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2,5-DIMETHYL-4-(p-AMINOBENZYL)PYRIDINE IN THE SYNTHESIS OF SUBSTITUTED QUINOLINES, PYRIDOINDAZOLES, AND ISOQUINOLINOQUINOLINES

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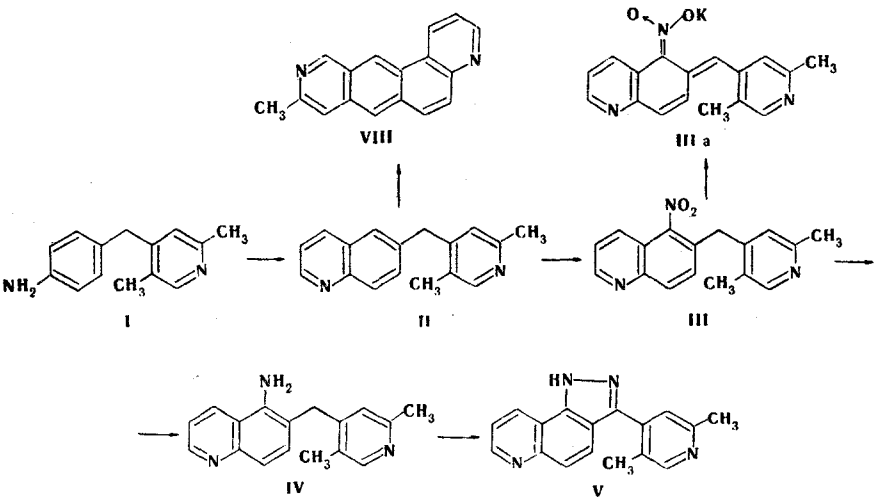
2,5-Dimethyl-4-pyridyl(6-quinolyl)methane was obtained from 2,5-dimethyl-4-(p-aminobenzyl)pyridine via the Skraup reaction. The product was nitrated to 2,5-dimethyl-4-pyridyl(5-nitro-6-quinolyl)methane, which was reduced to 2,5-dimethyl-4-pyridyl(5-amino-6-quinolyl)methane. It was established that the diazo compound formed from this amino derivative is converted to 1H,3-(2,5-dimethyl-4-pyridyl)-pyrido[2,3-g]indazole as a result of intramolecular cyclization. 9-Methylisoquinolino[7,6-f]quinoline was obtained by catalytic dehydrocyclization of 2,5-dimethyl-4-pyridyl(6-quinolyl)methane. 2,5-Dimethyl-4-pyridyl(5-nitro-6-quinolyl)methane has chemochromic properties.

A previously unknown substituted quinoline, viz., 2,5-dimethyl-4-pyridyl(6-quinolyl)-methane (II), was obtained from 2,5-dimethyl-4-(p-aminobenzyl)pyridine (I) [1] via the Skraup reaction. 2,5-Dimethyl-4-(p-nitrobenzyl)pyridine, from which amino derivative I was obtained, was used as the oxidizing agent in its synthesis.

We have accomplished the nitration of substituted quinoline II and subsequent transformations at the nitro and amino groups with allowance for the fact that some functionally substituted quinolines have specific physiological properties [2].

As a result of nitration under relatively severe conditions we isolated only one mononitro derivative, viz., 2,5-dimethyl-4-pyridyl(5-nitro-6-quinolyl)methane (III). Its PMR spectrum does not contain a signal of the 5-H proton, but the 7-H and 8-H protons of the



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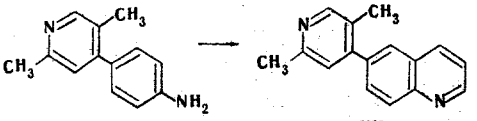
quinoline part of the molecule give a spectrum of the AB type, and this constitutes evidence that the nitro group is attached to the C_5 atom. An ortho orientation of the nitro group relative to the methylene group is confirmed [3] by the appearance in the mass spectrum of III of an $(M - OH)^+$ fragment with m/e 276, which has the maximum peak intensity.

Nitro derivative III has chemochromic properties. A colorless solution of III in methanol turns brick-red when potassium hydroxide or potassium carbonate is added to it. Nitro form III evidently is converted to nitronic acid salt IIIa in this case.

A significant decrease in the signal of the methylene group (δ 4.08 ppm), the appearance of two additional (as compared with III) signals of methylene groups, and complication of the structure of the spectrum in the aromatic region are observed in the PMR spectrum (for a solution in CD_3OD with tetramethylsilane as the standard) of III recorded after the addition of a solution of potassium carbonate. We have previously observed a similar conversion of the nitro form to the aci form in the case of 2,5-dimethyl-4-(p,o-dinitrobenzyl)pyridine [4]; however, in contrast to the latter, nitroquinolyl(pyridyl)methane III does not display photochromic properties when its crystals or a methanol solution are illuminated with an electronic photoflash at +30 to −50°C.

2,5-Dimethyl-4-pyridyl(5-amino-6-quinolyl)methane (IV) was obtained by reduction of nitro derivative III by means of hydrazine hydrate and Raney nickel. We made an attempt to replace the amino group in this compound by a hydroxy group by diazotization and subsequent decomposition of the diazo compound. However, evidently as a consequence of the relative stability of the resulting diazo compound, as well as the ease of deprotonation of the methylene group under alkaline conditions, the compound undergoes intramolecular cyclization, as a result of which 1H,3-(2,5-dimethyl-4-pyridyl)pyrido[2,3-g]indazole (V) — a representative of a new heterocyclic system — is formed in high yield. The position and the multiplicity of the signals of the protons of the quinoline and pyridine fragments in the PMR spectrum of pyridoindazole V are similar to the position and multiplicity of the signals of amino derivative IV. However, the absence in its spectrum of signals of the protons of the amino and methylene groups, as well as the appearance of a broad signal at δ 14.3 ppm (1-H), which is characteristic for indazole [5], confirms the pyridoindazole structure of V.

We obtained 6-(2,5-dimethyl-4-pyridyl)quinoline (VII) from the previously described 2,5-dimethyl-4-(p-aminophenyl)pyridine (VI) [6] via the Skraup reaction. The condensation was carried out in the presence of 2,5-dimethyl-4-(p-nitrophenyl)pyridine.



VI VII

Substituted quinoline II was used in the synthesis of a new polynuclear nitrogen-containing heterocyclic system of the isoquinolino-quinoline type, a representative of which is 9-methylisoquinolino[7,6-f]quinoline (VIII).

The dehydrocyclization of II was carried out on a K-16 dehydrogenating catalyst at 560-580°C. In the course of this reaction hydrogen may be split out from the quinoline ring at both C_7 (with the formation of a linear condensed system) and C_5 (with the formation of an angular structure). Only VIII was isolated in the experiment. The localization of the signal of the 1-H proton at weak field is explained by the angular structure of VIII, since in the spectra of quinolines the signal of the peri proton is located at stronger (by ∿0.9 ppm) field. The UV spectrum of VIII is also in agreement with its angular structure [7].

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Tesla BS-487C spectrometer (80 MHz) with tetramethylsilane as the internal standard [in the case of V, the solvent was dimethyl sulfoxide (DMSO), and the standard was hexamethyldisiloxane]. The UV spectra of solutions of the compounds in ethanol were obtained with a Specord UV-vis spectrophotometer. The mass spectra were obtained using an MKh-1303 mass spectrometer with a system for direct introduction of the samples into the ion source at an ionizing voltage of 70 V. Intense molecular-ion peaks are present in the mass spectra of all of the synthesized compounds. Activity II aluminum oxide was used for chromatographic analysis.

2,5-Dimethyl-4-pyridyl(6-quinolyl)methane (II). A 14-ml sample of sulfuric acid (sp. gr. 1.83) was added with stirring to a mixture of 2 g (0.013 mole) of ferrous sulfate, 16.7 g (0.18 mole) of glycerol, 4.8 g (0.022 mole) of I, and 8 g (0.034 mole) of 2,5-dimethyl-4-(p-nitrobenzyl)pyridine, and the flask containing the reaction mixture was heated with a burner flame for 1 h. The contents of the flask were then dissolved in 50 ml of water, the aqueous mixture was neutralized with sodium hydroxide solution, and the organic bases were extracted with ether. The ether was removed by distillation, and the residue was dissolved in chloroform. The chloroform solution was passed through a layer of aluminum oxide for purification. The glassy residue (6.8 g) that remained after removal of the chloroform by distillation was recrystallized five times from petroleum ether to give 4.1 g (71%) of substituted quinoline II as colorless crystals with mp 83-84°C. PMR spectrum, δ, ppm (quinoline ring signals): 8.56 dd (2-H, J = 4.2; 1.7 Hz), 7.9 dd (3-H, J = 9.0; 4.2 Hz), and 7.12 dd (4-H, J = 9.0; 1.7 Hz). Found: C 82.0; H 6.7; N 11.4%; M^+ 248. $C_{17}H_{16}N_2$. Calculated: C 82.2; H 6.5; N 11.3%; M 248.

2,5-Dimethyl-4-pyridyl(5-nitro-6-quinolyl)methane (III). A 5-g sample of potassium nitrate was added with stirring to a mixture of 2.48 g (0.01 mole) of II, 13 ml of fuming nitric acid (sp. gr. 1.5), and 20 ml of 30% oleum, and the mixture was heated at 100°C for 3 h. It was then cooled and poured over ice (100 g). The aqueous mixture was neutralized with potassium hydroxide solution and extracted with chloroform. The residue (1.4 g) that remained after removal of the chloroform by distillation was crystallized from acetone to give 0.8 g (27%) of nitro derivative III as colorless crystals with mp 138-140°C. PMR spectrum, δ, ppm (quinoline ring signals): 8.97 dd (2-H, J = 4.0, 1.0 Hz), 8.13 d (8-H, J = 9.0 Hz), 8.07 dd (4-H, J = 9.0, 1.0 Hz), 7.52 dd (3-H, J = 9.0, 4.0 Hz), and 7.33 d (7-H, J = 9.0 Hz). Found: C 69.4; H 5.3; N 14.5%; M^+ 293. $C_{17}H_{15}N_3O_2$. Calculated: C 69.6; H 5.2; N 14.3%; M 293.

2,5-Dimethyl-4-pyridyl(5-amino-6-quinolyl)methane (IV). A solution of 2.64 g (0.08 mole) of nitro compound III and 13.2 ml of hydrazine hydrate in 46 ml of ethanol to which a catalytic amount of Raney nickel was added was heated at 70°C for 9 h. The hot solution was filtered, water was added to the filtrate until it became slightly turbid, and the mixture was boiled until dissolving was complete, after which the solution was cooled slowly. The resulting crystals (1.6 g) were chromatographed (H = 40 cm, d = 2 cm, elution with chloroform) to give 1.6 g (60%) of amino derivative IV as colorless crystals with mp 209-210°C (from aqueous alcohol). PMR spectrum, δ, ppm (quinoline ring signals): 8.98 dd (2-H, J = 4.0, 1.7 Hz), 8.24 d (4-H, J = 9.0 Hz), 7.64 d (8-H, J = 9.0 Hz), 7.42 dd (3-H, J = 9.0, 4.0 Hz), 7.32 d (7-H, J = 9.0 Hz), and 4.14 br s (NH_2). Found: C 77.8; H 6.8; N 15.5%; M^+ 263. $C_{17}H_{17}N_3$. Calculated: C 77.6; H 6.5; N 16.0%; M 263.

The PMR spectra of II-IV contain singlet signals of two methyl groups at 2.2-2.5 ppm and of the α (at 8.1-8.7 ppm) and β protons (at 6.4-7.0 ppm) of the pyridine ring, as well as signals of a methylene group at 4.02, 4.22, and 3.98 ppm, respectively.

1H,3-(2,5-Dimethyl-4-pyridyl)pyrido[2,3-g]indazole (V). A solution of 0.3 g of sodium nitrate in 1 ml of water was added gradually at 0°C to a mixture of 1 g (3.8 mmole) of amino derivative IV and 1.8 g of sulfuric acid (sp. gr. 1.83) in 13 ml of water, after which a solution of 2 ml of sulfuric acid in 10 ml of water was added, and the mixture was maintained at 50°C for 3 h and refluxed for 30 min. The mixture was then made alkaline to pH 10 with a saturated solution of sodium carbonate and extracted with chloroform. Carbon dioxide was bubbled through the aqueous solution up to pH 7, and the mixture was extracted with chloroform. Workup of the chloroform solutions gave 0.83 g (83%) of V as colorless crystals with mp 250-251°C [from ethyl acetate–heptane (2:3) and from toluene]. PMR spectrum, δ, ppm: 8.97 dd (7-H, J = 4.0, 1.0 Hz), 8.66 dd (9-H, J = 4.0, 1.0 Hz), 7.94 d (5-H), 7.67 dd (8-H, J = 8.0, 4.0 Hz), 7.65 d (4-H, J = 9.0 Hz), and 14.3 br s (NH); pyridine ring signals: 8.44 s (6-H), 7.43 s (4-H), 2.37 s (5-CH_3), and 2.54 s (2-CH_3). Found: C 74.4; H 5.2; N 19.8%; M^+ 274. $C_{17}H_{14}N_4$. Calculated: C 74.5; H 5.1; N 20.4%; M 274.

6-(2,5-Dimethyl-4-pyridyl)quinoline (VII). This compound was obtained in 80% yield from amino derivative VI by the method used to synthesize II. The colorless crystals had mp 165-166°C [from ethyl acetate–heptane (1:2)]. PMR spectrum, δ, ppm: 8.74 dd (2-H, J = 4.2, 1.7 Hz), 8.10 dd (3-H, J = 9.0, 4.2 Hz), and 7.35 dd (4-H, J = 9.0, 1.7 Hz); pyridine ring signals: 8.32 s (6-H), 6.97 s (3-H), 2.50 s (2-CH_3), and 2.20 s (5-CH_3). Found: N 11.9%; M^+ 234. $C_{16}H_{14}N_2$. Calculated: N 11.7%; M 234.

9-Methylisoquinolino[7,6-f]quinoline (VIII). A solution of 2.48 g (0.01 mole) of substituted quinoline II in 60 ml of benzene was passed at a constant rate in the course of 2 h through K-16 catalyst (10 cm^3). The temperature in the catalyst zone was 580°C. The residue from the catalyzate was crystallized from petroleum ether to give 0.7 g of starting II. Chromatography (H = 30 cm, d = 2.5 cm, elution with ether) of the residue from the mother liquor gave an additional 0.8 g of II (R_f 0.4) and 0.15 g (16% on the basis of the converted II) of dehydrocyclization product VIII as pale-orange crystals with mp 177-178°C [from carbon tetrachloride–chloroform (1:1)] and R_f 0.18. PMR spectrum, δ, ppm: 9.26 s (11-H), 8.80 d (3-H), 8.70 d (1-H), 7.97 s (7-H), 7.41 dd (2-H), and 2.62 s (9-CH_3). UV spectrum, λ_{max} (log ε): 210 (4.6), 264 (4.45), 296 (4.21), 330 (2.84) sh, and 380 (2.42) sh. Found: N 11.2%; M^+ 244. $C_{17}H_{12}N_2$. Calculated: N 11.4%; M 244.

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AMINOMETHYLATION OF SUBSTITUTED 5-HYDROXYPYRIMIDINES

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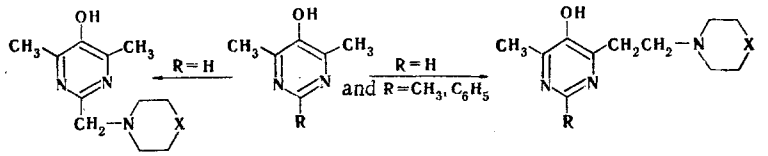
Conditions that make it possible to obtain aminomethyl derivatives of 2-R-4,6-dimethyl-5-hydroxypyrimidine that are substituted both in the pyrimidine ring (R = H) and at the methyl group of the side chain (R = H, CH_3, C_6H_5) were found. The facts established in this research make it possible to propose various substitution mechanisms.

We have shown the fundamental possibility of the incorporation of an electrophilic substituent in the 2 position of 4,6-dimethyl-5-hydroxypyrimidine (Ia) by aminomethylation and diazo coupling [1]. However, methyl groups bonded to a pyridine or pyrimidine ring have increased activity [2]. For example, the formation of products of substitution in the side chain have been noted for 4-nitro-2-methyl- and 2-nitro-6-methyl-3-hydroxypyridines [3].

Using piperidine and morpholine as the secondary amines we investigated the aminomethylation of 2,4,6-trimethyl- (Ib) and 2-phenyl-4,6-dimethyl-5-hydroxypyrimidine (Ic),



IIIa, b Ia-c IIa-d

Ia, IIa, b R=H; Ib, IIc R=CH_3; Ic, IId R=C_6H_5; IIa, c, d, IIIb X=O; IIb, IIIa X=CH_2

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