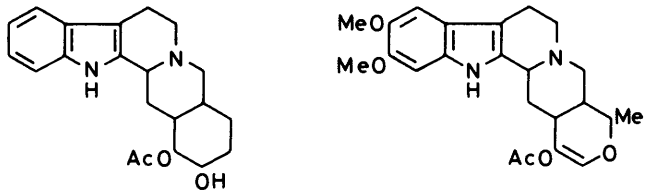
Kinetics of Yohimbine and Reserpiline Oxidations by Peroxodisulphate

Manuel Balón,* Marice A. Muñoz, M. Carmen Carmona, and Miguel Sánchez
Departamento de Fisicoquímica Aplicada, Facultad de Farmacia, Universidad de Sevilla, 41012 Sevilla, Spain

The kinetics of yohimbine and reserpiline oxidations by peroxodisulphate in aqueous solution have been investigated. The results suggest that the reactions proceed *via* reversible formation of a 3*H*-indole (indolenine) intermediate, which subsequently decomposes to yield a 3,4-didehydro derivative. The values of the equilibrium and rate constants are reported. Potassium chloride showed a retarding effect on the reaction; the effect of Ag^+ cations was negligible. A mechanism involving nucleophilic displacement on peroxide oxygen is proposed.

Although the oxidations of indole alkaloids by various oxidizing agents have been thoroughly studied,[1,2] the action of peroxodisulphate upon these compounds has not received detailed attention. However, potassium peroxodisulphate is well known as an excellent and versatile oxidant for a variety of organic compounds;[3–5] indeed it has been reported to be an effective reagent for oxidation of indoles.[6,7]

In this paper we report a kinetic study of the oxidations of the Rauwolfia alkaloids yohimbine (**1**) and reserpiline (**2**) by peroxodisulphate. Rauwolfia alkaloids[8] have achieved significance as sympatholytic, antihypertensive, and sedative agents.



(1) Yohimbine (2) Reserpiline

Scheme 1.

Experimental

Materials.—Yohimbine and reserpiline hydrochlorides (C. H. Boehringer Sohn) were used as received. Stock solutions (10^{-3}M) were prepared by weighing; the samples were dissolved in 5 cm^3 of methanol, diluted with distilled water to 250 cm^3, and stored in the dark. Precipitation was not observed on further dilution. Potassium peroxodisulphate and all other chemicals used were of analytical grade.

Product Analysis.—A typical reaction mixture of each alkaloid was monitored by u.v.–visible spectrometry in the region 240—400 nm. At zero time the only absorption peaks, corresponding to the aqueous solutions of yohimbine and reserpiline, were at 278 and 300 nm respectively. During the reactions decreasing absorbance was observed at these wavelengths, and new absorption bands appeared at 350 (yohimbine) and 394 nm (reserpiline). At the end of the reaction, slow absorbance decreases were observed at these wavelengths. At much longer reaction times the spectra suggested that the indole ring had been cleaved.

Characterization of the products was attempted by t.l.c. analysis. Samples of the reaction mixtures were chromatographed on Kieselgel 60G (Merck) using chloroform–methanol (4:1) as the mobile phase. These samples were taken at the first stage of the reaction in order to avoid the effects of secondary reactions. Chromatograms showed two spots, corresponding to the starting alkaloid and product. The products were identical (t.l.c.) with those obtained by treating the alkaloids with nitrous acid in sulphuric acid medium. It is well known that this reagent oxidizes Rauwolfia alkaloids to the corresponding 3,4-didehydro derivatives.[9]

The formation of these latter products was confirmed by fluorescence spectroscopy. The fluorescence spectra of the reaction mixtures (Perkin-Elmer 650-40 spectrophotofluorometer) exhibited excitation maxima at 350 (yohimbine) and 397 nm (reserpiline) and emission maxima at 504 and 497 nm, respectively. These bands correspond fairly well with those reported for similar compounds.[10]

Kinetic Measurements.—Kinetic measurements were made with a Lambda-5 spectrophotometer equipped with a thermostatted cell compartment. The temperature was maintained at the desired value to within ± 0.1 °C. After the reagents had reached thermal equilibrium, the reactions were initiated by addition of the alkaloid solution to a solution containing an appropriate concentration of peroxodisulphate. The mixtures were transferred into a silica cell as quickly as possible.

Kinetic runs were carried out under pseudo-first-order conditions with peroxodisulphate in large excess. The reactions were usually followed at the absorption maxima of the alkaloid. It was also verified, in experiments in which alkaloid disappearance and product appearance were followed simultaneously, that rate constant values were the same within experimental error. Pseudo-first-order rate constants, k_{obs}, were obtained by non-linear least-squares fitting of the absorbance *vs.* time measurements to equation (1); A_0, A_∞, and k_{obs} were taken as floating parameters and excellent agreement between experimental and calculated A_t values was obtained for about 80—90% of the reaction. This method always gave reproducible results; rate constants in duplicate runs were reproducible to within better than 5%.

$$A_t = A_\infty + (A_0 - A_\infty) \exp(-k_{obs}t) \qquad (1)$$

Results

To evaluate the order of reaction with respect to oxidant, reactions were carried out at different concentrations of peroxodisulphate. The results are recorded in Table 1. The rate constants presented are the averages obtained from at least two independent runs. It is apparent that k_{obs} values increase with peroxodisulphate concentration, although plots of k_{obs} *vs.* $[S_2O_8^{2-}]$ are curved.

In order to clarify the reaction mechanism, the catalytic effect of Ag^+ ions on the reaction rates was examined. This cation is known to be an effective catalyst for peroxodisulphate reactions.[3–5] However, there was no detectable effect on k_{obs}

Table 1. Pseudo-first-order rate constants for the oxidation reactions of yohimbine and reserpiline by peroxodisulphate at 25 °C ([alkaloid] = 2.5×10^{-4}M)

Yohimbine		Reserpiline	
$10^2[S_2O_8^{2-}]$/M	k_{obs}/min^{-1}	$10^3[S_2O_8^{2-}]$/M	k_{obs}/min^{-1}
5	0.077	10	0.272
4	0.066	8	0.238
3	0.058	5	0.173
2.5	0.053	4	0.139
2	0.045	3	0.105
1.5	0.037	2.5	0.089
1	0.031	2	0.073
0.75	0.022	1.5	0.056
0.50	0.017	1	0.038
0.25	0.009	0.50	0.019

Table 2. Dependence of [KCl] on k_{obs} at 25 °C

	k_{obs}/min^{-1}	
[KCl]/M	Yohimbine[a]	Reserpiline[b]
0	0.053	0.089
0.2	0.041	0.036
0.4	0.036	0.028
0.6	0.032	0.024
0.8	0.029	0.019

[a] [Yohimbine] = 2×10^{-4}M; $[S_2O_8^{2-}] = 2.5 \times 10^{-2}$M. [b] [Reserpiline] = 2.5×10^{-4}M; $[S_2O_8^{2-}] = 2.5 \times 10^{-3}$M.

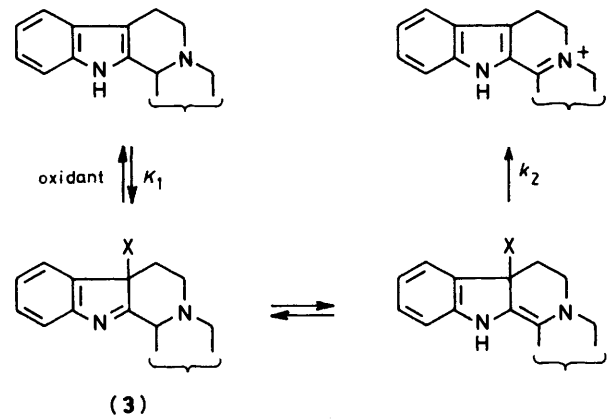
with Ag^+ ion concentrations in the range 10^{-5}—10^{-6}M. The influence of potassium chloride concentration on k_{obs} was also investigated. A negative effect (Table 2) was observed. Plots of ln k_{obs} *vs* $I^{1/2}$ (I = ionic strength) are linear. However, the application of simple electrostatic theory to solutions of high ionic strength and to reactants of large size is doubtful.

The temperature dependence of the rate constants is shown in Table 3. Activation energies of 40.5 and 52.3 kJ mol^{-1} (reserpiline and yohimbine respectively) were calculated from plots of ln k_{obs} *vs* $1/T$.

Table 3. Effects of temperature on k_{obs}

	k_{obs}/min^{-1}	
t/°C	Yohimbine[a]	Reserpiline[b]
20	0.021	0.068
25	0.030	0.089
30	0.043	0.119
35	0.061	0.153
40	0.083	0.199

[a] [Yohimbine] = 2×10^{-4}M; $[S_2O_8^{2-}] = 1 \times 10^{-2}$M. [b] [Reserpiline] = 2.5×10^{-4}M; $[S_2O_8^{2-}] = 2.5 \times 10^{-3}$M.



Scheme 2.

$$v = \frac{k_2K_1[S_2O_8^{2-}]\cdot[\text{Alkaloid}]_T}{1 + K_1[S_2O_8^{2-}]} \quad (2)$$

$$k_{obs} = \frac{k_2K_1[S_2O_8^{2-}]}{1 + K_1[S_2O_8^{2-}]} \quad (3)$$

$$\frac{1}{k_{obs}} = \frac{1}{k_2K_1[S_2O_8^{2-}]} + \frac{1}{k_2} \quad (4)$$

Discussion

The oxidation of indole alkaloids containing a tetrahydro-β-carboline nucleus to 3,4-didehydro-β-carbolines by a variety of oxidizing agents has received considerable attention. However, while widely used synthetically, these reactions have not been the subject of kinetic studies. The general mechanism shown in Scheme 2 has been put forward by Taylor[11,12] for these reactions.

This mechanism initially involves the formation *via* a reversible step of a 3*H*-indole (indolenine) intermediate (**3**) by electrophilic attack of the oxidant at the 3-position of the indole ring. Decomposition of the intermediate may be fast or slow depending upon its stability. The isolation and characterization of such intermediates supports this mechanism.[12,13]

It seems reasonable to assume a similar mechanism for the yohimbine and reserpiline oxidations by peroxodisulphate. If $[\text{Alkaloid}]_T = [\text{Alkaloid}] + [\text{Intermediate}]$, the rate law (2) is obtained; hence k_{obs} is given by equation (3).

Equation (3) can be rearranged as equation (4), which shows that a plot of the reciprocal of k_{obs} against the reciprocal of the peroxodisulphate concentration should give a straight line with an intercept equal to $1/k_2$ and a slope equal to $1/k_2K_1$. Such plots (Figure) confirm the consistency of the experimental data with this mechanism. Values of K_1 and k_2 obtained by a fit of equation (4) are 35 l mol^{-1} and 1.85×10^{-3} s^{-1} (yohimbine) and 39.5 l mol^{-1} and 1.67×10^{-2} s^{-1} (reserpiline), respectively.

The K_1 values are very similar, but there is a great difference between the k_2 values. The higher reactivity of the 3*H*-indole from reserpiline than that from yohimbine may be due to the influence of the methoxy substituents. It has been demonstrated that methoxy substitution at the 6-position of the indole ring has a marked effect on the properties of indole derivatives.[14,15] This substitution would be expected to facilitate the decomposition of the 3*H*-indole, probably *via* intramolecular electron transfer.

We now consider the nature and formation of the proposed 3*H*-indole intermediate. Taking into account the nature of the oxidizing agent, it appears that *O*-sulphates are reasonable 3*H*-indole intermediates (X = $-OSO_3^-$) in these reactions. Similar intermediates have been proposed in other oxidations of indole derivatives by peroxodisulphate.[6] On the other hand, there are at least two possible mechanisms for intermediate formation: (a) cleavage of the peroxodisulphate molecule and subsequent attack of the sulphate ion radicals formed on C-3 of the indole, and (b) peroxodisulphate attack at this position with displacement of sulphate ion.

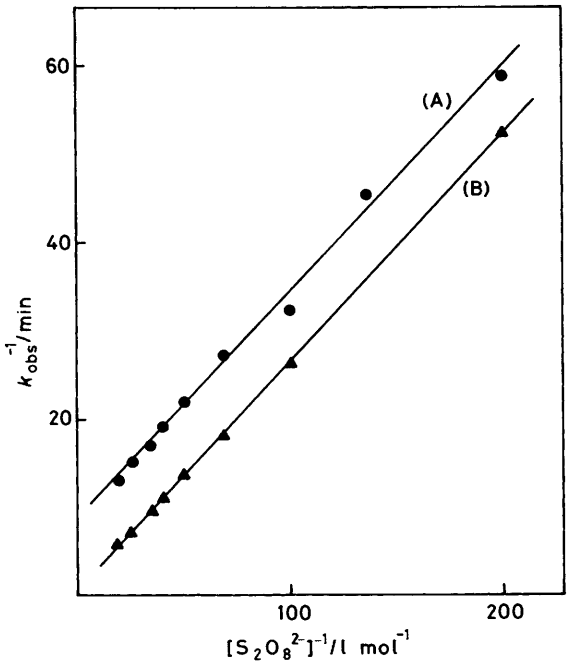
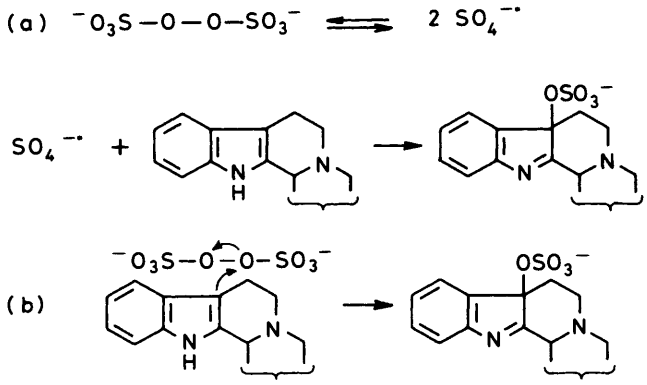


Figure. Plots of $1/k_{obs}$ against (A) $1/[S_2O_8^{2-}]$ for yohimbine and (B) $10^{-1}/[S_2O_8^{2-}]$ for reserpiline

Sulphate ion radicals, $SO_4^{-\bullet}$, have been invoked as intermediates in a variety of peroxodisulphate reactions,[3-5] these are usually accelerated by trace-metal ions, of which Ag^+ is the most thoroughly investigated. The rates of the reactions catalysed by these ions are independent of reductant concentration. A salient feature of our experimental results is the absence of catalysis in the presence of Ag^+. This observation eliminates a mechanism depending on homolysis of peroxodisulphate, and suggests that these reactions proceed *via* nucleophilic displacement at the peroxidic linkage of peroxodisulphate rather than by a radical mechanism. In addition, the kinetic evidence alone precludes homolysis as a unimolecular initiation step since neither mechanism of this type predicts first-order dependence on alkaloid concentration.

The activation energies provide additional support for a non-radical mechanism. These results clearly indicate that the rate-limiting step does not involve peroxodisulphate homolysis, which has an activation energy near 120 kJ mol^{-1}; on the contrary, the calculated values for these parameters are of the magnitude expected for nucleophilic displacement on peroxide oxygen.[4] Although peroxodisulphate ions are not typical electrophilic reagents, a variety of peroxodisulphate nucleophilic reactions are known, *e.g.*, the oxidations of phenols



Scheme 3.

(Elbs oxidation[16]) and of aromatic amines (Boyland–Sims oxidation[17]).

Acknowledgements

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