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ON THE GIF OXIDATION OF ALICYCLIC TERTIARY AMINES

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Abstract : Oxidation of various tertiary amines by the Gif^{IV} system based on an iron catalyst associated with a reductant (zinc) and molecular oxygen, led to a mixture of the keto-derivatives and the corresponding lactams . Steric hindrance and electron withdrawing substituents exert a deactivating effect on the oxidation .

The successful oxidation of saturated hydrocarbons by the Gif system to the corresponding ketones as major products[1,2] prompted us to extend the scope of this reaction to a family of alicyclic tertiary amines . Recently, it has been reported[3] that oxidation of *N*-acylpiperidine or pyrrolidine by different systems, including the Gif^{IV} system, leads exclusively to the corresponding lactam . We have studied the behaviour of various *N*-methylamines towards the Gif system (iron catalyst, zinc powder, acetic acid and pyridine, in air)[2], in order to establish the differences between *N*-acyl and *N*-alkyl substituents .

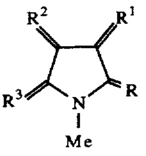
The Gif oxidations performed in the usual manner[2,4] on *N*-methyl pyrrolidine **1**, nicotine **2**, codeine **3** and mesembrane **4** have led to the corresponding lactams together with the corresponding ketones . The structures of all oxidation products were established via an extensive series of GC-MS and high resolution MS studies (VG 7070, EI PI, capillary column PCsil, 50 m), including comparison with reference samples, when available . Pyrrolidine **1** produced a mixture of *N*-methyl 2-pyrrolidone **5** and *N*-methyl 3-pyrrolidone **6** (ratio 3 : 1, yield 17 %), as well as traces of nicotine **2** and its two other regio isomers resulting from the pyridine-pyrrolidine coupling at positions 2 and 4 . Other products identified in the mixture were *N*-methyl succinimide **7** and *N*-methyl 2,4-pyrrolidinedione **8** (ratio 1 : 1.5, yield 0.2 %) . Under the same conditions, nicotine **2** gave products which correspond to oxidation of all three methylenes (total yield of this fraction 15 %) : 5'-(lactam), 4'-ketone (ratio 4 : 1), and traces of 3'-ketone .

The highly hindered codeine **3** produced small amounts (0.3 %) of codeine 6-acetate and an oxidised product which was tentatively identified as lactam **9** . It is worthy of note that the oxidation site differs from that attacked by Cp450 or other mono-oxygenases[6]. Furthermore, the sole formation of 9 means that there is a deactivation of the methylene at C-10 by the 3-methoxyl group and of the methylene at C-15 lying in the proximity of the hydroxyl on C-6 . The only oxidation site available (methylene at C-16) then furnished lactam 9 .

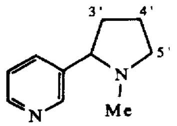
The last molecule, mesembrane 4 led to the formation of two oxidised products : 2-lactam 10 and a small quantity of 6-keto-mesembrane 11 (ratio 3 : 1, yield 2 %) . The other methylene at C-3 and C-4 are not oxidised easily because of the severe steric hindrance due to the aryl moiety . In this perspective it was interesting to investigate the oxidation of 6-hydroxy-mesembrane 12 . The anticipated deactivation of the methylene adjacent to the nitrogen by the hydroxyl group takes place and neither lactam nor ketone were formed .

Apart from the usually observed quantities of bipyridines we have identified, for the first time, in some reaction mixtures hydroxy-pyridine and its acetate . The presence of these two products is a valuable confirmation of the proposed specific role of pyridine in trapping hydroxyl radicals[7] as well as a demonstration of the utility of GC-MS techniques in mechanisti investigations .

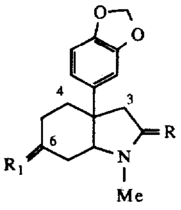
The formation of ketones in the presence of tertiary amines is another illustration of the remarkable penchant of the Gif system for the oxidation of methylene groups . The results indicate that oxidation of the methylene groups cannot involve electron transfer or radical attack . If these mechanisms were involved then only lactams would have been formed[7] .



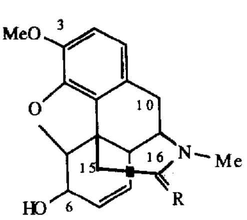
1 $R=R_1=R_2=R_3=H_2$
5 $R=O, R_1=R_2=R_3=H_2$
6 $R_1=O, R=R_2=R_3=H_2$
7 $R=R_3=O, R_1=R_2=H_2$
8 $R=R_2=O, R_1=R_3=H_2$



2



4 $R=R_1=H_2$
10 $R_1=H_2, R=O$
11 $R_1=O, R=H_2$
12 $R_1=H,OH, R=H_2$



3 $R=H_2$
9 $R=O$

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