THE S-OXIDATIVE DEGRADATION OF TIPREDANE PROMOTED BY THE ANTIOXIDANT SODIUM METABISULPHITE

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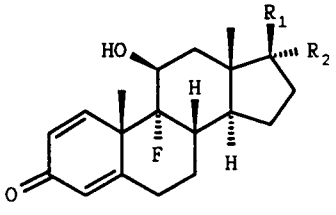
Tipredane (I) is a novel corticosteroid, which possesses a C-17 asymmetric dithioketal moiety and is susceptible to acid hydrolysis resulting in the C-17 monomethyl and monoethyl vinyl sulphide derivatives (IIa,b), these then undergo further hydrolysis to the C-17 keto derivative (Ia).
Our research has also shown that tipredane is susceptible to peroxide oxidation yielding epimeric C-17 monomethyl and monoethyl vinyl sulphoxides (IIc,d). The major products, however, are those of the epimeric methylthio sulphoxide derivatives of tipredane (Ib). The oxidation occurs exclusively on the methylthio moiety of tipredane, whereas oxidation of the corresponding C-17 epimer (Ic) yields the ethylthio sulphoxide epimers (Id). This suggests that oxidation is sterically unfavourable on the C-17 α-substituent. The epimeric methylthio sulphoxides (Ib) are produced in a ratio of approximately 80:20. X-Ray crystallography has shown that the major epimer possesses the S-configuration at sulphur. All the sulphoxide derivatives were highly susceptible to acid hydrolysis ultimately resulting in the formation of the C-17 keto derivative (Ia).



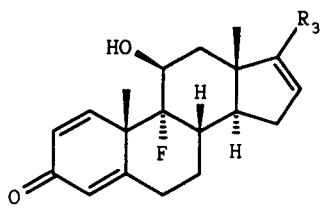
I R_1 = MeS, R_2 = EtS

Ia R_1,R_2 = O

Ib R_1 = MeS(O), R_2 = EtS

Ic R_1 = EtS, R_2 = MeS

Id R_1 = EtS(O), R_2 = MeS



IIa R_3 = MeS

IIb R_3 = EtS

IIc R_3 = MeS(O)

IId R_3 = EtS(O)

The problem of S-oxidation of tipredane was encountered in many pharmaceutical formulations and was particularly prevalent in PEG/saline/ethanol formulations in which the former excipient contained varying levels of peroxides.
In an attempt to prevent oxidation, various classes of antioxidants were incorporated into the formulation. L-Ascorbic acid and the antioxidant synergist EDTA failed to confer protection against oxidation; N-acetylcysteine prevented oxidation but caused hydrolysis. Butylated hydroxy toluene successfully retarded the oxidation of tipredane; in contrast sodium metabisulphite accelerated the oxidative degradation. Further research has shown this to be a common effect of sulphurous acid salts. Preliminary investigations have shown that the parameters important in controlling this anomolous reaction are sodium metabisulphite level, peroxide containing co-solvents and ionic strength. The peroxide/sodium metabisulphite oxidation of tipredane can be arrested with the concomitant addition of hydroquinone which suggests that the oxidation involves a free radical mechanism. Sulphite radical anions have been postulated to be formed by the autoxidation of sulphite to sulphate and to be involved in the biological oxidation of methionine (Mottley 1988; Hayatsu 1971), a similar mechanism may explain the accelerated degradation observed here and research is at present underway to verify this.

Mottley, C., Mason, R.P.(1988) Arch. Biochem. Biophys. 267: 681-689
Hayatsu, H., Inoue, M. (1971) Chem. Pharm. Bull. 19: 1286-1289