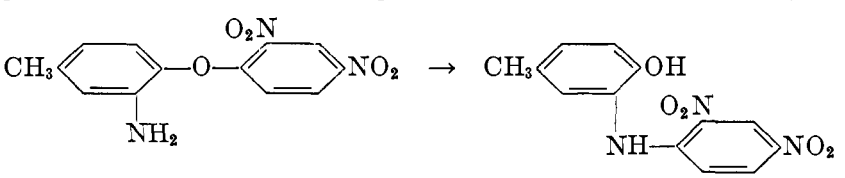
LXXV



LXXVI

made the YH group too acidic.

The rearrangements of *o*-aminodiphenyl ethers into *o*-hydroxydiphenylamines, exemplified by the conversion of LXXVII into LXXVIII, differ from the usual Smiles rearrangements in not appearing to require conversion of the amino groups to amide ion functions as a prerequisite to rearrangement (489).

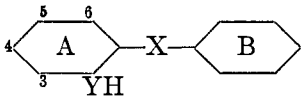


LXXVII LXXVIII

Rearrangement of LXXVII occurred most readily in hydroxylic solvents and was somewhat *retarded* by aqueous alkali. It is reasonable that the amino group as such should participate in the rearrangement reaction, for cleavage of suitably activated diphenyl ethers by amines is well known (Section II,F). The fact that *N*-acyl derivatives of LXXVII reacted progressively more slowly the more electron-withdrawing the character of the acyl group is in accord with the conclusion that the amino group as such enters into the displacement reaction (490). Smiles observed or attempted the rearrangement of several *o*-amino sulfides and sulfones; his papers refer only to base-promoted rearrangement reactions and he appears not to have investigated the effect of heat alone on them. Many of them would be expected to undergo thermal rearrangement.

D. THE EFFECTS OF SUBSTITUENTS IN AN AROMATIC RING JOINING X AND Y

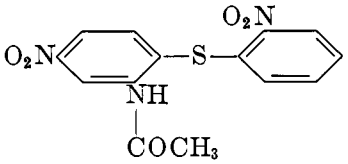
Most of the compounds whose rearrangement was studied by Smiles were of the structural type LXXIX. The effects of substituents introduced into ring A are not so easily and simply predicted as in the case of substituents in ring B.



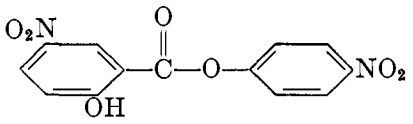
LXXIX

A substituent in ring A can affect the rate of reaction by its electronic effect on X or on Y. With regard to their effect on X, electron-withdrawing groups should promote reaction and electron-furnishing groups should hinder, and these effects should be strongest for groups in the 4- and 6-positions. The overall consequence of their effect on Y will depend on whether YH is more or less acidic than the optimum for most rapid rearrangement. If YH is on the insufficiently acidic side of the optimum, electron-withdrawing groups should assist rearrangement, but if YH is rather too acidic, electron-withdrawing groups in ring A should retard reaction; electron-furnishing groups should have opposite effects, and in all cases except the halogens these effects should operate most strongly from the 3- and 5-positions. It is worth noting that, with respect to their effects on both X and Y, electron-withdrawing groups should assist rearrangement if YH is less acidic than the optimum. If YH is more acidic than the optimum, an ambiguity arises, and one hesitates to predict what the effect of a substituent would be.

An instance in which an electron-withdrawing group in position 4 of ring A assisted rearrangement is provided by LXXX, which rearranged more rapidly



LXXX



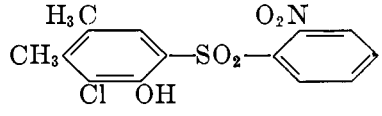
LXXXI

than its mononitro parent (171). The contrary effect of a nitro group is illustrated by the behavior of 4-nitrophenyl 5-nitrosalicylate (LXXXI), which remained unaltered under conditions sufficient for rearrangement of 4-nitrophenyl salicylate to 2-carboxy-4′-nitrodiphenyl ether (552). From information previously considered, the hydroxy group appears to be a YH group of the rather too acidic sort, and thus the deactivating effect of the 5-nitro group is in accord with the discussion in the previous paragraph.

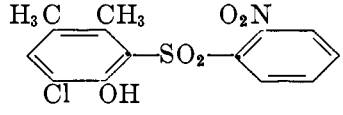
Since removal of a proton from YH is not prerequisite to the rearrangement of *o*-aminodiphenyl ethers, the effect of a substituent introduced into the A ring would always be difficult to predict, for an electron-withdrawing group, for instance, would facilitate reaction by increasing the displaceability of the phenoxy group and retard reaction by decreasing the basicity of the amino group. It is therefore not surprising that as the nature of the substituent in the 4-position of 2-amino-2′,4′-dinitrodiphenyl ethers is varied from one electronic extreme to the other, there should be a stage of maximum reactivity with substituents of intermediate electronic character (table 55). A stage of maximum reactivity is also observed in rearrangement of 5-substituted-2-amino-2′,4′-dinitrodiphenyl ethers (487).

E. STERIC EFFECTS

McClement and Smiles (418) determined the time for complete rearrangement of some *o*-hydroxysulfones substituted in the A ring with methyl and/or chlorine groups. Generally speaking, chlorine atoms retarded reaction and methyl groups assisted it; this is not surprising in a substance in which YH is on the rather too acidic side of the optimum. The accelerating effect of methyl groups in the 6-position was very much stronger than that of methyl groups in other positions of the A ring; 3-chloro-2-hydroxy-4,5-dimethyl-2′-nitrodiphenyl sulfone (LXXXII), for instance, took more than 150 min. to rearrange, while 3-chloro-2-hydroxy-5,6-dimethyl-2′-nitrodiphenyl sulfone (LXXXIII) rearranged completely in 12



LXXXII



LXXXIII

min. Since the electronic make-up of these two isomers is nearly the same, the electronic explanation of the phenomenon offered by McClement and Smiles is difficult to accept. The phenomenon can, however, be easily understood from steric considerations.

The shape of a diphenyl sulfone molecule is perhaps best compared to that of a bird in flight; the sulfur atom represents the body of the bird, the oxygen atoms its head and tail, and the two benzene rings its wings. Such a sulfone has an infinite number of possible configurations which may be realized by rotation about the carbon–sulfur single bonds. In the case of 2-hydroxy-2′-nitrodiphenyl sulfones (structure LXXXIV), these configurations may profitably be sorted

into five categories which approximate five extreme configurations. Only one of these extremes (J in figure 5) is similar to the natural configuration of a bird in flight. In the other four, one of the wings (benzene rings) is turned so as to present its flat side to the direction of flight. Configuration L involves a great deal of strain between the nitro group of ring B and the carbon atoms of ring A, and is much disfavored when other less strained configurations are possible. In the case of the 6-position being unsubstituted (R being H), configurations approxi-

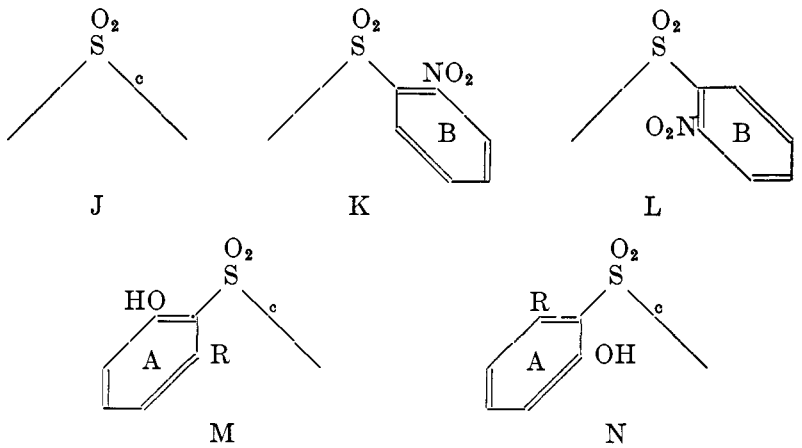
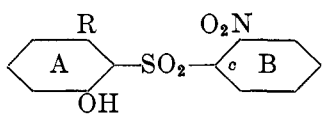


FIG. 5. Configurations of 2-hydroxy-2′-nitrodiphenyl sulfones

mating the other four extremes are possible, but only those resembling N can lead to rearrangement. Thus, in sulfones with a free 6-position, there are four



LXXXIV

probable types of configurations, of which only one has the orientation prerequisite to reaction.

Now when a large group, such as methyl, is introduced into the 6-position, configuration M becomes highly strained (as well as configuration L), and there remain only three probable configurational types of which one can lead to rearrangement. The probability of the molecular configuration being such as would lead to rearrangement is thus increased by the presence of a large group in position 6, and so the rate of reaction increases. This is steric acceleration of reaction.

The above argument can be refined and strengthened by taking account of the interaction of the sulfone oxygen atoms with the groups in the ortho positions of the two rings. In those configurations in which the "wings" of the sulfone are edgewise to the direction of flight (ring A in J, K, and L; ring B in J, M, and N) there will be some strain between large ortho substituents and the sulfone

bridge. For sulfones with an unsubstituted 6-position, this effect will operate to disfavor configurations J, M, and N, the nitro group being the only large group ortho to the sulfone linkage. This leaves configurations resembling K as the most probable, and these do not lead to rearrangement. In 6-methyl sulfones, interaction of the methyl group with the sulfone link will tend to disfavor J and K, configurations which do not lead to rearrangement. The bias in favor of configuration K is thus removed, and configuration N, the only one which can lead to rearrangement, becomes an equal competitor in a field of three instead of a less favored competitor in a field of four.

McClement and Smiles (418) pointed out that 2-hydroxy-1-naphthyl sulfones are also unusually prone to rearrangement. This is in accord with the above discussion.

F. REVERSE SMILES REARRANGEMENTS

Coats and Gibson (126) found that many of the sulfinic acids which Smiles and his associates prepared by rearrangement of *o*-hydroxysulfones were capable of rearranging back to the original sulfones. These reverse Smiles rearrangements occurred, as one might expect, at low pH (pH 2–6) at which sulfino but not hydroxyl groups are in their ionized forms. (Aromatic sulfinic acids have K_a about 2×10^{-2}.) The optimum pH for rearrangement varied from one *o*-sulfino-

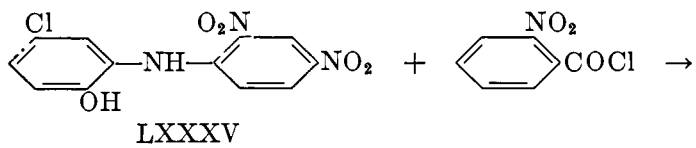
TABLE 55

Time for complete rearrangement of 4-substituted-2-amino-2′,4′-dinitrodiphenyl ethers at 50°C. (Roberts, de Worms, and Clark (491))

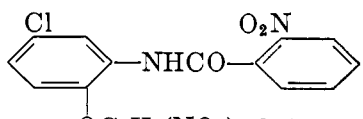
Group in 4-position..	NH_2	OCH_3	CH_3	H	I	Br	Cl	CO_2Ar	COOH
Time, min.....	50	13	7	5	15	30	60	No reaction	

diphenyl ether to another. There was evidence that, even under these acidic conditions, the forward Smiles rearrangement also occurred; that is, there was an equilibrium.

Rearrangement of *o*-hydroxydiphenylamines to *o*-aminodiphenyl ethers has not been observed, though *o*-aminodiphenyl ethers have been found to rearrange (table 55). However, treatment of 5-chloro-2-hydroxy-2′,4′-dinitrodiphenylamine (LXXXV) with *o*-nitrobenzoyl chloride in hot acetone solution produces 4-chloro-2′,4′-dinitro-2-(*o*-nitrobenzamido)diphenyl ether (LXXXVI); in cold acetone there was no rearrangement but only *O*-acylation (490).



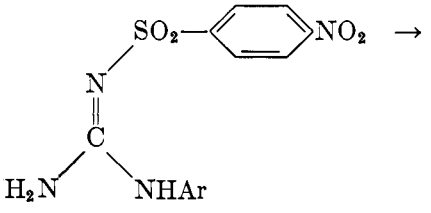
LXXXV



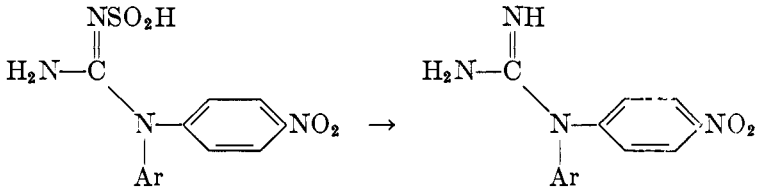
LXXXVI

G. SOME RELATED REARRANGEMENTS

The decomposition of *o*- or *p*-nitrophenylsulfonylguanidines (but not their *m*-isomers) in basic solution is quite analogous to the Smiles rearrangement of *o*-aminodiphenyl sulfones, the —C═C— linkage between X and Y in the sulfones being replaced by a —N═C— linkage. An example is the transformation of LXXXVII into LXXXIX; the unstable *N*-sulfinic acid LXXXVIII is probably an intermediate (11, 12).

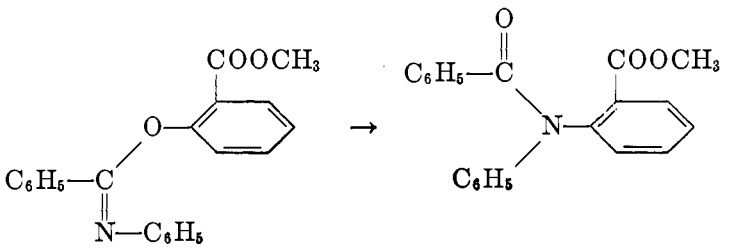


LXXXVII



LXXXVIII LXXXIX

The thermal rearrangement of aryl imido esters of type XC to amides of type XCI is known as the Chapman rearrangement (118). It has been used to advantage in the synthesis of *N*-arylanthranilic acids (143, 310).



XC XCI

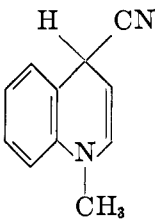
IX. Reactions Effecting Replacement of Hydrogen

Nucleophilic substitution reactions leading to replacement of nuclear hydrogen atoms appear in this special section because they are mechanistically rather different from most of the reactions previously considered. The distinction arises from the low anionic stability of the hydride ion, making it difficult to eject from the intermediate. In some cases the hydride ion is apparently eliminated as such, but more often the substitution is completed by oxidation of the intermediate either intramolecularly or by the action of an external oxidizing agent.

One might question the propriety of classifying as a nucleophilic substitution a process which cannot be consummated without the action of an oxidizing agent. Without answering the question, we classify all these displacements of hydrogen together because their first stage, formation of the intermediate, is the same sort of process as in other nucleophilic substitutions and quite essential to the overall reaction.

A. REACTIONS ACTIVATED BY HETERO NITROGEN ATOMS

The introduction of the cyano group into quaternary quinolinium salts is a process the separate stages of which are easily isolable and readily understood. *N*-Methylquinolinium iodide and potassium cyanide form the adduct XCII and potassium iodide; the adduct can in turn be oxidized by iodine to 4-cyano-*N*-methylquinolinium iodide, the overall result being introduction of a cyano group in place of hydrogen (45c). The reaction can be used for the preparation of 4-cyanoquinoline from quinoline, for the cyanoquinolinium salt is demethylated by heating, methyl iodide being evolved.



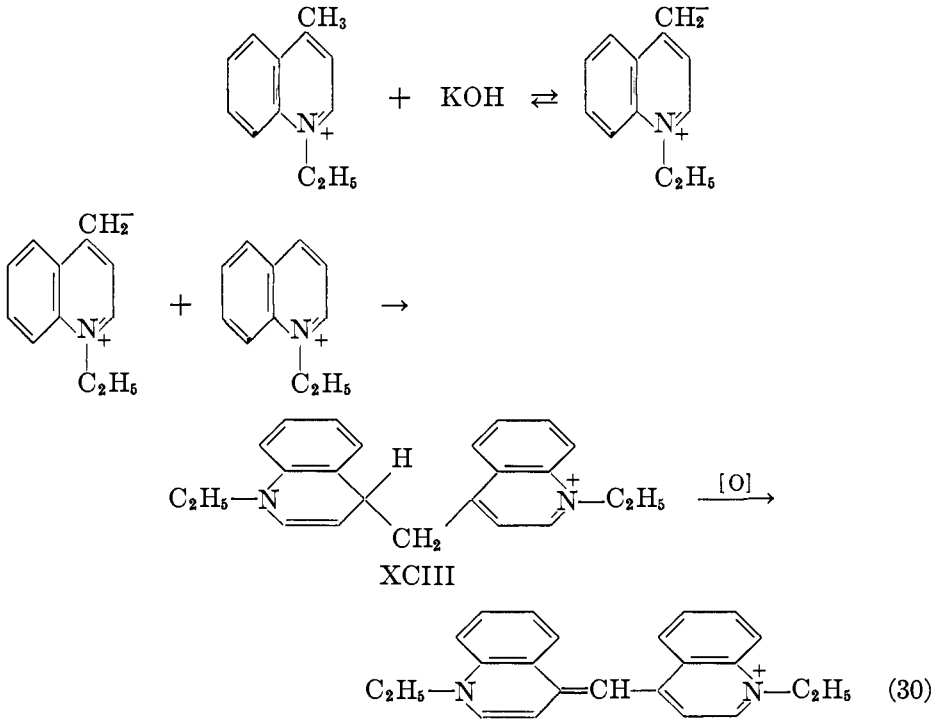
XCII

Quite analogous is the formation of 1-alkyl-2-quinolones from 1-alkylquinolinium salts *via* the intermediate pseudo-bases (*cf.* page 306); potassium ferricyanide is the oxidizing agent commonly used for the second stage of the reaction (45d). Pseudo-bases derived from other heterocyclic systems are similarly oxidizable.

The formation of cyanine dyes is another example of the same sort (equation 30). The intermediate leuco-base XCIII is oxidized by other constituents of the reaction mixture (45e).

The introduction of alkyl or aryl groups into pyridine, quinoline, and related heterocyclic bases by means of organolithium compounds is a valuable synthetic method. The first product of reaction (equation 17) is an adduct in which the alkyl or aryl group is bonded to the α- or γ-carbon, and the lithium atom is attached to nitrogen. (1,2-Addition always predominates unless, as in acridine, it is not possible.) In the case of the *n*-butyllithium–pyridine adduct, the substitution can be completed by heating, which causes lithium hydride to be split out quantitatively, yielding 2-*n*-butylpyridine (610). Adducts from quinoline, isoquinoline, and acridine were reported by Ziegler and Zeiser (611) to furnish on heating only moderate to negligible amounts of lithium hydride, and a more satisfactory preparative procedure was to hydrolyze the adduct to an alkyldihydroquinoline, for instance, which was then oxidized to the alkylquinoline

by nitrobenzene. In the general preparative application of this method (215, 329, 544) dihydro compounds are sometimes isolated (requiring oxidation), while in other cases the fully aromatic product is obtained directly. The latter

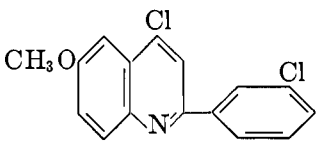


XCIII

(30)

is probably due either to the splitting out of lithium hydride subsequent to addition but in the same vessel, or to air oxidation of the intermediate dihydro compound.

A remarkable application of this synthesis was the preparation (217) of 4-chloro-2-*m*-chlorophenyl-6-methoxyquinoline (XCIV) by the reaction of *m*-chlorophenyllithium and 4-chloro-6-methoxyquinoline. One would expect the 4-chlorine atom to be displaced. This is reminiscent of the failure of 2-chloroquinoline to react with *n*-butyllithium (216).

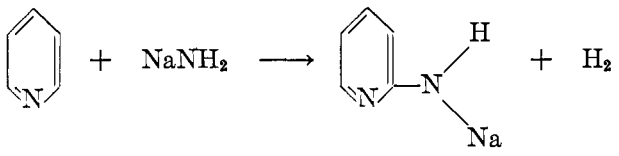


XCIV

Grignard reagents also effect the introduction of alkyl and aryl groups into the α- and γ-positions of pyridine and quinoline, but more severe conditions are necessary and yields are not as good (45a, 49).

The amination of heterocyclic bases by sodium amide is the best known nucleo-

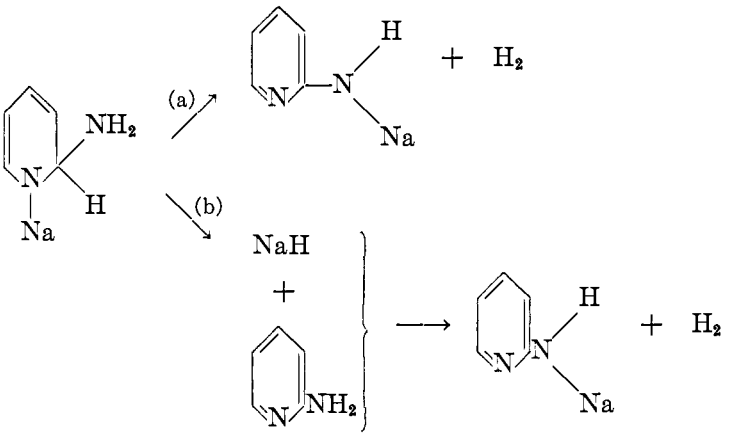
philic displacement of aromatic hydrogen. A familiar example is the synthesis of 2-aminopyridine (equation 31). In the usual synthetic procedure (at tempera-



(31)

tures of 100–200°C.) (360) hydrogen gas is evolved, but at lower temperatures in liquid ammonia it is sometimes necessary to add potassium nitrate in order to complete the substitution (44). These two classifications appear to represent once again the two methods of completing the replacement of hydrogen—direct elimination of hydride and oxidation.

The mechanism is presumably (147, 360) the formation of adduct XCV, followed by formation of hydrogen gas either directly (equation 32a) or indirectly by splitting out sodium hydride, which then acts upon the aminopyridine (equation 32b). Bergstrom (44) has produced evidence that an adduct is formed in



(32)

liquid ammonia solution but its structure and even its composition are unknown.

Other unsolved questions are the nature of catalysis by impurities present in ordinary sodium amide and by amides themselves, the specificity of potassium nitrate as an oxidizing agent in liquid ammonia, and the production of potassium amalgam when the potassium amide amination of quinoline is run in the presence of mercury (44). Deasy (147) has discussed the mechanism of these reactions in greater detail. Leffler's article (360) reviews their preparative application.

Hydroxylation of pyridine and quinoline by potassium hydroxide is analogous to amination, and like amination was discovered by Chichibabin (120, 121, 556). Quinoline and very dry, finely pulverized potassium hydroxide at 200–250°C. give carbostyril in over 80 per cent yield; hydrogen gas is evolved nearly quantitatively. Barium oxide containing barium hydroxide can also be used,

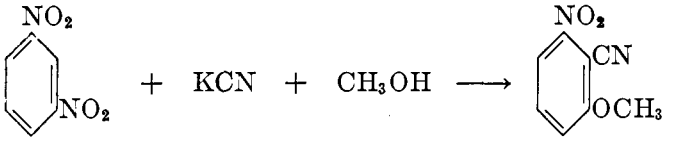
but sodium hydroxide is ineffective. Above 300°C., more than one mole of hydrogen is evolved per mole of quinoline and 2,4-dihydroxyquinoline is produced. Pyridine also reacts, but with greater difficulty, and so do isoquinoline and other related bases (121). 3-Hydroxypyridine has been converted to 2,5-dihydroxypyridine by a similar procedure (343).

B. REACTIONS ACTIVATED BY NITRO GROUPS

Nucleophilic displacement of hydrogen from aromatic nitro compounds has in every case been completed by oxidation rather than by hydride displacement. In most cases nitro compounds themselves, being oxidizing agents, oxidize the metastable intermediates (such as XCVI). Sometimes the oxidation occurs intramolecularly, in which case a compound containing a nitroso group or further stage of reduction may be isolated. In other instances an external oxidizing agent has been necessary.

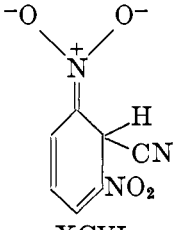
Because nitro groups are often partially reduced during reaction, and because the nitro groups sometimes react directly with nucleophilic reagents, these reactions are seldom tidy. Yields are often small with a complicated mixture of by-products. These complications are so severe in the case of interaction of aromatic nitro compounds with Grignard reagents that direct reaction with the nitro group is exclusively observed and there is no introduction of alkyl or aryl groups into nuclear positions (501).

The cyano group has several times been introduced into aromatic nitro compounds in place of hydrogen. The best-known example is the formation of 6-methoxy-2-nitrobenzonitrile from *m*-dinitrobenzene and methanolic potassium cyanide (equation 33) (372). This reaction appears to go through intermediate



(33)

XCVI, which is oxidized by other molecules of the nitro compound to a dinitro-

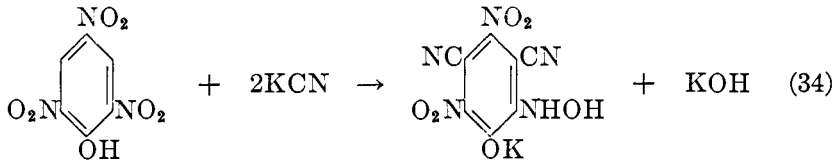


XCVI

benzonitrile, from which a nitro group is then displaced by methoxide from the alkaline methanolic solvent. The formation of 3-chloro-6-methoxy-2-nitrobenzonitrile from 1-chloro-2,4-dinitrobenzene (equation 29) (58, 260) and of 5-cyano-6-methoxyquinoline from 6-nitroquinoline (293) are instances of the same sort.

In the formation of potassium isopurpurate from picric acid and potassium cyanide (equation 34), two cyano groups are introduced and each time the inter-

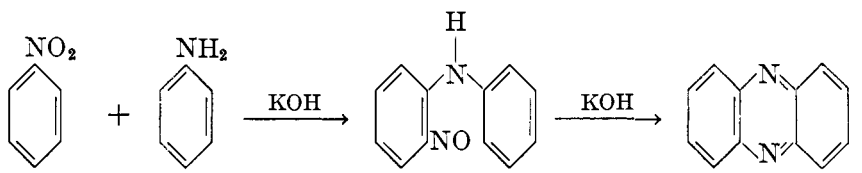
mediate is oxidized intramolecularly so that the product is a substituted phenylhydroxylamine (76). A number of other polynitrophenols react similarly.



(34)

By analogy with pyridine, one might expect the action of sodium amide upon nitrobenzene in liquid ammonia to give *o*- or *p*-nitroaniline, but a very complicated mixture of unidentified products is obtained (88). The expected reaction does occur with substituted amide ions. Nitrobenzene with potassium carbazole gives *N*-*p*-nitrophenylcarbazole (436); from nitrobenzene, sodium amide, and piperidine (sodium piperidide the active agent), *N*-*p*-nitrophenylpiperidine is formed (88); and sodium diphenylamide and nitrobenzene in liquid ammonia give *p*-nitrotriphenylamine (47). The sodium amide–piperidine reagent also converts 1-nitronaphthalene into 1-nitro-4-piperidinonaphthalene and 8-nitroquinoline into a nitropiperidinoquinoline whose orientation has not been established (88). In all these cases the intermediate appears to be oxidized by other molecules of the nitro compound.

The formation of phenazine from aniline and nitrobenzene in the presence of sodium hydroxide (606) possibly occurs by introduction of an anilino group ortho to the nitro group, followed by ring closure of the resulting *o*-nitrosodiphenylamine (equation 35). Some *p*-nitrosodiphenylamine was isolated from such a reaction (604).



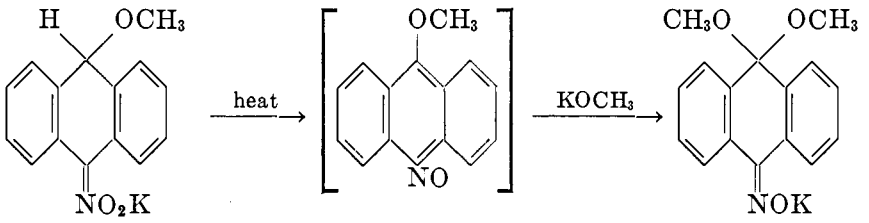
(35)

The production of *o*-nitrophenol (603) by the action of finely divided dry potassium hydroxide on nitrobenzene at 60–70°C. is a prominent example of the displacement of hydrogen by hydroxide. Yields up to 50 per cent of theory are obtained even in a hydrogen atmosphere, showing that air oxidation is not involved. Although Wohl (603) was unable to isolate any reduction product of nitrobenzene, it is probable that some of the nitrobenzene acted as an oxidizing agent. This would account for the rather low yield and for the impurities in the crude reaction mixture. A report by Lepsius that from five moles of nitrobenzene there were obtained three moles of *o*-nitrophenol and one mole of azoxybenzene could not be verified by Wohl and Aue (606).

The formation of 2,4- and 2,6-dinitrophenols from *m*-dinitrobenzene and of picric acid from *s*-trinitrobenzene, in each case in reaction with potassium ferricyanide and aqueous alkali (254), are related examples. Here the substitution plainly is completed by the oxidizing action of the ferricyanide.

Potassium methoxide and 9-nitroanthracene at low temperatures give a simple

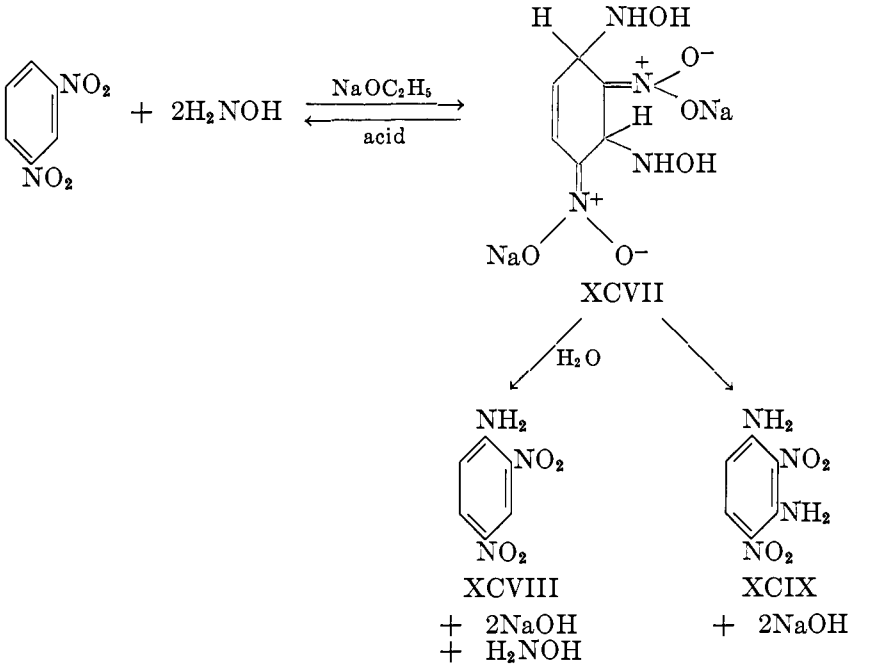
adduct but at higher temperatures this reacts further (424), as shown in equation 36. The intermediate methoxynitrosoanthracene was not isolated, but there is



(36)

no doubt that it was formed. Its formation represents the introduction of a methoxy group into 9-nitroanthracene, accompanied by intramolecular oxidation of the intermediate.

Ethanolic hydroxylamine and *m*-dinitrobenzene in the presence of sodium ethoxide form a salt, $C_6H_8N_4O_6Na_2$, which precipitates (425). Acidification of it regenerates *m*-dinitrobenzene, but treatment with water produces, according to the conditions, 2,4-dinitroaniline (XCVIII) or 2,6-dinitro-1,3-phenylenediamine (XCIX). It is possible that in the salt the hydroxylamine fragments are directly bonded to the nitro group, but the following scheme is a more attractive representation of the reactions:



The rearrangement of salt XCVII into the dinitrophenylenediamine XCIX is an internal oxidation–reduction process whose mechanism is open to speculation.

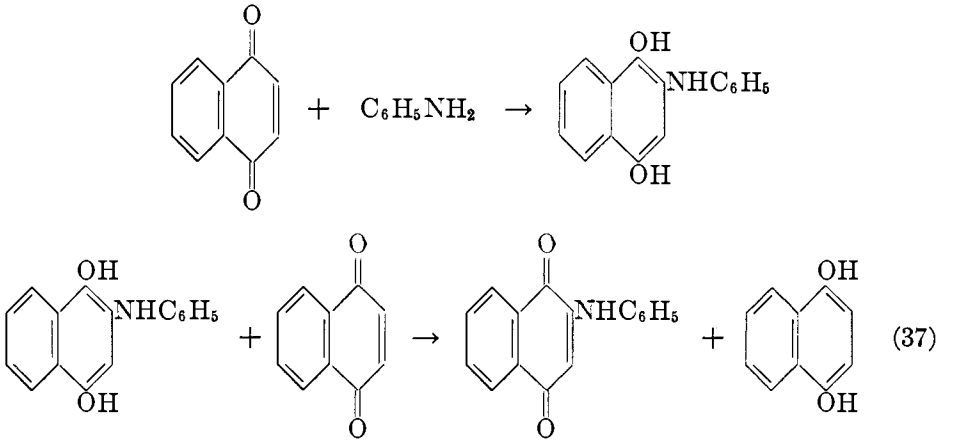
In like manner 2-nitronaphthalene and hydroxylamine form 2-nitro-1-naph-

thylamine (425), *s*-trinitrobenzene forms picramide (425), and 1-nitronaphthalene is transformed into 4-nitro-1-naphthylamine (5, 460).

The action of the 2-quinolyl anion (formed during decarboxylation of quinaldinic acid) on *m*-dinitrobenzene to give 2-(2,6-dinitrophenyl)quinoline (the orientation was assumed) (99) is an example of nitro-activated replacement of hydrogen by a carbanion. The 2-quinolyl anion is considered (99) to be similar to the cyanide ion in its nucleophilic reactivity.

C. REACTIONS IN QUINONES

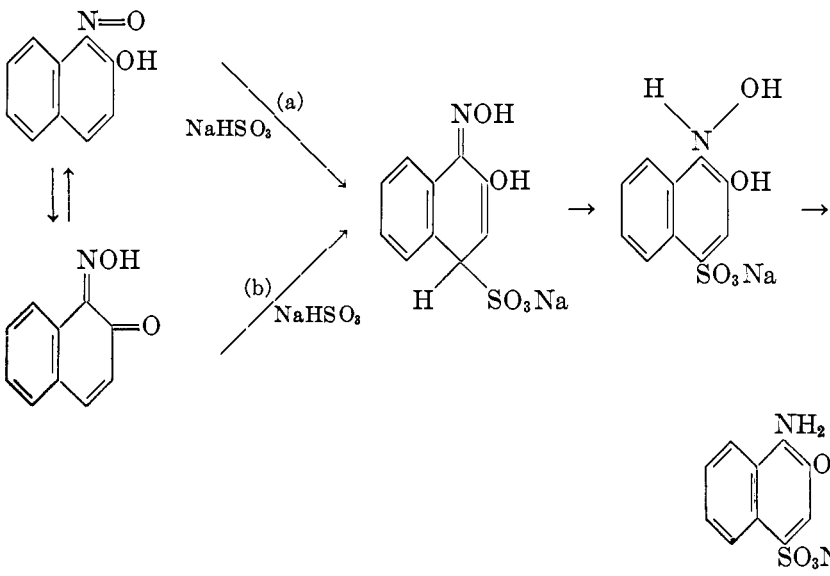
The introduction of chlorine atoms and of amino, methoxy, cyano, and other groups into quinones by a combination of 1,4-addition and oxidation processes is well known and is mentioned briefly because of its close similarity to reactions by means of which hydrogen is displaced from more properly aromatic compounds. An example is the reaction of aniline with 1,4-naphthoquinone (equation 37). The intermediate anilinonaphthohydroquinone is oxidized by unreacted



(37)

naphthoquinone, because the unsubstituted quinone has the higher oxidation potential. In other cases the oxidation potential of the substituted quinone is higher and it can be obtained only by addition of an external oxidizing agent. This and similar reactions have been discussed by Fieser and Fieser (182).

The reactions of 1-nitroso-2-naphthol with potassium cyanide, *p*-toluenesulfinic acid, and sodium bisulfite to give, respectively, 4-cyano-, 4-*p*-tolylsulfonyl-, and 4-sulfo-1-amino-2-naphthols have been described (88, 89, 182) as proceeding by addition to the quinone oxime tautomeric form of 1-nitroso-2-naphthol (equation 38b). This is an attractive representation of the mechanism, but direct 1,6-addition to the nitroso form (activated by the nitroso group) is equally appealing (equation 38a). In either case the same adduct is obtained; it probably undergoes internal oxidation–reduction to a 4-substituted-2-hydroxynaphthylhydroxylamine, which is then reduced to the amine by one of the several reducing agents present in the reaction mixtures.

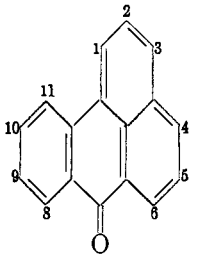


(38)

D. REACTIONS ACTIVATED BY OTHER STRUCTURES

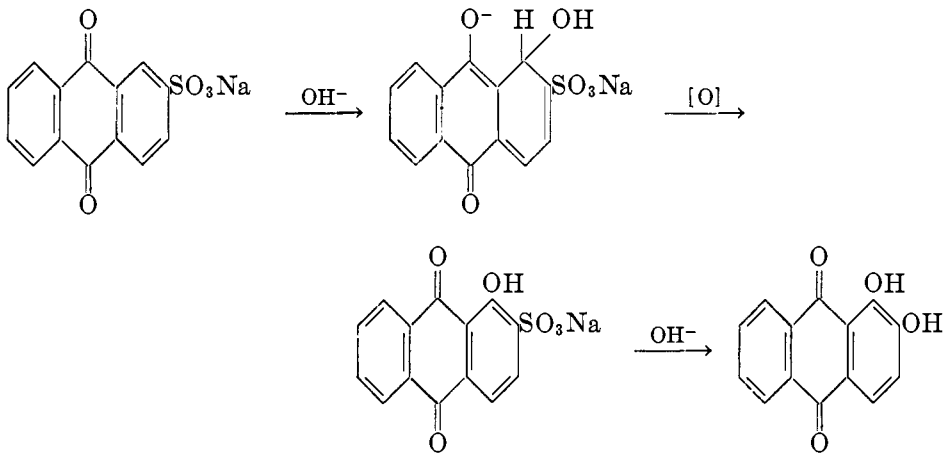
Reactions of Grignard reagents with hindered aromatic ketones and anils often effect introduction of alkyl or aryl groups into unsubstituted aromatic positions. These reactions have been discussed briefly in Section III,D of this review and at length by Gaertner (205).

Mesobenzanthrone is activated at the 4- and 6-positions (*Chemical Abstracts*



numbering) for nucleophilic substitution. With piperidine a 4-piperidino derivative is formed in a reaction that is catalyzed by potassium hydroxide or sodium amide and proceeds more rapidly in an oxygen atmosphere (86). The function of the oxygen is to oxidize the intermediate; reaction in a nitrogen atmosphere gives strongly basic by-products which seem to indicate that the intermediate disproportionates, forming some hydroaromatic amines as well as the usual product. Fusion of mesobenzanthrone with potassium hydroxide and potassium chlorate (oxidant) gives a mixture of 6- and 4-hydroxymesobenzanthrones in which the latter predominates (87). Other cases of the introduction of a substituent into mesobenzanthrone by use of a nucleophilic reagent are referred to by Bradley (86). The Grignard reagent gives 6-substitution, evidently due to preliminary coördination with the carbonyl group.

The preparation of alizarin by the fusion of 2-anthraquinonesulfonic acid with alkali in the presence of a nitrate or chlorate has been depicted as follows (587):



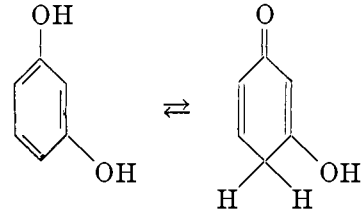
The similarity to substitutions in mesobenzanthrone is marked. The indicated order of introduction of the two hydroxy groups is assumed.

Sachs (503) found that fusion of naphthols, naphthylamines, and naphthalene itself with sodium amide brought about the introduction of amino groups, accompanied by the evolution of hydrogen gas. From 2-naphthol principally 5-amino-2-naphthol was obtained, and 1-naphthol also gave a 5-amino derivtive. 1-Naphthylamine was converted into 1,5-naphthylenediamine, and 2-naphthylamine yielded mainly the 2,5-diamine. Yields were in the range 20 to 50 per cent. From naphthalene, 1-naphthylamine and 1,5-naphthylenediamine resulted; in this case hydrogen evolution did not occur until water was added at the end of the reaction. Reaction with naphthalene occurred best in the presence of sodium phenoxide and somewhat less well in the presence of sodium amoxide or sodium glyceroxide, but naphthalene and sodium amide alone gave only traces of amination.

It is noteworthy that throughout Sachs's experiments there was a preference for substitution in the α-positions of naphthalene, and that the reactions occurred so readily with compounds containing the highly deactivating ionized hydroxy ($—O^-$) and ionized amino ($—NH^-$) substituent groups. This is less alarming when one considers that substitution occurred in the ring not containing the deactivating group, and recalls the fact that transmission of electronic effects from one ring to another is inefficient.

Fusion of sodium hydroxide with phenol causes evolution of hydrogen gas and the formation of phloroglucinol, resorcinol, and catechol (26, 27). Resorcinol under the same conditions is converted to phloroglucinol. Bradley and Robinson (88) have interpreted this reaction as one activated by the quinonoid system in the tautomer of resorcinol (equation 39), but the explanation is not convincing,

because it is difficult to believe that there would be any appreciable amount of free resorcinol under such highly alkaline conditions. The observed orientation



(39)

of substitution is in accord with the usual electronic behavior of the ionized hydroxy (—O^-) group, but it is strange that a reaction so greatly deactivated occurs at all. Boswell and Dickson (82) discovered that the reaction would not occur in the absence of oxygen, and that in the presence of oxygen approximately one volume of hydrogen was produced for two volumes of oxygen absorbed. The importance of oxygen suggests a free-radical mechanism.

Fusion of potassium benzoate with potassium hydroxide produces *p*-hydroxybenzoic acid and smaller amounts of salicylic acid and other products (28).

X. Cine-Substitution

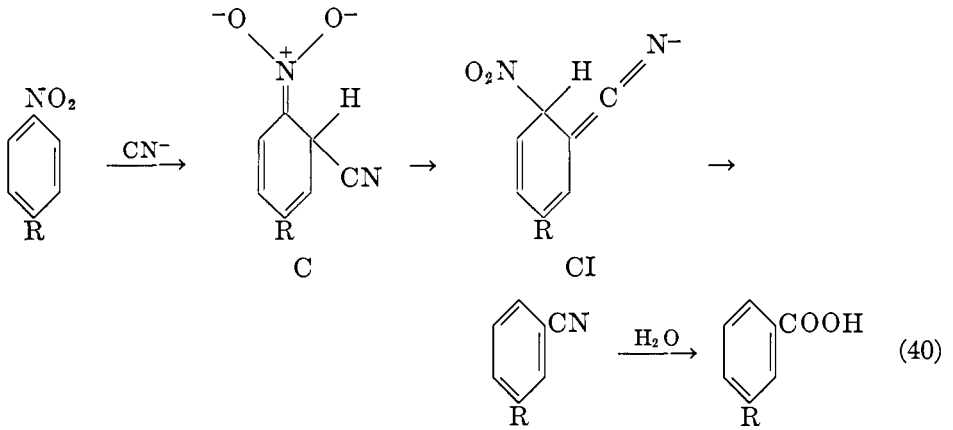
There are a number of aromatic nucleophilic substitution reactions in which the ring position taken by the entering group is not the same as that vacated by the displaced group. For reactions of this type we propose the descriptive and convenient term "cine-substitution" (from the Greek *cine*, to move). This term is meant to embrace reactions in which the entry of one group and the expulsion of the other occur essentially as a single process (which, however, might pass through metastable intermediates). It excludes processes of a desubstitution–resubstitution type, in which the two steps can be performed independently, as well as "normal" substitutions preceded or followed by a true rearrangement. For none of the cine-substitutions has a mechanism been rigorously established, and therefore it is difficult to apply these distinctions in practice. There are, however, two examples of reactions which at first glance seem to be cine-substitutions but which on closer inspection show definite indications of going through a sequence of removal of one group, followed, in an independent stage, by introduction of another. These deceptive cases are considered briefly at the end of the section.

A. The von Richter reaction

The oldest and in some respects the strangest cine-substitution reaction was discovered by von Richter (473, 474, 475) in 1871. It is the conversion of an aromatic nitro compound to a carboxylic acid under the influence of alcoholic potassium cyanide. The carboxyl group appears ortho to the position vacated by the nitro group (that the carboxyl group might in some cases have entered para to the position of the nitro group cannot be denied, but is improbable (104)). The most familiar example of the von Richter reaction is the conversion

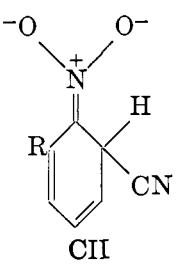
of *p*-bromonitrobenzene to *m*-bromobenzoic acid (in 22 per cent yield). *m*-Bromonitrobenzene gives a mixture of *o*- and *p*-bromobenzoic acids, while *o*-bromonitrobenzene gives no acidic products (104, 473, 474, 475, 612). The chloronitrobenzenes and iodonitrobenzenes react quite analogously (473, 474, 475, 476). The nitroanisoles also react according to the same pattern, *m*-anisic acid being obtained from *p*-nitroanisole and *p*-anisic acid from *m*-nitroanisole (104). Nitrobenzene gives benzoic acid (21 per cent), though here of course the difference in position cannot be detected. *m*-Nitrobenzenesulfonic acid gives *o*- and *p*-sulfobenzoic acids, together with one or more aminosulfobenzoic acids (277).

The mechanism shown in equation 40 has been proposed for the von Richter reaction (104).



(40)

This mechanism accounts for the observed products and for the failure of ortho-substituted nitrobenzenes to react (steric interference with stabilization of the intermediate CII by the nitro group). The critical step (C → CI) is analogous to hydrogen migration in the rearrangement of phenylglyoxal to mandelic acid



CII

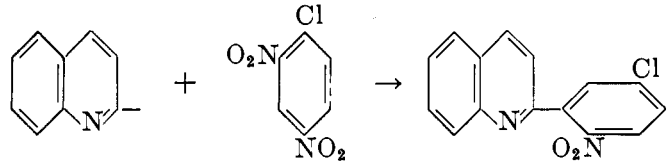
(161, 448). The mechanism assumes the exclusive attack of cyanide ortho to a nitro group; the assumption is open to dispute but is strongly supported by analogy with the reaction of *m*-dinitrobenzene with cyanide (equation 33).

In this connection, it should be recalled that *m*-dinitrobenzene, 1-chloro-2,4-dinitrobenzene, *s*-trinitrobenzene, and 6-nitroquinoline do not undergo cine-substitution in reaction with alcoholic cyanide. These compounds possess more activation than simple mononitrobenzenes and react at lower temperatures at

which there would seem to be insufficient thermal activation for the step in which hydrogen migrates.

Bunnett, Cormack, and McKay (104) have given a complete survey of the von Richter reaction and a detailed consideration of its mechanism.

The reaction (equation 41) of the 2-quinolyl anion (from the decarboxylation of quinaldinic acid) with 1-chloro-2,4-dinitrobenzene to form 2-(2-nitro-5-chlorophenyl)quinoline is remarkably similar to the von Richter reaction (99). With



(41)

m-dinitrobenzene, replacement of hydrogen rather than the nitro group occurs (page 379).

B. REACTIONS OF AMIDE IONS WITH ARYL HALIDES

The condensation of amide and substituted amide ions with aromatic halogen compounds sometimes follows a "normal" course but at other times cine-substitution occurs. The earliest examples are more than half a century old, but the phenomenon did not receive much attention until recent studies in the schools of Gilman and Bergstrom.

Kym (345) in 1894 found that the reaction of *p*-dibromobenzene with *p*-toluidine and soda lime at 350°C. gives some *m*-ditoluidinobenzene. A more extensive early study by Haeusserman (233, 234) showed that *o*-, *m*-, and *p*-dichlorobenzenes all give, on reaction with potassium diphenylamide, the same product, *N,N,N',N'*-tetraphenyl-*m*-phenylenediamine. *p*-Dichlorobenzene also produced some tetraphenyl-*p*-phenylenediamine as a by-product.

The more extensive recent work on this reaction is summarized in table 56. It will be observed that ortho-substituted halobenzenes underwent cine-substitution in all cases, regardless of the electronic nature of the substituent. One can correlate attack meta to an ether linkage with the *o,p*-deactivating effect of alkoxy groups, but it is most surprising that attack occurred meta to groups such as methylsulfonyl and trifluoromethyl which are *o,p*-activating for nucleophilic substitution. There are fewer examples of the reaction of *p*-substituted halobenzenes with amides; in some cases only the "normal" product was isolated, while in others the composition of the product revealed a mixture of normal and cine-substitution. *m*-Substituted halobenzenes have given "normal" substitution exclusively.

With one exception, naphthyl halides give β-naphthylamines preferentially, regardless of the orientation of the starting halide. This contrasts with the formation of α-naphthylamine in the reaction of naphthalene with sodium amide (503). The exception is the reaction of α-fluoronaphthalene with potassium amide to give α-naphthylamine; this is especially interesting, because the same halide gives the cine-product with lithium diethylamide.

TABLE 56

Reactions of aryl halides with metal amides

A. Cine-substitutions

ARYL HALIDE	METAL AMIDE	SOLVENT	PRODUCT AND YIELD	REFERENCE
o-Iodoanisole	$NaNH_2$	NH_3	*m*-Anisidine (33%)	(208)
o-Bromoanisole	$NaNH_2$	NH_3	*m*-Anisidine (33%)	(208)
p-Bromoanisole	$LiN(C_2H_5)_2$	Ether	*N*,*N*-Diethyl-*m*-anisidine (mainly) + *N*,*N*-diethyl-*p*-anisidine (total 34%)	(211)
o-Chloroanisole	$NaNH_2$	NH_3	*m*-Anisidine (57.5%)	(208)
2-Iododiphenyl ether	$NaNH_2$	NH_3	3-Aminodiphenyl ether (22%)	(208)
o-Iodoanisole	$LiN(C_2H_5)_2$	Ether	*N*,*N*-Diethyl-*m*-anisidine	(209)
4-Iododibenzofuran	$NaNH_2$	NH_3	3-Aminodibenzofuran (48%)	(208)
4-Bromodibenzofuran	$NaNH_2$	NH_3	3-Aminodibenzofuran (31%)	(208)
4,6-Diiododibenzofuran	$NaNH_2$	NH_3	3-Amino-6-iododibenzofuran (61%) + 3,6-diaminodibenzofuran (5%)	(208)
4,6-Diiododibenzofuran	$NaNH_2$	NH_3 + ether	3-Aminodibenzofuran (42%)	(208)
4-Iododibenzothiophene	$NaNH_2$	NH_3	3-Aminodibenzothiophene (50%)	(214)
o-Bromothioanisole	$NaNH_2$	NH_3	*m*-Thioanisidine (45%)	(414)
o-Chlorothioanisole	KNH_2	NH_3	*m*-Thioanisidine (35%)	(414)
o-Bromophenyl methyl sulfone	$NaNH_2$	NH_3	*m*-Aminophenyl methyl sulfone (15%)	(414)
o-Bromodimethylaniline	$LiN(C_2H_5)_2$	Ether	*N*,*N*-Dimethyl-*N'*,*N'*-diethyl-*m*-phenylenediamine (29%)	(212)
o-Chlorobenzotrifluoride	$NaNH_2$	NH_3	*m*-Aminobenzotrifluoride (52%)	(38)
p-Bromotetraphenylsilane	$LiN(CH_3)_2$	Ether	*m*-Dimethylaminotetraphenylsilane (15%)	(213)
1-Bromonaphthalene	$LiN(C_2H_5)_2$	Ether	2-Diethylaminonaphthalene (27%)	(209)
1-Chloronaphthalene	$LiN(C_2H_5)_2$	Ether	2-Diethylaminonaphthalene (27%))	(209)
1-Fluoronaphthalene	$LiN(C_2H_5)_2$	Ether	2-Diethylaminonaphthalene (40%)	(209)
1-Chloronaphthalene	KNH_2	NH_3	2-Naphthylamine (45%) + 1-naphthylamine (2%)	(569)

TABLE 56—*Concluded*

A. Cine-substitutions—*Concluded*

ARYL HALIDE	METAL AMIDE	SOLVENT	PRODUCT AND YIELD	REFERENCE
1-Bromonaphthalene....	KNH_2	NH_3	2-Naphthylamine (43%) + 1-naphthylamine (2%)	(569)
1-Iodonaphthalene.....	KNH_2	NH_3	2-Naphthylamine (45%) + 1-naphthylamine (2%)	(569)
1-Chloronaphthalene....	*p*-Toluidine–soda lime		2-*p*-Toluidinonaphthalene	(345)
1-Bromonaphthalene....	Aniline–soda lime		2-Anilinonaphthalene	(345)
o-Chlorotoluene.....	$KN(C_6H_5)_2$	$(C_6H_5)_2NH$	*N*,*N*-Diphenyl-*m*-toluidine	(234)

B. Some related "normal" substitutions

ARYL HALIDE	METAL AMIDE	SOLVENT	PRODUCT AND YIELD	REFERENCE
2-Iododibenzofuran.....	$NaNH_2$	NH_3	2-Aminodibenzofuran (30%)	(208)
2,8-Diiododibenzofuran.	$NaNH_2$	NH_3	2,8-Diaminodibenzofuran (6%)	(208)
2-Chloroquinoline.....	$LiN(CH_3)_2$	Ether	2-Dimethylaminoquinoline (58%)	(209)
1-Fluoronaphthalene....	KNH_2	NH_3	1-Naphthylamine (64%)	(569)
2-Fluoronaphthalene....	KNH_2	NH_3	2-Naphthylamine (11%)	(569)
2-Chloronaphthalene....	KNH_2	NH_3	2-Naphthylamine (49%) + 1-naphthylamine (3%)	(569)
2-Bromonaphthalene....	KNH_2	NH_3	2-Naphthylamine (53%)	(569)
2-Iodonaphthalene.....	KNH_2	NH_3	2-Naphthylamine (48%) + 1-naphthylamine (3%)	(569)
p-Chlorophenetole.....	KNH_2	NH_3	*p*-Phenetidine (41%)	(48)
m-Chlorobenzotrifluoride.....	$NaNH_2$	NH_3	*m*-Aminobenzotrifluoride (35%)	(38)

These appear to be clean-cut cine-substitutions because (*a*) recovered unreacted starting materials retain their original orientation, (*b*) from naphthyl halides sometimes α- and sometimes β-naphthylamine was produced, showing that rearrangement of products did not occur, and (*c*) although dehalogenation sometimes accompanied amination it is not possible to aminate the halogen-free compounds under the conditions used.

C. REACTIONS OF THE CHLOROTOLUENES WITH HYDROXIDE

The three nuclearly chlorinated toluenes each give, on reaction with aqueous caustic at temperatures in the vicinity of 350°C., mixtures of cresols in which

m-cresol always predominates (table 57). Shreve and Marsel (523) were at first inclined to believe that true rearrangement of either chlorotoluene starting material or cresol product was responsible for the change in orientation during these reactions, but concluded that it occurred "during actual hydrolysis." Analysis of recovered unreacted chlorotoluenes "revealed no appreciable rearrangement" and "tests on the cresols themselves showed that they did not isomerize readily."

TABLE 57

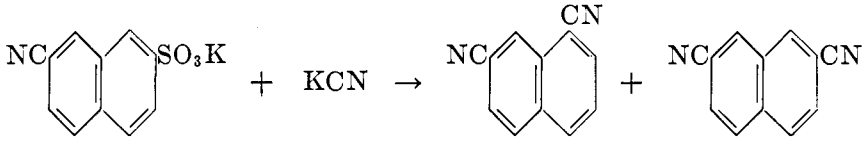
Reactions of chlorotoluenes with sodium hydroxide solution

CHLOROTOLUENE	TEMPERATURE	COMPOSITION OF CRESOLS OBTAINED			REFERENCE
		Ortho	Meta	Para	
	°C.	*per cent*	*per cent*	*per cent*	
Ortho	315–320*		25.3		(423)
	380†		52		(523)
Meta	325†	21	66	13	(523)
Para	315–320*		38.2		(423)
	360†		62		(523)

* Copper powder catalyst used.
† No catalyst used.

D. OTHER CASES OF CINE-SUBSTITUTION

In the course of preparation of some dicyanonaphthalenes by cyanide fusion of cyanonaphthalenesulfonic acids or naphthalenedisulfonic acids, King and Wright (328) encountered two cases of anomalous behavior, which are shown in



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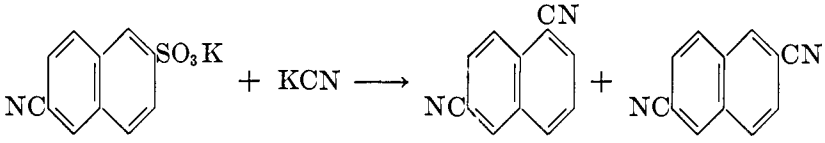
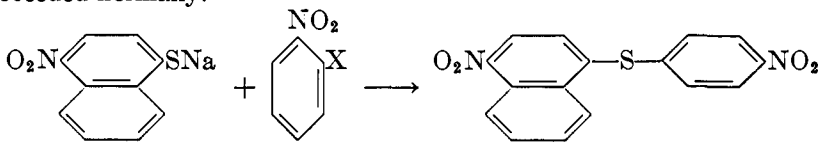


(43)

equations 42 and 43. Other preparations went entirely in the "normal" fashion, as did a number of similar experiments by Bradbrook and Linstead (85). Reactions 42 and 43 appear to qualify as cine-substitutions, for neither sulfonic acids nor nitriles rearrange under the conditions employed and, although desulfonation might occur, replacement of hydrogen by a cyano group under such conditions is unknown.

Hodgson and Leigh (267, 268) encountered cine-substitution in the reaction of some nitrothionaphthols with halonitrobenzenes and halonitronaphthalenes.

Their reactions[7a] are shown in equations 44 and 45; other closely related reactions proceeded normally.



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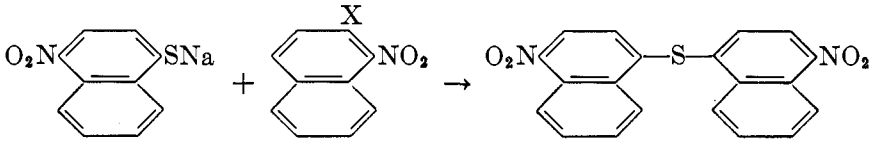

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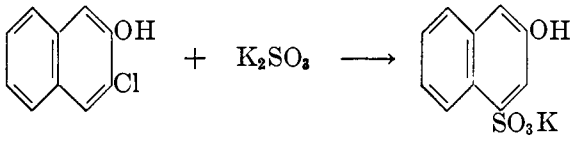
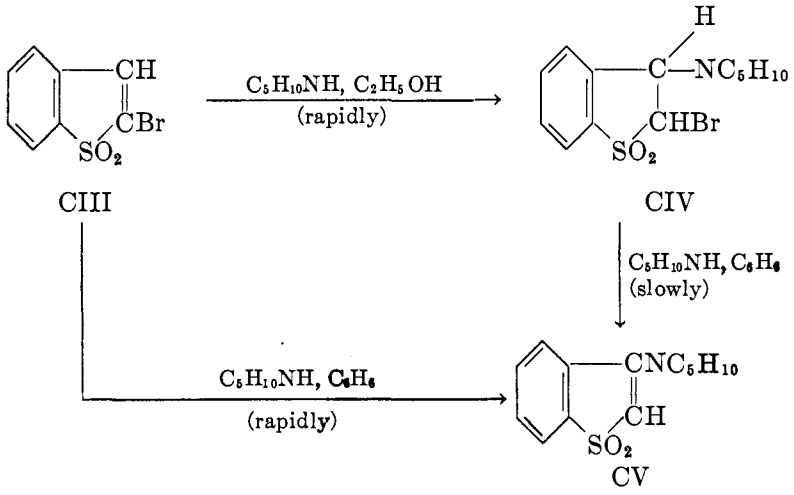
Another case (412) of apparent cine-substitution is shown in equation 46.



(46)

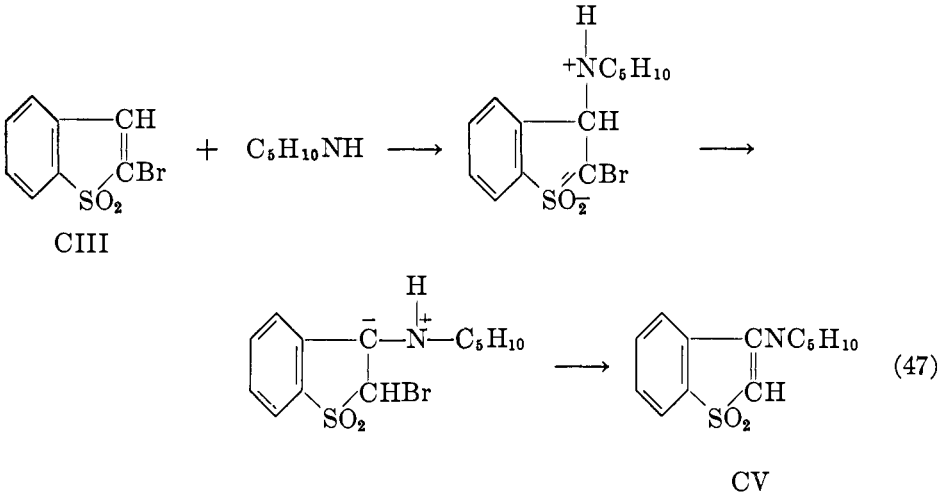
E. RELATED REACTIONS IN ALIPHATIC SYSTEMS

2-Bromothianaphthene-1-dioxide (CIII) reacts with piperidine to form 3-piperidinothianaphthene-1-dioxide (CV). Some of the addition product CIV is



[7a] *Note added in proof:* A recent paper by Lukashevich and Chlenova (619) claims that sodium 4-nitro-1-thionaphthoxide disproportionates to form bis(4-nitro-1-naphthyl) sulfide, m.p. 235–237°C., and that this same product is formed when sodium 4-nitro-1-thionaphthoxide is combined with 2-chloro-1-nitronaphthalene, much of the chloro compound being recovered unchanged. Thus, the product of equation 45 is claimed to be derived entirely from the first reactant. Also, the Russian workers obtained the normal product, 4-nitro-1-naphthyl *o*-nitrophenyl sulfide, from sodium 4-nitro-1-thionaphthoxide and *o*-chloronitrobenzene (*cf.* equation 44). The substance, m.p. 236–238°C., which Hodgson and Leigh obtained in reaction 44 is said to be bis(4-nitro-1-naphthyl) sulfide, and authentic 4-nitro-1-naphthyl *p*-nitrophenyl sulfide is claimed to melt at 147–148.5°C. The latter claim derives support from Hodgson's own work (272); the reaction of sodium *p*-nitrothiophenoxide with 1,4-dinitronaphthalene gave material melting at 152–153°C. In short, there is serious doubt of the validity of equations 44 and 45.

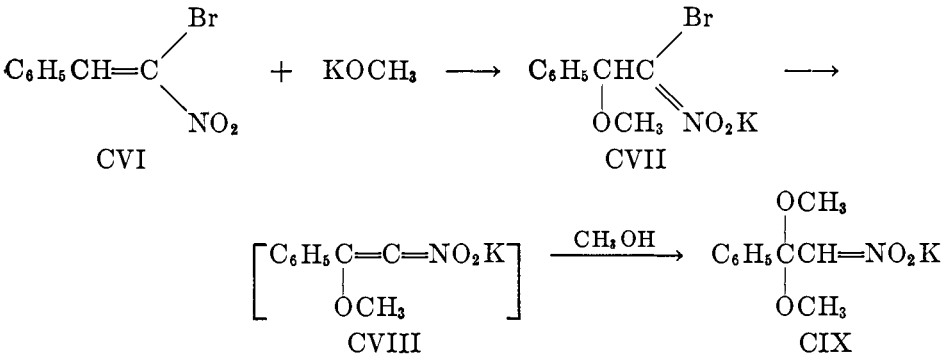
obtained as a by-product, and CIV can be obtained in good yield from the same reactants in alcohol (70). However, *the reaction of adduct CIV with piperidine in benzene to give CV is only one-fifth as fast as the reaction of CIII with piperidine in benzene.* Therefore, CIV cannot be an intermediate in the main reaction producing CV from CIII. It has been suggested by Hayes (249) that a stereoisomer of CIV may be an intermediate in the main reaction in benzene. It is equally possible that the reaction is a genuine cine-substitution, the mechanism of which might be as sketched in equation 47.



CIII CV (47)

The conversion of methyl α-chloroacrylate to methyl β-cyanoacrylate by the action of sodium cyanide (133, 444) is another possible aliphatic cine-substitution. An addition–elimination mechanism has been suggested (443) for it, but the suggestion does not appear to have experimental support.

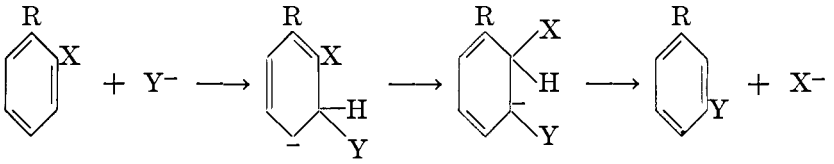
The formation of ω-nitroacetophenone dimethylacetal (CIX) from ω-nitro-ω-bromostyrene (CVI) and potassium methoxide resembles cine-substitution, but has been shown (546) to involve an addition–elimination sequence. The adduct CVII was isolated but CVIII, the dehydrobromination product, was not isolable because it added methanol so rapidly under the conditions employed.



CVI CVII CVIII CIX

F. MECHANISM

A reasonable mechanism has been proposed for the von Richter reaction, but the other instances of cine-substitution seem more mysterious. Their course often shows considerable disregard for the usual activating patterns of substituents. Except for the reactions of Hodgson and Leigh (equations 44 and 45), it is possible to regard every case cited above as the result of occupation by the entering group of a position ortho to that vacated by the displaced group[7b]. Ignoring for the moment the possibility that, for instance, the conversion of *o*-iodoanisole to *m*-anisidine might have involved entry of the amino group par to the position of the halogen, we can sketch the following tentative mechanism:



There is little to say for this mechanism except that it is in agreement with the facts now available and that it accomplishes the necessary hydrogen transfer in a fairly agreeable fashion.

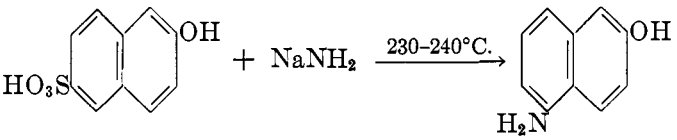
Another mechanism which is possible for all the reactions in this section, with the exception of that of Hodgson and Leigh, is an addition–elimination sequence. This mechanism would accommodate entry of the reagent para to the group which is displaced, if such entry is ever established. There is, however, no experimental support for it.

For the reactions of chlorotoluenes with hot caustic, the S_N1 mechanism needs to be given some consideration. As discussed on page 295, the kinetics of the production of phenol from chlorobenzene and alkali suggest this possibility.

G. DECEPTIVE CASES OF APPARENT CINE-SUBSTITUTION

There are two groups of reactions which appear at first glance to be cine-substitutions but which on closer inspection show symptoms of proceeding through a sequence of the reductive removal of one group, followed by introduction of another in a separate reaction.

Sachs (503) found that fusion of 2-naphthol-6-sulfonic acid with sodium amide



(48)

gave 5-amino-2-naphthol (equation 48). However, the same ingredients at a lower temperature produce only 2-naphthol, and 2-naphthol at 230°C. is aminated

[7b] *Note added in proof:* Benkeser and Buting (615) have recently concluded, from a study of the reaction of sodium amide with *o*-bromoanisoles carrying a third ring substituent, that "the only position taken by the entering group is the one adjacent to the halogen atom and that when this position is already occupied the halogen is not replaced."

to 5-amino-2-naphthol. Sachs's suggestion that 2-naphthol is an intermediate in reaction 48 is sensible, and for the time being the reaction cannot be classed as a cine-substitution. The production of 5-amino-2-naphthol from 2-naphthol-8-sulfonic acid probably represents another sequence of reductive desulfonation followed by amination. Sachs found other naphtholsulfonic acids to give the expected "normal" products.

Fusion of aromatic halogen compounds or sulfonic acids with alkali results in replacement of the halogen atom or sulfo group by a hydroxy group. These reactions were widely used by German chemists in the decade before 1875 in work on the orientation relationships amongst disubstituted benzenes, and their use caused considerable confusion because resorcinol is obtained not only from *m*-halogenated phenols, for instance, but also (along with catechol or hydroquinone) from *o*- and *p*-halogenated phenols. To Fittig and Mager is due credit for first recognizing the ambiguous course of these reactions. These investigators (186, 187) carefully purified both starting materials and products, and showed that *p*-bromophenol gave only one dihydroxybenzene product—namely, resorcinol—while *o*-bromophenol and *m*-bromophenol gave mainly resorcinol and some catechol. Other workers obtained resorcinol from *p*-chlorophenol (178) and from *p*-iodophenol (451) but *o*-iodophenol gave only catechol. None of these early papers reported yields, and most of them suggest that the reported products were accompanied by others not identified.

Fierz-David and Stamm (181) made a more systematic examination of the products from the alkali treatment of 1,4-benzenedisulfonic acid, 4-phenolsulfonic acid, 4-chlorobenzenesulfonic acid, and *p*-chlorophenol. Only fusion of *p*-chlorophenol with sodium hydroxide gave any substantial yield (38 per cent) of resorcinol. The same ingredients autoclaved in an aqueous medium gave only traces of resorcinol, together with much phenol and 2,4′-dihydroxybiphenyl. From the first three compounds under various conditions again only small yields (<5 per cent) of resorcinol were obtained in the presence of greater amounts of phenol.

Classification of these reactions as cine-substitutions is not entirely justified on the basis of evidence presently available. Experiments by Blanksma (62) and Tijmstra (547) show that production of resorcinol from *o*- and *p*-chlorophenol does not occur by rearrangement of these to *m*-chlorophenol or by rearrangement of catechol or hydroquinone to resorcinol. However, it is significant that phenol generally exceeded resorcinol in quantity amongst the products in the experiments of Fierz-David and Stamm, and that phenol may be converted into resorcinol by alkali fusion (26). Present evidence does not allow a decision between proper cine-substitution and desubstitution–resubstitution (*via* phenol) as a mechanism for resorcinol formation.

XI. Related Reactions of Uncertain Mechanism

There are a number of aromatic susbtitution reactions which bear a strong resemblance to those properly within the scope of this review, usually in response to the same sort of activation, but for which other mechanisms are conceivable.

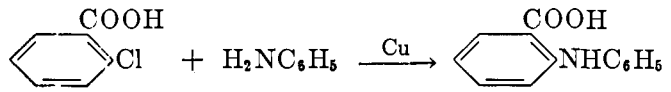
In the following discussion, principal emphasis is placed on the theoretical problems that these reactions present.

A. ULLMANN REACTIONS

Fritz Ullmann discovered two very useful copper-catalyzed reactions of aryl halides, and both bear his name in common usage. Here, main attention is devoted to the copper-catalyzed condensation of aryl halides with common nucleophilic reagents, and less to his biaryl synthesis.

1. Copper-catalyzed condensation of aryl halides with common nucleophilic reagents

Ullmann (559) found in 1903 that *o*-chlorobenzoic acid and copper powder in refluxing aniline give *N*-phenylanthranilic acid (equation 49). Subsequent study (560) showed that pure *o*-chlorobenzoic acid does not react with aniline,



(49)

but that minute quantities of copper salts are sufficient to catalyze the reaction, leading to a very satisfactory yield. Salts of iron, nickel, platinum, and zinc also had some catalytic activity, but manganese and tin salts were ineffective. Performing the reaction in the presence of potassium carbonate gave superior results, because alkali salts of *N*-phenylanthranilic acid are less prone to undergo decarboxylation and because acid-catalyzed resinification reactions are avoided. Additional papers (221, 222, 224, 567) from Ullmann's laboratory showed that a wide variety of anthranilic acids and other diarylamines can be prepared by condensing anilines with *o*-chlorobenzoic acids or other aryl halides, or by employing, for instance, anthranilic acid and bromobenzene. These variations of the synthesis were usually run in refluxing amyl alcohol or nitrobenzene.

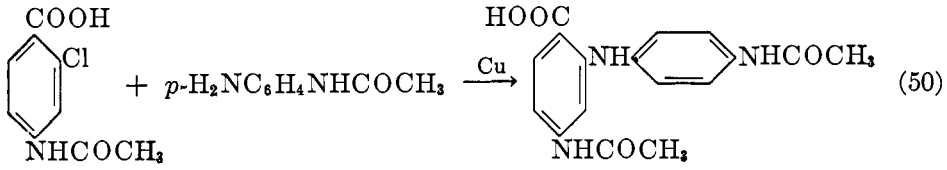
It was soon recognized that copper catalysis facilitates the condensation of unactivated or slightly activated aryl halides with all sorts of nucleophilic reagents. For instance, the reaction of bromobenzene with potassium phenoxide at 200°C. for 12 hr. gives only a trace of diphenyl ether, but the same ingredients with a little copper powder give an 87 per cent yield of diphenyl ether in only 2.5 hr. (566). Copper catalysis of condensations of slightly activated aryl halides with amines, ammonia, phenoxides, alkoxides, and hydroxide has since found wide application in synthetic work.

The Rosenmund–von Braun nitrile synthesis, which involves the condensation of aryl halides with cuprous cyanide, must be regarded as a special case of the Ullmann reaction. Good yields of aromatic nitriles are obtained by means of it, but in the absence of ions of copper (or neighboring metals) scarcely any nitrile is produced from aryl halides and alkali cyanides. The synthesis has been recently reviewed by Mowry (443).

Another interesting variation is the copper-catalyzed condensation of sodium *o*-bromobenzoate with the sodium derivatives of ethyl malonate and similar active methylene compounds (296). Both copper metal and copper acetate were

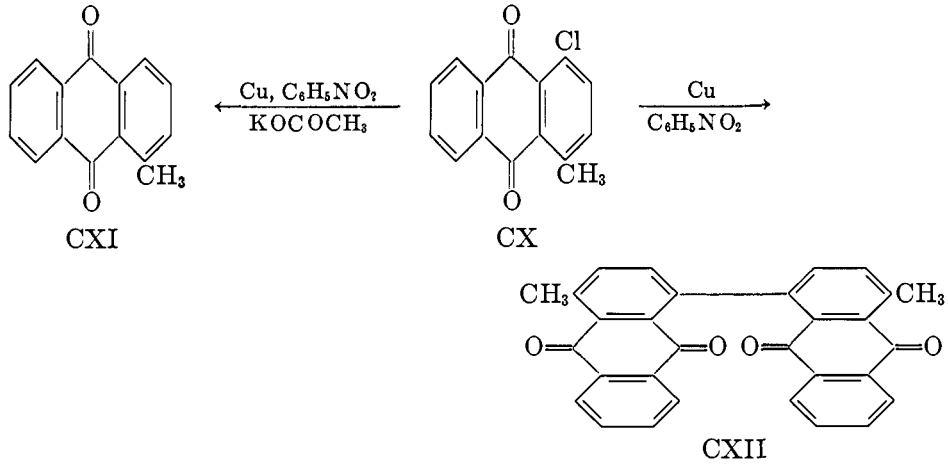
effective; the latter also catalyzed the hydrolysis of *o*-bromobenzoic acid to salicylic acid by only 30 min. boiling in aqueous sodium acetate solution. Strangely, ethyl *o*-bromobenzoate would enter into none of these reactions, nor would *p*-bromobenzoic acid.

Ullmann condensations are frequently accompanied by reductive dehalogenation of the aryl halide. Dehalogenation is strongly dependent both on the extent to which the halogen atom is activated, the more activated halogens being the more sensitive, and on the nature of other substances present in the reaction mixture. For example, 4-acetamido-2-chlorobenzoic acid condenses normally with *p*-aminoacetanilide through a range of reaction temperatures (equation 50), but with *p*-phenylenediamine only reduction occurs at 140°C., the usual reaction temperature (223). However, *p*-phenylenediamine condenses properly



(50)

at 100°C. 1-Chloro-4-methylanthraquinone (CX) refluxed with copper powder in nitrobenzene gives the expected biaryl (CXII); if potassium acetate is also present, no biaryl is formed but 1-methylanthraquinone (CXI) is obtained in good yield (563). This same treatment with copper and potassium acetate



converts 1,2,3,4-tetrachloroanthraquinone into 2,3-dichloroanthraquinone.

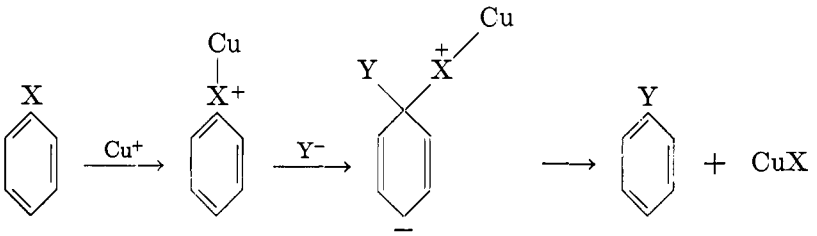
Fusion of 1-chloro-2,4-dinitronaphthalene with benzoic acid and copper powder has been developed (529) as a synthesis of 1,3-dinitronaphthalene (74 per cent yield). The technique has also been applied successfully to the dehalogenation of 1-chloro-2,4-dinitrobenzene and of *o*-chloronitrobenzene, but it fails on *p*-chloronitrobenzene. This, together with the above-mentioned selective removal of the 1- and 4-chlorine atoms from 1,2,3,4-tetrachloroanthraquinone, appears

to indicate that an oxygen-containing group such as nitro, carbonyl, or carboxyl in the ortho position favors dehalogenation.

The real catalysts in Ullmann condensations are probably cuprous compounds. Satisfactory catalysis is obtained by use of copper salts without any of the metal. Furthermore, the metal itself is inactive unless there is also present elemental oxygen (593), the function of which is evidently to oxidize the metal to a salt which possesses catalytic activity. Cuprous iodide is an active catalyst in the presence of potassium iodide, a circumstance in which cupric ions cannot exist (222). This, of course, does not rule out the possibility that cupric ions may also have catalytic activity if they are present.

Potassium iodide in trace amounts greatly increased the yields in the copper-catalyzed condensation of 3-chloro-2-naphthoic acid with chloroanilines (110). It is probable that the potassium iodide operated to maintain the copper compounds in a state of high catalytic activity, and did not of itself interact with the aryl chloride.

The following scheme is a possible formulation of the mechanism of Ullmann condensations:



Representation of the cuprous compound as Cu^+ and of the nucleophilic reagent (Y) as an anion are for purposes of convenience only. This mechanism assigns to the copper catalyst the role of increasing the replaceability of the halogen atom by converting it to an onium condition. This is similar to increasing the replaceability of an amino group by converting it to the quaternary ammonium condition.

An alternative possibility, suggested by Waters (586b), is a free-radical mechanism. Waters' formulation (equation 51) of the generation of free aryl radicals

$$ArCl + Cu^0 \rightarrow Ar\cdot + Cu^+ + Cl^- \qquad (51)$$

is not in accord with Weston and Adkins' (593) observation that the metal itself lacks catalytic activity. However, cuprous compounds conceivably could reduce the aryl halide to a free radical. It is nevertheless difficult to accept a free-radical mechanism, because the copper-catalyzed condensations behave in so many respects similarly to the properly ionic aromatic nucleophilic substitutions that occur in the absence of copper. However, a free-radical mechanism may well pertain to the reductive dehalogenation which often accompanies Ullmann condensations.

The discovery of Rosenmund, Luxat, and Tiedemann (498) that condensation of slightly activated or unactivated aryl halides with alkoxides is accelerated

by ultraviolet radiation, with or without catalysis by copper compounds, is surprising. They found, for instance, that the ultraviolet-irradiated and copper-catalyzed reaction of bromobenzene with sodium isoamoxide in isoamyl alcohol at 128°C. gave, in 6 hr., 76 per cent of the theoretical liberation of bromide ion. Phenyl isoamyl ether was isolated, though in much lower yield. Application of the same technique to the reaction of *p*-chlorobenzoic acid with cuprous cyanide and potassium cyanide gave 70 per cent of terephthalic acid in 8 hr. refluxing in water solution; without irradiation, temperatures above 180°C. are necessary for comparable conversions. However, the ultraviolet-irradiated, copper-catalyzed reaction of 1-bromonaphthalene with sodium isoamoxide gave pure naphthalene in nearly quantitative yield.

Acceleration by ultraviolet irradiation suggests a free-radical mechanism, but it is also conceivable that the aryl halide, in its excited state following absorption of radiation, might react with a nucleophilic reagent to form a transition state such as would be formed in an ionic mechanism.

2. The Ullmann biaryl synthesis[8]

Aryl iodides react with copper powder at elevated temperatures to form biaryls according to equation 52.

$$2\mathrm{ArI} + 2\mathrm{Cu} \rightarrow \mathrm{ArAr} + 2\mathrm{CuI} \tag{52}$$

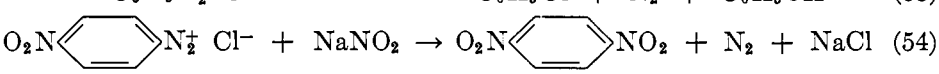
Aryl bromides and chlorides may also be employed, but reaction is very slow unless the halogen is activated by an *o*- or a *p*-nitro group or by other structures with similar electronic characteristics.

Possibilities of both ionic and free-radical mechanisms for the Ullmann biaryl synthesis have been advanced. The ionic mechanisms at some stage involve nucleophilic attack on an aromatic carbon, and if valid would place the synthesis within the field of this review. However, as Fanta (176) has said, the available experimental evidence does not allow a decision on mechanism at present.

B. REPLACEMENTS OF THE DIAZONIUM GROUP

Equations 53, 54, and 55 illustrate reactions bearing a strong formal resemblance to bimolecular aromatic nucleophilic substitution, but regarding the mechanism of which there is great controversy. For detailed information on these reactions, in which the diazonium salt group is eventually replaced by a group

$$\mathrm{C_6H_5N_2^+\ Cl^-} \xrightarrow{\mathrm{H_2O,\ HCl}} \mathrm{C_6H_5Cl} + \mathrm{N_2} + \mathrm{C_6H_5OH} \tag{53}$$



$$\mathrm{O_2N\text{-}C_6H_4\text{-}N_2^+\ Cl^-} + \mathrm{NaNO_2} \rightarrow \mathrm{O_2N\text{-}C_6H_4\text{-}NO_2} + \mathrm{N_2} + \mathrm{NaCl} \tag{54}$$

$$\mathrm{C_6H_5N_2^+\ Cl^-} \xrightarrow{\mathrm{CuCl,\ HCl}} \mathrm{C_6H_5Cl} + \mathrm{N_2} \tag{55}$$

of anionic origin, the reader is referred to the review of Hodgson (262) and the book by Saunders (512c). The present discussion is limited to an outline of the main features of the controversy in its present state.

[8] For further information, the reader is referred to the recent comprehensive review by Fanta (176).

Three principal mechanisms of scission of the carbon–nitrogen bond in diazonium compounds are envisaged: (*1*) Decomposition of the diazonium cation or of some derivative thereof to give an aryl cation; this is the first step of unimolecular aromatic nucleophilic substitution, evidence for which was discussed on page 294. (*2*) Decomposition of the diazonium cation or some derivative thereof to give a phenyl radical; since nitrogen (N_2) is the other product of decomposition, this requires that something else be oxidized. (*3*) Displacement of the diazonium group by nucleophilic attack on the aromatic carbon atom.

Waters (586a) and Saunders (512a) support mechanism 1 for the decomposition of diazonium cations in acid solutions. As discussed on page 294, this is a rational suggestion. It is, however, not clear how generally this mechanism may prevail.

Hodgson (262) favors for a wide range of these replacements mechanism 3, involving bimolecular displacement of the diazonium group. For reactions leading to the introduction of a halogen atom, he advocates mechanism 3 for processes as diverse as the decomposition of diazonium salts in strong hydrochloric acid, the Sandmeyer reaction in its general sense (including catalysis by metal chlorides other than cuprous chloride), and the reaction of sodium benzenediazotate with carbon tetrachloride to give chlorobenzene (271). He believes that covalently bound chlorine is uniquely active in effecting such replacements, whereas chloride ion is ineffective. He also proposes mechanism 3 for the formation of aromatic nitro compounds by the decomposition of neutralized diazonium salts in solutions rich in sodium nitrite (266, 271); in support of this view, he cites the greater yields obtained when there is a nitro group ortho or para to the site of replacement (76 per cent of *p*-dinitrobenzene as compared to 35 per cent of nitrobenzene and 16 per cent of *p*-nitroanisole).

For the Sandmeyer reaction in its narrow sense, concerning only catalysis by cuprous salts, Waters (586a) has proposed the mechanism shown in equations 56 and 57. Here, cuprous chloride first reduces the diazonium ion to an aryl

$$ArN_2^+ + CuCl \rightarrow Ar\cdot + N_2 + Cu^{++} + Cl^- \qquad (56)$$

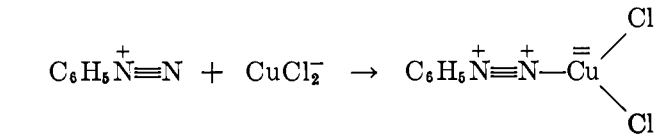
$$Ar\cdot + Cl^- + Cu^{++} \rightarrow ArCl + Cu^+ \qquad (57)$$

free radical, being oxidized to cupric ion in the process. Then the free radical reacts with the cupric ion and a chloride ion, forming an aryl chloride molecule and regenerating a cuprous ion. All this is imagined to occur within a complex between the diazonium cation and cuprous chloride. Waters associates the preëminent catalytic efficiency of cuprous salts with the oxidation potential of the cuprous–cupric couple which, in his view, is just right for the electron transfers in his mechanism.

Cowdrey and Davies (129) have shown, from an extensive kinetic study, that the Sandmeyer reaction of diazonium chlorides with cuprous chloride is of first order with respect to each of the two species ArN_2^+ and $CuCl_2^-$, that the ion $CuCl_4^{--}$ is catalytically inactive, and that para-substituents affect the rate in the following decreasing order: $NO_2 > Cl > H > CH_3 > OCH_3$. They ob-

serve that these kinetics are compatible with three principal mechanisms: (*a*) slow decomposition of a complex $(ArN_2)(CuCl_2)$, which is in mobile equilibrium with the two ions, (*b*) slow formation of a complex of the same formula followed by rapid decomposition into aryl chloride and other products, and (*c*) direct collision of the $CuCl_2^-$ ion with aromatic carbon, leading to straightforward displacement of the diazonium group by a chlorine atom (Hodgson's mechanism).

Cowdrey and Davies observe that if mechanism (*c*) were valid, the $CuCl_4^{--}$ ion should be even more effective than $CuCl_2^-$, and therefore they prefer a coordination mechanism. They formulate formation of the complex as in equation



(58)

58. They prefer mechanism (*b*) of the two which involve a complex, ascribing the accelerating effect of the nitro group to its increasing the positive charge on the terminal nitrogen atom which attacks the negative $CuCl_2^-$ ion. If so, this is puzzling, for in reaction 58 the diazonium ion, though positively charged, acts as a nucleophilic reagent. The alternative mechanism (*a*) is in their opinion disfavored because the *p*-nitro substituent would make the equilibrium concentration of the complex so low that decomposition of the *p*-nitro complex could not conceivably be rapid enough to overcompensate for its reduced concentration and thus drastically increase the overall rate. However, it must be admitted that, if the equilibrium is truly mobile, the magnitude of the equilibrium concentration of the complex is immaterial because the activation energy of the process is the difference between the energy of the separate ions on the one hand and the energy of the transition state for complex decomposition on the other. Thus mechanism (*a*) cannot be so lightly dismissed. The effects of substituents are in accord with a variation of (*a*) in which decomposition occurs by intramolecular nucleophilic displacement of the diazonium group by chlorine.

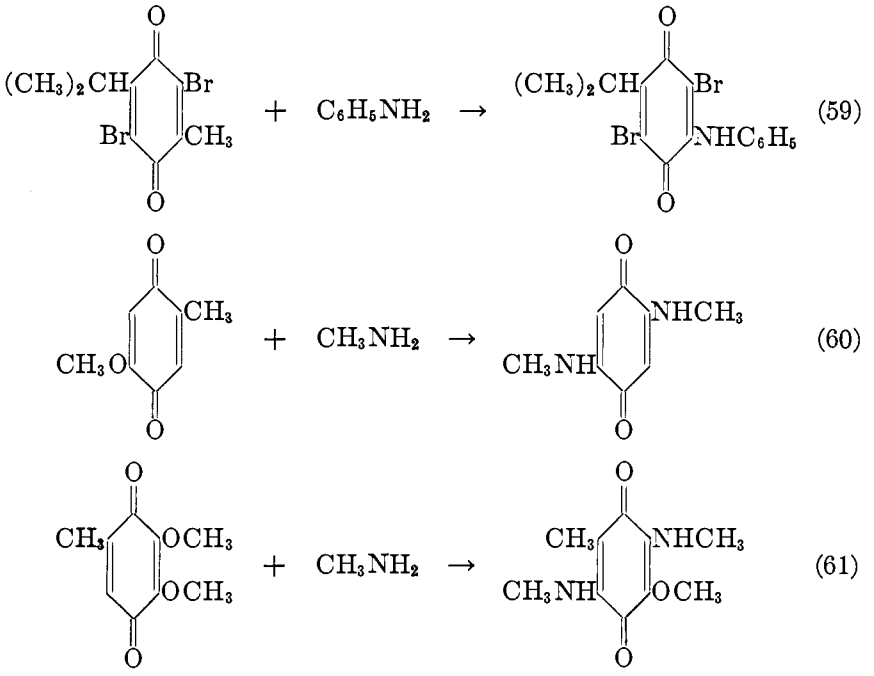
Although Cowdrey and Davies do not favor Waters' mechanism for the Sandmeyer reaction, their kinetics are not incompatible with it and arguments against it must be made on other grounds. For variations of the Sandmeyer reaction employing metal chlorides other than cuprous chloride, variations which their experiments did not touch, Cowdrey and Davies were inclined to accept Hodgson's mechanism.

Thus it does not seem possible to reject in their entirety any of the conflicting theories about these reactions. Clarification of their mechanisms must await further experimental and theoretical consideration.

C. DISPLACEMENT OF ALKYL GROUPS FROM QUINONES

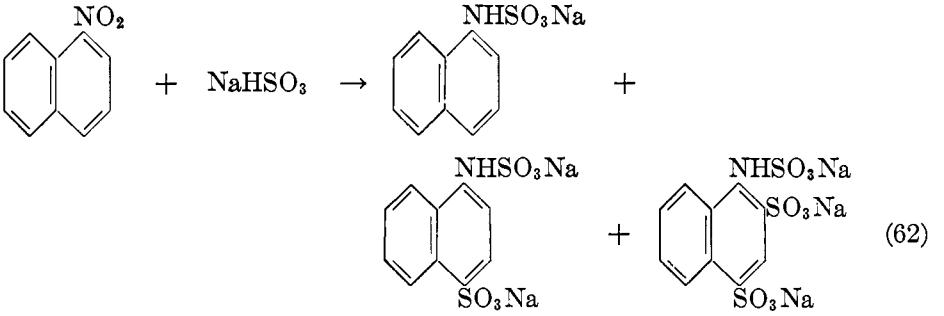
Although this review does not in general concern itself with nucleophilic substitution in quinones, we shall briefly describe two instances (6, 68, 274) in which alkyl groups have been displaced from quinones by amine reagents. Examples are shown in equations 59 and 60; equation 61 shows a very similar

reaction in which the methyl group was not disturbed. No work has been done on the mechanism of these peculiar reactions. They have been briefly discussed by Smith, Arnold, and Nichols (530).



D. THE PIRIA REACTION

Treatment of aromatic nitro compounds with bisulfites produces mixtures of the corresponding amines and their nuclearly-sulfonated derivatives, both in the form of *N*-arylsulfamic acids. Acid hydrolysis liberates the free amines and aminosulfonic acids. For example, 1-nitronaphthalene and sodium bisulfite form (294) the *N*-sulfo derivatives of 1-naphthylamine, naphthionic acid, and 1-aminonaphthalene-2,4-disulfonic acid (equation 62). At one time it was thought that



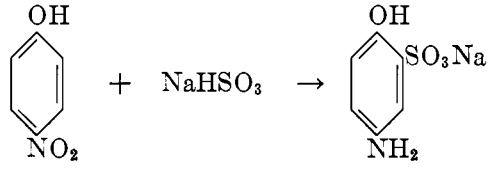
nuclear sulfonation occurred during the acid-catalyzed hydrolytic cleavage of the sulfamic acid groups, but experiments by Hunter and Sprung (295) demon-

strated that *N*-arylsulfamic acids do not rearrange to aminosulfonic acids during hydrolysis by acids under a variety of conditions.

Usually the sulfo group is introduced ortho or para to the amino group. *A priori*, sulfonation might initiate by attack on any of four stages of reduction of the nitro group: on the nitro compound itself, on a nitroso compound, on an arylhydroxylamine, or on the *N*-sulfo amine. Sulfonation initiated by attack on the nitro or nitroso compound would presumably involve nucleophilic attack of bisulfite ions on positions ortho or para to the activating group. Sulfonation initiated at a later stage of reduction would require electrophilic attack in order for the observed orientation to be achieved.

Nucleophilic attack on the nitro compound has been favored by Smith, Arnold, and Nichols (530). Attack on the nitroso compound is at least as plausible, for nitrosobenzene and *p*-nitrosotoluene give, with bisulfite, the same products as the corresponding nitro compounds (356). Disulfonation during the Piria reaction on 1-nitronaphthalene (equation 62) might appear to require attack on both the nitro compound and the resulting nitroso compound, sodium 1-nitroso-4-naphthalenesulfonate. It is, however, conceivable that the arylhydroxylamine resulting from nucleophilic sulfonation of 1-nitrosonaphthalene could be oxidized back to the nitroso stage, which could undergo further sulfonation. The yields of aminosulfonic acids obtained from *p*-nitrobenzoic acid and *m*-dinitrobenzene are significantly higher than from nitrobenzenes substituted with electron-furnishing groups (294); this fact lends support to the nucleophilic sulfonation mechanism.

The Piria reaction on *p*-nitrophenol forms, eventually, 1-amino-4-hydroxybenzene-3-sulfonic acid (equation 63) (356). This entry of the sulfo group ortho to the hydroxy rather than to the nitro group is suggestive of an electrophilic mechanism. Sulfonation ortho to the hydroxy rather than to the nitro group was also observed in the Piria reaction on 5-nitrosalicylic acid.



(63)

Additional work is required to establish the mechanism.

XII. References

(1) Adamson and Billinghurst: J. Chem. Soc. **1950**, 1039.
(2) Allan and Loudon: J. Chem. Soc. **1949**, 821.
(3) Amstutz: J. Am. Chem. Soc. **71**, 3836 (1949).
(4) Andrisano and Casoni: Boll. sci. facoltà chim. ind. Bologna **1943**, No. 1, 1; Chem. Abstracts **41**, 723 (1947).
(5) Angeli and Angelico: Gazz. chim. ital. **31**, I, 27 (1901).
(6) Anslow and Raistrick: J. Chem. Soc. **1939**, 1446.
(7) Austen: Ber. **9**, 621 (1876).
(8) Austen: Ber. **9**, 919 (1876).

(9) AUSTEN AND SMITH: Am. Chem. J. **8,** 89 (1886).
(10) AUTENRIETH AND GEYER: Ber. **41,** 146 (1908).
(11) BACKER AND MOED: Rec. trav. chim. **66,** 689 (1947).
(12) BACKER AND WADMAN: Rec. trav. chim. **68,** 595 (1949).
(13) BACON AND RICHARDSON: J. Chem. Soc. **1932,** 884.
(14) BADDILEY AND TOPHAM: J. Chem. Soc. **1944,** 678.
(15) BADGER, COOK, AND VIDAL: J. Chem. Soc. **1947,** 1109.
(16) BAKER: Trans. Faraday Soc. **37,** 632 (1941).
(17) BAKER AND SMITH: J. Chem. Soc. **1936,** 346.
(18) BALBIANO: Gazz. chim. ital. **11,** 396 (1881).
(19) BANKS: J. Am. Chem. Soc. **66,** 1127 (1944).
(20) BANKS: J. Am. Chem. Soc. **66,** 1131 (1944).
(21) BANKS AND CONTROULIS: J. Am. Chem. Soc. **66,** 944 (1946).
(22) BANKS, GRUHZIT, TILLITSON, AND CONTROULIS: J. Am. Chem. Soc. **66,** 1771 (1944).
(23) BANTLIN: Ber. **11,** 2105 (1878).
(24) BARBER: J. Chem. Soc. **1929,** 2333.
(25) BARBER, WILKINSON, AND EDWARDS: J. Soc. Chem. Ind. **66,** 411 (1947).
(26) BARTH AND SCHREDER: Ber. **12,** 417 (1879).
(27) BARTH AND SCHREDER: Ber. **12,** 503 (1879).
(28) BARTH AND SCHREDER: Monatsh. **3,** 799 (1882).
(29) BASFORD, CURD, AND ROSE: J. Chem. Soc. **1946,** 713.
(30) BATEMAN, CHURCH, HUGHES, INGOLD, AND TAHER: J. Chem. Soc. **1940,** 979.
(31) BAUDET: Rec. trav. chim. **43,** 707 (1924).
(32) BEILSTEIN AND KURBATOW: Ann. **182,** 97 (1876).
(33) BEILSTEIN AND KURBATOW: Ann. **182,** 108 (1876).
(34) BEILSTEIN AND KURBATOW: Ann. **192,** 235 (1878).
(35) BEILSTEIN AND KURBATOW: Ann. **196,** 221 (1879).
(36) BEILSTEIN AND KURBATOW: Ann. **197,** 79 (1879).
(37) BEILSTEIN AND KURBATOW: Ann. **197,** 82 (1879).
(38) BENKESER AND SEVERSON: J. Am. Chem. Soc. **71,** 3838 (1949).
(39) BENNETT: Ann. Repts. Progress Chem. (Chem. Soc. London) **1929,** 132.
(40) BENNETT AND VERNON: J. Chem. Soc. **1938,** 1783.
(41) BENSON AND SAVELL: Chem. Revs. **46,** 45 (1950).
(42) BERCKMANS AND HOLLEMAN: Anales soc. españ. fís. y quím. **23,** 358 (1925); Chem. Abstracts **19,** 2482 (1925).
(43) BERCKMANS AND HOLLEMAN: Rec. trav. chim. **44,** 851 (1925).
(44) BERGSTROM: J. Org. Chem. **2,** 411 (1937).
(45) BERGSTROM: Chem. Revs. **35,** 77 (1944): (a) p. 111; (b) p. 140; (c) p. 189; (d) p. 194; (e) p. 208.
(46) BERGSTROM AND AGOSTINHO: J. Am. Chem. Soc. **67,** 2152 (1945).
(47) BERGSTROM, GRANARA, AND ERICKSON: J. Org. Chem. **7,** 98 (1942).
(48) BERGSTROM AND HORNING: J. Org. Chem. **11,** 334 (1946).
(49) BERGSTROM AND MCALLISTER: J. Am. Chem. Soc. **52,** 2845 (1930).
(50) BERGSTROM, WRIGHT, CHANDLER, AND GILKEY: J. Org. Chem. **1,** 170 (1936).
(51) BERLINER AND MONACK: Private communication (July 25, 1950).
(52) BERLINER, QUINN, AND EDGERTON: J. Am. Chem. Soc. **72,** 5305 (1950).
(53) BERNSTEIN, STEARNS, SHAW, AND LOTT: J. Am. Chem. Soc. **69,** 1151 (1947).
(54) BEVAN, HUGHES, AND INGOLD: Private communication.
(55) BLANKSMA: Beilstein, first supplement, Vol. X, p. 53.
(56) BLANKSMA: Rec. trav. chim. **20,** 399 (1901).
(57) BLANKSMA: Rec. trav. chim. **21,** 419 (1902).
(58) BLANKSMA: Rec. trav. chim. **21,** 424 (1902).
(59) BLANKSMA: Rec. trav. chim. **23,** 113 (1904).
(60) BLANKSMA: Rec. trav. chim. **23,** 119 (1904).

(61) BLANKSMA: Rec. trav. chim. **25**, 174 (1906).
(62) BLANKSMA: Chem. Weekblad **5**, 93 (1908); Chem. Zentr. **1908, I**, 1051.
(63) BLANKSMA: Chem. Weekblad **5**, 789 (1908); Chem. Abstracts **3**, 780 (1909).
(64) BLANKSMA: Rec. trav. chim. **27**, 46 (1908).
(65) BLANKSMA AND SCHREINEMACHERS: Rec. trav. chim. **52**, 428 (1933).
(66) BLAU: Monatsh. **7**, 621 (1886).
(67) BOEHRINGER AND SOEHNE: German patents 269,544 (1914), 284,533 (1915), and 286,266 (1915); quoted in reference 236.
(68) BÖTERS: Ber. **35**, 1502 (1902).
(69) BONNER, JAMES, LOWEN, AND WILLIAMS: Nature **163**, 955 (1949).
(70) BORDWELL, LAMPERT, AND MCKELLIN: J. Am. Chem. Soc. **71**, 1702 (1949).
(71) BORODKIN: Zhur. Priklad. Khim. (J. Applied Chem.) **21**, 987 (1948); Chem. Abstracts **43**, 6175 (1949).
(72) BORROWS, CLAYTON, AND HEMS: J. Chem. Soc. **1949**, S199.
(73) BORROWS, CLAYTON, HEMS, AND LONG: J. Chem. Soc. **1949**, S190.
(74) BORSCHE: Ber. **56**, 1488 (1923).
(75) BORSCHE: Ber. **56**, 1494 (1923).
(76) BORSCHE AND BÖCKER: Ber. **37**, 4388 (1904).
(77) BORSCHE AND EXSS: Ber. **56**, 2353 (1923).
(78) BORSCHE AND FESKE: Ber. **60**, 157 (1927).
(79) BORSCHE, STACKMANN, AND MAKAROFF-SEMLJANSKI: Ber. **49**, 2222 (1916).
(80) BORSCHE AND TRAUTNER: Ann. **447**, 1 (1926).
(81) BOST, TURNER, AND NORTON: J. Am. Chem. Soc. **54**, 1985 (1932).
(82) BOSWELL AND DICKSON: J. Am. Chem. Soc. **40**, 1786 (1918).
(83) BOURGEOIS AND HUBER: Bull. soc. chim. [4] **9**, 944 (1911).
(84) BOYER, SPENCER, AND WRIGHT: Can. J. Research **24B**, 200 (1946).
(85) BRADBROOK AND LINSTEAD: J. Chem. Soc. **1936**, 1739.
(86) BRADLEY: J. Chem. Soc. **1937**, 1091.
(87) BRADLEY AND JADHAV: J. Chem. Soc. **1937**, 1791.
(88) BRADLEY AND ROBINSON: J. Chem. Soc. **1932**, 1254.
(89) BRADLEY AND ROBINSON: J. Chem. Soc. **1934**, 1484.
(90) BRADLOW AND VANDERWERF: J. Org. Chem. **14**, 509 (1949).
(91) BRADY AND BOWMAN: J. Chem. Soc. **119**, 898 (1921).
(92) BRADY AND CROPPER: J. Chem. Soc. **1950**, 507.
(93) BRAND: J. prakt. Chem. [2] **67**, 145 (1903).
(94) BREWIN AND TURNER: J. Chem. Soc. **1928**, 332.
(95) BREWSTER: *Organic Chemistry*, p. 613. Prentice-Hall, Inc., New York (1950).
(96) BROOKER, HESELTINE, VAN LARE, AND VAN ZANDT: Abstracts of Papers presented at the 117th meeting of the American Chemical Society, Philadelphia, Pennsylvania, April, 1950, p. 34L.
(97) BROWN: J. Am. Chem. Soc. **67**, 1452 (1945).
(98) BROWN, BARTHOLOMAY, AND TAYLOR: J. Am. Chem. Soc. **66**, 435 (1944).
(99) BROWN AND HAMMICK: J. Chem. Soc. **1949**, 173.
(100) BROWN AND PEARSALL: J. Am. Chem. Soc. **67**, 1765 (1945).
(101) BRUCE AND PEREZ-MEDINA: J. Am. Chem. Soc. **69**, 2571 (1947).
(102) BUCHMANN AND HAMILTON: J. Am. Chem. Soc. **64**, 1357 (1942).
(103) BÜTTNER: Ber. **36**, 2234 (1903).
(104) BUNNETT, CORMACK, AND MCKAY: J. Org. Chem. **15**, 481 (1950).
(105) BUNNETT, DRAPER, RYASON, NOBLE, TONKYN, AND ZAHLER: Unpublished work.
(106) BUNNETT AND LEVITT: J. Am. Chem. Soc. **70**, 2778 (1948).
(107) BURTON AND KENNER: J. Chem. Soc. **119**, 1047 (1921).
(108) CAIN: Ber. **38**, 2511 (1905).
(109) CAIN AND SCHENKER: Abstracts of Papers presented at the 117th meeting of the American Chemical Society, Philadelphia, Pennsylvania, April, 1950, p. 41L.

(110) CAIRNS AND KERMACK: J. Chem. Soc. **1950**, 1322.
(111) CAMPBELL, ANDERSON, AND GILMORE: J. Chem. Soc. **1940**, 446.
(112) CAMPBELL, DICK, FERGUSON, AND LOUDON: J. Chem. Soc. **1941**, 747.
(113) CARMACK, BULLITT, HANDRICK, KISSINGER, AND VON: J. Am. Chem. Soc. **68**, 1220 (1946).
(114) CATCHPOLE, HUGHES, AND INGOLD: J. Chem. Soc. **1948**, 10.
(115) CHALKLEY: J. Am. Chem. Soc. **51**, 2489 (1929).
(116) CHALLENGER AND COLLINS: J. Chem. Soc. **125**, 1377 (1924).
(117) CHALLENGER AND LIU: Rec. trav. chim. **69**, 334 (1950).
(118) CHAPMAN: J. Chem. Soc. **1930**, 2462.
(119) CHEMISCHE FABRIK GRIESHEIM-ELEKTRON: German patent 120,585; Beilstein, Vol V, p. 556.
(120) CHICHIBABIN: J. Russ. Phys.-Chem. Soc. **55**, 7 (1924); Chem. Abstracts **19**, 1572 (1925).
(121) CHICHIBABIN AND KURSANOVA: J. Russ. Phys.-Chem. Soc. **62**, 1211 (1930); Chem. Abstracts **25**, 2727 (1931).
(122) CHRISTENSEN, GRAHAM, AND TOMISEK: J. Am. Chem. Soc. **68**, 1306 (1946).
(123) CLARK AND BALL: Trans. Roy. Soc. Can. [3] **21**, Sect. 3, 311 (1927).
(124) CLAUS AND SCHALLER: J. prakt. Chem. [2] **56**, 204 (1897).
(125) CLINTON AND SUTER: J. Am. Chem. Soc. **70**, 491 (1948).
(126) COATS AND GIBSON: J. Chem. Soc. **1940**, 442.
(127) COLONNA: Pubbl. inst. chim. univ. Bologna **1943**, No. 2, 3; No. 3, 3; No. 4, 3; No. 5, 3; No. 6, 3; No. 7, 3; Chem. Abstracts **41**, 754 (1947).
(128) COOPER, DHAR, HUGHES, INGOLD, MACNULTY, AND WOOLF: J. Chem. Soc. **1948**, 2043.
(129) COWDREY AND DAVIES: J. Chem. Soc. **1949**, S48.
(130) COWDREY, HUGHES, INGOLD, MASTERMAN, AND SCOTT: J. Chem. Soc. **1937**, 1252.
(131) CRAIG: Private conversation at University College, London.
(132) DE CRAUW: Rec. trav. chim. **50**, 753 (1931).
(133) CRAWFORD, MCLEISH, AND WOOD: U. S. patent 2,293,969 (August 25, 1942); Chem. Abstracts **37**, 2748 (1943).
(134) CROSSLEY, KIENLE, AND BENBROOK: J. Am. Chem. Soc. **62**, 1400 (1940).
(135) CURD, HOGGARTH, LANDQUIST, AND ROSE: J. Chem. Soc. **1948**, 1766.
(136) CURD, LANDQUIST, AND ROSE: J. Chem. Soc. **1947**, 775.
(137) CURD, RAISON, AND ROSE: British patent 592,928 (1947); Chem. Abstracts **42**, 2291 (1948).
(138) CURD, RAISON, AND ROSE: J. Chem. Soc. **1947**, 899.
(139) CUTHBERTSON AND MOFFATT: J. Chem. Soc. **1948**, 561.
(140) CUTLER, SURREY, AND CLOKE: J. Am. Chem. Soc. **71**, 3375 (1949).
(141) DADSWELL AND KENNER: J. Chem. Soc. **1927**, 580.
(142) DAUBEN: J. Am. Chem. Soc. **70**, 2420 (1948).
(143) DAUBEN AND HODGSON: J. Am. Chem. Soc. **72**, 3479 (1950).
(144) DAVIES AND HICKOX: J. Chem. Soc. **121**, 2640 (1922).
(145) DAVIES AND LEEPER: J. Chem. Soc. **1926**, 1413.
(146) DAVIES AND WOOD: J. Chem. Soc. **1928**, 1122.
(147) DEASY: J. Org. Chem. **10**, 141 (1945).
(148) DECKER AND KAUFMANN: J. prakt. Chem. [2] **84**, 425 (1911).
(149) DE DEGIORGI: Anales asoc. quím. argentina **24**, 3 (1936); Chem. Abstracts **30**, 8181 (1936).
(150) DE KOCK: Rec. trav. chim. **20**, 112 (1901).
(151) DESVERGNES: Chimie & industrie **26**, 1271 (1931).
(152) DETAR AND SAGMANLI: J. Am. Chem. Soc. **72**, 965 (1950).
(153) DEY AND DORAISWAMI: J. Indian Chem. Soc. **10**, 309 (1933).
(154) DEY, GOVINDACHARI, AND RAJAGOPALAN: Current Sci. **15**, 161 (1946); Chem. Abstracts **40**, 7174 (1946).

(155) DEY, GOVINDACHARI, AND UDUPA: J. Sci. Ind. Research (India) **4**, 369 (1945); Chem. Abstracts **40**, 6448 (1946).
(156) DEY, GOVINDACHARI, AND UDUPA: J. Sci. Ind. Research (India) **1B**, 25 (1946); Chem. Abstracts **41**, 2407 (1947).
(157) DIECKMANN AND KÄMMERER: Ber. **40**, 3737 (1907).
(158) DIPPY: Chem. Revs. **25**, 183 (1939).
(159) DIRSTINE AND BERGSTROM: J. Org. Chem. **11**, 55 (1946).
(160) DOERING AND PASTERNAK: J. Am. Chem. Soc. **72**, 143 (1950).
(161) DOERING, TAYLOR, AND SCHOENEWALDT: J. Am. Chem. Soc. **70**, 455 (1948).
(162) DOHRN AND DIEDRICH: Ann. **494**, 284 (1932).
(163) DRAKE: *Organic Reactions*, Vol. I, p. 105. John Wiley and Sons, Inc., New York (1942).
(164) DRAKE, CREECH, GARMAN, HAYWOOD, PECK, VAN HOOK, AND WALTON: J. Am. Chem. Soc. **68**, 1208 (1946).
(165) EHRLICH AND BENDA: Ber. **46**, 1931 (1913).
(166) ELDERFIELD, GENSLER, WILLIAMSON, GRIFFING, KUPCHAN, MAYNARD, KREYSA, AND WRIGHT: J. Am. Chem. Soc. **68**, 1584 (1946).
(167) EMERY: Ber. **34**, 4178 (1901).
(168) ENGELHARDT AND LATSCHINOW: J. Russ. Phys.-Chem. Soc. **2**, 118 (1870); Beilstein, Vol. V, pp. 242 and 244.
(169) ENGELHARDT AND LATSCHINOW: Z. Chem. **1870**, 234; Beilstein, Vol. V, p. 265.
(170) EVANS: *The Reactions of Organic Halides in Solution*, p. 67. Manchester University Press, Manchester, England (1946).
(171) EVANS AND SMILES: J. Chem. Soc. **1935**, 181.
(172) EVANS AND SMILES: J. Chem. Soc. **1936**, 329.
(173) FAIRBOURNE AND FAWSON: J. Chem. Soc. **91**, 1942 (1907).
(174) FAIRBOURNE AND FAWSON: J. Chem. Soc. **1927**, 46.
(175) FALCO, HITCHINGS, AND RUSSELL: J. Am. Chem. Soc. **71**, 362 (1949).
(176) FANTA: Chem. Revs. **38**, 139 (1946).
(177) FARR, BARD, AND WHELAND: J. Am. Chem. Soc. **71**, 2013 (1949).
(178) FAUST: Ber. **6**, 1022 (1873).
(179) FEHNEL: J. Am. Chem. Soc. **72**, 1404 (1950).
(180) FEHNEL AND CARMACK: J. Am. Chem. Soc. **72**, 1292 (1950).
(181) FIERZ-DAVID AND STAMM: Helv. Chim. Acta **25**, 364 (1942).
(182) FIESER AND FIESER: *Organic Chemistry*, p. 733. D. C. Heath and Company, Boston, Massachusetts (1944).
(183) FISCHER: Ber. **24**, 3785 (1891).
(184) FISCHER AND HEPP: Ber. **19**, 2991 (1886).
(185) FISCHER AND HEPP: Ber. **20**, 2471 (1887).
(186) FITTIG AND MAGER: Ber. **7**, 1175 (1874).
(187) FITTIG AND MAGER: Ber. **8**, 362 (1875).
(188) FORREST AND WALKER: J. Chem. Soc. **1948**, 1939.
(189) FORSTER AND FIERZ: J. Chem. Soc. **91**, 1942 (1907).
(190) FOX AND TURNER: J. Chem. Soc. **1930**, 1115.
(191) FRANZEN AND BOCKHACKER: Ber. **53**, 1175 (1920).
(192) FREIDLIN, BALANDIN, AND FRIDMAN: Bull. acad. sci. U.R.S.S., Classe sci. chim. **1945**, 655: Chem. Abstracts **40**, 4687 (1946).
(193) FREUND: Ber. **37**, 4666 (1904).
(194) FREUND AND RICHARD: Ber. **42**, 1101 (1909).
(195) FRIEDLAENDER AND OSTERMAIER: Ber. **15**, 332 (1882).
(196) FRIES: Ann. **454**, 159 (1927); Beilstein, second supplement, Vol V, p. 303.
(197) FRIES AND NOLL: Ann. **389**, 371 (1912); Beilstein, first supplement, Vol. V, p. 188.
(198) FROMM AND MARTIN: Ann. **401**, 177 (1913).
(199) FUSON, ARMSTRONG, AND SPECK: J. Org. Chem. **7**, 297 (1942).
(200) FUSON AND GAERTNER: J. Org. Chem. **13**, 496 (1948).

(201) FUSON, GAERTNER, AND CHADWICK: J. Org. Chem. **13**, 489 (1948).
(202) FUSON AND SPECK: J. Am. Chem. Soc. **64**, 2446 (1942).
(203) GABRIEL: Ber. **19**, 2354 (1886).
(204) GABRIEL: Ber. **34**, 3363 (1901).
(205) GAERTNER: Chem. Revs. **45**, 493 (1949).
(206) GALBRAITH AND SMILES: J. Chem. Soc. **1935**, 1234.
(207) GEIGY AND COMPANY: German patents 91,818 and 198,909; Beilstein, Vol. VII, pp. 237 and 238.
(208) GILMAN AND AVAKIAN: J. Am. Chem. Soc. **67**, 349 (1945).
(209) GILMAN, CROUNSE, MASSIE, BENKESER, AND SPATZ: J. Am. Chem. Soc. **67**, 2106 (1945).
(210) GILMAN AND GAINER: J. Am. Chem. Soc. **69**, 877 (1947).
(211) GILMAN AND KYLE: J. Am. Chem. Soc. **70**, 3945 (1948).
(212) GILMAN, KYLE, AND BENKESER: J. Am. Chem. Soc. **68**, 143 (1946).
(213) GILMAN AND MELVIN: J. Am. Chem. Soc. **72**, 995 (1950).
(214) GILMAN AND NOBIS: J. Am. Chem. Soc. **67**, 1479 (1945).
(215) GILMAN AND SHIRLEY: J. Am. Chem. Soc. **72**, 2181 (1950).
(216) GILMAN AND SPATZ: J. Am. Chem. Soc. **63**, 1553 (1941).
(217) GILMAN AND SPATZ: J. Am. Chem. Soc. **66**, 621 (1944).
(218) GIUA AND RUGGERI: Gazz. chim. ital. **53**, 290 (1923).
(219) GIUA AND RUGGERI: Gazz. chim. ital. **53**, 341 (1923).
(220) GODFREY AND LEWIS: Abstracts of Papers presented at the 115th Meeting of the American Chemical Society, San Francisco, California, April, 1949, p. 62-O.
(221) GOLDBERG: Ber. **39**, 1691 (1906).
(222) GOLDBERG: Ber. 40, 4541 (1907).
(223) GOLDBERG AND KELLEY: J. Chem. Soc. **1946**, 102.
(224) GOLDBERG AND NIMEROVSKY: Ber. **40**, 2448 (1907).
(225) GOMBERG: Ber. **35**, 2403 (1902).
(226) GOMBERG: Ber. **42**, 406 (1909).
(227) GOTTLIEB: J. Am. Chem. Soc. **58**, 532 (1936).
(228) GOULEY, MOERSCH, AND MOSHER: J. Am. Chem. Soc. **69**, 303 (1947).
(229) GRAHAM, HUGHES, AND INGOLD: Private communication.
(230) GROHMANN: Ber. **23**, 3445 (1890).
(231) GROHMANN: Ber. **24**, 3808 (1891).
(232) GROVES, TURNER, AND SHARP: J. Chem. Soc. **1929**, 512.
(233) HAEUSSERMANN: Ber. **33**, 939 (1900).
(234) HAEUSSERMANN: Ber. **34**, 38 (1901).
(235) HAITINGER AND LIEBEN: Monatsh. **6**, 319 (1885).
(236) HALE AND BRITTON: Ind. Eng. Chem. **20**, 114 (1928).
(237) HALL: J. Am. Chem. Soc. **52**, 5115 (1930).
(238) HALL AND SPRINKLE: J. Am. Chem. Soc. **54**, 3469 (1932).
(239) HAMILTON AND MORGAN: *Organic Reactions*, Vol. II, p. 431. John Wiley and Sons, Inc., New York (1944).
(240) HAMMETT: *Physical Organic Chemistry*, p. 189. McGraw-Hill Book Company, Inc., New York (1940).
(241) HANTZSCH: Ber. **30**, 2334 (1897).
(242) HANTZSCH AND HIRSCH: Ber. **29**, 947 (1896).
(243) HANTZSCH AND KISSEL: Ber. **32**, 3137 (1899).
(244) HANTZSCH AND SMYTHE: Ber. **33**, 505 (1900).
(245) HARRINGTON AND BARGER: Biochem. J. **21**, 169 (1927).
(246) HASS, FEUER, AND HARBAN: J. Am. Chem. Soc. **72**, 2282 (1950).
(247) HAUSER AND WEISS: J. Org. Chem. **14**, 310 (1949).
(248) HAWORTH AND ROBINSON: J. Chem. Soc. **1948**, 777.
(249) HAYES: Footnote to reference 70.

(250) HECKMANN: Ann. **220**, 128 (1883).
(251) HEIM: Ber. **16**, 1771 (1883).
(252) HENLEY AND TURNER: J. Chem. Soc. **1930**, 928.
(253) HENRIQUES: Ann. **215**, 339 (1882).
(254) HEPP: Ann. **215**, 352 (1882).
(255) HEPP: Ann. **215**, 361 (1882).
(256) HERTEL AND LÜHRMANN: Z. Elektrochem. **45**, 405 (1939).
(257) DEN HERTOG: Rec. trav. chim. **67**, 381 (1948).
(258) DEN HERTOG, FALTER, AND VAN DER LINDE: Rec. trav. chim. **67**, 377 (1948).
(259) DEN HERTOG, SCHOGT, DE BRUYN, AND DE KLERK: Rec. trav. chim. **69**, 673 (1950).
(260) VAN HETEREN: Rec. trav. chim. **20**, 107 (1901).
(261) HIRSCH: Ber. **31**, 1253 (1898).
(262) HODGSON: Chem. Revs. **40**, 251 (1947).
(263) HODGSON AND HABESHAW: J. Chem. Soc. **1942**, 45.
(264) HODGSON AND HANDLEY: J. Chem. Soc. **1926**, 542.
(265) HODGSON AND HANDLEY: J. Soc. Chem. Ind. **46**, 435-T (1927).
(266) HODGSON, HEYWORTH, AND WARD: J. Chem. Soc. **1948**, 1512.
(267) HODGSON AND LEIGH: J. Chem. Soc. **1938**, 1031.
(268) HODGSON AND LEIGH: J. Chem. Soc. **1939**, 1094.
(269) HODGSON AND MOORE: J. Chem. Soc. **1927**, 630.
(270) HODGSON AND SMITH: J. Chem. Soc. **1933**, 500.
(271) HODGSON AND WARD: J. Chem. Soc. **1948**, 556.
(272) HODGSON AND WARD: J. Chem. Soc. **1948**, 2017.
(273) HODGSON AND WILSON: J. Chem. Soc. **127**, 440 (1925).
(274) HOFFMANN: Ber. **34**, 1558 (1901).
(275) HOGGARTH: J. Chem. Soc. **1949**, 3311.
(276) HOLLEMAN: Proc. K. Akad. Wetensch. Amsterdam **6**, 659 (1904); Brit. Chem. Abstracts **86**, i, 486 (1904).
(277) HOLLEMAN: Rec. trav. chim. **24**, 194 (1905).
(278) HOLLEMAN: Rec. trav. chim. **39**, 435 (1920).
(279) HOLLEMAN AND BEEKMAN: Proc. K. Akad. Wetensch. Amsterdam **6**, 327 (1903); Brit. Chem. Abstracts **86**, i, 232 (1904).
(280) HOLLEMAN AND BEEKMAN: Rec. trav. chim. **23**, 253 (1904).
(281) HOLLEMAN AND VAN HAEFTEN: Rec. trav. chim. **40**, 67 (1921).
(282) HOLLEMAN AND DEN HOLLANDER: Rec. trav. chim. **39**, 435 (1920).
(283) HOLLEMAN, DE MOOY, AND TER WEEL: Rec. trav. chim. **35**, 1 (1915).
(284) HOLMES AND LOUDON: J. Chem. Soc. **1940**, 1521.
(285) HORNING AND BERGSTROM: J. Am. Chem. Soc. **67**, 2110 (1945).
(286) VAN HOVE: Bull. sci. acad. roy. Belg. [5] **12**, 801 (1926).
(287) VAN HOVE: Bull. sci. acad. roy. Belg. [5] **13**, 206 (1927); Chem. Zentr. **1927**, II, 51.
(288) HÜCKEL AND HAVEKOSS: Ber. **62**, 2041 (1929).
(289) HÜFFER: Rec. trav. chim. **40**, 451 (1921).
(290) HUGHES: Trans. Faraday Soc. **37**, 603 (1941).
(291) HUGHES AND INGOLD: J. Chem. Soc. **1941**, 608.
(292) HUGHES, INGOLD, AND REED: J. Chem. Soc. **1950**, 2400.
(293) HUISGEN: Ann. **559**, 101 (1948).
(294) HUNTER AND SPRUNG: J. Am. Chem. Soc. **53**, 1432 (1931).
(295) HUNTER AND SPRUNG: J. Am. Chem. Soc. **53**, 1443 (1931).
(296) HURTLEY: J. Chem. Soc. **1929**, 1870.
(297) IBBOTSON AND KENNER: J. Chem. Soc. **123**, 1260 (1923).
(298) ILLUMINATI AND GILMAN: J. Am. Chem. Soc. **71**, 3349 (1949).
(299) INGHAM AND HAMPSON: J. Chem. Soc. **1939**, 981.
(300) INGOLD: J. chim. phys. **45**, 159 (1948).
(301) JACKSON AND BOOS: Am. Chem. J. **20**, 444 (1898).

(302) JACKSON AND CALHANE: Am. Chem. J. **28,** 456 (1902).
(303) JACKSON AND CALHANE: Am. Chem. J. **28,** 472 (1902).
(304) JACKSON AND FISKE: Am. Chem. J. **30,** 53 (1903).
(305) JACKSON AND ITTNER: Am. Chem. J. **19,** 199 (1897).
(306) JACKSON AND WARREN: Am. Chem. J. **15,** 607 (1893).
(307) JACKSON AND WARREN: Am. Chem. J. **16,** 28 (1894).
(308) JACKSON AND WARREN: Am. Chem. J. **16,** 33 (1894).
(309) JAMES AND TURNER: J. Chem. Soc. **1950,** 1515.
(310) JAMISON AND TURNER: J. Chem. Soc. **1937,** 1954.
(311) JOHNSON AND MACKENZIE: Am. Chem. J. **42,** 353 (1909).
(312) KADESCH: J. Am. Chem. Soc. **66,** 1207 (1944).
(313) KADESCH AND WELLER: J. Am. Chem. Soc. **63,** 1310 (1941).
(314) VAN DER KAM: Rec. trav. chim. **45,** 564 (1926).
(315) KAUFMANN AND ALBERTINI: Ber. **42,** 2004 (1909).
(316) KAUFMANN AND ALBERTINI: Ber. **42,** 3776 (1909).
(317) KAUFMANN AND ALBERTINI: Ber. **44,** 2052 (1911).
(318) KEHRMANN AND BAUER: Ber. **29,** 2362 (1896).
(319) KENEFORD, MORLEY, SIMPSON, AND WRIGHT: J. Chem. Soc. **1950,** 1104.
(320) KENNER: J. Chem. Soc. **105,** 2717 (1914).
(321) KENNER AND PARKIN: J. Chem. Soc. **117,** 852 (1920).
(322) KENNER, TOD, AND WITHAM: J. Chem. Soc. **119,** 1700 (1921).
(323) KENNER, TOD, AND WITHAM: J. Chem. Soc. **127,** 2343 (1925).
(324) KENT AND SMILES: J. Chem. Soc. **1934,** 422.
(325) KENYON, WIESNER, AND KWARTLER: Ind. Eng. Chem. **41,** 654 (1949).
(326) KING AND KING: J. Chem. Soc. **1947,** 726.
(327) KING, KING, AND MUIR: J. Chem. Soc. **1946,** 5.
(328) KING AND WRIGHT: J. Chem. Soc. **1939,** 253.
(329) KLEIN AND SPOERRI: J. Am. Chem. Soc. **72,** 1844 (1950).
(330) KLINGSBERG: J. Am. Chem. Soc. **72,** 1031 (1950).
(331) KOENIGS AND GREINER: Ber. **64,** 1049 (1931).
(332) KOENIGS AND JUNG: J. prakt. Chem. **137,** 157 (1933).
(333) KÖRNER: Gazz. chim ital. **4,** 305 (1874).
(334) KÖRNER AND CONTARDI: Atti accad. Lincei [5] **15, I,** 526 (1906); Brit. Chem. Abstracts **90,** i, 641.
(335) KÖRNER AND CONTARDI: Atti accad. Lincei [5] **22, II,** 626 (1913).
(336) KÖRNER AND CONTARDI: Atti accad. Lincei [5] **22, II,** 632 (1913).
(337) KÖRNER AND CONTARDI: Atti accad. Lincei [5] **23, I,** 283 (1914).
(338) KOHN AND GRAUER: Monatsh. **34,** 1751 (1913).
(339) KRAAY: Rec. trav. chim. **49,** 1082 (1930).
(340) KREMS AND SPOERRI: Chem. Revs. **40,** 330 (1947).
(341) KRÖHNKE AND SCHMEISS: Ber. **70,** 1728 (1937).
(342) KRYUGER AND BEDNOVA: J. Gen. Chem. (U.S.S.R.) **3,** 67 (1933).
(343) KUDERNATSCH: Monatsh. **18,** 613 (1897).
(344) KYM: Ber. **32,** 3539 (1899).
(345) KYM: J. prakt. Chem. [2] **51,** 325 (1894).
(346) KYM AND RATNER: Ber. **45,** 3238 (1912).
(347) LA COSTE: Ann. **208,** 9 (1881).
(348) VAN DE LANDE: Rec. trav. chim. **51,** 98 (1932).
(349) DE LANGE: Rec. trav. chim. **38,** 101 (1919).
(350) LANGE, ROUSH, AND ASBECK: J. Am. Chem. Soc. **52,** 3696 (1930).
(351) LANGE AND SHEIBLEY: J. Am. Chem. Soc. **55,** 1188 (1933).
(352) LAUBENHEIMER: Ber. **7,** 1600 (1874).
(353) LAUBENHEIMER: Ber. **11,** 1155 (1878).
(354) LAUBENHEIMER: Ber. **11,** 1159 (1878).
(355) LAUBENHEIMER: Ber. **15,** 597 (1882).

(356) LAUER, SPRUNG, AND LANGKAMMERER: J. Am. Chem. Soc. **58**, 225 (1936).
(357) LE FEVRE: J. Chem. Soc. **1931**, 810.
(358) LE FEVRE, SAUNDERS, AND TURNER: J. Chem. Soc. **1927**, 1168.
(359) LE FEVRE AND TURNER: J. Chem. Soc. **1927**, 1113.
(360) LEFFLER: *Organic Reactions*, Vol. I, p. 91. John Wiley and Sons, Inc., New York (1942).
(361) LEIS AND CURRAN: J. Am. Chem. Soc. **67**, 79 (1945).
(362) LEONARD: Chem. Revs. **37**, 269 (1945).
(363) LEONARD AND CURTIN: J. Org. Chem. **11**, 349 (1946).
(364) LE ROUX, LU, SUGDEN, AND THOMSON: J. Chem. Soc. **1945**, 586.
(365) LEVI AND SMILES: J. Chem. Soc. **1932**, 1488.
(366) LEVI, WARREN, AND SMILES: J. Chem. Soc. **1933**, 1490.
(367) LEVY, RAINS, AND SMILES: J. Chem. Soc. **1931**, 3264.
(368) LEWIS AND SEABORG: J. Am. Chem. Soc. **62**, 2122 (1940).
(369) LEYMANN: Ber. **15**, 1233 (1882).
(369a) LINKE: Ber. **56**, 848 (1923).
(370) LIPPMANN AND FLEISSNER: Monatsh. **4**, 788 (1883).
(371) LIVINGSTON AND LOUDON: J. Chem. Soc. **1937**, 246.
(372) LOBRY DE BRUYN: Rec. trav. chim. **2**, 205 (1883).
(373) LOBRY DE BRUYN: Rec. trav. chim. **2**, 210 (1883).
(374) LOBRY DE BRUYN: Rec. trav. chim. **9**, 190 (1890).
(375) LOBRY DE BRUYN: Rec. trav. chim. **9**, 193 (1890).
(376) LOBRY DE BRUYN: Ber. **24**, 3749 (1891).
(377) LOBRY DE BRUYN: Rec. trav. chim. **13**, 101 (1894).
(378) LOBRY DE BRUYN: Rec. trav. chim. **23**, 47 (1904).
(379) LOBRY DE BRUYN AND BLANKSMA: Rec. trav. chim. **20**, 115 (1901).
(380) LOBRY DE BRUYN AND VAN GEUNS: Rec. trav. chim. **23**, 26 (1904).
(381) LOBRY DE BRUYN AND VAN LEENT: Rec. trav. chim. **14**, 150 (1895).
(382) LOBRY DE BRUYN AND VAN LEENT: Rec. trav. chim. **15**, 84 (1896).
(383) LOBRY DE BRUYN AND STEGER: Rec. trav. chim. **18**, 41 (1899).
(384) LONGUET-HIGGINS: Nature **166**, 139 (1950).
(385) LONGUET-HIGGINS AND COULSON: J. Chem. Soc. **1949**, 971.
(386) LORANG: Rec. trav. chim. **46**, 891 (1927).
(387) LOUDON: J. Chem. Soc. **1935**, 537.
(388) LOUDON: J. Chem. Soc. **1936**, 218.
(389) LOUDON: J. Chem. Soc. **1939**, 902.
(390) LOUDON: J. Chem. Soc. **1940**, 1525.
(391) LOUDON, ROBERTSON, WATSON, AND AITON: J. Chem. Soc. **1950**, 55.
(392) LOUDON AND ROBSON: J. Chem. Soc. **1937**, 242.
(393) LOUDON AND SHULMAN: J. Chem. Soc. **1938**, 1618.
(394) LOUDON AND SHULMAN: J. Chem. Soc. **1941**, 722.
(395) LUCAS, KENNEDY, AND WILMOT: J. Am. Chem. Soc. **58**, 157 (1936).
(396) LÜTGERT: Ber. **70**, 151 (1937).
(397) LULOFS: Rec. trav. chim. **20**, 292 (1901).[9]
(398) LUTHY, BERGSTROM, AND MOSHER: J. Org. Chem. **14**, 322 (1949).
(399) MACBETH AND PRICE: J. Chem. Soc. **1937**, 982.
(400) MACLEOD, PFUND, AND KILPATRICK: J. Am. Chem. Soc. **44**, 2260 (1922).
(401) MAGIDSON AND GRIGOROVSKI: Ber. **66**, 866 (1933).
(402) MANGINI: Gazz. chim. ital. **66**, 675 (1936).
(403) MANGINI AND CASONI: Boll. sci. facoltà chim. ind. univ. Bologna **3**, 173 (1942); Chem. Abstracts **38**, 4916 (1944).
(404) MANGINI AND COLONNA: Gazz. chim. ital. **68**, 543 (1938).

[9] Rate coefficients given in reference 397 must be divided by 2, since the expression used to calculate them was incorrect; *cf.* Lorang (386) and Talen (542).

(405) MANGINI AND COLONNA: Gazz. chim. ital. **73**, 313 (1943).
(406) MANGINI AND FRENGUELLI: Gazz. chim. ital. **67**, 358 (1937).
(407) MANGINI AND FRENGUELLI: Gazz. chim. ital. **69**, 86 (1939).
(408) MARCINKOW AND PLAZEK: Roczniki Chem. **16**, 395 (1936).
(409) MARCKWALD AND MEYER: Ber. **33**, 1885 (1900).
(410) DE LA MARE: Thesis, University of London, 1948.
(411) MARIELLA AND KVINGE: J. Am. Chem. Soc. **70**, 3126 (1948).
(412) MARSCHALK: Bull. soc. chim. [4] **45**, 651 (1929).
(413) MARSHALL AND ACREE: Am. Chem. J. **49**, 127 (1913).
(414) MARTIN: Iowa State Coll. J. Sci. **21**, 38 (1946); Chem. Abstracts **41**, 952 (1947).
(415) MATSUKAWA AND OHTA: J. Pharm. Soc. Japan **69**, 489 (1949); Chem. Abstracts **44**, 3455 (1950).
(416) MATTAAR: Rec. trav. chim. **41**, 103 (1922).
(417) MCBEE, BOLT, GRAHAM, AND TEBBE: J. Am. Chem. Soc. **69**, 947 (1947).
(418) MCCLEMENT AND SMILES: J. Chem. Soc. **1937**, 1016.
(419) MCCORMACK AND STOCKMAN: Ind. Eng. Chem. **31**, 278 (1939).
(420) MCKEE, MCKEE, AND BOST: J. Am. Chem. Soc. **68**, 1904 (1946).
(421) MCLEISH AND CAMPBELL: J. Chem. Soc. **1937**, 1103.
(422) MCMASTER AND MAGILL: J. Am. Chem. Soc. **50**, 3038 (1928).
(423) MEHARG AND ALLEN: J. Am. Chem. Soc. **54**, 2920 (1932).
(424) MEISENHEIMER: Ann. **323**, 205 (1902).
(425) MEISENHEIMER AND PATZIG: Ber. **39**, 2533 (1906).
(426) MELANDER: Arkiv för Kemi **2**, 211 (1950).
(427) MELDOLA AND STEPHENS: J. Chem. Soc. **87**, 1199 (1905).
(428) MEYER: Monatsh. **36**, 723 (1915).
(429) MEYER AND BERGIUS: Ber. **47**, 3155 (1914).
(430) MEYER AND WURSTER: Ber. **5**, 632 (1872).
(431) MIGRDICHIAN: *The Chemistry of Organic Cyanogen Compounds*, Chap. 7. Reinhold Publishing Corporation, New York (1947).
(432) MILLER, KNIGHT, AND ROE: J. Am. Chem. Soc. **72**, 4765 (1950).
(433) MILLER AND WRIGHTSON: Abstracts of Papers presented at the 112th meeting of the American Chemical Society, New York, N. Y., September, 1947, p. 16J.
(434) MOELWYN-HUGHES: *The Kinetics of Reactions in Solution*, 2nd edition. Oxford University Press, Oxford and London (1947).
(435) MOELWYN-HUGHES AND JOHNSON: Trans. Faraday Soc. **36**, 948 (1940).
(436) DE MONTMOLLIN AND DE MONTMOLLIN: Helv. Chim. Acta **6**, 94 (1923).
(437) MORGAN AND CHALLENOR: J. Chem. Soc. **119**, 1537 (1921).
(438) MORGAN AND DREW: J. Chem. Soc. **117**, 784 (1920).
(438a) MORGAN AND GLOVER: J. Chem. Soc. **119**, 1700 (1921).
(439) MORGAN AND JONES: J. Chem. Soc. **119**, 187 (1921).
(440) MORLEY AND SIMPSON: J. Chem. Soc. **1949**, 1014.
(441) MORTON: Chem. Revs. **35**, 32 (1944).
(442) MOSHER: In Elderfield's *Heterocyclic Compounds*, Vol. 1, John Wiley and Sons, Inc., New York (1950): (a) p. 397; (b) p. 425.
(443) MOWRY: Chem. Revs. **42**, 189 (1948): (a) p. 203; (b) p. 207.
(444) MOWRY AND ROSSOW: J. Am. Chem. Soc. **67**, 927 (1945).
(445) MÜLLER AND WEISBROD: J. prakt. Chem. [2] **113**, 30 (1926).
(446) MUNCH, THANNHAUSER, AND COTTLE: J. Am. Chem. Soc. **68**, 1297 (1946).
(447) NAGORNOFF: J. russ. chem. Ges. **29**, 699; Brit. Chem. Abstracts **76**, i, 425 (1899).
(448) NEVILLE: J. Am. Chem. Soc. **70**, 3499 (1948).
(449) NIETZKI AND KONWALDT: Ber. **37**, 3893 (1904).
(450) NOELTING, GRANDMOUGIN, AND MICHEL: Ber. **25**, 3328 (1892).
(451) NÖLTING AND STRICKER: Ber. **20**, 3018 (1887).
(452) OGATA AND OKANO: J. Am. Chem. Soc. **71**, 3211 (1949).

(453) OGATA AND OKANO: J. Am. Chem. Soc. **71**, 3212 (1949).
(454) VAN OPSTALL: Rec. trav. chim. **52**, 901 (1933).
(455) PARYS: Rec. trav. chim. **48**, 560 (1929).
(456) PERNA: J. Russ. Phys.-Chem. Soc. **35**, 114 (1903); Brit. Chem. Abstracts **84**, i, 406 (1903).
(457) PETRENKO-KRICHENKO: Ber. **62**, 581 (1929).
(458) PLOQUIN: Compt. rend. **226**, 339 (1948); Chem. Abstracts **42**, 4462 (1948).
(459) PRICE AND STACY: J. Am. Chem. Soc. **68**, 498 (1946).
(460) PRICE AND VOONG: Org. Syntheses **28**, 80 (1948).
(461) PULLMAN, RUMPF, AND KIEFFER: J. chim. phys. **45**, 150 (1948).
(462) QUICK: J. Am. Chem. Soc. **42**, 1033 (1920).
(463) RAIFORD AND COLBERT: J. Am. Chem. Soc. **48**, 2652 (1926).
(464) RARICK, BREWSTER, AND DAINS: J. Am. Chem. Soc. **55**, 1289 (1933).
(465) REINDERS AND RINGER: Rec. trav. chim. **18**, 326 (1899).
(466) REITSEMA: Chem. Revs. **43**, 63 (1948).
(467) REMICK: *Electronic Interpretations of Organic Chemistry*, 2nd edition, John Wiley and Sons, Inc., New York (1949): (a) p. 77.
(468) RENFREW: J. Am. Chem. Soc. **68**, 1433 (1946).
(469) REVERDIN: Org. Syntheses **7**, 28 (1927).
(470) RHEINLANDER: J. Chem. Soc. **123**, 3099 (1923).[10]
(471) RICHARDSON: J. Chem. Soc. **1926**, 522.
(472) RICHTER: Ber. **44**, 3472 (1911).
(473) VON RICHTER: Ber. **4**, 21 (1871).
(474) VON RICHTER: Ber. **4**, 459 (1871).
(475) VON RICHTER: Ber. **4**, 553 (1871).
(476) VON RICHTER: Ber. **8**, 1418 (1875).
(477) VON RICHTER: Ber. **21**, 2470 (1888).
(478) RICHTZENHAIN: Ber. **77**, 1 (1944).
(479) RICHTZENHAIN AND NIPPUS: Ber. **77**, 566 (1944).
(480) RICHTZENHAIN AND NIPPUS: Ber. **82**, 408 (1949).
(481) VAN RIJN: Rec. trav. chim. **45**, 259 (1926).
(482) RIKLIS: J. Gen. Chem. (U.S.S.R.) **15**, 825 (1945).
(483) RIKLIS: J. Gen. Chem. (U.S.S.R.) **17**, 1511 (1947).
(484) RINGER: Rec. trav. chim. **18**, 330 (1899).
(485) ROBERTS: J. Chem. Soc. **1932**, 2358.
(486) ROBERTS AND CLARK: J. Chem. Soc. **1935**, 1312.
(487) ROBERTS AND RHYS: J. Chem. Soc. **1937**, 39.
(488) ROBERTS, WEBB, AND MCELHILL: J. Am. Chem. Soc. **72**, 408 (1950).
(489) ROBERTS AND DE WORMS: J. Chem. Soc. **1934**, 727.
(490) ROBERTS AND DE WORMS: J. Chem. Soc. **1935**, 1309.
(491) ROBERTS, DE WORMS, AND CLARK: J. Chem. Soc. **1935**, 196.
(492) VAN ROMBURGH: Rec. trav. chim. **2**, 35 (1883).
(493) VAN ROMBURGH: Rec. trav. chim. **2**, 103 (1883).
(494) VAN ROMBURGH: Rec. trav. chim. **4**, 189 (1885).
(495) VAN ROMBURGH AND WENSINK: Verslag. K. Acad. Wetenschappen **23**, 966 (1914); Chem. Abstracts **9**, 1175 (1915).
(496) ROSENMUND: Ber. **54**, 438 (1921).
(497) ROSENMUND AND HARMS: Ber. **53**, 2226 (1920).
(498) ROSENMUND, LUXAT, AND TIEDEMANN: Ber. **56**, 1950 (1923).
(499) ROUCHE: Bull. sci. acad. roy. Belg. **1921**, 534.
(500) ROWLETT AND LUTZ: J. Am. Chem. Soc. **68**, 1288 (1946).

[10] Rate coefficients given in reference 470 must be multiplied by 6.67 if they are to be expressed in liters $mole^{-1}$ $min.^{-1}$

(501) RUNGE: *Organo-Metallverbindungen*, p. 531. Wissenschaftliche Verlagsgesellschaft m.b.H., Stuttgart (1944).
(502) RUSSELL, ELION, FALCO, AND HITCHINGS: J. Am. Chem. Soc. **71**, 2279 (1949).
(503) SACHS: Ber. **39**, 3006 (1906).
(504) SALKIND: Ber. **64**, 289 (1931).
(505) SALKOWSKI: Ann. **174**, 257 (1874).
(506) SANDIN AND BROWN: J. Am. Chem. Soc. **69**, 2253 (1947).
(507) SANDIN, CHRISTIANSEN, BROWN, AND KIRKWOOD: J. Am. Chem. Soc. **69**, 1550 (1947).
(508) SANDIN AND LISKEAR: J. Am. Chem. Soc. **57**, 1304 (1935).
(509) SANE AND JOSHI: J. Chem. Soc. **125**, 2481 (1924).
(510) SANGER: Biochem. J. **39**, 507 (1945).
(511) SARGENT AND SMALL: J. Org. Chem. **11**, 359 (1946).
(512) SAUNDERS: *The Aromatic Diazo Compounds and Their Technical Applications*, 2nd edition, Edward Arnold and Company, London (1949): (a) p. 108; (b) p. 117; (c) p. 275.
(513) SCHIEMANN AND ROSELIUS: Ber. **64**, 1336 (1931).
(514) SCHIFF: Monatsh. **11**, 329 (1890).
(515) SCHMIDT AND LADNER: Ber. **37**, 4402 (1904).
(516) SCHMIDT AND WAGNER: Ann. **387**, 164 (1912).
(517) SCHÖPFF: Ber. **22**, 903 (1889).
(518) SCHÖPFF: Ber. **22**, 3281 (1889).
(519) SCHÖPFF: Ber. **23**, 3440 (1890).
(520) SCHÖPFF: Ber. **24**, 3771 (1891).
(521) SEELIG: Ann. **237**, 140 (1887).
(522) SEN: J. Indian Chem. Soc. **23**, 383 (1946).
(523) SHREVE AND MARSEL: Ind. Eng. Chem. **38**, 254 (1946).
(524) SIDGWICK: *The Chemical Elements and their Compounds*, p. 766. Oxford University Press, Oxford and London (1950).
(525) SINGH AND PEACOCK: J. Chem. Soc. **1935**, 1410.
(526) SINGH AND PEACOCK: J. Chem. Soc. **1935**, 1411.
(527) SINGH AND PEACOCK: J. Phys. Chem. **40**, 669 (1936).
(528) SKRAUP: Monatsh. **10**, 726 (1889).
(529) SMITH: J. Am. Chem. Soc. **71**, 2855 (1949).
(530) SMITH, ARNOLD, AND NICHOLS: J. Am. Chem. Soc. **65**, 2131 (1943).
(531) SPITZER AND WHELAND: J. Am. Chem. Soc. **62**, 2995 (1940)
(532) SPRUNG: J. Am. Chem. Soc. **52**, 1650 (1930).
(533) STAEDEL: Ann. **217**, 170 (1883); Beilstein, Vol. VI, p. 415.
(534) STEGER: Rec. trav. chim. **18**, 13 (1899).[11]
(535) STEVENS, PFISTER, AND WOLF: J. Am. Chem. Soc. **68**, 1035 (1946).
(536) SUTER: *The Organic Chemistry of Sulfur*, John Wiley and Sons, Inc., New York (1944): (a) p. 362; (b) p. 420; (c) p. 670.
(537) SUTER AND SCRUTCHFIELD: J. Org. Chem. **1**, 189 (1936).
(538) SWARTS: Bull. acad. roy. Belg. **1913**, 241; Chem. Abstracts **8**, 680 (1914).
(539) SWARTS: Rec. trav. chim. **35**, 154 (1915).
(540) SWEET, CALKINS, AND BANKS: J. Am. Chem. Soc. **69**, 2260 (1947).
(541) TADROS AND LATIF: J. Chem. Soc. **1949**, 3337.
(542) TALEN: Rec. trav. chim. **47**, 329 (1928).
(543) TALEN: Rec. trav. chim. **47**, 782 (1928).
(544) TARBELL, BUNNETT, CARLIN, AND WYSTRACH: J. Am. Chem. Soc. **67**, 1582 (1945).
(545) THEOBALD AND SCHOFIELD: Chem. Revs. **46**, 171 (1950).
(546) THIELE AND HAECKEL: Ann. **325**, 1 (1902).

[11] Rate coefficients given in reference 534 must be divided by 2, since the expression used to calculate them was incorrect, just as in reference 397; *cf.* footnote 9.

(547) TIJMSTRA: Chem. Weekblad **5**, 96 (1908); Chem. Zentr. **1908, I**, 1051.
(548) TISCHCHENKO AND CHURBAKOV: J. Applied Chem. (U.S.S.R.) **7**, 764 (1934); Chem. Abstracts **29**, 2520 (1935).
(549) TODD AND SHRINER: J. Am. Chem. Soc. **56**, 1382 (1934).
(550) TOMISEK AND CHRISTENSEN: J. Am. Chem. Soc. **67**, 2112 (1945).
(551) TOPCHIEV: Compt. rend. acad. sci. U.R.S.S. [N.S.] **4**, 201 (1935); Brit. Chem. Abstracts **1936A**, 838.
(552) TOZER AND SMILES: J. Chem. Soc. **1938**, 1897.
(553) TOZER AND SMILES: J. Chem. Soc. **1938**, 2052.
(554) TRÖGER AND MEINECKE: J. prakt. Chem. **106**, 203 (1923).
(555) TRONOV AND KRYUGER: J. Russ. Phys.-Chem. Soc. **58**, 1270 (1926).
(556) TSCHITSCHIBABIN: Ber. **56**, 1879 (1923).
(557) TWISS: J. Chem. Soc. **105**, 1672 (1914).
(558) UHLEMANN: Ber. **11**, 1162 (1878).
(559) ULLMANN: Ber. **36**, 2382 (1903).
(560) ULLMANN: Ann. **355**, 312 (1907).
(561) ULLMANN AND BRUCK: Ber. **41**, 3932 (1908).
(562) ULLMANN, ENGI, WOSNESSENSKY, KUHN, AND HERRE: Ann. **366**, 79 (1909).
(563) ULLMANN AND MINAJEFF: Ber. **45**, 687 (1912).
(564) ULLMANN AND NADAI: Ber. **41**, 1870 (1908).
(565) ULLMANN AND PASDERMADJIAN: Ber. **34**, 1150 (1901).
(566) ULLMANN AND SPONAGEL: Ber. **38**, 2211 (1905).
(567) ULLMANN AND WAGNER: Ann. **355**, 359 (1907).
(568) UNGNADE: Chem. Revs. **38**, 405 (1946).
(569) URNER AND BERGSTROM: J. Am. Chem. Soc. **67**, 2108 (1945).
(570) VAUGHAN: Chem. Revs. **43**, 447 (1948).
(571) VERMEULEN: Rev. trav. chim. **25**, 14 (1906).
(572) VAN DE VLIET: Rec. trav. chim. **43**, 606 (1924).
(573) VOMPE AND TURITSYNA: Doklady Akad. Nauk S.S.S.R. **64**, 341 (1949); Chem. Abstracts **43**, 4671 (1949).
(574) VONGERICHTEN: Ber. **32**, 2571 (1899).
(575) VORLÄNDER: Ber. **70**, 146 (1937).
(576) VORLÄNDER AND SPRECKELS: Ber. **52**, 309 (1919).
(577) VOROZHTSOV AND KOBELEV: J. Gen. Chem. (U.S.S.R.) **4**, 310 (1934).
(578) VOROZHTSOV AND KOBELEV: J. Gen. Chem. (U.S.S.R.) **9**, 1465 (1939); Chem. Abstracts **34**, 2688 (1940).
(579) VOROZHTSOV, KOZLOV, AND TRAVKIN: J. Gen. Chem. (U.S.S.R.) **9**, 522 (1939); Chem. Abstracts **34**, 410 (1940).
(580) VOROZHTSOV AND SHEMYAKIN: Ber. **69**, 148 (1936).
(581) WALKER: J. Chem. Soc. **1947**, 1552.
(582) WARREN AND SMILES: J. Chem. Soc. **1931**, 914.
(583) WARREN AND SMILES: J. Chem. Soc. **1931**, 2207.
(584) WARREN AND SMILES: J. Chem. Soc. **1932**, 1040.
(585) WATERS: J. Chem. Soc. **1942**, 266.
(586) WATERS: *The Chemistry of Free Radicals*, 2nd edition, Oxford University Press, Oxford and London (1948); (a) p. 162; (b) p. 171.
(587) WATERS: *Physical Aspects of Organic Chemistry*, 4th edition, p. 492. Routledge and Kegan Paul, Ltd., London (1950).
(588) WATSON: Ann. Repts. Progress Chem. (Chem. Soc. London) **36**, 197 (1939).
(589) WEDEKIND: Ber. **33**, 426 (1900).
(590) WEIDEL AND BLAU: Monatsh. **6**, 651 (1885).
(591) WENDER: Gazz. chim. ital. **19**, 234 (1889).
(592) WENZEL: Monatsh. **15**, 453 (1894).
(593) WESTON AND ADKINS: J. Am. Chem. Soc. **50**, 859 (1928).

(594) WHALLEY: J. Chem. Soc. **1950**, 2241.
(595) WHEELER AND LIDDLE: Am. Chem. J. **40**, 557 (1908).
(596) WHELAND: *The Theory of Resonance*, John Wiley and Sons, Inc., New York (1944): (a) p. 133; (b) p. 256; (c) p. 259; (d) p. 269; (e) p. 272.
(597) WHELAND: *Advanced Organic Chemistry*, 2nd edition, p. 378. John Wiley and Sons, Inc., New York (1949).
(598) WIBAUT AND BROEKMAN: Rec. trav. chim. **58**, 885 (1939).
(599) WIGHT AND SMILES: J. Chem. Soc. **1935**, 340.
(600) WILLGERODT: Ber. **9**, 977 (1876).
(601) WILLGERODT: Ber. **15**, 1002 (1882).
(602) WIZINGER AND COENEN: J. prakt. Chem. [2] **153**, 127 (1939).
(603) WOHL: Ber. **32**, 3486 (1899).
(604) WOHL: Ber. **36**, 4135 (1903).
(605) WOHL: Ber. **39**, 1951 (1906).
(606) WOHL AND AUE: Ber. **34**, 2442 (1901).
(607) WOLF, BEUTEL, AND STEVENS: J. Am. Chem. Soc. **70**, 4264 (1948).
(608) WRIGHT AND BERGSTROM: J. Org. Chem. **1**, 179 (1936).
(609) ZAKI AND FAHIM: J. Chem. Soc. **1942**, 270.
(610) ZIEGLER AND ZEISER: Ber. **63**, 1847 (1930).
(611) ZIEGLER AND ZEISER: Ann. **485**, 174 (1931).
(612) ZINCKE: Ber. **7**, 1502 (1874).
(613) ZINCKE, HEUSER, AND MÖLLER: Ann. **333**, 296 (1904).
(614) ZINCKE AND WEISPFENNIG: J. prakt. Chem. [2] **82**, 1 (1910).

References added in proof

(615) BENKESER AND BUTING: Abstracts of Papers presented at the 119th meeting of the American Chemical Society, Cleveland, Ohio, April, 1951, p. 73M.
(616) GILMAN AND BEEL: J. Am. Chem. Soc. **73**, 774 (1951).
(617) GOLD, J.: Chem. Soc. **1951**, 1430.
(618) ITAI: J. Pharm. Soc. Japan **65**, No. 9/10A, 8 (1945); Chem. Abstracts **45**, 5688 (1951).
(619) LUKASHEVICH AND CHLENOVA: Doklady Akad. Nauk S.S.S.R. **73**, 711 (1950); Chem. Abstracts **45**, 1565 (1951).
(620) OCHIAI, ISHIKAWA, AND KATADA: J. Pharm. Soc. Japan **63**, 307 (1943); Chem. Abstracts **45**, 5153 (1951).
(621) OCHIAI AND KATADA: J. Pharm. Soc. Japan **63**, 265 (1943); Chem. Abstracts **45**, 5152 (1951).