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A SYNTHESIS OF A NEW-TYPE HETEROCYCLIC COMPOUND BY USING DIELS-ALDER REACTION OF 2-METHYLENE-1,2-DIHYDROPYRIDINE DERIVATIVE

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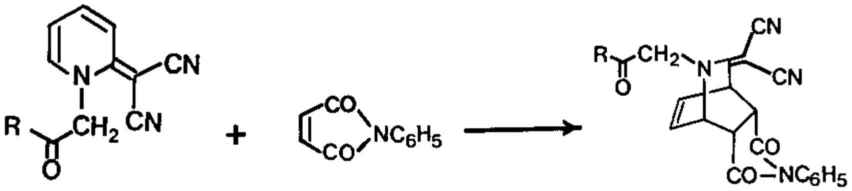
Abstract —— The Diels-Alder reaction of 2-dicyanomethylene-1,2-dihydropyridines having an active methylene group at the 1-position (Ia-d) with N-phenylmaleimide gave isoquinuclidine derivatives (IIa-d), which were treated with triethylamine to afford new-type heterocyclic ring system, 2-azatricyclo$[5.2.2.0^{2,6}]$undecane derivatives (IIIa-d).

Isoquinuclidine derivatives prepared by Diels-Alder reaction of 1-substituted 2(1H)-pyridones with dienophiles are interesting as possible intermediates[1] for iboga alkaloids. Therefore, we have developed a synthetic route toward this heterocyclic ring system having various substituents[2] by the reaction. Moreover, we recently reported a simple synthetic method[3] leading to isoquinuclidines having a carbon side-chain at the 3-position by the reaction of 2-methylene-1,2-dihydropyridine derivatives with dienophiles such as maleic anhydride, maleimide, and N-phenylmaleimide, and the reaction is the first example of 2-methylene-1,2-dihydropyridine derivative used as diene. In order to expand the synthetic utility of the above reaction, we investigated the reaction of 2-dicyanomethylene-1,2-dihydropyridines having an active methylene group at the 1-position (Ia-d) with N-phenylmaleimide, and cyclization of the adducts (IIa-d) obtained gave a new-type heterocyclic ring system, which shared the nitrogen between pyrrole and isoquinuclidine rings. These compounds (IIIa-d) are expected to possess the interesting pharmacological activities being similar as pyrrole and isoquinuclidine derivatives.

Dedicated to Professor Derek H. R. Barton on the occation of his 70th birthday.

Table I. Preparation of Adducts (IIa-d)

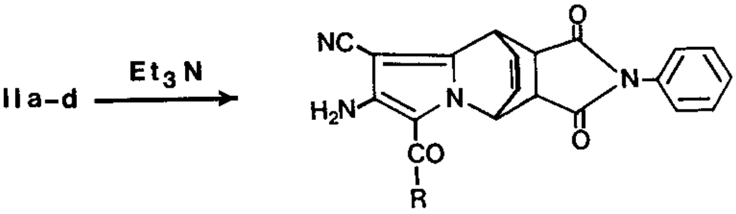


I

II

Compd.	R	Product	Yield (%)
Ia	Me	IIa	60
Ib	C_6H_5	IIb	50
Ic	OMe	IIc	85
Id	OEt	IId	34

Table II. Cyclization of Adducts (IIa-d)



III

Product	R	Yield (%)
IIIa	Me	90
IIIb	C_6H_5	87
IIIc	OMe	80
IIId	OEt	84

A mixture of Ia-d[4] and 20 equiv of *N*-phenylmaleimide was heated at 95-100°C for 72 h, and the *endo*-adducts (IIa-d)[4] were stereoselectively obtained in moderate yields as shown in Table I. The structures of IIa-d were confirmed by their spectral analyses. The configuration of two substituents at 5- and 6-positions in IIa-d was determined to be *endo* from the coupling constant value (J_{16} = 4 Hz) in their ^{1}H-nmr spectra, respectively. Next, cyclization of the adducts (IIa-d) was investigated as follows. A solution of IIa-d and 3 equiv of triethylamine in *N*,*N*-dimethylformamide was heated at 60-70°C for 10 h to give new-type heterocyclic ring system, 2-azatricyclo[$5.2.2.0^{2,6}$]undecane derivatives (IIIa-d)[4] in excellent yields as shown in Table II. The structures of IIIa-d were determined by their spectral analyses. The ir spectra of IIIa-d showed two absorption bands due to the amino group in the 3500-3400 cm^{-1} region, respectively.

Further investigation for the extension of these reactions is now in progress.

REFERENCES AND NOTES

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2. a) H. Tomisawa and H. Hongo, *Chem. Pharm. Bull.*, 1970, **18**, 925; b) H. Tomisawa, R. Fujita, K. Noguchi, and H. Hongo, *ibid*., 1970, **18**, 941; c) H. Hongo, *ibid*.,1972, **20**, 226; d) H.Tomisawa, H. Hongo, H. Kato, R. Fujita, and A. Sato, *ibid*., 1978, **26**, 2312; e) H. Tomisawa, H. Hongo, H. Kato, T. Naraki, and R. Fujita, *ibid*., 1979, **27**, 670.
3. H. Tomisawa, H. Nakano, and H. Hongo, *Chem. Parm. Bull*., 1988, **36**, 1692.
4. All new compounds (Ic,d, IIa-d, and IIIa-d) gave satisfactory spectral and analytical data. Selected data are as follows:

   Ic : mp 141-143°C (benzene); ir (Nujol): 2230, 2200, 1760 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.77 (3H, s), 5.35 (2H, s), 6.90 (1H, t, J=7 Hz), 7.30 (1H, d, J=8 Hz), 7.75 (1H, dd, J=7, 8 Hz), 7.97 (1H, d, J=7 Hz); ms m/z 215 (M^+).

   Id : mp 169-172°C (benzene); ir (Nujol): 2230, 2200, 1755 cm^{-1}; ^{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=7, 8 Hz), 7.93 (1H, d, J=7 Hz); ms m/z 229 (M^+).

IIa : mp 200-202°C (EtOAc); ir (Nujol) : 2220, 2200, 1780, 1715 cm^{-1}; ^{1}H-nmr (DMSO-$\underline{d}_6$): 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); ms m/z 372 (M^{+}).

IIb : mp 218-221°C (acetone); ir (Nujol): 2220, 2200, 1780, 1710, 1690 cm^{-1}; ^{1}H-nmr (DMSO-$\underline{d}_6$): 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); ms m/z 434 (M^{+}).

IIc : mp 124-125°C (benzene); ir (Nujol): 2220, 2200, 1970, 1745, 1720 cm^{-1}; ^{1}H-nmr (DMSO-$\underline{d}_6$): 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); ms m/z 388 (M^{+}).

IId : mp 177-178°C (EtOAc); ir (Nujol): 2220, 2200, 1785, 1740, 1715 cm^{-1}; ^{1}H-nmr (DMSO-$\underline{d}_6$): 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); ms m/z 402 (M^{+}).

IIIa : mp 197-199°C (benzene); ir (Nujol): 3480, 3400, 2230, 1775, 1715 cm^{-1}; ^{1}H-nmr (DMSO-$\underline{d}_6$): 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); ms m/z 372 (M^{+}).

IIIb : mp 198-201°C (benzene); ir (KBr): 3500, 3400, 2250, 1785, 1720 cm^{-1}; ^{1}H-nmr (DMSO-$\underline{d}_6$): 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); ms m/z 434 (M^{+}).

IIIc : mp 206-208°C (benzene); ir (Nujol): 3480, 3400, 2230, 1785, 1715, 1685 cm^{-1}; ^{1}H-nmr (DMSO-$\underline{d}_6$): 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); ms m/z 388 (M^{+}).

IIId : mp 174-176°C (EtOAc); ir (Nujol): 3500, 3400, 2230, 1775, 1700, 1680 cm^{-1}; ^{1}H-nmr (DMSO-$\underline{d}_6$): 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); ms m/z 402 (M^{+}).

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