tillation. This oily product was converted into 2 g. of an oxime identical with the oxime later obtained from the main portion of the adduct. The dark viscous oil from the distillation residue was separated from the water and was taken up in methanol, whereupon a considerable amount of methanol-insoluble resin separated out. The methanol solution of adduct was poured into water and the adduct extracted with petroleum ether. After removal of the solvent, 14 g. of the adduct distilled at 154–156° (7 mm.). This finally solidified and was recrystallized from ethanol–water mixture.

A portion of this ketonic adduct was converted into its oxime by warming with hydroxylamine hydrochloride and sodium acetate in ethanol–water solution. The oxime was recrystallized from ethanol–water mixture.

Attempted Reaction with Chloromaleic Anhydride.—A mixture of 27.3 g. (0.1 mole) of hexachlorocyclopentadiene, 26.5 g. (0.2 mole) of chloromaleic anhydride, and 5 ml. of xylene was refluxed for twelve hours. On steam distillation practically all of the diene was recovered unchanged and no adduct could be isolated.

Action of Alkali on the Adducts.—Hexachlorocyclopentadiene itself was very easily decomposed by even weak alkali with the liberation of ionic chlorine. The acid from the maleic anhydride adduct was remarkably stable toward alkali; boiling its salt with 10% aqueous or alcoholic potassium hydroxide for six hours liberated no significant amount of ionic chlorine. The adducts made with *p*-benzoquinone, acrylonitrile, and methyl vinyl ketone produced ionic chlorine quite easily when warmed with alcoholic potassium hydroxide. The interesting observation was made that the acrylonitrile adduct on heating with alcoholic alkali produced an intense clear red color.

Summary

Hexachlorocyclopentadiene has been found capable of acting as the diene component in the Diels–Alder diene synthesis with certain dienophiles, in which respect it appears to differ from comparably chlorinated, and even some less highly chlorinated, acyclic dienes. Compounds prepared through the additions of maleic anhydride, ethyl maleate, *p*-benzoquinone, acrylonitrile and methyl vinyl ketone to hexachlorocyclopentadiene are described.

YONKERS, N. Y. RECEIVED SEPTEMBER 11, 1946

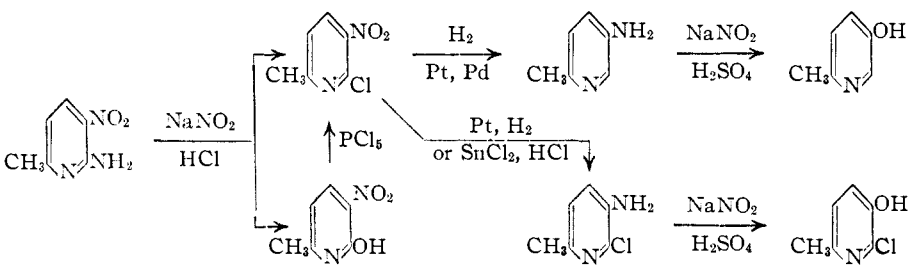
[CONTRIBUTION FROM THE RICHARDSON CHEMISTRY LABORATORY, THE TULANE UNIVERSITY OF LOUISIANA]

Substituted 2-Picolines Derived from 6-Amino-2-picoline[1]

BY EDWIN D. PARKER[2] AND WILLIAM SHIVE[3]

In connection with investigations concerning utilization of coal tar bases, a number of substituted 2-picolines derived from 6-amino-2-picoline have been synthesized for various purposes.

One of these products, 5-hydroxy-2-picoline, was prepared for comparison with the "β-hydroxy-α-picoline"[4] which Wulff[5] obtained by alkali fusion of the sulfonation product of 2-picoline. The following equations indicate the methods by which this hydroxy compound and 6-chloro-5-hydroxy-2-picoline were prepared. The 5-hydroxy-2-picoline prepared by this method and the "β-hydroxy-α-picoline" of Wulff[5] were found to be identical. Wulff[6] also nitrated his "β-hydroxy-α-picoline" but did not report the structure of the "nitro-β-hydroxy-α-picoline" which he obtained. Since further investigation in this Laboratory has led to the conversion of this nitrohydroxypicoline to the corresponding chlorohydroxypicoline,[7] the synthesis of 6-chloro-5-hydroxy-2-picoline as indicated above was carried out in order to compare the product with that obtained from the "nitro-β-hydroxy-α-picoline." The two compounds were found to be identical.



The 6-amino-5-nitro-2-picoline used in the above syntheses was obtained from 2-picoline by amination and nitration similar to the method of Zeide[8] except that the nitration of 6-amino-2-picoline and isomerization of the 6-nitroamino-2-picoline were carried out in the same reaction mixture instead of isolating the intermediate nitroamino compound before isomerization. Both 6-amino-5-nitro-2-picoline and 6-amino-3-nitro-2-picoline, the latter being obtained in larger amounts, resulted from the nitration and isomerization and were separated by steam distillation, the former compound being volatile with steam and the latter remaining in the residue.

(1) From a thesis submitted by Edwin D. Parker in partial fulfillment of the requirements for the degree of Master of Science.

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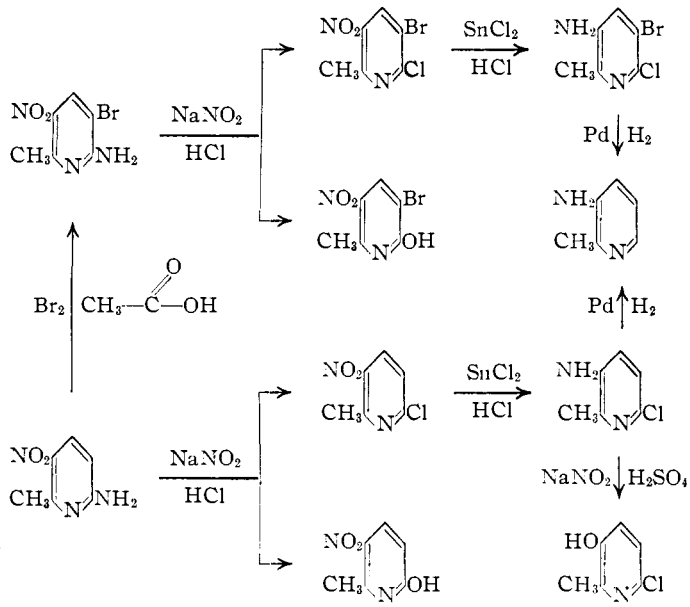
(4) This product has been indexed as 2-picolin-3-ol, *C. A.*, Decennial Index, **21–30** (1927–1936), and has been listed as 3-hydroxy-2-picoline, *C. A.*, **26**, 2471 (1932).

(5) Wulff, U. S. Patent, 1,880,645, Oct. 4, 1932.

(6) Wulff, U. S. Patent 1,889,303, Nov. 29, 1932.

(7) Ballweber and Shive, unpublished work.

(8) Zeide, *J. Russ. Phys.-Chem. Soc.*, **50**, 534 (1920); *C. A.*, **18**, 1497 (1924).



Diazotization of 6-amino-5-nitro-2-picoline was effected by mixing the compound in concentrated hydrochloric acid at 0° with a slight excess of sodium nitrite in a sealed Carius tube. After standing for several hours at low temperatures, the reaction mixture was finally heated for two hours at 60–80° and neutralized. 6-Chloro-5-nitro-2-picoline was isolated by steam distillation of the mixture. Isolated from the residue of the steam distillation, 6-hydroxy-5-nitro-2-picoline was converted to the corresponding 6-chloro compound with phosphorus pentachloride.

Catalytic reduction with Adams platinum catalyst and a palladium catalyst afforded 5-amino-2-picoline, m. p. 95.0–95.6°, which corresponds closely to the product, m. p. 95–96°, which Graf[9] has obtained from 6-methylnicotinic acid by the Curtius method. Following the method of Graf,[9] 5-amino-2-picoline was converted through the diazonium sulfate to 5-hydroxy-2-picoline, m. p. 166–167°, which showed no depression in melting point when mixed with the "3-hydroxy-α-picoline," m. p. 165–166°, prepared by the method of Wulff.[5] Graf reported the melting point of his sample to be 165–167°.

Attempts to hydrogenate 6-chloro-5-nitro-2-picoline to 5-amino-6-chloro-2-picoline in the presence of Adams platinum catalyst resulted in a mixture of that compound with some 5-amino-2-picoline hydrochloride. However, stannous chloride in concentrated hydrochloric acid reduced the nitro group with the formation of 5-amino-6-chloro-2-picoline in excellent yields. Conversion of the 5-amino-6-chloro-2-picoline to 6-chloro-5-hydroxy-2-picoline was effected only by diazotization of low concentrations of the amino compound in dilute sulfuric acid followed by decomposition of the diazonium sulfate through heating the reaction mixture. The yields were low because of side reactions. The 6-chloro-5-hydroxy-2-picoline obtained in this manner did not depress the melting point of the chlorohydroxy-2-picoline[7] obtained by heating the "nitro-β-hydroxy-α-picoline" of Wulff[6] with concentrated hydrochloric acid.

Parallel with the synthesis of 6-chloro-5-hydroxy-2-picoline, a series of derivatives of 2-picoline including 6-chloro-3-hydroxy-2-picoline for further comparative purposes was prepared from 6-amino-3-nitro-2-picoline as indicated in the following equations.

The synthesis of 6-chloro-3-hydroxy-2-picoline was analogous to that of the 5-hydroxy isomer. 3-Amino-6-chloro-2-picoline, an intermediate in this synthesis, was reduced with hydrogen in the presence of a palladium catalyst to 3-amino-2-picoline in order to compare this product with that obtained on hydrogenation of 3-amino-5-bromo-6-chloro-2-picoline. The two products were found to be identical and corresponded to the 3-amino-2-picoline, m.p. 115–116°, obtained by Dornow[10] from 2-methylnicotinamide by Hofmann's method. Dornow also prepared 3-hydroxy-2-picoline, m.p. 167–168°, through diazotization of the 3-amino-2-picoline.

Bromination or chlorination of 6-amino-3-nitro-2-picoline was easily effected in acetic acid to form 6-amino-5-bromo-3-nitro-2-picoline or 6-amino-5-chloro-3-nitro-2-picoline, respectively. Depending upon the conditions of bromination, varying yields of a perbromide of 6-amino-3-nitro-2-picoline were also obtained; however, this perbromide was easily decomposed by heating with concentrated sulfuric acid. The formation of the brominated product occurred with the evolution of hydrogen bromide when the perbromide was so treated.

5-Bromo-6-chloro-3-nitro-2-picoline and 5-bromo-6-hydroxy-3-nitro-2-picoline were obtained from the corresponding 6-amino compound through the diazonium salt by a method analogous to the preparation of 6-chloro- and 6-hydroxy-5-nitro-2-picoline. Reduction of 5-bromo-6-chloro-3-nitro-2-picoline with stannous chloride in concentrated hydrochloric acid gave excellent yields of the corresponding 3-amino compound.

The 3-amino-5-bromo-6-chloro-2-picoline was synthesized in order to determine which of the two halogens was easier to remove by hydrogenation with a palladium catalyst. Absorption of one molecular equivalent of hydrogen resulted in the formation of a mixture of approximately equal amounts of the original compound and 3-amino-2-picoline. Hence, upon removal of the first halogen atom from the compound, the re-

(9) Graf, *J. prakt. Chem.*, **133**, 19 (1932).

(10) Dornow, *Ber.*, **73B**, 78 (1940).

maining halogen was easier to remove than the first.

Experimental

6-Amino-2-picoline.[8]—Commercial grade 2-picoline obtained from the Pittsburgh Coke and Chemical Co. was fractionated through a 6-foot Stedman packed column. Sodium amide, from 92 g. of sodium added to 1.5 liters of liquid ammonia containing a trace of ferric nitrate, was covered with 300 cc. of anhydrous xylene. After addition of 186 g. of 2-picoline, the mixture was heated under dry nitrogen at 125–130° for four hours, then at 130–135° for another four hours and finally refluxed for an additional four hours. The reaction mixture was cooled and treated with cracked ice. The upper xylene layer was separated from two lower layers and washed with water. The aqueous washings, water layer and the dark middle layer which was insoluble in xylene and water were combined and extracted with chloroform. The chloroform layer was washed with water and combined with the xylene layer. After initial solvent removal from the extracts, the 6-amino-2-picoline was fractionated under reduced pressure to obtain a yield of 132 g., or 61.1% of the theoretical, of 6-amino-2-picoline, b. p. 124–125° (20 mm.), m. p. 39–40°.

Nitration of 6-Amino-2-picoline.[8]—Solution of 254 g. of 6-amino-2-picoline in 1200 cc. of concentrated sulfuric acid was effected at 0° by slowly stirring molten 6-amino-2-picoline into the sulfuric acid surrounded by an ice-salt cooling bath. To this solution maintained at 0°, a cooled mixture of 175 cc. of concentrated nitric acid and 175 cc. of concentrated sulfuric acid was added dropwise. The reaction mixture was stirred for an additional hour at 0° and then allowed to warm overnight to room temperature. The 6-nitroamino-2-picoline thus formed was rearranged by heating the reaction mixture to 60° in a water-bath for one hour and finally in a boiling water-bath for one hour. The mixture was then poured over cracked ice, neutralized with concentrated sodium and potassium hydroxide solution to a *p*H 5 to 6 and steam distilled. From the cooled distillates, 81 g. of 6-amino-5-nitro-2-picoline was obtained while the residual liquid contained 210 g. of 6-amino-3-nitro-2-picoline. The distillates were used as the source of water for the boiler of the steam distillation apparatus after the volatile nitro compound had been removed. The residual part of the reaction mixture after steam distillation and filtration was evaporated to dryness, and the residue was extracted with chloroform and alcohol to obtain 10 g. of material, m. p. 150–153°, which was largely the 5-nitro compound. The yield of 6-amino-3-nitro-2-picoline was 210 g. or 58.4% of the theoretical; the yield of 6-amino-5-nitro-2-picoline was 91 g. or 25.3% of the theoretical; the over-all yield of nitro compounds was 83.7% of the theoretical.

6-Chloro-5-nitro-2-picoline.—A solution of 1.56 g. of 6-amino-5-nitro-2-picoline was effected in 20 cc. of concentrated hydrochloric acid in a Carius tube. A small tube containing 0.77 g. of sodium nitrite was placed in the Carius tube in such a manner that the acid and nitrite did not come in contact. The tube was sealed, and its contents were cooled to 0°, mixed and allowed to stand in an ice-bath for several hours. The reaction mixture was heated for two hours at 80°, removed from the sealed tube, poured into 50 cc. of water and neutralized with sodium hydroxide after destruction of any excess nitrite. 6-Chloro-5-nitro-2-picoline was separated from the mixture by steam distillation, sublimed under reduced pressure and recrystallized from acetone to obtain pale yellow, almost colorless, plates, m. p. 70.0–70.8°, yield, 0.67 g. or 38% of the theoretical.

Anal. Calcd. for $C_6H_5ClN_2O_2$: N, 16.23. Found: N, 16.27.

6-Hydroxy-5-nitro-2-picoline.—The residue from steam distillation of 6-chloro-5-nitro-2-picoline was filtered to obtain a yellow precipitate which was recrystallized from water to obtain large elongated yellow prisms, m. p. 226–227° with decomposition, decolorization occurring at 220°. The yield varied in different experiments but was usually in the range of 25–30% of the theoretical.

Anal. Calcd. for $C_6H_6N_2O_3$: N, 18.18. Found: N, 17.88.

For the purpose of identification, a small amount of 6-hydroxy-5-nitro-2-picoline was treated with an equivalent weight of phosphorus pentachloride in dry xylene to obtain 6-chloro-5-nitro-2-picoline which was identical with that obtained as described above.

5-Amino-2-picoline.—A solution of 0.878 g. of 6-chloro-5-nitro-2-picoline in ethyl acetate containing a small amount of ethyl alcohol was hydrogenated at atmospheric pressure in the presence of Adams platinum catalyst and palladium on barium carbonate catalyst. After the calculated quantity of hydrogen to reduce the nitro- and chloro-groups was absorbed, no further reduction proceeded at any appreciable rate. The catalyst was filtered from the solution which was evaporated under reduced pressure. The viscous red-colored residue was treated with 2 cc. of 12% sodium hydroxide to liberate the amine which was then extracted with chloroform. The extracts were evaporated under reduced pressure to obtain a viscous liquid which was dissolved in a small amount of benzene and petroleum ether. From the cooled solution, 0.330 g., 60% of the theoretical yield, of 5-amino-2-picoline, m. p. 95.0–96.5°, was obtained. Graf[9] reported the preparation of 5-amino-2-picoline, m. p. 95–96°, from 6-methylnicotinic acid by the Curtius method.

Anal. Calcd. for $C_6H_8N_2$: N, 25.91. Found: N, 25.67.

5-Hydroxy-2-picoline.—By the method described by Graf,[9] 5-amino-2-picoline was diazotized in dilute sulfuric acid. The 5-hydroxy-2-picoline isolated by this procedure melted at 166–167°. The hydroxy-2-picoline obtained by sulfonation of 2-picoline followed by fusion of the sodium 2-picoline sulfonate with potassium hydroxide as described by Wulff[5] was found to melt at the same temperature, and the mixed melting point of the two samples showed no depression.

5-Amino-6-chloro-2-picoline.—A solution of 1.85 g. of 6-chloro-5-nitro-2-picoline in ethyl acetate containing a small amount of absolute ethanol was hydrogenated at atmospheric pressure in the presence of Adams platinum catalyst. The absorption of hydrogen slowed considerably when approximately the amount necessary to reduce the nitro group had been absorbed. The catalyst was filtered from the solution which was evaporated under reduced pressure to obtain a dark red viscous liquid which failed to crystallize when cooled. After extracting with boiling benzene, the insoluble portion crystallized and was removed by filtration. The benzene layer was diluted with petroleum ether and cooled on an ice-bath. Colorless plates, 1.0 g. or 65% of the theoretical yield, which melted at 82–83° after two recrystallizations from benzene–petroleum ether, were thus obtained.

Anal. Calcd. for $C_6H_7ClN_2$: Cl, 24.87. Found: Cl, 25.18.

The benzene insoluble material (0.3 g. or 20% of the theoretical) was dissolved in water and treated with a small amount of 15% sodium hydroxide. The precipitated material after two recrystallizations from benzene melted at 95–97° and did not depress the melting point of 5-amino-2-picoline as prepared above.

An alternate method of reduction was carried out as follows: A solution of 0.320 g. of 6-chloro-5-nitro-2-picoline in 5 cc. of concentrated hydrochloric acid was treated with 1.5 g. of stannous chloride. The solution was then heated for thirty minutes on a steam-bath. The reaction mixture was made just sufficiently alkaline with sodium hydroxide to dissolve the tin salts. The reaction mixture was extracted several times with chloroform, and the chloroform layer was dried over anhydrous sodium sulfate. On evaporation of the chloroform, a residue of crude material, 0.219 g. or 83% of the theoretical yield, melting at 78–82° was obtained. After two recrystallizations from benzene, the compound melted at 82–83° and did not depress the melting point of the 5-amino-6-chloro-2-picoline obtained by hydrogenation.

6-Chloro-5-hydroxy-2-picoline.—Diazotization of 0.40 g. of 5-amino-6-chloro-2-picoline was carried out in 75

cc. of 1 *N* sulfuric acid by slow addition of 0.20 g. of sodium nitrite dissolved in 10 cc. of water. The solution became deep red on addition of the nitrite, and when heated to decompose the diazonium sulfate, a brown precipitate formed. The solution was made alkaline with dilute sodium hydroxide and filtered. The filtrate was concentrated to 15 cc. and saturated with carbon dioxide. Ethanol was added to precipitate the inorganic salts which were removed by filtration and washed with ethanol. The combined alcohol solutions were then evaporated, and the resulting residue was sublimed under reduced pressure to obtain 40 mg. of slightly yellow crystalline material which after two recrystallizations from benzene appeared as colorless prisms, m. p. 194–196°. A mixture of this compound with the chlorohydroxy-2-picoline, m. p. 196–198°, of Ballweber and Shive[7] melted at 195–197°.

6-Chloro-3-nitro-2-picoline.—A solution of 0.92 g. of 6-amino-3-nitro-2-picoline in 10 cc. of concentrated hydrochloric acid was diazotized with 0.47 g. of sodium nitrite in a sealed tube as described above in the preparation of 6-chloro-5-nitro-2-picoline. The reaction mixture was poured into approximately 50 cc. of water and neutralized with 15% sodium hydroxide. On steam distillation, the mixture yielded 0.30 g., or 29% of the theoretical yield, of 6-chloro-3-nitro-2-picoline as pale yellow, almost colorless, prisms, m. p. 54–55° after further purification by sublimation.

Anal. Calcd. for $C_6H_5ClN_2O_2$: Cl, 20.55. Found: Cl, 20.55.

6-Hydroxy-3-nitro-2-picoline.—A crystalline material was filtered from the residue of the steam distillation of 6-chloro-3-nitro-2-picoline. The material, 0.45 g. or 49% of the theoretical yield, was recrystallized from acetone to obtain light yellow microscopic needles, m. p. 234–236°.

Anal. Calcd. for $C_6H_6N_2O_3$: N, 18.18. Found: N, 18.34.

3-Amino-6-chloro-2-picoline.—A solution of 0.56 g. of 3-nitro-6-chloro-2-picoline in 6 cc. of concentrated hydrochloric acid was cooled in an ice-bath and treated with 2.5 g. of stannous chloride. The mixture was then heated on the steam-bath for thirty minutes, cooled and treated with sufficient concentrated sodium hydroxide just to dissolve the tin salts. The aqueous solution was then extracted with three 30-cc. portions of chloroform. The chloroform extracts were combined and dried over anhydrous sodium sulfate. Upon removal of the solvent, the residue crystallized and was recrystallized from benzene to obtain colorless elongated prisms, m. p. 93–94°, yield 0.42 g. or 91% of the theoretical.

Anal. Calcd. for $C_6H_7ClN_2$: Cl, 24.87. Found: Cl, 24.64.

6-Chloro-3-hydroxy-2-picoline.—Diazotization of 3-amino-6-chloro-2-picoline (0.32 g.) was effected in 85 cc. of 1 *N* sulfuric acid by the dropwise addition of 0.16 g. of sodium nitrite in 5 cc. of water. The reaction mixture was faintly yellow and became orange in color on standing overnight. The solution was heated on a water-bath, made alkaline with sodium hydroxide, and evaporated to about 5 cc. The mixture was neutralized by passing carbon dioxide through the solution, and the inorganic salts were removed to a large extent by diluting with ethanol. The precipitated inorganic salts were leached with ethanol, and the combined ethanol solutions were evaporated to dryness. The residue was treated with charcoal in ethanol solution and recrystallized from ethyl acetate yielding 0.07 g., or 22% of the theoretical yield, of colorless plates, which melted at 208° after two additional recrystallizations from ethyl acetate and sublimation.

Anal. Calcd. for C_6H_6ClNO: Cl, 24.70. Found: Cl, 24.67.

When mixed in approximately equal amounts with the chlorohydroxy-2-picoline (m. p. 196.5–198.0°) prepared by Ballweber and Shive,[7] the mixture melted from 173–187°.

6-Amino-5-chloro-3-nitro-2-picoline.—To a solution of 1.53 g. of 6-amino-3-nitro-2-picoline in 15 cc. of acetic acid, a solution of one molecular equivalent of chlorine in 25 cc. of acetic acid was added. The reaction mixture was allowed to stand at room temperature overnight before the acetic acid was removed by distillation. The residue was treated with water and filtered. The precipitate was recrystallized from acetone to obtain light yellow needles, m. p. 215.4–216.0°, yield 0.94 g. or 50% of the theoretical. Some 6-amino-3-nitro-2-picoline (0.6 g.) was recovered on neutralizing the filtrate.

Anal. Calcd. for $C_6H_5ClN_3O_2$: N, 22.40. Found: N, 22.68.

6-Amino-5-bromo-3-nitro-2-picoline.—A solution of 5.0 g. of 6-amino-3-nitro-2-picoline was effected in about 25 cc. of glacial acetic acid by heating the mixture. A solution of 5.7 g. of bromine in glacial acetic acid was added slowly, and the reaction mixture was allowed to stand overnight before removal of the solvent by distillation. The residue was treated with water and filtered. The precipitated crystals were recrystallized from acetone to obtain 6.0 g., or 79% of the theoretical yield, of yellow needles, m. p. 211.6–212.4°.

Anal. Calcd. for $C_6H_5BrN_3O_2$: Br, 34.44. Found: Br, 34.18.

In a similar experiment, 2.98 g. of light yellow, almost colorless, crystals which decomposed at 230° separated from the acetic acid solution on standing. This material was insoluble in hot or cold water, 5% sodium hydroxide, 5% hydrochloric acid, ether or chloroform, but was soluble in 20% hydrochloric acid or acetic acid. On treating with concentrated sulfuric acid, hydrogen bromide was evolved, and 6-amino-5-bromo-3-nitro-2-picoline identical with the above product was isolated on neutralization of the sulfuric acid solution. The compound was apparently a perbromide of 6-amino-3-nitro-2-picoline, and its formation appears to be dependent upon the temperature and concentration of amino compound during bromination.

Anal. Calcd. for $C_6H_7N_3O_2Br_2$: Br, 51.07. Found: Br, 51.11.

5-Bromo-6-chloro-3-nitro-2-picoline.—By the sealed tube method described above, 2.112 g. of 6-amino-5-bromo-3-nitro-2-picoline in 15 cc. of concentrated hydrochloric acid was diazotized with 0.697 g. of sodium nitrite. The reaction mixture was diluted to 50 cc. and neutralized with sodium hydroxide after the excess nitrite was destroyed. The chloro compound was isolated from the mixture by steam distillation and was recrystallized from benzene and petroleum ether to obtain 0.734 g., or 32.1% of the theoretical yield, of light yellow flat prisms, m. p. 93°.

Anal. Calcd. for $C_6H_4BrClN_2O_2$: N, 11.14. Found: N, 11.11.

5-Bromo-6-hydroxy-3-nitro-2-picoline.—The hydroxy compound, 0.568 g. or 26.8% of the theoretical yield, was filtered from the neutral residue following steam distillation of the 5-bromo-6-chloro-3-nitro-2-picoline, and was recrystallized from acetone to obtain light yellow, almost colorless, elongated prisms, m. p. 261° with decomposition.

Anal. Calcd. for $C_6H_5BrN_2O_3$: Br, 34.29. Found: Br, 34.52.

3-Amino-5-bromo-6-chloro-2-picoline.—To a mixture of 1.59 g. of 5-bromo-6-chloro-3-nitro-2-picoline in 5 cc. of concentrated hydrochloric acid, 4.0 g. of stannous chloride was added slowly. Since the compound failed to go into solution, a small quantity of ethanol and a few pieces of metallic tin were added. The reaction mixture was then warmed on a steam-bath for about thirty minutes. The solution was decanted from the unreacted tin and treated with sodium hydroxide until the tin hydroxides just dissolved. The solution was extracted with chloroform, and the chloroform extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The residue, 1.35 g. or 96.4% of the theoretical yield, was recrystallized from benzene and petroleum ether to obtain colorless crystals, m. p. 162.5–164.0°.

Anal. Calcd. for $C_6H_6N_2ClBr$: total halogen, 52.09.

Found: total halogen, 51.72 (silver halide calcd. as Ag_2BrCl).

Hydrogenation of 3-Amino-5-bromo-6-chloro-2-picoline and of 3-Amino-6-chloro-2-picoline.—A solution of 0.53 g. of 3-amino-5-bromo-6-chloro-2-picoline in 10 cc. of ethanol was hydrogenated at atmospheric pressure in the presence of palladium supported on charcoal as a catalyst. The hydrogenation was stopped when the calculated quantity of hydrogen necessary to remove one halogen had been absorbed. After filtration to remove the catalyst, the solvent was evaporated under reduced pressure. Extraction of the residue with ether yielded only a minute amount of material; so, the residue was treated with water which changed the insoluble material noticeably. The insoluble material was then removed by extraction with ether, and the residue from evaporation of the dried ether extracts consisted of 0.20 g. (38%) of colorless crystals, m. p. 161–163°, which did not depress the melting point of 3-amino-5-bromo-6-chloro-2-picoline.

The aqueous layer was made alkaline with dilute sodium hydroxide and evaporated at room temperature to dryness. The residue was extracted with chloroform, and the chloroform extracts were evaporated to obtain 0.10 g. (39%) of crystalline material which after sublimation and two recrystallizations from benzene–petroleum ether melted at 114–116°; picrate, m. p. 236° with decomposition. This material corresponded in properties to the 3-amino-2-picoline of Dornow.[10]

Hydrogenation of 48 mg. of 3-amino-6-chloro-2-picoline was carried out in ethanol at atmospheric pressure in the presence of palladium-on-charcoal as the catalyst. Following removal of the catalyst by filtration, the solvent was removed under reduced pressure. The residue was dissolved in a small amount of water, made alkaline and extracted with chloroform. The chloroform extracts were dried with anhydrous sodium sulfate and evaporated to dryness. The residue, m. p. 112–114°, amounted to 13 mg. or 37% of the theoretical yield. After recrystallization from benzene containing a small amount of petroleum ether the material melted at 114–116° and did not depress the melting point of the analogous product obtained on reduction of 3-amino-5-bromo-6-chloro-2-picoline.

Acknowledgment.—The authors gratefully acknowledge financial aid from the Pittsburgh Coke and Chemical Co., Pittsburgh, Pa., and the aid of Gwyn White Shive who carried out some of the analyses.

Summary

1. 5-Hydroxy-2-picoline has been synthesized from 6-amino-2-picoline and found to be identical with the hydroxy-2-picoline obtained by alkali fusion of the sulfonation product of 2-picoline.

2. 6-Chloro-5-hydroxy-2-picoline has been prepared from 6-amino-2-picoline and shown to be identical with the chloro-5-hydroxy-2-picoline obtained by nitration of 5-hydroxy-2-picoline and treatment of the nitro-5-hydroxy-2-picoline with concentrated hydrochloric acid.

3. Catalytic reduction of 3-amino-5-bromo-6-chloro-2-picoline with an equimolecular amount of hydrogen resulted in a mixture of the original compound and 3-amino-2-picoline in approximately equal amounts.

4. A number of substituted 2-picolines have been synthesized from 6-amino-2-picoline and characterized.

NEW ORLEANS, LA. RECEIVED SEPTEMBER 3, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE, AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PITTSBURGH]

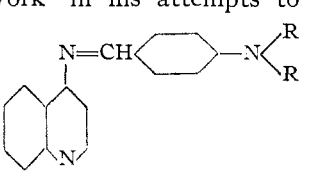
Studies in the Quinoline Series. VI. Synthesis of Certain 4-Substituted Quinoline Derivatives[1]

BY VIRGINIA G. RAMSEY,[2] WILMER E. BALDWIN AND R. STUART TIPSON

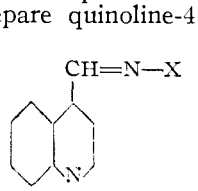
The extensive work of Browning, *et al.*,[3] on the chemotherapeutic properties of "anil quinolinium salts" suggested to us the desirability of preparing some of the related quinoline bases for testing as antimalarial agents.

The 4-aminoquinolines used in the formation of several 4-(*p*-dialkylaminobenzylidene)-aminoquinolines (I) were obtained by well-established procedures mentioned in the experimental section and their condensation with the respective aldehydes conducted at 120–125° in the presence of piperidine as catalyst. The resulting azomethines were readily hydrolyzed to the parent aldehyde and amine by hydrolysis with 10% hydrochloric acid at 100°. Since few, if any, 4-benzylaminoquinolines appear to have been examined for antimalarial activity, a series of corresponding 4-(*p*-diethylaminobenzylamino)-quinolines was prepared from the benzylidene-amino compounds by reduction of the azomethine double bond with hydrogen under pressure, in the presence of Adams catalyst.

Quinoline-4-azomethines (II) of another type were prepared by causing quinoline-4-aldehyde to react with selected amines; in II, X was *p*-hydroxyphenyl, *p*-dimethylaminophenyl, or diethylaminoethyl. In agreement with the experience of Work[4] in his attempts to prepare quinoline-4-



(I)



(II)

(1) Based on a thesis submitted by Virginia G. Ramsey to the Graduate School of the University of Pittsburgh, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1946. Contribution No. 617 of the Department of Chemistry, University of Pittsburgh.

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(3) Browning, Cohen, Ellingworth and Gulbransen (a) *J. Path. Bact.*, **27**, 121 (1924); (b) **29**, 317 (1926); (c) *Proc. Roy. Soc.* (London), **B103**, 404 (1928); (d) **B105**, 99 (1929).

(4) Work, *J. Chem. Soc.*, 429 (1942).