STEREOCHEMICAL FEATURES OF DITERPENE ALKALOIDS IN ACYLATION AND ALKALINE HYDROLYSIS REACTIONS

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We have previously [1] shown the difficulty of saponifying an acetoxy group at C_1 in alkaloids with the lycoctonine skeleton. We have now obtained additional information on the hydrolysis of a C_1-acetoxy group (Table 1). In addition, using the alkaloids karakoline (I, $R_1=R_2=R_3=R_4=H$) and karakolidine (I, $R_1=R_2=R_3=H$, $R_4=OH$) as examples, we have shown the relative ease of esterification of the hydroxy group in this position in comparison with a hydroxy group at C_{10}. The presence in the hydrolysis or esterification products of an acyloxy group at C_1 was shown by the appearance in their NMR spectra of the signal of the geminal proton in the form of a one-proton quartet at ~5 ppm [1] and in the mass spectra of a maximum peak due to the ejection of the acyloxy residue from the molecular ion [2]. By selective acylation, monoacetyl karakoline (I), monobenzoylkarakoline (II), and monoacetylkarakolidine (III) have been obtained.

The relative ease of occurrence of the acylation reaction observed for the C_1-hydroxy group and the difficulty of the saponification of the acetoxy group in this position apparently follow from the mechanisms of these reactions. A consideration of models shows that in the acylation reaction, where the attack of the reagent takes place at an electron pair of the oxygen atom of the hydroxy group, access to this group at C_1 is hindered to a considerably smaller extent than to the C_{10}-hydroxy group where steric screening by the cis-alkyl substituents at C_8 and C_{15} is exhibited. On alkaline hydrolysis, attack by the nucleophilic agent takes place at the carbonyl carbon which, in the C_{10}-acetoxy group, is fairly remote from the plane of the ring and steric screening by the substituents mentioned is small. Conversely, access to the electrophilic center of the C_1-acetoxy group is, as shown by a study of models, hindered by the protons at C_{12}, C_{17}, and C_{13}, which causes its saponification to be difficult.

Table 1 shows that the saponification of the acetates of karakolidine takes place with anomalous ease as compared with other C_1-acetoxy derivatives. In view of the similar times of hydrolysis of the tetra- and diacetates of karakolidine, the ease of hydrolysis of the sterically hindered acetoxy group at C_1 can be explained by the influence of the neighboring C_{13}-hydroxy group [3, 4].

TABLE 1

Compound	Positions of the acetoxy groups	Time of complete hydrolysis, min
Karakoline diacetate (I, $R_1=R_3=COCH_3$; $R_2=R_4=H$)	C_1 (α); C_{10}	150
Talatisidine diacetate (IV)	C_1 (β); C_{10}	130
Lappaconidine tetraacetate (V)	C_1 (α); C_4, C_8, C_9	165
Lappaconine triacetate (V, $R_1=CH_3$)	C_4, C_8, C_9	45
Talatisamine diacetate (IV)	C_8, C_{10},	45
Karakolidine tetraacetate (I, $R_1=R_2=R_3=COCH_3$, $R_4=OCOCH_3$)	C_1 (α); C_8, C_{10} C_{13}	20
Karakoline tetraacetate (I, $R_1=R_3=COCH_3$, $R_2=R_4=H$)	C_1 (α); C_{10}	20

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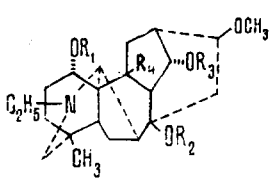

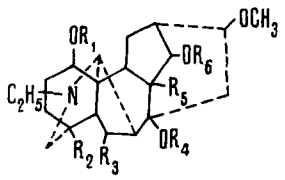

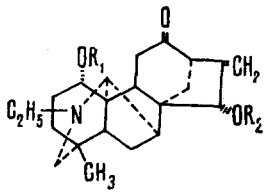

I R_1 = COCH$_3$; R_2 = R_3 = R_4 = H.
II R_1 = COC$_6$H$_5$; R_2 = R_3 = R_4 = H.
III R_1 = COCH$_3$; R_2 = R_3 = H; R_4 = OH.
IV R_1 = R_6 = COCH$_3$; R_2 = CH$_2$OCH$_3$.
V R_1 = R_4 = COCH$_3$; R_2 = R_5 = OCOCH$_3$; R_3 = OCH$_3$.
VI R_4 = R_6 = COCH$_3$; R_1 = CH$_3$; R_2 = CH$_2$OCH$_3$.
Not specified R=H.
VII R_1 = R_2 = COCH$_3$.
VIII R_1 = COCH$_3$; R_2 = H.

It can be seen from a consideration of the structure of songorine (VII, R_1 = R_2 = H) that the spatial environment of the substituent at C_1 in it is practically the same as in alkaloids with a lycoctonine skeleton. It was interesting to check whether the saponification of the C_1-acetoxy group would be difficult in the hydrolysis of its diacetate (VII). On hydrolyzing (VII) for 45 min, we isolated monoacetylsongorine (VIII) containing, according to NMR and mass spectra, an acetoxy group at C_1 [2].

EXPERIMENTAL METHOD

The melting points are not corrected. The mass spectra were taken on an MKh-1303 instrument fitted with a system for direct introduction of the sample into the ion source, and the NMR spectra were taken on a JNM-4H-100/100 MHz instrument in deuterochloroform with HMDS as internal standard (the values are given in the δ scale). The homogeneity of the products was checked in a thin layer of type KSK silica gel in the benzene–methanol (4 : 1) system.

Saponification of Karakolidine Tetraacetate. A mixture of 45 mg of karakolidine tetraacetate and 2 ml of a 5% solution of KOH in methanol was boiled under reflux for 20 min. The solvent was evaporated off and after the usual treatment with acetone, 17 mg of karakolidine was isolated. The mother liquor showed one spot with a R_f value identical with that of karakolidine.

Karakolidine Diacetate. A mixture of 85 g of karakolidine, 2 ml of acetic anhydride, and 0.2 ml of pyridine was kept at room temperature for 6 days. The acetic anhydride was evaporated off, the residue was dissolved in water, and the solution was made alkaline with sodium carbonate with cooling and was extracted with ether. A product was obtained which, after recrystallization from a mixture of ether and acetone (4 : 1), had mp 226-229° C. Yield 65 mg. NMR spectrum: 2.01 ppm (3H, CH_3COO), 2.03 ppm (3H, CH_3COO), M^+ 477.

Saponification of Karakolidine Diacetate. A mixture of 25 mg of karakolidine diacetate and 1 ml of a 5% solution of KOH in methanol was boiled under reflux for 20 min. After the usual working up, the only reaction product obtained was karakolidine (TLC).

Monoacetylkarakoline (I). A mixture of 0.15 g of karakoline, 3 ml of acetic anhydride, and 0.3 ml of pyridine was kept at room temperature for 15 min. Then the acetic anhydride was evaporated off, the residue was dissolved in water, the solution was made alkaline by the addition of sodium carbonate with cooling, and the reaction product was extracted with ether. The solvent was distilled off, and by means of hexane 0.13 g of a product was isolated which, from a mixed melting point and TLC, was identified as the monoacetylkarakoline isolated by the partial hydrolysis of karakoline diacetate [1].

Monobenzoylkarakoline (II). To 0.15 g of karakokine in 2 ml of pyridine was added five drops of benzoyl chloride, and the mixture was left at room temperature for 40 h. The pyridine was distilled off under vacuum and after the usual working up a product was obtained which, after recrystallization from ether, had mp 164-166° C. Yield 95 mg. NMR spectrum: 7.48 and 7.93 ppm (5H, multiplet), 5.13 ppm (1H, quartet, J_1 = 10 Hz, J_2 = 7 Hz). IR spectrum: 1725 cm^{-1}. M^+ 481.

Monoacetylkarakolidine (III). Karakolidine (65 mg) was acetylated under the conditions described above for the preparation of monoacetylkarakoline. After the usual working up, ether isolated 45 mg of a product with mp 193-195° C. NMR spectrum: 1.98 ppm (3H, CH_3COO), 5.44 ppm (1H, quartet, J_1 = 10 Hz, J_2 = 7 Hz). M^+ 419.

Saponification of Songorine Diacetate. A mixture of 0.14 g of songorine diacetate and 7 ml of 5% methanolic solution of KOH was boiled for 45 min. The product obtained after the usual working up was separated preparatively in a layer of silica gel in the benzene–methanol (4 : 1) system. This gave mono-

acetylsongorine (VIII) in the form of a powder. NMR spectrum: 205 ppm (3H, CH_3COO); 5.01 ppm (1H, quartet); M^+ 399.

SUMMARY

Relative difficulty of saponifying an acetoxy group at C_1 and ease of acylation of a hydroxy group in this position as compared with a hydroxy group C_{10} has been shown for alkaloids with a lycoctonine skeleton.

The anomalously easy saponification of a C_1-acetoxy group in karakolidine acetates is due to the influence of the neighboring C_{13}-hydroxy group.

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