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STRUCTURE OF ISOHYPERECTINE — AN ALKALOID FROM *Hypecoum erectum*

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A base with the composition $C_{24}H_{21}O_6N_3$ isomeric with hyperectine which has been called isohyperectine, has been isolated from the epigeal part of Hypercoum erectum *L., and its structure has been established by chemical and spectral methods.*

Hypecoum erectum L. attracted our attention as a source of new biologically active compounds that are of interest for more profound study [1, 2]. From it, in addition to spiroaminoketal alkaloids, an unusual spirobenzylisoquinoline alkaloid hyperectine (I) containing an aminomaleimide substituent has been isolated [9-11]. Although compound (I) has two centers of chirality, it was isolated in the racemic form. An x-ray structural analysis of its methiodide showed its (8R,9S−8S,9R)-configuration [12, 13]. Attempts to separate the racemate into optically active antipodes led only to partial success on the use of chiral sorbents. Although on plates with a thin layer of chiral sorbent a clear separation was observed, no individual compounds were isolated on columns but only fractions enriched with an optically active substance because of partial racemization during the chromatographic process [13]. Hyperectine methiodide (II) formed a blue anion of the des-base under the action of alkali with the opening of ring *C* (III).

The unusual structure and properties of hyperectine induced us to carry out additional investigations in the search for new compounds in this plant. As a result, from the hyperectine fraction we isolated, together with (I), a new base with the same elementary composition as hyperectine, $C_{24}H_{21}O_6N_3$, mp 239-240°C (decomp., from a mixture of chloroform and methanol) [14], which differed from the former by its sparing solubility in organic solvents. It followed from its NMR spectrum that the alkaloid contained the same functional groups as hyperectine. However, it was impossible to make a comparative study of the spectra of compounds (IV) and (I) because of the pronounced differences in their solubility. The PMR spectrum of isohyperectine (IV) ($CDCl_3-CF_3COOH$) showed the signals of the protons of methylammonium group at 2.97 ppm (3H, d), of the proton of a benzyl methylene $ArCH_2C\equiv$ at 3.40 and 3.98 ppm (2 × 1 H, d, J = 16.09 Hz), of $CH_2N=$ methylene protons at 3.15 ppm (2 H, m), of the protons of an $ArCH_2CH_2$ group at 4.12 and 3.50 ppm (2 H, m), of a C_8-H methine proton at 4.55 ppm (1 H, s), of the methylene protons of OCH_2O groups at 5.92, 5.94, and 5.97 ppm (4 H, m), of the C_1-H and C_4-H aromatic protons at 6.28 and 6.66 ppm (2 × 1H, s), of the $C_{11}-H$ and C_{12}-H *ortho*- protons at 6.90 ppm (2 H, s), and of mobile protons on nitrogen atoms at 8.34 and 9.09 ppm (broadened signals).

The mass spectra of (I) and (IV) showed analogous fragmentation under the action of electron impact (Fig. 1). On hydrolysis with alkali, hyperectine (I) was partially converted into isohyperectine (IV), which confirmed their structural relationship. However, compound (IV) did not undergo isomerization under analogous conditions. An alkaline hydrolysate of (IV) yielded a dicarboxylic acid with mp 202-203°C (decomp.), isomeric with an acid having mp 262-263°C (decomp.) obtained from (I) in admixture with the former. Acids (V) and (VI) were separated chromatographically.

On interaction with diazomethane, isohyperectine (IV), like (I) formed a N-methyl derivative (VIII), with the composition $C_{25}H_{23}O_6N_3$, a N-methylmaleimide derivative) but it did not give a methiodide (IX) with methyl iodide, which can be explained by steric hindrance to attack of the unshared pair of electrons of the nitrogen atom in the tetrahydroisoquinoline nucleus because of the propinquity of the amino group of the aminomaleimide fragment, which forms a hydrogen bond. Thus, in isohyperectine (IV), unlike hyperectine (I), the $N-CH_3$ fragment and the NH_2 group are in the cis-position with respect to one another, and therefore compound (IV) was the (8R,9R−8S,9S)- isomer.

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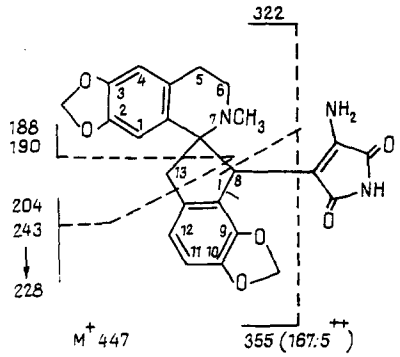
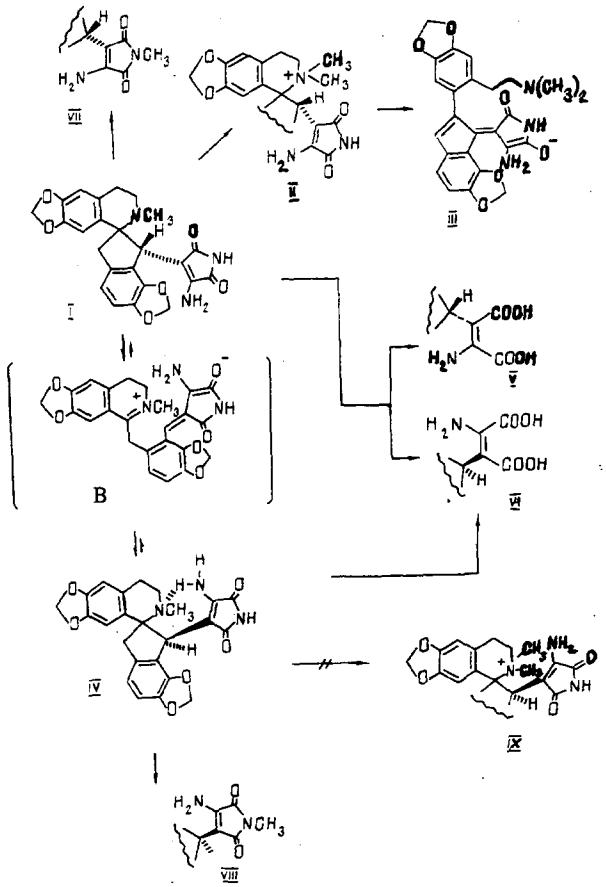


Fig. 1



Scheme 1. Fragmentation of hyperectine (I) and isohyperectine (IV) under the action of electron impact.

The absence of optical activity in hyperectine and isohyperectine can be explained by an equilibrium of the tautomeric forms A and B, one of which (the bipolar B) has no centers of chirality. The anion of the des-base (III) also has no centers of chirality (see Scheme 1).

It was shown by chromatography in a thin layer of silica gel that isohyperectine (IV) is present, together with hyperectine (I), in extracts of *H. erectum* that had not been subjected to additional chemical treatments. Thus, isohyperectine is apparently a native compound.

EXPERIMENTAL

PMR spectra were determined on a M-360 instrument (Bruker) with a working frequency of 360 MHz using TMS as internal standard, the chemical shifts being given in ppm on the δ scale. Melting points were determined on a Boetius instrument. Mass spectra were recorded on a CH-8 spectrometer (Varian) with an ionizing energy of 70 eV.

Isolation of Hyperectin (IV). After the separation of the hyperectin, the fraction of alkaloids from *H. erectum* obtained at pH 5.5-6.0 was recrystallized from chloroform–methanol (1:1). The alkaloid isolated had a chromatographic mobility close to that of hyperectine (LSL_{254} 5/40 silica gel; chloroform–methanol (9:1) system). Recrystallization from methanol gave a substance with a faint yellow color, mp 239-240 (decomp.). In the presence of chloroform, the substance became yellow, mp 240-241°C (decomp.). However, the two forms of the alkaloid scarcely differed in terms of their IR spectra.

Hydrolysis of Isohyperectin. A solution of 60 ml of the substance in 10 ml of 0.1 N caustic soda solution was heated in the boiling water bath for 3 h. The unchanged substance was extracted with chloroform. The aqueous alkaline solution was neutralized with 0.1 N hydrochloric acid, and the resulting substance was extracted with chloroform. After the chloroform had been distilled off, the residue was recrystallized from methanol, giving a dicarboxylic acid having mp 202-203°C (decomp.).

Hydrolysis of Hyperectin. A solution of 0.5 g of hyperectine in 100 ml of 0.1 N caustic soda was heated in the boiling water bath for 5 h. The cooled solution was treated with chloroform. Hyperectine and isohyperectine in approximately equal amounts were detected in the organic phase by chromatography in a thin layer of silica gel. The aqueous phase was then neutralized with 0.1 N hydrochloric acid (about 100 ml), and the hydrolysis products were extracted with chloroform, these consisting, according to chromatography in a thin layer of silica gel, of a mixture of two compounds in approximately equal amounts. These substances were separated on a column of silica gel (40/100). Elution was carried out successively with benzene, benzene–chloroform, chloroform, and chloroform–methanol mixtures in various ratios. Chloroform–methanol eluted a yellow substance with mp 262-263°C (decomp.) — a product of the hydrolysis of hyperectine (V). Methanol eluted a cream-colored substance with mp 202-203°C (decomp.), identical with the product (VI) of the hydrolysis of isohyperectine.

Methylation of Isohyperectine with Diazomethane. A solution of 50 mg of the substance in 50 ml of methanol was heated with an ethereal solution of diazomethane taken in excess, and then the solution was left to stand for two days and the solvent was distilled off. The residue, which consisted of the methylation product contaminated with a small amount of the initial substance, was purified on a column of silica gel (40/100). The N-methyl derivative was eluted with benzene–chloroform (1:1). Yellow amorphous substance. N-methyl-(IV) differed in its chromatographic mobility from N-methyl-(I) and, thus, was not a product of the isomerization of the alkaloid.

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