A SYNTHESIS OF A NEW TYPE HETEROCYCLIC COMPOUND USING DIELS-ALDER CYCLOADDITION OF 2-METHYLENE–1,2-DIHYDROPYRIDINES[1]

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Abstract - Diels-Alder cycloaddition of 2-methylene-1,2-dihydropyridines having an active methylene group at the 1-position with *N*-phenylmaleimide gave isoquinuclidines, and cyclization of the adducts obtained afforded a new type of heterocyclic ring system, 2-azatricyclo[5.2.2.0^{2,6}]undecanes.

Isoquinuclidines prepared by Diels-Alder cycloaddition of 1-substituted 2(1*H*)-pyridones with dienophiles are interesting as possible intermediates[2] for iboga alkaloids. Therefore, we have developed a synthetic route toward this heterocyclic ring system having various substituents[3] by the cycloaddition. In the previous paper,[4] we reported a simple synthetic method leading to isoquinuclidines having a carbon side chain at the 3-position by the cycloaddition of 2-methylene-1,2-dihydropyridines with dienophiles such as maleic anhydride, maleimide, and *N*-phenylmaleimide (**5**), and the cycloaddition is the first example of 2-methylene-1,2-dihydropyridines acting as diene. In order to expand the synthetic utility of the above cycloaddition, we investigated the cycloaddition of 2-methylene-1,2-dihydropyridines (**1a-e**) having an active methylene group at the 1-position with dienophile (**5**), followed by the cyclization of the adducts (**6a-e**) obtained to give a new type of heterocyclic ring system, 2-azatricyclo[5.2.2.0^{2,6}]undecanes (**7a-e**), which share the nitrogen between pyrrole and isoquinuclidine rings. These compounds (**7a-e**) are expected to possess the interesting pharmacological activities[5] being similar as pyrrole and isoquinuclidine derivatives.

N-Acylmethyl-1,2-dihydropyridines (**1a,b**) were prepared according to Kröhnke's procedure,[6] and *N*-alkoxycarbonylmethyl-1,2-dihydropyridines (**1c-e**) were synthesized from 2-hydroxypyridine (**2**) as shown in Scheme 1. Reactions of **2** with methyl bromoacetate or ethyl bromoacetate in the

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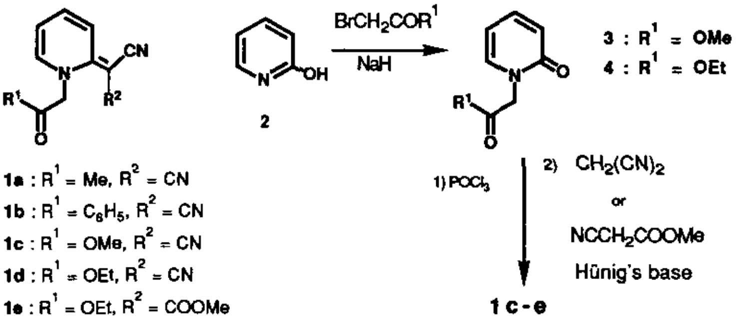
Dedicated to Dr. Masatomo Hamana on the occasion of his 75th birthday.

Scheme 1

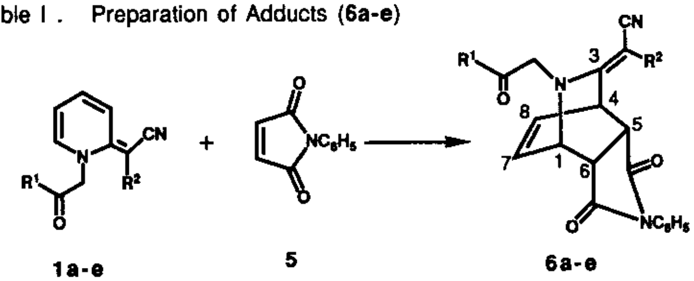


presence of sodium hydride gave the corresponding products, 1-methoxycarbonylmethyl-(**3**)[7] and 1-ethoxycarbonylmethyl-2(1*H*)-pyridones (**4**), in 68% and 64% yields, respectively. The pyridones (**3** and **4**) were heated with $POCl_3$ for 2 h at 70-80°C, and excess reagent was removed *in vacuo.* Treatments of the residues derived from **3** with malononitrile and from **4** with malononitrile or methyl cyanoacetate in THF at room temperature for 12 h in the presence of Hünig's base gave the corresponding 2-methylene-1,2-dihydropyridines (**1c-e**), in 56, 52 and 53% yields, respectively. The structures of **1c-e, 3** and **4** were confirmed by their ms, ir and ^{1}H-nmr spectral analyses. The geometorical configuration of **1e** can be deduced as *Z* form by nOesy.

A mixture of **1a-e** and **5** was heated at 95-100°C for 72 h, and the *endo*-adducts (**6a-e**) were stereoselectively obtained in moderate yields as shown in Table I.

Ms of the products (**6a-e**) suggested that the cycloaddition of **1a-e** with **5** gave the 1:1 cycloadducts, and the ir spectra of **6a-e** showed the corresponding carbonyl and cyano absorptions. ^{1}H-Nmr spectra of **6a-e** revealed characteristic signals of a isoquinuclidine system (H-1,4,5,6,7 and 8). The *endo* stereochemistry of **6a-e** followed from the coupling constant ($J_{1,6}$ = 4 Hz)[4] in their ^{1}H-nmr spectra. The geometorical configuration of the methoxycarbonyl group in the side chain of the adduct (**6e**) can be deduced to be *E* form with respect to the nitrogen at the 2-position from ^{1}H-nmr spectral data. Namely, although the proton at the 4-position of **6a-d** resonated at 4.53, 4.60, 4.57 and 4.53 ppm, respectively, that of **6e** resonated considerably at lower field (6.05 ppm) than those of **6a-d**, because of deshielding effect of ester carbonyl.

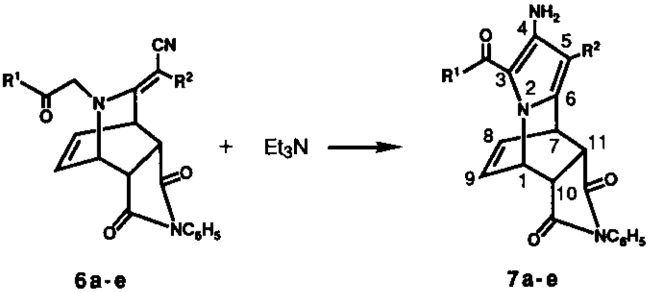
Table I . Preparation of Adducts (**6a-e**)



Compd	Adduct	Yield (%)
1a	**6a**	60
1b	**6b**	50
1c	**6c**	85
1d	**6d**	34
1e	**6e**	70

Next, we investigated the cyclization of the adducts (**6a-e**). A mixture of **6a-e** and Et_3N in DMF or 1-propanol was heated at 60-70°C for 10 h to give a new type of heterocyclic ring system, 2-azatricyclo-[5.2.2.$0^{2,6}$]undecanes (**7a-e**) in excellent yields as shown in Table II. The structures of the cycloproducts (**7a-e**) were confirmed by their spectral analyses (ms, ir, and ^{1}H-nmr). Ir spectra of **7a-e** showed two absorption bands due to the amino group in the 3500-3400 cm^{-1} region. Uv spectra of **7a-e** provided an absorption maximum in the 271-304 nm region,[8] suggesting pyrrole

Table II . Preparation of Cycloproducts (**7a-e**)



Adduct	Product	Yield (%)
6a	**7a**	90
6b	**7b**	87
6c	**7c**	80
6d	**7d**	84
6e	**7e**	80

ring having an electron-withdrawing group.

EXPERIMENTAL

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Ir spectra were measured with a Shimadzu IR-430 and PERKIN ELMER 1725X spectrophotometers. ^{1}H-Nmr spectra were recorded on JEOL JMN-PMX 60 and JEOL JMN-GSX 400 spectrometers with TMS as internal standard. The coupling patterns are indicated as follows: singlet=s, doublet=d, triplet=t, quartet = q, multiplet=m, and broad=br. Ms were taken on Hitachi RMG-6MG and JEOL-DX 303 spectrometers. Uv were recorded on a Hitachi 150-20 spectrophotometer.

2-Dicyanomethylene-1,2-dihydro-1-methoxycarbonylmethylpyridine (1c): To a suspension of 2-hydroxypyridine (1 g, 11 mmol) and NaH (0.32 g, 13 mmol) in THF (40 ml) was added methyl bromoacetate (2.5 g, 17 mmol) at 0°C under N_2, and the mixture was stirred for 36 h at room temperature. The reaction mixture was quenched with H_2O (50 ml) and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give **3**[7] (1.3 g, 68%), colorless oil. Ir (Nujol)cm^{-1}: 1745, 1660. ^{1}H-Nmr ($CDCl_3$) δ : 3.70 (3H, s), 4.67 (2H, s), 6.20 (1H, t, J = 7 Hz), 6.48 (1H, d, J = 9 Hz), 7.40 (1H, dd, J = 9, 7 Hz), 7.43 (1H, d, J = 7 Hz). A mixture of **3** (1.3 g, 7.4 mmol) and $POCl_3$ (10 ml, 110 mmol) was heated at 70-80°C for 1.5 h, and excess reagent was removed *in vacuo.* To a mixture of the resulting residue and malononitrile (0.72 g, 11 mmol) in THF (40 ml) was added Hünig's base (1.7 g, 13 mmol) at –50°C, and the mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with H_2O (60 ml), and then the resulting precipitate was filtered to give **1c** (0.9 g, 56%), yellow prisms (benzene), mp 141-143°C. High resolution ms m/z : Calcd for $C_{11}H_9N_3O_2$ (M^+) : 215.0694. Found : 215.0710. Ir (Nujol) cm^{-1} : 2230, 2200, 1760. ^{1}H-Nmr δ (DMSO-d_6) : 3.77 (3H, s), 5.34 (2H, s), 6.90 (1H, t, J = 7 Hz), 7.30 (1H, d, J = 8 Hz), 7.75 (1H, dd, J = 8, 7 Hz), 7.97 (1H, d, J = 7 Hz).

2-Dicyanomethylene- and (*Z*)-2-[Cyano(mthoxycarbonyl)methylene]-1,2-dihydro-1-ethoxycarbonylmethylpyridines (1d,e): To a suspension of 2-hydroxypyridine (2 g, 21 mmol) and NaH (0.32 g, 13 mmol) in THF (40 ml) was added ethyl bromoacetate (5.3 g, 32 mmol) at 0°C under N_2, and the mixture was heated for 7 h at 40-50°C. The reaction mixture was quenched with H_2O (60 ml), and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give **4** (3.5 g, 64%), mp 32-33°C, colorless prisms (isopropyl ether). High resolution ms m/z :

Calcd for $C_9H_{11}NO_3$ (M^+) : 181.0739. Found : 181.0747. Ir (Nujol)cm^{-1}: 1735, 1660. ^{1}H-Nmr ($CDCl_3$) δ : 1.22 (3H, t, J = 7 Hz), 4.17 (2H, q, J = 7 Hz), 4.68 (2H, s), 6.18 (1H, t, J = 7 Hz), 6.50 (1H, d, J = 9 Hz), 7.40 (1H, dd, J = 9, 7 Hz), 7.43 (1H, d, J = 7 Hz). A mixture of **4** (1.7 g, 9.2 mmol) and $POCl_3$ (20 ml, 220 mmol) was heated at 70-80°C for 1.5 h, and excess reagent was removed *in vacuo*. To a mixture of the resulting residue and malononitrile (0.9 g, 14 mmol) or methyl cyanoacetate (1.39 g, 14 mmol) in THF (50 ml) was added Hünig's base (2.2 g, 17 mmol) at –50°C, and the mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with H_2O (60 ml), and then the precipitate was filtered to give **1d** (1.1 g, 52%) or **1e** (1.2 g, 53%), respectively. **1d** : mp 169-172°C, yellow prisms (benzene). High resolution ms m/z : Calcd for $C_{11}H_9N_3O_2$ (M^+) : 229.0351. Found : 229.0870. Ir (Nujol) cm^{-1} : 2230, 2200, 1755. ^{1}H-Nmr (DMSO-d_6) δ : 1.25 (3H, t, J = 7 Hz), 4.23 (2H, q, J = 7 Hz), 5.32 (2H, s), 6.87 (1H, t, J = 7 Hz), 7.27 (1H, d, J = 8 Hz), 7.72 (1H, dd, J = 8, 7 Hz), 7.93 (1H, d, J = 7 Hz). **1e** : mp 99-100°C, yellow prisms (benzene). High resolution ms m/z : Calcd for $C_{13}H_{14}N_2O_4$ (M^+) : 262.0954. Found : 262.0924. Ir (KBr) cm^{-1} : 2175, 1751. ^{1}H-Nmr ($CDCl_3$) δ : 1.20 (3H, t, J = 7 Hz), 3.60 (3H, s), 4.17 (2H, q, J = 7 Hz), 5.22 (2H, s), 7.00 (1H, t, J = 7 Hz), 7.70 (1H, J = 9 Hz), 8.03 (1H, t, J = 7 Hz), 8.10 (1H, d, J = 7 Hz).

General Procedure for the Preparation of the Diels-Alder Adducts (6a-e). A mixture of **1a-e** (3 mmol) and **5** (10.4 g, 60 mmol) was heated at 95-100°C for 72 h. The reaction mixture was worked up in the following way to give the corresponding products (**6a-e**).

***N*-Phenyl-2-acetonyl-3-dicyanomethylene-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (6a)** : To the reaction mixture was added benzene. The precipitate was filtered to afford **6a** (60%), colorless prisms (AcOEt), mp 200-202°C. High resolution ms m/z : Calcd for $C_{21}H_{16}N_4O_3$ (M^+) : 372.1222. Found : 372.1166. Ir (Nujol) cm^{-1}: 2220, 2200, 1780, 1715 ; ^{1}H-nmr (DMSO-d_6) δ: 2.13 (3H, s), 3.42 (1H, dd, J = 3, 8 Hz), 3.82 (1H, dd, J = 4, 8 Hz), 4.53 (1H, m), 4.92 (2H, s), 5.05 (1H, m), 6.43-6.97 (2H, m), 7.02-7.73 (5H, m).

***N*-Phenyl-3-dicyanomethylene-2-phenacyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (6b)** : The reaction mixture was treated in the same manner as described for the preparation of **6a**, and gave **6b** (50%), colorless prisms (acetone), mp 218-221°C. High resolution ms m/z : Calcd for $C_{26}H_{18}N_4O_3$ (M^+) : 434.1380. Found : 434.1400. Ir (Nujol) cm^{-1}:

2220, 2200, 1780, 1710, 1690 ; ^{1}H-nmr (DMSO-d_6) δ: 3.57 (1H, dd, J = 3, 8 Hz), 3.97 (1H, dd, J = 4, 8 Hz), 4.60 (1H, m), 5.27(1H, m), 5.67 (2H, s), 6.53-7.00 (2H, m), 7.07-8.20 (10H, m).

***N*-Phenyl-3-dicyanomethylene-2-methoxycarbonylmethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (6c)** : The reaction mixture was chromatographed on a column of silica gel. The fraction eluted with $CHCl_3$ was evaporated to give **6c** (85%), colorless prisms (benzene), mp 124-125°C. High resolution ms m/z : Calcd for $C_{21}H_{16}N_4O_4$ (M^+) : 388.1172. Found : 388.1156. Ir (Nujol) cm^{-1}: 2220, 2200, 1770, 1745, 1720 ; ^{1}H-nmr (DMSO-d_6) δ: 3.45 (1H, dd, J = 3, 8 Hz), 3.73 (3H, s), 3.90 (1H, dd, J = 4, 8 Hz), 4.57 (1H, m), 4.83 (2H, s), 5.22(1H, m), 6.47-7.00 (2H, m), 7.05-7.67 (5H, m).

***N*-Phenyl-2-ethoxycarbonylmethyl-3-dicyanomethylene-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (6d)** : The reaction mixture was chromatographed on a column of silica gel. The fraction eluted with $CHCl_3$ was evaporated, and the residue was rechromatographed on a column of alumina. The fraction eluted with $CHCl_3$ was evaporated to give **6d** (34%), colorless prisms (AcOEt), mp 177-178°C. High resolution ms m/z : Calcd for $C_{22}H_{18}N_4O_4$ (M^+) : 402.1329. Found : 402.1396. Ir (Nujol) cm^{-1}: 2220, 2200, 1785, 1740, 1715 ; ^{1}H-nmr (DMSO-d_6) δ: 1.23 (3H, t, J = 7 Hz), 3.43 (1H, dd, J = 3, 8 Hz), 3.83 (1H, dd, J = 4, 8 Hz), 4.20 (2H, q, J = 7 Hz), 4.53 (1H, m), 4.80 (2H, s), 5.20(1H, m), 6.50-6.97 (2H, m), 7.03-7.67 (5H, m).

***N*-Phenyl-3-[(*Z*)-cyano((*E*)-methoxycarbonyl)]-2-ethoxycarbonylmethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (6e)** : The reaction mixture was chromatographed on a column of silica gel. The fraction eluted with $CHCl_3$ was evaporated to give **6e** (70%), colorless prisms (benzene), mp 196-197°C. High resolution ms m/z : Calcd for $C_{23}H_{21}N_3O_6$ (M^+) : 435.1430. Found : 435.1468. Ir (Nujol) cm^{-1}: 2198, 1783, 1737, 1714 ; ^{1}H-nmr (DMSO-d_6) δ: 1.22 (3H, t, J = 7 Hz), 3.27 (1H, dd, J = 3, 8 Hz), 3.68 (3H, s), 3.84 (1H, dd, J = 4, 8 Hz), 4.17 (2H, q, J = 7 Hz), 4.74 (1H, d, J = 19 Hz), 4.83 (1H, d, J = 19 Hz), 5.11 (1H, m), 6.05 (1H, m), 6.54 (1H, m), 6.80 (1H, m), 7.14-7.17 (2H, m), 7.40-7.50 (3H, m).

General Procedure for the Preparation of 2-Azatricyclo[5.2.2.0^{2,6}]undecanes (7a-e). A mixture of **6a-d** (1 mmol) in DMF (3 ml) or **6e** (0.44 g, 1 mmol) in 1-propanol (5 ml) and Et_3N (3 mmol) was heated at 60-70°C for 10 h. The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on a column of alumina. The fraction eluted with $CHCl_3$ was evaporated to give **7a-e**.

***N*-Phenyl-3-acetyl-4-amino-5-cyano-2-azatricyclo[5.2.2.$0^{2,6}$]undec-3,5,8-triene-10,11-*exo*-dicarboximide (7a)** : 90% yield, colorless prisms (benzene), mp 197-199°C. High resolution ms m/z : Calcd for $C_{21}H_{16}N_4O_3$ (M^+) : 372.1222. Found : 372.1209. Uv (λ_{max}, EtOH) nm (log ε) : 288 (4.13); ir (Nujol) cm^{-1}: 3480, 3400, 2230, 1775, 1715 ; ^{1}H-nmr (DMSO-d_6) δ: 2.40 (3H, s), 3.43 (1H, dd, J ≈ 3, 8 Hz), 3.68 (1H, dd, J = 4, 8 Hz), 4.63 (1H, m), 6.10 (2H, br s), 6.50 (1H, s), 6.65-6.98 (2H, m), 7.05-7.70 (5H, m).

***N*-Phenyl-4-amino-3-benzoyl-5-cyano-2-azatricyclo[5.2.2.$0^{2,6}$]undec-3,5,8-triene-10,11-*exo*-dicarboximide (7b)** : 87% yield, colorless prisms (benzene), mp 198-201°C. High resolution ms m/z : Calcd for $C_{26}H_{18}N_4O_3$ (M^+) : 434.1379. Found : 434.1392. Uv (λ_{max}, EtOH) nm (log ε) : 295 (3.88); ir (KBr) cm^{-1}: 3500, 3400, 2250, 1785, 1720 ; ^{1}H-nmr (DMSO-d_6) δ: 3.40-3.73 (2H, m), 4.67 (1H, m), 5.17(1H, m), 6.23 (2H, br s), 6.53-6.90 (2H, m), 6.96-7.77 (10H, m).

***N*-Phenyl-4-amino-5-cyano-3-methoxycarbonyl-2-azatricyclo[5.2.2.$0^{2,6}$]undec-3,5,8-triene-10,11-*exo*-dicarboximide (7c)** : 80% yield, colorless prisms (benzene), mp 206-208°C. High resolution ms m/z : Calcd for $C_{21}H_{16}N_4O_4$ (M^+) : 388.1172. Found : 388.1156. Uv (λ_{max}, EtOH) nm (log ε) : 271.6 (3.99); ir (Nujol) cm^{-1}: 3480, 3400, 2230, 1785, 1715, 1685 ; ^{1}H-nmr (DMSO-d_6) δ: 3.45 (1H, dd, J = 3, 8 Hz), 3.67 (1H, dd, J = 4, 8 Hz), 3.83 (3H, s), 4.67 (1H, m), 5.97 (2H, br s), 6.40 (1H, m), 6.70-7.02 (2H, m), 7.10-7.77 (5H, m).

***N*-Phenyl-4-amino-5-cyano-3-ethoxycarbonyl-2-azatricyclo[5.2.2.$0^{2,6}$]undec-3,5,8-triene-10,11-*exo*-dicarboximide (7d)** : 84% yield, colorless prisms (AcOEt), mp 174-176°C. High resolution ms m/z: Calcd for $C_{22}H_{18}N_4O_4$ (M^+) : 402.1329. Found : 402.1396. Uv (λ_{max}, EtOH) nm (log ε) : 272.6 (3.94); ir (Nujol) cm^{-1}: 3500, 3400, 2230, 1775, 1715, 1700, 1680 ; ^{1}H-nmr (DMSO-d_6) δ: 1.33 (3H, t, J = 7 Hz), 3.45 (1H, dd, J = 3, 8 Hz), 3.65 (1H, dd, J = 4, 8 Hz), 4.30 (2H, q, J = 7 Hz), 4.65 (1H, m), 5.83 (2H, br s), 6.38 (1H, m), 6.65-7.00 (2H, m), 7.07-7.67 (5H, m).

***N*-Phenyl-4-amino-3-ethoxycarbonyl-5-methoxycarbonyl-2-azatricyclo-[5.2.2.$0^{2,6}$]undec-3,5,8-triene-10,11-*exo*-dicarboximide (7e)** : 80% yield, colorless prisms (benzene), mp 195-197°C. High resolution ms m/z : Calcd for $C_{23}H_{21}N_3O_6$ (M^+): 435.1431. Found : 435.1361. Uv (λ_{max}, EtOH) nm (log ε) : 303.4 (4.33); ir (Nujol) cm-1: 3503, 3399, 1781, 1710, 1689 ; ^{1}H-nmr ($CDCl_3$) δ: 1.42 (3H, t, J = 7 Hz), 3.17 (1H, dd, J = 4, 8 Hz), 3.40 (1H, dd, J = 3, 8 Hz), 3.88 (3H, s), 4.37 (2H, q, J = 7 Hz), 5.27 (1H, m), 5.73 (2H, br s), 6.43-6.93 (3H, m), 7.03-7.63 (5H, m).

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