CYCLOADDITION OF AZEPINE DERIVATIVES WITH

METHOXYCARBONYL-2-PYRONES[1]

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Cycloaddition reactions of 5- or 3-methoxycarbonyl-
2-pyrone with 1-ethoxycarbonyl-1H-azepine and 1-eth-
oxycarbonyl-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 de-
rivatives 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 C_4H_4 unit increase.[2] Exten-
sion 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 heterepins with
2-pyrone and exploited a new procedure for the C_4H_4 homologation
of the heterepins using their photo-valence isomers.[3] 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 heterepins such as (1)
and (2).[2] We report here an outline of these studies including
the synthesis of benzazepine derivatives (3) and (4).[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)[5] 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[6] 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. $C_{14}H_{16}O_4N_2$) 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),
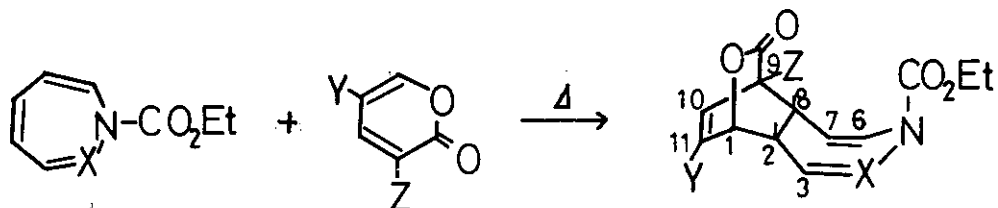
(1) X = CH

(2) X = N
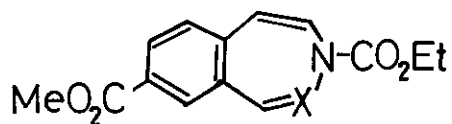
(5) Y = CO₂Me
    Z = H
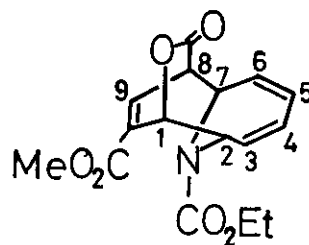
(9) Y = H
    Z = CO₂Me

(6) X = CH, Z = H
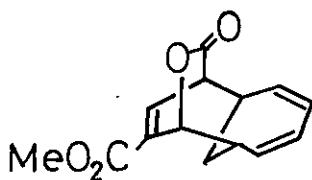   Y = CO₂Me

(10) X = CH, Y = H
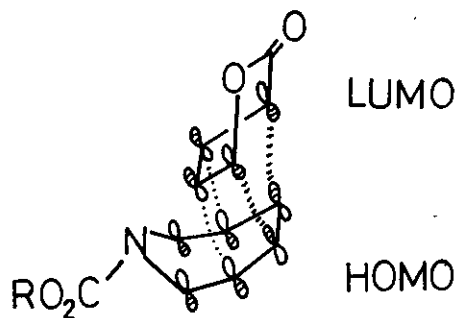   Z = CO₂Me

(3) X = CH

(4) X = N

(7)

(8)

LUMO

HOMO

(11)

435 (2.70 sh), 467 (2.36 sh).   For $\underline{4}$; m/e, 274 (M$^+$, 100%), 202

(96%); ir (KBr), 1730, 1710 cm^{-1}; uv max (cyclohexane), 217 nm

(log ε, 4.49), 268 (4.38 sh), 275 (4.46), 327 (3.44).   For $\underline{6}$;

m/e, 319 (M$^+$, 1%), 165 (100%); ir (CCl$_4$), 1780, 1735 cm^{-1}.   For

$\underline{7}$; m/e, 319 (M$^+$, 1%), 165 (100%); ir (CCl$_4$), 1760, 1705 cm^{-1}.

The endo formula of the adduct $\underline{6}$ 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 $\underline{7}$ was deduced by the resemblance

of its nmr spectrum to that of adduct $\underline{8}$ which was derived from

cycloheptatriene and $\underline{5}$.[2]   At room temperature, adduct $\underline{7}$ exhibits

three pairs of signals with slight differences in chemical shift

for the protons of the ethoxycarbonyl group and at the C_1 and C_8

positions.   These three pairs of signals coalesced to three inde-

pendent signals at 70°C supporting the presence of two rotamers

owing to the ethoxycarbonyl group.[8]   The structures of benzaze-

pines, $\underline{3}$ and $\underline{4}$, 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 $\underline{4}$, location of the methoxycarbonyl

group at the C_8 position is cofirmed by appearance of the NOE bet-

ween the C_5-H and C_6-H, and the C_1-H and C_9-H with 15 and 17% in-

creases, respectively.   The formation of $\underline{3}$ and $\underline{4}$ should result

from the decarboxylation and dehydrogenation of the corresponding

(4+2) type adducts.

   For comparisons the cycloaddition reaction of $\underline{1}$ with 3-methoxy-

Table 1. Nmr Spectral Data for 3,4,6,7, and 10. Chemical Shift (δ, ppm)

H / compd	1	2	3	4	5	6	7	8	9	10 & 11	coupling constants, (Hz)
3a)	5.14 or 5.19 d	6.09 or 6.14 d		6.14 or 6.09 d	5.19 or 5.14 d	7.20 d		7.48 dd	6.57 d		$J_{1,2}=J_{4,5}=10.3$, $J_{6,8}=1.8$, $J_{8,9}=8.0$
4a)	7.31 s			6.47 d	5.55 d	6.86 dd	7.77 dd		7.61 d		$J_{4,5}=9.0$, $J_{6,7}=8.0$, $J_{7,9}=1.8$
6a)	5.46 dd	3.30 ddd	4.77 or 4.82 dd	6.81 d		6.81 d	4.82 or 4.77 dd	3.11 ddd	3.62 dd	7.10 dd	$J_{1,2}=3.0$, $J_{2,3}=J_{7,8}=4.3$, $J_{2,8}=8.1$, $J_{3,4}=J_{6,7}=11.3$, $J_{8,9}=2.3$, $J_{9,10}=6.0$, $J_{1,10}=2.3$
7b)	5.54 and 5.62 dd	5.06–5.43 m		6.07 brs ↕			5.06–5.43 m	3.82 and 3.79 dd	7.23 dd		$J_{1,2}=4.8$, $J_{1,9}=1.4$, $J_{7,8}=4.0$, $J_{8,9}=6.9$
10a)	5.00 ddd	3.33 m	4.67 m	6.82 d		6.82 d	4.67 m	3.33 m		6.70 dd 6.36 dd	$J_{1,2}=2.2$, $J_{1,10}=2.0$, $J_{1,11}=4.7$, $J_{2,3}=J_{7,8}=4.0$, $J_{3,4}=J_{6,7}=10.0$, $J_{10,11}=8.0$

a) measured in CCl_4. b) measured in $CDCl_3$

carbonyl-2-pyrone ($\underline{9}$) was carried out under the same conditions, in which case the (4+2) type adduct $\underline{10}$ [oil; m/e, 305 (M^+, 1%), 151 (100%); ir (CCl_4), 1775, 1740 cm^{-1}] was isolated in only 5% yield in addition to the (6+4) type dimer of $\underline{1}$.[6]

Thermal decarboxylation of $\underline{6}$, $\underline{7}$, and $\underline{10}$ was attempted to produce the C_4H_4 homologation products of $\underline{1}$ and $\underline{2}$ and to confirm the formation mechanism of $\underline{3}$ and $\underline{4}$. Heating of $\underline{6}$ in refluxing xylene for 50 min afforded $\underline{3}$ 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 $\underline{7}$ at 240°C, however, resulted in the cycloreversion to give $\underline{1}$ and $\underline{5}$, the behavior of which was also expected from its mass spectrum. Heating of $\underline{10}$ in boiling xylene caused the Cope rearrangement.[10]

As shown above, it became clear that 2-pyrones ($\underline{5}$ and $\underline{9}$) reacted with heterepins ($\underline{1}$ and $\underline{2}$) though in small yields. The trend of low yields was also observed in the reaction of cyclohepta-triene 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 heterepins

and the LUMO of 2-pyrones.   Extended Hückel Mo calculations on
the net charge distribution of the 2-pyrones predict that 3-methoxy-
carbonyl derivative (9) should react with dienophiles easier than
the 5-isomer (5),[12] 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 secon-
dary orbital interaction in the transition state as shown in 11.

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