[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Studies in the Quinoline Series. IV. Quinolyl Mercaptans and Sulfides

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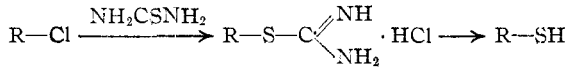
The marked influence of the position of a substituent in determining the therapeutic properties of quinoline derivatives gives significance to all information on the reactivity of quinoline isomers. The differing antimalarial specificity of plasmochin and SN 7618[1] and the absence of antimalarial action in the position isomers of hydrocinchonine[2] are facts awaiting explanation.

The present study expands the general knowledge of quinolyl derivatives possessing simple functional groups; it also presents certain properties of the mercapto-quinolines which might make a more extensive series of 6- and 7-substituted quinolylmercaptans of value in considering energy relationships of isomeric structures. The preparation of the mercaptans and symmetrical sulfides is based on the reaction of halides with thiourea to form isothiouronium salts and subsequently mercaptans.[3]



R = a substituted chloroquinoline.

Rosenhauer and associates[4] synthesized quinolyl-, lepidyl- and quinaldyl-mercaptans by the interaction of thiourea with chloroquinolines. However, they encountered varying amounts of diquinolyl sulfides in replacing the chlorine of 4-chloroquinolines. Surrey and Lindwall,[5] also, found that certain reaction conditions favor the formation of bis-(6-nitro-2-pyridyl) monosulfide.

In the experience of this Laboratory, 2-chloro-7-methylquinoline and 2,7-dichloro-4-methylquinoline were converted to the corresponding isothiouronium salts, and subsequently to mercaptans, in good yield. In the titration of the three isothiouronium salts, which we were able to separate and identify analytically, it was observed that the aqueous solution was faintly alkaline to litmus, or became alkaline with a very small portion of 0.1 *N* sodium hydroxide; as was expected, titration to an end-point with phenolphthalein required the calculated amount of 0.1 *N* sodium hydroxide.

The 2-mercaptans were yellow, crystalline products of low solubility in alcohol, aqueous-alcoholic alkali, and chloroform; complete oxidation to the disulfides was rather slow. Symmetrical 2,2′-quinolyl sulfides were obtained only by direct synthesis. In contrast, 4,4′-quinolyl sulfides were invariably encountered among the reaction products from treatment of 4-chloroquinolines with thiourea.

With the use of thiourea to introduce the sulfur linkage in the 4-position, only one pure isothiouronium salt was isolated: 7-methyl-4-quinolylisothiouronium chloride was obtained in a 45% yield. However, even in this case the hydrochloride of bis-(7-methyl-4-quinolyl) sulfide also was obtained. In two other examples, analyses indicated that the crystalline reaction product was mainly the hydrochloride of bis-(7-chloro-2-methyl-4-quinolyl) sulfide and of bis-(6-methoxy-2-methyl-4-quinolyl) sulfide, respectively. During titration the hydrochlorides of the sulfides remained acid to litmus until nearly all the calculated amount of alkali had been added. This afforded a rough distinction between quinolyl sulfides and isothiouronium salts as crude reaction products. The present experimental work gives no data concerning the course of the formation of symmetrical sulfides. It may be that dissociation of the isothiouronium salt provides a small amount of mercaptan to react with residual chloroquinoline and this subsequent reaction determines the extent of dissociation of the isothiouronium salt. Or it may be that the essential point in the chain reaction is initiating the dissociation of the isothiouronium salt.[6] However, Watt[7] in the preparation of 2,2′-benzothiazolyl sulfide has postulated the sulfide formation as a direct reaction between the isothiouronium salt and residual chlorobenzothiazole.

Slight yields of mercaptan were isolated in decomposing the crude bis-(4-quinolyl)-sulfide hydrochlorides. The orange 4-quinolyl mercaptans dissolved fairly readily in alcohol, chloroform, and ether.

Even the few mercaptans under discussion show that interesting comparisons are possible between the 2-mercapto and 4-mercapto structures. The 4-mercaptans were orange or deep yellow in contrast to the canary yellow of the 2-mercaptans; but in all cases studied, alkaline solutions were colorless. In the light of the closely similar melting points of 7-methyl-(2- or 4-)quinolinethiol, the low solubility of 7-methyl-2-quinolinethiol marks it as the more rigid structure,[8] possibly suggesting hydrogen bonding. Traditionally, the quinolone structure is assigned to the oxygen

(1) The Board for Co-ordination of Malarial Studies, *Science*, **103**, 8 (1946). SN = survey number, an identifying number for compounds which will appear in a forthcoming monograph entitled, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, *Editor*.

(2) Nandi, *Proc. Indian Acad. Sci.*, **12A**, 1 (1940); *C. A.*, **34**, 7918 (1940).

(3) F. Arndt, *Ber.*, **54**, 2236 (1921).

(4) Rosenhauer, Hoffmann and Heuser, *ibid.*, **62**, 2730 (1929).

(5) Surrey and Lindwall, THIS JOURNAL, **62**, 1697 (1940).

(6) We are indebted to a referee for the suggestion that the chloroquinoline may be sufficiently basic to decompose the isothiouronium salt.

(7) Watt, *J. Org. Chem.*, **4**, 436 (1939).

(8) Gilman, "Organic Chemistry," second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. II, p. 1737.

analogs[9]; tautomeric and resonance forms are summarized by Bergstrom.[10]

Experimental

2- and 4-Chloro-7-methylquinoline.—7-Methylquinoline was converted to the N-oxide, which was isolated as the solid hydrochloride. The N-oxide was prepared by the action of hydrogen peroxide on 7-methylquinoline, dissolved in glacial acetic acid.[11] The free oxide melted at 60–62° and was very hygroscopic. Chlorination with phosphorus oxychloride gave substitution in the 2- and the 4-position in about equal quantities; sulfuryl chloride gave about 3 parts of 4-chloro to 1 part of 2-chloro-7-methylquinoline.

The chloro derivative which separated on partial neutralization of the chlorination mixture was assumed to be 2-chloro-7-methylquinoline; m. p., 79–81°. On further neutralization an oil was obtained which distilled at 97–100° at 1 mm. and crystallized in the ice-box. This oil was irritating to the skin and caused persistent itching and vesicle formation. The oil was identified as 4-chloro-7-methylquinoline by conversion to 4-amino-7-methylquinoline; m. p., 163–164°. A specimen of 4-amino-7-methylquinoline[12] prepared through 7-methylcinchoninamide melted at 163.4–164.5°.

7-Methyl-2-quinolylisothiouronium Chloride.—Five grams of 2-chloro-7-methylquinoline was partially dissolved in 30 cc. of absolute alcohol; 8 cc. of ether was added to clear the solution. The mixture was shaken frequently after the addition of 2 g. of thiourea, and after thirty minutes at room temperature a soft, white precipitate was noted. After three to four hours a dense precipitate had settled and the supernatant solution was yellow. The isothiouronium salt was filtered off after 48 hours, in 86% yield; the white salt turned yellow at 150° and melted at 173–174° with decomposition. The aqueous solution of 7-methyl-quinoline-2-isothiouronium chloride was alkaline to litmus but not alkaline to phenolphthalein. *Anal.* Calcd. for $C_{11}H_{11}N_3S\cdot HCl$: HCl, 14.2; S, 12.64. Found: HCl, 14.8; S, 12.59.

7-Methyl-2-quinolinethiol.—A solution of 2.5 g. of the above isothiouronium salt in 15 cc. of water was decomposed with 4% sodium hydroxide and the mercaptan was taken up in chloroform; yield, 91%. Aqueous alkaline solutions are colorless; acidic solutions, yellow. The lemon-yellow, crystalline mercaptan is slightly soluble in ether, fairly soluble in chloroform, but not soluble in alcohol to the extent of 1%; decomposition at 205°, with liquefaction at 207°. *Anal.* Calcd. for $C_{10}H_9NS$: S, 18.28. Found: S, 18.35.

Bis-(7-methyl-2-quinolyl) Disulfide.—Iodine oxidation of the mercaptan proceeds somewhat slowly. The disulfide was prepared by adding iodine to a solution of 7-methyl-2-quinolinethiol in chloroform (or of the sodium salt of the mercaptan in 60% alcohol). After eighteen hours, the chloroform solution was washed with alkali and thiosulfate and concentrated. The disulfide crystallized as faintly-yellow leaves, difficultly soluble in hot alcohol, fairly soluble in ether, readily soluble in chloroform, and insoluble in aqueous alkali. It decomposed at 177–178°; 1:1 mixtures with 7-methyl-2-quinolinethiol or with the symmetrical monosulfide showed a lowering of at least 20° in the mixed melting point. *Anal.* Calcd. for $C_{20}H_{16}N_2S_2$: S, 18.38. Found: S, 17.94.

7-Methyl-4-quinolylisothiouronium Chloride.—The reactants were entirely soluble in absolute alcohol at room temperature. From 5 g. of 4-chloro-7-methylquinoline only 3 g. of white isothiouronium salt was obtained (45%). An aqueous solution of the salt was alkaline to litmus after the first tenth of the titration, m. p., 140°. *Anal.* Calcd. for $C_{11}H_{11}N_3S\cdot HCl$: HCl, 14.2; N, 16.60; S, 12.64. Found: HCl, 14.7; N, 16.41; S, 12.67.

From the alcoholic mother liquor of the reaction mixture, a considerable yield of the hydrochloride of bis-(7-methyl-4-quinolyl) sulfide separated on addition of water.

7-Methyl-4-quinolinethiol.—After alkaline hydrolysis of the corresponding isothiouronium salt, the mercaptan was obtained as an orange solid from careful neutralization of alkaline solutions with acetic acid, or from concentrated chloroform solutions; yield, 70%; m. p., 204°. The mercaptan is soluble in 30 volumes of alcohol; difficultly soluble in ether. *Anal.* Calcd. for $C_{10}H_9NS$: N, 8.0; S, 18.28. Found: N, 8.25; S, 18.12.

Bis-(7-methyl-4-quinolyl) Disulfide.—An alcoholic solution of 7-methyl-4-quinolinethiol was neutralized with 0.1 *N* sodium hydroxide and treated with an iodine–potassium iodide solution. The white disulfide, which separated immediately, was washed with water and triturated with ether; it was very soluble in chloroform; m. p., 170° with softening at 167°.

Bis-(7-methyl-4-quinolyl) Sulfide.—The hydrochloride of the symmetrical sulfide (light yellow in color) was the main product when the reaction of the chloroquinoline with thiourea was carried out in boiling alcohol. At room temperature, as noted above, the hydrochloride of the symmetrical sulfide was found in the alcoholic mother liquor. The titration value for the latter preparation corresponded to 18.2% of HCl (the solution remained acid to litmus until nearly the end of the titration); the calculated HCl value for the dihydrochloride would be 18.8%.

The free base crystallized from ether as a white powder or from alcohol as hard, transparent rods, melting at 115°. *Anal.* Calcd. for $C_{20}H_{16}N_2S$: S, 10.12. Found: S, 9.94.

7-Chloro-4-methyl-2-quinolylisothiouronium Chloride, SN-10,738.—A solution of 16 g. of 2,7-dichlorolepidine[13] and 5.8 g. of thiourea in 90 cc. of absolute alcohol was refluxed for several minutes before the sudden appearance of a yellow precipitate. Refluxing was continued for thirty minutes. The isothiouronium salt was obtained in 90% yield and melted at 204–205°. *Anal.* Calcd. for $C_{11}H_{10}N_3SCl\cdot HCl$: HCl, 12.6; N, 14.58; S, 11.11. Found: HCl, 10.36; N, 14.46; S, 10.78.

7-Chloro-4-methyl-2-quinolinethiol, SN-10737.—A suspension of the isothiouronium salt was stirred with an excess of 10% ammonium hydroxide until the bright yellow color seemed uniform. The mercaptan is scarcely soluble in aqueous alkali, but is somewhat soluble in alcoholic alkali. The base is soluble in 100 parts of boiling alcohol, 200 parts of boiling benzene, and in 10 parts of hot pyridine; m. p., 275°. *Anal.* Calcd. for $C_{10}H_8NSCl$: N, 6.7; S, 15.31. Found: N, 6.7; S, 15.38.

This mercaptan was also prepared by refluxing 0.04 mole of 2,7-dichlorolepidine in 30 cc. of alcohol with 0.04 mole of sodium thiosulfate in 20 cc. of water.[14] Two layers were observed in the actively refluxing solution; after six hours, crystallization started and several hours later the two layers were no longer noticeable. The product was well washed with water and with alcohol and macerated with ether.

Bis-(7-chloro-4-methyl-2-quinolyl) Disulfide, SN-14,830.—A hot, saturated solution of 7-chloro-4-methyl-2-quinolylmercaptan was treated with an iodine–potassium iodide solution. A white solid, which separated gradually, was collected on a funnel and triturated with ammonia. The disulfide was recrystallized from chloroform; m. p., 196–198°. *Anal.* Calcd. for $C_{20}H_{14}N_2S_2Cl_2$: S, 15.34. Found: S, 15.33.

Bis-(7-chloro-2-methyl-4-quinolyl) Sulfide.—4,7-Dichloroquinaldine was prepared through ring-closure of ethyl β-(*m*-chloroanilino)-crotonate and subsequent treatment with phosphorus oxychloride. Several crystallizations of the dichloroquinaldine from 5 volumes of alcohol gave a 72% yield of 4,7-dichloroquinaldine (melting 102°).

(9) Sidgwick, Taylor and Baker, "Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1942.

(10) Bergstrom, *Chem. Rev.*, **35**, 77 (1944), p. 132. See also Ewing and Steck, paper presented before the Division of Organic Chemistry at the Atlantic City Meeting, April, 1946.

(11) Directions for the procedure were generously supplied us by Dr. A. M. Van Arendonk of the Eli Lilly Research Laboratories.

(12) V. Ramsey, private communication.

(13) German Patent 556,324; *C. A.*, **26**, 5573 (1932).

(14) Westlake and Dougherty, THIS JOURNAL, **64**, 149 (1942).

A second product melting at 80° (possibly 4,5-dichloroquinaldine[15] was recovered from the alcoholic filtrates.

The reaction of 4,7-dichloroquinaldine with thiourea in 15 volumes of absolute alcohol and 2 volumes of ether gave a 60% yield of solid. This proved to be largely the monohydrochloride of the symmetrical sulfide. *Anal.* Calcd. for $C_{20}H_{14}N_2Cl_2S\cdot HCl$: HCl, 8.55; N, 6.65; S, 7.60. Found: HCl, 9.64; N, 6.71; S, 7.61.

When the hydrochloride was neutralized with alkali, the symmetrical sulfide was obtained in 80% yield along with a slight amount of the yellow alkali-soluble mercaptan, melting at 207°. Bis-(7-chloro-2-methyl-4-quinolyl) sulfide is a white powder, soluble in ether and very soluble in chloroform; it crystallized from alcohol as glistening, transparent rods; m. p., 171–172°. *Anal.* Calcd. for $C_{20}H_{14}N_2Cl_2S$: S, 8.31; Found: S, 8.53.

Bis-(6-methoxy-2-methyl-4-quinolyl) Sulfide, SN-10,739.—Whether the reaction of thiourea with 4-chloro-6-methoxyquinaldine was carried out in refluxing absolute alcohol or at room temperature (in 20 volumes of absolute alcohol and 2 volumes of ether) the product was a mixture. At room temperature the yield corresponded to 60% of the weight of the reactants. In titration of the salt nearly half of the 0.1 *N* sodium hydroxide had been added, before the solution was alkaline to litmus. If the acidic reaction were attributed to hydrochloride of the symmetrical sulfide, the base might contain about two parts of sulfide to one part of mercaptan. *Anal.* Calcd. for $C_{12}H_{13}N_3OS\cdot HCl$ (isothiouronium salt): HCl, 12.72; N, 14.84; S, 11.31. Calcd. for $C_{22}H_{20}O_2N_2S\cdot HCl$ (monosulfide): HCl, 8.73; N, 6.79; S, 7.79. Calcd. for $C_{11}H_{11}NOS\cdot HCl$ (mercaptan): N, 5.80; S, 13.3. Found: (refluxing) HCl, 12.22; N, 9.50; S, 10.90. (Room temp.): HCl, 12.7; N, 10.64; S, 10.62.

When the above salt was decomposed with alkali, the odor of mercaptan was noticeable and some deep yellow mercaptan (m. p. 231–232°) was isolated. Two grams of bis-(6-methoxy-2-methyl-4-quinolyl) sulfide was obtained as white solid from 3.1 g. of the salt. The monosulfide is difficultly soluble in ether or hot alcohol, but rather readily soluble in chloroform or pyridine; m. p., 205°. *Anal.* Calcd. for $C_{22}H_{20}O_2N_2S$: N, 7.44; S, 8.51. Found: N, 7.67; S, 8.56.

6-Methoxy-2-methyl-4-quinolinethiol.—A small amount of mercaptan was obtained along with the bis-(6-methoxy-2-methyl-4-quinolyl) sulfide, when the initial salt was carefully neutralized in the presence of chloroform. Aqueous alkaline solutions of the mercaptan are colorless, but a deep yellow solid separated on neutralization. 6-Methoxy-2-methyl-4-quinolinethiol was recrystallized from 15 volumes of boiling alcohol; m. p., 231–232°. A slight residue was insoluble in alcohol or chloroform. *Anal.* Calcd. for $C_{11}H_{11}NOS$: N, 6.83; S, 15.60. Found: N, 6.83; S, 15.88.

The bis-(2-quinolyl) sulfides were prepared by direct synthesis according to the procedure used for the synthesis of unsymmetrical quinolyl thioethers. Refluxing molecular equivalents of the mercaptan and the appropriate chloroquinoline in chloroform or *p*-cymene, or heating in mineral oil, provided a simple method for obtaining the hydrochloride of the desired quinolyl sulfide. Often the hydrochloride was fairly soluble even in cold chloroform. This type of condensation was successful where poor results were obtained with traces of alkali or an equivalent of alkali in alcoholic solutions. Banks[16] has discussed cases when H^+ ion favors the replacement of chlorine from the 2,4-positions of heterocyclic compounds. However, the direct addition of acid was of no value in the present study.

(15) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(16) Banks, *ibid.*, **66**, 1127 (1944).

Bis-(7-methyl-2-quinolyl) Sulfide.—The mercaptan and chloroquinoline were refluxed for fifteen hours in 30 volumes of chloroform, in which the mercaptan dissolved slowly. The hydrochloride crystallized as a white solid from the concentrated chloroform solution in a 73% yield; m. p., 200–202°. The base crystallized from ether in rosets of glistening yellow rods, m. p., 161–162°. *Anal.* Calcd. for $C_{20}H_{16}N_2S$: S, 10.12. Found: S, 10.41.

Bis-(7-chloro-4-methyl-2-quinolyl) Sulfide.—The hydrochloride of the sulfide was obtained by refluxing the reactants in chloroform for eighteen hours as above. *p*-Cymene was a better solvent for the mercaptan; refluxing for three hours gave a 50% yield of the hydrochloride of the symmetrical sulfide. The salt crystallized from *p*-cymene on cooling, and was washed with ether to remove unchanged 2,7-dichlorolepidine. Prolonged heating caused discoloration. The hydrochloride was suspended in aqueous alkali, and the liberated base was crystallized twice from 30 volumes of alcohol. The sulfide crystallized as soft balls of white needles; m. p., 165–167°. *Anal.* Calcd. for $C_{20}H_{14}N_2SCl_2$: S, 8.31. Found: S, 8.40.

4-(*p*-Tolylmercapto)-6-methoxy-2-methylquinoline, SN-11,411-4.—A chloroform solution (80 cc.) of 8 g. of 4-chloro-6-methoxyquinaldine was saturated with nitrogen before the addition of 8.5 g. of *p*-tolylmercaptan. The solution was refluxed for six hours. No solid crystallized on cooling, so chloroform was removed and the solid allowed to stand with 150 cc. of ether overnight. The yellow, crystalline hydrochloride, obtained in 83% yield, melted at 218°. Two recrystallizations from absolute alcohol raised the melting point to 220°. *Anal.* Calcd. for $C_{18}H_{17}NOS.HCl$: S, 9.66. Found: S, 9.70.

The base was obtained when a chloroform solution of the hydrochloride was washed with aqueous alkali, and the chloroform layer evaporated to small volume. The base crystallized as a white powder, or as large, transparent prisms, m. p., 115–116°. *Anal.* Calcd. for $C_{18}H_{17}ONS$: S, 10.84. Found: S, 11.08.

4-(2-Benzothiazolylmercapto)-6-methoxy-2-methylquinoline, SN-10598.—A 10% excess of 2-mercaptobenzothiazole was refluxed for twelve hours with a chloroform solution of 4-chloro-6-methoxyquinaldine. Refluxing alcoholic solutions of the reactants in the presence of potassium hydroxide or barium oxide failed to bring about condensation. The hydrochloride of the reaction product remained in the chloroform solution at room temperature and formed a rather gummy residue when chloroform was removed. Ether extracted very little unchanged methoxychloroquinaldine. The residue dissolved completely in an equal weight of warm methyl alcohol, but on dilution some crystallization occurred. In several runs, 0.5–1.5 g. of mercaptobenzothiazole, or the disulfide, crystallized from a 12% solution in methyl alcohol on standing overnight. The hydrochloride of benzothiazolylmercapto-6-methoxyquinaldine (melting 138–142°) was recovered by removing methyl alcohol under reduced pressure, and was crystallized from absolute ethyl alcohol.

To obtain the free base, the hydrochloride was dissolved in 12 volumes of chloroform, filtered from a slight residue, and shaken with aqueous alkali. The thioether, which crystallized from concentrating chloroform solutions, was suspended in ether and collected in 80% yield from the salt. The base is not very soluble in ether, alcohol or acetone; m. p., 135–136°. *Anal.* Calcd. for $C_{18}H_{14}ON_2S_2$: S, 18.93. Found: S, 19.11.

2-(1-Methylheptyl)-mercaptobenzothiazole.—Molecular equivalents of potassium hydroxide and mercaptobenzothiazole were refluxed in 5 volumes of absolute alcohol for six hours with a small excess of 2-bromo-*n*-octane. After removal of potassium bromide and alcohol, an ether solution of the residue was washed with water, dried, and fractionated. At 1 mm. pressure, the 2-(1-methylheptyl)-mercaptobenzothiazole boiled at 162–165°. *Anal.* Calcd. for $C_{16}H_{21}NS_2$: S, 22.94. Found: S, 23.19.

Acknowledgment.—The author wishes to thank Dr. L. H. Cretcher for his generous interest in this problem.

Summary

7-Substituted quinolyl isothiouronium salts and mercaptans have been synthesized. Greater intensity of color, as well as greater chemical reactivity, were observed for the 4-quinolyl thiols as compared with the 2-quinolyl thiols.

The 2-thiols and the intermediate isothiouronium salts were isolated in good yield. In only one of three syntheses, was the pure 4-isothiouronium chloride identified, whereas the formation of sulfide hydrochlorides was more or less extensive.

Symmetrical and unsymmetrical sulfides are described and a second method of preparation is given.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Arsenicals in the Isoquinoline Series

BY BILL ELPERN AND CLIFF S. HAMILTON

Stimulated by the success in the corresponding field of sulfanilamides[1] and by the discovery of Friedheim[2] that arsenicals derived from *s*-triazines have trypanocidal and spirochetocidal activity, workers[3] in this and other laboratories have recently studied the preparation of a number of aminobenzenearsonic acids substituted on the nitrogen by various heterocycles.

A search of the literature revealed that although there are a great many complex compounds containing the isoquinoline nucleus, *e. g.*, the opium and morphine alkaloids, but few simple derivatives have been reported. It seemed of interest, therefore, to prepare several simple haloisoquinoline derivatives and study their reaction with various aminobenzenearsonic acids.

According to the mechanism proposed by Banks[4] it could be predicted that a halogen in the 1-position of the isoquinoline nucleus should be more reactive toward replacement by an amino group in the presence of hydrogen ions. This prediction was fulfilled when 1-chloroisoquinoline and 1-chloro-4-bromoisoquinoline were condensed with various aminobenzenearsonic acids. In several cases, however, equally good yields were obtained by merely fusing the dry reactants in the absence of solvent and mineral acid. No condensation was effected by either of these methods in the case of 1-chloro-5-nitroisoquinoline. The deactivating influence of the nitro group has been previously noted, *e. g.*, the condensation of *p*-aminobenzenearsonic acid with 2-chloropyridine is very much faster than with 2-chloro-5-nitropyridine.[5] A small degree of condensation was effected in a large excess of aqueous alkali, the principal product being 1-hydroxy-5-nitroisoquinoline. The deactivating influence of the nitro group was probably modified through formation of its sodium salt.

(1) Northey, *Chem. Rev.*, **27**, 85 (1940).

(2) Friedheim, *Schweiz. Med. Wochschr.*, **71**, 116 (1941); THIS JOURNAL, **66**, 1775 (1944).

(3) Banks, Gruhzit, Tillitson and Controulis, THIS JOURNAL, **66**, 1771 (1944); Cragoe and Hamilton, *ibid.*, **67**, 536 (1945); Andres and Hamilton, *ibid.*, **67**, 946 (1945).

(4) Banks, *ibid.*, **66**, 1127 (1944).

(5) Banks, personal communication.

Azo compounds containing arsenic have been prepared in the benzene,[6] naphthalene[6] and quinoline[7] series. However, no analogs have been synthesized in the isoquinoline series. 5-Amino-, 4-bromo-5-amino-, 4-bromo-8-amino- and 1-chloro-5-aminoisoquinoline were coupled with one or more of the following diazotized arsonic acids: *o*-, *m*-, *p*-aminobenzenearsonic acids, and 3-amino-4-nitrobenzenearsonic acid. These azo compounds were isolated in a fairly high state of purity from the reaction mixture but were difficult to crystallize. All were deep red dyes that gave colored solutions ranging from purple in concentrated acid through red, to yellow in alkali.

It is assumed that coupling took place *para* to the amino group in the isoquinoline nucleus. Fieser and Martin[8] have reported the coupling of 5(8)-hydroxyisoquinoline with diazotized aniline and reducing the azo-group to form 5(8)-hydroxy-8(5)-aminoisoquinoline. They also prepared the isomeric compound with the hydroxyl and amino groups reversed, in order to make studies of the quinone structures. Their work indicates the absence of *ortho* quinones in these two compounds

Experimental

The preparation of 5-nitroisoquinoline,[9] 4-bromoisoquinoline,[10] 4-bromo-5-nitroisoquinoline,[11] 4-bromo-8-nitroisoquinoline,[11] *o*-arsanilic acid,[12] *m*-arsanilic acid,[12] *p*-arsanilic acid,[12] 3-amino-4-hydroxyphenylarsonic acid,[13] 3-nitro-4-aminophenylarsonic acid[14] and 1-arsono-4-naphthylamine[15] is adequately described in the literature.

2-Methyl-1-isoquinolone.—Dimethyl sulfate (252 g., 2 moles) was added dropwise with stirring to isoquinoline (258 g., 2 moles). The mixture nearly all solidified at the completion of the addition. After refluxing on a steam-bath for two hours, water (425 ml.) was added and the yellow solution cooled to 0°.

While cooling, two solutions were prepared: A, sodium

(6) Jacobs and Heidelberger, THIS JOURNAL, **43**, 1646 (1921).

(7) Berlingozzi, *Ann. chim. applicata*, **18**, 31, 333 (1928).

(8) Fieser and Martin, THIS JOURNAL, **57**, 1840 (1935).

(9) LeFèvre and LeFèvre, *J. Chem. Soc.*, 1470 (1933).

(10) Craig and Cass, THIS JOURNAL, **64**, 783 (1942).

(11) Edinger and Bossung, *J. prakt. Chem.*, (2) **43**, 190 (1891).

(12) Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1583 (1918).

(13) Ehrlich and Bertheim, *Ber.*, **45**, 757 (1912).

(14) Bertheim, *ibid.*, **44**, 3095 (1911).

(15) Saunders and Hamilton, THIS JOURNAL, **54**, 636 (1932).