Synthesis of 2-Substituted 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones

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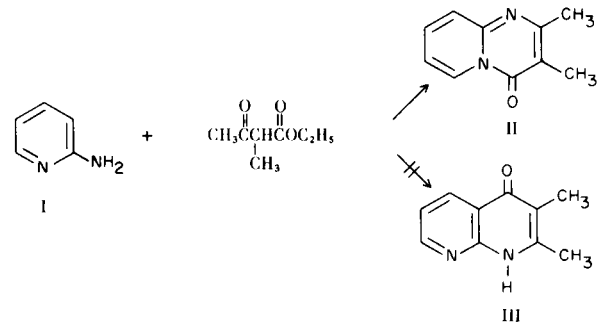
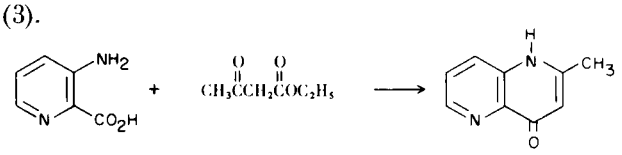
The reaction of 2-aminopyridine (I) with β-ketoesters in the presence of polyphosphoric acid ethyl ester affords pyridopyrimidinone (II) (1) and not a naphthyridone (III) as reported earlier (2).



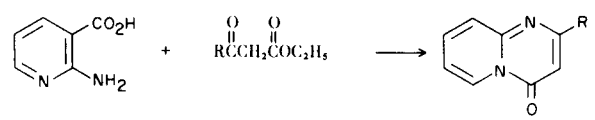
I II III

It was of interest to determine if 2-aminonicotinic acid (IV) would react similarly, especially since its isomer, 3-aminopicolinic acid (V) on heating with ethyl acetoacetate yielded 2-methyl-1,5-naphthyridine-4(1*H*)one (VI) (3).



V VI

In the present investigation, reaction of compound IV with refluxing ethyl acetoacetate and with ethyl benzoylacetate in refluxing *N*,*N*-dimethylformamide (DMF) gave 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (VII) (1) and 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (VIII) (4) respectively. Decarboxylation probably occurred during the heating period analogous to that reported by Baumgarten and co-workers (3).



IV

VII, R = CH_3
VIII, R = C_6H_5

When compound IV was refluxed with a mixture of ethyl trifluoroacetoacetate and molecular sieves (to scavenge water and/or alcohol) (5,6), or with an ethyl trifluoroacetoacetate-DMF-molecular sieves mixture, ethyl 2-aminonicotinate (7) was isolated. In other experiments, addition of molecular sieves to the respective reaction mixture did not affect the yield of compounds VII or VIII.

EXPERIMENTAL (8)

Preparation of 2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (VII).

A magnetically-stirred mixture of 5 g. (0.036 mole) of 2-aminonicotinic acid (9) and 25 ml. (25.6 g., 0.2 mole) of ethyl acetoacetate was refluxed for 1 week. The cooled product was diluted with chloroform; unreacted compound IV was removed by dilute aqueous sodium carbonate extraction (acidification of the separated alkaline wash led to the recovery of 1.1 g. of compound IV). The chloroform solution was dried (anhydrous magnesium sulfate) and chromatographed on 125 g. of silica gel. Elution of the column with acetone afforded 2 g. (35% yield) of off-white solid which was recrystallized from heptane, m.p. 119-120°. An analytical sample was prepared by sublimation (100°/0.05 mm.) to give white sublimate, m.p. 121-122.5°, lit. (1), m.p. 121-122.5°. No NH- or OH-type absorption noted in the ir, ν max cm^{-1}: 1710 (C=O); nmr: CH_3, 2.46 (s); 3-H, 6.32 (s); 5-H, 9.02 (dt); 6,7,8-H, 6.98-7.90 (m).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.5; H, 4.9; N, 17.7.

Preparation of 2-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (VIII).

A moisture-protected mixture of 6.9 g. (0.05 mole) of compound IV, 9.6 g. (0.05 mole) of ethyl benzoylacetate, 10 g. of molecular sieves, and 50 ml. of molecular sieves-dried DMF was magnetically stirred under reflux for 8 days. The cooled material was filtered and the residue was washed several times with chloroform. The combined organic liquid was concentrated to give a semi-solid. It was leached with four 50 ml. portions of hot benzene to leave 3.7 g. of recovered compound IV (by ir, m.p.). The combined benzene extract was chromatographed on 300 g. of silica gel. Elution of the column with ether followed by acetone yielded an off-white to yellow solid, m.p. 138-142°. It was further purified by sublimation (135°/0.07 mm.) followed by recrystallization of the sublimate from carbon tetrachloride to give 2.2 g. (20% yield) of white crystals, m.p. 147.5-148°, lit. (4), m.p. 149.5-150°. No NH- or OH-type absorption noted in the ir, ν max cm^{-1}: 1680 (C=O); nmr: 3-H, 6.86 (s); 5-H, 8.88 (dt); 5-ArH and 6,7,8-H, 6.95-8.20 (m).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.7; H, 4.5; N, 12.6. Found: C, 75.6; H, 4.4; N, 12.6.

Isolation of Ethyl 2-Aminonicotinate.

A mixture of 6.9 g. (0.05 mole) of compound IV, 9.2 g. (0.05 mole) of ethyl trifluoroacetoacetate, 10 g. of molecular sieves, and 50 ml. of molecular sieves-dried DMF was magnetically stirred and refluxed for 8 days under a Drierite-protected drying tube. The cooled material was diluted with water and extracted with several portions of chloroform. The separated, dried (anhydrous magnesium sulfate), and filtered organic extract was chromatographed on 100 g. of silica gel. Elution of the column with ether afforded a light yellow solid (m.p. 91-92°) which was sublimed (80°/0.1 mm.). Recrystallization of the sublimate from cyclohexane gave 1.6 g. of ethyl 2-aminonicotinate (by ir, nmr, CHN analyses) as stout white crystals, m.p. 93-95°, lit. (7), m.p. 94-96°.

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(8) Melting points are uncorrected and were determined using a Thomas-Hoover capillary m.p. apparatus. Molecular sieves (type 4A, pellet form) were purchased from the Linde Corporation. Column chromatography was carried out on Davison grade 923 silica gel (100-200 mesh); fractions were monitored by tlc on Mallinckrodt silica gel (SilicAR® 7GF). Infrared spectra were recorded as hydrocarbon oil mulls on a Perkin Elmer model 21 spectrophotometer. Nmr spectra were taken as 20% wt./vol. solutions in deuteriochloroform containing 1% TMS as an internal standard using a Varian model A-60 spectrometer. Chemical shifts are reported in δ units and coupling constants (J) are stated in Hz. This paper represents contribution No. 660 from Minnesota Mining and Manufacturing Company.

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