[Chem. Pharm. Bull. 16(11)2195—2199(1968)]

UDC 547.859.1.07 : 615.225.2

Studies on Pyrimidine Derivatives and Related Compounds. LIX.[1] Syntheses of 2,3-Dihydro-1H-pyrazolo[5,1-*b*]purin-2-ones

Akira Takamizawa, Yoshio Hamashima, Sadao Hayashi, and Shoji Sakai

Shionogi Research Laboratory, Shionogi & Co., Ltd.[2]

(Received March 22, 1968)

Syntheses of 2,3-dihydro-1H-pyrazolo[5,1-*b*]purin-2-ones (Va—c) from 7-aminopyrazolo[1,5-*a*]pyrimidin-6-carbohydrazides (IVa—c) involving a ring formation were described. Acid hydrolysis of Va—b gave 6,7-diaminopyrazolo[1,5-*a*]pyrimidines (VIa,b). Both VIa and VIb reproduced Va and Vb by the reaction with phosgene respectively.

Hydrolytic decomposition of Vb under more vigorous condition afforded 6-amino-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine (VIII), which was identified with the compound synthesized by another method. In Va—c remarkable hypocholesteric activity and enhancement effect of lypolitic activity on ACTH were observed.

We reported in our previous paper[3] that some C-substituted 7-aminopyrazolo[1,5-*a*] pyrimidines showed remarkable antipyretic and antiinflammatory activities. It appeared of interest to investigate further the pharmacological properties of 7-aminopyrazolo[1,5-*a*] pyrimidine derivatives based on the facts mentioned above.

Many studies have been done on the syntheses of purine derivatives but it seems to be little on the syntheses of polycyclic purine derivatives with heterocycles. The present investigation was undertaken in order to synthesize some new pyrazolopurine derivatives.

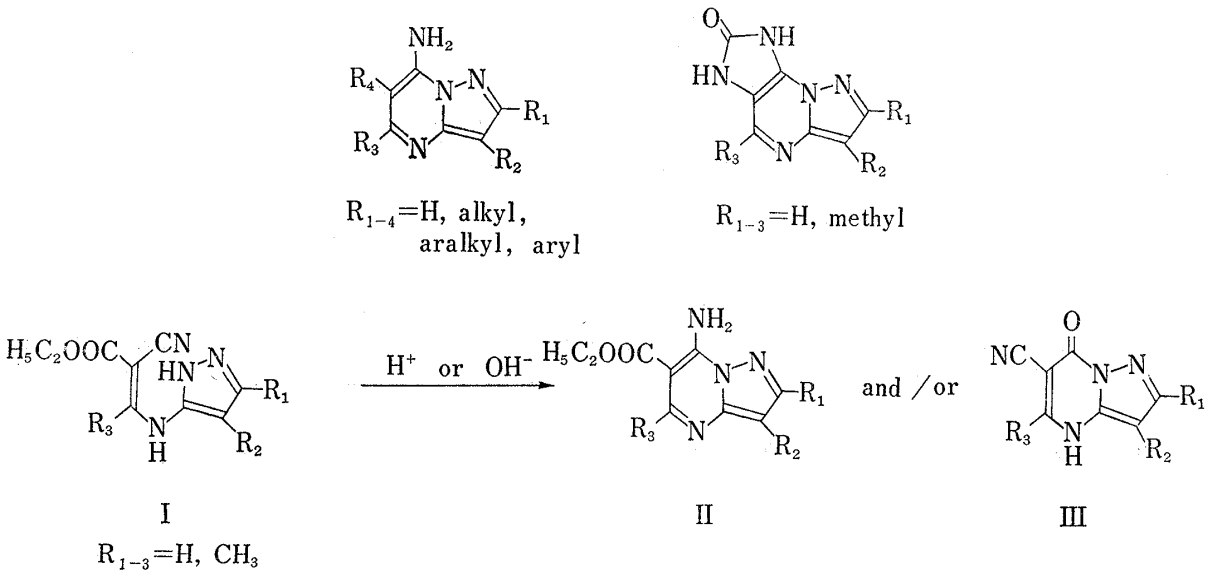

Chart 1

Recently[4] we have revealed that the orientation of the cyclization reaction of ethyl 1-cyano-2-(5-pyrazolyl)amino-2-alkylcrotonate was controlled by the acid or base catalyst

1) Part LVIII: A. Takamizawa, Y. Hamashima, and H. Sato, *J. Org. Chem.*, in contribution.
2) Location: *Sagisu, Fukushima-ku, Osaka.*
3) A. Takamizawa, Y. Hamashima, S. Hayashi, and R. Kido, *Yakugaku Zasshi*, **83**, 745 (1963).
4) A. Takamizawa, Y. Hamashima, S. Sakai, and S. Nagakura, *Bull. Chem. Soc. Japan*, **41**, 2141 (1968).

used. Ethyl 7-aminopyrazolo[1,5-*a*]pyrimidine-6-carboxylates derived from ethyl 1-cyano-2-(5-pyrazolyl)amino-2-crotonates were used as starting materials. A step of the imidazoline ring formation was conveniently carried out by modifying the method of the Curtius reaction.

Refluxing of ethyl 2,3-dimethyl-7-aminopyrazolo[1,5-*a*]pyrimidine-6-carboxylate (IIa) with large excess of hydrazine hydrate in ethanol afforded IVa, mp 287° (decomp.), in 95% yield. The elemental analysis of IVa indicated the empirical formula of $C_9H_{12}ON_6$. The ultraviolet absorption spectrum had similar curve to that of IIa and showed maxima at 234 (4.73) and 313 mμ (4.20). These data concluded the structure of IVa to be 2,3-dimethyl-7-aminopyrazolo[1,5-*a*]pyrimidine-6-carbohydrazide. The reaction of IVa with nitrous acid gave light green crystals (Va), mp >290°, in good yield. The elemental analysis of Va was in agreement with the expected formula, $C_9H_9ON_5$, which corresponded to the constitution of losing ammonia from IVa. The infrared spectrum showed strong carbonyl bands at 1720 and 1692 cm^{-1}. The ultraviolet absorption spectrum showed maxima at 243 (4.46), 290.5 (3.53), 300 (3.43), and 354 mμ (3.77) resembling to that of 7-acylaminopyrazolo[1,5-*a*]pyrimidines.[5] The nuclear magnetic resonance (NMR) spectrum showed a one-proton singlet methine signal at τ 1.87 and two three-proton singlet methyl signals at τ 7.63 and 7.82. These physical data suggested that the structure of Va to be 6,7-dimethyl-2,3-dihydro-1H-pyrazolo [5,1-*b*]purin-2-one. This will be reasonably described as follows: the Curtius reaction firstly occurred at the C_6-position and followed the cyclization between isocyanate, which might be produced, and C_7 amino group. Furthermore, the structure of Va was unequivocally supported by the chemical experiments, too. Namely, the hydrolytic decomposition of Va by hydrochloric acid gave VIa. The elemental analysis of Va was in agreement with the formula of $C_8H_{11}N_5 \cdot 2HCl$ and assumed to be 6,7-diaminopyrazolo[1,5-*a*]pyrimidine dihydrochloride. The reaction of VIa with phosgene reproduced Va in 40% yield. From the data mentioned above, the structures of Va and VIa were determined. Acetylation of Va with acetic anhydride in pyridine gave monoacetate (VII) in 78.8% yield. The infrared spectrum showed carbonyl bands at 1745 and 1703 cm^{-1}. The ultraviolet absorption spectrum was similar to that of Va and showed maxima at 237.5 (4.41), 245.5 (4.38), 258 shoulder (4.27), 292 (3.75), 307 (3.63), and 358 mμ (3.83). NMR spectrum showed a one-proton singlet methine signal at τ 0.77 and three-proton singlet methyl signals at τ 7.18, 7.53, and 7.67. Although the substitution position of the acetyl group may be considered at the C_2-position of imidazolinone moiety in accord with the ultraviolet and infrared spectral findings, further examinations on it were not undertaken. The convenient Curtius reaction in IVa was also quite analogously occurred in IVb and IVc. The reactions of IIb–c with hydrazine hydrate produced IVb–c in good yields. The structures of IVb—c were confirmed by their elemental analyses respectively. The Curtius reaction in IVb proceeded as similar as IVa and produced Vb, mp>290°, $C_7H_5ON_4$, in 70.5% yield. The infrared spectrum showed bands at 1710 and 1685 cm^{-1}. The ultraviolet absorption spectrum showed maxima at 240 (4.42), 286 (3.63), 296.5 (3.50), and 341 mμ (3.71).

These data indicated that Vb had a similar structure to that of Va, consequently, the structure of Vb was confirmed to be 2,3-dihydro-1H-pyrazolo[5,1-*b*]purin-2-one. 7-Methyl-2,3-dihydro-1H-pyrazolo[5,1-*b*]purin-2-one (Vc), mp >290°, was also obtained by the reaction of IVc with nitrous acid in 82.2% yield (see Experimental Section). Decomposition of Vb by aqueous hydrochloric acid at 100° gave 6,7-diaminopyrazolo[1,5-*a*]pyrimidine (VIb) in good yield, whose structure was confirmed by reproducing Vb in the reaction of VIb with phosgene. On the other hand, Vb was decomposed to give VIII as yellow crystals by heating at 150° with conc. hydrochloric acid in a sealed tube. The elemental analysis of VIII indicated an empirical formula of $C_6H_6ON_4 \cdot HCl$. The ultraviolet absorption spectrum showed maxima at 243 and 283 mμ, indicating [3,5] the structure might be 6-amino-7-oxo-4,7-dihydro-

5) A. Takamizawa and Y. Hamashima, *Chem. Pharm. Bull.* (Tokyo), **13**, 1207 (1965).

pyrazolo[1,5-*a*]pyrimidine. The structure of VIII obtained here was shown to be identical with the compound prepared by another synthetic route described later. We intended to confirm the structure of VIII. It was accomplished by using ethyl 7-oxo-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-6-carboxylate (IX)[6] as the starting material and treating the similar method to those of described above. The reaction of IX with hydrazine hydrate gave corresponding carbohydrazide (X), mp >300°, in good yield, whose structure was confirmed by the elemental analysis ($C_7H_7O_2N_5 \cdot H_2O$), infrared [ν_{max}^{Nujol} cm^{-1}: 3340, 3280 (NH), and 1660 (C=O)] and ultraviolet absorption spectral [λ_{max}^{EtOH} mμ (log ε): 221 (4.32), 306 (4.23)] consideration. The reaction of X with nitrous acid afforded yellow crystals, which showed identical infrared spectrum in every respect with that of VIII obtained from Vb.

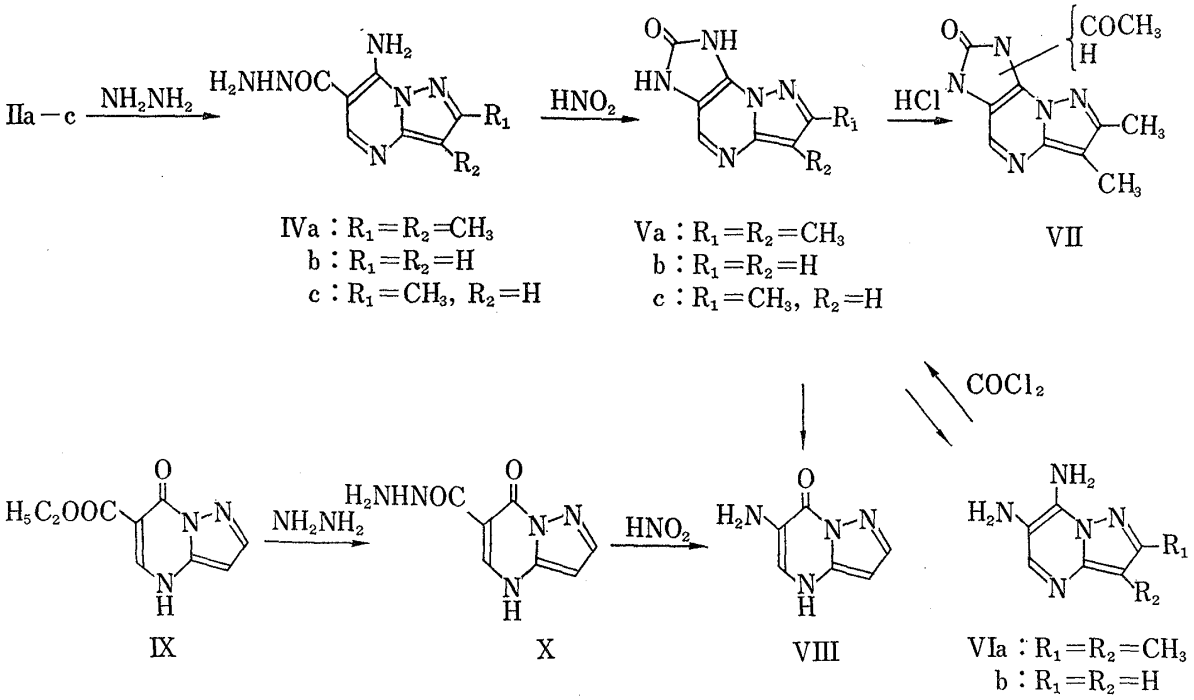

Chart 2

As described above we favorably succeeded in obtaining 2,3-dihydro-1H-pyrazolo[5,1-*b*] purin-2-ones from 7-aminopyrazolo[1,5-*a*]pyrimidine-6-carbohydrazides presumably *via* isocyanates as intermediate.

Va—c showed no significant antipyretic or anti-inflammatory activity in mice, but it was found that they had remarkable hypocholesteric activity and enhancement effect of lypolitic activity on ACTH or norepinephrine in rats. Further experiments are now in progress.

Experimental[7]

2,3-Dimethyl-7-aminopyrazolo[1,5-*a*]pyrimidine-6-carbohydrazide (IVa)——A mixture of 4 g of IIa and 100 ml of 80% hydrazine hydrate in 300 ml of ethanol was heated to reflux on a steam bath for 8 hr. After cooled, the precipitated solid was filtered and recrystallized from ethanol to give IVa as colorless sticks, mp 287° (decomp.). Yield, 4.57 g (95%). IR ν_{max}^{Nujol} cm^{-1}: 3375, 3273, 3215, 1635, 1616. UV λ_{max}^{EtOH} mμ (log ε): 234 (4.73), 313 (4.20). *Anal.* Calcd. for $C_9H_{12}ON_6$: C, 49.08; H, 5.49; N, 38.16. Found: C, 49.05; H, 5.73; N, 38.13.

6) Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), **10**, 620 (1962).
7) All melting points are uncorrected. NMR spectra were obtained on the Varian A-60 spectrometer using tetramethylsilane (TMS) as internal reference.

6,7-Dimethyl-2,3-dihydro-1H-pyrazolo[5,1-*b*]purin-2-one (Va)——To a mixture of 4.4 g of IVa, 100 ml of EtOH and 100 ml of 10% hydrochloric acid was added 1.38 g of sodium nitrite in 30 ml of H_2O under ice water cooling and stirring. The mixture was stirred at the temperature for 2 hr, after that the mixture was heated to reflux for 2 hr. To the residue, after being evaporated to dryness, was added 200 ml of H_2O. The precipitated solid was filtered and recrystallized (dimethyl sulfoxide) to give Va as light yellow fine crystalline powders, mp >280°. Yield, 3.0 g (74%). IR ν_{max}^{Nujol} cm^{-1}: 3125, 2680, 1720, 1692, 1685. UV λ_{max}^{EtOH} mμ (log ε): 243 (4.46), 290.5 (3.53), 300 (3.43), 354 (3.77). τ (d_6–DMSO): 1.87 (singlet, 1H, C_5–H), 7.63 (singlet, 3H, C_2–CH_3), 7.82 (singlet, 3H, C_3–CH_3). *Anal.* Calcd. for $C_9H_9ON_5$: C, 53.19; H, 4.46; N, 34.47. Found: C, 52.99; H, 4.53; N, 34.12.

Treatment of Va with Hydrochloric Acid——A suspension of 0.5 g of Va in 15 ml of 10% hydrochloric acid was heated at 100° for 1 hr. To the residue after being evaporated was added H_2O, the suspension was filtered (starting material 0.29 g recovered) and the filtrate was concentrated to leave colorless solid, which was recrystallized from EtOH affording VIa as colorless needles, mp >280°, yield, 0.35 g (69.3%). *Anal.* Calcd. for $C_8H_{11}N_5 \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 37.08; H, 5.42; N, 27.03. Found: C, 37.31; H, 5.38; N, 26.95.

Treatment of VIa with Phosgene——VIa was dissolved in small amount of H_2O and neutralized with sodium carbonate. Phosgene was passed into the solution under cooling, after that the reaction mixture was filtered and the residue was recrystallized from dimethylsulfoxide to give Va, which was proved to be identical with Va obtained above by the infrared comparison. Yield, 0.098 g (40%).

Acetylation of Va——A mixture of 1 g of Va, 60 ml of pyridine, and 30 ml of acetic anhydride was heated to 110° for 30 min until it became clear, the mixture was concentrated. The residue was washed with $CHCl_3$ leaving light brown crystals, which was recrystallized from pyridine affording VI as colorless needles, mp >280°. Yield, 0.95 g (78.8%). IR ν_{max}^{Nujol} cm^{-1}: 3076, 1745, 1703, 1621, 1259. UV λ_{max}^{EtOH} mμ (log ε): 237.5 (4.41), 245.5 (4.38), 258 sh (4.27), 292 (3.75), 307 (3.63), 358 (3.83). τ (in d_5–pyridine): 2.40 (singlet, 1H, C_5–H), three methyl signals at 7.18, 7.53, and at 7.68 as singlet signals. *Anal.* Calcd. for $C_{11}H_{11}O_2N_5$: C, 53.87; H, 4.52; N, 28.56. Found: C, 53.40; H, 4.28; N, 28.16.

7-Aminopyrazolo[1,5-*a*]pyrimidine-6-carbohydrazide (IVb)——A mixture of 10 g of IIb and 200 ml of 80% hydrazine hydrate in 550 ml of EtOH was heated to reflux on a steam bath for 5 hr. After cooling, the precipitated solid was filtered and recrystallized (EtOH) to give IVb as colorless plates, mp 253° (decomp). Yield, 5.8 g (60%). IR ν_{max}^{Nujol} cm^{-1}: 3340, 1660, 1623, 1602. UV λ_{max}^{EtOH} mμ (log ε): 219.5 (4.39), 306 (4.23). *Anal.* Calcd. for $C_7H_8ON_6$: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.60; H, 4.65; N, 43.64.

2-Methyl-7-aminopyrazolo[1,5-*a*]pyrimidine-6-carbohydrazide (IVc)——IVc was obtained by the similar treatment as described above using 10 g of IIc, 220 ml of 80% hydrazine hydrate, and 550 ml of EtOH. Colorless plates, mp 256° (decomp.). Yield, 6.3 g (65%). IR ν_{max}^{Nujol} cm^{-1}: 3370, 3246, 1665, 1608. UV λ_{max}^{EtOH} mμ (log ε): 229.5 (4.42), 305 (4.16). *Anal.* Calcd. for $C_8H_{10}ON_6$: C, 46.59; H, 4.89; N, 40.76. Found: C, 46.38; H, 5.01; N, 40.63.

2,3-Dihydro-1H-pyrazolo[5,1-*b*]purin-2-one (Vb)——To a mixture of 3.13 g of IVb and 50 ml of 10% hydrochloric acid in 50 ml of EtOH was added dropwise 1.25 g of sodium nitrite in 10 ml of H_2O under ice water cooling and stirring. After being stirred at the temperature for 3 hr, the mixture was heated to reflux for 3 hr. To the mixture after being evaporated to dryness was added 100 ml of 2% hydrochloric acid, the precipitated solid was filtered. Recrystallization of the residue from EtOH gave Vb as yellow brown plates, mp >290°. Yield, 2.07 g (72.5%). IR ν_{max}^{Nujol} cm^{-1}: 3126, 2610, 1710, 1684, 1592. UV λ_{max}^{EtOH} mμ (log ε): 240 (4.42), 286 (3.63), 296.5 (3.50), 341 (3.71). *Anal.* Calcd. for $C_7H_5ON_5$: C, 48.00; H, 2.88; N, 39.99. Found: C, 47.93; H, 3.02; N, 40.04.

7-Methyl-2,3-dihydro-1H-pyrazolo[5,1-*b*]purin-2-one (Vc)——Light brown rhombs (dimethyl sulfoxide), mp >290°. Yield, 82.2%. IR ν_{max}^{Nujol} cm^{-1}: 3100, 2650, 1705, 1685. UV λ_{max}^{EtOH} mμ (log ε): 241 (4.46), 290 (3.52), 295 (3.51), 344 (3.70). *Anal.* Calcd. for $C_8H_7ON_5$: C, 50.79; H, 3.73; N, 37.02. Found: C, 50.06; H, 4.09; N, 36.95.

Acid Hydrolysis of Vb——A suspension of 1.0 g of Vb in 30 ml of 10% hydrochloric acid was heated at 100° for 1 hr. To the residue after being evaporated was added H_2O, the suspension was filtrated and the filtrate was concentrated to leave colorless solid, which was recrystallized from EtOH–acetone affording VIb as colorless plates, mp >300°. Yield, 0.62 g. *Anal.* Calcd. for $C_6H_7N_5 \cdot 2HCl$: C, 32.45; H, 4.08; N, 31.53. Found: C, 32.26; H, 4.26; N, 31.90.

6-Amino-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine (VIII)——i) One gram of Vb dissolved in 50 ml of 20% hydrochloric acid was heated at 150° in a sealed tube for 4 hr. The residue after being evaporated was recrystallized from 5% hydrochloric acid to give VIII hydrochloride as yellow crystalline powder, mp >300°. Yield, 0.735 g (62%). IR ν_{max}^{Nujol} cm^{-1}: 3060, 2520, 1678, 1619. *Anal.* Calcd. for $C_6H_6ON_4 \cdot HCl$: C, 37.68; H, 3.73; N, 29.30; Cl, 20.89. Found: C, 37.54; H, 4.13; N, 29.32; Cl, 20.29.

ii) To a solution of 0.7 g of X in 50 ml of 10% hydrochloric acid was added dropwise 0.31 g of sodium nitrite in 5 ml of H_2O, under ice water cooling. After being stirred at the temperature for 3 hr, the mixture was heated on a steam bath for 3 hr. The reaction mixture was concentrated to dryness and recrystallized from 10% hydrochloric acid affording yellow crystals, mp >300°, which was proved to be identical with VIII obtained i) by their infrared comparison.

7-Oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carbohydrazide (X)——A mixture of 3 g of IX and 50 ml of 80% hydrazine hydrate was heated on a steam bath for 4 hr. To a residue after being evaporated to dryness was added 50 ml of H_2O and neutralized with 10% hydrochloric acid precipitating colorless solid. Recrystallization of the solid from H_2O gave X as colorless crystalline powders, mp >300°. Yield, 2.35 g (78%). IR ν_{max}^{Nujol} cm^{-1}: 3370, 3290, 3050, 1661, 1600. *Anal.* Calcd. for $C_7H_7O_2N_5 \cdot H_2O$: C, 39.81; H, 4.30; N, 33.17. Found: C, 40.18; H, 4.45; N, 33.67.