BENZYLATION OF 2,5-DIMETHYL-4-PHENYL(p-ALKYLBENZYL)PYRIDINES

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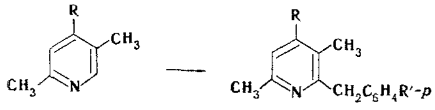
New substituted 4-phenyl-2-benzyl- and 2,4-dibenzylpyridines were obtained, and some of their transformations were studied.

In one of our previous communications [1], we described the synthesis of 3,6-dimethyl-4-phenyl-2-benzylpyridine (II) by means of the Ladenburg–Chichibabin reaction from 2,5-dimethyl-4-phenylpyridine (I). Continuing our study of similar substituted pyridine systems, we used the same route to obtain 3,6-dimethyl-4-phenyl-2-(p-methylbenzyl)- and p-ethylbenzylpyridines (III and IV) from I. Compounds of the aryl-γ-pyridylmethane type (V–VII), which we previously described in [2, 3], were used as other substituted pyridine bases, in the case of which, the same benzylation of the α-position of the pyridine ring was carried out.



I, V–VII — II–IV, VIII–X

I $R=C_6H_5$; II $R=C_6H_5$, $R'=H$; III $R=C_6H_5$, $R'=CH_3$; IV $R=C_6H_5$, $R'=C_2H_5$; V $R=C_6H_5CH_2$;
VI $R=p\text{-}CH_3C_6H_4CH_2$; VII $R=p\text{-}C_2H_5C_6H_4CH_2$; VIII $R=C_6H_5CH_2$, $R'=H$;
IX $R=p\text{-}CH_3C_6H_4CH_2$, $R'=H$; X $R=p\text{-}C_2H_5C_6H_4CH_2$, $R'=H$

The IR spectra of dibenzylpyridines IX and X contain bands in the region of the out-of-plane vibrations of the aromatic C–H bonds at 747 and 707 cm^{-1}, which are characteristic for a monosubstituted benzene ring. These bands are absent in the spectra of starting VI and VII. The PMR spectrum of VIII has a singlet at δ 6.59 ppm caused by the β-hydrogen atom of the pyridine ring, singlets at 1.96 and 2.37 ppm (the β- and α-methyl hydrogens, respectively), and singlets at 3.73 and 4.07 ppm (the γ- and α-methylene hydrogens, respectively).

Benzyl-substituted pyridine II was introduced into condensation with benzaldehyde in acetic acid in the presence of acetic anhydride. The condensation occurs at both the α-methyl and α'-methylene groups. We were able to identify distilbazole-1,2-diphenyl-1-[3'-methyl-4'-phenyl-6'-(β-styryl)-2'-pyridyl]ethylene (XI) in the form of the picrate. 3-Methyl-4-phenyl-2-benzoyl-6-carbethoxypyridine (XII) was obtained by the oxidation of XI (without isolation of the reaction products) under mild conditions with subsequent esterification of the keto acid formed in the process. The IR spectrum of XII in the region of the stretching vibrations of the C = O group contains two intense bands at 1736 and 1665 cm^{-1}, which are related, respectively, to the ester grouping in the α position of the pyridine ring and to the stretching vibrations of a carbonyl group of the benzophenone type. (See scheme on the following page.)

We attempted to accomplish the catalytic dehydrocyclization of II, as a result of which we were able to obtain complex, nitrogen-containing, condensed, polynuclear compounds. The dehydrocyclization of II can proceed in different directions depending on whether the dehydrocyclization occurs through the β-methyl group and the ortho hydrogen of the α-benzyl radical, through the same methyl group and the ortho

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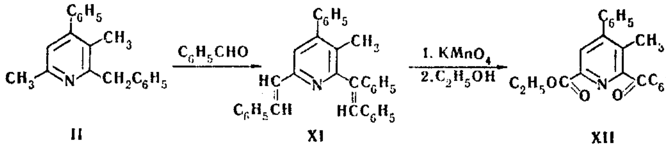
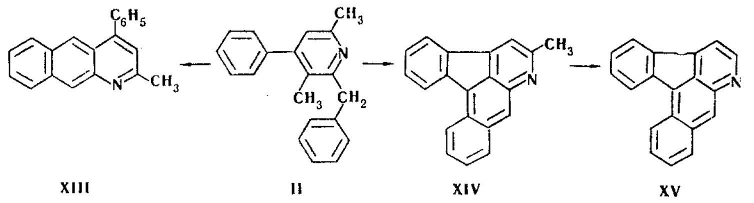


hydrogen of the γ-phenyl radical, or simultaneously through the methyl group and the ortho hydrogens of the benzyl and phenyl groups. The dehydrocyclization of II was carried out with a K-16 dehydrating catalyst at 500-510°C. Column chromatography was used to isolate two substances from the reaction products – yellow crystals with mp 108-109° and orange crystals with mp 172-173°.



On the basis of the spectral and analytical data, the 6-methyl-7-azaindeno[1,2,3-d, e]anthracene structure (XIV) can be assigned to the substance with mp 172-173°. The IR spectrum of XIV in the region of the out-of-plane vibrations of the aromatic C–H bonds does not contain bands at 690-710 cm^{-1} that are related to the monosubstituted benzene ring. This region contains only a band at 879 cm^{-1}, characteristic for single C–H bonds, and bands at 715 and 742 cm^{-1}, which are related to four adjacent aromatic bonds. Maxima at 242 nm (log ε 4.34), 276 nm (log ε 4.34), 288 nm (log ε 4.40), 298 nm (log ε 4.34), 369 nm (log ε 3.86), and 395 nm (log ε 3.62) are observed in the UV spectrum of XIV. As compared with the UV spectrum of 3,8-dimethylanthracene, all of the bands are shifted to the long-wave region. A signal corresponding to the methylene group (δ 4.13 ppm) is not present in the PMR spectrum of XIV. The signal at 2.95 ppm corresponds to the α-methyl group of the pyridine ring.

The substance with mp 108-109° apparently has the 2-methyl-4-phenylbenzo[g]quinoline structure (XIII). Its molecular weight, as determined by mass spectrometry, is 269. The UV spectrum of XIII is similar to the spectrum of azaanthracene and anthracene systems. There are bands corresponding to a monosubstituted benzene ring and a methyl group in the IR spectrum. The position of the methyl group in the structure of XIII is indicated arbitrarily. The PMR spectrum of XIII contains two proton signals at 8.3 and 8.57 ppm, which can be assigned to the α-hydrogen of the pyridine ring. It is possible that migration of the methyl radical occurs during the dehydrocyclization.

The dehydrocyclization of II at 620° proceeds to a greater extent; in addition to cyclization products XIII and XIV, a dark-red crystalline substance with mp 149-150° was isolated. On the basis of analytical data and the PMR spectrum, the 7-azaindeno[1,2,3-d,e]anthracene structure (XV) can be conjecturally assigned to this dark-red substance. Under these conditions, dehydrocyclization is apparently accompanied by cleavage of an α-methyl group. The molecular weight of XV, as determined by mass spectrometry, is 253. The IR spectrum of XV does not contain bands corresponding to a monosubstituted benzene ring and a methyl group. The UV spectrum of XV is close to the UV spectrum of the condensed XIV system and differs very much from the UV spectrum of XIII. It was chromatographically established that XV is formed from XIV under the same conditions.

EXPERIMENTAL

3,6-Dimethyl-4-phenyl-2-(p-methylbenzyl)pyridine (III). The method in [1] was used to obtain 5 g (50%) of III with bp 185-190° (1 mm) from 10 g (54 mmole) of I and 8 g (57 mmole) of p-methylbenzyl chloride in the presence of 0.25 g copper powder. Found: C 88.0; H 7.5; N 5.0%. $C_{21}H_{21}N$. Calculated: C 87.9; H 7.3; N 4.9%.

3,6-Dimethyl-4-phenyl-2-(p-ethylbenzyl)pyridine (IV). The reaction of 20 g (110 mmole) of I, 9.81 g (63 mmole) of p-ethylbenzyl chloride, and 0.15 g of copper powder gave 5.5 g (40%) of IV with bp 195-200° (1 mm). Found: N 4.7%. $C_{22}H_{23}N$. Calculated: N 4.6%.

3,6-Dimethyl-2,4-dibenzylpyridine (VIII). A mixture of 100.6 g (507 mmole) of V, 40.5 g (320 mmole) of freshly distilled benzyl chloride, and 0.15 g of copper powder was held at 250-260° for 7.5 h and at 280-290° for 2 h. The hot reaction mass was poured into 200 ml of saturated aqueous sodium hydroxide solution, and the mixture was heated for 1 h on a boiling-water bath. The mixture was then cooled, and the organic bases were extracted with ether. The organic bases were extracted from the extract with 15% sulfuric acid. The acid extract was brought up to pH 12 by means of sodium hydroxide, and the organic bases were extracted with ether. Two distillations of the ether extract yielded 58.3 g (0.296 mole) of the starting pyridine V and the following fractions: the first fraction (1.1 g) boiled at 180-186° (1.5 mm), the second fraction (29.1 g) boiled at 186-196° (1.5 mm), and the third fraction (5.7 g) boiled at 196-220° (1.5 mm). The still residue was 26 g.

A 4.1-g sample of the second fraction was subjected to chromatographic separation (with a 115-cm-high column with a diameter of 1.5 cm, packed with activity II Al_2O_3, with elution by petroleum ether, gradual addition of ether and, at the end, pure ether) to give 1.96 g of a substance with R_f 0.60 [activity II Al_2O_3, ether—petroleum ether (2:1)] from which 2.35 g of the perchlorate of VIII with mp 68-69° (from alcohol) was obtained. Found: N 3.8; Cl 8.9%. $C_{21}H_{21}N \cdot HClO_4$. Calculated: N 3.6; Cl 9.2%. The perchlorate yielded 1.3 g of free base VIII with bp 187-188° (1.5 mm), n_D^{20} 1.6018, d_4^{20} 1.070, and MR_D 92.20. Found: C 87.7; H 7.2; N 5.1%. $C_{21}H_{21}N$. Calculated: C 87.8; H 7.3; N 4.9%; MR_D 92.31. The yield of VIII was 30% (based on the converted V).

The same method was used to obtain 3,6-dimethyl-2-benzyl-4-(p-methylbenzyl)pyridine (IX) [in 32% yield with bp 196-198° (1.5 mm), n_D^{20} 1.5980, and d_4^{20} 1.059]. Found: C 87.9; H 7.8; N 4.7%; MR_D 96.95. $C_{22}H_{23}N$. Calculated: C 87.7; H 7.6; N 4.6%; MR_D 96.93 and 3,6-dimethyl-2-benzyl-4-(p-ethylbenzyl)pyridine (X) [in 25% yield with bp 199-204° (1.5 mm), n_D^{20} 1.5887, and d_4^{20} 1.035]. Found: C 87.6; H 8.0; N 4.6%; MR_D 102.6. $C_{23}H_{25}N$. Calculated: C 87.6; H 7.9; N 4.4%; MR_D 101.6.

3-Methyl-2-benzoyl-4-phenyl-6-carbethoxypyridine (XII). A mixture of 5 g (16 mmole) of II, 5.82 g (55 mmole) of benzaldehyde, 3.8 g of acetic anhydride, and 2.2 g of acetic acid was heated at 185-190° for 20 h. The unchanged benzaldehyde was removed by steam distillation, and 100 ml of 40% sodium hydroxide was added to the residue. The organic compounds were extracted with ether to give 8.25 g of hygroscopic crystals, from which the picrate of pyridine XI with mp 208-210° (from alcohol) was obtained. Found: N 8.0%. $C_{34}H_{27}N \cdot C_6H_3N_3O_7$. Calculated: N 8.2%.

Potassium permanganate (19.8 g) was added at 0° to a solution of 5.37 g (11 mmole) of XI in 200 ml of acetone. After the solution was decolorized, the manganese dioxide was removed by filtration and washed twice with hot water. The aqueous solution was partially evaporated and neutralized with 50% sulfuric acid. The resulting precipitate (3.63 g) was dried and heated for 8 h with 40 ml of alcohol and 5 ml of sulfuric acid. The mixture was neutralized with sodium carbonate solution. The organic bases were extracted with ether, and the alcohol—ether solution yielded 3.14 g (76%) of ester XII with mp 171-173° (from methanol). Found: C 76.5; H 5.4; N 3.9%. $C_{22}H_{19}NO_3$. Calculated: C 76.5; H 5.5; N 4.0%.

Dehydrocyclization of 3,6-Dimethyl-4-phenyl-2-benzylpyridine. A) A solution of 20 g of II in 60 ml of benzene was passed at a constant rate for 5 h over a K-16 catalyst (100 ml). The temperature in the catalyst zone was 500-510°. A total of 4.5 liters of gas was collected. The catalyzate yielded 9.4 g of a substance, which was vacuum distilled to give a fraction (4.1 g) with bp 185-210° (1 mm). This fraction was chromatographed with a column filled with activity II aluminum oxide with elution by ether to give, successively, 0.54 g of XIII and 0.05 g of XIV. Compound XIII was obtained as yellow crystals with mp 108-109° (from ligroin) and R_f 0.82 (ether). Found: C 88.5; H 6.3; N 5.1%. $C_{20}H_{15}N$. Calculated: C 89.2; H 5.6; N 5.2%. The picrate had mp 237-238° (from alcohol). Found: N 11.4%. $C_{20}H_{15}N \cdot C_6H_3N_3O_7$. Calculated: N 11.2%. Compound XIV was obtained as orange crystals with mp 172-173° (from ligroin) and R_f 0.72 (ether). Found: C 89.1; H 5.6; N 5.2%. $C_{20}H_{13}N$. Calculated: C 89.9; H 4.9; N 5.2%.

B) In this case, 21 g of II in 120 ml of benzene was allowed to react for 4 h. The temperature in the catalyst zone was 620°, and 7.75 liter of gas (96.4% H_2, 3.6% C_nH_{2n+2}) was collected. Chromatography of the catalyzate gave 0.76 g of starting II, 5 g of XIII, 1.3 g of XIV, and at the end of the chromatography, 1.01 g of XV as dark-red crystals with mp 149-150° (from ligroin). Found: C 89.8; H 5.6; N 5.0%. $C_{19}H_{11}N$. Calculated: C 90.1; H 4.3; N 5.5%. The picrate had mp 274-276° (from alcohol). Found: N 11.1%. $C_{19}H_{11}N \cdot C_6H_3N_3O_7$. Calculated: N 11.5%.

C) A solution of 11.3 g of XIV and 100 ml of benzene was passed over the same catalyst at 620-640° for 3 h. A total of 7 liter of gas (97% H_2 and 3% of C_nH_{2n+2}) was collected. The catalyzate yielded 2.53 g of starting XIV. The presence of approximately equal amounts of XIV and XV was established in the residual reaction products by means of chromatography on activity II aluminum oxide with elution by ether.

The IR spectra were measured with a UR-20 spectrophotometer. The samples were prepared as mineral oil pastes. The UV spectra of absolute alcohol solutions were measured with an SF-4A spectrophotometer.

The PMR spectra were obtained with a Varian HA-100 spectrometer (100 MHz). The solvents were CCl_4 and $CDCl_3$, and the internal standard was tetramethylsilane.

LITERATURE CITED

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