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# Ring Transformation Reaction of 1,4,6-Trisubstituted 2(1H)-Pyrimidinones and -Thiones with Hydroxylamine

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1,4,6-Trisubstituted 2(1H)-pyrimidinones (Ia—e) underwent ring transformation with hydroxylamine to afford 3,5-disubstituted isoxazoles (IIa—e) in high yields. On the other hand, 2(1H)-pyrimidinethiones (IIIa, b, f—k) underwent ring transformation to give mainly a new type of N-substituted 2-aminopyrimidine 1-oxides (IVa, b, f—k) as well as isoxazoles.

The reaction of pyrimidinium salts (VII, VIII and IX) with hydroxylamine is also discussed.

**Keywords**——ring transformation reaction; hydroxylamine; nucleophilic reaction; 3,5-disubstituted isoxazoles; N-substituted 2-aminopyrimidine 1-oxides; pyrimidinium salts

There are many reviews on the synthesis of isoxazoles$^{1)}$ and pyrimidine N-oxides.$^{2)}$ Isoxazoles were also obtained by the ring transformation of pyrimidines$^{3)}$ and pyrimidine N-oxides.$^{4)}$ On the other hand, no attempts to prepare isoxazoles and pyrimidine N-oxides by the ring transformation of 2(1H)-pyrimidinones and -thiones have been carried out, to our knowledge. Further, the preparation of N-substituted 2-aminopyrimidine 1-oxides has not been reported, except for the preparation of 2,4,6-triaminopyrimidine N-oxides.$^{5)}$

Previously, we reported$^{6)}$ on the reaction of 2(1H)-pyrimidinones and -thiones with nucleophiles such as Grignard reagents, organolithium reagents, sodium borohydride, or lithium aluminum hydride to give dihydro- and tetrahydro-2(1H)-pyrimidinones and -thiones.

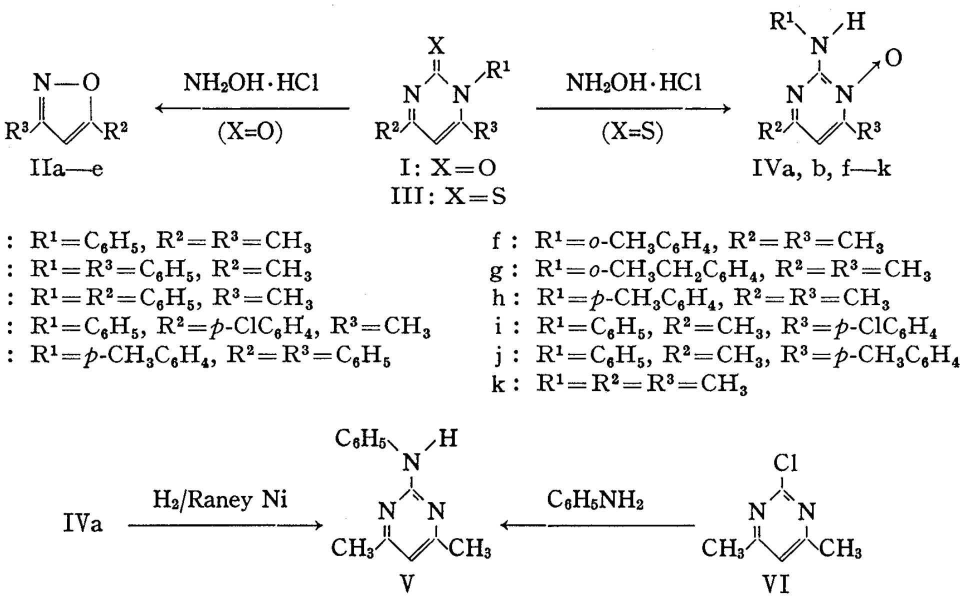
As a part of our works on nucleophilic reactions, we described here the ring transformation reaction of 1,4,6-trisubstituted 2(1H)-pyrimidinones and the corresponding thiones to 3,5-disubstituted isoxazoles and a new type of N-substituted 2-aminopyrimidine 1-oxides by using hydroxylamine as a nucleophile.

## Results and Discussion

4,6-Dimethyl-1-phenyl-2(1H)-pyrimidinone (Ia) reacted with hydroxylamine hydrochloride in the presence of sodium hydroxide to give 3,5-dimethylisoxazole (IIa) and N-phenylurea. The former compound was identical with an authentic sample obtained from acetylacetone and hydroxylamine hydrochloride.$^{7)}$ 4-Methyl-1,6-diphenyl-2(1H)-pyrimidinone (Ib) also underwent the ring transformation reaction to give only 5-methyl-3-phenylisoxazole (IIb)

TABLE I. Isoxazoles (IIa—e)

| Isoxazole | Formula | Yield (%) | mp[or bp] (°C) | Lit. mp[or bp] (°C) |
|---|---|---|---|---|
| IIa | $C_5H_7NO$ | 80 | [139—140.5] | [136—140]$^{7)}$ |
| IIb | $C_{10}H_9NO$ | 71 | 67—68 | 65$^{8)}$ |
| IIc | $C_{10}H_9NO$ | 66 | 42—44 | 42$^{8)}$ |
| IId | $C_{10}H_8ClNO$ | 75 | 90—91 | 91—92$^{9)}$ |
| IIe | $C_{15}H_{11}NO$ | 80 | 142—143 | 141—142.5$^{10)}$ |



a : $R^1=C_6H_5$, $R^2=R^3=CH_3$
b : $R^1=R^3=C_6H_5$, $R^2=CH_3$
c : $R^1=R^2=C_6H_5$, $R^3=CH_3$
d : $R^1=C_6H_5$, $R^2=p\text{-}ClC_6H_4$, $R^3=CH_3$
e : $R^1=p\text{-}CH_3C_6H_4$, $R^2=R^3=C_6H_5$
f : $R^1=o\text{-}CH_3C_6H_4$, $R^2=R^3=CH_3$
g : $R^1=o\text{-}CH_3CH_2C_6H_4$, $R^2=R^3=CH_3$
h : $R^1=p\text{-}CH_3C_6H_4$, $R^2=R^3=CH_3$
i : $R^1=C_6H_5$, $R^2=CH_3$, $R^3=p\text{-}ClC_6H_4$
j : $R^1=C_6H_5$, $R^2=CH_3$, $R^3=p\text{-}CH_3C_6H_4$
k : $R^1=R^2=R^3=CH_3$

Chart 1

in 71% yield. The ring transformation of other 2(1H)-pyrimidinones (Ic—e) was carried out and the results are summarized in Table I.

When 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (IIIa) was treated with hydroxylamine hydrochloride in the manner described above, a product, mp 155.5—156°C, was obtained. The product had the formula $C_{12}H_{13}N_3O$ and displayed strong bands at 3240 and 1240 $cm^{-1}$ due to N–H and N–O stretching in the infrared (IR) spectrum. In the preceding paper,[11] we reported that C-6 methyl protons of 1-aryl-4,6-dimethyl-2(1H)-pyrimidinethiones resonated at higher field by about 0.4 ppm than C-4 methyl protons due to the anisotropic effect of the benzene ring. By examination of the proton magnetic resonance (PMR) spectrum, we found that this anisotropic effect had disappeared in this reaction product, and the C-4 and C-6 methyl protons showed sharp signals at $\delta$ 2.41 (3H, s) and 2.52 (3H, s). In addition, the $C^{13}$ nuclear magnetic resonance (CMR) spectrum of the product still indicated the structure unit, $CH_3\text{-}\overset{\|}{C}\text{-}CH{=}\overset{|}{C}\text{-}CH_3$. From these spectral data, the product was assigned to be 2-anilino-4,6-dimethylpyrimidine 1-oxide (IVa). The structure of IVa was also confirmed by chemical reaction. It is well known[12] that pyrimidine N-oxides are easily deoxygenated with Raney nickel or phosphorus trichloride to give the corresponding pyrimidines. Thus, IVa was treated with Raney nickel to afford 2-anilino-4,6-dimethylpyrimidine (V), which was identical (spectral data and mixed melting point) with an authentic sample prepared from 2-chloro-4,6-dimethylpyrimidine (VI) and aniline.[13] The ring transformation reaction of other 2(1H)-pyrimidinethiones (IIIb, f—k) was examined and the results are shown in Table II.

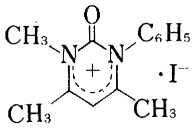
In the case of 4-methyl-1,6-diphenyl-2(1H)-pyrimidinethione (IIIb), pyrimidine 1-oxide (IVb, 30%) and a mixture of isoxazoles (IIb and IIc, 33%) were obtained. Yamanaka *et al.* reported[14] that pyrimidine N-oxides were converted into isoxazoles in good yields by acid hydrolysis with 20% sulfuric acid. The conversion of IVb into IIb and IIc did not occur even upon prolonged reaction and acid hydrolysis with 20% sulfuric acid. A possible mechanism for the ring transformation reaction of 2(1H)-pyrimidinones and -thiones is illustrated in Chart 2.

The reaction of pyrimidinium salts with hydroxylamine was examined. 3,4,6-Trimethyl-2-oxo-1-phenyl-1,2-dihydropyrimidinium iodide (VII) gave an intractable mixture, while 4,6-dimethyl-2-methylthio-1-phenyl-1,2-dihydropyrimidinium iodide (VIII) and 4-methyl-2-methylthio-1,6-diphenyl-1,2-dihydropyrimidinium iodide (IX) afforded pyrimidine 1-oxides IVa and IVb in 49 and 27% yields, respectively.

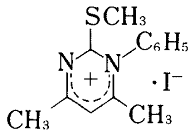
TABLE II. Pyrimidine 1-Oxides (IVa, b, f—k)

| Compound No. | Yield (%) | mp (°C) | Formula | Analysis (%) Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|
| IVa | 80 | 155.5—156[a] | $C_{12}H_{13}N_3O$ | 66.95<br>(66.98 | 6.08<br>6.02 | 19.52<br>19.58) |
| IVb | 30 | 176—176.5[a] | $C_{17}H_{15}N_3O$ | 73.62<br>(73.55 | 5.45<br>5.42 | 15.15<br>15.12) |
| IVf | 28 | 110—111[a] | $C_{13}H_{15}N_3O$ | 68.10<br>(67.89 | 6.59<br>6.58 | 18.32<br>18.36) |
| IVg | 43 | 108—110[a] | $C_{14}H_{17}N_3O$ | 69.11<br>(68.98 | 7.04<br>6.99 | 17.27<br>17.19) |
| IVh | 39 | 199—200[b] | $C_{13}H_{15}N_3O$ | 68.10<br>(68.00 | 6.59<br>6.61 | 18.32<br>18.24) |
| IVi | 35 | 189—190[c] | $C_{17}H_{14}ClN_3O$ | 65.49<br>(65.30 | 4.52<br>5.56 | 13.47<br>13.44) |
| IVj | 44 | 157—158[a] | $C_{18}H_{17}N_3O$ | 74.20<br>(74.06 | 5.88<br>5.81 | 14.42<br>14.41) |
| IVk | 30 | 143.5—144[a] | $C_7H_{11}N_3O$ | 54.88<br>(54.82 | 7.23<br>7.17 | 27.43<br>27.30) |

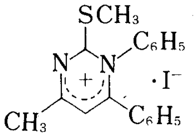
a) Recrystallized from benzene–hexane.
b) Recrystallized from benzene.
c) Recrystallized from ethanol.



VII



VIII



IX

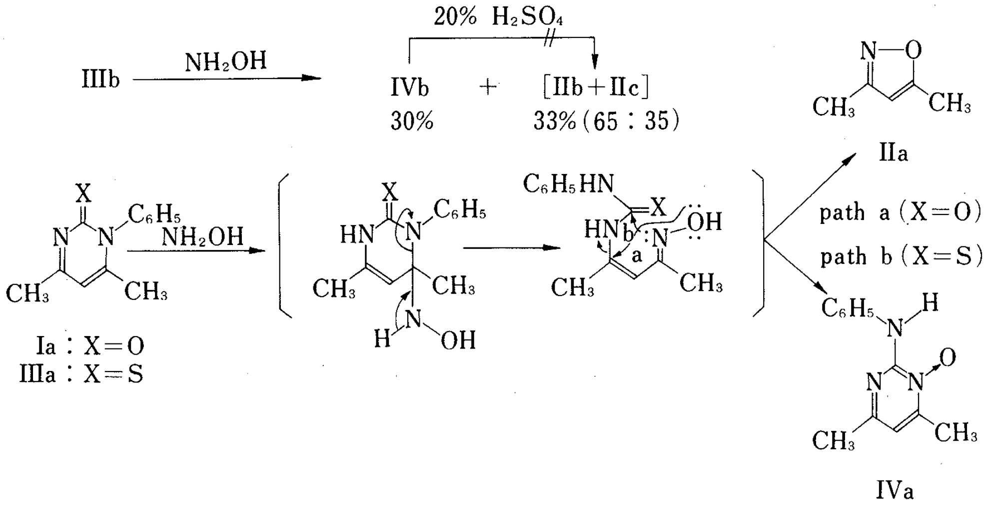


Chart 2

It is concluded from these results that 1,4,6-trisubstituted 2(1H)-pyrimidinones easily undergo ring transformation on treatment with hydroxylamine to give 3,5-disubstituted isoxazoles in good yields, and 2(1H)-pyrimidinethiones afford mainly N-substituted 2-aminopyrimidine 1-oxides in considerable yields.

## Experimental

All melting points and boiling points are uncorrected. IR and ultraviolet (UV) spectra were obtained on a Jasco ITA-1 infrared spectrometer and a Shimadzu UV-365 UV-VIS-NIR recording spectrophotometer, respectively. PMR and CMR spectra were recorded on a Hitachi R-20 spectrometer and a JEOL-100 NMR spectrometer, respectively, using tetramethylsilane as an internal standard.

**General Procedure for the Reaction of 2(1H)-Pyrimidinones (Ia—e) with Hydroxylamine**——A mixture of 2(1H)-pyrimidinone (2 mmol), hydroxylamine hydrochloride (2.2 mmol), and sodium hydroxide (4.4 mmol) in absolute ethanol (30 ml) was refluxed for 2 h. The reaction mixture was poured into water, and extracted with dichloromethane, then the extract was dried over anhydrous magnesium sulfate. The products (IIa—e) were identified by comparison with authentic samples (spectral data and mixed melting point) (Table I).

**General Procedure for the Reaction of 2(1H)-Pyrimidinethiones (IIIa, b, f—k) or Pyrimidinium Salts (VIII and IX) with Hydroxylamine**——The reaction was carried out in the manner described above. The crude products were chromatographed on silica gel with benzene–ethyl acetate (4: 1) for compounds IVb, IVi, and IVj or with chloroform–acetone–ethanol (100: 20: 4) for compounds IVa, IVf—h, and IVk.

**2-Anilino-4,6-Dimethylpyrimidine 1-Oxide (IVa)**——IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3240, 1600, 1445, 1245, 1205, 1165; UV $\lambda_{\max}^{\text{EtOH}}$ nm (log $\varepsilon$): 246 (4.32), 283 (4.30), 330 (3.70); PMR (CDCl$_3$) $\delta$: 2.41 (3H, s), 2.52 (3H, s), 6.60 (1H, s), 7.1—7.6 (3H, m), 7.6—7.9 (2H, m), 9.7 (1H, br s); CMR (CDCl$_3$) $\delta$: 17.7 (q), 23.6 (q), 110.9 (d), 119.6 (d), 123.6 (d), 128.9 (d), 137.7 (s), 149.9 (s), 152.8 (s), 154.1 (s).

**2-Anilino-4-methyl-6-phenylpyrimidine 1-Oxide (IVb)**——IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3240, 1585, 1560, 1440, 1140, 1100; UV $\lambda_{\max}^{\text{EtOH}}$ nm (log $\varepsilon$): 239 (4.32), 280 (4.44), 354 (3.56); PMR (CDCl$_3$) $\delta$: 2.47 (3H, s), 6.70 (1H, s), 7.0—8.2 (10H, m), 9.9 (1H, br s).

**4,6-Dimethyl-2-(*o*-toluidino)pyrimidine 1-Oxide (IVf)**——IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3240, 1580, 1260, 1220, 1165, 740; UV $\lambda_{\max}^{\text{EtOH}}$ nm (log $\varepsilon$): 242 (4.20), 279 (4.18), 327 (3.70); PMR (CDCl$_3$) $\delta$: 2.38 (6H, s), 2.50 (3H, s), 6.54 (1H, s), 7.0—7.5 (3H, m), 8.1—8.4 (1H, m), 9.6 (1H, br s).

**4,6-Dimethyl-2-(*o*-ethylanilino)pyrimidine 1-Oxide (IVg)**——IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3130, 1590, 1555, 1440, 1210, 1165; UV $\lambda_{\max}^{\text{EtOH}}$ nm (log $\varepsilon$): 242 (4.16), 278 (4.16), 324 (3.61); PMR (CDCl$_3$) $\delta$: 1.30 (3H, t, $J=7.0$ Hz), 2.33 (3H, s), 2.50 (3H, s), 2.77 (2H, q, $J=7.0$ Hz), 6.50 (1H, s), 7.0—7.5 (3H, m), 8.2—8.4 (1H, m), 9.8 (1H, br s).

**4,6-Dimethyl-2-(*p*-toluidino)pyrimidine 1-Oxide (IVh)**——IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3230, 1595, 1560, 1245, 1205, 1170; UV $\lambda_{\max}^{\text{EtOH}}$ nm (log $\varepsilon$): 243 (4.15), 282 (4.31), 322 (3.64); PMR (CDCl$_3$) $\delta$: 2.32 (3H, s), 2.40 (3H, s), 2.51 (3H, s), 6.54 (1H, s), 7.0—7.4 (2H, m), 7.5—7.8 (2H, m), 9.5 (1H, br s).

**2-Anilino-6-(*p*-chloro)phenyl-4-methylpyrimidine 1-Oxide (IVi)**——IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3200, 1590, 1560, 1140, 1085, 815, 750; UV $\lambda_{\max}^{\text{EtOH}}$ nm (log $\varepsilon$): 243 (4.29), 280 (4.48), 357 (3.54); PMR (CDCl$_3$) $\delta$: 2.42 (3H, s), 6.70 (1H, s), 7.0—8.1 (9H, m), 9.9 (1H, br s).

**2-Anilino-4-methyl-6-(*p*-tolyl)pyrimidine 1-Oxide (IVj)**——IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3140, 1585, 1560, 1140, 1100, 805; UV $\lambda_{\max}^{\text{EtOH}}$ nm (log $\varepsilon$): 243 (4.18), 282 (4.47), 352 (3.65); PMR (CDCl$_3$) $\delta$: 2.40 (3H, s), 2.42 (3H, s), 6.74 (1H, s), 7.1—7.6 (7H, m), 7.7—8.0 (2H, m), 9.9 (1H, br s).

**4,6-Dimethyl-2-methylaminopyrimidine 1-Oxide (IVk)**——IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 3270, 1610, 1430, 1160, 1125; UV $\lambda_{\max}^{\text{EtOH}}$ nm (log $\varepsilon$): 231 (4.29), 254 (3.81), 327 (3.81); PMR (CDCl$_3$) $\delta$: 2.30 (3H, s), 2.42 (3H, s), 3.07 (3H, d, $J=5.0$ Hz), 6.38 (1H, s), 7.4 (1H, br s).

**Deoxygenation of 2-Anilino-4,6-dimethylpyrimidine 1-Oxides (IVa)**——The reaction mixture of IVa (1 mmol) in methanol (30 ml) was deoxygenated in the presence of Raney nickel (Ni–Al 50% alloy, 2 g) under hydrogen at room temperature. After removal of the catalyst, the solvent was evaporated off. The crude product was recrystallized from hexane to give V (75% yield). The product V was identical (spectral data and mixed melting point) with an authentic sample.13)

## References and Notes

1) *a*) A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17, ed. by A. Weissberger, Interscience Publisher, Inc., New York, 1962, pp. 1—94; *b*) C. Kashima, *Heterocycles*, **12**, 1343 (1979).
2) T. Kato, H. Yamanaka, and T. Shibata, *Yakugaku Zasshi*, **87**, 1096 (1967) and references cited therein.
3) H.C. van der Plas, M.C. Vollering, H. Jonegejan, and B. Zuurdeeg, *Rec. Trav. Chim.*, **93**, 225 (1978).
4) T. Kato, H. Yamanaka, and N. Yasuda, *J. Org. Chem.*, **32**, 3593 (1967).
5) J.M. McCall and R.E. Tenbrink, *Synthesis*, **1978**, 673.
6) C. Kashima, A. Katoh, Y. Yokota, and Y. Omote, *J. Chem. Soc. Perkin I*, **1981**, 489.
7) R.G. Micetich, *Can. J. Chem.*, **48**, 2006 (1970).
8) G. Bianchi and P. Grunanger, *Tetrahedron*, **21**, 817 (1965).
9) P.V. Finzi and P. Gruenager, *Chim. Ind.* (Milan), **47**, 516 (1965) [*Chem. Abstr.*, **63**, 18062c (1965)].
10) C.F. Beam, M.C.D. Dyer, R.A. Schwarz, and C.R. Hauser, *J. Org. Chem.*, **35**, 1806 (1970).
11) C. Kashima and A. Katoh, *J. Chem. Soc. Perkin I*, **1980**, 1599.
12) H. Yamanaka, S. Ogawa, and S. Konno, *Chem. Pharm. Bull.*, **28**, 1526 (1980).
13) *a*) F.H.S. Curd and F.L. Rose, *J. Chem. Soc.*, **1964**, 343; *b*) R.A. Abramovitch, R.B. Rogers, and G.M. Singer, *J. Org. Chem.*, **40**, 41 (1975).
14) T. Sakamoto, S. Niitsuma, M. Mizugaki, and H. Yamanaka, *Chem. Pharm. Bull.*, **27**, 2653 (1979).