Chemistry of *o*-Amino Aldehydes. Reaction of 4-Aminopyrimidine-5-carboxaldehyde and 1,3-Cyclohexanedione

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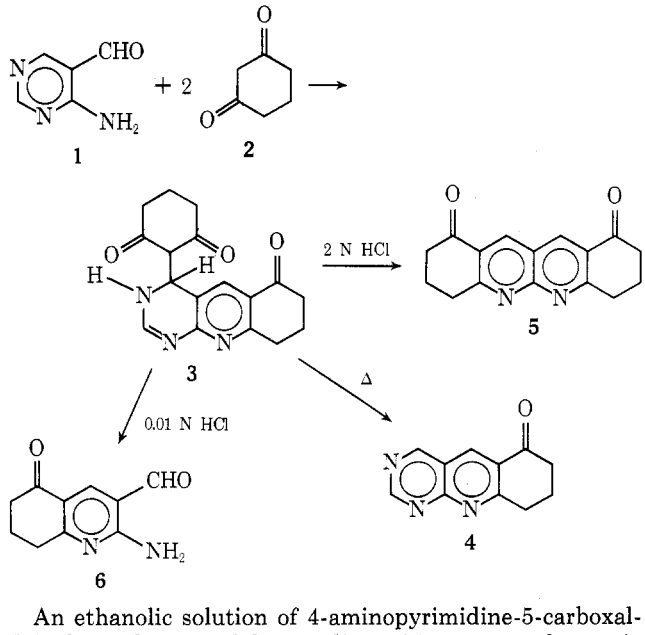
4-Aminopyrimidine-5-carboxaldehyde and 1,3-cyclohexanedione react in a 1:2 molar ratio with formation of an addition product in quantitative yield. Spectroscopic data and chemical evidence are in agreement with a 1,3-cyclohexanedione-substituted dihydropyrimidine structure (**3**). Its transformation in 2 N HCl results in a very efficient annelation sequence leading to four linearly fused rings (**5**) from monocyclic starting materials in high yield. Reactions in 0.01 N HCl, on the other hand, give 2-amino-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxaldehyde (**6**). The accumulation of functional groups in this simple molecular framework is noteworthy. Pyrolysis of **3** results in the elimination of the 1,3-cyclohexanedione moiety with formation of 6-oxo-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (**4**). The mechanism of the formation of **3** and its transformation into products is discussed.

The versatility of 4-aminopyrimidine-5-carboxaldehyde (**1**) in the synthesis of substituted 2-aminonicotinaldehydes and of polycondensed 1,8-naphthyridines was explored previously in this laboratory.[1,2] Friedländer condensations of this *o*-amino aldehyde and aromatic ketones led to the formation of the pyrido[2,3-*d*]pyrimidine system, which upon hydrolysis generated a new *o*-amino aldehyde functional group. This sequence, however, was not successful for aliphatic ketones such as acetone and cyclohexanone. In related investigations leading to 1,8-naphthyridines it was demonstrated that 2-aminonicotinaldehyde and cyclohexanediones condensed readily with formation of mono or bis condensation products depending on the molar ratio of the reagents.[3] It was hoped that a similar sequence with **1** would result in the formation of polycyclic systems containing the pyrido[2,3-*d*]pyrimidine moiety. Hydrolysis of this heterocyclic unit would then yield *o*-amino aldehydes for further elaboration of N-heterocyclic compounds. This paper deals with the reaction of 4-aminopyrimidine-5-carboxaldehyde (**1**) and 1,3-cyclohexanedione (**2**).



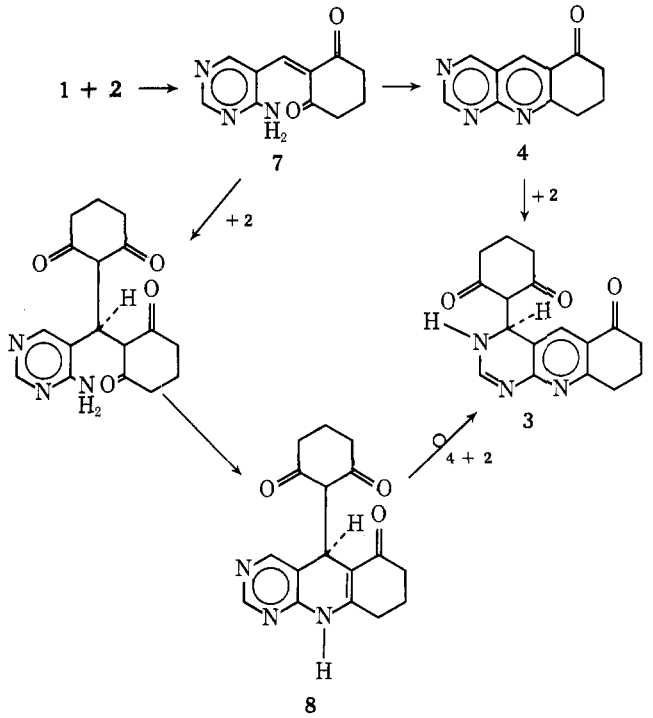
An ethanolic solution of 4-aminopyrimidine-5-carboxaldehyde and 1,3-cyclohexanedione in a 1:2 molar ratio formed a white, thick precipitate in quantitative yield after a few hours at 75 °C. Isolation proved it to be a 1:2 addition product of the amino aldehyde and the 1,3-dione, with loss of two molecules of water. Such addition products are typically formed in the reaction of aldehydes and **2** or dimedone. In the present case the second molecule of water would be lost by intramolecular Schiff base formation. A product of the same molar composition was formed in the reaction of **2** and 2-aminonicotinaldehyde.[3] Strong absorptions in the infrared spectrum for the NH and C=O functional groups are observed at 3200–3100, 1680, 1640, and 1555 cm−1.

Two structures, **3** and **8**, can be envisioned for the addition product. NMR data are consistent with structure **3**. A singlet at δ 6.37 is assigned to the methine proton in the dihydropyrimidine ring. In structure **8** the corresponding proton would be incorporated in a dihydropyridine system and would absorb at higher field, as observed previously in the addition product of **2** and 2-aminonicotinaldehyde.[3] A singlet at δ 8.41 is assigned to the proton on the pyridine ring in **3**, whereas the absorption at δ 7.89 agrees well for the amidine type proton.[4] As expected, both the NH and the enolic OH are exchanged in deuterated acetic acid. Chemical transformations of the 1:2 addition product are in agreement with its formulation as a dihydropyrimidine derivative (see below).

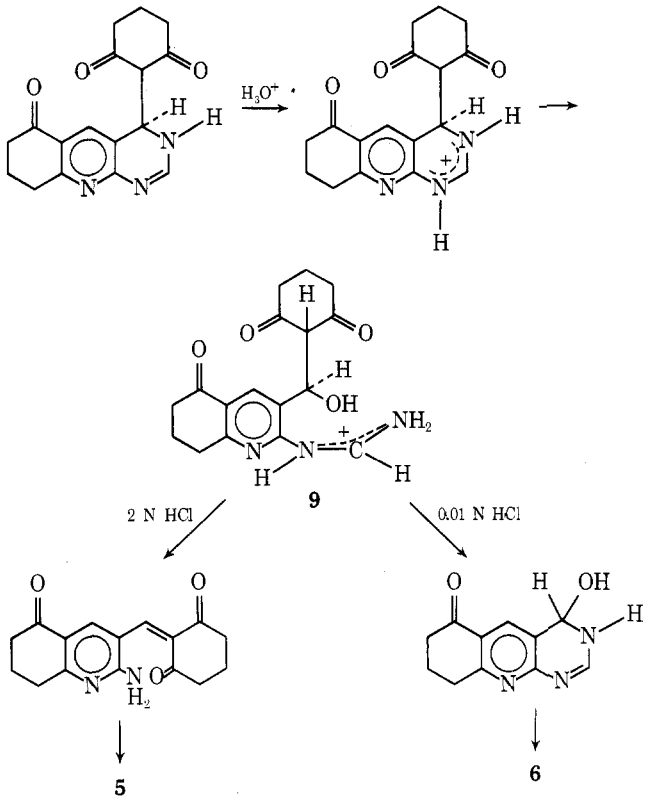
The formation of **3** results from intramolecular Schiff base formation on the α,β-unsaturated carbonyl system (**7**), followed by Michael addition of 1,3-cyclohexanedione on the electron-deficient pyrimidine ring of **4** (Scheme I). An alternative pathway, based on the known tendency of 1,3-cyclohexanediones to form 2:1 addition products with aldehydes, cannot be excluded. Michael addition of **2** on **7** followed by ring closure would lead to **8**, which would then rearrange to its thermodynamically more stable isomer **3**. All attempts to isolate **8** from the reaction mixture were unsuccessful.[5] The second mole of 1,3-cyclohexanedione required in both reaction sequences is readily supplied by retroaldol condensation.

The thermal decomposition of **3** was of interest in order to evaluate the mechanism proposed in Scheme I. Pyrolysis of **3**, carried out in a sublimation apparatus at 170 °C and 1 mmHg, resulted in a mixture of 6-oxo-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (**4**) and 1,3-cyclohexanedione (**2**), identified by their ir, NMR, and mass spectrum. This dissociation can be observed directly by introducing **3** in the direct inlet of a mass spectrometer. The molecular ions and typical fragmentation patterns of **2** and **4** were observed, whereas no peak at *m/e* 311, corresponding to **3**, was found. Dissolving the sublimate in ethanol resulted in rapid formation of a precipitate (**3**), identical in all respects with the product obtained from **1** and **2**. Fractional sublimation, followed by benzene extraction of the sublimate, gave pure **4** in 20% yield.[6] Addition of 1,3-cyclohexanedione to an ethanolic solution of this material resulted equally in the fast formation of **3** in quantitative yield. Nucleophilic additions

Scheme I



Scheme II



of dimedone on similar fused pyrimidines, such as pteridine[7] and quinazoline,[8] have been reported.

The tedious pyrolysis of 3, the low yield, and the difficulties encountered in the purification of 4, prompted us to investigate alternative pathways for the utilization of the pyrimidine moiety in 3. Refluxing a solution of 3 in 2 N HCl for a brief period of time gave 1,10-dioxo-1,2,3,4,7,8,9,10-octahydrodibenzo[*b,g*]-1,8-naphthyridine (5) in 90% yield. Analytical and spectroscopic data are in full agreement with the proposed structure. This facile transformation results in an efficient annelation reaction wherein four linearly fused rings are formed from readily available monocyclic reagents in a two-step synthesis in excellent yield. Refluxing a solution of 3 in 0.01 N HCl, on the other hand, gave a different product identified as 2-amino-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxaldehyde (6), in 70% yield. The accumulation of functional groups in a simple structural framework and the mild reaction conditions used for their introduction is noteworthy.

Apparently the 1,3-cyclohexanedione moiety in 3 is retained under the reaction conditions leading to 5, while it is lost during the synthesis of 6. The high-yield synthesis of 5 further substantiates the structural assignment of the 1:2 addition product 3. Indeed, an adduct of the alternative structure 8 would have to dissociate in order to form the diketone 5. However, the instability of 1,3-cyclohexanedione[9] in boiling strong acid would prevent its complete readdition to 4. Furthermore, formation of 4 under these reaction conditions would result in its rapid hydrolysis to 6. This was established by the quantitative hydrolysis of 4, obtained from 3 by pyrolysis, in boiling 2 N HCl. However, this o-amino aldehyde (6) was not formed under the reaction conditions employed for the synthesis of 5. Furthermore, experiments directed toward displacement of the 1,3-cyclohexanedione moiety in 3 by the analogous dimedone, carried out by adding an excess of dimedone to the reaction mixture, did not result in the incorporation of the latter in the final product (5), as evidenced by the absence of methyl absorptions in the NMR spectrum of the diketone. The transformations of 3 in acid medium further support the structural assignment made earlier for the 1:2 addition product of 4-aminopyrimidine-5-carboxaldehyde and 1,3-cyclohexanedione.

The products obtained from 3 at different pH are clearly determined by the acidity of the reaction medium. It is noteworthy that increasing acidity of the reaction mixture (from 0.01 to 2 N HCl) resulted in a gradual increase in the formation of 5 and a corresponding decreasing yield of 6. The concentration of 3 itself did not affect the type of product formed; in fact 5 and 6 can by synthesized at identical concentration of 3, as described in the Experimental Section. The key element in the mechanism of the facile transformations of 3 is the loss of the 1,3-dione moiety at intermediate pH and its incorporation into the final product at low pH. Protonation of 3 and subsequent hydrolytic cleavage of the pyrimidine moiety results in the formation of a resonance stabilized N-substituted formamidinium ion (9) (Scheme II). At low pH dehydration of the β-hydroxy ketone moiety leads to the formation of an α,β-unsaturated ketone. This sequence of reaction steps irreversibly retains the 1,3-cyclohexanedione moiety, since protonation of the basic formamidine system prevents the backward reaction (via Michael addition of the terminal amine on the α,β-unsaturated ketone). Hydrolysis of the formamidine moiety followed by ring closure results in the diketone 5. At pH ≃3, however, a free terminal amine in the amidine moiety of 9 is available for nucleophilic displacement to regenerate a pyrimidine system, with loss of the 1,3-dione moiety. The instability of 1,3-cyclohexanedione[9] in hot mineral acid makes this step essentially irreversible. Further hydrolysis of the newly formed pyrimidine nucleus results in the formation of 6 along well-established pathways.[10] The proposed mechanism leading to 6 implies that the product derived from the protonated formamidine should also be observed at intermediate pH. Indeed 5 was isolated in 20% yield from the reaction conducted in 0.01 N HCl. An alternative formulation for the sequence leading to 6 or its im-

mediate precursor would be retro-aldol condensation of the intermediate β-hydroxy ketone, followed by hydrolysis of the formamidine moiety.

Finally, it should be noted that the base-catalyzed reaction of **3** modeled after the transformations of Michael adducts with similar fused pyrimidines,[11] resulted in the formation of **5** in poor yield, while **6** was not obtained under these reaction conditions.

Experimental Section

General. NMR spectra were recorded with a Varian A-60 and/or Varian XL-100 with FT spectrometer using Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU6E instrument; infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. All melting points are uncorrected. Microanalyses were done by Instranal Laboratory Inc., Rensselaer, N.Y.

4-(2′,6′-Dioxocyclohexyl)-6-oxo-3,4,6,7,8,9-hexahydropyrimido[4,5-*b*]quinoline (3). A solution of 5.0 g (40 mmol) of 4-aminopyrimidine-5-carboxaldehyde (**1**) and 9.2 g (82 mmol) of 1,3-cyclohexanedione in 125 ml of absolute ethanol was heated for 6 h at 75 °C and then refluxed for 15 min. The white, voluminous precipitate was collected and washed extensively with ethanol to yield 12.75 g (100%) of analytically pure **3**: mp 255 °C dec; ir (Nujol) 3200–3100, 1680, 1640, 1555 (broad), 1420, 1345, 1310, 1290, 1260, 1225, 1150, 1070, 1000, 900, 850–800 (broad), 770, 735 cm^{-1}; NMR δ (CD_3COOD) 8.41 (s, 1) 7.89 (s, 1), 6.37 (s, 1) 3.00 (unresolved m, 2) 2.65–1.90 (unresolved m, 10).

Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.49; H, 5.47; N, 13.62.

6-Oxo-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (4). Thermal decomposition of **3** was conducted in an efficient sublimation apparatus at 170 °C and 1 mmHg. The sublimate was removed frequently. The combined fractions were extracted with benzene and the benzene evaporated to dryness. The residue was recrystallized from cyclohexane to yield **4** in 20% yield (decomposes without melting). An analytical sample was prepared by sublimation at 150 °C and 1 mmHg: ir (Nujol) 1680, 1590, 1535, 1430, 1250, 1225, 1195, 1175, 1125, 1075, 1000, 985, 935, 910, 885, 820, 805, 740 cm^{-1}; NMR δ ($CDCl_3$) 9.68 (s, 2, H2–H4) 9.1 (s, 1, H5) 3.48 (t, 2, H9, J_{H8-H9} = 6 Hz), 2.88 (t, 2, H7, J_{H7-H8} = 6 Hz), 2.38 (m, 2, H8); mass spectrum M^+ at *m/e* 199.

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.25; H, 4.61; N, 21.03

1,10-Dioxo-1,2,3,4,7,8,9,10-octahydrodibenzo[*b,g*]-1,8-naphthyridine (5). A solution of 5.0 g of **3** in 4 l. of 2 N HCl was refluxed for 45 min. The solution was cooled rapidly, neutralized (Na_2CO_3), and extracted thoroughly with ethyl acetate. The solvent was evaporated and the residue recrystallized from ethanol to yield 3.75 g (88%) of **5**, mp 245 °C dec. An analytical sample was prepared by sublimation at 120 °C and 1 mmHg: ir (Nujol) 1685, 1600, 1530, 1460, 1415, 1405, 1355, 1310, 1250, 1230, 1200, 1165, 1120, 1010, 1000, 970, 900, 810 cm^{-1}; NMR δ ($CDCl_3$) 8.86 (s, 2, H11, H12) 3.42 (t, 4, H4, H7, J_{H3-H4} = 6 Hz), 2.86 (t, 4, H2, H9, J_{H2-H3} = 6 Hz), 2.36 (m, 4, H3, H8); mass spectrum M^+ at *m/e* 266 (60%), 238 (100%).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.19; H, 5.32; N, 10.57

2-Amino-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxaldehyde (6). A solution of 5.0 g of **3** in 4 l. of 0.01 N HCl was refluxed for 45 min. The solution was cooled rapidly, neutralized, and extracted continuously with ether. The ether was evaporated and the residue washed with 25 ml of methanol (to remove diketone **5**) to yield 2.1 g (70%) of **6**, recrystallized from ethanol, mp 236–237 °C. An analytical sample was prepared by sublimation at 90 °C and 1 mmHg: ir (Nujol) 3360, 3260, 3100, 2720, 1655, 1620, 1585, 1535, 1400, 1350, 1265, 1195, 1160, 1120, 1000, 950, 900, 795, 770, 745, 720 cm^{-1}; NMR δ ($CDCl_3$) 9.88 (s, 1, HCO) 8.50 (s, 1, H4) 2.95 (t, 2, H8, J_{H7-H8} = 6 Hz), 2.65 (t, 2, H6, J_{H6-H7} = 6 Hz), 2.18 (m, 2, H7); mass spectrum M^+ at *m/e* 190 (80%), 162 (100%).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.27; N, 14.77.

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References and Notes

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(5) Even when excess **1** is used, **4** could not be isolated from the reaction medium; the only product observed was **3**. 1,3-Cyclohexanedione became the limiting reagent under these reaction conditions.
(6) It proved difficult to remove 1,3-cyclohexanedione from the sublimate, even by resublimation. Any remaining **2** reacted rapidly with **4** in organic solvents with re-formation of **3**. This is responsible for the low yield.
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(10) See ref 1 and references cited therein.
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