Tetrahedron Letters No.2, pp. 195-198, 1971. Pergamon Press. Printed in Great Britain.

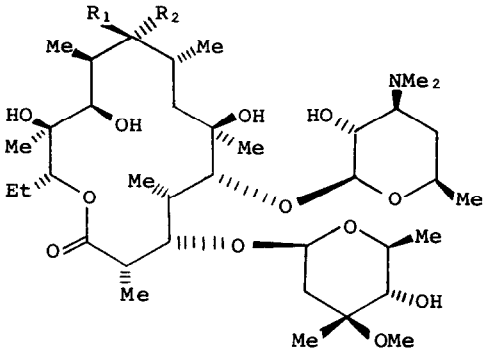
THE REDUCTION OF OXIMES WITH TERVALENT TITANIUM, A MILD DEOXIMATION PROCEDURE AND THE PARTIAL SYNTHESIS OF ERYTHROMYCYLAMINE.

Graham H. Timms and Eric Wildsmith[1]

Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey

(Received in UK 21 November 1970; accepted for publication 10 December 1970)

The conversion of erythromycin (I) into erythromycylamine (9-amino-3-O-cladinosyl-5-O-desosaminyl-6,11,12-trihydroxy-2,4,6,8,10,12-hexamethylpentadecane-13-olide) (IV) has been the object of considerable synthetic effort.[2-4] The best published procedure[4] requires reduction of erythromycin oxime (II) with hydrogen over PtO_2 and is effective only when an uneconomically high ratio of catalyst to substrate (1:2 w/w) is used. Both epimers are produced and (IVa) predominates over (IVb).



I $R_1R_2 = =O$

II $R_1R_2 = =N^{OH}$

III $R_1R_2 = =NH$

IVa $R_1 = NH_2$, $R_2 = H$

IVb $R_1 = H$, $R_2 = NH_2$

We have examined the possibility of a non-catalytic reduction of (II) and have found the oxime group resistant to reduction by a variety of dissolving metal systems. Such systems, like the above hydrogenation, are heterogeneous and it is reasonable that these methods all fail because of the inaccessibility of the metal surface to the hindered oxime group.

We chose, therefore, to examine the homogeneous reaction of the oxime (II) with various transition metal ions in low valence states.[5]

Addition of aqueous $TiCl_3$ [6] to a solution of oxime (II) in aqueous methanol buffered with acetate led to decolorisation of two equivalents of Ti^{3+} within five minutes at room temperature. T.l.c. showed clean conversion to a new compound which was inert to further reagent. This was isolated by solvent extraction and identified as erythromycin imine (III) on the basis of its elemental analysis and infra-red spectrum (ν_{max} 1640 cm^{-1}, KBr).

Similar reduction was observed with divalent vanadium (prepared by Zn/Hg/HCl reduction of vanadyl sulphate). Reduction with divalent chromium was unsuccessful in the presence of acetate but proceeded satisfactorily otherwise.

The isolation of a stable imine is compatible with the lack of reactivity of the carbonyl group of erythromycin (I), which forms an oxime and a hydrazone but is inert to semicarbazide, phenyl hydrazine and reductive amination.

The formulation of the product as imine (III) is strongly supported by its ready reduction with $NaBH_4$ in methanol to the desired amine (IV). This reduction is highly stereoselective giving only one detectable isomer, which was identified (m.p., m.m.p., i.r., n.m.r., pKa, X-ray powder diffraction pattern) with the major isomer reported by Massey *et al.*[4] and which is believed to be the 9S isomer (IVa) by analogy with the stereochemical outcome of the borohydride reduction of erythromycin itself.[7]

Deoximation Reactions

There have been several recent reports of methods for the regeneration of carbonyl compounds from the corresponding oximes.[8] In the case of a normal aldehyde or ketone, where the imine undergoes rapid hydrolysis in an aqueous medium (pH $\sim$ 5), reduction with tervalent titanium, with or without added buffer, provides a convenient method for achieving this conversion under extremely mild conditions.

During the course of this work Corey and Richman[9] have published a similar deoximation procedure which involves the conversion of the oxime to its O-acetate derivative followed by reduction with chromous acetate. In the case of saturated ketoximes a reaction temperature of 65° C. is required.

The present procedure offers several advantages:-

(i) Reaction proceeds readily with oximes themselves and thus prior

acetylation is not necessary.

(ii) In all cases studied reaction may be carried out at room temperature and is complete within one hour.

(iii) Reaction is successful for aldehydes and di-aryl ketones where the chromous acetate method fails.

(iv) Commercially available $TiCl_3$ solution may be used and the reaction followed conveniently by loss of the dark colour of Ti^{3+} complexes.

The chromous acetate procedure fails for oximes of α-diketones because of over reduction to basic products. A small amount of a basic compound is produced in the deoximation of biacetyl monoxime with Ti^{3+}, which nevertheless gives biacetyl as the principal product.

Typical Procedure

Acetophenone oxime (5.4 g., 0.05 mole) was dissolved in dioxan (100 ml.) and ammonium acetate (50 g.) added. 50% aqueous acetic acid (20 ml.) was added as a solvent aid. The mixture was stirred under nitrogen and aqueous titanium trichloride (125 ml., ∿ 0.12 mole) added gradually. After one hour t.l.c. indicated no remaining oxime. The product was extracted into ether, washed with sat.NaCl, $NaHCO_3$ and then a little water and dried over $MgSO_4$. The solvent was removed by distillation and n.m.r. analysis on the residue (ketone + dioxan) showed that the yield of ketone was 96%. Distillation under reduced pressure gave acetophenone (4.2 gms., 87.5%).

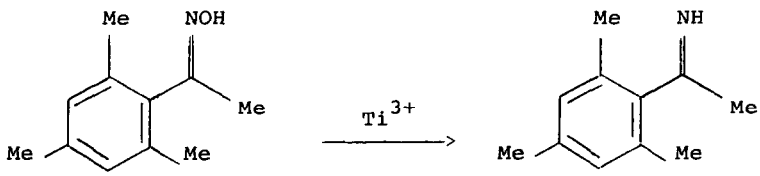
Similar successful deoximations have been carried out on the oximes of the following: cyclohexanone, 2,6-dimethyl cyclohexanone, phenyl (1-adamantyl) ketone, benzophenone, di-isopropyl ketone, mesityl oxide and benzaldehyde.

The choice of solvent is determined largely by the solubility of the oxime. Successful deoximations have been achieved in aqueous dioxan, acetic acid, dimethyl formamide and acetone. The use of alcoholic solvents leads to ketal formation.

All the oximes studied were reduced at approximately the same rate. This differs markedly from the chromous acetate reduction in which conjugated ketoximes are much more reactive.

Isolation of Imine Intermediate

Several hindered ketones were studied with the object of isolating the postulated imine intermediate. The oximes of 2,6-dimethyl cyclohexanone and phenyl (1-adamantyl) ketone gave the ketone as the only detectable product. Benzophenone oxime gave rise to a small spot on t.l.c. with the same R_f as authentic benzophenone imine[10] but this was not isolated. Methyl mesityl ketoxime (V), however, gave clean conversion to the imine (VI) which was isolated as a liquid and identified by spectroscopic methods and by conversion to the known hydrochloride[11]. In addition, the hydrochloride could be converted to the ketone by boiling in water.



V. VI.

We thank Drs. K. Gerzon and E.H. Massey for samples of the erythromycylamines (IVa) and (IVb) and Miss D.M. Prime for experimental assistance.

References:

1. To whom correspondence should be addressed.
2. S. Djokic and Z. Tamburasev, *Tetrahedron Letters*, 1645 (1967)
3. S. Djokic and Z. Tamburasev, *British Patent* 1,100,504 (1968)
4. E.H. Massey, B. Kitchell, L.D. Martin, K. Gerzon and H.W. Murphy, *Tetrahedron Letters*, 157 (1970)
5. E. Wildsmith, *United Kingdom Patent Application* No.17529/70, April 1970
6. A 15% aqueous solution of $TiCl_3$ containing $ZnCl_2$ and HCl (B.D.H. Chemicals Ltd.) was used throughout this work.
7. P.V. Demarco, *Tetrahedron Letters*, 383 (1969)
8. See reference 9. for collected references to mild deoximation methods.
9. E.J. Corey and J.E. Richman, *J.Amer.Chem.Soc.*, 92, 5276 (1970)
10. G.E.P. Smith, Jr. and F.W. Bergstrom, *J.Amer.Chem.Soc.*, 56, 2095 (1934)
11. C.R. Hauser and D.S. Hoffenberg, *J.Amer.Chem.Soc.*, 77, 4885 (1955)