SUBSTITUTED PYRIDINES

Synthesis of 2-Azafluorenone, 3-Methyl-6,7-Benzoisoquinoline, and 7-Methyl-2,3-Benzo-1,6-Naphthyridine

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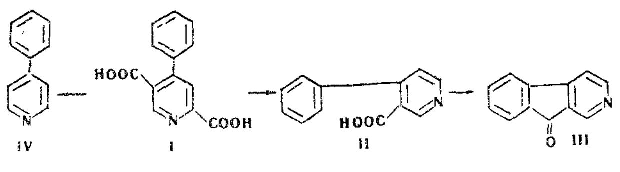
From γ-pyridones have been obtained substituted pyridine bases serving as the starting materials for the synthesis of polycyclic nitrogen-containing compounds. 2-Azafluorenone has been obtained by the cyclization of 4-phenylpyridine-3-carboxylic acid. The dehydrocyclization of 4-benzyl-2,5-dimethylpyridine has given 3-methyl-6,7-benzoisoquinoline and that of N-(2,5-dimethyl-4-pyridyl)aniline has given 7-methyl-2,3-benzo-1,6-naphthyridine.

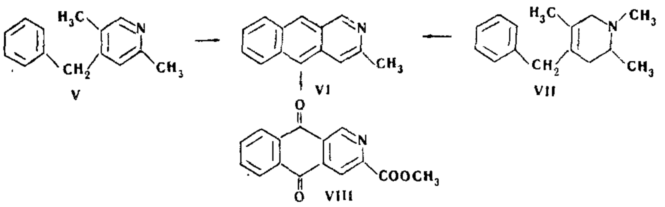
By a method developed in our laboratory starting from γ-pyridones it is comparatively easy to obtain individual substituted pyridine bases including polycyclic bases containing an uncondensed pyridine nucleus [1]. A particularly widely used substance for the syntheses is 1,2,5-trimethyl-4-pyridone—an intermediate for one of the products of the pharmaceutical industry. Having available a suitable method for obtaining substituted pyridine bases of given structure, we have turned our attention to the synthesis from them of condensed heterocyclic compounds, derivatives of which may be of pharmacological or other interest.

In preceding communications, we have described the syntheses of 4-phenylpyridine-2,5-dicarboxylic acid (I) [1] and 4-benzyl-2,5-dimethylpyridine (V) [2]. The acid I was used to obtain 2-azafluorenone (III). When it was heated in the autoclave in the presence of water at 180° C, 4-phenylpyridine-3-carboxylic acid (II) was obtained. If the reaction was carried out at temperatures above 200° C, complete decarboxylation took place with the formation of 4-phenylpyridine (IV). When the acid II was heated with concentrated sulfuric acid at 100° C, 2-azafluorenone (III) was obtained.



The conversion of 4-benzyl-2,5-dimethylpyridine (V) into 3-methyl-6,7-benzoisoquinoline (VI) was effected by its dehydrocyclization on type K-12 dehydrogenation catalyst at 480–500° C. On the same catalyst and under the same conditions, the same benzoisoquinoline VI was obtained from 4-benzyl-1,2,5-trimethyl-Δ^4-piperidine (VII) [3].

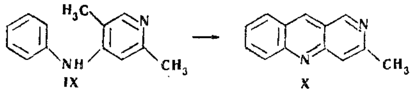
The oxidation of compound VI and subsequent esterification with methanol of the acid so formed gave 2-methoxycarbonyl-4,5-phthaloylpyridine (VIII).



To confirm the structure of the compounds described, we studied their IR and UV spectra. The IR spectrum of 4-benzyl-2,5-dimethylpyridine (V) had strong bands in the low-frequency region at 751 and 712 cm^{-1}, assigned to the nonplanar deformation vibrations of five adjacent C—H bonds of a benzene ring and a band at 858 cm^{-1} relating to the same vibrations of two isolated C—H bonds of a pyridine ring [4]. In the IR spectrum of 3-methyl-6,7-benzoisoquinoline (VI) the band at 755 cm^{-1} is characteristic for four adjacent C—H bonds (benzo group). The split band (892, 905 cm^{-1}) is apparently due to nonplanar vibrations of the isolated C—H bonds (5, 8 positions) [4]. As was to be expected, the doublet (892, 905 cm^{-1}) was not present in the spectrum of 2-methoxycarbonyl-4,5-phthaloylpyridine (VIII). In the region of the stretching vibrations of the carbonyl groups, two bands are found at 1676 and 1719 cm^{-1}, the first of which belongs to a quinoid group C=O [4] and the second to a carbonyl group of an ester grouping of the type Ar—COOR [4].

The UV spectrum of 4-benzyl-2,5-dimethylpyridine (V) had an absorption band (λ_{max} 267 nm, ε_{max} 3300) typical for compounds with nonconjugated chromophores [5]. 3-Methyl-6,7-benzoisoquinoline (VI) has a short-wave band at 252 nm (ε_{max} 130 000) and a group of bands having a fine structure with the center at approximately 345 nm (ε_{max} 2600). UV spectra of this type are characteristic for linear condensed aromatic systems [5].

Subsequently, we carried out the analogous dehydrocyclization of N-(2,5-dimethyl-4-pyridyl)aniline (IX) [3] on type K-12 catalyst at 600° C. This gave a small yield of 7-methyl-2, 3-benzo-1, 6-naphthyridine (X).


IX X

In the region of the stretching vibrations of the NH group the IR spectrum of IX (solution in CCl_4) there is a band at 3435 cm^{-1} (integral intensity $0.51 \cdot 10^4$ $mole^{-1} \cdot l \cdot cm^{-2}$). These values are characteristic for an NH group in compounds of the type of Ar—NH—Ar [6]. It also follows from the UV spectrum of the aminopyridine IX (λ_{max} 286 nm, ε_{max} 15 900) that the benzene and the pyridine rings are not conjugated.

The UV spectrum of 7-methyl-2, 3-benzo-1, 6-naphthyridine (X) is characterized by a short-wave absorption band at 252 nm (ε_{max} 120 000) and a long-wave band (λ_{max} [approximate position of the center of the group of bands] 345 nm, ε_{max} 5300) having a vibrational structure which is characteristic for a linear condensed aromatic system [5]. In the low-frequency region the IR spectrum of X has two strong bands at 755 and 877 cm^{-1}. The first relates to the nonplanar deformation vibrations of four adjacent aromatic C—H bonds and the second shows the presence of isolated C—H bonds [4].

EXPERIMENTAL

4-Phenylpyridine-3-carboxylic acid (II). A mixture of 1 g (4.1 mM) of 4-phenylpyridine-2, 5-dicarboxylic acid (I) (mp 233°-234° C) and 20 ml of water was heated in the autoclave at 180° C for 2 hr. After the water had been distilled off, the residue was recrystallized from ethanol. This gave 0.45 g of II; mp 148°-150° C [1].

4-Phenylpyridine (IV). A mixture of 2 g (8.2 mM) of the acid I and 25 ml of water was heated in the autoclave at 240°-250° C for 3 hr. The reaction product was recrystallized from water. This gave 1.1 g of IV, mp 77°-78° C [7]. Similarly, heating 1 g (5.1 mM) of the acid II and 20 ml of water at 200° C for 3 hours gave 0.54 g of IV.

2-Azafluorenone (III). A mixture of 1 g (5.1 mM) of the acid II and 5 ml of concentrated sulfuric acid was heated at 100° C for 2 hr. The reaction products were diluted with water and made alkaline with potassium hydroxide. The bright yellow crystals that deposited were filtered off and recrystallized from gasoline. This gave 0.3 g of III; mp 151°-152° C. Found, %: N 7.44; 7.51. Calculated for $C_{12}H_7NO$, %: N 7.73. **Picrate:** 235°-236° C (from ethanol). Found, %: N 13.93; 13.66. Calculated for $C_{12}H_7NO \cdot C_6H_3N_3O_7$, %: N 13.59. **Hydrochloride:** mp 208° C (from acetone). Found, %: N 6.44; 6.15. Calculated for $C_{12}H_7NO \cdot HCl$, %: N 6.43.

The IR spectrum of crystalline 2-azafluorenone (III) has a strong band at 1712 cm^{-1} relating to the vibrations of the carbonyl group of the fluorenone nucleus [4]. A strong band at 740 cm^{-1} is due to the nonplanar deformation vibrations of four adjacent aromatic C—H bonds and a band at 860 cm^{-1} is apparently due to nonplanar vibrations of isolated C—H bonds [4].

3-Methyl-6, 7-benzoisoquinoline (VI). a) A solution of 15.45 g (0.078 mole) of 4-benzyl-2, 5-dimethylpyridine (V) in 100 ml of benzene was passed at constant rate over 2 hr through a tube containing 165 ml of type K-12 catalyst. The temperature in the catalyst zone was 480°-500° C. 1.5 *l* of gas was collected (18° C, 770 mm). The condensate was dried with fused potassium hydroxide. After the benzene had been distilled off, petroleum ether was added to the residue. The precipitate that formed was filtered off and recrystallized from absolute ethanol. This gave 2.73 g of VI in the form of bright yellow crystals with mp 197°-198° C. Its solutions in organic solvents possessed a violet fluorescence; in sulfuric and hydrochloric acids a yellow fluorescence was observed. Found, %: N 7.18; 7.18. Calculated for $C_{14}H_{13}N$, %: N 7.25. **Picrate:** mp 255°-256° C (from aqueous ethanol). Found, %: N 12.94; 13.27. Calculated for $C_{14}H_{13}N \cdot C_6H_3N_3O_7$, %: N 13.27. **Hydrochloride:** yellow crystals, mp 258°-259° C (from isopropanol).

From the residual solution of reaction products in petroleum ether, after vacuum distillation, 5.82 g of the initial 4-benzyl-2, 5-dimethylpyridine (mp 58°-59° C) was recovered.

b) A solution of 25.26 g (0.12 mole) of 4-benzyl-1, 2, 5-trimethyl-Δ^4-piperidine (VII) in 165 ml of benzene was passed through the same catalyst tube at the same temperature over 2.5 hr. 8.3 *l* of gas was collected (18° C, 768 mm). After similar working up, the reaction products yielded 1.6 g of VI (mp 197°-198° C) and 9.6 g of 4-benzyl-2, 5-dimethylpyridine (V) (mp 58°-59° C).

2-Methoxycarbonyl-4, 5-phthaloylpyridine (VIII). Slowly, in separate portions, 31 g (0.31 mole) of chromic anhydride in 750 ml of glacial acetic acid was added to a solution of 4 g (0.02 mole) of VI in 250 ml of glacial acetic acid at 115° C. After the acid had been distilled off from the reaction mixture, the residue was treated with sodium carbonate and then with sodium hydroxide until alkaline and then with ether. The ethereal layer was separated off. The reaction mixture was made acid with concentrated hydrochloric acid and evaporated to dryness. The residue, dried at 80°-90° C, was treated with 250 ml of absolute methanol. Dry hydrogen chloride was passed through the mixture without heating for 2 hr and then with heating (50° C) for 2 hr. The alcohol was distilled off. The residue was treated with water and then sodium carbonate was added. The organic bases were extracted with ether. This gave 0.2 g of VIII in the form of red-orange crystals, mp 204°-205° C (from methanol). Found, %: C 67.32; 67.35; H 4.07; 3.89; N 5.30; 5.05. Calculated for $C_{15}H_9NO_4$, %: C 67.42; H 3.39; N 5.24.

7-Methyl-2, 3-benzo-1, 6-naphthyridine (X). A solution of 5 g (0.025 mole) of N-(2, 5-dimethyl-4-pyridyl)aniline (IX) in 70 ml of benzene was passed over type K-12 catalyst at 600° C during 1.5 hr. 1020 ml of gas was collected (22° C, 737 mm). After the benzene had been distilled off from the condensate, 3.85 g of crystalline residue was obtained. By repeated recrystallization, first from heptane and then from ethyl acetate, this yielded 0.15 g of X in the form of bright yellow lustrous scales; mp 139.5°-140° C, with a strong irritating effect on the mucous membrane of the nose similar to that of acridine. Found, %: C 79.63; 79.97; H 5.46; 5.49; N 14.36; 14.70. Calculated for $C_{13}H_{10}N_2$, %: C 80.38; H 5.18; N 14.44. **Hydrochloride:** light brown crystals, mp 350° C (decomp. from ethanol). Found, %: N 10.46; 10.51; C 13.75. Calculated for $C_{13}H_{10}N_2 \cdot HCl \cdot 2H_2O$, %: N 10.50; Cl 13.32.

The IR spectra of compounds III, V, VI, VIII, IX, and X in the crystalline state were recorded on a UR-10 spectrometer with LiF, NaCl, and KBr prisms in the range from 3800 to 400 cm^{-1}. Samples were prepared in the form of mulls with paraffin oil. The measurements of the frequency and intensity of the stretching vibrations of the NH group of compound IX were carried out on a IKS-14 spectrometer with an LiF prism, using solutions of this compound in carbon tetrachloride with concentrations of 10^{-3}-$2 \cdot 10^{-4}$ M.

The UV absorption spectra of compounds V, VI, IX, and X were measured on a "Hitachi" spectrophotometer. The concentrations of the solutions in ethanol varied from $5 \cdot 10^{-6}$ to $2 \cdot 10^{-4}$ M.

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