TRANSFORMED STEROIDS.

114.* DIRECTION OF OPENING OXIDE RING OF 16,17α-EPOXY-17β-PHENYLANDROST-4-EN-3-ONE

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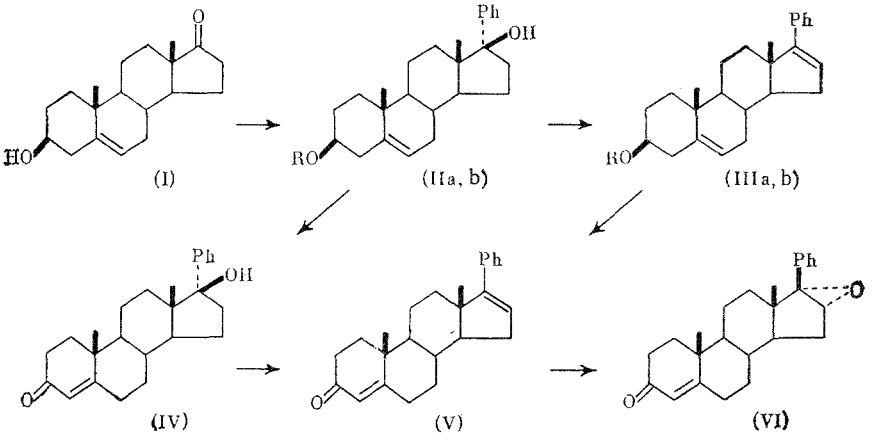
Previously we had shown that replacing the 20-keto group in 16,17α-epoxy-20-ketosteroids by the azomethine grouping (hydrazone, semicarbazone) leads, in the presence of nucleophilic reagents, to a strictly structural and stereospecific opening of the oxide ring [2]. Analogous results were also observed when going from the oxides to the corresponding aziridines [3]. The theory was expressed that such a reaction direction is explained by the formation of an intermediate bridge cation, which includes either one or both N atoms [2]. However, a viewpoint exists [4], according to which the cleavage of the 17-C–O bond, adjacent to the azomethine grouping, is determined by the presence of p–π conjugation, which facilitates formation of the 17 carbcation, stabilized by the conjugation. Here the reaction direction of hydrazone oxides is compared with the results of opening aryl oxides [4], while the stereospecificity observed for the former is explained by steric hindrance. In connection with this we undertook the synthesis and a study of the direction of opening the oxide ring of an aryloxysteroid, and specifically of 16,17α-epoxy-17β-phenylandrost-4-en-3-one (VI)

The condensation of epiandrostenolone (I) with phenyllithium in abs. ether [5] gave 17α-phenylandrost-5-en-3β,17β-diol (IIa) in ∿70% yield. 17-Phenylandrosta-4,16-dien-3-one (V) was synthesized in two ways, by the Oppenauer oxidation of phenylandrostendiol (IIa) and the subsequent dehydration of 17α-phenylandrost-4-en-17β-ol-3-one (IV) using $POCl_3$ in pyridine and, in contrast, by the dehydration of phenylandrostendiol 3-acetate (IIb) under the same conditions, alkaline hydrolysis of the phenyldiene 3-acetate (IIIb), and subsequent oxidation of the obtained phenylandrostadienol (IIIa). Although the second path is longer, still it gives a higher yield of diene (V) due to the smoother dehydration of the phenylandrostendiol 3-acetate (IIb) (∿90%) when compared with the dehydration of the Δ^4-3-ketone (IV) (∿50%)



R=H(a), Ac(b).

The oxidation of phenyldienone (V) with m-chloroperbenzoic acid leads to the formation of (VI), whose structure is confirmed by the PMR spectral data. It proved that phenyl epoxide (VI) is unstable in the presence of nucleophilic reagents. When (VI) is treated with AcOH the oxide ring is opened with the predominant formation of 17α-phenyl-17β-methyl-

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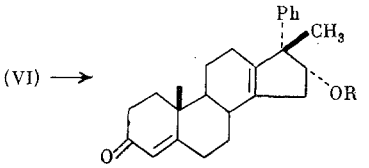
18-nor-androsta-4,13-dien-16α-ol-3-one (VIIa), a rearrangement product of the Wagner–Meerwein type.



(VIIa, b)

R = H(a), Ac(b).

The reaction proceeds in a similar manner with NH_3, and also with pyridine isocyanate in refluxing ethanol. The acetylation of the rearrangement product (VIIa) under the usual conditions leads to acetate (VIIb). The structure and stereochemistry of (VIIa) and its acetate (VIIb) were confirmed by the physicochemical analysis data. The IR spectrum of (VIIa), obtained from the reaction with AcOH, lacks the absorption band of the acetate group, which appears in the spectrum of (VIIb). The PMR spectra of compounds (VIIa) and (VIIb) lack the signals of the angular 18-CH_3 group, but display the signals from the CH_3 groups further downfield (respectively 1.48 and 1.56 ppm), which is characteristic for the spectrum of a rearrangement product of the Wagner–Meerwein type. The configuration of the 16-center was proved on the basis of the data of the PMR spectrum of (VIIb) and the ^{13}C NMR spectra of (VIIa) and (VIIb). Thus, the signal of the methyl of the acetyl group in the PMR spectrum of (VIIb) (δ 1.56 ppm) is shifted upfield when compared with its position (2.00 ppm) in the spectra of 17-keto-16(α,β)acetylated steroids [6]. This shift (Δδ 0.4 ppm) is possible only for the syn configuration of the aromatic nucleus and AcO group, where the methyl proton of the acetyl group falls within the cone of the shielding magnetic anisotropic effect of the aromatic nucleus. The ^{13}C NMR spectral data for compounds (VIIa) and (VIIb) show that the signal of the 18-C atom is shifted downfield by 0.3 ppm when the AcO group is replaced by OH (Table 1).

From an analysis of the data given in [7] it can be seen that with a cis configuration of the methyl (18-CH_3) and AcO groups in the spectra of 17β-substituted steroids the replacement of the AcO group by OH leads to an upfield shift of the 18-C signal by 0.9 ppm, while for the trans arrangement the replacement of the AcO group by OH leads to a downfield shift of the signal of the CH_3 group by 0.4 ppm, which is also observed in our case. As a result, it can be stated that the configuration at 16-C is α, i.e., the 18-C methyl and 16-C acetoxy groups or the hydroxyl are found in the trans position.

As a result, the presence of a phenyl nucleus in the 17-position facilitates, as was to be expected, the cleavage of the 17-C–O bond of the oxide ring, adjacent to this substitutent. However, the overall reaction result differs sharply from that for the case of the 20-hydrazone 16,17α-oxides. Actually, the formation of the 17-carbcation, stabilized by conjugation with the aromatic ring, facilitates the 1,2-migration of the angular CH_3 group, but not the insertion of a nucleophilic reagent, as occurs in the case of the hydrazone oxides.

EXPERIMENTAL

The melting points were determined on a Kofler block. The IR spectra were taken on a UR-10 instrument in KBr. For the TLC we used silica gel KSK deposited on microplates, with

TABLE 1. ^{13}C NMR Spectra of Compounds (VIIa) and (VIIb) (δ, ppm)

Compound	1-C	2-C	3-C	4-C	5-C	6-C	7-C	8-C	9-C	10-C
(VIIb)	36,6	33,8	199	124,6	170,0	33,3	31,1	35,5	51,7	38,6
(VIIa)	36,6	33,8	199	124,6	170,2	33,3	31,1	35,4	51,8	38,7

Compound	11-C	12-C	13-C	14-C	15-C	16-C	17-C	18-C	19-C
(VIIb)	22,5	23,5	139,5 * (140,5)	140,5 * (139,5)	37,4	81,1	56,2	22,9	16,9
(VIIa)	22,3	23,5	139,1 * (139,6)	139,6 * (139,1)	39,4	80,9	55,8	23,2	16,9

*The assignment is ambiguous.

detection by I_2 vapors. The PMR spectra were taken on a Tesla BS-497 spectrometer (100 MHz) in $CDCl_3$ solution. The ^{13}C NMR spectra were taken on a Bruker HX-90 spectrometer (90 MHz) in $CDCl_3$ solution, with TMS as the internal standard.

17α-Phenylandrost-5-en-3β,17β-diol (IIa). To a stirred solution of phenyllithium, prepared from 3.36 g of Li and 25.5 ml of bromobenzene in 350 ml of ether, was added a solution of 8.64 g epiandrostenolone (I) in 250 ml of ether and the mixture was refluxed for 12 h. The excess PhLi was decomposed with satd. NH_4Cl solution, the mixture was extracted with benzene, and the extract was washed with water, dried over Na_2SO_4, and evaporated. We obtained 7.40 g of (IIa), mp 176-178°C (from acetone–hexane). Infrared spectrum (ν, cm^{-1}): 3040, 3065, 3075, 3095, 3220-3500. Found: C 81.31; H 9.71%. $C_{15}H_{34}O_2$. Calculated: C 81.92; H 9.35%.

17α-Phenylandrost-5-en-3β,17β-diol 3-Acetate (IIb). Infrared spectrum (ν, cm^{-1}): 1735, 3030, 3060, 3090, 3500. PMR spectrum (δ, ppm): 0.90 s (3H, 18-CH_3), 1.0 s (3H, 19-CH_3), 1.93 s (3H, 3-OAc), 4.43 br.1 (1H, 3-H), 5.28 m (1H, 6-H), 7.25 s (5H, aromatic protons).

17-Phenylandrosta-5,16-dien-3β-ol 3-Acetate (IIIb). To a solution of 2.2 g of (IIb) in 50 ml of dry pyridine was added 2.2 ml of $POCl_3$ and the mixture was refined for 30 min, cooled, poured into ice water, extracted with $CHCl_3$, and the extract was washed in succession with dilute HCl solution, $NaHCO_3$ solution, and water, and then evaporated. The residue (semicrystalline brown oil) was forced by nitrogen through an SiO_2 column (1:1 ether–hexane system). We obtained 1.97 g of (IIIb), mp 146-147° (from methanol). Infrared spectrum (ν, cm^{-1}): 1245, 1495, 1735, 3035, 3070, 3090. PMR spectrum (δ, ppm): 0.97 s (3H, 18-CH_3), 1.0 s (3H, 19-CH_3), 1.94 s (3H, 3-OAc), 4.5 br.1 (1H, 3-H), 5.30 m (1H, 16-H), 7.3 s (5H, aromatic protons).

17-Phenylandrosta-5,16-dien-3β-ol (IIIa). To a solution of 2 g of (IIIb) in 50 ml of dioxane was added a solution of 0.5 g of KOH in 20 ml of water and the mixture was let stand overnight at ∿20°. The mixture was poured into water and the obtained precpiitate was filtered, washed with water, and dried. We obtained 1.8 g of (IIIa), mp 153-155° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1500, 3035, 3055, 3080, 3300-3520.

17-Phenylandrosta-4,16-dien-3-one (V). a) From a solution of 1.8 g of (IIIa) in 160 ml of abs. toluene and 20 ml of cyclohexanone we distilled off 30 ml of toluene, added a solution of 2 g of aluminum isopropoxide, and refluxed the mixture for 2 h. After cooling, the mixture was decomposed with 10% AcOH solution, extracted with $CHCl_3$, and the extract was washed in succession with $NaHCO_3$ solution and water, dried over Na_2SO_4, and evaporated. The residue was treated with hexane and the obtained amorphous precipitate was filtered to give 1.3 g of (V), mp 164-166° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1495, 1615, 1675, 3000, 3020, 3050. Found: C 86.27; H 8.54%. $C_{25}H_{30}O$. Calculated: C 86.65; H 8.73%. PMR spectrum (δ, ppm): 0.98 s (3H, 18-CH_3), 1.14 s (3H, 19-CH_3), 5.66 s (1H, 4-H), 5.8 m (1H, 16-H), 7.2 m (6H, aromatic protons).

b) A solution of 200 mg of (IV) in 10 ml of pyridine and 0.2 ml of $POCl_3$ was refluxed for 1 h. The mixture was poured into ice water, extracted with $CHCl_3$, and the extract was washed in succession with dilute HCl solution, $NaHCO_3$ solution, and water, and then evaporated. We obtained an oil, which was separated on an SiO_2 plate in the system 2:1 ether–hexane (2 passes). We obtained 100 mg of (V), mp 163-165° (from aqueous acetone), which did not depress the mixed melting point with the above described sample.

17α-Phenylandrost-4-en-17β-ol-3-one (IV). From a solution of 1 g of (IIa) in 80 ml of toluene and 10 ml of cyclohexanone we distilled off 20 ml of toluene, added a solution of 1 g of $Al(OPr\text{-}i)_3$, and refluxed the mixture for 1.5 h. Then the mixture was decomposed with 10% AcOH solution and extracted first with benzene, and then with $CHCl_3$. The combined extracts were washed in succession with $NaHCO_3$ solution and water, and then evaporated. The condensation products were steam-distilled in vacuo. The residue was treated with hexane and the obtained finely crystalline precipitate was filtered. We obtained 750 mg of (IV), mp 182-184°(from aqueous acetone), cf. [5].

16,17α-Epoxy-17β-phenylandrost-4-en-3-one (VI). To a solution of 870 mg of (V) in 10 ml of freshly distilled CH_2Cl_2 was added in drops, with stirring, at ∿20°, a solution of 550 mg of m-chloroperbenzoic acid in 10 ml of CH_2Cl_2 and the mixture was let stand for 4 h at ∿20°. The mixture was diluted with CH_2Cl_2, washed in succession with Na_2SO_3 and $NaHCO_3$ solutions, water, and saturated NcCl solution, and then it was evaporated, the residue was treated with hexane, and the obtained crystalline precipitate was filtered. We obtained 730 mg of (VI), mp 210-212° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1505, 1625, 1670,

3010, 3035, 3070. PMR spectrum (δ, ppm): 0.71 s (3H, 18-CH_3), 1.11 s (3H, 19-CH_3), 3.54 s (1H, 16-H), 5.66 s (1H, 4-H), 7.26 s (aromatic protons). M^+ 362.

17α-Phenyl-17β-methyl-18-nor-androsta-4,13-dien-16α-ol-3-one (VIIa). A solution of 500 mg of (VI) in 8 ml of AcOH was let stand overnight at ∿20°. The mixture was diluted with water and the obtained precipitate was filtered, washed with water, and dried. We obtained 300 mg of (VIIa), mp 220-222° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1500, 1620, 1660, 3420, 3490. PMR spectrum (δ, ppm): 1.19 s (3H, 19-CH_3), 1.48 s (3H, 18-CH_3), 4.10 (1H, 16-H; $J_{16,15} = J_{16,15'} = 7$ Hz), 5.79 s (1H, 4-H), 7.1 s (aromatic protons); $[\alpha]_D^{20}$ +1.91° (C 0.261, CH_3OH). M^+ 362.

17α-Phenyl-17β-methyl-18-nor-androsta-4,13-dien-16α-ol-3-one 16-Acetate (VIIb). A solution of 40 mg of (VIIa) in 1 ml of pyridine and 0.5 ml of Ac_2O was let stand overnight at 20°. After the usual workup we obtained 27 mg of (VIIb), mp 139-140° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1497, 1674, 1735; $[\alpha]_D^{20}$ +48° (C 0.172, $CHCl_3$). PMR spectrum (δ, ppm): 1.20 s (3H, 19-CH_3), 1.56 s and 1.59 s (3H each, 18-CH_3 and 16-OAc), 5.23 (1H, 16-H; $J_{16,15} = J_{16,15'} = 7$ Hz), 5.80 s (1H, 4-H).

CONCLUSIONS

Starting with androst-5-en-3β-ol-17-one, we synthesized 16,17α-epoxy-17β-phenylandrost-4-en-3-one. Cleavage of 17-C—O bond, adjacent to the phenyl ring, occurs during its nucleophilic opening, accompanied by 1,2-migration of the angular 18-CH_3 group.

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TRANSFORMED STEROIDS.

115.* STABILITY OF NITROGEN INVERTOMERS IN STEROIDO[16α,17α-d]-N-METHOXYISOXAZOLIDINE SERIES

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The regio- and stereodirectivity of the 1,3-dioplar cycloaddition of nitronic esters to various mono- and disubstituted dipolarophiles has been studied quite extensively [2-4]. On the basis of much experimental data it has been concluded that the given reaction is strictly regiospecific and that the dipolarophile can approach the dipole from both the exo and endo sides. The competition between the two possible approaches was considered to be a function of the nature of the substituents in the dipolarophile [3]. The cycloaddition products, namely N-methoxyisoxazolidines, have an additional center of asymmetry due to the high inversion barrier of the N atom, which was shown by physicochemical methods. The presence of stereoisomeric pairs, which arise as a result of such hindered inversion, the so-called invertomers, was proved by employing physicochemical emthods, in particular PMR, because of

*See [1] for Communication 114.

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