Pyrimidine Derivatives and Related Compounds. Part 42.[1] Isolation of the Intermediates in the Ring Transformation of 1,3-Oxazine-2,4-diones into Pyrimidines and Pyrazoles, and their Structure Determination by ^{15}N Nuclear Magnetic Resonance Analysis

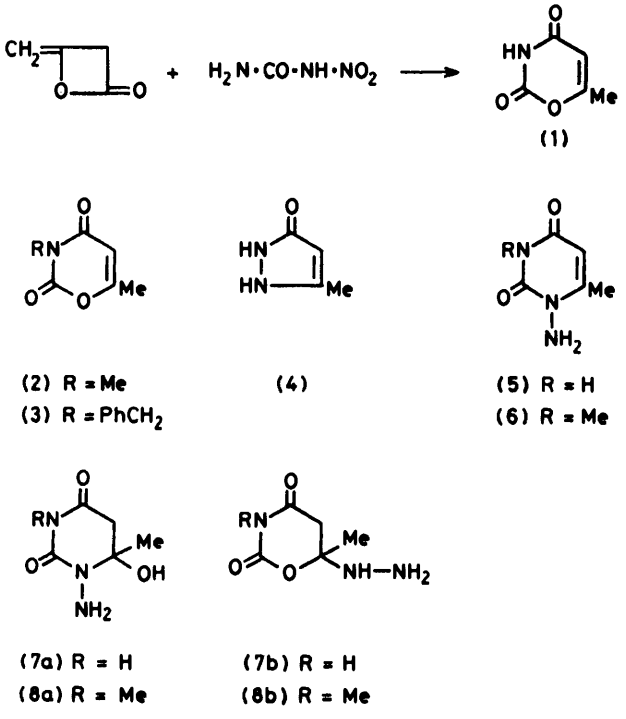
By **Motoi Yogo,*** Faculty of Pharmacy, Meijo University, Tempaku-cho, Tempaku-ku, Nagoya 468, Japan
Kosaku Hirota * and **Shigeo Senda**, Gifu College of Pharmacy, Mitahora-higashi, Gifu 502, Japan

Reaction of the 6-methyl-1,3-oxazine-2,4-diones (1) and (2) with hydrazine hydrate at room temperature gave the 6-hydroxy-5,6-dihydrouracils (7a) and (8a). The structures of the products were determined by ^{15}N n.m.r. analysis. The mechanism of the ring transformation of 1,3-oxazines into pyrimidines and pyrazoles is discussed.

SHAW and his co-workers [2] have reported that 6-methyl-1,3-oxazine-2,4-dione (1) reacts with hydrazine hydrate to give 5-methylpyrazol-3-one (4), whereas 3,6-dimethyl-1,3-oxazine-2,4-dione (2) transformed into 1-amino-3,6-dimethyluracil (6) under the same conditions. However, experimental details (such as reaction temperature and amounts of reagents) were not clearly stated. In contrast to these results, Kato *et al.*[3] have described the reaction of the oxazine (1) with hydrazine hydrate to give 1-amino-6-methyluracil (5), whereas 3-benzyl-6-methyl-1,3-oxazine-2,4-dione (3) gave the pyrazolone (4).

As part [4] of studies on the synthesis and reactions of 1,3-oxazine-2,4-dione derivatives, we have re-examined the reaction of the 6-methyl-1,3-oxazine-2,4-diones (1) and (2) with hydrazine hydrate. We have isolated the intermediates (7) and (8) in these reactions, and determined their structures by ^{15}N n.m.r. analysis.

Several reports [2,5] have been published on the synthesis of the starting 6-methyloxazine (1). However, we obtained it in much better yield simply by keeping the mixture of nitrourea, keten dimer, and pyridine at room temperature overnight. The reactions of the 6-methyloxazines (1) and (2) with hydrazine hydrate in ethanol at room temperature did not give the corresponding 1-aminouracils (5) and (6), or the pyrazolone (4) but afforded a new compound in 80 and 71% yield, respectively. Spectral data (^1H n.m.r., ^{13}C n.m.r., and mass) supported either of two possible structures [(7a or b), and (8a or b), respectively], a choice between which was made on the basis of ^{15}N n.m.r. Fourier transform spectra (Table). The decoupled spectrum of each product showed three signals. However, the off-resonance-decoupled spectrum of (7) showed a doublet for N-3, a singlet for N-1, and a triplet for NH_2, whereas the oxazine (7b) would show two doublets and a triplet. Similarly, that of (8) showed two singlets for N-3 and N-1, and a triplet for NH_2, whereas the oxazine (8b) would show a singlet, a doublet, and a triplet. Thus both adducts have the 6-hydroxy-5,6-dihydrouracil structure [(7a) or (8a)].

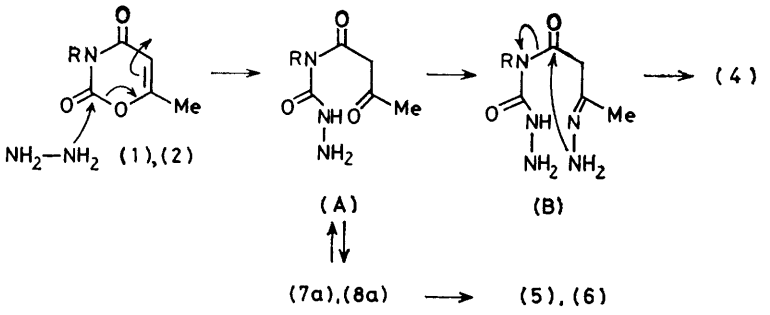


^{15}N N.m.r. chemical shifts [solvent $(CD_3)_2SO$] [a]

	NH_2	N-1	N-3
(1)			34.2 (d) (−231.3)
(2)			31.2 (s) (−234.3)
(5)	−45.4 (t) (−310.9)	40.5 (s) (−225.0)	43.0 (d) (−222.5)
(6)	−42.6 (t) (−308.1)	39.4 (s) (−226.1)	40.1 (s) (−225.4)
(7a)	−52.3 (t) (−317.8)	22.0 (s) (−243.5)	36.7 (d) (−228.8)
(8a)	−49.1 (t) (−314.6)	22.8 (s) (−242.8)	30.9 (s) (−234.6)

[a] Chemical shifts with respect to external $HCONH_2$; shifts with respect to NH_4NO_3 are in parentheses ($\delta_{NH_4{}^{15}NO_3} = \delta_{HCONH_2} - 265.5$).

Heating of the dihydrouracils (7a) and (8a) in ethanol gave the 1-amino-6-methyluracils (5) and (6) in 85 and 63% yield, respectively. On heating in ethanol in the presence of hydrazine hydrate, the dihydrouracil (7a) afforded the pyrazolone (4) as major product and the aminouracil (5) as a minor one, while in a similar reaction with (8a) the aminouracil (6) was obtained in 45% yield



SCHEME

and the pyrazolone (4) was detected by ^{1}H n.m.r. spectroscopy (although it could not be isolated). When the aminouracils (5) and (6) were refluxed in ethanol in the presence of hydrazine hydrate, the pyrazolone (4) was not obtained and the starting material was recovered. Therefore, the pyrazolone (4) is not formed *via* the uracils (5) and (6).

On the basis of the above-mentioned results, a mechanism for the ring transformation of the 6-methyloxazines (1) and (2) into the uracils (5) and (6) and the pyrazolone (4) is postulated (see Scheme). The initial step is an attack at the 2-position by hydrazine hydrate giving the intermediates (7a) and (8a) *via* the semicarbazide (A). Subsequent dehydration of (7a) and (8a) would afford the aminouracils (5) and (6). On the other hand, the pyrazolone (4) would be formed *via* the hydrazone (B).

EXPERIMENTAL

Mass spectra were measured with a JEOL TMS-D-300 spectrometer and ^{1}H n.m.r. spectra with a JEOL JNM-PS-100 spectrometer, with tetramethylsilane as internal standard. ^{13}C N.m.r. spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as internal standard. ^{15}N N.m.r. spectra of (7a) and (8a) were measured with a JEOL JNM-FX-90Q Fourier transform spectrometer operating at 9.03 MHz, and those of (1), (2), (5), and (6) with a JEOL JNM-FX-100 Fourier transform spectrometer operating at 10.05 MHz. ^{15}N N.m.r. chemical shifts are given in p.p.m. to lower frequency of external 90% $HCONH_2$ in $(CD_3)_2SO$.

6-*Methyl*-1,3-*oxazine*-2,4-*dione* (1).—To a stirred solution of nitrourea (2.1 g, 0.02 mol) in anhydrous pyridine (10 ml), keten dimer (2.2 g, 0.026 mol) was added dropwise at room temperature and the mixture was kept at room temperature overnight. The solvent was evaporated off *in vacuo* and the residue was washed with water to give the oxazine (1) (1.3 g, 52%), m.p. 241—242 °C (from ethyl acetate) (lit.,[2] 243 °C).

1-*Amino*-6-*hydroxy*-6-*methyl*-5,6-*dihydrouracil* (7a).—To a stirred suspension of the finely powdered oxazine (1) (1 000 mg, 7.9 mmol) in ethanol (10 ml) was added hydrazine hydrate (500 mg, 10 mmol) and the mixture was stirred for 10 h. The precipitate was filtered off and washed with a small amount of ethanol to give the 6-*hydroxydihydrouracil* (7a) (1 010 mg, 80%), m.p. 162—164 °C (Found: C, 37.7; H, 5.75; N, 26.4. $C_5H_9N_3O_3$ requires C, 37.7; H, 5.7; N, 26.4%); *m/z* 159 (M^+); δ_H [$(CD_3)_2SO$] 1.52 (3 H, s, Me), 2.55 (1 H, d, *J* 16 Hz, H-5), 2.88 (1 H, d, *J* 16 Hz, H-5), 4.30 (2 H, br, NH_2, exchanged in D_2O), and 7.50 (1 H, br, OH, exchanged in D_2O); δ_C [$(CD_3)_2SO$] 26.37 (q, Me), 45.18 (t, CH_2), 83.20 (s, HO-*C*-Me), 153.92 (s, N-*C*O-N), and 168.22 (s, C-*C*O-N).

1-*Amino*-6-*hydroxy*-3,6-*dimethyl*-5,6-*dihydrouracil* (8a).—The oxazine (2) (2 800 mg, 20 mmol), hydrazine hydrate (1 100 mg, 22 mmol), and ethanol (25 ml) were treated as in the preparation of (7a) to give the *dihydrouracil* (8a) (2 460 mg, 71%), m.p. 115—117 °C (Found: C, 41.6; H, 6.4; N, 24.3. $C_6H_{11}N_3O_3$ requires C, 41.6; H, 6.4; N, 24.3%); *m/z* 173 (M^+); δ_H [$(CD_3)_2SO$] 1.50 (3 H, s, Me), 2.63 (1 H, d, *J* 16 Hz, H-5), 2.93 (1 H, d, *J* 16 Hz, H-5), 3.00 (3 H, s, NMe), 4.35 (2 H, s, NH_2, exchanged in D_2O), and 6.01 (1 H, s, OH, exchanged in D_2O); δ_C [$(CD_3)_2SO$] 26.25 (q, Me), 27.25 (q, NMe), 45.12 (t, CH_2), 82.27 (s, HO-*C*-Me), 154.57 (s, N-CO-N), and 167.40 s, C-*C*O-N).

Heating of the 5,6-*Dihydrouracil* (7a).—(a) *In the absence of hydrazine hydrate.* A mixture of the 5,6-dihydrouracil (7a) (400 mg, 2.5 mmol) and ethanol (20 ml) was refluxed for 13 h. The precipitate was filtered off to give the aminouracil (5) (300 mg, 85%), m.p. 254—256 °C (lit.,[3] m.p. 245—246 °C) (Found: C, 42.7; H, 5.2; N, 29.8. Calc. for $C_5H_7N_3O_2$: C, 42.55; H, 5.0; N, 29.8%); *m/z* 141 (M^+); δ_H [$(CD_3)_2SO$] 2.19 (3 H, s, Me), 5.11 (2 H, s, NH_2, exchanged in D_2O), 5.36 (1 H, s, H-5), and 11.09 (1 H, br, s, NH, exchanged in D_2O).

(b) *In the presence of hydrazine hydrate.* A mixture of the 5,6-dihydrouracil (7a) (400 mg, 2.5 mmol), hydrazine hydrate (200 mg, 4 mmol) and ethanol (4 ml) was refluxed for 20 min. The solvent was evaporated off and the residue was triturated with propan-2-ol. The resulting solid was filtered off to give a mixture (200 mg) of the pyrazolone (4) (81%) and the aminouracil (5) (19%). The ratio of the products was determined by ^{1}H n.m.r. analysis.

Heating of the 5,6-*Dihydrouracil* (8a).—(a) *In the absence of hydrazine hydrate.* A mixture of the 5,6-dihydrouracil (8a) (500 mg, 2.9 mmol) and ethanol (5 ml) was refluxed for 28 h. Concentration of the mixture gave the aminouracil (6) (280 mg, 63%), m.p. 154—156 °C (lit.,[2] 112 °C; lit.,[6] 151—152 °C) (Found: C, 46.5; H, 5.9; N, 27.2. Calc. for $C_6H_9N_3O_2$: C, 46.4; H, 5.85; N, 27.1%); *m/z* 155 (M^+); δ_H [$(CD_3)_2SO$] 2.22 (3 H, s, Me), 3.16 (3 H, s, NMe), 5.24 (2 H, s, NH_2, exchanged in D_2O), and 5.54 (1 H, s, H-5).

(b) *In the presence of hydrazine hydrate.* A mixture of the 5,6-dihydrouracil (8a) (400 mg, 2.3 mmol), hydrazine hydrate (170 mg, 3.4 mmol) and ethanol (4 ml) was refluxed for 30 min. The solvent was evaporated off and the residue was triturated with propan-2-ol. The resulting

solid was filtered off to give the aminouracil (6) (160 mg, 45%), identical with the sample obtained in (a).

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