SUBSTITUTED PYRIDINES. 2,5-DIAROYL-4-PHENYLPYRIDINES AND 2,5-DIAMINO-4-PHENYLPYRIDINES

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 2, pp. 275–277, 1968

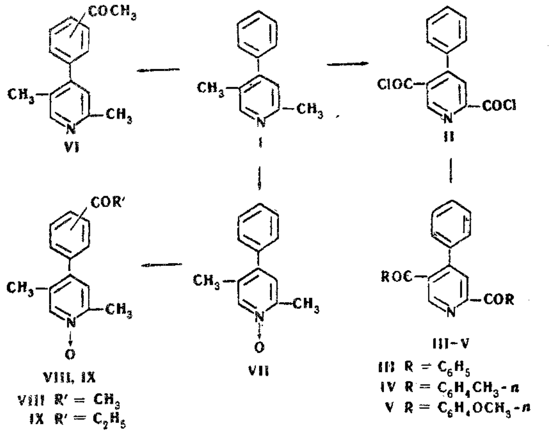
UDC 547.829'822.7'828.07

2,5-Dibenzoyl(di-p-toluoyl, di-p-anisoyl)-4-phenylpyridines, 2,5-dimethyl-4-acetyl(propionyl)phenylpyridine N-oxides, and 2,5-diamino-4-phenylpyridine have been obtained.

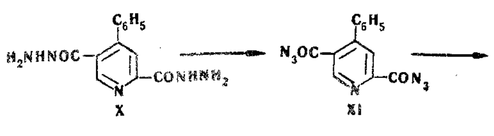
The present paper reports syntheses of substituted pyridine bases in which the 2,5-dimethyl-4-phenylpyridine (I) that we obtained previously [1] was used.

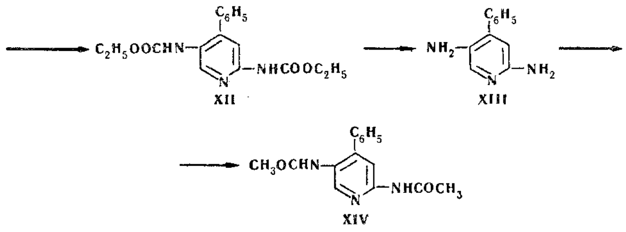
An attempt was made to obtain from this substituted pyridine some dicarbonyl compounds forming polyconjugated systems. The synthesis of the ketones was effected by the Friedel-Crafts method by treating benzene, toluene, and anisole with the dichloride of 4-phenylpyridine-2,5-dicarboxylic acid (II). This gave, respectively, 2,5-dibenzoyl-4-phenylpyridine (III), 2,5-di-p-toluoyl-4-phenylpyridine (IV), and 2,5-di-p-anisoyl-4-phenylpyridine (V). As was to be expected, the Friedel-Crafts acylation of 2,5-dimethyl-4-phenylpyridine (I) itself took place with difficulty. 2,5-Dimethyl-4-acetylphenylpyridine (VI) was obtained in low yield by the treatment of the phenyl-substituted pyridine I with acetyl chloride in nitrobenzene at 150° C.

The acylation of 2,5-dimethyl-4-phenylpyridine N-oxide (VII) also took place with difficulty. Under the same acylation conditions, 2,5-dimethyl-4-acetylphenylpyridine N-oxide (VIII) and 2,5-dimethyl-4-propionylphenylpyridine N-oxide (IX) were obtained in low yields.



The γ-phenyl-substituted pyridine base (I) was used for the synthesis of 2,5-diamino-4-phenylpyridine (XIII), which may also be of interest for obtaining polyconjugated systems.





The synthesis of the diamine XIII was carried out by the Curtius method. The starting material was the dihydrazide of 4-phenylpyridine-2,5-dicarboxylic acid (X) [2]. The diazide of this acid (XI) is unstable and decomposes on storage. Consequently, it was impossible to characterize it analytically. The conversion of the diazide XI into 2,5-di(ethoxycarbonylamino)-4-phenylpyridine (XII) took place with a satisfactory yield. When the urethane XII was hydrolyzed in hydrochloric acid and in alkali we were unable to obtain the diamine. Hydrolysis of the urethane XII with hydriodic acid gave the sparingly water-soluble trihydriodide of the base XIII. The hydriodide yielded the free base, 2,5-diamino-4-phenylpyridine (XIII), in the form of pale pink crystals. In spite of repeated purification, low analytical figures for the nitrogen content of the diaminopyridine XIII were obtained. It is possible that this is explained by its hygroscopicity, which is characteristic of polyamines. However, the analytical data of its diacetyl derivative XIV and its picrate were satisfactory.

EXPERIMENTAL

2,5-Dibenzoyl-4-phenylpyridine (III). A mixture of 9.76 g (0.04 mole) of 4-phenylpyridine-2,5-carboxylic acid and 100 ml of thionyl chloride was heated until the acid had completely dissolved. The excess of thionyl chloride was distilled off and the residue (11.2 g), consisting of crude 4-phenylpyridine-2,5-dicarbonyl chloride [3], was dissolved in 50 ml of dry benzene. This solution was added gradually at room temperature to a mixture of 13.3 g (0.1 mole) of aluminum chloride and 50 ml of benzene. The mixture was stirred at room temperature for 1 hr and was then heated to the boil for 4 hr. After this it was poured into 200 ml of ice water and acidified with 10 ml of concentrated hydrochloric acid. The benzene was distilled off from the benzene layer and the residue was added to the aqueous layer, and was then treated with sodium carbonate. The organic bases were extracted with ether. This gave 2.8 g of 2,5-dibenzoyl-4-phenylpyridine (III) in the form of colorless crystals with mp 115–118° C (from ethanol). Found, %: N 3.67, 3.87. Calculated for $C_{25}H_{17}NO_2$, %: N 3.58.

2,5-Di-p-toluoyl-4-phenylpyridine (IV). A reaction was carried out similarly with 18.2 g (0.075 mole) of 4-phenylpyridine-2,5-dicarboxylic acid, 200 ml of thionyl chloride, 100 ml of toluene, and 35 g (0.26 mole) of aluminum chloride. After the working up process, the organic bases were extracted with ether. The ethereal solution was dried and hydrogen chloride was passed into it. The free base was liberated from the hydrochloride obtained to give 5 g of IV in the form of colorless crystals with mp 96–99° C (from ethanol). Found, %:

N 3.62, 3.52. Calculated for $C_{27}H_{21}NO_2$, %: N 3.58. The IR spectrum of crystalline **IV** has an intense band with an absorption maximum at 1660 cm^{-1} which is characteristic for a carbonyl group conjugated with two aromatic nuclei.

2, 5-Di-p-anisoyl-4-phenylpyridine (V). In a similar manner, 1.92 g of 4-phenyl-2, 5-di-p-methoxybenzoylpyridine was obtained from 4.88 g (0.02 mole) of 4-phenylpyridine-2, 5-dicarboxylic acid, 25 ml of thionyl chloride, 5.58 g (0.042 mole) of aluminum chloride, and 50 ml of anisole. The hydrochloride of the base V had mp 136–138° C (from acetone). Found, %: N 2.85, 2.94. Calculated for $C_{27}H_{21}NO_4 \cdot HCl$, %: N 3.05.

From 1.92 g of the hydrochloride was isolated 1.68 g of the free base V in the form of colorless crystals with mp 113–114° C (from ethanol). Found, %: N 3.03, 3.02. Calculated for $C_{27}H_{21}NO_5$, %: N 3.31.

2, 5-Dimethyl-4-acetylphenylpyridine (VI). A solution of 5.49 g (0.03 mole) of 2, 5-dimethyl-4-phenylpyridine in 25 ml of nitrobenzene was gradually added to 20.35 g (0.15 mole) of aluminum chloride and 50 ml of nitrobenzene, and this was followed by 7.08 g (0.09 mole) of acetyl chloride in 25 ml of nitrobenzene. The reaction mixture was stirred at room temperature for 1 hr and was then heated at 150° C for 5 hr. After cooling, it was poured into 200 ml of cold water. The nitrobenzene was distilled off with steam. The residue was treated with sodium carbonate and extracted with ether. After it had been dried and the ether had been driven off, the residue was distilled to give 3.5 g of the initial 2, 5-dimethyl-4-phenylpyridine [bp 105–120° C (1 mm)] and 0.23 g of 2, 5-dimethyl-4-acetylphenylpyridine (VI); bp 120–125° C (1 mm); mp 140–141° C (from ethanol). Found, %: N 6.59, 6.50. Calculated for $C_{15}H_{15}NO$, %: N 6.22. The IR spectrum of crystalline **VI** had an intense band with an absorption maximum at 1673 cm^{-1}, which is characteristic for a carbonyl group conjugated with one aromatic ring.

2, 5-Dimethyl-4-acetylphenylpyridine N-oxide (VIII). To 26.6 g (0.2 mole) of aluminum chloride and 50 ml of nitrobenzene was gradually added a solution of 7.96 g (0.04 mole) of 2, 5-dimethyl-4-phenylpyridine N-oxide in 25 ml of nitrobenzene, followed by a solution of 9.48 g (0.12 mole) of acetyl chloride in 25 ml of nitrobenzene. The mixture was stirred at room temperature for an hour and then at 150° C for 4 hr. Then it was cooled and poured into 200 ml of cold water. The nitrobenzene was distilled off with steam. The residue was treated with sodium carbonate and extracted with chloroform. After drying, the chloroform was evaporated off and the residue was distilled. A fraction with bp 140–150° C (3 mm) was isolated, and on the addition of ether this crystallized. In this way, 0.57 g of **VIII** was obtained in the form of colorless crystals with mp 171–173° C (from ethanol). Found, %: N 5.65, 5.73. Calculated for $C_{15}H_{15}NO_2$, %: N 5.81.

2, 5-Dimethyl-4-propionylphenylpyridine N-oxide (IX). The reaction was carried out similarly with 26.6 g (0.2 mole) of aluminum chloride, 7.96 g (0.04 mole) of 2, 5-dimethyl-4-phenylpyridine N-oxide, 11.1 g (0.12 mole) of propionyl chloride, and 100 ml of nitrobenzene. This gave 0.1 g of **IX**; bp 150–160° C (3 mm), mp 172–174° C (from ethanol). Found, %: N 5.87, 5.75. Calculated for $C_{16}H_{17}NO_2$, %: N 5.49.

2, 5-Di-(ethoxycarbonylamino)-4-phenylpyridine (XII). A solution of 5.42 g (0.02 mole) of 4-phenylpyridine-2, 5-dicarboxylic acid dihydrazide in 500 ml of water and 15 ml of concentrated hydrochloric acid was cooled to −3° C and, with vigorous stirring, a solution of 4 g (0.058 mole) of sodium nitrite in 40 ml of water was added over 5 min. The colorless crystals formed were filtered off, washed with cold water (100 ml), and dissolved in ether. After brief drying with sodium sulfate, 60 ml of absolute ethanol was added to the solution of 4-phenylpyridine-2, 5-dicarboxylic acid diazide. The ether was distilled off and the residual ethanolic solution was boiled for 12 hr. On cooling, 7.0 g crystals of 2, 5-di(ethoxycarbonylamino)-4-phenylpyridine **(XII)** crystallized out; mp 179–181° C (from ethanol). Found, %: N 12.62, 12.65. Calculated for $C_{17}H_{19}N_3O_4$, %: N 12.76.

2, 5-Diamino-4-phenylpyridine (XIII). With the constant passage of a current of carbon dioxide, a solution of 7 g (0.021 mole) of **XII** in 15 ml of 57% hydriodic acid was boiled for 3 hr. On cooling, 7.8 g of the trihydriodide of the base **XIII** separated out in the form of long yellow needle-like crystals, mp 151–154° C (from ethanol). Found, %: N 7.93, 8.10. Calculated for $C_{11}H_{11}N_3 \cdot 3HI$, %: N 7.44. A solution of 20 g (0.015 mole) of potassium carbonate in 50 ml of water and 200 ml of benzene was added to 7.8 g (0.014 mole) of the trihydriodide of the base **XIII**. The mixture was heated at the boil for 3 hr with the constant passage of carbon dioxide through it. The hot benzene layer was separated off, and the aqueous alkaline solution was extracted with hot benzene (50 ml). The combined benzene extracts were dried with sodium sulfate and the solvent was distilled off in a current of carbon dioxide. This gave 2.3 g of 2, 5-diamino-4-phenylhydrazine; mp 104–106° C (after three recrystallizations from a mixture of benzene and petroleum ether.) Found, %: N 20.86, 20.94. Calculated for $C_{11}H_{11}N_3 \cdot 3C_6H_3N_3O_7$, %: N 19.26.

2, 5-Diacetylamino-4-phenylpyridine (XIV). With cooling, 5 g (64 mM) of acetyl chloride in 10 ml of benzene was slowly added to a mixture of 0.9 g (4.9 mM) of 2, 5-diamino-4-phenylpyridine and 10 ml of triethylamine in 20 ml of anhydrous benzene. The mixture was stirred at room temperature for 1 hr and was then heated to 50° C for 30 min and left overnight. The solvent and the excess of triethylamine were distilled off, and 50 ml of water and 10 ml of concentrated hydrochloric acid were added and the resulting mixture was extracted with ether. The aqueous layer was treated with alkali and extracted with ether and benzene. After drying, the ether and benzene were distilled off. This gave 0.5 g of **XIV** in the form of colorless crystals with mp 208–209° C (from ethyl acetate). Found, %: N 14.99, 14.92. Calculated for $C_{15}H_{15}H_3O_2$, %: N 15.60.

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15 April 1966

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