ARYLTHIAZATHIOLIUM SALTS AND *o*-AMINOARYL THIOLS

THE HERZ REACTION

W. K. WARBURTON[1]

Commonwealth Scientific and Industrial Research Organization, McMaster Animal Health Laboratory, Parramatta Road, Glebe, New South Wales, Australia

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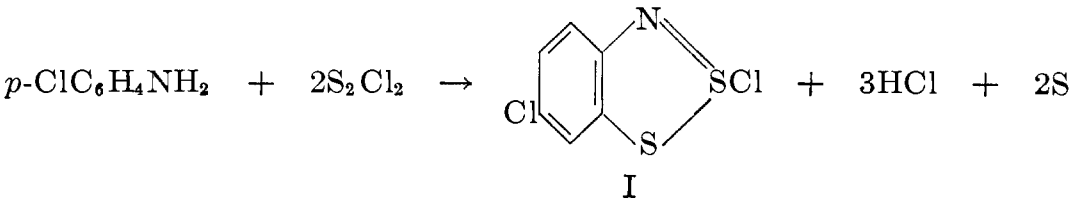
CONTENTS

I. INTRODUCTION

A. The nature of the reaction

In this review the term "Herz reaction" will be used to describe the overall reaction leading to the preparation of *o*-aminobenzenethiols by the condensation of aromatic amines with sulfur chloride and hydrolysis of the condensation product. There are three discernible steps.

In the first step the amine (e.g., *p*-chloroaniline) reacts with sulfur chloride to give a thiazathiolium chloride (I).

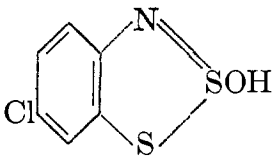


I

Hydrolysis of the thiazathiolium chloride (which is called a Herz compound) proceeds through the replacement of chlorine by hydroxyl to give a thiazathiolium hydroxide (IIA). This replacement can usually be carried out in neutral

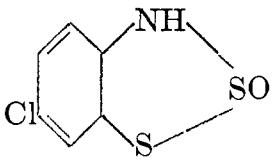
[1] Present address: Chemistry Unit, Glaxo Laboratories, Ltd., Greenford, Middlesex, England.

solution, but the hydroxy compound is not always isolated. Aqueous or aqueous-alcoholic alkali then opens the five-membered ring to give the sodium salt of the *o*-aminobenzenethiol (III) and sodium hydrogen sulfite.



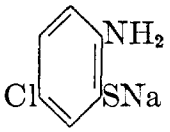
IIA

or



IIB

$+ \quad 2NaOH \rightarrow$



III

$+ \quad NaHSO_3$

The reaction mixture containing the hydrolysis product can be used directly in many syntheses, but the thiol can be precipitated and collected, if required, as the free base or as the zinc mercaptide.

B. Early attempts to thionate aniline

The chemical literature of the period from about 1870 to 1890 described many attempts to prepare dyes from aniline (and other aromatic amines) and sulfur or compounds of sulfur. Some interesting chemical discoveries arose from these experiments, of which an important example is the reaction between sulfur and *p*-phenylenediamine to give Lauth's Violet, the first phenothiazine to be prepared (35). In the same year (1874) Caro prepared methylene blue from sulfur and *p*-aminodimethylaniline. Caro's work has been reviewed by Bernthsen (5).

Claus (18) observed that sulfur chloride and aniline reacted violently in the cold, with destruction of the aniline, to produce a small amount of a violet-brown dye. The reaction was moderated by using carbon disulfide as a diluent and yielded several compounds which were investigated in 1871 by Claus and Krall (19).

Claus and Krall reported that the reaction proceeded in two steps, in the first of which the carbon disulfide took part as follows:

$$4C_6H_5NH_2 + S_2Cl_2 + CS_2 \rightarrow \underset{\text{Diphenylthiourea}}{C_{13}H_{12}N_2S} + 2C_6H_5NH_2 \cdot HCl + 3S$$

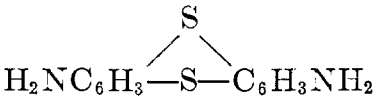
The diphenylthiourea was isolated from the reaction mixture and shown to take part in a second reaction with excess sulfur chloride to give triphenylguanidine and phenyl isothiocyanate, both of which were also isolated.

$$2C_{13}H_{12}N_2S + S_2Cl_2 \rightarrow C_{19}H_{17}N_3 \cdot HCl + C_7H_5NS + HCl + 3S$$

Roorda-Smit (39) used anhydrous ether instead of carbon disulfide as a diluent and obtained a product which was insoluble in ether and on distillation gave an oil of the composition $C_{12}H_{12}N_2S$. This oil formed a picrate. Roorda-

Smit called the compound "thioanilide" and thought that it probably had the structure $C_6H_5NHSNHC_6H_5$. It was different from the "thioaniline" described by Merz and Weith (36) and by Krafft (34), which was undoubtedly 4,4′-diaminodiphenyl sulfide.

Schmidt (40) heated aniline with "sulfur iodide" (possibly a mixture of sulfur and iodine) and reported a small yield of 4,4′-diaminodiphenyl sulfide. Sulfur bromide and aniline reacted vigorously in benzene to give a tarry mixture, from which acid extracted a base called "dithioaniline." This compound, which analyzed poorly for $C_{12}H_{10}N_2S_2$, was not obtained crystalline. Schmidt assigned to it the structure:



Sulfur chloride reacted with acetanilide at 100°C. to give a mixture which yielded, after hydrolysis, "pseudo-dithioaniline," to which Schmidt assigned the structure $H_2NC_6H_4SSC_6H_4NH_2$.

Edeleano (21) confirmed the formation of diphenylthiourea in the presence of carbon disulfide, as reported by Claus and Krall (19), and observed the formation of "thioanilide" when chloroform was used as a diluent.

Some of the reactions described in this section would undoubtedly repay further investigation.

II. THE DISCOVERY OF THE HERZ REACTION

A. Formation and hydrolysis of thiazathiolium compounds

In a German patent which was granted in 1914, but not published until 1922 (10), Richard Herz, working in the laboratories of Leopold Cassella and Co. in Frankfurt, announced the discovery of a reaction which was to prove of great value in the preparation of *o*-aminobenzenethiols and which opened the way for the systematic large-scale production of a variety of interesting dyes. By treating aniline hydrochloride, instead of the free base, with four or five equivalents of sulfur chloride, and allowing the mixture to react at a moderate temperature until all the amine was consumed, Herz directed the reaction so that the product was the thiazathiolium chloride (I). The introduction of chlorine into the benzene ring will be discussed later.

The characterization of the Herz compound as a thiazathiolium chloride was a remarkable feat, for the ring system was completely unknown, and the Herz compound from aniline cannot be recrystallized or obtained analytically pure. Herz stated that the reaction was not limited to aniline but was applicable generally to aromatic amines containing a free ortho position. He also described the reaction of Herz compounds with water, which led to the liberation of hydrogen chloride and the introduction of hydrogen and oxygen.

In later patents, Herz showed that the hydrolysis followed the course described above, to give compounds of the type of IIA or IIB, and that these compounds reacted with alkali, preferably in the dark and in the presence of sodium hydro-

sulfite, to give *o*-aminobenzenethiols (III) (12). Other patents protected variations of the process. For example, an acyl derivative of the amine may be used (12), and the free base may be used under suitable conditions if diluents are present (13). These diluents include carbon disulfide. Diluents are not necessary if the hydrochloride or the monoacyl derivative is used (14). *N*-Acyl and *N*-alkyl groups are lost in the reaction. The separation of the benzenethiol as the zinc salt, and the purification and decomposition of the latter, are mentioned (15).

Herz stated that the hydrolysis product (IIA or IIB) reacted with aromatic bases in water to give dyes (10). The *p*-chlorine atom is easily replaced by the anilido group (4, 44). The main application of the reaction—condensation of the *o*-aminobenzenethiol with chloroacetic acid—is described in a separate patent (16). A solution of the crude alkaline hydrolysis product is treated with sodium chloroacetate, when the *o*-aminoarylthioglycolic acid is formed. When heated, this loses water; the "inner anhydride" so formed is easily purified. Later patents (28, 29) protect the preparation of *o*-aminobenzenethiols as well as the use of substituted thioglycolic acids (30).

Various methods for the hydrolysis of Herz compounds have been described. Sometimes the Herz compound is converted to the hydroxide, which is collected (11) and may, in special cases, be purified by recrystallization before further hydrolysis. These cases are mentioned in Section III,A. Although sodium hydroxide is normally used, hydrolysis by making alkaline with sodium carbonate and subsequently heating with sodium hydrosulfite has also given good results (2).

B. Nuclear substitution

Substitution in the para position of the benzene nucleus usually occurs during a Herz reaction, and if this position is already occupied, replacement by chlorine may occur. Herz drew attention to this fact (10). He did not state specifically whether the Herz compound from aniline itself contained a chlorine atom para to the amino group, but used a symbol for an aromatic ring which might or might not have become substituted. Farrington and Warburton (22, 23) unsuccessfully tried to find conditions for the preparation of *o*-aminobenzenethiol from aniline by the Herz reaction but obtained only 2-amino-5-chlorobenzenethiol. König (33) prepared the same compound from aniline, and both König and Weinberg (43, 44) prepared 2-amino-5-chloro-3-methylbenzenethiol from *o*-toluidine. König (33) also observed that when *p*-anisidine underwent the Herz reaction and the thiol was treated with acetic anhydride, a small amount of a monochloro-6-methoxy-2-methylbenzothiazole was formed as a by-product; probably it was the 4-chloro isomer. This indicated some substitution by chlorine ortho to the amino group.

Farrington and Warburton (22) were not able to isolate any recognizable compound from the reaction between sulfur chloride and *m*-chloroaniline, but from *o*-chloroaniline they obtained a 20 per cent yield of 2-amino-3,5-dichloro-

benzenethiol. Substitution in the para position occurs also in 5-isopropyl-2-methylaniline (31).

Herz found (10) that nitro and carboxyl groups, as well as arsonic and sulfonic acid residues, were readily expelled from the para position and replaced by chlorine. A more remarkable observation is that of Blomquist and Duguid (9), who found that the nitro groups of 4-chloro-2-nitroaniline and *o*-nitroaniline were replaced by chlorine. Since ortho substitution has never been observed with *p*-chloroaniline, it seems that an ortho nitro group is more liable to expulsion than a hydrogen atom in the same position. Blomquist and Duguid repeated the Herz reaction with 2-nitro-*p*-toluidine and 4-amino-3-nitrobenzonitrile, but could not hydrolyze the products. The only groups which have been definitely reported to withstand replacement in the para position are bromo (41), dimethylamino (44), ethoxyl (20), methoxyl (2, 25, 33), and methyl (33).

III. THE MECHANISM OF THE REACTION

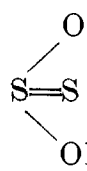
Little more is known of the mechanism of the Herz reaction than is contained in the patent announcing it (10), but confirmation of the structural types which are intermediates has been obtained by later workers who have isolated a few of them in a more or less analytically pure condition. Herz (10) considered that the origin of the group —S—S—Cl in the heterocyclic ring was the same group in sulfur chloride. He offered no opinion on the nature of the sulfur–chlorine bond.

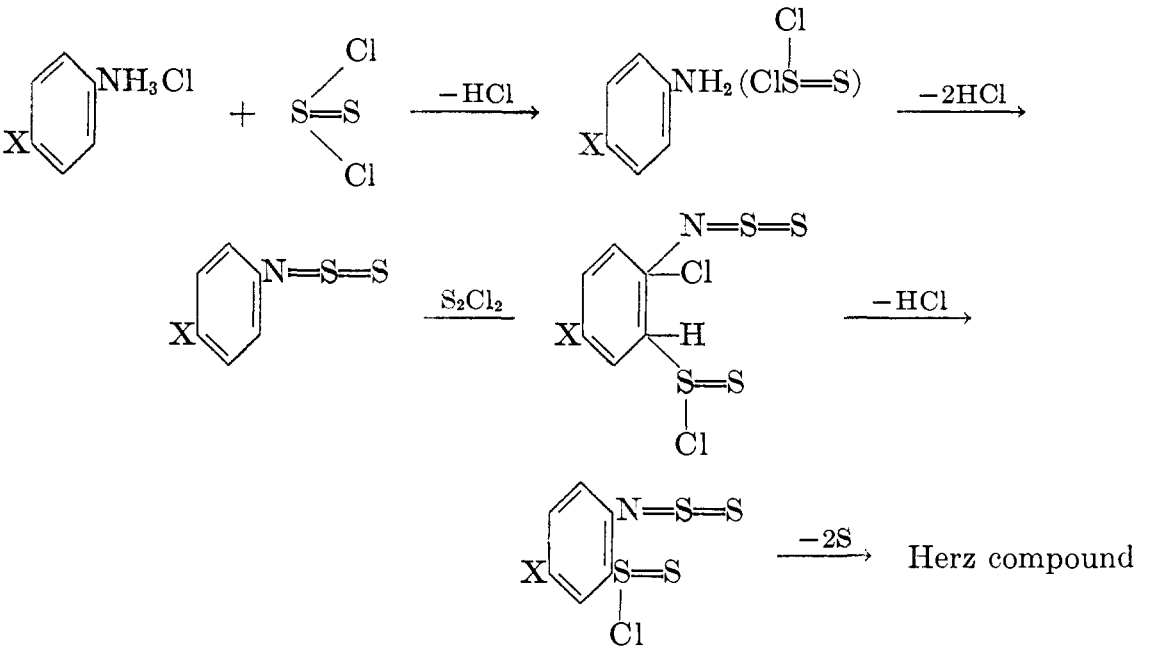
The composition of the Herz compound from 5-isopropyl-2-methylaniline has been confirmed by recrystallization and analysis (31). The analyses for sulfur and chlorine are only moderately good, and analyses for the other elements are not reported.

The Herz compound from 3-nitro-*p*-anisidine gave a hydrolysis product which analyzed well for carbon and hydrogen, but no analytical figures for the other elements are reported (25).

There are no grounds for deciding whether the hydrolysis product has structure IIA or structure IIB, and Herz left this question unanswered. Bezzubets and Ignatyuk-Maĭstrenko (8) used the form IIB, but gave no reasons for their choice. The Herz compound from *o*-anisidine has been written as shown in formula IV by Weinberg (43, 44), but again no reason for using this structure is given.

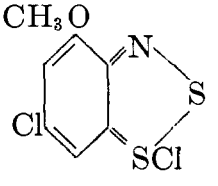
Bezzubets and Ignatyuk-Maĭstrenko (8) showed that the rate of formation of the Herz compound from *p*-chloroaniline was much greater in the polar solvent acetic acid than in benzene, ligroin, or carbon tetrachloride.

Bezzubets (7) explained the first step of the Herz reaction (formation of a thiazathiolium chloride) by considering sulfur chloride as the chloride of the hypothetical thiosulfinic acid  and suggested the possible reaction sequence:



A serious objection to this view is that sulfur chloride has the structure ClSSCl. Palmer's electron-diffraction studies (38) exclude the structure in which two chlorine atoms are attached to the same sulfur atom. Palmer found that the sulfur–sulfur distance was 2.05 A. and calculated the S—S—Cl angle at 103° 35′. Ackermann and Mayer (1) arrived at the same conclusion, and dipole-moment and Raman-spectrum studies (37) have given results consistent with the structure suggested by Palmer.

Bezzubets suggested that the thio-keto form of the cyclic hydrolysis product could be regarded as a lactam of the hypothetical *o*-aminoarylthiosulfinic acid (V), and that the sodium salt of this acid could split out sodium sulfite in an alkaline medium and form the sodium salt of the *o*-aminobenzenethiol. This suggestion conflicts with that of Drozdov and Ignatyuk-Maĭstrenko (20) that the initial hydrolysis products of Herz compounds are bases.



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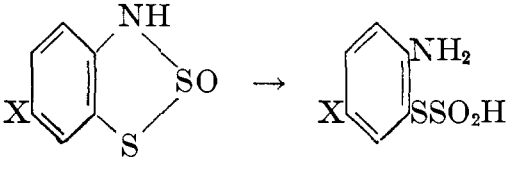


V

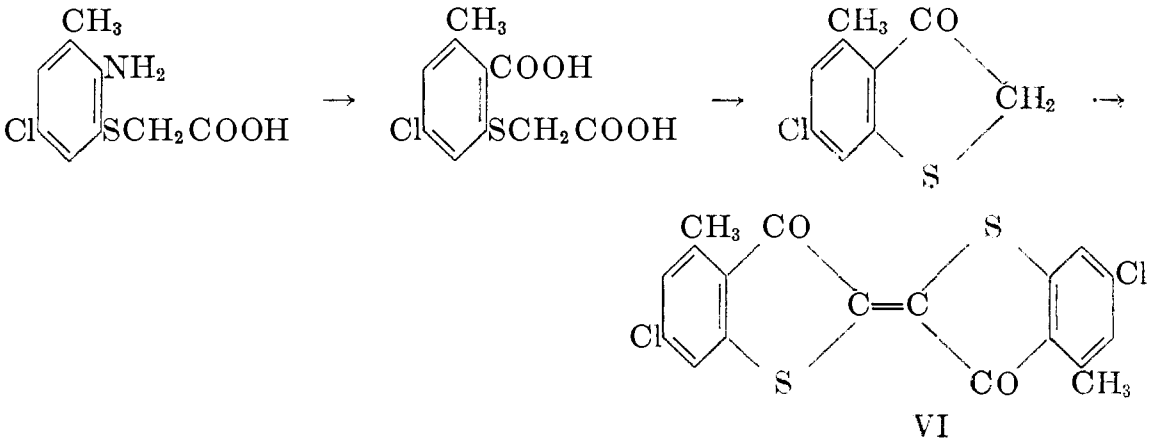
The mechanism of the substitution reaction is quite unknown. It is not even known whether the Herz compound is formed and then substituted, or whether an intermediate compound between the amine and sulfur chloride is formed and substituted before ring closure takes place. Some support for the latter course is found in the replacement of *o*-nitro groups (9), a reaction which indicates a greater reactivity at the ortho position than the Herz compounds themselves possess.

A few trial experiments using reactive aromatic compounds which are not amines have indicated that sulfur chloride is not a very effective chlorinating agent (42).

IV. SOME APPLICATIONS OF THE REACTION

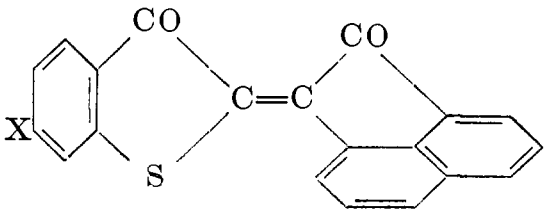
A. Dyes prepared from o-aminoarylthioglycolic acids

This section of the review is not comprehensive, and only a few representative types are mentioned. Sulfur dyes have been discussed more fully by Chapman (17). The amino group of an *o*-aminoarylthioglycolic acid may be converted by the Sandmeyer reaction to the nitrile, and thence to the dicarboxylic acid (30). Ring closure, decarboxylation, and oxidation give the thioindigo (VI) (26). The dye shown is Vat Pink F.F.R.

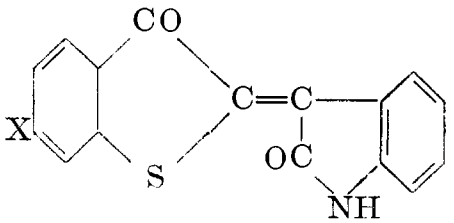


VI

The active methylene group in thioindoxyl will condense with diketones. Thioindoxyl and acenaphthenequinone give dyes of the Ciba Scarlet G type (VII) (27), and condensation with isatin in the 3-position of the latter compound gives dyes of the Thioindigo Scarlet type (VIII) (6, 14).



VII



VIII

Thioindoxyls will also condense with the 2-position of isatins if the latter are first treated with phosphorus pentachloride.

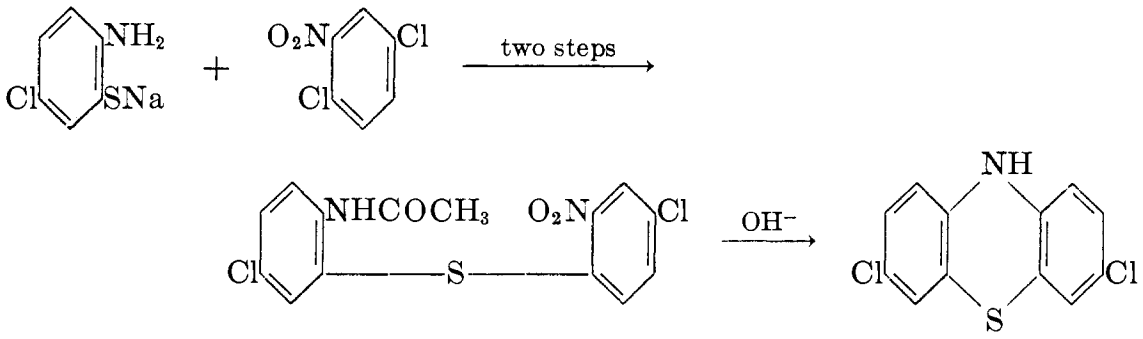
The importance of the thioindigo dyes is that substitution causes large changes in color, so that a large part of the visible spectrum can be covered, whereas in the indigo series the effect of substitution on color is small (31).

Metal salts of *o*-aminobenzenethiols condense readily with acid chlorides. With *p*-nitrobenzoyl chloride the product, after reduction, is a 2-(*p*-amino-

phenyl)benzothiazole. Treatment with methyl iodide gives a dye of the Thioflavine class, and treatment of the thiazole with sulfur and hypochlorite gives dyes of the Chloramine Yellow class (2). The dye Immedial Pure Blue has been prepared by condensing 2-amino-5-dimethylaminobenzenethiol with chloranil and treating the product with sodium polysulfide. Its structure is complex (4, 32).

B. Other heterocyclic compounds

Ring systems which can be prepared from *o*-aminobenzenethiols include benzothiazole and thionaphthene, which have already been mentioned, and phenothiazine. Phenothiazines are formed by the Smiles rearrangement (3) of 2-acylamino-2′-nitrodiphenyl sulfides and ring closure of the intermediate diphenylamine, which is not usually isolated. The acyl and nitro groups are expelled, and yields are often quantitative, as in the following example (22):



V. OTHER METHODS OF PREPARING *o*-AMINOBENZENETHIOLS

The Herz reaction cannot be used to prepare *o*-aminobenzenethiols with a free 5-position, whether substituted or not (22, 23). A few other useful synthetic methods will be briefly mentioned.

Formation of diphenyl disulfides from *o*-halonitrobenzenes and sodium disulfide, followed by reduction with zinc and acetic acid, gives zinc salts of *o*-aminobenzenethiols, but the method fails when applied to 2,4-dichloronitrobenzene (22). Alkaline hydrolysis of 2-mercaptobenzothiazole under pressure is the most useful method for the laboratory synthesis of *o*-aminobenzenethiol, but any halogen substituents in the benzene ring may be replaced by hydrogen (22).

VI. SCOPE AND LIMITATIONS OF THE HERZ REACTION

The reaction is limited to the preparation of *o*-aminobenzenethiols containing as substituents in the 5-position chlorine, or a group which is not replaced by chlorine (bromine, dimethylamino, ethoxyl, methoxyl, or methyl). Because nitro groups are replaced, it is not possible to protect the 5-position with a nitro group and subsequently reduce and remove or alter the protecting group in the usual way. This is a severe limitation, which might be overcome by closer study. For example, there is no report of a Herz reaction with *p*-iodoaniline, and no report of the use of sulfur bromide since 1878 (40).

In some cases the hydrolysis of Herz compounds has failed to give the expected thiols. These Herz compounds include those from *p*-chloroaniline (9)

TABLE 1

o-Aminobenzenethiols prepared by the Herz reaction

Starting Material	Product: Derivative of 2-Aminobenzenethiol	References
Aniline	5-Chloro	(22, 23, 33)
4-Bromoaniline	5-Bromo	(41)
2-Chloroaniline	3,5-Dichloro	(9)
4-Chloroaniline	5-Chloro	(8, 22)
4-Chloro-5-isopropyl-2-methylaniline	5-Chloro-6-isopropyl-3-methyl	(31)
4-Chloro-2-nitroaniline	3,5-Dichloro	(9)
2,4-Dichloroaniline	3,5-Dichloro	(9)
4-Dimethylaminoaniline	5-Dimethylamino	(44)
4-Ethoxyaniline	5-Ethoxy	(20)
2-Methoxyaniline	5-Chloro-3-methoxy	(43, 44)
4-Methoxyaniline	3-Chloro-5-methoxy (?)	(2, 25, 33)
4-Methoxy-3-nitroaniline	5-Methoxy-4-nitro	(25)
2-Methylaniline	5-Chloro-3-methyl	(33, 43, 44)
4-Methylaniline	3-Chloro-5-methyl	(33)
5-Isopropyl-2-methylaniline	5-Chloro-6-isopropyl-3-methyl	(31)
2-Nitroaniline	3,5-Dichloro	(9)
3-Aminocarbazole	3-Amino-4-mercaptocarbazole	(4)

(although other workers have obtained the expected thiol in this way (8, 22)), 2-nitro-*p*-toluidine and 4-amino-3-nitrobenzonitrile (9), and 3-nitro-*p*-anisidine (25).

Herz (10) gave, as examples of compounds suitable for use in the reaction, the following amines: *o*-toluidine, *m*-toluidine, *p*-xylidine, α-naphthylamine, β-naphthylamine, aminobiphenyl, the chloroanilines and chlorotoluidines, the nitroanilines, the aminophenols and their ethers, monoacetyl-*m*- and *p*-phenylene- and toluenediamines, monoacetylbenzidine, benzidineoxamic acid, *p*-phenylenediamine, benzidine, "and similar bases." The products are described, however, in only a few cases. It should be remembered that a patent frequently protects variations in a process which have not been worked out in detail. The Herz reaction has been used with 3-aminocarbazole to give an intermediate for the dye Hydron Blue (4). *p*-Phenylenediamine (42), 2-aminopyridine (21a), and 3-aminopyridine (21a) react with sulfur chloride to give products which do not contain sulfur.

Table 1 includes only *o*-aminobenzenethiols which have been adequately described or which have been converted to derivatives of known constitution. It does not include compounds mentioned only in patents. The physical properties of the thiols are not given, for the compounds have been isolated in the free condition in only a few cases.

VI. REFERENCES

(1) ACKERMANN, P. G., AND MAYER, J. E.: J. Chem. Phys. **4**, 377 (1936).
(2) AST, M. T., AND BOGERT, M. T.: Rec. trav. chim. **54**, 917 (1935).
(3) BENNETTS, G. M.: Obit. Not. Roy. Soc. (London) **8**, 593 (1953).
(4) BERNASCONI, E.: Helv. Chim. Acta **15**, 287 (1932).
(5) BERNTHSEN, A.: Ber. **45**, 2012 (1912).
(6) BEZDZIK, A., AND FRIEDLÄNDER, P.: Monatsh. **29**, 375 (1908).

(7) BEZZUBETS, M. K.: J. Gen. Chem. (U.S.S.R.) **17,** 685 (1947); Chem. Abstracts **42,** 6807 (1948).
(8) BEZZUBETS, M. K., AND IGNATYUK-MAĬSTRENKO, V. A.: J. Appl. Chem. (U.S.S.R.) **12,** 1137 (1942); Chem. Abstracts **34,** 3268 (1940).
(9) BLOMQUIST, A. T., AND DUGUID, L. I.: J. Org. Chem. **12,** 720 (1947).
(10) CASSELLA AND CO.: German patent 360,690; Frdl. **14,** 908 (1922).
(11) CASSELLA AND CO.: German patent 370,845; Frdl. **14,** 915 (1922).
(12) CASSELLA AND CO.: German patent 367,346; Frdl. **14,** 918 (1922).
(13) CASSELLA AND CO.: German patent 367,344; Frdl. **14,** 912 (1922).
(14) CASSELLA AND CO.: German patent 367,345; Frdl. **14,** 914 (1922).
(15) CASSELLA AND CO.: German patent 398,877; Frdl. **14,** 9 (1922).
(16) CASSELLA AND CO.: German patent 364,822; Frdl. **14,** 920 (1922).
(17) CHAPMAN, E.: In *Thorpe's Dictionary of Applied Chemistry,* 4th edition, Vol. 11, p. 245. Longmans, Green and Company, London (1954).
(18) CLAUS, A.: Ber. **3,** 527 (1870).
(19) CLAUS, A., AND KRALL, W.: Ber. **4,** 99 (1871).
(20) DROZDOV, N. S., AND IGNATYUK-MAĬSTRENKO, V. A.: J. Appl. Chem. (U.S.S.R.) **12,** 1065 (1939); Chem. Abstracts **34,** 3265 (1940).
(21) EDELEANO, L.: Bull. soc. chim. France **5,** 173 (1891); Ber. **24** (3), 192 (1891).
(21a) FARRINGTON, K. J., AND RYAN, A. J.: Unpublished work.
(22) FARRINGTON, K. J., AND WARBURTON, W. K.: Australian J. Chem. **8,** 545 (1955).
(23) FARRINGTON, K. J., AND WARBURTON, W. K.: Australian J. Chem. **9,** 480 (1956).
(24) FELIX, A., AND FRIEDLÄNDER, P.: Monatsh. **31,** 55 (1910).
(25) FOX, H. H., AND BOGERT, M. T.: J. Am. Chem. Soc. **61,** 2014 (1930).
(26) FRIEDLÄNDER, P.: Ber. **39,** 1060 (1906).
(27) GROB, A.: Ber. **41,** 3331 (1908).
(28) HERZ, R.: U. S. patent 1,637,023; Chem. Abstracts **22,** 1365 (1928).
(29) HERZ, R.: U. S. patent 1,699,432; Chem. Abstracts **23,** 1140 (1929).
(30) HERZ, R.: U. S. patents 1,243,170 and 1,243,171; Chem. Abstracts **12,** 227 (1918).
(31) HIXSON, A. W., AND CAUWENBERG, W. J.: J. Am. Chem. Soc. **52,** 2118 (1930).
(32) KELLER, E., AND FIERZ-DAVID, H. E.: Helv. Chim. Acta **16,** 585 (1933).
(33) KÖNIG, W.: Ber. **61,** 2067 (1928).
(34) KRAFFT, P.: Ber. **7,** 384 (1874).
(35) LAUTH, C.: Ber. **9,** 1035 (1876).
(36) MERZ, V., AND WEITH, W.: Ber. **4,** 384 (1871).
(37) MORINO, Y., AND MIZUSHIMA, S.: Sci. Papers Inst. Phys. Chem. Research (Tokyo) **32,** 220 (1937); Chem. Abstracts **31,** 7757 (1937).
(38) PALMER, K. J.: J. Am. Chem. Soc. **60,** 2362 (1938).
(39) ROORDA-SMIT, J. A.: Ber. **8,** 1445 (1875).
(40) SCHMIDT, E. B.: Ber. **11,** 1168 (1878).
(41) STEPHEN, F. F., AND WIBBERLEY, D. G.: J. Chem. Soc. **1950,** 3338.
(42) WARBURTON, W. K.: Unpublished work.
(43) WEINBERG, H. VON: Chem. Ztg. **42,** 404 (1930).
(44) WEINBERG, H. VON: Ber. **63A,** 117 (1930).