Pure & Appl. Chem., Vol. 66, Nos 10/11, pp. 2365–2368, 1994.
Printed in Great Britain.

Erythromycin: New chemistry on an old compound

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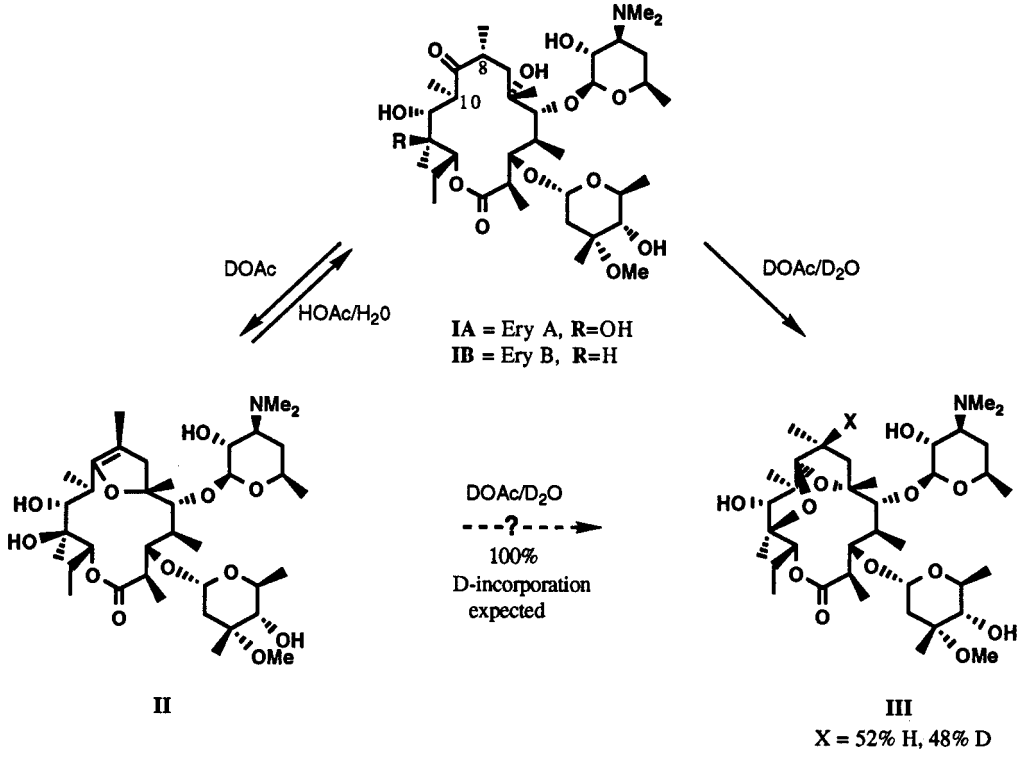
Abstract

Although Erythromycin A (Ery A) **IA** has been known for over 40 years(1) some of the chemical properties of this fermentation product are only now being revealed. For example, the acid degradation mechanism was studied in 1971(2). It was thought to proceed through the enol ether **II** ultimately to anhydroerythromycin A **III** as recently as 1986(3). In 1989(4), a more detailed kinetic study suggested that there is an equilibrium between **IA** and **II** coupled to a direct conversion from **IA** to **III**. We have confirmed this finding with a simple deuterium labelling experiment.

Ery A **IA** was treated with DOAc/D_2O to form **III**, while the reaction mixture was sampled for mass spectrum analysis and observed by ^{13}Cmr. After just a few minutes, there was about 50% deuterium labelling found to be on carbon 8 by ^{13}Cmr. No deuterium was detected on C-10. Furthermore, if naturally labelled **III** is dissolved in DOAc/D_2O, deuterium is slowly picked-up on C-8.

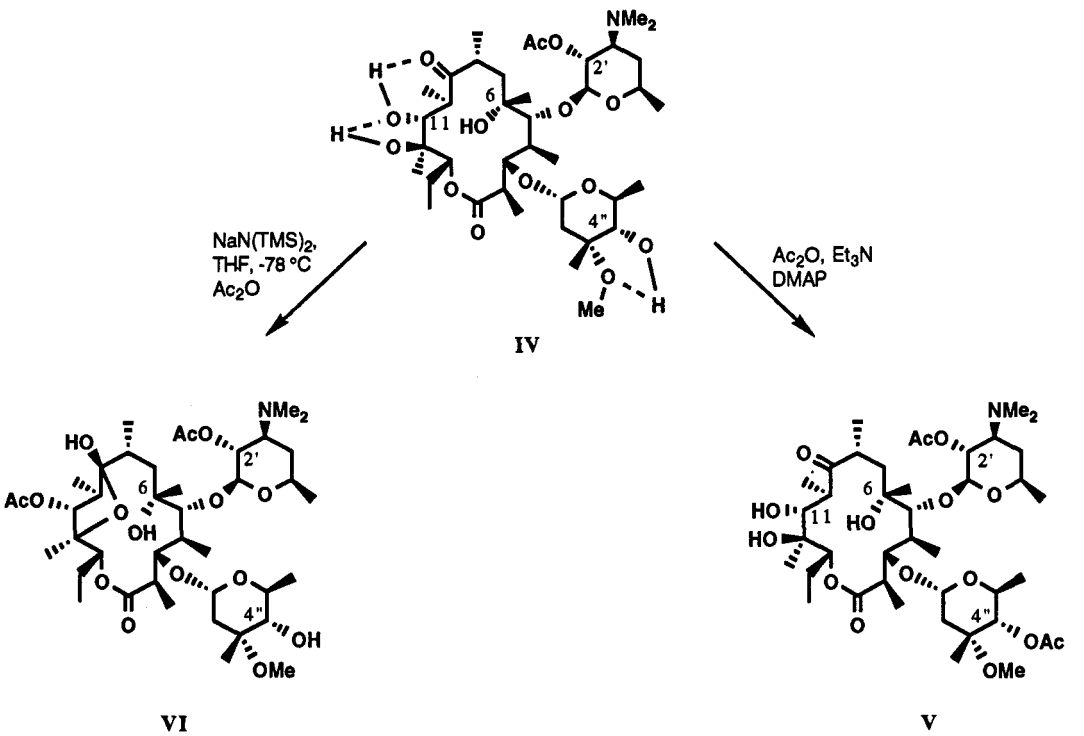
This simple study does not require a direct reaction from **II** to **III**, nor does it rule it out. However, it does confirm the direct pathway from **IA** to **III** is operative, since at least some of **III** was found to have been unlabelled. The kinetic studies on these labelling experiments will be reported elsewhere.

Scheme 1



Biologically active molecules often exhibit unusual chemical properties related to the interaction of functional groups. In Ery A **IA**, for example, the three secondary hydroxyl groups can easily be differentiated. The -OH on the desosamine moiety is the first to acetylate, with the 3"-dimethylamino group acting as an intramolecular catalyst. Indeed, the reaction of Ery A **IA** with acetic anhydride, using triethylamine as base, readily leads to the pure 2'-acetyl derivative **IV**. In order to effect reaction at the 4" hydroxyl group on the cladinose sugar, one must use a catalyst, such as N,N-dimethylaminopyridine (DMAP). The hydroxyl on the macrocycle itself, at C-11, can only be acetylated by heating with these reagents. However, if the 2'-acetyl derivative is treated with a strong base such as sodium hexamethyldisilazide in THF at -78 °C, and acetic anhydride is added, the hydroxyl group at C-11 is acetylated in preference to that at 4". This could be explained by the extensive hydrogen-bonding available to the various functionalities. An alkoxide at C-11 is stabilized by the neighboring proton on the C-12 hydroxyl, while an alkoxide at 4" is relatively less stable due to the lack of a possible hydrogen bond.

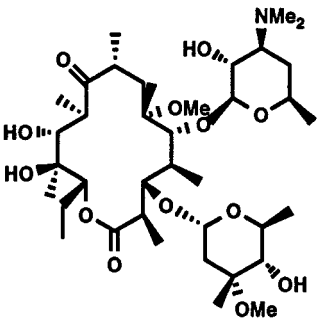
Scheme 2



Careful nmr analysis has shown that **VI** exists as a 12,9-hemiacetal and deuterium labelling experiments show a slow exchange of the proton on the C-6 hydroxyl with external solvent. A similar 12,9-hemiacetal was reported to be a major form of **IA** in aqueous solution(5).

A wide variety of ways have been found to prevent the acid degradation shown in scheme 1. Several second generation compounds have reached the commercial market place(6). These new compounds are all modified on the macrocycle to prevent acid degradation, and all show enhanced pharmacodynamics over **IA** and the early salts and 2' esters of **IA**. One example is Roxithromycin, the methoxyethoxymethyl ether of the 9-oxime. Reduction of the oxime leads to 9(S) or 9(R) erythromycilamines, and the 9(S) has been transformed to a prodrug called Dirithromycin. The oxime is also the starting material for production of Azithromycin, an ring-expanded 15-membered macrocycle with a second basic amine present. This compound shows low blood levels but excellent tissue levels.

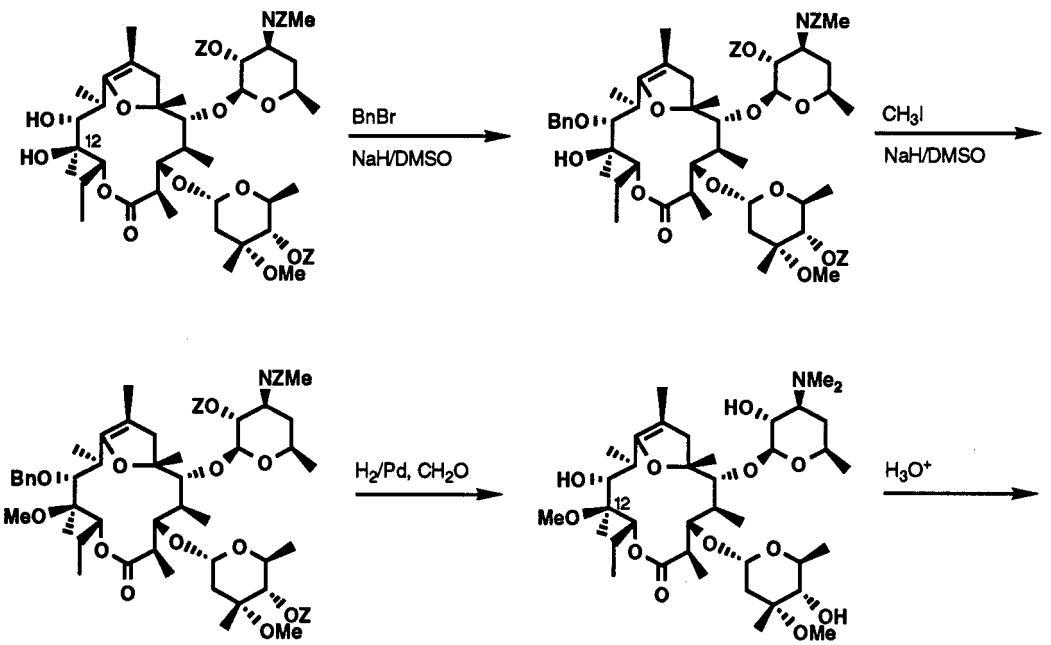
A very simple way to prevent acid degradation according to scheme 1 is to methylate the 6-OH group. Hence, treatment of **IV** with NaH in DMSO-THF at 0 °C, then adding CH_3I produces up to 30 % of 6-OMe erythromycin A **VII**. This compound, Clarithromycin, is now made commercially by a much more efficient route, starting with the 9-oxime.



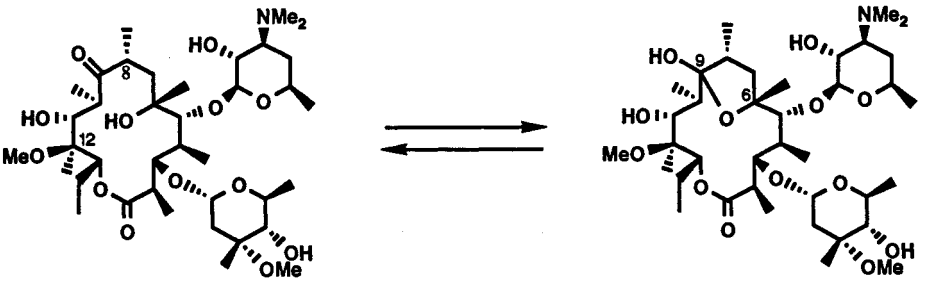
VII

In order to further explore the interaction of the macrocycle ring hydroxyls, we decided to block the 12-OH by methylation. The synthesis of this compound is shown in scheme 3.

Scheme 3



VIII



IX

After all the other hydroxyls were blocked, methylation of the 12-OH proceeded smoothly. After removal of the protecting groups and replacing the N-methyl lost when the Cbz-derivative was formed, the 12-OMe enol ether **VIII** was subjected to mild hydrolysis conditions. While **IB** exists largely as the 9-ketone in aqueous solution, 12-OMe erythromycin **IX** exists as a mixture of keto and 6,9-hemiacetal forms, and as with **IB**, the 8-methyl group slowly epimerizes. The microbiological acitvity of **IX** was found to be about one-half that of the parent structure **IA**, similar to **IB**. Hydrogen bonding may be responsible for the larger extent of hemiacetal form for **IX** relative to **IA**. Details of these various studies, along with possible implications to the biological activity of these analogs, will be published elsewhere.

References

1. R.C. Anderson, H.E. Boaz, R.L. Bunch, E.H. Flynn, J.M. McGuire, H.M. Powell and J.W. Smith, *Antibiot. Chemother.*, **2**, 281 (1952).
2. R.S. Egan, P.H. Jones, P. Kurath and T.J. Perun, Experientia, **27**, 362 (1971).
3. P.J. Atkins, T.O. Herbert and N.B. Jones, *Int. J. Pharm.*, **254**, 215 (1989).
4. T. Cachet, R. Hauchecorne, J. Hoogmartens, G. Van den Mooter and C. Vinckier, *Int. J. Pharm.*, **55**, 67 (1989).
5. J. Barber, J.I. Gyi, G.A. Morris, D.A. Pye and J.K. Sutherland, J. Chem. Soc. Chem. Comm., 1040 (1990).
6. A number of reviews have appeared on these second generation semisynthetic compounds. See, for example: P.A. Lartey and T.J. Perun in *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers B.V.: 1993; Vol. 13, pp 155-185.