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Studies on Diazepines. XXX.[1] Addition Reactions of Monocyclic Diazepines with Dimethyl Acetylenedicarboxylate Involving Diazonine Intermediates

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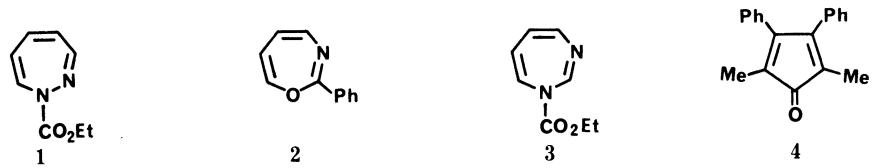
The reaction of the 1*H*-1,3-diazepines (**8a**—**c**) with dimethyl acetylenedicarboxylate (DMAD) gave the 3a,7a-dihydropyrrolo[3,2-*b*]pyridines (**9**), probably *via* the 1,5-diazonine intermediates **11** derived from the initially formed [2+2]π cycloadducts **10**. Similarly, the 1*H*-1,2-diazepines (**15a**—**c**), upon treatment with DMAD, produced the 3a,7a-dihydroindazoles (**20**), presumably *via* the [2+2]π cycloadducts **18** and the 1,2-diazonines **19** successively, but the dihydroindazoles (**20**) further reacted with the reagent to give the dimethyl phthalates (**16**) and the pyrazoles (**17**) as the final products *via* the [4+2]π cycloadducts **21**. These results are the first examples of the reaction of fully unsaturated seven-membered heterocyclic rings with acetylenes.

Keywords——1*H*-1,3-diazepine; 1*H*-1,2-diazepine; dimethyl acetylenedicarboxylate; cycloaddition; diazonine intermediate; 3a,7a-dihydropyrrolo[3,2-*b*]pyridine; 3a,7a-dihydroindazole; dimethyl phthalate; pyrazole

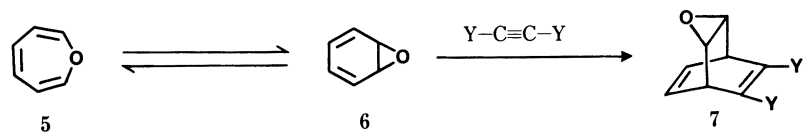
Fully unsaturated seven-membered heterocyclic compounds (heteroepines) are known[2] to undergo intermolecular cyclizations with a variety of dienophiles, dienes, and dipolar molecules, because they possess many reaction sites and thus can react as monoenes, dienes, trienes, or their hetero analogues such as imines and enamines, in addition to norcaradiene forms. Intermolecular cyclizations of seven-membered heterocyclic rings containing two hetero atoms (diheteroepines) have also been well studied. The 1,2-diazepines (**1**) undergo a broad spectrum of cycloaddition reactions[3] with many unsaturated compounds such as tetracyanoethylene,[4] 1,2,4-triazoline-3,5-diones,[5] singlet oxygen,[6] nitrile oxides,[7] α-pyrones,[8] cyclopentadienones,[9] isocyanates,[10] ketenes,[11] and diazoalkanes,[12] giving the corresponding 1 : 1 adducts. On the other hand, it has been reported that 2-phenyl-1,3-oxazepine (**2**) did not add to usual dienophiles, except for 2,5-dimethyl-3,4-diphenylcyclopentadienone (**4**).[9] Accordingly, we were prompted to examine the reactivity of 1*H*-1,3-diazepines such as **3**, prepared recently by us,[13] toward dienophiles, and we have reported that they react with the cyclopentadienone (**4**) to afford three kinds of 1 : 1 cycloadducts, *i.e.*, [6+4]π cycloadducts and [4+2]π cycloadducts.[14]

However, heteroepines have appeared to be unreactive with acetylenes, even highly activated acetylenecarboxylic acids, except for oxepin (**5**), which adds to acetylenes through the benzene oxide form (**6**) to give the adducts (**7**).[15] We report here that 1,2- and 1,3-diazepines can be forced to react with an acetylene derivative by prolonged heating, giving rise to products probably *via* cycloadduct and diazonine intermediates successively.[16]

The starting 1-ethoxycarbonyl-1*H*-1,3-diazepines (**8a**—**c**)[13] were prepared by the thermal ring conversion of the corresponding 1*H*-1,2-diazepines[17] obtained photochemically from pyridine *N*-imides. Treatment of the 1,3-diazepines (**8a**—**c**) with dimethyl acetylenedicarboxylate (DMAD) (1.5 mol eq) in benzene at 60—70 °C until almost all of the starting diazepines had been consumed (for 6—7 d) gave the corresponding 3a,7a-dihydropyrrolo[3,2-

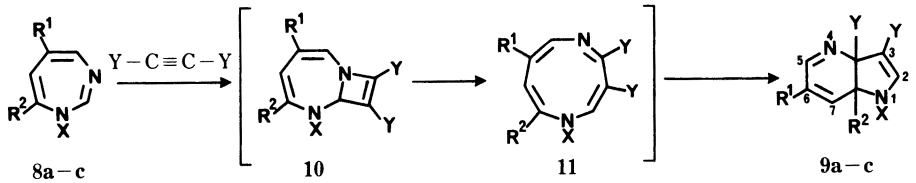


1 2 3 4



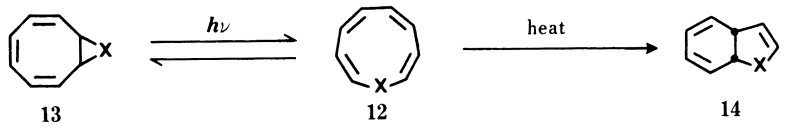
5 6 7

Chart 1



8a–c 10 11 9a–c

a : $R^1=R^2=Me$ $X=CO_2Et$
b : $R^1=Me$, $R^2=H$ $Y=CO_2Me$
c : $R^1=OMe$, $R^2=H$



13 12 14

a : X=O, b : $X=NCO_2Et$

Chart 2

b]pyridines (**9a**—**c**) in 50—80% yields, as the sole characterizable products.

The formation of the products **9** from **8** may proceed by initial addition of DMAD to the imine double bond of **8** to give the cycloadducts **10**. The adducts **10** might undergo ring expansion to the 1,5-diazonines (**11**), which might then cyclize to give the products **9**, although attempts to isolate the key intermediates **10** and **11** have been unsuccessful. Reaction times shorter than 6—7 d resulted in a decrease in the amount of the products **9** and an increase in the starting diazepines, and the yields of **9** calculated from the consumed **8** were nearly constant (50—80%). This observation may indicate that the formation of the cycloadducts **10** is the rate-determining step in this reaction. In all cases, the formation of other possible adducts such as $[4+2]\pi$ and $[6+4]\pi$ cycloadducts was not observed. The photochemical valence isomerization of the nine-membered heterocycles **12** to the 9-hetero-bicyclo-[6.1.0]nona-2,4,6-trienes (**13**) is known, and they are thermally labile and rearrange to the bicyclic compounds **14**.[18] This fact supports the hypothesis that the present reaction involves the diazonine intermediates **11**.

The products **9** gave high-resolution mass spectra (MS) consistent with formulations as the starting diazepines (**8**) plus one molecule of DMAD, indicating the initial formation of 1 : 1 adducts, and the structural assignments of **9** were mainly based on their nuclear magnetic

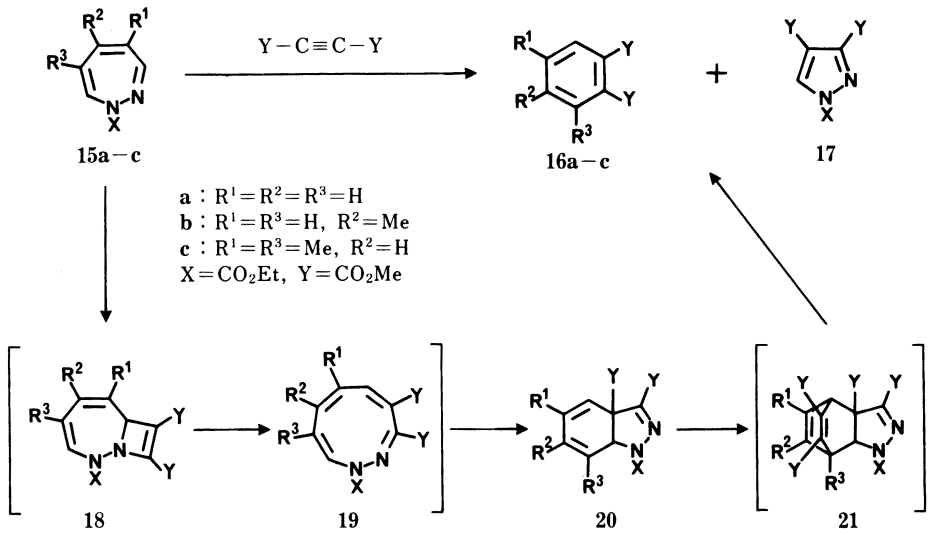


Chart 3

resonance (NMR) spectral data. Although the stereochemistry of this reaction is not clear, the products **9** are assumed to be *cis*-fused from their ^{1}H-NMR spectral data. It is known[19] that the 7a-proton of *cis*-1-ethoxycarbonyl-3a,7a-dihydroindole (**14b**) resonates at much lower field (δ 5.05) than that of its *trans*-isomer (δ 3.93). Therefore, the chemical shifts of 7a-H in **9** (δ 4.95 for **9a**; δ 5.10 for **9b**) suggest that the products **9** are *cis*-fused isomers, and consequently the intermediates **11** might be all-*cis*-diazonines, because all-*cis*-cyclononatetraene and its hetero analogues are known to undergo thermal isomerization to give the corresponding *cis*-fused bicyclic compounds such as **14**.[18,19]

On the other hand, the reaction of the 1*H*-1,2-diazepines (**15a**—**c**)[17] with DMAD (2.5 mol eq) under similar conditions at 55—60 °C for *ca.* 7 d resulted in the formation of the dimethyl phthalates (**16a**—**c**) and 1-ethoxycarbonyl-3,4-bismethoxycarbonylpyrazole (**17**) in 20—40% and 20—30% yields, respectively. When an equimolar amount of DMAD was used, the yields of the products **16** and **17** were extremely low and a large amount of the starting diazepines was recovered (*ca.* 50—60%).

This reaction may also involve the 1,2-diazonine intermediates **19** derived from the initially formed cycloadducts **18**, and the diazonines (**19**) might undergo intramolecular cyclization to give the 3a,7a-dihydroindazoles (**20**), by analogy with the case of the 1,3-diazepines (**8**). The dihydroindazoles (**20**) may further react with DMAD to afford the products **16** and **17** *via* the [4+2]π cycloadducts **21**. In addition, 3-methyl-1*H*-1,2-diazepines did not react with DMAD, even when heated for 2 weeks, suggesting that the 3-methyl group blocks the initial cyclization to DMAD.

This mechanistic assumption was confirmed by the following facts. When the reaction of the 5-methyl-1*H*-1,2-diazepine (**15b**) with DMAD (1.1 mol eq) was carried out at 40 °C for 10 d, the key dihydroindazole **20b** could be isolated in *ca.* 5% yield, together with **16b** (6%) and the starting **15b** (50%). The intermediate **20b** thus isolated was further treated with DMAD at 60 °C for 20 h to give a 1 : 1 mixture of **16b** and **17** in *ca.* 90% yield. This result indicates that the formation of **16** and **17** from **20** is much faster than that of **20** from the diazepines (**15**), and thus the latter is the rate-determining step for the overall reaction.

The difference in product pattern between 1,3-diazepines (**8**) and 1,2-diazepines (**15**) may depend on the different position of one of the two nitrogen atoms in the bicyclic compounds (**9** and **20**). The dihydroindazoles (**20**) having a diene function readily undergo Diels-Alder

reaction, whereas the dihydropyrrolopyridines (**9**) having an aza-diene function appear to be unreactive with the dienophile; indeed, the compounds **9** isolated did not react with DMAD even when heated at 60 °C for 3 d.

In conclusion, the present results are the first examples of the reaction of heteroepines with acetylenes, and the present reaction clearly involves $[2+2]\pi$ cycloadduct and diazonine intermediates.

Experimental

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. Infrared (IR) spectra were determined with a Hitachi 270-30 spectrometer and MS were measured with a JEOL DX-300 instrument. ^{1}H-NMR spectra were recorded on a JEOL JNM-MH100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard, and spectral assignments were confirmed by spin-decoupling experiments. ^{13}C-NMR spectra were recorded on a JEOL FX-100 spectrometer in $CDCl_3$.

Starting Diazepines——The 1*H*-1,3-diazepines (**8a—c**)[13] and the 1*H*-1,2-diazepines (**15a—d**)[17] were prepared by the reported methods.

Reaction of the 1*H*-1,3-Diazepines (8a—c) with DMAD: Formation of 3,3a-Bismethoxycarbonyl-3a,7a-dihydropyrrolo[3,2-*b*]pyridines (9a—c)——General Procedure: A solution of **8** (3—5 g) and DMAD (1.5 mol eq) in dry benzene (20—30 ml) was heated at 60—70 °C with stirring under an argon atmosphere. The reaction was followed in terms of the disappearance of the spot of the starting **8** on silica gel thin-layer chromatography, and was complete in 6—7 d. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel using hexane–ether (1 : 1) as an eluent to give **9**, which was recrystallized from benzene–isopropyl ether.

1-Ethoxycarbonyl-3,3a-bismethoxycarbonyl-6,7a-dimethyl-3a,7a-dihydropyrrolo[3,2-*b*]pyridine (**9a**): 66% yield, mp 145.5—146.5 °C, pale yellow prisms. IR (KBr): 1744 and 1710 (C=O), 1624 (C=N) cm^{-1}. ^{1}H-NMR δ: 1.36 and 4.28 (3H, t, and 2H, q, CO_2Et), 1.96 (3H, dd, 6-Me), 3.76 and 3.82 (each 3H, s, CO_2Me), 4.95 (1H, dd, 7a-H), 6.30 (1H, m, 7-H), 7.70 (1H, s, 2-H), 7.81 (1H, d, 5-H), $J_{5,7}=2$, $J_{6\text{-Me},7}=1.5$, $J_{6\text{-Me},7a}=1$, $J_{7,7a}=5$ Hz. ^{13}C-NMR δ: 14.5, 63.0, and 151.4 (q, t, and s, CO_2Et), 19.3 (q, 6-Me), 51.7 and 53.4 (each q, $CO_2\underline{Me}$), 58.4 (d, 7a-C), 71.6 (s, 3a-C), 115.6 (s, 3-C), 121.6 (d, 7-C), 128.7 (s, 6-C), 142.6 (d, 2-C), 157.4 (d, 5-C), 163.9 and 171.9 (each s, $\underline{C}O_2Me$). High-resolution MS *m/z*: M^+ Calcd for $C_{15}H_{18}N_2O_6$: 322.1165. Found: 322.1165.

1-Ethoxycarbonyl-3,3a-bismethoxycarbonyl-6-methyl-3a,7a-dihydropyrrolo[3,2-*b*]pyridine (**9b**): 81% yield, mp 153—154 °C, pale yellow prisms. IR (KBr): 1742, 1724, and 1708 (C=O), 1628 (C=N) cm^{-1}. ^{1}H-NMR δ: 1.35 and 4.26 (3H, t, and 2H, q, CO_2Et), 3.64 (3H, s, 6-OMe), 3.75 and 3.81 (each 3H, s, CO_2Me), 5.10 (1H, d, 7a-H), 5.43 (1H, m, 7-H), 7.70 (1H, s, 2-H), 7.75 (1H, d, 5-H), $J_{5,7}=3$, $J_{7,7a}=6$ Hz. ^{13}C-NMR δ: 14.5, 63.0, and 151.4 (q, t, and s, CO_2Et), 51.7 and 53.4 (each q, $CO_2\underline{Me}$), 54.8 (q, 6-OMe), 59.9 (d, 7a-C), 72.5 (s, 3a-C), 92.4 (d, 7-C), 115.0 (s, 3-C), 142.7 (d, 2-C), 148.7 (s, 6-C), 154.2 (d, 5-C), 163.9 and 171.5 (each s, $\underline{C}O_2Me$), High-resolution MS *m/z*: M^+ Calcd for $C_{15}H_{18}N_2O_7$: 338.1114. Found: 338.1117.

1-Ethoxycarbonyl-6-methoxy-3,3a-bismethoxycarbonyl-3a,7a-dihydropyrrolo[3,2-*b*]pyridine (**9c**): 52% yield, mp 115—116 °C, pale yellow prisms. IR (KBr): 1750, 1730, and 1714 (C=O), 1632 (C=N) cm^{-1}. ^{1}H-NMR δ: 1.32 and 4.23 (3H, t, and 2H, q, CO_2Et), 1.49 (3H, s, 7a-Me), 1.93 (3H, d, 6-Me), 3.75 and 3.77 (each 3H, s, CO_2Me), 6.21 (1H, m, 7-H), 7.73 (1H, s, 2-H), 7.81 (1H, d, 5-H), $J_{5,7}=1.9$, $J_{6\text{-Me},7}=2$ Hz. ^{13}C-NMR δ: 14.4, 62.6, and 150.3 (q, t, and s, CO_2Et), 19.0 (q, 6-Me), 23.0 (q, 7a-Me), 51.5 and 52.6 (each q, $CO_2\underline{Me}$), 63.1 (s, 7a-C), 76.8 (s, 3a-C), 114.0 (s, 3-C), 126.8 (s, 6-C), 127.1 (d, 7-C), 142.4 (d, 2-C), 157.1 (d, 5-C), 164.3 and 167.8 (each s, $\underline{C}O_2Me$). High-resolution MS *m/z*: M^+ Calcd for $C_{16}H_{20}N_2O_6$: 336.1319. Found: 336.1317.

Reaction of the 1*H*-1,2-Diazepines (15a—c) with DMAD——General Procedure: A solution of **15** (*ca.* 1 g) and DMAD (2.5 mol eq) in dry benzene (10 ml) was heated at 55—60 °C with stirring under an argon atmosphere for 7 d and worked up as described for the reaction of **8** to give the dimethyl phthalate (**16**) and 1-ethoxycarbonyl-3,4-bismethoxycarbonylpyrazole (**17**), successively.

Dimethyl phthalate (**16a**): 47% yield. This compound was identical with an authentic sample of dimethyl phthalate.

Dimethyl 4-methylphthalate (**16b**): 22% yield, colorless oil. IR ($CHCl_3$): 1728 (C=O) cm^{-1}. ^{1}H-NMR δ: 2.36 (3H, s, 4-Me), 3.86 (6H, s, 2 × CO_2Me), 7.27 (1H, d, $J=8$ Hz, 5-H), 7.43 (1H, s, 3-H), 7.64 (1H, d, $J=8$ Hz, 6-H). High-resolution MS *m/z*: M^+ Calcd for $C_{11}H_{12}O_4$: 208.0736. Found: 208.0735.

Dimethyl 3,5-dimethylphthalate (**16c**): 23% yield, colorless oil. IR ($CHCl_3$): 1734 (C=O) cm^{-1}. ^{1}H-NMR δ: 2.31 and 2.35 (each 3H, s, 3- and 5-Me), 3.87 and 3.93 (each 3H, s, CO_2Me), 7.22 (1H, s, 4-H), 7.64 (1H, s, 6-H). High-resolution MS *m/z*: M^+ Calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.0889.

1-Ethoxycarbonyl-3,4-bismethoxycarbonylpyrazole (**17**): 25% yield from 1*H*-1,2-diazepine (**15a**), 16% yield from 5-methyl-1*H*-1,2-diazepine (**15b**), and 22% yield from 4,6-dimethyl-1*H*-1,2-diazepine (**15c**), mp 67—68 °C, colorless plates (from isopropyl ether). IR (KBr): 1786, 1752, and 1732 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.40 and 4.54 (3H,

t, and 2H, q, CO_2Et), 3.81 and 3.92 (each 3H, s, CO_2Me), 8.56 (1H, s, 5-H). High-resolution MS *m/z*: M^+ Calcd for $C_{10}H_{12}N_2O_6$: 256.0695. Found: 256.0698.

Isolation of the Intermediate 20b——A solution of **15b** (805 mg) and DMAD (700 mg, 1.1 mol eq) in dry benzene (10 ml) was heated at 40 °C with stirring under an argon atmosphere for 10 d and worked up as described for the reaction of **8** to give **16b** (59 mg, 6.3% yield), **20b** (70 mg, 4.9% yield), and the starting **15b** (405 mg, 50% yield) successively.

1-Ethoxycarbonyl-6-methyl-3,3a-bismethoxycarbonyl-3a,7a-dihydroindazole (**20b**): mp 98—99 °C, colorless prisms (from isopropyl ether). IR (KBr): 1740 and 1708 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.36 and 4.36 (3H, t, and 2H, q, CO_2Et), 1.80 (3H, s, 6-Me), 3.77 and 3.85 (each 3H, s, CO_2Me), 5.30 (1H, m, 7a-H), 5.84 (1H, m, 7-H), 5.94 (1H, d, 5-H), 6.12 (1H, d, 4-H), $J_{4,5}$ = 9 Hz. ^{13}C-NMR δ: 14.6, 63.3 and 152.4 (q, t, and s, CO_2Et), 21.7 (q, 6-Me), 52.8 and 53.5 (each q, $CO_2\underline{Me}$), 59.0 (s, 3a-C), 64.3 (d, 7a-C), 113.9 (d, 7-C), 119.5 (d, 5-C), 127.7 (d, 4-C), 132.5 (s, 6-C), 144.9 (s, 3-C), 161.6 and 171.1 (each s, $\underline{C}O_2Me$). High-resolution MS *m/z*: M^+ Calcd for $C_{15}H_{18}N_2O_6$: 322.1165. Found: 322.1169.

Reaction of 20b with DMAD——A solution of **20b** (30 mg) and DMAD (20 mg, 1.5 mol eq) in dry benzene (3 ml) was heated at 55 °C for 20 h and worked up as described for the reaction of **8** with DMAD to give **16b** (17 mg, 88% yield) and **17** (20 mg, 83% yield) successively.

References and Notes

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