derivative, but the latter failed to give any definite oxidation product under a variety of working conditions, yielding only intractable, dark blue tarry substance.

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53. **Hideo Kanō and Yasuo Makisumi**: Studies on Isoxazole Derivatives. VIII.[1] Catalytic Hydrogenation of 5-Aminoisoxazoles.

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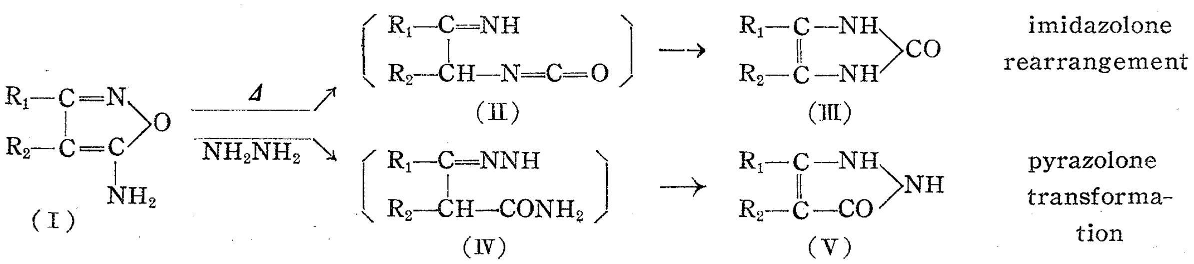
In part III[2] and V[3] of this series, one of the authors (Kanō) reported on the "imidazolone rearrangement" and "pyrazolone transformation" of 5-aminoisoxazoles (I). In both cases, it was considered that these transitions occurred with the ring cleavage of (I) at N—O bond, and each intermediate was assumed to be the isocyanate (II) and the amide (IV).



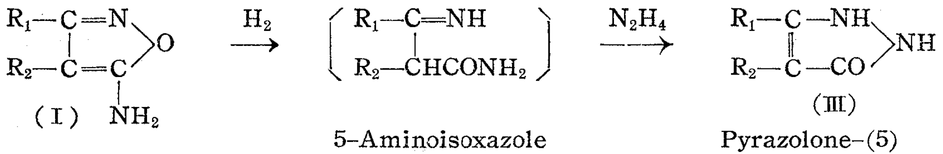
Recently, the catalytic hydrogenation of 3-pheyl-5-aminoisoxazole and its acyl derivatives was studied by Shaw and Sugowdz,[4] the former yielding β-aminocinnamide and the latter, a mixture of β-aminocinnamoyl acylamide and hydroxypyrimidine. These amides reacted with hydrazine or phenylhydrazine to give pyrazolones.

In the imidazolone rearrangement and pyrazolone transformation, the ring opening of (I) was affected by the substituents at 3- and 4-positions of 5-aminoisoxazoles. Such ring opening however did not occur with 3-phenyl-5-aminoisoxazole.

The present paper is a report on catalytic hydrogenation of 5-aminoisoxazoles (I) and its acyl derivatives (VI) which have substituents at 3- and 4-positions.

(I) readily absorbed 1 mole of hydrogen in the presence of Raney nickel in ethanol at room temperature, and after hydrogenation the basic products were treated with hydrazine. The pyrazolones (III) were obtained. The results of these reactions are shown in Table I. (VI) also easily absorbed 1 mole of hydrogen in the presence of

Table I



R_1	R_2	5-Aminoisoxazole No.	Pyrazolone-(5) No.	Pyrazolone-(5) m.p. °C
CH_3	H	(Ia)	(IIIa)[8]	218~219
CH_3	CH_3	(Ib)	(IIIb)[9]	271~272
C_2H_5	CH_3	(Ic)	(IIIc)	232~233

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* Imafuku, Amagasaki, Hyogo-ken (加納日出夫, 牧角徳夫).

1) Part VII: J. Pharm. Soc. Japan, **74**, 138(1954).

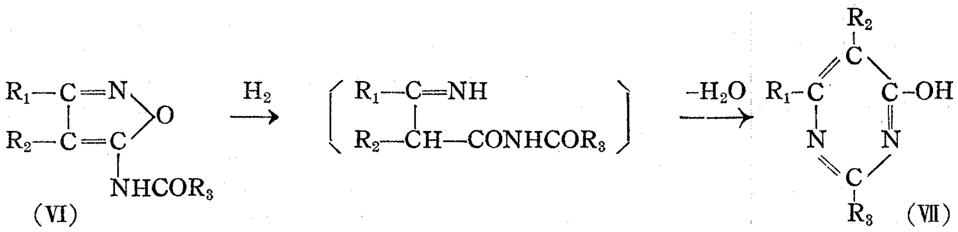
2) Part III: *Ibid.*, **72**, 1118(1952).

3) Part V: *Ibid.*, **73**, 383(1953).

4) G. Shaw, G. Sugowdz: J. Chem. Soc., **1954**, 665.

Raney nickel in ethanol. After removal of the catalyst by filtration, the solvent was evaporated on a steam bath to give hydroxypyrimidines (VII) in good yields. The results of these reactions are summarized in Table II.

TABLE II



R_1	R_2	R_3	5-Acetaminoisoxazole No.	5-Acetaminoisoxazole m.p. °C	6-Hydroxypyrimidine No.	6-Hydroxypyrimidine m.p. °C	
CH_3	H	CH_3	(VIa)5)	169	(VIIa)10)	193~194	(benzene)
CH_3	CH_3	CH_3	(VIb)6)	114~115	(VIIb)10)	174	(benzene)
C_2H_5	CH_3	CH_3	(VIc)7)	71~72	(VIIc)11)	168~169	(benzene)
CH_3	C_2H_5	CH_3	(VId)	oil	(VIId)10)	140~141	(benzene)
n-C_4H_9	n-C_3H_7	CH_3	(VIe)	oil	(VIIe)	118	(EtOH)
C_6H_5	CH_3	CH_3	(VIf)	103~104	(VIIf)	180~181	(MeOH)
$C_2H_5OCH_2$	CH_3	CH_3	(VIg)	75~76	(VIIg)	157~158	(benzene)
CH_3OCH_2	CH_3	CH_3	(VIh)	109~110	(VIIh)	159~160	(benzene+petr. ether)
CH_3	H	H	(VIi)	127~128	(VIIi)12)	149~150	(benzene)
CH_3	CH_3	H	(VIj)	102~103	(VIIj)13)	205~206	(EtOH)
C_2H_5	CH_3	H	(VIk)	78~79	(VIIk)	161~162	(benzene)

The authors are grateful to Dr. K. Takeda, Director of this Laboratory, for his helpful advice and encouragement. Their thanks are also due to the members of the analysis room of this Laboratory for the microanalytical work.

Experimental

I) Hydrogenation of 5-Aminoisoxazoles

3-Methylpyrazolone-(5)(IIIa)—A solution of (Ia) (2 g.) in ethanol (30 cc.) was shaken in H_2 stream with Raney Ni (1.5 cc.) at room temperature, 480 cc. H_2 being absorbed during 3 hrs. Evaporation of the filtered solution *in vacuo* gave a pale yellow oil, which was warmed on a water bath with $NH_2NH_2\cdot H_2O$ (2 cc. of 70%) for 30 mins. On cooling, (IIIa) (0.7 g.) was obtained. Recrystallization from hot water gave colorless prisms, m.p. 218~219°, undepressed on admixture with an authentic sample.8) *Anal.* Calcd. for $C_4H_6ON_2$: C, 48.98; H, 6.12; N, 28.57. Found : C, 48.90; H, 6.13; N, 28.60.

3,4-Dimethylpyrazolone-(5)(IIIb)—(Ib) (2.0 g.) was treated by the same procedure as for (IIIa). Yield, 0.8 g. Colorless prisms, m.p. 271~272°, undepressed on admixture with an authentic sample.9) *Anal.* Calcd. for $C_5H_8ON_2$: C, 53.51; H, 7.14; N, 24.98. Found : C, 53.17; H, 7.07; N, 25.49.

3-Ethyl-4-methylpyrazolone-(5)(IIIc)—(Ic) (2.0 g.) was treated by the same procedure as for (IIIa). Yield, 0.9 g. Colorless plates, m.p. 232~233°. *Anal.* Calcd. for $C_6H_{10}ON_2$: C, 57.12; H, 7.99; N, 22.21. Found : C, 56.90; H, 7.62; N, 22.43.

II) Acylation of 5-Aminoisoxazoles

3-Ethyl-4-methyl-5-acetaminoisoxazole (VIc)—A mixture of (Ic) (2.0 g.) and Ac_2O (6 cc.) was heated on a water bath for 30 mins. The excess Ac_2O was removed *in vacuo* to precipitate (VIc) (2.0 g.). Recrystallization from a mixture of benzene and petr. ether gave colorless prisms, m.p. 71~72°. *Anal.* Calcd. for $C_8H_{12}O_2N_2$: C, 57.14; H, 7.14; N, 16.67. Found : C, 57.59; H, 7.49; N, 16.95.

3-Methyl-4-ethyl-5-acetaminoisoxazole (VIa)— 3-Methyl-4-ethyl-5-aminoisoxazole was acetylated by the same procedure as for (VIc). A pale yellow oil was obtained which was used withoutfurther purification.

3-Butyl-4-propyl-5-acetaminoisoxazole(VIe)— 3-Butyl-4-propyl-5-aminoisoxazole was acetylated

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5) Burns : J. prakt. Chem., [2] **47**, 123(1893).
6) Kanō : J. Pharm. Soc. Japan, **72**, 1120(1952).
7) Hanriot : Compt. rend., **112**, 796(1891).
8) Knorr : Ber., **29**, 253(1896).
9) V. Rothenburg : J. prakt. Chem., [2] **52**, 40(1895).

by the same procedure as for (VIc). A colorless oil was obtained which was used without further purification.

3-Phenyl-4-methyl-5-acetaminoisoxazole (VIf)— 3-Phenyl-4-methyl-5-aminoisoxazole was acetylated by the same procedure as for (VIc). Colorless prisms, m.p. 103~104°. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.66; H, 5.59; N, 12.96. Found: C, 66.70; H, 5.66; N, 13.08.

3-Ethoxymethyl-4-methyl-5-acetaminoisoxazole (VIg)— 3-Ethoxymethyl-4-methyl-5-aminoisoxazole was acetylated by the same procedure as for (VIc). Colorless prisms, m.p. 75~76°. *Anal.* Calcd. for $C_9H_{14}O_3N_2$: C, 54.54; H, 7.07; N, 14.14. Found: C, 54.17; H, 6.89; N, 13.86.

3-Methoxymethyl-4-methyl-5-acetaminoisoxazole(VIh)— 3-Ethoxymethyl-4-methyl-5-aminoisoxazole was acetylated by the same procedure as for (VIc). Colorless needles, m.p. 109~110°. *Anal.* Calcd. for $C_8H_{12}O_3N_2$: C, 52.17; H, 6.52; N, 15.22. Found: C, 52.27; H, 6.51; N, 15.22.

3-Methyl-5-formylaminoisoxazole (VIi)—A mixture of 3-methyl-5-aminoisoxazole (2.0 g.) and formic acid (3 cc. of 80%) was heated on a water bath for 15 mins. The excess acid was removed *in vacuo* to precipitate (VIi) (1.8 g.). Recrystallization from benzene gave colorless needles, m.p. 127~128°. *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.76; N, 22.22. Found: C, 48.03; H, 4.85; N, 22.16.

3,4-Dimethyl-5-formylaminoisoxazole(VIj)— 3,4-Dimethyl-5-aminoisoxazole was treated by the same procedure as for (VIi). Colorless needles, m.p. 102~103°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.40; H, 5.70; N, 20.00. Found: C, 51.61; H, 6.00; N, 20.25.

3-Ethyl-4-methyl-5-formylaminoisoxazole(VIk)— 3-Ethyl-4-methyl-5-aminoisoxazole was treated by the same procedure as for (VIi). Colorless plates, m.p. 78~79°. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.54; H, 6.56; N, 18.18. Found: C, 54.24; H, 6.29; N, 18.36.

III) Hydrogenation of 5-Acylaminoisoxazole

2,4-Dimethyl-6-hydroxypyrimidine (VIIa)—A solution of (VIa) (2.0 g.) in EtOH was hydrogenated over Raney Ni (2 cc.) at room temperature, 230 cc. of H_2 being absorbed during 6 hrs. Evaporation of the filtered solution on a water bath gave a solid (1.6 g.), which recrystallized from benzene to colorless needles, m.p. 193~194°, undepressed on admixture with an authentic sample.[10] *Anal.* Calcd. for $C_6H_8ON_2$: C, 58.05; H, 6.49; N, 22.56. Found: C, 58.52; H, 6.96; N, 22.42.

2,4,5-Trimethyl-6-hydroxypyrimidine (VIIb)— (VIb) (3.0 g.) was hydrogenated by the same procedure as for (VIIa). White needles (1.6 g.), m.p. 174°, undepressed on admixture with an authentic sample.[10] *Anal.* Calcd. for $C_7H_{10}ON_2$: C, 60.90; H, 7.30; N, 20.29. Found: C, 60.85; H, 7.36; N, 20.29.

2,5-Dimethyl-4-ethyl-6-hydroxypyrimidine (VIIc)—(VIc) (2.0 g.) was hydrogenated by the same procedure as for (VIIa). White needles (1.75 g.), m.p. 168~169°, undepressed on admixture with an authentic sample.[11] *Anal.* Calcd. for $C_8H_{12}ON_2$: C, 63.16; H, 7.89; N, 18.42. Found: C, 63.16; H, 8.08; N, 18.35.

2,4-Dimethyl-5-ethyl-6-hydroxypyrimidine(VIId)—(VId) (1.0 g.) was hydrogenated by the same procedure as for (VIIa). White needles (0.9 g.), m.p. 140~141°, undepressed on admixture with an authentic sample.[10] *Anal.* Calcd. for $C_8H_{12}ON_2$: C, 63.16; H, 7.89; N, 18.42. Found: C, 63.04; H, 8.16; N, 18.05.

2-Methyl-4-butyl-5-propyl-6-hydroxypyrimidine (VIIe)—(VIe) (1.2 g.) was hydrogenated by the same procedure as for (VIIa). White needles (1.05 g.), m.p. 117~118°. *Anal.* Calcd. for $C_{12}H_{20}ON_2$: C, 69.23; H, 9.62; N, 13.46. Found: C, 69.24; H, 9.78; N, 13.52.

2,6-Dimethyl-4-phenyl-6-hydroxypyrimidine (VIIf)—(VIf) (0.5 g.) was hydrogenated by the same procedure as for (VIIa). White prisms (0.5 g.), m.p. 180~181°. *Anal.* Calcd. for $C_{12}H_{12}ON_2$: C, 71.55; H, 6.06; N, 13.90. Found: C, 71.99; H, 6.04; N, 14.00.

2,5-Dimethyl-4-ethoxymethyl-6-hydroxypyrimidine (VIIg)—(VIg) (1.0 g.) was hydrogenated by the same procedure as for (VIIa). White needles (0.9 g.), m.p. 157~158°. *Anal.* Calcd. for $C_9H_{14}O_2N_2$: C, 59.34; H, 7.74; N, 15.38. Found: C, 59.03; H, 7.63; N, 15.14.

2,5-Dimethyl-4-methoxymethyl-6-hydroxypyrimidine (VIIh)—(VIh) (1.0 g.) was hydrogenated by the same procedure as for (VIIa). White needles (0.9 g.), m.p. 159~160°. *Anal.* Calcd. for $C_8H_{12}O_2N_2$: C, 57.14; H, 7.14; N, 16.67. Found: C, 56.69; H, 6.68; N, 16.98.

4-Methyl-6-hydroxypyrimidine (VIIi)—(VIi) (0.4 g.) was hydrogenated by the same procedure as for (VIIa). White needles (0.35 g.), m.p. 149~150°, undepressed on admixture with an authentic sample.[12] *Anal.* Calcd. for $C_5H_6ON_2$: C, 54.54; H, 5.45; N, 25.45. Found: C, 54.37; H, 5.19; N, 25.32.

4,5-Dimethyl-6-hydroxypyrimidine (VIIj)—(VIj) (1.0 g.) was hydrogenated by the same procedure as for (VIIa). Colorless prisms, m.p. 205~206°, undepressed on admixture with an authentic

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[10] Pinner: Ber., **22**, 1616 (1889).

[11] Schwarze: J. prakt. Chem., [2] **42**, 17 (1890).

[12] Gabriel, Colman: Ber., **32**, 1533 (1899).

sample.[13] *Anal.* Calcd. for $C_6H_8ON_2$: C, 58.06; H, 6.45; N, 22.58. Found : C, 58.01; H, 6.41; N, 22.67.

4-Ethyl-5-methyl-6-hydroxypyrimidine (VIIk)—(VIk)(0.4 g.) was hydrogenated by the same procedure as for (VIIa). Colorless plates (0.35 g.), m.p. 161~162°. *Anal.* Calcd. for $C_7H_{10}ON_2$: C, 60.87; H, 7.24; N, 20.29. Found : C, 60.67; H, 7.25; N, 20.43.

Summary

Catalytic hydrogenation of 5-aminoisoxazoles (I) gave the amides, which was treated with hydrazine hydrate to yield the pyrazolones-(5) (V), but the acyl derivatives (VI) gave the hydroxypyrimidine (VII) in good yields. The hydrogenation was not affected by the substituents at 3- and 4-positions of (I) or (VI).

(Received April 30, 1955)

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13) Schlenker : *Ibid.*, **43**, 2823(1901).