RING-TRANSFORMATION OF 1,2,4-OXADIAZINE DERIVATIVES INTO 4-HYDROXYPYRIMIDINE DERIVATIVES: CATALYTIC HYDROGENATION OF 3-ARYL-5-ETHOXYCARBONYLMETHYLENE-5,6-DIHYDRO-4H-1,2,4-OXADIAZINE DERIVATIVES[1)]

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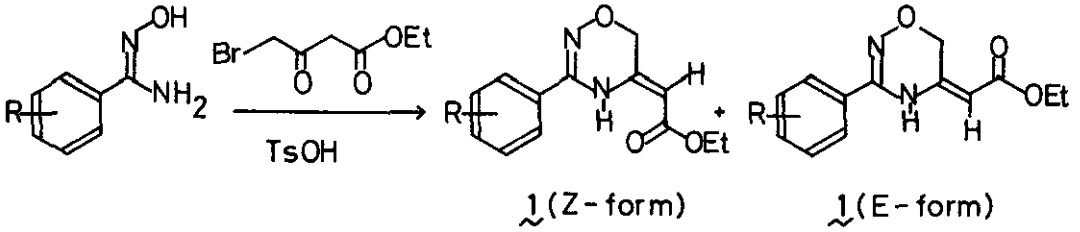
Abstract —— Catalytic hydrogenation of 3-aryl-5-ethoxycarbonylmethylene-5,6-dihydro-4H-1,2,4-oxadiazine derivatives (1) is described. The method leads to new synthesis of 2-aryl-4-hydroxypyrimidine derivatives (3) involving cyclization of ethyl 3-benzimidoylimino-4-hydroxybutanoate derivatives (2) by the elimination of ethanol. Nickel catalyzed hydrogenation of 1 gave ethyl 2-aryl-4-oxazolylacetate (4) as a by-product besides product 3.

We have recently reported the synthesis of 3-aryl-5-ethoxycarbonylmethylene-5,6-dihydro-4H-1,2,4-oxadiazine derivatives (1) by the reaction of benzamide oxime derivatives with ethyl γ-bromoacetoacetate in the presence of p-toluenesulfonic acid as a catalyst.[2)] In relation to the synthesis of exo-methylene-1,2,4-oxadiazine derivatives, Santilli et al.[3)] previously reported that reaction of benzamide



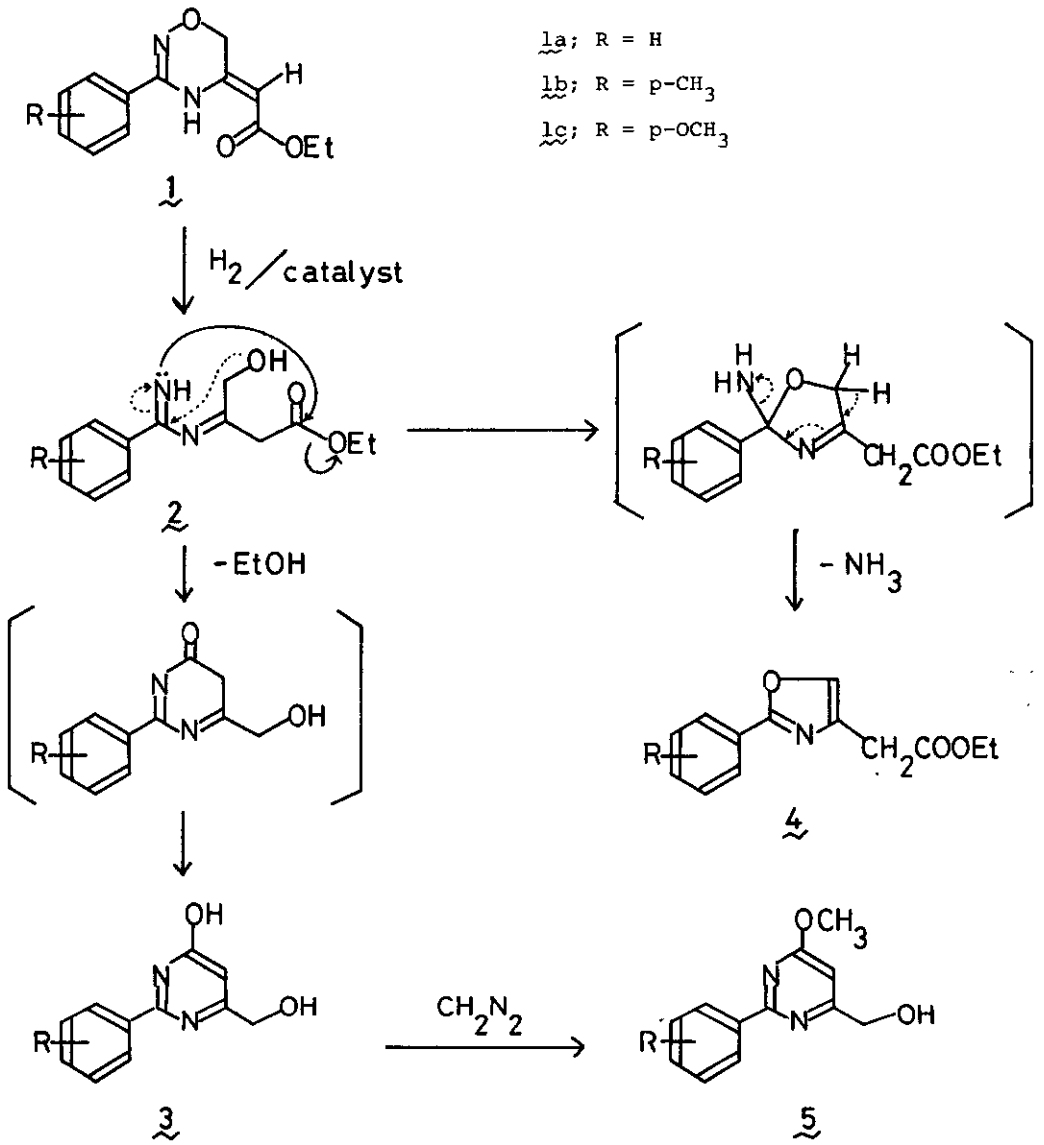
1 (Z-form) 1 (E-form)

oximes with dimethyl acetylenedicarboxylate gave methyl (3-aryl-4,5-dihydro-5-oxo-6H-1,2,4-oxadiazin-6-ylidene)acetate which, on heating with N,N-diethylethylenediamine, was transformed to methyl 2-aryl-5-[2-(diethylamino)ethylamino]-1,6-dihydro-6-oxo-4-pyrimidinecarboxylate. They have also mentioned the mechanism of the ring-transformation as proceeding through N-O bond fission by an attack of the amine to the 6-position of the oxadiazine ring. In this connection, we have intended the ring-transformation of our 1,2,4-oxadiazine derivatives into pyrimidine derivatives. Here, we wish to report some aspects on the hydrogenolytic ring-transformation of 5-exo-methylene-1,2,4-oxadiazines.

First, we attempted nickel catalyzed hydrogenation of 1, since compound 1 does not bear an exo-methylene group at the 6-position. According to the method described by Shaw et al.,[4] a suspension of (Z)-5-ethoxycarbonylmethylene-5,6-dihydro-3-phenyl-4H-1,2,4-oxadiazine (1a, R = H) (140 mg, 5.1 mmol) and Raney nickel catalyst (about 15 mg) in THF (50 ml) was stirred in hydrogen at room temperature and atmospheric pressure for 72 h to afford colorless precipitate, which on recrystallization from EtOH gave colorless needles of mp 240°C (3a), $C_{11}H_{10}N_2O_2$,[5] in 55.2 % yield with recovery of the starting material (9.5%). The structure of 3a was established to be 4-hydroxy-6-hydroxymethyl-2-phenylpyrimidine on the basis of its IR, NMR, and MS spectral data.[6] On treatment with diazomethane in EtOH, 3a was converted to 6-hydroxymethyl-4-methoxy-2-phenylpyrimidine (5a),[7] mp 110°C, in 97 % yield.

Treatment of 1a with hydrogen at about three atmospheric pressure in the presence of Raney nickel catalyst, on the other hand, afforded 3a in 75.7% yield and a colorless viscous oil of $C_{13}H_{13}NO_3$ (4a) in 5.6% yield. The structure of 4a was elucidated to be ethyl 2-phenyl-4-oxazolylacetate on the basis of its spectral data,[8] and identified by the comparison of IR spectrum with that of the authentic sample prepared by the method described in the literature.[9]

When palladium on charcoal was used as a catalyst, the yield of 3a decreased to 44.2% and an appreciable amount of the starting material was recovered even on carrying out the reaction for 72 h. By using Adam's platinum oxide as a catalyst, on the other hand, a small amount of 3a (7.1%) and a ring-opened product (2a), $C_{13}H_{16}N_2O_3$, mp 89°C, (13.8%), were obtained. The structure of 2a was assigned to be ethyl 3-benzimidoylimino-4-hydroxybutanoate on the basis of its spectral data.[10] On treatment with a trace of sodium hydroxude in EtOH, compound 2a was converted to 3a in almost quantitative yield and compound 4a could not be



isolated. A likely pathway is shown in the above chart.

The similar ring-transformation was carried out by using (Z)-5-ethoxycarbonylmethylene-5,6-dihydro-3-p-methylphenyl-4H-1,2,4-oxadiazine (1b, R = p-CH_3) and (Z)-5-ethoxycarbonylmethylene-5,6-dihydro-3-p-methoxyphenyl-4H-1,2,4-oxadiazine (1c, R = p-OCH_3) and results are listed in Table I.

When palladium chloride or platinum on charcoal was used as a catalyst, the reaction resulted in the recovery of the starting material. From the above results,

the present ring-transformation, especially the hydrogenation under three atmospheric pressure, seems to be useful in the synthesis of 4-hydroxypyrimidine derivatives. We are now presently investigating to optimize the reaction conditions and to control them in view of mechanistic points.

Table I Catalytic Hydrogenation of 1

Run	Reaction Conditions	Compounds	Products (Yield %)[11]
Ia-c	H_2 (1 atm)/ Ni / 72 h	1a	3a (55.2)
		1b	3b (57.7)
		1c	3c (74.0), 4c (1.5)
IIa-c	H_2 (3 atm)/ Ni / 24 h	1a	3a (75.7), 4a (5.6)
		1b	3b (77.3), 4b (6.2)
		1c	3c (42.2), 4c (22.0)
IIIa-c	H_2 (1 atm)/ Pd-C / 72 h	1a	3a (44.2)
		1b	3b (35.7)
		1c	3c (27.8)
IVa-c	H2 (1 atm)/PtO_2 / 72 h	1a	2a (13.8), 3a (7.1)
		1b	2b (55.2), 3b (8.0)
		1c	2c (57.9), 3c (1.2)

REFERENCES AND NOTES

1) A part of this work was presented at the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 3 (1982) p.468 (3Q 3-3).

2) K. Tabei, E. Kawashima, T. Takada, and T. Kato, Chem. Pharm. Bull., in press.

3) A. A. Santilli and A. C. Scotese, J. Heterocyclic Chem., 16, 213 (1979).

4) G. Shaw and G. Sugowdz, J. Chem. Soc., 665 (1954).

5) All new compounds gave satisfactory analyses and high resolution mass spectral data.

6) 3a: mp 240°C (from EtOH) [IR ν(KBr)cm^{-1}; 3350, 1660, 1640. NMR δ(DMSO-d_6)ppm; ~3.3 (1H, br, disappeared on addition of D_2O, OH), 4.41 (2H, s, -CH_2OH), ~5.5 (1H, br, disappeared on addition of D_2O, OH), 6.32 (1H, s, 5-H of pyrimidine

ring), 7.50 and 8.15 (3H and 2H, each m, phenyl). MS m/e; 202 (M^+)].

7) 5a: mp 110°C (from $CHCl_3$-hexane) [IR ν(KBr)cm^{-1}; 3250, 1600. NMR δ($CDCl_3$)ppm; ~3.5 (1H, br, disappeared on addition of D_2O, OH), 4.06 (3H, s, $-OCH_3$), 4.68 (2H, br s, $-CH_2OH$), 6.60 (1H, s, 5-H of pyrimidine ring), 7.50 and 8.45 (3H and 2H, each m, phenyl). MS m/e; 216 (M^+)].

8) 4a: viscous oil [IR ν($CHCl_3$)cm^{-1}; 1735. NMR δ($CDCl_3$)ppm; 1.30 and 4.25 (3H and 2H, t and q, J = 10 Hz, CH_3CH_2-), 3.61 (2H, s, $-CH_2COOEt$), 7.45 and 8.05 (3H and 2H, each m, phenyl), 7.71 (1H, s, 5-H of oxazole ring). MS m/e: 231 (M^+)].

9) D. M. O'Mant, Brit. Amended 1,139,940 (1966)[C.A., 75, 140825w (1971)].

10) 2a: mp 89°C (from hexane)[IR ν(KBr)cm^{-1}; 3250, 1720. NMR δ($CDCl_3$)ppm; 1.28 and 4.20 (3H and 2H, t and q, J = 8 Hz, CH_3CH_2-), ~1.7 (1H, br, disappeared on addition of D_2O, OH), 1.75 (2H, s, $-CH_2OH$), 2.75 and 3.00 (2H, ABq, J = 15 Hz, $-CH_2COOEt$), ~5.7 (1H, br, disappeared on addition of D_2O, NH), 7.45 and 7.63 (5H, m, phenyl). MS m/e; 248 (M^+)].

11) 2b: mp 116°C (from hexane) [IR ν(KBr)cm^{-1}; 3200, 1740. NMR δ($CDCl_3$)ppm; 1.30 and 4.15 (3H and 2H, t and q, J = 8 Hz, CH_3CH_2-), ~1.65 (1H, br. s, disappeared on addition of D_2O, OH), 1.75 (2H, s, $-CH_2OH$), 2.38 (3H, s, tolyl-CH_3), 2.70 and 3.00 (2H, ABq, J = 15 Hz, $-CH_2COOEt$), ~5.6 (1H, br, disappeared on addition of D_2O, NH), 7.30 and 7.65 (2H and 2H, ABq, J = 9 Hz, aromatic). MS m/e; 262 (M^+)].

2c: mp 107°C (from hexane) [IR ν(KBr)cm^{-1}; 3200, 1738. NMR δ($CDCl_3$)ppm; 1.33 and 4.21 (3H and 2H, t and q, J = 9 Hz, CH_3CH_2-), ~1.65 (1H, br, disappeared on addition of D_2O, OH), 1.70 (2H, s, $-CH_2OH$), 2.65 and 3.00 (2H, ABq, J = 18 Hz, $-CH_2COOEt$), 3.85 (3H, s, $-OCH_3$), ~5.6 (1H, br, disappeared on addition of D_2O, NH), 6.95 and 7.66 (2H and 2H, ABq, J = 8 Hz, aromatic). MS m/e; 278 (M^+)].

3b: mp 254°C (from EtOH) [IR ν(KBr)cm^{-1}; 3300, 1660, 1640. NMR δ(DMSO-d_6)ppm; 2.38 (3H, s, tolyl-CH_3), ~3.3 (1H, br, disappeared on addition of D_2O, OH), 4.36 (2H, s, $-CH_2OH$), ~5.5 (1H, br, disappeared on addition of D_2O, OH), 6.30 (1H, s, 5-H of pyrimidine ring), 7.31 and 8.06 (2H and 2H, ABq, J = 8 Hz, aromatic). MS m/e; 216 (M^+)].

3c: mp 250°C (from EtOH) [IR ν(KBr)cm^{-1}; 3400, 1670. NMR δ(DMSO-d_6)ppm; ~3.3 (1H, br, disappeared on addition of D_2O, OH), 3.80 (3H, s, $-OCH_3$), 4.31 (2H, s, $-CH_2OH$), ~5.45 (1H, br, disappeared on addition of D_2O, OH), 6.25 (1H, s, 5-H

of pyrimidine ring), 7.00 and 8.15 (2H and 2H, ABq, J = 9 Hz, aromatic). MS m/e; 232 (M^+)].

4b: viscous oil [IR ν(liq)cm^{-1}; 1738. NMR $\delta(CDCl_3)$ppm; 1.30 and 4.25 (3H and 2H, t and q, J = 9 Hz, CH_3CH_2-), 2.38 (3H, s, tolyl-CH_3), 3.65 (2H, s, -CH_2CO-OEt), 7.20 and 7.88 (2H and 2H, ABq, J = 8 Hz, aromatic), 7.65 (1H, s, 5-H of oxazole ring). MS m/e; 245 (M^+)].

4c: mp 50°C (from hexane) [IR ν(KBr)cm^{-1}; 1735. NMR $\delta(CDCl_3)$ppm; 1.30 and 4.25 (3H and 2H, t and q, J = 7 Hz, CH_3CH_2-), 3.65 (2H, s, -CH_2COOEt), 3.88 (3H, s, -OCH_3), 6.95 and 7.99 (2H and 2H, ABq, J = 9 Hz, aromatic), 7.65 (1H, s, 5-H of oxazole ring). MS m/e; 261 (M^+)].

5b: mp 75°C (from hexane-$CHCl_3$) [IR ν(KBr)cm^{-1}; 3200. NMR $\delta(CDCl_3)$ppm; 2.20 (3H, s, tolyl-CH_3), 3.60 (1H, br, disappeared on addition of D_2O, OH), 4.06 (3H, s, -OCH_3), 4.68 (2H, br s, -CH_2OH), 6.54 (1H, s, 5-H of pyrimidine ring), 7.28 and 8.35 (2H and 2H, ABq, J = 9 Hz, aromatic). MS m/e; 230 (M^+)].

5c: mp 93°C (from hexane) [IR ν(KBr)cm^{-1}; 3250. NMR $\delta(CDCl_3)$ppm; ~3.55 (1H, br, disappeared on addition of D_2O, OH), 3.85 (3H, s, -OCH_3), 4.05 (3H, s, -OCH_3), 4.71 (2H, s, -CH_2OH), 6.55 (1H, s, 5-H of pyrimidine ring), 6.95 and 8.41 (2H and 2H, ABq, J = 9 Hz, aromatic). MS m/e; 246 (M^+)].

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