SYNTHESIS AND PROPERTIES OF 1-ARYL-2,5,7-TRIMETHYL-4-OXO-1,4-DIHYDROPYRIDO[2,3-D]PYRIMIDINES

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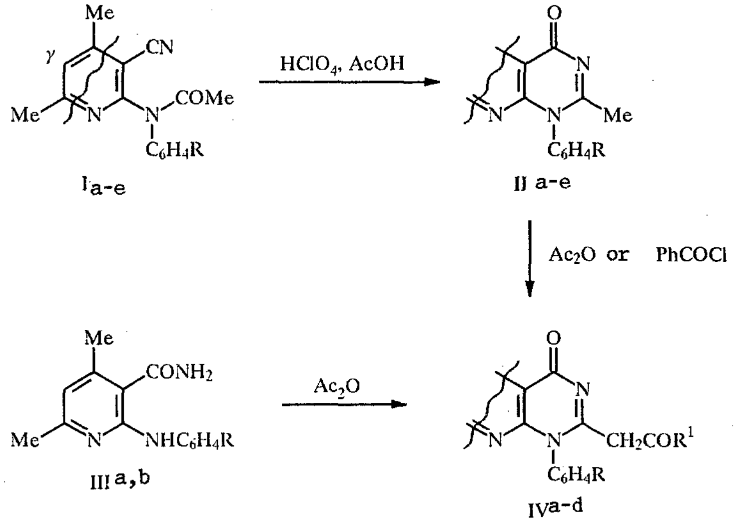
1-Aryl-2,5,7-trimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines are formed from the cyclization of N-acetyl-2-arylamino-4,6-dimethylnicotinonitriles by perchloric acid in a mixture of acetic acid and acetic anhydride. 1-Aryl-2-acetonyl-5,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines are formed on heating 2-arylamino-4,6-dimethylnicotinamides with acetic anhydride. These and analogous compounds were obtained by acylation of 1-aryl-2,5,7-trimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines with acetic anhydride or benzoyl chloride.

It was shown in a previous paper [1] that 1-aryl-2,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines are formed by the cyclization of N-acetyl-2-arylamino-6-methylnicotinonitriles with hydrogen chloride. An attempt has been made in the present work to extend this reaction to the N-acetyl-2-arylamino-4,6-dimethylnicotinonitriles (Ia-e).

In contrast to the N-acetyl-2-arylamino-6-methylnicotinonitriles, it is more difficult to convert compounds I(a-e) into derivatives of pyrido[2,3-d]pyrimidine with anhydrous hydrogen chloride in either ethanol or benzene. A mixture of starting materials and cyclization products was obtained. This is evidently caused by steric hindrance by the methyl groups at C(4) at one of the reaction centers, the nitrile group.



I—III a $R = H$, b $R = 4\text{-MeO}$, c $R = 4\text{-Me}$, d $R = 3\text{-Me}$, e $R = 2\text{-MeO}$; IV a $R = H$, $R^1 = Me$;
b $R = 4\text{-MeO}$, $R^1 = Me$; c $R = 4\text{-Me}$, $R^1 = Me$; d $R = 4\text{-Me}$, $R^1 = Ph$

We attempted to the stronger acid perchloric acid in a mixture of acetic acid and acetic anhydride to cyclize the nitrile Ia-e since it is known that its acid properties are increased in acetic acid medium [3]. The reaction with compounds Ia-e occurs easily at 20°C over 48 h to give 1-aryl-2,5,7-trimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines in high yield (Table 1).

Compound IIa has been obtained by boiling 2-anilino-4,6-dimethylnicotinamide in acetic anhydride [4]. However, our investigation of the reaction of the amides IIIa and b with acetic anhydride with or without sodium acetate showed that the 1-

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5,7-Dimethyl-1-(4′-tolyl)-4-oxo-2-phenacyl-1,4-dihydropyrido[2,3-d]pyrimidine (IVd). A solution of 0.01 mol of compound IIc and benzoyl chloride (3.0 g, 0.02 mol) in pyridine (15 ml) was boiled for 5 h. The mixture was poured into water (50 ml) and the residue filtered off and recrystallized from 1:1 ethanol–DMF. Ir spectrum: 1670 (heterocycle CO), 1600 cm^{-1} (phenacyl CO).

5,7-Dimethyl-1-phenyl-4-oxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (V). A mixture of 2-anilino-4,6-dimethylnicotinamide (2.4 g, 0.01 mol) and formamide (4.5 g, 0.1 mol) was heated at 190-200°C for 6 h. The mixture was cooled, poured into water (30 ml), the residue filtered off and crystallized from 1:1 ethyl acetate–toluene. IR spectrum: 1660 (CO), 3200 cm^{-1} (NH). ^1H NMR spectrum: 2.16, 2.53 (6 H, s, $2CH_3$), 4.83 (2 H, d, CH_2); 6.46 (s, pyridine H), 7.03-7.26 (m, 5 H, aromatic), 7.9 ppm (1 H, s, NH).

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