TOTAL SYNTHESIS OF dl-7-AMINO-3-DEACETOXYCEPHALOSPORANIC ACID(7-ADCA) INVOLVING A SHORT STEP SYNTHESIS OF A 4,5-DIHYDRO-6H-1,3-THIAZINE

Toshihiko Hashimoto, Taiichiro Watanabe, Yoichi Kawano, Teruo Tanaka, and Tetsuo Miyadera*

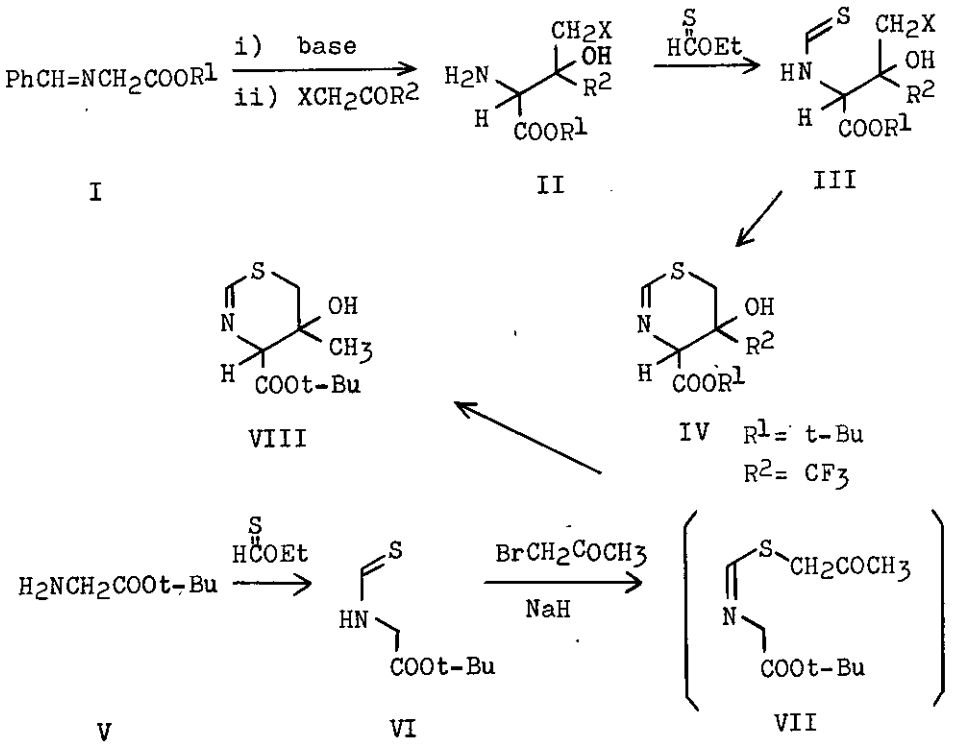
Central Research Laboratories, Sankyo Co., Ltd.
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan

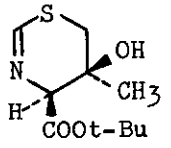
A 1,3-thiazine, tert-butyl 5-hydroxy-5-methyl-4,5-dihydro-6H-1,3-thiazine-4-carboxylate (VIII) was prepared by a two step process starting from glycine tert-butyl ester(V). Interestingly the thiazine formation proceeded stereoselectively to afford almost exclusively the cis isomer(VIIIa). Utilizing the 1,3-thiazine the title compound(XV) was synthesized by the established synthetic method.

In the course of a synthetic work on 3-trifluoromethyl-cephalosporins,[1] we found a new route to 4,5-dihydro-6H-1,3-thiazines which may be of use as key intermediates for cephalosporin synthesis. Following the previous synthesis of the 1,3-thiazines, our interest was directed to finding a new short step

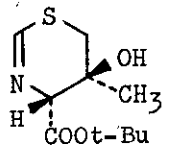
synthesis of 1,3-thiazines. A thiazine synthesis earlier reported[1] involves three steps in the order: reaction of a Schiff base anion with an α-haloketone(I→II); thioformylation(II→III); cyclization to a 1,3-thiazine(III→IV). Success in this synthesis prompted us to investigate an alternative route with a reversed sequence(V→VI→VII→VIII) of the three steps in which alkylation of the thioformyl derivative of a glycine ester is followed by cyclization between the carbonyl group and the methylene carbon of the resulting Schiff base. Although a 2-substituted thiazine has been similarly prepared,[2] to date there is no report concerning the synthesis of 2-unsubstituted thiazines by the same method.[3]

Thioformylation of glycine tert-butyl ester(V) with ethyl thioformate in carbon tetrachloride at room temperature afforded a thioformamide(VI), mp 50-51°, in a 82% yield. The amide VI was treated with one mole-equivalent of sodium hydride(NaH) in tetrahydrofuran(THF) at 0°C followed by addition of bromoacetone. After stirring for 30 min, the reaction mixture was poured into 10% aq. K_2HPO_4 with ice-cooling and extracted with ethyl acetate to give a 69% yield of the 1,3-thiazine VIII, mp 140-141° (from benzene), MS m/e: 231(M^+), NMR($CDCl_3$) δ: 1.38(s, Me), 1.54 (s, t-Bu), 2.88(d-d, J=12.5, 1.3 Hz, C_6-H), 3.01(d, J=12.5 Hz, C_6-H), 3.50(s, OH), 4.07(m, C_4-H), 8.33(d, J=2.5 Hz, C_2-H). The thiazine thus formed seemed to contain almost exclusively one diastereomer (VIIIa) in which the hydroxyl and carboxylate groups are cis. Treatment of the cis thiazine with NaH in THF at 0°C for 2 hr gave rise to a 3:1 mixture of the cis and trans isomers(VIIIa and VIIIb). The stereochemical assignments of the diastereomers were

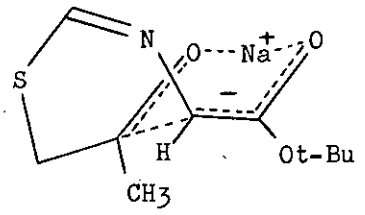




VIIIa



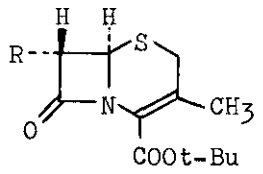
VIIIb



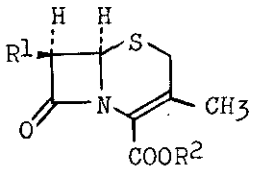
IX

possible based on the IR spectra(in CCl_4) in which the cis isomer VIIIa exhibited an absorption band at 3500 cm^{-1} due to intramolecular hydrogen bonding between the hydroxyl group and ester carbonyl. The other diastereomer VIIIb showed absorption bands at 3560 and 3460 cm^{-1} due to both the free hydroxyl group and the intramolecularly hydrogen-bonding hydroxyl group which possibly reflects a conformational change of the thiazine ring. Such a spectroscopic difference between the two isomers was similarly observed with the cis and trans 5-trifluoromethyl analogs(IV) whose stereochemistry was previously assigned by X-ray crystallographic analysis.[1] The stereochemistry of the cis isomer VIIIa was unambiguously confirmed by X-ray analysis.[4] The thiazine formation of the ketone VII seems to favor the transition state (IX) where the carboxylate group exists cis to the carbonyl oxygen. Similar stereochemical explanation has been made for a stereoselective aldol condensation reaction of a lithium enolate.[5]

The hydroxyl derivative VIII was acetylated with acetic anhydride in pyridine at 60°C for 48 hr followed by reaction with azidoacetyl chloride[6] in the presence of triethylamine in THF to give the trans 7-azido-3-cephem derivative (X, mp 82-83°, NMR($CDCl_3$)δ : 1.55(s, t-Bu), 2.07(d, J=1.0 Hz, Me), 3.16(d, J=18 Hz, C_2-H), 3.48(d-q, J=18, 1.0 Hz, C_2-H), 4.42(d, J=1.8 Hz, C_7-H), 4.59(d, J=1.8 Hz, C_6-H), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100(N_3), 1779(β-lactam), 1715(ester), MS m/e: 296(M^+)). On catalytic hydrogenation over 10% Pd-C in THF, X afforded the trans 7-amino derivative(XI, NMR($CDCl_3$) 100 MHz δ : 1.56(s, t-Bu), 1.96(s, NH_2), 2.01(splintered s, Me), 3.07(d, J=18 Hz, C_2-H), 3.47(d-q, J=18),



X: R= N_3
XI: R= NH_2
XII: R= o-$NO_2C_6H_4SNH$



XIII: R^1=o-$NO_2C_6H_4SNH$, R^2=t-Bu
XIV: R^1= NH_2, R^2= t-Bu
XV: R^1= NH_2, R^2= H

1.0 Hz, C_2-H), 4.07(d, J=2.0 Hz, C_7-H), 4.42(d, J=2.0 Hz, C_6-H), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3300(NH_2), 1775(β-lactam), 1720(ester)).

The conversion of the trans amine to the cis isomer(XIV) was performed by the established method of Hiraoka and Kobayashi[7] in our Laboratories. Treatment of XI with o-nitrobenzenesulfenyl chloride in the presence of triethylamine in THF at room temperature gave the o-nitrobenzenesulfenyl derivative(XII, mp 65-67°, NMR($CDCl_3$) δ: 1.42(s, t-Bu), 1.99(s, Me), 3.03, 3.51(AB-q, J=18.5 Hz, C_2-H_2), 4.03(d, J=7.0 Hz, NH), 4.41(d-d, J=2.0, 7.0 Hz, C_7-H), 4.68(d, J= 2.0 Hz, C_6-H), 7.1-8.4(m, C_6H_4). Following oxidation of XII to the imine derivative with excess MnO_2 in CH_2Cl_2 and successive reduction with sodium borohydride in DMSO-THF afforded the cis sulfenamido derivative(XIII), mp 208-209°. The sulfenamide XIII was treated with a solution of KI and $Na_2S_2O_3$ in methanol-acetic acid at room temperature to give the cis amine(XIV), mp 136-137°. The tert-butyl group was deprotected by treatment with trifluoroacetic acid at room temperature to obtain dl-7β-amino-3-deacetoxycephalosporanic acid(7-ADCA, XV) as the trifluoroacetic acid salt which was identified by comparison of the IR and NMR spectra with

those of an optically active authentic sample.

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