STEROIDS

XLII. THE REACTION OF 16α, 17α-EPOXYPREGNENOLONE WITH AROMATIC AMINES

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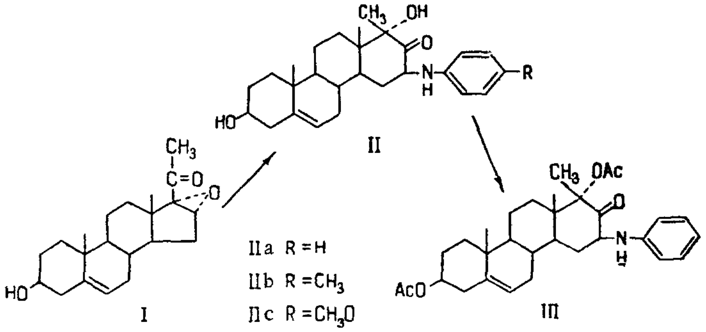
In a number of patents [1-3] it has been reported that the opening of the oxide ring of 20-oxo-16α, 17α-epoxysteroids under the action of primary and secondary aliphatic and cyclic amines leads to the formation of 16-amino-17α-hydroxy-20-oxosteroids. However, the structure and configuration of the compounds obtained has never been confirmed.

More recently, the hypothesis has been put forward [4] that the direct reaction of aliphatic and cyclic amines with 20-oxo-16α, 17α-epoxysteroids forms not 16-amino-17α-hydroxy-20-oxosteroids but, probably, rearrangement products which have a D-homosteroid structure, which has likewise not been confirmed.

In the present paper we give the results of an investigation of the reaction of primary aromatic amines (aniline, p-toluidine, and p-anisidine) with 16α, 17α-epoxypregnenolone (I) and of a determination of the structure and configuration of the reaction products. It has been found that the reaction gives not derivatives of 16-amino-17α-hydroxypregnenolone [1-3], but other compounds, namely the corresponding amino derivatives of D-homosteroids – 16β-anilino-(IIa), 16β-p-toluidino- (IIb), and 16β-p-anisidino-3β, 17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (IIc).



The structure and configuration of compounds IIa, b, and c was shown by a series of chemical reactions and by physicochemical methods.

Elementary analyses and IR spectra show the appearance in the molecules of the reaction products obtained of an additional hydroxy group and an arylamino group. The acetylation of IIa with acetic anhydride in pyridine at room temperature led to a diacetate the IR spectra of which show that only the hydroxyl groups acetylate. Since acetylation takes place readily, the newly introduced hydroxy group is not present in position 17; pregnan-17-ols acetylate under more severe conditions. Consequently, for compound IIa it

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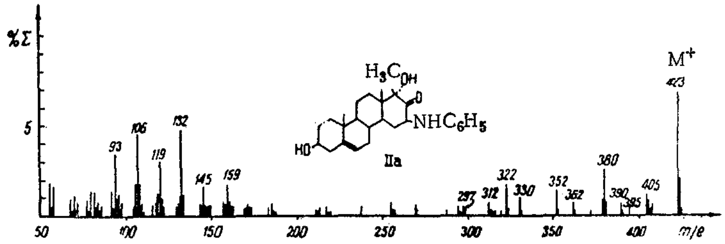
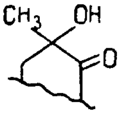


Fig. 1. Mass spectrum of compound IIa.

would be possible to propose the structure of 17-anilino-3β, 16-dihydroxypregn-5-en-20-one. However, in the PMR spectra of IIa, b,and c there are no signals of the protons of a methyl group at C-21, which are generally observed in the 1.9-2.1 ppm region and which are characteristic for pregnen-20-ones [4].

At the same time, in addition to the signals of angular methyl groups, the spectra have the signal of a methyl group in the 1.50-1.56 ppm region. This value of the chemical shift of the signal of a methyl group is characteristic for a fragment of the following type [4]:



This permits a D-homosteroid structure to be proposed for IIa, b, and c.

In the PMR spectra, the signal of the proton at C-16 found in the 4.40-4.85 ppm region has a half-width of 10 Hz which, according to the literature [6], corresponds to the axial position of the proton at C-16. Consequently, the amine residue is located equatorially, i.e., the compounds contain 16β-arylamino groups.

Spectropolarimetry shows that compounds IIa, b, and c have similar OD curves with a negative Cotton effect, which is in harmony with literature information [7] on D-homosteroids with a carbonyl group in position 17. The trough of the observed Cotton effect is in the region of about 320-330 nm. Thus, the usual carbonyl anomaly is shifted somewhat into the long-wave region. As is well known [7], this is observed in oxosteroids having an axial hydroxy group adjacent to the carbonyl.

There is also information in the literature [8] on the rotatory dispersion of 17-oxo-D-homosteroids containing an amine substituent in position 17a. Compounds of this type have OD curves with the first extremum at 317-332 nm. The sign of the Cotton effect depends both on the configuration at C-17a and also on the nature of the amine substituent. Apparently the nature of the amine substituent at C-16 also has a definite influence on the OD curves of the compounds that we studied: the positive Cotton effect is shifted somewhat in the long-wave region in the sequence aniline, p-toluidine, p-anisidine. The troughs are at 315, 322, and 332 nm, respectively.

The structures that we propose for IIa and b agree well with the features of their mass spectra (Fig. 1).

The mass spectra of compounds IIa and b have strong peaks of the molecular ions with m/e 423 and 437 corresponding to the molecular weights of IIa and IIb. The peaks of the ions of the high-molecular-weight part of the spectrum such as M − H_2O (m/e 405 and 419), M − 28 (m/e 395 and 409), M − H_2O − CH_3 (m/e 390 and 404), M − CH_3 − 28 (m/e 380 and 394, M − CH_3 − 28 − H_2O m/e 362 and 376), M − $ArNH_2$ (m/e 330), and M − $ArNH_2$ − H_2O (m/e 312), are connected with the elimination of the functional groups of the molecule. The main decomposition of the molecules of IIa and b under electron impact is governed by the arylamine substituent in ring D, as a result of which four amine fragments are formed in the low-molecular-weight part of the spectrum: a, b, c, and d, containing the arylamino group with the neighboring carbon atoms:

$Ar\overset{\cdot +}{N}H_2$	$CH_2{=}\overset{+}{N}HAr$	$CH_2{=}CH{-}\overset{\cdot +}{N}HAr$	$O{=}C{=}\overset{\cdot +}{N}HAr$
a	b	c	d
IIa m/e 93	IIa m/e 106	IIa m/e 119	IIa m/e 132
IIb m/e 107	IIb m/e 120	IIb m/e 133	IIb m/e 146

An analogous fragmentation is observed in the mass spectra of a series of steroid alkaloids with an alkylamino grouping in ring A or ring D [9].

The molecular models IIa and III were constructed on the basis of the results obtained. From a consideration of the models it can be seen that the diacetate III can be formed from IIa only if the anilino group is present in position 16β and the hydroxy group at 17aα. In the opposite case, i.e, that of the 16α-anilino-17aβ-hydroxy derivative (as can be seen from its model), acetylation should take place at the nitrogen atom and not at the 17aβ-hydroxy group, since a hydroxy group in the 17aβ position is strongly screened by the angular methyl group and the carbonyl group.

The information given confirms that the reaction of aromatic amines (aniline, p-toluidine, and p-anisidine) with 16α, 17α-epoxypregnenolone forms 16β-anilino- (IIa), 16β-p-toluidino- (IIb), and 16β-p-anisidino-3β, 17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (IIc).

EXPERIMENTAL

The IR spectra were obtained on a UR-10 instrument in paraffin oil, the PMR spectra on a JNM-4H-100 instrument in deuteropyridine, and the mass spectra on an MKh-1306 instrument fitted with a system for the direct introduction of the sample into the ion source at a temperature of 170°C with an ionizing voltage of 30 V. The rotatory dispersions were measured on a VNIÉKIPRODMASh [All-Union Scientific-Research Experimental Design Institute for Food Machinery] "SPU-M" semiautomatic spectropolarimeter in tubes 0.5 dm long at a concentration of 0.1% (dioxane). The purity of the substances isolated was checked by thin-layer chromatography. The analytical results for all the compounds corresponded to the calculated figures.

16β-Anilino-3β, 17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (IIa). A mixture of 10 g of 5-hydroxy-16α, 17α-epoxypregn-5-en-20-one (I) and 30 ml of aniline was boiled in a current of nitrogen under reflux with a calcium chloride tube for 6 h. The excess of aniline was distilled off in vacuum and the residue was crystallized from methanol with the addition of carbon. This gave 10.2 g of IIa. The methanol was evaporated off from the mother solution in vacuum until crystallization began, and then the solution was cooled. This gave another 1.5 g of IIa, mp 240-241.5°C $[\alpha]_D^{20}$ – 85° (here and below, for 1% solutions in chloroform), ν_{max}, cm^{-1}: 3550, 3540 (OH), 3380 (NH), 1710 (C = O),and 1610 (C = C). Yield 11.7 g (91.2%). Found, %: C 76.77; H 8.85; N 3.26. Calculated for $C_{27}H_{37}NO_3$, %: C 76.55; H 8.80; N 3.30.

3β, 17aα-Dihydroxy-16β-p-toluidino-17aβ-methyl-D-homoandrost-5-en-17-one (IIb). A solution of 10 g of I and 10 g of p-toluidine in 300 ml of ethanol was stirred in an autoclave at 180°C for 10 h. The reaction mixture was cooled, ethanol was added until the precipitate had dissolved completely, the solution was treated with carbon and filtered, and the carbon was washed with ethanol. The ethanol was evaporated off in vacuum to a volume of 200 ml and the residue was cooled at –5°C for 2 h, after which 10 g (75.5%) of IIb was filtered off; mp 210-212°C (from methanol), $[\alpha]_D^{20}$ – 69°, ν_{max} 3550, 3440 (OH), 3360 (NH), 1705 (C = O), and 1620 (C = C).

Found, %: C 76.57; H 8.92; N 3.22. Calculated for $C_{28}H_{39}NO_3$, %: C 76.84; H 8.98; N 3.20.

16β-p-Anisidino-3β, 17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (IIc). This was obtained like the preceding compound from 10 g of I and 10 g of p-anisidine in a yield of 12.8 g (84.7%); mp 198-199.5°C (from methanol); $[\alpha]_D^{20}$ – 70°, ν_{max}, cm^{-1}: 3520, 3430 (OH), 3380 (NH), 1700 (C = O), and 1615 (C = C).

Found, %: C 74.25; H 8.48; N 2.96. Calculated for $C_{28}H_{39}NO_4$, %: C 74.13; H 8.66, N 3.08.

16β-Anilino-3β, 17aα-diacetoxy-17aβ-methyl-D-homoandrost-5-en-17-one (III). A solution of 1.5 g of IIa and 15 ml of acetic anhydride in 30 ml of pyridine was left at room temperature for 24 h and diluted with water, and then the precipitate was filtered off, washed with water, and dried. This gave 1.45 g (81%) of III, mp 197-199°C (from absolute ethanol). $[\alpha]_D^{20}$ – 73°, ν_{max} 3350 (NH), 1735 (ester CO), 1705 (ketone CO), 1610 (C = C).

Found, %: C 73.10; H 7.94; N 2.77. Calculated for $C_{31}H_{41}NO_5$, %: C 73.34; H 8.14; N 2.75.

SUMMARY

1. The reaction of 16α, 17α-epoxypregnenolone with primary aromatic amines (aniline, p-toluidine, and p-anisidine) has been studied. The reaction products are amino derivatives of D-homosteroids: 16β-anilino- (IIa), 16β-p-toluidino- (IIb), and 16β-p-anisidino-3β, 17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (IIc).

2. The structure and configuration of the compounds (IIa, b, and c) obtained have been shown by a series of chemical reactions and by physicochemical methods.

3. The acetylation of IIa with acetic anhydride in pyridine leads to the formation of 16β-anilino-3β, 17aα-diacetoxy-17aβ-methyl-D-homoandrost-5-en-17-one (III).

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