SYNTHESIS OF CHUANGXINMYCIN ANALOGUES

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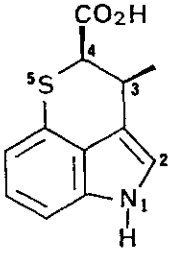
Abstract —— Chuangxinmycin analogues with 3-cyanomethyl, 3-ethoxycarbonylmethyl, and 3-nitromethyl groups were synthesized. They revealed antitumor activity against P388 leukemia cells *in vitro*.

Chuangxinmycin (1) is a new kind of antibiotic which has recently been isolated from *Actinoplanes tsinanensis* n. sp. and has been found to possess considerable biological activities.[1,2] The antibiotic 1 is comprised of a unique heterocyclic skeleton bearing an indole ring substituted at its 3- and 4-positions.

These facts prompted us to synthesize analogues of chuangxinmycin for evaluating their biological activities. As a preliminary work, we wish to report here the synthesis of some analogues, substituted at 3-methyl of 1, which exhibited antitumor activity against P388 leukemia cells *in vitro*.

The antibiotic 1 has been synthesized through dehydrochuangxinmycin ester 2 by two research groups.[3,4] The most burdensome problem seems to be yet remained



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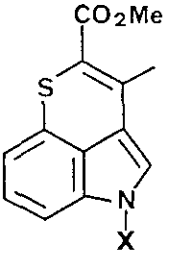
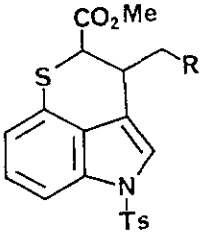


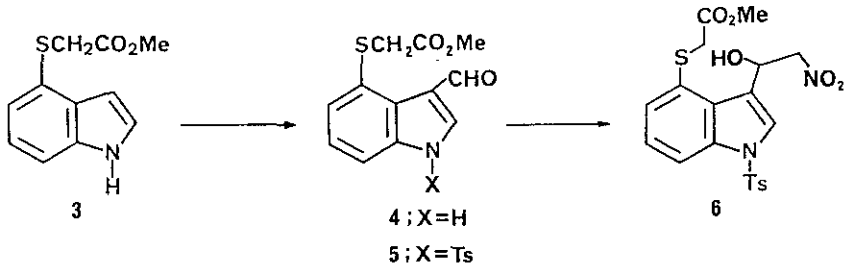
2; X=H or Ac

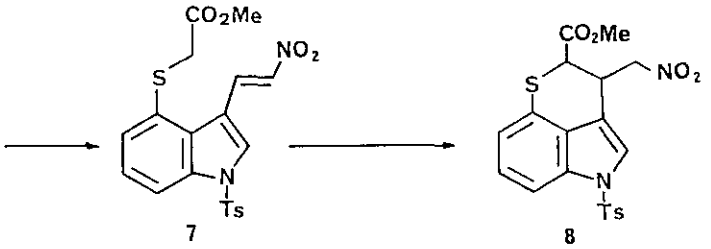


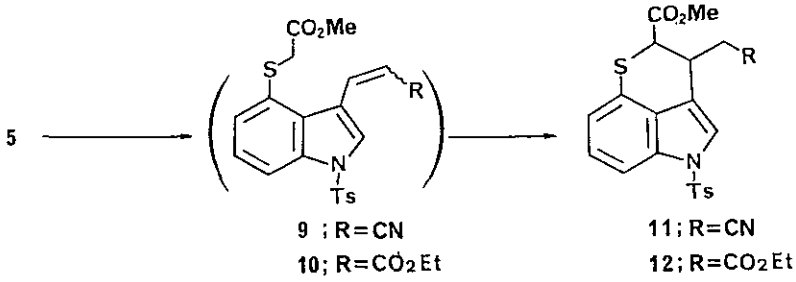
in the reduction of 2 to the ester of 1;[5,6] tetra-substituted C_3-C_4 double bond resists to the hydrogenation and moreover the divalent sulfur at 5-position of 2 tends to suffer reductive extrusion.[4] Thus, we attempted to construct directly the C_3-C_4 single bond in the synthesis of analogues of 1.

The starting material of our choice was 3-formyl-4-(methoxycarbonylmethylthio)indole (4), which was easily prepared by Vilsmeier-Haack reaction of methyl 4-indolylthioacetate (3)[3,4,5] with dimethylformamide/$POCl_3$ in tetrahydrofuran (THF) in 95% yield. For activation of the formyl group of 4, tosyl group was introduced (4/TsCl/K_2CO_3/acetone) to afford 5 in 99% yield.

When the aldehyde 5 was stirred together with K_2CO_3 in nitromethane at room temperature for 1 h, an oily alcoholic adduct 6 was produced in 91% yield. The



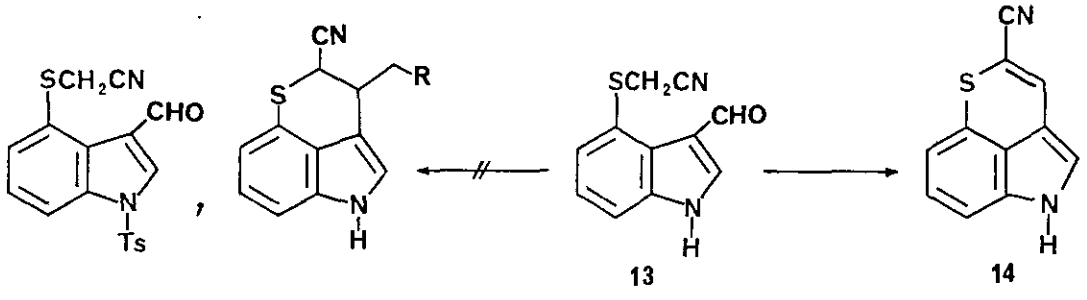




alcohol 6 was dehydrated with ammonium acetate in acetic acid (80 °C/13.5 h) to give a nitro compound 7 as yellow needles (from hexane - ethyl acetate, mp 143 - 143.5 °C) in 67% yield. Next, the olefin 7 was refluxed with triethylamine in methanol (20 min) to give stereoisomeric mixture 8a and 8b (8a/8b = 24/76), which were easily separated by chromatography on silica gel. Elution with dichloromethane - ether (100:1) gave 8a as colorless needles (from dichloromethane - hexane, mp 185-187 °C) and 8b as colorless granules (from dichloromethane - hexane, mp 151-152 °C). Major isomer 8b might be trans one though nmr analysis could not well decide the stereochemistry of the isomers.[7]

The analogues with 3-cyanomethyl and 3-ethoxycarbonylmethyl groups were far more easily synthesized than 8. When the aldehyde 5 was treated with anion of diethyl cyanomethylphosphorane, prepared from by the use of NaH, in THF under argon atmosphere at 0 °C for 2.5 h, a tricyclic product 11 was produced as stereoisomeric mixture (11a/11b = 41/59) in 76% yield. Similarly, treatment of 5 with triethyl phosphonoacetate gave 12 (12a/12b = 43/57) in 79% yield. As much the case of 8, the reaction leading to 11 and 12 might also proceed through olefins 9 and 10.

In place of 5, 4-cyanomethylthio derivative 13 was synthesized and used for the successive carbon chain extention and cyclization. Under the conditions of Horner-Wittig reaction and of condensation with nitromethane described above, the aldehyde 13 was, however, unstable to yield 14. The aldehyde 13 was also converted easily into 14 under the tosylation conditions (4 → 5).



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The chuangxinmycin analogues obtained here revealed antitumor activity against P388 leukemia cells in vitro and their IC_{50} values were as follows: 8a;14.7, 8b;3.1, 11a;3.1, 11b;3.4, 12a;3.3 and 12b;4.4 μg/ml. It is worth to point out that chuangxinmycin methyl ester (racemic, synthesized one)[6] exhibited scarely

the antitumor activity.

REFERENCES AND NOTES

1. H. -T. Liang, H. -D. Hsu, C. -P. Chang, H. -E. Ku, and W. -S. Wang, Hua Hsueh Hsueh Pao, 1976, 34, 129; Sci. Sin., 1977, 20, 106.
2. The antibiotic 1 was found to be active in vitro against a variety of Gram-positive and Gram-negative bacteria, and in vivo, against Escherichia coli and Shigella dysenteria infections.
3. C. -P. Chang, H. -D. Hsu, L. -C. Huang, Y. -C. Lin, H. -S. Li, C. -L. Yu, and C. -L. Chao, Hua Hsueh Hsueh Pao, 1976, 34, 133.
4. A. P. Kozikowski, M. N. Greco, and J. P. Springer, J. Am. Chem. Soc., 1982, 104, 7622.
5. We have recently found that Mg in methanol gave rather prefered result for the reduction of 2, though the desulfurization yet tended to occur.[6]
6. M. Matsumoto and N. Watanabe, Heterocycles, in press.
7. 8a: NMR(400MHz, $CDCl_3$) δ2.36(s, 3H9, 3.83(s, 3H), 4.35(broad d, J=2.9Hz, 1H), 4.43-4.49(m, 1H), 4.55-4.64(m, 1H), 4.80(dd, J=13.0 and 5.1Hz, 1H), 7.08(dd, J=7.6 and 0.5Hz, 1H), 7.25(broad d, J=8.4Hz, 2H), 7.27(dd, J=8.3 and 7.6Hz, 1H), 7.43(s, 1H), 7.72(dd, J=8.3 and 0.5Hz, 1H), 7.73(broad d, J=8.4Hz, 2H)ppm.

   8b: NMR(400MHz, $CDCl_3$) δ2.35(s, 3H), 3.58(s, 3H), 3.99(d, J=2.6Hz, 1H), 4.46(ddd, J=7.2, 6.6 and 2.6Hz, 1H), 4.50(dd, J=12.1 and 7.2Hz, 1H), 4.75(dd, J=12.1 and 6.6Hz, 1H), 7.08(dd, J=7.6 and 0.6Hz, 1H), 7.22-7.28(m, 3H), 7.51(s, 1H), 7.70(dd, J=8.3 and 0.6Hz, 1H), 7.73(d, J=8.3Hz, 2H)ppm.

   In the above case, comparison of coupling constants ($-C_3H-C_4H-$) between 8a(2.9Hz) and 8b(2.6Hz) were of little use. We could, however, conclude that the major isomer 8b is trans one, providing that proton at C_4 of trans isomer is found higher than that of cis isomer as in the case of chuangxinmycin methyl ester (4.0-4.1 ppm) and its trans isomer (3.6 ppm).[4,6]

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