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UNUSUAL ELECTROLYTIC REDUCTION OF α-AMINO KETONES

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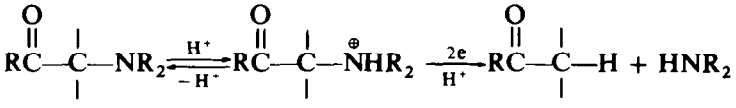
Abstract—The electrochemical reduction of the alkaloids quininone (I) and dihydrocinchoninone (II) on mercury and graphite electrodes was investigated. Electrolysis in CH_3CN caused cleavage of the C—N bonds, while normal reduction of the carbonyl functions occurred in 35% aq. H_2SO_4. A mechanism accounting for the behaviour of I and II in the two media is presented.

INTRODUCTION

REDUCTIVE cleavage of the C—N bond involving a two-electron charge transfer has been reported to take place during electrolysis of α-amino ketones (Eq. 1).[1–5] This cleavage occurs on the protonated compound and its rate is therefore enhanced by lowering the pH of the reaction medium.[4, 5] We observed such cleavage in preliminary



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electrolysis experiments of the alkaloids quininone (I) and dihydrocinchoninone (II) in CH_3CN solutions. However, in contrast to reports[4, 5] on other α-amino ketones, electroreduction of these two compounds in a strongly acidic medium resulted in the reduction of their carbonyl functions, leaving the C—N bonds intact. Although the polarographic curves of I and their dependence on pH has been previously investigated,[6, 7] the isolation and characterization of the electrolysis products have not been reported. Since the reaction pathway, namely, cleavage or carbonyl reduction, can be detected only by product studies, it was our main interest to isolate the cathodic reduction products of I and II.

RESULTS AND DISCUSSION

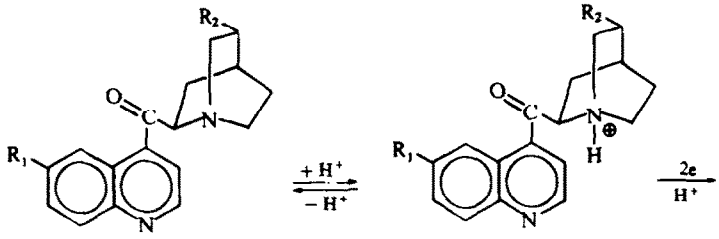
Optical reduction potentials of I and II in CH_3CN and aq. H_2SO_4 solutions were determined by potentiostatic steady state current potential measurements and preparative electrolyses were carried out. The reduction products of I and II in CH_3CN solutions were found to be the ring opened reduction products III and IV, respectively.

In spite of previous reports[4, 5] suggesting such ring-opening would occur more readily in strongly acidic medium, only the quinuclidine derivs. were formed when I and II were electrolyzed in 35% aq. H_2SO_4. Thus a mixture of the isomeric alcohols V and VI was formed from I and a similar mixture of VII and VIII was obtained from II. (Mixtures of rearranged and unrearranged products were formed at lower H_2SO_4 concentrations.)

The above observations may be accounted for by the following mechanism. In

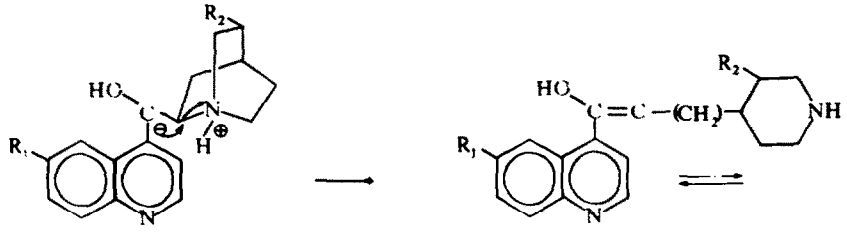
CH_3CN solutions only the more basic nitrogens of I and II, namely the quinuclidinic nitrogens, are partly protonated. The carbonyl functions of the protonated species (a) are electrolytically reduced and the resulting anions (b) undergo a fragmentation to yield the enols (c) isolated in their ketonic form as the final products III and IV.

SCHEME A

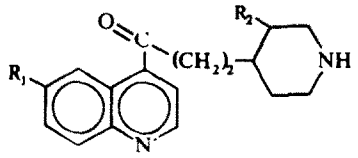


I: R_1 – OCH_3; R_2 – $CH=CH_2$
II: R_1 – H; R_2 – C_2H_5

(a)



(b) (c)



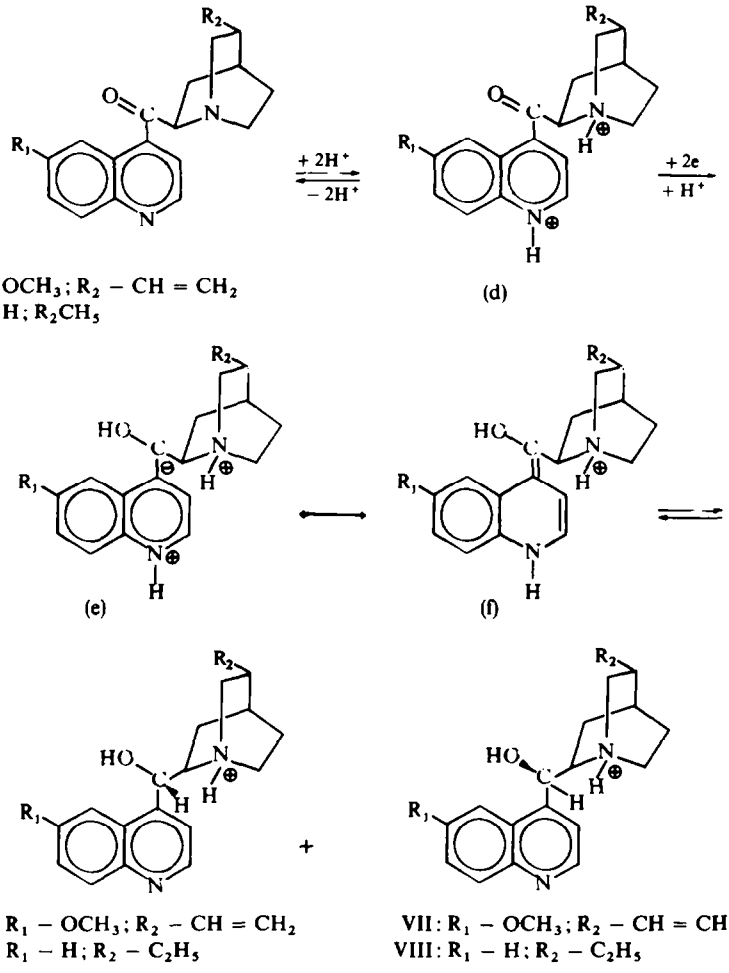
III: R_1 – OCH_3; R_2 – $CH=CH_2$
IV: R_1 – H; R_2 – C_2H_5

Whereas in CH_3CN no protonation of the quinolinic nitrogen takes place, in 35% aq. H_2SO_4 both nitrogens of I and II are protonated, and the electroreactive species is (d) instead of (a).

Due to the protonation of the quinolinic nitrogens, there is considerable contribution of the resonance forms (f) to the anions (e) formed by electrolysis. Since these resonance forms are but tautomers of the final products, Scheme A does not obtain, fragmentation is prevented, and normal reduction products are formed (V and VI from I, VII and VIII from II).

Alternatively, it may be argued that the formation of cleaved products in CH_3CN and alcohols in 35% aq. H_2SO_4 is a consequence of competition between cleavage, which is an internal collapse of charges, and direct protonation, which would be strongly dependent on the proton concentration. However, such an argument is refuted by the fact that the cleavage of other α-amino ketones (other than I and II) has been found to occur more readily in strongly acidic solutions.[4, 5]

SCHEME B



I: R_1 – OCH_3; R_2 – $CH=CH_2$
II: R_1 – H; R_2CH_5

V: R_1 – OCH_3; R_2 – $CH=CH_2$
VI: R_1 – H; R_2 – C_2H_5

VII: R_1 – OCH_3; R_2 – $CH=CH_2$
VIII: R_1 – H; R_2 – C_2H_5

It is noteworthy that the course of electrolytic reduction of α-amino ketones is altered by the presence of additional charged centers in the primarily formed anions (of the types (b) and (e)). The product composition and the extent of reaction via Schemes A and/or B appears to be controlled by the contribution of resonance forms of type (f) to the anion.

EXPERIMENTAL

Mercury "Merck" (G.R. and for polarography) filtered and redistilled before use and spectroscopic graphite "Ultra Carbon" were used as working electrodes. Platinized Pt was used as a counter electrode and a commercial (Radiometer K-601) saturated sulfate electrode was the reference. All potentials reported are vs. this reference electrode.

Purified[8] acetonitrile. H_2SO_4 "Merck" (anal.) and triple distilled water were used as solvents. The electrolyte tetraethylammonium-*p*-toluene sulfonate was prepared in quantitative yield in the following way: 200 g ethyl-*p*-toluene sulfonate and 120 g Et_3N in 300 ml absolute EtOH were stirred at room temperature for 48 hr. EtOH and excess Et_3N were removed under reduced pres. and the residue recrystallized from EtOH-EtOAc-Et_2O mixtures.

Quininone* (I) was purified by recrystallization from ether. Quinine and quinidine (V) bases were precipitated from water solutions of their sulfates* by means of 10% NaOH. Epiquinine and quinicine (III) were obtained and isolated from a rearrangement of quinine in AcOH.[9] Rearrangement of V under the same conditions[9] enabled isolation of epiquinidine (VI) and an additional amount of III.

Dihydrocinchoninone (II) was prepared by oxidation of dihydrocinchonine (VII). (VII and dihydrocinchonidine were prepared by catalytic hydrogenation over Pd/C of cinchonine* and cinchonidine* respectively, by the following procedure: 5 g starting compound and 50 mg catalyst in 200 ml EtOH were stirred under H_2 for 24 hr. After removal of catalyst and solvent, a quantitative yield of product was obtained.

Rearrangement[11] of (VII) in AcOH yielded dihydrocinchonicine (IV) and epidihydrocinchonine (VIII). Similarly, (IV) and epidihydrocinchonidine were obtained from dihydrocinchonidine.

Electrochemical measurements and preparative electrolyses.

The range of potentials available for reduction was determined[12] from steady state measurements of current-potential curves with a dropping mercury electrode of constant surface $3{\cdot}24 \times 10^{-3}$ cm^2 and a graphite electrode of 0·282 cm^2 rotated at a speed of 240 r/min. Measurements were performed potentiostatically using an "Elron" model CHP-1 potentiostat and recorded on an x-y recorder "Moseley" model 7030 AM.

Preparative electrolyses were carried out potentiostatically on a mercury pool of 15 cm^2 or on a rotating graphite cathode of 54 cm^2 for a period of time corresponding to the passage of 2e per mole. Each electrolysis was carried out several times to ensure reproducibility.† The yields of products were determined by independent separation of three samples from each electrolysis, by preparative TLC. The eluents for TLC were mixtures of C_6H_6:Et_2O:Et_2NH in the ratio 40:12:5 for products of quininone (I) and in the ratio 20:6:3 for products of dihydrocinchoninone (II). The electrolytically formed products were identified by comparison with authentic samples by means of TLC, IR, NMR and mass-spectrum.

Electrolysis of quinone (I) *in* CH_3CN. 0·01 moles (I) in 100 ml of a previously prepared solution of 0·5 M tetraethylammonium-*p*-toluene sulfonate in CH_3CN:H_2O (6:1) were electrolysed on a mercury cathode at − 1·05 V. After electrolysis, the CH_3CN was removed under reduced pressure at 50°, satd. aq. NaCl added and the mixture repeatedly extracted with CH_2Cl_2. The collected extracts were washed with satd. aq. NaCl, dried over $MgSO_4$ and solvent removed. The remaining oil consisted of 54–61% quinicine (III) and 38–29% starting compound I. Electrolysis of I under the described conditions on a mercury cathode at − 1·5 V, or on a graphite electrode at two extreme potentials − 1·2 V and − 1·9 V did not alter the products nor their yeild. The same results were obtained when the concentration of electrolyte was changed to 1·0 M.

Electrolysis of dihydrocinchonine (II) *in* CH_3CN. Electrolysis of II was carried out on a mercury cathode at − 1·65 V. The composition of the electrolysed solution and its work up were identical to that described for I (*cf.* (a)). 10–20% of the starting compound II was recovered and the only product formed (51–62%) was identified as dihydrocinchonicine (IV).

Electrolysis of quininone (I) *in aq.* H_2SO_4. A solution of 80 ml 0·01 M I in 35% aq. H_2SO_4 was electrolysed at − 0·9 V on a mercury pool cathode. After electrolysis 100 ml CH_2Cl_2 was added, the reaction mixture cooled, ice bath and neutralized to pH 7–8 with KOH pellets. The organic layer was separated, washed with satd. aq. NaCl, dried over $MgSO_4$ and the solvent was removed. 30–35% of I was recovered and the product (65–55%) was a mixture of the isomeric alcohols V and VI.

Electrolysis of dihydrocinchoninone (II) *in aq.* H_2SO_4. The potential of electrolysis and all other conditions were identical to that described for I (*cf.* (c)). The product was found to be a mixture of the isomers VII and VIII.

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* Plantex Ltd. Nathanya

† There is a small difference in the ratio of the products of different runs of the same electrolyses; the limiting percents are reported.

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