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CHEMICAL MODIFICATION BASED ON DITERPENE ALKALOIDS — NEW DERIVATIVES OF KARAKOLINE AND TALATISIDINE

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The preparation and spectral characteristics of five new derivatives of karakoline (1) and talatisidine (2) are described; 14-benzoylanhydrooxykarakoline (4), 8,14-dibenzoylanhydrooxykarakoline (5), 14-benzoylkarakoline (6), 14-O-methyltalatisidine (7), and 1-benzoyl-14-O-methyltalatisidine (8).

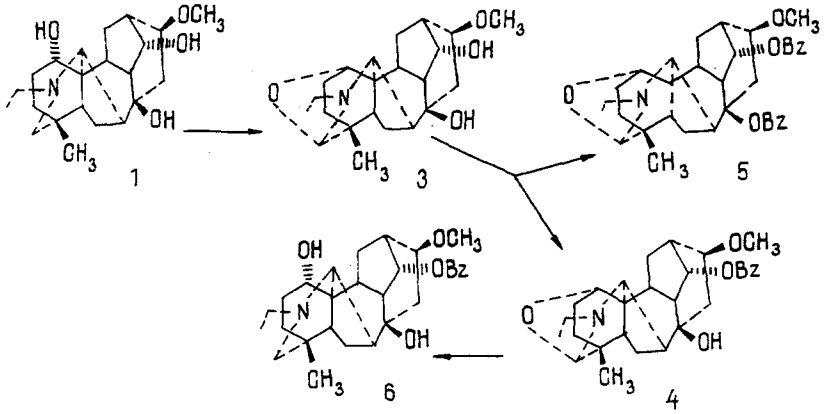
Originally, the chemical modification of diterpene alkaloids was connected mainly with the proof of their structures and the study of their chemical properties. Later, with the accumulation of information on the structures of the alkaloids and their biological activities, the necessity appeared for modifying the molecules with the aim of finding highly active drugs [1-4].

In the present paper we describe the preparation and spectral characteristics of a number of derivatives of karakoline (1) and talatisidine (2). Karakoline was isolated fron the plant *Aconitum karakolicum* [5], and talatisidine from *A. talassicum* [6].

The oxidation of karakoline (1) with potassium permanganate in aqueous acetone gave anhydrooxykarakoline (3), which has been described previously [1]. Benzoylation of the latter with benzoyl chloride in pyridine for 24 h led to a mixture of products, the chromatographic separation of which gave 14-benzoylanhydrooxykarakoline (IV) as the main product, and also 8,14-dibenzoylanhydroxykarakoline (5) and the initial compound as minor products.

The IR spectrum of (4) contained the absorption band of an ester carbonyl at 1725 cm^{-1}. The presence of a benzoyl group at C-14 was confirmed by the signals of five aromatic protons at 7.30-7.88 ppm and a downfield shift of the signal of the hemiacyl proton (5.05 ppm, t, J = 5 Hz) in the PMR spectrum. In the mass spectrum of (4) the maximum peak was that of the ($M^+ - 56$) ion (100%), showing the presence of the grouping of an internal α-carbinolamine ether [7].

The structure of (5) followed from the following facts. In the IR spectrum of (5) an absorption band of an ester carbonyl was observed at 1715 cm^{-1}. In the PMR spectrum there were the signals of 10 aromatic protons at 7.00-7.70 ppm and of a C-14-β-proton at 5.05 ppm (t, J = 5 Hz). The mass spectrum contained intensive peaks of the ions ($M^+ - 56$) (100%) and ($M^+ - 56 - 122$) (62%), arising on the successive ejection of an acrolein molecule and of benzoic acid at the expense of the benzoyl group at C-8.



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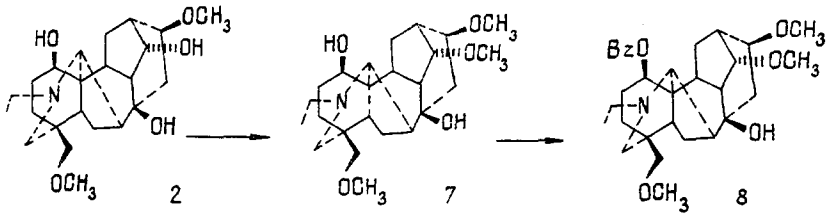
When talatisidine (2) was methylated with methyl iodide in dioxane in the presence of sodium hydride, 14-O-methyltalatisidine (7) was obtained. The latter was benzoylated with benzoyl chloride in pyridine, giving 1-benzoyl-14-O-methyltalatisidine (8). The PMR spectrum of (8) contained the signal of an α-proton at C-1 geminal to a benzoyl group (5.35 ppm, 1 H, br.s, C-1 — α-H). The mass spectrum agreed with the proposed structure.



EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer, mass spectra on a MKh-1310 spectrometer with a system for direct injection into the ion source, and PMR spectra on a Tesla BS-567 A instrument (100 MHz, δ scale, 0 - HMDS). Type KSKG silica gel and deactivated alumina were used for chromatography.

Anhydrooxykarakoline (3) was obtained by a procedure described previously [1].

Benzoylation of Anhydrooxykarakoline (3). A solution of 0.7 g of anhydrooxykarakoline in 6 ml of pyridine was treated with 3 ml of benzoylchloride and the mixture was left at room temperature for 28 h. Then the solvent was evaporated off, the residue was dissolved in water, and the solution was made alkaline with sodium carbonate and was extracted with ether. The ethereal extract was dried over sodium sulfate and evaporated. Yield 1 g.

The benzoylation product was chromatographed on a column of silica gel with elution by benzene to which acetone was gradually added. The fractions obtained yielded 8,14-dibenzoylanhydrooxykarakoline (0.03 g), the initial anhydrooxykarakoline (0.2 g), and 14-benzoylanhydrooxykarakoline (0.66 g).

14-Benzoylanhydrooxykarakoline (4), mp 77-79°C (acetone). IR spectrum, ν_{max} (KBr, cm^{-1}): 3490-3410, 1725, 1455, 1280, 1120, 1095, 1000, 890. Mass spectrum, *m/z* (%): M 479 (2.5), 464 (2), 424 (31), 423 (100), 408 (3), 105 (15). PMR spectrum (100 MHz, $CDCl_3$): 0.79 (3H, s, C-4$-CH_3$), 1.01 (3H, t, J = 2.5 Hz, H$-$C-1), 5.05 (1H, t, J = 5 Hz, H$-$C-14), 7.30 and 7.88 (Ar$-$H).

8,14-Dibenzoylanhydrooxykarakoline (5). Amorphous. IR spectrum, ν_{max} (KBr, cm^{-1}): 1715, 1450, 725, 2950, 1605, 1285, 1180, 1125, 1100, Mass spectrum, *m/z* (%): M 583 (4), 568 (2.6), 529 (10), 528 (62), 527 (100), 512 (2.3), 499 (1.2), 462 (4), 461 (5.4), 451 (2.5), 446 (2.6), 430 (3), 407 (27), 406 (23), 405 (62), 404 (33), 375 (19). PMR spectrum ($CDCl_3$): 0.75 (3H, s, C-4$-CH_3$), 1.05 (3H, t, J = 7.5 Hz, N$-C_2H_5$), 3.27 (3H, s, OCH_3), 3.64 (1H, s, H$-$C-19), 3.73 (1H, d, J = 2.5 Hz, H$-$C-1), 5.05 (1H, t, J = 5 Hz, H$-$C-14), 7.00-7.70 (10H, Ar$-$H).

Reduction of 14-Benzoylanhydrooxykarakoline (4). 14-Benzoylanhydrooxykarakoline (0.35 g) was subjected to Adams hydrogenation in 40 ml of alcohol. After the usual working up, 0.3 g of 14-benzoylkarakoline (6) was isolated with the aid of ether.

14-Benzoylkarakoline (6), mp 158-160°C (ether). IR spectrum ν_{max} (KBr, cm^{-1}): 3460, 2960, 1725, 1469, 1285, 1125, 11125, 720. Mass spectrum, *m/z* (%): M^+ 481 (19), 466 (24), 465 (31), 464 (100), 448 (19), 437 (5), 424 (7), 422 (8), 409 (10), 104 (19). PMR spectrum ($CDCl_3$): 0.83 (3H, s, C-4$-CH_3$), 1.06 (3H, t, J = 7.5 Hz, N$-C_2H_5$), 3.17 (3H, s, OCH_3), 5.08 (1H, t, J = 5 Hz, H$-$C-14), 7.39 and 7.90 (10H, Ar$-$H).

The methylation of talatisidine (2) (0.2 g) was conducted by the procedure described in [8]. This gave 0.16 g of 14-O-methyltalatisidine (7).

14-O-Methyltalitisidine (7) mp 176-178°C (acetone), IR spectrum, ν_{max} (KBr, cm^{-1}): 3400, 2940, 2835, 1715, 1650, 1460, 1390, 1200, 1120, 975. Mass spectrum, *m/z* (%): M^+ 421 (65), 407 (27), 406 (100), 405 (19), 404 ($CDCl_3$): 0.95 (3H, t, J = 7 Hz, N$-C_2H_5$), 3.22, 3.24, 3.31 (each 3H, s, 3xOCH_3), 3.66 (1H, t, J = 5 Hz, H$-$C-14).

Benzoylation of 14-O-Methyltalitisidine (7). A mixture of 14-O-methyltalitisidine (0.14 g), 2 ml of pyridine, and 1.5 ml of benzoyl chloride was left at room temperature for 48 h. The excess of solvent was evaporated off, and the residue was dissolved in 2.5% sulfuric acid. The acid solution was washed with benzene and was then made alkaline with sodium carbonate and extracted with ether. The ethereal extract was dried over sodium sulfate and evaporated. The product was

purified on a column of silica gel. Elution with hexane–ether (1:1) gave 0.09 g of chromatographically pure 1-benzoyl-14-O-methyltalatisidine (8).

1-Benzoyl-14-O-methyltalatisidine (8). Mass spectrum, *m/z* (%); M^+ 525 (12), 510 (6), 421 (24), 420 (82), 405 (29.4), 404 (100), 388 (12), 370 (9). PMR spectrum ($CDCl_3$): 1.00 (3H, t, J = 7.5 Hz, $N-C_2H_5$), 3.20, 3.23 (3H and 6H, $3xOCH_3$), 3.54 (1H, t, J = 5 Hz, H–C-14), 5.35 (1H, br.s, H–C-1), 7.40 and 7.92 (5H, m, Ar–H).

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