On the Reactions of 1,3,4-Oxadiazolium Salts with Dialkyl Acylphosphonates.\textsuperscript{1)}
A Novel Synthesis of 1,3,4-Oxadiazin-5-one Derivatives

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Reaction of 3-ethyl-5-aryl-1,3,4-oxadiazolium salts (X) with dialkyl acylphosphonates (V) in the presence of triethylamine afforded 2-aryl-4-ethyl-6-alkyl (or aryl)-5,6-dihydro-4H-1,3,4-oxadiazin-5-one derivatives (XII) \textit{via} an acyclic intermediate (XI) which is a 1:1 adduct of X and V. The mechanism of this novel reaction involving ring expansion is discussed briefly.

Reactions of thiazolium (I), 1,3,4-thiadiazolium (II), 1,2,4-thiadiazolium (III), and oxazolium salts (IV) with dialkyl acylphosphonates (V) to give the ring-expanded products 1,4-thiazine (VI),\textsuperscript{4)} 1,3,4-thiadiazine (VII),\textsuperscript{4)} 1,2,4-thiadiazine (VIII),\textsuperscript{5)} and 1,4-oxazine derivatives (IX),\textsuperscript{6)} respectively, have already been reported.

\begin{center}
\begin{tikzpicture}
\node[draw] (r1) at (0,0) {\(\text{R}_1\)};
\node[draw] (y) at (-1,0) {\(\text{Y}\)};
\node[draw] (z) at (-2,0) {\(\text{Z}\)};
\node[draw] (w) at (-3,0) {\(\text{W}\)};
\node[draw] (ro) at (1,0) {\(\text{R'O}\)};
\node[draw] (pcor) at (2,0) {\(\text{COR}\)};
\node[draw] (c) at (3,0) {\(\text{C}_3\text{H}_8\)};
\node[draw] (n) at (4,0) {\(\text{N}\)};
\node[draw] (r2) at (5,0) {\(\text{R}_2\)};
\node[draw] (x) at (6,0) {\(\text{X}^-\)};
\node[draw] (v) at (7,0) {\(\text{V}\)};
\node[draw] (o) at (8,0) {\(\text{O}\)};
\node[draw] (r) at (9,0) {\(\text{R}\)};
\node[draw] (w) at (10,0) {\(\text{W}\)};
\node[draw] (y) at (11,0) {\(\text{Y}\)};
\node[draw] (z) at (12,0) {\(\text{Z}\)};
\node[draw] (r1) at (13,0) {\(\text{R}_1\)};
\node[draw] (w) at (14,0) {\(\text{W}\)};
\node[draw] (y) at (15,0) {\(\text{Y}\)};
\node[draw] (z) at (16,0) {\(\text{Z}\)};
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tabular}{ll}
I : & \(Y = C - R_2, \ Z = C - R_3, \ W = S\) \\
II : & \(Y = N, \ Z = C - R_2, \ W = S\) \\
III : & \(Y = C - R_2, \ Z = N, \ W = S\) \\
IV : & \(Y = C - R_2, \ Z = C - R_3, \ W = O\) \\
V : & \(Y = C - R_2, \ Z = C - R_3, \ W = S\) \\
VI : & \(Y = C - R_2, \ Z = C - R_3, \ W = S\) \\
VII : & \(Y = N, \ Z = C - R_2, \ W = S\) \\
VIII : & \(Y = C - R_2, \ Z = N, \ W = S\) \\
IX : & \(Y = C - R_2, \ Z = C - R_3, \ W = O\)
\end{tabular}
\end{center}

Chart 1

In order to extend the scope of the reaction, application was directed toward some 1,3,4-oxadiazolium salts (X), and the present paper in concerned with these results.

Since the base-catalyzed deprotonation of the \(\text{C}_3\text{H}\) of 3-ethyl-1,3,4-thiadiazolium chloride proceeds faster than that of 3-ethylthiazolium iodide,\textsuperscript{5)} and the base-catalyzed deprotonation of the \(\text{C}_3\text{H}\) of 3,4-dimethylthiazolium iodide proceeds faster than that of 3,4-dimethylthiazolium iodide,\textsuperscript{5)} it seemed reasonable to expect that 1,3,4-oxadiazolium salts (X), in which a sulfur atom in the thiazolium nucleus is replaced by an oxygen atom and the carbon atom at its 4-position by a nitrogen atom, might also serve as very reactive materials toward dialkyl acylphosphonates.


2) Location: \textit{Fukushima-ku, Osaka, 553, Japan.}


3-Ethyl-5-phenyl-1,3,4-oxadiazolium tetrafluoroborate (Xa)\(^9\) reacted with dimethyl benzoylphosphonate (Va') in N,N-dimethylformamide (DMF) in the presence of triethylamine (Et\(_3\)N) at \(-50-60^\circ\) to give a colorless crystalline product (XIA') of mp 115-117\(^\circ\) in 64.5\% yield. The elementary analysis of XIA' was in agreement with the composition C\(_{15}\)H\(_{20}\)O\(_2\)N\(_2\)P suggesting that XIA' is a 1:1 adduct (free base) of Xa and Va'. The infrared (IR) spectrum of XIA' showed an NH band at 3420, two C=O bands at 1699 and 1685, a P=O band 1258, and P-O-C bands at 1055, 1038 and 1025 cm\(^{-1}\) in CDCl\(_3\); its ultraviolet (UV) spectrum in ethanol showed an absorption maximum at 225 nm (log \(\varepsilon\) 4.17). The nuclear magnetic resonance (NMR) spectrum in CDCl\(_3\) showed proton signals for an N-CH\(_2\)CH\(_3\) (\(\tau\) 8.89, 3H, t, \(J\) 7.2 Hz; \(\tau\) 5.93, 2H, q, \(J\) 7.2 Hz), two O-CH\(_3\) (\(\tau\) 6.48, d, \(J_{PH}=11.0\) Hz; \(\tau\) 6.17, d, \(J_{PH}=11.0\) Hz), two C\(_6\)H\(_5\) (\(\tau\) 2.8-2.1, m), and an NH (\(\tau\) 0.016, b-s, disappeared on the addition of deuterium oxide) group in addition to a characteristic 1H at \(\tau\) 3.80 as a doublet (\(J\) 7.5 Hz) due to hydrogen-phosphorus coupling. From these analytical and spectral data, the structure of XIA' could be assigned as O-[1-phenyl-2-oxo-2-(N\(^1\)-ethyl-N\(^2\)-benzoylhydrazino)ethyl]-O, O-dimethylphosphonate.

When XIA' was treated with a basic ion exchange resin, Amberlite IRA-400, in methanol at room temperatures, a colorless crystalline product (XIIa) of mp 74-77\(^\circ\) was produced in 60.8\% yield. Compound XIIa was readily assigned as 2,6-diphenyl-4-ethyl-5,6-dihydro-4H-1,3,4-oxadiazin-5-one, a compound whose formation was expected from the reaction behavior of other azolium salts reported previously,\(^3\)\(^-\)\(^6\) on the basis of the analytical and spectral data.

Similarly, when salts Xa-c reacted with dialkyl acylphosphonates (Va-g and Vb'), the corresponding 1,3,4-oxadiazin-5-one derivatives XIIa-i were obtained via intermediates XIA-i (Chart 2). In the reactions of Xa with diethyl aroylphosphonates Va (or Va') and Vd-g, a para-substituent on the aryl group showed no effect on the yield of product. With

Vb' and Vc, yields of products XIIb and XIIc fell to 11.5 and 2.5%, respectively. This can be considered as follows: the reactivity of Vb' is lower than those of Va and Vd—g, the reaction intermediate is unstably and there is loss in the purification step due to the oily nature of the product; while in the latter case an alternative product (XIII, yield 37.2%) is the main result.

The structure of vinylphosphonate XIII, mp 140—143°, was estimated on the basis of the following data. The elementary analysis of XIII indicated a formula \((\text{C}_{22}\text{H}_{37}\text{O}_8\text{N}_2\text{P})\) containing one molecule of water less than XIc. Its IR spectrum (CHCl₃) showed an NH band at 3400, a C=O band at 1693, a P=O band at 1257, and P–O–C bands at 1050, 1027.5 and 75 cm⁻¹ in addition to a strong C=O band N O C–C=CH–C₆H₅ at 1570—1562 cm⁻¹.

The UV spectrum showed an absorption maximum at 314.5 nm in ethanol, suggesting that XIII has a highly conjugated system in the molecule. Its NMR spectrum (CDCl₃) exhibited proton signals as follows: \(\tau\) 8.77 (NCH₂CH₃, t, \(J=7.0\) Hz), 8.66 (OCH₃CH₂×2, t, \(J=7.0\)), 6.44 (NCH₃, q, \(J=7.0\)), 5.80 (OCH₃×2, quint., \(J_{HH}=J_{HP}=7.0\)), 3.1—2.5 (C₆H₅×2, m), 1.50 (NH, b, disappeared on the addition of deuterium oxide), 1.28 (C₆H₅CH₂, s), but benzylic proton signals were not observed. A cyclic structure, i.e. XIV which would be expected from the formula for XIII, was ruled out because a doublet signal due to coupling with vicinal phosphorus, predicted from the NMR data (\(\tau\) 3.8—4.0, \(J_{HP}=7.8—8.0\) Hz) described previously, and above for the single proton in such a P–O–CH₃ system, was not detected in the NMR spectrum. The possibility of an acyclic lactim form \([\text{C}_6\text{H}_5–(\text{OH})\text{C}=\text{N}–\] as partial structure of XIII is at present under investigation.

\[
\begin{align*}
\text{XIII} & \quad \text{XIV} \\
\text{Et} & \quad \text{Et}
\end{align*}
\]

The treatment of intermediates XIa, d—g with NaOH in 95% ethanol gave XIIa, d—g together with the hydrolysis products XVa, d—f, though XIg did not give XVg.

To examine the route of the formation of XV and the effect of the kind of base used in the cyclization of XI to XII, we next tried the following experiments (see Table I). Interconversion of XIIa and XVa was not observed under the conditions described above. This fact shows that both compounds are formed from XIa via independent pathways and that the \((\text{R'}\text{O})_2\text{P(O)O}–\) group in XI is effective as a leaving group in the cyclization of XI to XII. On treatment of XIa with NaOEt in absolute ethanol or NaOMe in absolute methanol, XIIa and XVa were obtained but ether type compounds formed by replacement of the \((\text{EtO})_2\text{P}–(\text{O})\text{O}–\) group with an EtO or MeO group were not obtained. Consequently, it is obvious that
TABLE I

<table>
<thead>
<tr>
<th>Base (mole)</th>
<th>Solvent</th>
<th>React. time</th>
<th>Yield of products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amberl. IRA-400 (large excess)</td>
<td>MeOH</td>
<td>10 hr</td>
<td>XIIa: 65.8, XVa: —</td>
</tr>
<tr>
<td>NH₄ (23)</td>
<td>80% EtOH</td>
<td>24 days</td>
<td>78.3</td>
</tr>
<tr>
<td>NEt₃ (11)</td>
<td>80% EtOH</td>
<td>20 days</td>
<td>58.0</td>
</tr>
<tr>
<td>NaOH (10)</td>
<td>95% EtOH</td>
<td>20 hr</td>
<td>33.6, 29.2</td>
</tr>
<tr>
<td>NaOEt (10)</td>
<td>abs. EtOH</td>
<td>19 hr</td>
<td>46.8, 9.9</td>
</tr>
<tr>
<td>NaOMe (10)</td>
<td>abs. MeOH</td>
<td>20 hr</td>
<td>59.3, 1.7</td>
</tr>
</tbody>
</table>

XV is formed by an initial attack of EtO⁻, MeO⁻ or OH⁻ on phosphorus atom of XI. On the other hand, on treatment with NH₄ or NEt₃ in 80% ethanol, XIa gave XIIa slowly but no formation of XVa was observed. These results show that only XII is produced in the cyclization of XI when an ammonium type base is used as a catalyst, whereas with a metal cationic base accompanying hydrolysis gives XV in addition to XII.

![Chart 4](chart4.png)

The reaction mechanism of the present reactions may be considered as shown in Chart 4. First, the Cₓ-carbanion of the 1,3,4-oxadiazolium ylide A, produced by treatment of salt X with triethylamine in analogy with other azolium yldes, makes a nucleophilic attack on the carbonyl carbon of phosphonate V; intramolecular rearrangement follows to give betaine C, then addition of H₂O to C gives oxadiazoline D. Subsequently, Cₓ-O bond fission in D leads to intermediate XI. Here, action of an ammonium type base (R₄N⁺OH⁻)

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on XI affords XII via exclusive nucleophilic attack by aroyl oxygen anion, generated by deprotonation of the NH proton in XI, on the carbon atom attached to the R group (i.e., α-route); whereas with a metal cationic base, catalytic base (RŐ or OH̋) makes an attack on the phosphorus atom of XI as a nucleophile, P-O bond fission following to give XV (i.e., β-route) in addition to the formation of XII via the α-route.

The mechanism of the formation of XIII may be explained as follows (Chart 5): Although a part of betaine B', produced by reaction of XIa with Vc in analogy with other oxadiazolium betaines (B) described above, gives 1,3,4-oxadiazin-5-one derivative XIIc via the usual pathway, the major part of B' undergoes conversion of E' by elimination of benzylic proton, followed by addition of hydroxide ion to F', and ring-opening of G' to give XIII. The possibility of an alternative route for the formation of XIII, i.e., enol form Vc reacts with ylde A' to give F' which then produced XIII via G', was excluded by the fact that reaction of Xa with pure dimethyl 1-hydroxystyrylphosphonate (Vc') did not give the corresponding XIII' or XIIc under the conditions described above.
Experimental

Reaction of 1,3,4-Oxadiazolium Salts (Xa–c) with Dialkyl Aclyphosphonates (V) —— i) General Procedure for isolation of Intermediates (XI): To a stirred mixture of Xa–c (11.44 mmole) and V (11.70 mmole) in dry DMF (25 ml), Et₂N (dried over Na wire, 22.8 mmole) was slowly added dropwise at −70°—−60° in an atmosphere of dry argon. The mixture was then stirred for 5 hr at −60°—−50° and was left to stand overnight at −50°—−5°. DMF was removed in vacuo at 45°, and the residue was extracted with CHCl₃. The CHCl₃ extract was washed with water, dried over Na₂SO₄, and evaporated. After being washed with petroleum ether or ether, the residue was purified by recrystallization or preparative thin-layer chromatography (PLC) on SiO₂ developed with ether.


Xi: colorless oil. UV λₚₓmax nm: 235. IR νₚ₋ₓox cm⁻¹: 3310, 1690 (broad), 1251, 1030, 981.

XiI: light yellow oil. UV λₚₓmax nm: 238. IR νₚ₋ₓox cm⁻¹: 3180, 1690 (broad), 1250, 1035, 980.

ii) Treatment of Intermediates (XI) with Amberlite IRA-400: Amberlite IRA-400 (chloride form, ca. 30 g) was converted to its hydroxyl form by stirring for 45 min with an excess of 10% aqueous sodium hydroxide. The resin was washed with water until the washings were neutral to pH paper, then it was washed thoroughly with methanol to remove as much water as possible. The resin was suspended in methanol (50 ml) and stirred. XI (1.0 g) was added and the mixture was stirred overnight at room temperatures, then filtered. The resin was washed several times with methanol. The filtrate was reduced in vacuo and the residue was extracted with chloroform. The chloroform extract was washed with water, dried over Na₂SO₄, and evaporated. After being washed with petroleum ether, the residue was purified by recrystallization or PLC on SiO₂ developed with chloroform.

XII: mp 74°—77°, colorless needles (ether–petroleum ether). Anal. Calcd. for C₁₂H₁₄O₂N₄C: 72.84; H, 5.75; N, 9.99. Found: C, 72.56; H, 5.84; N, 10.18. IR νₚ₋ₓox cm⁻¹: 1675 (C=O), 1604 (C=N). UV λₚₓmax nm (log e): 294 (4.12). NMR: δ 8.67 (3H, t, J = 7.0), 6.10 (2H, d, J = 7.0), 4.22 (1H, s), 2.80—2.90 (10H, m).

XIII: Colorless oil. Anal. Calcd. for C₁₂H₁₄O₂N₄C: C, 66.08; H, 6.47; N, 12.84. Found: C, 66.21; H, 6.49; N, 12.82. UV λₚₓmax nm: 291.

XIV: mp 83°—85°, colorless crystals (ether–petroleum ether). Anal. Calcd. for C₁₂H₁₄O₂N₄Cl: C, 64.86; H, 4.80; N, 8.90. Found: C, 65.26; H, 4.79; N, 8.95. IR νₚ₋ₓox cm⁻¹: 1673, 1632. UV λₚₓmax nm (log e): 294 (4.11).

XV: Colorless oil. Anal. Calcd. for C₁₂H₁₄O₂N₄C: C, 73.45; H, 6.16; N, 9.52. Found: C, 72.86; H, 6.12; N, 10.03. IR νₚ₋ₓox cm⁻¹: 1673, 1632. UV λₚₓmax nm (log e): 294 (4.09).

XVI: mp 89°—94°. Anal. Calcd. for C₁₂H₁₄O₂N₄Br: C, 56.84; H, 4.21; N, 7.60. Found: C, 56.83; H, 4.03; N, 7.92. IR νₚ₋ₓox cm⁻¹: 1673, 1633. UV λₚₓmax nm (log e): 217.5 (4.28), 294 (4.10).


XIIIi: mp 76°—78°, colorless crystals. Anal. Calcd. for C₁₂H₁₄O₂N₄Cl: C, 64.86; H, 4.80; N, 8.90. Found: C, 64.93; H, 4.76; N, 8.78. IR νₚ₋ₓox cm⁻¹: 1651, 1625. UV λₚₓmax nm: 298.5.

Reaction of 1,3,4-Oxadiazolium Salts (Xa) with Diethyl Phenyacetylephosphonate (Vc) —— A mixture of Xa (10 g, 38.2 mmole), Vc (10 g, 39.0 mmole), dry DMF (80 ml), and triethylamine (7.9 g, 78.2 mmole)...

11) All melting points are uncorrected. All NMR spectra were taken with a Varian A-60 spectrometer in CDCl₃ containing tetramethylsilane as an internal reference. Chemical shifts are expressed in δ values and coupling constants in Hz. Multiplicities of signals are represented as s (singlet), d (doublet), t (triplet), b (broad), and m (multiplet).
was treated according to the procedure described above. DMF was removed in vacuo at 45°, and the residue was extracted with chloroform. The extract was washed with 5% NaHCO₃ and water successively, dried, and evaporated. The oily residue crystallized from ether to give colorless crystals (XIII, 6.1 g, 37.2%), mp 138—140°. Anal. Calcd. for C₁₂H₁₈O₅N₅P: (XIII) C, 61.39; H, 6.32; N, 6.51; P, 7.20; EtO, 20.90; mol. wt., 430.4. Found: C, 61.60; H, 6.38; N, 6.28; P, 6.67; EtO, 20.26; mol. wt. (chioroform), 436.6. UV λ<sub>max</sub> nm: 314.5. To the mother liquor of the above crude crystals 99% ethanol (10 g) and 10% sodium hydroxide (10 g) were added and the mixture was refluxed for 1 hr. The solution was concentrated in vacuo to leave an oily residue which was extracted with chloroform. The extract was washed with water, dried, and evaporated. The oily residue was submitted to PLC (SiO₂—chloroform) to give a light yellow oil (XIIc, 0.28 g, 2.5%). Anal. Calcd. for C₁₅H₁₆O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.29; N, 9.34. UV λ<sub>max</sub> nm: 293.5. IR ν<sub>max</sub> cm⁻¹: 1670, 1631.

**Treatment of XIA,d—g with NaOH in 95% Ethanol**—To a solution of NaOH (23 mmole) and H₂O (1.5 ml) in 99% ethanol (31.5 ml), XIA,d—g (2.3 mmole) was added and dissolved. The solution was allowed to stand at room temperatures for 20 hr, then neutralized with 10% H₂SO₄ under ice-cooling. Ethanol was removed in vacuo and the residue was extracted with CHCl₃. The extract was washed with H₂O, dried over Na₂SO₄, and evaporated. The residue was submitted to PLC on Al₂O₃ and developed with CHCl₃. The higher position band gave VIIIa,d—g, and the lower position band gave XVIIIa,d—f. The results are summarized in Chart 3 and Table II.

### Table II

<table>
<thead>
<tr>
<th></th>
<th>XVa</th>
<th>XVd</th>
<th>XVe</th>
<th>XVI</th>
</tr>
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<tbody>
<tr>
<td>R</td>
<td>H</td>
<td>Cl</td>
<td>Me</td>
<td>Br</td>
</tr>
<tr>
<td>mp (°C)</td>
<td>155—157</td>
<td>134—136</td>
<td>148—151</td>
<td>132—135</td>
</tr>
<tr>
<td>λ&lt;sub&gt;max&lt;/sub&gt; nm (e)</td>
<td>220&lt;sup&gt;mm&lt;/sup&gt; (14967)</td>
<td>225 (20965)</td>
<td>224.5 (17701)</td>
<td>228 (21282)</td>
</tr>
<tr>
<td>IR ν&lt;sub&gt;max&lt;/sub&gt; cm⁻¹</td>
<td>3444, 3240</td>
<td>3480, 3275</td>
<td>3390, 3225</td>
<td>3470, 3440, 1680, 1666, 1679, 1667, 3195, 1692, 3275, 1678, 1648, 1658, 1664, 1662, 1651</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Formula</th>
<th>Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcd.</td>
<td>Found</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>XVa</td>
<td>C₁₀H₁₂O₅N₄</td>
<td>68.44</td>
</tr>
<tr>
<td>XVd</td>
<td>C₁₀H₁₂O₅N₅Cl</td>
<td>61.35</td>
</tr>
<tr>
<td>XVe</td>
<td>C₁₀H₁₂O₅N₅Br</td>
<td>69.21</td>
</tr>
<tr>
<td>XVf</td>
<td>C₁₀H₁₂O₅N₅Br</td>
<td>54.12</td>
</tr>
</tbody>
</table>

**Treatment of XIA with MeONa in abs. MeOH (or EtONa in abs. EtOH)**—To a solution of 19.5 mmole of Na in 28 ml of abs. MeOH (or abs. EtOH), 1.95 mmole of XIa was added and dissolved. The solution was allowed to stand at room temperatures for 20 hr (or 19 hr), then treated according to the procedure (neutralization and PLC separation) described above to give XIIa and XV. Both products were shown to be identical with authentic samples obtained above by IR, UV and TLC comparisons (see Table I).

**Treatment of XIA with Et₃N in 80% EtOH**—To a solution of Et₃N (1.8 g, 17.8 mmole) and H₂O (5.0 g) in 99% EtOH (20 ml), XIa (706 mg, 1.624 mmole) was added. The mixture was allowed to stand for 20 days at room temperatures, then EtOH and H₂O were removed in vacuo and CHCl₃ (20 ml) was added to the residue. The CHCl₃ solution was dried over Na₂SO₄ and evaporated. The residue was submitted to PLC (Al₂O₃—CHCl₃) to give XIIa (mp 74—77°, 264 mg, 58%).