HETEROCYCLES FROM NITRILE OXIDES. PART IV1. 1,2,4,5-OXATRIAZINES2

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Abstract — The reaction of nitrile oxides with hydrazones is
found to constitute a convenient synthetic route to the
hitherto unknown 4,5-dihydro-6H-1,2,4,5-oxatriazines. Elemental
analysis and spectral data conform with the present oxatriazine
ring system and disprove the 1,2,4-triazole structure previously
assigned for such reaction products.

INTRODUCTION

The oxatriazine ring system has received limited attention in the literature. To
our knowledge, the only member of this class of heterocycles known so far is the
2H-1,3,4,5-oxatriazine system reported recently by Gainsford and Woolhouse3.
This prompted us to develop a convenient synthetic route for the hitherto
undescribed 1,2,4,5-oxatriazines. Our successful synthesis of oxadiazines from
nitrile oxides (I) and selected aza-nucleophiles4, led us to expect that oxatriazines
could be accessible via interaction of I with suitably functionalized
diaza-substrates. In the present work, we find that nitrile oxides (I) do react
with hydrazones (II) to give directly the expected 6H-1,2,4,5-oxatriazine deriva-
tives (IV) as quite stable crystalline solids (Scheme 1, Table 1).

RESULTS AND DISCUSSION

A. Mechanism

The addition of nucleophiles to nitrile oxides (I) is well known to proceed in a
stereospecific manner and results exclusively in the initial formation of the
corresponding (Z)-adducts5-7 in which the entering nucleophile and the forming
lone pair at the nitrogen atom are mutually trans. Accordingly, the formation of
compounds IV in the above reaction could also be assumed to involve a stereo-
specific syn-1,3-addition of II onto I which leads to the initial formation of the (Z)-hydrazoximes (III) as the kinetically controlled, nonisolable adducts. In these latter acyclic intermediates the reactive termini (the oximino oxygen and the azomethine carbon) are suitably located for intramolecular cyclization in an allowed "6-endo-trig" process\(^8\) to yield the corresponding 1,2,4,5-oxatriazines (IV). Related intramolecular cyclizations, following the initial nucleophilic addition step, have been reported for the reaction of nitrile oxides (I) with nucleophilic substrates incorporating suitably located electrophilic centers\(^4,7\). The nucleophilic addition, displayed in Scheme 1, takes precedence over a 1,3-dipolar cycloaddition at the azomethine-linkage in compounds II. This is because the latter \(\pi\)-bond is normally unreactive dipolarophile, except for its activated types\(^9\), towards nitrile oxides.

**Scheme 1**

\[
\text{Ar-} C\equiv N-\bar{\text{O}} \quad \xrightarrow{+} \quad \text{HN}-N=\text{CRR}^+ \\
\text{I} \quad \text{II} \quad \text{III} \quad \text{IV} \quad \text{V}
\]

B. Spectral Data

Structure (IV) is elucidated from spectral data and elemental analysis. The ir spectra of compounds IVa-o exhibit a sharp N-H stretching band in the range 3240-3280 cm\(^{-1}\) and an absorption band around 1640 cm\(^{-1}\) attributed to C\(_3\)-N stretching. The \(^1\)H-nmr data are also consistent with the assigned structure. Thus, in compounds IVb-e, j, n the N-H and the neighboring C\(_6\)-H protons are mutually coupled and appear as two doublets at about \(\delta\) 4.3 and 5.4 (\(J = 5\) Hz) respectively; upon addition of deuterium oxide, the N-H signal disappears, and the C\(_6\)-H doublet
Table 1. Physical and Analytical Data of Compounds IV.

<table>
<thead>
<tr>
<th>No</th>
<th>Ar</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Mp(°C)</th>
<th>Formula</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>C</th>
<th>H</th>
<th>N</th>
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<tr>
<td>IVa</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>-CH₂(CH₂)₃CH₂⁻</td>
<td>76-77°C</td>
<td>C₁₄H₁₉N₃O</td>
<td>68.54</td>
<td>7.81</td>
<td>17.13</td>
<td>68.88</td>
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<td>C₁₆H₁₇N₂O₂</td>
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<td>6.05</td>
<td>14.83</td>
<td>67.66</td>
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<td>o-HOC₆H₄</td>
<td>134-135°C</td>
<td>C₁₅H₁₅N₂O₂</td>
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<td>5.61</td>
<td>15.60</td>
<td>66.70</td>
<td>5.69</td>
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<td>IVd</td>
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<td>CH₃</td>
<td>C₆H₅</td>
<td>142-143°C</td>
<td>C₁₅H₁₄ClN₃O</td>
<td>62.61</td>
<td>4.90</td>
<td>14.60</td>
<td>62.73</td>
<td>5.07</td>
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<td>IVe</td>
<td>p-ClC₆H₄</td>
<td>CH₃</td>
<td>p-CH₃OC₆H₄</td>
<td>132-134°C</td>
<td>C₁₆H₁₆ClN₃O₂</td>
<td>60.48</td>
<td>5.08</td>
<td>13.32</td>
<td>60.45</td>
<td>5.11</td>
<td>13.20</td>
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<tr>
<td>IVf</td>
<td>p-ClC₆H₄</td>
<td>CH₃</td>
<td>o-CH₂OC₆H₄</td>
<td>145-146°C</td>
<td>C₁₆H₁₆ClN₃O₂</td>
<td>60.48</td>
<td>5.08</td>
<td>13.22</td>
<td>60.20</td>
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<td>IVg</td>
<td>p-ClC₆H₄</td>
<td>CH₃</td>
<td>o-HOC₆H₄</td>
<td>149-150°C</td>
<td>C₁₅H₁₄ClN₃O₂</td>
<td>59.31</td>
<td>4.65</td>
<td>13.83</td>
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<td>4.65</td>
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<td>IVh</td>
<td>p-ClC₆H₄</td>
<td>CH₃</td>
<td>-CH₂(CH₂)₃CH₂⁻</td>
<td>112-113°C</td>
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<td>60.11</td>
<td>6.49</td>
<td>15.02</td>
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<td>C₆H₅</td>
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<td>4.61</td>
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<td>o-CH₂OC₆H₄</td>
<td>172-173°C</td>
<td>C₁₆H₁₆ClN₃O₂</td>
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<td>5.08</td>
<td>13.22</td>
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<td>-CH₂(CH₂)₃CH₂⁻</td>
<td>84-85°C</td>
<td>C₁₄H₁₈ClN₃O</td>
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<td>15.02</td>
<td>60.56</td>
<td>6.54</td>
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<td>H</td>
<td>C₆H₅</td>
<td>158-159°C</td>
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<td>15.55</td>
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<td>IVm</td>
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<td>CH₃</td>
<td>CH(CH₃)₂</td>
<td>126-127°C</td>
<td>C₁₂H₁₆N₄O₂</td>
<td>54.54</td>
<td>6.10</td>
<td>21.20</td>
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<td>CH₃</td>
<td>o-CH₂OC₆H₄</td>
<td>143-145°C</td>
<td>C₁₆H₁₆N₄O₄</td>
<td>58.53</td>
<td>4.90</td>
<td>17.06</td>
<td>58.49</td>
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<td>IVo</td>
<td>m-NO₂C₆H₄</td>
<td>CH₃</td>
<td>-CH₂(CH₂)₃CH₂⁻</td>
<td>133-134°C</td>
<td>C₁₄H₁₈N₄O₃</td>
<td>57.92</td>
<td>6.25</td>
<td>19.30</td>
<td>57.82</td>
<td>6.28</td>
<td>19.20</td>
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aCrystallized from petroleum ether (40-60°C). bFrom dichloromethane/petroleum ether. cFrom diethyl ether/petroleum ether.
collapses to a sharp singlet. The cyclohexyl methylene protons in IVa,b,c,d appear as one broadened signal centered at δ1.7 (10 H); in contrast, these protons appear in the acyclic form (E)-IIIh (vide infra) as two distinct signals at δ 2.2 (4 H) and 1.6 (6 H) of which the low-field signal belongs to the α-methylene protons as influenced by the anisotropic effect of the neighbouring azomethine =-system. The isopropyl methyl protons in IVm appear as two distinct doublets indicating them to be diastereotopic; this pattern conforms with the cyclic structure (IV), but not with the acyclic form (E)-IIIm (vide infra) in which the isopropyl methyls appear as one doublet at δ 1.4. Furthermore, the C6-H proton in IVm appears as two doublets at δ 4.18 and 3.92 due to coupling with the vicinal NH (J = 5 Hz) and CH (J = 7 Hz). This signal collapses to one doublet upon addition of deuterium oxide.

13C-Nmr spectra of compounds IV exhibit two signals characteristic of the C6- and C7-carbons of the oxatriazine ring. The signal in the range δ 80-90 is assigned to the sp3-hybridized C6-carbon; this assignment is in good agreement with reported data for an sp3-carbon flanked by two electronegative atoms (nitrogen and oxygen) in related heterocycles10. The lowest field signal at 153-157 ppm is assigned to the sp2-hybridized C7-carbon, by analogy with several related azomethine systems11. The observed chemical shift of either signal conforms with structure IV, but not with the acyclic form (E)-III. The latter compounds exhibit two azomethine signals in the range δ 146-157, but lack the 13C-signal at δ 80-90.

In addition to the molecular ion peaks [M]+, the mass spectra of compounds IV are dominated by intense peaks corresponding to [M-17]+ fragment ions for which a stable triazole structure is suggested (Scheme 2). Two other significant fragments [A]+ and [B]+ are also observed in all cases. Ion [A]+ is probably formed either by expulsion of ArCN from [M-17]+, or alternatively, via elimination of ArCNO and H+ form [M]+ in a retro 1,3-dipolar addition process. Ion [B]+ originates from [M]+ by ring-opening, via bond rupture at C6-O, followed by elimination of R'R"C=NH and N=O.
In the present work, compounds IV were also obtained, though in low yields, by condensation of hydrazidoximes (V), accessible from the reaction of nitrile oxides (I) and methylhydrazine\textsuperscript{12}, with the appropriate carbonyl compounds (Scheme 3). The major products isolated from this condensation were the isomeric acyclic adducts (E)-III. By analogy to literature reports\textsuperscript{5,7} on the stereochemistry of the closely related amidoximes, the starting hydrazidoximes (V) are expected to exist as mixtures of both (Z)- and (E)-forms, in which the latter form predominates, being thermodynamically more stable. The stereochemistry of V is retained in the hydrazoximes (III) derived thereof. This explains the formation of both IV (produced by spontaneous cyclization of (Z)-III) and (E)-III from the condensation of hydrazidoximes (V) with carbonyl compounds. Compounds (E)-III\textsubscript{m} are quite stable and are recovered unchanged after prolonged reflux (24 h) in ether or ethanol. This behaviour lends support to the (E)-configuration assigned for these compounds. Cyclization of these acyclic adducts to the corresponding triazole derivatives VI, VII is unlikely (Scheme 3), as such step would involve a disfavoured "5-endo-trig." process\textsuperscript{8}. 

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Scheme 2

\[
\begin{align*}
\text{Ar} - \text{C} &= \text{N} - \text{R} \\
\text{[B]} \\
\text{Ar} - \text{C} &= \text{N} - \text{R} \\
\text{[M-17]}^+ \\
\rightarrow \\
\text{Ar} - \text{N} &= \text{N} - \text{C} \\
\text{[A]}^+ \\
\text{Ar} - \text{N} &= \text{N} - \text{C} \\
\text{[M]}^+ \\
\end{align*}
\]
C. Conclusion

Our present findings are contrary to the results reported by Risitano and coworkers\textsuperscript{13} who identified the reaction products, they obtained from the interaction of benzonitrile oxide with methylhydrazones, as 1,2,4-triazoles (VI). Reinvestigation of the reaction mixture revealed, in all cases, that the only by-products formed in the present study were furoxans (dimerization products of the nitrile oxides). Under the experimental conditions employed in the present study, triazoles were neither isolated nor detected.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer model 577 spectrophotometer, using potassium bromide pellets. A Varian T-60 A spectrometer was used for obtaining $^1$H-nmr spectra in CDCl$_3$ with TMS as internal reference. $^{13}$C-Nmr spectra (FT-mode) were recorded on a Bruker WM-250 spectrometer at 26.97 MHz using CDCl$_3$ as the solvent and TMS as internal reference. Mass spectra were determined on a Finnigan MAT 112 spectrometer using the direct inlet
technique (70 eV). Microanalysis was performed at the Mikroanalytisches Labor-Pascher (Bonn).

**Hydroxamoyl Chlorides (Precursors of Nitrile Oxides I).** Benzhydroxamoyl chloride, p-chlorobenzhydroxamoyl chloride, o-chlorobenzhydroxamoyl chloride and m-nitro-benzhydroxamoyl chloride, used in this study, were prepared by direct chlorination of the respective aldoximes following previously published procedures.\(^\text{14}\)

**Monomethylhydrazones (II).** Methylhydrazones employed in this work, were obtained by direct interaction between monomethylhydrazine and the corresponding carbonyl compound following literature procedures.\(^\text{15}\)

**Isobutyraldehyde Methylhydrazone.** This compound was obtained in 80% yield, bp 148-150°C/680 mmHg. Anal. Calcd. for C\(_5\)H\(_{12}\)N\(_2\): C, 59.95; H, 12.00; N, 27.97. Found: C, 59.78; H, 11.95; N, 27.70.

**General Procedure for the Preparation of \(6\)-E-1,2,4,5-Oxatriazines (IVa-g).** A solution of the appropriate hydroxamoyl chloride (0.01 mol) in chloroform (10 ml) was added dropwise to a stirred solution of the respective hydrazone (0.01 mol) and triethylamine (0.03 mol) in chloroform (40 ml) at -20°C. The temperature of the reaction mixture was then allowed to rise slowly to room temperature following the addition, and stirring was continued for 1 h. The solvent was finally removed in vacuo, and the residue washed with water (2 x 20 ml), dried and treated with absolute ethanol (20 ml). The insoluble furoxan by-product was removed by filtration and the alcoholic filtrate was evaporated in vacuo. The remaining solid product was recrystallized from the appropriate solvent. Yields were in the range of 45-65%.

**Hydrazidoximes (V).** These compounds were prepared from the reaction of hydrazine hydrate or methylhydrazine (0.1 mol) with the appropriate hydroxamoyl chloride (0.1 mol) in chloroform, in the presence of triethylamine at zero to -5°C.

**p-Chlorophenyl-N-methylhydrazidoxime (Va).** This compound was obtained in 40% yield, mp 98-100°C (decomp.), recrystallized from ether/petroleum ether.

m-Nitrophenyl-N-methylhydrazidoxime (Vm). This compound was obtained in 45% yield, mp 113-115°C (decomp.), recrystallized from dichloromethane/petroleum ether. Anal. Calcd. for C₈H₁₀N₄O₂: C, 45.70; H, 4.80; N, 26.66. Found: C, 45.77; H, 4.88; N, 26.50.

Condensation of Hydrazidoximes (Y) with Carbonyl Compounds. Cyclohexanone (0.01 mol) and the hydrazidoxime (Y, 0.01 mol) were refluxed in absolute ether (100 ml) for 1 h. The solvent was then evaporated leaving a solid residue composed of compounds IVh and IIIh. Separation of this mixture on preparative silica gel plates (using chloroform as the developing solvent) gave compounds IVh (26%) and (E)-IIIh (79%). Compound (E)-IIIh: mp 125-126°C, crystallized from ether/petroleum ether. Anal. Calcd. for C₁₄H₁₈ClN₂O: C, 60.11; H, 6.49; N, 15.02. Found: C, 59.94; H, 6.41; N, 15.03. Compounds IVm (12%) and (E)-IIIIm (80%) were similarly obtained from the reaction between isobutyraldehyde (0.01) and the hydrazidoxime (Vm) (0.01 mol). Compound (E)-IIIIm: mp 135-138°C, crystallized from ether/petroleum ether. Anal. Calcd. for C₁₂H₁₆N₄O₃: C, 54.54; H, 6.10; N, 21.20. Found: C, 54.40; H, 6.08; N, 21.14.

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REFERENCES
2. Part of this work was presented (A.Q. Hussein) at the Sixth International Conference on Organic Synthesis (IUPAC), Moscow, USSR, August 10-15, 1986.


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