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Autooxidation of $\Delta^{17(20)}$-20-Hydroxy Derivatives of Steroids. Synthesis of 3β-Acetoxy-17α-hydroperoxy-16α-methylpregn-5-en-20-one and Its Reduction to 17α-Hydroxy Derivative

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Abstract—An efficient procedure was proposed for the synthesis of 3β-acetoxy-17α-hydroperoxy-16α-methylpregn-5-en-20-one. Optimal conditions were found for the combined process including 1,4-addition of methylmagnesium bromide at the Δ^{16}-20-oxo fragment of dehydropregnenolone acetate and autooxidation of resulting bromomagnesium 3β-acetoxy-16α-methylpregna-5,17(20)-dien-20-olate. The subsequent reduction of the 17α-hydroperoxy group and hydrolysis of the 3β-acetoxy group afforded 17α-hydroxy-16α-methyl-substituted dehydropregnenolone acetate and its 3-hydroxy analog in high yield.

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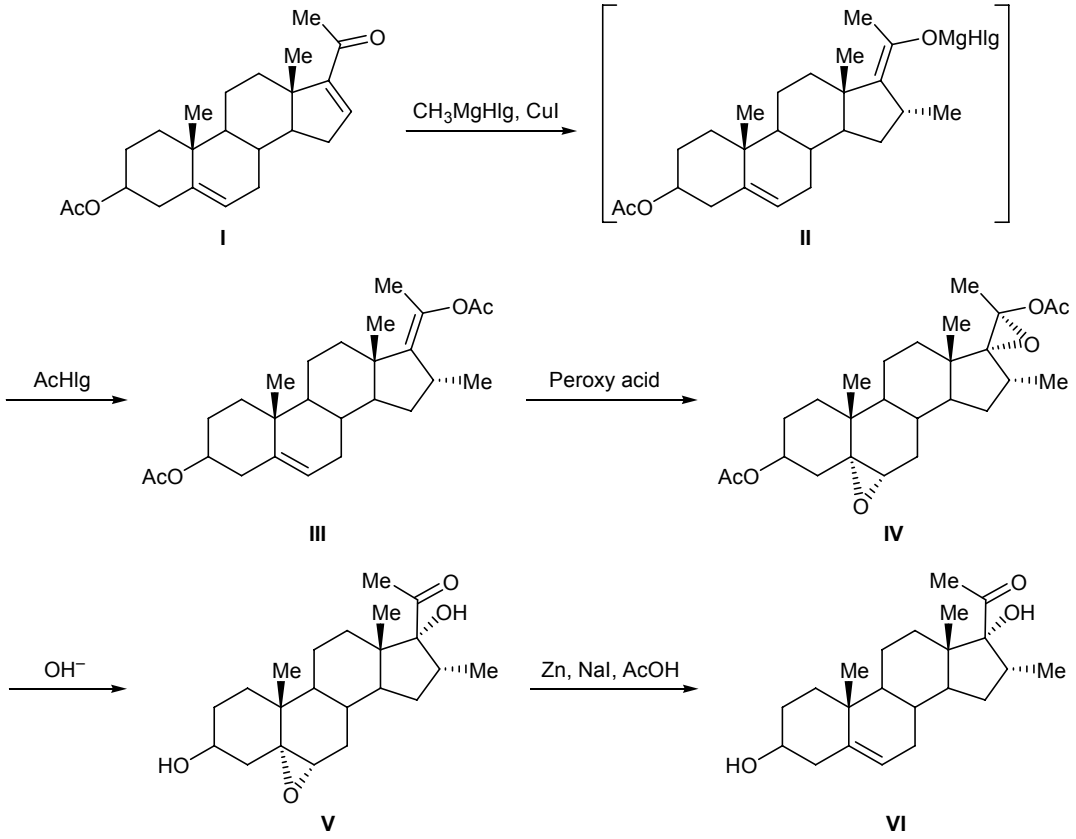
Corticosteroids occupy an important place among synthetic medicines. 16α-Methylcorticoids, e.g., Dexamethasone, Mometasone, Flumetasone, and their derivatives, have found wide application due to their strong anti-inflammatory and antiallergic activity. Such corticosteroids can be synthesized from pregnanes having a Δ^{16}-20-oxo fragment which is necessary for the introduction of 17α-hydroxy and 16α-methyl groups. An example is dehydropregnenolone acetate **I**; it is an important and most preferred intermediate in the synthesis of steroid drugs of the pregnane series. The presence of a Δ^{16}-20-oxo fragment in molecule **I** makes it possible to use it for the preparation of 17α-hydroxy-16α-methylpregnanes without additional modification. Compound **I** is obtained by cleavage of diosgenin, i.e., Δ^{5}-steroidal sapogenin [1]. Diosgenin is isolated on a large scale from renewable vegetable raw material, rhizomes of wild and cultivated plants belonging to the *Dioscoreaceae* R. Brown family, which occur mainly in tropical and subtropical regions, in particular in the Far East (Russia) and South-East Asia. Promising *Dioscoreaceae* species are *D. membranacea* and *D. colletti*; they contain 2.3 and 4.4% of diosgenin, respectively [2].

17α-Hydroxy and 16α-methyl groups are generally introduced in two steps, the first of these being 16α-alkylation. Attachment of a methyl group at the 16α-position of the Δ^{16}-20-oxo fragment in compound **I** is usually performed by 1,4-addition of methylmagnesium halide in the presence of copper(I) chloride [3]. The subsequent 17α-hydroxylation can be performed via direct oxidation according to [4] and by the Gallagher–Krichevsky method [5]. Both these procedures are based on the oxidation of $\Delta^{17(20)}$-20-hydroxy derivative, which is formed as a result of preliminary enolization of the C^{20}=O group. In the first version, enolization occurs in alkaline medium. The resulting $\Delta^{17(20)}$-20-hydroxy derivative is subjected to oxidation with molecular oxygen to obtain 17α-hydroperoxide which is then reduced to 17-hydroxy derivative [6]. In the second version, enolization is promoted by an organic acid (as a rule, *p*-toluenesulfonic acid) in acetic anhydride with simultaneous acetylation of $\Delta^{17(20)}$-20-hydroxy intermediate generated *in situ*. The subsequent oxidation of the $\Delta^{17(20)}$ double bond with a peroxy acid and mild alkaline hydrolysis of 17α,20-epoxide thus formed gave 17α-hydroxy-20-oxo compound.

However, acetylation of enolized 20-oxo group in 16α-methyl steroids is difficult to perform. The reaction is slow, and the yield is poor. 16α-Methyl-16,17-dihydro derivative of **I** undergoes enolization only

Scheme 1.



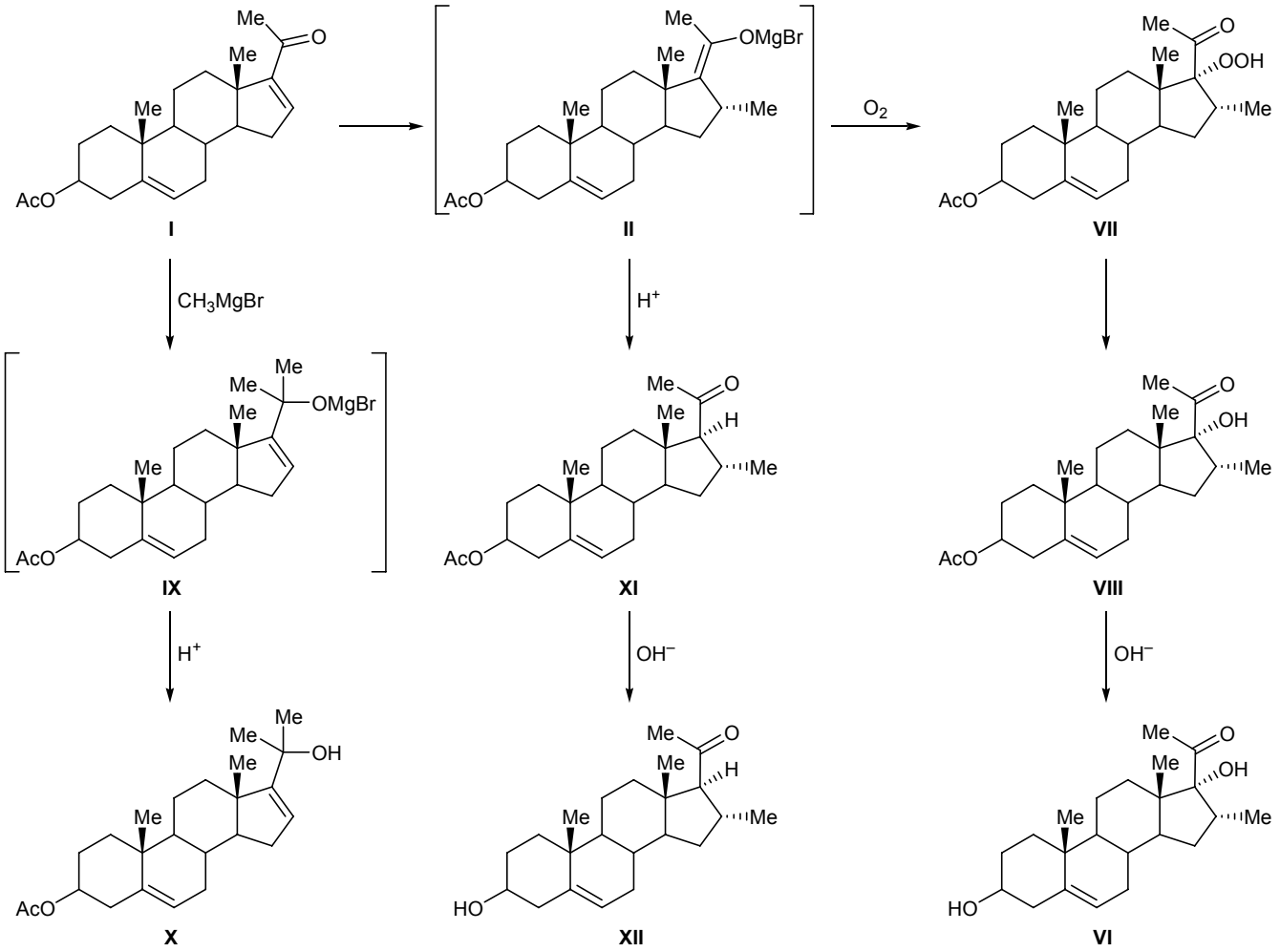
upon prolonged heating of the reaction mixture in acetic anhydride with slow removal of acetic acid by distillation (from 6 [7] to 18 h [8]). The subsequent epoxidation of the C^{17}=C^{20} double bond in 16α-methyl-20-enol acetate with peroxy acid required much longer time than that necessary for the oxidation of analogous enol acetate having no substituent on C^{16} [9]. The reaction was not selective: it also involved other double C=C bonds present in the steroid molecule. Therefore, the C^5=C^6 bond is protected via transformation into, e.g., 5,6-dichloro derivative [10]. In some cases, the C^5=C^6 bond is preliminarily hydrogenated over palladium catalyst to obtain compounds of the 5α series [11]. Nevertheless, despite a number of steps, this procedure was used for a long time for large-scale manufacture of 17α-hydroxy-16α-methylcorticosteroids.

Direct acylation of metal enolates is a modification of the Gallagher–Krichevsky procedure. It includes treatment of enolate **II** with an acylating agent. The latter may be not only carboxylic acid anhydrides and chlorides but also heteroelement halides, e.g., trimethylsilyl chloride [12]. Oxidation of $\Delta^{17(20)}$-20-enol ester **III** with an organic peroxy acid, alkaline hydrolysis of 16α-methyl-17α,20-epoxy ester **IV**, and regeneration of the C^5=C^6 double bond in **V** led to the formation of 17α-hydroxy-16α-methyl derivative **VI** [13, 14] (Scheme 1).

There are a few published data on the introduction of 17α-hydroxy and 16α-methyl groups into Δ^{16}-20-oxo steroids via reduction of 17α-hydroperoxy derivatives obtained by autooxidation with molecular oxygen of halomagnesium 16α-methyl-$\Delta^{17(20)}$-20-olate [15–17]. However, this rare procedure (unlike those described above) almost was not used in practice because of poor yield of 17α-hydroperoxy compounds and low reproducibility.

In the present article we report on the synthesis of 3β-acetoxy-17α-hydroperoxy-16α-methylpregn-5-en-20-one (**VII**) from dehydropregnenolone acetate **I**, transformation of **VII** into 17α-hydroxy derivatives **VIII** and **VI**, and on the effect of the Grignard reaction conditions on the efficiency of subsequent autooxidation (Scheme 2). The reaction of Δ^{16}-pregnan-20-one with methylmagnesium bromide is usually carried out in 9–10-fold amount (with respect to the substrate) of tetrahydrofuran in the presence of 9.2 wt % of copper chloride at –15 to 5°C in a stream of an inert gas using

Scheme 2.



2.5–3 mole of the Grignard compound per mole of the substrate [14, 17]. Our studies on the conjugate addition reaction were performed under the same conditions.

In order to obtain compound **XI** which was necessary as reference sample to estimate the purity of the autooxidation product of compound **VII**, magnesium enolate **II** was subjected to protolysis. It is known that protolysis of halomagnesium 16α-methyl-$\Delta^{17(20)}$-20-olate obtained in tetrahydrofuran gives different results, depending on the conditions. Addition to the reaction mixture of a dilute mineral acid (sulfuric [15] or hydrochloric [18]) or methanol [19] leads to protonation of the C^{17}-carbanion with formation of 17-deoxy-16α-methyl-20-oxo steroids in 75–95% yield. However, when the same reagents were used in the synthesis of compound **XI**, the reaction was always accompanied by formation of 17α-hydroperoxy derivative **VII** as impurity. Addition of methanol to the reaction mixture containing intermediate **II** on exposure to air (nitrogen was not passed through the reaction mixture) resulted in the formation of 10–15% of hydroperoxide **VII**. We succeeded in isolating 17-deoxy compound **XI** in 90–95% yield only when methanol was slowly added to the reaction mixture under a strong stream of nitrogen. Analogous result was obtained using a 10% aqueous solution of ammonium chloride instead of methanol.

Tetrahydrofuran is known to be the most preferable solvent for 1,4-addition of Grignard compounds to Δ^{16}-pregnan-20-one derivatives. However, the subsequent autooxidation gave 17-hydroperoxy compound in a yield not exceeding 50% [16, 20]. According to published data [17], 17α-hydroperoxide can be obtained in up to 86% yield by carrying out autooxidation under heterogeneous conditions, by adding diethyl ether to the reaction mixture after completion of the Grignard reaction. We examined the effect of solvent

Table 1. Composition (%) of the Grignard reaction and autooxidation products formed in different solvents [TLC: Sorbfil (Russia), sample amount 10 μg, development with a 5% solution of vanillin in 10% aqueous perchloric acid]

Solvent	Compound **X** (1,2-addition)	Compound **XI** (1,4-addition, protolysis)	Compound **VII** (1,4-addition, autooxidation, hydrolysis)
Tetrahydrofuran	–	50	50
Pyridine	–	80	20
Acetonitrile	–	80	20
1,4-Dioxane	30	55	15
Diethyl ether	30	20	50
Methylene chloride	30	–	70
Benzene	95	–	5
Toluene	95	–	5

nature in one-pot synthesis of 17α-hydroperoxy-16α-methyl derivative **VII** from compound **I** with a view to find optimal conditions ensuring the required selectivity of both 1,4-addition and subsequent autooxidation. As solvents we selected those characterized by different miscibilities with water (Table 1), and the autooxidation step was carried out in both homogeneous and heterogeneous media. If a water-miscible solvent was used, a solid separated from the reaction mixture and was filtered off. When the reaction was carried out in a water-immiscible solvent, the aqueous phase was extracted with that solvent, and the products were analyzed by thin-layer chromatography. The results are collected in Table 1.

As might be expected, the alkylation in tetrahydrofuran occurred at the C^{16} atom. However, the subsequent autooxidation of bromomagnesium 16α-methyl-$\Delta^{17(20)}$-20-olate **II** afforded no more than 50% of hydroperoxide **VII**. The use of pyridine which readily dissolves copper chloride to form coordination compounds [21, 22] improved the yield of the 1,4-addition product up to 80%, but hydroperoxide **VII** was formed in a poor yield (about 20%). Apart from pyridine, copper chloride is readily soluble in acetonitrile (13.4 g of CuCl in 100 g of the solvent) [23]. On the other hand, acetonitrile itself is capable of reacting with alkylmagnesium halides, so that it is not used as solvent in Grignard reactions. Our attempts to perform the reaction in acetonitrile gave unexpected results. The reaction at a temperature not exceeding 5°C involved predominant addition of methylmagnesium bromide at the Δ^{16}-20-oxo fragment of the initial steroid with selective formation of 1,4-addition product, but the subsequent autooxidation gave no more than 20% of hydroperoxide **VII**. Raising the temperature to 10°C sharply reduced the selectivity of the alkylation step (the reaction occurred at the α,β-unsaturated carbonyl fragment of the substrate or at the cyano group of the solvent), a considerable heat evolution was observed, and double amount of the Grignard compound was necessary to complete conjugate addition. At 20–22°C the main process was alkylation of acetonitrile. Thus we have found that selective alkylation of the Δ^{16}-20-oxo steroid in acetonitrile is possible at ≤5°.

The use of dioxane as solvent for the conjugate addition reaction did not ensure acceptable selectivity, and the reaction mixture contained 30% of 1,2-addition product **X**. Presumably, the reason is very poor solubility of copper chloride in that solvent. As in the above cases, the subsequent autooxidation gave only 15% of compound **VII**.

The data in Table 1 show that, on the one hand, aromatic hydrocarbons, ethers, and methylene chloride are inappropriate solvents from the viewpoint of selectivity in the conjugate addition of methylmagnesium bromide; on the other hand, these solvents favor complete autooxidation of the 1,4-addition product (except for diethyl ether). In the reactions carried out in aromatic hydrocarbons, the main process was 1,2-addition of the Grignard compound, whereas in the reactions in diethyl ether or methylene chloride the fraction of compound **X** in the reaction mixture did not exceed 30%. The subsequent autooxidation of **II** gave hydroperoxide **VII**. The autooxidation in methylene chloride was more effective, and the yield of **VII** reached 70%, while no compound **XI** was present. Methylene chloride has long been used as solvent in Grignard syntheses [24], but its analogous application in the chemistry of Δ^{16}-20-oxo steroids was not reported previously.

Thus our results indicated that the autooxidation process in heterogeneous medium is more successful,

Table 2. Selectivity and yields of 17α-hydroperoxide **VII** in the autooxidation process

Solvent[a]	Selectivity for compound **VII**, %		Yield of **VII**, mol %	
	a	*b*	*a*	*b*
THF–diethyl ether	75	50	68	–
THF–CH_2Cl_2	80	85	–	–
THF–ethyl acetate	75	–	65	–
THF–CCl_4	80	–	65	–
THF–benzene	90	90	85	88
THF–toluene	90	90	80	75
Pyridine–benzene	–	90	–	40
Acetonitrile–benzene	–	90	–	85

[a] Solvent ratio 0.7 : 1 (by volume).

which is very consistent with published data [17]. Therefore, both versions of the combined process were compared with a view to optimize conditions for the synthesis of compound **VII**. In the first case (method *a*), co-solvent (diluent) was added only at the autooxidation step (as in [17]); i.e., a component immiscible with water was added to the reaction mixture after the conjugate addition was complete; in the second case (method *b*), the alkylation step was performed in a mixture of solvents ensuring formation of heterogeneous medium in the subsequent autooxidation process. The selectivity in the formation of compound **VII** was estimated on the basis of the TLC data. The results are collected in Table 2.

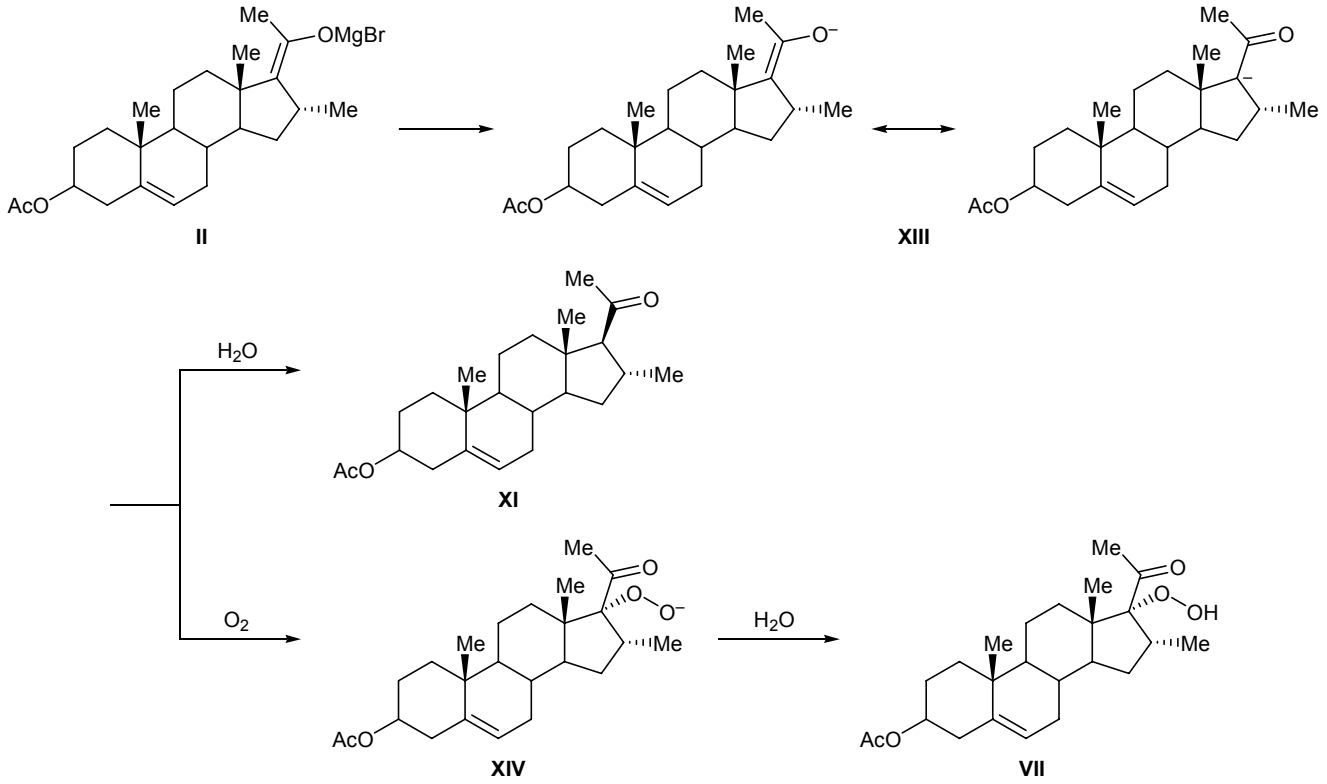
Diethyl ether and methylene chloride as diluents ensured comparable results. Addition of these solvents to the reaction mixture after completion of the Grignard reaction favored autooxidation. However, despite high selectivity for compound **VII** with the use of methylene chloride (80%, according to the TLC data), we failed to isolate the product as individual substance. Compound **VII** turned out to be very unstable in methylene chloride. The IR spectrum of a 1% solution of **VII** in CH_2Cl_2 indicated appreciable decomposition of this compound in 6 min. After 1 h at room temperature, compound **VII** underwent complete decomposition with formation of a complex mixture of products. Thus any water-immiscible solvent may be used as diluent for selective autooxidation (Table 2), but aromatic hydrocarbons are preferred.

The suitability of solvent mixtures for the 1,4-addition of Grignard compound was examined under analogous conditions. Binary solvent mixtures with a volume ratio of 0.5 : 1 to 1 : 1 were tried. The reaction in THF–diethyl ether, as in pure diethyl ether, was accompanied by formation of up to 30% of 1,2-addition product **X** and 20% of deoxy derivative **XI** together with target hydroperoxide **VII**. The best result was obtained using mixtures of THF with aromatic hydrocarbons: the selectivity for hydroperoxy compound **VII** attained 90%.

The Grignard reaction in acetonitrile–benzene or pyridine–benzene was characterized by regioselective alkylation at the C^{16} atom and fairly complete autooxidation (Table 2). However, in the second case, evaporation of the solution was accompanied by vigorous decomposition of hydroperoxide **VII**, so that the yield of **VII** did not exceed 40%. It is known that hydroperoxide in solution readily undergo decomposition at elevated temperature [25] and that copper salts are capable of not only catalyzing conjugate addition of Grignard compounds and initiating autooxidation (as low concentration of copper salt as ~10^{-5} M is sufficient to appreciably accelerate this process) [26] but also accelerating decomposition of hydroperoxides; the rate of decomposition increases in parallel with the concentration of copper salt [27, 28]. Therefore, fast removal of the catalyst from solution is necessary, which may be attained by washing. Insofar as the equilibrium concentration of pyridine in benzene layer is higher than in aqueous layer [29], removal of copper ions in such a way may be difficult, which may be a factor responsible for decomposition of hydroperoxide **VII** upon evaporation.

Thus the results of our study led us to conclude that selective autooxidation requires a heterogeneous medium consisting of an aqueous layer and organic layer containing enolate **II**. Hydrolysis of enolate **II** is likely to involve formation of intermediate conjugated anion **XIII**. Depending on the hydrolysis conditions,

Scheme 3.



protonation of **XIII** at the C^{17} atom to give 16α-methyl-17-deoxy derivative **XI** or autooxidation according to generally accepted mechanism [30] with formation of hydroperoxide **VII** is possible (Scheme 3). The low yield of the autooxidation product in homogeneous medium may be rationalized assuming that the rate of protonation is comparable with the rate of autooxidation. Thus, the solvent nature is an important factor affecting the selectivity of both conjugate addition of Grignard compound and subsequent autooxidation.

The structure of 3β-acetoxy-17α-hydroperoxy-16α-methylpregn-5-en-20-one (**VII**) was confirmed by its elemental composition and spectral data (an analytical sample was prepared by recrystallization from ethyl acetate). The IR spectrum of **VII** recorded from a 1% solution in methylene chloride contained a strong absorption band at 3530 cm^{-1}, which is typical of O–H stretching vibrations in OOH group [31] (the corresponding frequency of OH stretching vibrations in the spectrum of **VIII** is 3610 cm^{-1}). In the ^1H NMR spectrum of **VII** in $CDCl_3$ we observed a signal at δ 8.26 ppm, which was assigned to the OOH proton.

17α-Hydroperoxypregnanes can readily be reduced to the corresponding 17α-hydroxy derivatives by the action of zinc dust in acetic acid [17, 32] or via catalytic hydrogenation over Pd/C [17, 33]. Sodium thiosulfate and potassium or sodium iodide in acetic acid or aliphatic ketone (e.g., in acetone) can also be used as reducing agent. Hydroperoxide **VII** is thus converted to compound **VIII** in high yield (90% and more). Using zinc dust in acetic acid, potassium iodide in acetone, and sodium thiosulfate in acetone–methanol (1:1) we succeeded in obtaining compound **VIII** in 95–98% yield. The crude product isolated in the reduction of **VII** with sodium thiosulfate contained 2% of sulfur (according to the elemental analysis data), which may be regarded as a considerable disadvantage of this procedure.

EXPERIMENTAL

Analysis of compounds and monitoring of chemical processes by thin-layer chromatography were performed using Sorbfil PTSKh UV-254 plates (Russia) with hexane–acetone (10:3) and heptane–ethyl acetate–isopropyl alcohol (5:4:1) as eluents; spots were detected by treatment with a 1% solution of vanillin in 10% aqueous perchloric acid. The optical rotations $[\alpha]_D^{20}$ were determined on an FEP-02 polarimeter (USSR) from solutions in chloroform (c = 1). The IR spectra were recorded on a Perkin–Elmer 599 spectrometer. The mass spectra (electron impact, 50 eV) were obtained on a Varian MAT-112 instrument

(Germany). The ^{1}H NMR spectra were measured on a Varian XL-200 spectrometer (USA) at 200 MHz using $CDCl_3$ as solvent and TMS as internal reference.

17α-Hydroperoxy-16α-methyl-20-oxopregn-5-en-3β-yl acetate (VII). *a*. A suspension of 10 g of compound **I** and 0.25 g* of copper(I) chloride in 140 ml of THF was cooled to –10 to 0°C, and 60 ml of a 1.68 N solution of methylmagnesium bromide (3.6 equiv) in THF was slowly (over a period of ~15 min) added under stirring in a stream of an inert gas. The mixture was kept for 20 min at that temperature, and 200 ml of anhydrous benzene was slowly added, maintaining the temperature below –5°C. The mixture was stirred for 20 min and poured into 0.5 l of a 20% solution of ammonium chloride, cooled to 0°C, under vigorous stirring. The mixture was vigorously stirred for 20 min at 0–5°C, the organic layer was separated and washed with a 20% aqueous solution of ammonium chloride and water, the solvent was removed under reduced pressure at a temperature not exceeding ≤40°C, the residue was ground with hexane, and the precipitate was filtered off and washed with hexane on a filter. Yield 9.64 g (85%), mp 156°C (decomp.), 169°C (from ethyl acetate; decomp.), $[\alpha]_D^{20}$ = –35.9°. IR spectrum ν, cm^{-1}: in CH_2Cl_2: 3530 (OOH); in mineral oil: 3350 (OOH), 1740 (C=O), 1685 (C=O), 1240 (C–O). ^{1}H NMR spectrum, δ, ppm: 0.86 s (3H, 18-CH_3), 1.16 s (3H, 19-CH_3), 1.32 d (3H, 16-CH_3, J = 7.3 Hz), 2.19 s (3H, $COCH_3$), 2.44 s (3H, 21-CH_3), 4.70 m (1H, 3-H), 5.50 (1H, 6-H), 8.26 s (1H, OOH). Mass spectrum: m/z 404 $[M]^+$. Found, %: C 71.47; H 8.80. $C_{24}H_{36}O_5$. Calculated, %: C 71.25; H 8.96.

b. A 1.68 N solution of methylmagnesium bromide in tetrahydrofuran, 60 ml, was added under vigorous stirring at 0–5°C in a stream of an inert gas to a solution of 10 g of compound **I** in a mixture of 140 ml of THF and 200 ml of benzene containing 0.25 g of copper(I) chloride. After 20 min, the mixture was poured under vigorous stirring at 0–2°C into 500 ml of a 20% aqueous solution of ammonium chloride, kept for 20 min, and then treated as described above in *a*. Yield of **VII** 9.98 g (88%), mp 157.5°C (decomp.).

17α-Hydroxy-16α-methyl-20-oxopregn-5-en-3β-yl acetate (VIII). *a*. Zinc dust, 2.5 g, was added to a solution of 5 g of compound **VII** in 35 ml of glacial acetic acid. The mixture was stirred for 1 h at room temperature and poured into 300 ml of water, the precipitate was filtered off, washed on a filter with water, and dissolved in methanol–methylene chloride (1:1), and the solution was treated with activated charcoal and evaporated to dryness under reduced pressure. The residue was ground with water, and the precipitate was filtered off, washed on a filter with 1% hydrochloric acid and with water until neutral washings, and dried. Yield 4.56 g (95%), mp 204–206°C; published data [34]: mp 203–205°C.

b. Potassium iodide, 3.2 g, was added to a suspension of 8.2 g of compound **VII** in 160 ml of acetone. The mixture was stirred for 1 h at room temperature, a 10% solution of Na_2SO_3 was added (until the mixture turned colorless), and 160 ml of water was then added. The precipitate was filtered off and washed with water. Yield 7.72 g (98%), mp 205–206°C.

3β,17α-Dihydroxy-16α-methylpregn-5-en-20-one (VI). Potassium hydroxide, 3.5 g, was added to a suspension of 10 g of compound **VIII** in 330 ml of methanol under stirring in a stream of an inert gas. The mixture was kept for 1 h at room temperature, neutralized with acetic acid, and concentrated under reduced pressure. The precipitate was filtered off and washed with water. Yield 7.49 g (84%), mp 242–242.5°C; published data [34]: mp 245–250°C; $[\alpha]_D^{20}$ = –70° (c = 0.5, pyridine).

16α-Methyl-20-oxopregn-5-en-3β-yl acetate (XI). A suspension of 10 g of compound **I** and 0.92 g of copper(I) chloride in 92 ml of THF was cooled to –10 to 0°C, and 60 ml of a 1.68 N solution of methylmagnesium bromide in THF was added under stirring in a stream of an inert gas. The mixture was kept for 20 min at that temperature, 50 ml of anhydrous methanol was slowly added, maintaining the temperature below –5°C, and the mixture was stirred for 15 min and diluted with 200 ml of water. The resulting suspension was stirred for 2 h at 5–10°C, and the precipitate was filtered off and washed with aqueous methanol. Yield 9.9 g (95%), mp 183–185°C (from diethyl ether); published data [6]: mp 182–184°C.

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* Minimal amount necessary for the 1,4-addition reaction.

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