ALKALOIDS OF BUXUS BALEARICA. III

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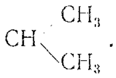
The isolation from Buxus balearica Lam. of seven alkaloids called A, B, C, D, E, F, and G has been reported previously [1]. The present paper gives the results of a further study of the alkaloids A, D, and G.

In a previous communication [2] we proposed for alkaloid A two possible structural formulas: Ia and Ib.

The NMR spectrum of alkaloid A has the singlets of four tertiary methyl groups at 0.70, 0.78, 0.83, and 0.96 ppm, three doublets of three secondary methyl groups at 0.79 ppm (J = 6.1 Hz), and 1.08 and 1.10 ppm (J = 6.8 Hz), and the signals of a $N(CH_3)_2$ group at 2.11 ppm, of a $CO{-}CH_2$ group at 2.34 ppm, and of a CO—NH group at 5.32 ppm.

The presence of a carbonyl group in position 11 is more likely than in position 1, since the protons of the $CO{-}CH_2$ group in the NMR spectrum of alkaloid A give a singlet [3–5].

The NMR spectrum of alkaloid A confirms structural formula Ib [2], where R =  $CH(CH_3)_2$.

A mixture of alkaloid A with the alkaloid baleabuxine kindly given to us by D. Herlem-Gaulier gave a depression. Alkaloid A is apparently an epimer of baleabuxine; we have called it "pseudobaleabuxine."

Alkaloid D, $C_{30}H_{50}N_2O_4$ (M^+ 502), contains a NH—C=O grouping, a C=O group (IR spectrum, cm^{-1}: 3250, 1650, 1540, and 1670), and a $N(CH_3)_2$ group (mass spectrum, peak with m/e 72). The NMR spectrum of this alkaloid has the singlets of three tertiary methyl groups at 0.51, 0.78, and 1.17 ppm, the doublets of three secondary methyl groups at 0.84, 1.07, and 1.15 ppm, and the signals of a $N(CH_3)_2$ group at 2.19 ppm and of a —CO—NH— group at 5.71 ppm. The signals of a proton on a C bearing a secondary OH group are present in the 3.96 ppm region (—CHOH, multiplet), and the signals of the protons attached to a C bearing a primary OH group (AB system) are at 2.92 ppm and 3.26 ppm (J = 12.83 Hz).

On the basis of these facts and also its physicochemical constants, alkaloid D was identified as N^3-isobutyrylcycloxobuxidine F, 2b [6, 7].

It was established by mass spectrometry that alkaloid G has the empirical formula $C_{26}H_{44}N_2O_3$, and not $C_{27}H_{46}N_2O_3$, as we considered previously [1]; mp 227–230° C (benzene), $[\alpha]_D^{20}$ +114° (c 0.80; chloroform. The alkaloid has the following groups: $N(CH_3)_2$ (mass spectrum, peak with m/e 72), OH, and C=O (IR spectrum, cm^{-1}: 3500, 3240, and 1670). The bands at 1640 and 1593 cm^{-1} in the IR spectrum are probably due to the deformation vibrations of an NH_2 group. This is confirmed by the disappearance of these bands in the spectrum of the product of the methylation of the alkaloid G. The UV spectrum (λ_{max} 221 mμ, log ε 3.95) shows conjugation (cyclopropane ring, C=O).

The NMR spectrum of alkaloid G has the singlets of three tertiary methyl groups at 0.77, 0.82, and 1.10 ppm; the doublet of a secondary methyl group at 0.80 ppm (J = 6.09 Hz) and the signal of a $N(CH_3)_2$ group at 2.16 ppm. The signals of the proton attached to the C bearing the secondary OH group appear in the 4.07 ppm region in the form of a multiplet. The signals of the two protons attached to the C bearing the primary OH group give a quartet in the 3.37 and 3.57 ppm region (CH_2OH, AB system, J = 12.74 Hz).

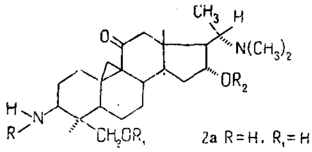
In the mass spectrum of the alkaloid, the maximum peak is that with m/e 72, due to the fragment of the side chain at C-17 ($CH_3CH{=}\overset{+}{N}(CH_3)_2$), and also the peak of the molecular ion with m/e 432.

The properties of alkaloid G that have been considered permit the conclusion that the alkaloid is a new substance isolated from this plant for the first time, and we have called it "buxidine F."

The acetylation of buxidine F led to a triacetate with the composition $C_{32}H_{50}N_2O_6$ (M^+ 558, N-acetyl di-O-acetate), which confirms the presence of two OH groups and an NH_2 group. IR spectrum, cm^{-1}: 3400, 1550, and 1540 (amide grouping); 1720 and 1745 (O-acetyl groups).

When buxidine F was heated with methyl iodide, a N-monomethyl derivative $C_{27}H_{46}N_2O_3$ was formed, the IR spectrum of which lacked the bands at 1640 and 1593 cm^{-1}, together with the methiodide of its N-monomethyl derivative $C_{27}H_{46}N_2O_3 \cdot CH_3I$. Further methylation with methyl iodide gave the N-dimethyl derivative of buxidine F $C_{28}H_{48}N_2O_3$ and its methiodide $C_{28}H_{48}N_2O_3 \cdot CH_3I$.

On the basis of these results we have proposed for buxidine F the structure 2a.



2a R = H, R_1 = H, R_2 = H

2b R = $(CH_3)_2$ CHCO; R_1 = H; R_2 = H

Structure 2a for buxidine F was confirmed by comparing the latter with the known alkaloid N^3-isobutyrylcycloxobuxidine F, 2b. The acid hydrolysis of N^3-isobutyrylcycloxobuxidine F gave a substance with mp 227–230° C, $[\alpha]^{20}_D$ +105 (c 0.90; chloroform) the IR and NMR spectra of which were identical with those for buxidine F.

EXPERIMENTAL

The IR spectra of the substances were recorded on a UR-10 spectrophotometer (paraffin oil), the UV spectra on an SF-4 spectrophotometer (ethanol), the NMR spectra on a Varian HA-100 spectrophotometer (deuterochloroform solution with hexamethyldisiloxane as internal standard) and the mass spectra on a MKh-1306 instrument fitted with a system for the direct introduction of the sample into the ion source at 130–150° C with an ionizing voltage of 25 V. All the melting points are uncorrected.

N-Acetyldi-O-acetylbuxidine F. 100 mg of the base in 400 ml of pyridine was acetylated with acetic anhydride (1 ml) at 20° C for 24 hr. The reaction product, after crystallization from a mixture of ethyl acetate and hexane, had mp 226–227° C.

IR spectrum, cm^{-1} 3400, 1720, 1745, 1660, 1540. Mass spectrum: M^+ 558; m/e 72, 100. NMR spectrum: signals of three tertiary methyl groups with δ 0.67, 0.78, and 1.11 ppm; doublet of a secondary methyl group at 0.78 ppm (J = 5.87 Hz), singlet of $N(CH_3)_2$ at 2.07 ppm; three $COCH_3$, singlets at 1.87, 1.92, and 2.03 ppm; CH_2OAc—AB system, 3.67 and 3.77 ppm (J = 11.9 Hz); CHOAc—5.07 ppm, multiplet; NH—CO—CH_3 5.61 ppm, doublet (J = 9.53 Hz).

Found, %: C 68.38; H 9.16; N 5.05. Calculated for $C_{32}H_{50}N_2O_6$, %: C 68.8; H 8.96; N 5.01.

Acid hydrolysis of N^3-isobutylcycloxobuxidine F: buxidine F. A mixture of 270 mg of N^3-isobutylcycloxobuxidine F; 25 ml of 2 N H_2SO_4, and 20 ml of methanol was boiled in the water bath for 2 hr. The methanol was distilled off and heating was continued for 1 hr. The solution was brought to pH 10 and extracted with methylene chloride. The reaction product, after crystallization from benzene, had mp 227–230° C; $[\alpha]^{D}_{20}$ +105° (c 0.90; chloroform).

IR spectrum, cm^{-1}: 3500, 3240, 1670, 1645, 1595. NMR spectrum: singlets of three tertiary methyl groups at 0.77 ppm (3H, 14α), 0.82 ppm (3H, 4α), and 1.13 ppm (3H, 18β), doublet of a secondary methyl group at 0.80 ppm (J ~ 6Hz); singlet of $N(CH_3)_2$ at 2.16 ppm; multiplet at 4.05 ppm (—CHOH, 16α, H); quartet, AB system (J = 12.7 Hz) at 3.37 and 3.57 ppm (—CH_2OH, 4β, 2H).

Found, %: N 6.40. Calculated, %: N 6.48.

N-Monomethylbuxidine F. To a solution of 0.6 g of buxidine F in 10 ml of methanol was added 6 ml of methyl iodide, and the mixture was boiled for 5 hr. A white precipitate deposited with mp 260° C (mixture of the hydriodide and the methiodide of the N-monomethyl derivative of buxidine F). The precipitate was dissolved in water and the solution was made alkaline and extracted with ether. The product obtained after the ether had been distilled off had mp 220–222° C (from acetone), $[\alpha]_D^{20}$ +120.6° (c 0.8; chloroform).

IR spectrum, cm^{-1}: 3480, 1670, and 1470. NMR spectrum: singlets of three tertiary methyl groups at 0.77 ppm (3H, 14α), 1.01 ppm (3H, 4α), and 1.14 ppm (3H, 18β); doublet of a secondary methyl group at 0.81 ppm (J = 6.12 Hz); singlet of $N(CH_3)_2$ at 2.19 ppm; singlet of $N{-}CH_3$ at 2.03 ppm; multiplet at 4.03 ppm ($-CH{-}OH$, 16α, H); quartet, AX system (J = 10.18 Hz) at 3.10 and 3.53 ppm ($CH_2{-}OH$, 4β, 2H).

Found, %: C 72.78; H 10.70; N 6.17. Calculated for $C_{27}H_{46}N_2O_3$, %: C 72.6; H 10.31; N 6.27.

N-Dimethylbuxidine F. To a solution of 0.35 g of N-monomethylbuxidine F in 10 ml of methanol was added 5 ml of methyl iodide and the mixture was boiled for 8 hr. After evaporation and washing with ether (0.1 g of unchanged N-monomethyl derivative passed into the ether), the product obtained (mixture of the hydriodide and methiodide of N, N-dimethylbuxidine F) was dissolved in water and the solution was made alkaline and extracted with ether. This gave 0.1 g of N, N-dimethylbuxidine F, mp 235–237° C (from acetone), $[\alpha]_D^{20}$ +90.6 (c 0.8; chloroform). IR spectrum: 1670 cm^{-1}.

Found, %: C 73.2; H 10.60; N 5.95. Calculated for $C_{28}H_{48}N_2O_3$, %: C 73.00; H 10.50; N 6.08.

The mass spectra were recorded and interpreted by V. I. Zaretskii (Institute of the Chemistry of Natural Compounds), and the IR and UV spectra by A. A. Kir'yanov and also by our colleagues of the Spectral Investigation Department of VILR [All-Union Scientific-Research Institute for Medicinal Plants].

CONCLUSIONS

1. Alkaloid D has been identified as N^3-isobutyrylcycloxobuxidine F.

2. A structure has been proposed for alkaloid A, which is apparently an epimer of baleabuxine, and we have called it pseudobaleabuxine.

3. A structure has been proposed for a new alkaloid which we have called buxidine F.

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