THE STRUCTURE OF HERBADINE AND HERBAMINE

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From the combined ethereal alkaloids obtained from the epigeal part of Vinca herbaceae [1], by solubility differences and chromatography on a column of alumina we have isolated two new alkaloids, which we have called herbadine and herbamine.

Herbadine has mp 206-208°C (decomp., acetone) (I). UV spectrum: λ_{max} 238, 292 nm (log ε 3.84, 3.55), which is characteristic for indoline alkaloids. The IR spectrum shows the absorption bands of a disubstituted benzene ring (760 cm^{-1}), of an ester carbonyl group (1720 cm^{-1}), and of a secondary nitrogen atom (3380 cm^{-1}), and a broad band at 3390-3460 cm^{-1} apparently due to a hydroxy group. The UV and IR spectra of (I) proved to be similar to those of vincarine [2].

The mass spectra of the base showed the peaks of ions with m/e 368 M^+ (32%), 252 (4), 251 (3), 168 (2), 167 (3), 166 (3), 158 (1), 157 (1), 143 (23), 130 (10), 117 (100), which are characteristic for alkaloids of ajmaline type [3, 4].

The NMR spectrum of (I) showed the signals of an ethylidene group (doublet at δ 1.55 ppm, 3H and a quartet with its center at δ 5.07 ppm, 1H), of a methoxy group (3.64; 3H), and of an NH group (6.07; 1H, singlet), and a broadened one-proton singlet at 4.57 ppm which we have assigned to $C_{21}H$.

The above facts show that herbadine is an indoline derivative and its structure is similar to that of vincarine and ajmaline. Acetylation of the base with acetic anhydride gave a N,O-diacetyl derivative (II), in the mass spectrum of which intense peaks of ions with m/e 452 M^+, 424 $(M-28)^+$, 410 $(M-42)^+$, 392 $(M-60)^+$ were observed. The IR spectrum of (II) contained an absorption band at 750 cm^{-1} and broad bands at 1640-1690, 1740-1760, and 3400-3460 cm^{-1} showing that the base has two hydroxy groups, one of them being secondary and the other tertiary.

Since the heterocyclic skeleton of (I) is based on the ajmaline nucleus, we may suggest two possible positions for the secondary hydroxy group: C_{21} and C_{17}. The choice was made on the basis of the results of a comparison of the chemical shifts of the protons at C_{17} and C_{21} in the NMR spectra of the alkaloids vincarine, ajmaline, and herbadine. The C_{21} position for the secondary hydroxy group in (I) proved to be the most acceptable. To confirm this, substance (I) was reduced with sodium tetrahydroborate giving a dihydro base (III). Its IR spectrum differed from that of the initial base by two absorption bands at 3330 and 3350 cm^{-1}, apparently showing the presence of two secondary nitrogen atoms in (III).

The NMR spectrum of (III) lacked the signal at 4.57 ppm ($C_{21}H$) and showed the signals of an ethylidene group (doublet at 1.50 ppm and quartet at 5.12 ppm), a $COOCH_3$ group (3.53 ppm, 3H), an NH group (singlet at 5.56 ppm, 2H), and two hydroxy groups (3.85 ppm, 1H, and 5.30 ppm, 1H).

When (III) was boiled with acetic anhydride in the presence of pyridine, a tetraacetyl derivative (IV) was formed (M^+ 538). Its NMR spectra showed two six-proton singlets, which we ascribed to $N-COCH_3$ (2.28 ppm) and $OCOCH_3$ (2.04 ppm). Consequently, the reduction of herbadine with sodium borohydride is similar to the reduction of ajmaline [3]. The secondary hydroxy group in (I) is located at C_{21}. On the basis of certain analogies with alkaloids of similar structure [5], the tertiary hydroxy group may be located at C_2 or C_3.

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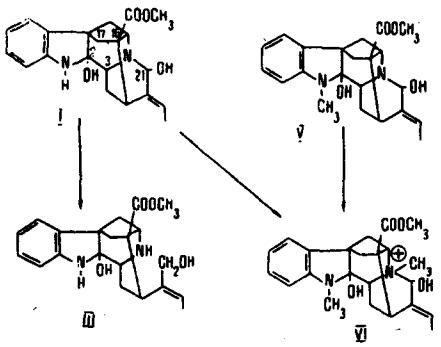
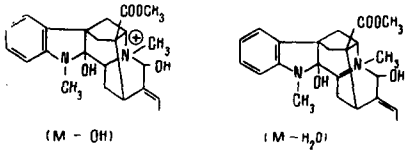


Herbamine (V) has mp 176-179°C (decomp.), and its UV spectrum [λ_{max} 250, 295 nm (log ε 3.82, 3.28)] is characteristic for substituted indoline bases. The IR spectrum shows a broad band of hydroxy groups (3400 cm^{-1}), the band of a nonconjugated carbonyl group (1740 cm^{-1}), and the band of a 1,2-disubstituted benzene ring (745 cm^{-1}).

The mass spectrum shows the peaks of ions with m/e 382 (50%), 168 (1), 167 (3), 158 (5), 157 (25), 144 (25) and 131 (100). The results of a comparative study of the mass spectra of the bases show that herbadine and herbamine are structurally similar, differing from one another by one $N-CH_3$ group.

The NMR spectrum of herbamine shows the signals of an ethylidene group (doublet at 1.50 ppm, 3H, and quartet with its center at δ 5.07 ppm, 1H), a $N-CH_3$ group (singlet at 2.72 ppm, 3H), a methoxy group (singlet at 3.54 ppm), and four aromatic protons (multiplet at 6.12-7.00 ppm).

The facts given show that herbamine is a N-methyl derivative of herbadine. To confirm this, the corresponding methiodides were obtained from herbamine and herbadine, and from these the quaternary derivatives (VI) were isolated by passage through a column of alumina. The products were identical in their R*f* values and mass spectra. The mass spectrum of (VI) showed a low-intensity peak with m/e 397 $(M-OH)^+$ and strong peaks at m/e 396 $(M-H_2O)^+$ and 382 $(M-CH_3OH)^+$. The formation of the peak with m/e 396 $(M-H_2O)^+$ permits the assumption that in herbamine and herbadine the tertiary hydroxy group is located at C_2.



The facts given above have permitted the structure of 2,21-dihydroxy-17-deoxyvincarine to be proposed for herbadine and N(a)-methyl-2,21-dihydroxy-17-deoxyvincarine for herbamine.

EXPERIMENTAL

Herbadine (I). The combined ethereal alkaloids (20 g) dissolved in 0.1 M citric acid were separated on a column of alumina. Benzene, benzene–ether, chloroform, and chloroform–methanol eluates were collected. The chloroform and the chloroform–methanol eluates were combined and rechromatographed through a column of alumina. The treatment of the benzene eluates with acetone gave 1.8 g of a faintly colored microcrystalline base – herbadine.

N,O-Diacetyl-(I) (II). A solution of 60 mg of the base in 10 ml of acetic anhydride was heated in the water bath for 8 h. This gave 45 mg of an amorphous substance with M^+ 452. NMR spectrum, ppm: 1.60 5.53 (=$CH-CH_3$), 2.13 ($OCOCH_3$), 2.27 ($N-COCH_3$), 3.50 ($COOCH_3$), 5.06 ($C_{21}H$).

Dihydro-(I) (III). With stirring, 0.5 g of sodium tetrahydroborate was added to a solution of 70 mg of the base (I) in 50 ml of methanol. The yield of the dihydroherbadine was 55 mg, mp 238-240°C (decomp., acetone), M^+ 370.

Tetraacetyl-(III) (IV). A solution of 50 mg of (III) in 10 ml of acetic anhydride was boiled in the presence of pyridine for 6 h. This gave 40 mg of (IV), M^+ 538. IR spectrum, cm^{-1}: 1600, 1650-1670, 1750-1760.

Herbamine (V). The fraction of the combined ethereal alkaloids soluble in 15% citric acid was separated in a column of alumina. After the vincarine had been eluted, the chloroform eluates by treatment with methanol deposited 2 g of herbamine, mp 176-179°C (decomp.), $[\alpha]_D^{20}$ 0 ± 5° (c 0.7; chloroform). The NMR spectra were taken on a JNM-4H-100/100 MHz instrument (HMDS as internal standard, δ scale), (I-IV) in D-pyridine and (V) in $CDCl_3$.

SUMMARY

The new bases herbadine and herbamine have been isolated from the epigeal part of Vinca herbaceae.

A comparative study of IR, UV, NMR, and mass spectra and chemical properties has established the structure of 2,21-dihydroxy-17-deoxyvincarine for herbadine and N(a)-methyl-2,21-dihydroxy-17-deoxyvincarine for herbamine.

LITERATURE CITED

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