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Cycloaddition Reactions of Azepines and Diazepines with Conjugated Double Bonds Possessing Electron-Withdrawing Groups

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Cycloadditions of 1-ethoxycarbonyl-1*H*-azepine with 5-methoxycarbonyl-2-pyrone gave [4+2] and [4+6] type adducts and a benzazepine derivative, while the reaction of the azepine derivative with 3-methoxycarbonyl-2-pyrone afforded only a [4+2] type adduct. Similarly, an addition of 1-ethoxycarbonyl-1*H*-1,2-diazepine with 5-methoxycarbonyl-2-pyrone gave a benzodiazepine derivative. Reactions of the azepine and the diazepine derivatives with tetrachlorocyclopentadienone dimethyl acetal afforded [4+2] type adducts.

Azepine and diazepine derivatives are known to be nonplaner compounds and to behave as olefinic compounds rather than aromatic materials.[1-4] The addition reactions of azepines and diazepines have received considerable attention from the viewpoint of a synthetic utility and an elucidation of the chemical reactivity. Azepines and diazepines are known to give [4+2] type adducts when allowed to react with dienophiles and afford [4+2] and [4+6] type adducts in reactions with enophiles.[2]

As a part of our research effort concerning the addition reactions of the heterocyclic compounds,[3] we have studied the cycloaddition reactions of azepine and diazepine derivatives with 2-pyrone derivatives and cyclopentadiene derivatives. We wish to report the results of these reactions.

Results

1-Ethoxycarbonyl-1*H*-azepine (**1a**) was allowed to react with 5-methoxycarbonyl-2-pyrone (**3**) in benzene at 80 °C for 57 h to give adducts **6** and **7** in yields of 25 and 20%, respectively. The same reaction under more drastic conditions (in toluene, 140 °C for 10 d) afforded the benzazepine derivative **8** and the [6+6] type dimer **9**[4] of **1a** in 5 and 36% yields, respectively. The reaction of 1-methoxycarbonyl-1*H*-azepine (**1b**) with 3-methoxycarbonyl-2-pyrone (**4**) at 80 °C for 68 h afforded adduct **10** and the [6+4] type dimer **11**[5] of **1b** in yields of 5 and 11%, respectively. The reaction of 1-ethoxycarbonyl-1*H*-1,2-diazepine (**2**) and **3** in benzene at 80 °C for 10 d gave no adduct but the reaction at 110 °C in toluene for 10 d gave a benzodiazepine derivative **12** in 12% yield. The reaction of **2** with **4** gave no adduct. Under conditions analogous to the above, **1** and **2** were allowed to react with 2-pyrone (**5**), but no adduct was obtained.

Upon heating in xylene at 140 °C for 50 min adduct **6** gave the benzazepine derivative **8** in 5% yield, which was obtained in better yield (17%) by a reaction of **6** with o-chloranil in anisole at 140 °C for 45 min. After heating, adduct 7 underwent a retro-Diels-Alder reaction to yield **1a** and **3**. The adduct **10** gave a resinous material upon heating, which was not further characterized.

The reaction of **1a** with tetrachlorocyclopentadienone dimethyl acetal (**13**) at 100 °C for 5 h afforded adduct **14** as crystalline material of mp 68—70 °C in yield of 48%.[5] The diazepine derivative **2** was also allowed to react with **13** at 100 °C for 15 h to give the adduct **15** in 39% yield. Under conditions analogous to the above **1** and **2** were allowed to react with cyclopentadienone diethyl acetal, however, no adduct was obtained. All attempts to hydrolyze the acetal components of **14** and **15** to the corresponding ketones and to substitute the chlorine atoms with hydrogen atoms were unsuccessful.

Elemental analyses and/or the molecular ion peaks in the mass spectra revealed that products **6**, **7**, and **10** are the 1 : 1 adducts of **1a** and **3**, and **1b** and **4**, respectively. The existence of lactone rings in these products is shown by the IR spectra (**6**; 1780, **7**; 1760, and **10**; 1775 cm^{-1}). The structures of the [4+2] type adducts **6** and **10** were determined on the basis of NMR spectral properties, employing the double- and triple-resonance technique. The small coupling constants between the bridgehead protons (**6**; $J_{1,2}$=3.0, $J_{2,3}$=$J_{7,8}$=4.3, and $J_{8,9}$=2.3 Hz, **10**; $J_{1,2}$=2.2 and $J_{2,3}$=$J_{7,8}$=4.0 Hz) indicate the endo structures of **6** and **10**.[6] These structures were further substantiated by the similarity of their NMR spectra to those of the [4+2] type adduct **14**.[5]

The IR absorption due to the urethane group of **7** appears at 1705 cm^{-1}, indicating that this urethane group is not conjugated with any unsaturated group. The [6+6] type dimer **9** also shows an absorption due to the urethane group at almost the same wave length (1700 cm^{-1}) in its IR spectrum.[4] The structure of **7** was determined mainly on the basis of NMR spectral properties and was confirmed by a comparison of its NMR spectrum to that of an analogous compound **16**.[7]

The signals due to the bridgehead protons, H_2 and H_7 (5.06—5.43 ppm) of **7** were observed at rather low field. The same tendency was observed with the [6+6] type dimer **9** (4.95 ppm)[4] substantiating the structure of 7. Each signal due to H_1, H_8, and the protons of ethoxycarbonyl group appears as a pair of signals at a slightly different chemical shift in the NMR spectrum at room temperature. At 70 °C, these three pairs coalesced to three independent signals. This phenom-

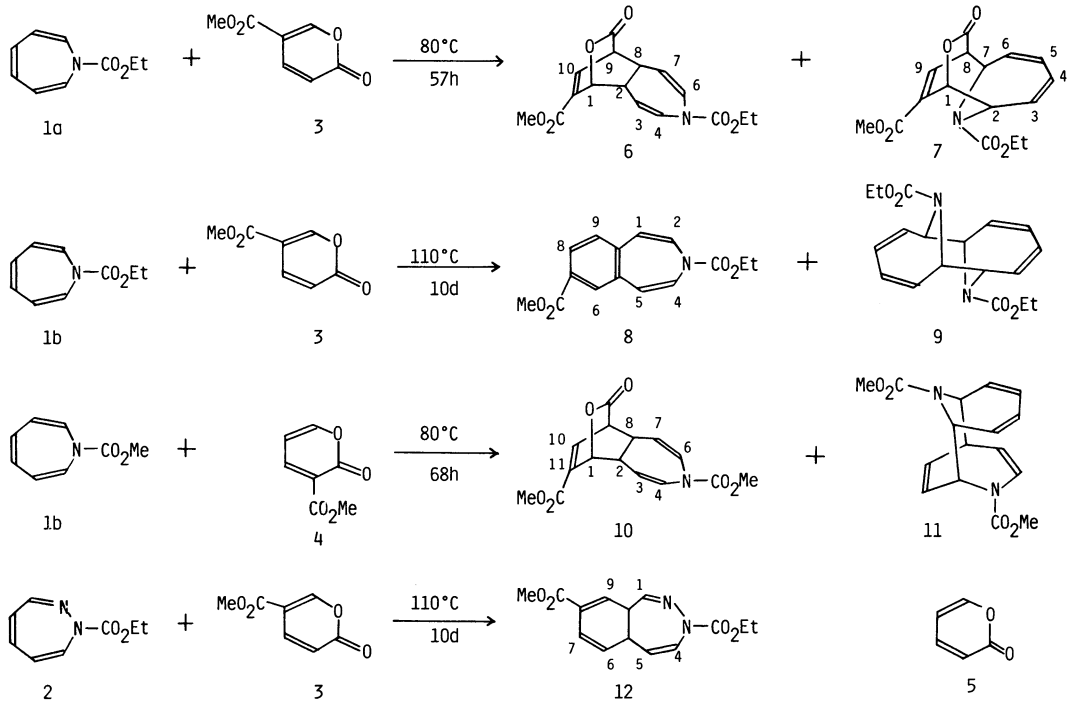


Fig. 1

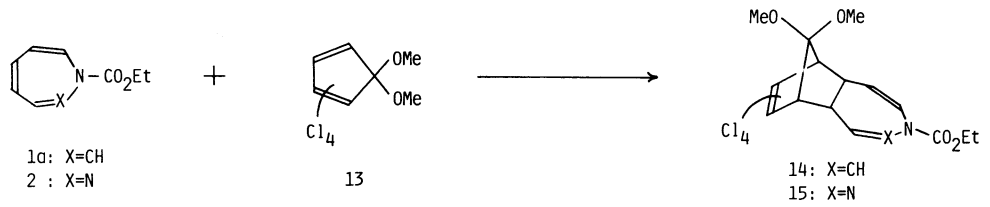


Fig. 2.

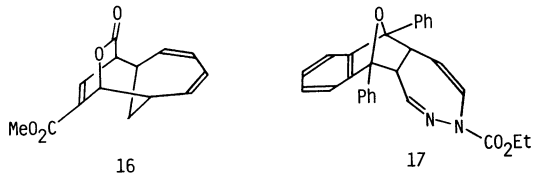


Fig. 3.

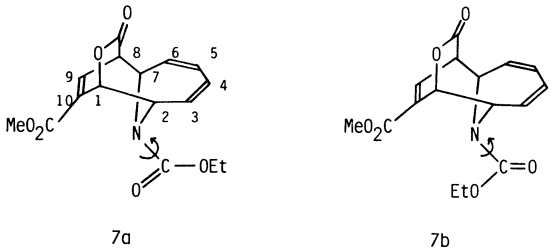


Fig. 4.

enon can be explained in terms of the existence of two rotamers (**7a** and **7b**) resulting from the rotation of the ethoxycarbonyl group as shown in Fig. 4.[3b,3d,8]

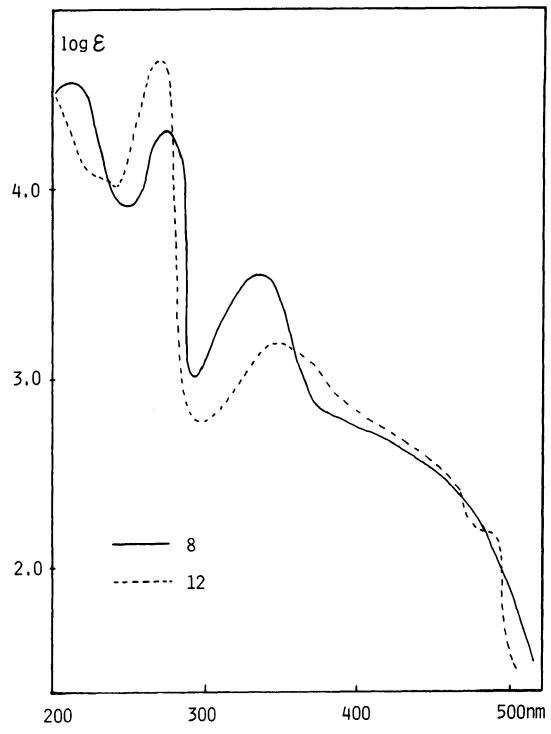
Elemental analyses and the molecular-ion peaks in the mass spectra indicate that **8** and **12** are the products of decarboxylations of the 1:1 adducts of **3** with **1a** and **2**, respectively. The UV spectra reveal that these products are the azepine and the diazepine derivatives.[9] The structure of **8** was determined on the basis of the NMR spectrum as well as the independent synthesis of **8** by the thermolysis of **6**. The NMR signals due to the protons on the seven-membered ring appear as two pairs of signals with slight differencies in chemical shift, showing **8** to be an almost symmetric compound.

In the NMR spectrum of **12**, the chemical shifts of H_1 (7.31 ppm), H_4 (6.47 ppm), and H_5 (5.55 ppm) closely resemble those of the corresponding protons (7.31, 6.22, and 5.67 ppm) of 2, suggesting the presence of the 3*H*-2,3-benzodiazepine skeleton. The position of the methoxycarbonyl group on the benzene ring was determined by the appearance of the NOE between H_5 and H_6, and H_1 and H_9 with 15 and 17%, respectively.

The structure of **14** was confirmed by a comparison of the physical properties with values found in the literature.[5] The Structure of **15** was elucidated on the basis of its NMR spectrum and was confirmed by a comparison of its NMR spectrum to that of an analogous compound **17**.[3]

Discussion

Though the yields of the products mentioned above



UV Spectra of 8 and 12 in Cyclohexane
Fig. 5.

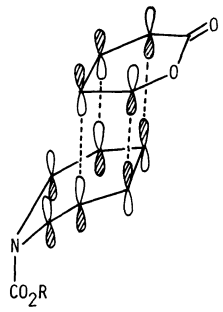


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Fig. 6.

are not high, it is significant that 2-pyrone derivatives reacted with azepine and diazepine derivatives since it has been previously reported by Anastassiou *et al.* that 2-pyrone is inert toward heterocyclic compounds such as **1** and **2**.[10] The experimental results obtained in our laboratory seem to suggest that the introduction of electron-withdrawing groups such as the methoxycarbonyl group increased the reactivity of the 2-pyrones with azepine and diazepine derivatives. This phenomenon can be rationalized by visualizing the reaction as an inverse electron-demanding Diels-Alder reaction in which the HOMO of the heterocyclic compounds interact with the LUMO of the 2-pyrones.[2c,11] In such cases, a lowering of the LUMO of the 2-pyrones or an elevation of the HOMO of the heterocyclic compounds are thought to promote the interaction of the transition state which allows the chemical reaction to proceed. Thus, the introduction of a methoxycarbouyl group,

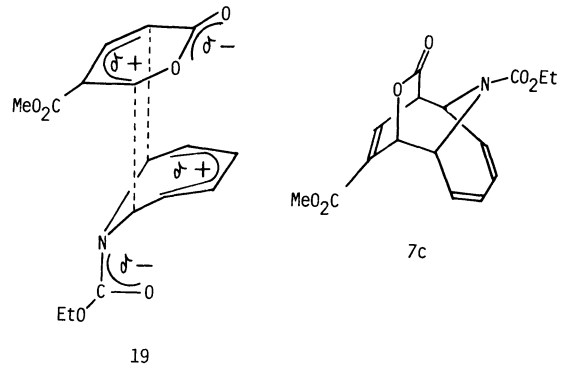

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Fig. 7.

which is known to lower the orbital energies of the system,[2c,12] is thought to be responsible for the success of the reaction.

The steric repulsion between the heterocyclic compounds and the methoxycarbonyl group at the reaction site of **4** may explain the lower yield of the reaction with **4** than with **3**. The endo mode of the reactions to form **6** and **10** is explained by the secondary orbital interaction in the transition state of **18**.

The preferential formation of **7**, and not **7c**, can be rationalized by the dipole-dipole interaction between the reactants in the transition state **19** as shown in Fig. 7.[2c,3c,13] The formation of **8** is a result of the decarboxylation reaction of **6** as shown by the experiment mentioned above. The benzodiazepine derivative **12** is also thought to be obtained through the decarboxylation reaction of the 1:1 adduct of **2** and **3**, corresponding to **6**.

The inactivity of cyclopentadienone diethyl acetal and the activity of **13** in the reactions with **1** and **2** can be explained by the following argument. Cyclopentadienone diethyl acetal contains an electron-rich conjugated double bond which is not suitable as an enophile in the inverse electron-demanding Diels-Alder reaction previously described.[2c] In fact, **13**, has an electron-defficient conjugated double bond substituted by chlorine atoms.

Experimental

All the reactions were carried out under a nitrogen stream. All melting and boiling points were uncorrected. NMR spectra were measured with a Varian HA-100 or Hitachi R-20B spectrometer with deuteriochloroform or carbon tetrachloride as solvents and tetramethylsilane as an internal standard. The IR spectra were measured in carbon tetrachloride solutions or potassium bromide disks and the UV spectra were measured in cyclohexane solutions. The mass spectra were measured with a Hitachi RMU 6D spectrometer at 70eV.

Reaction of ***1a*** *with 3 at 80°C.* A mixture of **1a** (1.52g, 9.2mmol) and **3** (7.10g, 46mmol) in benzene (20ml) was kept at 80°C for 57h. After evaporation of the solvent on a rotary evaporator, colorless crystals of recovered **3** were collected by filtration (4.67g, 66%). The filtrate was chromatographed on silica gel to give a red oil **1a** (120mg, 8%, pet ether–benzene 4:1 as an eluent), crystals **3** (1.19g, 17%, pet ether–benzene

1:1 as an eluent), a colorless viscous oil **6** (820mg, 25%, pet ether–benzene 1:2 as an eluent), and colorless crystals **7** (610 mg, 20%, ether as an eluent). The oil **6** and the crystals **7** were further purified by repeated chromatography on silica gel using benzene as an eluent and recrystallization from ethanol, respectively. **6**: Found: C, 60.19; H, 5.43; N, 4.14%. Calcd for $C_{16}H_{17}O_6N$: C, 60.18; H, 5.37; N, 4.39%. Ms *m/z* (rel intensity) 319 (M^+, 1), 165 (100), 127 (20), and 92 (54). IR (oil) 3050, 2950, 1780, and 1735 cm^{-1}. NMR (CCl_4) δ=1.31 (t, CH_3, J=7.0 Hz), 3.11 (ddd, H_8), 3.30 (ddd, H_2), 3.62 (dd, H_9), 3.70 (s, OCH_3), 4.20 (q, CH_2, J=7.0 Hz), 4.77 (dd, H_3 or H_7), 4.82 (dd, H_7 or H_3), 5.46 (dd, H_1), 6.81 (d, 2H, H_4 and H_6), and 7.10 (dd, H_{10}). Coupling constants in Hz, $J_{1,2}$=3.0, $J_{2,8}$=8.1, $J_{2,3}$=$J_{7,8}$=4.3, $J_{3,4}$=$J_{6,7}$=11.3, $J_{8,9}$=2.3, $J_{9,10}$=6.0, and $J_{10,1}$=2.3. **7**: mp 97.5—100 °C. Found: C, 60.14; H, 5.29; N, 4.11%. Calcd for $C_{16}H_{17}O_6N$: C, 60.18; H, 5.37; N, 4.39%. MS *m/z* (rel intensity) 319 (M^+, 1), 165 (100), 137 (14), and 92 (46). IR (KBr) 3030, 2950, 1760, and 1705 cm^{-1}. NMR ($CDCl_3$) δ=1.20 and 1.28 (t, CH_3, J=7.0 Hz), 3.79 and 3.82 (dd, H_8), 3.83 (s, OCH_3), 4.06 (q, CH_2, J=7.0 Hz), 5.06—5.43 (m, 2H, H_2 and H_7), 5.54 and 5.62 (dd, H_1), 6.07 (bs, 4H, H_3–H_6), and 7.23 (dd, H_9). Coupling constants in Hz, $J_{1,2}$=4.8, $J_{1,9}$=1.4, $J_{2,3}$=4.7, $J_{7,8}$=4.0, and $J_{8,9}$=6.9.

Reaction of ***1a*** *with* ***3*** *at 110 °C.* A mixture of **1a** (4.13g, 25mmol) and 3 (4.50g, 29mmol) in toluene (50ml) were kept at 110 °C for 10d. After evaporation of the solvent on a rotary evaporator, the residue was chromatographed on silica gel to afford a red oil of recovered **1a** (420mg, 10%, pet ether–ether 1:1 as an eluent), red crystals **8** (300mg, 5%, pet ether–ether 4:6 as an eluent), and colorless crystals **9** (1.46g, 35%, pet ether–ether 3:7 as an eluent). Recrystallization of **8** from ethanol gave pure crystals, mp 82—84 °C. Found: C, 65.61; H, 5.33; N, 5.10%. Calcd for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.33; N, 5.13%. MS *m/z* (rel intensity) 273 (M^+, 83), 201 (39), 200 (100), 173 (22), 142 (16), and 115 (9). IR (KBr) 3030, 2960, and 1720 cm^{-1}. NMR (CCl_4) δ=1.30 (t, CH_3, J=7.0 Hz), 3.78 (s, OCH_3), 4.17 (q, CH_2, J=7.0 Hz), 5.14 (d, H_1 or H_5), 5.19 (H_5 or H_1), 6.09 (d, H_2 or H_4), 6.15 (d, H_4 or H_2), 6.57 (d, H_9), 7.20 (d, H_6), and 7.48 (dd, H_8). Coupling constants in Hz, $J_{1,2}$=$J_{4,5}$=10.3, $J_{6,8}$=1.8, and $J_{8,9}$=8.0.

Reaction of ***1b*** *with* ***4***. A mixture of **1b** (900mg, 6.0 mmol) and **4** (4.62g, 30.0mmol) in benzene (10ml) was kept at 80 °C for 68h. After evaporation of the solvent on a rotary evaporator, the residue was chromatographed on silica gel to yield a red oil of recovered **1b** (300mg, 33%, benzene–ether 19:1 as an eluent) and a colorless resinous oil (220mg, benzene–ether 9:1 as an eluent), which was thin-layer chromatographed on alumina using pet ether–ether 1:4 as a developing solvent to give colorless crystals **11** (100 mg, 11%, R_f=0.7) and a colorless resinous oil **10** (95mg, 5%, R_f=0.6). The oil **10** was unstable toward distillation (0.05 Torr, bath temperature 135 °C) and was purified by repeated thin-layer chromatography on alumina using pet ether–ether 1:4 as a developing solvent; however, an analytically pure sample could not be obtained. MS *m/z* (rel intensity) 305 (M^+, 1), 151 (100), 123 (6), and 92 (46). IR (oil) 3030, 2980, 1775, and 1740 cm^{-1}. NMR (CCl_4) δ=3.33 (m, 2H, H_2 and H_8), 3.80 (s, OCH_3), 3.90 (s. OCH_3), 4.67 (m, 2H, H_3 and H_7), 5.00 (ddd, H_1), 6.36 (dd, H_{11}), 6.70 (dd, H_{10}), and 6.82 (d, H_4 and H_6). Coupling constatnts in Hz, $J_{1,2}$=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, and $J_{10,11}$=8.0.

Reaction of ***2*** *with* ***3***. A mixture of 2 (245mg, 1.5mmol) and **3** (350mg, 2.3mmol) in toluene (10ml) was kept at 110 °C for 10d. After evaporation of the solvent on a rotary evaporator, the residue was chromatographed on silica gel to afford orange crystals **12** (48mg, 12%, pet ether–ether 1:2 as an eluent), which were purified by recrystallization from ethanol. However, an analytically pure sample was not obtained because of a tendency to decompose to a resinous material. **12**: MS *m/z* (rel intensity) 274 (M^+, 100), 243 (12), 215 (34), 202 (96), 174 (28), 144 (42), and 116 (26). IR (KBr), 3030, 2960, 1730, and 1710 cm^{-1}. NMR (CCl_4) δ=1.34 (t, CH_3, J=7.0 Hz), 3.84 (s, OCH_3), 4.22 (q, CH_2), 5.55 (d, H_5), 6.47 (d, H_4), 6.86 (d, H_6), 7.31 (s, H_1), 7.61 (d, H_9), and 7.77 (dd, H_7). Coupling constants in Hz, $J_{4,5}$=9.0, $J_{6,7}$=8.0, $J_{7,9}$=1.8.

Thermal Reaction of ***6***. A solution of **6** (55mg, 0.17mmol) in xylene (2ml) was kept at 140 °C for 50min. After evaporation of the solvent on a rotary evaporator, the residue was thin-layer chromatographed on silica gel using pet ether–ether 1:1 as a developing solvent to give **8** (2mg, 4%, R_f=0.7) and the recovered **6** (27mg, 49%, R_f=0.5).

Reaction of ***6*** *with o-Chloranil.* A mixture of **6** (81mg, 0.25mmol) and *o*-chloranil (69mg, 0.28mmol) in anisole (5ml) was kept at 140 °C for 45min. The reaction mixture was chromatographed on alumina to yield an oil (150mg) using ether as an eluent. The oil was thin-layer chromatographed on silica gel using pet ether–ether 1:1 as a developing solvent to give **8** (12mg, 17%, R_f=0.7).

Reaction of ***2*** *with* ***13***. A mixture of **2** (1.00g, 6.0mmol) and **13** (3.20g, 12.1mmol) in benzene (3ml) was kept at 100 °C for 15h in a sealed ampoule. The reaction mixture was chromatographed on silica gel to give recovered **13** (2.46g, 77%, benzene as an eluent) and colorless crystals **15** (1.03g, 39%, benzene–ether 1:1 as an eluent), which were recrystallized from ether to give pure **15**; mp 77—77.5 °C. Found: C, 41.84; H, 3.64; N, 6.38%. Calcd for $C_{15}H_{16}O_4N_2Cl_4$: C, 41.88; H, 3.75; N, 6.51%. MS *m/z* (rel intensity) 430 (M^+, 1) and 165 (100). IR (KBr) 3030, 2970, and 1720 cm^{-1}. NMR ($CDCl_3$) δ=1.35 (t, CH_3, J=7.0 Hz), 3.48 (m, 2H, H_2 and H_8), 3.53 (s, OCH_3), 3.60 (s, OCH_3), 4.23 (q, CH_2, J=7.0 Hz), 4.95 (m, H_7), 6.93 (d, H_3), and 7.15 (d, H_6). Coupling constants, $J_{2,3}$=1.5, $J_{6,7}$=10.0, and $J_{7,8}$=2.5.

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