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REACTION OF BENZYLIDENE-2-NAPHTHYLAMINE WITH THE ETHYL ESTER OF 3-PYRIDYL-β-OXOPROPIONIC ACID

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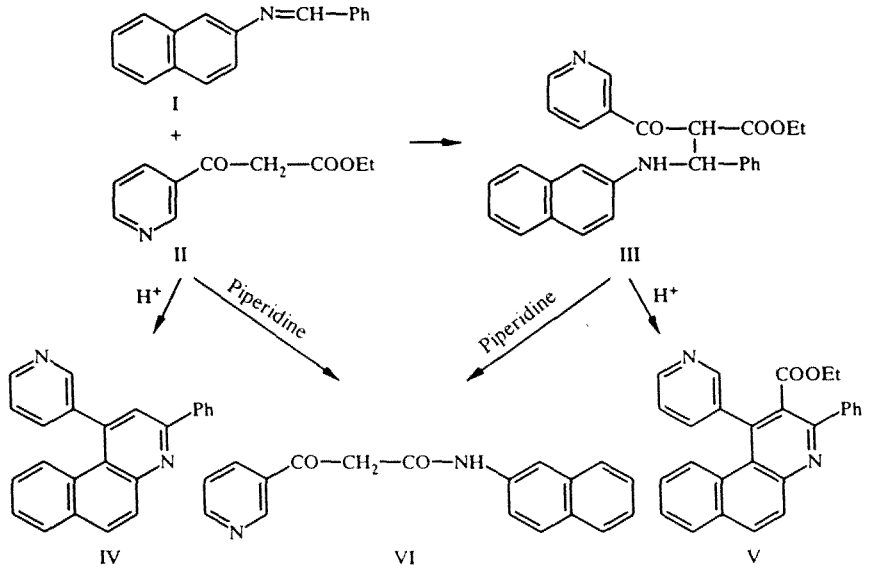
The reaction of benzylidene-2-naphthylamine with ethyl β-(3-ethyl)-β-oxopropionate under various conditions gave the ethyl ester of α-(2-naphthylamino)benzyl-β-(3-pyridyl)-β-oxopropionic acid, 1-(3-pyridyl)-3-phenylbenzo[f]quinoline, ethyl ester of 1-(3-pyridyl)-3-phenylbenzo[f]quinoline-2-carboxylic acid, and N-(2-naphthyl)amide of β-(3-pyridyl)-β-oxopropionic acid. The IR, UV, and mass spectra of the products were studied and the pathways for their formation were discussed.

In previous work [1-3], we showed that the reaction of arylidene-2-naphthylamines with ethyl acetoacetate and the ethyl esters of β-(2-furyl)- and β-(2-quinolinyl)-β-oxopropionic acids leads to biologically active esters of 1,3-disubstituted benzo[*f*]quinoline-2-carboxylic acids, which have not been readily available. The reaction of esters of β-pyridyl-β-ketoacids with 2-naphthylamine azomethines had not previously been studied. On the other hand, the introduction of a pyridine ring into compounds is known to expand its range of physiological activity [4].

In the present work, we studied the condensation of benzylidene-2-naphthylamine (I) with the pyridine analog of the previously used ketoesters, namely, ethyl β-(3-pyridyl)-β-oxopropionate (II) obtained from the ethyl ester of nicotinic acid and ethyl acetate through the Claisen reaction [5]. Ketoacid esters have CH-acid properties due to the labile hydrogen atoms of the methylene group. We have established that heating reagents I and II in ethanol at 40-60°C in the absence of catalyst gives the product of the addition of the CH-acid at the azomethine C=N bond, namely, the ethyl ester of α-(2-naphthylamino)benzyl-β-(3-pyridyl)-β-oxopropionic acid (III).



1-(3-Pyridyl)-3-phenylbenzo[*f*]quinoline (IV) is the only product when the reaction is carried out by heating the reagents at 100-150°C in the presence of concentrated hydrochloric acid in a sealed ampule. Under these conditions, hydrolysis and

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decarboxylation of the ester group of ethyl β-(3-pyridyl)-β-oxopropionate (II) presumably take place, leading to 3-acetylpyridine, whose subsequent condensation with benzylidene-2-naphthylamine I leads to benzo[*f*]quinoline IV.

Aminoketoester III is less capable of undergoing decarboxylation than ketoester II since the cyclization of III to give the ethyl ester of 1-(3-pyridyl)-3-phenylbenzo[*f*]quinoline-2-carboxylic acid (V) occurs upon heating this compound in the presence of hydrochloric acid.

When the reaction of benzylidene-2-naphthylamine I with ketoester II is carried out in toluene with piperidine as a base catalyst, pure N-(2-naphthyl)amide of β-(3-pyridyl)-β-oxopropionic acid (VI) was isolated after treatment of the reaction mixture. The formation of amide VI may occur due to the reaction of ethyl 3-pyridine-β-oxopropionate II with 2-naphthylamine, which is lost as the result of base-catalyzed hydrolytic cleavage of azomethine I. Substituted ethyl 3-phenyl- and 3-alkylaminopropionates are formed in the reaction of ketoacid esters with aniline or aliphatic amines in addition to ketoacid amides [6, 7]. The failure of the carbonyl group of ketoester II to participate in the reaction with liberated 2-naphthylamine in the reaction described above may be attributed to steric hindrance by the bulky naphthalene system and pyridine ring upon the approach of 2-naphthylamine to the carbonyl group.

Amide VI was also obtained in an attempt to cyclize aminoketoester III in the presence of piperidine. In this case, the C—C bond in aminoketoester III is probably cleaved, generating benzylidene-2-naphthylamine I and ethyl 3-pyridyl-4-oxopropionate II. Hydrolysis of azomethine I and the reaction of the resultant 2-naphthylamine with ketoester II according to the above scheme leads to amide VI. Cleavage of an aminoketoester at the C—C bond was described in our previous work [2].

The composition and structures of III—VI were supported by elemental analysis and spectral data.

The IR spectrum of aminoketoester III shows a characteristic NH group stretching band at 3400 cm^{-1}. The ν_{CO} bands of the ester moiety and carbonyl group next to the pyridine ring are found at 1735 and 1680 cm^{-1}, respectively. The bands for the ethyl group are at 2980-2850 cm^{-1}. The IR spectrum of benzo[*f*]quinoline IV lacks bands for these groups, which indicates hydrolysis and decarboxylation of the carboethoxy group and formation of a closed cyclic system. The C—H stretching bands for the aromatic rings in the spectrum of IV are found at 3090-3040 cm^{-1}. The spectrum of the ester of benzo[*f*]quinoline-2-carboxylic acid V has the ν_{CO} stretching band at 1715 cm^{-1}, ν_{C-H} bands of the ethyl fragment at 2965-2870 cm^{-1}, and ν_{C-H} bands of the aromatic rings at 3110-3060 cm^{-1}. The amide group carbonyl stretching vibrations in the IR spectrum of amide VI are seen as a strong, broad band at 1655 cm^{-1}. The stretching bands for the NH group and carbonyl group adjacent to the pyridine ring are found at 3310 and 1610 cm^{-1}, respectively. The downfield shift of these bands is probably related to a stable intramolecular hydrogen bond.

The electronic absorption spectrum of aminoketoester III is found in the UV region and proved similar to the spectrum of 2-naphthylamine. This spectrum has two bands characteristic for local excitation of the phenyl chromophore and a band due to transfer of an electron from the pyridine ring nitrogen atom ($n—\pi^*$ band) [8]. The electronic absorption spectrum of IV has structure typical for benzo[*f*]quinolines in the UV region [9]. This spectrum has a β-band (237-251 nm), *p*-band (284 nm), and α-band (348-369 nm), which has vibrational structure. Virtually no change is seen upon introducing carboethoxy groups into benzo[*f*]quinoline (V). Only a slight bathochromic shift of the α-band to 353-374 nm and a reduction in the intensity of the β-band are found in comparison with the spectrum of benzoquinoline IV. The four strong bands in the UV spectrum of amide VI are due to absorption of the naphthalene system and the conjugated amide group as well as $n—\pi^*$ transitions of the pyridine ring.

The intensity of the molecular ion peak in the mass spectrum of aminoketoester III (M^+, *m/z* 424) is 18%. The fragment peaks corresponding to starting compounds I and II and formed upon cleavage of the corresponding C—C bond and the peak for the $[M - C_{10}H_7NH_2]^+$ ion (*m/z* 281) are the strongest peaks in the spectrum (80-100%). The mass spectrum of benzo[*f*]quinoline IV has a molecular ion peak (M^+, *m/z* 332) with maximum intensity and low-intensity peaks (10-12%) for the $[M - C_6H_5]^+$, $[M - C_5H_4N]^+$, and $[M - HCN]^+$ ions. There are also peaks at the doubly-charged molecular (M^{++}) and $[M - CHN]^{++}$ ions, which is characteristic for condensed heteroaromatic compounds. The molecular ion peak in the mass spectrum of carboethoxybenzo[*f*]quinoline V (M^+, *m/z* 404) has maximum intensity. This spectrum of V has a peak for the $[M - CO_2C_2H_5]^+$ ion (*m/z* 331) (18%) along with peaks for the $[M - C_6H_5]^+$ and $[M - C_5H_4N]^+$ ions (12-15%). The loss of neutral HCN molecular ions is also observed in various stages of the decomposition. The mass spectrum of amide VI has a molecular ion peak (M^+, *m/z* 290, 35%) and fragment ions $[M - C_5H_4N - CO - CH_2CO]^+$ (*m/z* 142, 100%) and $[M - C_5H_4N - CO - CH_2]^+$ ions (*m/z* 169, 65%).

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for KBr pellets. The mass spectra were taken on a Varian MAT-311 spectrometer with direct inlet into the ion source. The ionizing voltage was 70 eV. The UV spectra were taken on a Specord UV-VIS spectrometer for ethanol solutions. A sample of ethyl 3-pyridyl-β-oxopropionate II was obtained according to Wunderlich [5].

Ethyl Ester of α-(2-Naphthylamino)benzyl-β-(3-pyridyl)-β-oxopropionic Acid (III). A mixture of 2.3 g (0.01 mole) azomethine I and 2.4 g (0.0125 mole) ketoester II in 30 ml ethanol was heated on a water bath for 30 min at 40-60°C. The precipitate formed upon cooling was filtered off and crystallized from 2-propanol to give 4.0 g (97%) III, mp 101-102°C. Found: C, 76.52; H, 5.28; N, 6.52%. Calculated for $C_{27}H_{24}N_2O_3$: C, 76.38; H, 5.71, N, 6.60%. UV spectrum, λ_{max}, nm (log ε): 232 (4.62), 248 (4.70), 271 (4.46), 318 (4.20).

1-(3-Pyridyl)-3-phenylbenzo[*f*]quinoline (IV). A mixture of 2.3 g (0.01 mole) azomethine I, 2.4 g (0.0125 mole) ketoester, 30 ml aliphatic alcohol (C_2—C_4), and 0.5 ml concentrated hydrochloric acid was heated in a sealed ampule for 2 h at 100-150°C. The precipitated product was treated with ethanolic NH_4OH and then with water and crystallized from 2-propanol to give 1.0 g (31%) IV, mp 180-181°C (181-182°C [9]). Found: 86.39; H, 4.96; N, 8.15%. Calculated for $C_{24}H_{16}N_2$: C, 86.70; N, 4.86; N, 8.43%. UV spectrum, λ_{max}, nm (log ε): 237 (4.54), 251 (4.48), 284 (4.56), 348 (3.80), 369 (3.76).

Ethyl 1-(3-pyridyl)-3-phenylbenzo[*f*]quinoline-2-carboxylate (V). A mixture of 2.1 g (0.005 mole) aminoketoester III, 30 ml ethanol, 0.5 ml concentrated hydrochloric acid, and 0.5 ml nitrobenzene was heated in a sealed ampule for 12 h at 100°C. The ampule contents were evaporated to 3/4 volume. The tarry residue was treated with ethanolic NH_4OH and water, dried, and triturated with 2-propanol. The product was filtered off and crystallized from ethanol to give 0.56 g (28%) V, mp 151-152°C. Found: C, 80.57; H, 5.26; N, 6.48%. Calculated for $C_{27}H_{20}N_2O_2$: C, 80.20; H, 4.95; N, 6.93%. UV spectrum, λ_{max}, nm (log ε): 234 (4.42), 250 (4.40), 282 (4.57), 353 (3.77), 374 (3.72).

N-(2-Naphthyl)amide of β-(3-Pyridyl)-β-oxopropionic Acid (VI). A sample of 2.1 g (0.005 mole) aminoketoester III or a mixture of 2.3 g (0.01 mole) azomethine and 2.4 g (0.0125 mole) ketoester II in 20 ml toluene with five drops of piperidine was heated for 3 h at 120-130°C. The precipitate formed upon cooling the reaction mixture was filtered off and crystallized from 2-propanol to give 0.23 g (16%) VI from III and 1.00 g (34%) from the mixture of I and II, mp 170-171°C. Found: C, 74.87; H, 4.89; N, 9.88%. Calculated for $C_{18}H_{14}N_2O_2$: C, 74.46; H, 4.87; N, 9.65%. UV spectrum, λ_{max}, nm (log ε): 216 (4.76), 245 (4.82), 278 (4.46), 330 (4.50).

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