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A Novel Synthesis of (\pm) -3-Aminonocardicinic Acid

By KATSUMI CHIBA, MIWAKO MORI, and YOSHIO BAN*

(Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, 060 Japan)

Summary (\pm) -3-Aminonocardicinic acid, which is an important starting material for the synthesis of nocardicin A and other biologically active analogues, has been synthesized by application of a new method for synthesis, of α -methylene- β -lactams.

NOCARDICIN A (1) has been isolated as the major product from the fermentation broth of *Nocardia uniforms* subsp. *tsuyamanensis* ATTC 21806 by Imanaka *et al.*;¹ its structure was elucidated by Kamiya *et al.*,² providing the first example of this new type of monocyclic β -lactam antibiotic. Much attention has been paid to these new antibiotics, since they have been found to be active against a broad spectrum of Gram-negative bacteria.

As (\pm) -3-aminonocardicinic acid (3-ANA, 2) is potentially an important starting material for the synthesis of biologically active nocardicin derivatives, this compound has been synthesized independently by Kamiya,³ Koppel,⁴ and Wasserman⁵ by different methods. We describe here a novel synthesis of 3-ANA using an extension of our method for the synthesis of β -lactams.⁶



Protection of the amino group of (\pm) -p-hydroxyphenylglycine (3) gave (4) in 81.7% yield (Scheme 1). Dibenzylation of (4) gave (5) (81.5%) and the protecting group was selectively removed by treatment with hydrogen chloride in CH₂Cl₂ to give (6) (m.p. 160—164 °C, 91.3%). Compound (6) was then condensed with 2,3-dibromopropene to give the amine (7) (m.p. 42—44 °C, 81.6%). Insertion of carbon monoxide into (7) was effected in the presence of 2 mol % of Pd(OAc)₂, 8 mol% of PPh₃, and 1.2 mol. equiv. of Buⁿ₃N in hexamethylphosphoramide at 100 °C for 3 h to afford the desired α -methylene- β -lactam (8b, m.p. 89.5—90.5 °C) in 36.5% yield. The yield was increased to 62.7% when the reaction was conducted under 4 atm of carbon monoxide at 80 °C for 38 h.



(8b)

As a trial method for the conversion of the α -methylene group into a 3-amino group, the 1-benzyl-3-methylene- β lactam (8a), which was easily prepared by the insertion of carbon monoxide into N-benzyl-2-bromoallylamine,¹ was oxidized with a catalytic amount of osmium tetraoxide in the presence of N-methylmorpholine N-oxide⁷ to furnish the diol (9a, m.p. 104—105 °C, 93.7%). This diol was cleaved with NaIO₄ in aq. tetrahydrofuran to give the ketolactam (10a, 96.7%), whose n.m.r. spectrum in CCl₄ showed it to be in a 1:1 equilibrium with the enol form. The ketolactam (10a) was immediately converted into the



SCHEME 1 Reagents, i, $Bu^{t}CO_{2}N_{3}$, n, $PhCH_{2}Br, K_{2}CO_{3}$, ini, $HCl(g) CH_{2}Cl_{2}$, iv, 2,3-dibromopropene, $K_{2}CO_{3}$, v, $Pd(OAc)_{2}$, PPh_{3} , $Bu_{3}^{n}N$.

oxime (11a, m p 140-144 °C, 65 2%), which was treated with acetic anhydride in the presence of NaOAc in ethyl acetate and then hydrogenated with PtO₂ under several atm of hydrogen to give the 1-benzyl-3-acetylamino- β lactam (12a, m p 101-104°, 58 2%)

Since the α -methylene group could be converted into 3acetamino group, the desired α -methylene- β -lactam (8b) was converted into the diol (9b, 83 0%) which was oxidized to the ketolactam (10b 72.8%) and then treated with $\rm NH_2OH~HCl$ to afford (11b, m p $~99{--}102~^\circ\!C,~65~4\%$), in the same manner The oxime (11b) was converted into a diastereomeric mixture of the desired 3-acetamino- β lactam which could be separated by preparative thin layer chromatography on silica gel into (12b) and (12b') (24 5%) and 28 0%, respectively) but it was not possible to cleave the N-acetyl group of (12) However, hydrogenation of the oxime (11b) with rhodium on alumina under several atm pressure of hydrogen afforded a mixture of diastereomers which was separated by preparative tlc on silica gel into (13) and (14) Each isomer was treated with

acetic anhydride in the presence of pyridine to give (12b') and (12b) The compound (13) was treated with toluene-p-sulphonic acid in ethyl acetate to give (13 TsOH, mp 163-166 °C), which was identical (nmr and ir spectrum, mixed mp) to an authentic sample The hydrotosylate of the other diastereoisomer (14) was also prepared (14 TsOH, m p 179-183 °C) and its structure was confirmed mainly by spectral data

Compound (13) is readily converted into (2),4 thus the present synthesis of dibenzyl 3-ANA hydrotosylate (13 TsOH) constitutes a formal synthesis of nocardicin A (1)

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