# REGIOSELECTIVE CYCLOADDITIONS OF 1*H*-AZEPINE AND 1*H*-1,2-DIAZEPINE DERIVATIVES WITH *N*,$\alpha$-DIPHENYLNITRONE AND NITROSOBENZENE

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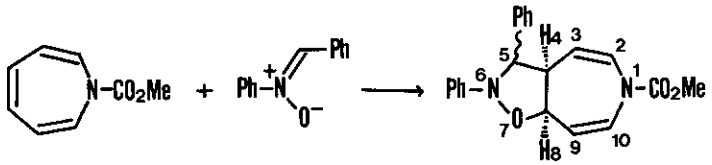
Abstaract Reactions of 1-carbomethoxy-1*H*-azepine with *N*,$\alpha$-diphenylnitrone afforded *endo*- and *exo*-[2+3]-type cycloadducts in almost the same ratio. Reactions of 1-carboethoxy-1*H*-azepine with nitrosobenzene in chloroform afforded [4+2]- and [6+2]-types of cycloadducts. Analogous results were obtained in the reactions using 1-carboethoxy-1*H*-1,2-diazepine.

Azepine and diazepine derivatives are known to be polyolefinics having partially enamine-type reactivities.[1] Because of their bending boat-form no special destabilization was detected which should be expected from the planar 8$\pi$-electrons anti-aromatic structure.[1] Azepines and diazepines are known to react with olefinic compounds through cycloadditions. However, the documents concerning the reactions with hetero-olefins containing 1,3-dipolar reagents are few in number.[2,3] Reactions of nitrones, one of 1,3-dipolar reagents, with five-membered heterocyclic compounds have been researched increasingly,[4] but no examples can be find on the reactions with seven-membered heterocycles such as azepines or diazepines.

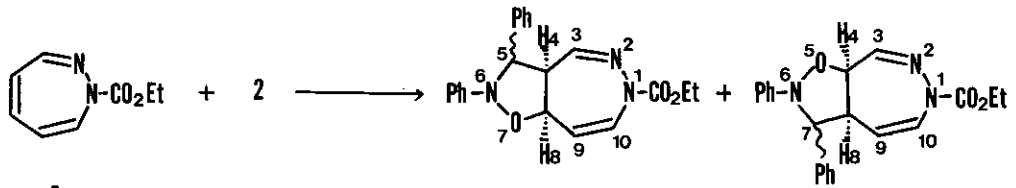
As a part of series of our studies on the reactivities of azepine and diazepine,[3,5] we carried out the reactions of 1*H*-azepine and 1*H*-1,2-diazepine derivatives with N,$\alpha$-diphenylnitrone and nitrosobenzene to form cycloadducts. Here the results will be discussed.

1-Carbomethoxy-1*H*-azepine (1a) and 1.5 equimolar amounts of *N*,$\alpha$-diphenylnitrone (2) were refluxed in toluene for 10 h. Chromatographic separation and purification of the reaction mixture gave cycloadducts (3) and (4) in 28 and 21% yields, respectively. Analogous reaction using 1-carboethoxy-1*H*-1,2-diazepine (5) gave the corresponding cycloadducts (6) and (7) in 22 and 26% yields, respectively, accompanied with small amounts of cycloadducts 8, 9, and 10 in 13, 3, and 3% yields, respectively. No interconversion between the products was observed under the reaction conditions, thus showing that all of these adducts were primary products.

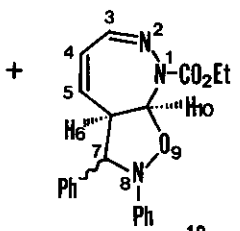
1-Carboethoxy-1*H*-azepine (1b) was allowed to react with 2 equimolar amount of nitrosobenzene (11) in refluxing chloroform for 15 min to give [4+2]- (12) and [6+2]-type cycloadducts (13) in 41 and 22% yields, respectively. The similar reaction with 1-carboethoxy-1*H*-1,2-diazepine (5) afforded a [4+2]-type cycloadduct (14) in 26% yield.



1a 2 3, 4



5 6, 7 8, 9



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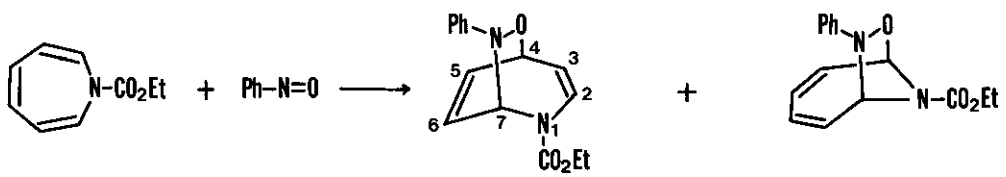
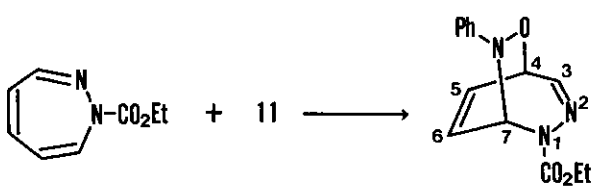
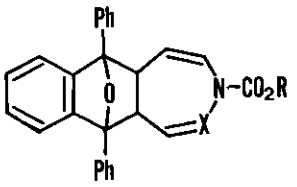


1b 11 12 13



5 14

Murphy *et al.* already studied the reaction of 1b with 11 in benzene solution to afford the same products as our case and revealed an absence of interconversion between the products.[2] The marked difference, however, is the considerable improvement in the yield of 12 in our case; *i. e.*, Murphy *et al.* obtained 12 in maximum 17% yield (at r. t., 8 weeks) or only 13 in 50% yield (at 20°C, 24 h).[2,6]

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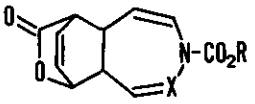


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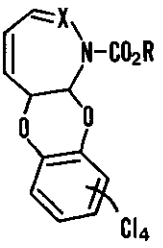


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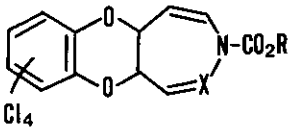


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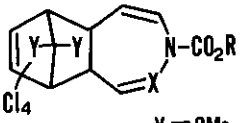
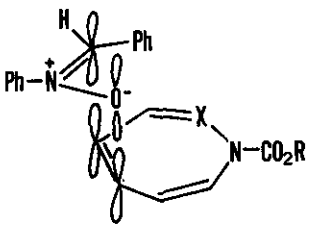



Y = OMe

18

The structure of 14 was deduced from a good resemblance of its nmr spectrum to that of 12, except a disappearance of the peak corresponding to H-2 proton. A down field shift of the peak of H-3 proton of 14 compairing to that of 12 was reasonably attributed to the inductive effect caused by the adjacent nitrogen atom in 14. The structures of 3 and 4 were also deduced based on their spectral, especially nmr, properties: The arrangements of the protons (H-2 - H-10) were decided using the decoupling technique of $^1$H nmr spectra. The *cis*-configurations of H-4 and H-8 in both 3 and 4 were supported by good coincidences of the coupling constant values between these protons to those of the analogous compounds (15-18).[3,4,7-9] The structures of 6, 7, 8, and 9 were also deduced from their spectral similarity with 3 and 4.[9] The structure of 10 was also deduced mainly on the basis of its nmr spectral properties which revealed a good coincidence to that of 19.[3]

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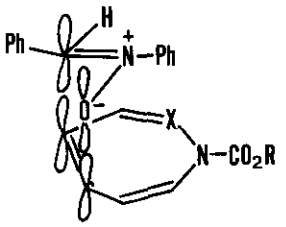


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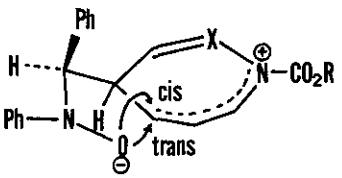


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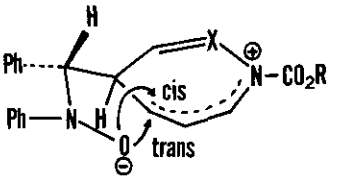
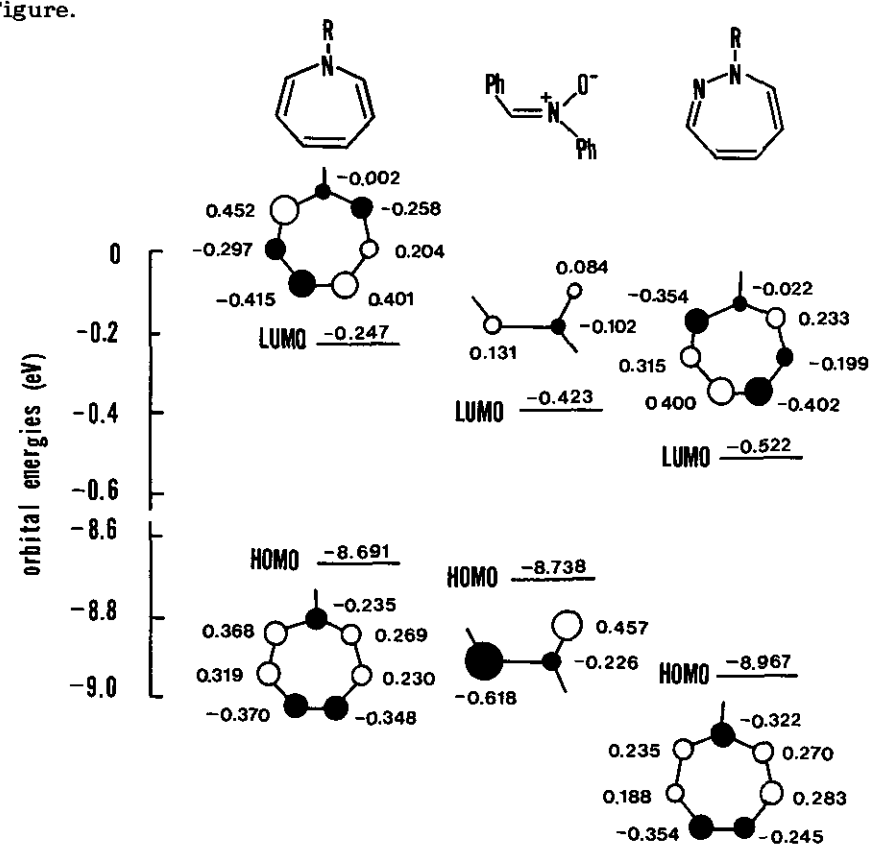



23

Concerted and ionic mechanisms are possible for the reactions of 1 and 5 with 2. The former is a [2+3]-type cycloaddition reaction *via* the *exo*- and *endo*-type transition states (20) and (21), respectively. An absence of the stabilization effects by secondary orbital interactions[10] and an absence of significant steric repulsions both in 20 and 21 make it possible to produce the both *exo*- and *endo*-types of the adducts in almost same yields. The another is a process through ionic intermediates (22) and (23), each of which can form the *exo*- and *endo*-adducts, respectively. However, the conformational flexiblity of the ionic intermediates (22 and 23) allow both *cis*- and *trans*-additions to proceed. Thus, considering that the configurations between H-4 and H-8 are cis for all of the cycloadducts, the concerted [2+3]-type cycloaddition process seems to be more plausible.

In order to examine the reaction mechanisms an MNDO calculation was carried out.[11] The energies and the coefficients of the LUMO and HOMO of 1, 2, and 5 were shown in the following Figure.



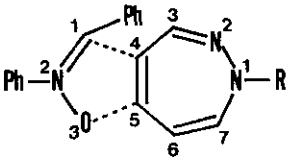

Previously, Klopman and Salem suggested that the regioselectivities could be predicted by the comparison of the values calculated by the following equation.[12]

$$\frac{\Sigma (C_{ra} \cdot C_{sa})^2}{E_r - E_s}$$

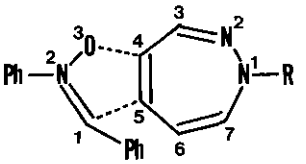
$C_{ra}$: coefficient on the atom "a" of molecular orbital "r"

$E_r$: energy of molecular orbital "r"

| Type 1 | | | | Type 2 | | | |
|---|---|---|---|---|---|---|---|
| | | Nitrone (HOMO) | | | | Nitrone (LUMO) | |
| | | 1, 3 | 3, 1 | | | 1, 3 | 3, 1 |
| Azepine (LUMO) | 2, 3 | 0.014 | 0.014 | Azepine (HOMO) | 2, 3 | 0.00037 | 0.00033 |
| | 4, 5 | 0.016 | | | 4, 5 | 0.00039 | |
| | 2, 7 | 0.005 | | | 2, 7 | 0.00034 | |
| Diazepine (LUMO) | 2, 3 | 0.011 | 0.011 | Diazepine (HOMO) | 2, 3 | 0.00014 | 0.00012 |
| | 4, 5 | 0.016 | 0.016 | | 4, 5 | 0.00030 | 0.00022 |
| | 6, 7 | 0.005 | 0.005 | | 6, 7 | 0.00022 | 0.00021 |
| | 2, 7 | 0.009 | 0.009 | | 2, 7 | 0.00017 | 0.00019 |



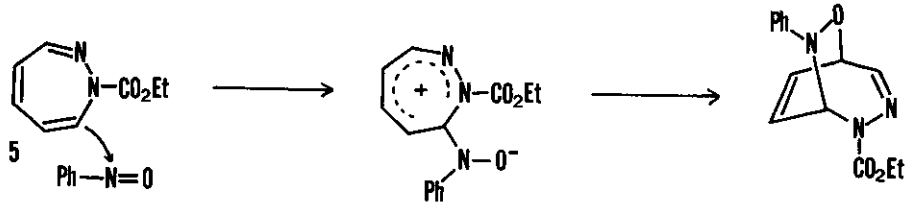
Nitrone Diazepine
1, 3 —— 4, 5



Nitrone Diazepine
3, 1 —— 4, 5

The values caluculated for LUMO of 1 and 5 and HOMO of 2 (Type 1) and the values for HOMO of 1 and 5 and LUMO of 2 (Type 2) according to the equation were summarized in the preceding Table. (The combinations of the position numbers in the Table show the combinations of the reaction sites of 1, 2, and 5 as exemplified in the figure under the Table). These results show the priorities of the additions to the 4,5-positions. The larger values in the Type 1 might suggest that the interactions between the LUMO of azepine and diazepine and the HOMO of nitrone controlled the reactions.[13]

The reaction of 1 and 11 is considered to proceed *via* a mechanism discussed by Murphy *et al.*[2] The reaction of 5 with 11 also proceeded through an ionic mechanism *via* an intermediate (24), which corresponds to the intermediate proposed by Murphy *et al.* in the reaction of azepine derivatives.[2] The improved yields in our case can be explained by the stabilization of the ionic intermediate (24) caused by a solvation by chloroform.[14]



11 24 14

## EXPERIMENTAL

Nmr spectra were measured with Varian XL-200 or Hitachi R-90 spectrometers with tetramethyl silane as an internal standard. Ir and ms spectra were measured with JASCO FT/IR 5300 spectrophotometer and Hitachi M-2000S spectrometer, respectively.

*Reaction of 1a with 2.* A mixture of 1a (310 mg, 2.1 mmol) and 2 (600 mg, 3.0 mmol) in toluene (5 ml) was refluxed for 10 h. After evaporation of the solvent, the reaction mixture was chromatographed on a silica gel column to give a mixed oil (hexane–ethyl acetate 95:5), which was subjected to thin-layer chromatography on silica gel (chloroform) to give oils 3 ($R_f$=0.65, 190 mg, 28%) and 4 ($R_f$=0.53, 145 mg, 21%).

3: Hrms: m/z 348.1480. Calcd for $C_{21}H_{20}N_2O_3$: m/z 348.1473. Ms m/z (rel intensity): 348 ($M^+$, 10), 332 (5), 195 (7), 182 (100). Ir (oil): 3030, 2980, 1720, 1600 $cm^{-1}$. $^1H$ Nmr ($CDCl_3$) $\delta$ 3.53 (m, $H_4$), 3.78 (s, 3H, $CH_3$), 4.39 (d, $H_5$), 4.80 (m, $H_3$), 4.81 (m, $H_8$), 4.98 (ddd, $H_9$), 6.76 (ddd, $H_{10}$), 6.97 (dd, $H_2$), 7.1–7.5 (m, 10H, Ph). Coupling constants in Hz: $J_{23}$=10.2, $J_{210}$=1.5, $J_{34}$=8.2, $J_{45}$=10.3, $J_{48}$=5.5, $J_{49}$=1.5, $J_{89}$=2.4, $J_{810}$=2.0, $J_{910}$=10.9.

4: Hrms: m/z 348.1472. Calcd for $C_{21}H_{20}N_2O_3$: m/z 348.1472. Ms m/z (rel intensity): 348 ($M^+$, 33), 240 (24), 180 (65), 151 (100). Ir (oil): 3030, 2980, 1723, 1600 $cm^{-1}$. $^1H$ Nmr ($CDCl_3$) $\delta$ 3.69 (s, 3H, $CH_3$), 3.80 (m, $H_4$), 4.57 (dd, $H_3$), 4.79 (ddd, $H_8$), 4.82 (d, $H_5$), 5.16 (dd, $H_9$), 6.56 (ddd, $H_2$), 6.84 (ddd, $H_{10}$), 7.1–7.5 (m, 10H, Ph). Coupling constants in Hz: $J_{23}$=10.3, $J_{24}$=1.6, $J_{210}$=1.3, $J_{34}$=5.5, $J_{45}$=8.2, $J_{48}$=5.4, $J_{89}$=4.4, $J_{810}$=1.3, $J_{910}$=10.5.

*Reaction of 5 with 2.* A solution of 5 (340 mg, 2.0 mmol) and 2 (590 mg, 3.0 mmol) in toluene (5 ml) was refluxed for 10 h. After evaporation of the solvent the reaction mixture was chromatographed on a silica gel column to give an oil of 4:1 mixture of 8 and 9 (120 mg, 16%, hexane–ethyl acetate (85:15)), an oil of *ca.* 1:1 mixture of 6 and 7 (350 mg, 48%, hexane–ethyl acetate (83:17)), and an oil 10 (24 mg, 3%, hexane–ethylacetate (6:4)).

6: Hrms: m/z 363.1581. Calcd for $C_{21}H_{21}N_3O_3$: m/z 363.1581. Ms m/z (rel intensity): 363 ($M^+$, 17), 255 (100), 197 (10), 182 (54). Ir (oil): 3040, 1970. 1723, 1600 $cm^{-1}$. $^1H$ Nmr ($CDCl_3$) $\delta$ 1.37 (t, 3H, $CH_3$, J=7.2 Hz), 3.81 (m, $H_4$), 4.37 (q, 2H, $CH_2$, J=7.2 Hz), 4.72 (d, $H_5$), 4.82 (ddd, $H_8$), 5.08 (ddd, $H_9$), 7.01 (d, $H_3$), 7.06 (dd, $H_{10}$), 7.1–7.5 (m, 10H, Ph). Coupling constants in Hz: $J_{34}$=5.9, $J_{45}$=9.0, $J_{48}$=6.0, $J_{49}$=1.1, $J_{89}$=2.8, $J_{810}$=1.3, $J_{910}$=10.8 .

7: Hrms: m/z 363.1624. Calcd for $C_{21}H_{21}N_3O_3$: m/z 363.1582. Ms m/z (rel intensity): 363 ($M^+$, 14), 255 (100), 197 (42), 182 (38). Ir (oil): 3030, 2970, 1720, 1650 $cm^{-1}$. $^1H$ Nmr ($CDCl_3$) $\delta$ 1.31 (t, 3H, $CH_3$, J=7.1 Hz), 3.89 (m, $H_4$), 4.30 (q, 2H, $CH_2$, J=7.1 Hz), 4.87 (ddd, $H_8$), 4.94 (d, $H_5$), 5.19 (dd, $H_9$), 7.10 (d, $H_3$), 7.17 (dd, $H_{10}$), 7.2–7.5 (m, 10H, Ph). Coupling constants in Hz: $J_{34}$=3.4, $J_{45}$=6.3, $J_{48}$=3.8, $J_{49}$=0, $J_{89}$=4.6, $J_{810}$=1.6, $J_{910}$=10.0.

8: Hrms: m/z 363.1572. Calcd for $C_{21}H_{21}N_3O_3$: m/z 363.1581. Ms m/z (rel intensity): 363 ($M^+$, 25), 333 (18), 197 (20), 181 (100). Ir (oil): 2982, 1728, 1597, 1489, 1454 $cm^{-1}$. $^1H$ Nmr ($CDCl_3$) $\delta$ 1.35 (t, 3H, $CH_3$, J=7.3 Hz), 3.64 (m, $H_8$), 4.29 (d, $H_7$), 4.33 (q, 2H, $CH_2$, J=7.3 Hz), 4.86 (dd, $H_9$), 5.03 (dd, $H_4$), 7.13 (dd, $H_{10}$), 7.17 (dd, $H_3$), 7.2–7.5 (m, 10H, Ph). Coupling constants in Hz: $J_{34}$=1.7, $J_{38}$=0.9, $J_{48}$=5.8, $J_{78}$=10.3, $J_{89}$=6.1, $J_{810}$=0.6, $J_{910}$=10.3.

9: $^1H$ Nmr ($CDCl_3$) $\delta$ 1.37 (t, 3H, $CH_3$, J=7.3 Hz), 4.05 (m, $H_8$), 4.29 (q, 2H, $CH_2$, J=7.3 Hz), 4.55 (dd, $H_9$), 4.67 (d, $H_7$), 5.13 (dd, $H_4$), 6.70–7.70 (m, 12H, $H_3$, $H_{10}$, and Ph). Coupling

constants in Hz: $J_{34}$=1.6, $J_{48}$=7.6, $J_{78}$=10.3, $J_{89}$=5.2, $J_{910}$=10.4. $^{13}$C Nmr($CDCl_3$) $\delta$ 14.4, 50.4, 63.6, 70.8, 75.8, 106.7, 116.0, 122.8, 128.0, 128.1, 128.7, 128.7, 128.9, 129.2, 138.1, 154.3, 158.3.

10: Hrms: m/z 363.1590. Calcd for $C_{21}H_{21}N_3O_3$: m/z 363.1582. Ms m/z (rel intensity): 363 ($M^+$, 22), 335 (17), 262 (100), 255 (99), 234 (29). Ir (oil): 3032, 2982, 1717, 1599, 1489, 1454 $cm^{-1}$. $^1$H Nmr ($CDCl_3$) $\delta$ 1.40 (t, 3H, $CH_3$, J=7.1 Hz), 3.68 (m, $H_6$), 4.40 (q, 2H, $CH_2$, J=7.1 Hz), 4.99 (d, $H_7$), 5.52 (ddd, $H_5$), 5.84 (ddd, $H_4$), 6.97 (d, $H_{10}$), 7.33 (d, $H_3$), 7.00–7.60 (m, 10H, Ph). Coupling constants in Hz: $J_{34}$=4.7, $J_{45}$=12.6, $J_{46}$=1.9, $J_{56}$=4.8, $J_{67}$=7.1, $J_{610}$=6.1.

*Reaction of 1b with 11.* A solution of 1b (340 mg, 2.1 mmol) and 11 (300 mg, 3.1 mmol) in chloroform (5 ml) was refluxed for 15 min. After evaporation of the solvent the reaction mixture was subjected to thin-layer chromatography on silica gel (hexane–ethyl acetate 1:1) to give crystals 13 ($R_f$=0.70, 120 mg, 22%, mp 115–116°C, lit.,[3] 115–116°C) and an oil 12 ($R_f$=0.60, 230 mg, 41%).

*Reaction of 5 with 11.* A solution of 5 (330 mg, 2.0 mmol) and 11 (440 mg, 4.1 mmol) in chloroform (5 ml) was refluxed for 4 h. After evaporation of the solvent the reaction mixture was chromatographed on a silica gel column to give an oil 14 (140 mg, 26%) by elution with hexane–ethyl acetate (3:1).

14: Hrms: m/z 273.1118. Calcd for $C_{14}H_{15}N_3O_3$: m/z 273.1113. Ms m/z (rel intensity): 273 ($M^+$, 16), 256 (74), 212 (40), 184 (100), 166 (78). Ir (oil): 3063, 2984, 1711, 1595, 1489, 1453 $cm^{-1}$. $^1$H Nmr ($CDCl_3$) $\delta$ 1.37 (t, 3H, $CH_3$, J=7.3 Hz), 4.37 (q, 2H, $CH_2$, J=7.3 Hz), 4.53 (ddd, $H_4$), 6.28 (2H, m, $H_5$, $H_6$), 6.80 (dd, $H_7$), 7.00–7.40 (m, 6H, $H_3$ and Ph). Coupling constants in Hz: $J_{34}$=6.1, $J_{45}$=9.0, $J_{57}$=4.2, $J_{67}$=4.2.

*Thermal Reactions of the Cycloadducts.* Only a typical reaction is mentioned and the results of the other reactions are summarized in the Table. A solution of 3 (100 mg) in toluene-$d_8$ (0.5 ml) was heated at 110°C for 24 h. Thin-layer chromatography of the reaction mixture on silica gel (chloroform) resulted in the recovery of 3 ($R_f$=0.75, 89 mg, 89%).

| | Solvent | Temp. | Time | Result (recovery) |
|---|---|---|---|---|
| 3 | toluene-d8 | 110°C | 24 h | 89 % |
| 4 | toluene-d8 | 110°C | 10 h | 93 % |
| 6 | toluene-d8 | 110°C | 10 h | 90 % |
| 7 | toluene-d8 | 110°C | 10 h | 72 % |
| 8 | toluene-d8 | 110°C | 10 h | 51 % |

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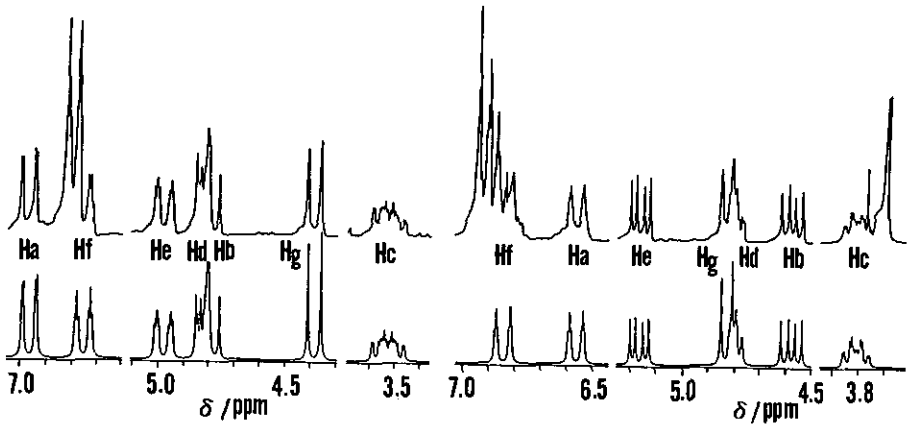


The observed (upper ones) and the simulated (lower ones) $^1$H nmr spectra of 3 (left side) and 4 (right side).

9. The small diferences in the coupling constant values of $J_{45}$ between 3 and 4, 6 and 7, and 8 and 9 made it hard to decide the full stereochemistries of the compounds.
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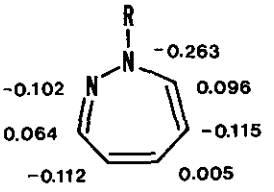
13. These calculations showed no difference between two directions of the nitrone to diazepine: *i. e.*, the interaction to give the adducts 6 and 7 and that to give 8 and 9 had the same value (0.016). The major formations of 6 and 7 is explained by examination of the electron densities of 5, which showed a negative charge at the 4-position and a positive one at 5-position. It is considered that the negatively charged oxygen atom of 2 should attack the positively charged 5-position of 5 to form 6 and 7 rather than the negatively charged 4-position.

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