CYCLOADDITION OF AZEPINE DERIVATIVES WITH
METHOXYCARBONYL-2-PYRONES\textsuperscript{1}

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Cycloaddition reactions of 5- or 3-methoxycarbonyl-2-pyrone with 1-ethoxycarbonyl-1H-azepine and 1-ethoxycarbonyl-1H-1,2-diazepine were investigated. The (4+2) and (4+6) type adducts such as 6, 7 and 10 were obtained in addition to the corresponding benzazepine derivatives, 3 and 4, which derived from the (4+2) type adducts.

Cycloaddition reactions of cycloheptatriene with 2-pyrone derivatives were of special interest because of a variety of the addition modes, as well as of synthetic utility for providing the ring fused derivatives with a \text{C}_4\text{H}_4 unit increase.\textsuperscript{2} Extension of this procedure to heterepins, such as 1H-azepine (1)
and 1H-1,2-diazepine (2), is expected to produce the correspond-
ing aza[11]annulenes. However, Anastassiou et al. reported
recently the failure to isolate adducts from the heteroepins with
2-pyrone and exploited a new procedure for the C,H homologation
of the heteroepins using their photo-valence isomers. Contrary
to this, we have found that an introduction of an electronega-
tive substituent such as methoxycarbonyl to 2-pyrone raised the
reactivity toward the cycloadditions with heteroepins such as (1)
and (2). We report here an outline of these studies including
the synthesis of benzazepine derivatives (3) and (4).

When a mixture of 1-ethoxycarbonyl-1H-azepine (1) and 5 molar
equiv of 5-methoxycarbonyl-2-pyrone (5) was heated at 80°C for
two days, two products 6 (oil) and 7 (mp 98-100°C) were obtained
in 25 and 20% yields, respectively. Under more drastic condi-
tions (1:1 mixture of 1 and 5, in refluxing toluene, for 7 days),
3-ethoxycarbonyl-7-methoxycarbonyl-3H-3-benzazepine (3) (mp 82-
84°C) was isolated in 5% yield accompanied by (6+6) cycloaddition
dimer of 1 in 35% yield. Heating of 1-ethoxycarbonyl-1H-1,2-
diazepine (2) and pyrone (5) at 80-110°C for 7 days produced
3-ethoxycarbonyl-8-methoxycarbonyl-3H-2,3-benzodiazepine (4) (mp
84-86°C) and an unidentified product (oil. C_{14}H_{16}O_{4}N_{2}) in 12 and
10% yields, respectively. The structure of the products, 3, 4, 6,
and 7 was elucidated mainly from the nmr spectra shown in
Table 1 as well as the following spectral properties: For 3;
m/e 273 (M^+, 83%), 200 (100 %); ir (KBr), 1720, 1680 cm^{-1}; uv
max (cyclohexane) 264 nm (log ε, 4.68), 339 (3.21), 354 (3.15 sh),

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$$\text{N-CO}_2\text{Et} + \text{Y-CO}_2\text{Et} \xrightarrow{\Delta} \text{Product}$$

(1) $X = \text{CH}$
(2) $X = \text{N}$
(3) $X = \text{CH}$
(4) $X = \text{N}$
(5) $Y = \text{CO}_2\text{Me}$
(6) $X = \text{CH}, \ Z = \text{H}$
(7) $Y = \text{CO}_2\text{Me}$
(8) $X = \text{CH}, \ Y = \text{H}$
(9) $Y = \text{H}$
(10) $X = \text{CH}, \ Y = \text{H}$
(11) $Z = \text{CO}_2\text{Me}$
(12) $Z = \text{CO}_2\text{Me}$

LUMO

HOMO
435 (2.70 sh), 467 (2.36 sh). For 4; m/e, 274 (M^+, 100%), 202 (96%); ir (KBr), 1730, 1710 cm\(^{-1}\); uv max (cyclohexane), 217 nm (log \(\epsilon\), 4.49), 268 (4.38 sh), 275 (4.46), 327 (3.44). For 6; m/e, 319 (M^+, 1%), 165 (100%); ir (CCl\(_4\)), 1780, 1735 cm\(^{-1}\). For 7; m/e, 319 (M^+, 1%), 165 (100%); ir (CCl\(_4\)), 1760, 1705 cm\(^{-1}\).

The endo formula of the adduct 6 is supported by small coupling constants between the bridgehead protons (\(J_1,2 = 3.0\) and \(J_8,9 = 2.3\) Hz),\(^7\) and the stereochemistry of 7 was deduced by the resemblance of its nmr spectrum to that of adduct 8 which was derived from cycloheptatriene and 5.\(^2\) At room temperature, adduct 7 exhibits three pairs of signals with slight differences in chemical shift for the protons of the ethoxycarbonyl group and at the C1 and C8 positions. These three pairs of signals coalesced to three independent signals at 70\(^\circ\)C supporting the presence of two rotamers owing to the ethoxycarbonyl group.\(^8\) The structures of benzazepines, 3 and 4, are also supported by the absence of the signals due to the saturated methine groups in their nmr spectra and by appearance of the uv absorption maxima at wavelength region from 350 to 450 nm.\(^9\) With adduct 4, location of the methoxycarbonyl group at the C8 position is confirmed by appearance of the NOE between the C5-H and C6-H, and the C1-H and C9-H with 15 and 17% increases, respectively. The formation of 3 and 4 should result from the decarboxylation and dehydrogenation of the corresponding (4+2) type adducts.

For comparisons the cycloaddition reaction of 1 with 3-methoxy-
Table 1. Nmr Spectral Data for 3,4,6,7, and 10. 
Chemical Shift (δ, ppm)

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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10 &amp; 11</th>
<th>coupling constants, (Hz)</th>
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<td>5.14</td>
<td>6.09</td>
<td>6.14</td>
<td>5.19</td>
<td>7.20</td>
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<td>6.47</td>
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<td>7.77</td>
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<td>3.11</td>
<td>3.62</td>
<td>7.10</td>
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<td>J\textsubscript{10,11}=8.0</td>
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</table>

a) measured in CCl\textsubscript{4}. b) measured in CDCl\textsubscript{3}
carbonyl-2-pyrone (9) was carried out under the same conditions, in which case the (4+2) type adduct 10 [oil; m/e, 305 (M⁺, 1%), 151 (100%); ir (CCl₄), 1775, 1740 cm⁻¹] was isolated in only 5% yield in addition to the (6+4) type dimer of 1.⁶

Thermal decarboxylation of 6, 7, and 10 was attempted to produce the C₄H₄ homologation products of 1 and 2 and to confirm the formation mechanism of 3 and 4. Heating of 6 in refluxing xylene for 50 min afforded 3 in a small yield (5%), but the yield raised to 17% by addition of dehydrogenation reagents such as DDQ or o-chloranil to the reaction mixture. The pyrolysis of 7 at 240°C, however, resulted in the cycloreversion to give 1 and 5, the behavior of which was also expected from its mass spectrum. Heating of 10 in boiling xylene caused the Cope rearrangement.¹⁰

As shown above, it became clear that 2-pyrone (5 and 9) reacted with heterpins (1 and 2) though in small yields. The trend of low yields was also observed in the reaction of cycloheptatriene with 2-pyrone derivatives,² and could be ascribed partially to a variety of the secondary thermal reactions. Nevertheless, it is noteworthy that 2-pyrone which did not react at all with azepines became reactive by introducing an electronegative substituent such as methoxycarbonyl group. Considering that the electronegative substituents are known to lower the orbital energies of the systems,¹¹ the results could be an experimental evidence for the inverse electron demanding Diels-Alder reactions which arose from the interaction between the HOMO of heterpins
and the LUMO of 2-pyrroles. Extended Hückel Mo calculations on the net charge distribution of the 2-pyrroles predict that 3-methoxy-carbonyl derivative (9) should react with dienophiles easier than the 5-isomer (5), but this was not the case. This discrepancy can be explained by the steric effect due to the methoxycarbonyl group located at the reaction site. The preferential formation of the endo adducts 6 and 10 can be rationalized in terms of the secondary orbital interaction in the transition state as shown in 11.

REFERENCES

1 Dedicated to Professor Tetsuo Nozoe on the occasion of his 77th birthday.


4 Presented at the Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1975; Proceedings Vol. III. p. 1663.

5 Satisfactory elemental analyses were obtained for all new compounds.

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