STEROIDS

XXXVI. The Opening of an Epoxide Ring with Organometallic Compounds

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The opening of an epoxide ring with organometallic compounds (Grignard reagents or organolithium compounds) is is a well-known synthetic method for obtaining α-alkyl substituted alcohols [1].

Thus, the opening of the epoxide ring of pregnane derivatives leads to the formation of 17α-hydroxy-16β-methyl derivatives [2, 3] and may be a promising route for the synthesis of 16β-substituted analogs of coticosteroid hormones (for example, betasone–16β-methyl-9α-fluoroprednisolone). However, there are cases where such reactions proceed anomalously [1, 4, 5].

We studied the effect of methyllithium on the 3, 20-diketal of 16α, 17α-epoxy-Δ^5-pregnene-3, 20-dione (I), described in a previous paper [6] as well as on the 3-acetate of the 20-ketal of 16α, 17α, epoxy-Δ^5-pregnene-3β-ol-20-one (II) [7, 8].

It was found that the products of the normal opening of the epoxy ring with methyllithium, i.e., 17α-hydroxy-16β-methyl-substituted pregnenes, were not present in the reaction mixture.

When compound (I) was used, the 3, 20-diketal of 16-methyl-$\Delta^{5,16}$-pregnadiene-3, 20-dione (III) and the 3, 20-diketal of $\Delta^{5,15}$-pregnadiene-17α-ol-3, 20-dione (IV) were found, which on deketalization, yielded 16-methyl-$\Delta^{4,16}$-pregnadiene-3, 20-dione (V) and $\Delta^{4,15}$-pregnadiene-17α-ol-3, 20-dione (VIII).

When compound (II) was used, 16-methyl-$\Delta^{5,16}$-pregnadiene-3β-ol-20-one (VI) and $\Delta^{5,15}$-pregnadiene-3β, 17α-diol-20-one (IX) were isolated from the reaction mixture after deketalization.

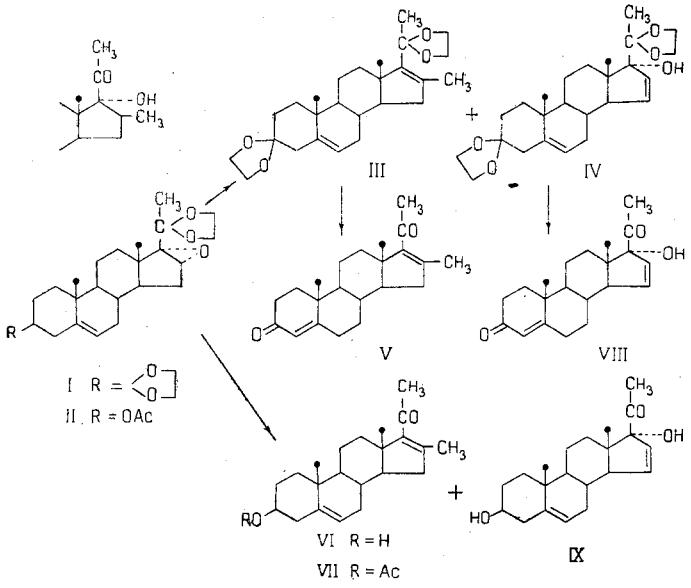
The structure of these compounds was established on the basis of elementary analysis and the IR and NMRspectra spectra. Thus, in the NMR spectra of compounds (III) and (V)–(VII) one observes singlets with intensities corresponding to 3 proton units with chemical shifts of 1.8 ppm (III), 1.99 ppm (V), 2.01 ppm (VI), and 2.03 ppm (VII), which indicates the presence of a methyl group on a double bond in each molecule (table). Absorption bands at 1660–1655 and 1600–1620 cm^{-1}, which are characteristic for a conjugated —C=C—C=O system, are present in the IR spectra of compounds (V)–(VII).

Compound	Chemical shifts, ppm**										
	$H_{C_{16}}$	$H_{C_{15}}$	$H_{C_{21}}$	$H_{C_{18}}$	$H_{C_{19}}$	H_{C_6}	H_{C_4}	H_{C_3}	H_{C_2}	H_{OH}	H_{CH_3CO}
III	1.8	—	1.47	0.89	1.04	5.30	—	—	3.9	—	—
IV	6.02 doublet	5.75 quartet	1.35	0.90	1.03	5.35	—	—	3.9	—	—
V	1.99	—	2.24	0.95	1.15	—	5.68	—	—	—	—
VI	2.01	—	2.26	0.91	0.98	5.35	—	3.48	—	2.59	—
VII	2.03	—	2.29	0.98	1.03	5.38	—	4.59	—	—	2.03
VIII	6.23 doublet	6.03 quartet	2.20	0.75	1.15	—	5.70	—	—	—	—
IX*	6.06 doublet	6.31 quartet	2.37	0.82	1.00	5.31	—	3.71	—	4.85	—

*NMR spectrum taken in deuteropyridine.

**L. A. Alekseeva and Professor Yu. N. Sheinker participated in the discussion of the NMR spectra.

Absorption frequencies in the 3600 cm^{-1} and 1700–1600 cm^{-1} regions are completely absent in the IR spectrum of diketal (III). Consequently, compounds (III) and (V)–(VII) have the structure of the 16-methyl-Δ^{16}-dehydro derivatives of the corresponding steroids.


III
IV
V
VIII
I R =
II R = OAc
VI R = H
VII R = Ac
IX

It is well known that 16-methyl-Δ^{16}-dehydrosteroids are readily converted into the corresponding 16-methylene-17α-hydroxy derivatives [10]. Compound (VI) was therefore converted into 16-methyl-16α,17α-epoxy-Δ^5-pregnene-3β-ol-20-one, from which the 3β,17α-diacetate of 16-methylene-Δ^5-pregnene-3β,17α-diol-20-one was obtained.

Absorption bands characteristic for OH groups (3535–3380 cm^{-1}) and specific narrow bands at 3080 cm^{-1} (ν C=C—H), which unambiguously indicate the appearance of an additional double bond in the molecule [11], were observed in the IR spectra of compounds (IV), (VIII), and (IX) (previously erroneously assigned the structure of 16β-methyl-Δ^5-pregnene-3β,17α-diol-20-one [9]). The position of this double bond can be judged from the NMR spectra. Two groups of signals in the vinyl proton region, each with intensity of 1 proton unit, are observed in the spectra of compounds (IV), (VIII), and (IX). The splitting of these signals is in good agreement with their assignment to the protons on the C_{15}–C_{16} double bond. Thus, for example, a doublet at 6.06 ppm with J = 7 Hz (proton on C_{16}, splitting due to interaction with the proton on C_{15}) and a quartet at 6.31 ppm with J = 7 Hz and J = 4 Hz (proton on C_{15}, splitting due to interaction with the protons on C_{16} and C_{14}) are found for compound (IX). It should also be added that the freshly formed hydroxy group in compounds (IV), (VIII), and (IX) is not acetylated under mild conditions. Thus, compounds (IV), (VIII), and (IX) are the 17α-hydroxy-Δ^{15}-dehydro derivatives of the corresponding steroids. After we had completed our investigation, a communication regarding the synthesis of 17α-hydroxy-Δ^{15}-dehydro derivatives of steroids appeared. The constants we obtained for compounds (VIII) and (IX) completely agreed with those described in this paper [12].

The occurrence of two competing reactions (opening of the epoxide ring with introduction of a methyl group into the steroid molecule and intramolecular isomerization of the epoxide to form an allyl alcohol) with no nucleophilic addition of methyllithium to the epoxide ring is due to the fact that methyllithium is a strong base and a weak nucleophilic agent.

The opening of the epoxide ring of acyclic and alicyclic epoxides by the action of organolithium compounds was recently studied by Cope and co-workers [13, 14] and Crandall and co-workers [15–18]. Two mechanisms for the isomerization were proposed, each of which is realized as a function of the nature of the epoxide taken for the reaction (the proofs were based on the use of deuterium-labeled compounds) [13, 14]. According to their data, two reaction mechanisms can be proposed for our case: in the first, it is assumed that a proton is removed from C_{15} under the action of a strong base with subsequent opening of the epoxide ring by the carbanion formed (carbanion mechanism or β-elimination); in the second, it is assumed that a proton is removed from the epoxide ring (α-elimination) resulting in a carbene with a subsequent 1,2-hydride shift [15, 16] (carbenoid mechanism or α-elimination)].

As far as the formation of 16-methyl-Δ^{16}-dehydro derivatives of steroids is concerned, it is not possible to assume their formation from the corresponding 17α-hydroxy-16β-methyl derivatives, since the latter are resistant to dehydration under the reaction conditions [19]. According to Crandall [17, 18], similar compounds are obtained through α-elimination of a proton from C_{16} to form a carbene, the addition of a second molecule of methyllithium, and subsequent splitting out of a lithium oxide molecule. One cannot exclude the carbenoid mechanism which leads to the formation of 16-oxo derivatives through reaction of the ketone with methyllithium and dehydration to the 16-methyl-Δ^{16}-dehydro derivative [17]. We cannot judge the reaction mechanisms with confidence since we do not have the experimental data at our disposal.

The opening of the epoxide ring makes it possible to obtain 16-methyl-Δ^{16}-dehydro derivatives of pregnane [19, 20] by a comparatively simple route, in which, by regulating the experimental conditions, we can increase the yield of these compounds. Thus, carrying out the reaction in tetrahydrofuran with the addition of the epoxides (I) and (II) to a methyllithium solution enables one to direct the reaction toward the predominant formation of compounds (V) and (VI). In addition, Δ^{15}-unsaturated derivatives of the 17α-hydroxypregnane series can be synthesized by this method [12].

EXPERIMENTAL

The instruments and conditions for the spectral and chromatographic analysis are described in [6]. The analytical results for all the compounds were in good agreement with the calculated values.

Reaction of methyllithium with the 3,20-diketal of 16α,17α-epoxy-Δ^5-pregnene-3,20-dione [1]. A solution of methyllithium prepared from 1.1 g of metallic lithium, 4.4 ml (10 g) of methyl iodide, and 70 ml of dry ether [21] was added to a solution of 0.84 g of (I) in 50 ml of dry benzene. The reaction mixture was heated to boiling, the solvent was distilled off until the temperature of the reaction mixture reached 70° C, and the mixture was boiled at this

temperature for 12 hr. The mixture was then cooled to 0° C, 30 ml of water was added, the benzene layer was removed, and the product was extracted from the aqueous layer with benzene. The combined benzene extracts were washed with water, dried, and evaporated to dryness. Acetone (70 ml) was added to 0.8 g of the crystalline residue, the suspension was boiled, and the insoluble residue was filtered off and washed with acetone. The 3,20-diketal of $\Delta^{5,15}$-pregnadiene-17α-ol-3,20-dione (IV) (0.3 g) was obtained with mp 246–248° C (decomp., from benzene), $[\alpha]_D$ −101° (chloroform), and R_f 0.65.

The mother-liquor was evaporated, and the residue was dissolved in benzene and chromatographed on a layer of silica gel (d = 3 cm, h = 4 cm). Benzene eluted 0.32 g of a substance which, after recrystallization from acetone, gave 0.21 g of the 3,20-diketal of 16-methyl-$\Delta^{5,16}$-pregnadiene-3,20-dione (III) with mp 207–210° C (from acetone), $[\alpha]_D$ −64° (chloroform), and R_f 0.83. Methylene chloride eluted 0.16 g of (I) with mp 178–180° C. The sample did not depress the melting point of an authentic sample.

Reaction of methyllithium with the 3-acetate of the 20-ketal of 16α,17α-epoxy-Δ^5-pregnene-3β-ol-20-one (II). A solution of 4.5 g of II in 145 ml of dry tetrahydrofuran was added during 15 min with stirring under nitrogen to an ether solution of methyllithium prepared from 7.5 g of metallic lithium and 35 ml of methyl iodide in 180 ml of absolute ether. The reaction mixture was boiled for 30 min, cooled to 0° C, and 200 ml of water was added. The ether-tetrahydrofuran layer was removed, and the product was extracted from the aqueous layer with ether. The combined extracts were washed with water, dried, and evaporated to dryness. The dry residue (4.05 g) was dissolved in 117 ml of methanol and added to a solution of 24 ml of 1 N H_2SO_4, and the mixture was boiled for 0.5 hr. The reaction mixture was cooled to 0° C, and the precipitate was filtered off and washed with water to give 3.16 g of (VI) (89%) [22] with mp 195–197° C (from methanol), $[\alpha]_D$ − 89° (ethanol) and R_f 0.53. The acetate of (VI) [compound (VII)] had mp 176–177° C, $[\alpha]_D$ − 85° (ethanol), and R_f 0.85.

The steroid was extracted with methylene chloride from the water–methanol mother liquor after removal of (VI) and the extract was evaporated to dryness to give 0.12 g of an oil which was treated with methylene chloride. The methylene-chloride-insoluble substance was recrystallized from ethyl acetate to give (IX) [12] with mp 263–264° C, $[\alpha]_D$ −168° (tetrahydrofuran), and R_f 0.36.

16-Methyl-$\Delta^{4,16}$-pregnadiene-3,20-dione (V) [23]. Compound III, 0.67 g, was boiled with 20 ml of 80% aqueous acetic acid for 10 min. The solvent was distilled off to dryness and the residue was recrystallized from aqueous acetone and aqueous methanol to give (V) with mp 164–166° C, $[\alpha]_D$ +92° (chloroform), and R_f 0.55.

$\Delta^{4,15}$-Pregnadiene-17α-ol-3,20-dione (VIII) [12]. Compound IV, 0.48 g, was boiled for 10 min with 20 ml of 85% aqueous acetic acid. The solvent was distilled off to dryness and the residue was recrystallized from ethyl acetate and 70% aqueous alcohol to give 0.2 g of (VIII) with mp 222–226° C (decomp.) and R_f 0.32.

CONCLUSIONS

The opening of the epoxide ring of the 3,20-diketal of 16α,17α-epoxy-Δ^5-pregnene-3,20-dione and of the acetate of the 20-ketal of 16α,17α-epoxy-Δ^5-pregnene-3β-ol-20-one with methyllithium has been studied. It was found that no products of the nucleophilic addition of methyllithium to the epoxide ring are formed, and after deketalization, 16-methyl-$\Delta^{4,16}$-pregnadiene-3,20-dione, $\Delta^{4,15}$-pregnadiene-17α-ol-3,20-dione, 16-methyl-$\Delta^{5,16}$-pregnadiene-3β-ol-20-one, and $\Delta^{5,15}$-pregnadiene-3β,17α-diol-20-one were isolated. The formation of the latter is due to alkali-catalyzed opening of the epoxide ring in the presence of the strong base, that methyllithium is.

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