Oxidation of Ellipticine with *Fremy's* Salt under Sonochemical Conditions

Oxidation von Ellipticin mit "*Fremy*-Salz" unter Ultraschallbedingungen

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Ellipticine (**E**) **1** is an indolic alkaloid with antitumor activity[1]. Some of its phenolic derivatives as *N*-methyl-9-hydroxyellipticine (celiptinium), obtained from 9-hydroxyellipticine (**9-OH E**), exhibit high cytotoxic activity[2]. Syntheses of **9-OH E** from 5-methoxyindole *via* 9-methoxyellipticine are not satisfactory if one considers yields and cost.

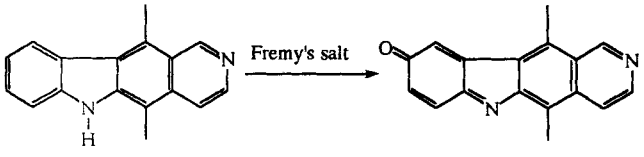
An interesting alternative route was to use indole, a less expensive product compared to 9-methoxyindole, to obtain **E** as starting compound for the hydroxyl derivative.

Recently, a regioselective formylation of **E** followed by *Baeyer-Villiger* oxidation has been reported as an expedient synthesis of **9-OH E**[3]. Before knowing this result, we tried to carry out the same conversion by direct oxidation of **1** as in the *in vivo* metabolism[4].

Results and discussion

In the present study we have found that ellipticine (**1**) is not oxidized to **9-OH E** by various P450 chemical models (metalloporphyrins activated by PhIO, NaOCl, mCPBA, H_2O_2, Bu_4NHSO_5; $VO(acac)_2/PhIO_2$; $H_2O_2/Fe(III)/CH_3CN$), whilst under the same conditions, **9-OH E** is easily transformed in 9-oxoellipticine (**9-OXO E**; **2**), in agreement with results obtained with the potassium hydrogenopersulfate-metalloporphyrin system[5].

So the potassium nitrosodisulfonate (*Fremy's* salt), a valuable oxidant for the synthesis of quinone-imines from heterocyclic amines[6,7], was studied. Under these conditions the first chemical conversion of **E** (**1**) to **9-OXO E** (**2**) was observed, then its reduction into **9-OH E** was easily realized with ascorbic acid[8].



1 **2**

Scheme

The radical nature of *Fremy's* salt led us to carry out the oxidation reaction under ultrasonic conditions in order to promote single electron transfers and so increase the yields. Some of our results are reported in the Table. The sensitivity of the heterogeneous oxidation reaction with *Fremy's* salt to ultrasonic effects was confirmed. Under optimal conditions (probe 4 mm and intensity 40W) 40% of the expected quinone-imine **2** was obtained.

Table: Experimental conditions and yields of **9-OXO E**

Conditions[a]	Solvent	Min	Yield (%)[b]
Stirring	Benzene	75	20
Stirring	Chloroform	75	15
))))[c], Bath	Benzene	30	20
))))), Probe, 4mm, 40W	Benzene	15	40
))))), Probe, 4mm, 40W	Chloroform	15	35
))))), Probe, 4mm, 20W	Benzene	15	35
))))), Probe, 9,5mm, 40W	Benzene	15	25
))))), Probe, 9,5mm, 40W	Chloroform	15	20
))))), Probe, 18mm, 100W	Benzene	15	10

[a] At 20°C.
[b] Calculated for isolated products.
[c]))))): Ultrasonic conditions.

The reactions are very sensitive to the solvent used; with acetone, acetonitrile, and THF only traces of **9-OXO E** (**2**) were obtained. With the more energetic probe (18 mm, used at 100 W) the lowest yield was obtained. In this case unidentified products, resulting probably of dimerisation, were formed. This reaction appears to be of type 3 (true sonochemical reaction in heterogeneous medium) in the classification established by *Luche*[9].

In conclusion, *Fremy's* salt is actually the only chemical oxidant known to carry out the direct conversion of **E** (**1**) into **9-OXO E** (**2**).

We thank the Sanofi group for the gift of **E** (**1**) and **9-OH E**

Experimental Part

Sonochemical reactions: Sonoclean S-1000 bath, Labsonic U generator (probes: 4 mm diameter, 0-50 W electrical power input; 9.5 mm, 0-45 W; 18 mm, 0-150 W). Reaction vessel: thermostated cylinder, 35 mm diameter, 80 mm depth. Column chromatography: Amicon silicagel Si60 (35-70 µm). Melting points: Büchi 510 (uncorr.). - IR spectra: Perkin-Elmer 1310.-^{1}NMR spectra: Bruker AM 300 (300 Mz, TMS int. stand.).

Oxidation of ellipticine (**1**)

To a solution of **1** (0.2 mmol) in solvent (20 ml) was added slowly, with a syringe, a solution of *Fremy's* salt (0.4 mmol) in 1 ml of a KH_2PO_4 aqueous solution (0.16 mol/l) diluted in 6 ml of water. After sonication the mixture was extracted with $CHCl_3$ (2 x 30 ml). The org. phase was evaporated after drying and the residue was chromatographied (eluent: C_6H_6, $CHCl_3$, EtOH, 3/2/1) to give pure **9-OXO E** (**2**) as a red solid. - m.p.: 345°C. - IR (KBr): $\tilde{\nu}$ = 1600 cm^{-1} (C=N); 1630 (C=O). - ^{1}H-NMR ($CDCl_3$): δ(ppm) = 9.39 (s; 1H, 1-H), 8.64 (d; J = 6 Hz, 1H, 3-H), 7.75 (d; J = 6, 1H, 4-H), 7.44 (d; J = 10, 1H, 7-H), 6.80 (s; 1H, 10-H), 6.51 (dd; J = 10 and 1, 1H, 8-H), 2.79 (s; 3H, 11-CH_3), 2.78 (s; 3H, 5-CH_3). - These data are in agreement with those already reported[10].

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Reduction of 9-OXO-E (2)

To a solution of **2** (0.2 mmol) in ethanol (20 ml) were added under stirring 0.20 mmol of ascorbic acid. After disappearence of the red tint the solvent was evaporated and the residue was purified as above to give 9-OH E as a yellow solid. - Yield 95%; m.p. >330°C. - IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (OH); 3100 (NH). - ^{1}H-NMR ([D_6]DMSO): δ(ppm) = 11.06 (s; 1H, OH), 9.65 (s; 1H, 1-H), 9.10 (s; 1H, NH), 8.41 (d; J = 6 Hz, 1H, 3-H), 7.89 (d; J = 6, 1H, 4-H), 7.77 (s; 1H, 10-H), 7.38 (d; J = 8.6, 1H, 7-H), 7.02 (d; J = 8.6, 1H, 8-H), 3.20 (s; 1H, 11-CH_3), 2.70 (s; 3H, 5-CH_3). - These data are identical to that of an authentic sample.

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