# SYNTHESIS AND PROPERTIES OF SUBSTITUTED 1-ARYL-1,4-DIHYDRO-4-OXOPYRIDO[2,3-d]-PYRIMIDINES

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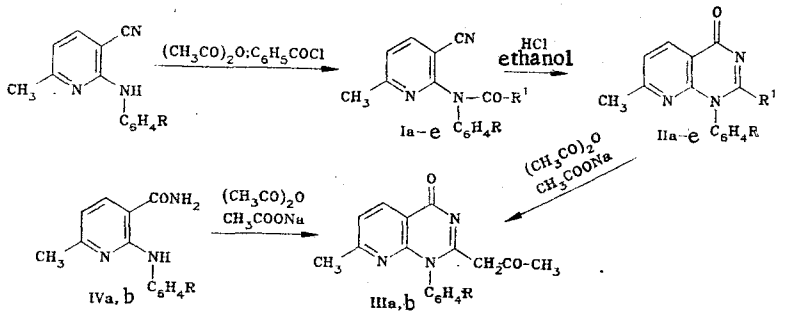
The reaction of 2-arylamino-6-methylnicotinonitriles with acetic anhydride or benzoyl chloride gives N-acyl-2-arylamino-6-methylnicotinonitriles. Upon treatment with hydrogen chloride in anhydrous ethanol, these products are converted to 2-substituted 1-aryl-1,4-dihydro-7-methyl-4-oxopyrido[2,3-d]pyrimidines. Heating amides of 2-arylamino-6-methylnicotinic acids or 1-aryl-2,7-dimethyl-1,4-dihydro-4-oxopyrido[2,3-d]-pyrimidines at reflux with acetic anhydride in the presence of anhydrous sodium acetate gives 1-aryl-2-acetonyl-7-methyl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines.

1-Aryl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines have not been subjected to intensive study. A synthetic method has been reported for these compounds which have anti-inflammatory and sedative action based on amides of 2-arylaminonicotinic acids and ethyl orthoformate [1]. The synthesis of 1,2-dimethyl-1,4-dihydro-4-quinazolones by the cyclization of N-acetyl-N-methylanthranylonitrile has been described [2].

In order to study the possibility of using this synthesis to obtain derivatives of 1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines, we prepared N-acyl-2-arylamino-6-methylnicotinonitriles (Ia-e, Table 1) by the acylation of previously described 2-arylaminonicotinonitriles [3, 4] using acetic anhydride or benzoyl chloride.



I—IV a R=H, $R^1=CH_3$; b R=*p*-$CH_3$, $R^1=CH_3$; c R=*p*-$CH_3O$, $R^1=CH_3$; d R=*m*-$CH_3$, $R^1=CH_3$; e R=H, $R^1=C_6H_5$

N-Acyl-2-arylamino-6-methylnicotinonitriles cyclize upon the action of hydrogen chloride in anhydrous ethanol to give 2-substituted 1-aryl-1,4-dihydro-7-methyl-4-oxopyrido[2,3-d]pyrimidines (IIa-e, Table 1) in 53-73% yield. The structures of IIa-e were supported by their IR spectra which have bands corresponding to carbonyl group stretching vibrations in the vicinity of 1700 $cm^{-1}$ and, in contrast to the spectra of nitriles Ia-e, the band at 2230 $cm^{-1}$ for the CN group is lacking.

The PMR spectrum of IIa has signals at 2.20-2.36 ppm (doublet for two methyl groups) and a multiplet centered at 7.3 ppm (aromatic and pyridine ring hydrogens).

An attempt was made to synthesize pyridopyrimidines Ia and IIb by the action of acetic anhydride on the amides of 2-anilino- (IVa) [4] and 2-(p-toluidino)-6-methylnicotinic (IVb) [5] acids. The reaction does not proceed in pyridine in the cold. A mixture of various products with a sharp melting point is formed upon heating of these compounds in excess acetic anhydride at reflux. Under more vigorous conditions involving heating IV and IVb for 8-10 hat

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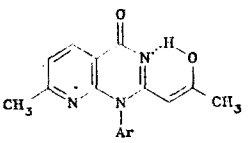
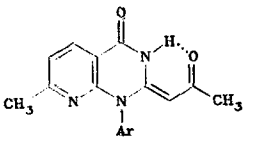
reflux in acetic acid in the presence of anhydrous sodium acetate, 2-acetonyl-7-methyl-1-phenyl-(IIIa) and 2-acetonyl-7-methyl-1-(p-tolyl)-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines (IIIb) are formed. The structures of IIIa and IIIb were supported by convergent synthesis under the same conditions involving the relatively facile and selective acylation of the methyl group at C-2 of the pyrimidine ring (the methyl group at C-7 remains free). An attempt to acetylate 7-methyl-1,2-diphenyl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidine (IIe) was unsuccessful. Noda et al. [6] have described the analogous acetylation of 1-alkyl-2-methyl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines upon heating at reflux in acetic anhydride. In contrast to these compounds, IIa and IIb are acetylated more slowly and under more vigorous conditions, likely as a consequence of their reduced nucleophilicity.

The IR spectra of IIIa and IIIb have bands at 1695 $cm^{-1}$ for the C=O group.

The PMR spectra of IIIa have signals at 2.30-2.32 ppm (six methyl group protons), a multiplet centered at 7.2 ppm and a doublet at 8.2 ppm (seven aromatic and pyridine ring protons) as well as a multiplet for one proton at 4.27 ppm and a signal for one proton at 14.1 ppm. A similar pattern is observed for IIIb. The PMR spectral data indicate that IIIa and IIIb exist either in enol form A or structure B. Both forms have a strong intramolecular chelate-type hydrogen bond. The signals at 4.27 ppm should be assigned to the methine group proton, while the signal at 14.1 ppm would be assigned to the chelate ring. The available spectral data do not indicate a preference for either A or B.


A


B

Rapid proton exchange is possible between the nitrogen and oxygen atoms as well and conversion of one form to the other.

## EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer. The PMR spectra were taken on an RS-60 spectrometer for 5% solutions of IIa,b,e,IIIa, b in deuterochloroform with HMDS as the internal standard.

The characteristics of the compounds synthesized are given in Table 1.

N-Acyl-2-arylamino-6-methylnicotinonitriles (Ia-e). The corresponding 2-arylamino-6-methylnicotinonitrile (10 mmoles) is heated at reflux in 10 ml acetic anhydride for 5 h and the mixture is poured into water. The precipitated product is filtered off and crystallized to give Ia-e.

TABLE 1. Characteristics of I, II, and III

| Compound | mp, °C | Found, % | | | Chemical formula | Calculated, % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | | C | H | N | |
| Ia | 83—85 | 71,7 | 5,4 | 16,9 | $C_{15}H_{13}N_3O$ | 71,7 | 5,2 | 16,7 | 50 |
| Ib | 115—117 | 72,0 | 6,1 | 15,5 | $C_{16}H_{15}N_3O$ | 72,4 | 5,7 | 15,8 | 71 |
| Ic | 101—103 | 69,0 | 5,8 | 15,1 | $C_{16}H_{15}N_3O_2$ | 68,3 | 5,4 | 14,9 | 66 |
| Id | 85—86 | 71,9 | 5,5 | 15,8 | $C_{16}H_{15}N_3O$ | 72,4 | 5,7 | 15,8 | 64 |
| Ie | 113—115 | 76,4 | 4,7 | 13,8 | $C_{20}H_{15}N_3O$ | 76,7 | 4,8 | 13,4 | 45 |
| IIa | 191—192 | 71,2 | 5,7 | 16,3 | $C_{15}H_{13}N_3O$ | 71,7 | 5,2 | 16,7 | 53 |
| IIb | 218—220 | 71,9 | 6,0 | 16,2 | $C_{16}H_{15}N_3O$ | 72,4 | 5,7 | 15,8 | 60 |
| IIc | 185—187 | 68,6 | 5,7 | 15,2 | $C_{16}H_{15}N_3O_2$ | 68,3 | 5,4 | 14,9 | 59 |
| IId | 200—202 | 71,9 | 6,1 | 16,3 | $C_{16}H_{15}N_3O$ | 72,4 | 5,7 | 15,8 | 60 |
| IIe | 256—258 | 76,5 | 5,1 | 13,3 | $C_{20}H_{15}N_3O$ | 76,7 | 4,8 | 13,4 | 73 |
| IIIa | 243—245 | — | — | 14,5 | $C_{17}H_{15}N_3O_2$ | — | — | 14,3 | 52 |
| IIIb | 244—246 | 70,6 | 5,9 | 14,2 | $C_{18}H_{17}N_3O_2$ | 70,3 | 5,6 | 13,7 | 50 |

2-Substituted 1-Aryl-7-methyl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines (IIa-e). Dry hydrogen chloride is introduced into a solution of 10 mmoles Ia-e in 40 ml anhydrous ethanol for 1.5 h and then, the reaction solution is heated for 0.5 h on a water bath. After cooling, the precipitate is filtered off and treated with aqueous sodium acetate. Crystallization from ethanol gives IIa-e.

1-Aryl-2-acetonyl-7-methyl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines (IIIa and IIIb). A solution of 10 mmoles 2-arylamino-6-methylnicotinamide (IVa or IVb) or 10 mmoles IIa or IIb and 0.7 g (8 mmoles) anhydrous sodium acetate in 10 ml acetic anhydride is heated at reflux for 10 h and poured into water. The residue is crystallized to yield IIIa or IIIb.

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# ELECTROCHEMICAL REDUCTION OF HYDROGENATED 2-PYRIMIDONES ON A GRAPHITE ELECTRODE


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E. L. Khanina, G. Ya. Dubur,
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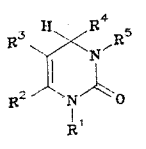
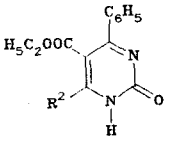
A rotating disk–ring graphite electrode was used to show that the first step in the electrochemical oxidation of substituted 2-oxo-1,2,3,4-tetrahydropyrimidines in anhydrous acetonitrile corresponds to a two-electron process and leads to the formation of the corresponding substituted 2-oxo-1,2-dihydropyrimidines. The electroreduction wave of 2-oxo-1,2-dihydropyrimidines on the ring electrode which appears at about −1.0 V is related to the reduction of the protonated oxidized species arising in the electrolysis. The electrochemical oxidation potentials of 11 hydrogenated 2-pyrimidones and electrochemical reduction potentials of two 2-pyrimidines were determined.


In a continuation of a study on the electrochemical oxidation of hydrogenated azines [1, 2], we investigated hydrogenated 2-pyrimidones in order to elucidate their capacity to undergo oxidation and to compare the electrochemical behavior of these compounds with that of previously studied 2-pyridones [3].



I-XI



XII,XIII

Table 1 shows that I-XI give a well-pronounced electrooxidation wave on a graphite disk in acetonitrile. The halfwave potentials lie in the range from 0.8 to 1.2 V. The linear de-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