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Chemical Modification of Erythromycin: Novel Reaction Observed by Treatment with Metalloporphyrins

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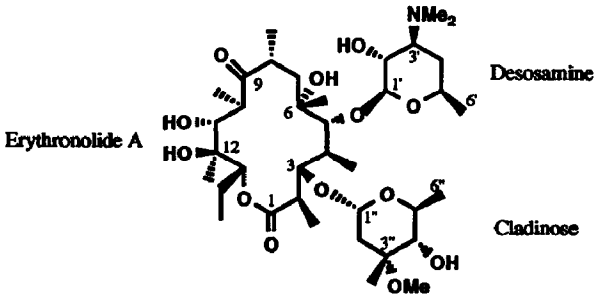
Abstract: Reaction of erythromycin and other macrolides with metalloporphyrins and exogenous co-oxidants leads to replacement of the N-dimethyl moiety in the desosamine sugar with complete retention of configuration. The resulting macrolides show antibacterial activity.

Erythromycin (I) is produced by the actinomycete *streptomyces erythroaeus*.[1] Since its introduction to clinical medicine[2] in 1952, erythromycin along with numerous analogs has been used in the medical and veterinary fields to combat a variety of infections caused by Gram-positive bacteria and mycoplasmas. The activity against Gram-negative species is marginal; susceptibility to acid degradation limits the pharmacokinetic profile.[3] New analogs are being prepared to extend the effectiveness of the macrolides to Gram-negative infections.

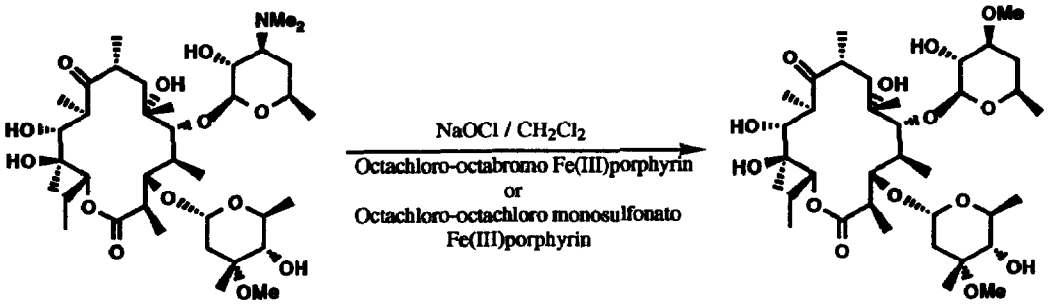


I

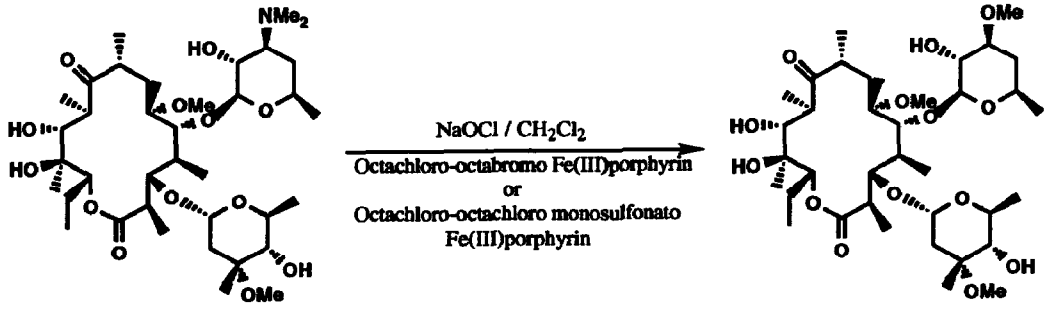
The desosamine and cladinose moieties in erythromycin have not been subjected to much synthetic modification. The N-oxide and dedimethylamino derivatives showed little antibacterial activity and no ribosomal binding activity.[4,5] It was suggested that the dimethylamino group should be considered as being extremely important for the antibacterial activity of erythromycin.[6,7,1]

Sterically protected and electronically activated metalloporphyrins have been studied as synthetic models for cytochrome P-450 mediated epoxidations and hydroxylations. These catalysts are robust, not destroyed under strongly oxidizing conditions and effect catalytic oxidations with high turnover numbers.[8-12]

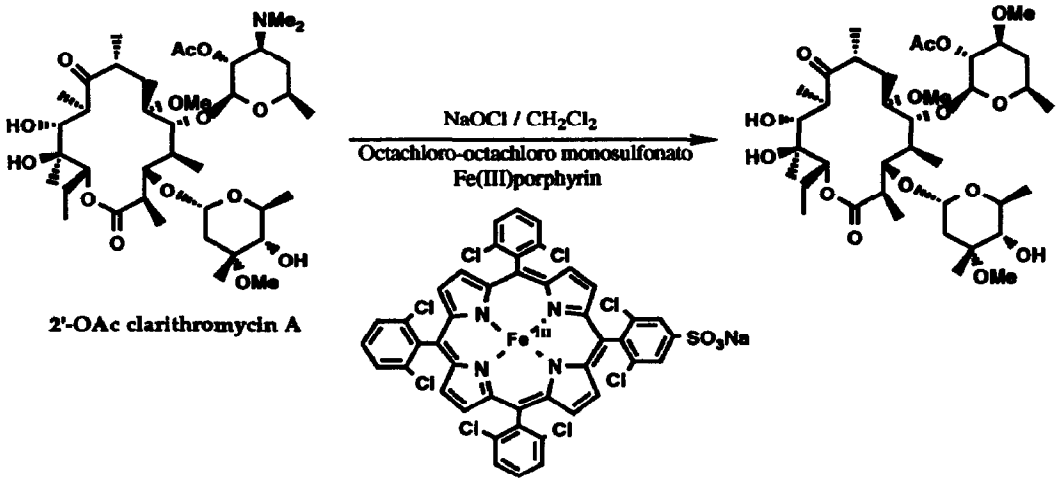
Metalloporphyrins[13] have been used in our laboratory to synthesize metabolites of pharmaceutical drugs.[14] During the course of these studies, we reacted macrolides with catalytic amount of metalloporphyrins and exogenous co-oxidants. Instead of the expected N-demethylated or C-hydroxylated products, an unexpected and novel reaction was observed. The N-dimethyl functionality on the desosamine sugar was replaced with an O-methyl group; the reaction occured with complete retention of configuration. The structure was confirmed by ^{1}H and ^{13}C spectra (COSY, ROESY, HMQC and HMBC). The stereochemistry at C3' was determined by NOE's in the ROESY spectrum from H3' and H1' and H5'.[15] Surprisingly, the compounds also retained significant anti-bacterial activity.[15] This unprecedented reaction occurs in absence of added methanol. Protection of the functionalities on the molecule is not necessary. Experiments to determine the scope and mechanism of the reaction are in progress. Several new macrolide analogs prepared by this method are being subjected to comprehensive biological screening. It is hoped that these will overcome the pharmacokinetic shortcomings of erythromycin.



Erythromycin A



Clarithromycin A



2'-OAc clarithromycin A

EXPERIMENTAL

A solution of 6-O-Methyl erythromycin A (Clarithromycin) (2.24 g, 3.0 mmol) in methylene chloride (30 ml) was treated with octachloro-octachloro Fe(III)porphyrin sulfonate, followed by 7.2% NaOCl (4.65 g, 4.5 mmol). Pyridine (25 μl) was added, and the reaction mixture was stirred overnight. Water (20 ml) was added. The organic layer was separated and evaporated to dryness *in vacuo*. The residue was dissolved in methylene chloride (4 ml) and chromatographed (silica gel) using acetone/hexane/triethylamine 30:100:2 (v:v:v). The major fraction was concentrated to dryness *in vacuo*. The product was crystallized from ethanol (4 ml) at -20 °C overnight. The crystals were filtered washed with cold ethanol and dried in a vacuum oven to yield (200 mg) of the product.

Spectral Data for 3'-OMe clarithromycin A.:

^{1}H Nmr (300 MHz, $CDCl_3$): 5.06 (dd, 1H, J=6.6, 1.5 Hz, H13), 4.92 (br d, 1H, J=3.1 Hz, H1"), 4.47 (d, 1H, J=4.5 Hz, H1'), 3.98 (dq, 1H, J=5.9, 2 Hz, H5"), 3.76 (br d, 1H, J=5.6 Hz, H11), 3.68 (d, 1H, J=4.5 Hz, H5), 3.54 (dq, 1H, J=5,3 Hz, H5'), 3.42 (dd, 1H, J=6, 4.5 Hz, H2'), 3.31 (s, 3H, H3"OMe), 3.03 (s, 3H, H6OMe), 2.98 (s, 3H, H3'OMe), 1.41 (s, 3H, H6Me), 0.84 (t, 3H, J=5.9 Hz, H15); ^{13}C Nmr (75 MHz, $CDCl_3$): 220.9 (C9), 175.7 (C1), 102.2 (C1'), 96.1 (C1"), 81 (C5), 78.4 (C3&C6), 77.9 (C13), 76.7 (C4"), 74.3 (C12), 72.8 (C3"), 72.2 (C2'), 70.3 (C3'), 69.1 (C11), 67.8 (C5'), 65.8 (C5"), 50.6 (C6OMe), 49.5 (C3"OMe), 48.7 (C3'OMe), 45.2 (C8), 45.1 (C2), 39.3 (C7), 39.1 (C4), 37.3 (C10), 34.9 (C2"), 30.5 (C4'), 21.5 (C3"Me), 21.3 (C6'), 21 (C14), 19.7 (C6Me), 18.7 (C6"), 18 (C8Me), 16 (C12Me), 15.9 (C2Me), 12.3 (C10Me), 10.6 (C15), 9.3 (C4Me); ms (DCI/NH_3) (m/e): 734 (M^+).

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14. (a) Andersen, K. E.; Begtrup, M.; Chorghade, M. S.; Lau, J.; Lee, E. C.; Lundt, B. F.; Petersen, H.; Sørensen, P. O.; Thøgersen, H. manuscript submitted to *Tetrahedron*. (b) Chorghade, M. S.; Lee, E. C.; Hansen, K., to be presented at the ACS National meeting in San Diego, in March 1994.
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