BENZYL CLEAVAGE IN THE OXIDATION OF CYCLEANINE BY MERCURIC ACETATE

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The dehydrogenation of cycleanine with mercuric acetate in 10% AcOH (at the boil) has been studied. It has been shown that it is accompanied by oxidative cleavage similar to benzyl cleavage under the action of electron impact. The main reaction product (without complexone) is the 8-(4-hydroxymethylphenoxy)-6,7-dimethoxy-2-methylisoquinolinium salt $C_{19}H_{20}NO_4Cl \cdot 1.5H_2O$, mp 196°C. The oxidation of cycleanine in the presence of ethylenediaminetetraacetic acid gave the mercuride $C_{19}H_{19}NO_3I_2Hg \cdot 2H_2O$, mp 240°C (water).

In alkaloid chemistry, the oxidation of organic bases with mercuric acetate to enamines and immonium derivatives is widely used to determine the configurations of the angular protons in quinolizidine alkaloids, for changing the configurations of bicyclic systems by the directed reduction of dehydrogenation products, and for introducing additional groups, such as methyl groups, into position 13 of protoberberine bases. Kupchan [3] has suggested that the antitumoral activity of the bisbenzylisoquinoline alkaloids is due to their oxidation in the organism to 1,2-dehydro derivatives. In view of this, it appears of definite interest to obtain quaternary 1,2-dehydro derivatives of bisbenzylisoquinoline alkaloids in order to study them in detail. However, in this case, on dehydrogenation with mercuric acetate, instead of the expected salts of the dehydro derivatives only mercurated derivatives were isolated [4]. In the presence of ethylenediaminetetraacetic acid as complexone the reaction took place smoothly with the formation of the desired tetradehydro derivatives [4].

Continuing a study of the chemical properties and of the modification of the structure of the alkaloid cycleanine (I) [5, 6], we have performed its reaction with mercuric acetate. It was observed that under the classical conditions and also according to the modification mentioned above [5] in the presence of a complexone, dehydrogenation took place slowly and the bulk of the alkaloid remained unchanged. In this case, the transformation products were isolated in the form of mercury compounds. Raising the temperature and increasing the time of the reaction led to the reduction of the mercury compounds to metallic mercury and to the formation of products of the deeper oxidation of the alkaloid containing no complexly bound mercury (Scheme 1).

A compound with mp 196°C (chloride) was isolated in good yield after the reaction in the absence of the complexone had been performed for 4-24 h. Its NMR spectrum (CD_3OD, δ) showed the signals of the protons of two methoxy groups at 3.76 ppm (C_7—OCH_3) and 4.17 ppm (C_6—OCH_3), of an immonium N-methyl group at 4.41 ppm, and of a methylene group at 4.57 ppm, the signals of the aromatic protons of a p-substituted benzyl group at 6.97 and 7.35 ppm (2 × 2 h, d, J = 8 Hz), a one-proton singlet at 7.67 ppm (C_5—H), the signals of heteroaromatic protons at 8.29 ppm (1 H, d, J = 6 Hz, C_4—H) and 8.44 ppm (1 H, qd, J_1 = 6, J_1 = 2 Hz, C_3—H), and the broadened signal of the C_1—H proton at 9.46 ppm. The presence of the weak-field signal of the C_1—H protons, and also of signals of the symmetrical protons of a benzyl group (in the initial cycleanine the C_{11}—H and C_{13}—H and the C_{10}—H and C_{14}—H protons are nonequivalent) shows the monomolecular structure of compound (II).

The mass spectrum confirmed the monomeric structure of the compound. In addition to the peaks M^+ (55%), M + 1 (44%), M − 1 − 15 (22%), M − 15 (24%), M − 15 − 31 (21%), and M − 30 (8%) there were the peaks of isoquinolinium ions at 204 (21%), 190 (100%), 188 (23%), 176 (8.8%), and 147 (5.9%) and characteristic for it were the peaks of doubly charged ions with m/e (M − 1)/2 (8%), (M − 2)/2 (60%), (M − 17)/2 (3%), and (M − 15)/2 (3%).

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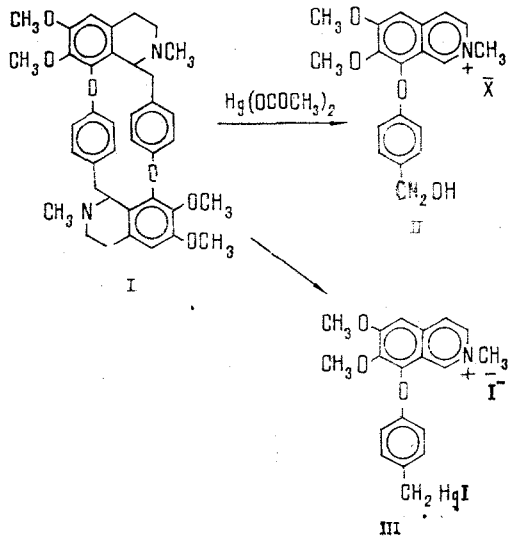
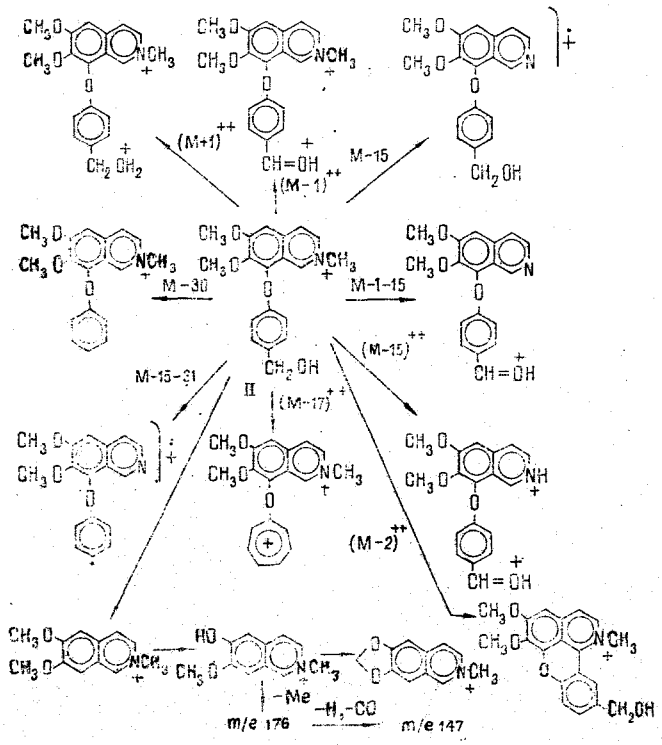
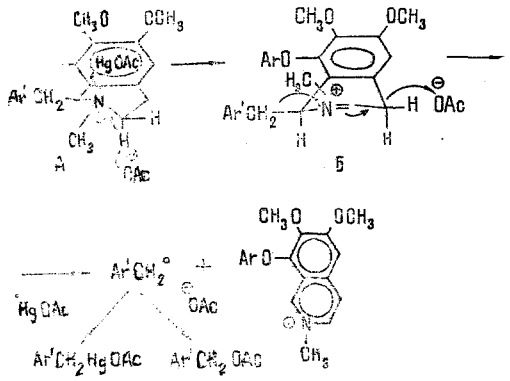


Scheme 1

The unusual direction of the oxidation of cycleanine can be explained by the predominant attack of the reagent on the C_{3a}—H proton, since the C_{1a}—H proton is sterically hindered, as follows from Stuart molecular models. Because of this, a 2,3-dehydro derivative is formed in which the quasi-equatorial benzyl bond is weakened and undergoes cleavage. This is favored by the coplanarity of the $C_{(15)}$—$C_{(1)}$—N—$C_{(3)}$—$C_{(4)}$—$H_{(e)}$ centers participating in the reaction in the intermediate compound (B).



Scheme 2. Scheme of the fragmentation of compound (II) under the action of electron impact.



Scheme 3. Stereochemical scheme of the cleavage of cycleanine.

The rigid macrocyclic structure of the dehydro derivative (B) prevents the conversion of the heterocycle into a conformation with a quasi-axial benzyl group in which the aromatization of the ring without the cleavage of a carbon–carbon bond is possible. On performing dehydrogenation in the presence of ethylenediaminetetraacetic acid, cleavage of the alkaloid was again observed, and the reaction product was isolated in the form of a mercurated derivative with the composition (in the case of the iodide) $C_{19}H_{19}NO_3I_2Hg \cdot 2H_2O$, mp 240°C, apparently having the structure (III).

EXPERIMENTAL

The NMR spectra were taken on a Varian HA-100D spectrometer (0 — TMS; δ scale) and the mass spectra on a Varian MAT CH-8 instrument at an energy of the ionizing electrons of 70 eV and a temperature of 180°C. Melting points were determined in evacuated capillaries in an electrically heated instrument.

Oxidation of Cycleanine in the Absence of a Complexone. A. A solution of 7.2 g of cycleanine and 3.6 g of mercuric acetate in 100 ml of 10% acetic acid was boiled under reflux for 2 h 10 min. Metallic mercury began to separate out 1 h after the beginning of the reaction. After the reaction mixture had cooled and the precipitate of metallic mercury had been removed, the pH of the aqueous solution was brought to 5 with ammonium hydroxide, and cycleanine was extracted with chloroform. Then a fraction of tertiary bases was separated by exhaustive extraction with chloroform at pH 7.5. The aqueous alkaline layer was acidified to pH 5 with acetic acid and was left for free evaporation. The crystalline precipitate that deposited was filtered off, and the solution was evaporated.

The crystalline deposit was treated with hot chloroform (60°C), and the extract was dried with sodium sulfate and evaporated. This gave 20 mg of a quaternary base with the composition $C_{36}H_{17}N_2O_6$, mp 155-156°C (ethanol) in the form of snow-white needles associated in the form of druses. Increasing the time of the reaction to 7, 19, and 24 h led to the formation of a mixture of compounds consisting of five compounds, including cycleanine, according to chromatography in a thin layer of alumina (activity grade IV) in the solvent system chloroform–methanol (9:1).

B. A solution of 11.96 g of cycleanine and 5.9 g of mercuric acetate in 100 ml of 10% acetic acid was boiled under reflux for 24 h. During the reaction, metallic mercury deposited. After the elimination of the deposit, the reaction mixture was exhaustively extracted with chloroform, which gave 8.86 g of cycleanine. The aqueous layer was brought to pH 7.5 with a solution of ammonium hydroxide and was treated with chloroform. In this process, a dark brown oily intermediate layer formed that was readily soluble in methanol and water and sparingly soluble in chloroform. It was separated off, evaporated, and chromatographed on a column of alumina (activity grade IV). The reaction products were eluted with benzene and chloroform. The fractions so obtained were rechromatographed in a thin layer of alumina (activity grade IV) in the chloroform–methanol (9:1) system.

The benzene fraction (0.34 g) contained a substance X with R_f 0.6, mp 120°C (undetermined structure). The chloroform fraction (0.73 g) contained dehydro derivatives with traces of substance X. This fraction was dissolved in water and chromatographed on a column of Sephadex G-50 (2.5 cm × 10 cm). The aqueous eluate was evaporated, and then the chloride of the

dehydro derivative with the composition $C_{19}H_{20}NO_4Cl \cdot 1.5H_2O$, mp 196°C (ethanol) was obtained with a yield of 50 mg. The mass spectrum of the salt was identical with that of the base obtained in experiment A.

Oxidation of Cycleanine in the Presence of a Complexone. A mixture of 1.2 g of cycleanine, 2.2 g of ethylenediaminetetraacetic acid, and 2 g of mercuric acetate was heated in 100 ml of 10% acetic acid at the boil under reflux. After cooling and separation of the precipitate of mercurous acetate, extraction with chloroform yielded cycleanine. The aqueous phase was brought to pH 9.5. The reaction products were extracted with chloroform and then the alkaline layer was acidified with acetic acid to pH 5 and was evaporated. The residue was dissolved in 5 ml of water and an excess of potassium iodide was added. A mercuride deposited with the composition $C_{19}H_{19}NO_3I_2Hg \cdot 2H_2O$, mp 240°C (water).

SUMMARY

It has been shown that the dehydrogenation of cycleanine with mercuric acetate is accompanied by oxidative cleavage similar to the benzyl cleavage observed under the action of electron impact. The main product of the reaction was an 8-(4'-hydroxymethylphenoxy)-6,7-dimethoxy-2-methylisoquinolinium salt, while when the reaction was performed in the presence of ethylenediaminetetraacetic acid it led to the corresponding mercuride with the composition $C_{19}H_{19}NO_3I_2Hg \cdot 2H_2O$.

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