

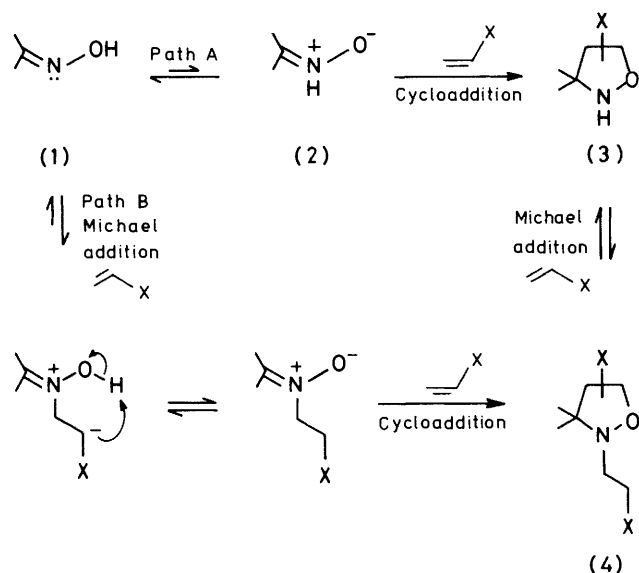
## X=Y-ZH Systems as Potential 1,3-Dipoles. Part 3. Isoxazolidines from the 1:1 Cycloaddition of Oximes with Dipolarophiles

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The 2-oximes of 1,2,3-tricarbonyl systems undergo cycloaddition to *N*-phenylmaleimide to give isoxazolidines. Proton transfer from oxygen to nitrogen, possible *via* an intramolecular 1,5-H shift, is believed to generate a 1,3-dipole as the reactive intermediate. The products are 1:1 adducts in contrast to the cycloadducts of simple aldehyde oximes and ketone oximes which incorporate a second molecule of dipolarophile on the isoxazolidine N-atom. Attempts to extend the cycloaddition to several other electro-negative olefins were unsuccessful, whilst dihydropyran gave Michael adducts.

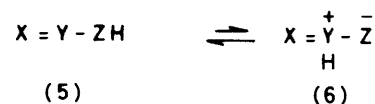
Aldehyde and ketone oximes may be classified as type III X=Y-ZH systems; they react with olefins bearing electro-negative substituents to give isoxazolidines in which a second molecule of the electronegative olefin is attached to the isoxazolidine N-atom.<sup>1</sup> A study of the reaction showed that the regio- and stereo-specificity of the reaction was low and that mixtures of all possible regio- and stereo-isomers are usually obtained. Two pathways for the formation of 2:1 adducts (4) were considered (Scheme 1) and path B was found to be the lower energy pathway and is thus responsible for the failure<sup>1</sup> to detect any intermediate 1:1 cycloadduct (3).



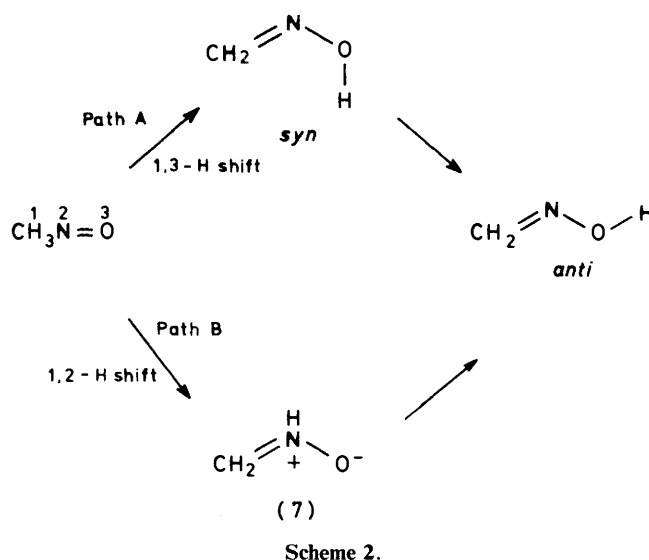
Our observations of the thermal tautomeric equilibration of imines (5a)<sup>2</sup> and hydrazones (5b)<sup>3</sup> with their 1,3-dipolar tautomers (6a) and (6b) respectively suggested a similar equilibration (5c)  $\rightleftharpoons$  (6c) should occur in oximes if the formal 1,2-proton transfer [Scheme 1, (1)  $\rightleftharpoons$  (2)] could be facilitated and the initial Michael addition *via* the nitrogen atom lone pair suppressed (Scheme 1, Path B).

*Ab initio* calculations have been carried out on two pathways for the intramolecular conversion of nitrosomethane into formaldehyde oxime (Scheme 2),<sup>4</sup> one of which (path B) involves 1,3-dipole formation (5c)  $\rightleftharpoons$  (6c).

The 1,3-H shift (path A) was calculated to be less energetically favourable than that involving two 1,2-H shifts (path B) but



- a; X = Z = C, Y = N  
 b; X = C, Y = Z = N  
 c; X = C, Y = N, Z = O



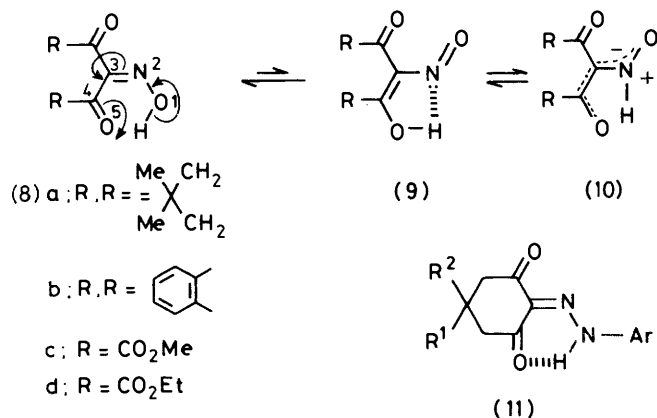
both paths were much too high in energy to be viable. However, the calculations did suggest that the 'NH' nitronium [(7) Scheme 2] should have sufficient stability to be observable. Thus, we were encouraged to seek oximes with structural features which might favour path A in Scheme 1.

The oximes (8) of 1,2,3-tricarbonyl compounds were selected for the following reasons. (i) The oxime configuration is not a problem. (ii) The oxime hydroxy group is hydrogen-bonded to the adjacent carbonyl group facilitating intramolecular transfer of the hydrogen atom from the oxime oxygen atom to the adjacent carbonyl oxygen atom *via* a thermal 1,5-H shift generating a nitroso enol (9). Intramolecular hydrogen-bonding (9) followed by proton transfer might then generate the desired 1,3-dipole (10). (iv) Michael addition *via* the nitrogen atom lone pair (path B, Scheme 1) is rendered less favourable by steric factors and by the reduced

**Table.**  $^{13}\text{C}$  N.m.r. Chemical shifts ( $\text{CDCl}_3$ , p.p.m.) of oximes (8a—d)

| Oxime | C=O          | C=N   | Others   |
|-------|--------------|-------|--|
| (8a)  | 199.2, 191.5 | 146.6 | 52.98 and 52.75 ( $\text{CH}_2$ )<br>30.41 ( $\text{CHMe}_2$ )<br>28.58 (Me) |
| (8b)* | 185.2, 181.4 | 146.9 | 141.3, 141.4, 136.7, 136.5,<br>123.9, 123.5 (all Ar<br>Carbon)               |
| (8c)  | 161.5, 161.1 | 144.2 | 53.47 and 53.2 (Me)  |

\* In  $\text{CD}_3\text{CN}$ .



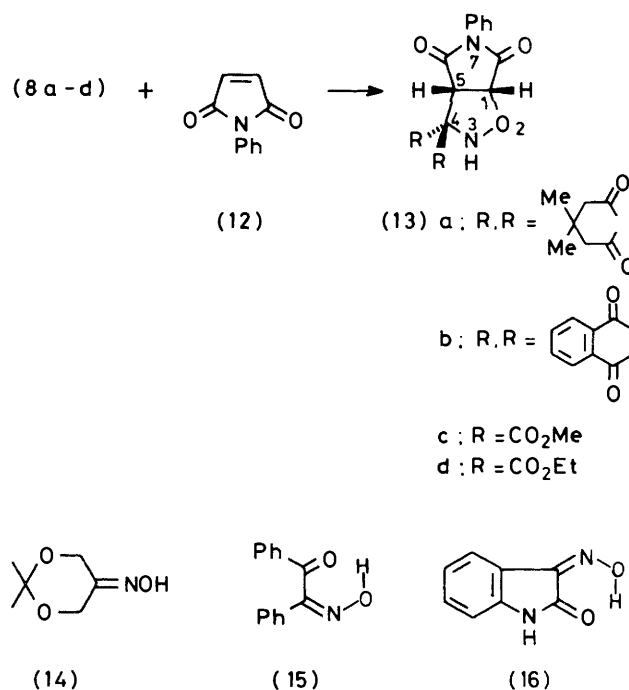
nucleophilicity of the nitrogen atom consequent on the flanking carbonyl groups.

The oximes (8a—d) were prepared by literature procedures<sup>5</sup> and their  $^{13}\text{C}$  n.m.r. spectra (Table) indicates no significant concentration of the nitroso enol (9) is present. The presence of an intramolecular hydrogen bond in (8a—d) is supported by the observation of two separate  $^{13}\text{C}$  n.m.r. signals for the carbonyl groups. The  $^{13}\text{C}$  n.m.r. signal for the hydrogen bonded carbonyl is expected to occur at lower field than the non-hydrogen-bonded carbonyl group.<sup>6</sup> Analogous hydrogen bonding has been observed in the hydrazone (11).<sup>6</sup>

When the oximes (8a, c, and d) were heated (5 h—2.5 days) at  $110^\circ\text{C}$  in toluene with *N*-phenylmaleimide (12), the corresponding 1 : 1 cycloadducts (13a) (32%), (13c) (67%), and (13d) (70%) were obtained. No 2 : 1 adducts analogous to those isolated in our previous work<sup>1</sup> could be detected. The oxime (8a) reacted at the fastest rate (5 h) but gave the lowest yield (32%) of cycloadduct owing to the temperature sensitivity of the oximes. The yield is improved somewhat (43%), by carrying out the reaction at  $35^\circ\text{C}$  for 8.5 days. The reaction of (8b) with (12) is best carried out in boiling acetonitrile for 4 days, when the adduct (13b) is formed in 50% yield.

Attempts to achieve analogous cycloadditions of (12) with (14), (15)<sup>7</sup> (toluene,  $120^\circ\text{C}$ , sealed tube, 5 days), and (16)<sup>8</sup> ( $100$ — $160^\circ\text{C}$ , sealed tube, acetonitrile, xylene or nitrobenzene) failed. The oxime (14) underwent thermal fragmentation (toluene,  $110^\circ\text{C}$ , 1 h) to give acetone (n.m.r.). Pyrolysis of Meldrum's acid derivatives to acetone, ketones, and carbon dioxide is well known,<sup>9</sup> whilst (15) and (16) are presumably sterically and electronically less favourable substrates for the hydrogen transfer sequence analogous to (8)  $\rightarrow$  (10).

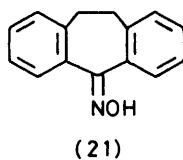
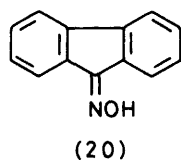
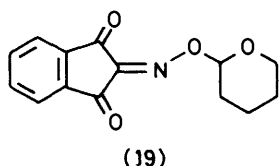
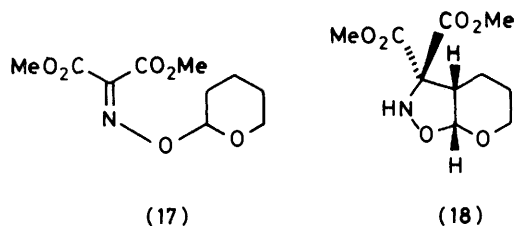
The oximes (8a—d) failed to give cycloadducts with a number of other dipolarophiles, e.g. dimethyl maleate, fumaronitrile, maleic anhydride, acenaphthene, diethyl



azodicarboxylate, and methyl acrylate. This may be due to a large energy gap between the frontier orbitals of the dipoles and these dipolarophiles. However, an n.m.r. study of the cycloaddition reaction between the oxime (8c) and dimethyl fumarate ( $[\text{H}_8]$ toluene,  $120^\circ\text{C}$ ) did show two weak doublets at  $\delta$  4.7 and 5.15 ( $J$  ca. 6 Hz) which is the normal region for the signals of 5-H and 1-H in the cycloadducts (13). However, the reaction seemed to stop after being heated for 29 h although both starting materials were still present. Similar behaviour was observed with the oxime (8d) and dimethyl fumarate, suggesting that the reactions might be catalysed by a trace of acid in the dimethyl fumarate. However, n.m.r. studies of the reaction of (8c) with dimethyl fumarate in the presence of 1 equivalent of either fumaric acid ( $[\text{H}_{10}]$ xylene,  $120^\circ\text{C}$ , 67 h) trifluoro[ $^2\text{H}$ ]acetic acid ( $[\text{H}_{10}]$ xylene,  $123^\circ\text{C}$ , 67 h), dry hydrogen chloride ( $\text{CD}_3\text{CN}$ ,  $90^\circ\text{C}$ , 45 h), or 2,4-dinitrophenol ( $\text{CD}_3\text{CN}$ ,  $90^\circ\text{C}$ , 78 h) showed no evidence for cycloadduct formation. These acid catalysts did not enhance the rate of cycloaddition of (8b) with (12) either. We have previously observed rate enhancements in the cycloaddition of imines and (12) by both Lewis and Bronsted acids.<sup>10</sup> Base catalysts (e.g. triethylamine or  $[\text{H}_5]$ pyridine) caused the decomposition of (8b) when heated with (12). The possible partial reaction of (8c) and (8d) with dimethyl fumarate is thus currently unexplained.

When the oxime (8c) was heated with dihydropyran (xylene,  $130^\circ\text{C}$ , 16 h) a 1 : 1 adduct (78%) was obtained which proved to be the Michael adduct (17) rather than the desired cycloadduct (18). The  $^{13}\text{C}$  n.m.r. spectrum provides the clearest distinction between (17) and (18), in particular, the observation of a resonance at  $\delta$  144.2 (C=N; compare Table). The oxime (8b) also gave a Michael adduct (19) (58%) when treated ( $80^\circ\text{C}$ , acetonitrile, 21 h) with dihydropyran. Michael addition reactions of  $\text{X}=\text{Y}-\text{ZH}$  systems involving the central nitrogen atom<sup>1</sup> or the terminal Z (or X) atom(s) are always likely to intervene if dipole formation and/or cycloaddition are slow. Thus we have observed both Michael addition and 1,3-dipolar cycloaddition with hydrazones depending on the nature of the dipolarophile.<sup>3,11</sup>

The cycloadditions of fluorenone oxime (20) and dibenzo-



tropone oxime (21) to (12) were also studied because it was thought that incipient transition state aromaticity might influence the ease of 1,3-dipole formation. Both oximes failed to react with (12). The corresponding *N*-methyl nitrones are known to undergo cycloaddition reactions<sup>12</sup> indicating a failure of the initial proton transfer step in the case of (20) and (21).

### Experimental

N.m.r. spectra were recorded on Bruker WH90 or Bruker WP250 instruments and refer to deuteriochloroform solutions, with tetramethylsilane as internal standard. I.r. spectra were measured for potassium bromide discs on Perkin-Elmer 157G or 598 instruments. Mass spectra were determined at 70 eV on an MS902 spectrometer. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer PE240 automatic analyser.

**4',4'-Dimethyl-7-phenyl-2-oxa-3,7-diazabicyclo[3.3.0]octane-4-spiro-1'-cyclohexane-2',6,6',8-tetraone (13a).**—A mixture of 5,5-dimethyl-2-hydroxyiminocyclohexane-1,3-dione (58 mg, 0.34 mmol) and *N*-phenylmaleimide (67 mg, 0.39 mmol) in dry [<sup>2</sup>H<sub>8</sub>]toluene (0.5 ml) was heated at 110 °C for 5 h in a sealed n.m.r. tube. The tube was then cooled, opened, the solution removed, and the solvent evaporated under reduced pressure. The resulting crude solid crystallised from ethyl acetate as colourless needles to give the cycloadduct (13a) (38 mg, 32%), m.p. 192–193 °C (Found: C, 62.9; H, 5.2; N, 8.15. C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub> requires C, 63.15; H, 5.30; N, 8.20%);  $\nu_{\max}$  3 200, 1 740, and 1 705 cm<sup>-1</sup>;  $m/z$  (%) 342 (*M*<sup>+</sup>, 5), 173 (38), and 98 (100);  $\delta_{\text{H}}$  7.5–7.2 (m, 1 H, ArH), 6.5 (br s, 1 H, NH), 5.22 (d, 1 H, 7-H, *J* 7.7 Hz), 4.19 (d, 1 H, 5-H), and 1.2 and 1.04 (2 × s, 2 × 3 H, Me).

**7-Phenyl-2-oxa-3,7-diazabicyclo[3.3.0]octane-4-spiro-2'-indan-1',3',6,8-tetraone (13b).**—A mixture of 2-hydroxyiminoindan-1,3-dione (860 mg, 4.9 mmol) and *N*-phenylmaleimide (900 mg, 5.2 mmol) was heated in boiling dry acetonitrile (50 ml) under an argon atmosphere for 4 days. Work-up as above afforded a crude solid product which was crystallised from

methanol to give the cycloadduct (13b) (850 mg, 50%), m.p. 215–217 °C (decomp.), as colourless plates (Found: C, 65.25; H, 3.35; N, 7.9. C<sub>19</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub> requires C, 65.20; H, 3.45; N, 8.05%);  $\nu_{\max}$  3 150 and 1 700 cm<sup>-1</sup>;  $m/z$  (%) 348 (*M*<sup>+</sup>, 51), 319 (10), and 200 (100);  $\delta_{\text{H}}$  8.11–7.4 (m, 9 H, ArH), 6.19 (s, 1 H, NH), 5.50 (d, 1 H, 1-H, *J* 7.7 Hz), and 4.11 (d, 1 H, 5-H).

**Dimethyl 7-Phenyl-2-oxa-3,7-diazabicyclo[3.3.0]octane-4,4-dicarboxylate (13c).**—A solution of dimethyl hydroxyiminomalonic acid (1.61 g, 0.01 mol) and *N*-phenylmaleimide (1.73 g, 0.01 mol) in dry toluene (70 ml) was boiled under reflux for 2 days. Removal of the solvent and crystallisation of the residue from methanol afforded the cycloadduct (13c) (2.3 g, 67%), m.p. 192–194 °C (decomp.), as colourless needles (Found: C, 53.7; H, 4.2; N, 8.4. C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>7</sub> requires C, 53.90; H, 4.20; N, 8.40%);  $\nu_{\max}$  3 180 and 1 715 cm<sup>-1</sup>;  $m/z$  (%) 334 (*M*<sup>+</sup>, 5), 304 (*M* – NO, 5), and 275 (*M* – CO<sub>2</sub>Me, 100);  $\delta_{\text{H}}$  7.53–7.25 (m, 5 H, ArH), 6.54 (s, 1 H, NH), 5.15 and 4.75 (2 × d, 2 × H, 1-H and 5-H respectively, *J* 7.4 Hz), 3.91 and 3.88 (2 × s, 2 × 3 H, OMe).

**Diethyl 5-Phenyl-2-oxa-3,7-diazabicyclo[3.3.0]octane-4,4-dicarboxylate (13d).**—This was prepared from diethyl hydroxyiminomalonic acid (63 mg, 0.33 mmol) and *N*-phenylmaleimide (58 mg, 0.33 mmol) in [<sup>2</sup>H]toluene (0.5 ml). After 2.5 days at 110 °C work-up gave the product (13d) (80 mg, 70%) as colourless needles from methanol, m.p. 133–135 °C (Found: C, 56.2; H, 4.85; N, 7.5. C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>7</sub> requires C, 56.35; H, 5.00; N, 7.35%);  $\nu_{\max}$  3 190 and 1 715 cm<sup>-1</sup>;  $m/z$  (%) 362 (*M*<sup>+</sup>, 11), 332 (*M* – NO, 2), and 289 (*M* – CO<sub>2</sub>Et, 100);  $\delta_{\text{H}}$  7.5–7.2 (m, 5 H, ArH), 6.5 (br s, 1 H, NH), 5.16 and 4.7 (2 × d, 2 × 1 H, 1-H and 5-H respectively, *J* 6.3 Hz), 4.49–4.27 (m, 4 H, 2 × CH<sub>2</sub>Me), 1.35 and 1.33 (2 × t, 2 × 3 H, CH<sub>2</sub>Me).

**Reaction of Dimethyl Hydroxyiminomalonic acid with Dihydropyran.**—A mixture of dimethyl hydroxyiminomalonic acid (160 mg, 1 mmol) and dihydropyran (84 mg, 1 mmol) in dry toluene (3 ml) was heated under an argon atmosphere at 130 °C for 16 h in a sealed tube. Removal of the solvent left an oil which was purified by preparative thin layer chromatography [silica gel, ether–light petroleum (b.p. 40–60 °C)] to give dimethyl tetrahydropyran-2-yloxyiminomalonic acid (17) (191 mg, 78%) as a colourless viscous oil (Found: C, 49.0; H, 6.3; N, 5.6. C<sub>10</sub>H<sub>15</sub>NO<sub>6</sub> requires C, 48.95; H, 6.15; N, 5.70%);  $\nu_{\max}$  (film) 1 745, 1 720, and 1 605 cm<sup>-1</sup> (C=N);  $m/z$  (%) 246 (*M* + 1, 32) and 85 (100);  $\delta_{\text{H}}$  5.54 (m, 1 H, OCHO), 3.93 and 3.90 (2 × s, 2 × 3 H, OMe), 3.76 (m, 2 H, CH<sub>2</sub>O), and 1.8–1.6 [m, 6 H, (CH<sub>2</sub>)<sub>3</sub>];  $\delta_{\text{C}}$  161 and 160.5 (2 × CO), 145.1 (C=N), 102.7 (OCHO), 62.4 (CH<sub>2</sub>O), 53.3 and 52.8 (2 × OCH<sub>3</sub>), 28.1, 24.9, and 18.54 (3 × CH<sub>2</sub>).

**Reaction of 2-Hydroxyiminoindan-1,3-dione and Dihydropyran.**—2-Hydroxyiminoindan-1,3-dione (175 mg, 1 mmol) and dihydropyran (84 mg, 1 mmol) in dry acetonitrile (40 ml) were boiled under reflux for 21 h, after which the solvent was removed and the residue purified by preparative thin layer chromatography, to afford 2-tetrahydropyran-2-yloxyiminoindan-1,3-dione (19) (150 mg, 58%) as yellow needles, m.p. 114–116 °C [Found: *M* + 1 (mass spectrum) 260.091 83. C<sub>14</sub>H<sub>13</sub>NO<sub>4</sub> + 1 requires 260.092 227];  $\nu_{\max}$  1 735, 1 705, and 1 600 (C=N) cm<sup>-1</sup>;  $\delta_{\text{H}}$  8.1–7.9 (m, 4 H, ArH), 5.74 (m, 1 H, OCHO), 3.84 (m, 2 H, CH<sub>2</sub>O), and 2.7–1.53 [m, 6 H, (CH<sub>2</sub>)<sub>3</sub>].

### Acknowledgements

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