GIF^{IV} OXIDATION OF SOME INDOLIC ALKALOIDS*

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Abstract - *The title oxidation was performed on four indolic alkaloids, β-carboline (1), reserpine (6), ajmaline (10) and ibogaine (11), leading to alicyclic hydroxylation of the starting materials. The numerous side products characterised during this reaction (due to reduction or coupling with solvent) as well as selective deuterium labelling experiments enabled us apart from the oxidation sites to study the Gif reaction mechanism.*

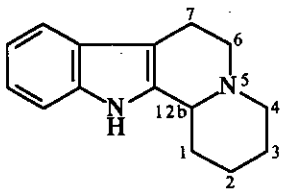
In previous papers on the Gif oxidation, we have observed the lactamisation and ketonisation of alicyclic amines together with their occasional hydroxylation.[1-3] Pursuing this study, we have performed a similar oxidation on four indolic alkaloids and their deuterated derivatives in order to determine the oxidation position as well as to study the mechanism of the Gif^{IV} reaction.[4]

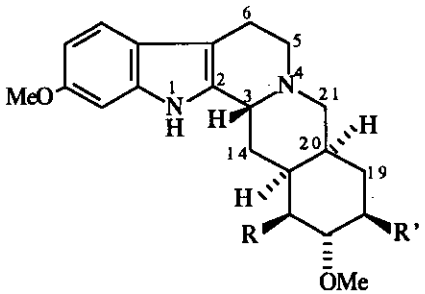
The crude mixtures obtained from Gif-oxidation process were analysed by GC-MS in order to confirm the structures of oxidation products and to quantify these products. Also, the structures of trace product provide further details on the controversial question of Gif system mechanism. The large quantities of pyridine and acetic acid in the Gif^{IV} oxidation reaction system (pyridine, acetic acid, Fe^{II} catalyst, zinc, O_2, room temperature) represent additional difficulties. A reliable work-up and preconcentration procedure is difficult to achieve without quantitative losses or modification of the Gif-reaction products. The Gif oxidation developed by D.H.R. Barton, and numerous related reactions, are the reactions employing complex redox systems. When applied to the sensitive indolic system, these systems can react either as reducing or as oxidating agents or as methylating agents ($CH_3^{\bullet}$ formation) or by coupling to the pyridine.

* To Professor Sir D.H.R. Barton without whom this work would not be possible for his 75th birthday.

An unprotected hydroxyl group usually acts as an inhibitor of Gif oxidation.[2,5] The indolic NR group can play a similar role, if we assume its participation in a Cp450-like complex e. g. in a Gif trinuclear catalyst.

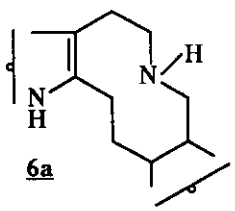
In this respect, it is conceivable that the hydroxylation can be favoured over lactam carbonylation for amines. The soft Gif oxidation conditions alone can explain the absence of indole rearrangement products.



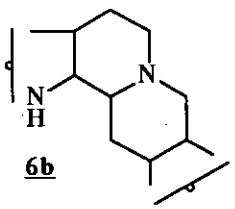


1 - d_0
2 - 6,6 - d_2
3 - 7,7 - d_2
4 - 3,3 - d_2
5 - 4,4 - d_2
12 - 6 - d_1

6 R = COOMe; R'=OCOTMP
(TMP = 3', 4', 5'- trimethoxyphenyl)



6a



6b

The oxidation of β-carboline (**1**)(1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine) leads to a mixture of compounds with preferential hydroxylation at C-6 methylene (yield 5%, 90% of starting material has been recovered). The hydroxylation position was confirmed by Gif^{IV} oxidation of a series of four dideuterated isomers (**2**-**5**) obtained from specifically designed syntheses[6] and from the mass spectrometric fragmentation pattern of the C,D rings of carboline. The 6,6-d_2 isomer (**2**) loses one deuterium from the C-6 methylene. Consequently, methane chemical ionisation leads to characteristic dehydration ions ($MH+CH_4-H_2O$) with an M-2 fragment. The 6-hydroxycarboline structure was also characterised as a silyl ether derivative using GC-MS technique. Some available hydroxycarbolines

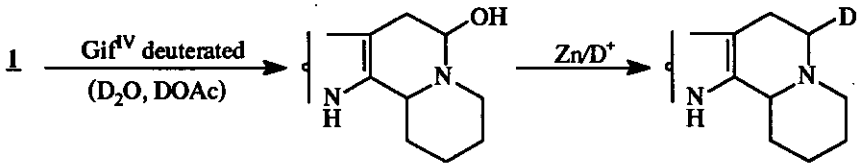
(e. g. 2-hydroxy-) were used as models for this comparison.[7]

The C-7 methylene and the other prolactam methylene at C-4 are equally accessibe to this oxidizing agent. However both lactams were absent in the mixture.

The presence of products of coupling to the pyridine was also observed. As we have already reported, methylene or methine-pyridine coupling easily takes place for several compouds under Gif conditions.[8] Using the same series of selectively deuterated β-carboline derivatives, coupling toward pyridine (in ortho or para position) at C-7 was observed together with trace amount of coupling products to the bipyridine and to the picoline at the same methylene. This observation is unexpected as the usual coupling site is the same as the oxidation site but it can be explained as a result of an independent reaction with Gif system. The pyridine is believed to be essential for Gif chemistry, its role being to quench $^{\bullet}OH$ and prevent Fenton's type reaction. Also the pyridine radical can react with the highly activated benzylic C-7, of the indolic base (2). The formation of all six bipyridine isomers (2,2'; 2,4'; 2,3'; 3,3'; 3,4'; 4,4') in the Gif reaction, as previously reported by our group,[8] nicely supports the hypothesis of random Py formation followed by polymerisation in an independent process.

The mixture obtained from Gif^{IV} oxidation also contained high yield (10%) of reduction product. Altough this was unexpected, it is obvious that the Gif^{IV} system, usually designed for oxidation and functionalisation of hydrocarbons, is a complex red-ox system which allows not only methylene or methine oxidation but also reduction of some functions by Zn/AcOH. The 2,3-indolic bond and the N5-C12b carboline bond are particularly susceptible to reduction by hydrides[9] and zinc dust/acid respectively.[10] The Gif^{IV} allows the second reduction under very mild conditions with a relatively high yield.

The low yield of hydroxylation of indoles under Gif oxidation may also be related to the room temperature zinc-acid induced reductive cleavage of the tertiary carbinolamine C-OH bond formed during oxidation. In order to further study this point, the Gif^{IV} (CD_3COOD, D_2O) system was used for the oxidation of β-carboline (1). The product was monodeuterated at C-6, providing additional confirmation of the hydroxylation position[11] (Scheme 1).



Scheme 1 **12**

Surprisingly the zinc-acid reduction of **1** at room temperature without the Gif Fe^{II} trinuclear catalyst leads to a dramatic loss of reduction product (**8**).

In order to complete this study the reduced indolic bases (**7**) and (**8**) were oxidised with the Gif^{IV} system. Lactamisation combined with hydroxylation at C-6 methylene was observed for compound (**7**) (yield 7 %, lactam / alcohol ratio 3:1); while the oxidation of compound (**9**) leads to a small yield of lactam tentatively assigned to methylene C-4.

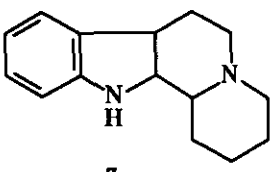
In this respect, Murata's conclusion[12] for the oxidation of the similarly activated *N*-acyl amines is confirmed. The reductive opening of the N5-C12b bond combined with *N*-acyl activation completely destroyed the β-carboline behavior of compound (**9**) on oxidation with Gif^{IV}.

Gif oxidation of reserpine (**6**) leads to the 5-hydroxy derivative together with traces of the correponding lactam detected via CI/CH_4. It is interesting to point out that biological oxidation of **6** usually occurs at B and C ring junction or on the aromatic moieties.[13] Another product identified in the postoxidation mixture has the mass of the starting materiel plus two units and has been identified as the product of C3-N4 bond of reserpine. The structure of this product, was established by compaison with two references compounds (**6a**) and (**6b**) prepared by reducing reserpine (**6**) with $CF_3COOH/NaBH_4$ and Zn/AcOH respectively.[9,10] The reduction product obtained during the Gif oxidation was identified as **6a**. This last result is a proof of the double nature (red-ox) of the Gif system.

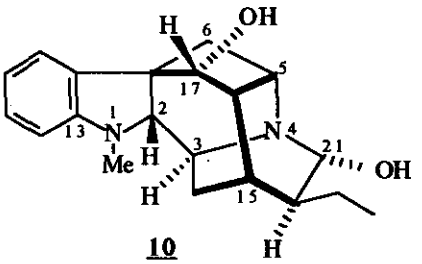
Under the same conditions, the highly hindered ajmaline (**10**) gave a hydroxylated product tentatively assigned as 6-hydroxyajmaline. Both ajmaline 21-acetate and ajmaline 17,21-diacetate were produced during this oxidation as well as a trace amount of a methylajmaline. The methyl radical is believed to come from the acetic acid, but the position of methylation was not determined.

The oxidation of ibogaine (**11**) produced a small amount (2%) of mono- and dihydroxy derivatives

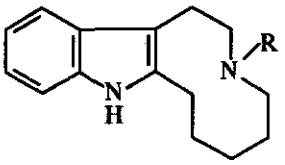
with the former tentatively identified as 7-hydroxyibogaine. We also found trace quantities of the correponding lactam and the reduction product (5%) resulting from reductive opening of the C5-C18 bond as confirmed by mass spectrometry and previously observed for β-carboline (1). Zinc-acetic acid reduction of 11 under Gif^{IV} conditions without the trinuclear catalyst leads again to a loss of yield of reduction product. It seems from both examples that the Gif^{IV} catalyst may be necessary even for reduction during this red-ox reaction.



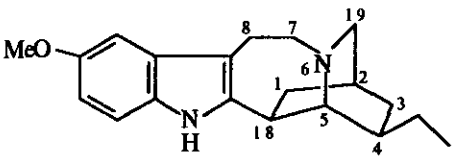
7



10



8 R = H
9 R = Ac



11

The predominent hydroxylation of indolic alkaloids under Gif^{IV} conditions and absence of carbonylated derivatives remain the newest and the most intriguing results of this study. The reduction and methylation of 1, 6 and 11, the absence of reduction for (10) together with the double hydroxylation of 11 and the first reported case of oxidation (hydroxylation) and methylation for the hydroxyalkaloid(10)add to the list of new and unpredictable results obtained from Gif reactions.

Coupling with pyridine and with bipyridines is observed for all indolic alkaloids, but does not take place on the oxidized methylene here. This coupling which increases with the aging of Gif^{IV} trinuclear catalyst could be suppressed by the successive addition of reducing agents (Zn, acid).

The results reported in this paper indicate that the indolic moiety interacts with the Gif catalyst, in a

manner similar to the Cp450 oxidation mechanism. In the absence of catalyst the reduction of indolic alkaloids as well as the reductive rearrangement of the ibogaine (11) azabicyclo[2,2,2]octane moiety to the less strained tertiary N5-piperidine structure is very weak or simply does not occur at room temperature. Finally the separation of the oxidation site from the pyridine coupling site presents another puzzling problem, tentatively rationalized as a result of two parallel reactions taking place during the Gif^{IV} oxidation of indolic alkaloids.

The biomimetic, soft Gif oxidation reaction applied to indolic alkaloids has produced enough interesting results to justify further development of new, more powerful and selective catalysts.

EXPERIMENTAL

General procedure for Gif ^{IV} oxidation. The substrate (2 mmol), the solvent [pyridine (28 ml)-acetic acid (2.3 ml), with or without water (1.85 ml)], trinuclear iron catalyst (7 μmol), and zinc powder (1.31 g, 20 mmol) were placed in a 125 ml conical flask and stirred at room temperature for 18 h under a static pressure of oxygen, provided by a balloon, or under a flow of air or oxygen blown over the surface of the reaction mixture, or simply with flask open to the air. The crude mixture was filtrated then concentrated under reduced pressure. The residue was treated with aqueous sodium hydroxide (0.1N), then extracted with ether to afford the reaction products which were analysed by GC-MS(Riber 1030, EI-PI, col. CPSIL 25 m, Φ 0.22 mm, 0.16 μ) and by hplc preparative.

ACKNOWLEDGEMENTS

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