[CONTRIBUTION FROM THE AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

Some Substituted 3,4-Dihydropyrido[2,3-d]pyrimidines

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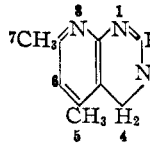
The synthesis of several new substituted 3,4-dihydropyrido[2,3-d]-pyrimidines is described. These compounds resulted from cyclization of acylated derivatives of 2-amino-3-aminomethyl-4,6-dimethylpyridine. The ease of cyclization was found to vary with the nature of the amide involved.

This paper describes the synthesis of substituted 3,4-dihydropyrido[2,3-d]pyrimidines.



IX, R = CH_3
X, R = C_6H_5
XI, R = H
XII, R = OH

Other workers[2] have synthesized a few substituted derivatives of this ring system.

In the present investigation, 3-cyano-4,6-dimethyl-2-pyridone[3] (I) was converted in two steps *via* the chloro derivative[4] (II) to 2-amino-3-cyano-4,6-dimethylpyridine (III). This nitrile was reduced to the corresponding primary amine, 2-amino-3-aminomethyl-4,6-dimethylpyridine (IV), by the action of lithium aluminum hydride. The reduction proceeded slowly and with some difficulty due to the precipitation of highly insoluble intermediate complexes. Nystrom and Brown[5] have previously noted difficulty in the reduction of bifunctional compounds.

A series of four acylated derivatives of IV was prepared by conventional methods. These were: 3-acetamidomethyl- (V), 3-benzamidomethyl- (VI), 3-formamidomethyl- (VII) and 3-carbethoxyaminomethyl-2-amino-4,6-dimethylpyridine (VIII).

The formyl derivative (VII) was synthesized by heating the formate salt of IV in toluene solution until the calculated amount of water had been collected in a trap. The product was contaminated by the cyclized 5,7-dimethyl-3,4-dihydropyrido-[2,3-d]pyrimidine and thus it was more feasible to proceed directly to the cyclized product in this case.

The cyclization of these acyl derivatives proceeded with variable ease. The acetamidomethyl compound (V) gave 2,5,7-trimethyl-3,4-dihydropyrido[2,3-d]pyrimidine (IX) when treated with phosphorus oxychloride in the cold whereas the ring closure of the benzamidomethyl derivative (VI) to 5,7-dimethyl-2-phenyl-3,4-dihydropyrido-[2,3-d]pyrimidine (X) required heating with a mixture of phosphorus pentachloride and phosphorus oxychloride. As previously mentioned, 5,7-dimethyl-3,4-dihydropyrido[2,3-d]pyrimidine (XI) was best prepared by heating the formate salt of IV in xylene solution. The cyclization of the substituted urethan (VIII) to 5,7-dimethyl-3,4-dihydropyrido[2,3-d]pyrimid-2-(1)-one (XII) was effected by heating in boiling diphenyl ether solution.

The dihydropyridopyrimidines, with the exception of XII, are fairly soluble in ethanol, benzene, chloroform and other organic solvents and are slightly soluble in water. They do not dissolve in ether or petroleum ether. The pyridopyrimidone (XII) is soluble in boiling cellosolve and glacial acetic acid. All of these compounds decompose slowly when heated unless the samples are inserted in the melting point bath just below their decomposition temperatures.

In contrast, the acyl derivatives of IV are less soluble in organic solvents than the cyclized products and they have characteristic melting points.

Experimental[6]

3-Cyano-4,6-dimethyl-2-pyridone.—This compound was prepared from acetylacetone and cyanoacetamide in 96% yield by following the directions of van Wagtendonk and Wibaut.[3]

2-Chloro-3-cyano-4,6-dimethylpyridine.—A modification of the method of Mariella and Leech[4] was employed for the preparation of this substance. 3-Cyano-4,6-dimethyl-2-pyridone (421 g., 2.85 moles) was heated under reflux with a mixture of phosphorus pentachloride (593 g., 2.85 moles) and phosphorus oxychloride (530 ml.) for 1 hour. After removal of the excess phosphorus oxychloride, the residue was poured onto ice to obtain the crude product. Recrystallization from 95% ethanol gave an analytically pure product (432 g., 91%) melting at 89–91°.

2-Amino-3-cyano-4,6-dimethylpyridine.—A mixture of 2-chloro-3-cyano-4,6-dimethylpyridine (200 g., 1.20 moles) and concentrated ammonium hydroxide (400 ml.) was placed in a steel pressure reaction vessel of 1100-ml. capacity. The vessel was equipped with an electrical heating jacket and a mechanical shaker. The contents of the bomb were heated to a temperature of 160° for 24 hours. After cooling, the contents of the bomb were removed and the solid collected by filtration. The crude product was dissolved in dilute hydrochloric acid, treated with activated carbon and then reprecipitated by the addition of dilute base. Recrystallization of this material from boiling cellosolve gave white crystals (116 g., 66%), m.p. 249–251°.

Anal. Calcd. for $C_8H_9N_3$: C, 65.27; H, 6.16; N, 28.57. Found: C, 65.48; H, 6.46; N, 28.74.

2-Amino-3-aminomethyl-4,6-dimethylpyridine.—A slurry of lithium aluminum hydride (38.0 g., 1.00 mole) and sodium-dried ether (1.0 l.) was prepared in a 3-l. three-necked flask which was equipped with a mercury-sealed stirrer and a reflux condenser. 2-Amino-3-cyano-4,6-dimethylpyridine (58.8 g., 0.40 mole) was added in small portions through the opened neck of the flask. A vigorous reaction took place after each addition and a yellow complex precipitated from solution. After the addition was completed, the contents of the flask were heated with stirring for 24 hours. The yellow solid which had originally separated had been replaced by a gray-green sticky solid. The excess lithium aluminum hydride was cautiously decomposed by the dropwise addition of water followed by the addition of excess 10% sodium hydroxide solution to destroy the complexes. The white lithium and aluminum salts which were thus obtained were removed by filtration and boiled with three 200-ml. portions of ethanol to extract the

(1) Parke, Davis and Company Fellow.

(2) (a) L. Klisiecki and E. Sucharda, *Roczniki Chem.*, **3**, 251 (1923) [*C. A.*, **19**, 72 (1925)]; (b) A. C. McLean and F. S. Spring, *J. Chem. Soc.*, 2582 (1949).

(3) H. M. van Wagtendonk and J. P. Wibaut, *Rec. trav. chim.*, **61**, 728 (1942).

(4) R. P. Mariella and J. L. Leech, THIS JOURNAL, **71**, 331 (1949).

(5) R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948).

(6) All melting points are uncorrected for stem emergence.

product. The combined ether and ethanol extracts were dried over anhydrous potassium carbonate and then evaporated under reduced pressure until the nearly colorless product began to crystallize. The crude product was recrystallized from benzene to give 41.3 g. (68%), m.p. 135–138°.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.53; H, 8.66; N, 27.79. Found: C, 63.45; H, 8.71; N, 27.54.

Acylation of 2-Amino-3-aminomethyl-4,6-dimethylpyridine (IV).—These derivatives were prepared by conventional methods.

The action of acetic anhydride on IV gave 2-amino-3-acetamidomethyl-4,6-dimethylpyridine in 92% yield, m.p. 185–187°.

Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.71. Found: C, 62.36; H, 7.89; N, 21.68.

2-Amino-3-benzamidomethyl-4,6-dimethylpyridine was obtained from IV by the action of benzoyl chloride in pyridine solution; m.p. 156–158°. The yield was 83%.

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.69; H, 7.03; N, 16.40.

The formate salt of IV (from equivalent amounts of 99% formic acid and IV), m.p. 172° dec., gave crude 2-amino-3-formamidomethyl-4,6-dimethylpyridine when heated in toluene solution until the calculated amount of water had been eliminated. Recrystallization from ethanol gave the analytically pure amide melting at 182–184° dec.

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.46; H, 7.41; N, 23.20.

2-Amino-3-carbethoxyaminomethyl-4,6-dimethylpyridine was obtained in 86% yield when IV and ethyl chlorocarbonate were allowed to stand at room temperature for 1 hour; m.p. 116–118°.

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59.16; H, 7.68; N, 18.82. Found: C, 59.30; H, 7.82; N, 18.82.

2,5,7-Trimethyl-3,4-dihydropyrido[2,3-d]pyrimidine.—A mixture of 2-amino-3-acetamidomethyl-4,6-dimethylpyridine (14.5 g., 0.075 mole) and phosphorus oxychloride (100 ml.) was allowed to stand at room temperature for 1 hour. The solid dissolved with warming during this time. The excess phosphorus oxychloride was removed under reduced pressure and the residue poured onto ice. The solution was rendered basic by the addition of dilute ammonium hydroxide and the white solid which separated was collected by filtration. The crude material was recrystallized from benzene to give 9.0 g. (69%), m.p. 203° dec.

Anal. Calcd. for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.49; H, 7.48; N, 23.83.

5,7-Dimethyl-2-phenyl-3,4-dihydropyrido[2,3-d]pyrimidine.—To a mixture of phosphorus pentachloride (5.0 g.) and phosphorus oxychloride (25 ml.) was added 2-amino-3-benzamidomethyl-4,6-dimethylpyridine (4.0 g., 0.0157 mole). The solution which formed was heated under reflux for 30 minutes, then cooled and poured slowly onto ice. The acidic solution was treated with activated carbon, filtered and then made basic by the addition of excess sodium carbonate solution. The crude yellow solid which separated was removed by filtration, dried and recrystallized from 95% ethanol to give 2 g. (61%) of pale yellow product melting at 190–193° dec.

Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.86; H, 6.50; N, 17.66.

5,7-Dimethyl-3,4-dihydropyrido[2,3-d]pyrimidine.—A mixture of 2-amino-3-aminomethyl-4,6-dimethylpyridine formate (5.0 g., 0.0254 mole) and xylene (75 ml.) was placed in a flask equipped with a water-trap and a condenser. The flask was heated by means of an oil-bath so that reflux was maintained. After 1.5 hours, the theoretical amount of water had been collected in the trap and the solid had dissolved to give a pale yellow solution. Cooling and addition of petroleum ether (30–60°) yielded 2.87 g. (70%) of slightly yellow product. Recrystallization from chloroform gave a product melting at 203° dec.

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 66.99; H, 6.92; N, 25.98.

5,7-Dimethyl-3,4-dihydropyrido[2,3-d]pyrimid-2(1)-one.—A solution of 2-amino-3-carbethoxyaminomethyl-4,6-dimethylpyridine (28.7 g., 0.128 mole) in diphenyl ether (200 ml.) was heated under reflux with brisk stirring for 70 minutes. The solution was cooled and, after the addition of 200 ml. of petroleum ether (30–60°), the tan solid which had separated was removed by filtration. The product (21.3 g., 94%) was purified by recrystallization from cellosolve to give white crystals, m.p. 271–274° dec.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 61.05; H, 6.51; N, 23.79.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Nitrogen Analogs of Ketenes. A New Method of Preparation[1]

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A novel synthesis of a nitrogen analog of a ketene (I) from the reaction of an α-choloroimino chloride (II) with sodium iodide in 84% yield is described. Some chemical and physical properties of I are also included.

The present paper is an initial report of an investigation of the chemistry of the nitrogen analogs of ketenes. The investigation resulted in the discovery of a novel method for the preparation of a ketenimine (I) in good yield by the reaction of an α-chloroimino chloride (II) with sodium iodide. The ketenimine (I) reacted smoothly with water, methanol and chlorine to give the amide (III), iminoester (IV) and α-chloroimino chloride (II) in good yield.

In 1921, Staudinger[3] prepared several ketenimines in unspecified yields by the interaction of a phosphinimine (VIII) with a ketene. The phosphinimines were prepared from the unstable phosphazides (VII) which were made from azides (VI) and phosphines (V). Staudinger characterized the ketenimines by reaction with water to give amides. In an attempt to prepare ketenimines, Staudinger[3,4] reported that zinc failed to dehalogenate an α-chloroimino chloride.

$$\underset{\text{V}}{R_3P} + \underset{\text{VI}}{R'N_3} \longrightarrow \underset{\text{VII}}{R_3P{=}N{-}N{=}N{-}R'} \xrightarrow{-N_2} \underset{\text{VIII}}{R_3P{=}N{-}R'}$$

$$\text{VIII} + R''_2C{=}C{=}O \longrightarrow R''_2C{=}C{=}N{-}R' + R_3PO$$

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(2) Parke, Davis and Co. Fellow, 1951–1952.

(3) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 887 (1921); see also H. Staudinger and J. Meyer, *Ber.*, **53**, 72 (1920).

(4) H. Staudinger, *Ann.*, **356**. 55 (1907).