SUBSTITUTED PYRIDINES. SYNTHESES BASED ON 2,5-DIMETHYL-4-PHENYL (β-PHENYLETHYL)PYRIDINE

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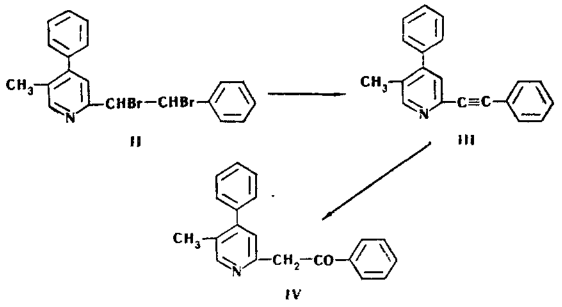
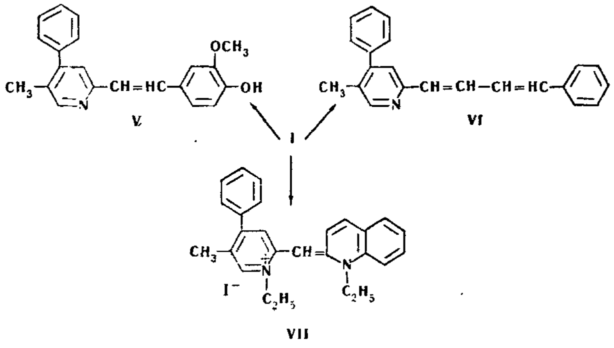
Condensation of the α methyl groups of 2,5-dimethyl-4-phenylpyridine and 2,5-dimethyl-4-β-phenylethylpyridine with some aromatic aldehydes is investigated. The cyclization of 2,5-dimethyl-4-phenylpyridine to 3-methyl-2-azafluorene and some derivatives of the latter is effected.

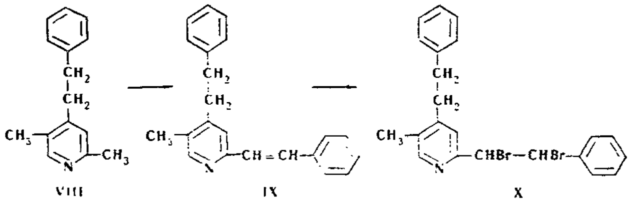
Condensation of 2,5-dimethyl-4-phenylpyridine (I) with benzaldehyde has been effected [1], and the resultant 5-methyl-4-phenyl-2-styryl-pyridine brominated to 1,2-dibromo-1-phenyl-2(5'-methyl-4'-phenylpyrid-2'-yl) (II). Heating II with alcoholic KOH led to the isolation of 5-methyl-4-phenyl-2-phenylethylpyridine (III). Hydration of the latter gave ω-(5-methyl-4-phenylpyrid-2-yl)acetophenone (IV).



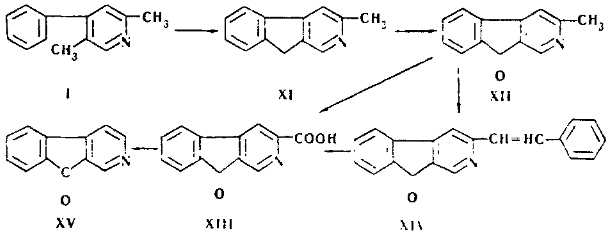
2,5-Dimethyl-4-phenylpyridine (I) was also condensed with vanillin and cinnamaldehyde, the products being 1-(3'-methoxy-4'-hydroxyphenyl)-2-(5''-methyl-4''-phenylpyrid-2''-yl)ethylene (V) and 1-phenyl-4-(5'-methyl-4'-phenylpyrid-2'yl)-1,3-butadiene (VI) respectively. Condensation of 2,5-dimethyl-4-phenylpyridine ethiodide with quinoline ethiodide gives an analog of cyanine dyes (VII).



The previously described 2,5-dimethyl-4-β-phenylethylpyridine (VIII) [3] was also condensed with benzaldehyde. The 5-methyl-4-β-phenylethyl-2-styrylpyridine (IX) was brominated to 1,2-dibromo-1-phenyl-2-(5'-methyl-4'-β-phenylethylpyrid-2'-yl)ethane (X).



2,5-Dimethyl-4-phenylpyridine (I) was used to synthesize polycyclic nitrogen compounds which are azafluorene derivatives. Dehydrocyclization of I over an industrial dehydrogenating catalyst, Mark K-16, at 500°, converted it to 3-methyl-2-azafluorene (XI), which by oxidation was converted to 3-methyl-2-azafluorenone (XII) and 2-azafluorenone-3-carboxylic acid (XIII). This acid was also obtained by a different method. 3-methyl-2-azafluorenone (XII) with benzaldehyde gave 3-styryl-2-azafluorenone (XIV), oxidized by $KMnO_4$ at 60-65° to acid XIII.



Decarboxylation of 2-azafluorenone-3-carboxylic acid gave 2-azafluorenone (XV), which we also obtained from 4-phenylpyridine-3-carboxylic acid.

The structures of the compounds prepared were proved not only by their synthetic reactions and analytical characteristics, but also by spectrum data, which, as a rule, were in good agreement with the results in the literature for similar compounds. Thus the IR spectra of 3-methyl-2-azafluorenone (XII) and 3-styryl-2-azafluorenone (XIV) were found to show intense bands at 1714 and 1710 cm^{-1} respectively, belonging to valence vibrations of a fluorenone-type carbonyl group.

The position of the styryl group in 5-methyl-4-β-phenylethyl-2-styrylpyridine (IX) is confirmed by comparing its UV spectrum with that of 2,5-dimethyl-4-styrylpyridine [3]. While the former of these has an absorption maximum at 312 nm, ε 27500, and the latter at 307 nm, ε 6500.

The IR spectra of 1-phenyl-4-(5'-methyl-4'-phenylpyrid-2'-yl)-1,3-butadiene (VI) and 3-styryl-2-azafluorenone (XIV) exhibit bands at 1625 and 1675 cm^{-1}, respectively, in the region of ethylene group valence vibrations. Furthermore, the IR spectrum of VI gas has a band with an absorption maximum at 1000 cm^{-1}, characteristic of valence vibrations of C—H bonds of the conjugated butadiene system.

The IR spectra were registered with a UR-10 spectrophotometer, in the region 3800–400 cm^{-1}, using LiF, NaCl, and KBr prisms. The specimens were made into mulls with vaseline. Absorption spectra were determined with an SF-4 instrument, in the 220–400 nm region. The measurements were made on ethanol solutions. Concentrations of the solutions 10^{-3}–10^{-5} M.

Detailed spectrum data for pyridine derivatives with unsubstituted substituents in the α-position, will be published separately.

EXPERIMENTAL

5-Methyl-4-phenyl-2-phenylethynylpyridine (III). 14 g (0.04 mole) 1,2-dibromo-1-phenyl-2-(5'-methyl-4'-phenylpyrid-2-yl)-ethane (II) was added to a stirred solution of 6.25 g (0.11 mole) KOH in 48 ml absolute EtOH at 40°, and the mixture then heated for 3 hr at 80°. 500 ml water was added. The orange bases were extracted with ether. The residue isolated from the ether extract, was crystallized from EtOH, yield 6 g **III**, mp 88–88.5°. Found: N 5.08; 5.09%, calculated for $C_{20}H_{15}N$: N 5.20%. Picrate mp 187–188°. Found: N 11.22; 11.01%, calculated for $C_{20}H_{15}N \cdot C_6H_3N_3O_7$: N 11.24%.

ω-(5-Methyl-4-phenylpyrid-2-yl) acetophenone (IV). 4.5 g (0.017 mole) III was added to 9 g 65% H_2SO_4 which was stirred and held at 120°. Then the mixture was heated for 3 hr at 160°. After cooling 300 ml water was added. The solution was neutralized with concentrated ammonia (to phenolphthalein). The organic bases were extracted with ether. The residue from the ether extract was recrystallized from petrol ether. Yield 3.5 g IV, bright yellow crystals, mp 73°. Found: C 84.05; 83.67; H 5.61; 5.61; N 4.84; 4.66%, calculated for $C_{20}H_{17}NO$: C 83.62; H 5.92; N 4.88%. Picrate mp 152° (ex EtOH). 2,4-Dinitrophenylhydrazone mp 222–223° (ex EtOH).

1-(3'-Methoxy-4'-hydroxyphenyl)-2-(5''-methyl-4''-phenylpyrid-2-yl)ethylene (V). A mixture of 5 g (0.027 mole) 2,5-dimethyl-4-phenylpyridine, 5 g (0.033 mole) vanillin, 2.79 g (0.027 mole) Ac_2O, and 1.64 g AcOH was heated for 9 hr at 180–185°. The Ac_2O was distilled off under a moderate vacuum. The residue was dissolved in water, and neutralized with Na_2CO_3. The organic base was extracted with ether. After drying the ether extract and distilling off the ether, the residue was washed with absolute EtOH. Yield 2.2 g V as yellowish green crystals mp 161–162° (ex acetone). Found: N 4.19, 4.24%, calculated for $C_{21}H_{19}NO_2$: N 4.41%.

1-Phenyl-4-(5'-methyl-4'-phenylpyrid-2-yl)-1,3-butadiene (VI). A mixture of 20 g (0.11 mole) 2,5-dimethyl-4-phenylpyridine, 17.4 g (0.13 mole) cinnamaldehyde, 11.2 g (0.11 mole) Ac_2O, and 6.6 g (0.11 mole) AcOH was heated for 12 hr at 170°. The Ac_2O was distilled off under a moderate vacuum, the residue dissolved in water, and neutralized with Na_2CO_3. The organic base and residual cinnamaldehyde were extracted with ether. The ether was distilled off, and the cinnamaldehyde removed from the residue by steam distillation, after which the organic bases were extracted with ether. The residue from the ether extract was crystallized from petrol ether. The crystals obtained were converted to 1-phenyl-4-(5'-methyl-4'-phenylpyrid-2-yl)-1,3-butadiene hydrochloride, mp 206–207°. Found: N 4.00%, calculated for $C_{22}H_{19}N \cdot HCl$: N 4.17%.

4 g free base was obtained from the hydrochloride, as light yellow crystals, mp 124° (ex EtOH–petrol ether). Found: C 88.54; 88.81; H 6.54; 6.60; N 4.59; 4.81%, calculated for $C_{22}H_{19}N$: C 88.88; H 6.40; N 4.71%.

Condensation of 2,5-dimethyl-4-phenylpyridine ethiodide with quinoline ethiodide. 35.4 ml 1 N KOH solution was added to a boiling solution of 6 g (0.018 mole) 2,5-dimethyl-4-phenylpyridine ethiodide and 10 g (0.035 mole) quinoline ethiodide in 140 ml EtOH, and the whole refluxed for 10 hr. The hot solution was filtered and left 2 days. The crystals which formed were filtered off, washed a few times with EtOH, and recrystallized from absolute EtOH–acetone. Yield of the analog VII of cyanine dyes 0.7 g, orange crystals, mp 281°–282°. Found: N 5.79; 5.57%; calculated for $C_{26}H_{27}IN_2$: N 5.67%.

5-Methyl-4-β-phenylethyl-2-styrylpyridine (IX). 10.5 g (0.05 mole) 2,5-dimethyl-4-β-phenylethylpyridine (VIII), 12.7 g (0.12 mole) benzaldehyde, and 12.2 g (0.12 mole) Ac_2O were refluxed together for 1 hr in a current of nitrogen. The acetic anhydride was distilled off under a moderate vacuum. The residue was dissolved in 40 ml water, and neutralized with Na_2CO_3. The benzaldehyde was steam distilled off. The organic bases were extracted with ether, and then distilled, to give a cut bp 180–210° (0.5 mm), mass 6.6 g. The fraction crystallized, and from it was obtained pale yellow crystals of IX, mp 118–120° (ex heptane–hexane 1:1). Found: N 4.42, calculated for $C_{22}H_{21}N$: N 4.68%. Hydrochloride mp 140–142° (ex EtOH). Found: N 3.85; 3.82%, calculated for $C_{22}H_{21}N \cdot HCl$: N 4.17%. Picrate mp 223–226° (ex EtOH). Found: N 10.42, 10.55%, calculated for $C_{22}H_{21}N \cdot C_6H_3N_3O_7$: N 10.60%.

1,2-Dibromo-1-phenyl-2-(5'-methyl-4'-β-phenylethylpyrid-2-yl)-ethane (X). A solution of 0.53 g (0.0033 mole) bromine in 20 ml $CHCl_3$ was added to a stirred solution of 1 g (0.003 mole) IX in 25 ml $CHCl_3$, and the whole then refluxed for 2 hr, after which the $CHCl_3$ was distilled off. Two recrystallizations of the residue from EtOH gave 0.63 g **X** as colorless crystals, mp 155–156°. Found: Br 35.05; 35.09; N 3.22; 3.01%, calculated for $C_{22}H_{21}Br_2N$: Br 34.83; N 3.05%.

3-Methyl-2-azafluorene (XI). 2,5-Dimethyl-4-phenylpyridine (I) was cyclodehydrogenated in a flow system, using a quartz reaction tube and end fittings. Industrial Mark K-16 catalyst was used (100 ml). Temperature in the catalyst zone was 500–510°. The catalyst was activated at 600° by drawing a slow stream of air through it, for 2 hr.

Over a period of 4 hr 30 g (0.164 mole) I in 60 ml benzene was passed through the tube at constant rate. 6 *l* gas (20°, 758 mm) was collected. Distillation of the condensate gave 12 g starting I, bp 123–128° (3 mm), and 6 g 3-methyl-2-azafluorene (XI), bp 130–135° (3 mm); mp 85.5–86° (ex ligroin). Found: C 86.02; 85.96; H 6.18; 6.43; N 7.43; 7.77%, calculated for $C_{13}H_{11}N$: C 86.20; H 6.08; N 7.73%. Picrate: mp 223–224° (ex EtOH), found: N 13.68; 13.52%, calculated for $C_{13}H_{11}N \cdot C_6H_3N_3O_7$: N 13.66%. Ethiodide mp 241–242° (ex EtOH).

3-Methyl-2-azafluorenone (XII). 7.5 g (0.048 mole) $KMnO_4$ was added in small portions, with vigorous stirring, to a mixture of 15 g (0.059 mole) Mg nitrate (6.H_2O), 500 ml water, and 5 g (0.0128 mole) XI at 60°, then heated to 90°, and rapidly filtered. The MnO_2 was carefully washed with hot acetone. The solution was concentrated to 100 ml. The precipitate was recrystallized from petrol ether, yield of **XII** 3.5 g, yellow crystals, mp 142°. Found: C 80.28; 79.64; H 5.08; 5.02; N 6.85; 7.13%, calculated for $C_{13}H_9NO$: C 80.00; H 4.62; N 7.18%. Picrate mp 225°. 2,4-Dinitrophenylhydrazone mp 232–233°.

2-Azafluorenone-3-carboxylic acid (XIII). 3 g (19 mM) $KMnO_4$ was gradually added to a stirred solution of 1 g (5.1 mM) XII in 700 ml water at 90°. The mixture was heated for 3 hr at 95°, until the color completely disappeared. The MnO_2 was filtered off, and washed three times on the filter with hot water. The aqueous solution was evaporated to 50 ml. The precipitate was filtered off. Recrystallization of it from petrol ether gave 0.15 g starting **XII**. The filtrate was treated with 50% H_2SO_4 (Congo Red). The resultant precipitate was filtered off, washed with water, and recrystallized from EtOH. Yield 0.2 g XIII, mp 217–218°. Found: N 5.88; 5.60%, calculated for $C_{13}H_7NO_3$: N 6.22%.

3-Styryl-2-azafluorenone (XIV). A mixture of 5 g (0.026 mole) **XII**, 3 g (0.029 mole) Ac_2O, and 1.8 g (0.03 mole) AcOH was heated for 10 hr at 150°. The Ac_2O was distilled off under a moderate vacuum. The residue was washed with a small amount of ether, and recrystallized from ligroin. Yield of **XIV** 2 g, mp 183–184°. Found: N 4.79; 4.67%, calculated for $C_{20}H_{13}NO$, N 4.95%.

Oxidation of 3-styryl-2-azafluorenone. A solution of 1 g (0.035 mole) XIV in 150 ml acetone was added gradually to a solution of 5 g (0.032 mole) $KMnO_4$ in 250 ml water. The mixture was heated for 3 hr at 60–65°. The MnO_2 was filtered off and carefully washed on the filter with hot acetone and hot water. The combined filtrates were evaporated to 50 ml and filtered. 0.2 g starting XIV was isolated from the solid. 50% H_2SO_4 was added to the filtrate until it was acid to Congo paper. The resultant precipitate was filtered off, washed with ether, and recrystallized from EtOH. Yield of XIII 0.25 g, mp 217–218°.

2-Azafluorenone (XV). 0.25 g (1.1 mM) XIII and 20 ml water were heated together in an autoclave for 3 hr at 210–215°. The crystalline precipitate was filtered off, and recrystallized from ligroin. Yield of XV 0.12 g, mp 151–152°. Found: N 7.52; 7.55%, calculated for $C_{12}H_7NO$: N 7.73%.

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