CLEAVAGE OF SOLASODINE TO DEHYDROPREGNENOLONE

IODINATION OF PSEUDOSOLASODINE DIACETATE

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Pseudosolasodine diacetate (I) is an intermediate in the industrial method for cleaving solasodine [1]. We reported earlier [2] a method for the quantitative determination of I by iodometric titration. The method is based on the tendency of I to add one molecule of iodine to the C_{20}-C_{22} double bond. We made an attempt to isolate the iodination product (II). However after titration [2] the aqueous layer gave a strongly acid reaction (pH 2.0). We isolated two compounds of similar chromatographic mobility, m.p. 192-194°C (IIIa) and 164-167°C (IIIb), from the organic layer by chromatography on silica gel; neither contained iodine. Since the titration was carried out in a neutral solvent system, the strongly acidic nature of the aqueous layer is due to the presence of hydriodic acid formed in the titration process. On the basis of analysis, mass, IR, and PMR spectra, and some chemical transformations of compounds IIIa and IIIb we assign them as the isomeric 23,27-cyclo-27-N-acetylamino-5,20(22)-furostadien-3β-ol acetates. Refluxing each of these compounds in glacial acetic acid forms an equal mixture of both isomers. The mass spectra of III show a general type of fragmentation: The molecular ions of IIIa and IIIb are identical at m/e 495, differing from the molecular ion of I by two. A reduction in the molecular weight of III by two in comparison with I and the acidic nature of the aqueous layer after titration imply the loss of two molecules of hydrogen iodide from I. The absence of absorption bands in the IR spectra of IIIa and IIIb in the 3000-3600 cm^{-1} region and the presence of amide group absorption bands point to the formation of a nitrogen ring from the open side chain. The mass spectrum indicates that this ring is five-membered: It has intense peaks at m/e 126 and 84, which can be attributed to fragments of structures A and B, respectively. The PMR spectra of IIIa and IIIb at 25°C show two sets of signals, which are unusually clear for methyl singlets near amide carbonyl, on C_{13} and C_{20}. This doubling of signals apparently arises because each of the compounds III exists as two conformers about the C−N bond, which tends to double-bond character. In the spectra of these compounds at high temperature (120°C in bromobenzene), coalescence of the signals of the majority of the groups occurs because of the rapid interconversion of conformers. However even at this temperature the signals of protons adjacent to the nitrogen atom remain broadened. Because of the doubling of

TABLE 1. Proton Chemical Shifts in Compounds IIIa, IIIb and VI (δ, ppm)

Compound	Angular CH_3	CH_3		OAc	NAc	H				2H on C_{26}
		on C_{20}	on C_{25}			on C_3	on C_6	on C_{16}	on C_{23}	
IIIa	0,65 0,96	1,64	0,95d	1,87	1,87	~4,5 m	5,21d	4,6m	4,4q	~3,9 t ~2,85t
IIIb	0,67 0,94	1,63	0,90d	1,87	1,90	~4,6 m	5,22d	4,6 m	4,5d	~3,5 d ~3,0t
VI	1,01 1,06	2,03	1,06 d	1,98	1,98	~4,40 m	5,25d	5,4 lm	4,39q	3,64q 2,98t

Notes. Abbreviations used: d) doublet; t) triplet; q) quartet; m) multiplet. The spectra of IIIa and IIIb were obtained in bromobenzene and that of VI in deuterochloroform at 25°C.

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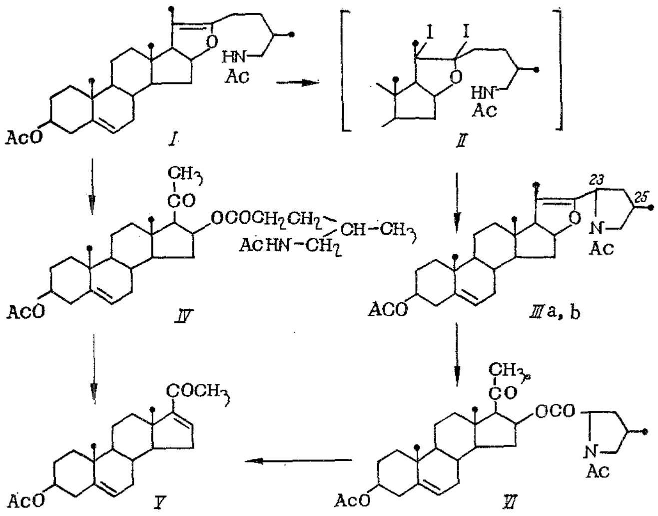

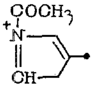

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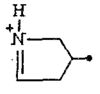

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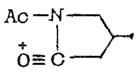

B

the signals at low temperature and the broadening of them at high temperature some parameters of the PMR spectra of IIIa and IIIb are only approximate (see Table 1). The assignment of the signals of the C_{23} and C_{26} protons is confirmed (apart from the multiplicity) by the large difference in chemical shift of identical protons in the two amide conformers.

The vicinal coupling constants for the C_{25} proton to the C_{26} protons (9 and 7 Hz) are not characteristic of six-membered rings, but are common enough for five-membered rings [3-5], which points to the structures assumed for compounds IIIa and IIIb.

We should particularly mention the considerable reduction of one of the vicinal coupling constants for the C_{23} proton in IIIb in comparison with IIIa, which results in a different multiplicity of the signal of this proton in these compounds (Table 1). This can be interpreted as due to the different orientation of the C_{23} proton in IIIa and IIIb and enables us to assume that these compounds are diastereoisometric at C_{23}. As the table shows, the signals in the region of 1.6 ppm in the PMR spectra of IIIa and IIIb were assigned to the methyl group on the C_{20}-C_{22} double bond. This position of the double bond was confirmed by oxidation of IIIa and IIIb by sodium dichromate in acetic acid.

We know from [1] that I, which has a C_{20}-C_{22} double bond, is oxidized by sodium dichromate in acetic acid with scission of this bond, forming the oxidation product (IV). This loses an ester group from position 16 when refluxed in acetic acid or when treated with alcoholic alkali, forming dehydropregnenolone acetate V.

We oxidized IIIb under the same conditions and isolated the hitherto unknown 16β-(N-acetyl-3'-methyl-5'-pyrrolidinylcarboxy)-3β-acetoxypregn-5-en-20-one (VI) and V. When VI was refluxed in glacial acetic acid, and also when it was treated with a solution of sodium hydroxide in tert-butanol at room temperature, we obtained V in good yield; we also got V by oxidation of IIIa with sodium dichromate in acetic acid followed by refluxing. The mass spectrum of VI shows the molecular ion at m/e 527 and intense peaks of fragments at m/e 154, 126, and 84. Peaks with m/e 126 and 84 are also observed in the mass spectra of IIIa and IIIb and are assigned to fragments A and B, respectively. The peak at m/e 154 can be assigned to the ion with structure B. The IR spectrum of VI contains ester and carbonyl absorption bands. The PMR spectrum of VI (see Table 1) shows signals characteristic of a five-membered nitrogen ring, like compounds IIIa and IIIb, together with a signal of the methyl group attached to carbonyl (C_{20}). It is interesting that the PMR spectrum of VI at 25°C, unlike the spectra of IIIa and IIIb, contains only one set of signals. Apparently in compounds IIIa and IIIb, where amide isomerism is observed, the barrier to rotation about the $C-N$ bond increases because of the steric hindrances associated with ring E, while in VI the lengthening of the chain linking the five-membered ring with the steroid residue leads to a reduction in the steric hindrances and hence in the barrier height.

The iodination of I, as studied by us, is an interesting case of spontaneous loss of a haloid acid from a molecule, due to the increased lability of the C_{23} proton located in the system of $O-CI-CH$ bonds. Loss of the proton is accompanied by cyclization of the amide chain into the N-acetylpyrrolidine ring and creation of a new asymmetric center at C_{23}, forming two stereoisomeric compounds IIIa and IIIb. These compounds cannot be titrated iodometrically.

EXPERIMENTAL

IR spectra were measured with a UR-10 instrument; PMR spectra were obtained with a JNM-4H-100 spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained with LKB-9000 and MX-1303 mass spectrometers by direct introduction of the sample into the source [at 50 eV (MX-1303) and 70 eV (LKB-9000)]. Chromatography was carried out on a thin layer of Silufol UV-254 with the system acetone–cyclohexane (1 : 1) with development by phosphomolybdic acid at 100°C. Preparative chromatography was carried out on L40/100 silica gel (Khemapol). The identity of the samples was established by the absence of freezing-point depression and comparison of IR spectra and chromatographic mobility (R_f values) with those of authentic samples.

Iodination of Pseudosolasodine Diacetate I. Preparative iodination was carried out under the conditions of the iodometric titration of I [2]. A solution of 15.4 g of iodine in 600 ml of technical isopropyl alcohol was poured into a solution of 10 g of I in 200 ml of technical isopropyl alcohol at room temperature. The reaction mixture was left in the dark for 30 min, and then 600 ml of chloroform and a freshly prepared solution of 5% sodium thiosulfate were added to the reaction mixture to decoloration. The chloroform layer was separated from the acidic aqueous layer (pH 2.0), washed with water to neutral reaction, dried, and evaporated to dryness in a vacuum. The oily residue was triturated with acetone. The crystalline precipitate was filtered, yield 3.84 g of IIIa, m.p. 192-194°C (from acetone). R_f 0.67. Found, %: C 75.30; H 9.10. $C_{31}H_{45}NO_4$. Calculated, %: C 75.11; H 9.15. IR, cm^{-1}: 1725 (ester CO), 1640, 1620 (amide CO). The mother liquor was evaporated; the residue was triturated with methanol and filtered to give 1.51 g of IIIb. R_f 0.74., m.p. 164-167°C (from methanol). Found, %: C 74.92; H 9.16. $C_{31}H_{45}NO_4$. Calculated %: C 75.11; H 9.18. IR, cm^{-1}: 1735 (ester CO), 1630 (amide CO). After iodometric titration of an aliquot of I [2] the aqueous layer was separated from the chloroform layer and titrated with 0.1 N sodium hydroxide. Calculation demonstrated that the aqueous layer contained 1.85 mole/liter HI.

Refluxing 23,27-Cyclo-N-acetylamino-5,20(22)-furostadien-3β-ol (IIIa, IIIb) in Acetic Acid. A solution of 0.3 g of IIIa in 10 ml of glacial acetic acid was refluxed for 3.5 h and then boiled to dryness; the residue was chromatographed on silica gel. Extraction with a 1 : 1 benzene–chloroform mixture gave 0.12 g of IIIb, while extraction with a chloroform–ethyl acetate mixture gave 0.13 g of IIIa; both were identical with authentic samples.

A solution of 0.3 g of IIIb in 10 ml of glacial acetic acid was refluxed for 4 h, and then boiled to dryness. The residue was triturated with methanol, and the crystalline precipitate was filtered, yield 0.15 g of IIIb. The mother liquor yielded 0.11 g of IIIa.

16β-(N-Acetyl-3'-methyl-5'-pyrrolidinylcarboxy)-3β-acetoxypregn-5-en-20-one (VI). To a solution of 2 g of IIIb in 15 ml of glacial acetic acid was added 2 g of a solution of sodium dichromate in 15 ml of acetic acid. The temperature was raised from 23 to 45°C. The solution was stirred for 1 h at room temperature, and then poured into a solution of 1 g of sodium sulfite. The solution was heated until the excess sodium dichromate had been removed. The reaction mixture was poured into water and extracted with chloroform. The extract was washed with water to neutral reaction and evaporated to dryness. The residue was triturated with ethyl acetate and the precipitate was filtered, yield 0.8 g of VI, m.p. 187-190°C (from ethyl acetate). R_f 0.7. Found, %: C 70.39; H 9.67; N 2.58. $C_{31}H_{45}NO_6$. Calculated, %: C 70.55; H 8.59; N 2.65. IR, cm^{-1}: 1730 (ester CO), 1710 (CO), 1640 (amide CO). The mother liquor was evaporated and the residue was chromatographed on silica gel. A 5 : 3 benzene–chloroform mixture extracted 0.12 g of V, which was identical to an authentic sample. A 3 : 4 benzene–chloroform mixture extracted 0.61 g of VI.

Cleavage of 16β-(N-Acetyl-3'-methyl-5'-pyrrolidinylcarboxy)-3β-acetoxypregn-5-en-20-one (VI). 1. In acidic solvent system. After 0.17 g of VI had been refluxed in 3 ml of acetic acid, the solution was boiled to dryness. The residue was triturated with methanol and the crystalline precipitate was filtered, yield 0.1 g of V, which was identical to an authentic sample. 2. In alkaline solvent system. A solution of 0.2 g of VI in 15 ml of tert-butanol and 12 ml of water was prepared, and 0.2 g of potassium hydroxide was added. The solution was allowed to stand at room temperature for 3 h. Then it was poured into 100 ml of water and neutralized with acetic acid. The precipitate was filtered, yield 0.1 g of V.

Dehydropregnenolone Acetate (V) from 23,27-Cyclo-27-N-acetylamino-5,20(22)-furostadien-3β-ol (IIIa, IIIb). To a solution of 4.8 g of IIIa in 50 ml of acetic acid was added a solution of 4.8 g of sodium dichromate in 30 ml of acetic acid. The temperature was increased from 20 to 48°C. The solution was stirred at room temperature for 2 h; 3 g of sodium sulfite was added and the reaction mixture was refluxed for 2.5 h. The cooled solution was diluted with 80 ml of water. The resulting precipitate was filtered, washed with 50% aqueous acetic acid and then water to neutral reaction, and dried. Yield 1.4 g of V. Similarly 1 g of IIIb yielded 0.41 g of V.

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METAL CANS IN AEROSOL PACKINGS

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In foreign pharmaceutical practice wide use is made of metal cans for aerosol preparations as well as glass cans. As examples we cite such preparations as the antiasthmatic alypent (Yugoslavia), novodrin spray (East Germany), the film-forming plastubol (Hungary), the inhalation nasivin (West Germany), ventolin (Britain), decatricina (Italy), and the dermatological sofradex and acidocort (France).

Metal cans are manufactured from steel and aluminum. The most efficient are considered to be monoblock aluminum cans, which are manufactured by successive drawing from slugs. These cans have a number of advantages over tin plate or composite aluminum cans: They are hermetic, display high resistance to impact and pressure, are light, and have a good external appearance.

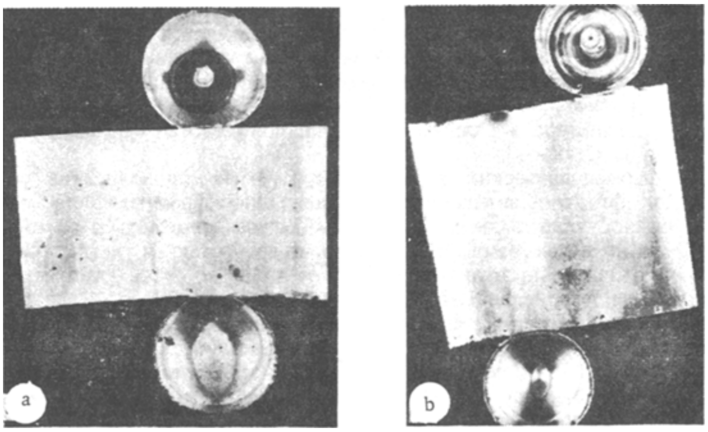

Fig. 1. Internal surfaces of aluminum cans after contact with a Freon-12/ethyl alcohol/water system; a) with tin valve; b) with aluminum valve.

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