Acrolein as a Synthon for 6-Hydroxytetrahydropyrimidines, 1,4(1,6)-Dihydropyrimidines, and Pyrimidines[1]

Alexander L. Weis* and Dov Zamir

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

Received December 8, 1986

A series of 6-hydroxytetrahydropyrimidines and 1,4(1,6)-dihydropyrimidines bearing a phenyl, methyl, or amino group at position 2, as well as the unsubstituted (parent) compounds of these families, were synthesized by reaction of acrolein with several amidines and guanidine. Acrolein containing 0.2–0.5% hydroquinone as a stabilizer and dry acetone as a solvent were found to be the optimal conditions for inhibition of polymerization and consequently gave the highest yields of 6-hydroxy-1,4,5,6-tetrahydropyrimidines. The latter were effectively dehydrated by using freshly activated molecular sieves in dimethoxyethane. The low yield of parent dihydropyrimidine is due to the intrinsic instability of this compound, since the high yield of 4-phenyl- and 4-phenyl-2-methyl-1,4-(1,6)-dihydropyrimidine indicated that the formamidine and acetamidine free bases used were stable enough under the conditions employed.

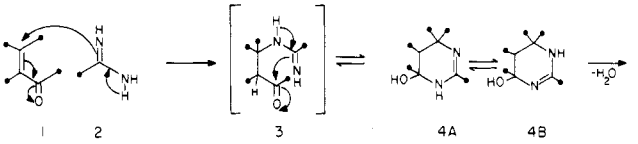
The reaction of readily available α,β-unsaturated aldehydes or ketones with compounds containing an amidine moiety[2] is an attractive [3 + 3]-fragment approach to the pyrmidine ring; it was used as early as 1899.[3] However, in only a few fortuitous cases, with specific α,β-unsaturated ketones, was the condensation successful.[3-6] About a decade ago, we developed a new one-pot synthesis using α,β-unsaturated carbonyl compounds and amidines[7] (or guanidine)[8] that enabled the facile preparation of various substituted pyrimidine derivatives. Moreover, a detailed study of this reaction enabled the preparation of a series of novel, reduced pyrimidines that are intermediates in the one-pot process.

A proposed mechanism for this reaction is given in Scheme I, in which the first step involves Michael-type 1,4-addition to give intermediate **4a**, which undergoes intramolecular ring closure to the cyclic carbinolamine derivative and then is dehydrated to the desired dihydropyrimidine. Thus, we also prepared 6-hydroxytetrahydropyrimidines,[9-12] as well as dihydropyrimidines.[10-13] In parallel, Austrian workers have reported on a series of reactions of α,β-unsaturated ketones with guanidines.[14]

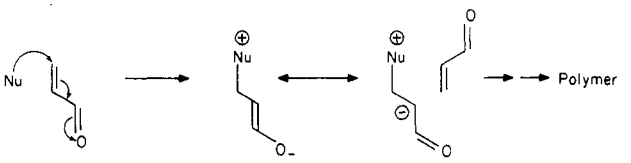
However, all attempts to use this method to prepare the parent pyrimidine or its reduced dihydro- and tetrahydropyrimidine derivatives from acrolein have failed.[3,5,6] We report here on the successful synthesis of parent hydroxytetrahydro- and dihydropyrimidines by use of acrolein and various amidines and guanidines.

When initiating this work, we supposed that the failure of previous attempts to synthesize pyrimidines from acrolein was probably the result of fast base-catalyzed polymerization of the acrolein, a well-known phenomenon.[15] The reaction between acrolein and strong organic bases, such as amidine and guanidine, was extensively examined in our laboratories during the past decade. According to experience gained, liquid acrolein, upon exposure to small amounts of the amidine or guanidine bases, polymerizes rapidly and exothermally. All attempts to slow polymerization by lowering temperature similarly hindered the condensation process, and no pyrimidine compounds were detected in the reaction mixture. We thus were most probably facing competition between at least two concurrent processes, polymerization and Michael-type addition. Moreover, the desired parent products, even if formed, were expected to be labile.

Scheme I



Scheme II



In our approach to control the polymerization reaction, we recalled the known mechanism of base-catalyzed

*To whom correspondence should be addressed at Research Laboratories, Eastman Kodak Co., Rochester, NY 14650.

(1) Dihydropyrimidines. 13. Part 12: Weis, A. L.; Vishkautsan, R.; Frolow, F. *J. Heterocycl. Chem.* **1986**, *23*, 705. This work is a part of: Zamir, D. M.Sc. Thesis, The Weizmann Institute of Science, Rehovot, Israel, 1984. For a preliminary communication, see: Weis, A. L.; Frolow, F.; Zamir, D.; Bernstein, M. *Heterocycles* **1984**, *22*, 657. This work was presented in part at the 9th International Congress of Heterocyclic Chemistry, Tokyo, Japan, 1983.

(2) Weis, A. L. *Adv. Heterocycl. Chem.* **1985**, *38*, 1.

(3) Traube, W.; Schwarz, R. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3163.

(4) Ruhemann, S. *J. Chem. Soc. Trans.* **1903**, *83*, 1371.

(5) Dodson, R. M.; Seyler, J. K. *J. Org. Chem.* **1951**, *16*, 461. Silversmith, E. F. *J. Org. Chem.* **1962**, *27*, 4090.

(6) Weis, A. L. Ph.D. Thesis, Institute of Organic Chemistry, Siberian Branch of the USSR Academy of Science, Novosibirsk, 1975.

(7) Weis, A. L.; Shyrina, V. M.; Mamaev, V. P. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1975**, 144. Weis, A. L.; Mamaev, V. P. *Ibid.* **1975**, 149.

(8) Mamaev, V. P.; Weis, A. L. *Khim. Geterotsikl. Soedin.* **1975**, 1555. Weis, A. L.; Mamaev, V. P. *Izv. Sib. Otd. Adad. Nauk SSSR, Ser. Khim. Nauk* **1975**, 91. Weis, A. L.; Mamaev, V. P. *Khim. Geterotsikl. Soedin.* **1976**, 1425.

(9) Weis, A. L.; Mamaev, V. P. *Khim. Geterotsikl. Soedin.* **1977**, 647. Weis, A. L.; Frolow, F. *J. Org. Chem.* **1984**, *49*, 3635.

(10) Weis, A. L. *Synthesis* **1985**, 528.

(11) Weis, A. L.; Frolow, F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 83.

(12) Weis, A. L.; Vishkautsan, R. *Isr. J. Chem.*, in press.

(13) Weis, A. L.; Mamaev, V. P. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1975**, 198. Weis, A. L.; Frolow, F. *J. Chem. Soc., Chem. Commun.* **1982**, 89; *Heterocycles* **1982**, *19*, 493.

0022-3263/87/1952-3421$01.50/0

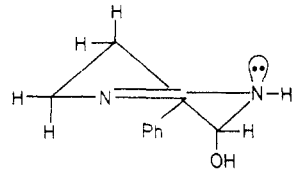


Figure 1. "Anomeric effect" in 6-hydroxy-2-phenyl-1,4,5,6-tetrahydropyrimidine.

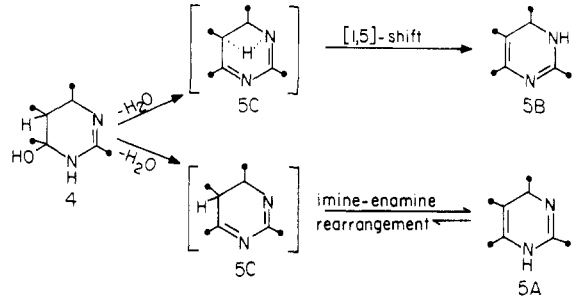
acrolein polymerization (Scheme II). It is clear that continuation of polymerization depends upon the existence of a negatively charged carbon in position 2, a species that, under the reaction conditions utilized, cannot be quenched. (Possible proton donors, such as the existing amidine molecules, are simply not acidic enough to transfer a proton to the carbanion.) We sought to develop conditions under which, on the one hand, polymerization does not take place, but, on the other hand, amidinic addition can still occur without competition from salt formation. To this end we examined a series of stronger proton donors with a wide range of pK_a's in a variety of organic solvents with various polarities. The best donor/solvent combination turned out to be hydroquinone in acetone.

Since the parent hydroxytetrahydro- and dihydropyrimidinic compounds were considered to be unstable, we utilized extremely mild reaction conditions and monitored the reaction very closely. On the basis of our accumulated past experience,[10-12] we chose to carry out the synthesis in two steps: synthesis of the hydroxytetrahydropyrimidine from amidine and acrolein, followed by dehydration to yield dihydropyrimidine. Furthermore, to simplify the task, we chose initially to study the reaction using a model compound with aromatic substitution in position 2, which should yield fairly stable tetrahydro- and dihydropyrimidine compounds. Only later did we attempt the less stable 2-alkyl, 2-amino, and completely unsubstituted materials.

In a preliminary communication, the preparation of 6-hydroxy-2-phenyl-1,4,5,6-tetrahydropyrimidine from stabilized acrolein and benzamidine was described.[1] Optimization of reaction conditions was carried out by varying solvents (acetone, benzene, ethanol, *tert*-butyl alcohol Me_2SO, DMF) and temperature (room temperature, −20 °C, −78 °C), as well as by altering the ratios of starting materials and the quantities of various stabilizers of acrolein.

The best results (96% yield) were obtained by slow addition of acrolein in acetone (stabilized by 0.2% hydroquinone) at −5 °C to stoichiometric amounts of benzamidine free base in acetone. The product that precipitated was a fairly stable white solid. However, on prolonged exposure to moist atmosphere at room temperature, it deteriorated into an amorphous, sticky, brownish yellow mass. Recrystallization from acetone gave colorless single crystals. Since carbinolamines are generally unstable, it was interesting to take advantage of this relatively stable material to use X-ray diffraction to determine its structure.[1] The structural analysis confirms that the product is a six-membered heterocycle containing the carbinolamine moiety. It has a half-chair conformation in which the hydroxyl group occupies a pseudoaxial position, and the hydrogen on nitrogen is pseudoequatorial. This situation exemplifies the "anomeric effect" in heteronitrogenous systems and can be explained by stereoelectronic control due to free-electron pairs on nitrogen and oxygen, antiperiplanar to the C–N bond (Figure 1).

Scheme III



The crystallographic analysis also shows that hydrogen bonds exist between the hydroxylic hydrogen of one molecule and the sp^3-hybridized nitrogen of its neighbor. This fact explains the solubility of this material in protic and polar solvents and its relative insolubility in aprotic and apolar media.

Following successful preparation of relatively stable **4** in high yields, we turned to the second and critical stage of the two-step synthesis, namely dehydration. For this reaction, various techniques are available, including (a) the use of an apolar solvent with azeotropic removal of water formed by use of the Dean–Stark apparatus and (b) employment of molecular sieves along with acid or base catalysis, as is common for Schiff-base preparation.

Refluxing the 6-hydroxytetrahydropyrimidine in benzene in the Dean–Stark apparatus gave an oily mixture, the ^1H NMR examination of which produced a spectrum characteristic of 2-phenyl-1,4(1,6)-dihydropyrimidine. However, chromatographic purification of this material on silica gel failed, most probably because of its basic, unstable character. Therefore, only low yields were obtained. The action of molecular sieves was also investigated by use of the following solvents from room temperature to their boiling points: benzene, ether, acetonitrile, toluene, DMF, Me_2SO, and dimethoxyethane. In most of the solvents, optimum dehydration occurred by refluxing the carbinolamine for 8 h in the presence of freshly activated 4-Å molecular sieves. Filtration of unreacted **4** followed by evaporation of solvent and drying under high vacuum for 2 h gave a yellow crystalline solid that was identified by spectral data and elemental analysis as a 2-phenyldihydropyrimidine. Dimethoxyethane was found to be an especially suitable solvent for this process because, along with its high volatility, it readily dissolves dihydropyrimidine, but not tetrahydropyrimidine. Therefore, the former could be prepared, analytically pure, as the lone product of dehydration without need for additional workup.

Mechanistically, it is possible that the initial products of dehydration are 4,5-dihydro isomers (which were too fleeting to be detected). Then, via thermally allowed [1,5]-sigmatropic hydrogen shift or imine–enamine tautomerism, they are transformed to 1,4- or 1,6-dihydropyrimidine (Scheme III). Gaussian 80 calculations also indicate that the energy of 1,4- (**5a**) and 1,6-dihydropyrimidines (**5b**) is lower than that of the 4,5 isomer (**5c**).

Moreover, we have prepared single crystals of 2-phenyldihydropyrimidine, the X-ray diffraction of which showed that the unit cell contained a 1:1 mixture of the 1,4 and 1,6 isomers. These data were further substantiated by IR spectra of the powdered crystals in KBr exhibiting two nearly equal absorption bands at 1638 cm^{-1} (1,6 form)

(14) Wendelin, W.; Harler, A. *Monatsh. Chem.* **1979**, *105*, 382, 563, 775; **1975**, *106*, 1479; **1976**, *107*, 133. Wendelin, W.; Schermanz, K.; Kersl, T. *Monatsh. Chem.* **1983**, *114*, 717. Wendelin, W.; Schermanz, K. *J. Heterocycl. Chem.* **1984**, *21*, 65. Wendelin, W.; Schermanz, K.; Schweiger, K.; Fuchsgruber, A. *Monatsh. Chem.* **1983**, *114*, 1371.

(15) Fisher, R. F. In *Acrolein*; Smith, C. W., Ed.; Wiley: New York, 1962; p 225.

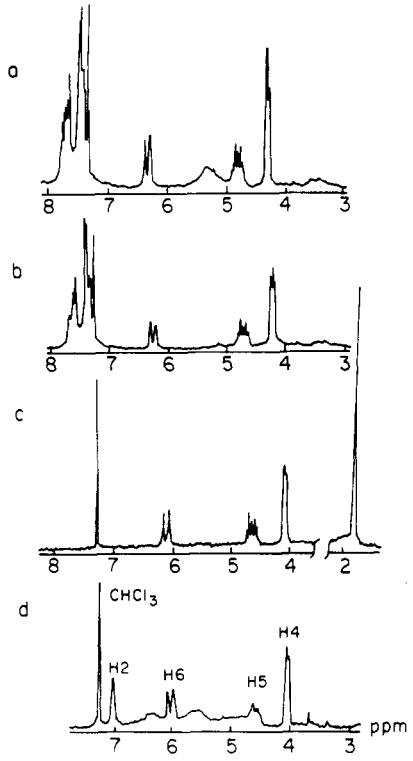


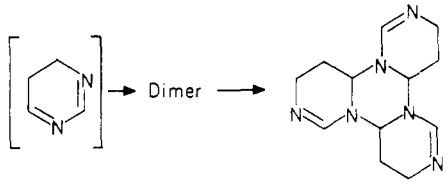
Figure 2. Fast-exchange-limit ^1H NMR spectra (80 MHz) of several 1,4(1,6)-dihydropyrimidines in $CDCl_3$: (a) 2-phenyldihydropyrimidine; (b) (a) + D_2O; (c) 2-methyldihydropyrimidine; (d) unsubstituted ("parent") dihydropyrimidine.

and at 1682 cm^{-1} (1,4 form). These two isomers were also observed in solution by ^1H NMR, in which the population of the two tautomers was very dependent upon solvent polarity. For instance, the ^1H NMR spectrum (Figure 2) of the carefully purified 2-phenyldihydropyrimidine **5a** in "ultrapure" $CDCl_3$[16] (270 MHz, 0.005 M, −56 °C) consists of two sets of signals, which were assigned as follows: [1,4-dihydropyrimidine (tautomer A)] 6.25 (NH), 6.16 (H^6), 4.61 (H^5), 4.32 (2 H^4) ppm; [1,4-dihydropyrimidine, (tautomer B, which is numerated as 3,4-dihydropyrimidine for the sake of convenient comparison)] 6.43 (H^6), 5.14 (NH), 5.0 (H^5), 4.25 (2 H^4) ppm. The population of B was about 20% higher than that of A in $CDCl_3$, whereas in Me_2SO-d_6 the ratio of tautomers changes, favoring formation of A. Moreover, the NH signals of both tautomers move in the 8–9 ppm region in Me_2SO-d_6 which indicates formation of the hydrogen-bonded associates with the solvent.

In progressing to the synthesis of 2-methyldihydropyrimidines, an initial difficulty was encountered, namely the extreme instability of the acetamidine free-base starting material. Attempts to carry out the reaction in benzene, toluene, or xylene gave unsatisfactory yield, owing to polymerization of acrolein. The best conditions eventually found were addition, under argon, of dry, cold acetone to a very concentrated solution of acetamidine free base in cold methanol, with a final volume ratio of acetone to methanol of 1:40–50. Dropwise addition of acrolein solution produced 6-hydroxy-2-methyltetrahydropyrimidine at a purity of ~85% and a calculated yield of 76%. Identification of the product was based upon ^1H NMR spectra and MS measurements.

The extremely hygroscopic nature of this intermediate was an additional problem. Upon exposure to the atmosphere, the material immediately turned amorphous and sticky, changing color to brown and then starting to decompose. It was also impossible to utilize conventional separation or purification techniques. The intermediate, for example, is very basic, rendering chromatographic separation impossible. Purification via salt formation and crystallization was also excluded because the salts formed were hygroscopic and could not be recrystallized. As a result, the only practical way to proceed was to utilize the crude mixture on hand.

Scheme IV



The formerly used conditions, namely reflux in dimethoxyethane (glyme) and freshly activated 4-Å molecular sieves, gave the best results among those checked. It should be noted that dehydration of 2-methyl-6-hydroxy-1,4,5,6-tetrahydropyrimidine was significantly slower than that of the 2-phenyl derivative. After 16 h of reflux, the unreacted starting material was filtered, and after evaporation of solvent, a yellow oil was produced, exhibiting the expected ^1H NMR spectrum and mass spectrum (MS) of the dihydropyrimidine. After evaporation and sublimation under high vacuum, the white crystals of 2-methyl-1,4-(1,6)-dihydropyrimidine were prepared, the formula of which was further confirmed by spectral and elemental analysis.

Even more severe problems were encountered in the preparation of unsubstituted dihydropyrimidine and 6-hydroxytetrahydropyrimidine. Formamidine is not stable as a free base even in solution. Because it is a strong base, formamidine catalyzes the polymerization of acrolein, particularly in aprotic, apolar solvents such as benzene and toluene. (This is the main reason why earlier attempts to prepare unsubstituted dihydropyrimidines failed.) Two methods to overcome these difficulties were eventually designed, the first involving use of *tert*-butyl alcohol as a solvent, and the second, acetone/methanol (50:1) at −17 °C. In both solvents, the parent 6-hydroxy-1,4,5,6-tetrahydropyrimidine was prepared in ~90% purity, though the yields in acetone/methanol were consistently superior. Attempts to further purify the product by either chromatography or salt formation were not successful. The product is a yellow powder that turns into a brown, sticky tar upon short exposure to moist air. In a closed container under argon, the compound is stable for a couple of weeks. It forms extremely hygroscopic salts with $CuSO_4$, H_2PtCl_6, $AgNO_3$, and picric acid.

Dehydration of the parent hydroxytetrahydropyrimidine is extremely sensitive, and many of our attempts have failed. Nevertheless, we found that 24 h of reflux in dimethoxyethane in the presence of molecular sieves, type 3-Å, followed by filtration and evaporation of the solvent, gave a yellow oil that exhibited the ^1H NMR signals expected for dihydropyrimidine (Figure 2) as well as its expected IR and UV spectra. Because of high instability, the compound was not obtained pure, despite various approaches to separation. However, upon heating the oil on a water bath in high vacuum, a white amorphous material was sometimes formed at the top of the vessel. This was taken up in dry $CDCl_3$ and found by quantitative ^1H NMR to contain 85% of the unsubstituted dihydropyrimidine. The material was unstable and decomposed completely within a few days, giving along with a signal

(16) Weis, A. L. *Tetrahedron Lett.* **1982**, *23*, 449. Weis, A. L.; Porat, Z.; Luz, Z. *J. Am. Chem. Soc.* **1984**, *106*, 8021.

at 7.2 ppm only aliphatic signals in ^1H NMR. Certainly, one can easily propose dimerization or trimerization of the intermediate of 4,5-dihydropyrimidines, as was observed with dihydropyridazine[17] (Scheme IV).

Therefore, it is quite possible that low yields of the 2-methyl and unsubstituted derivatives are a result of instability of free-base acetamidine, and particularly formamidine (compared with that of benzamidine and guanidine). In order to understand the difficulties in obtaining 2-methyl-6-hydroxytetrahydropyrimidines and their 2-unsubstituted congener, we synthesized analogues with the phenyl substituent at position 4. They were obtained by reaction of cinnamic aldehyde with the corresponding amidine. The 6-hydroxy-2-methyl-4-phenyl- and the 6-hydroxy-4-phenyl-1,4,5,6-tetrahydropyrimidine derivatives were prepared in high yields by the procedures described above. They were white solids, much more stable than the non-phenyl-substituted analogues, even though they were quite hygroscopic. Therefore, low yield in the case of acrolein was not due to instability of the starting free bases of acetamidine and foramamidine. It was found that these materials are dehydrated quantitatively to the corresponding dihydropyrimidine under previously described conditions.

The oxidation reactions of dihydropyrimidines and tetrahydropyrimidines were also studied. For instance, $KMnO_4$ in cold acetone oxidized 2-phenyldihydropyrimidine rapidly to 2-phenylpyrimidine (**6a**) in near quantitative yield, while under the same conditions 6-hydroxy-2-phenyl-1,4,5,6-tetrahydropyrimidine gave 6-oxo-2-phenyl-1,4,5,6-tetrahydropyrimidine (**7a**).

Because of the reported successful preparation of the guanidine free base in *tert*-butyl alcohol,[18] we began working with this solvent, with the same excellent results, and 2-amino-6-hydroxytetrahydropyrimidine was synthesized in 83% yield from acrolein and guanidine in *tert*-butyl alcohol and/or acetone. The resultant yellowish precipitate was extremely hygroscopic and very difficult to handle.

Experimental Section

Melting points were taken on a modified Fisher-Johns apparatus fitted with a thermocouple and digital thermometer (Lauda) and are uncorrected. ^1H NMR spectra were recorded with Varian FT-80A and WH-270 Bruker Fourier transform spectrometers. Microanalyses were performed by the microanalytical laboratory at the Weizmann Institute of Science.

The free base of benzamidine or acetamidine was prepared from the corresponding hydrochloride and sodium methoxide in dry methanol, followed by fast filtration of the precipitated sodium chloride under dry argon and evaporation of the solvent at room temperature under high vacuum. Acetamidine hydrochloride, mp 164–166 °C (acetonitrile), and formamidine hydrochloride were prepared by standard techniques. The free base of formamidine (very unstable) was prepared in situ from equimolar amounts of formamidine hydrochloride and sodium *tert*-butoxide and used after fast filtration under a dry atmosphere of the sodium chloride formed.

6-Hydroxy-1,4,5,6-tetrahydropyrimidines. General Procedure. A solution of the appropriate α,β-unsaturated carbonyl compound **1** (0.02 mol) in dry acetone (15 mol) was added dropwise (30 min) at 0–10 °C to a solution of amidine **2** (0.02 mol) in dry acetone (50 mL) with effective magnetic stirring under a dry inert atmosphere. Following the addition, the mixture was stirred for another 30 min, after which the cooling bath was removed and the mixture was stirred at room temperature, the course of the reaction being monitored by TLC. A white solid started to precipitate after the first hour. When the starting materials disappeared almost completely (TLC), the white copious precipitate was filtered and washed with dry diethyl ether. The mother liquid was evaporated to dryness, the crude residue triturated with a small amount of dry diethyl ether, and the additional portion of undissolved **3** filtered. The white solids (**3**) were combined, dried, and recrystallized.

Dihydropyrimidines. General Procedure. The hydroxytetrahydropyrimidines **4** (0.02 mol) were dehydrated in an aprotic solvent (50–70 mL; usually glyme, dimethylformamide, or acetonitrile) and freshly activated 4-Å molecular sieves (2–4 g). The transformation to dihydropyrimidine can be followed visually (the insoluble **4** transforms to soluble **5**). The reaction is very clean and evaporation of the solvent alone gives an analytically pure dihydropyrimidine product **5**.

6-Hydroxy-2-phenyl-1,4,5,6-tetrahydropyrimidine (4a). In dry acetone under nitrogen atmosphere 5.8 g (0.05 mol) of the free base of benzamidine was stirred and cooled to −5 °C in an ice/salt bath. The amidine produced a white suspension in the solvent. A solution of 3 g of stabilized acrolein in 50 mL of acetone was added dropwise (50 min). After 1 h, the white precipitate was filtered and the filtrate was warmed to room temperature. A second batch was filtered after 12 h, but to a lower degree of purity. The combined 8.4 g of product (mp 153–156 °C) was recrystallized from acetone, affording 7.4 g (84%) of **4a**: mp 156–158 °C; ^1H NMR (Me_2SO-d_6/$CDCl_3$, 2:1) 1.49–1.67 (dt, 2 H, J = 3.5, 5.6 Hz), 3.39 (t, 2 H, J = 5.6 Hz), 4.94 (t, 1 H, J = 3.5 Hz), 7.28–7.70 (m, 5 H) ppm; IR (KBr) 1083, 1308, 1491, 1597, 1618, 2985, 3300 cm^{-1}; UV (EtOH) λ_{max} 235 nm (ϵ 4540); MS, m/e 176 (M^+), 175, 158, 147, 131, 104, 77. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.81. Found: C, 68.24; H, 6.82.

6-Hydroxy-2-methyl-1,4,5,6-tetrahydropyrimidine (4b). Sodium methoxide was prepared under nitrogen atmosphere by reaction of 1.1 g of sodium (0.047 mol) in 50 mL of dry methanol, cooled to −10 °C in an ice/salt bath. Acetamidine hydrochloride (4.7 g) was added, and the mixture was stirred for 30 min. NaCl was filtered and the solvent evaporated under high vacuum (0.5 mmHg) at 30 °C. A white paste of free-base acetamidine in 5 mL of methanol was obtained, and it was removed from the evaporator under N_2 atmosphere, after which 200 mL of dry cool acetone was added. The mixture was stirred while cooling in an ice/salt bath, until a white suspension was obtained. A solution of stabilized acrolein (3.3 g in 50 mL of acetone) was added dropwise (1 h). A white precipitate appeared and was filtered under Ar atmosphere, giving a white-ivory powder (3.7 g). The degree of purity was 85%, according to the NMR spectrum (68% of theoretical yield). The product is very hygroscopic and unstable in water. It is insoluble in acetone, hexane, petroleum ether, methylene chloride, chloroform, and carbon tetrachloride. In water, methanol, ethanol, DMF, and Me_2SO, the product is soluble: ^1H NMR (Me_2SO-d_6/$CDCl_3$ 2:1) 1.66 (s, 3 H), 1.45–1.53 (m, 2 H), 3.12 (t, 2 H, J = 6.7 Hz), 4.74 (t, 1 H, J = 3.5 Hz) ppm; IR (KBr) 3402, 3292, 3226, 1633, 1620, 1534, 1434, 1303 cm^{-1}; UV (EtOH) λ_{max} 220 nm (ϵ 2380); MS, m/e 114 (M^+), 110, 97, 69, 56, 40.

6-Hydroxy-1,4,5,6-tetrahydropyrimidine (4c). Procedure A. Under Ar atmosphere and with heating, 0.99 g (0.025 mol) of potassium reacted with dry *tert*-butyl alcohol. Then 2.1 g (0.025 mol) of formamidine hydrochloride was dissolved in 15 mL of butanol and the resultant mixture added at room temperature to the potassium/*tert*-butyl alcohol solution. A white precipitate was obtained and filtered after 1 h. To the filtrate was added a solution of 1.4 g (0.025 mol) of stabilized acrolein in 30 mL of *tert*-butyl alcohol dropwise (30 min) while being stirred. A white precipitate began to appear within several minutes. After 30 min, filtration gave a white-ivory solid, which was rinsed with acetonitrile and dried under high vacuum; yield 0.5 g (20%).

Procedure B. A solution of the free base of formamidine in a mixture of acetone/methanol (1:40–50) was prepared according to the procedure utilized in preparing 6-hydroxy-2-methyl-1,4,5,6-tetrahydropyrimidine, using 6.9 g of formamidine hydrochloride (0.085 mol) and 200 mL of acetone. The suspension was cooled to −17 °C in an ice/salt bath and stirred. A solution of

(17) Bandlish, B. K.; Brown, J. N.; Timberlake, J. W.; Trefonas, L. M. *J. Org. Chem.* **1973**, *38*, 1102. Dodge, J.; Hedges, W.; Timberlake, J. W.; Trefonas, L. M.; Majeste, R. J. *J. Org. Chem.* **1978**, *43*, 3615. Wildi, E. A.; VanEngen, D.; Carpenter, B. K. *J. Am. Chem. Soc.* **1980**, *102*, 7994.
(18) Kim, Y. H.; Yoon, C. M.; Lee, N. J. *Heterocycles* **1981**, *16*, 49.
(19) Kametani, T.; Kano, S. *Yakugaku Zasshi* **1963**, *83*, 1043.

stabilized acrolein (4.8 g, 0.085 mol) in 20 mL of acetone was added dropwise (30 min), and a white solid precipitated immediately. Filtration after cooling for 2 h gave 7.36 g of the product. An additional 4.2 g of the product can be isolated from the mother liquor. The degree of purity was estimated at ca. 85% by quantitative ^{1}H NMR methods: ^{1}H NMR (Me_2SO-d_6/$CDCl_3$, 2:1) 1.61–1.70 (m, 2 H), 3.16 (t, 2 H, J = 6.1 Hz), 4.76 (t, 1 H, J = 3.2 Hz), 7.13 (s, 1 H) ppm; UV (EtOH) λ_{max} 206 nm (ϵ 1142); MS, m/e 100, (M^+), 96, 81, 80, 58, 54.

6-Hydroxy-4-phenyl-1,4,5,6-tetrahydropyrimidine (4d). The free base of formamidine (2.2 g, 0.05 mol) in a mixture of acetone/methanol (1:40–50) was prepared according to the above procedure B. After the mixture was cooled to −17 °C, a solution of distilled cinnamaldehyde, 7.2 g (0.05 mol) in 100 mL acetone, was added dropwise (1 h), after which the mixture was warmed to room temperature and stirred for 14 h. Evaporating the solvent (60 °C) left a yellow crude residue. Treatment with ether caused precipitation of a white hygroscopic solid, which was filtered off under Ar: mp 119–120 °C; ^{1}H NMR (Me_2SO-d_6/$CDCl_3$, 2:1) 7.30 (s, 5 H, aromatic), 4.69 (t, 1 H, J = 3 Hz), 4.29 (dd, 1 H, J = 11.5 Hz), 1.78 (dt, 1 H, J = 3 Hz), 1.38 (dt, 1 H, J = 11.3 Hz), 1.09 (d, 1 H, J = 1.8 Hz) ppm.

6-Hydroxy-2-methyl-4-phenyl-1,4,5,6-tetrahydropyrimidine (4e). The free base of acetamidine was prepared according to the procedure described above from 2 g of acetamidine hydrochloride (0.02 mol) and 60 mL of dry acetone (Ar, −50 °C). The suspension was stirred, and a solution of 2.7 g (0.02 mol) of cinnamaldehyde in 30 mL of dry acetone was added dropwise (30 min). After 24 h, the solvent was evaporated at room temperature. The yellow crude residue was treated with 30 mL of ether, and the additional precipitate was filtered (1.2 g): total yield 1.7 g, 46%; ^{1}H NMR 7.31 (s, 5 H, aromatic), 4.81 (t, 1 H, J = 2.5 Hz), 4.45 (dd, 1 H, J = 4.1, 12.2 Hz), 1.46 (dt, 1 H, J = 4.0, 12.2 Hz), 1.92 (s, 3 H) ppm.

2-Amino-6-hydroxy-1,4,5,6-tetrahydropyrimidine (4f). The free base of guanidine was prepared by a procedure similar to that used for formamidine. To a stirred solution of guanidine (0.02 M) was added dropwise acrolein (0.02 M) stabilized with hydroquinone, keeping the temperature below −20 °C. The product starts to precipitate after approximately 0.5 h. TLC analysis after 2 h shows disappearance of the acrolein. The beige precipitate was filtered off (~0.5 g); additional 1.4 g of product was obtained by dilution of the mother liquor with 300 mL of dry ether. All the manipulations with **4f** have to be carried out in a dry atmosphere, preferably under an inert atmosphere. In an attempt to open the flask to atmosphere, **4f** became a brownish sticky product, from which after 20 min only 10% of **4f** could be regenerated by treatment with dry ether: ^{1}H NMR (Me_2SO-d_6/$CDCl_3$, 2:1) 1.54 (m, 2 H), 3.17 (t, 2 H, J = 6.2 Hz), 4.67 (t, 1 H, J = 6.2 Hz) ppm; MS, m/e 115 (M^+); high-resolution MS 115.1264 ($C_{11}H_9N_3O$). Anal. Calcd for $C_4H_9N_3O$ (115.1355): C, 41.73; H, 7.88; N, 36.50. Found: C, 41.37; H, 7.68; N, 36.13.

2-Phenyl-1,4(1,6)-dihydropyrimidine (5a). Dry nitrogen (oxygen free) was bubbled for 10 min through 280 mL of 1,2-dimethoxyethane (glyme), 3 g of 6-hydroxy-2-phenyl-1,4,5,6-tetrahydropyrimidine was added, and the mixture was stirred with heating. Molecular sieves (4 Å, 60 g) were added, and the suspension was heated at 85 °C. After 8 h, the reaction mixture was cooled to room temperature, the molecular sieves were filtered off, and the solvent was evaporated at 30 °C under vacuum. The yellow crude residue was placed under high vacuum to remove volatile residues. Yellow crystals of **5a** (1.45 g, 54% theoretical yield) were obtained. The product was dried over KOH under vacuum. Needlelike yellow crystals (mp 131–132 °C) are formed when the product is recrystallized from hexane: ^{1}H NMR 7.30–7.70 (m, 5 H, aromatic), 6.31 (dt, 1 H, J = 11.6, 1.4 Hz), 4.8 (dt, 1 H, J = 11.6, 3.0 Hz), 4.23 (dd, 2 H, J = 3.0, 1.4 Hz) ppm; IR (KBr) 3437, 3048, 2809, 1676, 1638, 1539, 1305 cm^{-1}; UV (EtOH) λ_{max} 246 nm (ϵ 9976), 312 (2876); MS, m/e 158, (M^+), 156, 151, 110, 107, 80, 79. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.70; H, 6.20. Found: C, 75.90; H, 6.30.

2-Methyl-1,4(1,6)-dihydropyrimidine (5b). According to the procedure for 2-phenyl-1,4(1,6)-dihydropyrimidine, 2.5 g (0.02 mol) of 6-hydroxy-2-methyl-1,4,5,6-tetrahydropyrimidine was treated in 300 mL of dimethoxyethane and 60 g of molecular sieves (4 Å) in reflux, under Ar atmosphere, for 4 h. After the mixture was cooled to room temperature and filtered, the solvent was evaporated (30 °C, water vacuum), and a yellow crude residue remained. Sublimation gave white needlelike crystals, mp 82 °C. The elemental analyses of the white crystals and the yellow crude residue gave identical results: total weight 0.44 g (23%) of the theoretical yield); ^{1}H NMR 6.14 (dt, 1 H, J = 7.6, 1.1 Hz), 4.69 (dt, 1 H, J = 7.5, 3.2 Hz), 4.10 (dd, 2 H, J = 3.1, 1.0 Hz), 1.93 (s, 3 H) ppm; IR (KBr) 3461, 3447, 3425, 2312, 3200, 3000, 1700, 1670 cm^{-1}; IR ($CDCl_3$) (range 1600–1700 cm^{-1}) 1700, 1640, 1600 cm^{-1}; MS, m/e 96, (M^+), 95, 80, 79, 73, 64. Anal. Calcd for $C_5H_8N_2$: C, 62.49; H, 8.38. Found: C, 62.45; H, 8.32.

Unsubstituted Dihydropyrimidine (5c). To 500 mL of dimethoxyethane and 20 g of molecular sieves (3 Å) was added 500 mg of 6-hydroxy-1,4,5,6-tetrahydropyrimidine, and the mixture was heated to reflux under Ar according to the previous procedure. The solution turned yellow after 30 min. After 18 h, the solution was filtered, and the solvent was evaporated at 30 °C under water vacuum. A yellow crude residue was obtained, the ^{1}H NMR spectrum of which showed a mixture of the desired dihydropyrimidine with other materials. Heating the mixture to 100 °C, while cooling the walls of the bulb, gave off a very small amount of white vapor, which was taken in $CDCl_3$ under Ar and identified by NMR spectrum to be unsubstituted dihydropyrimidine. The product was unstable, and after 2 days in the tube, it decomposed or polymerized: ^{1}H NMR ($CDCl_3$) 7.1 (s, 1 H), 6.20 (d, 1 H, J = 5.9 Hz), 4.60 (m, 1 H), 4.07 (m, 2 H) ppm.

6-Oxo-2-phenyl-1,4,5,6-tetrahydropyrimidine (6a). To a stirred solution of 100 mg of 6-hydroxy-2-phenyl-1,4,5,6-tetrahydropyrimidine in 5 mL of acetone was added a saturated solution of $KMnO_4$ in acetone dropwise until a steady color was obtained. The mixture was filtered and the solvent evaporated. To the remaining black solid was added ether, and the mixture was stirred for 15 min. Filtration and evaporation of the ether gave the product as white crystals: mp 145 °C (lit.[13] mp 145 °C); ^{1}H NMR ($CDCl_3$) 7.75–7.42 (m, 5 H, aromatic), 3.89 (t, 2 H, J = 6.1 Hz), 2.57 (t, 2 H, J = 6.1 Hz) ppm.

2-Phenylpyrimidine (7a). One hundred milligrams of 2-phenyl-1,4(1,6)-dihydropyrimidine was treated with $KMnO_4$ in acetone according to the previous procedure. The product was obtained as white crystals in 98% yield: mp 37 °C (lit.[20] mp 38 °C); ^{1}H NMR ($CDCl_3$) 8.78 (d, 2 H, J = 4.9 Hz), 8.51–8.38 (m, 2 H, aromatic), 7.52–7.42 (m, 3 H, aromatic), 7.14 (t, 1 H, J = 2.4 Hz) ppm.

(20) Wagner, R. M.; Jutz, C. *Chem. Ber.* 1971, *104*, 2975.