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PREPARATION OF 21-ALDEHYDES OF $\Delta^{17(20)}$-STEROIDS

E. V. Popova, V. A. Andryushina, and G. S. Grinenko

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A method is described for the synthesis of 17(20)-unsaturated 21-aldehydes by the oxidation of 17β-hydroxy-17α-vinylsteroids with pyridine chlorochromate. The following compounds were obtained in the course of the investigation: 3-hydroxy-trans-pregna-5,17-dien-21-al acetate, mp 177-178°C (MeOH); trans-pregna-5,17(20)-diene-3β,21-diol 3-acetate (I), mp 150-153°C (MeOH); the 21-acetate of (I), with mp 130-133°C (ether–hexane); 3-oxo-trans-pregna-4,17(20)-dien-21-al, with mp 130-132°C (MeOH); and 3-oxo-trans-pregna-4,17(20)-dien-21-cic acid, $C_{21}H_{28}O_3$, mp 261-263°C. The IR and NMR spectra of the substances obtained are given.

In the use of some steroids (such as cholesterol and β-sitosterol) for the synthesis of hormone preparations, the question arises of the passage from compounds of the androstane series to the pregnane series, especially to corticosteroids. In this connection, interest is presented by 17(20)-unsaturated aldehydes, which are convenient intermediates for the construction of a dihydroxyacetone chain in position 17 of the molecule.

Among methods for the synthesis of $\Delta^{17(20)}$-21-aldehydes recently published in the litera ture we must mention the condensation of 17α-ethynyl-17β-hydroxysteroids with dimethylformamide acetal [1]. This reaction, giving a high yield (90%), has been described for the case of the methyl ether of ethynylestradiol. However, the greatest interest is presented by compounds containing the Δ^4-3-keto grouping that is a structural element of the articosteroids. But in this case, the condensation described above takes place with a low yield even when ethylene ketal protection is used for the 3-keto group as, for example, for 17α-ethynyl-17β-hydroxyandrost-4-en-3-one.

In the present paper we describe a method for the synthesis of 17(20)-unsaturated aldehydes by the oxidation of vinyl-substituted steroid alcohols with pyridine chlorochromate. As the initial compounds we selected 17α-vinylandrost-5-ene-3β,17β-diol 3-acetate (I) and 17β-hydroxy-17α-vinylandrost-4-en-3-one (V). Oxidation with pyridine chlorochromate with the aim of obtaining aldehydes has been proposed for vinyl-substituted acyclic alcohols. For steroid alcohols it has been described in the case of 3α-vinylcholestan-3β-ol, which contains a sterically unhindered equatorial hydroxy group in a six-membered ring. The product of oxidation was a mixture (1:1) of isomeric aldehydes with a yield of 70% [2].

We have studied the oxidation of vinyl-substituted alcohols with the alcohol group in the five membered ring of androstane derivatives. In our case, the reaction had to be performed at a sterically hindered group. Oxidation was carried out in methylene chlorine at room temperature. The reaction was monitored by the TLC method and was continued until the initial compound had disappeared (about 120 h). The reaction took place with 17α-vinylandrost-5-ene-3β,17β-diol 3-acetate with a satisfactory result (yield 50%).

The oxidation of 17β-hydroxy-17α-vinylandrost-4-en-3-one (V) formed a mixture of substances, from which it was possible to isolate the aldehyde (VI) only by chromatography on silica gel followed by preparative TLC of the corresponding fractions. The acid (VII), the structure of which agrees with the results of spectral analysis, was isolated at the same time. On the basis of literature analogy and the results of TLC, the formation of the oxide

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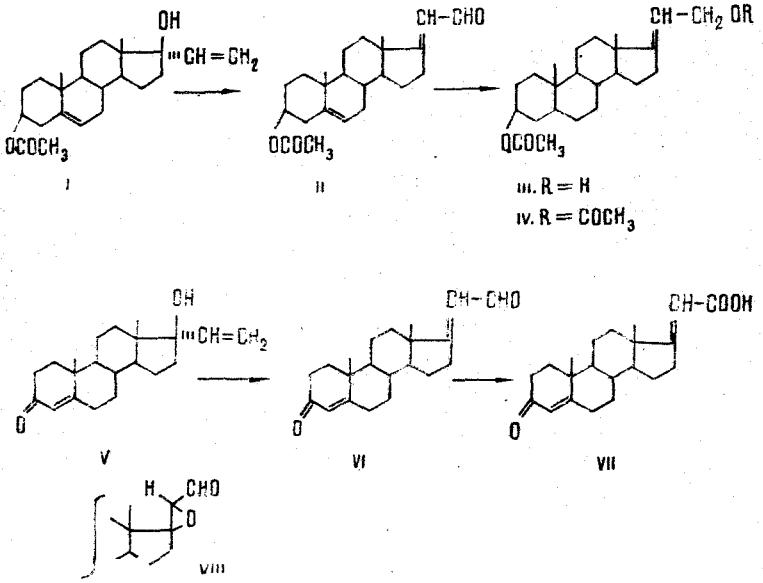
(VIII) as impurity may be assumed in both cases. However, we did not isolate it in the pure form



It was established by the NMR spectroscopy of the reaction mixture and of the products isolated that the oxidation took place stereospecifically with the formation of only the trans isomer. This was shown by the solitary singlet of the protons of the 18-angular methyl group (0.92 ppm for the aldehyde (VI) and 0.88 ppm for the aldehyde (II)) and the solitary doublet of aldehyde protons (9.83 ppm for (VI) and 9.84 ppm for (II)). The configuration of the substituents at the $C_{17(20)}$ double bond was suggested on the basis of a comparison of the results obtained with those given in the literature and, in particular, by a comparison of NMR spectral characteristics [1, 3, 4].

The aldehyde (II) was reduced with sodium tetrahydroborate to the alcohol (III), which was then converted into the acetate (IV). The construction of the dihydroxyacetone chain in the latter was performed by a published method [5] using N-methylmorpholine oxide in the presence of OsO_4, with the only difference that 33% H_2O_2 was used in place of 50% H_2O_2.

EXPERIMENTAL

IR spectra of mulls of the compounds in paraffin oil were taken on a UR-10 instrument, NMR spectra on a JNM-4H-100 instrument in $CDCl_3$ (with TMS as internal standard; δ scale), and mass spectra on a MAT-112 instrument (with an ionizing energy of 50 ev).

3-β-Hydroxypyregna-5,17(20)-dien-21-al Acetate (II). At room temperature, a solution of 2 g of 17α-vinylandrost-5-ene-3β,17β-diol acetate (I) in 30 ml of methylene chloride was added to a suspension of 2.9 g of pyridine chlorochromate [6] in 10 ml of methylene chloride. After 24 h, another 1 g of pyridine chlorochromate was added. The reaction mixture was kept at 20°C for 120 h (by which time the initial substance had disappeared, TLC), and was then diluted with 50 ml of ether. Chromium salts were filtered off through Celite, and the filtrate was evaporated in vacuum. The residue was dissolved in benzene and the solution was filtered through a layer of silica gel, which was carefully washed with benzene. Evaporation of the benzene left 1.9 g of a light yellow oil from which, by crystallization from MeOH, 0.75 g of the trans isomer of the aldehyde (II) was isolaed with mp 177-178°C (literature figures: mp 178-180°C [7]). IR spectrum (cm^{-1}): 2720, 1730, 1670, 1610. NMR spectrum (ppm): 0.88 (18-CH_3), 1.057 (19 CH_3), 2.033 ($COCH_3$), 5.402 ($C_5 = C_6H$–), 5.72 ($C = C_{20}H$–), 9.83 (C–CHO).

The mother solution yielded an additional 0.15 g of (II).

Pregna-5,17(20)-diene-3β,21-diol Diacetate (IV). The aldehyde (II) (0.14 g) was reduced with an excess of sodium tetrahydroborate in 7 ml of dimethylformamide at 20°C for two hours (the end of the reaction was determined by TLC). Then, with cooling, three drops of acetic acid and 14 ml of water were added. After this, 0.1 g of trans-pregna-5,17(20)-diene-3β,21-diol acetate (III) was filtered off with mp 150-153°C (MeOH) (literature figures: mp 177-178°C [3]). IR spectrum, cm^{-1}: 3320, 1730. NMR spectrum (ppm): 0.78 (18 CH_3), 1.04 (19

CH_3), 2.033 ($COCH_3$), 4.15 (CH_2OH), 4.6 (3 —H), 5.25 (C = C_{20}H—), 5.35 (C = C_6H—). The treatment of 0.1 g of the acetate (III) with acetic anhydride in pyridine at 20°C for 48 h gave 0.1 g of trans-pregna-5,17(20)-diene-3β,21-diol diacetate (IV), with mp 130-133°C (ether–hexane). According to the literature: mp 128-129°C (MeOH) [7].

Oxidation of 17β-Hydroxy-17α-vinylandrost-4-en-3-one (V). The oxidation of 5 g of the alcohol (V) was carried out with 5.8 g of pyridine chlorochromate, as for the alcohol (I). The oil obtained after dilution of the reaction mixture with ether (7 g) was filtered and evaporated and then it was passed in benzene through 10 g of silica gel. In this way, 4.5 g of a colorless oil was isolated, 3.5 g of which was chromatographed on 90 g of silica gel. Methylene chloride eluted fractions containing the aldehyde (VI) contaminated with substances of low polarity, and then methylene chloride and 5% of ether in methylene chloride eluted the aldehyde (VI) containing more polar compounds as impurities. After evaporation of the solven from these fractions, an oil retained which did not crystallize. By preparative TLC, 0.3 g of this oil yielded 0.12 g of 3-oxo-trans-pregna-4,17(20)-dien-21-al (VI), with mp 130-132°C (MeOH) (according to the literature: mp 142-147°C [1]). IR spectrum (cm^{-1}): 2720, 1670, 1610. NMR spectrum (ppm): 0.92 (18-CH_3), 1.22 (19-CH_3), 5.74 (C= C_{20}—H), 9.83 (CHO). Fractions containing 10-20% of ether in methylene chloride eluted from the column 0.3 g of 3-oxo-trans-pregna-4,17(20)-dien-21-cic acid (VII), $C_{21}H_{28}O_3$, mp 261-263°C. IR spectrum (cm^{-1}): 2500-2750, 1670, 1640, 1610. NMR spectrum (ppm): 0.89 (18-CH_3), 1.21 (19-CH_3), 5.62 (C=C_{20}—H). Mass spectrum: M 328.

SUMMARY

By oxidation with pyridine chlorochromate, 17α-vinylandrostene-3β,17β-diol has been converted into 3β-hydroxy-trans-pregna-5,17(20)-dien-21-al acetate.

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SYNTHESIS AND PHARMACOLOGY OF SOME DIISOQUINOLINE ALKALOIDS

V. I. Vinogradova, M. S. Yunusov, I. Khamdamov, and F. Sadritdinov

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A number of tetrahydrodiisoquinoline alkaloids has been synthesized by various routes. Some connections between the chemical structures of the compounds obtained and their pharmacological effects have been found.

Diisoquinoline alkaloids are physiologically active substances. Some of them are widely used in medical practice as sedatives and cholagogues [1].

The aim of the present work was to synthesize and find new physiologically active preparations among derivatives of the tetrahydroisoquinoline alkaloids, and also to find connections between their chemical structure and pharmacological action.

Several methods of obtaining photoberberine bases are known [2-10]. From the practical point of view, the most acceptable, in our opinion, is the following scheme of synthesis:

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