minimize the time it is in contact with the (moist) laboratory air.

SCHOOL OF CHEMISTRY
INSTITUTE OF TECHNOLOGY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 12, 1946

An Improved Procedure for the Replacement of Aromatic Amino Groups by Bromine

BY MELVIN S. NEWMAN AND WILLIAM S. FONES[1]

The replacement of aromatic amino groups by bromine by the Sandmeyer or Gattermann method is frequently unsatisfactory with regard to the time and apparatus required, the low yield, or

TABLE I

Amine	Product	Yield[a] pure (crude), %
o-Chloroaniline	o-Bromochlorobenzene	85 [89–95][a]
m-Chloroaniline	m-Bromochlorobenzene	46[b] [91–94]
p-Chloroaniline	p-Bromochlorobenzene	77 (81)[b] [83]
	4-Chloro-2,6-dibromo-phenol	8[b]
o-Nitroaniline	o-Bromonitrobenzene	83 (93) [80]
m-Nitroaniline	m-Bromonitrobenzene	87 (92) [75]
p-Nitroaniline	p-Bromonitrobenzene	79 (97) [90]
p-Nitroaniline	p-Chloronitrobenzene	33[c]
m-Toluidine	m-Bromotoluene	3[b]
Ethyl anthranilate	o-Bromobenzoic acid and	20 (32)
	3,5-Dibromosalicylic acid	23
Anthranilic acid	o-Bromobenzoic acid and 3,5-Dibromosalicylic acid	
3-Nitro-5-amino-benzoic acid	3-Nitro-5-bromoben-zoic acid	79
Ethyl 2,4-dichloro-5-aminophen-oxyacetate	2,4-Dichloro-5-bromo-phenoxyacetic acid	59[e]
Sulfanilic acid	2,4,6-Tribromophenol	40
p-Anisidine	p-Bromoanisole	7
1-Naphthylamine	1-Bromonaphthalene	20
2-Naphthylamine	Only tars	..
α-Aminopyridine	α-Bromopyridine	35
n-Butylamine	Mixture	..[d]

[a] The yields indicated are for pure product having properties in agreement with the literature values. Those yields were obtained by following the general procedure herein described. Since this was worked out for o-chloroaniline, the yields in the other cases are probably not the optimum. The figures in parentheses indicate crude yields and the yields in brackets are the best reported for the Sandmeyer procedure for the corresponding compounds in the following articles: Fry and Grote, THIS JOURNAL, **48**, 710 (1926); Hartwell, "Organic Syntheses," John Wiley & Sons, New York, N. Y., 1944, Vol. 24, pp. 22–24. [b] Anhydrous hydrogen bromide to saturation was used in place of 40% acid. [c] Concentrated hydrochloric acid was used instead of hydrobromic acid. [d] A mixture which contains some butyl bromide was obtained but was not further investigated. [e] New compound, m. p. 159–161°. Anal. (Arlington Laboratories). Calcd. for $C_8H_5O_3Cl_2Br$: C, 32.0; H, 1.7. Found: C, 32.4, 32.3; H, 2.3, 2.1.

---

(1) This material is taken from a thesis presented by William S. Fones to the Graduate School in partial fulfilment of the requirements for the Ph.D. degree, December, 1946.

both. The Schwechten[2] procedure is often considerably better but suffers from the high cost of reagents. Therefore an improved procedure is highly desirable.

In 1875, Hubner[3] converted 3-amino-5-nitrobenzoic acid into 3-bromo-5-nitrobenzoic acid in unstated yield by passing nitrogen trioxide into a cooled solution of the amine in acetic and hydrobromic acids followed by heating of the resulting mixture until the evolution of nitrogen ceased. On repetition of this experiment, we obtained an 80% yield. In view of the simplicity of this procedure and the high yield of product we have studied this method in some detail. The results we have obtained with nineteen amines are summarized in Table I.

General Procedure

A stirred solution or suspension of the amine hydrobromide prepared from 0.1 mole of amine, 125 cc. of acetic acid and 50 cc. of 40% hydrobromic acid is maintained at 5–10° while nitrogen trioxide[4] is passed in until a permanent dark color appears. This usually requires about forty-five minutes, during which time any solid amine hydrobromide disappears. The solution is then slowly heated until a brisk evolution of nitrogen occurs. This is usually in the 40–50° range and free bromine is evident in the escaping gas. When the gas evolution slows, the reaction mixture is heated to reflux for a few minutes after which it is cooled somewhat and poured into an excess of 20% sodium hydroxide. The product is then isolated by suitable means. The heating phase of the reaction requires about thirty minutes.

The yields in the case of o-chloroaniline were less if any of the following conditions prevailed: 1, no stirring during addition of nitrogen trioxide (78%); 2, nearly pure nitrogen tetroxide replaced nitrogen trioxide (72%); 3, no excess hydrobromic acid (<20%); 4, only 2 equivalents of nitrogen trioxide passed in (68%); 5, slight excess of amine hydrobromide over nitrogen trioxide (9%).

With p-chloroaniline, anhydrous hydrogen bromide in acetic acid improved the yield considerably (60 with 40% aqueous to 81% with anhydrous). No m- or p-bromotoluene was obtained when aqueous hydrobromic acid was used.

The results are consistent with the concept that a perbromide of the diazonium compound is formed and then decomposed by heat, as shown

$$RNH_2 \cdot HBr \xrightarrow{N_2O_3} RN_2Br + Br_2 \longrightarrow RN_2Br_3 \longrightarrow RBr + N_2 + Br_2$$
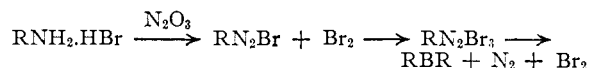
This explanation is supported by the following facts: (A) It is necessary to have hydrobromic acid in excess of that needed to form the amine hydrobromide. (B) Free bromine is present in large amount after the heating period but not before. (C) If sodium bisulfite is added before the heating period no organic bromide is formed. (D) It is known that diazonium salts react with bromine to form diazonium perbromides.[5]

(2) Schwechten. Ber., **65**, 1605 (1932); Newman and Wise. THIS JOURNAL, **63**, 2847 (1941).

(3) Hubner, Ann., **222**, 166 (1884). It is interesting that this publication appeared before Sandmeyer's article on the use of cuprous bromide, Ber., **17**, 1633 (1884).

(4) In our first experiments the oxides of nitrogen were generated by treating arsenic trioxide with nitric acid. Later nitrogen trioxide was obtained in steel cylinders from the du Pont Company.

(5) Griess, Ber., **18**, 965 (1885).

From our work we conclude that this method of replacement of amino groups by bromine is excellent in certain cases when the nucleus is not attacked by bromine under the conditions of the experiment, and when applicable is preferable to other procedures because of the simplicity of operation and the saving of time.
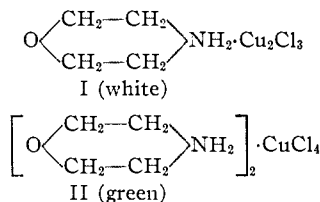
CHEMICAL LABORATORY
THE OHIO STATE UNIVERSITY
COLUMBUS 10, OHIO   RECEIVED DECEMBER 24, 1946

Morpholine Hydrochloride Complexes of Cuprous and Cupric Chloride

BY WALTER H. C. RUEGGEBERG, GORDON N. JARMAN AND RICHARD B. WEARN[1]

Complexes of morpholine with several divalent metals have been reported[2] but detailed data on copper complexes are lacking.

It was found that two complexes of cuprous chloride were obtained after reaction with morpholine hydrochloride. One of these substances, I, constituting about 90% of the reaction product, is the normal reaction product expected from cuprous chloride while the other, II, obtained in about 10% yield, is that derived from cupric chloride which was originally present in the cuprous chloride used.

$$O\underset{CH_2-CH_2}{\overset{CH_2-CH_2}{\Big\langle}} NH_2 \cdot Cu_2Cl_3$$

I (white)

$$\left[O\underset{CH_2-CH_2}{\overset{CH_2-CH_2}{\Big\langle}} NH_2 \right]_2 \cdot CuCl_4$$

II (green)

There are also strong indications that I can be transformed into II. This transformation can easily be observed visually by the color change from white to green occurring when I is exposed to the atmosphere.

The cuprous and cupric complexes are also differentiated by their solubility in water. While the green cupric complex is soluble in water, a 10% solution of hydrochloric acid is required to dissolve the cuprous complex.

Experimental

Preparation of Compound I.—To morpholine (728.6 g.), obtained from the Carbide and Carbon Chemicals Corporation was added dropwise concentrated hydrochloric acid (305.3 g.) in a round bottom flask equipped with a mechanical stirrer, dropping funnel, thermometer, gas inlet and gas escape tubes and at such a rate that by means of moderate cooling with an ice–water-bath, the temperature did not exceed 50°. After all of the hydrochloric acid had been added, a stream of nitrogen was passed through the flask and subsequently, cuprous chloride (655.4 g.), C. P. grade obtained from the Fischer Scientific Co., was added at 50°. The entire deep-brown reaction

(1) Present address: Southern Research Institute, Birmingham, Alabama.
(2) Haendler and Smith, THIS JOURNAL, 63, 1164 (1941).

mixture was stirred for several hours. All but about 10 to 20 g. of a solid material, probably cuprous chloride, went into solution. Upon cooling, a copious separation of crystals occurred. The yield was about 90%.

About 20 g. of the crude crystalline product was sucked dry on a Büchner funnel in an atmosphere of nitrogen. The crude crystals so obtained were washed with acetone and the acetone washings were set aside for the isolation of compound II. The cuprous chloride–morpholine hydrochloride complex so formed is a white crystalline material which tends to darken upon prolonged exposure to air. After some darkening at 103°, it was found to melt, with decomposition, at 110.5–112°.

Anal. Calcd. for $C_4H_{10}NOCu_2Cl_3$: Cu, 39.53; Cl, 33.07; N, 4.36. Found: Cu, 39.63; Cl, 32.62; N, 4.15.

It was found that compound I will react in concentrated solution with acetylene to form an orange-yellow substance which upon 5-fold dilution with water deposited a purplish red crystalline complex. This complex is probably $I \cdot C_2H_2$. Further work is required to identify this material.

Isolation of Compound II.—After concentrating and cooling the acetone washings obtained in the purification of the cuprous complex, I, above, a crop of fine bright green crystals was obtained. After drying, it was found that this complex melted to a dark brown liquid at 160–165°. If complex II is allowed to cool after having been heated to 160°, the green color characteristic of the cupric complex reappears. If, however, this material is heated above 160°, decomposition occurs to such an extent that, after cooling, only a brownish black fluid remains.

Anal. Calcd. for $C_8H_{20}N_2O_2CuCl_4$: Cu, 16.66; Cl, 37.16; N, 7.34. Found: Cu, 16.5; Cl, 36.81; N, 7.03.

CHEMICAL CORPS TECHNICAL COMMAND
EDGEWOOD ARSENAL, MD.   RECEIVED NOVEMBER 7, 1946

Derivatives of 5-Chloro-8-hydroxyquinoline

BY M. WEIZMANN AND E. BOGRACHOV

A number of syntheses in the series of 5-chloro-8-hydroxyquinoline was carried out. Derivatives of this substance were expected to have some antimalarial activity, and also to be effective against trypanosomae[1] and amoebae.[2] These compounds thus supplement the recent work by Lauer[3] and by Elderfield.[4]

The condensation of 4-chloro-2-aminophenol with ethyl acetoacetate proceeded easily at relatively low temperature, giving the substituted amino-crotonate, while 4-chloro-2-amino*anisole* reacted only at 160° and gave 2-methoxy-5-chloroacetoacetanilide. Cyclization of the two products led to 4,8-dihydroxy-5-chloroquinaldine (I) and 2-hydroxy-4-methyl-5-chloro-8-methoxyquinoline (II), respectively.

The corresponding Skraup syntheses of 8-hydroxy and 8-methoxy-5-chloroquinoline proceeded with equal ease (yield, 35 and 40%, respectively), as did the Doebner–Miller reaction (condensation with paraldehyde) which led to 8-hydroxy- and 8-methoxy-5-chloroquinaldine. The latter condensed with ortho and para-nitrobenzaldehyde

(1) Chiang and Hartung, *J. Org. Chem.*, **10**, 21 (1945); Browning and co-workers, *Proc. Roy. Soc.* (London), **113B**, 293 (1933); *J. Path. Bact.*, **27**, 121 (1924); *Brit. Med. J.*, II, 326 (1923).
(2) Vioform is a derivative of 5-chloro-8-hydroxyquinoline.
(3) Lauer, Arnold, Tiffany and Tinker, THIS JOURNAL, **68**, 1268 (1946).
(4) Elderfield and co-workers, *ibid.*, **68**, 1584 (1946).