[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF LOYOLA UNIVERSITY]

Synthesis of Some Substituted Pyridines[1]

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Three related series of bicyclic substituted pyridines have been prepared, differing from one another in the size of the carbocyclic ring fused in the 2,3-position. The cyclopentane, cyclohexane, and cycloheptane rings were the carbocyclic rings fused in the 2,3-positions. Other substituent groups have been placed in the 5-position, the 6-position, or the 5- and 6-positions of the pyridine nucleus. Evidence is also presented showing that it is possible to reduce selectively nitriles to primary amines or secondary amines, by adjusting the acidity of the solution.

The compounds synthesized during the present investigation were prepared in order to correlate the effect of the variation of substituents on the pyridine ring with changes in the infrared absorption spectra. In addition, these compounds might prove useful physiologically as they are related to some vitamins. The bioassays, which are being conducted, and the study of the infrared spectra will be reported elsewhere.

The general synthetic reaction scheme is illustrated in Fig. 1. The reactions were standard in nature, except for the hydrogenations, which are discussed later in this paper.

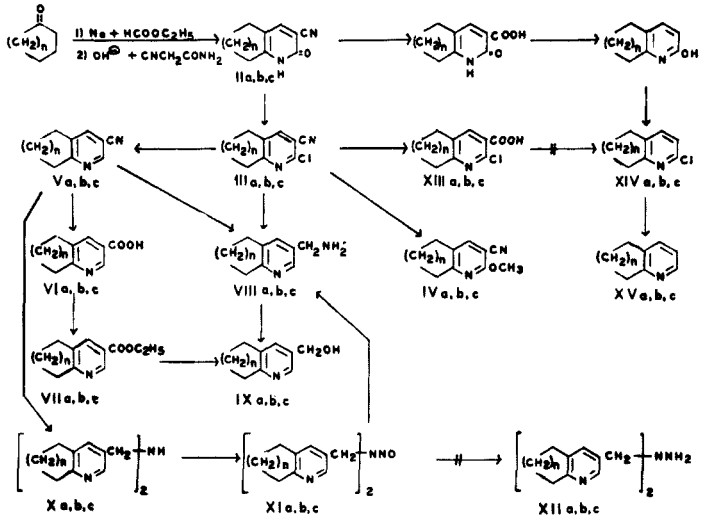

Fig. 1. Reaction scheme. For "a" compounds $n = 1$. For "b" compounds $n = 2$. For "c" compounds $n = 3$

EXPERIMENTAL

Compounds II through III were prepared as reported previously.[4]

6,7-Dihydro-2-methoxy-3-cyano-1,5-pyrindine (IVa). To 33 ml. of freshly prepared 1*N* sodium methoxide was added 3.0 g. of IIIa dissolved in 20 ml. of absolute alcohol. The flask containing the solution was stoppered loosely and placed on a hot plate at about 60° for 2 hr. The solution was filtered while warm to remove most of the sodium chloride, cooled in an ice bath and the white crystalline product was filtered. The solution developed a grayish color as the reaction proceeded. The yield was 2.5 g. (86%), m.p. 114–114.5° after one recrystallization from methanol.

Anal. Calcd. for $C_{10}H_{10}N_2O$: N, 16.1. Found: N, 16.1.

6,7-Dihydro-3-cyano-1,5-pyrindine (Va). To 160 ml. of a 1% solution of sodium hydroxide in absolute ethanol was added 3.0 g. of IIIa. To this solution was added 2.0 g. of a catalyst consisting of 5% palladium on charcoal. The mixture was hydrogenated using the Parr pressure reaction apparatus, under about 25 p.s.i. hydrogen pressure. The theoretical amount of hydrogen was taken up in 3 min., and after 1 more min. the shaker was turned off, 3 ml. concentrated hydrochloric acid was added, and the mixture filtered. The catalyst was washed three times with small portions of 95% ethanol. The resulting solution was evaporated at reduced pressure, and about 10 ml. of water containing 3 ml. concentrated hydrochloric acid added. The solution was filtered and brought to a *p*H of about 5 to precipitate the product. The white crystals were filtered and air dried. The yield in a typical run was 2.1 g. (87%), m.p. 88°. The product would not form a picrate.

Anal. Calcd. for $C_9H_8N_2$: N, 19.4. Found: N, 19.4.

6,7-Dihydro-1,5-pyrindine-3-carboxylic acid (VIa). This acid was prepared by refluxing 1.5 g. Va for 8 hr. with 20 ml. of 6*N* hydrochloric acid. After refluxing, the solution was cooled and 50% aqueous sodium hydroxide added dropwise

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(4) E. M. Godar and R. P. Mariella, *J. Am. Chem. Soc.*, 79, 1402 (1957).

until a precipitate formed. This occurred at about *p*H 5. The precipitate was filtered, washed with several small portions of water, and air dried. Yield, 1.5 g. (88.5%), m.p. 223–225°.

Anal. Calcd. for $C_9H_9NO_2$: N, 8.6. Found: N, 8.3.

6,7-Dihydro-3-carboethoxy-1,5-pyridine (VIIa). To 15 ml. of absolute ethanol in a 50-ml. flask was added 1.5 g. of Va. Then 6.8 ml. of conc. sulfuric acid was added and the reaction mixture heated at reflux for 12 hr. The solution was cooled, filtered, and made alkaline with 20% aqueous sodium hydroxide. The alkaline solution was extracted with three small portions of ethyl ether, the ether layer dried, and evaporated. Yield after one recrystallization from 95% ethanol was 1.3 g. (65.5%), m.p. 42°. This compound would not form a picrate.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.3. Found: N, 7.1.

6,7-Dihydro-3-aminomethyl-1,5-pyridine dihydrochloride (VIIIa). To a solution of 2.4 g. of Va in 100 ml. of absolute ethanol was added 3.0 g. of 5% palladium and 4.0 ml. of conc. hydrochloric acid. The pressure reaction flask containing the mixture was placed in the Parr hydrogenation apparatus and shaken at about 35 p.s.i. of hydrogen. The theoretical uptake occurred in about 3 min. and the shaking was continued for another 10 min. with no further reaction. The flask was removed from the apparatus and the contents filtered through a Buchner funnel. The catalyst was washed three times with 95% ethanol and the washings added to the filtrate. The ethanolic solution was evaporated under reduced pressure. Absolute ethanol was added during the evaporation in small portions until the amine dihydrochloride precipitated from the solution. At this time about 50 ml. of absolute ethyl ether was added and the powdery white crystals filtered from the solution. The dihydrochloride was allowed to dry in air. The yield in a typical reaction was 2.5 g. (85%), m.p. 208–210°.

Anal. Calcd. for $C_9H_{14}Cl_2N_2$: N, 12.7. Found: N, 12.7.

VIIIa *may also be prepared from* IIIa *as follows.* To about 160 ml. of a 1% solution of sodium hydroxide in absolute ethanol containing 2.0 g. of 5% palladium on charcoal was added 3.0 g. of IIIa. The mixture was placed in the low pressure hydrogenation apparatus and shaken at about 25 p.s.i. until one third of the theoretical amount of hydrogen was consumed. This occurred in 2 min. and the shaking was continued for 1 min. more. The shaker was turned off, 8 ml. of conc. hydrochloric acid was added and the hydrogenation was resumed. The theoretical amount of hydrogen was taken up in about 5 min. and the shaking was allowed to proceed for another 5 min. The bottle was removed from the apparatus and the contents filtered through a Buchner funnel. The precipitate was washed three times with 95% ethanol. The ethanol solution was evaporated as described above. The yield in a typical reaction was 2.8 g. (76%). The infrared spectrum of this compound was identical with that of the compound prepared by the alternate method.

6,7-Dihydro-3-hydroxymethyl-1,5-pyridine hydrochloride (IXa). A solution of 2.2 g. of the dihydrochloride of VIIIa in approximately 40 ml. of water was prepared. A solution of 3.4 g. sodium nitrite in about 40 ml. of water was also prepared. These solutions were placed in separate burets whose tips were immersed in 150 ml. of 20% hydrochloric acid in a 250-ml. beaker and run in slowly at room temperature. The reagents were added at a slow enough rate to keep the evolution of nitrogen oxides to a minimum. The solution was stirred until the evolution of gas ceased. Then it was heated to boiling for several minutes. The solution was evaporated under reduced pressure with the concurrent addition of absolute ethanol. When all the water had been displaced the remaining salts were extracted three times with hot absolute ethanol and the ethanol filtered. The resulting solution was reduced in volume and the hydrochloride of the alcohol completely precipitated by the addition of 25 ml. of absolute ethyl ether. The solution was filtered and the white crystalline solid dried in a desiccator. Yield 1.3 g. (60%), m.p. 130°.

Anal. Calcd. for $C_9H_{12}ClNO$: N, 7.6. Found: N, 7.8.

IXa may also be prepared from the corresponding ester VIIa, by reduction with lithium aluminum hydride. One-tenth g. of VIIIa was dissolved in 5 ml. anhydrous ether and 1.0 ml. of 0.584*N* lithium aluminum hydride in ether added. The mixture was stirred for several minutes and several drops of 50% aqueous sodium hydroxide solution added. The mixture was extracted several times with 2–3 ml. portions of ether and the ether evaporated. Yield 0.055 g. (71%). The infrared spectrum of the hydrochloride of this compound was identical with that of the compound prepared by the alternate method.

Di([6,7-dihydro-1,5-pyridine-β-yl]methyl) amine (Xa). A pressure bottle containing 3.0 g. of IIIa, 6 g. of ammonium carbonate, 2.0 g. of a catalyst consisting of 5% palladium on charcoal and about 80 ml. absolute ethanol was placed in the Parr low pressure hydrogenation apparatus and the contents shaken under a hydrogen pressure of about 15 p.s.i. The reaction was complete in 40 min. The solution was filtered and the catalyst washed three times with small portions of 95% ethanol. The ethanol was evaporated under reduced pressure with the concomitant addition of absolute ethanol to displace any water present. The amine hydrochloride precipitated from ethanol and was filtered. The free amine was obtained by dissolving the hydrochloride in dilute hydrochloric acid and making the resultant solution basic with sodium hydroxide. The alkaline solution was extracted with ether until no more oil was apparent; the ether solution was dried with anhydrous potassium carbonate. Upon evaporation of the ether the free amine was obtained, m.p. 118°, yield, 2.1 g. (89.5%).

Anal. Calcd. for $C_{18}H_{21}N_3$: N, 15.0. Found: N, 15.0.

Di([6,7-dihydro-1,5-pyrind-β-yl]methyl)-N-nitrosamine (XIa). To 1.5 g. of the monohydrochloride of Xa in a 25-ml. Erlenmeyer flask was added 6.7 ml. of a 10% solution of sodium nitrite in conc. sulfuric acid. The resulting solution was placed on a hot plate at about 50° for 1 hr. After this time the acid mixture was poured over about 100 g. ice and the solution allowed to come to room temperature. It was heated to boiling to expel any fumes from unreacted nitrite. The solution was cooled and neutralized with 50% aqueous sodium hydroxide. A precipitate formed which was allowed to settle overnight, and was filtered from the solution and washed with a small amount of water. The yield was 1.2 g. (82%), melting point after one recrystallization from absolute ethanol was 146–148°.

Anal. Calcd. for $C_{18}H_{20}N_4O$: C, 70.0; H, 6.5; N, 18.2. Found: C, 69.6; H, 6.4; N, 18.9.

The nitrosamine was difficult to purify as such, but readily formed a *dipicrate*, m.p. 203.5–204.5°. This was analyzed by titration in glacial acetic acid using perchloric acid as the titrant.

Anal. Calcd. for $C_{30}H_{26}N_{10}O_{13}$: Equivalent weight 384. Found: 387.

Attempted preparation of di([6,7-dihydro-1,5-pyrind-β-yl]-methyl)hydrazine (XIIa). To 7.2 ml. of 0.584*N* lithium aluminum hydride was added a solution of 1.2 g. of XIa in 20 ml. of dry ethyl ether. The mixture was stirred for an hour after all the reagents had been added. The excess hydride was decomposed with water and 0.3 g. sirupy phosphoric acid was added. The resulting mixture was extracted three times with ether. After the ether was evaporated 1.1 g. of an oil was recovered, which proved to have an infrared spectrum identical with that of the free base of compound VIIIa, and was therefore a primary amine. No hydrazine was obtained, although a small amount of the starting compound was recovered.

6,7-Dihydro-2-chloro-1,5-pyrindine-3-carboxylic acid (XIIIa). To 25 ml. of a 5% aqueous solution of sodium hydroxide in a 50-ml. flask was added 1.5 g. of IIIa. The mixture was heated under reflux for 4 hr. The solution was cooled and acidified. The white precipitate which formed was filtered and washed several times with small portions of water. Yield, 1.5 g. (96%), m.p. 206–208°.

Anal. Calcd. for $C_9H_8ClNO_2$: N, 7.1. Found: N, 7.2.

Attempted preparation of 6,7-dihydro-2-chloro-1,5-pyrindine (XIVa). This compound had been previously prepared by another route,[4] but it was thought that it could be prepared also by the decarboxylation of compound XIIIa. When an attempt was made to decarboxylate this compound by heating above the melting point, only hydrochloric acid was evolved. All attempts to separate material from the residue yielded only unchanged chloropyrindine. No attempts were made to identify the material resulting from the removal of hydrochloric acid from the molecule.

The remaining two series of compounds were prepared by the same methods as used for the 6,7-dihydropyrindines. Therefore, the yields and physical constants are noted here:

6,7,8,9-Tetrahydro-2-methoxy-3-cyanoquinoline (IVb). (79%), m.p. 106–106.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: N, 14.9. Found: N, 15.0.

6,7,8,9-Tetrahydro-3-cyanoquinoline (Vb). (96%), m.p. 81–82°.

Anal. Calcd. for $C_{10}H_{10}N_2$: N, 17.7. Found: N, 17.6.

6,7,8,9-Tetrahydroquinoline-3-carboxylic acid (VIb). (89.5%), m.p. 240° dec.

Anal. Calcd. for $C_{10}H_{11}NO_2$: N, 7.9. Found: N, 7.9.

6,7,8,9-Tetrahydro-3-carboethoxyquinoline (VIIb). (67%), $b_{1.1}$ 126°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: N, 6.8. Found: N, 6.9.

6,7,8,9-Tetrahydro-3-aminomethylquinoline dihydrochloride (VIIIb). (71.5%), m.p. 227–230°.

Anal. Calcd. for $C_{10}H_{16}Cl_2N_2$: N, 11.9. Found: N, 11.9.

6,7,8,9-Tetrahydro-3-hydroxymethylquinoline hydrochloride (IXb). (70%), m.p. 147°.

Anal. Calcd. for $C_{10}H_{14}ClNO$: N, 7.0. Found: N, 7.1.

Di-([6,7,8,9-tetrahydroquinol-β-yl]methyl)amine (Xb). (88%), m.p. 79–80°.

Anal. Calcd. for $C_{20}H_{25}N_3$: N, 13.7. Found: N, 13.8.

Di-([6,7,8,9-tetrahydroquinol-β-yl]methyl)-N-nitrosamine (XIb). (81.5%), m.p. 100–101°, picrate m.p. 180–182°. This compound was analyzed as the picrate, as the amine was difficult to obtain in crystalline form.

Anal. Calcd. for $C_{32}H_{30}N_{10}O_{15}$: N, 17.6. Found: N, 17.6.

6,7,8,9-Tetrahydro-2-chloroquinoline-3-carboxylic acid (XIIIb). (91.6%), m.p. 179–180°.

Anal. Calcd. for $C_{10}H_{10}ClNO_2$: N, 6.6. Found: N, 6.7.

6,7,8,9-Tetrahydro-2-methoxy-3-cyano-5-cyclohepta(b)pyridine (IVc). This compound formed much more slowly than did the other two compounds of this type, as evidenced by the time of appearance of color in the solution. The solution developed only a slight yellow color during the course of the reaction. (68%) after two recrystallizations from methanol. M.p. 82–84°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: N, 13.9. Found: N, 13.8.

6,7,8,9-Tetrahydro-3-cyano-5-cyclohepta(b)pyridine (Vc). (98%), m.p. 89–90°.

Anal. Calcd. for $C_{11}H_{12}N_2$: N, 16.3. Found: N, 16.1.

6,7,8,9-Tetrahydro-5-cyclohepta(b)pyridine-3-carboxylic acid (VIc). (90%), m.p. 218°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.3. Found: N, 7.5.

6,7,8,9-Tetrahydro-3-carboethoxy-5-cyclohepta(b)pyridine (VIIc). (78.5%), m.p. 52°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: N, 6.4. Found: N, 6.5.

6,7,8,9-Tetrahydro-3-aminomethyl-5-cyclohepta(b)pyridine dihydrochloride (VIIIc). (86.5%), m.p. 226–227°.

Anal. Calcd. for $C_{11}H_{18}Cl_2N_2$: N, 11.2. Found: N, 11.0.

6,7,8,9-Tetrahydro-3-hydroxymethyl-5-cyclohepta(b)pyridine hydrochloride (IXc). (80%), m.p. 127–128°.

Anal. Calcd. for $C_{11}H_{16}ClNO$: N, 6.6. Found: N, 6.6.

Di-([6,7,8,9-tetrahydro-5-cyclohepta(b)pyrid-β-yl]methyl) amine (Xc). (82.5%), m.p. 86–87°.

Anal. Calcd. for $C_{22}H_{29}N_3$: N, 12.5. Found: N, 12.6.

Di-([6,7,8,9-tetrahydro-5-cyclohepta(b)pyrid-β-yl]methyl)-N-nitrosamine (XIc). (84%), m.p. 168.5–169°.

Anal. Calcd. for $C_{22}H_{28}N_4O$: N, 15.4. Found: N, 15.6.

6,7,8,9-Tetrahydro-2-chloro-5-cyclohepta(b)pyridine-3-carboxylic acid (XIIIc). (92.5%), m.p. 168–170°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: N, 6.2. Found: N, 6.4.

Discussion of hydrogenation procedures. The first attempts to convert the cyanochloropyridines to aminomethylpyridines were made by the use of the procedure employed by Perez-Medina, Mariella, and McElvain.[5] These authors had used this method successfully to reduce some monocyclic cyanochloropyridines to the corresponding primary amines.

When this procedure (palladium on charcoal in acidic solution) was used with the bicyclic cyanochloropyridines, it was found that the uptake of hydrogen was very slow, the yields poor, several products were formed, and about half of the starting material was recovered.

Similar reductions in strongly basic solutions or in the presence of an excess of ammonium carbonate resulted in a reasonable rate of reduction (one hour and a half) with the formation of the *corresponding secondary amines.*

It was also discovered that in a slightly basic or neutral solution, the hydrogenations of the bicyclic cyanochloropyridines proceeded rapidly to about one third of theoretical and stopped. When an excess of acid was then added, the remainder of the theoretical amount of hydrogen was absorbed quickly. From this it follows that the halogen is rapidly removed in base (two to three minutes) and the nitrile easily and quickly reduced (three to six minutes) in acid to form the primary amine.

In order to check these procedures a series of halogen compounds were hydrogenated in the presence of sodium hydroxide. The compounds used were chlorobenzene, whose halogen was completely removed in forty-five minutes; bromobenzene, four minutes; iodobenzene, three minutes; and 2-bromopyridine in six minutes. Samples of benzonitrile and nicotinonitrile did not absorb hydrogen under the basic conditions used.

Using the acidic ethanolic medium the following nitriles were reduced to primary amines: nicotinonitrile in twenty-five minutes, 6,7-dihydro-3-cyano-1,5-pyrindine in five minutes, 6,7,8,9-tetrahydro-3-cyanoquinoline in ten minutes, and 6,7,8,9-tetra-3-cyano-5-cyclohepta(b)pyridine in three minutes.

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(5) L. A. Perez-Medina, R. P. Mariella, and S. M. McElvain, *J. Am. Chem. Soc.*, **69**, 2574 (1947).