THE CHEMISTRY OF THE DIARYL ETHERS

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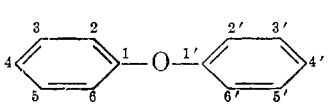
I. INTRODUCTION

The discussion of diphenyl ethers in this review is limited to those compounds in which two carbocyclic aromatic rings are linked by one oxygen atom. Special emphasis is given to the reactions which are peculiar to such compounds. Other nuclei—carbocyclic or heterocyclic—are regarded as substituents, whether they are fused with one of the "ether" rings or not. Natural products which belong to this category are not specifically treated, unless their reactions are of more general significance to the whole group of compounds.

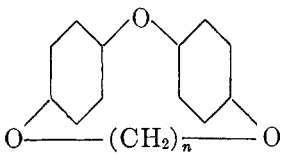
The compounds mentioned are named as derivatives of diphenyl ether when this system is practical; otherwise they are considered as phenoxy derivatives of the appropriate compounds. In *Chemical Abstracts* derivatives are listed under the heading "phenyl ether." For clarity and to avoid ambiguity the prefix di- is retained in the present review. This practice is useful in a discussion of substituted diphenyl ethers, since alkyl phenyl ethers are not the same as alkyldiphenyl ethers. The position of substituents is denoted in the literature by the use of *o*-, *m*-, *p*-, *o'*-, *m'*-, *p'*- and by the following numbering system:



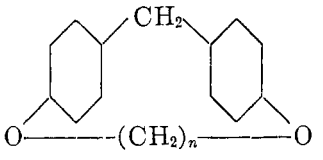
II. THE OXYGEN VALENCE ANGLE

Since oxygen can take the place of methylene and imino groups in cyclic compounds without appreciable change in the stability, strain, and ease of formation of the compounds involved, its valence angle must be similar in magnitude to the tetrahedral angle (178). Reasonably accurate methods give a value of 105° for the oxygen valence angle in water (110, 190). The angle is probably somewhat larger in dialkyl ethers, and apparently variable in size (90a). The determination of the oxygen valence angle in diphenyl ethers from studies of dipole moments has led to divergent values: e.g., 119° or 152° (31), 121° ± 5° (252), 110° (110), 128° ± 4° (265), and 142° ± 8° (111). The method is not free from criticism (131), and the results can be regarded only as approximations. X-ray crystal structure data for *p,p'*-diiododiphenyl ether give a valence angle of 118° ± 3° (31).

Lüttringhaus obtained evidence indicative of an angle larger than the tetrahedral angle by comparing the yield curves of the polycyclic systems I and II from the respective ω-bromoalkyl ethers.

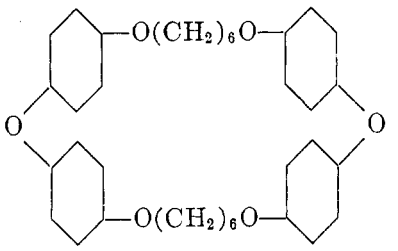


I



II

For $n = 10$ the yields of I and II were 36 and 68 per cent, respectively; for $n = 8$, 0 and 27 per cent; whereas for $n = 6$ the 34-membered ring system (III) was formed.



III

The difference between the valence angles of carbon and oxygen is further indicated by the formation of well-defined eutectics by diphenyl ether and diphenylmethane, their *p,p'*-dihydroxy compounds, and the decamethylene ethers (I and II). When the angles are forced to assume the same (or very nearly the same) value, as in fluorene and dibenzofuran, a continuous system of mixed crystals is observed (178) instead of eutectics.

III. DIPHENYL ETHER

Diphenyl ether was prepared in 1845 by List and Limpricht (172) by the dry distillation of copper benzoate. The product was shown to be a mixture of

diphenyl ether and diphenyl by Hoffmeister (128), who was the first to isolate the pure substance by separating this mixture. The ether was also prepared by the reaction of benzenediazonium sulfate with phenol (126, 127, 128). The yields were poor in either case. Thus, 5 lb. of copper benzoate gave only 30 g. of purified diphenyl ether. The product was apparently quite pure, since later workers have not succeeded in raising the melting point even after laborious purification (54). Improved yields of diphenyl ether from benzenediazonium chloride were claimed by Hirsch (124, 125), but his claims have not been entirely substantiated (276).

Gladstone and Tribe (89) prepared the ether by the dry distillation of aluminum phenoxide. The direct dehydration of phenol over aluminum chloride or zinc chloride at 350°C. gives only a very small amount of diphenyl ether (191, 211). The yields can be substantially increased when thorium dioxide is used as a catalyst. Sabatier and Mailhe obtained a 50 per cent yield of diphenyl ether in this manner in the temperature range of 390–450°C. (235), while later workers were able to raise the yield to 64 per cent (37). The reaction is reversible, and the optimum temperature is 450°C. (37).

Diphenyl ether is obtained among other products from the destructive distillation of calcium phenyl salicylate (136). It is formed in good yield (40–50 per cent) when a mixture of sodium benzenesulfonate and potassium phenoxide is distilled (204).

The best laboratory method for the preparation of diphenyl ether is due to Ullmann and Stein (284), who discovered in 1905 that copper (301) catalyzes the reaction between alkali phenoxides and aryl halides. The wide applicability of this method has made possible the synthesis of the majority of the compounds described in the following.

Diphenyl ether is available in commercial quantities as a by-product of the manufacture of phenol by the hydrolysis of chlorobenzene with aqueous sodium hydroxide (18, 192) or sodium carbonate (107) under pressure at elevated temperatures (Dow Process). The reaction is catalyzed by copper (107). The formation of diphenyl ether by this process is reversible (105, 105a) and can be restrained by adding the ether to the reaction mixture (106, 108).

The use of diphenyl ether as a heat-transfer medium is due to its extraordinary heat stability. A eutectic mixture of 73.5 per cent of diphenyl ether and 26.5 per cent of diphenyl (Dowtherm A) (290) and a eutectic mixture of 85 per cent of diphenyl ether and 15 per cent of naphthalene (Dowtherm B) are recommended for this purpose in the temperature range of 230–400°C. (119).

Pyrolysis of diphenyl ether at red heat causes mainly dehydrogenation to dibenzofuran (97, 193, 198). The by-products are benzene, phenol, carbon monoxide, carbon dioxide, hydrogen, methane, and ethane (198). When the pyrolysis is carried out in an autoclave at 500–550°C. (60 atm.), 65 per cent remains unchanged after 5 hr. The remainder of the reaction mixture consists of resin, gaseous material, some phenol, and a trace of benzene (133). Pyrolysis at 500°C. under 100 atm. of hydrogen yields benzene, phenol, and water (206).

Under moderate conditions the hydrogenation of diphenyl ether in the presence of nickel catalysts gives some dicyclohexyl ether (14–42 per cent) (2). More

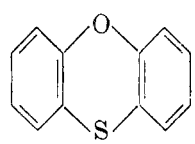
drastic conditions (150–250°C.) favor the formation of cyclohexane and cyclohexanol (134, 152, 188, 206). At 500°C. (100 atm.) the main products are methane, cyclopentane, and methylcyclopentane (206). Cyclohexane and cyclohexanol are obtained as chief reduction products when reduced copper is used as a catalyst (80–150 atm., 200–220°C.) (153), whereas the hydrogenation over molybdenum sulfide at 350°C. gives benzene, cyclohexane, and phenol (194).

Diphenyl ether is unaffected by hydriodic acid at 250°C. (133) and by heating with zinc dust (126, 133). It is stable toward oxidizing agents such as chromium trioxide in acetic acid (126), but in the animal organism (rabbit) it is converted to 4-hydroxydiphenyl ether (257).

Diphenyl ether forms a crystalline complex $((C_6H_5)_2O \cdot AlX_3)_2$ with aluminum chloride and aluminum bromide (150).

The ether linkage is cleaved slowly by heating diphenyl ether with dilute but not with concentrated sodium hydroxide solution at 300°C. (192), with aqueous sodium carbonate (105a), or with aqueous sodium phenoxide solution under pressure (105), or by fusing with potassium hydroxide at 300°C. (4). The product in each case is phenol or a phenoxide. A 50 per cent yield of phenol is obtained in $4\frac{1}{2}$ days by treating diphenyl ether with sodium in liquid ammonia (249). The reaction is quantitative when 2 atom-equivalents of sodium are added to 1 mole-equivalent of the ether in liquid ammonia (240). Cleavage can also be effected by boiling 1 mole of diphenyl ether with 2–3 atom-equivalents of sodium, potassium, or lithium in 4–6 moles of dry pyridine in a current of nitrogen (212), or by shaking the ether with sodium potassium alloy in benzene solution at room temperature (196). Heating with dimethyl sulfate at 155–160°C. gives a 40.5 per cent yield of methoxybenzenesulfonic acid and a 26 per cent yield of methyl methoxybenzenesulfonate (22). At higher temperatures sulfonation rather than cleavage becomes the main reaction. Ethylmagnesium bromide at 170–190°C. converts diphenyl ether to phenol and 2-hydroxybiphenyl (253). Some 2-hydroxybiphenyl is also obtained on cleavage of the ether with sodium acetylide (85).

The ether oxygen is replaced with sulfur when diphenyl ether is heated with sulfur for 15 hr. at 350°C. (156). In the presence of aluminum chloride at 100°C. diphenyl ether reacts with sulfur to give phenothioxin (IV) (261, 262).



IV

Phenothioxin

IV. ALKYLDIPHENYL ETHERS

The three symmetrical ditolyl ethers have been prepared by dehydration of the corresponding cresols over thorium dioxide at 400–450°C. (235). With the ex-

ception of the *o*-isomer the cresols give good yields of dimethyldiphenyl ethers. Higher temperatures favor dehydrogenation to dibenzofurans. The method has been applied to more complex compounds (237, 238) and even to mixed ethers (236). In the latter case the reaction products consist of mixtures which have to be separated.

Buch obtained 4,4′-dimethyldiphenyl ether by the dehydration of *p*-cresol with zinc chloride at 300°C. (41). Some *m*-cresyl ether was formed when *m*-cresol was dehydrated with 10 per cent of aluminum chloride (211).

Pyrolysis of the aluminum cresoxides gives fairly good yields of symmetrical dimethyldiphenyl ethers (55, 89, 90). More general are the method of Nollau and Daniels (204), which consists in heating a sodium arylsulfonate with a potassium aryloxide, and the Ullmann (285) method, the latter usually giving the best yields.

The direct alkylation of diphenyl ether with one equivalent of alkyl chloride in the presence of aluminum chloride (52) gives chiefly mixtures of mono-, di-, and tri-alkyldiphenyl ethers at 100–150°C. Aliphatic 1,1-dihalides condense with diphenyl ether under similar conditions to give bis(phenoxyphenylalkyl)-diphenyl ethers (51). A di(*s*-hexyl)diphenyl ether has been obtained by the alkylation of diphenyl ether with 3-hexene and hydrofluoric acid (45).

Methyldiphenyl ethers frequently serve for the preparation of acids into which they can be converted by oxidation. Higher alkylated diphenyl ethers have been suggested as dielectric agents for transformers and as plasticizers for resins (52).

On cleavage with sodium in liquid ammonia 2-methyldiphenyl ether gives nearly equal amounts of phenol and *o*-cresol, while 4-methyldiphenyl ether yields *p*-cresol as the main cleavage product and a small amount of phenol under the same conditions (240). The behavior of the 3-methyl isomer is intermediate between that of the *o*- and the *p*-methyl compounds. The order of increasing effectiveness of the three groups in strengthening the linkage between oxygen and the substituted phenyl group against cleavage is *o*-CH_3, *m*-CH_3, *p*-CH_3 (157). In 2,4′-dimethyldiphenyl ether the main product of the reaction with sodium in liquid ammonia is *p*-cresol (61 per cent), as would be predicted on the basis of the foregoing results (240). 4-*tert*-Butyl-4′-methyldiphenyl ether gives a slightly higher yield (52 per cent) of *p*-*tert*-butylphenol and a 48 per cent yield of *p*-cresol on cleavage, showing that the *tert*-butyl group has a slightly greater effect on the carbon–oxygen bond than the methyl group (300).

V. ARYLDIPHENYL ETHERS

Phenyl-substituted ethers (aryloxydi- and ter-phenyls) have been obtained by the Ullmann reaction (179), by rearrangement of diphenyl ether with phenylsodium (179), by treating a Grignard reagent of diphenyl ether with silver bromide (62), and as by-products in the preparation of phenylphenols (38).

The naphthyl ethers are best prepared by the dehydration of the naphthols with dilute sulfuric acid (94, 95), zinc chloride (191), or anhydrous hydrogen chloride (191). This method is superior to the Ullmann method, particularly

for the α-isomer (285). It is also used for the preparation of the phenanthryl ether from 9-phenanthrol (135). β-Naphthyl ether is obtained from the pyrolysis of aluminum β-naphthoxide (89), and both naphthyl ethers have been reported as by-products in the hydrolysis of chloronaphthalenes (38).

Naphthyl phenyl ethers have been prepared by the action of phenol upon the two naphthyldiazonium salts (129), and by the Ullmann reaction (285). β-Naphthol reacts with potassium nitroso-*p*-tolylsulfamate to give 30–40 per cent yields of β-naphthyl *p*-cresyl ether (208).

The phenyl (82, 279), methoxyphenyl (141), and naphthyl ethers (159) of anthraquinones are prepared by the sulfonate or Ullmann methods. 2-Phenoxyfluorene has been obtained in 18 per cent yield by heating 2-bromofluorene with potassium phenoxide and copper catalyst (176).

VI. PHENOXYQUINOLINES AND ISOQUINOLINES

The Ullmann reaction is used exclusively for the preparation of these ethers. 6-Phenoxyquinoline, 6-phenoxytetrahydroquinoline, and *N*-methyl-6-phenoxytetrahydroquinoline have been described as starting materials for a series of amines of therapeutic value (215). 6-Phenoxy-8-nitroquinoline and 6-phenoxy-8-aminoquinoline are the intermediates for the preparation of these amines (215). 5-Phenoxyisoquinoline has been described by Andersag (3).

VII. HALOGEN COMPOUNDS

The direct halogenation of diphenyl ether can be conducted in such a way that good yields of 4-halogenodiphenyl ethers are obtained. Chlorination is carried out in acetic acid (35) or in carbon tetrachloride at room temperature (186), bromination in carbon tetrachloride (258) or carbon disulfide in the presence of some iodine (186) or in acetic acid (34), and iodination with iodine monochloride in acetic acid (36). The 4,4′-dihalodiphenyl ethers are usually obtained in small amounts as by-products. A mixture of mono- and di-chlorodiphenyl ethers has been obtained by the chlorination of diphenyl ether with sulfuryl chloride (210). Halogenation of diphenyl ether with two molar equivalents of halogen or halogenation of the 4-halides gives good yields of the 4,4′-dihalogen compounds. The 4,4′-dichloro ether is accompanied by the 3,4-dichloro compound (35), whereas the 4,4′-dibromo compound is obtained free from isomers by the bromination of diphenyl ether in alcohol (291) and serves as a solid derivative for the identification of diphenyl ether. 4,4′-Diiododiphenyl ether can be prepared by iodination of the 4-iodo compound with iodine monochloride in acetic acid (36).

3,4,4′-Trichlorodiphenyl ether is produced in the chlorination of diphenyl ether, 4-chlorodiphenyl ether, and 3,4- and 4,4′-dichlorodiphenyl ethers (35).

A tetrabromodiphenyl ether of unknown orientation has been described by Cook (56). Halogenation with chlorine or bromine in the presence of aluminum chloride can be made to give diphenyl ethers containing more than four and less than ten halogens (39). With excess bromine and aluminum bromide, diphenyl ether can be exhaustively brominated. The resulting decabromo compound melts at 293°C. (26).

Monochloro, dichloro, monobromo, and dibromo derivatives of the three simple cresyl ethers have been described by Mailhe and Murat (187). Cook prepared both dibromo- (55) and tetrabromo-*m*-tolyl ethers (56), but the structures of the halogen tolyl ethers, all of which were obtained by direct halogenation, have not been determined.

Halogens can also be introduced into diphenyl ether by the diazotization of aminodiphenyl ethers and replacement of the diazonium group with chlorine (35), bromine (171), or iodine (36), or, in the case of bromine, by replacement of sodium sulfonate groups by direct bromination (259).

Halogenated phenols can be used in the Ullmann reaction for the preparation of halogenated diphenyl ethers if an excess of the phenol is used (228). Hydroxydiphenyl ethers are formed as by-products. The method works particularly well when the halogen in the aryl halide molecule is activated (242). The Ullmann reaction between dihalogenated benzenes and phenoxides can be limited to one of the halogens to give halogenated diphenyl ethers if two different halogens are present in the dihalogen derivative. 4-Chlorodiphenyl ether is obtained in this way by the reaction of *p*-chlorobromobenzene and potassium phenoxide (260). Some 4-phenoxydiphenyl ether is obtained as a by-product. The method has been used successfully for the preparation of a fluorodiphenyl ether from *m*-bromofluorobenzene (246).

Bromo- and iodo-diphenyl ethers have been prepared from acetoxymercuridiphenyl ethers by the action of bromine or iodine monochloride, respectively (247).

According to Rittler the halogenated diphenyl ethers are hydrolyzed to hydroxydiphenyl ethers by heating with aqueous alkali and copper catalyst under pressure (226). Heating with copper bronze at 200–220°C. converts 2-iododiphenyl ether to 2,2′-diphenoxydiphenyl (164). The bromodiphenyl ethers are used as halide components in the Ullmann reaction for the preparation of phenoxydiphenyl ethers (255).

The iododiphenyl ethers form Grignard reagents readily, the bromo compounds more slowly (66). The resulting reagents give the expected alcohols with carbonyl compounds (49, 66). Bromo- and iodo-diphenyl ethers react with alkyllithium by interconversion under mild conditions. The halogen may be ortho, meta, or para to the ether linkage (158).

The alkylation of halogenated diphenyl ethers with alkyl halides and aluminum chloride takes place much less readily than the corresponding alkylation of diphenyl ether. The products are predominantly monoalkyl derivatives (50).

In substitution reactions of halogenated diphenyl ethers the directive influence of the phenoxy groups largely determines the position of the new substituent (35).

VIII. NITRODIPHENYL ETHERS

The direct nitration of diphenyl ether with a slight excess of fuming nitric acid in a mixture of acetic acid and acetic anhydride at 25–30°C. gives a mixture of 2- and 4-nitrodiphenyl ethers and a small amount of dinitrodiphenyl ether (258). 4-Nitrodiphenyl ether can be partially frozen out of this mixture. When

a large excess of fuming nitric acid is used under the same conditions, the product consists mostly of dinitrodiphenyl ether (258). Cleavage and oxidation account for the formation of oxalic and picric acid as by-products (174). The nitration of diphenyl ether with potassium nitrate and concentrated sulfuric acid at 70°C. gives an 80 per cent yield of 2,4,2′,4′-tetranitrodiphenyl ether (189).

4,4′-Dimethyldiphenyl ether upon nitration undergoes considerable cleavage to 2-nitro- and 2,6-dinitro-*p*-cresols (223). Depending on the nitration conditions, the 2-nitro-, 2,2′-dinitro-, and 2,6,2′,6′-tetranitro-*p*-cresyl ethers are also obtained. The nitration of 2-nitro-*p*-cresyl ether gives a mixture of dinitro-*p*-cresol and 2,2′-dinitro-*p*-cresyl ether (220). 4-Methyldiphenyl ether is intermediate in stability between *p*-cresyl ether and diphenyl ether. It yields nitrophenols and cresols, owing to nitrative cleavage, and a single dinitrodiphenyl ether which probably has the nitro groups in the 2- and 4′-positions (224).

The nitrodiphenyl ethers are usually prepared from *o*- and *p*-nitrochlorobenzenes (32a), *p*-nitrofluorobenzene (219), *m*-nitrobromobenzene (285), 2,4-dinitrochlorobenzene (28), picryl chloride (302, 304), and the appropriate phenoxides. With the more highly activated halides the reaction takes place readily without a catalyst. The 2,4-dinitrodiphenyl ethers form rapidly when an alcoholic solution of 2,4-dinitrochlorobenzene is added to an aqueous alkaline solution of the phenol, and the mixture is refluxed on a steam bath. They are used for the identification of phenols (28).

Copper catalyst is usually required for the preparation of 3- and 4-nitrodiphenyl ethers from *m*-bromo- and *p*-chloro-nitrobenzenes (32a), whereas it is said to be neither helpful nor desirable in the preparation of 2-nitrodiphenyl ethers from *o*-chloronitrobenzene (120). Nitrophenols, which react only difficultly with *p*-chloronitrobenzene, give good yields of diphenyl ethers with *p*-fluoronitrobenzene (219). Both *o*- and *p*-nitrophenols react with 2,4-dinitrochlorobenzene (217) and picryl chloride without a catalyst (304).

Nitrodiphenyl ethers can be prepared in excellent yield by the reaction of *p*-dinitrobenzene with phenoxides (174). Heating *o*- or *p*-dinitrobenzene with dry potassium cyanide gives 2,2′- or 4,4′-dinitrodiphenyl ether (173).

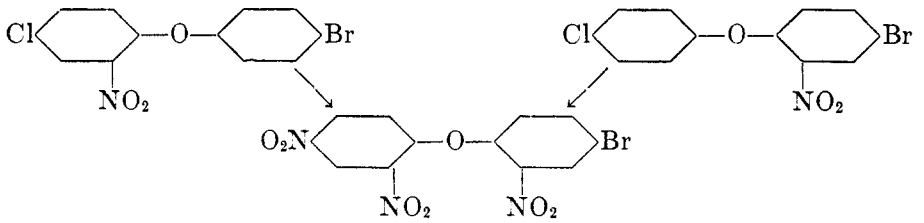
The nitro group in nitrodiphenyl ethers can be reduced in good yield to amino groups by means of stannous chloride (174), tin and hydrochloric acid (57), iron and acetic acid (99, 185), iron and ferric chloride (64), iron and hydrochloric acid (258), alkaline ferrous hydroxide (182), zinc and calcium chloride (258), ammonium sulfide (61, 183), or by catalytic reduction (36, 263). The electrolytic reduction in alcoholic alkali converts nitrodiphenyl ethers to azoxy compounds which separate out, owing to their low solubility (103). In acid solution the electrolytic reduction of the nitro compounds yields amines. Hydrazo compounds result from the reduction of nitrodiphenyl ethers with zinc dust and alcoholic alkali (104). The corresponding azo compounds can be obtained by oxidation with air or ferric chloride.

Nitro groups ortho or para to the oxide linkage weaken this linkage, thus allowing cleavage by sodium hydroxide (184, 189, 303), particularly in alcoholic solution (223), and by nitrogen bases. The latter case has been thoroughly in-

vestigated by a number of different workers. 2,4-Dinitrodiphenyl ether is cleaved to a small extent by aqueous alcoholic ammonia at 40–50°C. (27). When heated with aniline the 2,4-dinitrodiphenyl ethers give good yields of 2,4-dinitrodiphenylamine (27, 121, 203). If hydrazine is used instead, the cleavage is complete in a few minutes and gives a good yield of a benzotriazole and a phenol (27). Phenylhydrazine reacts more slowly, with the formation of 2-phenyl-2-benzotriazoles (27). A single nitro group in the 2-position of diphenyl ether activates the ether linkage sufficiently for cleavage by hydrazine but not by phenylhydrazine (27). The reaction with piperidine is most commonly applied for establishing the structures of nitrodiphenyl ethers. Cleavage takes place very slowly at 100°C. when one 2- or 4-nitro group is present but can be carried to completion in a few minutes with 2,4-dinitrodiphenyl ethers (43, 161). In all the cleavage reactions the amine nitrogen becomes attached to the more heavily nitrated ring and the second ring is isolated as a phenol (81, 161).

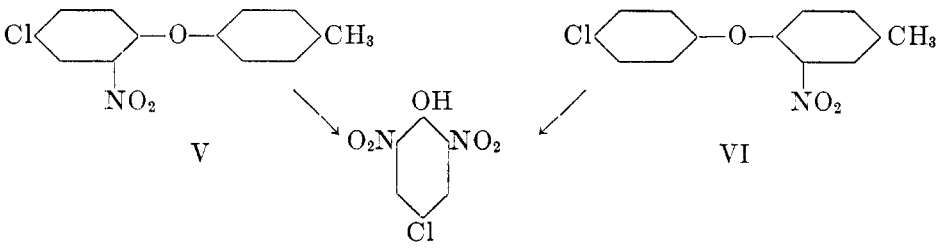
Nitrohalogenodiphenyl ethers can be prepared by nitrating halogenated diphenyl ethers. The phenoxy group orients the nitro groups to the 4-position when possible. When both 4-positions are blocked, the compound is usually nitrated in the 2-position. Two nitro groups in the 2- and 4-position of one ring inhibit further nitration in that ring (81).

In a few special cases chlorine and bromine are eliminated during nitration, as in the following examples (80),



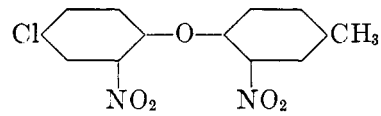
and in the nitration of 4-nitro-4′-bromodiphenyl ether, which gives 2,4,2′,4′-tetranitrodiphenyl ether (218). Iodine is more frequently eliminated (36).

Occasionally nitrative cleavage is also observed. The two nitro-4′-chloro-4-methyldiphenyl ethers (V and VI) react with cold fuming nitric acid to give 2,6-dinitro-4-chlorophenol as the main product.



Yet the dinitro ether (VII) which is obtained by the nitration of V and VI under mild conditions (fuming nitric acid diluted with acetic acid) cannot be cleaved

by cold fuming nitric acid (80). When VII is heated with fuming nitric acid, partial replacement of chlorine by a nitro group occurs.



VII

The halogenation of nitrodiphenyl ethers is considerably more limited in scope, since halogens cannot ordinarily be introduced into the nitrated rings. Raiford and coworkers were unable to introduce bromine into 2,2′,4-trinitro-, 2,3′,4-trinitro-, and 2-nitro-4′-bromo-diphenyl ethers (217).

In nitrodiphenyl ethers which contain a non-nitrated ring, second or third substituents, such as halogens, nitro, or other groups, tend to enter this ring. The mononitrodiphenyl ethers are first halogenated in the 4′-position (181, 242). Forced halogenation introduces a second halogen in the 2′-position (242). Under more rigorous conditions 2-nitrodiphenyl ether can be converted to 2-nitro-2,4,4′-tribromodiphenyl ether (180).

IX. HYDROXYDIPHENYL ETHERS

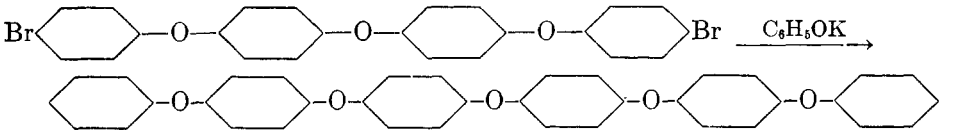
The Ullmann reaction can be used to prepare hydroxydiphenyl ethers directly from halogenated phenols and phenoxides (91, 147, 174, 213). Yields of 20–30 per cent may be obtained by the use of a large excess of phenoxide. In most cases the methyl ethers of the halogenated phenols are used instead, because of the higher yields of methoxydiphenyl ethers (286). Demethylation to the desired hydroxydiphenyl ethers is effected by heating with aluminum chloride in benzene (286), hydrobromic acid under pressure (269), hydriodic acid in acetic acid (174), or potassium hydroxide in ethylene glycol (293).

Small yields of hydroxydiphenyl ethers result when diazonium salts are decomposed with an excess of dihydric phenols such as catechol (205). 2-Hydroxydiphenyl ether has been isolated from the electrolytic oxidation of phenol (77), and 4,4′-dihydroxydiphenyl ether from the oxidation of phenol with chromyl chloride (71).

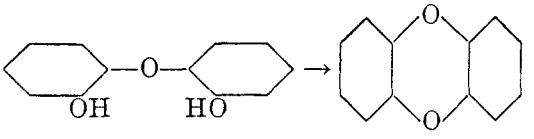
Hydroxydiphenyl ethers can be obtained from aminodiphenyl ethers through the diazonium reaction (101, 146, 174), and from chloro- or bromo-diphenyl ethers by high-pressure hydrolysis (226). A trinuclear hydroxydiphenyl ether has been described by Goldschmidt and coworkers as a product of the dehydrogenation of *o*-cresol with lead dioxide (91), but its structure has not been definitely established.

The three simple monohydroxydiphenyl ethers have been investigated most completely. Four dihydroxydiphenyl ethers and one simple trihydroxydiphenyl ether have also been described. The 2-, 3-, and 4-hydroxydiphenyl ethers have bactericidal properties (146, 147, 295), which can be further increased by halogenation or alkylation (295). 4-Hydroxydiphenyl ether has been suggested as an antioxidant (44).

The hydroxy groups in the foregoing compounds can be acylated (174), alkylated (123, 205), and allylated (295). The allyl ether of 4-hydroxydiphenyl ether has been rearranged to 3-allyl-4-hydroxydiphenyl ether by heating in diethylaniline (295). Aryl ethers of hydroxydiphenyl ethers may be prepared from the sodium salts of these compounds by heating with aryl halides and copper catalyst (102, 207). Staudinger and Staiger have built up chains of four, five, and six nuclei separated by oxygen by the reaction of *p*-dihalogen compounds with potassium phenoxide (255), e.g.:



2,2′-Dihydroxydiphenyl ether (VIII) is dehydrated to dibenzodioxin (IX) in good yield by heating with hydrobromic acid and a trace of red phosphorus at 190°C. (286). The dehydration may also be effected by heating with phosphorus oxychloride (286) or with zinc chloride (270).



VIII IX

Dibenzodioxin

The same product is obtained when 2,2′-dimethoxydiphenyl ether is heated with hydrobromic acid as above. The reaction is applicable to more complex ethers unless a third hydroxyl group occupies a position ortho or para to one of the hydroxyl groups involved in the cyclization (270). Tomita has reported the preparation of IX by the dehydrogenation of 2-hydroxydiphenyl ether with nitrobenzene and copper oxide (270).

Alkyl groups may be introduced into the phenolic ring of hydroxydiphenyl ethers by acylation and Clemmensen reduction of the resulting acylphenols or by hydrogenation of an allylphenol (295). Other alkylated hydroxydiphenyl ethers have been prepared through the Ullmann reaction with alkylphenoxides and alkylated aryl halides (213).

Chlorine or bromine may be introduced ortho or para to a hydroxyl group by chlorination with sodium hypochlorite or by direct bromination with bromine in acetic acid (295). Böhmer obtained a 13 per cent yield of 4′-bromo-4-hydroxydiphenyl ether by heating *p*-hydroxybenzenediazonium sulfate with hydrobromic acid (25). More commonly such halogen compounds are prepared by the halogenation of methoxydiphenyl ethers (171), or from aminomethoxydiphenyl ethers by diazotization, replacement, and demethylation (139).

4-Methoxydiphenyl ether is brominated in the phenoxy group more rapidly than 4-nitro, 4-bromo-, and 4-methyl-diphenyl ethers and even diphenyl ether

itself. These data constitute part of the evidence that the tautomeric or inductive effects of the substituent may be transmitted across the ether linkage from one ring to the other (34). In the halogenation of 4-methoxydiphenyl ether the halogen enters the 4′-position (32, 207). If this position is blocked the halogens go into the 3-position, unless the blocking group is more strongly directing than the methoxy group (32). 2-Methoxydiphenyl ether yields a mixture of 5-bromo-2-methoxydiphenyl ether and 4′,5-dibromo-2-methoxydiphenyl ether on bromination (171) but only 4′-iodo-2-methoxydiphenyl ether on iodination (32).

2′-Bromo-2-hydroxydiphenyl ether is dehydrohalogenated to dibenzodioxin by heating with copper and copper acetate (139).

Many nitromethoxydiphenyl ethers have been described, presumably because they are easily obtained by the condensation of nitrohalobenzenes with the alkali salts of methoxyphenols (29, 42, 207, 244). A few have been prepared by the nitration of methoxydiphenyl ethers. The nitration of 2-methoxydiphenyl ether gives the 5-nitro compound as main product (80 per cent) and a small amount (20 per cent) of the 4-nitro isomer (170). The structure of the single nitration product of 4-methoxydiphenyl ether (160) has been established as 3-nitro-4-methoxydiphenyl ether (32), but no data are available on the halogenation and nitration of 3-methoxydiphenyl ether.

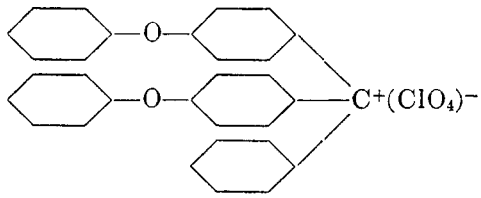
The results of the substitution reactions allow the conclusion that the methoxy group in the 2- and 3-positions has a somewhat stronger orienting effect than the phenoxy group. This effect becomes even greater when the phenoxy group carries a nitro substituent (42, 244). Nitration and halogenation of 2′-nitro-, 4′-nitro-, and 2′,4′-dinitro-2-methoxydiphenyl ethers give the 5-substituted compounds first. The second substituent goes usually to the 4-position. An exception is the nitration of 2′,4′-dinitro-2-methoxydiphenyl ether, where the second nitro substituent occupies the 3-position so that apparently the phenoxy group has no effect whatsoever (244). The chlorination of this same compound yields the 4,5-dichloro derivative. In 4′-nitro-2-hydroxydiphenyl ether the first bromine substitutes in the 5-position, the second in the 4-position (42).

Methoxy groups in the para-position strengthen the bond between the ether oxygen and the substituted phenyl group toward cleavage with sodium in liquid ammonia, while meta and particularly ortho methoxy groups weaken this linkage (157). Thus 2,3′-dimethoxydiphenyl ether yields 76 per cent of *m*-methoxyphenol and 24 per cent of guaiacol, while 3,4′-dimethoxydiphenyl ether is cleaved to give 92 per cent of *p*-methoxyphenol and 8 per cent of *m*-methoxyphenol (157).

X. ALCOHOLS

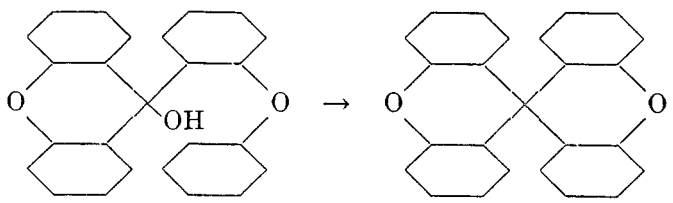
All known alcohols derived from diphenyl ether contain the hydroxyl group on a carbon directly connected to one of the rings. They have been prepared from hydroxydiphenyl ether by condensation with formaldehyde (295), from aldehydes by the Cannizzaro reaction (175), from ketones by reduction with aluminum isopropoxide (46) or by the Grignard reaction (49, 65, 66, 196), and from esters by the addition of Grignard reagents (280).

A few of these compounds are solid. Most of them are obtained in the form of oils which are difficult to purify. Dilthey and coworkers were able to isolate alcohols of the triarylcarbinol type in the form of colored crystalline carbonium salts such as X (66):

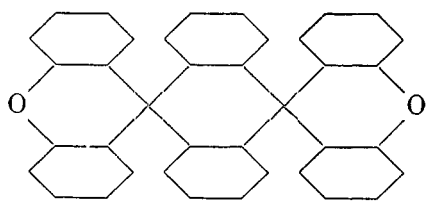


X

The reaction of the Grignard reagent from 2-iododiphenyl ether with xanthones or anthraquinone leads to alcohols which are readily cyclized to beautifully crystalline spiro compounds (XI and XII), which are characterized by high melting points and very low solubilities (49).



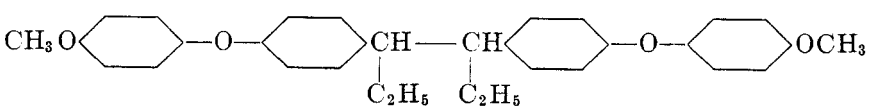
XI



XII

The secondary (46) and tertiary alcohols (196) are readily converted to halides. The bromide (XIII) reacts with sodium to give an analog of hexestrol (XIV) (46).

XIII



XIV

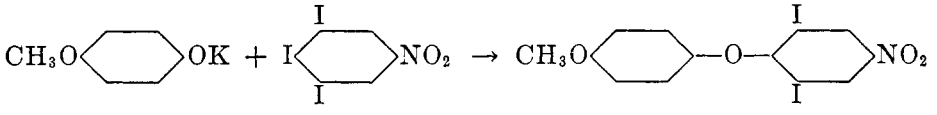
XI. ALDEHYDES

In 1898 Gattermann obtained 4-phenoxybenzaldehyde in approximately 50 per cent yield by the method which bears his name (84). According to Slotta and Soremba (250), the yield in this reaction can be raised to 70–80 per cent. The modification of Adams and Montgomery (1) gives a 50 per cent yield of the same compound. Lock and Kempter (175) prepared the three monoaldehydes by the Rosenmund reduction of the acid chlorides. The Etard reaction was unsuitable for the 3-isomer, since the intermediate double salt could not be decomposed (175).

Nitro aldehydes of diphenyl ether are obtained in good yield by condensing *p*-nitrofluorobenzene with the potassium salts of hydroxybenzaldehydes (219). The nitrochlorobenzenes (ortho or para) may be used for the same purpose. The reaction is carried out by adding the salt of the hydroxy aldehyde in small amounts to the hot halogen compound (36, 263).

The synthesis of the methoxy aldehydes is difficult. The Gattermann reaction is tedious and unsatisfactory (118), although it has been used for the preparation of various methoxy aldehydes (293). An attempt to use the *N*-methylformanilide method has met with failure (294), and the Etard reaction is impractical because of low yields (246). An example of the Ullmann reaction is reported by Robinson and Sugasawa (233), who condensed isovanillin with 3-bromo-4-methoxybenzaldehyde in pyridine in the presence of potassium carbonate and copper bronze. The method of McFayden and Stevens appears most promising for the synthesis of the methoxy aldehydes of diphenyl ether (118, 292).

The diiodomethoxy aldehyde required for the thyroxine synthesis is usually prepared from triiodonitrobenzene, which possesses sufficiently reactive halogen for the condensation with the monomethyl ether of hydroquinone under mild conditions.



XV

The resulting nitro compound (XV) is reduced to the amine, which is diazotized and treated with cuprous cyanide. The aldehyde is obtained by the Stephen reduction of the resulting nitrile (115).

4-Phenoxybenzaldehyde can be nitrated in the 4′-position by cautious nitration with concentrated nitric acid at 15–20°C. The 2′-nitro compound is obtained as a by-product. When 4-phenoxybenzaldehyde is nitrated with a mixture of nitric acid and sulfuric acid below 5°C., the 2,2′,4′-trinitroaldehyde is produced (250). An iodine atom can be introduced into the 4′-position of 4-phenoxybenzaldehyde by iodination with iodine monochloride and iodic acid (250).

The aldehyde group in aldehyde derivatives of diphenyl ether can be reduced

by the Clemmensen method (154) and oxidized with potassium permanganate (84), sodium dichromate and sulfuric acid (263), or silver oxide (175). These aldehydes form the usual derivatives, such as oximes, anils, phenylhydrazones (84, 175), and semicarbazones (118). They can be condensed with nitromethane (251), although sometimes in poor yield (256), with hydantoin (112, 251), glycine anhydride (112), acetylglycine (48), and hippuric acid (116, 251), and they undergo the Perkin reaction (112, 175). The products of these condensation reactions are intermediates in the preparation of β-arylethylamines (251, 256), α-amino acids (112), α-keto acids (48), and α-arylacetic acids (155).

Methoxy aldehydes can be demethylated with aluminum chloride. A side reaction sometimes causes the elimination of the formyl group as carbon monoxide. This reaction is dependent upon the relative positions of the groups involved (293).

XII. KETONES

4-Acyl- or 4-aroyl-diphenyl ethers are obtained in good yield from diphenyl ether through the Friedel–Crafts reaction (145). The acylating agents may be acid chlorides (145), anhydrides (21, 46, 145), or aryl esters (60). By using an excess of acyl halide (2.5–3 moles) and aluminum chloride (2 moles), two acyl groups can be introduced into diphenyl ether by this method. The second group enters the 4′-position (65). 4-Nitrodiphenyl ether undergoes the Friedel–Crafts reaction in the para-position of the non-nitrated ring (65, 263). When both para-positions are occupied by methyl groups, acetylation and benzoylation occur in the 2-position (221, 222). Benzoic and succinic anhydrides react with diphenyl ether and aluminum chloride with formation of *o*-(*p*-phenoxybenzoyl)benzoic acid and *o*-(*p*-phenoxybenzoyl)propionic acid (145). Cinnamoyl chloride reacts slowly under similar conditions but gives an excellent yield of 4-cinnamoyldiphenyl ether (151).

4-Alkoxydiphenyl ethers are acylated first in the 4′-position (66), and then ortho to the alkoxy group (272). 2-Alkoxydiphenyl ether undergoes the Friedel–Crafts acylation to give 4′,5-diacyl compounds (267, 268). When each ring contains one methoxy group, the methoxy groups determine the positions of the entering acyl groups. Thus, 2,2′-dimethoxydiphenyl ether yields 5,5′-diacyl compounds (267), and 4,4′-dimethoxydiphenyl ether gives 3,3′-diacyl derivatives (272). The methoxy or alkoxy groups may be retained in these reactions or cleaved to hydroxyl groups, depending on the reaction conditions (272).

4-Methoxydiphenyl ether was found to react with phosgene and aluminum chloride to give a good yield of 4,4′-di(4-methoxyphenoxy)benzophenone (66). Oxalyl chloride can be used in the place of phosgene in this case (15). Diphenyl ether and 4-methyldiphenyl ether are converted to substituted benzils by reaction with oxalyl chloride and aluminum chloride. 3-Methyl-, 3,3′-dimethyl-, 3-methoxy-, 3,4-dimethoxy-, and 3,4′-dimethoxydiphenyl ethers, on the other hand, yield xanthones with these reagents. 4,4′-Dimethoxy- and 4,4′-dinitro-diphenyl ethers do not react under the same conditions (15).

Acyl- and aroyl-diphenyl ethers can also be obtained in good yield by the

Ullmann reaction. The starting materials are halogenated aromatic ketones and phenols or hydroxyphenyl ketones and aryl halides (65, 66, 75).

Acetyldiphenyl ethers have been prepared from the corresponding acid chlorides of diphenyl ether by the acylation of ethyl sodioacetoacetate with the acid chloride, and hydrolysis of the resulting ester (294). Houben reports a 70 per cent yield of 4-trichloroacetyldiphenyl ether by the application of his ketone synthesis to diphenyl ether (130).

For proof of structure or for preparative purposes, acetyl- and chloroacetyldiphenyl ethers may be converted to acids by oxidation with alkaline permanganate (75, 245) or hypohalites (294). The Clemmensen reduction of the ketones yields alkyldiphenyl ethers (273), and the Meerwein reduction leads to the corresponding secondary alcohols (46).

Methyl ketones derived from diphenyl ethers can be converted to chalcones in good yield (65, 67). Some of the simpler ketones and particularly the chalcones form colored complex salts with sulfuric acid, stannic chloride, and perchloric acid (65).

Chloroacetyldiphenyl ethers have been used as intermediates in the preparation of amino alcohols of therapeutic importance (271).

XIII. ACIDS

4-Phenoxybenzoic acid was prepared by Klepl in 1883 by the hydrolysis of its phenyl ester, which was one of the pyrolysis products of *p*-hydroxybenzoic acid (148). The 2-phenoxy isomer was first obtained by Graebe in 1888 by heating the sodium salt of phenyl salicylate at 280–300°C. (96). The yield in this rearrangement was 25–30 per cent. Griess prepared all three isomers by decomposition of the diazonium salts of the three aminobenzoic acids with phenol (98) but reported no yields, and this method is not recommended for preparative purposes.

In 1904 Ullmann announced his copper-catalyzed reaction for the preparation of 2-phenoxybenzoic acid (278), and Fosse described the preparation of the same substance by the rearrangement of phenyl carbonate (78). The latter compound is stable to heating at 300°C. when pure, but rearranges with evolution of carbon dioxide and phenol when heated in the presence of sodium or potassium carbonate. Small amounts of carbonate give phenyl 2-phenoxybenzoate, while an excess of carbonate causes the formation of the free acid. Since salol gives the same products in the same ratio when pyrolyzed under these conditions, it has been suggested as an intermediate in the reaction (78). A recent patent (209) covers the preparation of phenyl 2-phenoxybenzoate by the pyrolysis of purified phenyl carbonate (from phosgene and sodium phenoxide) in the presence of 1 per cent of potassium carbonate at 230–270°C. The phenyl ester is hydrolyzed in good yield by heating with water and small amounts of sulfuric or sulfonic acids (149).

The Ullmann reaction involves heating the sodium or potassium salt of an *o*- or *p*-chlorobenzoic acid with a phenoxide and copper catalyst. With slight modifications the original procedure (278) is applicable to the preparation of larger amounts of acids in good yield (36). The method has been used for the

preparation of nitro acids (281), chloro acids (92, 287, 288), and methoxy acids of diphenyl ether (214, 282, 287, 289). The methoxy group may be located in either ring, while nitro groups are preferentially placed in such positions of the halogenated benzoic acids that they further activate the halogen. In dihalogenated benzoic acids the ortho halogen reacts in preference to the meta and para halogens, and the reaction is easily limited to one halogen.

Hydroxybenzoic acids are rarely used as phenolic components in the Ullmann reaction. An example of this kind is described by Haeussermann and Bauer (100). The esters of hydroxybenzoic acids, on the other hand, usually give good yields of diphenyl ethers when heated with aryl halides and copper catalyst (76, 118, 292, 294). When more complex esters are used the yields are decreased, owing to a number of side reactions. The most important of these is the replacement of halogen by hydrogen in the aryl halide molecule, a result which has been observed with bromomethoxybenzoic esters (75, 143), bromoalkoxyphthalic esters (142), and iodomethoxyphthalic esters (144), and may actually become the main reaction (75). Similar dehalogenations have also been described in the Ullmann reaction of 2-bromofluorene (176) and of 1,2,3,5-tetrabromobenzene with potassium phenoxide (285).

Another side reaction particularly pronounced in the phthalates or esters of other polycarboxylic acids consists in the alkylation by the ester of the free phenolic group required for the Ullmann reaction (142). This reaction can be used for alkylating phenols in a yield of 70–85 per cent. In its more general aspect it consists in heating the potassium salts of phenols with molecular proportions of alkyl phthalates at 190–200°C. (144). Methyl benzoate can be used as an alkylating agent in this manner, but the yield of phenol ether is much lower. Since the accumulation of carbomethoxy groups is largely responsible for this latter side reaction, Faltis and coworkers (75) suggest the synthesis of diphenyl ethers with methyl and (or) acetyl groups which can be converted to carboxyl groups after the diphenyl ether is formed. This indirect method has been widely used for the preparation of numerous acids.

The methyl groups in diphenyl ethers can be oxidized by dichromate, acetic acid, and sulfuric acid at 44°C. (34). The complete decomposition of 4′-nitro-4-methyldiphenyl ether by this reagent, as reported by Cook (53), is ascribed to cleavage caused by too high concentration of oxidizing agent and sulfuric acid (34). Some cleavage, however, is encountered in the oxidation of *p*-tolyl ethers even under mild conditions. According to Brewster and Slocombe, this is due to the shift of electrons from the ether oxygen atom to the *p*-tolyl nucleus. If the second nucleus is nitrated in the 2- or 4-position, the opposite shift of electrons hinders the cleavage reaction and the yields of acids increase (34). Permanganate has been used with good success for the oxidation of methyl groups to carboxyl groups in the diphenyl ether series. The yield in this case seems to depend to a great extent on the solvent used in the oxidation (292).

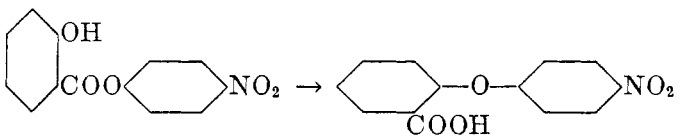
Acids of diphenyl ether have been obtained from the carbonation of sodium derivatives (179), lithium derivatives (85, 86, 158), and Grignard reagents of diphenyl ethers (158).

Suter and Oberg prepared *p*-(4-nitrophenoxy)benzoic acid by oxidation of the

corresponding aldehyde with sodium dichromate and sulfuric acid (263). This method is obviously limited to easily accessible aldehydes. The second method of Suter (258), which consists in introducing a cyano group by the Sandmeyer reaction and hydrolyzing the nitrile, is equally limited.

Hydroxy acids may be prepared by the demethylation of methoxy acids with hydriodic acid (292), hydrobromic acid (294), aluminum chloride (293), or alkali in high-boiling hydroxylic solvents (293). 3-Phenoxy-4-methoxybenzoic acid is resistant to hydriodic acid but can be demethylated with hydrobromic acid at 150°C. or with aluminum chloride (293). The demethylation of the methoxy acids with alkali may cause decarboxylation, depending upon the structure of the acids (293). Hydroxy acids may be obtained directly from hydroxydiphenyl ethers through the Kolbe reaction (225, 227). The carboxyl group enters a position ortho to each hydroxyl group in the original ether.

o-(*p*-Nitrophenoxy)benzoic acids (XVII) have been obtained by the rearrangement of *p*-nitrophenyl *o*-hydroxybenzoates (XVI) (274).

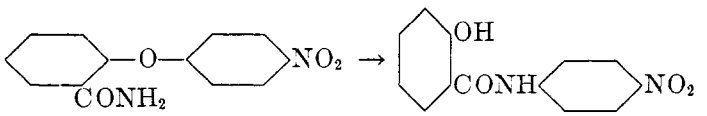


XVI XVII

The reaction gives a good yield (70 per cent) and takes place when the esters (XVI) are heated at 100°C. in a basic solution. It is inhibited by a nitro substituent para to the hydroxyl group in the esters (XVI). Salol requires much more drastic conditions for the analogous rearrangement (78).

Diphenyl ether acids with a carboxyl group in the 2-position are readily cyclized to xanthones by treating with phosphorus pentachloride and aluminum chloride (19) or by heating with concentrated sulfuric acid at 100°C. (5, 19, 70, 78, 79, 92, 96, 162, 281, 282, 283, 287, 289). Gottesmann (93) claims a quantitative yield of xanthones when the acids are heated for a few minutes with acetyl chloride and 1/40 of the amount of sulfuric acid.

The acids of diphenyl ethers are readily converted to acid halides, esters (263), and amides (6). The amide of *o*-(4-nitrophenoxy)benzoic acid (XVIII) rearranges when warmed with bases at 50°C. according to the following equation:



XVIII

The anilide corresponding to XVIII is rearranged more easily than XVIII, and the amide of *o*-(2,4-dinitrophenoxy)benzoic acid is converted to the *N*-nitrophenylsalicylamide by heat alone (275).

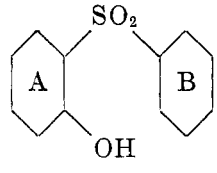
The carboxyl group in the acids of diphenyl ether can be eliminated by heating with barium hydroxide (96, 148) or by the Reichstein method (144). Alkali

fusion at 210–250°C. breaks the ether linkage and yields *o*- or *p*-hydroxybenzoic acid when the structure of the original acid permits (76, 112, 115). Sodium in liquid ammonia causes smooth cleavage of 2- and 4-phenoxybenzoic acids with the formation of phenol and benzoic acid or partially hydrogenated benzoic acid (240).

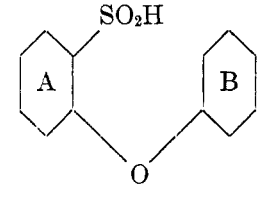
The nitration of 2-phenoxybenzoic acid gives a dinitro acid of unknown configuration, which undergoes nitrative cleavage when warmed with fuming sulfuric acid. The cleavage products are nitrosalicylic acid and 2,4-dinitrophenol (6). 2-Phenoxy-5-nitrobenzoic acid is nitrated and halogenated in the 4′-position (36).

XIV. SULFINIC, SULFONIC, AND SELENINIC ACIDS

p-Phenoxybenzenesulfinic acid was prepared by Suter by the reduction of the corresponding sulfonyl chloride with sodium sulfite and sodium carbonate. It was found to be quite unstable and could not be isolated in a pure state (259). Stable derivatives of *o*-phenoxybenzenesulfinic acid were synthesized by Krishna by the condensation of 2-chloro-5-nitrobenzenesulfinic acid with sodium phenoxides in boiling aqueous sodium hydroxide solution (157a). A number of *o*-phenoxybenzenesulfinic acids (XX) have been prepared by the rearrangement of *o*-hydroxysulfones (XIX) with alkali (140, 166, 167, 296, 298, 299).



XIX



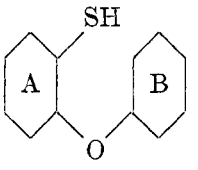
XX

This reaction takes place at room temperature if a nitro group occupies a position ortho to the sulfone linkage in ring B. A *p*-nitro group in this ring permits the rearrangement, but it takes place more slowly. In the absence of nitro substituents the sulfones (XIX) are stable even when heated to 250°C. with alkali. A carboxyl group in the 2-position or a nitro group in the 3-position of B fails to promote the rearrangement (140). Sulfones in which B is 2,4-dinitrophenyl, and *p*-hydroxysulfones undergo cleavage rather than rearrangement with alkali (140, 166). Bis-1-(2-hydroxynaphthyl) sulfone is converted to the sulfinic acid by heating with alkali at 150°C. (298). The acid cannot be isolated, however, since it loses sulfur dioxide under these conditions. The structures of the sulfinic acids are usually determined by permanganate oxidation and removal of the sulfonic acid grouping by steam distillation. The sulfur-free products have been synthesized in several cases (167, 296a). Sometimes the methyl sulfinate is accessible to synthesis (299).

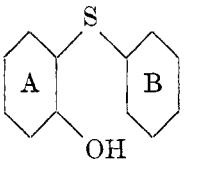
2-Phenoxybenzenesulfinic acids cyclize when they are treated in the cold with acetic anhydride containing a trace of sulfuric acid or with sulfuric acid. The products are mixtures of phenothioxins and their oxides (157a).

Sulfinic acids of diphenyl ether can be reduced to diphenyl ethers with zinc and acetic acid (296) and to phenoxythiophenols with zinc and hydrochloric

acid (296). The *o*-phenoxythiophenols (XXI) rearrange under the influence of alkali to give *o*-hydroxydiphenyl sulfides (XXII) if they contain a nitro group in the ortho-position of ring B (140).



XXI



XXII

Oxidation of the sulfides (XXII) with hydrogen peroxide in acetic acid regenerates the hydroxysulfones (XIX) (167, 299).

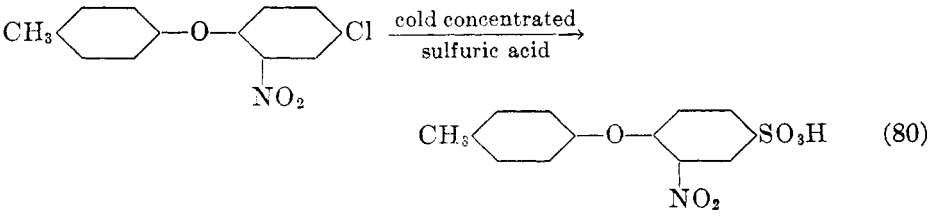
The direct sulfonation of diphenyl ether with 95 per cent sulfuric acid and acetic anhydride at 100°C. gives an excellent yield (93 per cent) of *p*-phenoxybenzenesulfonic acid (259), which can be isolated as the sodium salt. Its structure was established by conversion of the sodium sulfonate to 4,4′-dibromodiphenyl ether by direct bromination in water solution. The intermediate bromophenoxybenzenesulfonate can be isolated. Disulfonation takes place preferentially when diphenyl ether is sulfonated with concentrated sulfuric acid without a solvent at 100°C., because the monosulfonic acid which is first formed is soluble in concentrated sulfuric acid and is further sulfonated more rapidly than the almost insoluble diphenyl ether. The disulfonic acid is assigned the 4,4′-configuration, since its sodium salt yields 4,4′-dibromodiphenyl ether on bromination (259).

2-Nitro-, 2,4-dinitro-, and 2,4-dinitro-6-carboxydiphenyl ethers are sulfonated with concentrated sulfuric acid at temperatures at or above 100°C., presumably in the 4′-position (56, 138, 214). 4-Nitrodiphenyl ether requires 33 per cent fuming sulfuric acid for sulfonation (138). The position of the sulfonic acid group in these compounds has not been established. The structures of other sulfonic acids prepared by Cook and coworkers by sulfonating various diphenyl ethers are also unknown (53, 57, 58, 59).

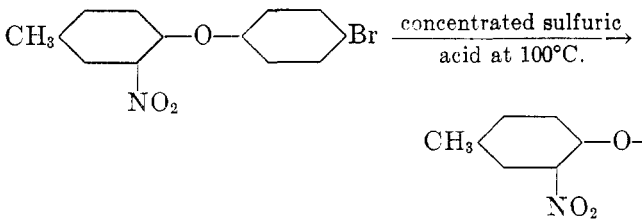
Chlorosulfonic acid acts on diphenyl ether at 25–30°C. with formation of the 4,4′-disulfonyl chloride (132, 259). The corresponding diamide is used as a solid derivative of diphenyl ether because of its sharp and characteristic melting point (132). 4,4′-Dibromodiphenyl ether is sulfonated in the 2- and 2′-positions with chlorosulfonic acid (261).

The sulfonation of diphenyl ether with aminosulfonic acid takes place when the mixture is heated to 160–170°C. The product is ammonium *p*-phenoxybenzenesulfonate (216).

The following unusual cases of sulfonation are described by Fox and Turner:

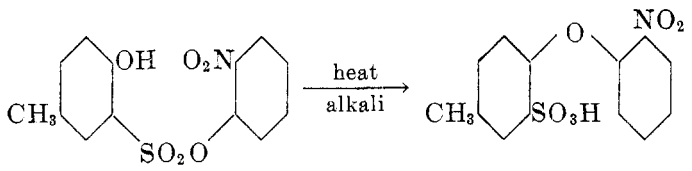


(80)



(81)

o-Nitrophenoxybenzenesulfonic acids (XXIV) can be prepared by the rearrangement of the *o*-nitrophenyl *o*-hydroxybenzenesulfonates (XXIII), a rearrangement which is analogous to that of the nitrophenyl salicylates (274).

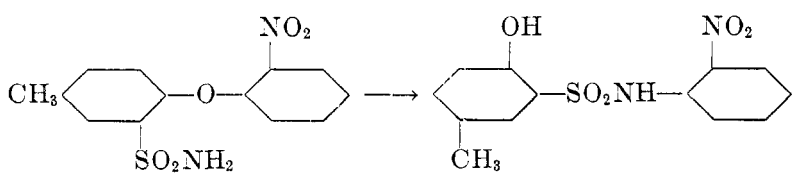


XXIII XXIV

Sodium phenoxybenzenesulfonates react with phosphorus pentachloride to give sulfonyl chlorides (259). This method constitutes the only good way to prepare 4-phenoxybenzenesulfonyl chloride, since chlorosulfonic acid causes disulfonation of diphenyl ether. 4-Phenoxybenzenesulfonyl chloride is brominated in the 4′-position, and the product is identical with the chlorosulfonation product of 4-bromodiphenyl ether. Amides and anilides of the sulfonic acids are readily prepared from the chlorides and serve as derivatives. Reduction of the sulfonyl chlorides with zinc and sulfuric acid or with stannous chloride, hydrochloric acid, and acetic acid gives thiophenols (259, 264), which can be converted to disulfides by oxidation with air or iodine (259).

Sodium hydroxide fusion of the sodium sulfonates of diphenyl ether does not give the desired hydroxy compounds but leads to cleavage, with the formation of sodium phenoxide (259).

o-Nitrophenoxybenzenesulfonamides (XXV) can rearrange according to the following equation:

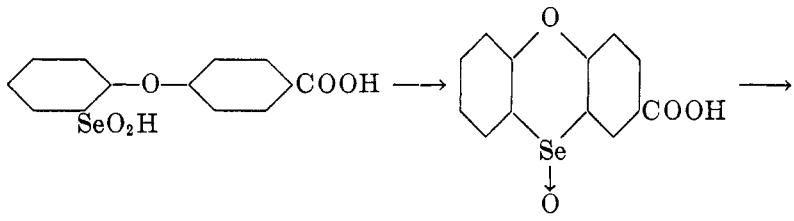


XXV

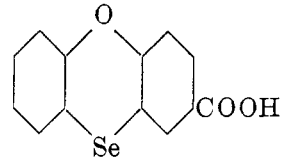
The reaction is inhibited if one of the amide hydrogens is substituted by phenyl (275).

A seleninic acid (XXVI) has been prepared by the diazotization of *p*-(*o*-amino-

phenoxy)benzoic acid, replacement of the diazonium group by the selenocyano group, and oxidation with nitric acid (266). Cyclization of this acid with 85



XXVI XXVII



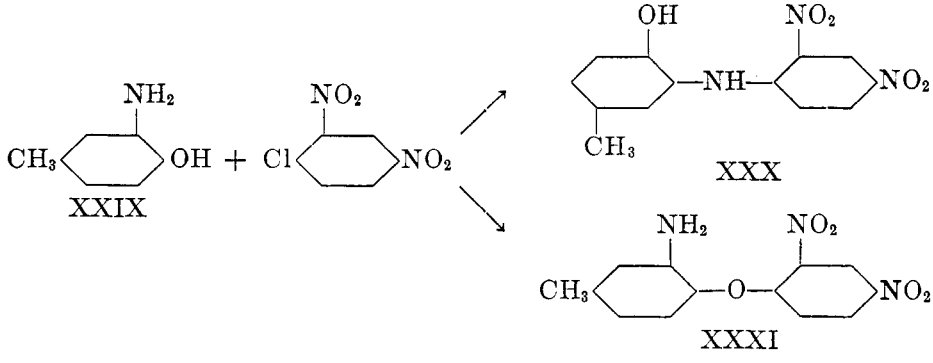
XXVIII

per cent sulfuric acid yields 2-carboxyphenoxaselenin-10-oxide (XXVII), which can be reduced to phenoxaselenin-2-carboxylic acid (XXVIII) by the action of potassium metabisulfite. Attempts to resolve this acid or a dichloro derivative which was also synthesized were unsuccessful (266).

XV. AMINODIPHENYL ETHERS

Amines in this series are prepared mostly by the reduction of the easily accessible nitro compounds, but they can also be obtained directly in good yields through the Ullmann reaction (285). Ullmann and Sponagel report a 57 per cent yield of *m*-phenoxyaniline and a 64 per cent yield of *p*-phenoxyaniline from the reaction of the bromoanilines with potassium phenoxide.

When aminophenols react with activated halogen compounds the reaction can yield either diphenyl ethers or diphenylamines, depending on the reaction conditions. Thus, the aminocresol XXIX reacts with 2,4-dinitrochlorobenzene to give an 85 per cent yield of the diphenylamine XXX when the mixture is heated with alcohol and sodium acetate. When the alcoholic solution of the



XXIX XXX XXXI

sodium salt of XXIX and 2,4-dinitrochlorobenzene is allowed to stand at room temperature, the ether (XXXI) may be isolated in 55 per cent yield (230).

Diamines are prepared by the reduction of dinitro compounds (100) or nitroamines of diphenyl ether (36). The reduction of dinitrodiphenyl ethers may be interrupted at the stage of the intermediate nitroamines if ammonium sulfide (61) or stannous chloride (234) is used as reducing agent.

Two β-(4-aryloxyphenyl)ethylamines have been prepared by the reduction of the corresponding nitrostyrenes (251, 256). Other side-chain amines of interest for the physiological action have been described by Pützer and Schönhöfer (215).

Amines of diphenyl ether are easily acetylated and benzoylated. The resulting amides are useful for identification purposes and permit the study of substitution reactions. The nitration of 2-acetaminodiphenyl ether gives the 5-nitro derivative (181). Chlorination and iodination yield mixtures, but the bromination in acetic acid solution yields the 5-bromo compound (180). In the 4-acetamino isomer the nitro group enters the 3-position. Chlorination leads to a dichloro derivative which contains one chlorine in the 4′-position; bromination and iodination yield the 4′-halogeno derivatives under ordinary conditions (242, 243). When a nitro group is present in the same ring as an acetamino group, additional substituents enter the non-nitrated ring. The substitution reactions of the acetamino compounds in general are governed by two factors,—the strong directive effect of the acetamino group, which exceeds that of any of the other groups considered, and a strong steric factor which tends to inhibit substitution ortho to the acetamino group (180).

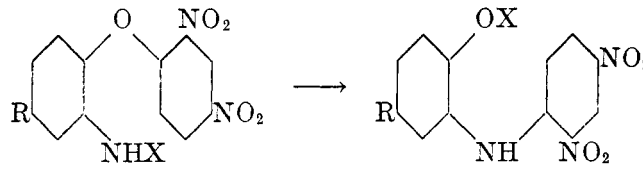
The amino groups in diphenyl ether are easily replaced by halogen by means of the Sandmeyer reaction, which is frequently used to establish the structures of various halogenation products (35). The replacement with the cyano group allows the preparation of acids (258). The amino group may be replaced by hydrogen in good yield when the diazonium salts are reduced with alkaline formaldehyde (33).

The diazonium salts of 2- and 4-aminodiphenyl ethers with chlorines substituted in positions ortho or para to the ether linkage can be salted out of an acid solution. They are stable when dry and mixed with standardizing diluents. These salts are valuable for the production of red and pink color shades with 2-hydroxy-3-naphthoic aryl amides (241).

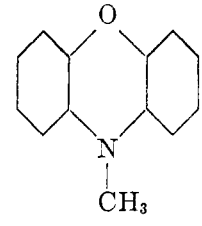
Jones and Cook (138) have described a series of seventy-two dyes derived from *o*- and *p*-aminodiphenyl ethers and their sulfonic acids.

2-Phenoxyanilines can be converted to dibenzofurans by heating their diazonium salts with 50 per cent sulfuric acid (97, 183). The reaction is apparently fairly general (181). It fails to give 4-substituted dibenzofurans unless the amino group is in the same ring as the group which is to be the 4-substituent (87). In the case of *o*-(2,5-dimethoxyphenoxy)aniline the amino group undergoes replacement with hydroxyl rather than cyclization to the dibenzofuran (88).

o-(2,4-Dinitrophenoxy)anilines are unstable to heat in hydroxylic or basic solvents and rearrange to diphenylamines (230):



The rearrangement proceeds readily when X=H and R=NH_2, OCH_3, CH_3, H, Cl, Br, or I, but not when R=COOH or $COOC_6H_3(NO_2)_2$ (232). The reaction takes place more slowly when X=acyl, the velocity being inversely proportional to the acid strength of the acids containing the acyl group (231). In the case of X=CH_3, the rearrangement gave the phenoxazine (XXXII), which was evidently formed by cyclization of the expected rearrangement product. Synthetic *N*-methyl-*o*-hydroxydiphenylamine cyclized to give XXXII under the



XXXII

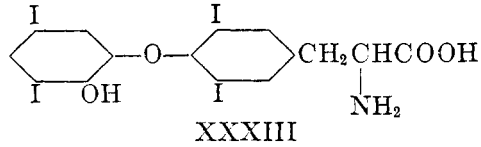
conditions of the rearrangement (229).

o-(2-Hydroxyphenoxy)aniline has been converted to dibenzodioxin by heating the diazonium salt with 50 per cent sulfuric acid and copper sulfate and to phenoxazine, although in small yield, by heating the free amine under pressure (61).

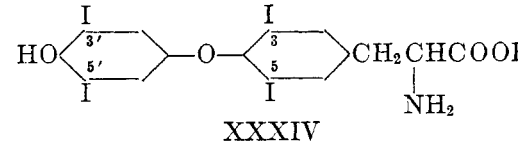
The ether linkage in the three monoamines of diphenyl ether is cleaved by sodium in liquid ammonia. The amino group stabilizes the linkage between oxygen and the aminated ring toward cleavage with this reagent, so that aminophenols are produced in good yield (157, 240, 300).

XVI. AMINO ACIDS

Most of the amino acids containing the diphenyl ether structure have been synthesized with the aim of preparing substances with thyroxine activity. With the exception of the synthesis of "ortho" thyroxine (XXXIII) by Niemann and Mead (200), all such attempts have failed. Thyroxine activity is thus highly specific and limited to thyroxine (XXXIV), the corresponding keto acid (48), and the ortho isomer (XXXIII).



XXXIII

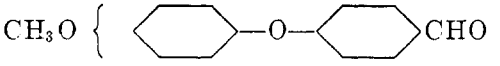


XXXIV

Both of the latter substances, however, possess only a fraction of the activity of thyroxine. The activity is likewise decreased when part or all of the iodine atoms in thyroxine are exchanged for chlorine or bromine (248). The physiological activity disappears when the iodine atoms in the 3- and 5-positions are removed (24), and is greatly decreased in 3,5-diiodothyronine (114).

The elucidation of the structure of thyroxine by Harington (112, 113, 114) was based on the degradation and synthesis of the desiodo compound, thyronine. The location of the iodine atoms was established by alkali fusion of the naturally occurring material and finally by the synthesis of thyroxine (114, 115).

The starting materials for the synthesis of amino acids of this type are the aldehydes (XXXV) or their 3,5-diiodo derivatives.

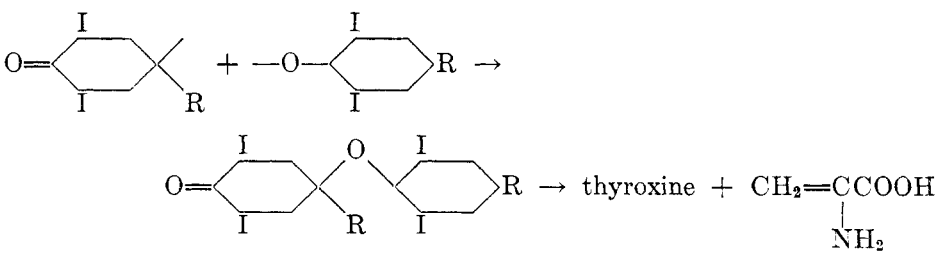


XXXV

The latter are prepared from 3,4,5-triiodonitrobenzene by the Ullmann reaction with appropriate methoxyphenols, and successive replacement of the nitro group with NH_2, CN, and CHO (30, 115, 199, 200, 201, 202). The halogen-free aldehydes are best prepared from the corresponding acids by the McFayden–Stevens method (118, 292).

The amino acids are usually prepared from the aldehydes by the Erlenmeyer synthesis (116). Other procedures involve the use of acetylglycine (30), hydantoin, or glycine anhydride (112).

Thyroxine-containing proteins can be prepared by the iodination of proteins such as casein at 37°C. in the pH range of 7–9 with a limited amount of iodine (177, 197). The intermediate in the reaction is believed to be diiodotyrosine (combined in the protein molecule), since the iodination of casein at lower temperatures causes only substitution of iodine, and because it is possible to produce thyroxine, although in small yield, by the incubation of diiodotyrosine at 37°C. and pH 8.8 (197). These results have been fully substantiated by other workers (23, 117, 137). The mechanism of the reaction proposed by Johnson and Tewkesbury (137) involves the addition of two free radicals derived from diiodotyrosine by dehydrogenation and elimination of one side chain:



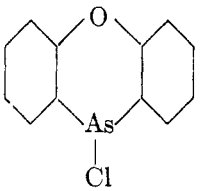
R = $-CH_2CH(NH_2)COOH$

The side-chain fragment was actually isolated in the form of pyruvic acid and ammonia (137). Other possible intermediates in the reaction, such as triiodophenol and 3,5-diiodo-4-hydroxybenzoic acid, have been eliminated (20).

XVII. PHOSPHORUS, ARSENIC, AND TELLURIUM COMPOUNDS

p-Phenoxydichlorophosphine was obtained by Davies and Morris by refluxing diphenyl ether with phosphorus trichloride and aluminum chloride (62). Its structure was established by conversion to tri-*p*-phenoxyphenylphosphine with *p*-phenoxyphenylmagnesium bromide. The same phosphine and methiodide were obtained by synthesis from *p*-phenoxyphenylmagnesium bromide and phosphorus trichloride. An independent proof of structure consisted in brominating the phosphonic acid obtained by hydrolyzing the dichlorophosphine dichloride. Bromine in carbon tetrachloride gave the 4′-bromo acid, which on heating with bromine at 160°C. yielded 4,4′-dibromodiphenyl ether (62). With aliphatic Grignard reagents 4-phenoxyphenyldichlorophosphine yielded dialkylphosphines which gave crystalline addition compounds with carbon disulfide (63).

Arsenic can be introduced into diphenyl ether in the same way as phosphorus, by refluxing with arsenic trichloride and aluminum chloride (169). Substitution in this case occurs in the 2-position, with simultaneous cyclization to give 10-chlorophenoxarsine (XXXVI):



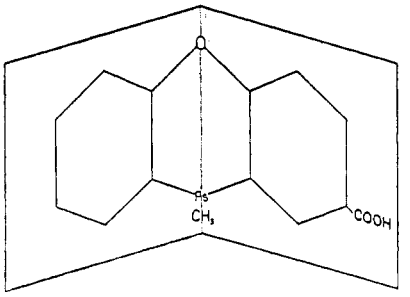
XXXVI

The structure of this chloroarsine has been established by an unambiguous synthesis from 2-aminodiphenyl ether (276) through the Bart reaction. This same reaction is used in the majority of the cases for the preparation of arsonic acids of diphenyl ether (109). It consists in decomposing diazonium salts with sodium arsenite in a buffered solution. The arsonic acids are converted to dichloroarsines by reducing with sulfur dioxide in warm hydrochloric acid in the presence of a little potassium iodide (228). *o*-Aryloxyphenyldichloroarsines are cyclized to chlorophenoxarsines by heating at 200°C. (195, 228). The cyclization rates have been determined for a number of these compounds by measuring the amount of hydrochloric acid produced (195). In some cases *o*-phenoxyphenylarsonic acids can be cyclized by heating with sulfuric acid. When cyclization does not take place, the acids usually sulfonate instead (228).

Chlorophenoxarsines can also be prepared by heating a chloromercuridiphenyl ether with arsenic trichloride and cyclizing the resulting dichloroarsine (195). 8-Chloro-10-phenylphenoxarsine-2-carboxylic acid and 10-methylphenoxarsine-2-carboxylic acid (XXXVII) have been resolved (163, 165). The optical activity of these compounds is due to the fact that the compound is non-planar and arranged in two planes intersecting about the oxygen–arsenic axis.

Arsonic acids of diphenyl ether may be prepared directly by the Ullmann reaction with *o*-chlorophenylarsonic acid and phenoxides, because the arsonic acid

group activates the halogen atom (72). 4-Bromo-3-nitrophenylarsonic acid reacts similarly with various phenoxides to give 3-nitro-4-aryloxyarsonic acids (182).

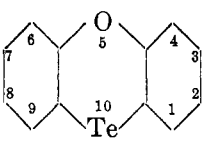


XXXVII

4-Phenoxyphenylarsonic acid is chlorinated and brominated in the 4′-position. The structures of the halogenated products have been established by synthesis from 4′-halo-4-aminodiphenyl ethers (64).

Dimethylarsines have been prepared from 2-phenoxyphenyldichloroarsines by the action of methylmagnesium iodide, and from 4-phenoxyphenylmagnesium bromide and iododimethylarsine. They can be characterized as methiodides (64).

Tellurium is introduced into diphenyl ether by treating the ether with tellurium tetrachloride in chloroform solution. At low temperatures the product is *p*-phenoxyphenyltelluriumtrichloride. When this is heated to 200°C., or when the original reaction mixture is heated to 200°C., 10,10-dichlorophenoxatellurin is produced (68). Reduction of the dichloride with potassium metabisulfite at 0°C. furnishes phenoxatellurin (XXXVIII) in excellent yield.



XXXVIII

Phenoxatellurin

On nitration with concentrated nitric acid XXXVIII yields a mixture of 4- and 8-nitro compounds. Fuming nitric acid produces the 4,8- and 2,8-dinitrotellurins. The nitro compounds readily lose tellurium when boiled with aqueous potassium hydroxide (69).

o-Tolyloxyphenyltelluriumtrichloride has been prepared from the chloromercuri compound by the action of tellurium tetrachloride (47). Attempts to resolve phenoxatellurin-2-carboxylic acid have been unsuccessful.

XVIII. MERCURY, LITHIUM, AND SODIUM COMPOUNDS

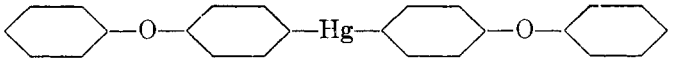
Mercuration of diphenyl ether with mercuric acetate in acetic acid at 100°C. was found to give approximately equal amounts of 4-acetoxymercuridiphenyl

ether and 4,4′-diacetoxymercuridiphenyl ether (247). The ratio of these products was about the same when the reaction was carried out at room temperature. 4-Bromo- and 4-iodo-diphenyl ethers were mercurated in the 4′-position by this method, while 4-hydroxydiphenyl ether gave a mixture of polymercury compounds. Individual mercury compounds could not be obtained from 4-methoxydiphenyl ether, but 4-benzoyloxydiphenyl ether gave the 4′-acetoxymercuri derivative (247).

The mercuri group in the pure acetoxymercuri compounds is replaced with iodine upon treatment with iodine monochloride in acetic acid solution. 4-Acetoxymercuridiphenyl ether reacts in the normal manner with warm mineral acids to give diphenyl ether, with sodium chloride solution to give 4-chloromercuridiphenyl ether, and with bromine to give 4-bromodiphenyl ether. In 4,4′-diacetoxymercuridiphenyl ether both groups are replaced by these same reagents with hydrogen, chloromercuri groups, or bromine, respectively (247). Chloromercuri compounds are also obtained in good yield by the decomposition of diazomercuric chlorides of diphenyl ether with copper powder (47).

Reactive alkyl halides and aroyl halides have been found to react with 4-chloromercuridiphenyl ether at 150°C. to give mercuric halides and alkylated or acylated diphenyl ethers. Benzylation yields 4-benzyl- and 4,4′-dibenzyldiphenyl ethers in this manner. In order to explain the formation of the dibenzyl compound, Schroeder and Brewster assume that the mercuric chloride which is liberated in the reaction between benzyl chloride and the chloromercuri compound mercurates the benzyldiphenyl ether in the 4′-position. Subsequent benzylation would lead to the 4,4′-dibenzyl compound. In support of this theory the authors were able to benzylate diphenyl ether with benzyl chloride and mercuric chloride. The two benzylation products were formed in approximately the same ratio as in the previous reaction (247). The rates of benzylation for diphenyl ether, *p*-bromodiphenyl ether, and *p*-nitrodiphenyl ether with mercuric chloride were in the same order as the rates of bromination for the same compounds. The reaction was of the first order, indicating that the rate-determining step was the speed of dissociation of a coördination compound which may be formulated as in the Friedel–Crafts reaction (34). Benzoyl chloride and *tert*-amyl chloride react with diphenyl ether and mercuric chloride to give the corresponding 4-substituted derivatives (247). Anhydrous cadmium chloride and zinc chloride are said to be even more efficient than mercuric chloride in reactions of this type with diphenyl ether (247).

4-Mercuribis(diphenyl ether) (XXXIX) is formed from 4-bromodiphenyl



XXXIX

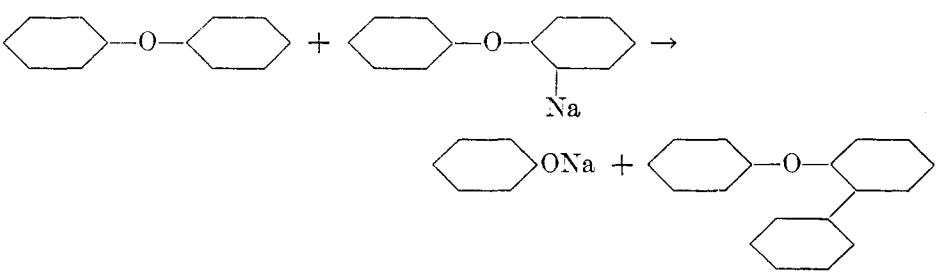
ether by heating with sodium amalgam in toluene containing some ethyl acetate at 120°C. (247) or by the action of mercuric chloride on 4-phenoxyphenylmagnesium bromide (62). The mercury compound (XXXIX) yields 4-acetoxydiphenyl ether when boiled with acetic acid, and 4-iododiphenyl ether on treatment with iodine monochloride (247).

Metalation with lithium occurs in fairly good yields when diphenyl ether is stirred with *n*-butyllithium in ether solution (85). The position of the metal has been established by isolation of 2-phenoxybenzoic acid as the carbonation product. The orientation of the metal to the 2-position in this case is quite unusual, since all other substitution reactions and also the mercuration of diphenyl ether involve the 4-position.

p-Bromodiphenyl ether undergoes metalation with *n*-butyllithium or metallic lithium in the 2-position, as evidenced by the formation of 2-phenoxy-5-bromobenzoic acid on carbonation. The reaction is interpreted as an autometalation involving the intermediate *p*-phenoxyphenyllithium, which is formed by halogen–lithium interchange (86). Further investigations have shown that under mild conditions iodo- and bromo-diphenyl ethers undergo mainly halogen–lithium interconversion, regardless of the position of the halogen. Iododiphenyl ethers give the reaction more readily than bromodiphenyl ethers, while chlorodiphenyl ethers are essentially unaffected. Under more drastic conditions, i.e., during during long periods of reaction or on refluxing in ether solution, the *p*-halogenodiphenyl ethers are metalated by *n*-butyllithium and phenyllithium (158).

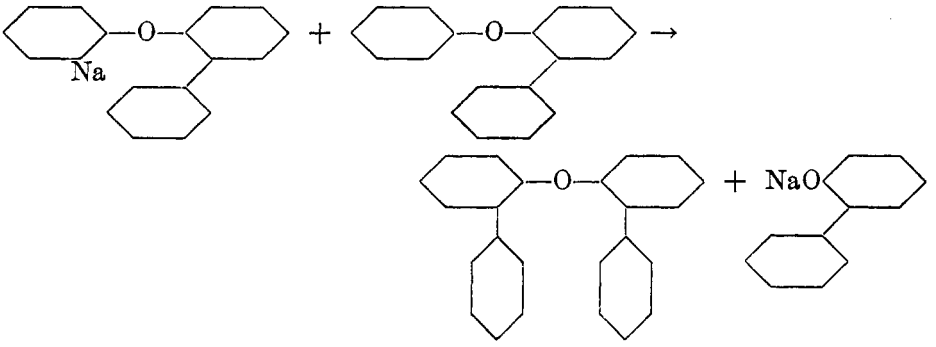
4-Methoxydiphenyl ether is metalated at least in part in the 3-position, since 2-methoxy-5-phenoxybenzoic acid has been isolated from the crude mixture of the carbonation acids. The same acid has been obtained from the carbonation of the reaction mixture from 3-bromo-4-methoxydiphenyl ether and *n*-butyllithium (158).

Treatment of diphenyl ether with ethynylsodium in liquid ammonia (85) or heating with ethylmagnesium bromide gives some *o*-phenylphenol (253). This same product has also been isolated from the reaction of diphenyl ether with phenylsodium (179), and its formation may probably be regarded as evidence for intermediate metalation products in these reactions. The existence of a metallic intermediate has been pretty well established in the last case, because carbonation of the reaction mixture yields an acid which has been identified as *o*-phenoxybenzoic acid. The end-products of the reaction in the order of decreasing yields are *o*-phenylphenol, phenol, *o*-phenoxydiphenyl, 2,2′-diphenyldiphenyl ether, and 2,6-diphenylphenol. Lüttringhaus and Sääf have shown that the phenol is derived exclusively from the diphenyl ether by cleavage with *o*-phenoxyphenylsodium:

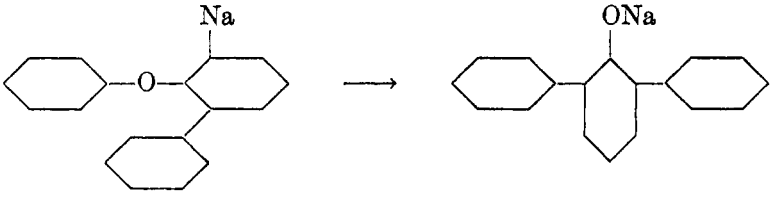


o-Phenylphenol may result from the cleavage of *o*-phenoxydiphenyl with either *o*-phenoxyphenylsodium or phenylsodium. The latter reaction could be demonstrated experimentally. The mechanism, which assumes an intermediate sodium

derivative of *o*-phenoxydiphenyl, also accounts for the formation of 2,2′-diphenyldiphenyl ether, which occurs in equivalent amounts. It is written as follows:

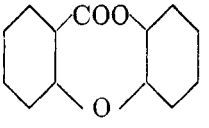


The formation of 2,6-diphenylphenol is postulated as a rearrangement of a third metallic intermediate (179):



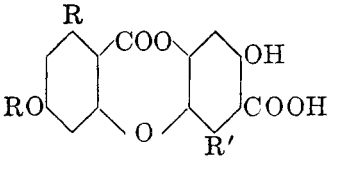
XIX. DEPSIDONES

Depsidones are substituted phenyl benzoates (depsides) in which the two nuclei are linked by an oxygen bridge so that a seven-membered ring is formed (7, 8). The basic ring system is therefore the lactone of *o*-(*o*-hydroxyphenoxy)benzoic acid (XL):

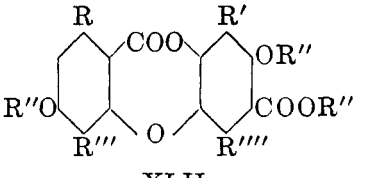


XL

The depsidones occur naturally along with depsides in various lichens. They may be grouped into two classes (XLI and XLII), depending on whether they are derived from homologs of orcinol or of β-orcinol (7).



XLI

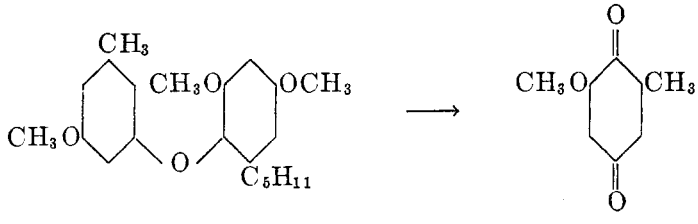


XLII

Depsidones of the first type (XLI) are distinguished by the length of the carbon chains R and R′ in the phenolic nuclei, which may contain one, three, five, or seven carbon atoms. These side chains are either paraffin chains or else contain a keto group in the alpha or beta position.

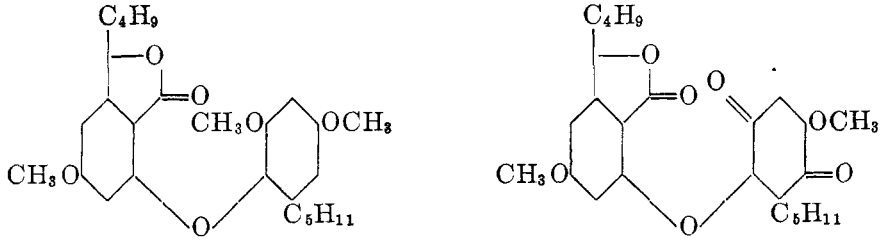
Mild hydrolysis usually opens the lactone ring in depsidones, while boiling with strong alkali or barium hydroxide causes the elimination of carbon dioxide. The ether linkage is broken by alkali fusion. The resulting fragments can be identified for proof of structure. In the case of lobaric acid, where alkali fusion fails to give fragments of both rings, thermal decomposition causes cleavage of the ether linkage with formation of two identifiable products (16).

The diphenyl ether skeleton of the compounds is usually obtained by methylation of all free hydroxyl groups and removal of the carboxyl groups by heating with strong alkali. The structure of these diphenyl ether skeletons can be ascertained from the products obtained on oxidation of the ether and of its bromination product. Protophysodon trimethyl ether (XLIII), for example, gives 6-methoxy-2-methyl-1,4-benzoquinone (XLIV) on oxidation with chromic acid, while its tribromo derivative yields 6-methoxy-2-amyl-3-bromo-1,4-benzoquinone (11).



XLIII XLIV

In the oxidation of the dimethyl ether of lobariolide (XLV), a degradation product of lobaric acid, chromic acid oxidation leaves the ether linkage intact, so that the complex aryloxyquinone (XLVI) may be isolated (16). 6-Methoxy-2-amyl-1,4-benzoquinone is also formed on oxidation.



XLV XLVI

The final proof for the structure of the diphenyl ether skeletons, which are polyalkylpolymethoxydiphenyl ethers, is by synthesis, which has been realized in a number of cases (9, 12, 13, 17).

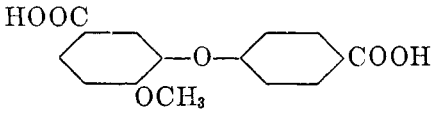
The phenolic nuclei in the depsidones of the second type (XLII) are charac-

terized by methyl side chains (R, R′, R‴, R⁗) in various stages of oxidation, that is, methyl, methylol, formyl, and carboxyl groups (7). All depsidones of this group known at the present time contain one aldehyde group which gives rise to various characteristic color tests.

For the determination of structures in this class of compounds the various methylol, formyl, and methylol ether groups are reduced to methyl groups (10, 14). The hydrogenated products are then investigated like the depsidones of the first type (9). Additional information can be obtained by submitting depsidones of the β-orcinol type to alkali fusion or pyrolysis.

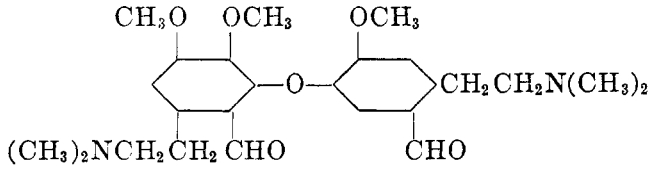
XX. ALKALOIDS

Diphenyl ether linkages occur in the isoquinoline alkaloids of the Berberidaceae, Menispermaceae, papeira bark, and curare (122). Examples of the alkaloids which occur in the first two groups are oxyacanthine and dauricine. Both are somewhat related and yield the same acid (XLVII) when the ammonium base obtained from the exhaustive methylation of the alkaloid is oxidized with potassium permanganate. The structure of the acid (XLVII) has been established by synthesis (155, 239, 254).



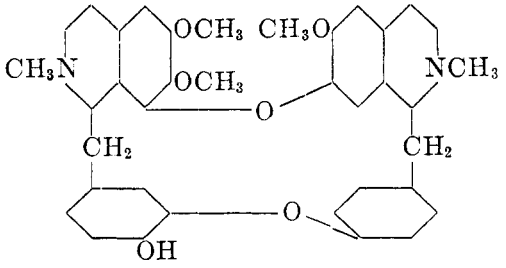
XLVII

A second fragment (XLVIII) of oxyacanthine was obtained along with the dialdehyde corresponding to XLVII by ozonizing the methine base formed in the first stage of the Hofmann degradation (40).

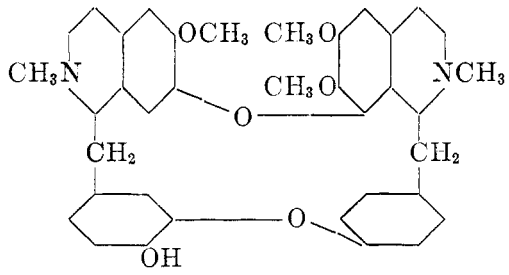


XLVIII

Treatment of the diamine (XLVIII) with alkali gave a nitrogen-free divinyldialdehyde which was reduced to 2,3,2′-trimethoxy-5′,6-dimethyl-4′,5-diethyldiphenyl ether. The structure of the latter was confirmed by synthesis. On the basis of these and other data oxyacanthine was assigned the configuration XLIX or L.

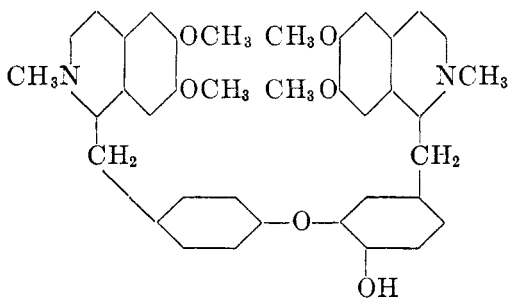


XLIX

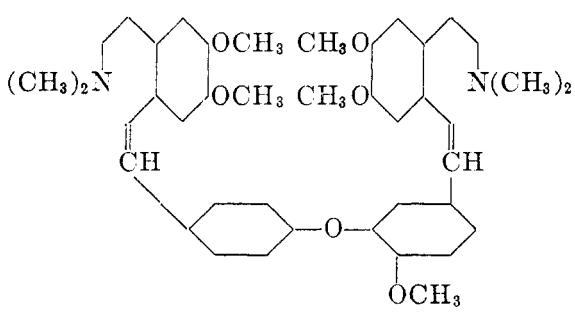


L

The structure of dauricine (LI) is based largely on the synthesis of the methine (LII) which is produced in the first stage of the Hofmann degradation of this alkaloid.

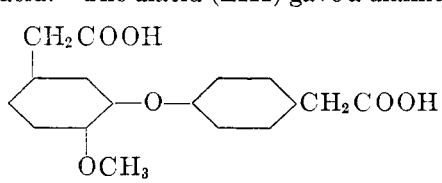


LI



LII

The starting material for this synthesis, 4′,5-diformyl-2-methoxydiphenyl ether, was obtained by the Rosenmund reduction of the corresponding diacid chloride. It was converted to the di(carboxymethyl)diphenyl ether (LIII) by way of the azlactone and diketo acid. The diacid (LIII) gave a diamide with homoveratryl-

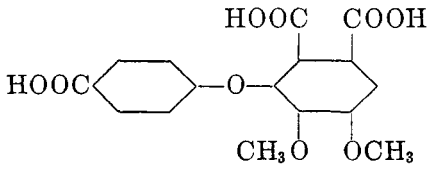


LIII

amine which was cyclized to the bisisoquinoline derivative by treatment with phosphorus pentachloride. Reduction followed by methylation yielded the methine (LII) (155).

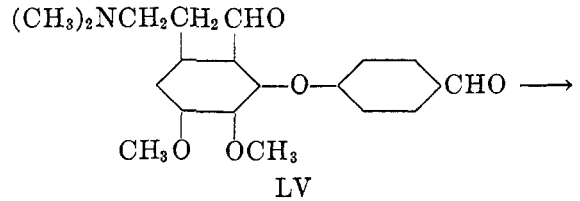
Alkali fusion of oxyacanthine yields *p*-hydroxybenzoic acid (254). The same reaction with tetrandrine and trilobine, two of the Menispermaceae alkaloids, furnishes protocatechuic acid (122).

The two papeira bark alkaloids isochondrodendrine and bebeerine give the same acid (LIV) on oxidation of the non-nitrogenous compounds obtained from the product of the exhaustive methylation of the alkaloids with base. The structure of LIV was established by synthesis (74, 76).

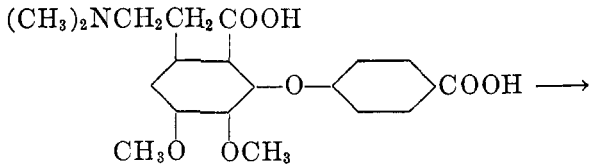


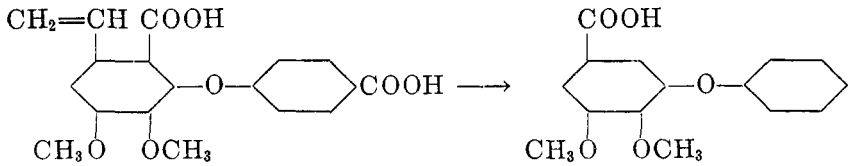
LIV

The structure of isochondrodendrine was based on the above degradation and the ozonization product (LV) of the methine base obtained by exhaustive methylation of the alkaloid. The dialdehyde (LV) was oxidized, deaminated with alkali, decarboxylated, and oxidized to the acid (LVII) which was also prepared from methyl bromoveratrate by the Ullmann reaction (73).



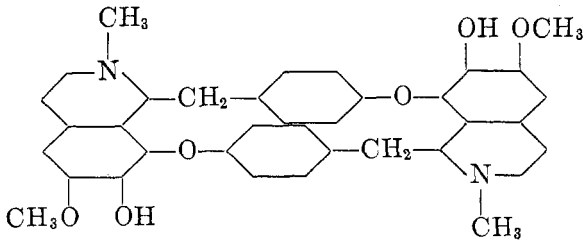
LV



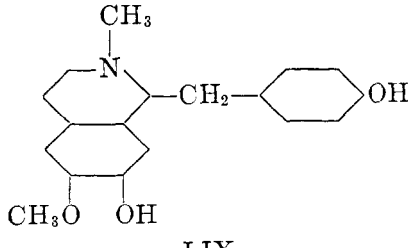


LVI LVII

In view of the excellent yield of the vinyl acid (LVI) in this degradation, isochondrodendrine was given the structure LVIII, which is built up from two identical fragments, and might be considered as a dehydrogenation product from two molecules of coclaurine (LIX), an alkaloid of the Menispermaceae.

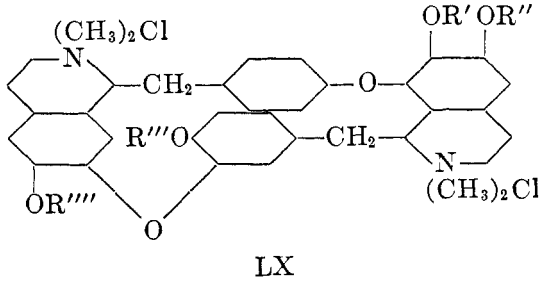


LVIII



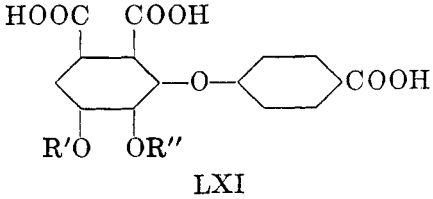
LIX

Bebeerine methochloride and the curare alkaloid tubocurarine chloride are diastereoisomers which have been assigned the structure LX largely on the basis of the oxidation acids (LXI and LXII, where the R groups are methyl)

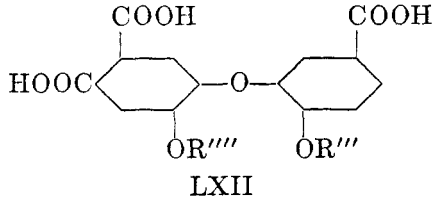


LX

obtained from the deaminated base which results from the exhaustive methylation of the alkaloids.



LXI



LXII

Two of the R groups in LX are methyl and two are hydrogen. The positions of the free hydroxyl groups were determined by King (142), who marked them by ethylation with ethyl iodide. The ethoxy acids (LXI: R′ = CH_3, R″ = CH_2CH_3; LXII: R‴ = CH_2CH_3, R⁗ = CH_3) were prepared by synthesis from

the potassium salt of methyl *p*-hydroxybenzoate and methyl 3-bromo-5-methoxy-4-ethoxyphthalate, and the potassium salt of methyl 3-hydroxy-4-ethoxy-benzoate and methyl 5-iodo-4-methoxyphthalate. Since they were found to be identical with the degradation acids, R″ and R‴ in the alkaloids LX must be hydrogens, and R′ and R⁗ must be methyl groups.

The methods used for the structural elucidation of other alkaloids containing diaryl ether linkages are very similar to those discussed in the preceding examples.

The author has made use of the historical part of a thesis submitted by E. F. Orwoll to the Faculty of the Graduate School of the University of Missouri in partial fulfilment of the requirements for the degree of Doctor of Philosophy in August, 1945.

XXI. REFERENCES

(1) ADAMS, R., AND MONTGOMERY, E.: J. Am. Chem. Soc. **46**, 1518 (1924).
(2) ADKINS, H.: *Reactions of Hydrogen*, p. 59. The University of Wisconsin Press, Madison (1937).
(3) ANDERSAG, H.: *Medizin und Chemie*, Vol. 2, p. 359. I. G. Farbenindustrie, Elberfeld (1934).
(4) AMATATSU, R., AND ARAKI, S.: J. Chem. Soc. Japan **52**, 484 (1931).
(5) ANSCHÜTZ, R., STOLTENHOFF, W., AND VOELLER, F.: Ber. **58B**, 1736 (1925).
(6) ARBENZ, C.: Ann. **257**, 76 (1890).
(7) ASAHINA, Y.: Acta Phytochim. (Japan) **8**, 33 (1934).
(8) ASAHINA, Y.: Fortschr. Chem. org. Naturstoffe **2**, 46 (1939).
(9) ASAHINA, Y., AND ASANO, J.: Ber. **66**, 1215 (1933).
(10) ASAHINA, Y., AND HAYASHI, H.: Ber. **70**, 810 (1937).
(11) ASAHINA, Y., AND NOGAMI, H.: Ber. **68**, 77 (1935).
(12) ASAHINA, Y., AND NOGAMI, H.: Ber. **68**, 1500 (1935).
(13) ASAHINA, Y., AND SHIBATA, S.: Ber. **72**, 1399 (1939).
(14) ASAHINA, Y., AND TANASE, Y.: Ber. **67**, 766 (1934).
(15) ASAHINA, Y., AND TANASE, Y.: Proc. Imp. Acad. (Tokyo) **16**, 297 (1940).
(16) ASAHINA, Y., AND YASUE, M.: Ber. **69**, 644 (1936).
(17) ASAHINA, Y., AND YASUE, M.: Ber. **70**, 206 (1937).
(18) AYLSWORTH, J. W.: U. S. patent 1,213,142 (January 23, 1917).
(19) BAEYER, A. v.: Ann. **372**, 99 (1910).
(20) BARKDOLL, A. E., AND ROSS, W. F.: J. Am. Chem. Soc. **66**, 898 (1944).
(21) BARNETT, E. B., AND GOODWAY, N. F.: Ber. **63**, 3048 (1930).
(22) BELOV, V. N., AND SHEPELENKOVA, E. I.: J. Gen. Chem. (U.S.S.R.) **11**, 757 (1941).
(23) BLOCK, P., JR.: J. Biol. Chem. **135**, 51 (1940).
(24) BLOCK, P., JR., AND POWELL, G.: J. Am. Chem. Soc. **64**, 1070 (1942).
(25) BÖHMER, C.: J. prakt. Chem. [2] **24**, 473 (1881).
(26) BONNEAUD, M. A.: Bull. soc. chim. [4] **7**, 779 (1910).
(27) BORSCHE, W.: Ber. **56**, 1488 (1923).
(28) BOST, R. W., AND NICHOLSON, F.: J. Am. Chem. Soc. **57**, 2368 (1935).
(29) BOUVEAULT, M. L.: Bull. soc. chim. [3] **17**, 949 (1897).
(30) BOVARNICK, M., BLOCH, K., AND FOSTER, G. L.: J. Am. Chem. Soc. **67**, 562 (1945).
(31) BRANCH, G. E. K., AND CALVIN, M.: *The Theory of Organic Chemistry*, p. 137. Prentice-Hall, Inc., New York (1941).
(32) BREWSTER, R. Q., AND CHOGUILL, H. S.: J. Am. Chem. Soc. **61**, 2702 (1939).
(32a) BREWSTER, R. Q., AND GROENING, T.: *Organic Syntheses*, Vol. 14, p. 66. John Wiley and Sons, Inc., New York (1934).

(33) BREWSTER, R. Q., AND POJE, J. A.: J. Am. Chem. Soc. **61,** 2419 (1939).
(34) BREWSTER, R. Q., AND SLOCOMBE, R.: J. Am. Chem. Soc. **67,** 562 (1945).
(35) BREWSTER, R. Q., AND STEVENSON, G.: J. Am. Chem. Soc. **62,** 3144 (1940).
(36) BREWSTER, R. Q., AND STRAIN, F.: J. Am. Chem. Soc. **56,** 117 (1934).
(37) BRINER, E., BRON-STALET, J., AND PAILLARD, H.: Helv. Chim. Acta **15,** 619 (1932).
(38) BRITTON, E. C.: U. S. patent 1,959,283 (May 15, 1934).
(39) BRITTON, E. C., STOESSER, W. C., AND GOERGEN, G. G.: U. S. patent 2,022,634 (November 26, 1935).
(40) BRUCHHAUSEN, F. v., OBEREMPT, H., AND FELDHAUS, A.: Ann. **507,** 145 (1933).
(41) BUCH, K.: Ber. **17,** 2634 (1884).
(42) BUCHAN, S., AND SCARBOROUGH, H. A.: J. Chem. Soc. **1934,** 705.
(43) CAHN, S.: J. Chem. Soc. **1931,** 1121.
(44) CALCOTT, W. S., DOUGLASS, W. A., AND WALKER, H. W.: U. S. patent 1,913,368 (1933).
(45) CALCOTT, W. S., TINKER, J. M., AND WEINMAYR, V.: J. Am. Chem. Soc. **61,** 1014 (1939).
(46) CAMPBELL, N. R., AND CHATTAWAY, F. W.: Proc. Roy. Soc. (London) **B130,** 435 (1942).
(47) CAMPBELL, I. G. M., AND TURNER, E. E.: J. Chem. Soc. **1938,** 37.
(48) CANZANELLI, A., GUILD, R., AND HARINGTON, C. R.: Biochem. J. **29,** 1617 (1935).
(49) CLARKSON, R. G., AND GOMBERG, M.: J. Am. Chem. Soc. **52,** 2881 (1930).
(50) COLEMAN, G. H., AND DREISBACH, R. D.: U. S. patent 2,170,989 (August 29, 1939).
(51) COLEMAN, G. H., AND HADLER, B. C.: U. S. patent 2,079,279 (May 4, 1937).
(52) COLEMAN, G. H., AND PERKINS, R. P.: U. S. patent 2,170,809 (August 29, 1939).
(53) COOK, A. N.: J. Am. Chem. Soc. **25,** 61 (1903).
(54) COOK, A. N.: J. Am. Chem. Soc. **26,** 302 (1904).
(55) COOK, A. N.: Am. Chem. J. **36,** 543 (1906).
(56) COOK, A. N.: J. Am. Chem. Soc. **32,** 1285 (1910).
(57) COOK, A. N., AND EBERLY, C. F.: J. Am. Chem. Soc. **24,** 1200 (1902).
(58) COOK, A. N., AND FRARY, G. G.: Am. Chem. J. **28,** 486 (1902).
(59) COOK, A. N., AND SHERWOOD, F. F.: J. Am. Chem. Soc. **37,** 1835 (1915).
(60) COX, E. H.: J. Am. Chem. Soc. **52,** 352 (1930).
(61) CULLINANE, N. M., DAVEY, H. G., AND PADFIELD, H. J. H.: J. Chem. Soc. **1934,** 716.
(62) DAVIES, W. C., AND MORRIS, C. J. O. R.: J. Chem. Soc. **1932,** 2880.
(63) DAVIES, W. C., AND MORRIS, C. J. O. R.: Bull. soc. chim. [4] **53,** 980 (1933).
(64) DAVIES, W. C., AND OTHEN, C. W.: J. Chem. Soc. **1936,** 1236.
(65) DILTHEY, W., BACH, E., GRÜTERING, H., AND HAUSDÖRFER, E.: J. prakt. Chem. **117,** 337 (1927).
(66) DILTHEY, W., AND HARENBERG, F.: J. prakt. Chem. **136,** 67 (1933).
(67) DILTHEY, W., NEUHAUS, L., REIS, E., AND SCHOMMER, W.: J. prakt. Chem. **124,** 81 (1929).
(68) DREW, H. D. K.: J. Chem. Soc. **1926,** 223.
(69) DREW, H. D. K., AND THOMASON, R. W.: J. Chem. Soc. **1927,** 116.
(70) ECKERT, A., AND SEIDEL, F.: J. prakt. Chem. [2] **102,** 344 (1921).
(71) ETARD, M. A.: Bull. soc. chim. [2] **28,** 276 (1877).
(72) ETZELMILLER, R. E., AND HAMILTON, C. S.: J. Am. Chem. Soc. **53,** 3085 (1931).
(73) FALTIS, F., AND DIETERICH, H.: Ber. **67B,** 231 (1934).
(74) FALTIS, F., AND FRAUENDORFER, H.: Ber. **63,** 806 (1930).
(75) FALTIS, F., HOLZINGER, L., ITA, P., AND SCHWARZ, R.: Ber. **74B,** 79 (1941).
(76) FALTIS, F., AND TROLLER, A.: Ber. **61B,** 345 (1928).
(77) FICHTER, F., AND BRUNNER, E.: Bull. soc. chim. [4] **19,** 280 (1916).
(78) FOSSE, R.: Bull. soc. chim [3] **31,** 253 (1904).
(79) FOSSE, R., AND ROBYN, A.: Bull. soc. chim. [3] **31,** 267 (1904).
(80) FOX, D. L., AND TURNER, E. E.: J. Chem. Soc. **1930,** 1115.
(81) FOX, D. L., AND TURNER, E. E.: J. Chem. Soc. **1930,** 1853.

(82) FREY, M.: Ber. **45,** 1359 (1912).
(83) FUZIKAWA, F.: Ber. **68,** 73 (1935).
(84) GATTERMANN, L.: Ann. **357,** 363 (1907).
(85) GILMAN, H., AND BEBB, R. L.: J. Am. Chem. Soc. **61,** 109 (1939).
(86) GILMAN, H., LANGHAM, W., AND JACOBY, A. L.: J. Am. Chem. Soc. **61,** 106 (1939).
(87) GILMAN, H., VAN ESS, M. W., AND HAYES, D. M.: J. Am. Chem. Soc. **61,** 643 (1939).
(88) GILMAN, H., AND VAN ESS, P. R.: J. Am. Chem. Soc. **61,** 1365 (1939).
(89) GLADSTONE, J. H., AND TRIBE, A.: J. Chem. Soc. **41,** 5 (1882).
(90) GLADSTONE, J. H., AND TRIBE, A.: J. Chem. Soc. **49,** 27 (1886).
(90a) GOLDSCHMIDT, S.: *Hand-und Jahrbuch der chemischen Physik*, Vol. 4, p. 161. Akademische Verlagsgesellschaft, Leipzig (1933).
(91) GOLDSCHMIDT, A., SCHULTZ, E., AND BERNARD, H.: Ann. **478,** 1 (1931).
(92) GOMBERG, M., AND CONE, L. H.: Ann. **370,** 183 (1909).
(93) GOTTESMAN, E.: Ber. **66,** 1168 (1933).
(94) GRAEBE, C.: Ber. **13,** 1851 (1880).
(95) GRAEBE, C.: Ann. **209,** 150 (1881).
(96) GRAEBE, C.: Ber. **21,** 501 (1888).
(97) GRAEBE, C., AND ULLMANN, F.: Ber. **29,** 1876 (1896).
(98) GRIESS, P.: Ber. **21,** 980 (1888).
(99) GROVES, L. G., TURNER, E. E., AND SHARP, G. I.: J. Chem. Soc. **1929,** 512.
(100) HAEUSSERMAN, C., AND BAUER, E.: Ber. **29,** 2085 (1896).
(101) HAEUSSERMAN, C., AND BAUER, E.: Ber. **30,** 738 (1897).
(102) HAEUSSERMAN, C., AND MÜLLER, A.: Ber. **34,** 1070 (1901).
(103) HAEUSSERMAN, C., AND SCHMIDT, O.: Ber. **34,** 3770 (1901).
(104) HAEUSSERMAN, C., AND TEICHMANN, H.: Ber. **29,** 1446 (1896).
(105) HALE, W. J., AND BRITTON, E. C.: U. S. patent 1,737,841 (December 3, 1929).
(105a) HALE, W. J., AND BRITTON, E. C.: U. S. patent 1,737,842 (December 13, 1929).
(106) HALE, W. J., AND BRITTON, E. C.: U. S. patent 1,806,798 (May 26, 1931).
(107) HALE, W. J., AND BRITTON, E. C.: U. S. patent 1,882,824 (October 18, 1933).
(108) HALE, W. J., AND BRITTON, E. C.: U. S. patent 1,925,321 (September 5, 1933).
(109) HAMILTON, C. S., AND MORGAN, J. F.: In *Organic Reactions*, Vol. 2, p. 417. John Wiley and Sons, Inc., New York (1944).
(110) HAMMETT, L. P.: *Physical Organic Chemistry*, p. 33. McGraw-Hill Book Co., Inc., New York and London (1940).
(111) HAMPSON, G. C., FARMER, R. H., AND SUTTON, L. E.: Proc. Roy. Soc. (London) **A143,** 150 (1933).
(112) HARINGTON, C. R.: Biochem. J. **20,** 300 (1926).
(113) HARINGTON, C. R.: *The Thyroid Gland*, pp. 93–111. Oxford University Press, London (1933).
(114) HARINGTON, C. R.: Fortschr. Chem. org. Naturstoffe **2,** 103 (1939).
(115) HARINGTON, C. R., AND BARGER, G.: Biochem. J. **21,** 169 (1927).
(116) HARINGTON, C. R., AND MCCARTNEY, W.: Biochem. J. **21,** 852 (1927).
(117) HARINGTON, C. R., AND RIVERS, R. P.: Nature **144,** 205 (1939).
(118) HARINGTON, C. R., AND RIVERS, R. P.: J. Chem. Soc. **1940,** 1101.
(119) HEINDEL, L.: Trans. Am. Inst. Chem. Engrs. **32,** 73 (1936).
(120) HENLEY, R. V.: J. Chem. Soc. **1930,** 1222.
(121) HENLEY, R. V., AND TURNER, E. E.: J. Chem. Soc. **1930,** 928.
(122) HENRY, T. A.: *The Plant Alkaloids*, pp. 352–83. P. Blakiston's Son and Co., Philadelphia (1939).
(123) HILLYER, H. W.: Am. Chem. J. **26,** 365 (1901).
(124) HIRSCH, R.: Ber. **23,** 3705 (1890).
(125) HIRSCH, R.: German patent 58,001 (June 10, 1890).
(126) HOFFMEISTER, W.: Ber. **3,** 747 (1870).
(127) HOFFMEISTER, W.: J. prakt. Chem. [2] **1,** 143 (1870).

(128) HOFFMEISTER, W.: Ann. **159,** 191 (1871).
(129) HÖNIGSCHMID, O.: Monatsh. **23,** 824 (1902).
(130) HOUBEN, J., AND FISCHER, W.: Ber. **64,** 2645 (1931).
(131) HÜCKEL, W.: *Theoretische Grundlagen der organischen Chemie*, 2nd edition, p. 55. Akademische Verlagsgesellschaft, Leipzig (1935).
(132) HUNTRESS, E. H., AND CARTEN, F. H.: J. Am. Chem. Soc. **62,** 603 (1940).
(133) IPATIEFF, W., AND ORLOW, N.: Ber. **60B,** 1963 (1927).
(134) IPATIEFF, W., AND PHILIPOV, O.: Ber. **41,** 1001 (1908).
(135) JAPP, F. R., AND FINDLAY, A. J.: J. Chem. Soc. **71,** 1119 (1879).
(136) JEITELES, B.: Monatsh. **17,** 65 (1896).
(137) JOHNSON, T. B., AND TEWKESBURY, L. B.: Proc. Natl. Acad. Sci. U. S. **28,** 73 (1942).
(138) JONES, H. I., AND COOK, A. N.: J. Am. Chem. Soc. **38,** 1535 (1916).
(139) KEIMATSU, I., AND YAMAGUCHI, E.: J. Pharm. Soc. Japan **56,** 680 (1936).
(140) KENT, B. A., AND SMILES, S.: J. Chem. Soc. **1934,** 422.
(141) KING, F. E.: J. Chem. Soc. **1934,** 1064.
(142) KING, H.: J. Chem. Soc. **1939,** 1157.
(143) KING, H.: J. Chem. Soc. **1939,** 1165.
(144) KING, H., AND WRIGHT, E. V.: J. Chem. Soc. **1939,** 1168.
(145) KIPPER, H.: Ber. **38,** 2490 (1905).
(146) KLARMAN, E., GATYAS, L. W., AND SHTERNOV, V. A.: J. Am. Chem. Soc. **53,** 3404 (1931).
(147) KLARMAN, E., GATYAS, L. W., AND SHTERNOV, V. A.: J. Am. Chem. Soc. **54,** 298 (1932).
(148) KLEPL, A.: J. prakt. Chem. [2] **28,** 199 (1883).
(149) KNAPP, W. A.: U. S. patent 2,251,743 (August 5, 1941).
(150) KOHLER, E. P.: Am. Chem. J. **27,** 241 (1902).
(151) KOHLER, E. P., HERITAGE, G. L., AND BURNLEY, M. C.: Am. Chem. J. **44,** 60 (1910).
(152) KOMATSU, S., AND MASUMOTO, M.: Bull. Chem. Soc. Japan **5,** 241 (1930).
(153) KOMATSU, S., SUGINO, K., AND HAGIWARA, M.: Proc. Imp. Acad. (Tokyo) **6,** 194 (1930).
(154) KONDO, H., AND KEIMATSU, I.: Ber. **71,** 2553 (1938).
(155) KONDO, H., NARITA, Z., AND UYEO, S.: Ber. **68,** 519 (1935).
(156) KRAFFT, F., AND STEINER, O.: Ber. **34,** 561 (1901).
(157) KRANZFELDER, A. L., VERBANC, J. J., AND SOWA, F. J.: J. Am. Chem. Soc. **59,** 1488 (1937).
(157a) KRISHNA, S.: J. Chem. Soc. **123,** 2782 (1923).
(158) LANGHAM, W., BREWSTER, R. Q., AND GILMAN, H.: J. Am. Chem. Soc. **63,** 545 (1941).
(159) LAUBE, E.: Ber. **39,** 2245 (1906).
(160) LEA, T. R., AND ROBINSON, R.: J. Chem. Soc. **1926,** 411.
(161) LEFEVRE, R. J. W., SAUNDERS, S. L. M., AND TURNER, E. E.: J. Chem. Soc. **1927,** 1168.
(162) LESPAGNOL, A., BERTRAND, J., AND DUPAS, J.: Bull. soc. chim. [5] **6,** 1625 (1939).
(163) LESSLIE, M. S.: J. Chem. Soc. **1938,** 1001.
(164) LESSLIE, M. S., AND TURNER, E. E.: J. Chem. Soc. **1932,** 281.
(165) LESSLIE, M. S., AND TURNER, E. E.: J. Chem. Soc. **1934,** 1170.
(166) LEVI, A. A., AND SMILES, S.: J. Chem. Soc. **1932,** 1488.
(167) LEVY, A. A., RAINS, H. C., AND SMILES, S.: J. Chem. Soc. **1931,** 3264.
(168) LEWIS, W. L., AND CHEETHAM, H. C.: J. Am. Chem. Soc. **43,** 2117 (1921).
(169) LEWIS, W. L., LOWRY, C. D., AND BERGEIM, F. H.: J. Am. Chem. Soc. **43,** 891 (1921).
(170) LIONS, F., AND WILLISON, A. M.: J. Proc. Roy. Soc. N. S. Wales **71,** 435 (1938).
(171) LIONS, F., AND WILLISON, A. M.: J. Proc. Roy. Soc. N. S. Wales **72,** 257 (1939).
(172) LIST, K., AND LIMPRICHT, H.: Ann. **90,** 209 (1854).
(173) LOBRY DE BRUYN, C. A., AND VANGEUNS, J. W.: Rec. trav. chim. **23,** 26 (1904).
(174) LOCK, G. M.: Monatsh. **55,** 167 (1930).

(175) LOCK, G., AND KEMPTER, F. H.: Monatsh. **67,** 24 (1935).
(176) LOEWENICH, J., BECKER, W., AND SCHRÖDER, T.: J. prakt. Chem. **127,** 248 (1930).
(177) LUDWIG, W., AND MUTZENBECHER, P.: Z. physiol. Chem. **258,** 210 (1939).
(178) LÜTTRINGHAUS, A.: Ann. **528,** 223 (1937).
(179) LÜTTRINGHAUS, A., AND SÄÄF, G. v.: Ann. **542,** 241 (1939).
(180) MCCOMBIE, H., MACMILLAN, W. G., AND SCARBOROUGH, H. A.: J. Chem. Soc. **1930,** 1202.
(181) MCCOMBIE, H., MACMILLAN, W. G., AND SCARBOROUGH, H. A.: J. Chem. Soc. **1931,** 529.
(182) MACLAY, W. D., AND HAMILTON, C. S.: J. Am. Chem. Soc. **54,** 3310 (1932).
(183) MAEYER, F., AND KRIEGER, W.: Ber. **55,** 1659 (1922).
(184) MAIKOPAR: Ber. **6,** 564 (1873).
(185) MAILHE, A., AND MOUREU, M. C.: Compt. rend. **154,** 1240 (1912).
(186) MAILHE, A., AND MURAT, M.: Compt. rend. **154,** 601 (1912).
(187) MAILHE, A., AND MURAT, M.: Bull. soc. chim. [4] **11,** 288 (1912).
(188) MARTY, A.: Compt. rend. **187,** 47 (1928).
(189) MATSUMURA, K.: J. Am. Chem. Soc. **52,** 3201 (1930).
(190) MECKE, R.: Z. physik. Chem. **261,** 253 (1939).
(191) MERZ, V., AND WEITH, W.: Ber. **14,** 187 (1881).
(192) MEYER, K. H., AND BERGIUS, F.: Ber. **47,** 3158 (1914).
(193) MEYER, H., AND HOFMAN, A.: Monatsh. **37,** 705 (1916).
(194) MOLDAVSKI, B. L., AND LIVSHITZ, S.: J. Gen. Chem. (U.S.S.R.) **4,** 948 (1934).
(195) MOLE, J. D. C., AND TURNER, E. E.: J. Chem. Soc. **1939,** 1720.
(196) MÜLLER, E., AND BUNGE, W.: Ber. **69,** 2164 (1936).
(197) MUTZENBECHER, P. v.: Z. physiol. Chem. **261,** 253 (1939).
(198) NAKAI, R.: Bull. Chem. Soc. Japan **5,** 136 (1930).
(199) NIEMANN, C., BENSON, A. A., AND MEAD, J. F.: J. Am. Chem. Soc. **63,** 2204 (1941).
(200) NIEMANN, C., AND MEAD, J. F.: J. Am. Chem. Soc. **63,** 2685 (1941).
(201) NIEMANN, C., MEAD, J. F., AND BENSON, A. A.: J. Am. Chem. Soc. **63,** 609 (1941).
(202) NIEMANN, C., AND REDEMANN, C. E.: J. Am. Chem. Soc. **63,** 1549 (1941).
(203) NIETZKI, R., AND SCHÜNDELEN, B.: Ber. **24,** 3586 (1891).
(204) NOLLAU, E. H., AND DANIELS, L. C.: J. Am. Chem. Soc. **36,** 1885 (1914).
(205) NORRIS, J. F., MACINTIRE, B. G., AND CORSE, W. M.: Am. Chem. J. **29,** 127 (1903).
(206) OGAWA, T.: Bull. Chem. Soc. Japan **6,** 174 (1931).
(207) ÖSTERLIN, M.: Monatsh. **57,** 31 (1931).
(208) PAAL, C., AND DEYBECK, S.: Ber. **30,** 884 (1897).
(209) PEARSON, J. H., AND HAMMAREN, B. W.: U. S. patent 2,349,459 (May 23, 1944).
(210) PERATONER, A., AND ORTOLEVA, G.: Gazz. chim. ital. **28,** 197 (1898).
(211) POSTOWSKY, J., AND LUGOWKIN, B.: J. prakt. Chem. [2] **122,** 141 (1929).
(212) PREY, V.: Ber. **76B,** 156 (1943).
(213) PUMMERER, R., MELAMED, D., AND PUTTFARCKEN, H.: Ber. **55B,** 3116 (1922).
(214) PURGOTTI, A.: Gazz. chim. ital. **44,** I, 643 (1914).
(215) PÜTZER, B., AND SCHÖNHÖFER, F.: German patent 550,327 (October 24, 1932).
(216) QUILICO, A.: Atti accad. Lincei [6] **6,** 512 (1927).
(217) RAIFORD, L. C., AND COLBERT, J. C.: J. Am. Chem. Soc. **48,** 2652 (1926).
(218) RAIFORD, L. C., THIESSEN, G. W., AND WERNERT, I. J.: J. Am. Chem. Soc. **52,** 1205 (1930).
(219) RARICK, M. J., BREWSTER, R. Q., AND DAINS, F. B.: J. Am. Chem. Soc. **55,** 1289 (1933).
(220) REILLY, J., AND BARRETT, H. S. B.: J. Chem. Soc. **1927,** 1399.
(221) REILLY, J., AND DRUMM, P. J.: J. Chem. Soc. **1927,** 2814.
(222) REILLY, J., AND DRUMM, P. J.: J. Chem. Soc. **1930,** 455.
(223) REILLY, J., DRUMM, P. J., AND BARRETT, H. S. B.: J. Chem. Soc. **1927,** 67.
(224) REILLY, J., DRUMM, P. J., AND GRAY, T.: Sci. Proc. Roy. Dublin Soc. **19,** 461 (1930).

(225) RITTLER, K. W.: German patent 588,650 (November 23, 1933).
(226) RITTLER, K. W.: German patent 609,080 (February 8, 1935).
(227) RITTLER, K. W., AND ROST, A.: German patent 611,400 (March 7, 1935).
(228) ROBERTS, E., AND TURNER, E. E.: J. Chem. Soc. **127**, 2004 (1925).
(229) ROBERTS, K. C., AND CLARK H. B.: J. Chem. Soc. **1935**, 1312.
(230) ROBERTS, K. C., AND DE WORMS, C. G. M.: J. Chem. Soc. **1934**, 727.
(231) ROBERTS, K. C., AND DE WORMS, C. G. M.: J. Chem. Soc. **1935**, 1309.
(232) ROBERTS, K. C., DE WORMS, C. G. M., AND CLARK, H. B.: J. Chem. Soc. **1935**, 196.
(233) ROBINSON, R., AND SUGASAWA, S.: J. Chem. Soc. **1931**, 3173.
(234) RYAN, H., KEANE, J., AND M'GAHON, J. C.: Proc. Roy. Irish Acad. **37B**, 368 (1927).
(235) SABATIER, P., AND MAILHE, A.: Compt. rend. **151**, 493 (1910).
(236) SABATIER, P., AND MAILHE, A.: Compt. rend. **155**, 261 (1912).
(237) SABATIER, P., AND MAILHE, A.: Bull. soc. chim. [4] **11**, 843 (1912).
(238) SABATIER, P., AND MAILHE, A.: Compt. rend. **158**, 611 (1914).
(239) SANTOS, A. C.: Dissertation Westfälischen Wilhelms-Universität, Münster, 1929, p. 5.
(240) SARTORETTO, P. A., AND SOWA, F. J.: J. Am. Chem. Soc. **59**, 603 (1937).
(241) SAUNDERS, K. H.: *The Aromatic Diazocompounds*, p. 33. Edward Arnold and Co., London (1936).
(242) SCARBOROUGH, H. A.: J. Chem. Soc. **1929**, 2361.
(243) SCARBOROUGH, H. A., AND SWEETEN, J. L.: J. Chem. Soc. **1934**, 52.
(244) SCARBOROUGH, H. A., AND SWEETEN, J. L.: J. Chem. Soc. **1934**, 867.
(245) SCHICKH, O. V.: Ber. **69**, 242 (1936).
(246) SCHIEMANN, G., AND WINKELMÜLLER, W.: J. prakt. Chem. **135**, 101 (1932).
(247) SCHROEDER, W. D., AND BREWSTER, R. Q.: J. Am. Chem. Soc. **60**, 751 (1938).
(248) SCHUEGRAF, K.: Helv. Chim. Acta **12**, 405 (1929).
(249) SHORYGIN, P., AND SKOBLINSKAYA, S. A.: Compt. rend. acad. sci. U. R. S. S. **14**, 505 (1937).
(250) SLOTTA, K. H., AND SOREMBA, K. H.: Ber. **68**, 2059 (1935).
(251) SLOTTA, K. H., AND SOREMBA, K. H.: Ber. **69**, 566 (1936).
(252) SMYTH, C. P., AND WALLS, W. S.: J. Am. Chem. Soc. **54**, 3230 (1932).
(253) SPÄTH, E.: Monatsh. **35**, 319 (1914).
(254) SPÄTH, E., AND PICKL, J.: Ber. **62**, 2251 (1929).
(255) STAUDINGER, H., AND STAIGER, F.: Ann. **517**, 67 (1935).
(256) STÖHR, R.: Z. physiol. Chem. **201**, 142 (1931).
(257) STROUD, S. W.: J. Endocrinol. **2**, 55 (1940).
(258) SUTER, C. M.: J. Am. Chem. Soc. **51**, 2581 (1929).
(259) SUTER, C. M.: J. Am. Chem. Soc. **53**, 1112 (1931).
(260) SUTER, C. M., AND GREEN, F. O.: J. Am. Chem. Soc. **59**, 2578 (1937).
(261) SUTER, C. M., MCKENZIE, J. P., AND MAXWELL, C. E.: J. Am. Chem. Soc. **58**, 717 (1936).
(262) SUTER, C. M., AND MAXWELL, C. E.: *Organic Syntheses*, Vol. 18, p. 64. John Wiley and Sons, Inc., New York (1938).
(263) SUTER, C. M., AND OBERG, E.: J. Am. Chem. Soc. **53**, 1567 (1931).
(264) SUTER, C. M., AND SCRUTCHFIELD, P. H.: J. Am. Chem. Soc. **58**, 54 (1936).
(265) SUTTON, L. E., AND HAMPSON, G. C.: Trans. Faraday Soc. **31**, 945 (1935).
(266) THOMPSON, M. C., AND TURNER, E. E.: J. Chem. Soc. **1938**, 29.
(267) TOMITA, M.: J. Pharm. Soc. Japan **54**, 897 (1934).
(268) TOMITA, M.: J. Pharm. Soc. Japan **56**, 492 (1936).
(269) TOMITA, M.: J. Pharm. Soc. Japan **56**, 683 (1936).
(270) TOMITA, M.: J. Pharm. Soc. Japan **56**, 814 (1936).
(271) TOMITA, M.: J. Pharm. Soc. Japan **56**, 906 (1936).
(272) TOMITA, M.: J. Pharm. Soc. Japan **57**, 689 (1937).
(273) TOMITA, M.: J. Pharm. Soc. Japan **58**, 510 (1938).
(274) TOZER, B. H., AND SMILES, S.: J. Chem. Soc. **1938**, 1897.

(275) TOZER, B. H., AND SMILES, S.: J. Chem. Soc. **1938,** 2052.
(276) TURNER, E. E., AND SHEPPARD, A. B.: J. Chem. Soc. **127,** 544 (1925).
(277) ULLMANN, F.: Ber. **29,** 1878 (1896).
(278) ULLMANN, F.: Ber. **37,** 854 (1904).
(279) ULLMANN, F., AND EISER, O.: Ber. **49,** 2162 (1916).
(280) ULLMANN, F., AND ENGI, G.: Ber. **37,** 2368 (1904).
(281) ULLMANN, F., ENGI, G., AND HERRE, E.: Ann. **366,** 86 (1909).
(282) ULLMANN, F., AND KIPPER, H.: Ber. **38,** 2122 (1905).
(283) ULLMANN, F., AND PANCHAUD, L.: Ann. **350,** 113 (1906).
(284) ULLMANN, F., AND SPONAGEL, P.: Ber. **38,** 2212 (1905).
(285) ULLMANN, F., AND SPONAGEL, P.: Ann. **350,** 87 (1906).
(286) ULLMANN, F., AND STEIN, A.: Ber. **39,** 623 (1906).
(287) ULLMANN, F., AND WAGNER, C.: Ann. **355,** 360 (1907).
(288) ULLMANN, F., AND WAGNER, C.: Ann. **371,** 388 (1909).
(289) ULLMANN, F., AND SLOKASOFF, M.: Ber. **38,** 2118 (1905).
(290) ULLOCK, D. S., GAFFERT, G. A., KONZ, P. R., AND BROWN, G. G.: Trans. Am. Inst. Chem. Engrs. **32,** 73 (1936).
(291) UNDERWOOD, H. W., BARIL, O. L., AND TOONE, G. C.: J. Am. Chem. Soc. **52,** 4087 (1930).
(292) UNGNADE, H. E.: J. Am. Chem. Soc. **63,** 2091 (1941).
(293) UNGNADE, H. E., AND ORWOLL, E. F.: J. Am. Chem. Soc. **65,** 1736 (1943).
(294) WALKER, J.: J. Chem. Soc. **1942,** 347 (231).
(295) WALTER, M.: Festschrift Emil C. Barell **1936,** 266; Chem. Zentr. **1937,** II, 380.
(296) WARREN, L. A., AND SMILES, S.: J. Chem. Soc. **1930,** 1327.
(296a) WARREN, L. A., AND SMILES, S.: J. Chem. Soc. **1930,** 962.
(297) WARREN, L. A., AND SMILES, S.: J. Chem. Soc. **1931,** 914.
(298) WARREN, L. A., AND SMILES, S.: J. Chem. Soc. **1931,** 2207.
(299) WARREN, L. A., AND SMILES, S.: J. Chem. Soc. **1932,** 1040.
(300) WEBER, F. C., AND SOWA, F. J.: J. Am. Chem. Soc. **60,** 94 (1938).
(301) WESTON, P. E., AND ADKINS, H.: J. Am. Chem. Soc. **50,** 859 (1928).
(302) WILLGERODT, C.: Ber. **12,** 1277 (1879).
(303) WILLGERODT, C.: Ber. **13,** 887 (1880).
(304) WILLGERODT, C., AND HÜETLIN, E.: Ber. **17,** 1764 (1886).
(305) WILLGERODT, C., AND KORNBLUM, A.: J. prakt. Chem. [2] **39,** 294 (1889).