ALKALOIDS OF Hypecoum erectum

STRUCTURE OF HYPECORINE AND HYPECORININE

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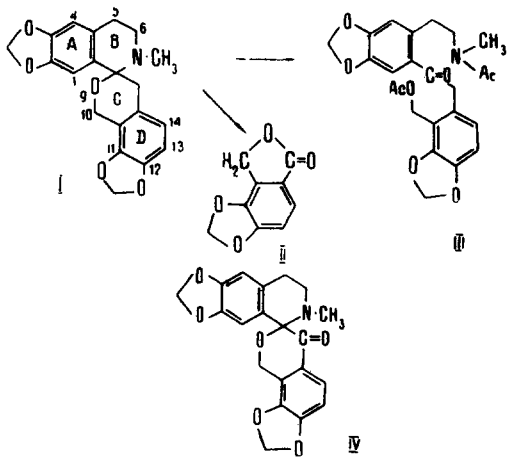
The alkaloid composition of plants of the genus Hypecoum (family Papaveraceae) has been little studied. There are reports in the literature on the isolation from Hypecoum pendulum L. of protopine [1], from H. trilobum Trautv., H. leptocarpum Hook f. et Thoms., and H. procumbens L. of protopine and sanguinarine [2, 3] and from H. procumbens, as well, of chelerythrine, allocryptopine, chelirubine, and coptisine [3]. From Hypecoum erectum L., collected in Transbaikalia in the flowering phase, in addition to protopine [4], we have isolated two new alkaloids, which we have called hypercorine and hypecorinine.

Hypecorine, $C_{20}H_{19}NO_5$, consists of white crystals with mp 154-156°C (from ethanol), optically inactive. The melting point of the hydrochloride $C_{20}H_{19}NO_5 \cdot HCl$ is 250-252°C (decomp., from ethanol).

The UV spectrum of this substance (λ_{max} 236 and 290 nm; log ε 3.93, 3.87) is characteristic for alkaloids having two isolated benzene nuclei with O-alkyl substituents. The IR spectrum of the alkaloid (Fig. 1) confirms the presence of aromatic rings in its molecule. The NMR spectrum of hypecorine in CCl_4 (Fig. 2) has the signals of a $N-CH_3$ group (2.19 ppm, singlet, 3H), of a $O-CH_2-Ar$ grouping (4.61 and 4.65 ppm, doublets, J = 15.0 Hz, 1H each), of two aromatic methylenedioxy groups (5.79 and 5.86 ppm, singlets, 2H each), and of four aromatic protons as two pairs in the ortho and para positions to one another (6.40 and 6.74 ppm, singlets; 6.38 and 6.52 ppm, doublets, J = 8.0 Hz). A six-proton multiplet in the 2.35-3.35 ppm range shows the presence in the hypecorine molecule of three methylene groups of the $C-CH_2-Ar$ and $C-CH_2-N$ type.

Oxidation of the alkaloid with potassium permanganate gave 4,5-methylenedioxyphthalide (II), which enables hypecorine to be assigned to the group of spirobenzylisoquinoline alkaloids. In addition, this shows that the ortho protons belong to ring D.

On the basis of its chemical and spectral characteristics, hypecorine may be considered to have the structure represented by formula I. A characteristic feature of this structure is the presence of a spiro amino ketal grouping ($O-C-N-CH_3$), which is absent from known alkaloids of the spirobenzylisoquinoline type.



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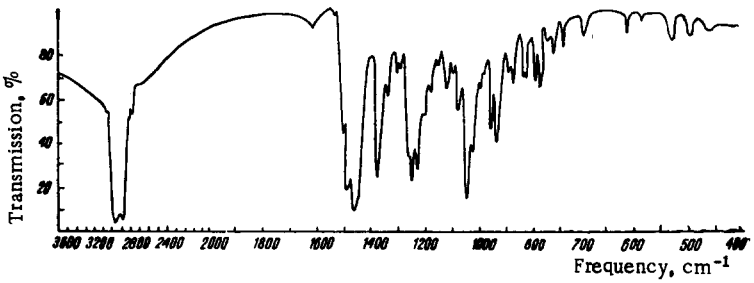

Fig. 1. IR spectrum of hypecorine.

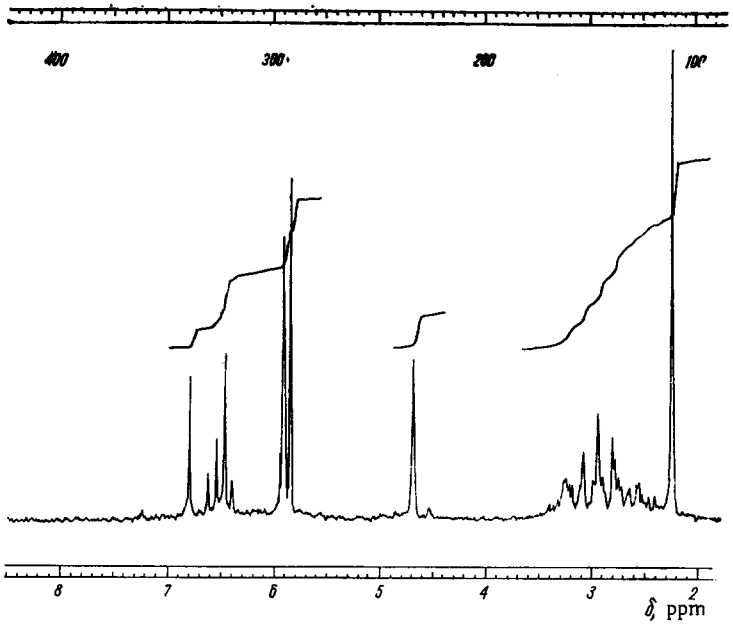

Fig 2. NMR spectrum of hypecorine.

Such a grouping must be responsible for the instability of the alkaloid to acid reagents and, in particular, to acetic anhydride. In actual fact, when hypecorine was heated with acetic anhydride in chloroform, the C–O and C–N bonds of the amino ketal grouping were cleaved with the formation of the N,O-diacetyl ketone (III). The IR spectrum of (III) has the carbonyl bands of a saturated ester (1748 cm^{-1}), of an oxo group conjugated with an aromatic nucleus (1679 cm^{-1}), and of a tertiary amide group (1651 cm^{-1}).

The NMR spectrum of (III) in CCl_4 corresponds completely to that expected for a compound of this structural formula: N–Ac, O–Ac (1.89 and 1.91 ppm, singlets, 3H each); $N-CH_3$ (2.93 ppm, singlet, 3H); $Ar-CH_2-CH_2-N-$ (2.70-3.00 ppm, multiplet, 2H; 3.15-3.45 ppm, multiplet, 2H); $CO-CH_2-Ar$ (4.10 ppm, singlet, 2H); $AcO-CH_2-Ar$ (4.95 ppm, singlet, 2H); two aromatic methylenedioxy groups (5.92 ppm, singlet, 4H); and aromatic protons H_4 (7.23 ppm, doublet, $J \simeq \sim 1.5$ Hz); H_1 (6.78 ppm, singlet); and H_{13} and H_{14} (6.50 and 6.62 ppm, doublets, J = 8.0 Hz).

Apart from these signals, the NMR spectrum of (III) shows additional signals at 1.78, 2.78, and 6.56 ppm making up together with the peaks from N–Ac, $N-CH_3$, and H_1 3, 3, and 1 proton units, respectively. The results of a study of the temperature dependence of the spectrum of (III) in deuteropyridine between 32 and 80°C showed that at 80°C there was a broadening and complete fusion of the signals from N–Ac and $N-CH_3$ with the corresponding satellites. Because of masking by the solvent, the region of aromatic solvents was not studied. Thus, the additional signals relate to a second conformer formed as a consequence of hindered rotation around the N–Ac and (or) Ar–C=O bonds.

Hypecorinine, $C_{20}H_{17}NO_6$, has a structure similar to that of hypecorine and consists of a colorless optically inactive crystalline substance with mp 197-198°C (from ethanol). Elementary analysis shows that hypecorinine has one more carbonyl group than substance (I). It can be seen from the IR spectrum of the alkaloid (Fig. 3) that its molecule has a carbonyl group conjugated with an aromatic nucleus (1690 cm^{-1}). The UV spectrum of hypecorinine (λ_{max} 240, 292, 322 nm; log ε 4.38, 4.10, 3.95) also shows that its chain of conjugated bonds is longer than that of (I).

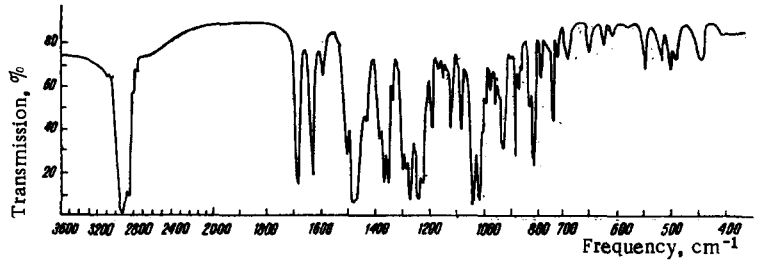

Fig. 3. IR spectrum of hypecorinine.

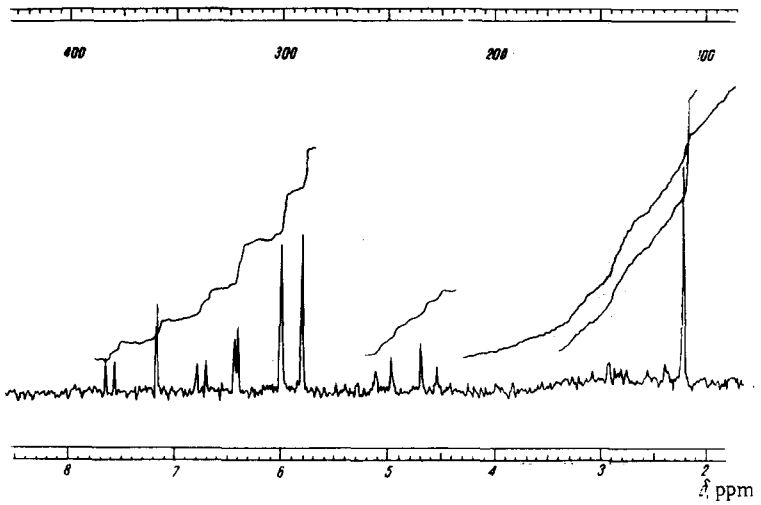

Fig. 4. NMR spectrum of hypecorinine.

In the NMR spectrum of hypecorinine in CCl_4 (Fig. 4) there are signals of the following structural elements: $N-CH_3$ (2.21 ppm, singlet, 3H); $Ar-CH_2-CH_2-N$ (2.3-3.4 ppm, multiplet, 4H); $O-CH_2-Ar$ (4.63 and 5.04, doublets, J = 15.5 Hz, 1H each); two aromatic methylenedioxy groups (5.81 and 6.01 ppm, singlets, 2H each); two aromatic para protons (6.41 and 6.45 ppm, singlets, 1H each); and two aromatic ortho protons (6.76 and 7.61 ppm, doublets, J = 8.2 Hz, 1H each). The positions of the signals of the ortho protons in hypecorinine show the conjugation of a C=O group with a benzene nucleus, and the chemical shift of the proton in the weakest field (7.61 ppm) shows that it is located in the α position to the site of attachment of the C=O group (such a pronounced descreening of the proton is the result of a combination of the effects of the reduced electron density on the carbon atom, the magnetic anisotropy of the C=O group, and dipole–dipole interaction with it).

As compared with (I), hypecorinine is more stable to the action of acetic anhydride and does not undergo acetylation with the opening of the spiro amino ketal grouping even on being boiled with acetic anhydride for 6 h.

It is obvious that in this case the amino ketal grouping is stabilized by the neighboring electron-accepting carbonyl group. All that has been said above permits us to propose structure (IV) for hypecorinine.

The mass spectrum of (IV) has, in addition to the molecular peak M^+ 367, a signal with m/e 177, which is characteristic for a 4,5-methylenedioxynaphthalene ion and a signal with m/e 190, relating to a 2-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline ion, which also corresponds to structure (IV).

The presence in hypecorine and hypecorinine of a spiro amino ketal grouping apparently explains the ease of racemization of these compounds and, therefore, the fact that (I) and (IV) are isolated from the natural raw material in the form of optically inactive compounds.

EXPERIMENTAL

The NMR spectra were obtained on an HA-100D (100 MHz) instrument with HMDS as standard. The IR spectra were taken on a UR-10 spectrophotometer and the UV spectra on an EPS-3T instrument (solvent ethanol).

The analyses of all the compounds corresponded to the calculated figures.

Isolation of Hypecorine and Hypecorinine. Dichloroethane extraction of 5 kg of the air-dry epigeal part of Hypecoum erectum gave 105 g of combined alkaloids. After the separation of the ethanol-insoluble protopine (51 g), the ethanolic solution of the combined alkaloids was evaporated. The residue was dissolved in 5% sulfuric acid, the solution was brought to pH 6.5 with saturated sodium carbonate solution, and the hypecorine (4.3 g) was extracted with ether. When the pH was raised further to 7.5, extraction with ether yielded hypecorinine (0.3 g).

Oxidation of Hypecorine with Potassium Permanganate. At room temperature, powdered potassium permanganate was added in 0.25-g portions to a solution of 1.5 g of the substance in 100 ml of acetone. A total of 6 g of $KMnO_4$ was added. After the separation of the manganese dioxide, the filtrate was evaporated and the residue (0.6 g) was repeatedly extracted with boiling ether. This gave 0.45 g of (II), $C_9H_6O_4$, mp 180-181°C (from ether); mol. wt. 178 (mass spectrometrically); IR spectrum: ν_{max} 1745 cm^{-1}; UV spectrum: λ_{max} 224, 270, 294 nm (log ε 4.44, 3.80, 3.71) [5].

NMR spectrum in $CDCl_3$: $Ar-CH_2-O$ (5.16 ppm, singlet, 2H); aromatic methylenedioxy group (6.04 ppm, singlet, 2H); two aromatic ortho protons (6.91 and 7.41 ppm, doublets, J = 8.0 Hz, 1H each).

Acetylation of Hypecorine. A solution of 0.2 g of the substance in 30 ml of chloroform was boiled with 1.2 ml of acetic anhydride for 4 h and was evaporated. The residue was washed with ethanol, giving 0.15 g of substance (III), $C_{24}H_{25}NO_8$, with mp 126-127°C (from ethanol).

SUMMARY

Two new alkaloids (hypecorine and hypecorinine) have been isolated from Hypecoum erectum L., and their structures have been determined.

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