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HYDROXYLATION OF INDOLINES AND INDOLES BY HYDROGEN PEROXIDE IN SUPERACIDS

Christian BERRIER, Jean-Claude JACQUESY*, Marie-Paule JOUANNETAUD and Alain RENOUX

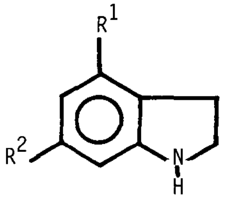
Laboratoire de CHIMIE XII - Faculté des Sciences
C.N.R.S. U.A. N° 489 "Synthèse et Réactivité de Produits Naturels"
40, Avenue du Recteur Pineau - 86022 POITIERS Cedex (France)

ABSTRACT - In SbF_5-HF, indolines and indoles are hydroxylated on the aromatic ring, protonated hydrogen peroxide $H_3O_2^+$ reacting on the protonated substrates.

Electrophilic hydroxylation of aromatics has been intensively studied and it has been shown that hydrogen peroxide in superacidic media is a convenient reagent to achieve the reaction[1]. Anilines being converted into aminophenols without oxidation or degradation of the nitrogen substituent[2], we have studied the reactivity of the model substrates 1a-7a whose frameworks are part of many natural bases.

Hydroxylation of compounds 1a-3a has been carried out as previously described for anilines : 70% hydrogen peroxide (6 mmoles) is added to a cold (-20°C) stirred solution of the substrate (4 mmoles) in SbF_5-HF (molar ratio : 0.04; 20 ml). After 10 to 20 minutes (see table) and usual work-up, products are isolated by column chromatography over SiO_2.

With the more reactive indoles 4a-6a and indolenine 7a, reaction time is only 3 minutes and more acidic conditions are used (SbF_5-HF : 0.08) to limit polymerisation processes.



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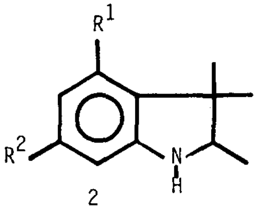

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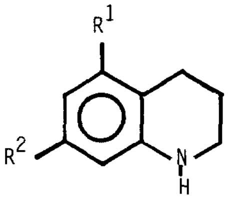

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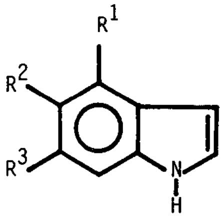
a $R^1 = R^2 = H$
b $R^1 = OH$, $R^2 = H$
c $R^1 = H$, $R^2 = OH$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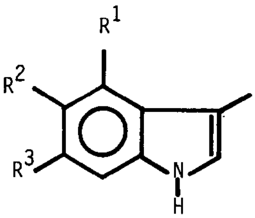
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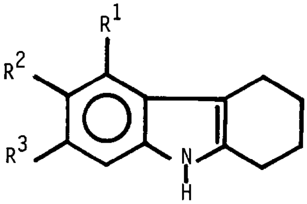
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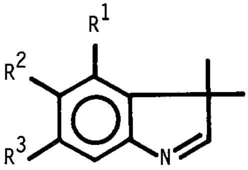
a : $R^1 = R^2 = R^3 = H$

b : $R^1 = OH$, $R^2 = R^3 = H$

c : $R^1 = R^3 = H$, $R^2 = OH$

d : $R^1 = R^2 = H$, $R^3 = OH$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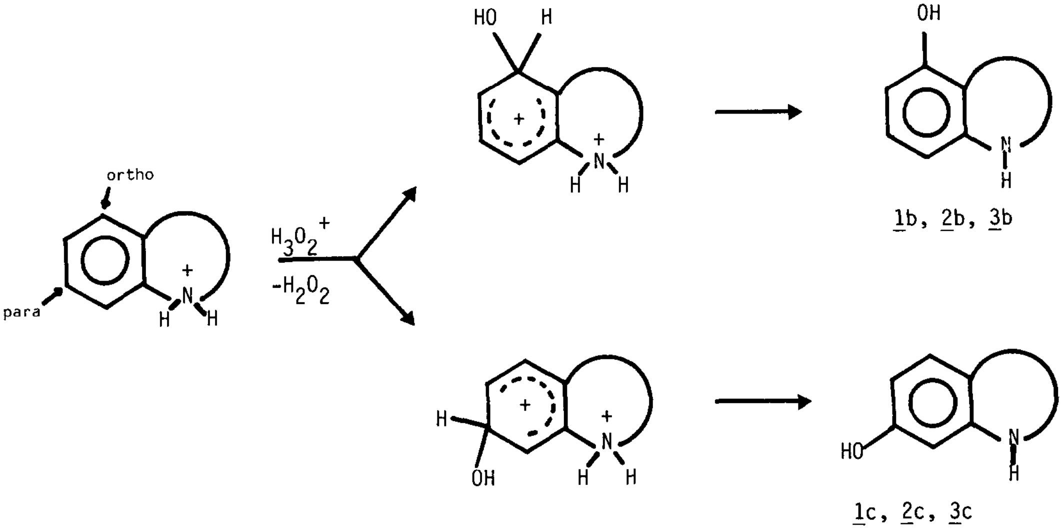
STARTING MATERIAL	REACTION TIME (min)	PRODUCTS (% yield)
1a	10	1b(33.5) + 1c(42.5)
2a	20	2b(20) + 2c(56)
3a	10	3b(44) + 3c(22)
4a	3	4a(5) + 4b(5) + 4c(20) + 4d(10)
5a	3	5a(5) + 5b(6) + 5c(31) + 5d(18)
6a	3	6b(9) + 6c(48) + 6d(20)
7a	3	7b(7) + 7c(55) + 7d(24)

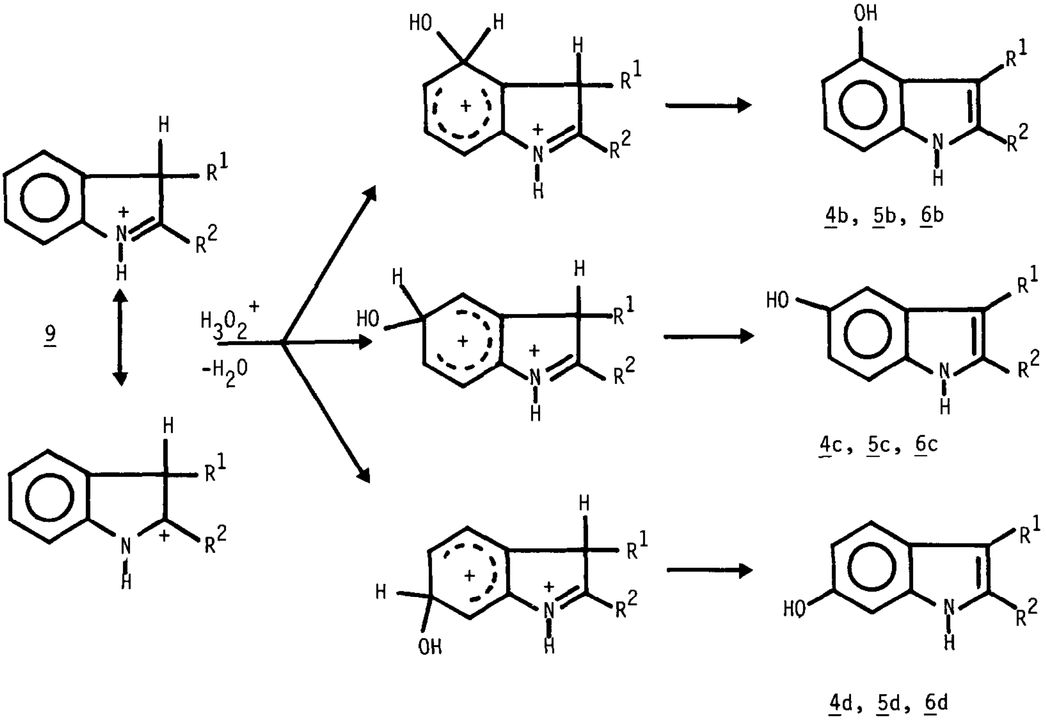
The results, reported in table show that only hydroxylation of the aromatic ring is observed, the process being more selective on substrates 1a-3a that on indoles 4a-6a and indolenine 7a. Furthermore, the products are stable in the reaction conditions ruling out an initial hydroxylation on the ring followed by isomerisation.

The observed regioselectivity can be accounted for by involvement of electrophilic protonated hydrogen peroxide $H_3O_2^+$ [1a,1f,2,3] reacting on the protonated substrate :

- indolines 1a and 2a and tetrahydroquinoline 3a are N-protonated[4] in superacids. On the resulting ammonium ions 8, substitution occurs ortho or para to the alkyl group which is prevailing over the deactivating protonated nitrogen substituent. Furthermore the observed ortho/para substitution ratio is lower in the indoline than in the tetrahydroquinoline series and this might be the result of he Mills-Nixon effect[5] (the observed 3b/3c ratio is quite "normal" as shown by hydroxylation of ortho-oluidine in the same conditions[6]).

- protonation of indoles 4a-6a on carbon 3 to give ions 9[7] protects them from polymerisation and analogous ion is obtained by N-protonation of indolenine 7a.





The observed high reactivity of these substrates and the poor regioselectivity of hydroxylation can be accounted for by reaction of ions 9, more delocalized than ions 8.

In usual conditions indolines and indoles are reacting with electrophiles on carbons 5 and (or 2) respectively. In superacidic media a completely different regioselectivity is operative, the electrophile reacting on the protonated substrates, as exemplified by the reaction with hydrogen peroxide.

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