STEROIDS

XLVIII. THE CLEAVAGE OF SOLASODINE TO PREGNA-5,16-DIEN-3β-OL-20-ONE. STUDY OF THE OXIDATION OF PSEUDOSOLASODINE DIACETATE BY SODIUM BICHROMATE IN ACETIC ACID

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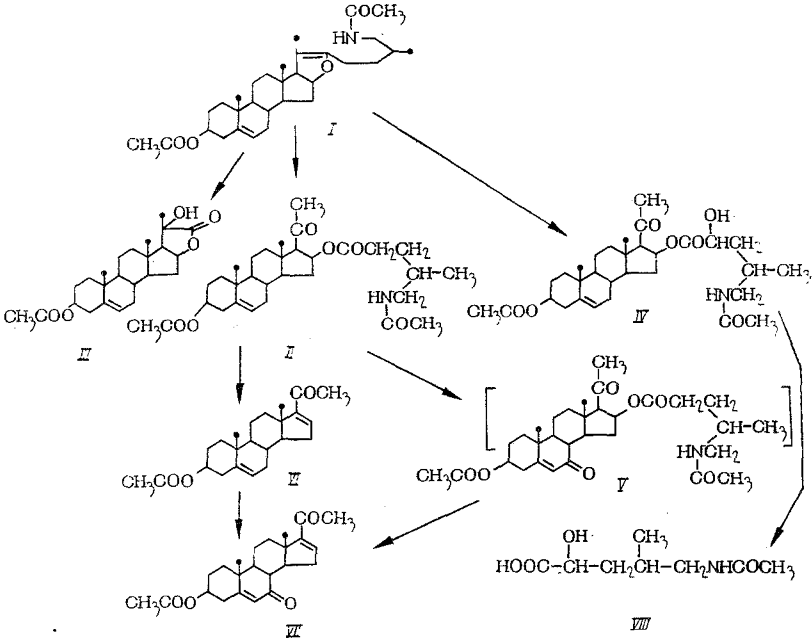
UDC 615.31.547.944.3

As we reported earlier [1, 2], in the four-step synthesis of dehydropregnenolone acetate from solasodine, the oxidation of pseudosolasodine diacetate (I) is the step with the lowest yield of all. To optimize the process we investigated the side reactions that occur in the oxidation of I by sodium bichromate in glacial acetic acid.



The end product of the oxidation of I, 16β-(δ-acetylamino-γ-methylvaleroyloxyl)-pregn-5-en-3β-ol-20-one acetate (II) was isolated earlier in crystalline form [3]. Its isolation from the reaction mass after oxidation involves great difficulties since it is extremely labile with respect to acid and alkaline agents, and also with respect to thermal influence. Under the indicated influences, it splits out an ester group in the 16-position, giving VI (see Scheme). Such lability of the basic reaction product, which is also manifested in chromatography of any significant amounts of the substance on various sorbents (aluminum oxide, silica gel), hinders the isolation of side products. It has been established that the use of permutit as a sorbent permits the avoidance of any appreciable decomposition of II. The separation was conducted on polyethylene columns, filled with permutit, and monitored by thin-layer chromatography. After the isolation of

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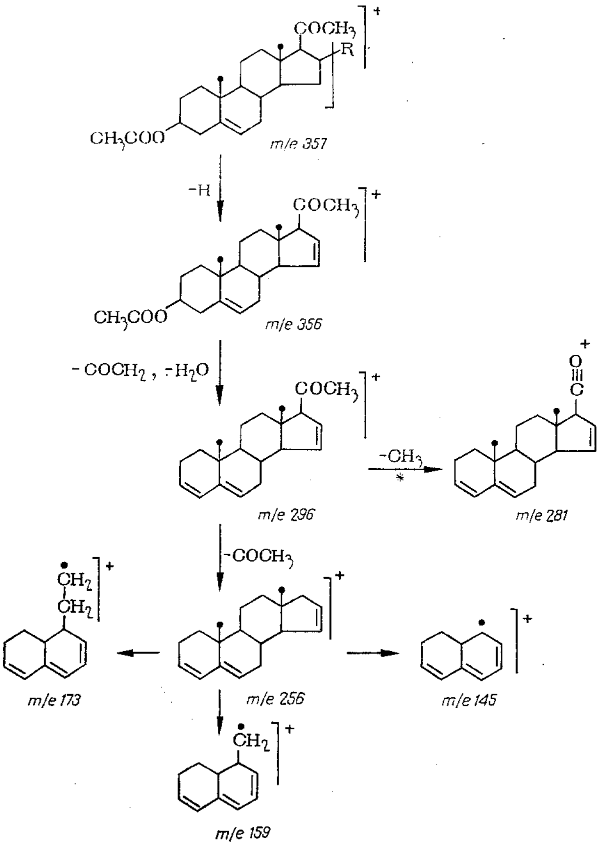
S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 8, No. 5, pp. 18-22, May, 1974. Original article submitted February 7, 1973.

II from the remaining fractions by repeated separations on permutit, two side products were isolated. One of them proved to be identical with the (22 →16)-lactone of 3β-acetoxy-16,20-dihydroxy-Δ^5-bis-norcholenoic acid (III), which we isolated earlier [1] from the mother liquors after the crystallization of technical (VI), produced according to an industrial method. Another compound was ascribed the structure IV – the acetate of 16β-(δ-acetylamino-γ-methyl-α-hydroxyvaleroyloxy)-pregn-5-en-3β-ol-20-one – on the basis of the data of analysis and the mass, PMR, and IR spectra. According to the data of the mass spectrum, IV has a molecular weight of 545, which is 16 greater than the molecular weight of II. It can be assumed that IV contains a free hydroxyl group. In the region of mass numbers below m/e 360, the mass spectrum of IV almost entirely coincides with the spectrum of II. This gives a basis for believing that in this region of the spectrum the ions II and IV have the same structure. A consideration of the values of the mass numbers of fragment ions and metastable ions, observed in the spectra of II and IV, permits us to compile a decay scheme which agrees with the concept that during the formation of an ion with mass number 356, the side chain in the 16-position is stripped off in the form of a neutral fragment:

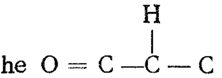


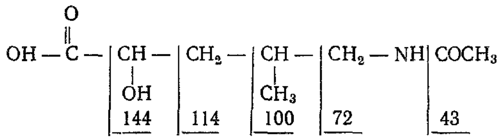
Consequently, the fragment in the molecules of II and IV differing in structure is precisely the side chain. The presence in the spectrum of IV of an intense peak with m/e 72, characteristic of the spectrum of II and possessing the structure $CH_2=\overset{+}{N}HCOCH_3$, shows that this group is preserved in the side chain of IV. To establish the structure of IV, we split out the ester group from the 16-position in IV and isolated 2-hydroxy-4-methyl-5-acetylaminovaleric acid (VIII) from the reaction mixture.

The acid VIII was isolated as follows. One of the fractions containing a mixture of the substances IV and VIII was subjected to boiling with glacial acetic acid. After evaporation of the acid to dryness and grinding of the oily residue with alcohol, VI was removed, the mother liquor was evaporated to dryness, and the acid VIII was isolated in crystalline form by grinding the residue with benzene. After chromatography of the benzene mother liquor on silica gel, the diketone VII was isolated. The structures of VII and VIII were established on the basis of the data of analysis, UV, IR, PMR, and mass spectra.

In the mass spectrum of VIII, a peak of a molecular ion with m/e 189 is observed. In the IR spectrum of VIII, there is a distinct absorption band at 3300 cm^{-1} (OH group) and two blurred absorption bands in the region of 2500 and 1950 cm^{-1} characteristic of acylamino acids [4]. In the PMR spectrum of VIII, signals of the protons of the amide group are observed at δ 1.94 ppm and the protons of the methylene group (δ =

3.32 ppm), bonded to the amide group. The signal of a proton geminally bonded to an OH group is also distinguished in the spectrum at $\delta = 4.63$ ppm. The distinct nature of the splitting of the signal – a quartet, $J_1 = 10$ Hz, $J_2 = 4$ Hz – is an indication of interaction with only two protons. Evidently, such a possibility is realized only in the case of the addition of OH to the carbon atom in the α-position to the carboxyl group.

The observed distinct multiplicity is associated with the absence of free rotation around the  $O=C-\overset{\displaystyle H}{\overset{|}{C}}-C$ bond on account of the intermolecular hydrogen bonds that arise. In the case of the addition of hydroxyl to the β-carbon atom, the multiplicity of the proton bonded to it would be complicated as a result of interaction with three neighboring protons. The addition of the OH group to the γ-position is excluded by the doublet nature of the signal of the methyl group at $\delta = 1.05$ ppm with $J = 7.5$ Hz. The nature of the mass spectrum also confirms this position of the hydroxyl group. According to the mass spectrum, the intense peaks of fragments with m/e 144, 114, 100, 72, 43 can be explained by a gradual breakdown of the molecule according to the scheme:

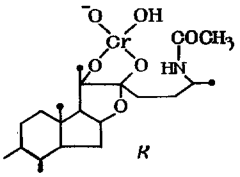

$$OH-\overset{\displaystyle O}{\overset{\|}{C}}-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-NH\,COCH_3$$

Ions with mass numbers 145, 143, 129, and 115 are easily interpreted as rearrangement ions. The appearance of intense peaks of ions with m/e 114 and 115 can be explained only on the assumption that the hydroxyl group is in the α-position to the double bond. Thus, all the data cited demonstrates that IV differs from II by the presence of a hydroxyl group in the side chain in the α-position to the carboxyl group.

The structure of VII as the acetate of pregna-5,16-dien-3β-ol-7,20-dione was established as follows. In its IR spectrum, similar to the IR spectrum of VI, absorption bands are observed at 1730 (CO, ester), 1670 (CO, conjugated) cm^{-1}; moreover, the latter is substantially more intense than that for VI. In the UV spectrum of VII there is an absorption maximum at 238 nm ($\varepsilon = 21{,}000$); for VI at the same wavelength, $\varepsilon = 9200$, i.e., in compound VII, in comparison with VI, there is a second carbonyl group conjugated with a double bond. The second carbonyl group may be in the 4, 7, or 15-position. The nature of the splitting of the signal of the proton at C_3 ($\delta = 4.77$ ppm) – a structure of seven lines with a halfwidth of 15 Hz, the result of the interaction with the four neighboring methylene protons – excludes the possibility of a position of the carbonyl group at C_4. The signals of the vinyl protons at $\delta = 5.74$ and 6.78 ppm indicate the position of the carbonyl group at C_7. The first (singlet) was assigned to the proton at C_6, and the second (singlet, broadened on account of interaction with two protons) was assigned to the proton at C_{16}. If the carbonyl group were situated at C_{15}, the signal of the proton at C_{16} should have been observed in a weaker field on account of the supplementary influence of the second carbonyl group in the α-position and should have taken the form of a singlet, while the signal of the proton at C_6 should have been observed in the region of 5.3 ppm.

Thus, in the oxidation of I, two side products were isolated from the reaction mixture, together with the oxidation product (II): the hydroxylactone (III) and (IV). The presence of VII in the reaction mass after boiling with acetic acid is evidence of the presence of still another side product V, which cannot be isolated directly from the reaction mass. Compound V is a product of allyl oxidation of II (with respect to the 5,6-double bond) with sodium bichromate, since in the oxidation of analytical pure IV with sodium bichromate in acetic acid, followed by boiling of the reaction mass (after reduction of the excess chromic with sodium sulfite), VII was also isolated. Compound VII was also isolated in the oxidation of VI. However, IV was not detected by thin-layer and column chromatograpny in the reaction mixture after the oxidation of II. This is an indication that IV is not the result of oxidation of the side chain of II, but arises as a result of allyl oxidation of I with respect to the 20,22-double bond.

As a result of a detailed study of the side products of the oxidation of I and on the basis of the literature data on the fact that the oxidation of the double bond by chromium salts in acetic acid proceeds through chromate esters [5], it can be imagined that the reaction of I with sodium bichromate in acetic acid proceeds through the formation of a tetravalent complex [6] of the indicated structure (K). (See scheme on following page.)



K

The latter decomposes forming II and III. Compound II experiences supplementary oxidation, giving V. Allyl oxidation of this kind, without displacement of the double bond, probably proceeds through a carbonium ion [7]. The formation of IV only in the oxidation of I indicates that allyl oxidation of I with respect to the 20,22-bond precedes the formation of the chromate complex.

EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument, the PMR spectra on a JNM-4H-100 instrument with tetramethylsilanex as the internal standard, the mass spectra on KB-9000 and CH-6 mass spectrometers, and the UV spectra on an EPS-3 instrument. Chromatography was conducted in a thin layer of UV-254 silufol in the system chloroform–acetone (9 : 1) with the appearance of phosphomolybdic acid at 100°.

Oxidation of Pseudosolasodine Diacetate (I). To 300 g I in 3 liters of glacial acetic acid at 20°, a solution of 130 g sodium bichromate in 1 liter of acetic acid was added with mixing. The temperature was raised to 38°. The reaction mixture was mixed for 10 min, 32 g sodium sulfite added, the solution poured out into 10 liters of water, extracted with benzene, the extract washed with a saturated solution of sodium bicarbonate and with water to a neutral pH. The benzene extract was evaporated to 1.5 liters. The oily residue, weighing 23 g, obtained after the evaporation of 100 ml of the benzene extract, was mixed with 20 g of permutit, dried to the air-dried state, and poured into a polyethylene column (d = 3.5 cm, *l* = 25 cm), filled with permutit. The column was washed with a mixture of chloroform and acetone (9 : 1). The eluate, containing a substance with $R_f = 0.11$, was evaporated to dryness and ground with a mixture of ethyl acetate and cyclohexane (1 : 2). The crystalline residue was filtered off, and 7-8 g II, mp 115-120°, was obtained. From 1.5 liters of the benzene extract, a total of 112 g II was obtained by the treatment indicated above. After crystallization from 1 liter of a mixture of ethyl acetate and hexane (1 : 2) with charcoal, 87 g II, mp 126-127°, was obtained [3]. After elution of the column, it was cut into four parts, and each part was eluted with acetone. The oily residues obtained after the evaporation of acetone consisted of four fractions: No. 1 ($R_f = 0.9$; 0.59; 0.11), No. 2 ($R_f = 0.9$; 0.59; 0.11; 0.0), No. 3 ($R_f = 0.59$; 0.11; 0.0), and No. 4 ($R_f = 0.11$; 0.0). After the treatment described above, 0.4 g IV (R_f 0.0 or 0.45; chloroform–acetone, 9 : 1 or 1 : 1) was isolated from fraction No. 4. Found, %: C 68.03; H 8.65; N 2.31. $C_{31}H_{47}NO_7$. Calculated, %: C 68.30; H 8.60; N 2.57. IR spectrum: 3300 (OH, NH), 1740 (CO, ester), 1715 (CO), 1660 (CO, amide), cm^{-1}. After chromatographic separation of fraction No. 1 on silica gel, 1.55 g III, mp 239-240°, R_f 0.59, was isolated; it gave no depression of the melting point in a mixed sample with the substance described in [1]; the IR spectra were identical. A portion of 8 g of the oily residue of fraction III was boiled with 60 ml of glacial acetic acid for 3 h, and the solvent distilled off to dryness. The residue was recrystallized from alcohol, 3.45 g VI, mp 169-171°, $R_f = 0.9$, was filtered off, and the mother liquor evaporated to dryness. The residue was dissolved in benzene, the benzene removed from the undissolved VIII and applied on a column with silica gel. Benzene eluted 0.5 g VI, and a mixture of benzene and chloroform (3 : 1) eluted 0.8 g of an oil ($R_f = 0.9$, 0.59; chloroform–acetone, 9 : 1). After grinding with acetone, 0.4 g VII, mp 226-228° (from ethanol), Rf = 0.45 (benzene–ethyl acetate, 8 : 2), was filtered off. Found, %: C 74.34; H 8.16; $C_{23}H_{30}O_4$. Calculated, %: C 74.54; H 8.16 IR spectrum: 1735 (CO, ester), 1665 (CO, conjugated), cm^{-1}. PMR spectrum ($CDCl_3$), δ, ppm: 0.85; 1.18 (CH_3, angular); 1.99; 2.20 (CH_3 at carbonyls); 4.77 (H at C_3); 5.74 (H at C_6); 6.78 (H at C_{15}).

The residue of VIII was dissolved in a mixture of chloroform and acetone (8 : 2), the crystalline residue filtered off and washed with chloroform. Yield 0.64 g VIII, mp 157.5-160° (from a mixture of acetone and ethanol, 9 : 1). Found, %: C 51.28; H 7.91; N 7.63. $C_8H_{15}NO_4$. Calculated, %: C 50.88; H 7.9; N 7.39. IR spectrum: 3340 (NH), 2500, 1950, 1710 (COOH), 1610 (CO, amide) cm^{-1}. PMR spectrum (in deuteromethanol), δ, ppm: 1.0 (CH_3, doublet); 1.95 (CH_3 at carbonyl, singlet); 3.33 (CH_2–NH, triplet); 4.63 (CH–OH, quartet).

Oxidation of II. A 3-g portion of II with mp 126-127° was dissolved in 30 ml of acetic acid and a solution of 1.69 g sodium bichromate in 10 ml acetic acid added. It was heated with mixing for 1 h at 50°. After cooling, 2.2 g sodium sulfite was added, and the mixture boiled for 3 h. Then 33 ml of water was added with mixing, and the precipitate filtered off. Yield 1.12 g (VI) (67.5%), mp 169-171°. The acetic acid solution was neutralized with sodium bicarbonate, extracted with benzene, washed with water, dried, and evaporated to dryness. A 0.41-g portion of the oily residue was ground with ethanol, and VII filtered off, mp 222-224.5°, identical with the sample of VII described above.

Oxidation of Pregna-5,16-dien-3β-ol-20-one Acetate (VI). To 5 g VI in 80 ml acetic acid, a solution of 3 g sodium bichromate in 20 ml acetic acid was added on one operation at 20° with mixing. The mixture was mixed for 1 h at 20°, 4.5 g sodium sulfite added, heated until reduction, and 100 ml of water added at 20°. The precipitated VI was filtered off, washed with 50% aqueous acetic acid, and with water. Yield 3.5 g (70%) VI, mp 169-171°. The acetic acid solution was treated as described above. Yield 0.18 g VII, mp 225-226° (from ethanol).

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