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Studies on Synthetic Methods for 5-Amino-4(3*H*)-pyrimidones. I. A Novel Ring Expansion Reaction of 4-Aminoantipyrines to 5-Amino-4(3*H*)-pyrimidones[1]

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4-Anilino(or amino)antipyrines (Ia, b) were transformed into 5-anilino(or amino)-4(3*H*)-pyrimidones (IIa, b) in the presence of bases such as sodium hydride, sodium amide, sodium hydroxide, or sodium ethoxide in refluxing xylene. Treatment of IIa with hydrazine hydrate gave 4-anilino-5-hydroxy-3-methyl pyrazole (V). However, the reaction of IIb with hydrazine hydrate gave 3,5-diamino-6-methyl-4(3*H*)-pyrimidone(VI) and 4-(5-oxo-3-methyl-pyrazolinyliden)amino-5-hydroxy-3-methyl pyrazole (VII).

Keywords——pyrazole; pyrimidine; 4-aminoantipyrine; 5-amino-4(3*H*)-pyrimidone; 4-anilino-5-hydroxy-3-methyl pyrazole; 3,5-diamino-6-methyl-4(3*H*)-pyrimidone

Various syntheses and reactions of pyrazolone derivatives have been studied previously in our laboratory, and some unusual reactions have been found.[3] We now describe in detail the novel transformations of 4-aminoantipyrines to 5-amino-4(3*H*)-pyrimidones which were reported in our preliminary communication.[1]

We previously synthesized 4-anilino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one[4] (Ia) and its derivatives for pharmacological evaluation.[5] In connection with this study, we examined the methylation of Ia. The reaction of Ia with dimethyl sulfate proceeded successfully to give 4-(*N*-methyl)anilino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (IV) in 61% yield, whereas the reaction of Ia with methyl iodide in the presence of sodium hydride in refluxing xylene gave 5-anilino-6-methyl-3-phenyl-4(3*H*)-pyrimidone (IIa) in 42% yield instead of the methylated product(IV). The structural assignment of IIa was carried out as follow: the mass spectrum [m/e=277 (M^+)] and the elemental analysis data gave the empirical formula $C_{17}H_{15}N_3O$, which suggested the elimination of two hydrogen atoms from the mother compound (Ia). The nuclear magnetic resonance (NMR) spectrum showed no *N*-methyl signal, and a signal (δ 7.90 ppm, 1H, singlet) attributable to the pyrimidine ring (C-2) proton was observed. A similar reaction of 4-aminoantipyrine (Ib) with sodium hydride in refluxing xylene gave 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidone (IIb) in 40% yield. Its structure was established in the following way: Sandmeyer reaction of IIb in the presence of cuprous chloride in hydrochloric acid gave 5-chloro-6-methyl-3-phenyl-4(3*H*)-pyrimidone (IIIa). Similarly the reaction of IIb in the presence of cuprous bromide, hydrobromic acid, and sodium nitrite gave 5-bromo-6-methyl-3-phenyl-4(3*H*)-pyrimidone (IIIb), which was identical with the compound[6] prepared by the reaction of β-aminocrotonanilide[7] and dimethylformamide diethylacetal, followed by bromination with bromine in acetic acid.

1) T. Ueda, N. Oda, and I. Ito, *Heterocycles*, **8**, 263 (1977).
2) Location: *3-1, Tanabe-dōri, Mizuho-ku, Nagoya, 467, Japan.*
3) I. Ito and T. Ueda, *Tetrahedron*, **30**, 1027 (1974); I. Ito and T. Ueda, *Chem. Pharm. Bull.*, **23**, 1646 (1975); T. Ueda, I. Ito, and Y. Iitaka, *Chem. Pharm. Bull.*, **24**, 596 (1976).
4) T. Ueda, N. Oda, and I. Ito, *Yakugaku Zasshi*, **96**, 236 (1976).
5) Compound (Ia) showed analgesic activity; pharmacological data will be reported separately.
6) S. Senda, K. Hirota, and O. Otani, *Yakugaku Zasshi*, **94**, 571 (1974).
7) L. Knorr, *Chem. Ber.*, **25**, 776 (1892).

The transformations of Ia or Ib to IIa or IIb proceeded in the presence of bases such as sodium hydride, sodium amide, sodium hydroxide, or sodium ethoxide in refluxing xylene, and the presence of methyl iodide was unnecessary. However, no reaction occurred in the case of 4-dimethylaminoantipyrine or IV, which have no hydrogen atom on the amino group in their molecules. Thus, we concluded that the presence of a hydrogen atom on the 4-amino group is essential for this ring expansion reaction. A plausible mechanism accounting for the above results may be formulated as shown in Chart 2 for the transformations of Ia or Ib to IIa or IIb.

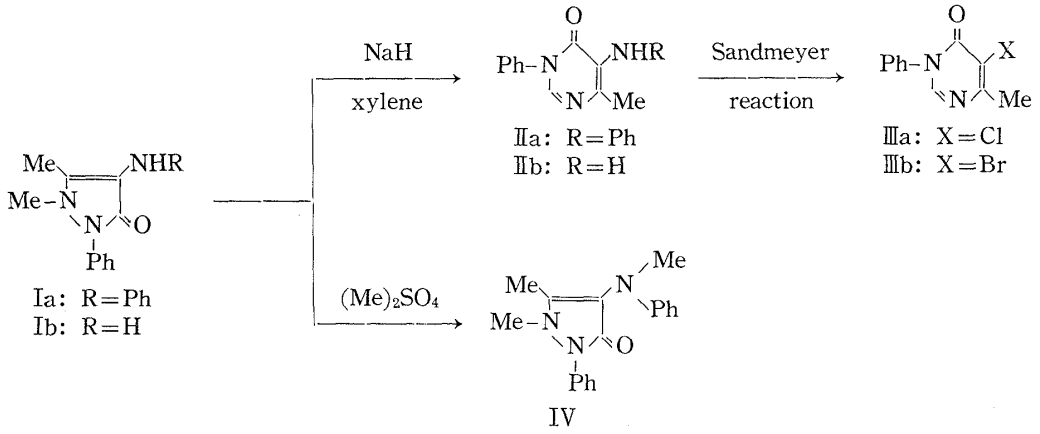

Chart 1

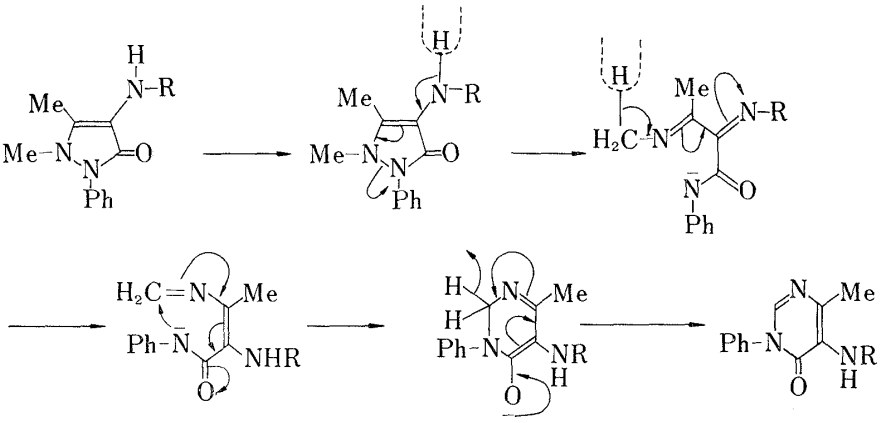

Chart 2

It is known that some pyrimidines can be transformed into pyrazoles by reaction with hydrazine hydrate.[8] Thus, it seemed of interest to investigate the reaction of pyrimidines (IIa, b) with hydrazine hydrate. The reaction of IIa with hydrazine hydrate gave 4-anilino-5-hydroxy-3-methyl pyrazole (V) in 47% yield; this structure was confirmed by the mass spectrum [*m/e*=189 (M^+)] and elemental analysis, and the presence of the enol–form was supported by the infrared (IR) absorption spectrum [3400 (NH), 3200—2400 (OH)]. However, the treatment of IIb with hydrazine hydrate gave 3,5-diamino-6-methyl-4(3*H*)-pyrimidone (VI) in 70% yield and 4-(5-oxo-3-methylpyrazolinyliden)amino-5-hydroxy-3-methyl pyrazole[9] (VII) in 15% yield. The IR and NMR spectra of VI indicated loss of the phenyl group and suggested the presence of two primary amines [IR: 3480, 3400, 3280, 3200(NH_2),

8) M.E.C. Biffin, D.J. Brown, and Q.N. Port, *J. Chem. Soc.* (*C*), **1968**, 2159.
9) M. Betti, *Gazz. Chim. Ital.*, **34**, 186 (1904) [*Beilsteins Hand Buch*, **25**, 458 (1936)]; F. Maria, *Gazz. Chim. Ital.*, **66**, 23 (1936) [*Chem. Abstr.*, **30**, 6388].

NMR (10% solution in $CDCl_3$) δ: 4.71 (2H, broad singlet, lost on D_2O exchange, C-NH_2 or N-NH_2) and 5.85 (2H, broad singlet, lost on D_2O exchange, N-NH_2 or C-NH_2)]. The mass spectrum [m/e=140 (M^+)] and elementary analysis data were consistent with the assigned structure (VI). Moreover, acetylation of VI with acetic anhydride gave 5-acetylamino-3-diacetylamino-6-methyl-4(3*H*)-pyrimidone (VIII). Similar replacements at the 3-position of 4-quinazolones on reaction with primary arylamines or other NH_2-functions have been reported.[10] Compound (VII) was identical with a sample prepared by the oxidation of 4-amino-5-hydroxy-3-methyl pyrazole.[9] Thus, it may be concluded that the reaction of IIb with hydrazine hydrate initially gave 4-amino-5-hydroxy-3-methyl pyrazole in addition to VI, and this was then oxidized during work-up to give VII. The proposed mechanism of formation of IV and V is shown in Chart 3.

The transformations of Ia, b into IIa, b and the conversion of IIb to VI appear to be useful, facile syntheses of 5-amino-4(3*H*)-pyrimidones.

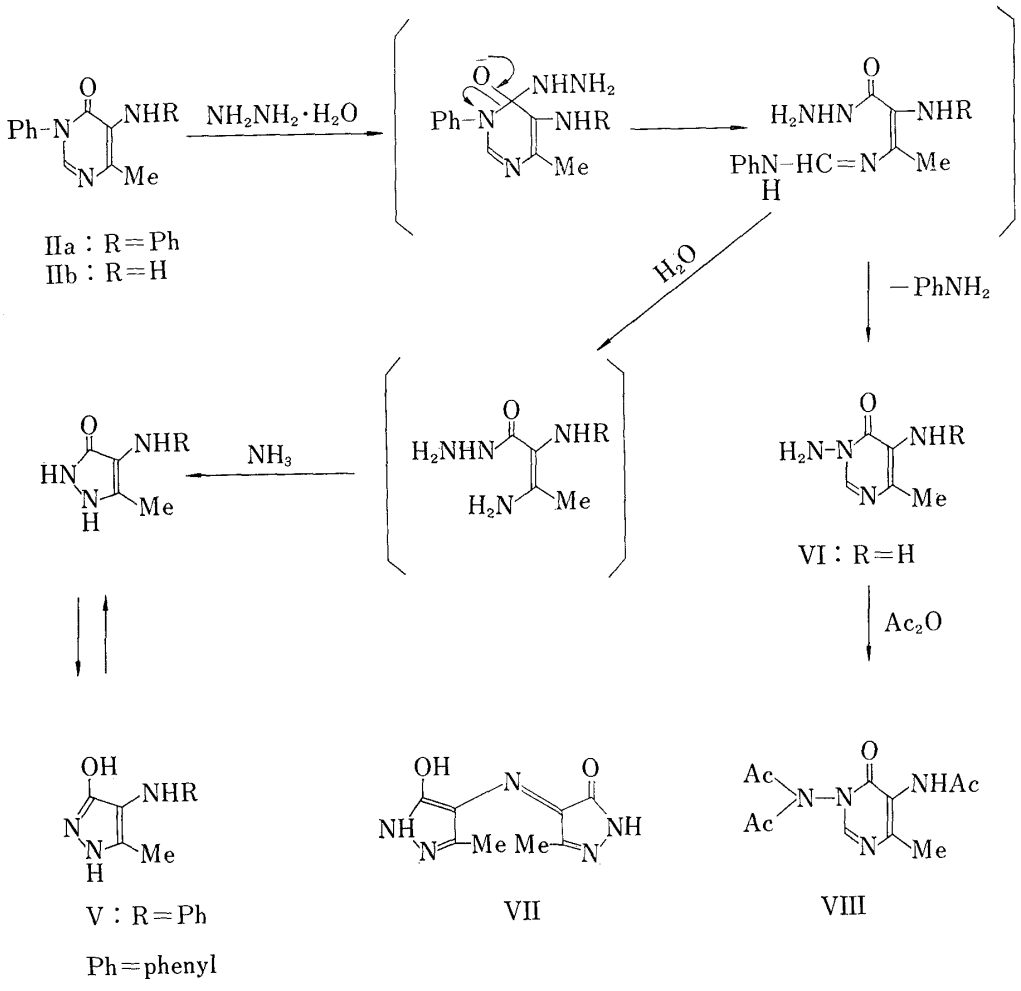

Chart 3

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with a Nihon Bunko IR-S spectrophotometer. NMR spectra were measured with a JEOL JNM-MH-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded with a Hitachi M-52 mass spectrometer. UV spectra were recorded with a Hitachi EPS-3T recording spectrophotometer.

10) "Fused Pyrimidines Part I," ed. by D.J. Brown, Interscience Publisher, New York, 1967, p. 339.

5-Anilino-6-methyl-3-phenyl-4(3*H*)-pyrimidone (IIa)——4-Anilino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (Ia) (1 g) was dissolved in 30 ml of refluxing xylene. Sodium hydride (50% mineral oil dispersion 1 g) was added to the stirred solution. Refluxing and stirring were continued for 5 hr. The hot reaction mixture was then filtered and cooled, and the resulting colorless crystals were collected by filtration. Concentration of the filtrate also gave crystals. The combined crystals were recrystallized from EtOH to give 417 mg (42%) of colorless prisms, mp 147—148°. *Anal.* Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.58; H, 5.77; N, 15.10. IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1670 (amide C=O). MS *m/e*: 277 (M^+). UV λ_{max}^{EtOH} (log ε): 243 (4.09), 280 (3.91), 335 (3.81). NMR (10% solution in $CDCl_3$) δ: 2.15 (3H, s, pyrimidone ring C-2 proton), 6.75—7.50 (10H, m, aromatic protons).

5-Amino-6-methyl-3-phenyl-4(3*H*)-pyrimidone (IIb)——4-Aminoantipyrine (Ib) (10 g) was dissolved in 200 ml of refluxing xylene, and sodium hydride (50% mineral oil dispersion 2.5 g) was added. The mixture was worked up by the procedure used for the synthesis of II to give 4 g (40%) of colorless prisms, mp 188—189° (from EtOH). *Anal.* Calcd for $C_{11}H_{12}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: 65.81; H, 5.48; N, 21.01. IR ν_{max}^{KBr} cm^{-1}: 3440, 3320 (NH_2), 1650 (C=O). MS *m/e*: 201 (M^+). NMR (10% solution in $CDCl_3$) δ: 2.20 (3H, s, C–Me), 3.95 (2H, broad s, NH_2, lost on D_2O exchange), 7.30—7.50 (5H, m, phenyl protons), 7.62 (1H, s, pyrimidone ring C-2 proton).

5-Chloro-6-methyl-3-phenyl-4(3*H*)-pyrimidone (IIIa)——A mixture of IIb (1 g), conc. HCl (5 ml), and Cu_2Cl_2 (1 g) was refluxed, and a solution of $NaNO_2$ (1 g) in 5 ml of H_2O was added to this mixture. After cooling, the mixture was extracted with chloroform. The extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was distilled off, and the residue was recrystallized from EtOH to give 368 mg (33.6%) of colorless needles, mp 165—166°. *Anal.* Calcd for $C_{11}H_9ClN_2O$: C, 59.86; H, 4.11; N, 12.69. Found: C, 59.89; H, 3.93; N, 12.88. NMR (10% solution in $CDCl_3$) δ: 2.50 (3H, s, C–Me), 7.30—7.55 (5H, m, aromatic protons), 8.01 (1H, s, pyrimidone ring C-2 proton).

5-Bromo-6-methyl-3-phenyl-4(3*H*)-pyrimidone (IIIb)——A mixture of IIb (1 g), hydrobromic acid (S.G.=1.43, 5 ml), and $CuCl_2$ (1 g) was refluxed, and a solution of $NaNO_2$ (1 g) in 5 ml of H_2O was added. The mixture was treated by the procedure described for IIIa, yield 440 mg (34%), mp 182—183° (lit.[7] 182.5°). The IR spectrum of this compound was identical with that of the compound[7] prepared by the reaction of β-aminocrotonanilide and dimethylformamide diethylacetal, followed by bromination with bromine in acetic acid. The mixed melting point did not show any depression.

4-(*N*-Methyl)anilino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (IV)——A mixture of Ia (279 mg) and dimethyl sulfate (1 ml) was heated on an oil bath (140—150°) for 30 min. After cooling, 20% NaOH (5 ml) was added to the mixture, and the whole was heated on a water-bath (70°) for 30 min. The reaction mixture was extracted with chloroform. The extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was distilled off, and the residue was recrystallized from EtOH to give colorless prisms of mp 103—104°, yield 180 mg (61%). NMR (10% solution in $CDCl_3$) δ: 2.08 (3H, s, C–Me), 3.08 (3H, s, N–Me or– $N\langle^{Ph}_{Me}$), 3.23 (3H, s, $-N\langle^{Ph}_{Me}$ or N–Me), 6.65—7.45 (10H, m, aromatic protons). *Anal.* Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: 73.78; H, 6.76; N, 14.24.

4-Anilino-5-hydroxy-3-methyl pyrazole (V)——A mixture of IIa (0.5 g) and hydrazine hydrate (5 ml) was refluxed on a mantle heater for 3 hr. The mixture became clear. Excess hydrazine hydrate was distilled off, and the residue was recrystallized from EtOH to give colorless needles of mp 229—230°, yield 320 mg (47%). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 3200—2400 (OH). MS *m/e*: 189 (M^+). *Anal.* Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.20; H, 5.78; N, 21.98.

3,5-Diamino-6-methyl-4(3*H*)-pyrimidone (VI)——A mixture of IIb (2 g) and 100% hydrazine hydrate (10 ml) was refluxed on a mantle heater for 3 hr. On cooling, crystals appeared and were collected by filtration. Recrystallization from EtOH gave colorless needles of mp 145—146°, yield 1.0 g (71%). *Anal.* Calcd for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.56; H, 5.70; N, 39.68. IR ν_{max}^{KBr} cm^{-1}: 3480, 3400, 3280, 3200 (NH_2), 1695, 1660 (amide C=O). Mass Spectrum *m/e*: 140 (M^+). NMR (10% solution in $CDCl_3$) δ: 2.10 (3H, s, C–Me), 4.71 (2H, broad s, C–NH_2 or N–NH_2, lost on D_2O exchange), 5.85 (2H, broad s, N–NH_2 or C–NH_2, lost on D_2O exchange), 7.80 (1H, s, pyridone ring C-2 proton).

4-(5-Oxo-3-methyl-pyrazolinyliden)amino-5-hydroxy-3-methyl pyrazole[9] (VII)——After removal of the crystals from the reaction mixture in the above experiment (VI), the filtrate was evaporated to dryness, and the residue was recrystallized from EtOH to give 0.4 g (19%) of red needles, mp>270°. MS *m/e*: 207 (M^+). *Anal.* Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.38; N, 33.80. Found: C, 46.27; H, 4.23; N, 33.63.

5-Acetylamino-3-diacetylamino-6-methyl-4(3*H*)-pyridone (VIII)——A mixture of VI (1 g) and acetic anhydride (5 ml) was refluxed on a mantle heater for 1 hr. Excess acetic anhydride was distilled off, and the residue was recrystallized from EtOH to give colorless prisms of mp 211—212°, yield 0.7 g (50%). MS *m/e*: 266 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.78; H, 5.53; N, 21.25. NMR (10% solution in $CDCl_3$) δ: 2.00 (3H, s, C–Me), 2.08 (3H, s, $NHCOCH_3$), 2.15 (6H, s, $N(COCH_3)_2$), 8.40 (1H, s, pyrimidone ring C-2 proton), 9.50 (1H, broad s, $NHCOCH_3$, lost on D_2O exchange).

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