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TRANSFORMED STEROIDS—65[1]

MECHANISM OF THE REARRANGEMENT OF STEROID OXIRANES BY TREATMENT WITH GRIGNARD REAGENTS

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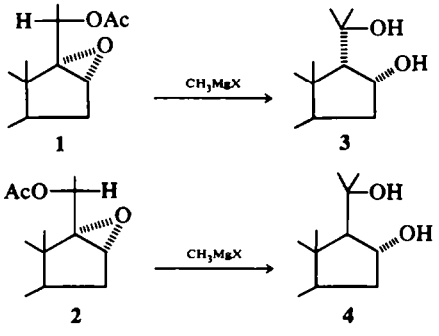
Abstract—Rearrangement of steroid acetoxy–epoxides under the action of MeMgX was studied with the use of deuterated analogs, epimeric at C-20 (20-deutero-20-acetoxy-16α,17α-epoxysteroids). 3β,16α,20-Trihydroxy-20-methylpregnenes resulting in this case contained all the deuterium. Thus this rearrangement is proved to involve a hydride shift. Interaction of a 16α-acetoxy-17α,20α-epoxysteroid with MeMgX does not lead to above compounds. This fact suggests the mechanism of this novel rearrangement as proceeding via the formation of chelate complex with the participation of the carbonyl oxygen atom of the acetoxy-group and oxygen atom of the oxide ring followed by intramolecular 20→17 hydride shift. Some stereochemical aspects of this reaction are discussed.

Some years ago Akhrem and Ilyukhina reported an atypical course of Grignard reaction for 16α,17α-epoxypregn-5-en-3β,20-diol 3,20-diacetates **1** and **2** resulting in 3,16α,20-trihydroxy-20-methylpregnenes **3** and **4** respectively.[2,3] A molecular rearrangement was suggested, which involved complete inversion of the side chain configuration at C-17, or complete retention, as apparently determined by the stereochemistry at C-20.[4,5]

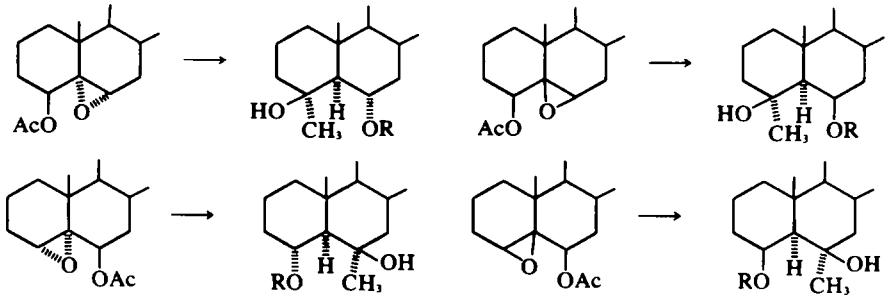


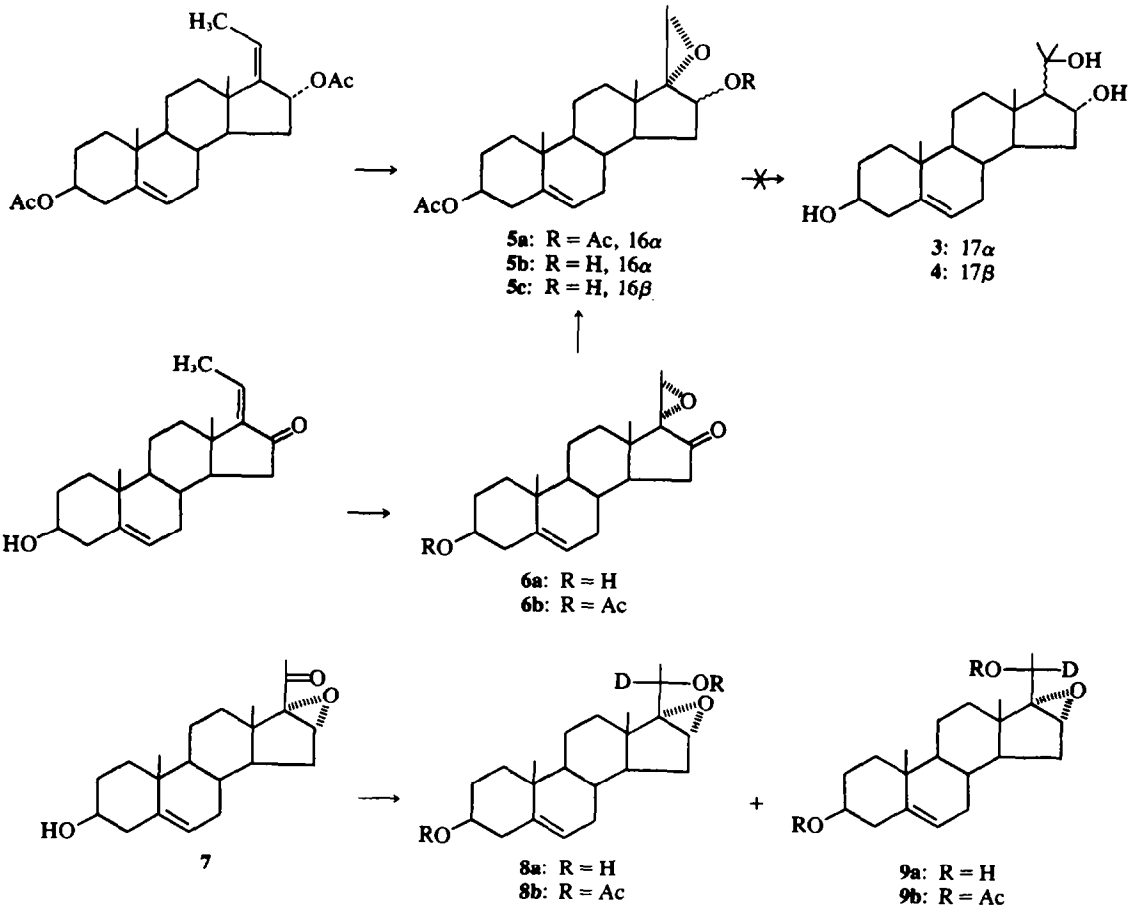
The general character of the rearrangement was later confirmed by Bull[6] with isomeric 4-acetoxy-5,6- and 6-acetoxy-4,5-epoxysteroids:

The mechanism could not proceed via the well-known isomerization of α-oxides to ketones[7,8] since the alkyl from the Grignard reagent added not to the oxide ring carbon, but to the next carbon atom, bearing the acetoxy group. An alternative reaction route involved epoxy group migration,[4,9] and looked quite reasonable, apart from the fact that the side chain inversion in **1** was somewhat unexpected. We prepared a 3,16-diacetate of 17α,20α-epoxypregn-5-en-3β,16α-diol(**5a**) according to the Scheme given below, and treated it with CH_3MgI. However we did not detect any **3** or **4** in the reaction mixture.

Further we reduced 16α,17α-epoxypregn-5-en-3β-ol-20-one(**7**) with $NaBD_4$ to obtain an epimeric mixture of 20-hydroxy-20-deuteroxy compounds. From this mixture 20β-deutero-16α,17α-epoxypregn-5-en-3β,20α-diol (**8a**) and 20α-deutero-16α,17α-epoxypregn-5-en-3β,20β-diol (**9a**) were isolated by fractional crystallization. It is noteworthy that reduction with $NaBD_4$ somewhat favours (**9a**) in comparison with the results reported for $NaBH_4$.[4]

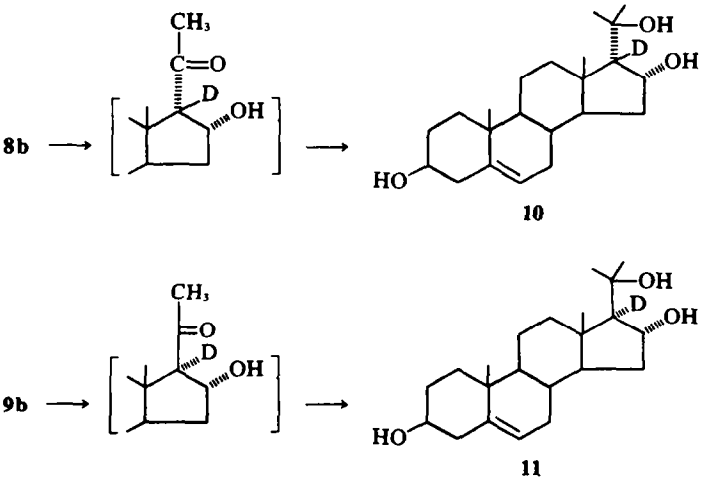
Epimeric **8a** and **9a** were acetylated to give 3,20-diacetates **8b** and **9b**, containing 0·9 atom D/mol as shown by mass spectrometry. The diacetates were





further treated with CH_3MgI yielding 17β-deutero-20-methyl-17α-pregn-5-en-3β,16α-20-triol (**10**) (0·89 atm D/mol) and 17α-deutero-20-methyl-pregn-5-en-3β,16α,20-triol (**11**) (0·87 atom D/mol). These deuterium exchange studies clearly show that the rearrangement is accompanied by a 20→17-hydride shift.

To elucidate the stereochemistry of the rearrangement it seemed interesting to compare it with the Serini reaction. Both are pinacol rearrange-



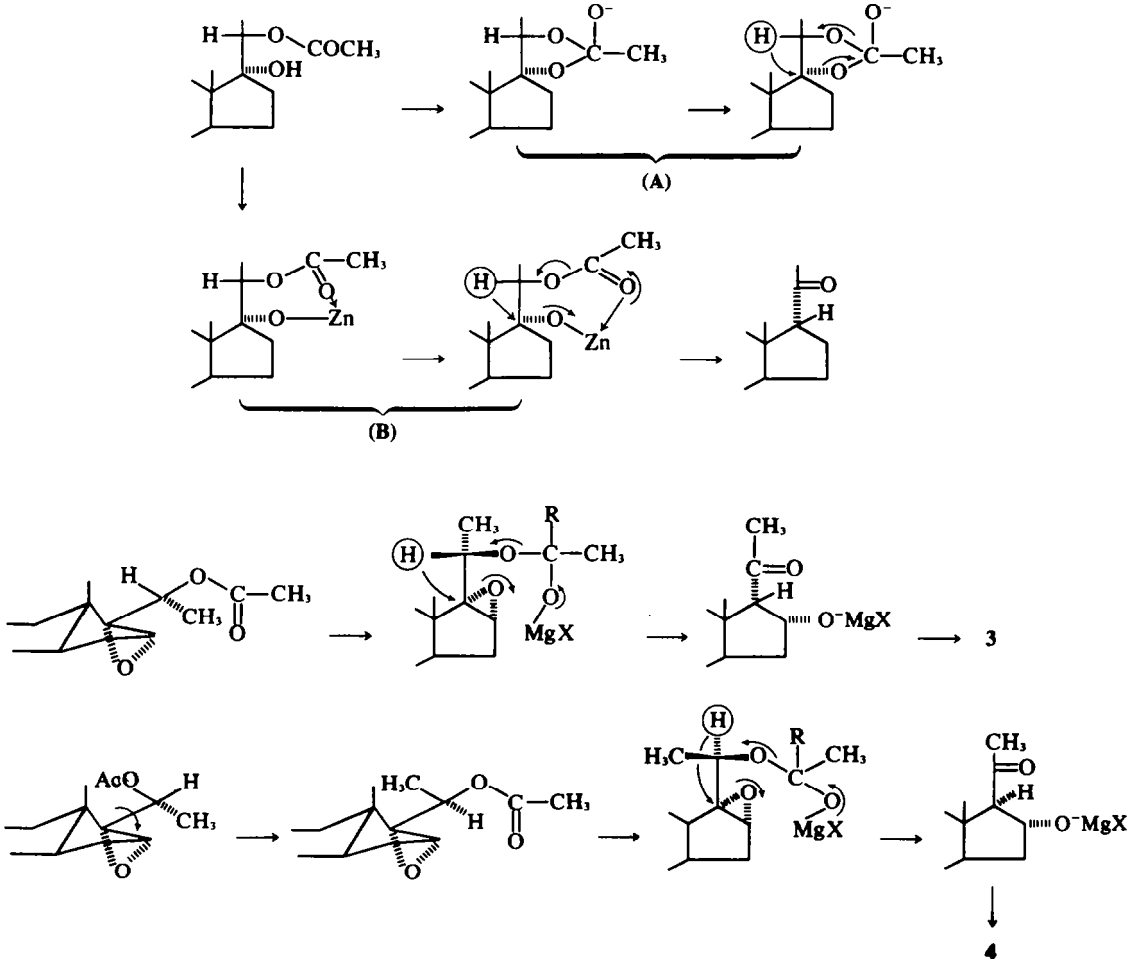
ments and both involve a 20→17-hydride shift.[10,11] However, if the Serini reaction always proceeds with a Walden inversion at C-17 irrespective of configuration of the 20-acetoxy group, the stereochemistry of the new rearrangement clearly depended on the configuration at C-20. However this stereochemical puzzle can be interpreted easily from conformational considerations.

The present conception of the Serini reaction[12] is that the C-17 hydroxyl and 20-acetoxy group are spatially very close, and might interact. Two pathways can be visualized for this interaction: orthoacetate formation (A)[11,13] and chelation (B), as usually proposed for 1,3 ketols.[14] The possibility of ZnOAc substitution for Zn in the Serini reaction is also suggestive of chelation.[12]

Conformational analysis shows that for the 17-hydroxyl and 20-acetate groups to be near to each other, the hydrogen attached to C-20 must be on the side opposite to C_{17}—O bond, so that the stereospecific 20→17 hydride shift will bring the configuration inversion at C-17. The situations with 20α-acetate (1) and its 20β-isomer(2) are not exactly identical. For 20α-acetate(1) quite a small rotation around the C_{17}—C_{20} bond is sufficient to bring the 20α-acetoxy group and oxirane oxygen into proximity, so that C_{20} hydrogen atom stays on the β-side. For 20β-acetate (2) the required rotation is much greater so that the C_{20}-hydrogen is shifted to the α-side.

Hence the 20→17 hydride shift which occurs with the retention of the migrating hydrogen configuration will in the case of 20α-acetate induce Walden inversion, and in the second case result in configuration retention at C-17.

As is to be anticipated, considerable side chain rotation required in the case of 20β-acetate is hindered and the reaction does not proceed by this route exclusively, but gives a whole set of side products.[2,4] The present rearrangement even more than the Serini reaction should favour chelation, since there is a possibility of the Grignard reagent addition to the carbonyl carbon of the acetate-group, which should facilitate CO group ionization.



From the above one can summarize that the main difference between the Serini reaction and the present rearrangement is that one proceeds with 1,2- and the other with 1,3-neighbouring group effect.

EXPERIMENTAL

M.ps (uncorrected) were measured with a Kofler apparatus. IR spectra were recorded for KBr discs with UR-10 Carl Zeiss (Jena) spectrometer (values in cm^{-1}). NMR spectra were measured at 60 MHz with a Varian A-60 and RS-60 spectrometers in $CDCl_3$. Chemical shifts are in ppm (δ), from hexamethyl disilane used as an internal standard. Mass spectra were determined on a Varian CH-6 mass spectrometer using an ionizing potential of 70 eV and a direct inlet system. GLC was carried out with a chromatograph model LHM-7A, provided with flame ionization detector on a glass column (2 m × 5 mm O.D.) packed with 5% SE-30 on 60/80 Chromosorb W at 220°, with N_2 as a carrier gas. Hydroxyl-substituted steroids were separated as trimethylsilyl ether derivatives.[16,17] TLC was carried out on silica gel KSK containing 15% gypsum, spray reagents being conc H_2SO_4 with 1% vanillin or a mixture of picric acid, $HClO_4$ and AcOH.[17] Heating of the plates and 254 nm light were used for visualization of TLC spots. Acetylations were realised with Ac_2O in pyridine at room temperature overnight.

17α,20α-Epoxypregn-5-en-3β,16α-diol diacetate (**5a**)

(a) A soln of Br_2 (0·71 g) in CCl_4 (39 ml) was added to a stirred soln of pregna-5,17 (20)-cis-dien-3β,16α-diol diacetate[18] (1·3 g) in 2:1 ether–CCl_4 mixture (390 ml) at − 15° for 1 h. Solvents were evaporated *in vacuo* at 25° to give an oily residue. This was dissolved in dry $CHCl_3$ (26 ml) and treated with soln of monoperphthalic acid in ether (60 ml, 8% MPA) at 0° for 2 h. After being allowed to stand during 18 h in the refrigerator the mixture was washed with sat $NaHCO_3$ aq and water, dried ($MgSO_4$) and concentrated *in vacuo* at 20°. The residue was dissolved in dry acetone (20 ml), treated with anhydrous NaI (2·7 g), left overnight at 0°. Acetone was partially removed from this mixture *in vacuo* at 20° and then to the residue a soln of sat $Na_2S_2O_3$ was added until the brown colour of the soln had disappeared. Water and $CHCl_3$ were then added and the layers were separated. The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were washed with water and then dried over $MgSO_4$. The solvents were removed and the resulting residue crystallized from MeOH to give 0·2 g of **5a**, m.p. 201–203°. A second crop, 0·2 g, (TLC pure) of **5a** was obtained from the mother liquors by preparative TLC on silicagel. Three recrystallizations from MeOH gave an analytical sample, m.p. 203–204°; ν_{max} 1250, 1730. (Found: C, 71·94; H, 8·68. Calc for $C_{25}H_{36}O_5$: C, 72·08; H, 8·71%).

(b) To a soln of 0·500 g of pregna-5,17(20)-cis-dien-3β-ol-16-one[18] in 45 ml MeOH at − 5° were added 1·2 ml 4N NaOH and 2·4 ml H_2O_2 (30%). After standing during 2 h at this temp the mixture was poured into the water and extracted by EtOAc. The organic phase was washed well with water, dried ($MgSO_4$) and evaporated. The residue (0·5 g) without further purification was acetylated and after usual work-up the oil product (0·52 g) was obtained, which was chromatographed on silica gel and afforded 0·17 g of 17α,20α-epoxypregn-5-en-3β-ol-16-one 3-acetate (**6**), m.p. 181–182° (acetone–hexane). (Found: C, 74·42; H, 8·67. Calc for $C_{23}H_{32}O_4$: C, 74·16; H, 8·66%). NMR: 0·88, 1·00 (each 3H,S, 18- and 19-CH_3), 1·25 (3H, d, 21-CH_3), 1·95 (3H,S, 3-OAc), 3·37 (1H,q, 20-H), 4·54 (1H, br.m, 3α-H), 5·34 (1H, m, 6-H). Besides acetate (**6**) from the other eluates was obtained an isomeric substance, which probably was 17β,20β-epoxy-pregn-5-en-3β-ol-16-one 3-acetate (0·110 g), m.p. 221–223°. (Found: C, 74·28; H, 8·70. Calc. for $C_{23}H_{32}O_4$: C, 74·16; H, 8·66%). NMR: 1·03 (6H,S, 18- and 19-CH_3), 1·37 (3H, d, 21-CH_3), 1·97 (3H,S, 3-OAc), 3·4 (1H, q, 20-H), 4·55 (1H, 3α-H), 5·33 (1H, m, 6-H).

$NaBH_4$ (0·315 g) was added to a soln of **6** (0·430 g) in tetrahydrofuran aq. The mixture was set aside for 20 h at a room temp, then poured into water. The precipitate was filtered off, washed well with water, dried in a desiccator and recrystallized twice from MeOH to give 0·026 g 17α,20α-epoxypregn-5-en-3β,16α-diol 3-acetate (**5b**), m.p. 204–206°; ν_{max}: 1280, 1722, 3455. From mother liquors an additional amount of **5b** (0·08 g) was obtained.

The filtrate, obtained above, was extracted with ether. The ether was washed with water, dried ($MgSO_4$), evaporated to give after preparative TLC on silica gel (solvents: hexane–ether, 1:2) 0·05 g of **5b** and 0·026 g of a more polar substance, which probably was 17α,20α-epoxypregn-5-en-3β,16β-diol 3-acetate, m.p. 187–190° (MeOH); ν_{max}: 1262, 1735, 3450. Acetylation of **5b** (0·080 g) gave rise to **5a** (0·02 g), m.p. 199–201° (MeOH) identical in all respects with the product obtained above using MPA.

Grignard reaction of 17α-20α-epoxypregn-5-en-3β,16α-diol 3,16-diacetate **5a**

Tetrahydrofuran (16 ml) and then a soln of **5a** (0·813 g) in 1:1 mixture of benzene and ether (20 ml) were added to a Grignard reagent prepared from Mg (2·34 g), CH_3I (7 ml) and ether (35 ml). Ether was distilled and the reaction mixture was stirred for 3 h at 67–70°, then the complex was decomposed with excess of sat NH_4Cl aq, extracted with $CHCl_3$. The extract was washed thoroughly with water. Filtration of the aqueous phase gave the precipitate. This was washed with water, dried and recrystallized from MeOH to give 0·120 g of the substance, m.p. 238–240° different from both triol **3** and triol **4** by R_f and by mixed m.ps which showed depression. Analytical sample of this substance, which probably was the D-homoisomer of **3** or **4**, had m.p. 243·5–244° (MeOH): ν_{MAX}: 3350 (OH). (Found: C, 75·86; H, 10·54. Calc. for $C_{22}H_{36}O_3$: C, 75·81; H 10·41%). The mother liquor from the recrystallization and from the $CHCl_3$- extract, obtained above, gave additional amounts of this substance (0·3 g), TLC pure.

Reduction of 16α,17α-epoxypregn-5-en-3β-ol-20-one **7** *with $NaBD_4$*

$NaBD_4$ (0·460 g, content of deuterium 96%), was added to a soln of keto-oxide (**7**, 7 g) in 95% ethanol at 25°. After standing for 46 h at a room temp the mixture was poured into water. The precipitate was filtered off, washed well with water, dried and twice recrystallized from MeOH to give 0·288 g 20α-hydroxyepoxide (**8a**), m.p. 196–210°. Mother liquors gave 0·183 g **8a**. Mass spectrum of **8a** exhibited a peak with *m/e* 333, thus showing the presence of deuterium in this product (substitution by deuterium 90·8%).

Mother liquors from the crystallisation of **8a** was combined, evaporated *in vacuo*. The residue was recrystallized from acetone to give **9a**, m.p. 181–183°. Mass spectrum: M^+ (333), substitution by deuterium 90·6%. Acetylation of **8a** and **9a** gave respectively 20β-deutero-16α,17α-epoxypregn-5-en-3β,20α-diol diacetate (**8b**), m.p.

163–165° (acetone) and 20α-deutero-16α,17α-epoxypregn-5-en-3β,20β-diol diacetate **9b**, m.p. 143–146° (acetone), each having a peak with *m/e* 357 (M-AcOH) and substitution by deuterium 90·7 and 90·1% respectively. Diols **8a** and **9a** as well as its diacetates **8b** and **9b** were shown to be identical with a corresponding nondeuterated samples by TLC and by mixed m.ps which showed no depression, but all these substances had different IR spectra.

Grignard reaction of 20β-deutero-16α,17α-epoxypregn-5-en-3β,20α-diol diacetate **8b**

A soln of **8b** (0·355 g) in benzene (10 ml) was added dropwise with stirring to a solution of Grignard reagent prepared from Mg (1·02 g), CH_3I (3 ml) and ether (15 ml). The mixture was stirred for 3·5 h at room temp, then the complex was decomposed with the excess of the sat soln of NH_4Cl. The precipitate filtered and was washed well with water, dried, then washed with hot MeOH. The methanol filtrate was evaporated *in vacuo* and the residue was twice recrystallized from MeOH to give 17β-deutero-20-methyl-17α-pregn-5-en-3β,16α,20-triol (**10**, 0·090 g), m.p. 239–242°. Mass spectrum: 331 (M-18), substitution by deuterium 89·4%. Additional amount of **10** (0·09 g, homogeneous on TLC) was obtained from the mother liquor. The content of **10** in the mother liquor was 76% (GLC).

Grignard reaction of 20α-deutero-16α,17α-epoxypregn-5-en-3β,20β-diol diacetate **9b**

A soln of diacetate (**9b**, 1·26 g) in benzene (70 ml) was added to a Grignard reagent prepared from Mg (3·65 g), CH_3I (10 ml) and ether (53 ml). The mixture was stirred for 2 h at 65°. After working-up described above the product was extracted with $CHCl_3$, washed with water. Solvent was removed *in vacuo*, the residue was three times recrystallized from MeOH to give 17α-deutero-20-methyl pregn-5-en-3β,16α,20-triol (**11**, 0·020 g), m.p. 228–232°. Mass spectrum: M^- (349), substitution by deuterium 87·7%. The mother liquor from recrystallization of **11** contained (GLC) 25% 11 and 75% 20α-deutero-18-nor-17β-methyl - 17α - pregna - 5,13 (14 - diene - 3β,16α,20β - triol, the latter resembling on TLC its nondeuterated analogue.[19] 17-Deutero-triols **10** and **11** showed no depression of mixed m.ps with **3** and **4** respectively, but all had different IR-spectra.

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REFERENCES

[1]Transformed steroids. Part 64 of this series, A. A. Akhrem, I. V. Vesela and A. V. Kamernitzkii, Submitted to *Izv. Akad. Nauk SSSR, Ser. khim.*
[2]A. A. Akhrem and T. V. Ilyukhina, *Izv. Akad. Nauk SSSR, Ser. khim.* 192 (1966)
[3]A. A. Akhrem and T. V. Ilyukhina, *Ibid.* 710 (1967)
[4]A. A. Akhrem and T. V. Ilyukhina, *Ibid.* 1577 (1968)
[5]A. A. Akhrem and T. V. Ilyukhina, *Ibid.* 1795 (1969)
[6]J. R. Bull, *J. Chem. Soc* (*C*) 1128 (1969)
[7]N. G. Gaylord and E. J. Becker, *Chem. Rev.* **49**, 413 (1951)
[8]M. S. Kharash and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, New York, 1954
[9]A. A. Akhrem and I. G. Reshetova, *Izv. Akad. Nauk SSSR, Ser. khim.* 79 (1965); 769 (1966)
[10]N. L. Wendler in *Molecular Rearrangements*, Vol. II, P. de Mayo, ed., Interscience Publishers, Inc., New York, N.Y., 1964, p. 1039
[11]N. L. Wendler, *Proc. Chem. Soc.* 422 (1960)
[12]E. Ghera, *J. Org. Chem.* **35**, 660 (1970)
[13]F. Goto and L. F. Fieser, *J. Am. Chem. Soc.* **83**, 251 (1961)
[14]E. Ghera and S. Shoua, *Chem. Commun.* 398 (1971)
[15]T. Luukkainen, W. J. A. Vanden Heuvel, E. O. A. Haahti and E. C. Horning, *Biochem. Biophys. Acta*, **52**, 599 (1961)
[16]H. L. Lau, *J. Gas Chromatogr.* **4**, 136 (1966)
[17]W. R. Eberlein, *J. Clin. Endocrinol. Metab.* **25**, 288 (1965)
[18]S. N. Kessar and A. L. Rampal, *Tetrahedron* **24**, 887 (1968)
[19]A. A. Akhrem and T. V. Ilyukhina, *Izv. Akad. Nauk SSSR, Ser. khim.* 909 (1969)