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THE STRUCTURES OF TALATISAMINE AND CAMMACONINE BY CORRELATION WITH ISOTALATIZIDINE*

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Abstract—The structures of talatisamine (**1**) and cammaconine (**3**) were established by correlation with isotalatizidine (**2**)—a diterpenoid alkaloid with known structure and stereochemistry. It has been established that 1,8,14-tri-O-methylisotalatizidine is identical with di-O-methyltalatisamine as well as with tri-O-methylcammaconine, thus proving that **1** is 1-O-methyl ether of isotalatizidine. From the oxidation reactions and the above mentioned correlation the structure **3** is assigned to cammaconine. It is the first known member among the highly oxygenated diterpenoid alkaloids with a C-16 hydroxyl group.

THE alkaloid talatisamine (**1**), isolated from some Aconitum species[1,2] and from *Aconitum variegatum*,[3] is a highly oxygenated diterpenoid alkaloid with molecular formula $C_{24}H_{39}NO_5$ and one N-Et, two OH and three OMe groups. It can be oxidized with Sarett complex to a ketolactam—dehydrooxotalatisamine, which contains a 5-membered ring ketone and a 6-membered tertiary lactam. Hence, one of the OH groups is secondary and the second one is tertiary. Dehydrooxotalatisamine can not be oxidized with lead tetraacetate, thus proving that there are no vicinal OH groups in the original alkaloid. These facts go to show that talatisamine is an alkaloid with the aconitine-type skeleton. On the basis of the above data and some biogenetical considerations we suggested a partial structure of talatisamine[3] with two OH groups situated at C-8 and C-14, and one of the three OMe groups located at C-18. The position of the two remaining OMe groups was not established.

Recently Yunusov and Yunusov[4,5] gave evidence for the assignment of these two OMe groups at C-1 and C-16 on the skeleton as well as determining the α-configuration of the OH at C-14 and the β-configuration of the OMe at C-16.

Talatisamine was first isolated from *Aconitum talassicum*[1] together with isotalatizidine (**2**) and its C-1 epimer talatizidine, two alkaloids with known structure and stereochemistry.[6] Among the highly oxygenated diterpenoid alkaloids isotalatizidine and talatizidine as well as talatisamine contain only five oxygen functions. These facts suggest a probable structural relationship and a possibility that talatisamine is correlated either with isotalatizidine or with talatizidine. Now we report the results of this correlation.

Talatisamine on refluxing with methyl iodide and sodium hydride was smoothly converted into di-O-methyltalatisamine, a crystalline compound with m.p. 103·5–105°.

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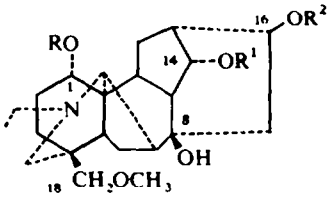
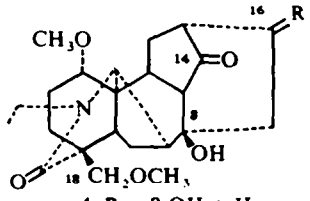
The IR spectrum shows no absorption in the OH region and the NMR spectrum contains signals for five OMe groups at δ 3·11 (3H), 3·26 (3H), 3·29 (3H) and 3·35 (6H) and a triplet at δ 1·03 (J = 7 cs) indicative of an N-Et group.

Under the same conditions, isotalatizidine gave rise to two products in approximately equal amounts. They were separated by column chromatography on alumina. The more polar one was 1,8,14-tri-O-methylisotalatizidine (m.p. 103–5°) which was found to be identical with di-O-methyltalatisamine by means of mixed m.p., TLC, IR and NMR spectra and Debye-Scherrer diagrams. The less polar product was an oil. Its IR spectrum shows no absorption in the OH region and its NMR spectrum contains signals for four OMe groups at δ 3·14 (3H), 3·31 (3H) and 3·34 (6H) and for N-Et group at δ 1·09 (J = 8 cs). At this stage the compound was not further investigated.

Talatisamine when heated under reflux in a solution of sodium hydride and then treated with methyl iodide yielded an oily mixture of two products. One, was identified by means of TLC as di-O-methyltalatisamine. The correlation of talatisamine with isotalatizidine proves that the former is 1-O-methylisotalatizidine and establishes also the same stereochemistry of both alkaloids. Hence, the structure of talatisamine is 1.



1: R = R² = CH₃, R¹ = H
2: R = R¹ = H, R² = CH₃
3: R = CH₃, R¹ = R² = H



4: R = β-OH + H
5: R = O

A second alkaloid isolated from *Aconitum variegatum* is cammaconine, a crystalline compound with m.p. 135–137° and molecular formula $C_{23}H_{37}NO_5$. It contains according to its NMR spectrum one N-Et, three OH and two OMe groups. The elemental and functional composition of cammaconine is the same as that of the epimers isotalatizidine and talatizidine and its m.p. is close to the former. However, a comparison by means of TLC and IR spectra shows that these two alkaloids are different.

Cammaconine on methylation under the above conditions was converted into tri-O-methylcammaconine, identical in all respects with 1,8,14-tri-O-methylisotalatizidine. Therefore, it was proved that cammaconine has the same skeleton, oxygen location and stereochemistry as isotalatizidine but a different pattern of O-methylation.

Oxidation of cammaconine with Sarett reagent gave rise to a mixture of products. The separation by column chromatography yielded a ketolactam with m.p. 228–230°. Its IR spectrum shows CO absorption for a cyclic 5-membered ketone (1735 cm^{-1}), for a cyclic 6-membered tertiary lactam (1620 cm^{-1}) and a broad OH absorption in the region of 3400 cm^{-1}. The NMR spectrum contains a singlet at δ 3·30 (6H) corresponding to two OMe groups and a triplet centered at δ 1·18 (J = 7 cs), indica-

tive of a N–Et group. All spectral data as well as the elemental analysis supported this compound as dehydrooxocammaconine (**4**).

A careful separation of the above mixture by preparative TLC on silica gel enabled the isolation of a second crystalline product of oxidation (m.p. 194–195°). The same product was obtained together with dehydrooxocammaconine when cammaconine was oxidized with potassium permanganate. The IR spectrum of this product shows absorption for a cyclic 6-membered tertiary lactam (1620 cm^{-1}), CO absorption for a 6-membered ring ketone or an aldehyde group (1725 cm^{-1}) and for a 5-membered ring ketone (1750 cm^{-1}) and a broad OH absorption in the region of 3400 cm^{-1}. The NMR spectrum of this compound contains signals for two OMe groups at δ 3·25 (3H) and 3·38 (3H) and for a N-Et group at δ 1·16 (J = 7 cs). There is no signal confirming the presence of an aldehyde group in the compound. The IR and NMR spectra as well as the molecular formula show that this compound is a diketo-lactam—didehydrooxocammaconine (**5**). Therefore, cammaconine contains two secondary and one tertiary OH group.

Since no aldehyde group is present in didehydrooxocammaconine, the oxygen function at C-18 in cammaconine must be a OMe. The tertiary OH group must be situated at C-8 and one of the secondary OH groups at C-14. The last OH group can be located either at C-1 or at C-16. The first position is ruled out because it leads to the structure of isotalatizidine. The only possible position is at C-16.

Hence, cammaconine is a highly oxygenated diterpenoid alkaloid containing an OH group at an unusual position, namely at C-16, and its structure is **3**. It is the first known member of lycoctonine-aconitine group of alkaloids to bear a β-C-16 OH instead of a β-C-16 OMe group.

EXPERIMENTAL

The m.ps unless specifically stated, were taken on a Koffler hot-stage and not corrected. IR spectra were measured on a UR-10 (Zeiss) spectrometer in $CHCl_3$. NMR spectra were recorded on a JEOL JNM-C-60-S spectrometer in $CDCl_3$. The chemical shifts are expressed as δ units and are referred to TMS as an internal standard. The column chromatography was carried out on alumina (of activity II) and the TLC on silica gel DG (Riedel de Haen) and alumina D (Chemiewerck Greiz-Dölau/DDR). Systems of solvents used were: ether–acetone–methanol–ethanol (10:10:1:1) (Syst A), light petroleum-ether–acetone–methanol (10:10:1:1) (syst B), benzene–acetone–methanol (100:100:3) (syst C) and benzene–acetone (1:1) (syst D).

O-*Methylation of talatisamine* (**1**)

8,14-*Di*-O-*methyltalatisamine*. A 50% suspension of NaH in paraffin (100 mg) was treated with dry light petroleum and the soln was decanted. Then dioxan (7 ml), 51 mg of **1** and MeI (0·35 ml) were added. The mixture was refluxed for 6 hr and evaporated *in vacuo* to dryness. The residue was left overnight and afterwards treated with water. A solid product (46 mg) was obtained, filtered off and washed with water. It was recrystallized from petzol as colourless crystals (28 mg)* with m.p. 103·5–105°, R_f 0·47 (on alumina, syst A). (Found: C, 69·72; H, 9·90. $C_{26}H_{43}NO_3$ requires: C, 69·45; H, 9·64%).

O-*Methylation of isotalatizidine*

1,8,14-*Tri*-O-*methylisotalatizidine*. The methylation of **2** (200 mg) was carried out in the manner described. In this case a semi-solid product was obtained and the mixture after adding water was extracted with benzene, the soln dried and the solvent evaporated. An oily residue in quantitative yield was obtained and passed through a basic Al_2O_3 (30 g) column. With ether-light petroleum (1:4) 40 mg of a product displaying by TLC a main spot with R_f 0·85 (alumina, syst A) was eluted. The ether-light petroleum (1:1) eluent gave 29 mg of a second product producing by TLC a main spot with R_f 0·47 (alumina, syst A). When the first

* Refluxing the reaction mixture for only 30 min afforded also 8,14-di-O-methyltalatisamine in good yield.

product (40 mg) was purified by preparative TLC on alumina, developed thrice with syst B, 28 mg of a colourless oil with R_f 0·85 was obtained. From the second product (29 mg) a substance (20 mg) with R_f 0·47 was isolated by preparative TLC (on alumina, syst A). Recrystallization from petzol gave 15 mg of 1,8,14-tri-O-methylisotalatizidine, m.p. 103·5–105°. This compound is identical by mixed m.p., TLC, IR and NMR spectra and Debye-Scherrer diagrams with 8,14-di-O-methyltalatisamine.

In some of the experiments carried out in the same manner but in batches of 50 mg of **2** the oily product (R_f 0·85) predominated and the crystalline one was present only in traces.

O-Methylation of cammaconine (**3**)

8,14,16-Tri-O-methylcammaconine. From 52 mg of **3** a crude product (38 mg) was obtained. Recrystallization gave 19 mg of a crystalline substance with m.p. 103·5–105°, R_f 0·47. A mixture with 1,8,14-tri-O-methylisotalatizidine produced a single spot in TLC and had an undepressed m.p. Their IR and NMR spectra and Debye-Scherrer diagrams were identical.

Oxidation of cammaconine with Sarett reagent

Dehydrooxocammaconine (**4**). A soln of 200 mg of **3** in 4·2 ml dry pyridine at 0° was added to Sarett reagent, prepared by stirring 180 mg CrO_3 in 1·8 ml dry pyridine at 0°. The mixture was stirred at 0° for 1 hr, then at room temp for 11 hr and left overnight. The solvent was removed *in vacuo*, dissolved in 10 ml 5% H_2SO_4 and saturated with SO_2 till the excess of CrO_3 was destroyed. The aqueous soln was extracted thoroughly with $CHCl_3$, the combined extracts were dried and the solvent removed under reduced pressure to give an oily residue. It was applied to an alumina (10 g, neutral) column. With ether 40 mg of a product (R_f 0·51, silica gel, syst C, twice developed) was obtained. Recrystallization from benzene gave 20 mg of **4**, m.p. 228–230° (Found: C, 65·99; H, 8·25. $C_{23}H_{33}NO_6$ requires: C, 65·85; H, 7·93%).

Oxidation of cammaconine with potassium permaganate

Dehydrooxocammaconine (**4**) *and didehydrooxocammaconine* (**5**). To 50 mg of **3** dissolved in 7 ml acetone and 0·3 ml glacial AcOH 50 mg $KMnO_4$ in 7 ml acetone was added. The mixture was stirred at room temp for 2 hr and then evaporated *in vacuo* to dryness. One more sample of 50 mg of **3** was oxidized in the same manner and the whole batch was extracted with acetone. The solvent was removed and the residue (48 mg) was separated by preparative TLC on silica gel, developed twice with syst D. From the most intensive strip a mixture (20 mg) of two substances was isolated. The rechromatography on silica gel (syst C, twice developed) afforded the separation of both substances yielding 10 mg of **4**, R_f 0·51, m.p. 228–230° (from benzene). This compound was identical with the above **4** by mixed m.p., TLC and IR spectra. The second product obtained was **5** (7 mg), R_f 0·62, m.p. 194–195° (from benzene). (Found: *m/e* 417. $C_{23}H_{31}NO_6$ requires mol. wt. 417·49).

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