SUBSTITUTED PYRIDINES. PREPARATION OF SUBSTITUTED STILBAZOLES AND THEIR REACTIONS

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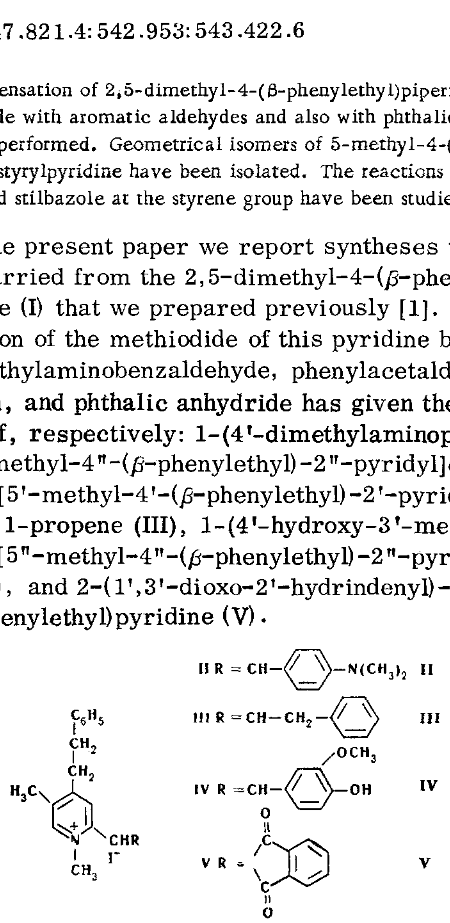
The condensation of 2,5-dimethyl-4-(β-phenylethyl)piperidine methiodide with aromatic aldehydes and also with phthalic anhydride has been performed. Geometrical isomers of 5-methyl-4-(β-phenylethyl)-2-styrylpyridine have been isolated. The reactions of this substituted stilbazole at the styrene group have been studied.

In the present paper we report syntheses that have been carried from the 2,5-dimethyl-4-(β-phenylethyl) pyridine (I) that we prepared previously [1]. The condensation of the methiodide of this pyridine base with p-dimethylaminobenzaldehyde, phenylacetaldehyde, vanillin, and phthalic anhydride has given the methiodides of, respectively: 1-(4'-dimethylaminophenyl), 2-[5"-methyl-4"-(β-phenylethyl)-2"-pyridyl]ethene (II), 1-[5'-methyl-4'-(β-phenylethyl)-2'-pyridyl]-3-phenyl-1-propene (III), 1-(4'-hydroxy-3'-methoxyphenyl)-2-[5"-methyl-4"-(β-phenylethyl)-2"-pyridyl]ethene (IV), and 2-(1',3'-dioxo-2'-hydrindenyl)-5-methyl-4-(β-phenylethyl)pyridine (V).



The compounds obtained were characterized by their absorption spectra in the UV region, or, in the case of colored compounds, in the visible region. The spectroscopic data are given in the experimental part.

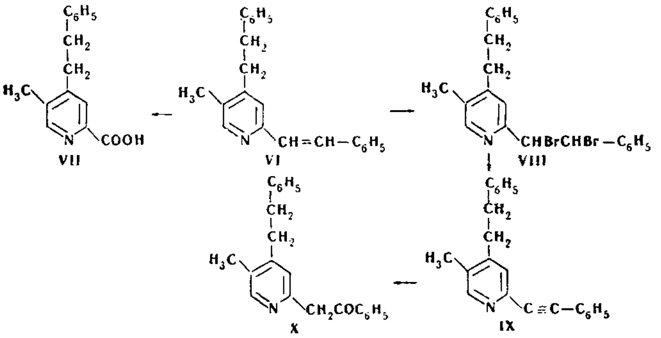
When the synthesis of 5-methyl-4-(β-phenylethyl)-2-styrylpyridine (VI) [2] was repeated, its two isomers were isolated. The main product was the high-melting isomer (mp 118°–120° C), which, if one takes steric factors into account, is obviously the trans isomer. The second isomer (mp 90°–93° C) apparently has the cis structure. The geometrical isomers were characterized by their IR and UV spectra.

In view of the fact that the molecule of 2,5-dimethyl-4-(β-phenylethyl)pyridine has not only an α-methyl group but also an active γ-methylene group, it might have been expected that the condensation of this pyridine base would take place not through the α-methyl group but through the γ-methylene group.

To answer the question of the structure of the condensation products obtained, we used a comparison of the UV spectra of 2,5-dimethyl-4-styrylpyridine [3] and the isomeric 5-methyl-4-(β-phenylethyl)-2-styrylpyridines (VI) described in the present paper. The UV spectrum of the 4-stilbazole exhibited a single characteristic absorption maximum at 305 nm, ε 6500, and spectra of the isomeric 2-stilbazoles (VI) had a characteristic maximum at 312 nm, ε 27500 [4,5]. The oxidation of the substituted stilbazole VI under mild conditions gave 5-methyl: 4-(β-phenylethyl)pyridine-2-carboxylic acid (VII), which was also characterized spectroscopically (1330, 1411, 1456, 1605, 1762, 3696 cm^{-1}) [6, 7]. Consequently, it must be assumed that it is the α-methyl group that takes part in the condensation of benzaldehyde with 2,5-dimethyl-4-(β-phenylethyl)pyridine.

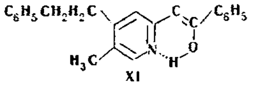
An attempt was also made to perform the condensation of 5-methyl-4-β-(phenylethyl)-2-styrylpyridine (VI) with benzaldehyde under severe conditions (170° C, reaction time 25 hr). However, no distyrene derivative was formed. The initial pyridine VI was recovered from the reaction mixture. The reaction products underwent resinification to a considerable extent

The conversion of 5-methyl-4-(β-phenylethyl)-2-styrylpyridine (VI) into 5-methyl-4-(β-phenylethyl)-2-phenylethynylpyridine (IX) was performed via 1,2-dibromo-1-[5'-methyl-4'-(β-phenylethyl)-2'-pyridyl]-2-phenylethane (VIII) [2]. Didehydrobromination of the dibromide VIII gave the acetylenic compound IX which, by hydration, was converted into ω-[5-methyl-4-(β-phenylethyl)-2-pyridyl]acetophenone (X), a compound similar in structure to deoxybenzoin.



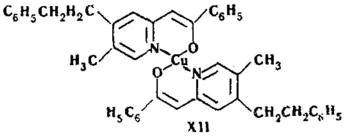
With ferric chloride, ω-[5-methyl-4-(β-phenylethyl)-2-pyridyl]acetophenone (X) gives a clear reaction for an enolic grouping. The tautomeric system of ω-[5-methyl: 4-(β-phenylethyl)-2-pyridyl]acetophenone (X) may be regarded as analogous to the system of β-diketones [8].

The ketone X dissolves in ether to a very small extent. Apparently its enolic form forms an intramolecular hydrogen bond which leads to an internally complex structure XI of low polarity [9].



XI

ω-[5-methyl-4-(β-phenylethyl)-2-pyridyl]acetophenone (X) forms a chelate complex with copper oxide (XII) comparatively readily, this formation apparently taking place through the enolic form XI in which the copper atom replaces the hydroxyl hydrogen atom and is coordinately bound to the nitrogen [10]. In its structure, this complex is similar to that of copper with 9-hydroxyquinoline [11].



XII

The similarity of the UV spectra of ω-[5-methyl-4(β-phenylethyl)-2-pyridyl]acetophenone (X) and of the chelate complex XII, apart from the bathochromic shift in the latter due to an increase in complexity, can be regarded as a confirmation of the proposed structures of XI and XII.

EXPERIMENTAL

Condensation of 2,5-dimethyl-4-(β-phenylethyl)pyridine methiodide with aromatic aldehydes and phthalic anhydride. 2,5-Dimethyl-4-(β-phenylethyl)pyridine methiodide (I) forms colorless crystals with mp 217–222° C. Found, %: N 3.64, 3.77. Calculated for $C_{16}H_{20}IN$, %: N 3.96.

a) A mixture of 2 g (5.7 mM) of the methiodide I, 1.04 g (7 mM) of p-dimethylaminobenzaldehyde, 0.5 ml of piperidine, and 30 ml of absolute ethanol was heated to the boil for 8 hr. The precipitate formed (2 g) was separated off and recrystallized from ethanol three times. The product was 1-(4'-dimethylaminophenyl): 2-(5"-methyl-4"-β-phenylethyl-2"-pyridyl)ethene (II) methiodide in the form of dark red crystals with mp 251–253° C. Yield 73%. λ_{max} 450 nm, ε 19600. Found, %: N 5.48, 5.53. Calculated for $C_{25}H_{29}IN_2$, %: N 5.78.

b) Similarly, 1.2 g (3.4 mM) of the methiodide I, 4.7 g (6.7 mM) of phenylacetaldehyde, 0.4 ml of piperidine, and 20 ml of ethanol yielded 0.85 g (56%) of 1-[5'-methyl-4'-(β-phenylethyl)-2'-pyridyl]-3-phenyl-1-propene (III). Colorless crystals with mp 214–216° C, λ_{max} 270 nm, ε 9570. Found, %: N 3.07, 3.14. Calculated for $C_{28}H_{26}IN$, %: N 3.07.

c) Similarly, 1.2 g (3.4 mM) of the methiodide I, 0.76 g (0.5 mM) of vanillin, 0.4 ml of piperidine, and 20 ml of ethanol yielded 1.31 g (79%) of the methiodide of 1-(4'-hydroxy-3'-methoxyphenyl)-2-(5"-methyl-4"-β-phenylethyl-2'-pyridyl)ethene (IV). Light yellow crystals with mp 236–238° C (from methanol), λ_{max}, nm, (ε): 390 (19500), 512 (14500). Found, %: N 1.80, 2.59. Calculated for $C_{24}H_{26}INO_2$, %: N 2.87.

d) The condensation reaction was performed with 1.5 g (4.2 mM) of the methiodide I, 0.74 g (5 mM) of phthalic anhydride, 0.2 ml of piperidine, and 25 ml of ethanol. This gave 1.18 g (57%) of the methiodide of 2-(1',3': dihydroxy-2'-hydrindenyl)-5-methyl-4-(β-phenylethyl)pyridine (V). Light yellow crystals with mp 207–211° C (from ethanol), λ_{max} 270 nm, ε 16 000. Found, %: N 3.14, 2.96. Calculated for $C_{24}H_{22}INO_2$, %: N 2.90.

5-Methyl-4-(β-phenylethyl)-2-styrylpyridine (VI). A mixture of 10.5 g (0.05 mole) of 2,5-dimethyl-4-(β-phenylethyl)pyridine, 12.7 g (0.12 mole) of benzaldehyde, and 12.2 g (0.12 mole) of acetic anhydride was distilled off in a slight vacuum. The residue was dissolved in 40 ml of water and neutralized with sodium carbonate. The benzaldehyde was distilled off with steam. The organic bases were extracted with ether and distilled, a fraction boiling at 180–210° C (0.5 mm) being collected, weight 6.6 g. Its recrystallization from a mixture of heptane and hexane (1:1) gave 6.1 g (45%) of light yellow crystals of one of the isomers of 5-methyl-4-(β-phenylethyl)-2-styrylpyridine (VI), with mp 118–120° C, λ_{max} 312 nm, ε 27500, ν 1638, 1592, 1485, 982, 850, 768, 755, 737, 694, 509, 494 cm^{-1}. Calculated, %: C 88.04; 88.14; H 6.74; 6.77; N 4.42; 4.71%. Calculated for $C_{22}H_{21}N$, %: N 4.68%.

The mother liquor yielded crystals (0.05 g) of the second isomer of 5-methyl-4-(β-phenylethyl)-2-styrylpyridine (VI), with mp 90–93° C, λ_{max} 314 nm, ε 27400, ν 1638, 1596, 1498, 978, 847, 765, 751, 731, 700, 692, 500 cm^{-1}. Found, %: C 88.23; 88.19; H 6.68; 7.15; N 4.71; 4.61%. Calculated for $C_{22}H_{21}N$, %: C 88.29; H 7.02; N 4.68%.

5-Methyl-4-(β-phenylethyl)pyridine-2-carboxylic acid (VII). In three portions (at 30–40 minute intervals), 4.6 g (0.029 mole) of potassium permanganate was added at 0° C to a solution of 3.3 g (0.01 mole) of 5-methyl-4-(β-phenylethyl)-2: styrylpyridine (VI) in 80 ml of acetone. The mixture was stirred at the same temperature for 3 hr. The manganese dioxide was filtered off and washed with acetone. Then 70 ml of water was added to the filterate and it was heated to the boil for an hour. The precipitate was filtered off and washed with 20 ml of hot water. Concentrated hydrochloric acid was added dropwise to the aqueous solution (pH 8.7; pH-meter). At pH 4.2–4.0, a precipitate formed, which was separated off and washed with hot water. This gave 1.1 g (40%) of compound VII in the form of colorless crystals with mp 120–123° C from heptane. Found, %: C 74.29; 74.28; H 6.60; 6.61; N 5.46; 5.43%. Calculated for $C_{15}H_{15}NO_2$, %: C 74.69; H 6.23; N 5.80%.

The phenacyl ester of 5-methyl-4-(β-phenylethyl)pyridine-2-carboxylic acid formed colorless crystals with mp 155–157° C.

5-Methyl 4-(β-phenylethyl)-2-phenylethynylpyridine (IX). To a solution of 7 g (0.125 mole) of potassium hydroxide in 50 ml of anhydrous methanol heated to 50° C was added 7.3 g (0.017 mole) of 1,2-dibromo-1-[5'-methyl-4'-(β-phenylethyl)-2'-pyridyl]: 2-phenylethane (VIII) (mp 155–156° C) [2]. The mixture was heated to the boil for 4 hr and was then poured into 300 ml of water. The organic bases were extracted with ether. This yielded 3.8 g (80%) of the pyridine IX with mp 133–134° C (from heptane). Found, %: N 4.52, 4.42. Calculated for $C_{22}H_{12}N$, %: N 4.71.

ω-[5-Methyl-4-(β-phenylethyl)-2-pyridyl]acetophenone (X). A mixture of 2.3 g (7.8 mM) of IX, 36 ml of 60% sulfuric acid, and 0.4 g of mercuric sulfate was heated at 120° C for 8 hr (with stirring). The reaction mixture was treated with ammonia. The organic bases were extracted with chloroform. The residue after the chloroform had been driven off (2.4 g) formed a noncrystallizing oil from which the hydrochloride of ω-[5-methyl-4-β-phenylethyl-2-pyridyl]acetophenone was obtained with mp 184–185° C (from a mixture of ethyl acetate and ethanol). Found, %: N 3.61, 3.79. Calculated for $C_{22}H_{21}NO \cdot HCl$, %: N 3.98. The free base X was isolated from the hydrochloride in the form of yellow crystals with mp 73–75° C, λ_{max}, nm (ε): 241 (17500), 334 (17400). Found, %: C 83.41; 83.45; H 6.64; 6.42; N 4.73; 4.43%. Calculated for $C_{22}H_{21}NO$, %: C 83.80; H 6.66; N 4.44%.

A solution of 0.1 g (0.3 mM) of X in 1 ml of acetone was treated with 3 ml of saturated aqueous copper acetate solution. The mixture was heated for 15 min, and the precipitate that deposited was filtered off and washed with hot water. This gave 0.11 g of the brown chelate complex of compound XII; mp 198–201°C, λ_{max}, nm (ε): 310 (26800), 380 (29100) (the spectrum was taken in chloroform solution). Found, %: N 3.85, 3.80. Calculated for $(C_{22}H_{20}NO)_2 \cdot Cu$, %: N 4.04.

The IR spectra were recorded on a UR-10 spectrophotometer in the 3800–400 cm^{-1} region with LiF, NaCl, and KBr prisms. The samples were prepared in the form of mulls in paraffin oil.

The UV spectra were determined on a SF-4 spectrophotometer in the 220–400 nm region and a SF-2 instrument in the 400–750 nm region. The measurements were carried out on ethanol solutions with concentrations of 10^{-3}–10^{-5} M.

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