phor-π-sulfonate[22] (32.8 g., 0.1 mole) were dissolved in 100 cc. of warm 1 *N* hydrochloric acid. The solution soon deposited the essentially pure L-methionine salt (21.1 g., 85.5%) as narrow transparent prisms with $[\alpha]^{25}D$ +61.7° (*c* 4, water), not substantially changed (+61.5°) after one or more crystallizations from 2.5 parts of water with small loss; solubility in water 5.4. The salt is a hydrate, stable at ordinary temperatures in air or over calcium chloride. Analytical data accord closely with a 7:4 hydration ratio.

Anal. Calcd. for $(C_{15}H_{26}O_6NS_2Br)_4 \cdot 7H_2O$: C, 36.53; H, 6.04; H_2O, 6.42. Found: C, 36.68; H, 6.04; H_2O, 6.47, 6.44, 6.44.

The anhydrous salt has $[\alpha]^{25}D$ +65.8°.

Additional crops (14.8 g.) from the original solution had $[\alpha]^{25}D$ +82° to +84° and consisted principally of ammonium (+)-α-bromocamphor-π-sulfonate dihydrate, $[\alpha]^{25}D$ +84.3° (*c* 4, water). This salt is apparently less soluble than the corresponding D-methionine salt, leaving D-methionine hydrochloride in the final liquors.

L-Methionine.—Pure L-methionine salt (12.4 g.) was dissolved in 2 parts of hot water and the amino acid was precipitated by addition of ammonia to *p*H 6, followed by 4 volumes of methanol. Recrystallization from 80% methanol removed traces of ammonium bromocamphorsulfonate and gave L-methionine (78%) having $[\alpha]^{25}D$ +23.4° (*c* 3, 1 *N* HCl). Evaporation of the methanol from filtrates gave a solution of ammonium bromocamphorsulfonate suitable for re-use.

D-Methionine (6.6 g.) having $[\alpha]^{25}D$ −17.5° (about 84% D-form) was obtained similarly from the foot liquors of the resolution.

(b).—DL-Methionine (119.3 g., 0.8 mole) and ammonium (+)-α-bromocamphor-π-sulfonate (131.2 g., 0.4 mole) were dissolved in 600 cc. of water containing 0.8 mole of hydrochloric acid and the warm solution was seeded. The initial crop of L-methionine salt (145 g.) and further crops obtained by successive concentrations to 200 cc. totaled 182 g. One crystallization series from 2.5 parts of water gave 163 g. (83%) of pure L-methionine salt (hydrate) as large prisms, $[\alpha]^{25}D$ +61.5°. Decomposition of this salt with ammonia gave 44.2 g. (74% based on the DL-form) of L-methionine, $[\alpha]^{25}D$ +23.4° (*c* 3, 1 *N* HCl). The combined mother liquors from the resolution and recrystallization gave 60.5 g. of D-methionine, $[\alpha]^{25}D$ −19.2°.

(c).—D-Methionine (0.05 mole) from (b) was purified by use of ammonium (−)-α-bromocamphor-π-sulfonate.[18] Except for the sign of rotation the constants of the salt and amino acid were substantially identical to those given for the antipodes.

(22) W. J. Pope and J. Read, *J. Chem. Soc.*, **97**, 2199 (1910).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FORDHAM UNIVERSITY]

The Preparation of Pyridine Azo Compounds[1]

BY ROBERT W. FAESSINGER AND ELLIS V. BROWN

Two simple and closely related methods for the preparation of 2- and 4-pyridineazo compounds are described, based upon the reactions of (a) the sodium derivative of 2-aminopyridine with *p*-nitrosodimethylaniline, and (b) the disodium derivative of nitrobenzene or *p*-substituted nitrobenzenes with 2-aminopyridine. By these methods, a variety of new azo compounds have been prepared in which the azo linkage is attached to the 2- position of the pyridine nucleus. Application of the above methods to 3-aminopyridine, aniline and α-naphthylamine did not produce the desired azo compounds.

In investigating the synthesis of pyridine analogs of *p*-dimethylaminoazobenzene (Butter-yellow), which were to be tested for carcinogenic activity, it was observed that 3-aminopyridine easily diazotized and then readily coupled with dimethylaniline to form pyridine-3-azo-*p*-dimethylaniline.[2]

On the other hand, when either 2-aminopyridine or 4-aminopyridine was treated in a similar manner, coupling with dimethylaniline failed to occur to form the expected pyridine azo compound.

Tschitschibabin[3] investigated the preparation of pyridine-2-azoaryl compounds. He successfully prepared pyridine-2-azo-α-naphthol and pyridine-2-azoresorcinol by the reaction of sodium pyridine-2-diazotate with an alcoholic solution of α-naphthol or resorcinol while bubbling CO_2 through the mixture. However, Tschitschibabin reported that no azo product was obtained when dimethylaniline was used. We have since experimentally verified this claim and have found that coupling of 2- and 4-aminopyridine with dimethylaniline also failed when these amines were diazotized with nitrosylsulfuric acid, amyl nitrite or with nitric acid and potassium metabisulfite. In addition, it was observed that *p*-nitrosodimethylaniline in glacial acetic acid does not couple with the pyridylamines in question.

Koenigs, Kinne and Weiss[4] have prepared pyridine-4-azo-*m*-phenylenediamine, pyridine-4-azoresorcinol and the dinitrate of pyridine-4-azo-*p*-dimethylaniline by the reaction of 4-aminopyridine with nitrosylsulfuric acid in concd. nitric acid, followed by coupling with the arylamines. Our investigations of this method on 2-aminopyridine and 4-aminopyridine indicate that this process is of no value for the preparation of the pyridineazo-*p*-dimethylanilines.

Koenigs, Fieigang, Lobmayer and Zscharn[5] have reported the preparation of pyridine-4-azobenzene by the oxidation of pyridine-4-hydrazobenzene with nitrous acid. M. Martynoff[6] has prepared azo compounds in the benzene series with some outstanding results. By heating a mixture of an arylamine and an arylnitro compound with powdered sodium hydroxide, aryl azo compounds were obtained. This process, when applied to the pyridine series using 2-aminopyridine and *p*-nitrodimethylaniline, yielded a viscous, black oil which showed no tendency to crystallize.

A series of pyridine azoaryl compounds has been prepared by two somewhat related processes. In the first method, the sodium derivative of 2-aminopyridine reacted with *p*-nitrosodimethylaniline in dry toluene under an atmosphere of nitrogen to yield the desired product with the azo linkage at the 2-position on the pyridine nucleus. The same results, with a slightly lower percentage yield,

(1) Paper presented at the 118th Meeting, American Chemical Society, Chicago, Ill., Sept. 7, 1950.

(2) C. Rath, *Ann.*, **486**, 95 (1931).

(3) A. E. Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, **50**, 512 (1920).

(4) E. Koenigs, G. Kinne and W. Weiss, *Ber.*, **57**, 1172 (1924).

(5) E. Koenigs, W. Fieigang, G. Lobmayer and A. Zscharn, *ibid.*, **59**, 321 (1926).

(6) M. Martynoff, *Compt. rend.*, **227**, 1371 (1948).

TABLE I

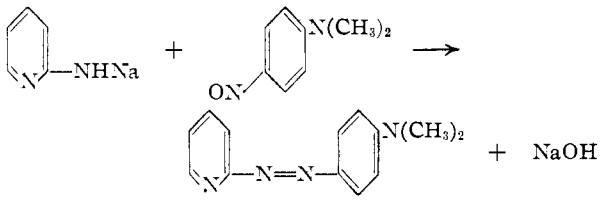
PYRIDINE AZO COMPOUNDS (CONTAINING *p*-DIMETHYLANILINE MOIETY)

Pyridine compound	Azo product	M.p. in °C.[b]	Yield[c] with *p*-nitroso-dimethyl-aniline, %	Yield[d] with *p*-nitrodi-methyl-aniline, %	Nitrogen, % Calcd.	Found
2-Amino-	Pyridine-2-R[a]	111–112	47.3	52.3	24.77	25.02
4-Amino-	Pyridine-4-R	207–209	44.3	53.8	24.77	24.64
3-Methyl-2-amino-	3-Methylpyridine-2-R	158–160	45.8	57.8	23.33	23.62
4-Methyl-2-amino-	4-Methylpyridine-2-R	151–153	45.8	53.5	23.33	23.32
5-Methyl-2-amino-	5-Methylpyridine-2-R	154–147	42.5	55.6	23.33	23.40
6-Methyl-2-amino-	6-Methylpyridine-2-R	107–108	45.8	61.9	23.33	23.67
2,6-Diamino-	6-Aminopyridine-2-R	210–213	31.2	..	29.04	28.95

[a] R = -azo-*p*-dimethylaniline. [b] Uncorrected. [c] Based on *p*-nitrosodimethylaniline used. [d] Based on *p*-nitrodimethylaniline used.

could be obtained by refluxing a mixture of 2-aminopyridine, *p*-nitrosodimethylaniline and metallic sodium under nitrogen. The reaction of the sodium derivatives of the 2-aminopicolines and 4 aminopyridine proceeded in the same manner producing the corresponding azo compounds.

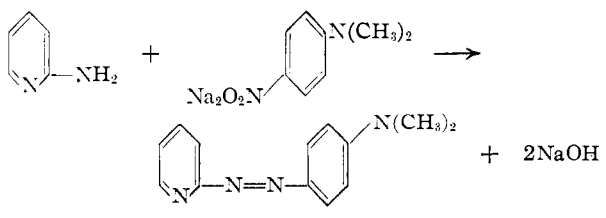
The equation for this preparative method for pyridine azo compounds may be shown as



Small amounts of 4,4′-azobis-(N,N-dimethylaniline) and 4,4′-azoxybis-(N,N-dimethylaniline) were formed as by-products. The results obtained by using this method on aminopyridines and aminopicolines are reported in Table I.

The second method for the preparation of pyridineazo-*p*-dimethylanilines and other pyridine-2-azo compounds involved the reaction of the disodium derivative of *p*-nitrodimethylaniline[7] or other nitrobenzene derivatives with 4-amino- or 2-aminopyridine. This method might be termed a modification of M. Martynoff's process.[6] The pyridylamine was added to the disodium derivative of *p*-nitrodimethylaniline with heating and the product obtained was the expected azo compound. Some unreacted *p*-nitrodimethylaniline can be recovered from the reaction mixture. Similar results were obtained when a mixture of the pyridylamine and *p*-nitrodimethylaniline in toluene was refluxed with sodium.

The equation for this reaction might be shown as



No 4,4′-azoxybis- or 4,4′-azoxybis-(N,N-dimethylaniline) could be isolated from this reaction; however, unreacted *p*-nitrodimethylaniline was recovered. The results of the reaction of *p*-nitrodimethylaniline with various pyridylamines and picolylamines are shown in Table I.

Nitroaryl compounds, other than *p*-nitrodimethylaniline, have reacted with 2-aminopyridine in the manner reported above with varying degrees of success. Arylnitro compounds such as *p*-nitrophenol and *p*-nitrobenzoic acid could not be used since the reactants settled out of the solvent as sodium nitrophenolate and sodium nitrobenzoate before coupling could occur. Ethyl *p*-nitrophenylacetate and ethyl *p*-nitrobenzoate appeared to hydrolyze during the reaction yielding a complex mixture of products. The results obtained with other substituted nitrobenzenes are listed in Table II.

It was noticed, especially in the case of pyridine-2-azo-*p*-dimethylaniline, that two isomeric forms occurred, when azo compounds were prepared by the above methods. This is in agreement with the results of Kirpal, *et al.*,[8a,b] for the case of 2,2′-azopyridine. One form of the isomeric pyridine-2-azo-*p*-dimethylanilines was isolated as yellow-orange plates, m.p. 108–109°, and the other form as red needles, m.p. 111–112°. The plate variety, which had the lower melting point, is believed to be in the *cis* form since prolonged boiling with an aqueous alkali solution converted it to the higher melting needle variety which is considered to have the more stable *trans* configuration.

TABLE II

PYRIDINE-2-AZO COMPOUNDS FROM VARIOUS ARYL NITRO COMPOUNDS WITH 2-AMINOPYRIDINE

No azo compounds were isolated from the reactions with *p*-nitroaniline, *m*-nitroaniline, *p*-dinitrobenzene and *p*-nitrocyanobenzene.

Aryl nitro compound	Pyridineazo product	M.p. in °C.[b]	Yield[c] %	Nitrogen, % Calcd.	Found
Nitrobenzene	R′-Benzene[a]	Oil	41.0	12.92	12.85[d]
p-Nitrotoluene	R′-*p*-Toluene	72.74	42.5	21.32	21.40
p-Nitroanisole	R′-*p*-Anisole	50–52	55.3	19.71	19.60
p-Chlorobenzene	R′-*p*-Chlorobenzene	115–118	44.8	19.31	19.10

[a] R′ = pyridine-2-azo. [b] Uncorrected. [c] Based on nitro compound used. [d] Methiodide derivative.

The separation of these two isomers was effected on an aluminum oxide adsorption column; the *cis* form remained on the column when washed with low-boiling petroleum ether (30–60°).

The behavior of 3-aminopyridine in the reactions just described was radically different from that ob-

(7) V. O. Lukashevich, *Ann.*, **521**, 198 (1936); *J. Gen. Chem. (U. S. S. R.)*, **11**, 1007 (1924).

(8) (a) A. Kirpal and E. Reiter, *Ber.*, **60**, 664 (1927); (b) A. Kirpal and W. Bohm, *ibid.*, **65**, 680 (1932).

served for 2-amino- and 4-aminopyridine. 3-Aminopyridine,[9] like aniline and α-naphthylamine, reacted with *p*-nitrosodimethylaniline under the same conditions mentioned, but did not produce the expected azo compound and yielded instead 4,4′-azoxybis-(N,N-dimethylaniline) and 4,4′-azobis-(N,N-dimethylaniline), neither of which contains the pyridine ring.

Experimental

Pyridine-2-azo-*p*-dimethylaniline by the Sodamide Method.—2-Aminopyridine (4.7 g.) (0.05 mole) and 6.4 g. of naphthalene[10] (0.05 mole) were dissolved in 75 ml. of dry toluene and to this mixture was added 1.15 g. (0.05 mole) of clean sodium with stirring, under an atmosphere of N_2. The reaction mixture was refluxed, with vigorous stirring, until no free sodium was apparent (approx. 1.5 hr.). Then 7.5 g. (0.05 mole) of *p*-nitrosodimethylaniline was added to this suspension of the sodium derivative of 2-aminopyridine, all at once, and refluxing was continued for an additional hour.

The solvent was removed under vacuum, the residue dissolved in 200 ml. of 25% acetic acid, the resultant purple solution diluted with 500 ml. of water and the precipitate of naphthalene and 4,4′-bisazoxydimethylaniline removed by filtration. The azoxy compound (0.6 g., m.p. 244°) was obtained from the mixture by washing with concd. HCl and diluting the resulting solution. Upon neutralizing the original filtrate with ice-cold 20% sodium hydroxide solution, there was obtained a precipitate of crude azo compound (6.3 g.) which was recrystallized several times from petroleum ether (90–100°), 5.3 g., red needles, m.p. 111–112°, yellow plates, m.p. 108–109°. By benzene extraction of the alkaline filtrate, further product, consisting mainly of the plate form, was recovered. The azo compounds listed in Table I may be prepared by treating the respective commercially available aminopicolines in the above manner.

Pyridine-2-azo-*p*-dimethylaniline by the Disodium *p*-nitrodimethylaniline Method.—*p*-Nitrodimethylaniline (8.3 g.) (0.05 mole) was dissolved in 75 ml. of dry toluene and 2.4 g. of clean sodium (0.1 mole) added with stirring under an atmosphere of N_2. The mixture was carefully warmed until reaction occurred but subsequent cooling was necessary to control the reaction. After the reaction subsided, the mixture was refluxed for 1 hr. or until no free sodium was observed. To this suspension of the disodium derivative 4.7 g. (0.05 mole) of 2-aminopyridine was added all at once, the mixture refluxed for 1 hr., the solvent removed under vacuum and the residue treated in the same manner as reported above for the sodamide reaction. The precipitate filtered from the dilute acetic acid solution of the azo compound was found to be essentially unreacted *p*-nitrodimethylaniline (3 g.). Recrystallization of the crude azo compound (4.4 g.) from petroleum ether (90–100°) yielded 4 g. of red needles, m.p. 111–112°. The azo compounds listed in Table I may be prepared by treating the respective aminopicolines or aminopyridines in the above manner.

Pyridine-2-azobenzene.—To a solution of 12.3 g. of dry freshly distilled nitrobenzene (0.1 mole) and 9.4 g. of 2-aminopyridine (0.1 mole) in 150 ml. of dry toluene was added 4.6 g. of clean sodium (0.2 mole) while stirring vigorously under an atmosphere of N_2. This mixture was carefully warmed until a reaction occurred and, after the activity had subsided, again heated to reflux for 3 hr. with continued stirring. The resulting mixture was then filtered hot[11] and the cooled filtrate extracted twice with 25-ml. portions of 17% hydrochloric acid. The acidic solution was diluted to 300 ml. with ice-water, filtered, made basic with cold sodium hydroxide solution (20%), and extracted 4 times with 100-ml. portions of petroleum ether (90–100°). The combined ether extracts were washed 3 times with 50-ml. portions of water, dried over anhydrous sodium sulfate and the dried extract was then evaporated *in vacuo* to remove the solvent. The dark-red liquid residue was then dried over paraffin wax shavings in a vacuum desiccator for 48 hr. and consisted of 7.5 g. of pyridine-2-azobenzene. The picrate of pyridine-2-azo-*p*-dimethylaniline melted at 135–137°; the methiodide at 162–163°.

Pyridine-2-azo-*p*-toluene.—*p*-Nitrotoluene (13.7 g.) (0.1 mole), 9.4 g. of 2-aminopyridine (0.1 mole) and 4.6 g. of clean sodium (0.2 mole) were treated as in the preparation of pyridine-2-azobenzene. The acid extract was made basic with sodium hydroxide solution and allowed to stand for 1 hr. The crude pyridine-2-azo-*p*-toluene (9.8 g.) was filtered, washed with water, air-dried and recrystallized from petroleum ether (90–100°) yielding 8.3 g. (42%) red needles of pyridine-2-azo-*p*-toluene, m.p. 72–74°.

Pyridine-2-azo-*p*-anisole and pyridine-2-azo-*p*-chlorobenzene were prepared by treating the respective nitro compounds with 2-aminopyridine in the above manner.

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(9) Prepared by the action of NaOCl on nicotinamide. We are grateful to Charles Pfizer & Co., Inc., for a generous supply of nicotinamide.

(10) Karl Ziegler, German Patent 615,468 (July 6, 1935).

(11) The black precipitate should be treated with alcohol before disposal to insure the destruction of any free sodium which may not have reacted.