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AN EFFICIENT SYNTHESIS OF DES-N-METHYL-N-ACETYL ERYTHROMYCIN DERIVATIVES VIA THE N-OXIDE

Yi-Yin Ku,* David Riley, Hemant Patel, ChengXi Yang and Jih-Hua Liu

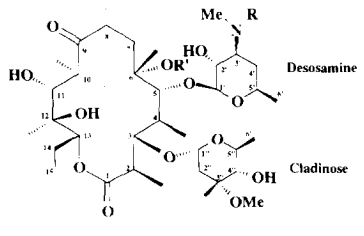
D-54P, Chemical Process Research, Chemical and Agricultural Products Division

Abbott Laboratories, North Chicago, IL 60064-4000

Abstract: An efficient synthesis of des-N-methyl-N-acetyl erythromycin derivatives has been developed, it involves the Polonovsky reaction of erythromycin N-oxide derivatives. The reaction conditions have been established so that the desired products can be prepared in high quality and in good yields. This provides a convenient way to prepare des-N-methyl-N-acetylerythromycin-based macrolides.

Erythromycin A, one of the most important macrolide antibiotics discovered,[1,2] was produced by a fermentation process.[3] Since its discovery in 1952,[4] numerous semi-synthetic erythromycin derivatives have been prepared to improve the parent's antibacterial activity and pharmacokinetic profile. [3,5,6]

It was reported that the reaction between erythromycin and ethyl chloroformate produced O,N-dicarbethoxy-des-N-methylerythromycin.[7] In this reaction, a methyl group is displaced with a carbethoxy group from the dimethylamino function in the desosamine. Subsequently, this reaction was extended to prepare O,N-dicarbobenzoxy des-N-methylerythromycin,[8] the carbobenzoxyl group can be easily hydrogenolyzed to give des-N-methylerythromycin. These modifications have made it possible to study the structure effects of dimethylamino function of the desosamine on the antibacterial activities of erythromycin derivatives.

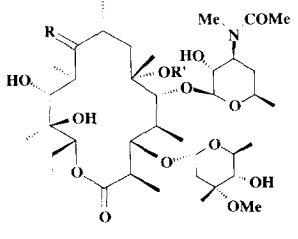


1: R = Me, R'= H, Erythromycin A

2: R = Me, R'= Me, Clarithromycin

3: R = H, R'= H, Des-N-methylerythromycin

4: R = H, R'= Me, Des-N-methylclarithromycin



5: R = O, R'= Me

6: R = N-O-iPrO

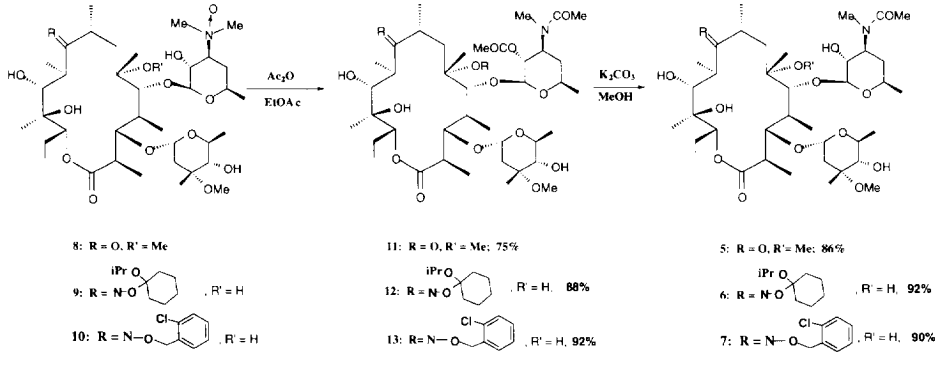
7: R = N-O-Cl

Another reported method for demethylation of the dimethylamino function of erythromycin derivatives is via an iodine-mediated reaction.[9] The erythromycin derivative was treated with I_2/NaOAc to give des-N-methylerythromycin. This reaction was used to prepare a series of macrolides whose methyl group of the dimethylamino function was displaced by other groups including acyl function. The des-N-methyl-N-acyl macrolides were used for structure-activity studies of the gastrointestinal motor stimulating effects.[10]

Although the Polonovsky reaction has been widely used in organic synthesis to prepare a variety of interesting compounds [11,12], it has not been used in the erythromycin-based macrolides. We wish to report an efficient process for preparing several des-N-methyl-N-acylerythromycin derivatives via Polonovsky reactions of erythromycin N-oxide derivatives.

Erythromycin A derivatives, including clarithromycin **8**, 9-(isopropylcyclohexylketal) erythromycin oxime **9**, and 9-(2-chlorobenzyl)erythromycin oxime **10**, can be easily oxidized using m-CPBA or hydrogen peroxide as oxidizing reagents to produce the N-oxide derivatives in a typical yield of 85% ~ 95%.[7,13] The Polonovsky reactions were carried out by treating the corresponding N-oxides with acetic anhydride in EtOAc at room temperature for 4 h. After aqueous workup, the rearrangement products were hydrolyzed to remove the 2'-O-acetyl functionality by reacting with aqueous methanol in the presence of K_2CO_3 at 60°C. Thus, the des-N-methyl-N-acetylerythromycin derivatives: des-N-methyl-N-acetylclarithromycin **5**, des-N-methyl-N-acetyl-9-(isopropylcyclohexylketal) erythromycin oxime **6,** and des-N-methyl-N-acetyl-9-(2-chlorobenzyl)erythromycin oxime **7,** were obtained in good yields (Scheme 1).

Scheme 1.



It was found that the best results were obtained when the N-oxides were treated with acetic anhydride in EtOAc without addition of any other reagents. For example, when the reactions were carried out in CH_2Cl_2 or

EtOAc using acetic anhydride in the presence of Et_3N, pyridine, or dimethylamino pyridine, complex reaction mixtures were obtained. Since erythromycin derivatives possess several hydroxy groups (i.e. 2'-OH, 4"-OH and 11-OH groups) they potentially all can be acetylated under the forcing acetylation reaction conditions. Furthermore 4"-O-acetyl and 11-O-acetyl groups are difficult to hydrolyze.[14] It was also found that hydrolysis of the 2'-O-acetyl group of the des-N-methyl-N-acetylerythromycin derivatives requires stronger conditions than the corresponding dimethyl compound. For example, the normal hydrolysis of 2'-O-acetyl of erythromycin A derivatives only requires stirring in MeOH at room temperature, while under this condition, the 2'-O-acetyl, des-N-methyl-N-acetylerythromycin derivatives were unreactive, even when base K_2CO_3 was added to facilitate the reaction. The difference observed in the hydrolysis must be due to the lack of base catalysis of the dimethylamino group. The nucleophilicity of the nitrogen of des-N-methyl-N-acetylerythromycin derivatives has been greatly reduced by the formation of the amide.

In a typical experiment: To a solution of 9-(2-chlorobenzyl)erythromycin oxime N-oxide (888 mg, 1.0 mmol) in EtOAc (10 mL) was added acetic anhydride (0.28 mL, 3.0 mmol), and the resulting solution was stirred at room temperature for 4 h. The solution was poured into 5% $NaHCO_3$ (20 mL), and the mixture was stirred for 10 min, then the product was extracted with EtOAc (20 mL). The organic layer was separated, washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo to give the 2'-O-acetyl-9-(2-chlorobenzyl)-des-N-methyl-N-acetylerythromycin oxime **13** (866 mg, 92% yield). MS (APCI): $[M+H]^+/z$ = 943. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.23 (3H, 3"-CH_3), 1.38 (3H, 6-CH_3), 1.94 (3H, s, 2'-OAc), 2.01 (3H, 3'-NAc), 2.81 (3H, s, 3'-NCH_3), 3.36 (3H, s, 3'-OCH_3), 5.13 (2H, -OCH_2Ar), 7.17~7.37 (4H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 10.5 (15-C), 14.4 (10-CH_3), 30.4 (NCH_3), 33.0 (10-CH), 83.7 (5-OCH), 126.7~135.1 (Ar-C), 170.1 (2'-O<u>C</u>OCH_3), 171.8 (3'-N<u>C</u>OCH_3), 172.3 (C=N), 175.0 (1-C). The hydrolysis was carried out as follows: To a solution of 2'-O-acetyl-9-(2-chlorobenzyl)-des-N-methyl-N-acetylerythromycin oxime **13** (500 mg, 0.53 mmol) in MeOH (8 mL) was added K_2CO_3 (500 mg) followed by H_2O (3 mL). The resulting solution was stirred at 60 °C for 4 h, and the solvent was removed. The residue was extracted with EtOAc (20 mL) and H_2O (10 ml) /brine (10 mL). The organic layer was separated, washed with brine and dried over Na_2SO_4, the solvent was removed in vacuo to give the 9-(2-chlorobenzyl)-des-N-(methyl)-N-acetylery oxime **7** (432 mg, 90% yield) as a white solid. The structural confirmations were made based on the ^1H and ^{13}C spectra (COSY, HMQC, and HMBC) and mass spectra.

In conclusion, we have successfully prepared a series of des-N-methyl-N-acetyl erythromycin derivatives via the Polonovsky reaction of erythromycin N-oxides. The reaction conditions have been established so that the desired des-N-methyl-N-acetylerythromycin derivatives can be prepared in high quality and in good yields. This procedure provides a convenient way to prepare des-N-methyl-N-acetylerythromycin-based macrolides.

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