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ALKALOIDS OF Aconitum coreanum.

IV. 14-HYDROXY-2-ISOBUTYRYLHETISINE N-OXIDE

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A new alkaloid has been isolated from the epigeal part of Aconitum coreanum (Levl.) Rapaics, for which the structure of 14-hydroxy-2-isobutyrylhetisine N-oxide has been established on the basis of spectral characteristics and a chemical transformation.

Aconitum coreanum (Levl.) Rapaics grows in the south of Maritime Territory and is known as a poisonous plant [1] possessing antibacterial activity [2]. We have reported the isolation of a series of diterpene alkaloids from this plant previously [3].

Continuing our investigation, we have isolated a new optically active base crystallizing in the form of needles with mp 317-319°C, composition $C_{24}H_{33}NO_6$ (I). Its IR spectrum showed the absorption bands of hydroxy (3600-3200 cm^{-1}), ester carbonyl (1730 cm^{-1}), and exomethylene (1680 cm^{-1}) groups. Its PMR spectrum contained the signals from tertiary methyl (δ 1.15 ppm, 3 H, singlet), gem-dimethyl (1.16 ppm, 6 H, doublet, J = 6 Hz), and exomethylene (4.75 and 4.65 ppm; broadened singlets, 1 H each) groups. These facts permitted the conclusion that (I) belonged to the C_{20}-diterpene alkaloids with an isobutyryl substituent.

Base (I) differed in composition from the 14-hydroxy-2-isobutyrylhetisine (II) isolated from this plant [3] (the so-called Guan-Fu base Z [4]) by an oxygen atom. A comparison of the mass spectra of (I) and (II) showed that in (I), together with the M^+, M − 17, M − 28, M − 45, M − 56, and M − 87 peaks characteristic for (II) [5], there were the peaks of the ions M − 16, M − 18, M − 16 − 17, M − 16 − 28, M − 16 − 45, M − 15 − 56, and M − 16 − 87, which gave grounds for the assumption that (I) was the N-oxide of an isobutyryl derivative of 14-hydroxyhetisine.

According to TLC results, the alkaloid did not possess the high polarity characteristic of N-oxides. Furthermore, it did not dissolve in water, was sparingly soluble in chloroform and moderately in ethanol and methanol, and crystallized readily from the latter and also when water was added to its dilute ethanolic solutions. The presence of a N→O group and the position of the isobutyryl substituent in (I) were established by ^{13}C NMR spectroscopy.

The results of a comparison of the ^{13}C NMR spectra of (I) and (II) (Table 1) showed

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TABLE 1. Chemical Shifts of the Carbon Atoms of 14-Hydroxy-2-isobutyrylhetisine N-oxide (I) and of Guan-Fu Base Z (II) (δ ppm, O–HMDS)

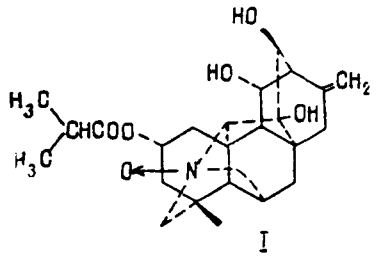
C atom	Multiplicity	I (CD_3OD)	I ($CDCl_3$)*	II ($CDCl_3$)*
1	t	31,07	30.18	31,37
2	d	69,69	68,20	69,69
3	t	37,27	36,60	36,82
4	s			37,65
5	d	56.02	54,98	60,05
6	d	75,52	75.21	63.12
7	t	29,28	28,46	32,04
8	s	45,63	44,52	44,37
9	d	53,86	52,88	53.63
10	s			46,39
11	d	72,98	71,41	76.04
12	d	53,33	51.46	52,81
13	d	74.77	73,35	79.92
14	s	84,78	83,51	80,37
15	t	32,49	31,89	31,15
16	s	146.63	143,56	144,91
17	t	108,53	108,91	108,16
18	q	29,50	29,50	29,73
19	t	77.38	76,19	63,12
20	d	83.06	82,24	69,24
1′	s	177.63	179,64	176.65
2′	d	35,55	34,21	34.51
3′	q	19,49	19,05	19,12

*The chemical shifts were measured at an increased concentration with the addition of a methanolic solution of (I).

that the effect of the N → O group caused considerable downfield shifts of the C-6, C-19, and C-20 signals (Δδ = 12.40, 14.26, and 13.82 ppm, respectively), which corresponded in magnitude and direction to the α-contributions of a N-oxide [6]. The β- and γ-effects are, as a rule, diamagnetic [7] and are considerably smaller in magnitude than the α-contributions. Descreening is frequently observed for a tetrasubstituted β-carbon atom [8, 9]. The remaining signals were identified in the light of these facts and of the multiplicities of the signals in the spectrum of (I) obtained under conditions of incomplete suppression of interactions with protons, and also by means of a comparison with CSs of Guan-Fu base Z (II) given in [4]. The absence of appreciable changes in the CSs of the C-1, C-2, and C-3 signals permitted the conclusion that (I) was 14-hydroxy-2-isobutyrylhetisine N-oxide.

The PMR spectrum of (I) exhibited the signals of the protons at carbon atoms present in the α-positions to the N-oxide function in the form of a singlet at 3.93 ppm (H-20), two doublets at 4.02 ppm (H-19α) and 2.91 ppm (H-19β) with a gem coupling constant of 12 Hz, and an unresolved two-proton signal in the 3.83-3.63 ppm region (H-6 and H-13); i.e. downfield shifts were observed of the H-20, H-19β, and H-6 signals by Δδ = +0.42–0.44 ppm, and of the H-19α signal by Δδ = +1.10 ppm.

When 14-hydroxy-2-isobutyrylhetisine was oxidized with 30% hydrogen peroxide, a single product was formed which, according to GLC, IR spectra, and melting point proved to be identical with the base that had been isolated. This confirmed the structure (I) proposed for the new alkaloid.



I

EXPERIMENTAL

General Observations. Melting points were determined on a Boetius PHMK 05 instrument and optical rotations on a JASCO J-20 spectropolarimeter; IR spectra were obtained on a UR-20 spectrometer (KBr), mass spectra on a MKh-1310 instrument, and NMR spectra on a Tesla 567A 100 MHz spectrometer.

The separation and purification of the alkaloids were carried out on columns filled with alumina (Brockmann activity grade II, neutral, deactivated, 1:100).

For TLC we used LSL 5/40 alumina, neutral, in the solvent systems chloroform–methanol (25:1; and 20:1).

For the isolation and separation of the alkaloids, see [3]. The hexane–ether eluates containing the N-oxide (I) and Guan-Fu base Z (II) were combined and the Guan-Fu base Z was separated by crystallization from methanol and ethanol: mp 228-229°C. The mother liquors were chromatographed on a column of alumina. Ethereal eluates yielded 140 mg of (II) and chloroform eluates 80 mg of (I).

14-Hydroxy-2-isobutyrylhetisine N-oxide (I), mp 317-319°C, $[\alpha]_D^{20}$ +25° (c 0.34; ethanol). Crystallized in the form of colorless needles. Mass spectrum, m/z (%): 431 (M^+ 64), 415(50), 414(100), 413(10), 403(36), 398(23), 387(25), 386(43), 375(10), 370(19), 359(14), 358(16), 344(44), 328(20), 326(54) gem-dimethyl group. PMR spectrum, δ (ppm CD_3OD); 5.10 (1H, m, H-2). 4.75 and 4.65 (br. s, 1H each, $=CH_2$), 4.14 (1H, br. d, J = 9 Hz, H-11), 4.02 (1H, d, J = 12 Hz. H-19α), 3.93 (1H, br. s., H-20), 3.73 (2H, m, H-6, H-13), 2.91 (1 H, d, J = 12 Hz, H-19β), 1.15 (3H, s, CH_3-18), 1.16 (6H, d, J=6 Hz). The other signals appeared in the 3.05-1.40 ppm region.

Preparation of 14-Hydroxy-2-isobutyrylhetisine N-Oxide from (II). Hydrogen peroxide (30%, 5 ml) was added to 100 mg of Guan-Fu base Z in 5 ml of methanol, and the mixture was left at room temperature for two days. On evaporation in the air, colorless needles deposited, which were separated off and crystallized from ethanol and methanol, mp 317-319°C. The compound obtained was identical with (I) according to its melting point, TLC, and mass and IR spectra.

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