SUBSTITUTED PYRIDINES

Synthesis of α-Substituted 5-Methyl-4-Phenylpyridines and 3,7-Dimethyl-2-Azafluorene

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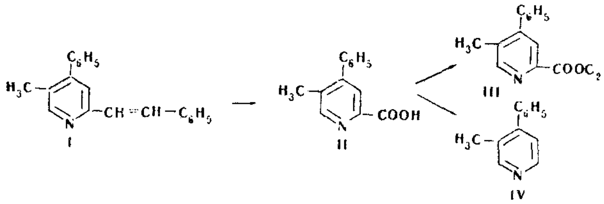
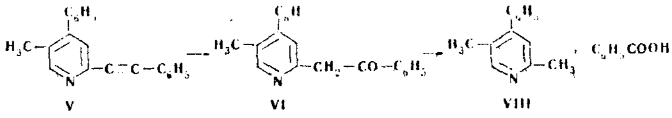
5-Methyl-4-phenyl-2-styrylpyridine has been oxidized to 5-methyl-4-phenylpyridine-2-carboxylic acid. The decarboxylation of this acid has given 3-methyl-4-phenylpyridine. To prove the structure of ω-(5-methyl-4-phenyl-2-pyridyl)acetophenone, it has been converted into 2,5-dimethyl-4-phenylpyridine. The reaction of benzyl chloride with the lithium derivative of 2,5-dimethyl-4-phenylpyridine has been studied. 3,7-Dimethyl-2-azafluorene has been obtained from 2,5-dimethyl-4-p-tolylpyridine.

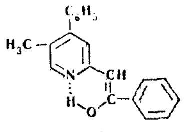
To synthesize an analog of picolinic acid, 5-methyl-4-phenylpyridine-2-carboxylic acid (II), we have used 5-methyl-4-phenyl-2-styrylpyridine (I), which we have described previously [1]. The acid II was obtained by the oxidation of the styryl derivative I with potassium permanganate in acetone.

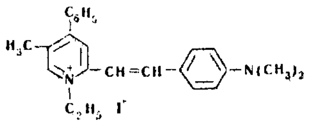
Acid II was converted by the usual method into the ethyl ester III. The decarboxylation of 5-methyl-4-phenylpyridine-2-carboxylic acid (II) gave 3-methyl-4-phenylpyridine (IV).



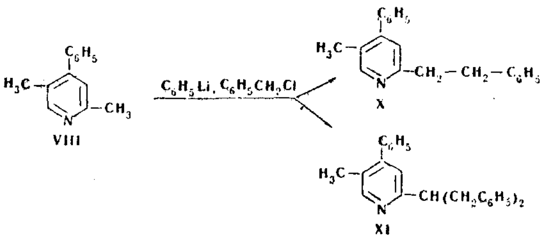
The second pyridine base the reactions of which have been studies in the present work is ω-(5-methyl-4-phenyl-2-pyridyl)acetophenone (VI), obtained by the hydration of 5-methyl-4-phenyl-2-phenylethynylpyridine (V) [2]. The amino ketone VI contains the structural elements of deoxybenzoin. This bright yellow substance, on reaction with ferric chloride, shows a clear reaction for an enol grouping, and is very slightly soluble in ether. The enolic form of this compound apparently has the structure of the chelate complex VII. The ω-(2,5-dimethyl-4-pyridyl)acetophenone obtained in our laboratory is a colorless substance which also gives the enol reaction and dissolves in ether with difficulty. A proof of the order of the addition of water to 5-methyl-4-phenyl-2-phenylethynylpyridine (V) is the decomposition of the ketone VI in the presence of 70% potassium hydroxide, which yielded 2,5-dimethyl-4-phenylpyridine (VIII) and benzoic acid. When the ethiodide of the pyridine base VIII was condensed with p-dimethylaminobenzaldehyde, the ethiodide of 2-(p-dimethylaminostyryl)-5-methyl-4-phenylpyridine (IX) was obtained.




VII

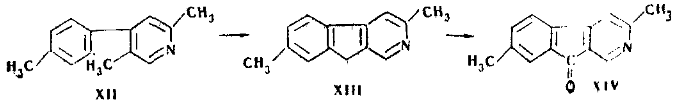

IX

In order to introduce benzyl radicals into the α-methyl group of 2,5-dimethyl-4-phenylpyridine (VIII), we used the reaction of its lithium derivatives with benzyl chloride. As a result, we obtained 1-(5'-methyl-4'-phenyl-2'pyridyl)-2-phenylethane (X) and 2-(5'-methyl-4'-phenyl-2'-pyridyl)-1,3-diphenylpropane (XI).



It has been shown in our laboratory [2] that uncondensed bicyclic compounds containing a pyridine nucleus and a methylene group in the β-position of the pyridine ring undergo catalytic dehydrogenation to nitrogen-containing condensed polycycles comparatively readily. Thus, from 2,5-dimethyl-4-phenylpyridine (VIII) we have obtained 3-methyl-2-azafluorene.

In the present communication, we report the similar conversion of 2,5-dimethyl-4-p-tolylpyridine (XII) [3] into 3,7-dimethyl-2-azafluorene (XIII).



The dehydrocyclization reaction was carried out on type K-16 industrial dehydrogenation catalyst at 550° C. The oxidation of the azafluorene XIII gave 3,7-dimethyl-2-azafluorenone (XIV).

EXPERIMENTAL

5-Methyl-4-phenylpyridine-2-carboxylic acid (II). In small portions, 15 g (0.094 mole) of potassium permanganate was added to a stirred solution of 5 g (0.018 mole) of 5-methyl-4-phenyl-2-styrylpyridine (I) in 200 ml of acetone at 0° C. After the oxidizing agent has been added, the mixture was stirred at 0° C for 3 hr and was then filtered. The manganese dioxide was washed with acetone and then repeatedly with hot water. The aqueous solution was evaporated to 50 ml and treated with 50% sulfuric acid to neutrality. The precipitate that deposited was filtered off and washed with cold water. This gave 4.5 g of a mixture of 5-methyl-4-phenylpyridine-2-carboxylic and benzoic acids.

The mixture was treated with 100 ml of dilute (1:1) hydrochloric acid. The benzoic acid was extracted with ether. The yield of benzoic acid was 1.5 g, mp 121° C. The acid solution was neutralized with sodium carbonate. The precipitate that deposited was filtered off and recrystallized from heptane. This gave 2 g of the acid II, mp 152° C. Found, %: N 6.30; 6.47. Calculated for $C_{13}H_{11}NO_2$, %: N 6.57. **Hydrochloride:** mp 191°–192° C (from acetone). Found, %: N 5.06; 5.24. Calculated for $C_{13}H_{11}NO_2 \cdot HCl$, %: N 5.61.

Ethyl 5-methyl-4-phenylpyridine-2-carboxylate (III). A mixture of 5 g (0.023 mole) of acid II, 40 ml of absolute ethanol, and 3 ml of concentrated sulfuric acid was boiled for 8 hr. Then the ethanol was distilled off. The residue was treated with aqueous sodium carbonate solution in the presence of ether. The ethereal extract yielded 2.7 g of compound III; mp 107°–108° C (from gasoline). Found, %: N 5.39; 5.38. Calculated for $C_{15}H_{15}NO_2$, %: N 5.81.

3-Methyl-4-phenylpyridine (IV). A mixture of 1 g (4.7 mM) of 5-methyl-4-phenylpyridine-2-carboxylic acid (II) and 15 ml of water was heated in the autoclave at 210°–215° C for 3 hr. The organic base was extracted with ether. After the ether had been distilled off, the residue yielded 3-methyl-4-phenylpyridine (IV) in the form of the picrate and hydrochloride. **Picrate:** mp 152°–153° C (from ethanol). Found, %: N 13.75; 13.67. Calculated for $C_{12}H_{11}N \cdot C_6H_3N_3O_7$, %: N 14.07. **Hydrochloride:** mp 187°–188° C (from acetone). Found, %: N 6.55, 6.32. Calculated for $C_{12}H_{11}N \cdot HCl$, %: N 6.81.

2,5-Dimethyl-4-phenylpyridine (VIII). A mixture of 0.5 g (1.7 mM) of ω-(5-methyl-4-phenyl-2-pyridyl)acetophenone (VI) and 15 ml of 70% potassium hydroxide solution was heated in the autoclave at 185° C for 6 hr. After dilution with water, the organic base was extracted with ether. The ethereal extract yielded 2,5-dimethyl-4-phenylpyridine (VIII) in the form of the picrate with mp 172° C (from ethanol). Found, %: N 13.40; 13.61. Calculated for $C_{13}H_{13}N \cdot C_6H_3N_3O_7$, %: N 13.59. The aqueous solution was treated with dilute (1:1) hydrochloric acid. The precipitate that deposited was extracted with ether, yielding 0.15 g of benzoic acid, mp 121° C (from water).

Ethiodide of 5-methyl-2-(p-dimethylaminostyryl)-4-phenylpyridine (IX). A mixture of 1.5 g (4.4 mM) of the ethiodide of 2,5-dimethyl-4-phenylpyridine, 0.66 g (4.4 mM) of p-dimethylaminobenzaldehyde, 1 ml of piperidine, and 25 ml of absolute ethanol was boiled for 7 hr. The ethanol was distilled off under slight vacuum. The residue was recrystallized from ethanol. This gave 1.3 g of the ethiodide IX in the form of bright red crystals with mp 238° C. Found, %: C 61.43; 61.60; H 5.35; 5.17; N 5.80; 5.61. Calculated for $C_{24}H_{27}IN_2$, %: C 61.28; H 5.74: N 5.96.

1-(5'-Methyl-4'-phenyl-2'-pyridyl)-2-phenylethane (X) and 2-(5'-methyl-4'-phenyl-2'-pyridyl)-1,3-diphenylpropane (XI). At room temperature, a solution of 18.3 g (0.1 mole) of 2,5-dimethyl-4-phenylpyridine (VIII) in 30 ml of ether was slowly added to a solution of phenyllithium prepared from 15.7 g (0.1 mole) of bromobenzene and 1.4 g (0.2 g-atom) of lithium in 100 ml of absolute ether. The reaction mixture was heated for 30 min, and then 12.6 g (0.1 mole) of benzyl chloride dissolved in 25 ml of ether was added. After being heated for an hour, the mixture was treated with 50 ml of water and 100 ml of 18% hydrochloric acid. The aqueous layer was treated with sodium carbonate. The organic bases were extracted with ether and were then distilled, three fractions being collected: 118°–160° C (2.5 mm), 10.5 g; 180°–220° C (3 mm), 2.4 g; 220°–260° C (3 mm), 6.2 g.

Vacuum distillation of the second fraction yielded 1-(5'-methyl-4'-phenyl-2'-pyridyl)-2-phenylethane (X) in the form of a viscous liquid with bp 185°–190° C (1 mm). Found, %: N 4.84; 4.87. Calculated for $C_{20}H_{19}N$, %: N 5.13. **Picrate:** mp 152°–153° C (from ethanol). Found, %: N 11.20; 11.26. Calculated for $C_{20}H_{19}N \cdot C_6H_3N_3O_7$, %: N 11.15.

In the same way, the third fraction yielded 2-(5'-methyl-4'-phenyl-2'-pyridyl)-1,3-diphenylpropane (XI) in the form of a very viscous liquid with bp 240°–245° C (2 mm). Found, %: N 4.02; 4.15. Calculated for $C_{27}H_{25}N$, %: N 3.86. **Picrate:** mp 174°–175° C (from ethanol). Found, %: N 9.70; 9.74. Calculated for $C_{27}H_{25}N \cdot C_6H_3N_3O_7$, %: N 9.46.

3,7-Dimethyl-2-azafluorene (XIII). The dehydrocyclization of 2,5-dimethyl-4-p-tolylpyridine (XII) was carried out in a continuous system. The catalyst tube and the packing were quartz. The catalyst was type K-16 industrial catalyst (100 ml). The temperature in the catalyst zone was 550° C. The catalyst was activated in a gentle current of air at 600° C for 2 hr.

A solution of 20 g (0.1 mole) of 2,5-dimethyl-4-p-tolylpyridine (XII) in 50 ml of benzene was passed through the catalyst tube at a constant rate for 3 hr. Five liters of gas was collected (20° C, 759 mm). Distillation of the condensate yielded 8.1 g of the initial pyridine XII [bp 120°–125° C (2 mm)] and 2.9 g of 3,7-dimethyl-2-azafluorene (XIII). Bp 148°–153° C (2 mm); mp 101°–101.5° C (from gasoline). Found, %: C 85.56; 85.83; H 6.77; 6.43; N 6.81; 6.92. Calculated for $C_{14}H_{13}N$, %: C 86.15; H 6.67; N 7.18. **Hydrochloride:** mp 290° C (from ethanol). Found, %: N 5.70; 5.92. Calculated for $C_{14}H_{13}N \cdot HCl$, %: N 6.04.

3,7-Dimethyl-2-azafluorenone (XIV). In small portions, 4.5 g (0.028 mole) of potassium permanganate was added with vigorous stirring to a mixture of 10 g (0.052 mole) of magnesium nitrate (hexahydrate), 4 g (0.021 mole) of 3,7-dimethyl-2-azafluorene (XIII) and 200 ml of water heated to 60° C. After the addition of the oxidizing agent, the mixture was stirred at 60° C for 2 hr and was then heated to 90° C and filtered rapidly. The manganese dioxide was carefully washed with hot acetone. The filtrate was evaporated to 50 ml. The precipitate that formed was recrystallized from gasoline giving 3 g of 3,7-dimethyl-2-azafluorenone (XIV) in the form of bright yellow crystals with mp 173° C. Found, %: C 80.01; 80.29; H 5.04; 5.06; N 6.62; 6.72. Calculated for $C_{14}H_{11}O$, %: C 80.40; H 5.28; N 6.69. **Hydrochloride:** mp 229°–230° C (from ethanol).

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