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STRUCTURE AND FEATURES OF THE FRAGMENTATION OF THE PRODUCTS OF THE REDUCTION OF DUBINIDINONE

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Structures (I) and (II) have been put forward for dubinidine and the product of its periodic acid oxidation [1]. Structure (I) has been confirmed by the synthesis of dubinidine [2]. The present paper reports on the structure of products (III) and (IV) obtained previously in the Clemmensen reduction of (II) [3].

The UV spectra of (III) and (IV) are characteristic for 2-quinolone derivatives [4]. The phenolic nature of (IV) is confirmed by a hypsochromic shift of the UV spectrum in alkaline solution, which is typical for 4-hydroxy-2-quinolone bases [5], and also by the preparation of an O-methyl derivative (V) by the action of diazomethane on (IV).

The IR spectra of (III) and (IV) show intense adsorption with maxima at 1660 and 1655 cm^{-1}, respectively, which are due to the amide carbonyl of a 2-quinolone.

The molecular weights of products (III) and (IV), determined mass spectrometrically (245 and 231), differ by a methylene group. However, the methylation product (V) was not identical with (III). In the spectra of (IV) (Fig. 1a), and of (V), the ions $(M-43)^+$ (m/e 188 and 202, respectively) far exceed all the other peaks, which possibly shows the presence of an open chain. In the spectrum of (III) (Fig. 1c), a more uniform distribution of the intensities of the peaks of the ions M^+, $(M-15)^+$, and $(M-57)^+$ is observed, which indicates the cyclic structure of this molecule. The formation of the ion $(M-31)^+$, which is characteristic for an OCH_3 group at C_4 [6], shows the presence of a methoxy group of a different type. On deuteration with deuterodiethylamine $[ND(C_2H_5)_2]$, leading to the replacement of the hydrogens on the carbons adjacent to the carbonyl group [7], in compound (IV) the peak of the M^+ ion shifted by 7 m.u. (Fig. 1b). In view of the presence of the phenolic hydroxyl and the NH group in the 4-hydroxy-2-quinolone nucleus, the exchange of the additional five hydrogens means that substance (IV) has a $-CH_2-CO-CH_3$ grouping. The displacement of the maximum peak with m/e 188 by 4 m.u. confirms that the formation of this ion involved the elimination of a $COCD_3$ group. The peak of the ion with m/e 174 was displaced by two units,

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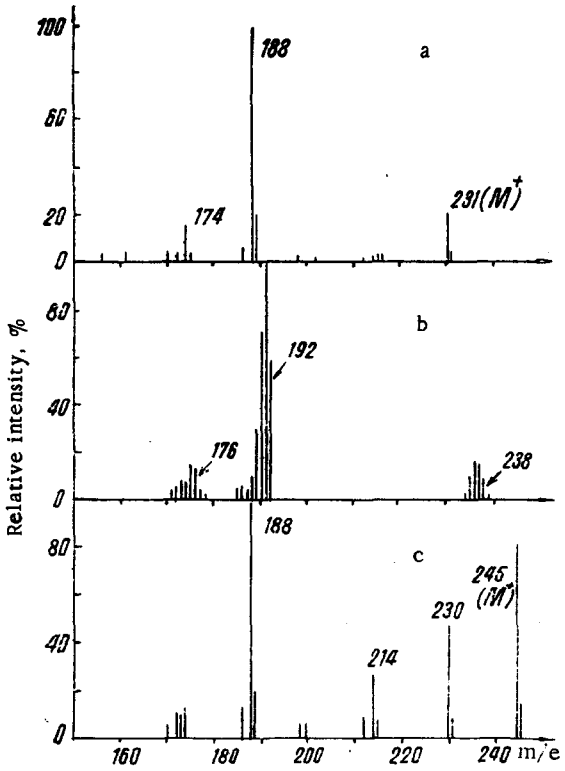


Fig. 1. Mass spectra of the products of the reduction of dubinidinone: (IV) (a); D_7-(IV) (b), and (III) (c).

i.e., this fragment arises with the elimination of a $-CD_2COCD_3$ group. The suitability of this method of deuteration is shown by the fact that when dubinidinone (II) was treated with deuterodiethylamine, the peak of the M^+ ion was displaced by 4 m. u. Analysis of the spectrum of the deuterium analog (II) showed that the formation of the maximum peak of the ion $(M - 43)^+$ takes place to the extent of 99% through the ejection of the $COCH_3$ side chain of the dihydrofuran ring.

A similar experiment with compound (III) gave a shift of the peak of the M^+ ion by only 1. m. u., through the replacement of the hydrogen of the NH group. The absence of hydroxy and ketonic carbonyl groups from compound (III), and also its nonidentity with the methylation product (V), permits the assumption that under the conditions of the Clemmensen reaction hydrogenolysis of the dihydrofuran ring takes place with the simultaneous formation of the ketal (III). The structure of the latter agrees with the features of the NMR spectrum, in which there are the signals from four adjacent aromatic protons of a benzene ring at 2.14 (H_5), 2.61 ($H_{6,7}$), and 2.80 (H_8), the signals of the protons of an α,α=disubstituted dihydrofuran ring at 7.35 ppm (2 H, γ-methylene protons) and 7.85 and 8.22 ppm (multiplets, 1 H each, β-methylene protons), and two three-proton singlets at 6.75 and 8.41 ppm ($-OCH_3$ and $-CH_3$ group on a quaternary carbon atom). The axial displacement of the signal of the protons of the methoxy group by 0.8 ppm relative to their position in the initial dubinidinone [1] confirms the formation of a ketal.

The spectra of compounds (III) and (IV) taken in trifluoroacetic acid coincide, with the exception of an additional three-proton singlet at 6.37 ppm in the spectrum of (III), which is due to the protons of the methanol formed in the hydrolysis of the ketal by trifluoroacetic acid. An examination of a sample obtained after the evaporation of the acid showed its identity with the phenolic compound (IV). We also found that (III) was converted into (IV) when it was heated in dioxane in the presence of sulfuric acid. Thus, trifluoroacetic acid saponifies the ketal (III) to the ketone (IV).

The absence of appreciable differences in the region of carbonyl absorption in the IR spectra of (III) and (IV) could be evidence in favor of the assumption that (IV) is present in the semiketal form (IVa). However, it is known that semiketals are stable to bases. The change in the UV spectrum of (IV) in an alkaline medium, the deuterium exchange with $ND(C_2H_5)_2$ described above, and also the formation of (V) and (VI) from (IV) show that the compound has structure (IV). Consequently, the shift of ν_{max} C=O of the ketone group in the IR spectrum of (IV) into the region of absorption of an amide carbonyl is probably due to a

hydrogen bond between the C=O and OH groups of compound (IV), since in the spectrum of the acetyl derivative (VI), where there is no hydrogen bond of this type, the maximum of the carbonyl band of the ketone is observed at 1720 cm^{-1} and that of the ester at 1770 cm^{-1}.

The NMR spectrum of (VI) (in $CDCl_3$) contains the signals of four adjacent aromatic protons and three singlets at 7.22 ppm (4 H, Ar—CH_2—CH_2—CO), 7.54 ppm (3 H, Ar—O—$COCH_3$), and 7.88 ppm (3 H, R—$COCH_3$).

On treatment with amalgamated zinc in hydrochloric acid, dubinidine underwent no change. Consequently, the hydrogenolysis of the dihydrofuran ring under the conditions of the Clemmensen reaction takes place when there is a carbonyl group in the α position with respect to the ring. The catalytic hydrogenation of (II) by the Adams method led to the reduction of the carbonyl group to an alcohol group with the formation of compound (VII).

The UV and IR spectra of (VII) are typical for 4-methoxydihydrofuranoquinoline alkaloids [8].

The NMR spectrum contains signals at 2.10-2.80 ppm (4 H, multiplet, $H_{5,6,7,8}$), 5.37 and 6.15 ppm (multiplets, 1 H each, α-proton of a dihydrofuran ring and proton geminal to a hydroxy group), 6.50 ppm (2 H, doublet, J = 7.5 Hz, β-protons of a dihydrofuran ring), 5.91 ppm (3 H, singlet, OCH_3), and 8.59 ppm (3 H, doublet, J = 6.5 Hz, CH—CH_3).

As in the case of dubinidinone (II) and other α-hydroxy-substituted 4-methoxydihydrofuranoquinoline alkaloids [8], the maximum peak of the ion with m/e 200 in the spectrum of (VII) is formed by the splitting off of the side chain. The two-stage splitting $M^+ \rightarrow 201^+ \rightarrow 200^+$ that is characteristic for dubinidine is not observed for (VII). In the decomposition of this compound there is a two-stage process of the formation of a pyrylium cation with m/e 212 [9] (see Scheme 1).

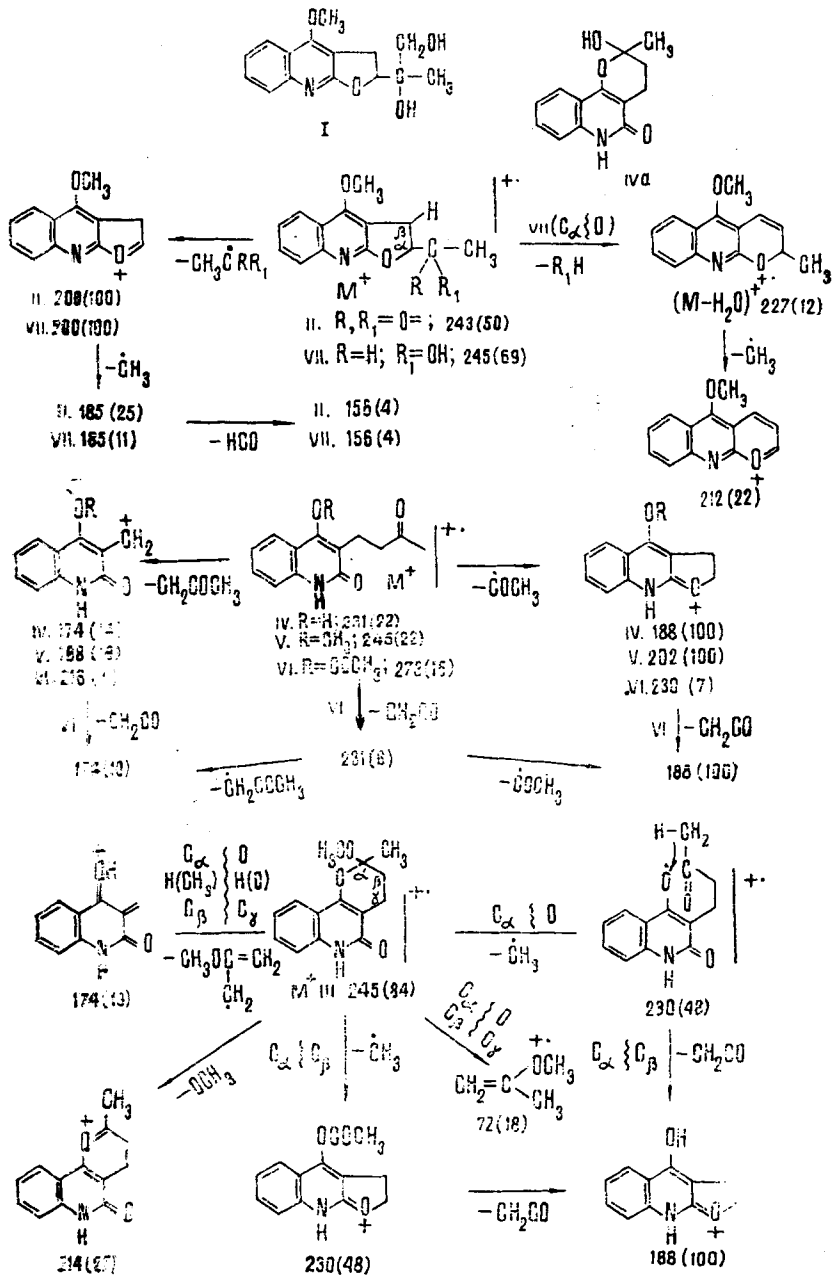
The features of the fragmentation of the products of the reduction of dubinidinone (III) and (IV), and also of the derivatives (V) and (VI), can be explained on the basis of the structures of these compounds. In the decomposition of the M^+ ion of (IV), cleavage of the γ bond is favored by two factors: the propinquity of the C=O group and the stabilization of the fragment formed with m/e 188 in the cyclic form (see Scheme 1). Here it is appropriate to draw an analogy with the mass spectrum of 4-phenylbutan-2-one [10], in which the ion with m/e 105 is approximately one and a half times more intense than the tropylium ion with m/e 91. The possibility of cyclization of the ion with m/e 188 leads to the situation that the ion with m/e 174 formed as the result of β-cleavage amounts to only 14% of the ion with m/e 188.

In the spectrum of the methylation product (V), a distribution of intensities similar to that of (IV) is retained.

The spectrum of the acetyl derivative (VI) has a doublet of ions with m/e 230 and 231. Consequently, the decomposition of this compound takes place through the alternative elimination of a $\dot{C}OCH_3$ radical and a ketene molecule, leading in the final account to the ion with m/e 188. The elimination of $\dot{C}H_2COCH_3$ from M^+ gives a weak peak with m/e 216 (1%), and the ion with m/e 174 amounts to 10% of the ion with m/e 188.

Although there are all the types of ions characteristic for the dihydropyranoquinolines in the spectrum of (III) [11], we must discuss the causes of the unusual distribution of their intensities. The deciding factor is the presence of a methoxy group at C_α. In this case, the initial cleavage of the C_α—O bond that is characteristic of the dihydropyranoquinolines [11] may be accompanied by the elimination of $\dot{C}H_3$ from OCH_3 (see Scheme 1). The resulting fragment $(M - 15)^+$ does in fact have the structure of the ion-radical of the phenol (IV), and by the elimination of a molecule of ketene with the simultaneous migration of $\dot{H}$ to C_4—O it can be converted into the cyclic form of the ion with m/e 188. If the possibility of initial C_α—C_β cleavage is assumed, this also leads in the first stage to the elimination of $\dot{C}H_3$ from the methoxy group. It is obvious that this variety of $(M - 15)^+$ ions, by losing a molecule of ketene, can also be converted into an ion with m/e 188. In addition to this, a methyl radical can be split off from C_α, as in the dimethylchromans [12]. Consequently, the high intensity of the peak of the $(M - 15)^+$ ion is due to the multiplicity of the pathways by which it originates.

The elimination from M^+ of the C_α—C_β chain together with the substituents that are most characteristic for the dihydropyranoquinolones [11, 12] is represented in the present case



Scheme 1. Fragmentation of dubinidinone and the products of its reduction.

by the peaks of ions of medium intensity with m/e 174 and 173. The decrease in the contribution of this process is apparently due to the fact that the splitting off of $\dot{C}H_3$ from OCH_3 described above leads to more stable fragments. On the other hand, the spectrum of (III) contains an ion with m/e 72 including the C_α–C_β chain which is characteristic for dihydropyranoquinolones [11]. This ion is absent from the spectrum of (IV).

EXPERIMENTAL METHOD

The UV spectra were taken on a Hitachi spectrophotometer, the IR spectra on a UR-20 instrument (tablets with KBr), the NMR spectra on a JNM-4H 100/100 MHz spectrometer, and the mass spectra on an MKh 1303 instrument fitted with a device for the direct introduction of the sample, at a temperature of the inlet system of 120-130°C and an ionizing voltage of 40 V.

Deuteration was performed by keeping a solution of the sample in $ND(C_2H_5)_2$ for a short time (5 min), followed by the pumping off of the solvent in the lock part of the mass spectrometer.

The preparation of compounds (II), (III), (IV), and (VI) has been described previously [3].

Dubinidinone (II), mp 86-87°C. UV spectrum: λ_{max} 230, 237, 265 inflection, 274, 383 inflection, 308, 321 nm (log ε 4.57, 4.40, 3.70, 3.79, 3.68, 3.42, 3.57); λ_{max} (H^+) 212, 237, 298, 305, 312 nm (log ε 4.45, 4.44, 3.75, 3.68, 3.45). The spectrum did not change when the solution was made alkaline.

Substance (III), mp 223°C (ethanol) UV spectrum: λ_{max} 216 inflection, 229, 242 inflection, 262 inflection, 271, 281, 306 inflection, 315, 328 nm (log ε 4.41, 4.54, 4.00, 3.48, 3.74, 3.74, 3.48, 3.71, 3.56). The spectrum did not change on acidification or alkalinization.

Substance (IV), mp 189°C (ethanol). UV spectrum: λ_{max} 217 inflection, 224, 242 inflection, 262 inflection, 272, 282, 306 inflection, 315, 325 inflection nm (log ε 4.57, 4.64, 4.29, 3.89, 4.04, 3.99, 3.84, 3.94, 3.88). The spectrum did not change on acidification. In an alkaline medium: λ_{max} 238 inflection, 255 inflection, 310 nm (log ε 4.28, 4.08, 4.06).

The O-methyl derivative (V) was formed when an ethereal solution of diazomethane was added to a solution of (IV) (0.1 g) in absolute methanol (3 ml); mp 181-182°C (from acetone).

Hydrolysis of the Ketal (III). To 0.1 g of (III) in 10 ml of dioxane was added three drops of concentrated sulfuric acid. After an hour's heating in the water bath, the solution was made alkaline with anhydrous sodium carbonate, filtered, and evaporated. The residue consisted of a crystalline substance with mp 188°C (from methanol) which did not fluoresce in UV light, was not revealed by the Dragendorff reagent, and dissolved in alkali. The substance was identical with (IV) according to a mixed melting point and its IR spectrum.

Adams Reduction of Dubinidinone (II). In 5 ml of ethanol, 0.1 g of (II) was hydrogenated over platinum black until the absorption of hydrogen ceased. After the removal of the catalyst, the evaporated ethanolic solution deposited crystals of (VII) with mp 191-192°C (from acetone).

UV spectrum: λ_{max} 231, 239, 254 inflection, 264, 273, 283, 308, 321 nm (log ε 4.61, 4.73, 3.28, 3.46, 3.58, 3.48, 3.28, 3.38). In an acid medium: λ_{max} 217, 237, 293, 306, 317 nm (log ε 4.41, 4.44, 3.79, 3.73, 3.54).

SUMMARY

The Clemmensen reduction of dubinidinone (II) leads to the hydrogenolysis of the dihydrofuran ring with the predominant formation of α-methoxy-α-methyl-α,β-dihydropyrano-2-quinolone.

An explanation of the characteristics of the fragmentation of the products of the reduction of dubinidinone has been found.

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