STRUCTURE OF THE ISOCOUMARIN ARTEMIDIN

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For the substance artemidin (I) isolated previously we proposed an isocoumarin structure with a butylene side chain in position 3 of the α-pyrone ring [1].

This paper gives a proof of the structure of I on the basis of a chemical study of it.

The IR spectrum of artemidin (Fig. 1) has the absorption band of a trans-disubstituted double bond (970 cm^{-1}), whose presence is confirmed by bromination and hydrogenation reactions. The bromination of I gave dibromoartemidin with the composition $C_{13}H_{12}O_2Br_2$ (II). The hydrogenation of artemidin in the presence of platinum oxide forms a dihydro derivative $C_{13}H_{14}O_2$ (III). The IR spectra of dibromoartemidin and dihydroartemidin lack the absorption band of a double bond. The UV spectrum of III retains the maxima characteristic for isocoumarin [2] (Fig. 2), and in its NMR spectrum the signals of the olefinic protons are shifted upfield [1].

When dihydroartemidin was heated with an aqueous solution of caustic potash, a keto acid (IV) was obtained, which shows that the substance has an isocoumarin, but not a coumarin, skeleton [3]. The IR spectrum of the ketoacid has absorption bands at 1595, 1570, and 1490 cm^{-1} (aromatic ring), 1685 cm^{-1} (C=O of a carboxy group), 1705 cm^{-1} (C=O of a ketone), and 2650 cm^{-1} (OH group of a dimerized acid). The presence of a ketone group in the saponification product of dihydroartemidin was confirmed by the formation of the 2,4-dinitrophenylhydrazone (V).

The elementary compositions, melting points, and UV spectra of dihydroartemidin, the ketoacid, and its hydrazone agree with those for the corresponding derivatives of capillarin [4-6] (Table 1).

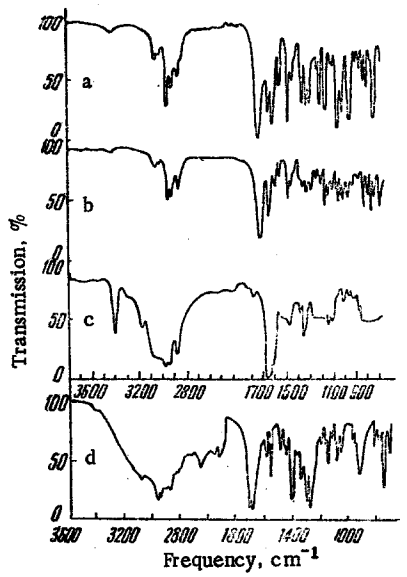

Fig. 1. IR spectra of: a) artemedin (I); b) dihydroartemidin (III); c) the isocarbostyryl (VI); d) the ketoacid (IV).

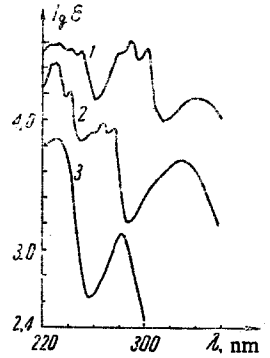

Fig. 2. UV spectra of: 1) artemidin (I); 2) dihydroartemidin (III); 3) the ketoacid (IV).

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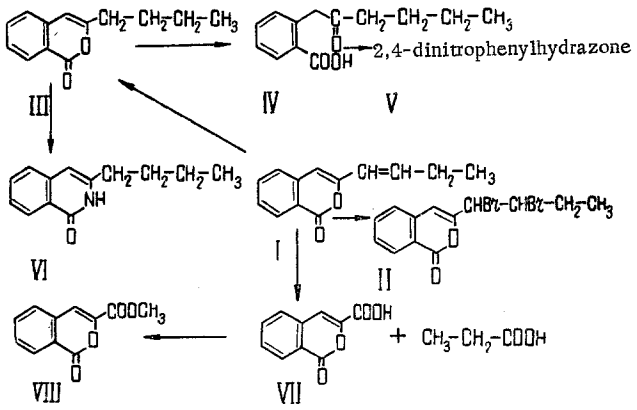
TABLE 1.

Artemidin derivatives	mp,°C	Capillarin derivatives	mp, °C
Dihydroartemidin	45- 46	Tetrahydrocapillarin	45.5-46.5
Ketoacid from dihydro-artemidin	85- 86	Tetrahydrocapillaric acid	85.5-86.5
2,4-Dinitrophenyl-hydrazone of ketoacid	174-175	2,4-Dinitrophenylhydrazone of tetrahydro-capillaric acid	174-175

When dihydroartemidin was heated in a sealed tube with ammonia, the oxygen of the pyrone ring was replaced by NH with the formation of an isocarbostyryl [4], $C_{13}H_{15}ON$ (VI). In the IR spectrum (in $CHCl_3$) of this compound the band of the carbonyl group shifted from 1725 to 1665 cm^{-1} and, in addition, a sharp band of an NH group appeared at 3400 cm^{-1}.

To establish the position of the double bond in the side chain, artemidin was oxidized with chromic anhydride in acetic acid. Propionic acid and isocoumarin-3-carboxylic acid (VII) were isolated from the oxidation products. The methyl ester of the acid (VIII) had the same melting point as authentic methyl isocoumarin-3-carboxylate [7]. Consequently, the double bond in the butylene chain is present in the 1,2 position.

The spectral and chemical information obtained permits structure I to be proposed for artemidin.



EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrophotometer, the UV spectra on an SF-4A instrument, and the NMR spectra on a JNM-100 instrument. The analytical results of the compounds corresponded to the calculated figures.

Isolation of Artemidin. A 10-kg sample of the epigeal part of Artemisia dracunculus was extracted with chloroform. The residue after the chloroform had been distilled off (yield 5%) was dissolved in ether. The ethereal solution was extracted with 0.5% KOH solution to eliminate acidic products and then distilled, and the residue was chromatographed on neutral alumina (activity grade IV, ratio 1 : 10). The column was eluted successively with petroleum ether, benzene, chloroform, and ether. One-liter fractions were collected. Fractions 2-6 were rechromatographed on silica gel (activity grade I, 1 : 40) and eluted with petroleum ether and a petroleum ether–ether mixture (9 : 1). When the petroleum ether–ether eluate was concentrated, a crystalline precipitate of artemidin was obtained. The precipitate was separated preparatively on plates with a fixed layer of silica gel in a petroleum ether–acetone (20 : 1) system. The zones with R_f 0.45 were eluted with ether, giving colorless needles of artemidin $C_{13}H_{12}O_2$, mp 49-50°C (from petroleum ether), mol. wt. 200 (mass spectrometry).

Hydrogenation of Artemidin. One gram of artemidin in solution in 10 ml of absolute ethanol was hydrogenated in the presence of 0.1 g of platinum oxide, 200 ml of hydrogen being absorbed in 30 min. After

removal of the catalyst and the solvent, colorless crystals of dihydroartemidin were obtained with mp 45-46°C (from petroleum ether). A mixture with artemidin showed a depression of the melting point.

Bromination of Artemidin. A 3% solution of bromine in $CHCl_3$ was added dropwise to a solution of 0.073 g of artemidin in 2 ml of $CHCl_3$ until it was no longer decolorized. The dibromo derivative had mp 139-140°C (from methanol), mol. wt. 360 (mass spectrometry).

Saponification of Dihydroartemidin. A mixture of 0.2 g of dihydroartemidin and 50 ml of 5% KOH solution was boiled for 20 min. When the cooled mixture was acidified with 5% HCl, crystals of the keto-acid of dihydroartemidin deposited with mp 85-86°C (from petroleum ether).

2,4-Dinitrophenylhydrazone of the Ketoacid. The ketoacid (0.05 g) was treated with a saturated HCl solution of 2,4-dinitrophenylhydrazine. On standing, crystals appeared in the form of yellow needles (hydrazone) with mp 174-175°C (from ethanol).

Amination of Dihydroartemidin. A mixture of 0.1 g of dihydroartemidin and 2 ml of conc. NH_3 was heated in a sealed tube at 130-150°C for 5 h. After cooling, crystals of the isocarbostyryl with mp 137-138°C (from acetone) deposited.

Oxidation of Artemidin. A solution of 0.3 g of artemidin in 8 ml of glacial acetic acid was treated with a solution of 0.4 g of chromic anhydride in 10 ml of 50% acetic acid, and the mixture was left to stand for 3 days. Propionic acid was identified in the reaction mixture on a fixed layer of cellulose [in a tertiary butanol–ammonia–water (25 : 3 : 5) system] from its R_f value of 0.55 (with a marker), being shown up by bromphenol blue as a blue spot on a yellow background. The acetic acid was driven off from the mixture at 40-50°C, the residue was treated with a 5% solution of sodium carbonate, the carbonate extract was washed with ether and acidified with 5% HCl, and the isocoumarin-3-carboxylic acid was extracted with ether. Mp of the acid 236-237°C (from ethyl acetate).

Methylation of Isocoumarin-3-carboxylic Acid. An ethereal solution of diazomethane was added to 0.01 g of the acid in 20 ml of ether. The mixture was left for 24 h, after which the solvent was driven off. The residue consisted of methyl isocoumarin-3-carboxylate with mp 172-173°C (from methanol).

CONCLUSIONS

Structure I has been proposed for artemidin on the basis of the preparation of a number of derivatives and spectral characteristics.

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