A NOVEL SYNTHESIS OF ISOQUINOLINE DERIVATIVES

Hideki Kato, Reiko Fujita, Hiroshi Hongo, and Hiroshi Tomisawa*
Tohoku College of Pharmacy, Komatsushima, Sendai 983, Japan

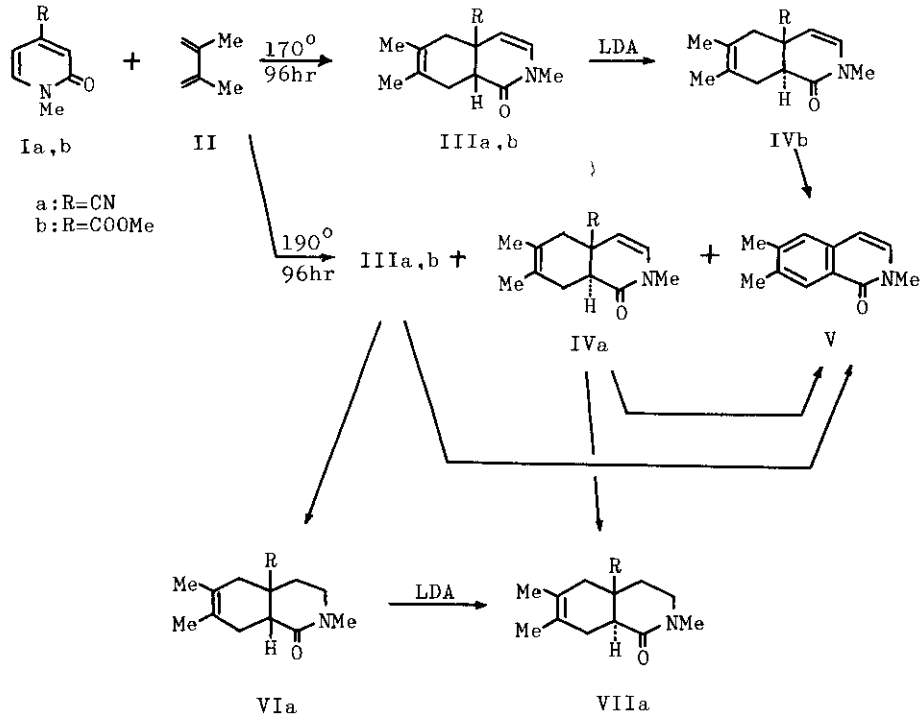
Abstract —— Reaction of 4-cyano-1-methyl-2(1H)-pyridone (Ia) with 2,3-dimethyl-1,3-butadiene (II) at 170° gave cis-4a-cyano-4a,5,8,8a-tetrahydro-2,6,7-trimethyl-1(2H)-isoquinolone (IIIa) in a good yield and at 190° gave IIIa, trans-4a-cyano-4a,5,8,8a-tetrahydro-2,6,7-trimethyl-1(2H)-isoquinolone (IVa), and 2,6,7-trimethyl-1(2H)-isoquinolone (V). Heating of 4-methoxycarbonyl-1-methyl-2(1H)-pyridone (Ib) with II gave cis-4a,5,8,8a-tetrahydro-4a-methoxycarbonyl-2,6,7-trimethyl-1(2H)-isoquinolone (IIIb) in a high yield.

Almost all methods[1] that have been described for the preparation of isoquinolines depend upon closing the heterocyclic ring from a pre-formed benzenoid derivatives. We wish to describe here the first successful isoquinoline synthesis by the Diels-Alder reaction of 1-alkyl-2(1H)-pyridone derivatives used as dienophiles. Diels-Alder reactions of 4-cyano- and 4-methoxycarbonyl-1-methyl-2(1H)-pyridone (Ia and Ib) with 2,3-dimethyl-1,3-butadiene (II) gave hydroisoquinoline derivatives. These reactions will be an advantageous synthetic method for isoquinoline derivatives, since the procedure is not tedious and the products were obtained in satisfactory yields.

Reaction of Ia with II at 170° gave cis-4a-cyano-4a,5,8,8a-tetrahydro-2,6,7-trimethyl-1(2H)-isoquinolone (IIIa) [$C_{13}H_{16}N_2O$, colorless needles, mp 79-81°. MS m/e: 216 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2240 (CN), 1670 (CO). NMR ($CDCl_3$) δ: 1.63, 1.71 (3H, 3H, s, s, C-Me x2), 2.2-2.9 (4H, m, CH_2 x 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).] in 71.6% yield, while the same reaction was carried out at 190° to give IIIa, trans-4a-cyano-4a,5,8,8a-tetrahydro-2,6,7-trimethyl-1(2H)-isoquinolone (IVa) [$C_{13}H_{16}N_2O$, colorless prisms, mp 154-156°. MS m/e: 216 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2210 (CN), 1660 (CO). NMR ($CDCl_3$) δ:

1.68, 1.73 (3H, 3H, s, s, C-Me x 2), 2.32-2.6 (5H, m, CH_2 x 2, C_{8a}-H), 3.14 (3H, N-Me), 5.09 (1H, d, J=7.5 Hz, C_4-H), 6.25 (1H, d, J=7.5 Hz, C_3-H).], and 2,6,7-trimethyl-1(2H)-isoquinolone (V) [$C_{12}H_{13}NO$, colorless needles, mp 149-150°. MS m/e: 187 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1635 (CO). NMR ($CDCl_3$) δ : 2.37 (6H, s, C-Me x 2), 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).] in 31.0%, 7.5%, and 17.6% yield, respectively.

The structures of these products were confirmed by the following way. The empirical formulae, nuclear magnetic resonance (NMR), infrared (IR), and mass (MS)



spectra of IIIa and IVa showed that these were the Diels-Alder adducts of Ia and II. Dehydrocyanation and dehydrogenation of IIIa and IVa were accomplished at 210° with palladium-asbestos to give the same compound (V). The ultraviolet (UV) spectrum of V [UV λ_{max}^{EtOH} nm (log ε): 227 (4.48), 247 (4.08), 277 (3.93), 287 (3.96), 312 (3.51), 324 (3.61), 340 (3.47).] was closely similar to that of 2-methyl-1(2H)-isoquinolone[2] and further, the structure of V was supported by the NMR spectrum. Therefore, the structures of IIIa and IVa were assumed to be cis and trans stereoisomers of hydro-

isoquinolone derivatives. The configurations of the ring junctures of IIIa and IVa were determined as follows. As mentioned above, IIIa was prepared under the milder reaction conditions than those in case of synthesis of IVa. This fact suggested the stereochemistry of the ring juncture in IIIa to be cis, which is supported by the well-known Alder-Stein rule for diene system (cis principle)[3]. Heating of IIIa at 190° gave IVa, however the same treatment of IVa did not afford IIIa. VIa [$C_{13}H_{18}N_2O$, colorless pillars, mp 53-55°. MS m/e: 218 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2245 (CN), 1645 (CO). NMR ($CDCl_3$) δ: 1.64 (6H, s, C-Me x 2), 1.9-2.6 (6H, m, CH_2 x 3), 2.76 (1H, t, J=6.5 Hz, C_{8a}-H), 2.92 (3H, s, N-Me), 3.45 (2H, m, N-CH_2-CH_2).] obtained by catalytic reduction of IIIa was isomerized with lithium diisopropylamide (LDA) to give VIIa [$C_{13}H_{18}N_2O$, colorless prisms, mp 110-111°. MS m/e: 218 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2230 (CN), 1640 (CO). NMR ($CDCl_3$) δ: 1.62, 1.68 (3H, 3H, s, s, C-Me x 2), 1.8-2.7 (7H, m, CH_2 x 3, C_{8a}-H), 2.94 (3H, s, N-Me), 3.15-3.83 (2H, m, N-CH_2-CH_2).] in 60.8% yield. VIIa was identified by the mixed melting point determination and the spectral comparison with an authentic sample, which was prepared by catalytic reduction of IVa. 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 IIIa is cis and that of IVa is trans.

Reaction of Ib with II at 170° gave cis-4a,5,8,8a-tetrahydro-4a-methoxycarbonyl-2,6,7-trimethyl-1(2H)-isoquinolone (IIIb) [$C_{14}H_{19}NO_3$, oil, bp 151° (3 mm Hg). IR ν_{max}^{neat} cm^{-1}: 1725 (CO-OMe), 1668 (N-CO). NMR ($CDCl_3$) δ: 1.60 (6H, s, C-Me x 2), 1.85-2.70 (4H, m, CH_2 x 2), 3.0 (1H, m, C_{8a}-H), 3.06 (3H, s, N-Me), 3.71 (3H, s, COOMe), 5.03 (1H, d, J=8 Hz, C_4-H), 6.06 (1H, d, J=8 Hz, C_3-H). MS m/e: 249 (M^+).] in 85.3% yield. The empirical formula, NMR, IR, and MS spectral data of IIIb showed that IIIb was the Diels-Alder adduct of Ib and II.

IIIb was isomerized with LDA to give the more stable isomer, trans-4a,5,8,8a-tetrahydro-4a-methoxycarbonyl-2,6,7-trimethyl-1(2H)-isoquinolone (IVb) [$C_{14}H_{19}NO_3$, colorless needles, mp 107-108°. MS m/e: 249 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1740(CO-OMe), 1665 (N-CO). NMR ($CDCl_3$) δ: 1.63 (6H, s, C-Me x 2), 2.11-2.90 (5H, m, CH_2 x 2, C_{8a}-H), 3.05 (3H, s, N-Me), 3.60 (3H, s, COOMe), 4.93 (1H, d, J=8 Hz, C_4-H), 6.09 (1H, d, J=8 Hz, C_3-H).] in 78.9% yield. Treatments of IIIb and IVb with palladium-charcoal at 220° gave the same compound (V). Therefore, the structures of IIIb and IVb were determined as described above.

Thus, this method provides a new and facile synthetic route to isoquinoline derivatives containing electrophilic groups at C_{4a} position. Further exploitation of this method to other systems and the synthetic applications to isoquinoline alkaloids are now in progress.

REFERENCES

1. S. Coffey (ed.), "Rodd's Chemistry of Carbon Compounds," 2nd ed., Vol. IV, part F, Elsevier Scientific Publishing Company, Amsterdam, 1976, p. 358.
2. G. W. Ewing and E. A. Steck, J. Am. Chem. Soc., 1964, 68, 2181.
3. K. Alder and G. Stein, Angew. Chem., 1937, 50, 510.

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