

SUBSTITUTED PYRIDINES

5-METHYL-4-BENZYL-2-STYRYL(PHENYLETHYNYL)PYRIDINES

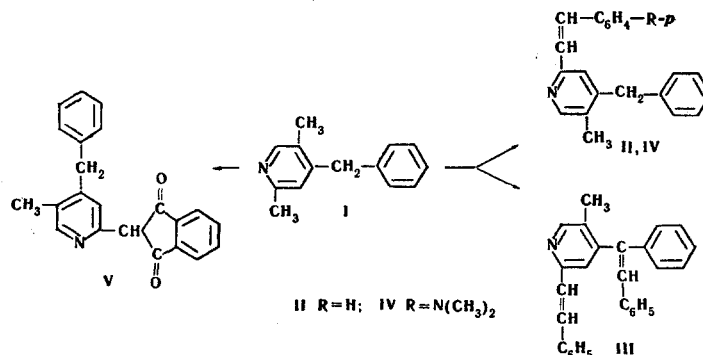
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5-Methyl-4-benzyl-2-styrylpyridine (II), its p-dimethylaminostyryl analog IV, and 5-methyl-4-benzyl-2-(1',3'-dioxo-2'-hydrindenyl)pyridine (V) have been prepared. II has been converted into 5-methyl-4-benzyl-2-phenylethynylpyridine (VII), 5-methyl-4-benzylpyridine-2-carboxylic acid (VIII), and 3-styryl-6,7-benzisoquinoline (X).

2,5-Dimethyl-4-benzylpyridine, obtained by us previously [1], has been used as starting material for the synthesis of the corresponding α -substituted stilbazoles and the similarly substituted phenylethynyl derivative. The condensation of I with benzaldehyde in the presence of zinc chloride, and with acetic anhydride, has been studied. In the latter case, the 5-methyl-4-benzyl-2-styrylpyridine (II) was best isolated as the hydrochloride. In this case, the yield of II was 57%.

It is necessary to bear in mind that I, in its reaction with benzaldehyde, may react either at the activated α -methyl group or at the γ -methylene group. However, the reaction in the latter sense proceeds only to an insignificant extent. The product of condensation at both the α -methyl and γ -methylene groups (1,2-diphenyl-1-(5'-methyl-2'-styryl-4'-pyridyl)ethene (III)) was isolated in small amounts, approximately 10% of the amount of II.



The occurrence of reaction at the methylene group was confirmed by IR and NMR spectroscopy (the authors thank L. I. Petrovskaya for NMR spectra). The IR spectra of II and III in the stretching and deformational regions of the C-H bonds in the CH₂ and CH₃ groups are almost identical. Bands in the spectrum of II corresponding to the CH₂ group were not observed, being apparently superimposed on the CH₃ bands. The presence of the CH₃ group in II and III was established unequivocally by the occurrence in the IR spectrum of II of the bands ν_{as} 2965, ν_s 2875 cm⁻¹, δ_{as} 1455, δ_s 1383 cm⁻¹, and in that of III, ν_{as} 2965, ν_s 2880 cm⁻¹, δ_{as} 1450, δ_s 1387 cm⁻¹. In the NMR spectrum of II, signals were observed due to the protons of the

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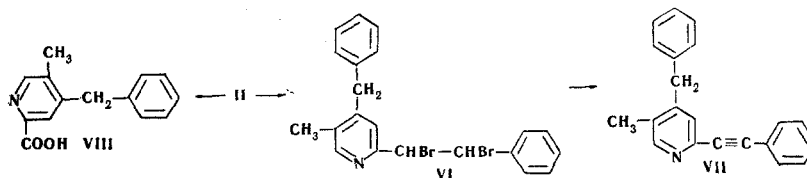
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CH₃ group (δ 2.25 ppm, relative to TMS), and of the CH₂ group (δ 3.95 ppm). The relative intensities were 3:2. The NMR spectrum of III showed only signals due to the protons of the CH₃ group (δ 2.15 ppm), and no signals due to the CH₂ group, which confirms the participation of this group in the condensation.

An analog of II, 5-methyl-4-benzyl-2-p-dimethylaminostyrylpyridine (IV) was isolated as the methiodide on condensation of I methiodide with p-dimethylaminobenzaldehyde in the presence of piperidine.

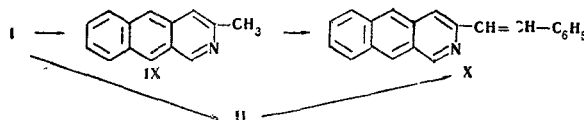
Condensation of I with phthalic anhydride gave 5-methyl-4-benzyl-2-(1', 3'-dioxo-2'-hydrindenyl)pyridine (V).

II was converted into 1-phenyl-2-(5'-methyl-4'-benzyl-2'-pyridyl)ethyne (VII) by bromination to 1, 2-dibromo-1-phenyl-2-(5'-methyl-4'-benzyl-2'-pyridyl)ethane (VI), followed by dehydrobromination.



An attempt was made to oxidize II at the ethylene group, the oxidation being carried out with potassium permanganate in acetone at 0°. It is a characteristic of this reaction that it affords readily-isolable benzoic acid, which was isolated in 45% yield. 5-Methyl-4-benzylpyridine-2-carboxylic acid (VIII) was isolated both in the free state and as its ethyl ester.

In a previous communication [2] there was described the catalytic dehydrocyclization of I to give 3-methyl-6, 7-benzisoquinoline (IX). The latter was allowed to react with benzaldehyde in the presence of zinc chloride, giving a 43% yield of 3-styryl-6,7-benzisoquinoline (X). A similar cyclization was carried out with II, resulting in the formation of the same styryl derivative of benzisoquinoline (X).



This conversion (I \rightarrow II \rightarrow X) is not only a new method for the synthesis of X, but it also proves that the styryl group in the starting material II is located in the α -position of the pyridine ring.

EXPERIMENTAL

5-Methyl-4-benzyl-2-styrylpyridine (II). a) [10 g (0.051 mole)], 26.8 g (0.252 mole) of benzaldehyde, and 1.74 g (0.0127 mole) of anhydrous zinc chloride were heated for 21 h (bath temperature 210–215°). The reaction mixture was treated with 100 ml of water, and 18% HCl was added until acid to Congo. There was obtained 12.3 g of yellow crystals (after washing with ether and acetone), which were treated with 40% sodium hydroxide. The organic bases were extracted with ether to give 9.8 g (67.8%) of II, mp 84–85° (from n-heptane). Found: C 88.30, 88.37; H 6.61, 6.39; N 4.79, 4.71%. C₂₁H₁₉N. Calculated: C 88.40; H 6.66; N 4.91%. IR spectrum, ν , cm⁻¹: 3095 s., 3077 s., 3043 v.s., 3015 w., 2965 s., 2940 s., 2880 m., 1595 s., 1550 v.w., 1495 s., 1455 s., 1393 m., 1080 w., 1030 m., 1010 w., 968 v.s., 937 w., 890 w., 766 s., 740 v.s., 703 v.s. Hydrochloride of II, mp 228–229° (from alcohol). Found: Cl 11.12, 11.15; N 4.66, 4.49%. C₂₁H₁₉N · HCl. Calculated: Cl 11.04; N 4.40%. Picrate of II, mp 219° (from alcohol). Found: N 10.50%. C₂₁H₁₉N · C₆H₃N₃O₇. Calculated: N 10.89%.

b) A portion of I [15 g (0.076 mole)], 19.35 g (0.180 mole) of benzaldehyde, and 7.8 g (0.076 mole) of acetic anhydride were heated at the boil for 12 h. The acetic anhydride was distilled off, and 100 ml of water was added to the residue, followed by sodium carbonate until alkaline. The benzaldehyde was removed by steam distillation, and the organic bases were extracted with ether. The residue obtained from the ether extracts was distilled to give 3.51 g of I (mp 58–59°). Repeated crystallization of the distillation residue from light petroleum gave 4.8 g (22%) of II (mp 84–85°) and 0.5 g (1.7%) of III, mp 174–175° (from alcohol). Found: C 89.68, 89.99; H 5.59, 5.61; N 3.72, 3.64%. C₂₈H₂₃N. Calculated: C 90.08; H 6.16; N 3.75%. IR spectrum,

ν , cm^{-1} : 3094 s., 3073 s., 3040 s., 3010 w., 2965 s., 2940 s., 2875 m., 1595 m., 1585 m., 1495 m., 1480 m., 1450 s., 1387 m., 1200 v.w., 1080 w., 1035 w., 1016 w., 978 s., 930 w., 880 w., 790 m., 770 s., 752 s., 730 m., 703 v.s.

c) A portion of I [40 g (0.201 mole)], 51.6 g (0.490 mole) of benzaldehyde, and 20.4 g (0.200 mole) of acetic anhydride were heated at the boil for 14 h. The acetic anhydride was distilled off, and the residue was treated with 50 ml of water and 18% hydrochloric acid until acid to Congo. The yellow crystals of II hydrochloride were isolated (42.3 g, after washing with ether and acetone). From the hydrochloride there was obtained 33.1 g (57.5%) of II, mp 84-85° (from n-heptane).

5-Methyl-4-benzyl-2-p-dimethylaminostyrylpyridine (IV). A portion of the methiodide of I [5 g (0.0147 mole)] (mp 170° from alcohol. Found: N 3.81, 4.00%. $\text{C}_{14}\text{H}_{15}\text{N} \cdot \text{CH}_3\text{I}$. Calculated: N 4.10%), 4.31 g (0.0290 mole) of p-dimethylaminobenzaldehyde, and 5 ml of piperidine in 50 ml of ethanol were boiled for 4 h. There was obtained 5.68 g (81.8%) of bright red crystals of the methiodide of IV, mp 255-258° (from methanol). Found: C 61.20, 61.61; H 6.27, 5.91; N 5.73, 5.62%. $\text{C}_{23}\text{H}_{24}\text{N}_2 \cdot \text{CH}_3\text{I}$. Calculated: C 61.30; H 5.74; N 5.94%.

5-Methyl-4-benzyl-2-(1', 3'-dioxo-2'-hydrindenyl)pyridine (V). A portion of I [6.0 g (0.030 mole)], 5.4 g (0.036 mole) of phthalic anhydride, and 3.1 g (0.030 mole) of acetic anhydride were heated in an autoclave at 200° for 14 h, to give 3.4 g (34.2%) of yellow crystals of V, mp 255-255.5° (from methanol). Found: C 81.36, 81.19; H 4.83, 5.25; N 3.90, 4.17%. $\text{C}_{22}\text{H}_{17}\text{NO}_2$. Calculated: C 80.73; H 5.19; N 4.28%.

1, 2-Dibromo-1-phenyl-2-(5'-methyl-4'-benzyl-2'-pyridyl)ethane (VI). To a solution of 3 g (0.0105 mole) of II in 20 ml of benzene was added a solution of 0.6 ml (0.0105 mole) of bromine in benzene. The solution was kept for 28 h in the light, to give 0.27 g of yellow crystals, mp 220-221° (from benzene), the identity of which was not established. The benzene solution afforded 3.21 g (68.5%) of white crystals of VI, mp 154-155° (from alcohol). Found: C 57.05, 57.32; H 4.70, 4.17; Br 36.20, 36.28; N 2.92, 2.71%. $\text{C}_{21}\text{H}_{19}\text{Br}_2\text{N}$. Calculated: C 56.62; H 4.27; Br 36.00; N 3.14%.

1-Phenyl-2-(5'-methyl-4'-benzyl-2'-pyridyl)ethyne (VII). To a solution of 16.9 g (0.290 mole) of potassium hydroxide in 130 ml of anhydrous ethyl alcohol was added at 40° a suspension of 20 g (0.045 mole) of VI in 230 ml of alcohol. The mixture was boiled for 4 h, then the alcohol was distilled off, and the residue was treated with 100 ml of water. The organic bases were extracted with ether, to give 8.12 g (64.0%) of white crystals of VII, mp 64-65.5° (from light petroleum). Found: C 88.88, 89.16; H 6.25, 6.21; N 4.98, 4.75%. $\text{C}_{21}\text{H}_{17}\text{N}$. Calculated: C 89.04; H 6.00; N 4.94%. Picrate of VI, mp 207-207.5° (from alcohol). Found: N 10.98%. $\text{C}_{21}\text{H}_{17}\text{N} \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$. Calculated: N 10.96%.

5-Methyl-4-benzylpyridine-2-carboxylic Acid (VIII). To a solution of 25 g (0.088 mole) of II in 150 ml of acetone at 0° was added slowly 35 g (0.220 mole) of potassium permanganate in portions, the mixture being stirred vigorously throughout. The manganese dioxide was filtered off and washed with 300 ml of hot 40% potassium hydroxide. The alkaline solution was partly evaporated, and treated with dilute (1:1) sulfuric acid to pH 12. Extraction with ether gave 4.8 g of benzoic acid (mp 121°). The acid solution was evaporated, and the residue crystallized to give 2 g (10.1%) of VIII, mp 145° (from water). Found: C 73.37, 73.13; H 5.44, 5.34; N 5.69, 5.59%. $\text{C}_{14}\text{H}_{13}\text{NO}_2$. Calculated: C 74.00; H 5.72; N 6.16%.

The mother liquors from the recrystallization of VIII were evaporated, and the residue was heated with 50 ml of absolute alcohol and 10 ml of sulfuric acid for 5 h. Seventy milliliters of water was added, the alcohol distilled off, and the residue treated with sodium carbonate solution. The organic bases were extracted with ether, and the residue after removal of the ether was distilled to give a first fraction (2 g), bp 145-205° (3 mm), and a second fraction (0.53 g), bp 174-190° (0.5 mm). From the second fraction there was obtained the hydrochloride of the ethyl ester of the acid VIII, mp 122-127° (from acetone). Found: C 66.06; H 5.65; N 4.80, 4.83; Cl 12.23, 12.45%. $\text{C}_{16}\text{H}_{17}\text{NO}_2 \cdot \text{HCl}$. Calculated: C 65.86; H 6.17; N 4.80; Cl 12.17%.

3-Styryl-6, 7-benzisoquinoline (X). a) A portion of IX [10 g (0.052 mole)], 8 ml (0.066 mole) of benzaldehyde, and 3.6 g (0.026 mole) of anhydrous zinc chloride were heated for 5 h at a bath temperature of 220-240°. The reaction products were washed with hydrochloric acid, water, and ether to give 6.3 g (43.3%) of bright yellow crystals of X, mp 250.5-251° (from chloroform). Found: C 89.69, 89.63; H 5.78, 5.60; N 4.75, 4.63%. $\text{C}_{21}\text{H}_{15}\text{N}$. Calculated: C 89.67; H 5.33; N 4.99%.

b) A solution of 46.4 g (0.163 mole) of II in 200 ml of benzene was passed at a constant rate during 8 h 30 min over type K-16 catalyst (volume of catalyst 100 ml) at 500°. 7.6 liters of gas was evolved (754 mm, 22°). From the catalyst there was obtained 3.8 g (8.3%) of crystals of X (insoluble in benzene), mp 250-251°.

The IR spectra were obtained on a UR-20 in the 3800-700 cm^{-1} range as KBr disks. The NMR spectra were measured on a "Hitachi" 60 MHz spectrometer, in CCl_4 .

LITERATURE CITED

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