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SYNTHESIS OF 5-(4-PYRIDYL) DERIVATIVES OF 2-AMINO- 4H-PYRAN AND 2-AMINOPYRIDINE

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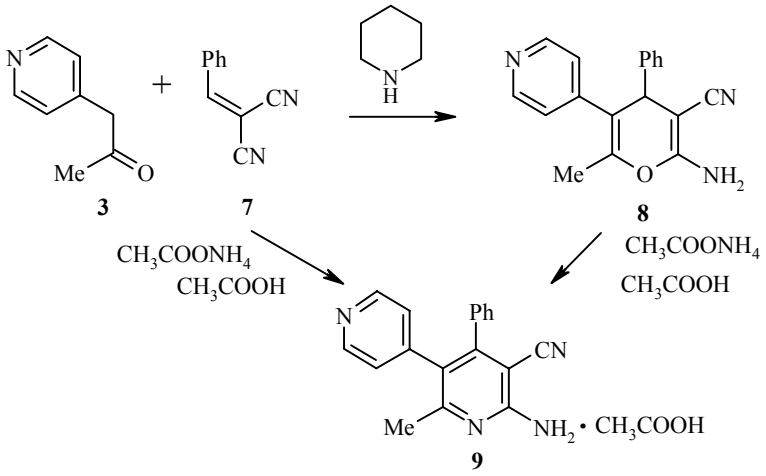
3-Cyano-6-methyl-5-(4-pyridyl)-2(1H)-pyridinone (Milrinone) (**1**) is an efficient cardiotonic drug, whose clinical use has been unfortunately limited due to its toxicity and side effects [1].

We have developed a synthesis for 4-aryl-3-cyano-6-methyl-5-(4-pyridyl)-2(1H)-pyridinones (**2**) [2]. These compounds are not as active as Milrinone but differ favorably in their low toxicity and lack of side effects (in this stage of investigation) [3]. Unfortunately, 2(1H)-pyridinones **2** are formed in the condensation of 4-pyridylacetone (**3**) with 2-ylidenecyanoacetamides **4** only in low yields due to the formation of alternative products, namely, 3-carbamoyl-3,4-dihydro-2(1H)-pyridinones (**5**) [3]. Thus, both the cyano and carbamoyl groups react in the intramolecular cyclization of 3-acetyl-1-carbamoyl-1-cyanopropanes **6**. The formation of only 3-cyano-2(1H)-pyridinones **2** might be expected if 2-ylidenemalononitriles **7** are used instead of compound **4**.



We have shown that the condensation of 4-pyridylacetone (**3**) with 2-benzylidenemalononitrile (**7**) in the presence of equimolar amount of piperidine in ethanol solution (under conditions analogous to the preparation of **2**) proceeds to give **8** in 45% yield. Pyridine **9** was obtained in 17% yield when this reaction was carried out in the presence of ammonium acetate in acetic acid solution at reflux for 2 h and forms a crystal solvate with one acetic acid molecule. Heating pyran **8** with ammonium acetate also gives pyridine **9** in 27% yield.

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Products **8** and **9** do not display significant cardiotonic activity.

2-Amino-3-cyano-6-methyl-4-phenyl-5-(4-pyridyl)-4H-pyran (8) was obtained in 45% yield; mp 195-197°C. IR spectrum (vaseline mull), ν, cm^{-1}: 2190 (C≡N); 3316, 3380 (NH_2). ^1H NMR spectrum (90 MHz, DMSO-d_6), δ, ppm: 1.88 (3H, s, 6-Me); 4.38 (1H, s, 4-H); 6.74 (2H, s, NH_2); 7.1-8.4 (9H, complex, 4-C_6H_5 and 5-C_5H_4N). Found, %: C 74.48; H 5.42; N 14.69. $C_{18}H_{15}N_3O$. Calculated, %: C 74.72; H 5.23; N 14.52.

2-Amino-3-cyano-6-methyl-4-phenyl-5-(4-pyridyl)pyridine (9) was obtained in 27% yield; mp 310-311°C. IR spectrum (vaseline mull), ν, cm^{-1}: 1662 (δNH_2); 1718 (C=O, in CH_3CO_2H); 2226 (C≡N); 3330, 3388 (NH_2). ^1H NMR spectrum (90 MHz, DMSO-d_6), δ, ppm: 1.85 (3H, s, 6-Me); 2.12 (3H, s, $\underline{CH_3}CO_2H$); 6.9-8.4 (9H, complex, 2-NH_2, 4-C_6H_5, and 5-C_5H_4N). Found, %: C 69.65; H 5.12; N 16.39. $C_{18}H_{14}N_4 \cdot CH_3CO_2H$. Calculated, %: C 69.35; H 5.24; N 16.17.

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