The Preparation of Certain Trisubstituted 2,6-Bis(2′-pyridyl)pyridines[1]

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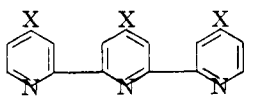
In view of the sensitiveness of the color[2] given by ferrous complexes of certain alkyl and aryl substituted 2,6-bis(2′-pyridyl)pyridines prepared in this laboratory,[3] it was considered desirable to introduce other substituents into this molecule in the positions *para* to the ring-nitrogen. This was accomplished by a method analogous to that previously used[4] in the preparation of similar derivatives of bipyridine.



I. X = H
II. X = NO_2

The tri-*N*-oxide of I was prepared in satisfactory yield by the action on I of hydrogen peroxide in acetic acid. Nitration of the oxide yielded the trinitro oxide in relatively poor yield. This could be converted to 2,6-bis(4′-amino-2′-pyridyl)-4-aminopyridine directly by catalytic reduction in acetic acid. Removal of oxygen from II to form the trinitro compound was accomplished by refluxing with phosphorus trichloride. It was found that with these trioxides removal of oxygen is more difficult than with the dioxides of bipyridine, so that phosphorus trichloride must be used either undiluted or in more concentrated solutions in chloroform than previously.

Treatment of II with acetyl chloride followed by phosphorus trichloride in chloroform yielded 2,6-bis(4′-chloro-2′-pyridyl)-4-chloropyridine. Trimethoxy- and -ethoxy-2,6-bis(2′-pyridyl)pyridines resulted from the action of sodium methoxide and ethoxide on II followed by removal of oxygen by phosphorus trichloride in chloroform.

A previous attempt[4] to hydrolyze 4,4′-dimethoxy-2,2′-bipyridine with hydriodic acid resulted in the formation of the 4-hydroxy-4′-methoxy derivative. We have now obtained 4,4′-dihydroxybipyridine by the action of nitrous acid on diamino bipyridine. The latter compound was conveniently prepared by catalytic reduction of 4,4′-dinitrobipyridine dioxide in acetic acid.

By a process similar to that described above, 2,6-bis(4′-hydroxy-2′-pyridyl)-4-hydroxypyridine was obtained from the corresponding triamino derivative.

EXPERIMENTAL

2,6-Bis(2′-pyridyl)pyridine trioxide. A solution of 8 g. of 2,6-bis(2′-pyridyl)pyridine in 42 ml. of glacial acetic acid and 27 ml. of 30% hydrogen peroxide was heated for 2 hr. at 80°. After addition of a further 27-ml. portion of hydrogen peroxide the temperature was raised to 90° and maintained there for 18 hr. The mixture was then poured into 400 ml. of acetone. After standing several hours, the precipitate was washed with acetone and removed by filtration. From two such runs 17 g. (88.1%) of pure product was obtained melting at 320–321° dec. It can be crystallized from methyl cellosolve–water.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94. Found: C, 63.80; H, 4.06.

2,6-Bis(4′-nitro-2′-pyridyl)-4-nitropyridine trioxide. To a cooled mixture of 5.7 g. of 2,6-bis(2′-pyridyl)pyridine trioxide, 20 ml. of concd. sulfuric acid, and 4.8 ml. of 20% fuming sulfuric acid was added 9.6 ml. of fuming nitric acid (sp. gr. 1.6). The mixture was heated under a reflux condenser at 100° for 1 hr. and then at 120° for 4 hr. The contents of the flask were then poured into ice water and filtered. The precipitate, after washing first with sodium bicarbonate solution and then with water, was dried, and crystallized from aqueous pyridine. The yield of nitro oxide, melting at 268–269° was 1.9 g. (22.6%). An analytical sample melted at 272–273°.

Anal. Calcd. for $C_{15}H_8N_6O_9$: C, 43.27; H, 1.92. Found: C, 43.32; H, 2.06.

2,6-Bis(4′-nitro-2′-pyridyl)-4-nitropyridine. A mixture of 1.5 g. of 2,6-bis(4′-nitro-2′-pyridyl)-4-nitropyridine trioxide and 15 ml. of phosphorus trichloride was refluxed for 18 hr., then poured on ice and made alkaline with ammonium hydroxide. The precipitate was removed, dried, and crystallized from benzene. The yield of pure product, melting at 225–226° was 0.7 g. (53.8%).

Anal. Calcd. for $C_{15}H_8N_6O_6$: C, 48.91; H, 2.17. Found: C, 48.86; H, 2.42.

2,6-Bis(4′-amino-2′-pyridyl)-4-aminopyridine. A mixture of 2.2 g. of 2,6-bis(4′-nitro-2′-pyridyl)-4-nitropyridine trioxide, 5.0 ml. of glacial acetic acid, 1 ml. of acetic anhydride, and 2 g. of 10% palladium-on-carbon was shaken at 30 lbs. pressure of hydrogen in a Parr reduction apparatus until no more hydrogen was absorbed (5 hr.). After removal of catalyst by filtration the solution was evaporated to dryness using an aspirator. Enough water was added to dissolve the resulting solid, followed by concd. ammonium hydroxide. On standing in a refrigerator, crystals of the monohydrate separated (1.2 g. or 75%), which melted at 288°. An analytical sample was prepared (m.p. 292–293°) by crystallization from water.

Anal. Calcd. for $C_{15}H_{14}N_6 \cdot H_2O$: C, 60.81; H, 5.41; N, 28.38. Found: C, 60.25; H, 5.31; N, 28.03.

2,6-Bis(4′-methoxy-2′-pyridyl)-4-methoxypyridine. To a cooled solution of 0.8 g. of sodium in 100 ml. of anhydrous methanol was added 1.9 g. of 2,6-bis(4′-nitro-2′-pyridyl)-4-nitropyridine. After stirring for 4 hr. at 35–40°, solution was nearly complete. The filtered methanolic solution was then evaporated to dryness using an aspirator, and the residue was extracted twice with chloroform. The cold solution obtained by evaporating the chloroform to a volume of 50 ml. was treated with 10 ml. of phosphorus trichloride and refluxed for 4 hr. After cooling and pouring on ice, the solution was made alkaline with sodium hydroxide and filtered. The precipitate was dissolved in ether and the solution added to the chloroform layer in the filtrate. The residue

(1) This work was supported by Grant G 9645 from the National Science Fonndation.

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

from the evaporation of the mixed solvents was then crystallized from methanol, yielding 0.9 g. (47.4%) of pure product, melting at 171–172°.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 66.87; H, 5.26; N, 13.00. Found: C, 66.70; H, 5.40; N, 13.11.

2,6-Bis(4'-ethoxy-2'-pyridyl)-4-ethoxypyridine. To a cooled solution of 0.68 g. of sodium in 91 ml. of anhydrous ethanol was added 2.2 g. of 2,6-bis(4'-nitro-2'-pyridyl)-4-nitropyridine. After stirring for 4 hr. at 60–65°, solution was nearly complete. The filtered alcoholic solution was evaporated to dryness using an aspirator and extracted with chloroform. After evaporation to a volume of 45 ml., 9 ml. of phosphorus trichloride was added and the mixture refluxed for 3 hr. It was then poured on ice and made alkaline. The precipitate obtained, which was insoluble in ether and chloroform was dried and again treated with chloroform and phosphorus trichloride as before. After again pouring on ice and making alkaline, the product dissolved in ether and was recovered by evaporation of the mixed solvents; yield, 0.8 g. (42.1%) of pure product melting at 157–158°.

Anal. Calcd. for $C_{21}H_{22}N_3O_3$: C, 69.04; H, 6.30. Found: C, 68.96; H, 6.49.

2,6-Bis(4'-chloro-2'-pyridyl)-4-chloropyridine. To a suspension of 2 g. of 2,6-bis(4'-nitro-2'-pyridyl)-4-nitropyridine in 20 ml. of glacial acetic acid at 60° was added 12 ml. of acetyl chloride. After heating for 1 hr. on the steam bath, an additional 4 ml. of acetyl chloride was added and heating continued for 1 hr. The mixture was poured on ice and the solution neutralized with sodium bicarbonate. The crude oxide precipitating after separation by filtration and drying was suspended in 35 ml. of chloroform. To the cold mixture was added 4.5 ml. of phosphorus trichloride. After standing for 1 hr., it was refluxed for one hour on the steam bath, and then poured on ice and made alkaline. The resulting precipitate, after drying, was crystallized from benzene yielding 1.2 g. (75.0%) of product, m.p. 210–211°. An analytical sample melted at 212–213°.

Anal. Calcd. for $C_{15}H_8N_3Cl_3$: C, 53.51; H, 2.38. Found: C, 53.49; H, 2.24.

4,4'-Dihydroxy-2,2'-bipyridine. To 7.5 ml. of concd. sulfuric acid at 0° was added 0.95 g. of sodium nitrite. The mixture was allowed to warm to room temperature and then heated at 65° until a clear solution resulted. To this solution was then added a solution of 1.2 g. of 4,4'-diamino-2,2'-bipyridine in 5 ml. of concd. sulfuric acid at 0–5°. After standing for 15 min., the reaction mixture was poured on 40 g. of ice, and the solution was allowed to stand overnight whereupon considerable evolution of nitrogen was observed. On adjusting to *p*H 6 with sodium hydroxide, a precipitate formed which was separated and crystallized from water. The yield of pure hemihydrate melting at 342–343° was 0.7 g. (58.3%).

Anal. (sample dried at 100°). Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.26. Found: C, 63.69; H, 4.30. Calcd. for $C_{10}H_8N_2O_2 \cdot {}^1/_2H_2O$: H_2O, 12.56. Found: H_2O, 12.57.

2,6-Bis(4'-hydroxy-2'-pyridyl)-4-hydroxypyridine. The procedure for this preparation was the same as for that of 4,4'-dihydroxy-2,2'-bipyridine. From 1.2 g. of the triamino compound was obtained 1.2 g. of crude trihydroxy compound. The pure product was obtained as a dihydrate by crystallization from water, in which it is very sparingly soluble. It melts over 400°.

Anal. Calcd. for $C_{15}H_{11}N_3O_3 \cdot 2H_2O$: C, 56.78; H, 4.73; H_2O, 11.36. Found: C, 56.92; H, 4.85; H_2O, 10.97.

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Piperidine Derivatives with a Sulfur-Containing Function in the 4- Position[1]

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A series of 1-methylpiperidines having a functional group containing sulfur at the 4- position was desired for screening as potential antiradiation compounds. The obvious approach to the synthesis of these compounds, the nucleophilic substitution of 1-methyl-4-chloropiperidine, failed to give the desired product.[3] An alternate route to 1-methyl-4-mercaptopiperidine (VIII) was suggested by the ease of formation of the hydrate of 1-methyl-4-piperidone hydrochloride,[4] which would suggest that the reaction of 1-methyl-4-piperidone with hydrogen sulfide should form a *gem*-dithiol with an ease similar to that observed with dibenzyl ketone.[5] The *gem*-dithiol thus formed could readily be converted to the corresponding mercaptan by reduction.

The reaction of 1-methyl-4-piperidone (I) with hydrogen chloride and hydrogen sulfide in ether, the procedure used for the conversion of dibenzyl ketone to the *gem*-dithiol,[5] failed to cause the introduction of sulfur, for the amine salt II precipitated before reaction with hydrogen sulfide occurred. By using a solvent, isopropyl alcohol, in which the amine salt would be soluble and precipitation of the product with ether the reaction led to a colorless, sulfur-containing product which released hydrogen sulfide on heating in aqueous solution. The color tests for sulfur-containing functional groups[6–8] were inconclusive; however, the elemental analyses corresponded to the formula of 1-methyl-4-thiopiperidone hydrochloride (V) which was assumed to be a trimer because of lack of color and analogy with polymerization of other thiones.[9] Molecular weight determinations on V were incon-

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(2) On leave from Extractos Curtientes y Productos Quimicos, S. A., Barcelona, Spain, 1959–1960, as Research Associate at the University of New Hampshire.

(3) Unpublished results, H. Barrera and R. E. Lyle. With the exception of potassium xanthate, nucleophiles led to cleavage of the heterocyclic ring of 1-methyl-4-chloropiperidine.

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