THE SIDE REACTIONS TAKING PLACE IN THE SAPONIFICATION OF ACYLCARDENOLIDES WITH AMMONIA

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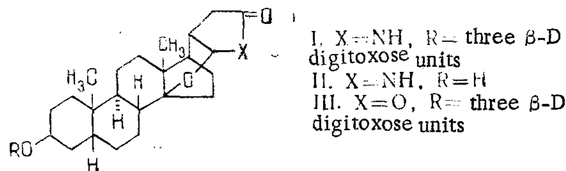
The hydrolysis of acyl groups in cardenolides with the aid of ammonia solutions is used fairly frequently. At the same time, it is impossible to achieve a yield of the desired product approximating to quantitative by this method of deacetylation because of side reactions.

In the process of obtaining digitoxin from lanatoside A, we attempted to use the method of saponifying the acetyl group in the latter with a methanolic-aqueous solution of ammonia followed by the enzymatic hydrolysis of the D-glucose unit. It was found that a digitoxin obtained in this way contained not more than 80% of the glycoside in spite of the absence of other cardenolides from it. Analysis of the product with the aid of thin-layer chromatography in the methylene chloride—ethanol—water (85:15:0.7) system with three runs of the solvent on a Silufol plate and the staining of the chromatograms with trichloroacetic acid showed that the digitoxin was accompanied by three other steroid compounds with extremely similar polarities. We have isolated two of them in the pure state by adsorption chromatography.

Compound (I) mp 236-238/248-252°C, $[\alpha]_D^{20}$ −3.6 ± 2° (c 1.0; chloroform—methanol). Acid hydrolysis of glycoside (I) was performed in 0.05 N H_2SO_4. The usual working up of the hydrolysate gave D-digitoxose and an aglycone (II).

The aglycone (II) had mp 230-234/245-246°C, $[\alpha]_D^{20}$ −39.0 ± 2° (c 0.84; chloroform). The elementary analyses of the glycoside (I) and its aglycone (II) corresponded to the calculated figures for the compositions $C_{41}H_{65}O_{12}N$ and $C_{23}H_{35}O_3N$, respectively. The presence of nitrogen in (I) and (II) and the absence of reactions for cardenolides (Raymond and Kedde) permitted the assumption that these products were products of ammonolysis at the lactone ring. Of the possible products of ammonolysis — amide and lactam — the choice was made unambiguously in favor of the lactam on the basis of the results of spectral studies.



The mass spectrum of the aglycone (II) had the peak of the molecular ion with m/z 373 and was also characterized by the following fragments, m/z: 358 (M − CH_3), 355 (M − H_2O), 345 (M − CO), 340 (M − CH_3 − H_2O), 327 (M − H_2O − CO), 289, 271, 249, 203, 193, 178. In the PMR spectrum of (II), recorded for a solution in deuteropyridine, there was a signal in the 9.1 ppm region consisting of a one-proton singlet corresponding to the NH group of a lactam ring. The IR spectra of (I) and (II) (tableted in KBr) lacked the band in the 1620-1630 cm^{-1} that is characteristic for the C=C bond of the butenolide ring of a natural carbenolide. The C=O groups of the lactams (I) and (II) absorbed in the 1708 and 1690 cm^{-1} regions, respectively, and the lactam NH group in the 3260 cm^{-1} region.

The absence of double C=C bonds in (I) and (II) shows that the ammonolysis of the lactone ring in digitoxin was accompanied by isomerization with the formation of a 14β,21-epoxylactam derivative.

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Compound (III), mp 247-253°C, $[\alpha]_D^{20}$ −5.9 ± 2° (c 1.0; chloroform—methanol). The elementary analysis corresponded to the figures calculated for the composition $C_{41}H_{64}O_{13}$. Since the initial digitoxin had the same composition, we assume that (III) was isodigitoxin, i.e., 14β,21-epoxycardenolide. An independent isomerization of digitoxin with the aid of KOH led to an identical compound.

Thus, the saponification of acylcardenolides by ammonia is accompanied by the formation of by-products — 14β,21-epoxycardenolides and their lactam analogues. Both these types of cardiotonic derivatives have low activities [1, 2]. We consider that the method of deacetylating cardiac glycosides with ammonia is unsuitable in industrial practice since it greatly complicated the purification of the desired substances and lowers the yield.

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ALKALOIDS OF *Veratrum lobelianum*.

X. STRUCTURE OF VERDINE

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Continuing the separation of the total alkaloids of the epigeal part of *Veratrum lobelianum* Bernh., collected in the Caucasus, Alma-Ata province, according to their basicities and also by column chromatography, we have isolated veralodine, germinaline, jervine, veratroylzygadenine, germbudine, veralosine, veralomine, [1-3], and the new alkaloid verdine with mp 218-220°C, $C_{27}H_{41}NO_5$ (I) [4].

The IR spectrum of (I) contained absorption bands at (cm^{-1}) 3400 (OH), 1710, and 1630 (CO—C=C—).

The UV spectrum [λ_{max} 252 nm (log ε 4.07)] was characteristic for an α,β-unsaturated ketone [5]. The mass-spectrometric fragmentation of verdine (I) took place in a similar manner to that of the alkaloids of the jervine group [6] (m/z: 97, 110 (100%), 112, 113, 124, 125, 328, 346, 426, 430, 441, 444, 459, M^+).

The PMR spectrum contained signals of the 19-CH_3, 18-CH_3, 21-CH_3, and 27-CH_3 methyl groups (Table 1).

The acetylation of (I) formed O,O',O",N-tetraacetylverdine (II) [M^+ 627, ν_{max}, cm^{-1}, 1710, 1635 (CO—C=C—), 1635 (N—Ac), 1740, 1245 (O—Ac)]. The saponification of (II) led to O,N-diacetylverdine (III) [M^+ 543; ν_{max}, cm^{-1}: 3450 (OH), 1710, 1635 (CO—C=C—), 1740, 1250 (O—Ac), 1635 (N—Ac)] and N-acetylverdine (IV) [M^+ 501; ν_{max}, cm^{-1}: 3420 (OH), 1710, 1630 (CO—C=C—), 1630 (N—Ac)].

The reduction of (I) by Adams' method and with palladium on carbon gave isomeric dihydroverdines with M^+ 461 the IR spectra of which lacked the absorption band of a —C=C— bond but contained the absorption band of a carbonyl group in a five-membered ring (1730 cm^{-1}). The Huang-Minlon reduction of (I) gave deoxodihydroverdine with M^+ 445, the IR spectrum of which lacked the absorption band of a carbonyl group. Details of the PMR spectra of compounds (I-III) are given in Table 1.

In the PMR spectra of compounds (I-III), the signals from the protons of the 18-CH_3 groups are observed in the weak field at 2.17-2.27 ppm. Consequently, the double bond in (I) is located at C_{12}-C_{13}, as in jervine [7].

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