Note

Substitution Reaction on the Indole Ring of (–)-Indolactam V, the Fundamental Structure of Teleocidins

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(–)-Indolactam V (**1**) has the basic ring-structure of teleocidins¹⁾ (teleocidin A-1, A-2, B-1, B-2, B-3, and B-4^{2,3)}), which are potent skin tumor promoters.⁴⁾ This compound was first synthesized,^{5,6)} and immediately after isolated from *Streptovorticillium blastmyceticum* NA34-17 as an Epstein-Barr virus early antigen (EBV-EA) inducer^{7~9)} together with (–)-14-*O*-acetylindolactam V,⁷⁾ (–)-2-oxy-indolactam V,¹⁰⁾ and (–)-*N*¹³-desmethylindolactam V¹¹⁾ as new microbial metabolites.

(–)-Indolactam V (**1**) is a key compound for structure-activity studies of teleocidin-related compounds because its structure is fundamental to teleocidins and it has various activities itself,^{12~14)} for example, induction of EBV-EA, induction of ornithine decarboxylase (ODC), adhesion of HL-60 cells, binding to a 12-*O*-tetradecanoylphorbol-13-acetate (TPA) receptor, activation of protein kinase C, and tumor-promoting activity. These activities of (–)-indolactam V (**1**) are lower than those of teleocidin B-4 (**2**) which carries a terpenoid moiety at positions 6 and 7 of the indole ring, suggesting that the monoterpenoid moiety in **2** acts to amplify the activity. Fujiki *et al.* examined these activities of (±)-*N*¹-prenyl and geranylindolactam V and indicated that the imino group at N-1 of **1** must be free for full expression of tumor-promoting activities.¹⁴⁾ Recently, we prepared a series of (–)-*N*¹-alkylindolactam Vs and tested their EBV-EA-inducing activity.¹⁵⁾ As a result it proved necessary to introduce an alkyl substituent at a position other than N-1 of **1** to obtain a more active compound than **1**. So we examined the substitution reaction on the indole ring of **1** in order to investigate in detail the structure-activity relationship.

First, **1** was halogenated. Electrophilic aromatic substitution of bromine into **1** in dioxane-pyridine gave (–)-

7-bromoindolactam V and (–)-2,7-dibromoindolactam V in 24.7% and 4.1% yield, respectively. The same reaction using iodine gave (–)-7-iodoindolactam V in 35.4% yield. These suggest that position 7 of **1** is most active in the electrophilic aromatic substitution reaction. However, radical reaction of **1** with *N*-chlorosuccinimide in dioxane gave predominantly (–)-5-chloroindolactam V in 40% yield. The same reactions using *N*-bromosuccinimide or *N*-iodosuccinimide gave no products.

Introduction of an alkyl substituent into the indole ring of **1** was examined. Friedel-Crafts alkylation using aluminum chloride and alkyl chloride in nitrobenzene was unsuccessful. Introduction of the first alkyl group may increase the reactivity of the ring toward further substitution and polymerization. Then Friedel-Crafts acylation was attempted. Treatment of (–)-14-*O*-acetylindolactam V with aluminum chloride and acetic anhydride in nitrobenzene, followed by hydrolysis, afforded (–)-7-acetylindolactam V (**3**) in 40% yield. (+)-2,7-Diacetyl, 5,7-diacetyl, and 5-acetylindolactam V were obtained as minor products. Reduction of **3** with lithium aluminum hydride and aluminum chloride in ether gave (–)-7-ethylindolactam V (**4**) in a quantitative yield. The same reaction using (–)-14-*O*-acetylindolactam V and octanoic anhydride afforded (–)-7-octanoylindolactam V (**5**) and (–)-7-octylindolactam V (**6**), respectively. The structures of all derivatives synthesized above were confirmed by spectral measurements (UV, IR, ¹H NMR, EIMS, and HR-EIMS). A series of (–)-7-alkylindolactam Vs can be obtained by this method, which will be useful for structure-activity studies.

It is known that teleocidins exist as two stable conformers, conformer A of the sofa type and B of the twist type, in solution at room temperature.¹⁶⁾ Introduction of an acyl group into position 7 will increase the resonance among the lone-pair electrons on N-13, aromatic elec-

FIG. 1. Synthetic Scheme of (–)-7-Alkylindolactam V.

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trons, and the acyl group, to fix the molecule in conformer B in which the lone-pair electrons on N-13 are more delocalizable onto the indole ring. While a large substituent at position 5 will hinder the resonance by a steric interaction between the large substituent and the N-methyl group, to fix the molecule in conformer A. As expected, in the ^1H NMR spectrum of (–)-7-acetylidolactam **5** (**3**) and (–)-5-acetylidolactam **5** (**7**) in chloroform, the signals were not doubled. It is possible to determine which conformer is predominant in solution because several signals of the two conformers differ largely in chemical shift and coupling constant¹⁶; for example, in the ^1H NMR spectrum of (–)-indolactam **5** (**1**) in chloroform, the signals ascribable to protons 5 and 10 of conformer A were observed at δ ca. 7.0 and δ 4.74 (J = 11.6 Hz), those of conformer B at δ 6.50 and δ 7.36 (J = 0 Hz), respectively. On the basis of the spectral features of **3** (δ 6.48 for H-5; δ 7.12, J = 0 Hz for H-10) and **7** (δ 4.89, J = 10.4 Hz for H-10), the fixed conformers of **3** and **7** were deduced to be conformers B and A, respectively. The sign of $[\alpha]_D$ of **3** ($[\alpha]_D^{24} - 670^\circ$, c = 0.181, EtOH) was opposite to that of **7** ($[\alpha]_D^{19} + 57^\circ$, c = 0.395, EtOH), and the CD peak at 230 nm ascribable to the lactam carbonyl group of **3** ($[\theta]_{231} - 34,300$, MeOH) was almost antipodal to that of **7** ($[\theta]_{229.5} + 76,100$, MeOH). These indicate that there exists a large difference in the configuration of the two conformers. Thus, one of them is likely responsible for the biological activity. Compounds fixed as conformer A or B, such as **3** and **7** will give a clue to this proposition.

Biological activities of these compounds and a series of (–)-7-acyl and alkyl derivatives will be published elsewhere.

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