A NOVEL RING EXPANSION REACTION OF 4-AMINOANTIPYRINES TO 5-AMINO-4(3*H*)-PYRIMIDINONES

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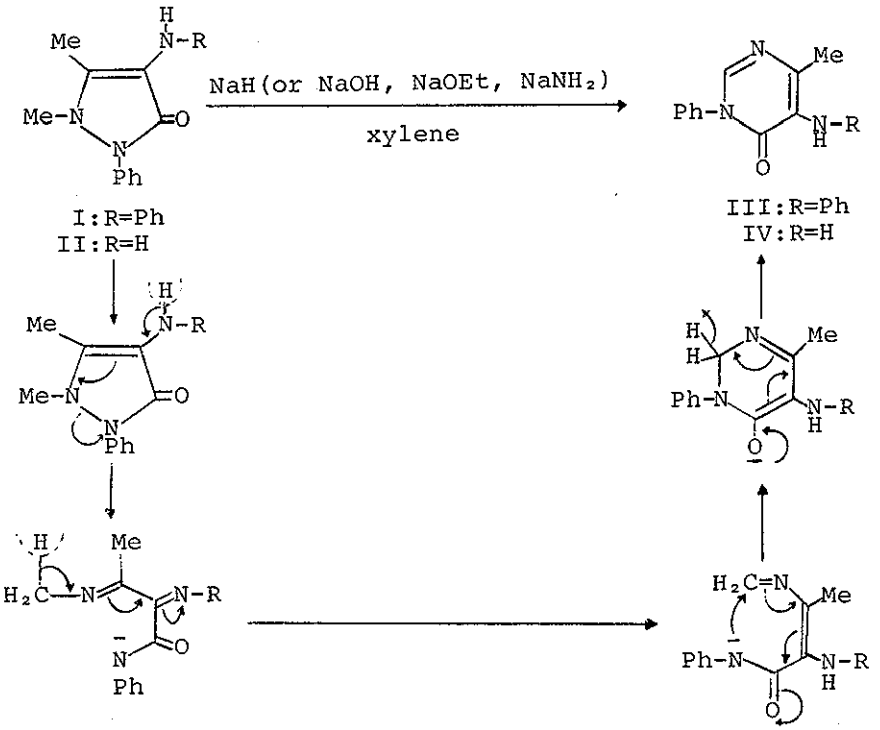
4-Amino(or anilino)antipyrines(I,II) were transformed into 5-amino(or anilino)-4(3*H*)-pyrimidinones(III,IV) in the presence of bases such as sodium hydride, sodium amide, sodium hydroxide, or sodium ethoxide in refluxing xylene. Treatment of III with hydrazine hydrate gave 4-anilino-5-hydroxy-3-methyl-pyrazole(V). However, the reaction of IV with hydrazine hydrate gave 3,5-diamino-6-methyl-4(3*H*)-pyrimidinone(VII) and 4-(5-oxo-3-methyl-pyrazolinyliden-4-amino)-5-hydroxy-3-methyl-pyrazole(VIII).

We have studied the syntheses and the reactivities of pyrazolone derivatives, and some unusual reactions have been reported previously[1]. We now wish to report the first observation of the ring expansion of 4-aminoantipyrines to 5-amino-4(3*H*)-pyrimidinones. This novel reaction was found during the investigation of aminopyrine. The methylation of 2,3-dimethyl-1-phenyl-4-anilino-3-pyrazolin-5-one[2](I) with methyl iodide and sodium hydride gave 5-anilino-6-

methyl-3-phenyl-4(3*H*)-pyrimidinone(III)(mp 147-8°, 42%) instead of the methylated product. The structual assignment of III was carried out as follows: The mass spectrum[m/e=277(M^+)] and the elemental analysis gave the empirical formula $C_{17}H_{15}N_3O$, which suggested the loss of two hydrogen atoms from the mother compound(I). The IR (ν_{max}^{KBr}) spectrum showed absorption bands at 3240(NH) and 1670 cm^{-1} (C=O). The UV[λ_{max}^{EtOH}(log ε)] spectrum exhibited absorption maxima at 243(4.09), 280(3.91), and 335(3.81) nm. The NMR spectrum revealed no N-methyl signal, and a signal(δ 8.08 ppm, 1H, singlet) attributable to the pyrimidine C-2 proton was observed. Similar reaction of 4-aminoantipyrine(II) with sodium hydride in refluxing xylene gave 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone(IV) in 40% yield:

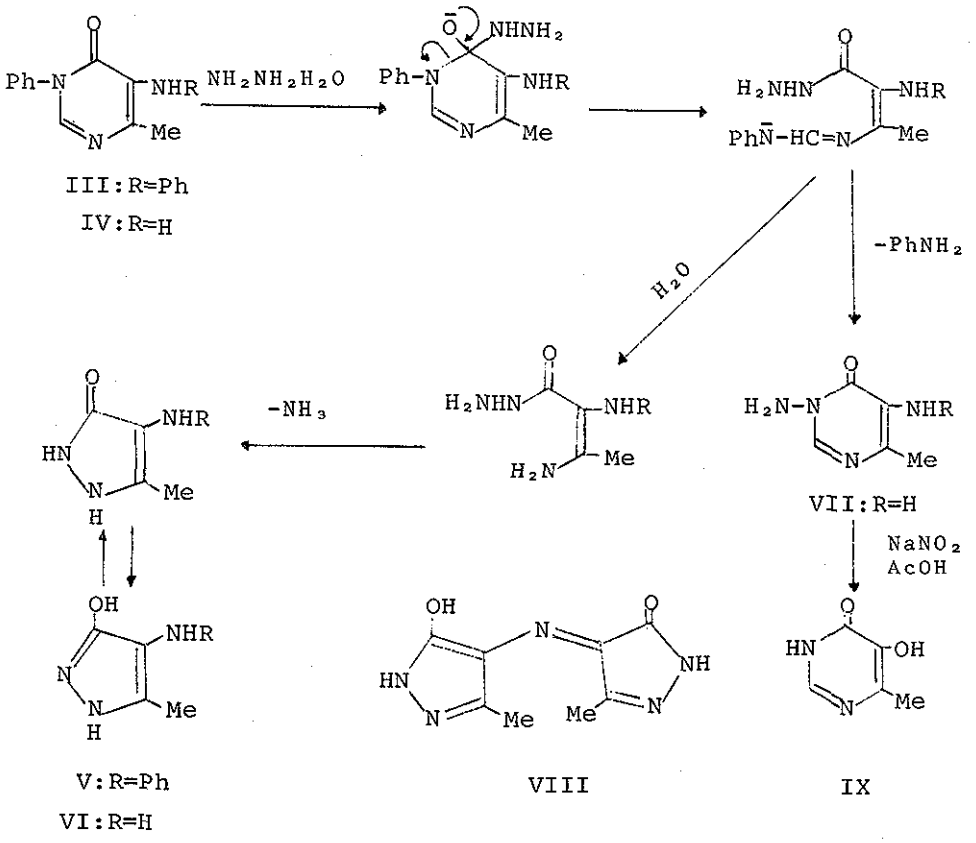


colorless prisms, mp 188-189° (EtOH), m/e=201(M^+), IR: 3440, 3320 cm^{-1}(NH_2), 1650(C=O). NMR $\delta_{ppm}^{CDCl_3}$: 2.20(3H, singlet, C-Me), 3.95 (2H, broad singlet, NH_2, erased on D_2O-exchange), 7.62(1H, singlet, pyrimidine C-2 proton), 7.30-7.50(5H, multiplet, phenyl protons). The structure of IV was also established by the following way: Sandmeyer reaction of IV in the presence of cuprous bromide, hydrobromic acid, and sodium nitrite gave 5-bromo-6-methyl-3-phenyl-4(3*H*)-pyrimidinone(mp 182-183°, 34% yield), which was identical with the compound[4] prepared by the reaction of β-aminocrotonanilide[5] and dimethylformamide diethylacetal followed by the bromination with bromine in acetic acid.

These transformations proceeded in the presence of bases such as sodium hydride, sodium amide, sodium hydroxide, or sodium ethoxide in refluxing xylene. However, no reaction proceeded in the case of 4-dimethylaminoantipyrine or 4-(N-methylanilino)antipyrine[3] which have no hydrogen atom on the amino group in their molecules. Thus it is concluded that the presence of hydrogen atom on the 4-amino group is the essential function in this ring expansion reaction.

It is known that some pyrimidines can be transformed into pyrazoles by the reaction with hydrazine hydrate[6]. Thus it appeared interesting for us to investigate the reaction with pyrimidinones (III, IV) with hydrazine hydrate.

The reaction of III with hydrazine hydrate gave 4-anilino-5-hydroxy-3-methyl-pyrazole(V)[mp 229-230°, colorless needles(EtOH), 82% yield] whose structure was confirmed by the mass spectrum[m/e =189(M^+)], elemental analysis, and IR spectrum[3400 cm^{-1}(NH), 3200



-2400(OH)]. However, the treatment of IV with hydrazine hydrate gave 3,5-diamino-6-methyl-4(3*H*)-pyrimidinone(VII)[mp 145-6°, colorless needles(EtOH), 70% yield] and 4-(5-oxo-3-methyl-pyrazolinyliden-4-amino)-5-hydroxy-3-methyl-pyrazole[7](VIII)[red needles(EtOH), mp>300°, 15% yield]. The structual assignment of VII was carried out by the spectral and the elemental analysis: IR, 3480, 3400, 3280,3200 cm^{-1}(NH_2), 1695, 1660 cm^{-1}(amide C=O), mass spectrum m/e=140(M^+), NMR $\delta_{ppm}^{CDCl_3}$ 2.10(3H, singlet, C-Me), 4.71(2H, broad singlet, C-NH_2 or N-NH_2, erased on D_2O-exchange), 5.85(2H, broad

singlet, N-NH_2 or C-NH_2, erased on D_2O-exchange), 7.80(1H, singlet, pyrimidine C-2 proton).

The reaction of VII with sodium nitrite in acetic acid gave 5-hydroxy-6-methyl-4(3*H*)-pyrimidinone(IX) [mp 230-231°, colorless prisms(EtOH), 60% yield, mass spectrum m/e=126(M^+), IR, 3460 cm^{-1} (OH), 1660 cm^{-1}(C=O)]. Baddar et al.[8] reported a similar reaction on 2-pyridone derivatives.

Scine it is known that the oxidation of the 4-aminopyrazole(VI) gives VIII[7], it may be concluded that the reaction of IV with hydrazine hydrate also gave the pyrazole(VI) at first and then VI was oxidized during the treatment[9] of the reaction mixture to give VIII.

The transformation of I or II into III or IV and the conversion of IV to VII seem to be useful as the facile syntheses of 5-amino-4(3*H*)-pyrimidinones. Detailed investigations of these reactions are currently in progress.

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3. This compound was obtained by the reaction of I with dimethyl sulfate

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9. The mixture of IV and hydrazine hydrate was refluxed for 1 hr. On cooling crystals(VII) appeared and were collected by filtration. The filtrate was evaporated to dryness, and the residue was recrystallized from EtOH to give VIII.

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