

Summary

7-Substituted quinolyl isothiuronium 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 isothiouro-

nium salts were isolated in good yield. In only one of three syntheses, was the pure 4-isothiuronium 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 sulfanilamides¹ and by the discovery of Friedheim² that arsenicals derived from *s*-triazines have trypanocidal and spirochetocidal activity, workers³ 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 Banks⁴ 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, Gruhitz, 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 naphthalene⁶ and quinoline⁷ 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 Martin⁸ 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 acid¹⁴ and 1-arsono-4-naphthylamine¹⁵ 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 Heidelberg, *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, Heidelberg 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).

hydroxide (379 g., 9.5 moles) in water (550 ml.), and B, potassium ferricyanide (1317 g., 4 moles) in water (2600 ml.).

Solution A was added during one and a half hours simultaneously with half of solution B, maintaining the temperature below 20°. The remainder of solution B was added during the next thirty minutes. After standing overnight, the dark oil that formed was salted out with sodium carbonate and separated. The aqueous portion was divided into three equal portions and each extracted with two 200-ml. portions of isoamyl alcohol. The alcohol extracts were combined with the oil and fractionated; yield, 196 g. (62%), boiling at 161–165° (3 mm.). The product was stored under nitrogen and solidified after standing several days in a refrigerator; m. p. 53–54°.¹⁶

1-Chloroisoquinoline.—This compound was prepared by modifying the procedure of Fisher and Hamer.¹⁶ The yield was increased from 66 to 91% by chlorinating 2-methyl-1-isoquinoline in a sealed tube instead of merely refluxing the mixture.

1-Chloro-5-nitroisoquinoline was prepared by nitrating 1-chloroisoquinoline using the same procedure as for nitrating isoquinoline.⁹

1-Chloro-4-bromoisoquinoline was synthesized by brominating 1-chloroisoquinoline in the same manner as isoquinoline was brominated.¹⁰

1-Chloro-5-amino-, 5-amino-,¹⁰ 4-bromo-5-amino-¹¹ and 4-bromo-8-aminoisoquinoline were prepared by reducing the corresponding nitro compounds dissolved in absolute ethanol, using molecular hydrogen at 50 pounds pressure and Raney nickel catalyst.

Arsonoarylaminoisoquinolines: Method I.—Equivalent amounts (0.1 mole) of the appropriate aminoarylarsonic

acid and 1-chloroisoquinoline or 1-chloro-4-bromoisoquinoline were suspended or dissolved in water (1 liter) containing hydrochloric acid (0.1 mole) and the mixture refluxed until a test for a primary amine was negative (R salt test). After concentrating the solution to 250 ml. and cooling, the product was precipitated by careful neutralization with alkali. Purification was effected by dissolving the arsonic acid in dilute sodium bicarbonate solution, filtering and precipitating the product with dilute acetic acid.

Method II.—Equivalent amounts of the appropriate aminoarylarsonic acid and 1-chloroisoquinoline or 1-chloro-4-bromoisoquinoline were heated together in an oil-bath at 175–185° for fifteen minutes. The melt was then dissolved in alkali, treated with charcoal and precipitated with dilute acetic acid. Purification was effected as in Method I.

Method III.—Equivalent amounts (0.01 mole) of the appropriate aminoarylarsonic acid and 1-chloro-5-nitroisoquinoline were dissolved in water (400 ml.) containing sodium hydroxide (0.05 mole) and refluxed for forty-eight hours. The clear red solution was cooled and 1-hydroxy-5-nitroisoquinoline (m. p. 250–251°) was filtered off. The filtrate was acidified with dilute acetic acid and the product was precipitated. It was purified as in Method I.

A summary of the results of the condensations appears in Table II.

Isoquinolineazobenzene arsonic Acids.—The appropriate aminoarylarsonic acid (0.1 mole) was dissolved in water (100 ml.) containing sodium hydroxide (0.1 mole). To this solution was added, all at once, a solution of sodium nitrite (0.1 mole) in water (50 ml.). After cooling to 0° the solution was poured into dilute hydrochloric acid (40 ml. of concentrated acid in 250 ml. of water) and kept at 0° until used. To couple, the cold diazonium solution was poured into a dilute acetic acid solution (150 ml.) of the appropriate isoquinolineamine. The dark red product formed at once. It was collected and washed thoroughly with water.

A summary of the results of the couplings appears in Table III.

TABLE I
HALOISOQUINOLINES

Isoquinoline	Yield, %	De-comp., °C.	Formula	N analyses, %	
				Calcd.	Found
8-Amino-4-bromo-	44	112	C ₉ H ₇ BrN ₂	12.56	12.50
4-Bromo-1-chloro-	41	97	C ₉ H ₆ BrClN	5.77	5.85
1-Chloro-5-nitro-	62	183–184	C ₉ H ₆ ClN ₂ O ₂	13.43	13.37
5-Amino-1-chloro-	32	154	C ₉ H ₇ ClN ₂	15.68	15.63

TABLE II
ARSONOARYLAMINOISOQUINOLINES

Isoquinoline	Method	Yield, %	Decomp., °C.	Formula	As analyses, %	
					Calcd.	Found
1-(4'-Arsonoanilino)-	I	58	300	C ₁₅ H ₁₃ AsN ₂ O ₃	21.76	21.62
1-(3'-Arsonoanilino)-	I	52	195–196	C ₁₅ H ₁₃ AsN ₂ O ₃	21.76	21.51
1-(2'-Arsonoanilino)-	II	13	195–200	C ₁₅ H ₁₃ AsN ₂ O ₃	21.76	21.58
1-(5'-Arsono-2'-hydroxyanilino)-	I	65	207–209	C ₁₅ H ₁₃ AsN ₂ O ₄	20.80	20.83
1-(4'-Arsono-1'-naphthylamino)-	II	20	202–205	C ₁₉ H ₁₆ AsN ₂ O ₃	19.05	19.19
1-(4'-Arsonoanilino)-4-bromo-	I	46	203–205	C ₁₅ H ₁₂ AsBrN ₂ O ₃	17.72	17.75
1-(3'-Arsonoanilino)-4-bromo-	II	57	215–218	C ₁₅ H ₁₂ AsBrN ₂ O ₃	17.72	17.52
1-(4'-Arsonoanilino)-5-nitro-	III	11	225–226	C ₁₅ H ₁₂ AsN ₃ O ₅	19.25	19.10
1-(3'-Arsonoanilino)-5-nitro-	III	11	220–221	C ₁₅ H ₁₂ AsN ₃ O ₅	19.25	19.32
1-(2'-Arsonoanilino)-5-nitro-	III	13	242–245	C ₁₅ H ₁₂ AsN ₃ O ₅	19.25	19.35

TABLE III
ISOQUINOLINEAZOBENZENE ARSONIC ACIDS

Arsonic acid	Yield, %	Decomp., °C.	Formula	As analyses, %	
				Calcd.	Found
5-Aminoisoquinoline-8-azobenzene-4'-	95	300	C ₁₃ H ₁₃ AsN ₄ O ₃	20.13	20.33
5-Amino-4-bromoisoquinoline-8-azobenzene-4'-	47	219–221	C ₁₅ H ₁₂ AsBrN ₄ O ₃	16.61	16.46
8-Amino-4-bromoisoquinoline-5-azobenzene-4'-	66	206–207	C ₁₅ H ₁₂ AsBrN ₄ O ₃	16.61	16.66
5-Amino-1-chloroisoquinoline-8-azobenzene-4'-	82	260	C ₁₅ H ₁₂ AsClN ₄ O ₃	18.42	18.31
5-Aminoisoquinoline-8-azobenzene-3'-	46	180–182	C ₁₅ H ₁₃ AsN ₄ O ₃	20.13	19.95
5-Amino-4-bromoisoquinoline-8-azobenzene-3'-	73	180–182	C ₁₅ H ₁₂ AsBrN ₄ O ₃	16.61	16.62
5-Aminoisoquinoline-8-azobenzene-2'-nitro-4'-	79	300	C ₁₅ H ₁₂ AsN ₅ O ₅	17.96	17.71

(16) Fisher and Hamer, *J. Chem. Soc.*, 1905 (1934), prepared this compound using methyl *p*-toluenesulfonate instead of methyl sulfate but their product melted at 38°.

Summary

1. 4-Bromo-8-aminoisoquinoline, 1-chloro-5-

nitroisoquinoline, 1-chloro-5-aminoisoquinoline, 1-chloro-4-bromoisoquinoline and 1-hydroxy-5-nitroisoquinoline were synthesized for the first time.

2. A number of isoquinoline derivatives bearing an active chlorine atom in the 1-position were condensed with several different aminobenzene-arsonic acids.

3. The chlorine in 1-chloro-5-nitroisoquinoline was found to be non-reactive in acid solution but somewhat reactive in alkaline solution.

4. Several isoquinoline amines were coupled with various diazotized aminobenzene-arsonic acids.

LINCOLN, NEBRASKA

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4-Amino-4'-hydroxylaminodiphenyl Sulfone, its Acetyl and D-Glucosyl Derivatives

BY ERNEST L. JACKSON

The pronounced antibacterial activity¹ of 4,4'-diaminodiphenyl sulfone (I), especially its inhibitive action in experimental tuberculosis,² has stimulated the synthesis and biological study of a variety of derivatives³ in an effort to reduce its toxicity and provide a drug suitable for clinical application. Certain N-glycosyl derivatives⁴ have been tried and the therapeutic efficacy of sodium 4,4'-diaminodiphenylsulfone-N,N'-didextrose-sulfonate (promin) in experimental tuberculosis and in leprosy⁵ has been demonstrated. This investigation concerns the synthesis, constitution and chemical properties of 4-amino-4'-hydroxylaminodiphenyl sulfone (II), two acetyl derivatives and a di-N-glucoside.

4-Amino-4'-hydroxylaminodiphenyl sulfone, m. p. 191-192°, is produced in high yield through reduction of 4-amino-4'-nitrodiphenyl sulfone in aqueous ethanol solution of ammonium chloride by zinc⁶ at 48-50°. The reduction of 4-acetyl-amino-4'-nitrodiphenyl sulfone in a similar way yields 4-acetyl-amino-4'-hydroxylaminodiphenyl sulfone (III), m. p. 194-195°. Both of these compounds, in dry crystalline condition, apparently are stable at room temperature. Acetylation⁷ of II under suitable conditions yields crystalline 4-acetyl-amino-4'-(N-acetyl-O-acetyl-hydroxylamino)-diphenyl sulfone (IV), m. p. 171-172°.

By virtue of the reducing action of the hydrox-

(1) (a) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **232**, 1331 (1937); *Biochem. J.*, **32**, 1101 (1938); (b) Fourneau, Tréfouël, Nitti, Bovet and Tréfouël, *Compt. rend.*, **204**, 1763 (1937); **205**, 299 (1937).

(2) Rist, Bloch and Hamon, *Ann. Inst. Pasteur*, **64**, 203 (1940); Smith, Emmart and Westfall, *J. Pharmacol.*, **74**, 163 (1942); Smith, N. Y. *State J. Med.*, **45**, 1665 (1945); Feldman, Hinshaw and Moses, *Am. Rev. Tuberc.*, **45**, 303 (1942); *Am. J. Med. Sci.*, **207**, 290 (1944).

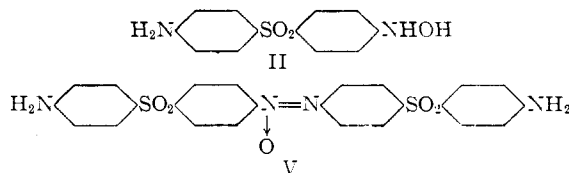
(3) See, for example: (a) Roblin; Williams and Anderson, *THIS JOURNAL*, **63**, 1930 (1941); (b) Heymann and Fieser, *ibid.*, **67**, 1979 (1945); Heymann and Heidelberger, *ibid.*, **67**, 1986 (1945); (c) patent literature; cf. Bambas, *THIS JOURNAL*, **67**, 668, 671 (1945).

(4) Cavallini and Saccarello, *Chimica e industria (Italy)*, **24**, 425 (1942); *C. A.*, **38**, 4257 (1944); Burnet, Cuénod and Natéf, *Bull. acad. med.*, **121**, 317 (1939); Tschesche and Bohle, German Patent 735,560 (1943); *C. A.*, **38**, 2668 (1944); Domagk, *Med. u. Chem.*, **4**, 82 (1942); *C. A.*, **38**, 6377 (1944).

(5) Faget and Pogge, *Pub. Health Repts.*, **60**, 1165 (1945).

(6) Bamberger, *Ber.*, **27**, 1548 (1894).

(7) Cf. Bamberger, *ibid.*, **51**, 636 (1918).



ylamino group, compound II in aqueous dioxane solution consumes 0.9 molecular equivalent of sodium periodate. This reaction, it will be noted, differs in type from the characteristic periodate cleavage of α -glycols.⁸ The hydroxylamine also is oxidized readily in aqueous organic solvents by atmospheric oxygen to yield 4,4'-bis-(*p*-aminobenzenesulfonyl)-azoxybenzene (V). The conversion to the azoxy derivative occurs in high yield in aqueous pyridine solution or in 95% methanol containing a trace of sodium bicarbonate. Similarly, 4,4'-bis-(*p*-acetylaminobenzenesulfonyl)-azoxybenzene (VI), identical with the product of acetylation of V, crystallizes from aqueous methanol solution of III. Heymann and Fieser^{3b} have noted polymorphism among certain derivatives of I; also the dimorphism of 4,4'-bis-(dipiperidylphosphorosoamino)-diphenyl sulfone⁹ has been reported. Two crystalline forms were observed in the case of V and its diacetyl derivative (VI); the melting points of the forms of V are 298-299° (dec.) and 306-307° (dec.), of its acetate 274-275° and 310-311° (dec.). The oxidation of 4-acetyl-amino-4'-aminodiphenyl sulfone by hydrogen peroxide¹⁰ in acetic acid solution produced VI with a melting point of 274-275°.

Another crystalline form of 4,4'-bis-(*p*-aminobenzenesulfonyl)-azoxybenzene was isolated⁹ previously from the products of the reaction of aqueous sodium bicarbonate solution with 4,4'-bis-(dichlorophosphorosoamino)-diphenyl sulfone; it melts at 245-246° and is almost colorless in contrast to the yellow color of V. The crystals melting at 245-246° upon acetylation yielded a

(8) (a) Malaprade, *Bull. soc. chim.*, (4) **43**, 683 (1928); (b) Jackson in R. Adams, "Organic Reactions," Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1944, p. 341.

(9) Jackson, *J. Org. Chem.*, **9**, 457 (1944).

(10) Cf. Carrara and Monzini, *Chimica e industria (Italy)*, **23**, 391 (1941); *C. A.*, **36**, 6510 (1942); Seikel, *THIS JOURNAL*, **62**, 1214 (1940).