Notes

Quinazolines. II. 2-Guanidino-4,6,7-trimethylquinazoline as a By-Product in the Three-Component Synthesis of 4,6-Diamino-2,2-dimethyl-1-(3,4-xylyl)-1,2-dihydro-*s*-triazine[1,2]

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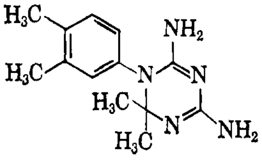
A high-melting, biologically active substance, identified as 3-guanidino-1-methylbenzo[*f*]quinazoline hydrochloride,[2] was isolated in these laboratories as a by-product in the three-component synthesis[3,4] of 4,6-diamino-2,2-dimethyl-1-(2-naphthyl)-1,2-dihydro-*s*-triazine from 2-naphthylamine hydrochloride, dicyandiamide, and acetone. We now wish to describe the only other anomalous guanidinoquinazoline by-product that we have encountered thus far in our considerable experience with the three-component dihydrotriazine synthesis. Careful work-up of the reaction mixture from the condensation of 3,4-xylidine hydrochloride with dicyandiamide and acetone revealed that the desired three-component synthesis product, 4,6-diamino-2,2-dimethyl-1-(3,4-xylyl)-1,2-dihydro-*s*-triazine (I·HCl), was accompanied by a small quantity (<5%) of 2-guanidino-4,6,7-trimethylquinazoline hydrochloride (II·HCl). The experimental basis for the formulation of II·HCl is given below.

Compounds I·HCl and II·HCl could be separated by repeated fractional crystallization from 20% aqueous ethanol, but the most satisfactory method of purification was found to be fractional crystallization of the free bases I and II from 95% ethanol. Compound II, m.p. 259–260°, formed a pale green precipitate with alkaline copper ammonium sulfate and a deep red color (positive test for the guanidine function) with the Sakaguchi reagent. Acidification of an alcoholic solution of II with dilute hydrochloric acid regenerated the hydrochloride salt II·HCl, m.p. 316–317° dec. The empirical formula of II ($C_{12}H_{15}N_5$) differed from that of dihydrotriazine I ($C_{13}H_{19}N_5$) only by the elements of methane and was thus consistent with the pattern observed previously when the three-component synthesis was carried out with 2-naphthylamine.[2] Moreover, the properties of II·HCl closely resembled those of 2-guanidino-4-methylquinazoline hydrochloride (III·HCl), prepared for comparison from *o*-aminoacetophenone hydrochloride and dicyandiamide according to the procedure of Theiling and McKee.[5]

Proof that the by-product is correctly represented by II, rather than by the alternative structure IV, was secured by the unambiguous synthesis depicted in Chart I. Acetylation of 3,4-xylidine,[6] followed by reaction with chloroacetyl chloride in the presence of aluminum chloride according to the procedure of Künckell and Schneider,[7] yielded 2-acetamido-ω-chloro-4,5-dimethylacetophenone, the structure of which was confirmed by its n.m.r. spectrum (only two unsplit peaks in the aromatic region at τ 2.37 and 2.60, corresponding to the C-3 and C-6 protons, respectively). Acid hydrolysis, followed by dehalogenation with zinc and ethanol according to the method of Schofield and coworkers,[8] then furnished 2-amino-4,5-dimethylacetophenone, which, on condensation with dicyandiamide and hydrochloric acid,[5] afforded a high-melting, colorless solid (m.p. 316–317° dec., 40% yield), identical in every respect with the by-product isolated from the three-component synthesis of I·HCl.



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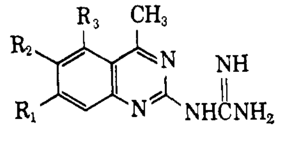
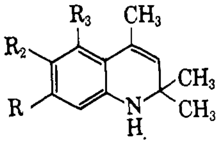


II, $R_1 = R_2 = CH_3$; $R_3 = H$
III, $R_1 = R_2 = R_3 = H$
IV, $R_1 = H$; $R_2 = R_3 = CH_3$



V, $R_1 = R_2 = CH_3$; $R_3 = H$
VI, $R_1 = H$; $R_2 = R_3 = CH_3$

The formation of II·HCl during the three-component synthesis of I·HCl is believed to be a competitive process occurring in the manner shown in Chart I. The initial reaction of 3,4-xylidine may take place either with dicyandiamide (path A), giving N^1-(3,4-xylyl)-biguanide hydrochloride (VII·HCl),[9] or with 2 equiv. of acetone (path B), giving "acetone anil" V·HCl.[10,11] Further condensation of VII·HCl with acetone[12] would lead to the expected three-component synthesis product

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[1] This investigation was supported in part by Research Grant C6516 and Research Career Development Award 1-K6-CA-22,151-01 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

[2] Paper I: A. Rosowsky, H. Kangur Protopapa, P. J. Burke, and E. J. Modest, *J. Org. Chem.*, **29**, 2881 (1964).

[3] E. J. Modest, *ibid.*, **21**, 1 (1956), and references cited therein.

[4] E. J. Modest, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, pp. 697-701.

(5) L. F. Theiling and R. L. McKee, *J. Am. Chem. Soc.*, **74**, 1834 (1952).

(6) L. Limpach, *Ber.*, **21**, 643 (1888).

(7) F. Künckell and H. Schneider, *J. prakt. Chem.*, **86**, 430 (1912).

(8) K. Schofield, T. Swain, and R. S. Theobald, *J. Chem. Soc.*, 2399 (1949).

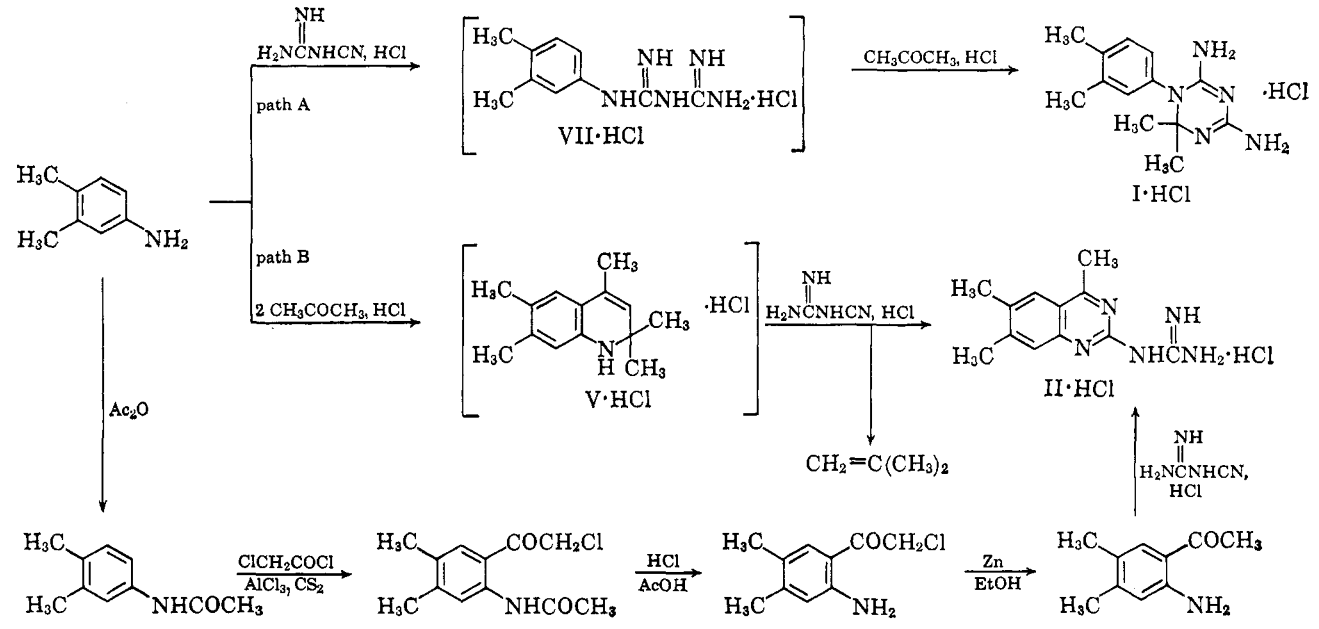
(9) H. King and I. M. Tonkin, *ibid.*, 1063 (1946).

(10) E. Knoevenagel, *Ber.*, **54**, 1722 (1921); see also ref. 11.

(11) For recent discussions concerning the structure and mechanism of formation of arylamine "acetone anils," see (a) I. W. Elliott, Jr., and P. Yates, *J. Org. Chem.*, **26**, 1287 (1961); (b) C. C. Tung, *Tetrahedron*, **19**, 1685 (1963).

(12) E. J. Modest and P. Levine, *J. Org. Chem.*, **21**, 14 (1956).

CHART I



I·HCl, while reaction of V·HCl with dicyandiamide[2,13] would furnish the observed by-product II·HCl. A similar mechanistic argument can be made for the previously reported formation of 3-guanidino-1-methylbenzo[*f*]quinazoline hydrochloride during the three-component synthesis with 2-naphthylamine.[2]

Supporting evidence for path B was obtained by the preparation of 2,2,4,6,7-pentamethyl-1,2-dihydroquinoline (V), and its conversion into II·HCl in 73% yield by condensation with dicyandiamide.[2,13] Compound V, the hitherto unreported "acetone anil" of 3,4-xylidine, was prepared by condensation with acetone in the presence of iodine.[10,11] That the structure of this substance is V, and not the sterically less-favored cyclization product VI, was shown by its n.m.r. spectrum (only two peaks in the aromatic region at τ 3.18 and 3.83, corresponding to the C-5 and C-8 protons, respectively, in V).

It should be emphasized that, among the numerous arylamines employed in these laboratories for the three-component dihydrotriazine synthesis,[3,4] only two, 2-naphthylamine and 3,4-xylidine, have given isolable quantities of guanidinoquinazoline by-products. Nevertheless, we believe that path B may be a more common side reaction than is now apparent and that it may escape detection in most instances because it is a low-yield process. In certain cases the two-component synthesis[12] may actually be a more desirable approach, since it obviates the possibility of "acetone anil" formation (path B). This point was illustrated, in the present work, by the preparation of I·HCl from VII·HCl and acetone in 84% yield without by-product formation.

The various factors affecting the degree to which guanidinoquinazoline formation can be expected to compete with dihydrotriazine formation in the three-component synthesis are currently under study and will be discussed in a future report.

Experimental[14]

4,6-Diamino-2,2-dimethyl-1-(3,4-xylyl)-1,2-dihydro-*s*-triazine (I). A. Standard Three-Component Synthesis.—A mixture of 3,4-xylidine (72.7 g., 0.6 mole), dicyandiamide (54 g., 0.64 mole) concentrated hydrochloric acid (50 ml., 0.6 mole), and acetone (300 ml.) was stirred magnetically for 5.5 hr. under reflux and then at room temperature overnight. A golden yellow solution was obtained in 10 min. and colorless solid began to form shortly thereafter. After refrigeration of the reaction mixture for approximately 4 hr., the solid was collected and washed with acetone. The small colorless prisms (89.6 g., 53%) melted at 211–218° and gave a negative biguanide test (no precipitate with alkaline copper ammonium sulfate).[3,12] Four crystallizations from 20% ethanol removed traces of II·HCl and afforded I·HCl as colorless shiny prismatic plates, m.p. 189–191°. The ultraviolet absorption spectrum of I·HCl showed λ_{max} in mμ (ϵ) at pH 1: 233–236 plateau (5920), 271 inflection (720); at pH 10: 241 (11,040), 271 (920); in EtOH: 244 (12,730).

Anal. Calcd. for $C_{13}H_{19}N_5 \cdot HCl \cdot 0.5H_2O$: C, 53.69; H, 7.28; Cl, 12.19; N, 24.09. Found: C, 53.19; H, 7.33; Cl, 12.27; N, 24.10.

For the preparation of I free base, a solution of 4 g. of once-crystallized I·HCl in 30 ml. of water was brought to pH 11 with 5 *N* sodium hydroxide at room temperature. Small colorless prismatic crystals were obtained (1.93 g., 57%) of m.p. 153–198°. According to the melting point and ultraviolet absorption spectrum, this solid was contaminated with a small amount of II. The volume of the original mother liquor was therefore reduced to 25 ml. at room temperature, and after overnight refrigeration a second crop of colorless thick prismatic rods (0.26 g., 7.7%) was obtained of m.p. 140–147°. Two crystallizations of this solid from 95% ethanol afforded I as small colorless prismatic rods, m.p. 131–133°.

Anal. Calcd. for $C_{13}H_{19}N_5$: C, 63.64; H, 7.81; N, 28.55. Found: C, 63.48; H, 7.78; N, 28.69.

Another crop (0.6 g., 18%) of crude I free base, contaminated with a small amount of II, was obtained from the original aqueous wash upon evaporation to dryness at room temperature; the total crude yield of I was 83%.

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(13) J. P. Brown, *Chem. Ind.* (London), 233 (1960).

(14) Ultraviolet absorption spectra were measured with a Cary Model 11 spectrophotometer. Spectra at pH 1 were taken in 0.1 *N* hydrochloric acid and at pH 10 in 0.05 *M* sodium carbonate-sodium borate buffer. Infrared spectra were taken in potassium bromide disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer (sodium chloride prism). N.m.r. spectra were measured in carbon tetrachloride or deuteriochloroform with a Varian A-60 instrument, with tetramethylsilane as the internal reference. Unless otherwise stated, analytical samples were dried at 70–100° for 17 hr. *in vacuo* over phosphorus pentoxide. Melting points were determined at 2°/min. in sealed Pyrex capillary tubes in a modified Wagner-Meyer melting point apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938)] and are corrected wherever possible. Decomposition points are not reproducible unless conditions are rigidly controlled. Microchemical analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and by Galbraith Laboratories, Knoxville, Tenn.

The impure crop melting at 153–198° was extracted with hot water to remove most of the I still present, and the remaining solid (0.57 g.) was washed with ether and crystallized twice from 95% ethanol. The pale yellow prisms (0.06 g.) were identical with II obtained from other runs (*vide infra*).

B. Two-Component Synthesis.—A mixture of N^1-(3,4-xylyl)-biguanide hydrochloride (VII·HCl) (12.1 g., 0.05 mole), concentrated hydrochloric acid (2.1 ml., 0.025 mole), and acetone (100 ml.) was stirred under reflux for 2 days, and at room temperature for an additional 4 days, at which time a negative biguanide test indicated completion of the reaction. The solid was collected and washed with acetone. The yield of small colorless prisms was 11.8 g. (84%), m.p. 189–200°. Crystallization of 9 g. from 25 ml. of water afforded colorless prismatic plates, 4.3 g., m.p. 204–209°. Two more crystallizations from water gave colorless thin prismatic plates (II·HCl) which melted at 189–191° after having been dried *in vacuo* for 1 week over phosphorus pentoxide at 100°.

Anal. Calcd. for $C_{13}H_{19}N_5 \cdot HCl \cdot 0.5H_2O$: C, 53.69; H, 7.28; N, 24.09. Found: C, 54.03, 54.05; H, 7.14, 7.24; N, 24.16.

2-Guanidino-4,6,7-trimethylquinazoline (II). A. Modified Three-Component Synthesis.—A mixture of 3,4-xylidine (12.1 g., 0.1 mole), dicyandiamide (9.0 g., 0.11 mole), concentrated hydrochloric acid (8.4 ml., 0.1 mole), and acetone (60 ml.) was stirred under reflux for 1.5 hr. An additional 2.5 ml. (0.03 mole) of concentrated hydrochloric acid was added, and reflux was resumed for 1 hr. The clear solution was refrigerated overnight and the solid (II·HCl) was collected, washed with acetone, and dried *in vacuo* at 65°; crude yield 1.21 g. (4.6%). Crystallization of 100 mg. from 2 ml. of water afforded a colorless powder, m.p. 314–315° dec. A pale greenish precipitate was observed on addition of alkaline copper ammonium sulfate,[2] and a positive Sakaguchi reaction was obtained.[2]

Anal. Calcd. for $C_{12}H_{15}N_5 \cdot HCl \cdot 0.75H_2O$: C, 51.54; H, 6.35; N, 25.18. Found: C, 51.71; H, 6.40; N, 24.57.

On prolonged refrigeration, the original filtrate yielded several crops of solids (combined weight 5.28 g.), which appeared, on the basis of infrared spectra and biguanide tests, to consist mainly of **4,6-diamino-2,2-dimethyl-1-(3,4-xylyl)-1,2-dihydro-*s*-triazine hydrochloride (I·HCl)**. The mother liquor gave a positive biguanide test, indicating the presence of **N^1-(3,4-xylyl)biguanide hydrochloride (VII·HCl)**.

B. Reaction of 3,4-Xylidine "Acetone Anil" with Dicyandiamide.—A solution of 12.1 g. (0.1 mole) of 3,4-xylidine and 1 g. of iodine in 65 ml. of anhydrous acetone was refluxed for 24 hr. and the acetone was removed *in vacuo*. The dark oily residue was dissolved in 130 ml. of benzene and the solution was extracted with several portions of 10% aqueous sodium thiosulfate (400 ml. total), rinsed with distilled water, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. A solution of dicyandiamide (8.5 g., 0.1 mole) and concentrated hydrochloric acid (12.5 ml., 50% excess) in 50% ethanol (100 ml.) was added to the semicrystalline residue (V), and the mixture was stirred under reflux for 2 hr. A heavy precipitate formed upon cooling to room temperature. After overnight refrigeration the product was collected and washed with water and acetone. The off-white solid (14.8 g., 54%) melted at 316–319° dec. Another crop (5.4 g., 19%) of solid was obtained from the combined mother liquor and wash upon concentration to approximately one-half the original volume; total crude yield 20.2 g. (73%). A solution of 14.7 g. of crude product in 160 ml. of 20% ethanol was treated with Darco[15] and concentrated to approximately 80 ml. After overnight refrigeration the solid was collected, washed with acetone, and dried in a vacuum oven at 50° for 5 hr.; yield 12.6 g. Two more crystallizations from 20% ethanol afforded II·HCl as small colorless prismatic needles, m.p. 316–317° dec.

Anal. Calcd. for $C_{12}H_{15}N_5 \cdot HCl \cdot 0.5H_2O$: C, 52.45; H, 6.24; Cl, 12.90; N, 25.49. Found: C, 52.52, 52.30; H, 6.13, 6.16; Cl, 13.04; N, 25.65.

For the preparation of II free base, a solution of 1 g. of II·HCl in 35 ml. of 35% ethanol was brought to pH 11 with 5 *N* sodium hydroxide and cooled. The product was collected and washed with water and acetone: small off-white prismatic rods (0.74 g., 89%), m.p. 262–263° dec. Two crystallizations from 95% ethanol afforded II free base as nearly colorless prismatic rods: m.p. 259–260° dec.; λ_{max} in $m\mu$ (ϵ) at pH 1: 249 (65,860), 328 (3930); at pH 10: 250 (39,800), 264 (30,260), 282 inflection (13,640), 341 (4010); in EtOH: 249 (57,600), 264 inflection (18,510), 331 (3390), 340 plateau (3930); at pH 13: 264 and 346 only, no peak at 249–250.

Anal. Calcd. for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.55. Found: C, 62.90; H, 6.56; N, 30.52.

Acidification of an ethanolic solution of II free base with hydrochloric acid yielded II·HCl identical with the material obtained in procedures A and B.

In another run, 3,4-xylidine "acetone anil" was prepared from 2.42 g. (0.02 mole) of 3,4-xylidine as described in the preceding experiment. A solution of the crude, partly crystalline product in 30 ml. of 50% ethanol was treated with Darco and concentrated to 10 ml. Overnight refrigeration gave **2,2,4,6,7-pentamethyl 1,2-dihydroquinoline (3,4-xylidine "acetone anil") (V)**, 2.28 g. (57%), m.p. 63–65°. Two further crystallizations from 50% ethanol afforded slightly off-white, thin prismatic plates, m.p. 64–65°, which were dried for 5 days over phosphorus pentoxide in a closed evacuated drying pistol at room temperature; λ_{max} in $m\mu$ (ϵ) at pH 1: 222 inflection (17,480), 264 (11,700), 294 inflection (970); at pH 10: 228 (30,110), 265 inflection (3070); 330 (3330); in EtOH: 231 (32,660), 265 inflection (2760), 339 (3070).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.60; H, 9.55; N, 6.97.

The τ-values for the n.m.r. spectrum (in carbon tetrachloride) of V [8.82 (singlet), 8.04 (doublet,) 7.88 (singlet), 6.75 (broad), 4.80 (broad), 3.83 (singlet), 3.18 (singlet); relative peak areas 6:3:6:1:1:1:1] correspond to *gem*-dimethyl, vinyl methyl, aromatic methyl, amine, vinyl and aromatic protons, respectively. Except for the additional aromatic methyl peak at τ 7.83, the above spectrum conforms well to that reported by Elliott and Yates[11a] for aniline "acetone anil."

C. Fusion of 2-Amino-4,5-dimethylacetophenone with Dicyandiamide.—3,4-Xylidine was acetylated in excess acetic anhydride[6] and the resulting 3,4-xylidide (colorless prismatic needles, yield 86%, m.p. 97–100°, lit.[6] m.p. 96–98°) was dried for 4 hr. at 40–50° *in vacuo* and used without purification for the preparation of 2-acetamido-ω-chloro-4,5-dimethylacetophenone (pale orange flat prismatic needles, yield 96%, m.p. 166–168°, lit.[7,8] m.p. 166–167°) by condensation with chloroacetyl chloride and aluminum chloride in carbon disulfide.[7] Acid hydrolysis and dehalogenation with zinc[8] furnished 2-amino-4,5-dimethylacetophenone (pale yellow thin prismatic rods, yield 93%, m.p. 125–127°, lit.[8] m.p. 125–126°). A mixture of the latter compound (1.0 g., 6.1 mmoles), dicyandiamide (0.24 g., 2.8 mmoles), and concentrated hydrochloric acid (0.51 ml., 6.1 mmoles) was heated in an oil bath for 4 hr. at 137–140° (internal temperature) while a gentle stream of nitrogen was passed through the reaction system. The nearly solid product was dissolved in 50 ml. of boiling water containing a few drops of hydrochloric acid, and the solution was treated with Darco. Concentration to 8 ml. under reduced pressure, acidification to pH 1 with hydrochloric acid, and refrigeration produced 0.31 g. (40%) of nearly colorless prismatic needles. One crystallization from 10% ethanol containing a few drops of hydrochloric acid afforded colorless prismatic needles, m.p. 316–317° dec. These crystals of II·HCl were shown, on the basis of their melting point and mixture melting point (316–317° dec.), and ultraviolet and infrared absorption spectra, to be identical with those prepared by procedure A.

The n.m.r. spectrum (in deuteriochloroform) of 2-acetamido-ω-chloro-4,5-dimethylacetophenone showed τ 7.76 (singlet), 7.70 (singlet), 7.65 (singlet), 5.19 (singlet), 2.60 (singlet), 2.37 (singlet); relative peak areas 3:3:3:2:1:1.

2-Guanidino-4-methylquinazoline Hydrochloride (III·HCl).—A sample of III·HCl, m.p. 319–321° dec. (lit.[5] m.p. 319–320° dec.), was prepared from *o*-aminoacetophenone hydrochloride and dicyandiamide according to the procedure of Theiling and McKee.[5] The free base III was prepared in the manner used for II. The ultraviolet absorption spectrum of III showed λ_{max} in $m\mu$ (ϵ) at pH 1: 245 (58,080), 264 inflection (5800), 323 (2960); at pH 10: 245 (28,810), 261 (24,180), 338 (3210); in EtOH: 245 (42,760), 266 (18,560), 284 (11,940), 292 inflection (10,990), 327–331 plateau (2720), 339 (2940).

N^1-(3,4-Xylyl)biguanide Hydrochloride (VII·HCl).—VII·HCl was prepared from 3,4-xylidine hydrochloride and dicyandiamide by a modification of the procedure of King and Tonkin,[9] and melted at 223–224° (lit.[9] m.p. 225–226°).

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(15) Darco G-60 activated carbon, Atlas Chemical Industries, Inc., Wilmington, Del.

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Transformations in the 1,10-Phenanthroline Series

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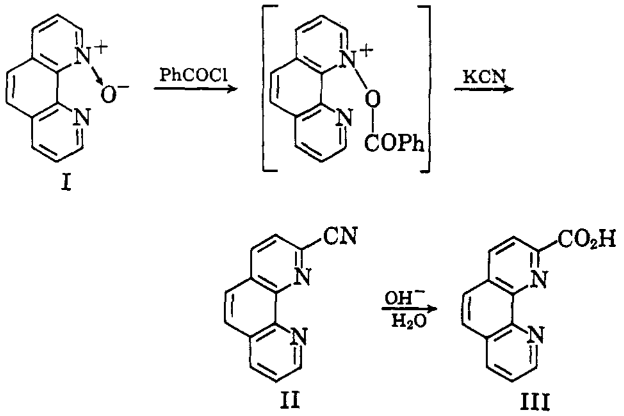
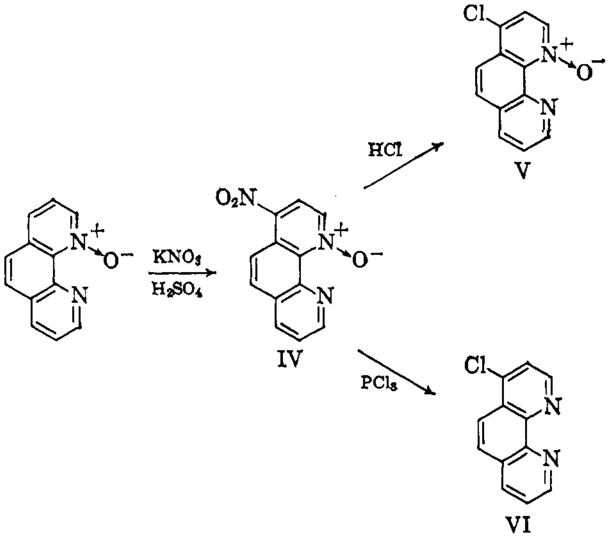
In conjunction with a study of metal ion coordination with 1,10-phenanthroline derivatives and macrocycles derived therefrom we have investigated some of the properties and reactions of 1,10-phenanthroline 1-oxide (I). This substance, which had been prepared previously by Maerker and Case in 26.5% yield,[1] is now readily available (70–80% yields) using a modified procedure described herein. The N-oxide is a tan solid, soluble in cold water, pK_a = 6.6 at 22°, significantly more basic than 1,10-phenanthroline[2] (pK_a = 4.8) or pyridine 1-oxide[3] (pK_a = 0.8).

1,10-Phenanthroline 1-oxide allows the introduction of a cyano group into the 2-position of the phenanthroline ring system. Treatment of the 1-oxide with benzoyl chloride and potassium cyanide at room temperature furnished 2-cyano-1,10-phenanthroline (II) in good yield. Hydrolysis of II under basic conditions gave 1,10-phenanthroline-2-carboxylic acid (III), a hitherto unknown and very useful substance. It is interesting to note that the observed reaction takes precedence over the Reissert reaction[4] at C-9,N-10. The latter course would require the attachment of benzoyl to N-10 which is sterically unfavorable. In addition it should be noted that we have found 1,10-phenanthroline itself not to undergo the Reissert reaction under the conditions useful for quinolines.



Although N-oxides in general are nitrated readily,[5] 1,10-phenanthroline 1-oxide has been reported to fail to undergo nitration.[1] On the other hand, the parent ring system nitrates to give 5-nitro-1,10-phenanthroline in 90% yield.[6] The apparent lack of reactivity of the N-oxide toward electrophilic substitution was reinvestigated. With potassium nitrate in sulfuric acid as a nitrating medium, the N-oxide was actually found to afford a mononitro compound in about 10% yield at 90°. The low yield was not improved by increasing the reaction temperature or time. The product of the reaction was assigned the structure 4-nitro-1,10-phenanthroline 1-oxide (IV) from the following observations. (1) The nitro group is very labile and is replaced by chloride when the compound is heated to reflux in concentrated hydrochloric acid to give 4-chloro-1,10-phenanthroline 1-oxide (V).[7] (2) Reaction of IV with phosphorus trichloride in refluxing chloroform resulted in both deoxygenation and replacement of the nitro group by chlorine. The product, 4-chloro-1,10-phenanthroline, had been prepared previously[8] by a different method. In agreement with the previous report[8] we found the compound to be hygroscopic, but the melting point which we observed was 163–165° (lit.[8] m.p. 180–230°). Hawkins and co-workers[9] recently repeated the original preparation, successfully purified the compound, and reported a melting point of 165–166°. The picrate of our specimen had m.p. 203–204° (reported originally for the picrate of 4-chloro-1,10-phenanthroline,[8] m.p. 203–206°).



The conditions which effect the conversion of 1,10-phenanthroline to the 5-nitro derivative[6] (150–160°, mixture of concentrated nitric and sulfuric acid) lead to gross degradation of 1,10-phenanthroline N-oxide. At lower temperatures the N-oxide is converted to the 4-nitro derivative in low yield and an insoluble acidic by-product is formed in considerable amount.

Our experience with N-oxide I confirms its exceptional unreactivity under the ordinary conditions of electrophilic substitution for aza-aromatic N-oxides. In all probability this effect stems from the relatively great stability of the conjugate acid of I and the consequence that the concentration of free unprotonated I, a much

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(1) G. M. Maerker and F. H. Case, *J. Am. Chem. Soc.*, **80**, 2745 (1958).

(2) T. S. Lee, I. M. Kolthoff, and D. L. Leussing, *ibid.*, **70**, 2348 (1948).

(3) H. H. Jaffe and G. O. Doak, *ibid.*, **77**, 4441 (1955).

(4) See W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

(5) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(6) G. F. Smith and F. W. Cagle, *ibid.*, **12**, 781 (1947).

(7) Nitro groups *para* to an N-oxide function are known to induce facile nucleophilic displacement. See H. J. den Hertog and W. P. Combé, *Rec. trav. chim.*, **70**, 581 (1951).

(8) H. R. Snyder and H. E. Freier, *J. Am. Chem. Soc.*, **68**, 1320 (1946).

(9) C. J. Hawkins, H. Duewell, and W. F. Pickering, *Anal. Chim. Acta*, **25**, 257 (1961).