dil. EtOH gave yellow crystals (11.4 g.), m.p. 72~74°, IR cm^{-1} : $\nu_{C=O}$ 1800 ($CHCl_3$). *Anal.* Calcd. for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84; N, 21.37. Found : C, 50.86; H, 4.00; N, 21.00.

4-(*p*-Nitrophenylazo)-3,4-dimethyl-5(4*H*)-isoxazolone (VIIIc)——By the same procedure as for Ⅷa, Ⅷc (10.7 g.) was obtained from Ia (5.6 g.) and *p*-nitrobenzenediazonium chloride. Recrystallization from EtOH gave greenish yellow crystals, m.p. 91~93°, IR cm^{-1} : $\nu_{C=O}$ 1800 ($CHCl_3$). *Anal.* Calcd. for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84; N, 21.37. Found : C, 49.70; H, 4.05; N, 20.95.

***o*-, *m*-, and *p*-Nitrophenylhydrazone of 2,3-Butanedione Monooximes (IXa, b, c)**——The solution of Ⅷa, Ⅷb, or Ⅷc in 10% NH_4OH and EtOH (1:1) was heated on a water bath for a few minutes. After cooling, the corresponding oxime was precipitated.

o-Nitrophenylhydrazone of 2,3-butanedione monooxime (Ⅸa) : Colorless needles (Me_2CO), m.p. 221° (decomp.). *Anal.* Calcd. for $C_{10}H_{12}O_3N_4$: C, 50.84; H, 5.12; N, 23.72. Found : C, 50.96; H, 5.34; N, 23.61. Ⅸa was identified with the sample prepared from 2,3-butanedione monooxime and *o*-nitrophenylhydrazine.

m-Nitrophenylhydrazone of 2,3-butanedione monooxime (Ⅸb) : Colorless needles (Me_2CO), m.p. 257~258°. *Anal.* Calcd. for $C_{10}H_{12}O_3N_4$: C, 50.84; H, 5.12; N, 23.72. Found : C, 50.83; H, 5.33; N, 23.18. Ⅸb was identical with a sample prepared from 2,3-butanedione monooxime and *m*-nitrophenylhydrazine.

p-Nitrophenylhydrazone of 2,3-butanedione monooxime (Ⅸc) : Colorless needles (dil. EtOH), m.p. 251~252°. *Anal.* Calcd. for $C_{10}H_{12}O_3N_4$: C, 50.84; H, 5.12; N, 23.72. Found : C, 51.11; H, 5.32; N, 23.40. Ⅸc was identified with an authentic sample.[5]

The authors are deeply grateful to Prof. Emeritus E. Ochiai of the University of Tokyo and Dr. K. Takeda, Director of this Laboratory, for their kind encouragement. Thanks are due to the members of the Analysis Room of this Laboratory for elemental analysis.

Summary

The reaction products of nitrous acid on 5-amino-3,4-dialkylisoxazoles (Ia, b, c) has been formulated as 4-(3,4-dialkyl-5-isoxazolyl)azo-3,4-dialkyl-5(4*H*)-isoxazolones (Ⅳa, b, c) rather than the azoxy structure (Ⅱ) which was originally proposed by Hanriot. To gain insight into this reaction mechanism, the behavior of *o*-, *m*-, and *p*-nitrobenzenediazonium chlorides on Ia has been also investigated.

(Received May 16, 1964)

[Chem. Pharm. Bull. 12 (9) 1024 ~ 1030]

UDC 612.398.145-064

141. Kuniyoshi Tanaka, Toshio Sugawa, Ritsuo Nakamori, Yasushi Sanno, Yasuo Ando, and Kin-ichi Imai : Studies on Nucleic Acid Antagonists. VI. Synthesis of 1,4,6-Triazaindenes(5*H*-Pyrrolo[3,2-*d*]pyrimidines).*1

(*Research Laboratories, Takeda Chemical Industries, Ltd.**2)

1,4,6-Triazaindene is a condensed heterobicyclic ring isosteric to both purine and indole, and therefore its properties, especially its behaviors to various chemical reactions intrigued us. Besides, purine and indole are the basic substances of a number of important metabolites, and it may well be that some triazaindene compounds might be active as

*1 Part V : K. Tanaka, T. Sugawa, Y. Kuwada, K. Imai, M. Morinaga, J. Watanabe, T. Komeda, T. Usui, H. Yokotani, H. Ito, S. Hemmi, M. Kato, H. Mima, K. Kaziwara : Ann. Rept. Takeda Res. Lab., 22, 192 (1963).

*2 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (田中邦喜, 須川利男, 中守律夫, 三野 安, 安藤康雄, 今井欣一).

antimetabolites or as chemotherapeutics. In this connection, we have reported[1] the synthesis of 1,4,6-triazaindenes by two different methods, which involved the ring-closure of 5-acylamido-6-methylpyrimidines and the reductive condensation of 5-nitro-6-ethoxalylmethylpyrimidines. Rose[2] reported the synthesis of four derivatives of 1,4,6-triazaindan-2-one, which, however, were 2-oxo-2,3-dihydro compounds and accordingly different from our compounds. Thereafter Pfleiderer[3] synthesized some analogs by a different method. This paper gives detailed account of the work previously reported[1] and presents some additional arguments on the synthetic approaches.

First of all, we attempted the synthesis of the 1,4,6-triazaindene ring from 5-acylamido-6-methylpyrimidine by the Madelung method of indole synthesis, which has so far been extended only to the synthesis of 4-, 5-, 6-, or 7-azaindole derivatives from pyridine compounds.[4,5]

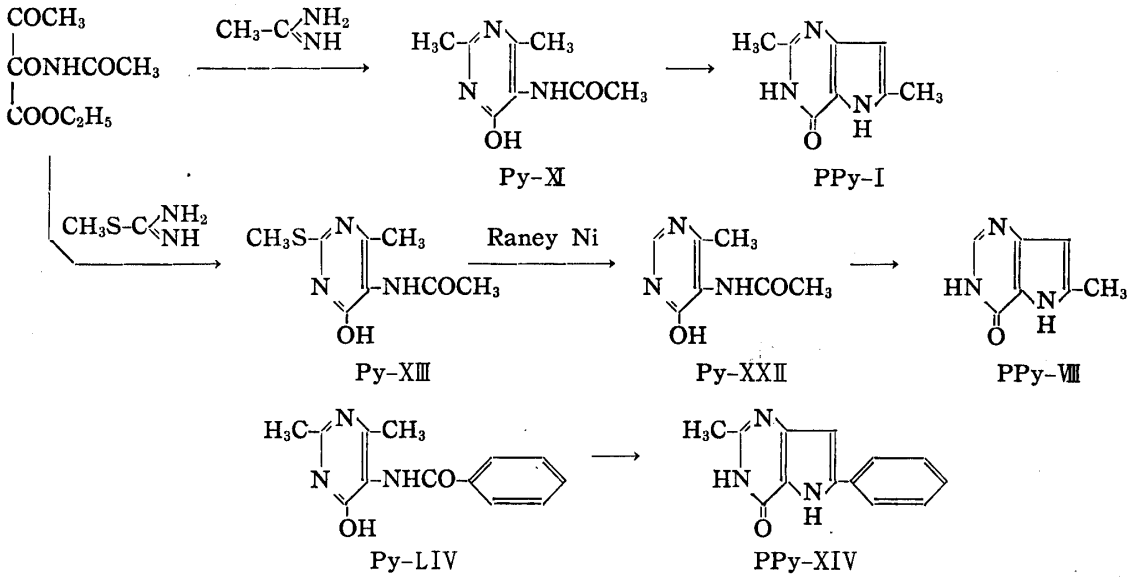
To this end, 5-formamido-6-methylpyrimidine (Py-XVII) produced by heating 5-amino-6-methylpyrimidine (Py-XVI) with formic acid was selected as starting material, and the substance was subjected to the Madelung condensation by heating with sodium methoxide in an atmosphere of nitrogen at 300°. However, this approach turned out to be fruitless because the reaction mixture became resinous.

The second approach we attempted was the cyclization of 5-acetamido-6-methylpyrimidines. Three new pyrimidine compounds,[6] namely, 2,6-dimethyl-4-hydroxy-5-acetamidopyrimidine (Py-XI), 2-amino-4-hydroxy-5-acetamido-6-methylprimidine (Py-XII), and 2-methylmercapto-4-hydroxy-5-acetamido-6-methylpyrimidine (Py-XIII) were synthesized by condensing ethyl acetamidoacetacetate with acetamidine, guanidine and methylisothiourea, respectively. When Py-XI was then submitted to the ring-closure reaction by heating in an atmosphere of nitrogen at 320~325° in the presence of sodium ethoxide, 2,5-dimethyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-I)[7] was obtained. Similar reactions with Py-XII or Py-XIII, however, recovered the starting materials at low temperatures or simply caused the decomposition at high temperatures. 2,4-Dihydroxy-5-acetamido-6-methylpyrimidine (Py-XVIII), which was synthesized by the acetylation of 2,4-dihydroxy-5-amino-6-methylpyrimidine (Py-IV), did not undergo ring-closure under similar conditions. Efforts were also directed toward the cyclization of compound having ethoxy groups instead of hydroxyls at 2,4-positions of Py-XVIII. For this purpose, 2,4-diethoxy-5-nitro-6-methylpyrimidine (Py-XIX) was catalytically reduced, and the resulting 2,4-diethoxy-5-amino-6-methylpyrimidine (Py-LIX) was acetylated to produce 2,4-diethoxy-5-acetamido-6-methylpyrimidine (Py-LX). The compound, however, did not give the expected compound on heating with sodium ethoxide. While it would be rash to conclude from these results, however, it might be pertinent to assume that pyrimidines substituted at least at 2-position by electron-releasing groups such as OH, OC_2H_5, NH_2, or SCH_3 are refractory toward the ring-closure to give 1,4,6-triazaindenes. For example, when 2-amino-4,6-dimethyl-5-acetamidopyrimidine (Py-XXVIII) was heated with sodium ethoxide at 320°, only the starting material was recovered unchanged or composition took place at 350°. This would indicate that the success of the reaction is primarily dependent on the nature of the substituent at the 2-position rather than the 4-position of the pyrimidines. If this argument is correct, 4-hydroxy-5-acetamido-6-methylpyrimidine (Py-XXII), in which the methyl at 2-position of Py-XI is replaced by hydrogen, should certainly

1) K. Tanaka, T. Sugawa, R. Nakamori, Y. Sanno, Y. Ando : Yakugaku Zasshi, **75**, 770 (1955).
2) F. L. Rose : J. Chem. Soc., **1954**, 4116.
3) W. Pfleiderer, H. Mosthaf : Chem. Ber., **90**, 728, 738 (1957).
4) G. R. Clemo, G. A. Swan : J. Chem. Soc., **1945**, 603; **1948**, 198.
5) E. Koenigs, A. Fulde : Ber., **60**, 2106 (1927).
6) K. Tanaka, T. Sugawa, R. Nakamori, Y. Sanno : Japan. Pat., 212, 795 (April 9, 1955).
7) *Idem* : *Ibid.*, 213, 592 (May 18, 1955).

undergo the reaction. In fact, Py-XIII was desulfurated with Raney nickel and the resulting Py-XXII was subjected to the Madelung reaction to give 2-methyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-VIII).

It is of interest to note that Py-XVII, which bears the 5-formamido group rather than the acetamido group, did not undergo the Madelung reaction under the conditions, where the acetamido derivatives (Py-XI, Py-XXII) were cyclized. Similarly, 2,4-dihydroxy-5-formamido-6-methylpyrimidine (Py-XV) and 2,6-dimethyl-4-hydroxy-5-formamidopyrimidine (Py-LV) failed to yield the 1,4,6-triazaindenes, but 2,6-dimethyl-4-hydroxy-6-benzamidopyrimidine (Py-LIV) gave 2-phenyl-5-methyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XIV) (Chart 1).



The ring-closure was unsuccessful with following compounds.

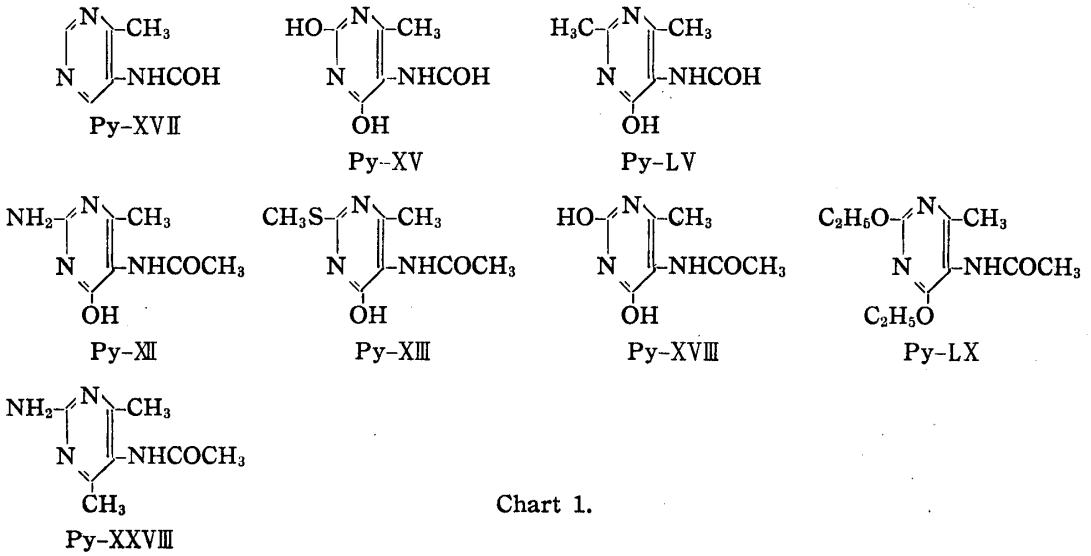


Chart 1.

These results demonstrated that there would be few possibility for synthesizing the triazaindene and its derivatives, which were isosteric to the naturally occurring purines, that is, the compounds having a hydroxyl or amino group at 2-position of the pyrimidine ring, by the above method.

In order to overcome this shortcoming, an alternative synthesis was investigated. Thus 5-nitro-6-ethoxalylmethylpyrimidines, which were synthesized by the Claisen

condensation of 5-nitro-6-methylpyrimidines with ethyl oxalate, were subjected to reductive condensation under the conditions of the indole synthesis by Reissert. The methyl group at 6-position of the starting materials may be activated when the substituents at 2- and 4-positions are properly selected, coupled with the influence of the ntiro-group at the 5-position. In fact, 2,4-diethoxy-5-nitro-6-methylpyrimidine (Py-XIX) was allowed to react with diethyl oxalate to give 2,4-diethoxy-5-nitro-6-ethoxalylmethylpyrimidine (Py-XX). The reaction was also applied to the alloxy derivatives from which the hydroxyl groups might be easily regenerated by the catalytic reduction. 2,4-Dialloxy-5-nitro-6-methylpyrimidine (Py-XLIII) was prepared by the reaction of 2,4-dichloro-5-nitro-6-methylpyrimidine (Py-V) with sodium alloxide, but the reaction of the product with diethyl oxalate in the presence of sodium ethoxide gave rise to Py-XX rather than 2,4-dialloxy-5-nitro-6-ethoxalylmethylpyrimidine (Py-XLIV). The reaction was conducted using sodium alloxide as condensing agent to yield Py-XLIV. For the purpose of investigating the influence of the substituents at 2- and 4-positions on the reaction, 2-ethoxy-4-amino-5-nitro-6-methylpyrimidine (Py-XXIX) and 2,4-diamino-5-nitro-6-methylpyrimidine (Py-IX) were reacted with diethyl oxalate. Consequently, it was found that 2-ethoxy-4-amino-5-nitro-6-ethoxalylmethylpyrimidine (Py-XXXI) was obtained from Py-XXIX, but with Py-IX only the starting material was recoverd. When the 2-position is substituted by such a group as amino, the activity of the methyl group at 6-position seems to be reduced. The Claisen reaction on the methyl group of the pyrimidine ring was first recorded in our previous paper,[1] but thereafter Sullivan[8] stated the Claisen reaction with 2,4,6-trimethylpyrimidine and Pfleiderer[3] with 2,4-diethoxy- and 2,4-dimethoxy-5-nitro-6-methylpyrimidine to introduce the ethoxalyl group into the methyl group at the 6-position.

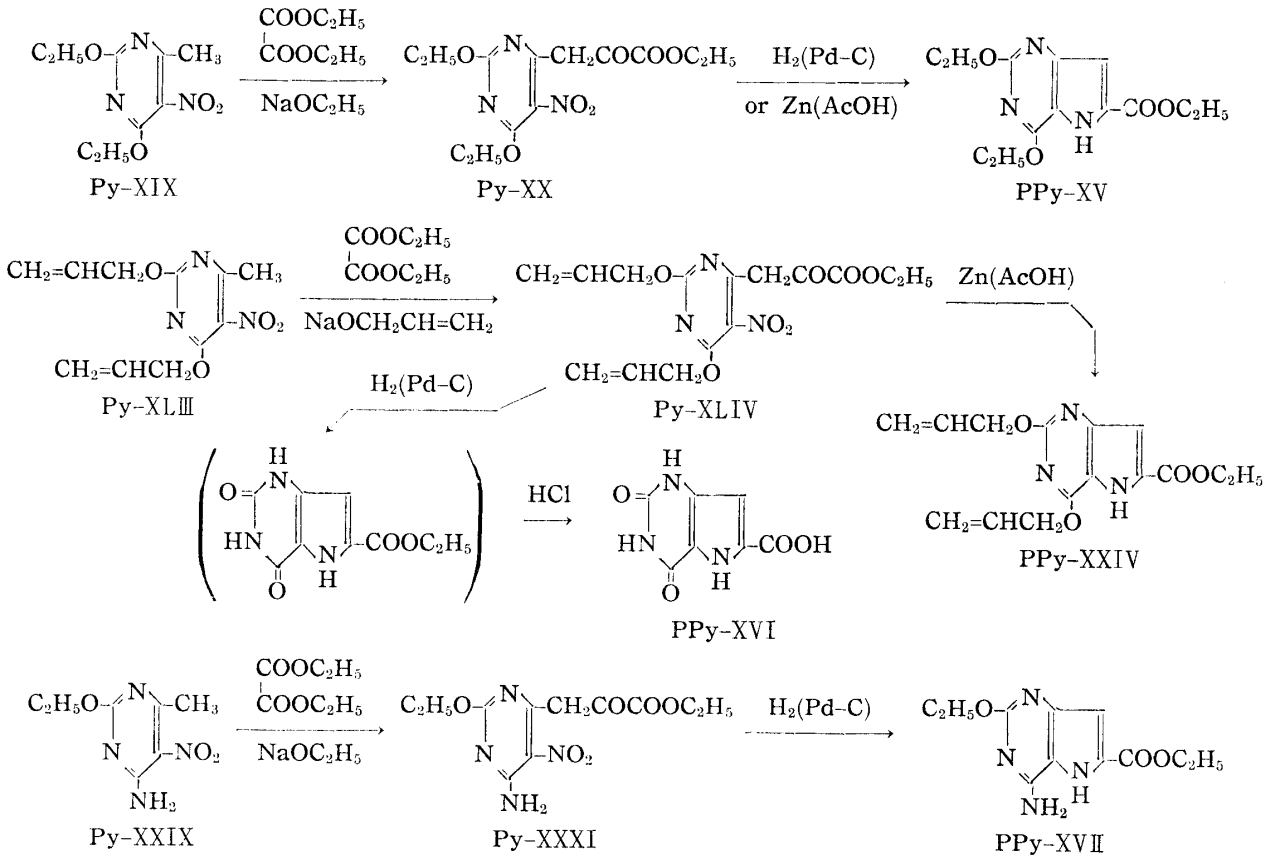


Chart 2.

8) H. R. Sullivan, W. T. Caldwell : J. Am. Chem. Soc., **77**, 1559 (1955).

The reductive ring-closure of these 5-nitro-6-ethoxalylmethylpyrimidines was carried out as follows: First of all, a solution of Py-XX in ethanol or ethyl acetate was reduced on palladium-charcoal, when 3 moles of hydrogen were absorbed, producing the expected ethyl 5,7-diethoxy-1,4,6-triazaindene-2-carboxylate (PPy-XV) in good yield. The reduction was also operative with zinc and glacial acetic acid. On the other hand, catalytic reduction of Py-XLIV resulted in ethyl 5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylate. Hydrolysis of the product with hydrochloric acid gave 5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylic acid (PPy-XVI). Reduction of Py-XLIV with zinc and glacial acetic acid yielded ethyl 5,7-dialloxy-1,4,6-triazaindene-2-carboxylate (PPy-XXIV). Furthermore, catalytic reduction of Py-XXXI produced ethyl 5-ethoxy-7-amino-1,4,6-triazaindene-2-carboxylate (PPy-XVII) (Chart 2).

As mentioned above, two methods for the synthesis of 1,4,6-triazaindene derivatives were established for the first time and it became possible to prepare more extensive derivatives.

Experimental*3

2,6-Dimethyl-4-hydroxy-5-acetamidopyrimidine (Py-XI)——A solution of metallic Na (4.2 g.; 0.18 atm.) in EtOH (85 ml.) was mixed with acetamidine hydrochloride (11.8 g.; 0.13 mole) and the separated NaCl was filtered. To the filtrate was added ethyl α-acetamidoacetacetate (23 g.; 0.12 mole) and the mixture was heated on a water bath for 4 hr. After cooling, the reaction mixture was diluted with H_2O (80 ml.), adjusted to pH 5 with HCl, and concentrated *in vacuo*. The residue was extracted with hot EtOH (400 ml.) and the extract was cooled to separate colorless needles, m.p. 275~277° (13.5 g. or 60%). The product was purified by recrystallization from MeOH. *Anal.* Calcd. for $C_8H_{11}O_2N_3$: C, 53.04; H, 6.08; N, 23.20. Found: C, 52.70; H, 6.11; N, 23.21.

2-Amino-4-hydroxy-5-acetamido-6-methylpyrimidine (Py-XII)——To a solution of metallic Na (1.15 g.; 0.05 atm.) in EtOH (20 ml.) was added guanidine carbonate (4.5 g.; 0.05 mole) and the mixture was heated for 30 min. and the separated Na_2CO_3 was filtered. To the filtrate was added a solution of ethyl α-acetamidoacetacetate (9.35 g.; 0.05 mole) in EtOH (20 ml.) and the mixture was heated on a water bath for 8 hr. The solvent was distilled off *in vacuo*, the residue was dissolved in *N* NaOH (45 ml.) and the solution was neutralized with AcOH. The resulting crystals were filtered and purified by recrystallization from MeOH to give colorless needles, m.p. 295~298° (decomp.) (3.4 g. or 37%). *Anal.* Calcd. for $C_7H_{10}O_2N_4$: C, 46.15; H, 5.33; N, 30.76. Found: C, 46.36; H, 5.36; N, 30.61.

2-Methylmercapto-4-hydroxy-5-acetamido-6-methylpyrimidine (Py-XIII)——To a mixture of thiourea (720 mg.; 9.5 mmoles) and H_2O (0.5 ml.) was added with stirring dimethylsulfate (700 mg.; 5.5 mmoles) and the resulting clear solution was treated with a solution of NaOH (500 mg.) in H_2O (1 ml.) and ethyl α-acetamidoacetacetate (1.87 g.; 0.01 mole). The mixture was left standing overnight and then heated on a water bath for 1 hr. After cooling the reaction mixture was filtered and the filtrate was neutralized with AcOH to separate crystals (700 mg. or 35%), which were purified by recrystallization first from EtOH then from H_2O to give colorless needles, m.p. 248~252°. *Anal.* Calcd. for $C_8H_{11}O_2N_3S$: C, 45.05; H, 5.20; N, 19.71. Found: C, 44.23; H, 5.44; N, 19.39.

2,5-Dimethyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-I)——To a solution of metallic Na (1.9 g.; 0.083 atm.) in EtOH (40 ml.) was added Py-XI (5 g.; 0.028 mole) and the mixture was heated on a metal bath in an atmosphere of N_2. The solvent was removed *in vacuo* and the colorless residue, after being kept at 320~325° (outer temp. 360~365°) in an atmosphere of N_2 for 20 min., was dissolved in H_2O (100 ml.) and adjusted to pH 8~9 with HCl. The separated crystals were filtered and dissolved in *N* HCl (90 ml.), and the solution was treated with charcoal. The solution was finally adjusted to pH 8 with 10% NaOH to yield colorless needles, m.p. 336° (decomp.) (2.4 g. or 53%). Recrystallization from H_2O-MeOH (12:5) raised melting point to 337°. *Anal.* Calcd. for $C_8H_9ON_3$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.72; H, 5.84; N, 26.13.

2-Methyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-VIII)——To a solution of metallic Na (2.2 g.; 0.096 atm.) in EtOH (40 ml.) was added 4-hydroxy-5-acetamido-6-methylpyrimidine (Py-XXII) (5 g.; 0.03 mole). The solvent was rapidly evaporated under the N_2 stream and the resulting mixture was gradually heated to 315~320°. When the contents became effervescent, the reaction was stopped. After cooling the mixture was dissolved in H_2O (50 ml.), filtered and adjusted to pH 8.5 with HCl. The resulting brown precipitate was filtered, dried (1.9 g.) and dissolved in 0.5*N* HCl, and the solution was adjusted

*3 All melting points are uncorrected.

to pH 7 with NaOH to afford precipitates which, after drying, became a colorless crystalline powder, m.p. >360° (1.5 g., or 31%). The product was found to be recrystallized from EtOH. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.37; H, 4.73; N, 28.18. Found : C, 56.10; H, 4.59; N, 27.90.

2-Phenyl-5-methyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XIV)——To a solution of metallic Na (1 g.; 0.044 atm.) in EtOH (20 ml.) was added 2,6-dimethyl-4-hydroxy-5-benzamidopyrimidine (Py-LIV) (3.4 g.; 0.014 mole). The mixture was heated on a metal bath to distill the EtOH under the N_2 stream, and the colorless residue was kept at 310° (outer temp. 350~355°) for 15 min. After cooling the reaction mixture was dissolved in H_2O (50 ml.), the solution was adjusted to pH 6 with AcOH. The resulting pale brown precipitate was dissolved in warm *N* NaOH and the solution was acidified with AcOH to separate precipitates, which were recrystallized from EtOH to give a colorless crystalline powder, m.p. 325° (decomp.) (1.8 g., or 56%).

The same product was also obtained from metallic Na (400 mg., 0.017 atm.), iso-PrOH (10 ml.), and Py-LIV (1.1 g.; 0.0045 mole) in a similar manner as described above, m.p. 322° (decomp.) (600 mg., or 60%). *Anal.* Calcd. for $C_{13}H_{11}ON_3$: C, 69.32; H, 4.92; N, 18.66. Found : C, 69.21; H, 4.66; N, 18.68.

2,4-Diethoxy-5-nitro-6-ethoxalylmethylpyrimidine (Py-XX)——To a solution of metallic Na (1 g.; 0.044 atm.) in EtOH (20 ml.) were added diethyl oxalate (6 g.; 0.041 mole) and 2,4-diethoxy-5-nitro-6-methylpyrimidine (Py-XIX) (9.1 g.; 0.04 mole) to separate a yellow precipitate, which was filtered after heating on a water bath for 1 hr., m.p. 305° (decomp.) (14 g., or 100%). A mixture of the yellow precipitate (13 g.; 0.37 mole), Me_2CO (50 ml.), HCl (10 ml.), and H_2O (20 ml.) was heated for 30 min. and the Me_2CO was distilled, leaving an oily substance, which solidified on cooling, m.p. 115° (decomp.) (11 g., or 91%). The product was recrystallized from EtOH into pale yellow needles, m.p. 120° (decomp.). *Anal.* Calcd. for $C_{13}H_{17}O_7N_3$: C, 47.71; H, 5.23; N, 12.84. Found : C, 47.70; H, 5.31; N, 12.90.

2,4-Dialloxy-5-nitro-6-ethoxalylmethylpyrimidine (Py-XLIV)——To a solution of metallic Na (3.2 g.; 0.14 atm.) in allylalcohol (80 ml.) were added diethyl oxalate (20 ml.; 0.15 mole) and a solution of 2,4-dialloxy-5-nitro-6-methylpyrimidine (Py-XLIII) (10 g.; 0.04 mole) in a small amount of allylalcohol with cooling to separate yellow needles. After being kept standing overnight at room temperature the crystals were filtered, dissolved in Me_2CO and heated with 10% HCl, and the solvent was distilled to leave an oily substance, which solidified on cooling. The product was recrystallized from aq. EtOH to yield yellow needles, m.p. 45° (12 g., or 85%). *Anal.* Calcd. for $C_{15}H_{17}O_7N_3$: C, 51.28; H, 4.88; N, 11.96. Found : C, 51.30; H, 4.58; N, 11.63.

2-Ethoxy-4-amino-5-nitro-6-ethoxalylmethylpyrimidine (Py-XXXI)——To a solution of metallic Na (800 mg.; 0.035 atm.) in EtOH (30 ml.) were added diethyl oxalate (5 ml.; 0.038 mole) and a solution of 2-ethoxy-4-amino-5-nitro-6-methylpyrimidine (Py-XXIX) (2 g.; 0.01 mole) in EtOH (100 ml.), and the mixture was refluxed on a water bath for 3 hr. After being kept standing overnight the separated crystals were filtered and heated with Me_2CO (50 ml.) and HCl (15 ml.), and the solvent was distilled to leave yellow crystals, which were recrystallized from EtOH into yellow needles, m.p. 220° (2.5 g., or 84%). *Anal.* Calcd. for $C_{11}H_{14}O_6N_4$: C, 44.30; H, 4.73; N, 18.79. Found : C, 44.42; H, 4.92; N, 19.07.

Ethyl 5,7-Diethoxy-1,4,6-triazaindene-2-carboxylate (PPy-XV)——A solution of Py-XX (10 g.; 0.031 mole) in AcOEt (100 ml.) was shaken in an atmosphere of H_2 in the presence of Pd-C prepared from 2% $PdCl_2$ solution (20 ml.) and charcoal, when 106% of the theoretical volume of H_2 was absorbed. The catalyst was filtered, and the solvent evaporated to yield a yellow product, which was recrystallized from Me_2CO into pale yellow crystals, m.p. 141° (8 g., or 94%). *Anal.* Calcd. for $C_{13}H_{17}O_4N_3$: C, 55.90; H, 6.14; N, 15.05; OC_2H_5, 48.42. Found : C, 55.63; H, 6.81; N, 14.89; OC_2H_5, 48.49.

Ethyl 5,7-Dialloxy-1,4,6-triazaindene-2-carboxylate (PPy-XXIV)——To a solution of PPy-XLIV (3.5 g.; 0.01 mole) in glacial AcOH (35 ml.) was added Zn dust (7 g.) in small portions at 70~80°. After 2 hr. the reaction mixture was diluted with H_2O, the separated oil was extracted with AcOEt, and the AcOEt solution, after washing with a $NaHCO_3$ solution and H_2O and drying over anhyd. Na_2SO_4, was concentrated, leaving an oily substance (3.1 g.). A portion of the product was converted to the picrate, which was purified by recrystallization from aq. EtOH into yellow needles, m.p. 144°. *Anal.* Calcd. for $C_{15}H_{17}O_4N_3 \cdot C_6H_3O_7N_3$: C, 47.37; H, 3.79; N, 15.78. Found : C, 47.28; H, 3.99; N, 15.92.

5,7-Dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylic Acid (PPy-XVI)——A solution of Py-XLIV (4 g.; 0.011 mole) in EtOH (200 ml.) was catalytically reduced in the presence of Pd-C prepared from 2% $PdCl_2$ solution (10 ml.) and charcoal, when 2500 ml. of H_2 was absorbed. The catalyst was filtered, the solvent was evaporated, and the residue was extracted with 50% hot EtOH. The crystals (1.5 g.) separated from the extract on cooling was heated with HCl for 6 hr. and the deposited colorless crystalline substance was purified by recrystallization from H_2O, m.p. >360°. *Anal.* Calcd. for $C_7H_5O_4N_3$: C, 43.08; H, 2.58; N, 21.54. Found : C, 43.09; H, 2.87; N, 20.87.

Ethyl 5-Ethoxy-7-amino-1,4,6-triazaindene-2-carboxylate (PPy-XVII)——A solution of Py-XXXI (2 g.; 0.0067 mole) in EtOH (300 ml.) was catalytically reduced for 3 hr. in the presence of Pd-C prepared from $PdCl_2$ (200 mg.) and charcoal, when 134% of the theoretical volume of H_2 was absorbed. The catalyst was filtered, the solvent was evaporated, and the remaining yellowish brown substance was purified by recrystallization from EtOH into colorless needles, m.p. 232°. *Anal.* Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79;

H, 5.64; N, 22.39. Found : C, 52.74; H, 5.87; N, 22.16.

Summary

Two methods of synthesizing 1,4,6-triazaindene, which was isosteric to purine and to indole were described. The first method involves the ring-closure of 5-acylamido-6-methylpyrimidines. The second method involves the Claisen reaction of 5-nitro-6-methylpyrimidines followed by reductive condensation.

(Received February 28, 1964)

[Chem. Pharm. Bull. 12 (9) 1030 ~ 1042]

UDC 612.398.145-064

142. Kin-ichi Imai : Studies on Nucleic Acid Antagonists. VII. Synthesis and Characterization of 1,4,6-Triazaindenes (5*H*-Pyrrolo[3,2-*d*]pyrimidines).*1

(*Research Laboratories, Takeda Chemical Industries, Ltd.**2)

As reported in the preceding paper Tanaka, *et al.**1 synthesized 1,4,6-triazaindene derivatives by two methods, *viz.* by the ring-closure of 5-acylamido-6-methylpyrimidines and the reductive condensation of 5-nitro-6-ethoxalylmethylpyrimidines. The present paper deals with the synthesis of 1,4,6-triazaindene and its derivatives : 9-Deaza-counterparts of the naturally occurring purine bases (purine, adenine, guanine, and hypoxanthine).

Ethyl 5,7-diethoxy-1,4,6-triazaindene-2-carboxylate (PPy-XV) was converted to ethyl 4,6-diethyl-5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylate (PPy-V) by intramolecular rearrangement on heating with copper powder at 200°. PPy-XV and PPy-V had the same composition, but they had markedly different ultraviolet absorption spectra (Fig. 1 and Fig. 2). Hydrolysis of PPy-V with ethanolic sodium hydroxide or with concentrated hydrochloric acid (in a sealed tube at 140°) gave the corresponding 2-carboxylic acid (PPy-VI), reflecting the stability of the two of three ethyl groups against the hydrolyzing agent. Because of the stability, the two ethyl groups should be attached to nitrogen 4 and 6. Heating of PPy-V with alcoholic ammonia (in a sealed tube) afforded 4,6-diethyl-5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxamide (PPy-XII).

On treatment with concentrated hydrochloric acid, PPy-XV was hydrolyzed to afford 5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylic acid (PPy-XVI) which was in turn decarboxylated into 5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene (PPy-XVIII) on heating at 300° in the presence of copper. PPy-VI in the same reaction gave rise to 4,6-diethyl-5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene (PPy-VII) (Chart 1).

Treatment of 5-oxo-4,5-dihydro or 7-oxo-6,7-dihydro-1,4,6-triazaindenes with phosphoryl chloride (in the presence of dimethylaniline) gave rise to a low yield of the corresponding chlorinated derivatives; the yield was improved when pyrophosphoryl chloride[1] (instead of phosphoryl chloride) was employed. Thus, 2,5-dimethyl-7-chloro-

*1 Part VI. K. Tanaka, T. Sugawa, R. Nakamori, Y. Sanno, Y. Ando, K. Imai : This Bulletin, **12**, 1024 (1964).

*2 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (今井欣一).

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