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Total Syntheses of (±)-N-Nordasycarpidone and (±)-Dasycarpidone (Studies on the Syntheses of Heterocyclic Compounds. CDXVIII[1])

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The stereoselective total syntheses of (±)-N-nordasycarpidone (I) and (±)-dasycarpidone (II) are herein described. The key step in the approach to these syntheses involved *cis* addition with catalytic reduction of a hydrochloride (VIII).

In the previous papers[3,4] we reported the syntheses of de-ethyldasycarpidone (IV), (±)-dasycarpidone (II) and (±)-3-epi-dasycarpidone (III). We now wish to report the stereoselective total syntheses of (±)-N-nordasycarpidone (I) and (±)-dasycarpidone (II). This synthesis gave a considerable improvement on those reported earlier,[4] because the hydrochloride (VIII) was reduced easily in a very short time and stereoselectively.

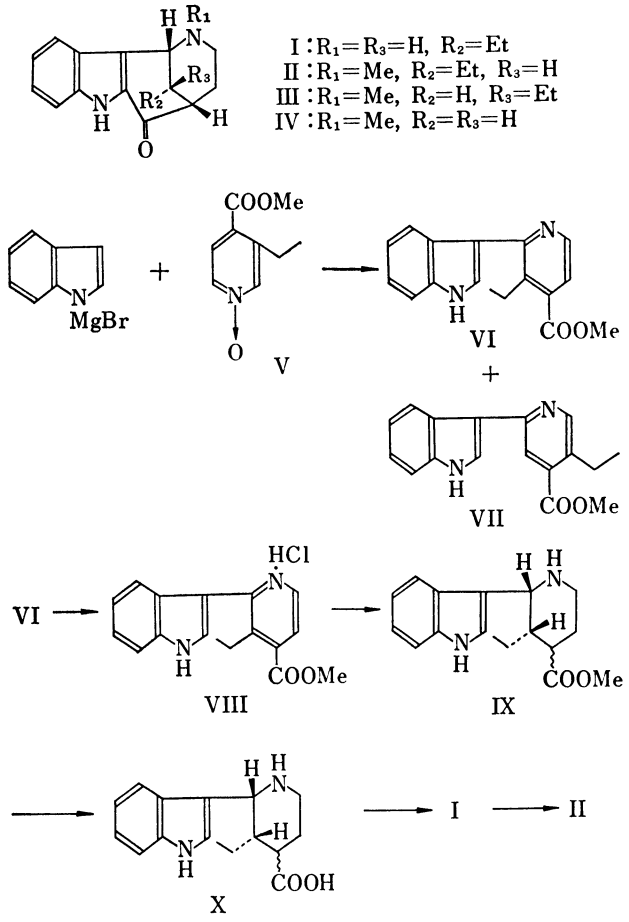

Chart 1

Grignard condensation of indolyl magnesium bromide with methyl 3-ethylisonicotinate-1-oxide (V) in tetrahydrofuran and methylene dichloride in the presence of benzoyl chloride was carried out to give a mixture of the desired condensation product (VI) and its structural isomer (VII), both of which could be separated.[4] Treatment of VI with an excess of ether including hydrogen chloride gas gave a hydrochloride (VIII), the infrared (IR) spectrum of which showed an absorption band due to ester–carbonyl at 1740 cm^{-1}. The catalytic reduction of the compound (VIII) yielded an aminoester (IX) as one of the diastereoisomers. In this method, another diastereoisomers were not obtained. In the nuclear magnetic

1) Part CDXVII: T. Kametani and H. Nemoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1325 (1971).
2) Location: *Aobayama, Sendai.*
3) T. Kametani and T. Suzuki, *J. Chem. Soc.* (*C*), **1971**, 1053.
4) T. Kametani and T. Suzuki, *J. Org. Chem.*, **36**, 1291 (1971).

resonance (NMR) spectrum (δ) of IX, the methyl signal due to the ethyl group was observed at 0.3 ppm, the signal of methyl group of methoxycarbonyl resonated at 3.68 ppm, and the C_2-proton resonated at 4.20 ppm as a doublet with $J=2.5$ Hz. Furthermore, the ring closure of X with polyphosphoric acid afforded only (±)-N-nordasycarpidone (I). These facts show that the bulkiest group of the indolyl group is *equatorial*, the C_4-proton is *cis* to that of C_2 and its dihedral angle is about 60°. Since the ethyl group lies over the aromatic π-electron system, we would expect a methyl signal at a higher field due to shielding by the π-electron system. After normal saponification, the resulting amino acids (X) were heated with polyphosphoric acid at 90—95° in accordance with Dolby's method[5] to yield the crude 2-acylindole, which, on preparative thick layer chromatography afforded (±)-N-nordasycarpidone (I). The IR spectrum showed the absorption bands at 3430 (indole NH) and 1645 cm^{-1} (conjugated C=O), respectively. In the NMR (δ) spectrum, the methyl protons due to the ethyl group resonated at 0.86 ppm and the C_3-proton revealed a doublet with 2.5 Hz at 4.62 ppm. The mass spectrum showed the molecular ion at *m/e* 254. (±)-N-Nordasycarpidone (I) was methylated by Eschweiler-Clarke reaction and the resulting (±)-dasycarpidone (II) was superimposable with its IR and NMR spectral data of an authentic sample.[4]

Experimental[6]

3-Ethyl-2-(3-indolyl)-4-methoxycarbonylpyridine Hydrochloride (VIII)——An excess of ether saturated with HCl gas was added to an ethanolic solution of 350 mg of VI to give a hydrochloride of 560 mg of VIII, which was recrystallized from various solvents but did not crystallize. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=O).

3-Ethyl-2-(3-indolyl)-4-methoxycarbonylpiperidine (IX)——The hydrochloride of 560 mg of VIII was reduced with H_2 in MeOH over Adams' catalyst at atmospheric pressure and room temperature. The solution was filtered and then evaporated to give a residue which was suspended in 10% NH_4OH and extracted with ether. The extract was washed with saturated NaCl solution, dried over K_2CO_3, and distilled off to give 350 mg of IX. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (indole NH) and 1720 (C=O). NMR (in $CDCl_3$) δ (ppm): 0.30 (CH_2-CH_3, 3H, triplet, $J=7$ Hz), 3.68 (3H, singlet, OCH_3), 4.20 (C_2-H, 1H, doublet, $J=2.5$ Hz), 7.0—7.8 (aromatic protons).

3-Ethyl-4-hydroxycarbonyl-2-(3-indolyl)piperidine (X) and (±)-N-Nordasycarpidone (I)——A mixture of 350 mg of aminoester (IX), 1 g of KOH, 10 ml of H_2O, and 20 ml of EtOH was refluxed for 4 hr. The above mixture was then neutralized with conc. HCl, and the solvent was evaporated completely to give a residue, which was extracted with dry EtOH to give 280 mg of the carboxylic acid (X) as a powder. Without purification, the acid of X was treated with polyphosphoric acid [prepared from 2 ml of phosphoric acid and 4 g of phosphrous pentoxide] at 90—95° for 1.5 hr. After the addition of 10 ml of water, the reaction mixture was basified with conc. NH_4OH and then extracted with EtOAc. The extract was washed with saturated NaCl solution, dried over K_2CO_3, and distilled off to give 150 mg of a brown syrup. Preparative thick layer chromatography (EtOAc–benzene–MeOH, 2:2:1) on silica gel afforded 65 mg of (±)-N-nordasycarpidone (I), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (indole NH) and 1645 (conjugatedC=O). NMR (in $CDCl_3$) δ (ppm): 0.86 (CH_2-CH_3, 3H, triplet, $J=7$ Hz), 4.62 (C_3-H, 1H, doublet, $J=2.5$ Hz), 7.0—7.8 (aromatic protons). Mass Spectrum *m/e*: 254 (M^+), 225, 211, 197, 184, 169.

(±)-Dasycarpidone (II)——To a mixture of 0.4 ml of 98% formic acid and 0.4 ml of 37% formalin was added 15 mg of (+)-N-nordasycarpidone and the mixture was heated on a water bath for 5 hr. After cooling, the mixture was decomposed with 20 ml of water, basified with conc. NH_4OH on cooling, and extracted with ether. The extract was distilled off to give 13 mg of (±)-dasycarpidone of II as a pale yellow syrup, whose IR and NMR spectra were superimposable with that of the authentic sample.[4]

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5) L.J. Dolby and H. Biere, *J. Am. Chem. Soc.*, **90**, 2699 (1968).
6) IR spectra were recorded on a type EPI-S2 Hitachi recording spectrometer in $CHCl_3$ solution. NMR spectra were measured on a Hitachi H-60 instrument. Mass spectra were measured on a Hitachi RMU-7 mass spectrometer.