

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 DERIVATIVES¹⁾

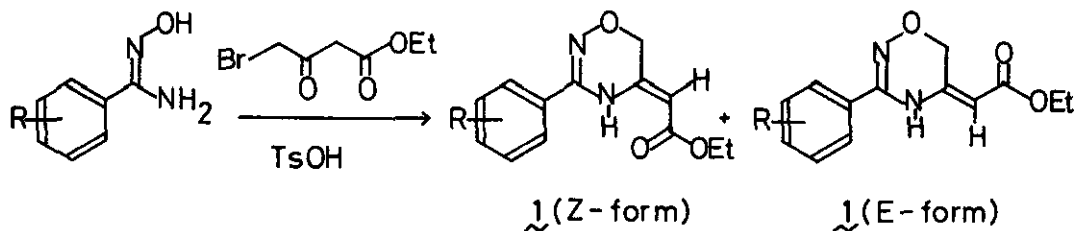
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Abstract— Catalytic hydrogenation of 3-aryl-5-ethoxycarbonyl-
methylene-5,6-dihydro-4H-1,2,4-oxadiazine derivatives (1) is
described. The method leads to new synthesis of 2-aryl-4-
hydroxypyrimidine derivatives (3) involving cyclization of ethyl
3-benzimidoylimino-4-hydroxybutanoate 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 de-
rivatives 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

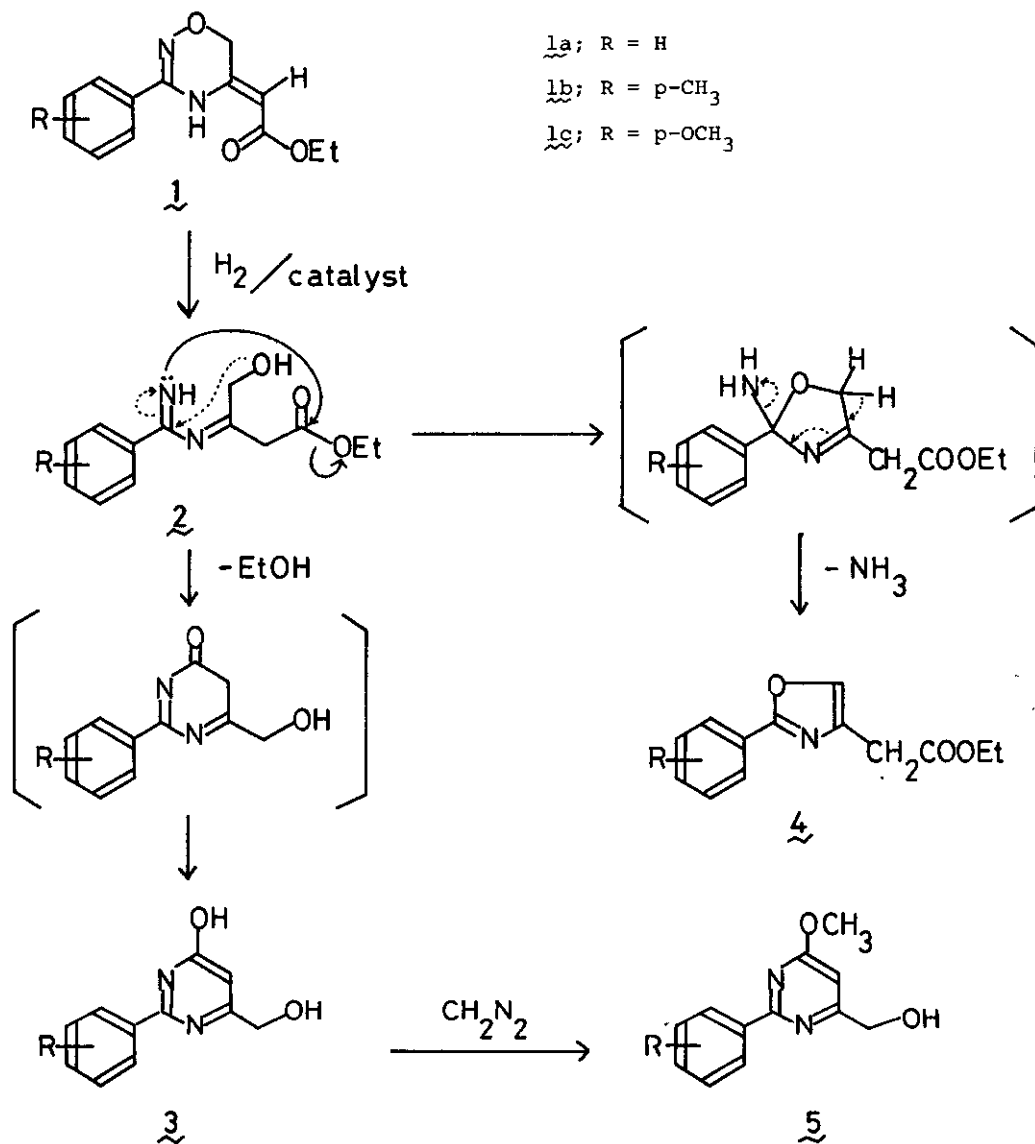


oximes with dimethyl acetylenedicarboxylate gave methyl (3-aryl-4,5-dihydro-5-oxo-6H-1,2,4-oxadiazin-6-ylidene)acetate which, on heating with N,N-diethylethylenediamine, was transformed to methyl 2-aryl-5-[2-(diethylamino)ethylamino]-1,6-dihydro-6-oxo-4-pyrimidinecarboxylate. They have also mentioned 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), C₁₁H₁₀N₂O₂,⁵⁾ 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 C₁₃H₁₃NO₃ (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), C₁₃H₁₆N₂O₃, 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 hydroxide 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 ($\underline{1b}$, R = p-CH₃) and (Z)-5-ethoxycarbonylmethylene-5,6-dihydro-3-p-methoxyphenyl-4H-1,2,4-oxadiazine ($\underline{1c}$, R = p-OCH₃) 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 %) ¹⁾
Ia-c	H ₂ (1 atm) / Ni / 72 h	<u>1a</u>	<u>3a</u> (55.2)
		<u>1b</u>	<u>3b</u> (57.7)
		<u>1c</u>	<u>3c</u> (74.0), <u>4c</u> (1.5)
IIa-c	H ₂ (3 atm) / Ni / 24 h	<u>1a</u>	<u>3a</u> (75.7), <u>4a</u> (5.6)
		<u>1b</u>	<u>3b</u> (77.3), <u>4b</u> (6.2)
		<u>1c</u>	<u>3c</u> (42.2), <u>4c</u> (22.0)
IIIa-c	H ₂ (1 atm) / Pd-C / 72 h	<u>1a</u>	<u>3a</u> (44.2)
		<u>1b</u>	<u>3b</u> (35.7)
		<u>1c</u>	<u>3c</u> (27.8)
IVa-c	H ₂ (1 atm) / PtO ₂ / 72 h	<u>1a</u>	<u>2a</u> (13.8), <u>3a</u> (7.1)
		<u>1b</u>	<u>2b</u> (55.2), <u>3b</u> (8.0)
		<u>1c</u>	<u>2c</u> (57.9), <u>3c</u> (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-d₆)ppm: ~3.3 (1H, br, disappeared on addition of D₂O, OH), 4.41 (2H, s, -CH₂OH), ~5.5 (1H, br, disappeared on addition of D₂O, 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 $\nu(\text{KBr})\text{cm}^{-1}$; 3250, 1600. NMR $\delta(\text{CDCl}_3)\text{ppm}$; ~3.5 (1H, br, disappeared on addition of D_2O , OH), 4.06 (3H, s, $-\text{OCH}_3$), 4.68 (2H, br s, $-\text{CH}_2\text{OH}$), 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 $\nu(\text{CHCl}_3)\text{cm}^{-1}$; 1735. NMR $\delta(\text{CDCl}_3)\text{ppm}$; 1.30 and 4.25 (3H and 2H, t and q, $\underline{J} = 10$ Hz, CH_3CH_2-), 3.61 (2H, s, $-\text{CH}_2\text{COOEt}$), 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 $\nu(\text{KBr})\text{cm}^{-1}$; 3250, 1720. NMR $\delta(\text{CDCl}_3)\text{ppm}$; 1.28 and 4.20 (3H and 2H, t and q, $\underline{J} = 8$ Hz, CH_3CH_2-), -1.7 (1H, br, disappeared on addition of D_2O , OH), 1.75 (2H, s, $-\text{CH}_2\text{OH}$), 2.75 and 3.00 (2H, ABq, $\underline{J} = 15$ Hz, $-\text{CH}_2\text{COOEt}$), -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 $\nu(\text{KBr})\text{cm}^{-1}$; 3200, 1740. NMR $\delta(\text{CDCl}_3)\text{ppm}$; 1.30 and 4.15 (3H and 2H, t and q, $\underline{J} = 8$ Hz, CH_3CH_2-), -1.65 (1H, br. s, disappeared on addition of D_2O , OH), 1.75 (2H, s, $-\text{CH}_2\text{OH}$), 2.38 (3H, s, tolyl- CH_3), 2.70 and 3.00 (2H, ABq, $\underline{J} = 15$ Hz, $-\text{CH}_2\text{COOEt}$), -5.6 (1H, br, disappeared on addition of D_2O , NH), 7.30 and 7.65 (2H and 2H, ABq, $\underline{J} = 9$ Hz, aromatic). MS m/e; 262 (M^+)].
- 2c: mp 107°C (from hexane) [IR $\nu(\text{KBr})\text{cm}^{-1}$; 3200, 1738. NMR $\delta(\text{CDCl}_3)\text{ppm}$; 1.33 and 4.21 (3H and 2H, t and q, $\underline{J} = 9$ Hz, CH_3CH_2-), -1.65 (1H, br, disappeared on addition of D_2O , OH), 1.70 (2H, s, $-\text{CH}_2\text{OH}$), 2.65 and 3.00 (2H, ABq, $\underline{J} = 18$ Hz, $-\text{CH}_2\text{COOEt}$), 3.85 (3H, s, $-\text{OCH}_3$), -5.6 (1H, br, disappeared on addition of D_2O , NH), 6.95 and 7.66 (2H and 2H, ABq, $\underline{J} = 8$ Hz, aromatic). MS m/e; 278 (M^+)].
- 3b: mp 254°C (from EtOH) [IR $\nu(\text{KBr})\text{cm}^{-1}$; 3300, 1660, 1640. NMR $\delta(\text{DMSO}-d_6)\text{ppm}$; 2.38 (3H, s, tolyl- CH_3), -3.3 (1H, br, disappeared on addition of D_2O , OH), 4.36 (2H, s, $-\text{CH}_2\text{OH}$), -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, $\underline{J} = 8$ Hz, aromatic). MS m/e; 216 (M^+)].
- 3c: mp 250°C (from EtOH) [IR $\nu(\text{KBr})\text{cm}^{-1}$; 3400, 1670. NMR $\delta(\text{DMSO}-d_6)\text{ppm}$; -3.3 (1H, br, disappeared on addition of D_2O , OH), 3.80 (3H, s, $-\text{OCH}_3$), 4.31 (2H, s, $-\text{CH}_2\text{OH}$), -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 $\nu(\text{liq})\text{cm}^{-1}$; 1738. NMR $\delta(\text{CDCl}_3)\text{ppm}$; 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, $-\text{CH}_2\text{CO}-\text{OEt}$), 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 $\nu(\text{KBr})\text{cm}^{-1}$; 1735. NMR $\delta(\text{CDCl}_3)\text{ppm}$; 1.30 and 4.25 (3H and 2H, t and q, $J = 7$ Hz, CH_3CH_2-), 3.65 (2H, s, $-\text{CH}_2\text{COOEt}$), 3.88 (3H, s, $-\text{OCH}_3$), 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 $\nu(\text{KBr})\text{cm}^{-1}$; 3200. NMR $\delta(\text{CDCl}_3)\text{ppm}$; 2.20 (3H, s, tolyl- CH_3), 3.60 (1H, br, disappeared on addition of D_2O , OH), 4.06 (3H, s, $-\text{OCH}_3$), 4.68 (2H, br s, $-\text{CH}_2\text{OH}$), 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 $\nu(\text{KBr})\text{cm}^{-1}$; 3250. NMR $\delta(\text{CDCl}_3)\text{ppm}$; ~3.55 (1H, br, disappeared on addition of D_2O , OH), 3.85 (3H, s, $-\text{OCH}_3$), 4.05 (3H, s, $-\text{OCH}_3$), 4.71 (2H, s, $-\text{CH}_2\text{OH}$), 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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