UDC 547.8:633.88+581.9

ALKALOIDS OF BUXUS BALEARICA. II

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Khimiya Prirodnykh Soedinenii, Vol. 5, No. 5, pp. 406-409, 1969

The isolation of seven alkaloids, denoted by A, B, C, D, E, F, and G, from Buxus balearica Lam. has been reported previously [1]. This paper reports further study of the alkaloids A, C, and F. It has been established by mass spectrometry that the alkaloid C has the empirical formula $C_{26}H_{39}NO$, and not $C_{26}H_{41}NO$, as we proposed previously [1]. Alkaloid C contains two absorption bands of an α,β-unsaturated ketone (1669 and 1596 cm^{-1}). Absorption bands of hydroxyl groups are absent. UV spectrum of alkaloid C: λ_{max} 239 and 247 mμ (log ε 4.52 and 4.48, respectively), which is the sum of those of an unsaturated ketone and of conjugated double bonds. The mass-spectrometric decomposition of alkaloid C corresponds completely to that described in the literature for the alkaloid buxamideine K [3] and buxpsiine. To identify alkaloid C as buxamideine K, the IR spectrum was recorded [2, 3] and it was also subjected to catalytic hydrogenation giving the known alkaloid buxamidine K [4].

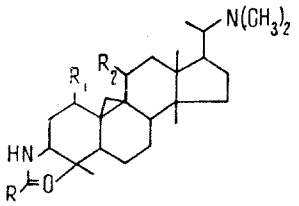
NMR spectrum of alkaloid C: 4-Me_2) doublet at 0.69 ppm; 14-Me) 0.86 ppm; 18-Me) 1.08 ppm; $COCH_3$) 2.20 ppm; $N(CH_3)_2$) 2.34 ppm. Signals of the protons on the double bonds: 11-H) 5.52 ppm; 19-H) 5.84 ppm; 16-H) 6.62 ppm. The spectrum of the hydrogenation product lacked the signal in the 6.62 ppm region which is characteristic for the 16-H proton at the double bond [3]. In the mass spectrum of the product of the hydrogenation of alkaloid C, the mass numbers are displaced by two units as compared with the spectrum of alkaloid C.

Alkaloid F, with the composition $C_{27}H_{46}N_2O_2$, contains NH and OH groups (IR spectrum: 3320, 3410 cm^{-1}) and, on acetylation, gives a triacetate with the composition $C_{33}H_{52}N_2O_5$ (N-acetyl, di-O-acetate), which confirms the presence of two hydroxyl groups and a secondary nitrogen atom. The methylation of alkaloid F by Hess's method gave a base with the composition $C_{28}H_{48}N_2O_3$, which was identified as cyclomicrophylline A [4, 5]. Consequently, alkaloid F is identical with cyclomicrophylline B [4, 5] and with cyclobaleabuxine [6].

Alkaloid A, with the composition $C_{30}H_{50}N_2O_2$, contains a carbonyl group and a secondary nitrogen (IR spectrum: 1683, 3460 cm^{-1}) which does not undergo acetylation or methylation by Hess's method. Reduction with lithium aluminum hydride led to an alcohol with the composition $C_{30}H_{52}N_2O_2$ (IR spectrum: 3490 cm^{-1} for OH), the acetylation of which gave an amorphous O-acetyl derivative. The UV spectrum (λ_{max} 219 mμ, log ε 3.86) shows slight conjugation (probably cyclopropyl ring, C=O). The mass-spectrometric decomposition of alkaloid A takes place in accordance with that described for derivatives of 20-dimethylaminopregnane [7]. In actual fact, the maximum peak is that with m/e 72, due to the side chain at C-17 ($CH_3CH{=}\overset{+}{N}(CH_3)_2$); the other peaks do not exceed 1.5% of the maximum peak. In the region of high mass numbers there are peaks of approximately equal magnitude with m/e 469, 470, and 471.

Consequently [7], the molecular peak of the alkaloid A is that with m/e 470. After the first stage of the Hofmann degradation of alkaloid A, a neutral des-base was obtained in which an amide group was present (IR spectrum: 3390, 1660, 1640 cm^{-1}).

In its mass spectrum there are peaks of ions with m/e M^+ 425, 410 (M − CH_3), 354 (M − 71), and 338 (M − 87) formed by a well-known mechanism [8]. The properties of alkaloid A are very close to those of the alkaloid baleabuxine [6] but are not identical with them (difference in the melting points of the bases and their solubilities, and the properties of the des-bases and the products of reduction with lithium aluminum hydride). It is most likely that these alkaloids are epimeric. The possibility of their differing with respect to the position of the carbonyl group (C-1 instead of C-11) and the radical R in the amide group is also not excluded. The two possible structural formulas Ia and Ib may be proposed for alkaloid A.



Ia R=C_3H_7; R_1=O; R_2=H_2

Ib R=C_3H_7; R_1=H_2; R_2=O

Experimental

The IR spectra of the substances were recorded on a UR-10 spectrophotometer in paraffin oil, the UV spectra on an SF-4 spectrophotometer (in ethanol), the NMR spectra of a JNM-3H-60 spectrophotometer in chloroform and benzene solutions (with hexamethyldisiloxane as internal standard), and the mass spectra of a MKh-1306 instrument fitted with a system for the direct introduction of the sample into the ion source [9] at 130–150° C with an ionizing voltage of 25 V. All the melting points are uncorrected. Chromatography was carried out on alumina of activity grade II; the system for the thin-layer chromatography of the alkaloids (silica gel) was butanol–acetic acid–water (10 : 1 : 3).

Alkaloid C (buxamideine K). This was obtained from the fraction extracted at pH 6.5 by chromatography and crystallization from acetone [1]; mp 180–183° C; $[\alpha]_D^{20}$ +118° (c 0.68; chloroform).

UV spectrum: λ_{max} 239, 247 mμ, log ε 4.52, 4.48. IR spectrum: 1669, 1596 cm^{-1}. NMR spectrum, δ, ppm: 0.69 (4-Me_2), 0.86 (14-Me), 1.08 (18-Me), 2.20 ($COCH_3$), 2.34 ($N(CH_3)_2$), 5.52 (11-H), 5.84 (19-H), 6.62 (16-H). Mass spectrum, m/e: M^+ 381, 71, 58, 43, and 84.

Found, %: C 81.57, 81.81; H 10.68, 10.56; N 3.65, 3.65. Calculated for $C_{26}H_{39}NO$, %: C 81.83; H 10.36; N 3.67; mol. wt. 381 (mass spectrum).

Catalytic hydrogenation of alkaloid C (buxamideine K). 100 mg of alkaloid C in 13 ml of 95% ethanol was hydrogenated over platinum (from 0.02 g of PtO_2). This gave 100 mg of a mixture of two substances the chromatography of which on a column of alumina (with methylene chloride as eluate) yielded 60 mg of a substance with mp 140° C, [α] +60 (c 0.5; chloroform).

UV spectrum: λ_{max}, 240, 247 mμ, log ε 4.32, 4.37. The NMR spectrum lacked a signal in the 6.62 ppm region for the 16-H proton. Mass spectrum, m/e: M^+ 383, 58, 71, and 84.

Elution with methylene chloride containing 5% methanol yielded 31 mg of an amorphous substance giving two spots on a thin-layer chromatogram.

Alkaloid F (cyclomicrophylline B). The alkaloid was obtained from an ethereal extract at pH 9 [1], mp 246–248° C (ethanol), $[\alpha]_D^{20}$ −60° (c 1.2; chloroform).

IR spectrum, cm^{-1}: 3320 (NH), 3410 (OH).

Found, %: C 76.08; H 11.00; N 6.45. Calculated for $C_{27}H_{46}N_2O_2$, %: C 75.3; H 10.75; N 6.5.

Methylation of alkaloid F. 100 mg of the substance was methylated by Hess's method. The reaction product had mp 228–230° C (from acetone), $[\alpha]_D^{20}$ − 90° (c 0.1; chloroform).

Found, %: C 75.59; H 10.81; N 6.10. Calculated for $C_{28}H_{48}N_2O_3$, %: C 75.6; H 10.9; N 6.3.

Acetylation of alkaloid F. 100 mg of the base in 4 ml of pyridine was acetylated with acetic anhydride (1 ml) at 20° C. After crystallization from a mixture of acetone and hexane the reaction product had mp 193–195° C, $[\alpha]_D^{20}$ — −145° (c 1.0; chloroform).

Found, %: C 72.06, 72.01; H 9.62, 9.51; N 4.68, 4.59. Calculated for $C_{33}H_{52}N_2O_5$, %: C 71.2; H 9.4; N 5.05.

Alkaloid A. This was obtained by the chromatography on alumina of the fraction extracted by chloroform from acid solution [1], mp 236–240° C (from acetone), $[\alpha]_D^{20}$ +120.7° (c 1.23; chloroform).

IR spectrum, cm^{-1}: 3400, 3030, 1660, 1685, 1530, 1427, 830. UV spectrum: λ_{max} 217 mμ (log ε 3.86). Mass spectrum, m/e: M^+ 470 and 72 (84%).

Found, %: C 76.17; H 10.72; N 5.82. Calculated for $C_{30}H_{50}N_2O_2$, %: C 76.52; H 10.71, N 5.95.

Reduction of the alkaloid A. In 20 ml of absolute ether, 206 mg of the substance was reduced with lithium aluminum hydride at room temperature, giving 200 mg of a white crystalline substance with mp 226–230° C (from acetone), $[\alpha]_D^{20}$ +53° (c 0.487; chloroform).

IR spectrum, cm^{-1}: 3380, 3340, 1650, 1530, 1560.

Found, %: C 76.05, 76.10; H 11.06, 11.18; N 5.71. Calculated for $C_{30}H_{52}N_2O_2$, %: C 76.22, H 11.09; N 5.93.

Acetylation of the product of the reduction of alkaloid A. At 20° C, 80 mg of the substance in 3 ml of pyridine was acetylated with acetic anhydride (1 mg). A chromatographically homogeneous amorphous substance was obtained.

IR spectrum: 1740 cm^{-1} (O-acetyl).

Hofmann degradation of alkaloid A. To a solution of 0.1 g of the substance in 4 ml of methanol was added 4 ml of methyl iodide, and the mixture was boiled for 4 hr. After evaporation, 0.12 g of methiodide with mp 261–264° C was obtained, and this was dissolved in water and treated with freshly-prepared silver oxide (from 0.1 g of $AgNO_3$) with

shaking for half an hour. After the separation of the solid matter and the elimination of the water in vacuum at 100° C, the residue was extracted with ether. This gave a white crystalline substance with 176–178° C. The residue of unchanged quaternary base was heated further in vacuum at 100° C for half an hour. After extraction with ether, another 8 mg of methine base was obtained. The reaction was neutral.

Found, %: N 3.48. Calculated, %: N 3.39.

Mass spectrum, m/e: M^+ 425; 338 (M – 87); 354 (M – 71); 410 (M – CH_3).

The IR and UV spectra were taken by M. E. Perel'son's group. The elementary composition was determined by E. A. Nikonova's group.

The mass spectra were recorded and interpreted by V. I. Zaretskii.

Conclusions

1. Alkaloid C has been shown to be identical with buxamideine K, and alkaloid F with cyclomicrophylline B.
2. Two possible structural formulas have been proposed for alkaloid A.

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7 June 1968

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