SUBSTITUTED PYRIDINES

2-BENZYL-3,6-DIMETHYL-4-PHENYLPYRIDINE AND ITS REACTIONS

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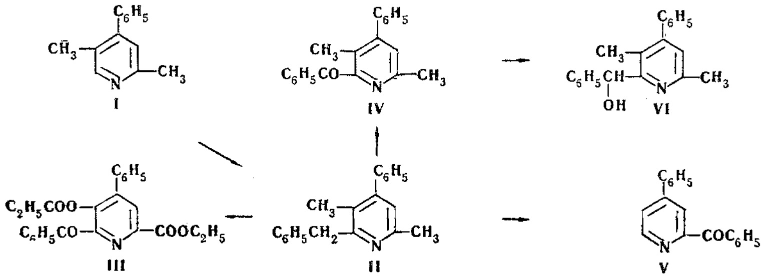
2-Benzyl-3,6-dimethyl-4-phenylpyridine has been obtained from 2,5-dimethyl-4-phenylpyridine by the Ladenburg–Chichibabin reaction. The compounds formed in its oxidation have been studied.

Continuing work on the synthesis of substituted pyridine bases which we shall use subsequently to obtain condensed nitrogen-containing polycyclic systems, we have turned to the synthesis of 2-benzyl-3,6-dimethyl-4-phenylpyridine (II). The starting material used was 2,5-dimethyl-4-phenylpyridine (I), which we have described previously [1].

The tetrasubstituted pyridine base II was obtained from I and benzyl chloride by the Ladenburg–Chichibabin reaction. Copper powder was used as the catalyst [2]. Without a catalyst the reaction gives a very low yield. As a rule, part of the initial pyridine I was recovered from the reaction mixture.

Compound II was oxidized with potassium permanganate in an acid medium [3]. Under these conditions the following substances are formed: a product of partial oxidation – 2-benzoyl-3,6-dimethyl-4-phenylpyridine (IV) – and a product corresponding to the oxidation of the two methyl groups and the methylene group of the benzyl radical – 2-benzoyl-4-phenylpyridine-3,6-dicarboxylic acid, which was isolated in the form of the diethyl ester III – and also benzoic acid. The latter is formed by the oxidative degradation of the pyridine ring [4].



The isolation of 2-benzoyl-4-phenylpyridine-3,6-dicarboxylic acid itself is associated with considerable difficulties. Consequently, its decarboxylation was carried out on the unpurified reaction product. This gave 2-benzoyl-4-phenylpyridine (V). The keto group of the benzoyl-substituted pyridine base IV was reduced with lithium aluminum hydride. This gave 3,6-dimethyl-4-phenylpyridine-2-yl(phenyl)methanol (VI). The corresponding carbamate was obtained from this alcohol and phenyl isocyanate.

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The IR spectrum of the substituted pyridine base II has bands with the maximum absorption at 3083, 3059, and 3025 cm^{-1} due to the stretching vibrations of the C–H aromatic bonds [5]. Bands at 2954, 2923, and 2867 cm^{-1} relate to the stretching vibrations of the aliphatic C–H bonds. The presence of benzene rings is also confirmed by bands at 1593, 1547, and 1498 cm^{-1} relating to the vibrations of the aromatic C=C bonds and the presence of CH_3 and CH_2 groups by bands of deformation vibrations at 1453 and 1384 cm^{-1}. In the region of nonplanar deformation vibrations of the aromatic C–H bonds there are strong bands at 778, 750, and 704 cm^{-1} caused by the vibrations of five adjacent hydrogen atoms of benzene rings. This nature of the substitution in the ring is also confirmed by the presence of four bands of the overtones of these vibrations at 1952, 1890, 1810, and 1760 cm^{-1}, which are characteristic for a monosubstituted aromatic ring.

It is impossible to say definitely from the IR spectrum of II whether a methylene group is present in its molecule. An answer to this question is given by a consideration of the spectrum of the product of its oxidation, III. In the spectrum of the diester III there is a well-defined doublet at 1723 and 1736 cm^{-1} and a band at 1683 cm^{-1} in the region of the vibrations of a carbonyl group, which is of the greatest interest.

As we have shown previously [6] for the case of 2,5-dimethyl-4-p-nitrobenzoyl pyridine, the band at 1683 cm^{-1} may be assigned to the stretching vibrations of the C=O group of a structure of the type of Ar–CO–Ar. To confirm this assignment, we studied the IR spectra of compounds IV and V. An increase in the frequency of the stretching vibrations of the carbonyl group in the series of compounds V, IV, and III (1657, 1672, and 1683 cm^{-1}, respectively) is connected with a weakening of the conjugation of the CO group with the aromatic rings which is probably due to a disturbance of the coplanarity of the system. The bands of the doublet at 1736 and 1723 cm^{-1} relate to the vibrations of the C=O bonds of two ester groups present in positions 2 and 5. This assignment is confirmed by the IR spectra of model compounds – 3-ethoxycarbonyl-4-pyridine, having one ester group in the β position ($\nu_{C=O}$ 1722 cm^{-1}) and 2-ethoxycarbonyl-5-ethyl-4-phenylbenzoylpyridine, in which the C=O group is present in the α position ($\nu_{C=O}$ 1736 cm^{-1}).

Thus, the bands in the region of the stretching vibrations of the C=O group at 1683, 1723, and 1736 cm^{-1} in the IR spectrum of compound III must be ascribed to the stretching vibrations of the carbonyl group of a structure of the Ar–CO–Ar type and those of ester groups in positions 5 and 2.

From what has been said it must be concluded that the molecule of compound II contains a methylene group.

In the IR spectrum of the carbinol VI, there is a band at ~3330 cm^{-1} relating to the stretching vibrations of a bound OH group. The presence of a phenyl radical is confirmed by the bands of the stretching vibrations of aromatic C–H bonds at 3062 and 3030 cm^{-1}. The frequency of 1596 cm^{-1} relates to the stretching vibrations of aromatic C=C bonds, and those of 703, 754, 764, and 778 cm^{-1} to the nonplanar deformation vibrations of five adjacent hydrogen atoms of a benzene ring.

EXPERIMENTAL

2-Benzyl-3,6-dimethyl-4-phenylpyridine (II). A mixture of 50 g (0.27 mole) of 2,5-dimethyl-4-phenylpyridine (I), 18.5 g (0.146 mole) of benzyl chloride, and 0.15 g of copper powder was heated at 250°C for 7 h and at 280°C for 1 h. Then it was treated with caustic soda. The reaction products were extracted with ether. After drying (magnesium sulfate), hydrogen chloride was passed into the ethereal solution. The hydrochlorides of the bases were separated off and dissolved in water, and the solution was treated with caustic soda and extracted with ether. The residue from the dried ethereal extract was distilled. This gave 25.1 g of the initial I [bp 110-120°C (1 mm)] and 27.6 g of II [bp 179-181°C (1 mm)] – a light yellow viscous liquid. Yield 74% on the I that had reacted. Found, %: C 87.67; 87.72; H 6.99; 7.26; N 5.27; 5.37. $C_{20}H_{19}N$. Calculated, %: C 87.59; H 6.95; N 5.12. Perchlorate: mp 160-162°C (from ethanol). Found, %: Cl 9.06; 9.19; N 3.69; 3.52. $C_{20}H_{19}N \cdot HClO_4$. Calculated, %: Cl 9.46; N 3.74.

2-Benzoyl-3,6-diethoxycarbonyl-4-phenylpyridine (III) and 2-Benzoyl-3,6-dimethyl-4-phenylpyridine (IV). With vigorous stirring and heating (100°C), 40 g (0.22 mole) of potassium permanganate was slowly added to 5.4 g (0.019 mole) of II in 750 ml of water. In proportion as the oxidizing agent was added to the reaction mixture, 100 ml of 10% sulfuric acid was added in 2-ml portions, and after this the dioxide was filtered off from the hot solution and was washed with hot water and with ether. The ethereal extracts yielded 2.14 g of IV in the form of colorless crystals with mp 81-82°C (from gasoline). Found, %: C 84.06; 84.30; H 6.04; 6.23; N 4.67; 4.59. $C_{20}H_{17}NO$. Calculated, %: C 84.32; H 5.92; N 4.87. Perchlorate: mp 195-

196°C (from ethanol). Found, %: Cl 8.73; 8.57; N 3.33; 3.29. $C_{20}H_{17}NO \cdot HClO$. Calculated, %: Cl 8.78; N 3.62. 2,4-Dinitrophenylhydrazone: mp 199.5-200°C (from a mixture of ethanol and acetone). Found, %: N 15.18; 14.87. $C_{26}H_{21}N_5O_4$. Calculated, %: N 14.99.

The aqueous solution was evaporated to 150 ml and treated with 50% sulfuric acid to an acid reaction. The reaction products were extracted with ether. A mixture of the residue from the ethereal extract (3 g), 40 ml of ethanol, and 4 ml of concentrated sulfuric acid was boiled for 12 h. Then 25 ml of water was added to the mixture and the ethanol was distilled off. The reaction products were extracted from the residue with ether. This gave 2.38 g of III in the form of colorless crystals with mp 97-98°C (from gasoline or petroleum ether). Found, %: C 71.72; 71.67; H 5.53; 5.50; N 3.53; 3.29. $C_{24}H_{21}NO_5$. Calculated, %: C 71.43; H 5.21; N 3.47.

2-Benzoyl-4-phenylpyridine (V). 5.4 g (0.019 mole) of II was oxidized as described above. After the separation of the manganese dioxide and extraction with ether, the aqueous solution was acidified with sulfuric acid to Congo Red. The reaction products were repeatedly extracted with ether. The residue from the ethereal extract was boiled with water (20 ml each time) twice. On cooling, the aqueous extract deposited 0.29 g of benzoic acid (mp 120-121°C). The residue, insoluble in water, was heated with 25 ml of water in an autoclave at 240-250°C for 4 h. Then the reaction mixture was treated with caustic soda and the organic bases were extracted with ether. This gave 0.54 g of V in the form of a viscous liquid with mp 200-203°C (1 mm). It crystallized from gasoline, giving crystals with mp 62-63°C. Found, %: C 83.61; 83.66; H 5.38; 5.06; N 5.43; 5.42. $C_{18}H_{13}NO$. Calculated, %: C 83.50; H 5.25; N 5.40. Picrate, mp 161-163°C (from ethanol). Found, %: N 11.45; 11.26. $C_{18}H_{13}NO \cdot C_6H_3N_3O_7$. Calculated, %: N 11.47.

3,6-Dimethyl-4-phenylpyridine-2-yl(phenyl)methanol (VI). A solution of 1.59 g (0.0055 mole) of IV in 20 ml of ether was gradually added to 0.16 g of lithium aluminum hydride in 50 ml of absolute ether. The mixture was boiled for 1 h and was then treated successively with 20 ml of aqueous ether, 30 ml of 10% sulfuric acid, and 40 ml of concentrated caustic soda solution. The ethereal layer was separated off and the products were twice extracted from the aqueous layer with ether. The ethereal extract yielded 1.26 g of VI in the form of colorless crystals with mp 74-76°C (from gasoline). Found, %: C 82.94; 82.87; H 6.65; 6.78; N 4.93; 4.63. $C_{20}H_{19}NO$. Calculated, %: C 83.03; H 6.57; N 4.84.

The IR spectra of compounds described were obtained on a UR-20 spectrophotometer. The samples of compound II were prepared in the form of a liquid film and those for the other compounds in the form of mulls in paraffin oil.

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