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GIF OXIDATION OF SOME ALICYCLIC AMINES

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Abstract. The Gif oxidation of seven alicyclic tertiary amines leads essentially to the formation of lactams. The structure of the products present in trace amounts supports the mechanistic hypothesis previously advanced. The structures of the oxidation products were investigated using high performance GC-MS system.

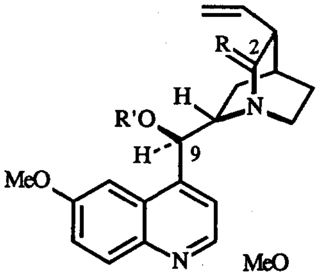
Broad studies of the Gif oxidation system (iron catalyst $Fe_3O(OAc)_6Pyr_{3.5}$, zinc powder, acetic acid, and pyridine, in air) for selective functionalisation of saturated hydrocarbons[1a], have led us to apply this process successfully to some tertiary alicyclic amines[1b]. As a result, the corresponding lactams as well as the aminoketones were obtained. In this Letter we would like to report on the oxidation of various heterocyclic compounds such as quinine 1, its O-acetate 2, quinuclidine 3, N-methylmorpholine 4, codeine 6-acetate 5, and finally mesembrane 6. The formation of lactams via the Gif system, even in the case of highly hindered amines (e.g. 1, 2, 3, and 6), remains the most interesting feature of the oxidation.

The oxidation of quinine 1 by the Gif system did not give any identifiable product in substantial amount. The presence of the secondary hydroxy group prevents the reaction which occurred on the corresponding protected quinine 9-acetate 2, leading to lactam 8 (yield 1-2%). The same phenomenon has previously been observed for the couples mesembrine 6 / 6-hydroxy mesembrane and for codeine 7 / codeine 6-acetate 5. The latter was oxidised to the corresponding lactam 9 with a slightly improved yield (0.5%) as compared to the oxidation of 7 (0.3%)[1].

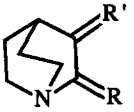
The low molecular weight simple amines 3 and 4 produced both lactams and ketones (3:1 ratios, 2-4% overall yields). The formation of the amino lactone 12 from N-methylmorpholine is an interesting observation. This compound was previously synthetised by opening ethylene oxide with sarkosinate[2]. In the case of N-methylmorpholine 4, the imide structure 13 was tentatively assigned to the double oxidation product (trace amounts). The isomeric lactam and quinuclidin-3-one 14[3] were used as reference compounds.

In both cases, the presence of the β-picoline and of the corresponding hydroxymethylene derivative was confirmed. Trifluoromethylation of the pyridine under electrochemical conditions (Gif-Orsay system) was previously reported when trifluoroacetic acid was used[4]. The formation of $CF_3^{\bullet}$ radicals at the anode was proposed to account for this observation. Pursuing this issue, we have detected a trace level of double methylation of the pyridine (lutidines, m/z 107) and a dipicoline fraction (m/z 194) as well. The methyl groups originate from the acetic acid used in the Gif oxidation as the pyridine utilised in the reaction was shown to be picoline-free (on a ppm level).

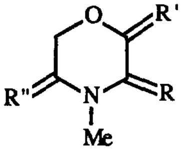
Finally, we have identified traces of a third oxidation product of mesembrane 6, mesembr-5-one 11, which was identified by comparison with a recently available reference sample[5]. This study of the oxidation by the Gif system of natural tertiary bases was made possible by the high performance GC-MS system (VG 7030, capillary columns CPSil 5, 0.4 m, 0.22 OD 25 m)[6].



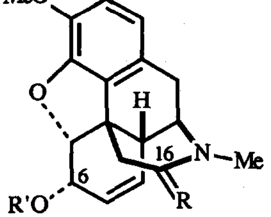
1 $R = H_2$, $R' = H$
2 $R = H_2$, $R' = Ac$
8 $R = O$, $R' = Ac$



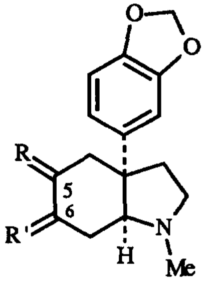
3 $R = R' = H_2$
10 $R = O$, $R' = H_2$
14 $R = H_2$, $R' = O$



4 $R = R' = R'' = H_2$
11 $R = O$, $R' = R'' = H_2$
12 $R' = O$, $R = R'' = H_2$
13 $R = R'' = O$, $R' = H_2$



5 $R = H_2$, $R' = Ac$
9 $R = O$, $R' = Ac$
7 $R = H_2$, $R' = H$



6 $R = R' = H_2$
11 $R = O$, $R' = H_2$

References and Notes.

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6. Full experimental details and product structures establishment will be given in a forthcoming paper.

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