

**2-Amino-4-hydroxy-1,4,5,6-tetrahydropyrimidine,
Its Preparation and Reaction¹⁾**EJI SUZUKI, SHOJI INOUE,^{2a)} and TOSHIO GOTO^{2b)}*Faculty of Pharmacy, Meijo University^{2a)} and Department
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2-Amino-4-hydroxy-1,4,5,6-tetrahydropyrimidine (I), the cyclic guanidine moiety of tetrodotoxin, and its derivatives were prepared to examine their chemical and physical properties in comparison with the toxin and its derivatives.

1. Oxidation of I with chromium trioxide-pyridine gave β -alacreatinine (III).
2. Etherification of I with alcohols in the presence of acid catalyst afforded the corresponding 4-alkoxy derivatives (IV and V).
3. Acetylation of I under various conditions gave N-acetyl derivative (VI), O-acetyl derivative (VII), and N-acetyl-1,6-dihydro derivative (VIII) respectively.
4. Interconversion of the acetyl derivatives is also described.

The structure of 2-amino-4-hydroxy-1,4,5,6-tetrahydropyrimidine (I) is found in tetrodotoxin, which is a strongly poisonous substance isolated from a fish, *Spherooides*. Present study is to prepare the compound (I) and its derivatives and to examine their chemical behaviors and physical properties in comparison with those of tetrodotoxin and its derivatives, since the toxin exhibits many interesting and curious reactions, some of which would be attributable to the cyclic guanidine moiety.

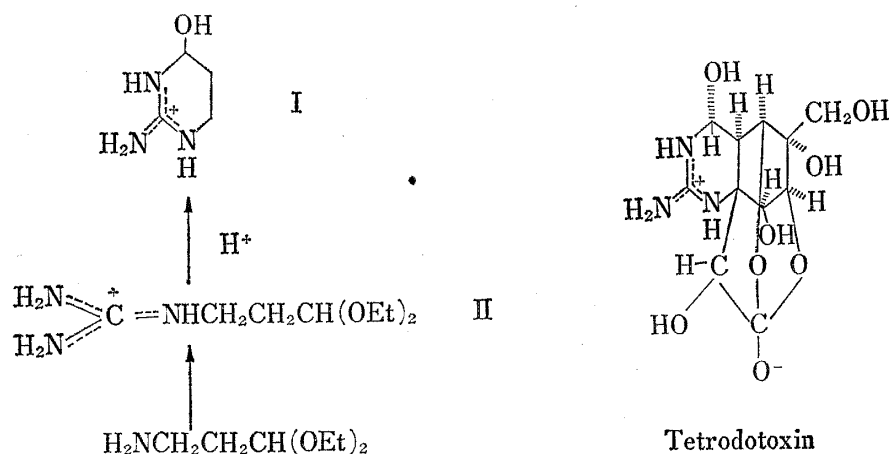


Chart 1

β -Aminopropionaldehyde diethyl acetal³⁾ prepared from β -chloropropionaldehyde diethyl acetal was treated with S-methylisothiurea to give β -guanidinopropionaldehyde diethyl acetal (II), which is recrystallized as its picrate. When being refluxed with a catalytic amount of aqueous hydrochloric acid, the acetal (II) is smoothly hydrolyzed to give 2-amino-4-hydroxy-1,4,5,6-tetrahydropyrimidine hydrochloride (I) without isolation of the intermediate aldehyde.

1) Tetrodotoxin. XII. Preceding paper (Part XI): *Tetrahedron*, **21**, 2059 (1965).

2) Location: a) *Yagotourayama, Tempaku-cho, Nagoya*. b) *Furo-cho, Chikusa-ku, Nagoya*.

3) Badische Aniline and Soda-Fabrik, *Chem. Abstr.*, **47**, 5426 (1953).

The structure of I was confirmed as follows. Elemental analysis indicates the molecular formula, $C_4H_{10}ON_3Cl$. It shows no absorption maximum in its UV spectrum but exhibits a pair of strong absorption bands in its IR spectrum at 1666 and 1628 cm^{-1} , which are characteristic to the N,N' -disubstituted guanidino group⁴⁾: The NMR spectrum (in D_2O) also suggests the cyclic structure; a triplet at 5.17 ppm ($1H$, $J=3$ c/s), which is assigned to the proton on the carbon bearing the hydroxyl and guanidino group; a multiplet centered at 1.98 ($2H$); and a quartet at 3.42 ($2H$, $J=7.0$ and 5.5 c/s).

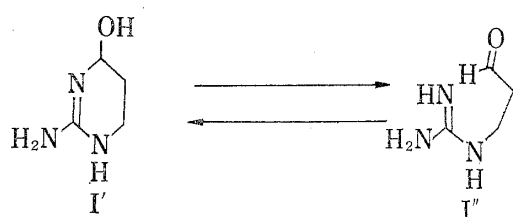


Chart 2

The compound (I) has a pK_a' at 11.8 , which is attributable to the guanidino group. Although I does not reduce the Fehling reagent, it shows a positive Sakaguchi reaction (for monosubstituted guanidine), indicating that the above equilibrium may exist (I' and I'').

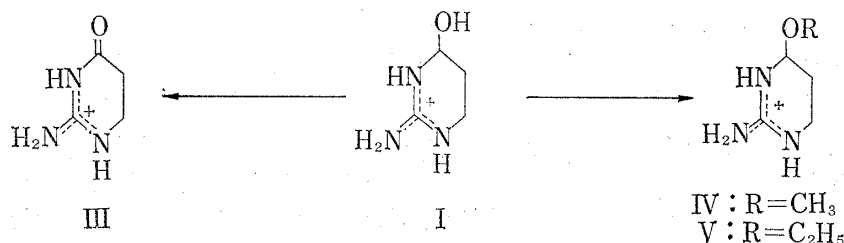


Chart 3

Oxidation of the compound (I) with chromium trioxide-pyridine gave the corresponding amide, β -alacreatinine (III, as picrate) identical with that obtained from β -alacreatine by cyclization with concentrated hydrochloric acid.⁵⁾

Etherification of the hydroxyl group in I was easily achieved by standing the compound in methanol containing 1% hydrochloric acid or *p*-toluenesulfonic acid at room temperature to afford 2-amino-4-methoxy-1,4,5,6-tetrahydropyrimidine hydrochloride (IVa) or *p*-toluenesulfonate (IVb). The presence of the methoxy† group is evident from NMR spectrum of IVa, which shows a sharp singlet at 3.34 ppm (in D_2O).

When ethanol was used instead of methanol, 2-amino-4-ethoxy-1,4,5,6-tetrahydropyrimidine *p*-toluenesulfonate (V) was obtained. Such ease of etherification at C₄ position has been observed in the case of tetrodotoxin.⁶⁾

Since the acetylation of tetrodotoxin in a variety of conditions gave complicated results,^{6,7)} acetylation of the compound (I) was examined using several different conditions. When the compound (I) was treated with acetic anhydride and pyridine at room temperature, 2-acetamido-4-hydroxy-1,4,5,6-tetrahydropyrimidine hydrochloride (VI) was produced. Its IR spectrum shows the presence of an acetyl (1721 cm^{-1}) and a guanidino group (1672 and 1611 cm^{-1}).⁴⁾ In the NMR spectrum (in $CDCl_3$), it exhibits a three-proton signal of an acetyl group at 2.27 ppm. Incidentally, pentaacetylanhydroepitetrodotoxin shows a signal at 2.27 ppm

- 4) a) T. Goto, K. Nakanishi, and M. Ohashi, *Bull. Chem. Soc. Japan*, **30**, 723 (1957); b) S. Takahashi, T. Goto, and Y. Hirata, *Nippon Kagaku Zasshi*, **85**, 586 (1964).
5) E. Mulder, *Ber.*, **8**, 1266 (1875). cf. I. S. Bengelsdorf, *J. Am. Chem. Soc.*, **75**, 3138 (1953).
6) K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, K. Sasaki, C. Tamura, and O. Amakasu, *Chem. Pharm. Bull. (Tokyo)*, **12**, 634 1367 (1964).
7) a) T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Nippon Kagaku Zasshi*, **85**, 667 (1964); b) K. Tsuda, M. Kawamura, and R. Hayatsu, *Chem. Pharm. Bull. (Tokyo)*, **8**, 257 (1960); c) R.B. Woodward, *Pure Appl. Chem.*, **9**, 49 (1964); d) H.S. Mosher, F.A. Fuhrman, H.D. Buchwald, and H.G. Fischer, *Science*, **144**, 1100 (1964).

for the N-acetyl group.^{7a)} pK_a' of the compound (VI) is 7.6, which is close to those of acetyl guanidine derivatives.

Acetylation of I with acetic anhydride in acetic acid containing *p*-toluenesulfonic acid at room temperature gave rise to white amorphous 4-acetoxy-2-amino-1,4,5,6-tetrahydropyrimidine *p*-toluenesulfonate (VII). From the IR spectrum, it evidently has a guanidino (1682 and 1620 cm^{-1}) and a carbonyl group (1747 cm^{-1}), whose absorption appears at a higher frequency by more than 25 cm^{-1} comparing with that of acetamido derivative (VI). This suggests that the acetyl group is introduced into the hydroxyl group of I. The NMR spectrum (in CDCl_3) exhibits the acetyl signal at 2.02 ppm, and the $\text{C}_4\text{-H}$ signal at 5.94, which appears at a lower field by about 0.54 ppm than that of 2-acetamido-4-hydroxy compound (VI), indicating that the compound (VII) has an acetoxy rather than an acetamido group. This compound (VII) is considerably unstable to acids and bases. Thus, deacetylation occurs during titration for measurement of pK_a' , and hence a pK_a' 4.82, which is attributable to acetic acid formed by hydrolysis, was obtained.

When the 2-amino-4-hydroxy compound (I) was acetylated with acetic anhydride at 125–135° for two hours, dehydration occurred and 2-acetamido-1,6-dihydropyrimidine hydrochloride (VIIIa) was obtained. The same compound was also prepared by treatment of I with acetic anhydride and pyridine at 73–77°. The IR spectrum reveals the existence of an N-acetyl group (1724 cm^{-1}) and a guanidino group (1692 and 1605 cm^{-1}). $\Delta\nu$ value (87 cm^{-1}) between the two guanidine bands suggests the presence of a double bond in the molecule,^{4b)} which is supported by the UV absorption at 280.5 $\text{m}\mu$ ($\log \epsilon$, 3.34). An alternate structure VIII' having a double bond at 3,4-position can be eliminated by inspection of its NMR spectrum (in D_2O). Thus, besides of the signal for the acetyl group (singlet at 2.21 ppm), signals for $-\text{CH}_2\text{-CH=CH-}$ system is observed; quartet at 4.18 ppm (2H, $J=3$ and 1.7 c/s), a pair of triplets at 6.19 ppm (1H, $J=8$ and 3 c/s), and a pair of triplets at 5.19 ppm (1H, $J=1.7$ and 8 c/s). Its pK_a' value (7.50) is similar to that of VI.

Treatment of the hydrochloride (VIIIa) with diluted aqueous ammonia at room temperature gave the free base, 2-acetamido-1,6-dihydropyrimidine (VIIIb). The double bond of 2-acetamido-1,6-dihydropyrimidine (VIII) is easily hydrated to form 2-acetamido-4-hydroxy compound (VI). Thus, treatment of 2-acetamido compound (VIIIa) with 0.01% aqueous hydrochloric acid at 78–85° for 24 hours gave white crystals which were found to be identical with VI by comparison of the UV and IR spectra. On the other hand, when a solution of the free base (VIIIb) in two moles of aqueous sodium hydroxide was warmed at 58–68° for three hours, the product was 2-amino-4-hydroxy compound (I). Similar addition reactions of the

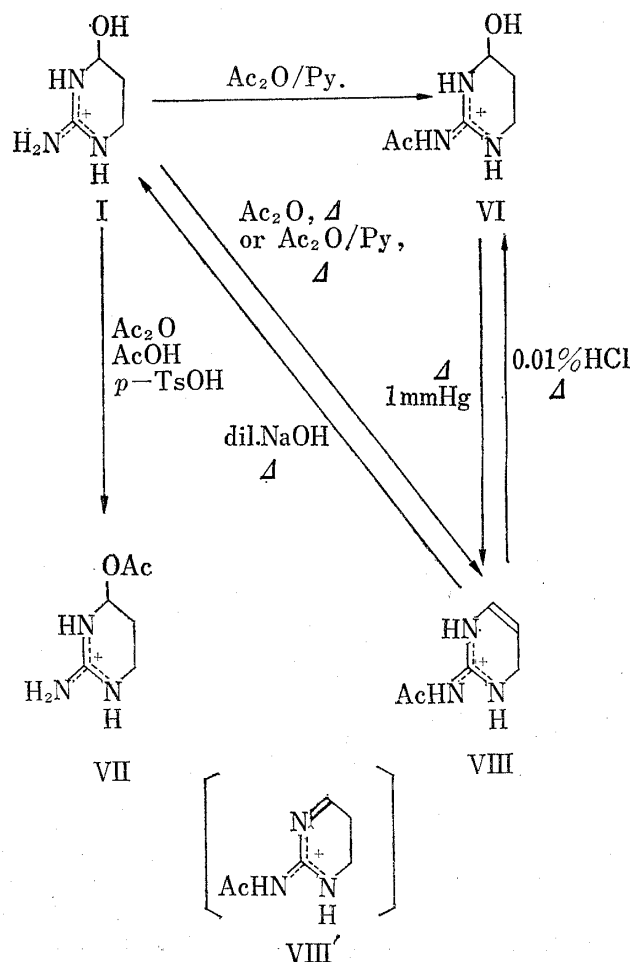


Chart 4. Interconversion of Acetyl Derivatives

double bond have been observed: a solution of VIIIa in water or chloroform consumed one mole of bromine giving rise to the bromohydrin, 2-acetamido-5-bromo-4-hydroxy-1,4,5,6-tetrahydropyrimidine hydrobromide (IX). Absence of UV absorption indicates disappearance of the double bond. The structure is also confirmed by means of NMR spectrum which shows a signal at 4.5 ppm for one proton at C₅ bearing bromine atom, as well as the other signals at the expected positions. Although the configuration is not proved, the *trans* addition is assumed. Reaction of the compound (VIIIa) with N-bromosuccinimide in methanol at room temperature for three days or under reflux for two hours afforded 2-acetamido-5-bromo-4-methoxy-1,4,5,6-tetrahydropyrimidine (X, as picrate), which was also prepared from the bromohydrin (IX) by treatment with a catalytic amount of hydrobromic acid in methanol. The ease of etherification also suggests that the hydroxyl group in IX is attached at C₄ rather than at C₅.

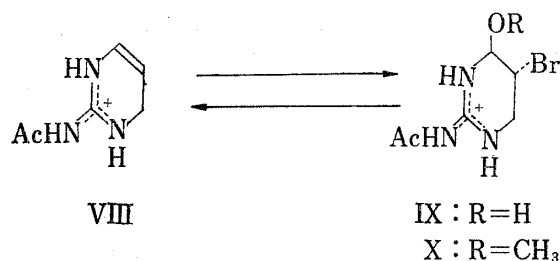


Chart 5

These addition reactions are somewhat unusual since the intermediate carbonium ion must have its positive charge at C₄, which is adjacent to the positively charged guanidinium group. Conversely, in spite of its positive charge, guanidinium group has an electron-donating effect to the adjacent carbon atom. On the other hand, elimination of hydroxyl and bromine

in the bromohydrin (IX) was effected by reducing with zinc powder and 0.01% hydrochloric acid to give 2-acetamido-1,6-dihydropyrimidine (VIIIc, as picrate).

Dehydration of 2-acetamido-4-hydroxy compound (VI) could be achieved by heating at 120–130° under vacuum (1 mm Hg) for 18 hours, the product which was purified by chromatography on silica gel was proved to be identical with 2-acetamido-1,6-dihydropyrimidine (VIIIa), although dehydration of 2-amino-4-hydroxy compound (I) was unsuccessful.

Experimental⁸⁾

β -Guanidinopropionaldehyde Diethyl Acetal Picrate (II)—S-Methylisothiurea sulfate (41 g) was dissolved in 150 ml of H₂O and neutralized with calculated amount of 20% NaOH under cooling. The mixture was added to a solution of 43.4 g of β -aminopropionaldehyde diethyl acetal⁹⁾ in 200 ml of H₂O. After the reaction mixture was allowed to stand at room temperature for 2 days, the guanidino compound was collected as its picrate by adding an equivalent mole of aq. solution of picric acid to the reaction mixture. Yellow needles, mp 136–137°, were obtained by recrystallization from H₂O. Yield, 88.8 g.

This compound gave a negative Dragendorff test, but a positive Sakaguchi reaction. *Anal.* Calcd. for C₁₄H₂₂O₉N₆: C, 40.19; H, 5.30; N, 20.09. Found: C, 39.97; H, 5.37; N, 20.27.

2-Amino-4-hydroxy-1,4,5,6-tetrahydropyrimidine Hydrochloride (I)—To a solution of 13.1 g of II in the minimum amount of H₂O was added 1.3 ml of 10% HCl. The mixture was refluxed for 10 min, treated with a small amount of charcoal and cooled. The yellow crystals separated were collected by filtration and washed with cold water. A small amount of the product was obtained from the mother liquor. Recrystallization from H₂O afforded yellow needles, mp 163–164° (decomp.). *Anal.* Calcd. for C₁₀H₁₂O₃N₂: C, 34.89; H, 3.51; N, 24.42. Found: C, 35.13; H, 3.50; N, 24.53.

2-Amino-4-hydroxy-1,4,5,6-tetrahydropyrimidine picrate (4 g) thus obtained was triturated with 3 equivalent moles of 3% HCl. After a while, picric acid was removed by extracting with ether. The H₂O layer was brought to pH 6 by treatment with Amberlite IR-4B resin (amine type). The resulting aq. solution was treated with a small amount of Norit and evaporated to dryness under reduced pressure at 40–45°. The residue was dissolved in a minimum amount of methanol and precipitated by addition of ether to produce colorless crystals. Recrystallization from MeOH-ether gave the product I as colorless needles, mp 115–116° (decomp.) (in a sealed tube). Yield, 1.2 g. This compound was hygroscopic. pK_a' 11.8. Sakaguchi reaction:

8) All melting points are uncorrected. The spectra were recorded on the following instruments: IR (in KBr pellets), Nihon-Bunko DS-402G and IR-S; UV, Beckman DK-2; NMR, Varian A-60 using TMS as an internal standard (TMS=0 ppm). The pK_a's were measured by Radiometer TTT-1 pH meter with an automatic recorder.

positive; Fehling test: negative. IR cm^{-1} : 3500—3100, 1688, 1628, 1165, 1082, 984. NMR(D_2O): H_5 1.98 ppm (2H, multiplet), H_6 3.42 (2H, quartet, $J_{5,6}=5.5$ and 7.0 c/s) and H_4 5.17 (1H, triplet, $J_{4,5}=3$ c/s). *Anal.* Calcd. for $\text{C}_4\text{H}_{10}\text{N}_3\text{Cl}$: C, 31.58; H, 6.66; N, 27.58. Found: C, 31.68; H, 6.64; N, 27.72.

Oxidation of 2-Amino-4-hydroxy-1,4,5,6-tetrahydropyrimidine Hydrochloride (I)—To a suspension of 300 mg of I in 4 ml of pyridine was added a solution of 300 mg of CrO_3 in 6 ml of pyridine under cooling. After standing the reaction mixture at room temperature for one hour, it was concentrated to almost dryness at 40—45° under reduced pressure. The residue, after washing with ether, was taken up in MeOH to remove insoluble material. Evaporation of the solvent gave a viscous oil which was treated with aq. picric acid. Recrystallization of the picrate from H_2O gave yellow needles (74 mg), mp 254—256° (decomp.), which was identical with β -alacreatinine picrate by comparison of IR and the mixed mp with an authentic specimen.

2-Amino-4-methoxy-1,4,5,6-tetrahydropyrimidine Hydrochloride (IVa)—A solution of 500 mg of I in 10 ml of MeOH containing 1% HCl was allowed to stand at room temperature for 4 days. The pH of the reaction mixture was adjusted to 6 by treating with Amberlite IR-4B resin (amine type). Removal of the solvent at room temperature under reduced pressure gave a viscous oil which was dissolved in a minimum amount of MeOH and precipitated by addition of ether to give colorless feather-like crystals, mp 112—113° (decomp.). Yield of the crude product of IVa was 450 mg. It was considerably hygroscopic. Sakaguchi and Dragendorff tests were negative. IR cm^{-1} : 2823, 1676, 1624, 1168, 1090, 1082. NMR (D_2O): H_5 2.06 ppm (2H, multiplet), H_6 ca. 3.34 (2H, multiplet), CH_3O 3.41 (3H, singlet) and H_4 4.77 (1H, triplet, $J_{4,5}=3$ c/s). NMR (THF): H_5 2.02 ppm (2H, multiplet), H_6 ca. 3.4 (2H, multiplet), CH_3O 3.46 (3H, singlet) and H_4 5.25 (1H, triplet $J_{4,5}=3$ c/s). *Anal.* Calcd. for $\text{C}_5\text{H}_{12}\text{ON}_3\text{Cl}$: C, 36.26; H, 7.30; N, 25.37. Found: C, 36.12; H, 7.30; N, 25.36.

2-Amino-4-methoxy-1,4,5,6-tetrahydropyrimidine *p*-Toluenesulfonate (IVb)—A solution of 42 mg of I in 2 ml of MeOH containing 60 mg of *p*-toluenesulfonic acid monohydrate was kept at room temperature for 3 days. After evaporation to dryness, the residue was washed with ether and purified by recrystallization from MeOH. Colorless needles, mp 141—142° (decomp.). Yield, almost theoretical. *Anal.* Calcd. for $\text{C}_{12}\text{H}_{19}\text{O}_4\text{N}_3\text{S}$: C, 47.81; H, 6.35; N, 13.94. Found: C, 47.71; H, 6.39; N, 14.14.

2-Amino-4-ethoxy-1,4,5,6-tetrahydropyrimidine *p*-Toluenesulfonate (V)—This compound was prepared from I and EtOH by the same way as described above IVb. Colorless needles from EtOH, mp 161—162° (decomp.) *Anal.* Calcd. for $\text{C}_{13}\text{H}_{21}\text{O}_4\text{N}_3\text{S}$: C, 49.50; H, 6.71; N, 13.32. Found: C, 49.75; H, 6.56; N, 13.62.

2-Acetamido-4-hydroxy-1,4,5,6-tetrahydropyrimidine Hydrochloride (VI)—To a suspension of 305 mg of I in 4 ml of pyridine was added 1 ml of acetic anhydride with stirring, and the mixture was allowed to stand for 20 hr at room temperature. The pale yellow solution was concentrated to almost dryness at room temperature under reduced pressure. The residue was dissolved in MeOH and precipitated by addition of ether. For further purification the precipitate was dissolved in CHCl_3 and reprecipitated with ether to yield 338 mg of 2-acetamido derivative (VI) as white needles, mp 124—125°. Sakaguchi and Dragendorff tests were negative: $\text{p}K_a'$ 7.6. IR cm^{-1} : 3302, 3200, 1721, 1672, 1611, 1246, 1218, 1092. NMR (CDCl_3): H_5 2.08 ppm (2H, multiplet), CH_3CO 2.27 (3H, singlet), H_6 3.58 (2H, multiplet) and H_4 5.40 (1H, broad). *Anal.* Calcd. for $\text{C}_6\text{H}_{12}\text{O}_2\text{N}_3\text{Cl}$: C, 37.22; H, 6.25; N, 21.70. Found: C, 37.12; H, 6.45; N, 21.74.

4-Acetoxy-2-amino-1,4,5,6-tetrahydropyrimidine *p*-Toluenesulfonate (VII)—To a solution of 310 mg of I in 4 ml of AcOH was added dropwise with stirring a mixture of 400 mg of *p*-toluenesulfonic acid monohydrate in 4 ml of acetic anhydride under cooling. After standing for 3 days at room temperature, the reaction mixture was concentrated to almost dryness and the residue obtained was washed with ether. The resulting amorphous solid was dissolved in the minimum amount of CHCl_3 and precipitated with ether. Repeated reprecipitation gave a white amorphous solid, mp 112—113° (decomp.). Sakaguchi and Dragendorff tests were negative. A solution of 3.389 mg of VII in 2 ml of 0.01 N KOH was titrated with 0.1 N HCl to give $\text{p}K_a'$ 4.82, corresponding to that of acetic acid. IR cm^{-1} : 1747, 1682, 1620, 1126, 1034, 1011. NMR (CDCl_3): H_5 ca. 1.95 ppm (2H, broad, overlap with CH_3CO), CH_3CO 2.02 (3H, singlet), CH_3 in *p*-TsO⁻ 2.37 (3H, singlet) H_6 3.36 (2H, broad) and H_4 5.94 (1H, broad). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{19}\text{O}_5\text{N}_3\text{S}$: C, 47.38; H, 5.81; N, 12.76. Found: C, 47.19; H, 6.01; N, 12.74.

2-Acetamido-1,6-dihydropyrimidine Hydrochloride (VIIIa)—Method A: A suspension of 159 mg of I in 0.8 ml of acetic anhydride was heated at 125—135° for 2 hr. After the reaction mixture was evaporated to dryness, the residue was washed with ether. Recrystallization from EtOH gave colorless plates, mp 221—222° (decomp.). Yield, 146 mg. Sakaguchi and Dragendorff tests were negative. $\text{p}K_a'$ 7.50. $\text{UV}_{\text{max}}^{\text{H}_2\text{O}}$ $\text{m}\mu$ (log ϵ): 220 (3.92), 280.5 (3.40). IR cm^{-1} : 3200, 2880, 1724, 1692, 1605, 1405, 1255, 1185. NMR (D_2O): CH_3CO 2.21 ppm (3H, singlet), H_6 4.18 (2H, quartet, $J_{4,6}=1.7$ c/s, $J_{5,6}=3.1$ c/s), H_5 5.19 (1H, two triplets, $J_{4,5}=8$, $J_{5,6}=3.1$ c/s) and H_4 6.19 (1H, two triplets, $J_{4,5}=8$ c/s, $J_{4,6}=1.7$ c/s). *Anal.* Calcd. for $\text{C}_6\text{H}_{10}\text{ON}_3\text{Cl}$: C, 41.03; H, 5.74; N, 23.93. Found: C, 41.01; H, 5.61; N, 23.98.

Method B: To a suspension of 251 mg of I in 3 ml of pyridine was added 3 ml of acetic anhydride, and the mixture was warmed at 73—77° for 3 hr. After the solution was concentrated to almost dryness, the residue was taken up in CHCl_3 and chromatographed on silica gel. The product obtained from the eluates with CHCl_3 was recrystallized from EtOH to give the acetyl derivative (VIIIa) as colorless plates, mp 218—220° (decomp.), undepressed on admixture with the product obtained above.

Method C: To a suspension of 100 mg of I in 3 ml of pyridine was added with stirring 0.3 ml of acetyl chloride under cooling, and the mixture was kept for 4 days at room temperature. The reddish brown reaction mixture was treated in the same way as in method B. Colorless plates thus obtained were identical with VIIIa.

2-Acetamido-1,6-dihydropyrimidine (VIIIb)—To a solution of 200 mg of VIIIa in 0.6 ml of H₂O was added 0.15 ml of 28% NH₄OH to give white precipitate. The mixture was kept at room temperature for overnight. The deposited solid was collected and washed with H₂O. The filtrate was extracted with CHCl₃ and dried over Na₂SO₄. Removal of the solvent left another crop of colorless crystals. The combined products were recrystallized from acetone to give colorless needles, mp 158–159° (decomp.), which gave a negative Beilstein test. Yield, 111 mg. UV_{max}^{meo} mμ (log ε): 241 (4.16), 278 (3.59). *Anal.* Calcd. for C₆H₉ON₃: C, 51.78; H, 6.52; N, 30.19. Found: C, 51.59; H, 7.30; N, 29.93.

Hydration of 2-Acetamido-1,6-dihydropyrimidine (VIIIa)—A solution of VIIIa in excess of 0.01% HCl was heated at 78–85° for 24 hr. After the excess acid was neutralized with NaHCO₃, the mixture was evaporated to dryness, and the residue was taken up in EtOH. Evaporation of the solvent gave white crystals. The UV and IR spectra were identical with those of an authentic sample of 2-acetamido-4-hydroxy-1,4,5,6-tetrahydropyrimidine (VI).

Hydrolysis of VIIIa—VIIIa (128 mg) was dissolved in 2 ml of 2 N NaOH and the solution was diluted with 10 ml of H₂O. After warming at 58–68° for 2 hr, aq. solution of picric acid was added to the reaction mixture and kept overnight at room temperature. The separated yellow needles were collected. Yield, 94 mg as picrate. The IR spectrum of the picrate was identical with that of 2-amino-4-hydroxy-1,4,5,6-tetrahydropyrimidine picrate obtained during preparation of I.

2-Acetamido-5-bromo-4-hydroxy-1,4,5,6-tetrahydropyrimidine (IX)—To a solution of 300 mg of VIIIa in 20 ml of H₂O was added one mole of aq. Br₂ with stirring. After evaporation of the solvent to dryness, the residual amorphous solid was recrystallized from acetone-benzene to give colorless needles of IX, mp 152–153°. Yield 475 mg. Sakaguchi and Dragendorff tests were negative. pK_a' 7.03. IR cm⁻¹: 3210, 2970, 1715, 1672, 1625, 1355, 1062, 718. NMR (D₂O): CH₃CO 2.26 ppm (3H, singlet), H₆ 3.97 (2H, multiplet), H₅ ca. 4.5 (1H, multiplet, overlap with DOH) and H₄ 5.33 (1H, broad). *Anal.* Calcd. for C₆H₁₁O₂N₃Br₂: C, 22.55; H, 3.15; N, 13.15. Found: C, 22.80; H, 3.54; N, 13.74.

2-Acetamido-5-bromo-4-methoxy-1,4,5,6-tetrahydropyrimidine Picrate (X)

Method A: Two drops of AcOH and 224 mg of N-bromosuccinimide was added at once to a solution of VIIIa in 10 ml of MeOH. The mixture was left at room temperature for 3 days and the resulted solution was evaporated to dryness under reduced pressure. The residue was diluted with a small amount of H₂O and precipitated as the picrate by adding saturated aq. solution of picric acid. Recrystallization from 50% EtOH afforded yellow needles, mp 164–165°. Yield, 226 mg. Sakaguchi and Dragendorff tests were negative. *Anal.* Calcd. for C₁₃H₁₆O₆N₆Br: C, 32.58; H, 3.16; N, 17.54. Found: C, 32.83; H, 3.38; N, 17.56.

(When refluxing the above reaction mixture for 2 hr instead of standing at room temperature, the same product X was obtained).

Method B: A solution of 64 mg of IX in 4 ml of MeOH containing 2 drops of conc. HBr was kept at room temperature for 24 hr. Excess acid was neutralized by addition of Amberlite IR-4B resin (amine type). The solvent was removed and addition of aq. solution of picric acid to the residue produced yellow precipitate which was recrystallized from 50% EtOH to give yellow needles. This compound was identical with the product prepared above.

Conversion of 2-Acetamido-5-bromo-4-hydroxy-1,4,5,6-tetrahydropyrimidine (IX) to 2-Acetamido-1,6-dihydropyrimidine Picrate (VIIIc)—To a solution of 15 mg of IX in 0.01% HCl, a small amount of zinc powder was added. The mixture was warmed at 60° for 4 hr and then filtered. The filtrate was neutralized with NaHCO₃ and concentrated to almost dryness. The residue was treated with aq. solution of picric acid to give yellow needles which were identified as 2-amino-1,6-dihydropyrimidine picrate by comparison of IR spectrum with that of the picrate obtained from VIIIb and picric acid.

Pyrolysis of 2-Acetamido-4-hydroxy-1,4,5,6-tetrahydropyrimidine Hydrochloride (VI)—VI (25 mg) was heated under reduced pressure (1 mm Hg) at 120–130° for 18 hr. The resulting product was dissolved in CHCl₃ and chromatographed on silica gel, employing CHCl₃-MeOH (1:1) as the eluent. Removal of the solvent gave a colorless amorphous solid. The product thus obtained was identical as 2-acetamido-1,6-dihydropyrimidine hydrochloride (VIIIa) by comparison of the IR spectra and the mixed mp determination.

Acknowledgement We wish to express our deep gratitude to Prof. Y. Hirata, Nagoya University, for his encouragement.