SIMPLE SYNTHESIS OF 1,3,4,5a,6,10b,11,11a-OCTAHYDRO-2H-PYRAZINO[1',2':1,5]PYRROLO[2,3-b]INDOLE DERIVATIVES BASED ON 1-HYDROXYINDOLE CHEMISTRY

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Abstract — 3-Substituted (3S,6S)-6-(1-hydroxyindol-3-ylmethyl)-2,5-piperazinediones are prepared for the first time. They are shown to be suitable intermediates for the synthesis of 3,10b-disubstituted (3S,5aR,10bS,11aS)-1,3,4,5a,6,10b,11,11a-octahydro-2H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4-dione derivatives.

We have been much interested in indole alkaloids such as sporidesmin B, brevianamide E, okaramine C, etc., which have 2H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole as a common skeleton. In our hypotheses, we have speculated that biosyntheses of these indole alkaloids might occur through 1-hydroxytryptophan derivatives.

In the previous paper, we have established that pyrrolo[2,3-b]indoles can be prepared in one step from the 1-acyloxy- or 1-aryloxyindoles in accord with the speculation (Scheme 1). The mechanism is believed to proceed through initial rearrangement of the 1-acyloxy- or 1-aryloxy group to the 3-position of indole nucleus, followed by the nucleophilic addition of the Nβ-side chain to the resultant imine carbon atom of 6. In order to explore the scope of these findings, we have attempted in this communication a model reaction for the synthesis of core structure of 1–3.

Figure 1

First of all, 2,5-piperazinedione derivatives (9a–c) were prepared from (+)-N-benzylxycarbonyl-L-tryptophan[(+)–8] according to the reported procedures. The compound [(+)–9a]8a was prepared by the following sequence of reactions; 1) condensation of (+)-8 with glycine methyl ester in the presence of DCC, 2) catalytic hydrogenation of the resultant amide to remove the protecting benzyl group, 3) cyclization of the resultant dipeptide to 2,5-piperazinedione by heating in MeOH-Et3N at reflux. The condensations of (+)-8 with L-phenylalanine methyl ester and L-leucine methyl ester were conducted by mixed anhydride method with methyl chloroformate. Catalytic hydrogenation of both products over 10% Pd/C, followed by
cyclization in refluxing MeOH afforded (−)-9b8c and (+)-9c8d,e in 86 and 46% yields, respectively. Reduction of (+)-9a, (−)-9b, and (+)-9c with Et3SiH in TFA9 afforded 1:1 mixtures of diastereomers (10a), (10b), and (10c) in 74, 96, and 83% yields, respectively. Application of our 1-hydroxyindole synthetic method to 10a encountered with a solubility problem. To overcome the problem, a mixed solvent, DMF-MeOH-H2O, was chosen. Consequently, oxidation of 10a with Na2WO4·2H2O and 30% H2O2,6 followed by methylation with CH2N2 produced 1-methoxyindole derivative [(+)11b] in 53% yield. However, attempts to isolate 11a after oxidation process were unsuccessful mainly because of its insolvability to almost all organic solvents.

In contrast to the case of 11a, the desired (3S,6S)-(−)-6-(1-hydroxyindol-3-ylmethyl)-3-benzyl- [(−)-11c] and -3-isobutyl-2,5-piperazinedione [(−)-11e] were isolated smoothly in 78 and 63% yields, respectively, by the oxidation of 10b and 10c with Na2WO4·2H2O and 30% H2O2 in CH2Cl2-MeOH-H2O. The structures were proved by converting them to the corresponding 1-methoxyindoles [(−)-11d] and [(−)-11f] in 78 and 93% yields, respectively, by the reaction with CH2N2. Subsequent benzoylation of 1-hydroxy group of (−)-11c and (−)-11e with benzyol chloride provided (−)-12b and (−)-12c in 77 and 96% yields, respectively. Compound [(+)9c] is concluded to take the conformation as shown in Figure 2 in solution.8d Therefore, the rearrangement of 1-benzoyloxy group was expected to proceed stereoselectively. In fact, heating (−)-12c in DMF at reflux produced (3S,5aR,10bS,11aS)-(−)-10b-benzoyloxy-3-isobutyl-1,3,4,5a,6,10b,11,11a-octahydro-2H-pyrazino[1′,2′:1,5]pyrrolo[2,3-b]indole-1,4-dione [(−)-13c] as a sole product in 37% yield. The structure of (−)-13c was determined by spectral data, and its stereochemistry was confirmed by the nOe experimental results in 1H-NMR.
spectroscopy as shown in Figure 3. Under similar reaction conditions, (–)-12b afforded two products, which are considered to be stereoisomers at the 5a- and 10b-positions. Their structural determinations are now in progress. With the success in the above model experiment in hand, further efforts towards synthesis of the related alkaloids are under investigation.

REFERENCES AND NOTES

1. a) This is Part 110 of a series entitled “The Chemistry of Indoles”. b) Part 109: F. Yamada, M. Tamura, A. Hasegawa, and M. Somei, Chem. Pharm. Bull., submitted. c) All new compounds gave satisfactory spectral and elemental analysis data. 11b, mp 213—214°C, [α]D20 +4.2° (c=0.30, DMF); 11c, mp 248—251°C (decomp), [α] &p<sup>20</sup>–153° (c=0.30, DMF); 11d, mp 273—278°C (decomp), [α]D26 –154° (c=0.30, DMF); 11e, oil, [α]D20 +46.6° (c=0.30, DMF); 11f, mp 200—202°C, [α]D26 –47.5° (c=0.30, DMF); 12b, oil, [α]D21 –95.1° (c=0.30, DMF); 12c, oil, [α]D26 –8.2° (c=0.29, MeOH); 13c, oil, [α]D22 –45.6° (c=0.20, MeOH).

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