

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.

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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 chloride¹⁾ (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} Jusō-nishino-cho, Higashiyodogawa-ku, Osaka (今井欣一).

1) G. B. Elion, G. H. Hitchings: J. Am. Chem. Soc., 78, 3508 (1956).

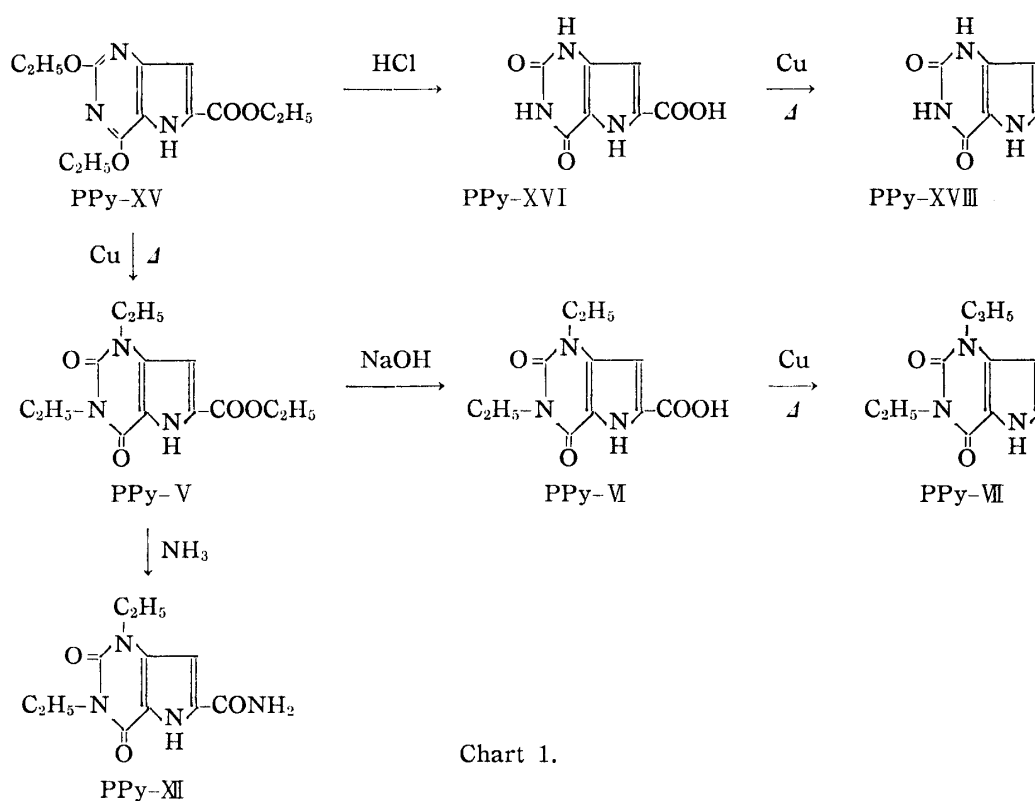


Chart 1.

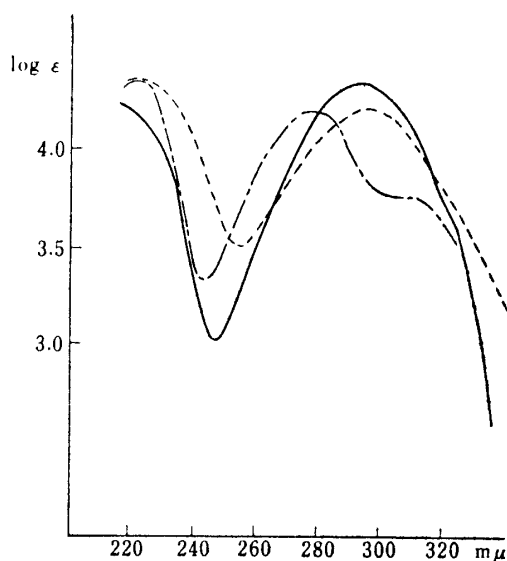


Fig. 1. Ultraviolet Absorption Spectra of Ethyl 5,7-Diethoxy-1,4,6-triazaindene-2-carboxylate (PPy-XV)

— 0.1N HCl
 --- 0.5N NaOH
 - · - MeOH

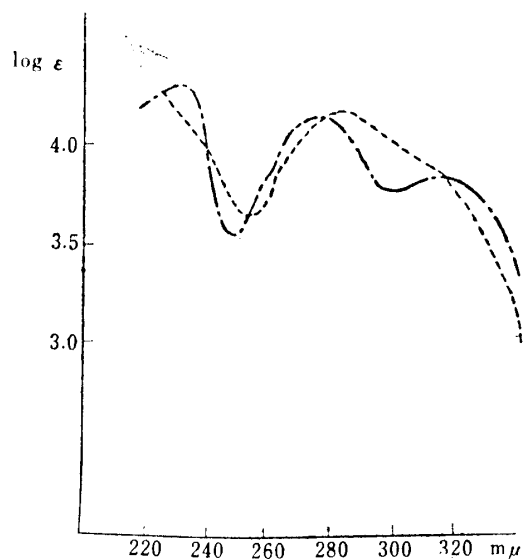


Fig. 2. Ultraviolet Absorption Spectra of Ethyl 4,6-Diethyl-5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylate (PPy-V)

--- N NaOH
 - · - MeOH

1,4,6-triazaindene (PPy-II) was obtained from 2,5-dimethyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-I), 2-methyl-7-chloro-1,4,6-triazaindene (PPy-K) from 2-methyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-VIII), 5,7-dichloro-1,4,6-triazaindene (PPy-XIX) from PPy-XVIII, and 7-chloro-1,4,6-triazaindene (PPy-XXXII) from 7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XXIX) which will be mentioned later.

The chlorine in the above derivatives was reactive enough to various nucleophilic reagents. With the dichloro compounds, the difference in reactivity was observed between 5- and 7-chlorine atoms. From analogy of purine and other condensed pyrimidine compounds, chlorine on 7-position is presumed to be more replaciable by the nucleophile. Accordingly, a product obtained from PPy-XIX by alkaline hydrolysis was assigned 5-chloro-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XXV^{III}).

Reaction of PPy-XIX with thiourea in ethanol gave the corresponding 5,7-diisothiuronium salt which was converted with alkali to 5,7-dimercapto-1,4,6-triazaindene (PPy-XX), from which 5,7-dimethylmercapto-1,4,6-triazaindene (PPy-XX^{III}) was given by reaction with either dimethyl sulfate or methyl iodide. PPy-XXX^{II} in the same treatment afforded 7-mercapto-1,4,6-triazaindene (PPy-XXX^{III}), an isostere of purine-6-thiol. More direct method of the preparation of PPy-XX was to treat PPy-XV^{III} with phosphorus pentasulfide-pyridine. PPy-I in a similar reaction (phosphorous pentasulfide-tetralin) gave 2,5-dimethyl-7-mercapto-1,4,6-triazaindene (PPy-X^{III}).

The ammonolysis of the chloro compounds showed that the chlorine at the 7-position was more reactive than the one at the 5-position. Thus, 2,5-dimethyl-7-amino-1,4,6-triazaindene (PPy-^{III}) was obtained from PPy-II, 2-methyl-7-amino-1,4,6-triazaindene (PPy-X) from PPy-X, and 5-chloro-7-amino-1,4,6-triazaindene (PPy-XXVI), and 5,7-diamino-1,4,6-triazaindene (PPy-XXXI) from PPy-XIX when temperature was kept at 120° and 200°, respectively. Treatment of PPy-XXV^{III} with alcoholic ammonia at 200° produced 5-amino-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XXX) (an isoster of guanine).

Catalytic reduction of chloro triazaindens on palladium-charcoal in the presence of magnesium oxide furnished the dechloro compounds. 2,5-Dimethyl-1,4,6-triazaindene (PPy-N) was obtained from PPy-II and 2-methyl-1,4,6-triazaindene (PPy-XI) from PPy-X. Similarly 7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XXIX) was produced from PPy-XXV^{III} and 7-amino-1,4,6-triazaindene (PPy-XXVII) from PPy-XXVI. PPy-XXIX and PPy-XXVII are the compounds isosteric to hypoxanthine and adenine, respectively.

With the aim of preparing 1,4,6-triazaindene having no substituent (PPy-XXI), PPy-XIX was reduced on palladium-charcoal in the presence of magnesium oxide, when hydrogen was absorbed far more than the theoretical amount and the expected product was not obtained from the reaction mixture. However, the desulfuration of 5,7-dimercapto compound (PPy-XX) with Raney nickel furnished 1,4,6-triazaindene (PPy-XXI) in poor yield. When the above-mentioned catalytic reduction was further scrutinized, it was noticed that 3 moles of hydrogen were uptaken. From its analytical values, ultraviolet absorption spectrum, and coloration to the Ehrlich reagent, the product was characterized as dihydro-1,4,6-triazaindene (PPy-XXI-H). Oxidation of the dihydro compound (PPy-XXI-H) with potassium ferricyanide afforded PPy-XXI in a better yield than in the desulfuration of PPy-XX.

The new condensed heterobicyclic compound, 1,4,6-triazaindene (PPy-XXI), was obtained as colorless prisms melting at 177° and showed strong ultraviolet absorption bands characteristic to the azaindens (Fig. 3). On the other hand, the absorption spectrum of dihydro-1,4,6-triazaindene (PPy-XXI-H) was quite different from this as shown in Fig. 4. Infrared absorption spectrum of PPy-XXI is shown in Fig. 5 (Chart 2).

In the above various reactions it was found that the pyrimidine portion of 1,4,6-triazaindenes had the same behaviors as those of purines. Attention was then turned to the pyrrole nucleus of 1,4,6-triazaindene. It was interesting to know whether or not the 3-position of 1,4,6-triazaindenes was reactive to electrophilic reagents like the β -position of indole. Since, however, the compound was negative to the Ehrlich reagent, the pyrimidine nucleus was supposed to have a great influence on the reaction at 3-position. When PPy-XV was allowed to react with 40% dimethylamine and 37% formalin in glacial acetic acid, the expected ethyl 3-dimethylaminomethyl-5,7-diethoxy-

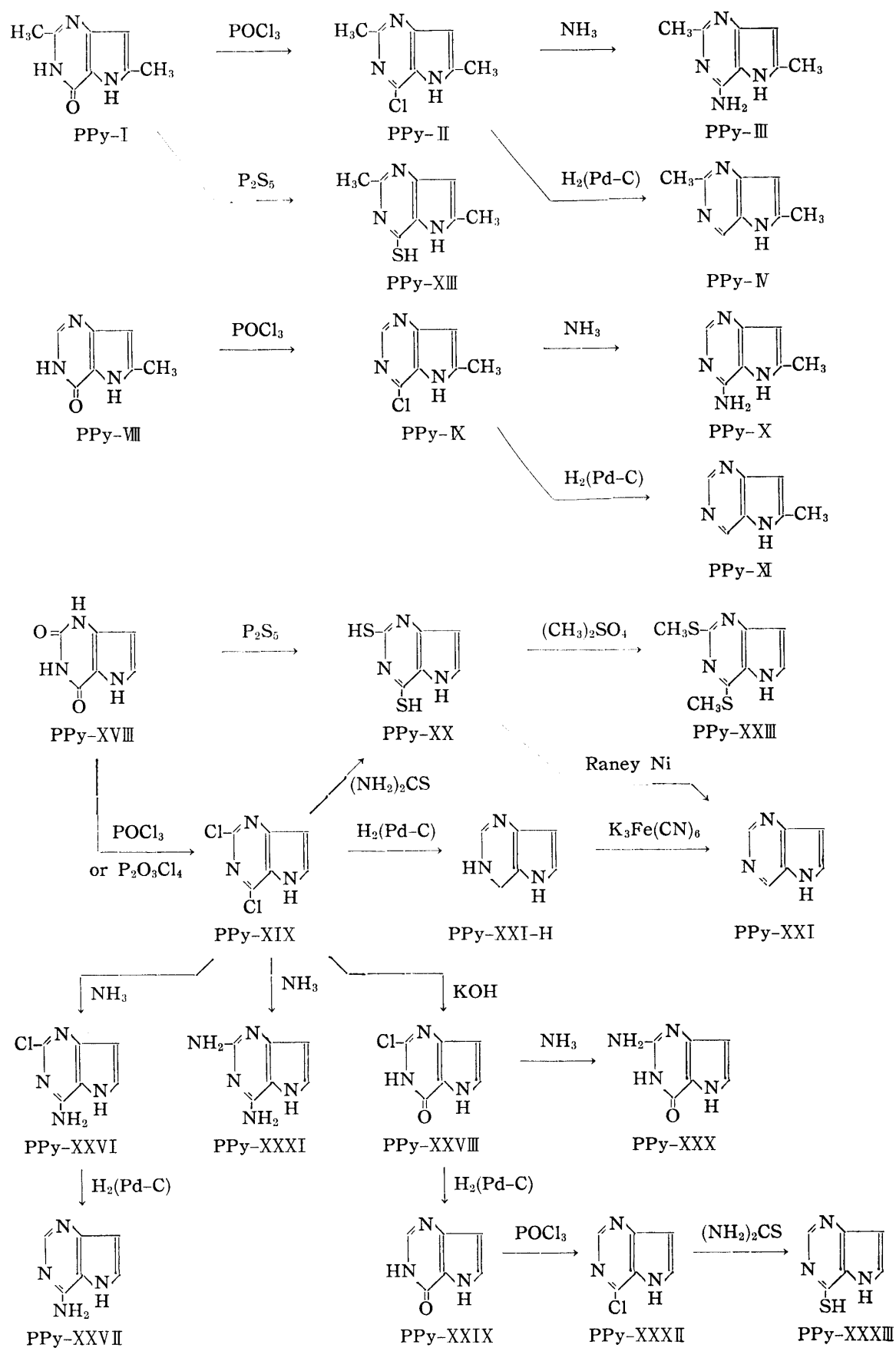


Chart 2.

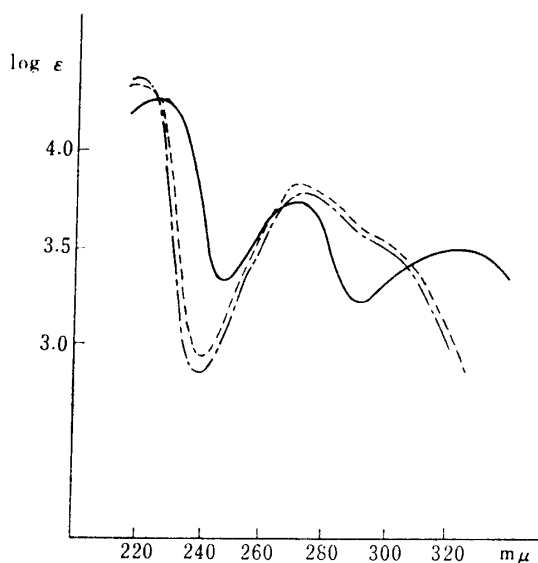


Fig. 3. Ultraviolet Absorption Spectra of 1,4,6-Triazaindene (PPy-XXI)

— pH 3.2
 --- pH 10.3
 - · - MeOH

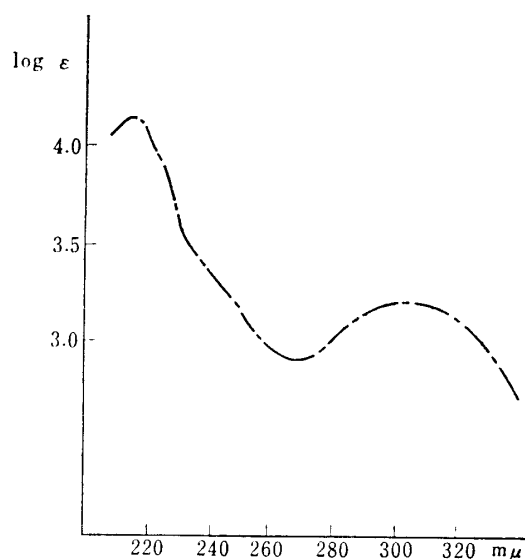


Fig. 4. Ultraviolet Absorption Spectrum of Dihydro-1,4,6-triazaindene Hydrochloride (PPy-XXI-H)

- · - MeOH

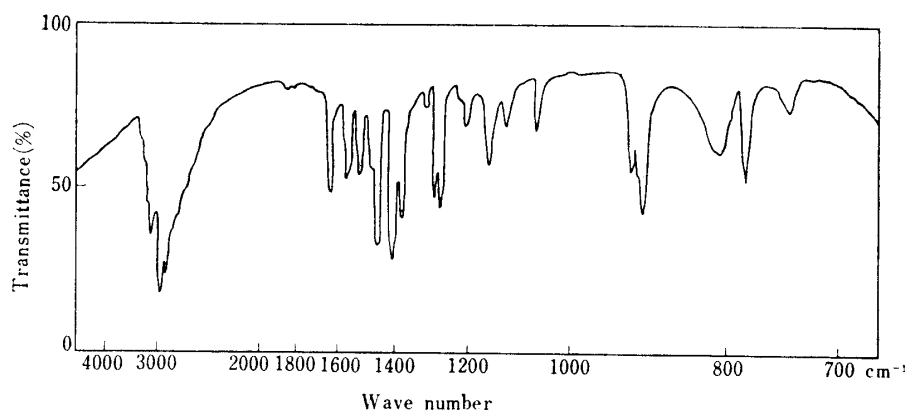


Fig. 5. Infrared Absorption Spectrum of 1,4,6-Triazaindene (PPy-XXI) in Nujol

1,4,6-triazaindene-2-carboxylate (PPy-XXXV) was obtained, which on further reaction with methyl iodide produced the methiodide (PPy-XXXVI) (Chart 3).

It has to be mentioned at this stage that the ultraviolet absorption spectra of 1,4,6-triazaindenes synthesized by two reactions, that is, by the Madelung and Reissert

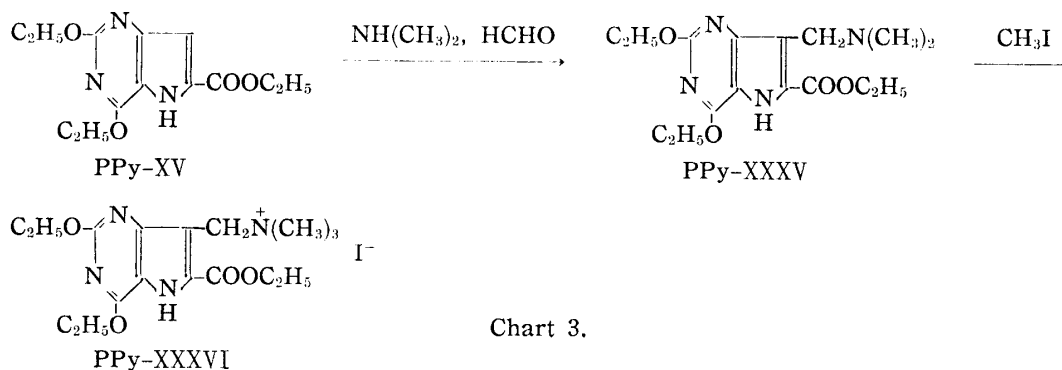


Chart 3.

methods showed a good identity. For example, PPy-IV and PPy-XI produced by the Madelung method were superimposable on those of PPy-XXI, which was synthesized by the Reissert method (Figs. 6, 7, and 3). A similar observation was made on PPy-VIII and PPy-XXIX (Figs. 8 and 9), and between PPy-X and PPy-XXVII (Figs. 10 and 11).

Confirmation of the structure assigned to 1,4,6-triazaindenes was further obtained from the nuclear magnetic resonance spectra measured in deuterium oxide, *N* sulfuric dideuterio acid and *N* sodium deuterioxide as shown in Table I. In the spectra of PPy-IV, VIII, X, and XI, one aromatic methyl signal (2-CH_3) and one aromatic proton (3-H)

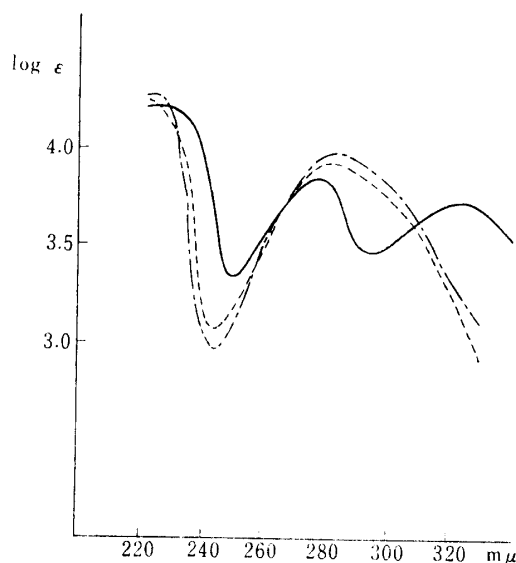


Fig. 6. Ultraviolet Absorption Spectra of 2,5-Dimethyl-1,4,6-triazaindene (PPy-IV)

— pH 3.1
 --- pH 10.3
 - - - MeOH

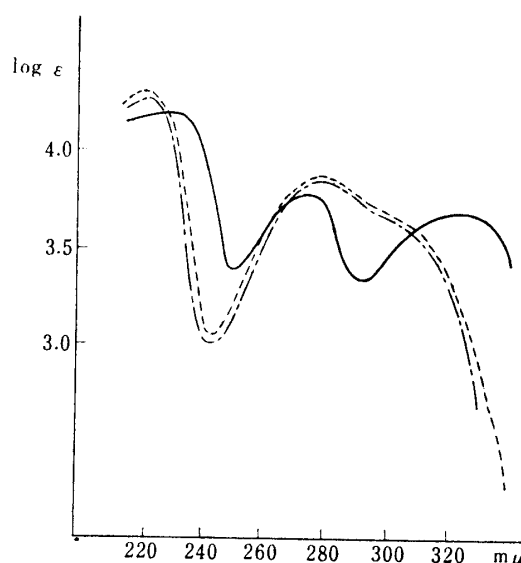


Fig. 7. Ultraviolet Absorption Spectra of 2-Methyl-1,4,6-triazaindene (PPy-XI)

— 0.001N HCl
 --- 0.001N NaOH
 - - - MeOH

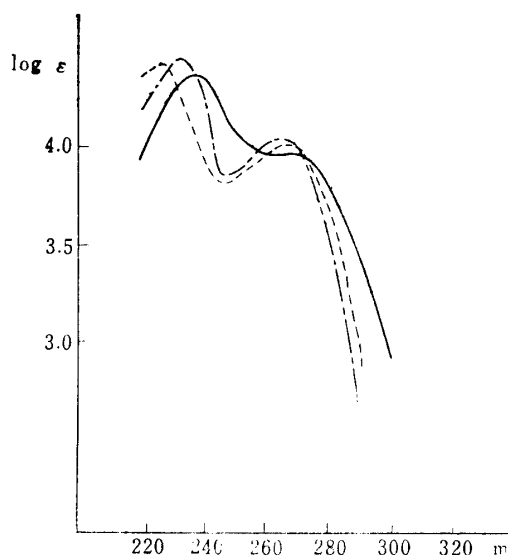


Fig. 8. Ultraviolet Absorption Spectra of 2-Methyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-VIII)

— 0.01N HCl
 --- 0.01N NaOH
 - - - MeOH

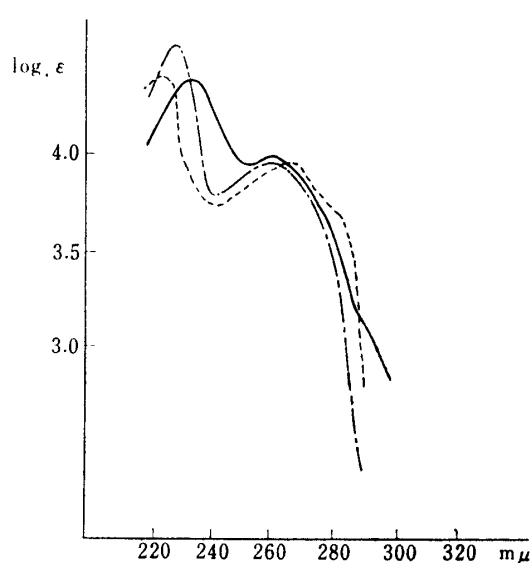


Fig. 9. Ultraviolet Absorption Spectra of 7-Oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XXIX)

— 0.01N HCl
 --- 0.01N NaOH
 - - - MeOH

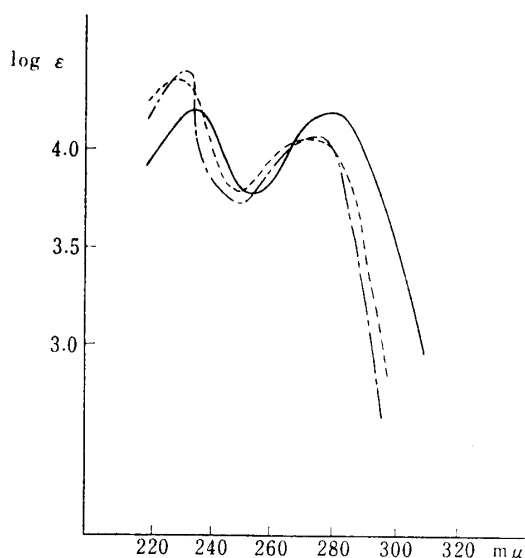


Fig. 10. Ultraviolet Absorption Spectra of 2-Methyl-7-amino-1,4,6-triazaindene (PPy-X)

— 0.01N HCl
 --- 0.01N NaOH
 - · - MeOH

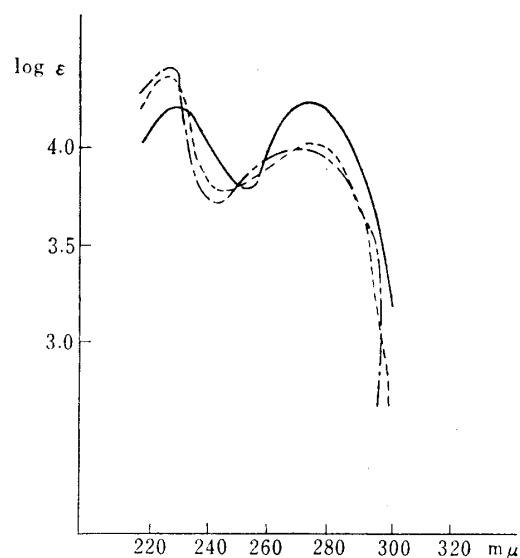


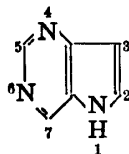
Fig. 11. Ultraviolet Absorption Spectra of 7-Amino-1,4,6-triazaindene (PPy-XXVII)

— 0.01N HCl
 --- 0.01N NaOH
 - · - MeOH

appeared at 2.33~2.74 and 6.10~6.75 as a single peak, respectively. In PPy-XVIII, XXI, XXVII, and XXIX, 2-H and 3-H appeared as doublet at 7.23~8.45 and 6.05~6.97. When the spectrum of PPy-XXI was measured in deuterium oxide, 5-H and 7-H overlapped and appeared as a single peak of two protons at 8.40, and 2-H and 3-H came out as doublet at 7.57 and 6.29 (Fig. 12). Recently Gatlin²⁾ stated with eight naturally occurring nucleosides that the nuclear magnetic resonance spectra measured in dimethyl sulfoxide revealed exchangeable protons. Measurements were made on nine triazaindenes shown in Table II. It was found that in PPy-IV, 1N-H of the pyrrole nucleus appeared as a broad peak at 11.4, and 3-H and 7-H as single peaks at 6.20 and 8.60. In the spectrum of PPy-VIII, 1N-H and 6N-H appeared as a broad peak overlapping at 11.7, suggesting that the 7-keto form is operative. In PPy-XVIII, two broad peaks appeared at 10.6 and 10.4, each corresponding to one proton. These may be due to 4N-H and 6N-H, and the finding indicates that the compound had the 5,7-diketo form. The spectrum of PPy-XXIX shows a broad peak of two protons at 12.0, which is also indicative of the presence of the 7-keto form. On the contrary the spectrum of PPy-X showed two protons signal at 6.37, suggesting the 7-amino form of the compound. Similarly in PPy-XXVII, two protons of 7-NH₂ appeared at 6.64. In PPy-XXX, 1N-H and 6N-H appeared as a broad peak overlapping at 11.4, and two protons of 5-NH₂ and one proton of 3-H appeared as a broad peak overlapping at 5.95, indicating the 5-amino-7-keto form of the compound. The spectrum of PPy-XXI shows one proton signal of 1N-H at 11.8 as a broad peak and 2-H signal at 7.09 as triplet, due to spin-spin interaction with 1N-H and 3-H, and the latter at 6.62 as a broad peak (Fig. 12).

From these nuclear magnetic resonance data, it was confirmed that 1,4,6-triazaindene had a fused heterobicyclic structure consisted of the pyrimidine ring and the pyrrole ring as described above. Furthermore it was made clear that the amino group at 5- or 7-position existed as such but the hydroxyl group it took the 5- or 7-keto form as in the purine nucleus.

2) L. Gatlin, J. C. Davis, Jr. : J. Am. Chem. Soc., 84, 4464 (1962).

TABLE I. Nuclear Magnetic Resonance of Derivatives of 1,4,6-Triazaindene in Deuterium Oxide, Sodium Deuterioxide and Sulfuric Dideuterio Acid^{a)}

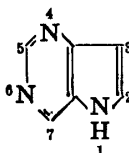
Compd.	Substituents				Solvent	Chemical shifts [δ (p.p.m.)] ^{b)} and coupling constants [J (c.p.s.)]				
	2	3	5	7		2	3	5	7	J _{2,3}
PPy-N	CH ₃	H	CH ₃	H	N D ₂ SO ₄	2.66	6.55	2.82	8.81	
PPy-VIII	"	"	H	OH	N NaOD	2.33	6.10	8.09		
PPy-X	"	"	"	NH ₂	N D ₂ SO ₄	2.42	6.16	8.28		
PPy-XI	"	"	"	H	"	2.74	6.75	8.94	8.94	
PPy-XVIII	H	"	OH	OH	N NaOD	7.23 (d) ^{c)}	6.05 (d)			3
PPy-XXI	"	"	H	H	D ₂ O	7.57 (d)	6.30 (d)	8.40	8.40	3
					N NaOD	8.04 (d)	6.57 (d)		{8.74 8.54 9.22 9.04	2
					N D ₂ SO ₄	8.45 (d)	6.97 (d)			3
PPy-XXVII	"	"	"	NH ₂	"	7.70 (d)	6.54 (d)	8.37		3
PPy-XXIX	"	"	"	OH	N NaOD	7.42 (d)	6.44 (d)	8.14		3

a) All spectra were obtained at 40° on a Varian A 60 NMR spectrometer operating at 60 Mc.p.s.

Each compound was dissolved in the solvent indicated in Table I to give a concentration of 5%.

b) All shifts in p.p.m. are reported relative to tetramethylsilane as external reference.

c) d: doublet.

TABLE II. Nuclear Magnetic Resonance of Derivatives of 1,4,6-Triazaindene in Dimethyl Sulfoxide^{a)}

Compd.	Substituents				Chemical shifts [δ (p.p.m.)] ^{b)} and coupling constants [J (c.p.s.)]							
	2	3	5	7	1N-H	2	3	4N-H	6N-H	5	7	J _{1,2} J _{1,3} J _{2,3}
PPy-N	CH ₃	H	CH ₃	H	11.4 (b) ^{c)}		6.20				8.60	
PPy-VIII ^{d)}	"	"	H	OH	11.7 (b)		6.10 (d) ^{c)}		11.7 (b)	7.73		2
PPy-X ^{d)}	"	"	"	NH ₂	10.7 (b)		6.07			8.03	6.37	
PPy-XVIII ^{d)}	H	"	OH	OH	11.7 (b)	7.07 (t) ^{c)}	5.87 (b)	{11.4 (b) 11.6 (b)				3 3
PPy-XXI	"	"	H	H	11.8 (b)	7.90 (t)	6.62 (b)			{8.92 8.82		3 3
PPy-XXVII	"	"	"	NH ₂	10.9 (b)	7.47 (d)	6.34 (d)			8.10	6.64	3
PPy-XXIX	"	"	"	OH	12.0 (b)	7.37 (t)	6.39 (t)		12.0 (b)	7.80		3 3 3
PPy-XXX	"	"	NH ₂	"	11.4 (b)	7.10 (t)	5.95 (b)		11.4 (b)	5.95 (b)		3 3
PPy-XXXI ^{e)}	"	"	"	NH ₂	12.3 (b)	7.45 (d)	6.14 (d)			{7.19 8.28 (b)		3

a) All spectra were obtained at 40° on a Varian A 60 NMR spectrometer operating at 60 Mc.p.s.

Each compound was dissolved in dimethyl sulfoxide to give a concentration of 5%.

b) All shifts in p.p.m. measured from tetramethylsilane as internal reference.

c) b: broad, d: doublet, t: triplet

d) Dissolved with warming.

e) PPy-XXXI was isolated as the hydrochloride.

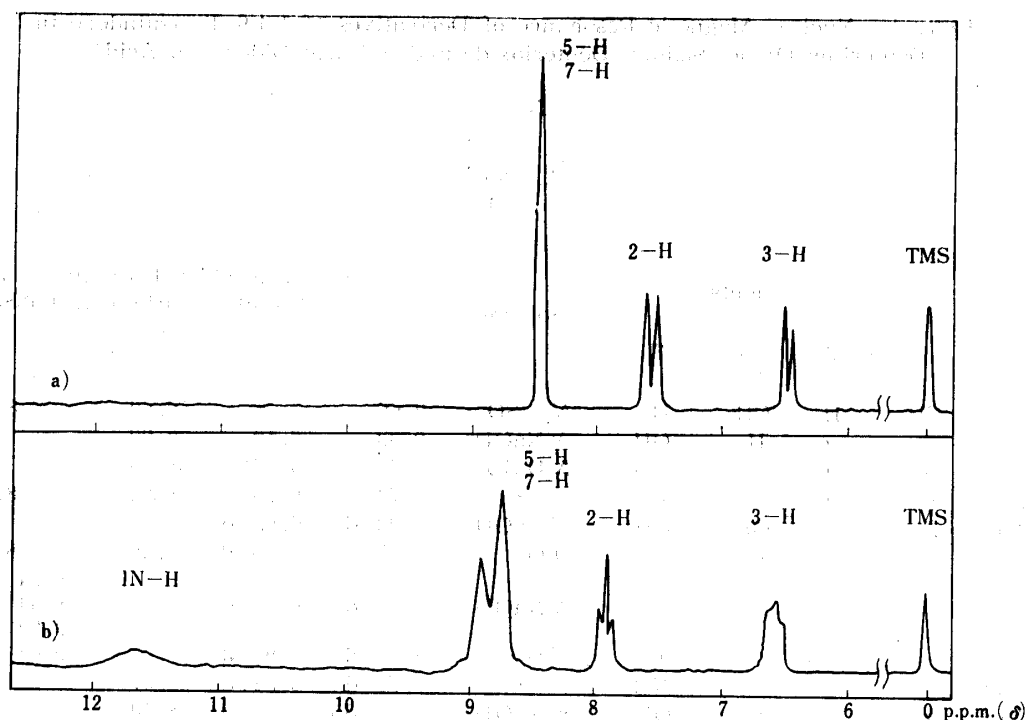


Fig. 12. Nuclear Magnetic Resonance Spectra of 1,4,6-Triazaindene (PPy-XXI) at 60 Mc.p.s., a) in D_2O , b) in Dimethyl Sulfoxide

The biological activities of 1,4,6-triazaindenes were tested by Kaziwara and Watanabe with their anticancer activities on Yoshida sarcoma, Ehrlich ascites carcinoma, and adenocarcinoma 755, by Ohmura and Hemmi with the growth inhibitory activities on *Lactobacillus casei*, *Streptococcus faecalis*, and *Tetrahymena geleii*, and by Araki and Ito with the inhibitory activities on the outgrowth of chick embryo fibroblast.

These tests eventually demonstrated that only PPy-XII showed a growth inhibitory activity on lactic acid bacteria and protozoa and was active against Yoshida sarcoma. However, 9-deazaadenine (PPy-XXVII), 9-deazahypoxanthine (PPy-XXIX), and 9-deazaguanine (PPy-XXX), which were isosteric to the naturally occurring purines, showed no such activities. Whereas PPy-XXXIII, an isoster of purine-6-thiol, showed no activity, PPy-XXXI, an isoster of 2,6-diaminopurine, exhibited a growth inhibitory activity on lactic acid bacteria and protozoa.

Experimental^{*3}

5,7-Dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylic Acid (PPy-XVI)—Ethyl 5,7-diethoxy-1,4,6-triazaindene-2-carboxylate (PPy-XV) (2 g.; 0.0072 mole) and HCl (10 ml.) were refluxed for 6 hr. and the resulting crystals (1.3 g. or 93%) was recrystallized from H_2O (3 L.) (m.p. $>360^\circ$). *Anal.* Calcd. for $C_7H_5O_4N_3$: C, 43.08; H, 2.58; N, 21.54. Found: C, 42.57; H, 2.98; N, 21.66.

IR absorption spectrum of the product was in accord with that of PPy-XVI produced from PPy-XLIV.^{*1}

5,7-Dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene (PPy-XVIII)—A mixture of PPy-XVI (1 g.; 0.0051 mole) and Cu powder (100 mg.) was heated in a metal bath at $330\sim 340^\circ$. After cease of the evolution of CO_2 was confirmed by $Ba(OH)_2$ solution, the reaction mixture was extracted with $NNaOH$ and the yellow needles separated from the extract were dissolved in H_2O , and the solution was acidified with AcOH to give a colorless precipitate, which was recrystallized from H_2O into colorless needles, m.p. $>360^\circ$ (600 mg. or 78%). *Anal.* Calcd. for $C_6H_3O_2N_3$: C, 47.68; H, 3.34; N, 27.81. Found: C, 47.02; H, 3.41; N, 27.91.

^{*3} All melting points are uncorrected.

Ethyl 4,6-Diethyl-5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylate (PPy-V)—A mixture of PPy-XV (1 g.; 0.0036 mole) and Cu powder (500 mg.) was heated at 200° then at 220–240° for 10 min. *in vacuo*. The reaction mixture was extracted with EtOH and the extract was concentrated and mixed with H₂O to deposit a pale brown precipitate, m.p. 205° (700 mg. or 70%), which was recrystallized from aq. EtOH into colorless needles, m.p. 205°. *Anal.* Calcd. for C₁₃H₁₇O₄N₃: C, 55.90; H, 6.14; N, 15.05. Found: C, 56.21; H, 6.46; N, 14.95.

4,6-Diethyl-5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxylic Acid (PPy-VI)—A solution of NaOH (1.5 g.) in H₂O (2 ml.) was heated with EtOH (15 ml.) and PPy-V (840 mg.; 3 mmoles) on a water bath for 2 hr. The EtOH was distilled and the residue was diluted with H₂O, acidified with HCl, and the separated colorless precipitate, m.p. 303–305° (700 mg. or 93%), was recrystallized from MeOH, m.p. 306°. *Anal.* Calcd. for C₁₁H₁₃O₄N₃: C, 52.58; H, 5.22; N, 16.73. Found: C, 51.90; H, 5.23; N, 16.71.

4,6-Diethyl-5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene (PPy-VII)—Heating of PPy-VI (150 mg.; 0.6 mmole) at 310–320° evolved CO₂. After 10 min., the residue was scrubbed against the wall with petr. benzin and the resulting powdery substance, m.p. 130–135° (100 mg. or 80%), was purified by dissolving in benzene and precipitating with petr. benzin into colorless needles, m.p. 142°. *Anal.* Calcd. for C₁₀H₁₃O₂N₃: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.31; H, 6.43; N, 20.14.

4,6-Diethyl-5,7-dioxo-4,5,6,7-tetrahydro-1,4,6-triazaindene-2-carboxamide (PPy-XII)—PPy-V (300 mg.; 1.1 mmoles), EtOH (5 ml.), and 28% NH₄OH (3 ml.) were heated in a sealed tube at 140–150° for 5 hr. The reaction mixture was extracted with EtOH, the extract was concentrated, and the substance precipitated by addition of H₂O to the concentrated extract was purified by recrystallization from aq. EtOH into colorless powdery crystals, m.p. 298° (200 mg. or 74%). *Anal.* Calcd. for C₁₁H₁₄O₃N₄: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.73; H, 5.92; N, 22.81.

2,5-Dimethyl-7-chloro-1,4,6-triazaindene (PPy-II)—2,5-Dimethyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-I) (4.7 g.; 0.029 mole) was refluxed with POCl₃ (27 ml.) for 3 hr. and the excess POCl₃ was distilled. The residue was poured into ice water (80 ml.) and made alkaline with NH₄OH, and the resulting precipitate was filtered and extracted with AcOEt (130 ml.). The extract was concentrated and the separated pale yellow substance, m.p. 157–158° (4.8 g. or 92%), was recrystallized from AcOEt into colorless needles, m.p. 158–160°. *Anal.* Calcd. for C₈H₈N₃Cl: C, 52.80; H, 4.44; N, 23.14; Cl, 19.52. Found: C, 52.58; H, 4.15; N, 22.82; Cl, 20.02.

2-Methyl-7-chloro-1,4,6-triazaindene (PPy-IX)—2-Methyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-VIII) (5 g.; 0.034 mole) was refluxed with POCl₃ (24 ml.) for 3 hr. and the excess chloride was distilled. The residue was poured into ice water (40 ml.), adjusted to pH 7 with NH₄OH and placed in a cool place overnight, and the resulting precipitate was filtered and dissolved in AcOEt. The filtrate was extracted with AcOEt and the extract was combined with the above AcOEt solution and concentrated to give colorless needles, m.p. 178° (decomp.) (4 g. or 71%). The product was purified by recrystallization from AcOEt, m.p. 182° (decomp.). *Anal.* Calcd. for C₇H₆N₃Cl: C, 50.16; H, 3.61; N, 25.07. Found: C, 50.24; H, 3.84; N, 25.03.

5,7-Dichloro-1,4,6-triazaindene (PPy-XIX)—i) A mixture of PPy-XVIII (5 g.; 0.033 mole), POCl₃ (400 ml.), and dimethylaniline (10 ml.) was refluxed for 2 hr., the excess POCl₃ was distilled and the residue was poured into ice water (300 ml.). The solution was adjusted to pH 8 with NH₄OH, the resulting precipitate was filtered and extracted with Et₂O (1 L.), and the residue of the extract was recrystallized from 50% MeOH into colorless needles, m.p. 224° (2 g. or 32%). *Anal.* Calcd. for C₆H₃N₃Cl₂: C, 38.39; H, 1.61; N, 22.34; Cl, 37.72. Found: C, 38.42; H, 1.90; N, 21.62; Cl, 38.89.

ii) PPy-XVIII (3 g.; 0.02 mole) and pyrophosphoryl chloride (the upper layer of the mixture which was prepared by adding 0.5 equivalent H₂O to POCl₃ and heating for 1.5 hr.) (24 ml.) were heated in a sealed tube at 165° for 12.5 hr. The resinous substance was removed and the solution, after being concentrated, was poured into ice water (120 ml.) and extracted with Et₂O (1.2 L.). The extract was dried over K₂CO₃ and concentrated, and the resulting pale yellow substance, m.p. 225–227° (2.1 g. or 56%), was recrystallized from aq. MeOH into colorless needles, m.p. 226–228°. The product showed no depression in melting point when mixed with the product in (i).

7-Chloro-1,4,6-triazaindene (PPy-XXXII)—PPy-XXIX (850 mg.; 6.3 mmoles) was refluxed with POCl₃ (20 ml.) for 2 hr. and the excess POCl₃ was distilled *in vacuo*. The residue was poured in to ice water, the solution was adjusted to pH 7 with NH₄OH and placed in a cool place overnight, and the separated product was recrystallized from 50% EtOH into pale yellow needles, m.p. 186–188° (decomp.). (Positive to flame reaction of Cl). *Anal.* Calcd. for C₆H₄N₃Cl: C, 46.91; H, 2.63; N, 27.35. Found: C, 46.87; H, 2.91; N, 27.09.

5-Chloro-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XXVIII)—PPy-XIX (3 g.; 0.016 mole) was refluxed in 2N KOH (30 ml.) for 4.5 hr. and acidified with glacial AcOH to give a colorless precipitate, which was recrystallized from H₂O (1.5 L.), m.p. 270° (decomp.) (1.6 g. or 59%). *Anal.* Calcd. for C₆H₄ON₃Cl: C, 42.48; H, 2.38; N, 24.77; Cl, 20.91. Found: C, 42.10; H, 2.31; N, 24.61; Cl, 20.57.

5,7-Dimercapto-1,4,6-triazaindene (PPy-XX)—i) A solution of PPy-XIX (500 mg.; 2.7 mmoles) and thiourea (400 mg., 5.2 mmoles) in EtOH (13 ml.) was refluxed for 5 hr. to yield a pale yellow precipitate. The precipitate was dissolved in N NaOH (10 ml.) and acidified with AcOH, and the resulting precipitate

was recrystallized from H₂O into pale yellow needles, m.p. $>360^{\circ}$ (250 mg. or 51%), (positive to S reaction). *Anal.* Calcd. for C₆H₅N₃S₂: C, 39.33; H, 2.75; N, 22.94. Found: C, 39.41; H, 2.87; N, 23.19.

ii) A mixture of PPy-XVIII (500 mg.; 3.3 mmoles), P₂S₅ (3 g.), and tetralin (20 ml.), was heated at 170–200° for 1.5 hr. and at 200–205° for 4 hr. with stirring to separate a precipitate. The precipitate was dissolved in 3*N* NaOH (20 ml.), acidified with glacial AcOH, and the resulting product was recrystallized from H₂O (300 ml.) to give pale yellow needles, m.p. $>360^{\circ}$ (150 mg. or 25%). *Anal.* Calcd. for C₆H₅N₃S₂: C, 39.33; H, 2.75; N, 22.94; S, 34.95. Found: C, 39.87; H, 2.92; N, 23.27; S, 34.18.

5,7-Dimethylmercapto-1,4,6-triazaindene (PPy-XXIII)—A solution of PPy-XX (70 mg.; 0.38 mmole) in 0.5*N* NaOH (2 ml.) was vigorously shaken with dimethylsulfate (0.1 ml.), and the resulting colorless precipitate was recrystallized from 60% MeOH, m.p. 230°. *Anal.* Calcd. for C₈H₉N₃S₂: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.75; H, 4.20; N, 19.23.

7-Mercapto-1,4,6-triazaindene (PPy-XXXIII)—A solution of PPy-XXXII (700 mg.; 4.6 mmoles) and thiourea (350 mg.; 4.6 mmoles) in EtOH (20 ml.) was refluxed for 4 hr. and the resulting substance was dissolved in *N* NaOH and acidified with glacial AcOH to separate a pale yellow precipitate, which was recrystallized from H₂O (300 ml.) into pale yellow needles, m.p. $>300^{\circ}$ (300 mg. or 43%), (positive to S reaction). *Anal.* Calcd. for C₆H₅N₃S: C, 47.65; H, 3.33; N, 27.78. Found: C, 47.66; H, 3.59; N, 27.99.

2,5-Dimethyl-7-mercapto-1,4,6-triazaindene (PPy-XIII)—2,5-Dimethyl-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-I) (700 mg.; 4.3 mmoles) and P₂S₅ (3.8 g.) were heated in tetralin (16 ml.) at 190–200° for 12 hr. The separated precipitate was washed with petr. ether and extracted with hot water (70 ml.), the extract was adjusted to pH 4 with NH₄OH, and the resulting substance was recrystallized from 30% MeOH into a colorless crystalline powder, m.p. 314–315° (decomp.). *Anal.* Calcd. for C₈H₉N₃S: C, 53.60; H, 5.06; N, 23.45. Found: C, 53.38; H, 4.77; N, 23.23.

2,5-Dimethyl-7-amino-1,4,6-triazaindene (PPy-III)—A mixture of PPy-II (1.5 g.; 0.0083 mole), Cu powder (40 mg.), EtOH-NH₃ (6.3 ml.), and saturated NH₄OH (2 ml.) was heated in a sealed tube at 160–170° for 13 hr. The Cu powder was filtered, the filtrate was evaporated to dryness, and the residue was treated with 0.5*N* NaOH (25 ml.). The insoluble substance was extracted with EtOH and the EtOH solution was concentrated, remaining a pale brown substance, which was recrystallized from MeOH to give colorless needles, m.p. 300–302° (750 mg. or 56%). *Anal.* Calcd. for C₈H₁₀N₄: C, 59.24; H, 6.22; N, 34.55. Found: C, 59.25; H, 6.38; N, 34.85.

2-Methyl-7-amino-1,4,6-triazaindene (PPy-X)—A mixture of PPy-IX (400 mg.; 2.4 mmoles), Cu powder (20 mg.), EtOH-NH₃ (1.8 ml.), and saturated NH₄OH (6 ml.) was heated in a sealed tube at 150–160° for 12 hr. The Cu powder was filtered, the filtrate was evaporated to dryness, and the remaining greenish brown substance was treated with 0.5*N* NaOH (5 ml.). The insoluble product was extracted with EtOH and the EtOH solution was concentrated to leave a pale brown substance (250 mg. or 71%), which was recrystallized from MeOH, m.p. 327–328° (decomp.). *Anal.* Calcd. for C₇H₈N₄: C, 56.74; H, 5.44; N, 37.82. Found: C, 56.61; H, 5.54; N, 36.97.

5-Chloro-7-amino-1,4,6-triazaindene (PPy-XXVI)—A mixture of PPy-XIX (3 g.; 0.016 mole) and EtOH-NH₃ (60 ml.) was heated in an autoclave at 120° for 12 hr., the solvent was distilled and the remaining substance was recrystallized from H₂O (2.5 L.) into colorless needles, m.p. 264° (decomp.) (1.6 g. or 59%). *Anal.* Calcd. for C₆H₅N₄Cl: C, 42.73; H, 2.99; N, 33.25; Cl, 21.04. Found: C, 42.97; H, 3.10; N, 33.10; Cl, 21.39.

5,7-Diamino-1,4,6-triazaindene Hydrochloride (PPy-XXXI)—PPy-XIX (4 g.; 0.021 mole) and EtOH-NH₃ (60 ml.) were heated in an autoclave at 200° for 20 hr. and the solvent was distilled. The residual brown substance was extracted with hot water and the aqueous solution was treated with charcoal and concentrated to give colorless needles, m.p. 285° (decomp.) (3.6 g. or 92%), which were recrystallized from H₂O, m.p. 287° (decomp.). *Anal.* Calcd. for C₆H₇N₅·HCl: C, 38.83; H, 4.34; N, 37.73; Cl, 19.10. Found: C, 38.50; H, 4.66; N, 36.70; Cl, 18.21.

5-Amino-7-oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XXX)—PPy-XXVIII (4 g.; 0.024 mole) and EtOH-NH₃ (50 ml.) were heated in an autoclave at 200° for 20 hr. and the solvent was distilled to leave a gray powder. The powder was stirred with 50% KOH (5 ml.) and the mixture was diluted with 5 times its volume of H₂O and acidified with glacial AcOH to deposit a precipitate, which was recrystallized from H₂O (70 ml.) into colorless fine crystals, m.p. $>300^{\circ}$ (850 mg. or 24%). *Anal.* Calcd. for C₆H₆ON₄: C, 48.01; H, 4.03; N, 37.33. Found: C, 48.15; H, 4.33; N, 37.16.

2,5-Dimethyl-1,4,6-triazaindene (PPy-IV)—To a suspension of PPy-II (2.2 g.; 0.012 mole) and MgO (1.2 g.) in 50% EtOH (120 ml.) was added Pd-C prepared from 2% PdCl₂ solution (12 ml.) and charcoal (1.2 g.) and the mixture was shaken in an atmosphere of H₂ for 2 hr., when 115% of the theoretical volume of H₂ was absorbed. The catalyst was filtered, the filtrate was evaporated to dryness *in vacuo*, and the remaining pale yellow substance was stirred with 10% NaOH (22 ml.) to give a precipitate. The precipitate was extracted with hot AcOEt and the extract was cooled to yield colorless prisms (1.2 g.). Another crop was obtained from the filtrate, and the combined crude product (1.5 g.) was recrystallized from AcOEt into colorless needles, m.p. 211–212° (1.3 g. or 73%). *Anal.* Calcd. for C₈H₉N₃: C, 65.28; H, 6.16; N, 28.56. Found: C, 65.58; H, 6.04; N, 28.47.

2-Methyl-1,4,6-triazaindene (PPy-XI)—To a suspension of PPy-X (1.7 g.; 0.01 mole) and MgO (1.02 g.) in 50% EtOH (100 ml.) was added Pd-C prepared from 2% PdCl₂ solution (10.2 ml.) and charcoal (1.02 g.) and the mixture was shaken in an atmosphere of H₂ for 1 hr., when 122% of the theoretical volume of H₂ was absorbed. The catalyst was filtered, the filtrate was concentrated *in vacuo*, and the remaining substance (1.15 g.) was recrystallized from AcOEt to afford colorless needles, m.p. 237° (decomp.) (900 mg. or 66%). *Anal.* Calcd. for C₇H₇N₃: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.10; H, 5.37; N, 31.28.

7-Oxo-6,7-dihydro-1,4,6-triazaindene (PPy-XXIX)—To a suspension of PPy-XXVIII (300 mg.; 1.8 mmoles) in EtOH (40 ml.) was added Pd-C prepared from 2% PdCl₂ solution (5 ml.) and charcoal (500 mg.), and the mixture was shaken in an atmosphere of H₂ for 4.5 hr., when 135% of the theoretical volume of H₂ was absorbed. The catalyst was filtered, the EtOH was distilled, and the residual colorless powder (300 mg.) was dissolved in hot NNaOH and filtered. The solution was acidified with glacial AcOH and the resulting precipitate was recrystallized from H₂O to give colorless prisms, m.p. >300°. The product was colored from about 290° and showed no distinct melting point. *Anal.* Calcd. for C₆H₅ON₃: C, 53.34; H, 3.73; N, 31.10. Found: C, 53.46; H, 3.79; N, 31.00.

7-Amino-1,4,6-triazaindene (PPy-XXVII)—To a suspension of PPy-XXVI (300 mg.; 1.8 mmoles) in EtOH (40 ml.) was added Pd-C prepared from 2% PdCl₂ solution (5 ml.) and charcoal (500 mg.), and the mixture was shaken in an atmosphere of H₂, when 125% of the theoretical volume of H₂ was absorbed in 15 min. The catalyst was filtered, the EtOH was distilled, the residual colorless powder was treated with NNaOH, and the insoluble substance was recrystallized from H₂O to yield colorless needles, m.p. >300°. The product browned from about 280° and decomposed at 320°. *Anal.* Calcd. for C₆H₆N₄: C, 53.72; H, 4.51. Found: C, 53.43; H, 4.42.

1,4,6-Triazaindene (PPy-XXI)—i) To a solution of PPy-XX (400 mg., 2.2 mmoles) in EtOH (30 ml.) was added Raney Ni (4 g.) and the mixture was refluxed on a water bath for 2 hr. and left standing overnight. The catalyst was filtered and washed with hot EtOH, and the washing and the filtrate were combined and concentrated *in vacuo* to 1/3 of the original volume. The concentrate was treated with charcoal and further concentrated to 1 ml. and the separated product (210 mg.) was recrystallized from AcOEt to yield colorless prisms, m.p. 177°. *Anal.* Calcd. for C₆H₅N₃: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.72; H, 4.02; N, 35.09.

ii) a) Catalytic Reduction of 5,7-Dichloro-1,4,6-triazaindene (PPy-XIX): Formation of Dihydro-1,4,6-triazaindene (PPy-XXI-H).

To a solution of PPy-XIX (1 g., 0.0053 mole) in MeOH (80 ml.) was added Pd-C prepared from 2% PdCl₂ solution (12 ml.) and charcoal (800 mg.), and the mixture was shaken in an atmosphere of H₂, when 0.0106 mole of H₂ was absorbed soon and 0.0053 mole of H₂ gradually (the theoretical is 0.0106 mole). The catalyst was filtered, and the UV absorption spectrum of the filtrate (Fig. 4) showed a broad absorption maximum at 305 mμ and exhibited no distinct absorption at λ_{max} 270 mμ which was characteristic to 1,4,6-triazaindenes. The solvent was evaporated to dryness in an atmosphere of N₂ and the residue was stirred with 10% NaOH, when it once came into solution but soon a colorless precipitate separated. The precipitate was filtered, washed with H₂O and dissolved in a little EtOH. Pale yellow prisms, m.p. 175° (decomp.), precipitated on addition of a great amount of Et₂O. The product was positive to the Ehrlich reagent and unstable in the air but kept unchanged in N₂. *Anal.* Calcd. for C₆H₇N₃: C, 59.51; H, 5.83; N, 34.70. Found: C, 59.61; H, 5.99; N, 33.94.

b) To a solution of PPy-XIX (3 g., 0.016 mole) in MeOH (120 ml.) was added Pd-C prepared from 2% PdCl₂ solution (30 ml.) and charcoal (2 g.) and the mixture was shaken in an atmosphere of H₂, when 1180 ml. of H₂ (0.016 × 3 mole) was absorbed in 1.5 hr. The catalyst was filtered, the filtrate was concentrated in an atmosphere of N₂, and a solution of the residue in H₂O (40 ml.) was mixed with 30% KOH (18 ml.) to separate crystals. To the reaction mixture was added dropwise a solution of potassium ferri-cyanide (11.8 g.; 0.036 mole) in hot water (50 ml.), when the crystals dissolved to make a clear yellowish brown solution. The solution was stirred for 30 min. at room temperature, neutralized with glacial AcOH and extracted with AcOEt (410 ml.). The extract was dried over anhyd. Na₂SO₄ and concentrated to leave a pale yellow powder (1.3 g.) negative to the Ehrlich reagent. The product was recrystallized from AcOEt, m.p. 172~174° (950 mg. or 50%). *Anal.* Calcd. for C₆H₅H₃: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.59; H, 4.27; N, 35.34.

The product showed no depression in melting point when mixed with PPy-XXI obtained in (i) and its IR and UV absorption spectra were in accord with those of PPy-XXI.

Ethyl 3-Dimethylaminomethyl-5,7-diethoxy-1,4,6-triazaindene-2-carboxylate (PPy-XXXV)—To a suspension of PPy-XV (1.1 g.; 0.004 mole) in glacial AcOH (1.5 ml.) was added a mixture of 40% dimethylamine (500 mg.; 4.4 mmoles), glacial AcOH (1.5 ml.), and 37% formalin (440 mg.; 4.4 mmoles) with cooling. After 20 min. the mixture was heated on a water bath for 2 hr. and left standing overnight at room temperature. The resulting pale yellow solution was diluted with H₂O (6 ml.) and extracted with Et₂O to remove non-basic substance. The aqueous layer was made alkaline with 10% NaOH and the separated oily substance, which solidified gradually, was recrystallized from petr. ether (ca. 50 ml.) into

colorless needles, m.p. 103~104° (500 mg. or 37%). *Anal.* Calcd. for $C_{16}H_{24}O_4N_4$: C, 57.14; H, 7.19; N, 16.66; C_2H_5O , 40.20. Found: C, 57.40; H, 7.10; N, 16.34; C_2H_5O , 40.21.

Ethyl 3-Dimethylaminomethyl-5,7-diethoxy-1,4,6-triazaindene-2-carboxylate Methiodide (PPy-XXXVI)—A mixture of PPy-XXXV (200 mg.; 0.6 mmole), EtOH (2 ml.), and CH_3I (100 mg.; 0.7 mmole) was kept in a closed vessel, when a small amount of colorless crystals separated out soon. After being kept standing overnight the crystals were filtered off, the filtrate was concentrated, and the remaining syrupy substance was dissolved in a little MeOH. To the MeOH solution was added a great amount of petr. ether, the separated resinous substance was scrubbed against the wall, and the solidified product was recrystallized from Me_2CO -AcOEt (1:2) into colorless needles, m.p. 180° (positive to flame reaction of I). *Anal.* Calcd. for $C_{17}H_{27}O_4N_4I$: C, 42.69; H, 5.69; N, 11.71. Found: C, 43.00; H, 5.91; N, 11.60.

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Summary

1,4,6-Triazaindene and its derivatives corresponding to the naturally occurring purine bases were synthesized from the 1,4,6-triazaindenes reported in the preceding paper. The structures of these derivatives were confirmed by investigating them on their physico-chemical properties such as ultraviolet absorption and nuclear magnetic resonance spectra.

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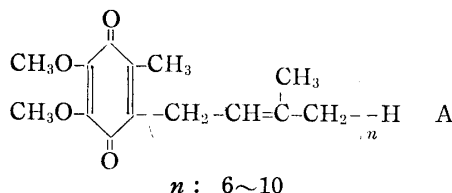
143. Isuke Imada, Yasushi Sanno, and Hiroshi Morimoto :

Photochemical Reaction of Ubiquinone (35). I.*¹

Photochemical Reaction of Ubiquinone (35).*²

(Research Laboratories, Takeda Chemical Industries, Ltd.*³)

In 1957, one of quinones was isolated from beef heart by Crane, *et al.* and made clear that the quinone was involved in the electron transport system. The quinone was named coenzyme Q by Lester, *et al.* On the other hand, a substance having an absorption peak at 272 mμ was isolated from the liver of vitamin A-deficient rats by Heaton, *et al.* and was referred to as ubiquinone by



*¹ This paper constitutes Part II of a series entitled "On the Components of Yeast"; Part I: Biochem. Z., **340**, 155 (1964).

*² A brief report of this work was published as a Communication to the Editor in this Bulletin, **11**, 815 (1963).

*³ Juso-nishino-cho, Higashiyodogawa-ku, Osaka (今田伊助, 三野 安, 森本 浩).