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

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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-arylt-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
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-diethylethlenediamine, was transformed to methyl 2-aryl-5-[2-(diethylamino)ethylamino]-1,6-
dihydro-6-oxo-4-pyrimidinocarboxylate. 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 (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 (2), C11H10N2O2, in 55.2% yield with recovery of the starting material (9.5%). The structure of 2 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, 2 was converted to 6-hydroxymethyl-4-methoxy-2-phenylpyrimidine (3), mp 110°C, in 97% yield.

Treatment of 1 with hydrogen at about three atmospheric pressure in the presence of Raney nickel catalyst, on the other hand, afforded 3 in 75.7% yield and a colorless viscous oil of C13H13N03 (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 3 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 3 (7.1%) and a ring-opened product (2a), CI3H16N203, 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 (\(\text{1b}, R = p-\text{CH}_3\)) and (Z)-5-ethoxycarbonylmethylene-5,6-dihydro-3-p-methoxypyphenyl-4H-1,2,4-oxadiazine (\(\text{1g}, R = p-\text{OCH}_3\)) 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 atmos-
pheric pressure, seems to be useful in the synthesis of 4-hydroxypyrimidine deri-
vatives. We are now presently investigating to optimize the reaction conditions
and to control them in view of mechanistic points.

<table>
<thead>
<tr>
<th>Run</th>
<th>Reaction Conditions</th>
<th>Compounds</th>
<th>Products (Yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia-c</td>
<td>H₂ (1 atm)/ Ni / 72 h</td>
<td>1ₐ</td>
<td>2ₐ (55.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1ₖ</td>
<td>3ₜ (57.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1ₜ</td>
<td>3c (74.0), 4c (1.5)</td>
</tr>
<tr>
<td>IIa-c</td>
<td>H₂ (3 atm)/ Ni / 24 h</td>
<td>1ₐ</td>
<td>3ₜ (75.7), 4a (5.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1ₖ</td>
<td>3ₜ (77.3), 4b (6.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1ₜ</td>
<td>3c (42.2), 4c (22.0)</td>
</tr>
<tr>
<td>IIIa-c</td>
<td>H₂ (1 atm)/ Pd-C / 72 h</td>
<td>1ₐ</td>
<td>3a (44.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1ₖ</td>
<td>3b (35.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1ₜ</td>
<td>3c (27.8)</td>
</tr>
<tr>
<td>IVa-c</td>
<td>H₂ (1 atm)/PtO₂ / 72 h</td>
<td>1ₐ</td>
<td>2ₐ (13.8), 3a (7.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1ₖ</td>
<td>2ₜ (55.2), 3b (8.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1ₜ</td>
<td>2c (57.9), 3c (1.2)</td>
</tr>
</tbody>
</table>

REFERENCES AND NOTES
1) A part of this work was presented at the 102nd Annual Meeting of the Pharmace-
utical Society of Japan, Osaka, April 3 (1982) p.468 (3Q 3-3).
5) All new compounds gave satisfactory analyses and high resolution mass spectral
data.
6) 2ₐ: 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
7) $\text{A}_3$: mp 110°C (from CHCl$_3$-hexane) [IR $\nu$(KBr) cm$^{-1}$; 3250, 1600. NMR $\delta$(CDCl$_3$) ppm; -3.5 (1H, br, disappeared on addition of D$_2$O, OH), 4.06 (3H, s, -OCH$_3$), 4.68 (2H, br s, -CH$_2$OH), 6.60 (1H, s, 5-H of pyrimidine ring), 7.50 and 8.45 (3H and 2H, each m, phenyl). MS m/e: 202 (M$^+$)].

8) $\text{A}_9$: viscous oil [IR $\nu$(CHCl$_3$) cm$^{-1}$; 1735. NMR $\delta$(CDCl$_3$) ppm; -3.5 (1H, br, disappeared on addition of D$_2$O, OH), 4.06 (3H, s, -OC$_3$), 4.68 (2H, br s, -CE$_2$0H), 6.60 (1H, s, 5-H of pyrimidine ring), 7.50 and 8.45 (3H and 2H, each m, phenyl). MS m/e: 216 (M$^+$)].

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

10) $\text{A}_2$: mp 89°C (from hexane) [IR $\nu$(KBr) cm$^{-1}$; 3250, 1720. NMR $\delta$(CDCl$_3$) ppm; 1.28 and 4.20 (3H and 2H, t and q, $\tilde{J}$ = 10 Hz, CH$_3$CH$_2$), -1.75 (1H, br, disappeared on addition of D$_2$O, OH), 1.75 (2H, s, -CH$_2$OH), 2.75 and 3.00 (2H, ABq, $\tilde{J}$ = 15 Hz, -CH$_2$COOEt), -5.7 (1H, br, disappeared on addition of D$_2$O, NH), 7.45 and 7.63 (5H, m, phenyl). MS m/e: 248 (M$^+$)].

11) $\text{A}_3$: mp 116°C (from hexane) [IR $\nu$(KBr) cm$^{-1}$; 3200, 1740. NMR $\delta$(CDCl$_3$) ppm; 1.30 and 4.15 (3H and 2H, t and q, $\tilde{J}$ = 8 Hz, CH$_3$CH$_2$), -1.65 (1H, br, disappeared on addition of D$_2$O, OH), 1.75 (2H, s, -CH$_2$OH), 2.38 (3H, s, tolyl-CH$_3$), 2.70 and 3.00 (2H, ABq, $\tilde{J}$ = 15 Hz, -CH$_2$COOEt), -5.6 (1H, br, disappeared on addition of D$_2$O, NH), 7.30 and 7.65 (2H and 2H, ABq, $\tilde{J}$ = 9 Hz, aromatic). MS m/e: 262 (M$^+$)].

$\text{A}_2$: mp 107°C (from hexane) [IR $\nu$(KBr) cm$^{-1}$; 3200, 1738. NMR $\delta$(CDCl$_3$) ppm; 1.33 and 4.21 (3H and 2H, t and q, $\tilde{J}$ = 9 Hz, CH$_3$CH$_2$), -1.65 (1H, br, disappeared on addition of D$_2$O, OH), 1.70 (2H, s, -CH$_2$OH), 2.65 and 3.00 (2H, ABq, J = 15 Hz, -CH$_2$COOEt), 3.85 (3H, s, -OCH$_3$), -5.6 (1H, br, disappeared on addition of D$_2$O, NH), 6.95 and 7.66 (2H and 2H, ABq, $\tilde{J}$ = 8 Hz, aromatic). MS m/e: 278 (M$^+$)].

$\text{A}_3$: mp 254°C (from EtOH) [IR $\nu$(KBr) cm$^{-1}$; 3300, 1660, 1640. NMR $\delta$(DMSO-d$_6$) ppm; 2.38 (3H, s, tolyl-CH$_3$), -3.3 (1H, br, disappeared on addition of D$_2$O, OH), 4.36 (2H, s, -CH$_2$OH), -5.5 (1H, br, disappeared on addition of D$_2$O, OH), 6.30 (1H, s, 5-H of pyrimidine ring), 7.31 and 8.06 (2H and 2H, ABq, $\tilde{J}$ = 8 Hz, aromatic). MS m/e: 216 (M$^+$)].

$\text{A}_3$: mp 250°C (from EtOH) [IR $\nu$(KBr) cm$^{-1}$; 3400, 1670. NMR $\delta$(DMSO-d$_6$) ppm; -3.3 (1H, br, disappeared on addition of D$_2$O, OH), 3.80 (3H, s, -OCH$_3$), 4.31 (2H, s, -CH$_2$OH), -5.45 (1H, br, disappeared on addition of D$_2$O, OH), 6.25 (1H, s, 5-H
of pyrimidine ring), 7.00 and 8.15 (2H and 2H, ABq, $\tilde{J} = 9$ Hz, aromatic). MS m/e; 232 (M$^+$).  

4b: viscous oil [IR v(liquid) cm$^{-1}$; 1738. NMR $\delta$(CDCl$_3$)ppm; 1.30 and 4.25 (3H and 2H, t and q, $\tilde{J} = 9$ Hz, CH$_3$CH$_2$-), 2.38 (3H, s, tolyl-CH$_3$), 3.65 (2H, s, $-\text{CH}_2\text{COOEt}$), 7.20 and 7.88 (2H and 2H, ABq, $\tilde{J} = 8$ Hz, aromatic), 7.65 (1H, s, 5-H of oxazole ring). MS m/e; 245 (M$^+$)].  

4c: mp 50°C (from hexane) [IR v(KBr) cm$^{-1}$; 1735. NMR $\delta$(CDCl$_3$)ppm; 1.30 and 4.25 (3H and 2H, t and q, $\tilde{J} = 7$ Hz, CH$_3$CH$_2$-), 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, $\tilde{J} = 9$ 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 v(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$_2$O, 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, $\tilde{J} = 9$ Hz, aromatic). MS m/e; 230 (M$^+$)].  

5c: mp 93°C (from hexane) [IR v(KBr) cm$^{-1}$; 3250. NMR $\delta$(CDCl$_3$)ppm; -3.55 (1H, br, disappeared on addition of D$_2$O, 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, $\tilde{J} = 9$ Hz, aromatic). MS m/e; 246 (M$^+$)].  

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