SYNTHESIS OF THE METHIODIDE OF (±)-7-HYDROXY-1-(4'-HYDROXYPHENETHYL)-6-METHOXY-2-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE

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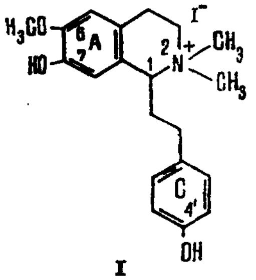
In order to identify one of the alkaloids isolated from Berberis oblonga, we have synthesized the methiodide of (±)-7-hydroxy-1-(4'-hydroxyphenethyl-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (I) from β-(4-hydroxy-3-methoxyphenyl)ethylamine (II) and β-(4-hydroxyphenyl)propionic acid (II) by the Bischler–Napieralski reaction. The corresponding tertiary base (IV) has been synthesized previously [1], but the authors did not give the method of obtaining the starting materials.

In contrast to the previous workers [1], we performed the condensation and cyclization by an improved method without the protection of the phenolic groups [2]. The amine (II) was synthesized by condensing vanillin with nitromethane [3] followed by the reduction of the nitrostyrene formed with hydrogen under a pressure of 40 atm in the presence of 10% Pd/C [2].

To obtain the acid (III) we alkylated phenol with acrylonitrile [4] and saponified the reaction product with ethanolic caustic soda [5]. The condensation of (II) and (III) under Teitel and Brossi's conditions [2] gave the corresponding amide (V) with a yield of 95% which, on cyclization under the action of phosphorus oxide-chloride, gave the dihydroisoquinoline (VI) (yield 85%). When (VI) was treated with methyl iodide followed by reduction with $NaBH_4$ of the quaternary base (VII) [6], we obtained 7-hydroxy-1-(4'-hydroxyphenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV). The intermediate products (V-VII) were not characterized; (IV) crystallizes from a mixture of petroleum ether and methanol with mp 96-97°C. Its mass spectrum lacked M^+ and contained ions with m/e 192, 177, and 107, which are characteristic for the fragmentation of phenethylisoquinoline bases [7].

The methiodide (I) was obtained by treating an ethanolic solution of (IV) with methyl iodide at room temperature; mp 217-218°C (chloroform–methanol).



I

The mass spectrum of (I) has peaks with m/e 327 (M – HI), 312, 206, 192 (100%), 177, 142, 127, 107, and 58. The NMR spectrum (deuteropyridine) shows three-proton singlets at 3.36 and 3.56 ppm [$= \overset{+}{N}(CH_3)_2$] and 3.69 ppm (OCH_3), a one-proton multiplet at 5.00 ppm (C_1–H), and multiplets of four methylene groups at 2.5-4.4 ppm. In the region of aromatic protons there is a four-proton doublet at 7.1 ppm from ring C, and a one-proton singlet at 6.72 is given by one of the hydrogens of ring A, the second signal being masked by the doublet.

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The results given confirm the structure of the base synthesized (I).

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ALKALOIDS OF THE SEEDS OF Lolium cuneatum

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Continuing the separation of the mixture of alkaloids of the seeds of L. cuneatum we have isolated two more new alkaloids. By chromatographing the water-soluble fraction of the total alkaloids on a column of alumina, we isolated a base with the composition $C_{10}H_{16}N_2O_3$ (I), oil, $[\alpha]_D^{20}$ +21.6° (c 0.9; methanol), R_f 0.14 [in a thin layer of silica gel in the chloroform–methanol (4:1) system]. The base (I) is readily soluble in ethanol and water and sparingly soluble in organic solvents. In the NMR spectrum of (I) (D_2O, δ scale, JNM 100/100 MHz) there are signals of protons from $=N-COCH_3$ at 2.45 ppm (3H, singlet) and from $=N-CH_3$ at 3.43 ppm (3H, singlet), and other signals characteristic for alkaloids of the loline group [1].

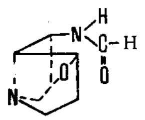
Its good solubility in water and the characteristics of its NMR spectrum show that (I) is probably lolinine N-oxide. The reduction of (I) with zinc in hydrochloric acid gave lolinine and a very small amount of loline. It is possible that in this reaction in addition to the reduction of the $N\rightarrow O$ bond, partial hydrolysis of the lolinine formed took place. The R_f value and the other properties of (I) coincide completely with those of the synthetic N-oxide obtained by oxidizing lolinine with hydrogen peroxide.

When the total alkaloids of the seeds of the introduced plant was separated, we isolated a base $C_8H_{12}N_2O_2$ (II) (M^+ 168), oil $[\alpha]_D^{20}$ +31.3° (c 0.96; acetone); hydrochloride with mp 181°C, R_f 0.44 [chloroform–methanol (4:1)].

The IR spectrum of (II) showed absorption bands at 1640 cm^{-1} (amide carbonyl) and a broad band at 3300-3360 cm^{-1} (NH).

The mass spectrum of (II) showed the peaks of ions with m/e 168 (M^+), 139 (M – CHO), 125, and others characteristic for the alkaloids of this group [2].

Hydrolysis with hydrochloric acid formed norloline, which was identified chromatographically. All these facts permitted the conclusion that our base had the structure of N-formylnorloline. We synthesized N-formylnorline by the reaction of norloline with ethyl formate. A mixture of the hydrochloride of N-formylnorloline with the hydrochloride of (II) gave no depression of the melting point.



II

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