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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XXVIII.[1] Diels-Alder Reaction of 4-Cyano-1-methyl-2(1*H*)-pyridone with 2,3-Dimethyl-1,3-butadiene

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The Diels-Alder reaction of 4-cyano-1-methyl-2(1*H*)-pyridone (I) with 2,3-dimethyl-1,3-butadiene (II) was carried out. The products obtained were *cis* and *trans*-4a-cyano-4a,5,8,8a-tetrahydro-2,6,7-trimethyl-1(2*H*)-isoquinolone (III and IV) and 2,6,7-trimethyl-1(2*H*)-isoquinolone (V).

Keywords——4-cyano-1-methyl-2(1*H*)-pyridone; 2,3-dimethyl-1,3-butadiene; Diels-Alder reaction; hydroisoquinoline; isoquinolone

There are considerable literatures dealing with the Diels-Alder reactions of 1-alkyl-2(1*H*)-pyridone derivatives used as dienes.[1,3] However, none of references are available concerning the reaction employing 1-alkyl-2(1*H*)-pyridone derivatives as dienophiles. Hereby, we wish to report the first successful result of the Diels-Alder reaction of 4-cyano-1-methyl-

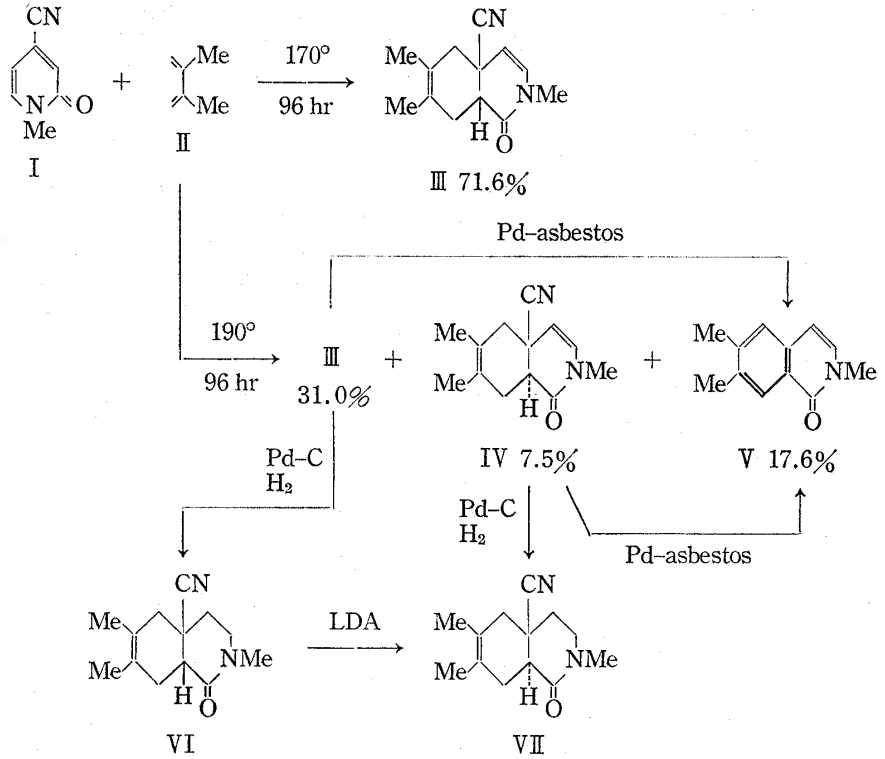

Chart 1

1) Part XXVII: H. Tomisawa, H. Hongo, H. Kato, T. Naraki, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **27**, 670 (1979).
2) Location: *Komatsushima, Sendai 983, Japan.*
3) H. Tomisawa, H. Hongo, H. Kato, R. Fujita, and A. Sato, *Chem. Pharm. Bull.* (Tokyo), **26**, 2312 (1978), and references cited therein; K. Somekawa, T. Watanabe, and S. Kumamoto, *Nippon Kagaku Zasshi*, **1978**, 412.

2(1*H*)-pyridone (I) with 2,3-dimethyl-1,3-butadiene (II). The hydroisoquinoline derivatives obtained have cyano and carbonyl groups at the appropriate positions, which are versatile in terms of synthetic utilization. Consequently, the hydroisoquinoline derivatives obtained will be useful as an intermediate for the syntheses of isoquinoline alkaloids. Moreover, the procedure is not tedious and the product is obtained in a good yield. Therefore, this reaction will be the novel synthetic method for the isoquinoline derivatives.

Reaction of I with II at 170° gave III ($C_{13}H_{16}N_2O$, colorless needles, mp 79—81°) in 71.6% yield, while the same reaction was carried out at 190° to give III, IV ($C_{13}H_{16}N_2O$, colorless prisms, mp 154—156°), and V ($C_{12}H_{13}NO$, colorless needles, mp 149—150°) in 31.0%, 7.5%, and 17.6% yield, respectively (Chart 1).

The structures of these products were confirmed to be *cis*-4a-cyano-4a,5,8,8a-tetrahydro-2,6,7-trimethyl-1(2*H*)-isoquinolone (III), *trans*-4a-cyano-4a,5,8,8a-tetrahydro-2,6,7-trimethyl-1(2*H*)-isoquinolone (IV), and 2,6,7-trimethyl-1(2*H*)-isoquinolone (V) by the following way. The empirical formulae, nuclear magnetic resonance (NMR) and infrared (IR) spectra of III and IV showed that these were the Diels-Alder adducts of I and II. Treatments of III and IV with palladium-asbestos at high temperature gave the same compound (V). As shown in Fig. 1, the ultraviolet (UV) spectrum of V was closely similar to that of 2-methyl-1(2*H*)-isoquinolone[4] and further, the structure of V was supported by the NMR spectrum. Therefore, the structures of III and IV were assumed to be *cis* and *trans* stereoisomers of hydroisoquinolone derivatives.

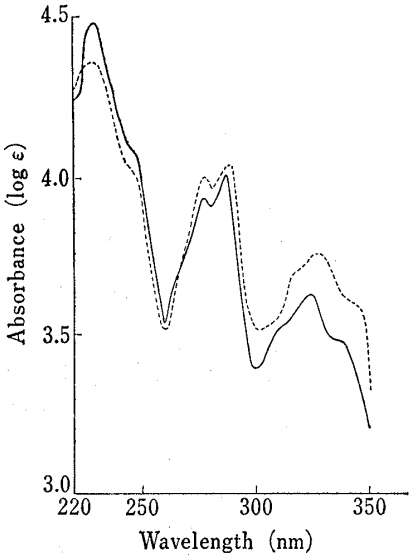

Fig. 1. UV Spectra of V and 2-Methyl-1(2*H*)-isoquinolone (in EtOH)

——: V,
-----: 2-methyl-1(2*H*)-isoquinolone.

The configuration of the ring junctures of III and IV were determined as follows. As mentioned above, III was prepared under the milder reaction conditions than that under which IV was obtained. This fact suggested that the stereochemistry of the ring juncture in III would be *cis* according to the well-known Alder-Stein rule for diene system (*cis* principle).

Heating of III at 190° gave IV, however the same treatment of IV did not afford III. VI ($C_{13}H_{18}N_2O$, colorless pillars, mp 53—55°) obtained by catalytic reduction of III was isomerized with lithium diisopropylamide (LDA) to give VII ($C_{13}H_{18}N_2O$, colorless prisms, mp 110—111°) in 60.8% yield. VII was identified by the mixed melting point determination and the spectral comparison with an authentic sample, which was prepared by catalytic reduction of IV. It has been well known that *trans* decaline derivatives in general are stereochemically more preferable than *cis* decaline derivatives. Therefore, the above facts support the ring juncture of III is *cis* and that of IV is *trans*.

Experimental[5]

The Diels-Alder Reaction of I with II——a) A mixture of I (1 g) and II (9.3 g) was heated in a sealed tube at 170° (an oil bath) for 96 hr. The reaction mixture was chromatographed on a column of silica gel. The solvent of the fraction eluted with benzene was evaporated, and the residue was recrystallized from hexane to give III (1.153 g), mp 79—81°, as colorless needles in 71.6% yield. The solvent of the fraction eluted with $CHCl_3$ was evaporated to recover I (157 mg) in 15.7% yield. *Anal.* Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.03; H, 7.43; N, 12.88. IR ν_{max}^{Nujol} cm^{-1}: 2240 (CN), 1670 (CO). MS

4) G.W. Ewing and E.A. Steck, *J. Am. Chem. Soc.*, **68**, 2181 (1946).
5) All melting points were uncorrected. δ: ppm from tetramethylsilane as an internal standard. Abbreviation used: s=singlet, d=doublet, t=triplet, m=multiplet.

m/e: 216 (M^+). NMR ($CDCl_3$) δ: 1.63, 1.71 (3H, 3H, s, s, C_6-Me, C_7-Me), 2.2—2.9 (4H, m, C_5-H_2, C_8-H_2), 2.95 (1H, m, C_{8a}-H), 3.10 (3H, s, N-Me), 5.30 (1H, d, J=8 Hz, C_4-H), 6.15 (1H, d, J=8 Hz, C_3-H).

b) A mixture of I (1 g), II (9.3 g), and *o*-xylene (6 ml) was heated in a sealed tube at 190° (an oil bath) for 96 hr. The reaction mixture was chromatographed on a column of silica gel, and the column was eluted with benzene–acetone (40: 1). The first fraction gave III (500 mg) in 31.0% yield. The second fraction was evaporated and the residue was recrystallized from benzene to give IV (121 mg), mp 154—156°, as colorless prisms in 7.5% yield. The third fraction was evaporated and the residue was recrystallized from benzene to afford V (245 mg), mp 149—150°, as colorless needles in 17.6% yield. The column was further eluted with $CHCl_3$ to recover I (210 mg) in 21.0% yield.

IV: *Anal.* Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.10; H, 7.43; N, 12.86. IR ν_{max}^{Nujol} cm^{-1}: 2210 (CN), 1660 (CO). MS *m/e*: 216 (M^+). NMR ($CDCl_3$) δ: 1.68, 1.73 (3H, 3H, s, s, C_6-Me, C_7-Me), 2.32—2.6 (5H, m, C_5-H_2, C_8-H_2, C_{8a}-H), 3.14 (3H, s, N-Me), 5.09 (1H, d, J=7.5 Hz, C_4-H), 6.25 (1H, d, J=7.5 Hz, C_3-H).

V: *Anal.* Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.89; H, 7.03; N, 7.41. IR ν_{max}^{Nujol} cm^{-1}: 1635 (CO), 895 (δ C-H), 802 (δ C-H). MS *m/e*: 187 (M^+). NMR ($CDCl_3$) δ: 2.37 (6H, s, C_6-Me, C_7-Me), 3.60 (3H, s, N-Me), 6.43 (1H, d, J=7 Hz, C_4-H), 7.03 (1H, d, J=7 Hz, C_3-H), 7.3 (1H, s, C_5-H), 8.25 (1H, s, C_8-H).

2,6,7-Trimethyl-1(2*H*)-isoquinolone (V)——a) A suspension of III (108 mg), 10% Pd-asbestos (50 mg), and nitrobenzene (2 ml) was refluxed under nitrogen atmosphere for 14.5 hr. The reaction mixture was chromatographed on a column of silica gel. The solvent of the first fraction eluted with $CHCl_3$ was evaporated to recover III (25 mg) in 23.1% yield. The solvent of the second fraction eluted with $CHCl_3$ was eavporated to afford V (49 mg) in 52.4% yield.

b) A suspension of IV (108 mg), 10% Pd-asbestos (50 mg), and nitrobenzene (2 ml) was refluxed under nitrogen atmosphere for 14.5 hr. The reaction mixture was chromatographed on a column of silica gel. IV (16 mg) was recovered from the fraction eluted with $CHCl_3$–benzene (1: 1) in 17.1% yield, and V (56 mg) was obtained from the fraction eluted with $CHCl_3$ in 59.9% yield.

Heating of III——A solution of III (432 mg) in *o*-xylene (8 ml) was heated in a sealed tube at 190° (an oil bath) for 96 hr. The reaction mixture was chromatographed on a column of silica gel. The solvents of the fractions eluted with benzene, benzene–$CHCl_3$ (1: 1), and $CHCl_3$ were evaporated to give III (360 mg, 83.3%), IV (28 mg, 6.5%), and V (16 mg, 4.3%), respectively.

Heating of IV——A solution of IV (432 mg) in *o*-xylene (8 ml) was heated in a sealed tube at 190° (an oil bath) for 96 hr. The reaction mixture was treated as the above-mentioned III to give IV (60 mg, 13.9%) and V (315 mg, 84.2%).

***cis*-4a-Cyano-3,4,4a,5,8,8a-hexahydro-2,6,7-trimethyl-1(2*H*)-isoquinolone (VI)**——A suspension of III (2.16 g), 5% Pd-C (0.5 g), and EtOH (40 ml) was shaken under H_2 for 3.5 hr at room temperature. The catalyst was filtered off. The filtrate was evaporated, and the residue was chromatographed on a column of silica gel. The solvent of the fraction eluted with $CHCl_3$ was evaporated, and the residue was recrystallized from ether to give VI (2.0 g), mp 53—55°, as colorless pillars in 91.7% yield. *Anal.* Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.70; H, 8.48; N, 12.91. IR ν_{max}^{Nujol} cm^{-1}: 2245 (CN), 1645 (CO). MS *m/e*: 218 (M^+). NMR ($CDCl_3$) δ: 1.64 (6H, s, C-Me×2), 1.9—2.6 (6H, m, C_4-H_2, C_5-H_2, C_8-H_2), 2.76 (1H, t, J=6.5 Hz, C_{8a}-H), 2.92 (3H, s, N-Me), 3.45 (2H, m, C_3-H_2).

***trans*-4a-Cyano-3,4,4a,5,8,8a-hexahydro-2,6,7-trimethyl-1(2*H*)-isoquinolone (VII)**——A suspension of IV (216 mg), 5% Pd-C (50 mg) and MeOH (30 ml) was shaken under H_2 until 25 ml of H_2 was absorbed. An equivalent amount of H_2 was 24 ml at 23°. The reaction mixture was treated as the above-mentioned VI. The solvent of the fraction eluted with $CHCl_3$ was evaporated, and the residue was recrystallized from benzene–hexane to afford VII (217 mg), mp 110—111°, as colorless prisms in 99.5% yield. *Anal.* Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.58; H, 8.33; N, 12.94. IR ν_{max}^{Nujol} cm^{-1}: 2230 (CN), 1640 (CO). MS *m/e*: 218 (M^+). NMR ($CDCl_3$) δ: 1.62, 1.68 (3H, 3H, s, s, C_6-Me, C_7-Me), 1.8—2.7 (7H, m, C_4-H_2, C_5-H_2, C_8-H_2, C_{8a}-H), 2.94 (3H, s, N-Me), 3.15—3.83 (2H, m, C_3-H_2).

Isomerization of VI——Butyl lithium solution [2.56 ml (10% solution in hexane)] was added to a cooled solution (−30°) of diisopropyl amine (0.56 ml) in THF (3 ml). After being stirred at the same temperature for 15 min, the mixture was cooled to −78°. A solution of VI (436 mg) in THF (3 ml) was added to the cooled solution, and the mixture was stirred at −78° for 80 min. To the reaction mixture, MeOH (0.5 ml) was added, and after 5 min, the mixture was treated with saturated aq. NH_4Cl (1 ml). The mixture was stirred to come at room temperature, and poured into 10% HCl (20 ml). The acidic mixture was extracted with benzene (5×20 ml). The benzene extract was dried over $MgSO_4$, evaporated, and the residue was chromatographed on a column of silica gel. The solvent of the fraction eluted with benzene–$CHCl_3$ (1: 1) was evaporated, and the residue was recrystallized from benzene–hexane to give VII (256 mg), mp 110—111°, as colorless prisms in 60.8% yield. Mixed melting point on admixture with the authentic sample showed no depression.

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