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# Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XXXI.[1] Syntheses of Isoquinoline Derivatives Using Diels–Alder Reactions of 4-Acetyl-, 4-Cyano-, and 4-Methoxycarbonyl-1-methyl-2(1*H*)-pyridones with 1,3-Butadiene Derivatives

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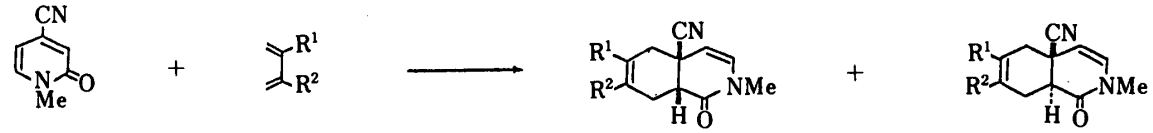
The Diels–Alder reactions of 4-cyano-, 4-methoxycarbonyl-, and 4-acetyl-2(1*H*)-pyridones (I, II, and IV) with 1,3-butadiene derivatives (III and V) were carried out to give 4a-substituted tetrahydro-1(2*H*)-isoquinolone derivatives (VI—IX, XV, XIX, and XX).

**Keywords**——4-substituted 1-alkyl-2(1*H*)-pyridone; Diels–Alder reaction; butadiene derivative; 4a-substituted tetrahydroisoquinolone

The Diels–Alder reaction of 1-alkyl-2(1*H*)-pyridone derivatives, dienophiles, with dienes has utility in the synthesis of isoquinoline derivatives. Our previous reports[2,3] in this series showed that the reactions of 4-cyano- and 4-methoxycarbonyl-1-methyl-2-(1*H*)-pyridones (I[2] and II[3]) with 2,3-dimethyl-1,3-butadiene (III) gave 4a-substituted-4a,5,8,8a-tetrahydroisoquinolones. In this paper we wish to describe the Diels–Alder reactions of 1-methyl-2(1*H*)-pyridones (I, II and IV[4]) with butadienes (III and V); the results demonstrate that this method is effective for the synthesis of tetrahydroisoquinolones.

The Diels–Alder reaction of I and 2-methyl-1,3-butadiene (V) at 160 °C for 96 h was carried out to give four products, *cis*- and *trans*-4a-cyano-2,6-dimethyl-4a,5,8,8a-tetrahydro-1(2*H*)-isoquinolones (VI and VII) in 4.0% and 1.4% yields, and *cis*-and *trans*-4a-cyano-2,7-dimethyl-4a,5,8,8a-tetrahydro-1(2*H*)-isoquinolones (VIII and IX) in 5.9% and 3.8% yields, respectively (Chart 1). The structures of these products were confirmed in the following way.



I

III : $R^1=R^2=Me$
V : $R^1=H$, $R^2=Me$

VI : $R^1=Me$, $R^2=H$
VIII : $R^1=H$, $R^2=Me$
X : $R^1=R^2=Me$

VII : $R^1=Me$, $R^2=H$
IX : $R^1=H$, $R^2=Me$
XI : $R^1=R^2=Me$

Chart 1

The products (VI—IX) have the same molecular formulae, $C_{12}H_{14}N_2O$, respectively, based on the mass spectra (MS). The proton nuclear magnetic resonance ($^1$H-NMR) spectra of VI—IX were similar to those of *cis*- and *trans*-4a-cyano-tetrahydroisoquinolone derivatives (X and XI)[2] (Chart 1) formed from I and III, respectively, From these results, the products (VI—IX) are suggested to be regio- and stereoisomeric adducts. The locations of the methyl

groups were determined as follows. Heating of VIII and IX with Pd-asbestos gave the same compound, 2,7-dimethyl-1(2*H*)-isoquinolone (XII), and the similar treatment of VI afforded 2,6-dimethyl-1(2*H*)-isoquinolone (XIII) (Chart 2). These results indicated that VI and VIII would be stereoisomers of VII and IX, respectively. The $^1$H-NMR spectra of XII and XIII were similar to that of 2,6,7-trimethyl-1(2*H*)-isoquinolone (XIV)[2] (Chart 2), and the signals due to $C_8$-H in those of XII and XIII were observed as a singlet at $\delta$ 8.27 and a doublet ($J$=8 Hz) at $\delta$ 8.33, respectively. Therefore, the methyl groups on the benzene rings in XII and XIII were determined to be at the 7- and 6-positions, respectively. Consequently, the products (VI, VII, VIII, and IX) were 2,6-dimethyl- and 2,7-dimethyl-tetrahydroisoquinolone derivatives, respectively.

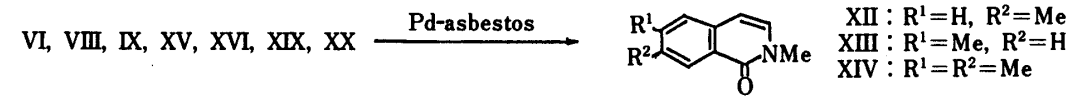



Chart 2

Next, the stereochemistries of the ring junctures in VI—IX were determined by examination of the $^1$H-NMR spectra. The signal due to $C_{8a}$-H in the *cis*-adduct (X) appeared at $\delta$ 2.95,[2] and that in the *trans*-adduct (XI), which overlapped with the signals due to the methylene protons, was located at $\delta$ 2.32—2.6.[2] The corresponding signals of VI and VIII appeared at $\delta$ 2.97 and 2.95, respectively, while those of VII and IX appeared at $\delta$ 2.3—2.6 and $\delta$ 2.2—2.8, respectively, although they overlapped with other signals. Based on a comparison of the signals due to $C_{8a}$-H in VI—IX with those in X and XI, the stereochemistries of the ring junctures in VI and VIII were deduced as *cis*, and those in VII and IX were deduced as *trans*.

The Diels–Alder reaction of II and V at 190 °C for 96 h regioselectively produced only *cis*-2,7-dimethyl-4a-methoxycarbonyl-4a,5,8,8a-tetrahydro-1(2*H*)-isoquinolone (XV) in 50.5% yield, and this was isomerized with lithium diisopropylamide (LDA) at −78 °C to give the *trans*-isomer (XVI) in 67.8% yield (Chart 3). Heating of XV and XVI with Pd-asbestos gave XII. The $^1$H-NMR spectra of XV and XVI were similar to those of the *cis*- and *trans*-4a-methoxycarbonyl-tetrahydroisoquinolone derivatives (XVII and XVIII)[3] (Chart 3), respectively. The signals due to $C_{8a}$-H at $\delta$ 2.97 and $\delta$ 2.0—2.7 (overlapped) in XV and XVI corresponded to those at $\delta$ 3.0[3] and $\delta$ 2.11—2.90[3] (overlapped) in XVII and XVIII, respectively, From the above facts, XV and XVI were established as the *cis*- and *trans*-2,7-dimethyl compounds, respectively.

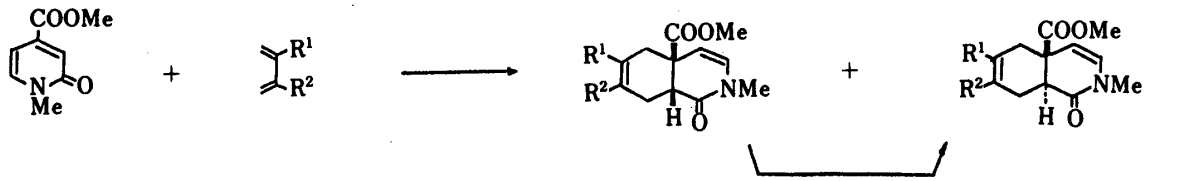



Chart 3

The Diels–Alder reactions of 4-acetyl-1-methyl-2(1*H*)-pyridone (IV)[4] with III at 160 °C for 96 h and V at 180 °C for 72 h gave *cis*-2,6,7-trimethyl- and *cis*-2,7-dimethyl-4a-acetyl-4a,5,8,8a-tetrahydro-1(2*H*)-isoquinolones (XIX and XX) in 98.7% and 42% yields, respectively (Chart 4), and these products were converted upon heating with Pd-asbestos to aromatized lactams (XIV and XII, respectively). The empirical formulae, and infrared (IR),

MS, and $^1$H-NMR spectral data of XIX and XX proved that they were 4a-acetyltetrahydroisoquinolone derivatives. The $^1$H-NMR spectra of XIX and XX showed the signals due to $C_{8a}$-H at $\delta$ 2.84 and 2.88, respectively, supporting the *cis*-form. From the above results, the products (XIX and XX) were determined to be the *cis*-adducts, thus establishing the Diels–Alder reaction of IV and V as proceeding regioselectively.

IV III : $R^1=R^2=Me$; V : $R^1=H$, $R^2=Me$ XIX : $R^1=R^2=Me$; XX : $R^1=H$, $R^2=Me$

Chart 4

## Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-430 spectrometer. MS were taken on Hitachi RMU-6MG and JEOL JMS-D-300 spectrometers. $^1$H-NMR spectra were taken at 60 MHz with tetramethylsilane (TMS) as an internal standard on a JEOL JMN-PMX 60 spectrometer in $CDCl_3$. The chemical shifts are expressed as ppm downfield from TMS. The following abbreviations are used, s = singlet, d = doublet, m = multiplet. The unit (Hz) of coupling constants ($J$ Hz) is omitted.

**The Diels–Alder Reaction of I with V**——A mixture of I (3 g), V (7.6 g), and *o*-xylene (9 ml) was heated in a sealed tube at 160 °C for 96 h. The reaction mixture was chromatographed on a column of silica gel. The four fractions eluted with benzene–actone (30 : 1) gave the products (VI—IX). The first fraction gave VIII, and the second, third, and fourth fractions afforded VI, IX, and VII, respectively. Furthermore, the column was eluted with $CHCl_3$ to recover I (2.3 g, 76.8%).

VI: The second fraction. Yield (180 mg, 4.0%). mp 121—123 °C, colorless prisms (isopropyl ether). High-resolution MS: Found 202.1101, Calcd for $C_{12}H_{14}N_2O$ ($M^+$) 202.1106. MS *m/z*: 202 ($M^+$), 134 ($M^+ - C_5H_8$, base peak). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 2250 (CN), 1685 (N–C=O). $^1$H-NMR $\delta$: 1.67 (3H, s, $C_6$-Me), 2.2—2.8 (4H, m, $CH_2 \times 2$), 2.97 (1H, m, $C_{8a}$-H), 3.07 (3H, N-Me), 5.23 (1H, d, $J$=8, $C_4$-H), 5.45 (1H, m, $C_7$-H), 6.10 (1H, d, $J$=8, $C_3$-H).

VII: The fourth fraction. Yield (63 mg, 1.4%). mp 120—122 °C, colorless plates (benzene–acetone). High-resolution MS: Found 202.1101, Calcd for $C_{12}H_{14}N_2O$ ($M^+$) 202.1106. MS *m/z*: 202 ($M^+$, base peak). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 2240 (CN), 1690 (N–C=O). $^1$H-NMR $\delta$: 1.69 (3H, s, $C_6$-Me), 2.3—2.6 (5H, m, $CH_2 \times 2$, $C_{8a}$-H), 3.15 (3H, s, N-Me), 5.02 (1H, d, $J$=8, $C_4$-H), 5.50 (1H, m, $C_7$-H), 6.20 (1H, d, $J$=8, $C_3$-H).

VIII: The first fraction. Yield (265 mg, 5.9%). mp 63—65 °C, colorless plates (isopropyl ether), High-resolution MS: Found 202.1098, Calcd for $C_{12}H_{14}N_2O$ ($M^+$) 202.1106. MS *m/z*: 202 ($M^+$), 134 ($M^+ - C_5H_8$, base peak). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 2250 (CN), 1660 (N–C=O). $^1$H-NMR $\delta$: 1.77 (3H, s, $C_7$-Me), 2.2—2.8 (4H, m, $CH_2 \times 2$), 2.95 (1H, m, $C_{8a}$-H), 3.08 (3H, s, N-Me), 5.30 (1H, d, $J$=8, $C_4$-H), 5.33 (1H, m, $C_6$-H), 6.17 (1H, d, $J$=8, $C_3$-H).

IX: The third fraction. Yield (172 mg, 3.8%). mp 153—155 °C, colorless plates (benzene). High-resolution MS: Found 202.1110, Calcd for $C_{12}H_{14}N_2O$ ($M^+$) 202.1106. MS *m/z* : 202 ($M^+$, base peak). IR $\nu_{max}^{Nijol}$ cm$^{-1}$: 2250 (CN), 1675 (N–C=O). $^1$H-NMR $\delta$: 1.77 (3H, s, $C_7$-Me), 2.2—2.8 (5H, m, $CH_2 \times 2$, $C_{8a}$-H), 3.16 (3H, s, N-Me), 5.10 (1H, d, $J$=8, $C_4$-H), 5.40 (1H, m, $C_6$-H), 6.27 (1H, d, $J$=8, $C_3$-H).

**The Diels–Alder Reaction of II with V**——A mixture of II (3 g), V (6.1 g), and *o*-xylene (9 ml) was heated in a sealed tube at 190 °C for 96 h, and the reaction mixture was treated in the same manner as described for the reaction of I and V. The fraction eluted with benzene–acetone (30 : 1) gave XV (2.13 g, 50.5%) as a pale yellow oil of bp 142—145 °C (2 Torr). High-resolution MS: Found 235.1207, Calcd for $C_{13}H_{17}NO_3$ ($M^+$) 235.1208. MS *m/z*: 235 ($M^+$), 167 ($M^+ - C_5H_8$, base peak). IR $\nu_{max}^{neat}$ cm$^{-1}$: 1720 (C=O), 1660 (N–C=O). $^1$H-NMR $\delta$: 1.63 (3H, s, $C_7$-Me), 2.1—2.6 (4H, m, $CH_2 \times 2$), 2.97 (1H, m, $C_{8a}$-H), 3.07 (3H, s, N-Me), 3.63 (3H, s, COOMe), 4.96 (1H, d, $J$=8, $C_4$-H), 5.28 (1H, m, $C_6$-H), 6.03 (1H, d, $J$=8, $C_3$-H).

**The Diels–Alder Reaction of IV with V**——A mixture of IV (0.76 g), V (5.19 g), and *o*-xylene (3 ml) was heated in a sealed tube at 180 °C for 72 h, and the reaction mixture was treated in the same manner as described for the preparation of XV. The fraction eluted with benzene–acetone (5 : 1) gave XX (0.46 g, 42%) as a colorless oil of bp 138 °C (1.8 Torr). *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.29; H, 7.83; N, 6.44. MS *m/z*: 219 ($M^+$). IR $\nu_{max}^{neat}$ cm$^{-1}$: 1705 (C=O), 1675 (N–C=O). $^1$H-NMR $\delta$: 1.66 (3H, s, $C_7$-H), 1.9-2.4 (4H, m, $CH_2 \times 2$), 2.20 (3H, s, CO–Me), 2.88 (1H, m, $C_{8a}$-H), 2.96 (3H, s, N-Me), 4.99 (1H, d, $J$=8, $C_4$-H), 5.35 (1H, m, $C_6$-H), 6.02 (1H, d, $J$=8, $C_3$-H).

**The Diels–Alder Reaction of IV with III**——A solution of IV (1.51 g) and III (12.3 g) in *o*-xylene (5 ml) was heated in a sealed tube at 160 °C for 96 h. After removal of the solvent, the residue was recryctallized from isopropyl ether to give XIX (2.3 g, 98.7%) as colorless prisms of mp 70.5—71 °C. *Anal.* Calcd for $C_{14}H_{19}NO_2$: C, 72.02; H, 8.21; N, 6.00. Found: C, 72.11; H, 8.36; N, 6.11. MS *m/z*: 233 ($M^+$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1705 (C=O), 1675 (N–C=O). $^1$H-NMR $\delta$: 1.50 (6H, s, C–Me×2), 1.9—2.5 (4H, m, $CH_2$×2), 2.20 (3H, s, CO–Me), 2.84 (1H, m, $C_{8a}$-H), 2.94 (3H, s, N–Me), 4.66 (1H, d, $J$=8, $C_4$-H), 5.94 (1H, d, $J$=8, $C_3$-H).

**Isomerization of XV**——Butyl lithium solution 2.56 ml (10% solution in hexane) was added to a cooled solution (−30 °C) of diisopropylamine (0.56 ml) in tetrahydrofuran (THF) (3 ml). After being stirred at the same temperature for 15 min, the mixture was cooled to −78 °C. A solution of XV (0.47 g) in THF (3 ml) was added to the cooled solution, and the mixture was stirred at −78 °C for 80 min. Next, MeOH (0.5 ml) was added, and after 5 min, the mixture was treated with saturated aqueous $NH_4Cl$ (1 ml). The mixture was stirred at room temperature, and poured into 10% HCl (20 ml). The acidic mixture was extracted with benzene. The benzene extract was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a column of silica gel. The fraction eluted with benzene–$CHCl_3$ (3:1) gave *trans*-2,7-dimethyl-4a-methoxycarbonyl-4a,5,8,8a-tetrahydro-1(2*H*)-isoquinolone (XVI) (0.319 g, 67.8%), as colorless prisms of 118—120 °C (isopropyl ether). High-resolution MS: Found 235.1197, Calcd for $C_{13}H_{17}NO_3$ ($M^+$) 235.1208. MS *m/z*: 235 ($M^+$), 176 ($M^+$ −COOMe, base peak). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1720 (C=O), 1675 (N–C=O). $^1$H-NMR $\delta$: 1.67 (3H, s, $C_7$-Me), 2.0—2.7 (5H, m, $CH_2$×2, $C_{8a}$-H), 3.06 (3H, s, N–Me), 3.60 (3H, s, COOMe), 4.90 (1H, d, $J$=8, $C_4$-H), 5.35 (1H, m, $C_6$-H), 6.10 (1H, d, $J$=8, $C_3$-H).

**Preparation of Isoquinolones (XII, XIII, and XIV)**——a) XII: A suspension of XV (0.05 g, 0.2 mmol), 10% Pd-asbestos (0.04 g) and naphthalene (0.2 g) was refluxed under a nitrogen atmosphere for 15 h. The reaction mixture was chromatographed on a column of silica gel. The fraction eluted with benzene-$CHCl_3$ (5:1) afforded XII (17 mg, 39.7%) as a pale yellow oil of bp 150 °C (2 Torr). *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.28; H, 6.43; N, 8.12. MS *m/z*: 173 ($M^+$). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 1655 (N–C=O). $^1$H-NMR $\delta$: 2.50 (3H, s, $C_7$-Me). 3.60 (3H, s, N–Me), 6.47 (1H, d, $J$=7, $C_4$-H), 7.03 (1H, d, $J$=7, $C_3$-H), 7.43 (2H, m, $C_5$-, $C_6$-H), 8.27 (1H, s, $C_8$-H).

The compounds (VIII, IX, XVI, and XX) were treated in the same manner as described above to give XII in 39.7%, 59.4%, 13.5%, and 23% yields, respectively.

b) XIII: A suspension of VI (0.04 g, 0.2 mmol), 10% Pd-asbestos (0.04 g), and naphthalene (0.2 g) was treated in the same manner as described for the preparation of XII. The fraction eluted with benzene–$CHCl_3$ (5:1) from the column afforded XIII (12 mg, 35.7%), as colorless needles of mp 85—87 °C (hexane). *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.28; H, 6.41; N, 8.10. MS *m/z*: 173 ($M^+$). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 1655 (N–C=O). $^1$H-NMR $\delta$: 2.47 (3H, s, $C_6$-Me), 3.60 (3H, s, N–Me), 6.43 (1H, d, $J$=8, $C_4$-H), 7.06 (1H, d, $J$=8, $C_3$-H), 7.30 (2H, m, $C_5$-, $C_7$-H), 8.33 (1H, d, $J$=8, $C_8$-H).

c) XIV: A suspension of XIX (0.14 g, 0.6 mmol), 10% Pd-asbestos (0.12 g), and naphthalene (0.8 g) was treated in the same manner as described for the preparation of XIII. The fractions eluted with benzene–$CHCl_3$ (5:1) and with $CHCl_3$ from the column gave XIV[2] (10 mg, 9.3%) and IV[4] (45 mg, 49.8%), respectively.

## References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