REACTIONS OF 21-ACETOXY-16α,17α-EPOXYPREGN-4-ENE-3,20-DIONE WITH NITROGEN-CONTAINING NUCLEOPHILIC AGENTS

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21-Acetoxy-16α,17α-epoxypregn-4-ene-3,20-dione (**1**) enters a reaction with acetonitrile catalyzed by perchloric acid, giving unusual products with the furostane skeleton. In contrast to analogous reactions, the reaction with sodium azide results in the azido derivative possessing the non-rearranged ring D. The ^{1}H NMR, ^{13}C NMR, and mass spectra are discussed.

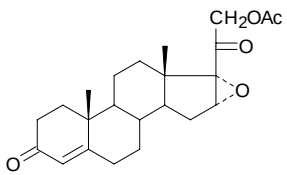
Key words: Pregnenes; Nitrogen-containing nucleophiles; NMR spectra.

Seeking for new applications of 21-acetoxy-16α,17α-epoxypregn-4-ene-3,20-dione (**1**) we investigated the possibilities of opening the epoxy ring with nitrogen-containing nucleophilic agents. The epoxy ring in the molecule of **1** is sterically hindered, while additional unprotected functional groups limit severely the choice of reaction conditions.

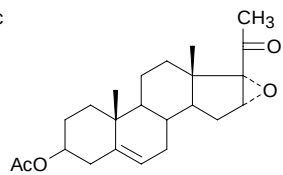
All reactions of the epoxide **1** with various amines in various reaction conditions gave mixtures of no preparatory value, whereas in the zinc iodide-catalyzed reaction with trimethylsilyl cyanide (giving rise to isonitriles[1]) the epoxy ring was absolutely resistant. The consecutive reactions appeared interesting.

The reaction of 3β-acetoxy-16α,17α-epoxypregn-5-en-20-one (**2**) with sodium azide was studied in ref.[2]. This reaction led to a single product which was obtained in a high yield, *viz.* the azido derivative with ring D rearranged to a six-membered ring. The reaction of the epoxide **1** with sodium azide in the same conditions led to a mixture of three products. The major product was 21-acetoxy-16β-azido-17α-hydroxypregn-4-ene-3,20 dione (**3**), hence the product of epoxy ring opening followed by no rearrangement. The non-rearranged structure is borne out by the ^{1}H NMR spectrum: hydrogen atoms in position 21 constitute an AB system appearing at δ 4.89 and 5.09 ppm, J = 16.9 Hz. The chemical shift of the signals is 0.35 ppm higher than for the starting substance **1** (4.59 and 4.69 ppm). If the rearrangement had taken place (structure **3a**), the chemical shifts of the hydrogens would be lower than for the starting substance and

the interaction constant would be about 10 Hz. The signal of the hydrogen atom in position 16 at 4.01 ppm (dd, J = 6.5 Hz, J' = 7.2 Hz) suggests that this hydrogen is bonded to a five-membered ring, as indicated by the interaction constants. The ^{13}C NMR spectrum (Table I) compared to that of the starting compound exhibits a 0.2 ppm downfield shift of the signal of the carbonyl group in position 20; this shift would certainly be larger (5 ppm at least) for substance **3a**. The C-21 signal was shifted 2.6 ppm downfields against the starting substance; for substance **3a** this shift would be upfields. Substance **3** does not react with acetic anhydride (while the acetylation of the rearranged product was successful[2]); its reaction with periodic acid in methanol, aimed at splitting the bond between the C-17 and C-20 carbon atoms, also failed – substance **3** did not react.



1



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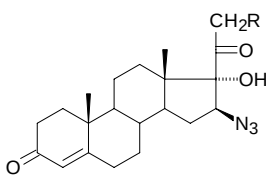
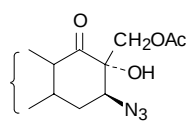
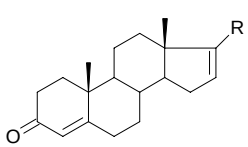
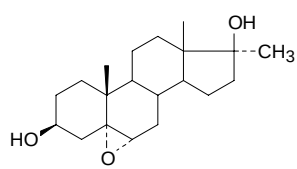




3a

	R
3	OAc
4	OH





7

	R
5	$CONH_2$
6	CN

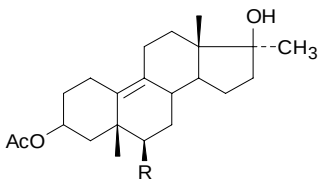
The second reaction product was the dihydroxy derivative **4**. Its structure was elucidated based on spectral data and acetylation which gave the acetate of **3**. The third product was presumably 3-oxoandrosta-4,16-diene-17-carboxamide (**5**). The molecular ion in the mass spectrum, *m/z* 313 ($C_{20}H_{27}NO_2$), loses the $^{\bullet}CONH_2$ radical to produce the most abundant ion *m/z* 269. Of importance in the ^{1}H NMR spectrum is the one-proton triplet at δ 6.42 ppm (*J* = 2.3 Hz), belonging to the olefinic hydrogen atom in position 16. Two amidic protons give rise to a superbroad singlet at 5.92 ppm. The ^{13}C NMR spectrum displays the amidic carbonyl group signal at 167.3 ppm and signals of the double bond between C-16 and C-17 at 136.2 and 149.1 ppm. Chemical evidence of the structure **5** was obtained by dehydration with acetic anhydride, resulting in the known[3] nitrile **6**.

Reaction of steroid epoxides with acetonitrile catalyzed by boron fluoride etherate or perchloric acid at room temperature results in *N*-acetamino-hydroxy derivatives[4]. We tested this reaction first on the model 5,6α-epoxy-17α-methyl-5α-androstane-3β,17β-diol (**7**), which has the epoxy group in the same position as in the cited paper[4], applying the same conditions. Two products were obtained, identified after consecutive acetylation as 3β,6β-diacetoxy-5,17α-dimethyl-5β-estr-9-en-17β-ol (**8**) and 6β-acetamino-3β-acetoxy-5,17α-dimethyl-5β-estr-9-en-17β-ol (**9**). The structure of the major product **8** was suggested based on spectral data analysis. The ^{13}C NMR spectrum indicates the presence of one tetrasubstituted double bond with signals at 134.6 and 142.1 ppm. Applying the well-known procedure[5], the shifts for C-9 and C-10 were calculated to be 136.2 ppm and 142.9 ppm, respectively, which is in a good agreement with the observed values. The C-19 signal is shifted more than 10 ppm downfields, which is indicative of a change in the environment (steric release) due to rearrangement. The C-6 signal appears at 76.4 ppm. The hydroxy group has 2 infrared absorption bands, *viz.* at 3 588 cm^{-1} and at 3 479 cm^{-1}. In the ^{1}H NMR spectrum the hydrogen atom of the hydroxy group gives rise to a one-proton singlet at 2.13 ppm (as evidenced by measuring the spectrum in the presence of CD_3COOD). Hydrogen in position 6 appears as a triplet at 4.72 ppm (*J* = 2.9 Hz).

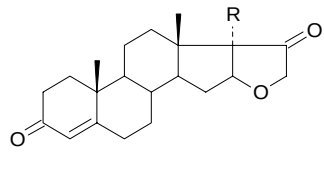
The by-product of substance **9** exhibits spectra very similar to those of this substance. The replacement of one acetoxy group by the acetamide group gives rise to new IR bands at 1 508 (C=N), 1 671 (C=O), and 3 421 (N–H) cm^{-1}, as well as to a new ^{1}H NMR doublet at 5.72 ppm, *J* = 9.6 Hz (N–H), which interacts with the signal of the equatorial hydrogen atom in position 6 at 4.20 ppm and vanishes on the addition of CD_3COOD. In the ^{13}C NMR spectrum the C-6 signal shifts to 54.1 ppm. The two products are astonishing and can be explained in terms of axial opening of the epoxy ring by acetonitrile (or water) followed by the Westphalen rearrangement[6] in acid medium.

In the same reaction with the epoxide **1**, boron fluoride etherate appeared unsuitable (unseparable mixtures emerged). Perchloric acid was therefore used, and temperature was increased to accelerate the process. Three substances were isolated from the

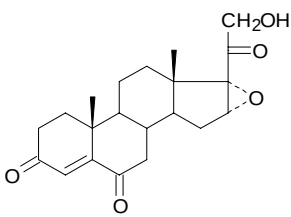
reaction mixture: 16β,21-epoxy-17α-hydroxypregn-4-ene-3,20-dione (17-hydroxy-21,23,24,25,26,27-hexanorfurost-4-ene-3,20-dione) (**10**), 16α,17α-epoxy-21-hydroxy-pregn-4-ene-3,6,20-trione (**11**), and 16α,17α-epoxy-21-acetoxy-5α-pregnane-3,6,20-trione (**12**). The structure of the major product **10** was proposed based on spectral data analysis. The ^{1}H NMR and ^{13}C NMR spectra give evidence of the presence of a five-membered ring with a CH_2 group between the oxygen atom and the carbonyl group. The formation of this derivative with the natural furostane skeleton[7] can be explained by a higher nucleophilicity of the ester group oxygen as compared to the acetonitrile nitrogen and energy favouring of the intramolecular opening of the epoxy ring. Efforts made to increase the yield of **10** and shorten the reaction period resulted in the finding that **10** can also be obtained by perchloric acid-catalyzed reaction of substance **1** in acetone (28% yield). Attempts at dehydration of substance **10** with acetic anhydride failed, which is indicative of the *cis*-annellation of the D/E rings. Substance **10** does not react at room temperature, and gives the acetylation product **13** and the starting epoxy derivative **1** at elevated temperatures.



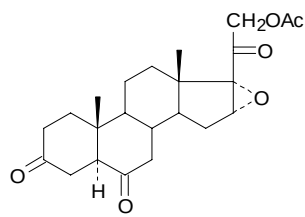
	R
8	OAc
9	NHAc



	R
10	OH
13	OAc



11



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Spectra give evidence that substance **11** possesses 3 keto groups: the ^{13}C NMR spectrum exhibits signals at 199.1, 201.0, and 205.5 ppm, and the IR spectrum displays two very strong bands at 1 690 and 1 710 cm^{-1} in the 2 : 1 ratio. The new carbonyl group in the 6-position causes the one-proton singlet of the olefinic hydrogen in position 4 to shift 0.5 ppm downfields as compared to the starting substance (6.20 ppm *vs* 5.70 ppm). Against the starting substance **1**, the acetoxy group signals are absent from all spectra.

TABLE I
^{13}C NMR spectra of substances **3**, **5**, **6**, and **8–12** in $CDCl_3$

Carbon	**3**	**5**	**6**	**8**	**9**	**10**	**11**	**12**
1	35.6	35.1	35.5	36.5	36.8	35.6	35.4	37.8[a]
2	33.9	33.5	33.8	26.5	26.8	33.7	33.9	36.9[a]
3	199.6	199.0	199.2	70.8	71.1	199.5	201.0	207.9
4	124.0	123.4	124.2	39.5	39.5	124.0	126.0	37.2[a]
5	170.6	170.8	170.0	38.6	38.6	170.5	160.1	57.6
6	31.9	31.3	32.5	76.4	54.1	31.7	205.5	210.7
7	30.5	31.2	31.5	30.6	32.3	30.1	46.2	46.0
8	34.9	33.4	34.0	31.5	31.8	35.2	31.6	35.3
9	53.1	53.6	53.9	134.6	134.4	53.1	50.9	53.6
10	38.6	38.3	38.6	142.1	142.4	38.5	39.7	41.2
11	20.0	20.3	20.6	22.1	22.1	19.7	20.3	21.0
12	32.6	32.3	32.8	29.7	29.7	33.8	30.7	30.8
13	47.7	45.9	48.0	45.4	45.4	45.9	42.5	42.9
14	47.5	55.4	55.2	42.8	42.5	51.5	45.0	45.0
15	32.5	34.0	33.9	22.7	22.7	32.6	27.5	27.5
16	68.8	136.2	147.2	31.3	31.2	89.4	61.6	61.1
17	88.5	149.1	127.2	74.9	75.3	86.9	69.6	70.0
18	14.4	15.8	16.2	15.8	17.3	13.9	15.1	12.6
19	17.3	16.8	17.2	26.6[b]	26.6	17.3	17.6	15.2
20	202.4	167.3	115.6	26.5[b]	26.6	217.3	199.7	198.7
21	67.9	–	–	–	–	73.6	65.6	65.7
CH_3 (Ac-3)	–	–	–	21.4	21.5	–	–	–
CO (Ac-3)	–	–	–	170.8[c]	170.5	–	–	–
CH_3 (Ac-6)	–	–	–	21.4	23.9	–	–	–
CO (Ac-6)	–	–	–	170.2[c]	169.6	–	–	–
CH_3 (Ac-21)	20.5	–	–	–	–	–	–	20.4
CO (Ac-21)	170.6	–	–	–	–	–	–	170.3

[a–c] Signals labelled by the same letter are mutually interchangeable.

In the ^{1}H NMR spectrum, the hydroxy group hydrogen in position 21 forms an ABX system with hydrogen atoms in that position. The X part appears as a triplet at 2.93 ppm (J = 4.8 Hz); this is the signal of the hydroxy group hydrogen. The epoxy group hydrogen gives rise to a one-proton singlet at 3.75 ppm. In the ^{13}C NMR spectrum, the C-3 signal shifts 2 ppm downfields and the C-4 and C-5 signals also shift 2.5 ppm and 9.7 ppm, respectively, downfields as compared to substance **1**. This is indicative of the presence of a keto group coupled with a double bond, hence, to position 6; this is consistent with the signal shift value of this keto group.

The ^{1}H NMR spectrum of substance **12** lacks the signal of the hydrogen at the double bond which is observed in the spectrum of the starting substance **1**. The AB quartet of the CH_2 group in position 21 and the singlet due to hydrogen at the epoxy ring remain virtually constant, giving evidence that the grouping at ring D has been preserved. The signals due to carbon atoms in this ring do not exhibit any changes in the ^{13}C NMR spectrum either. As with the substance **11**, this spectrum contains signals of three ketonic carbonyl groups but against the compound **11**, the signals of carbonyl groups in positions 3 and 6 exhibit downfield shifts of 8 ppm and 5 ppm, respectively. Furthermore, signals of double bond carbonyl groups are lacking, and instead them, signals of CH and CH_2 carbonyl groups are observed. At C-5, the α configuration is thermodynamically more stable (3,6-dioxo-5β-derivatives are spontaneously transformed to the 5α-derivatives on the action of acids or bases[8]). This has been demonstrated by comparing the molecular rotatory powers of 3,6-dioxo derivatives and steroids possessing the same substituent arrangement at ring D as substance **12** (ref.[9]).

EXPERIMENTAL

The melting points were determined on a Kofler stage and have not been corrected. Optical rotatory power in chloroform was measured on a Bendix–Ericson ETL-NPL automatic polarimeter at a precision of ±2°. Infrared spectra (ν in cm^{-1}) in chloroform solutions were scanned on a Perkin–Elmer 684 spectrophotometer, ^{1}H and ^{13}C NMR spectra (δ in ppm, J in Hz) of deuteriochloroform solutions were run on a Varian Unity instrument (200.057 MHz for ^{1}H and 50.306 MHz for ^{13}C) using tetramethylsilane as the internal standard. Mass spectra were recorded on an Incos 50 instrument; ionizing electron energy 70 eV, ionizing current 800 mA, ion source temperature 150 °C, samples evaporated from a direct expose probe applying a temperature gradient of 5 or 10 mA/s.

What is referred to as conventional reaction mixture treatment encompassed: evaporation to dryness in a vacuum, extraction of the residue with ether, washing the ethereal solution with water (or 5% sodium carbonate), drying the ethereal solution with anhydrous sodium sulfate, filtration, and evaporation of the solution to dryness in a vacuum. Chromatography was performed on silica gel 30–60 μm particle size.

Reaction of Epoxide **1** with Sodium Azide

Epoxide **1** (1.0 g, 2.6 mmol) and sodium azide (0.2 g, 3 mmol) were added to dimethyl sulfoxide (35 ml), concentrated sulfuric acid (0.15 ml) was added, and the constantly stirred mixture was heated at 90 °C for 2 days. Subsequently, the mixture was poured onto ice, and the precipitate formed was filtered

out, rinsed with 5% sodium hydrogen carbonate and water, and dried in air to obtain 550 mg of product. Additional 30 mg was reclaimed from the filtrate by extraction with ether. The combined products were chromatographed on a silica gel column (20 g).

21-Acetoxy-16β-azido-17α-hydroxypregn-4-ene-3,20-dione (**3**). Elution with a benzene–ether 3 : 1 mixture gave 450 mg (41%) of substance **3**, m.p. 182–184 °C, $[\alpha]_D$ +24° (*c* 0.53). Mass spectrum, *m/z* (%): 429 (M^+, $C_{23}H_{31}N_3O_5$; 0.1), 401 (0.6), 387 (0.8), 341 (3.8), 326 (1.8), 325 (0.9), 324 (0.8), 313 (2.1), 300 (28.2), 271 (14.1), 243 (15.5), 231 (20.4), 229 (8.5), 211 (4.9), 197 (3.5), 187 (5.6), 173 (5.6), 159 (5.7), 147 (9.2), 131 (11.3), 121 (14.1), 107 (19.7), 105 (19.7), 91 (18.3), 79 (19.7), 67 (13.4), 55 (15.5), 43 (100), 41 (18.3). IR spectrum: 3 450 (OH); 2 950, 2 864 (CH); 2 104 (N_3); 1 745 (CO, acetate); 1 732 (CO-20); 1 702 (N_3); 1 661 (CO-3); 1 615 (C=C); 1 234 (O–CO, acetate); 1 072 (C–O); 1 048 (C–O, acetate). ^{1}H NMR spectrum: 1.04 s, 3 H (3 × H-18); 1.20 s, 3 H (3 × H-19); 2.18 s, 3 H (OAc); 3.66 s, 1 H (OH); 4.01 dd, 1 H, J = 6.5, J' = 7.2 (H-16); 4.89 and 5.09 AB system, 2 H, J = 16.9 (2 × H-21); 5.74 s, 1 H (H-4). For $C_{23}H_{31}N_3O_5$ (429.6) calculated: 64.30% C, 7.29% H, 9.78% N; found: 64.18% C, 7.33% H, 9.59% N.

16β-Azido-17α,21-dihydroxypregn-4-ene-3,20-dione (**4**). Elution with a benzene–ether 1 : 1 mixture gave 10 mg (1%) of substance **4**, m.p. 199–200 °C (ethanol). Mass spectrum, *m/z* (%): 387 (M^+, $C_{21}H_{29}N_3O_4$, 0.7), 356 (0.9), 345 (0.7), 341 (2.8), 329 (1.9), 326 (3.7), 314 (3.3), 300 (25.5), 286 (9.5), 272 (15.1), 243 (14.2), 231 (18.8), 211 (8.0), 205 (4.2), 201 (7.3), 197 (7.3), 187 (10.3), 173 (12.9), 165 (7.0), 159 (12.9), 149 (60.6), 131 (20.4), 121 (29.6), 105 (49.3), 97 (36.6), 91 (60.6), 83 (50.0), 79 (50.0), 69 (45.1), 55 (70.4), 43 (100), 41 (73.2). IR spectrum: 3 600, 3 500 (OH); 2 949, 2 854 (CH); 2 105 (N_3); 1 725 (CO-20); 1 719 (N_3); 1 664 (CO-3); 1 614 (C=C); 1 087 (C–O). For $C_{21}H_{29}N_3O_4$ (387.5) calculated: 65.08% C, 7.56% H, 10.85% N; found: 65.17% C, 7.40% H, 10.71% N.

3-Oxoandrosta-4,16-diene-17-carboxamide (**5**). Elution with an ether–acetone 2 : 1 mixture gave 80 mg (10%) of substance **5**, m.p. 246–247 °C (acetone), $[\alpha]_D$ +127.7° (*c* 0.45). Mass spectrum, *m/z* (%): 313 (M^+, $C_{20}H_{27}NO_2$, 71.0), 298 (31.2), 296 (13.5), 281 (17.7), 271 (10.6), 269 (89.4), 256 (5.0), 253 (12.8), 228 (11.3), 190 (32.4), 173 (22.5), 159 (12.7), 147 (27.5), 145 (29.6), 128 (28.2), 119 (33.8), 105 (56.3), 91 (100), 79 (64.8), 77 (62.0), 67 (28.2), 55 (34.5), 44 (33.8), 41 (43.0). IR spectrum: 3 532, 3 411 (NH_2); 2 943, 2 861 (CH); 1 669 (CON); 1 664 (CO-3); 1 615 (C=C); 1 608 (C–N); 1 578 (C=C). ^{1}H NMR spectrum: 1.04 s, 3 H (3 × H-18); 1.23 s, 3 H (3 × H-19); 5.73 s, 1 H (H-4); 5.61–6.23 bs, 2 H (NH_2); 6.42 t, 1 H, J = 0.7 (H-16). For $C_{20}H_{27}NO_2$ (313.5) calculated: 76.62% C, 8.70% H, 4.47% N; found: 76.51% C, 8.48% H, 4.52% N.

Acetylation of substance **4**. Azide **4** (10 mg) was dissolved in pyridine (0.2 ml), acetic anhydride (0.2 ml) was added, and the whole was allowed to stand overnight at room temperature. The reaction mixture was decomposed with water and extracted with ether. The extract was treated conventionally, and the evaporation residue was crystallized from ethanol; m.p. 181–183 °C, the R_F values in TLC using 2 systems were identical with those of substance **3**. IR spectrum: 3 450 (OH); 2 950, 2 864 (CH); 2 105 (N_3); 1 745 (C–O, acetate); 1 732 (CO-20); 1 702 (N_3); 1 660 (CO-3); 1 615 (C=C); 1 235 (C–O, acetate); 1 072 (C–O); 1 046 (C–O, acetate).

3-Oxoandrosta-4,16-diene-17-carbonitrile (**6**)

Amide **5** (100 mg, 0.3 mmol) was dissolved in pyridine (1.5 ml), acetic anhydride (1.5 ml) was added, and the whole was heated at 60 °C for 4 h. The mixture was decomposed with ice and extracted with chloroform, and the extract was treated conventionally. The residue was taken up in benzene and filtered through a silica gel layer. Crystallization from a heptane–chloroform mixture gave 41 mg (44%) of substance **6**, m.p. 154–156.5 °C (ref.[3]: 156–158 °C), $[\alpha]_D$ +157° (*c* 0.24) (ref.[3]: +168° (*c* 2)). Mass spectrum, *m/z* (%): 295 (M^+, $C_{20}H_{25}NO$, 74.6), 280 (15.5), 267 (10.7), 253 (67.6), 238 (19.4), 224 (7.0), 210 (30.7), 196 (7.0), 124 (94.4), 109 (58.9), 105 (43.7), 91 (100), 83 (29.6), 79 (65.5), 77

(73.2), 65 (31.0), 55 (43.7), 41 (60.6). IR spectrum: 2 945, 2 860 (CH); 2 215 (C=N); 1 664 (CO-3); 1 617 (C=C); 1 592 (C=C); 1 454, 1 436 (=CH–); 1 377 (=CH–); 840 (=CH–). ^{1}H NMR spectrum: 0.97 s, 3 H (3 × H-18); 1.23 s, 3 H (3 × H-19); 5.74 d, 1 H, *J* = 2.0 (H-4); 6.64 dd, 1 H, *J* = 2.0, 3.42 (H-16).

Reaction of Epoxide **7** with Acetonitrile

To the epoxide **7** (1.0 g, 3.1 mmol) were added acetonitrile (10 ml), dichloromethane (10 ml), and perchloric acid (70%, 0.2 ml), and the whole was stirred at room temperature for 18 h. The solvents were removed by evaporation, and the residue was taken up in pyridine (2 ml). Acetic anhydride (2 ml) was added, and the mixture was allowed to stand overnight. The system was decomposed with ice and treated conventionally. Crystallization from ethanol gave 280 mg of product, which was a mixture of two substances as evidenced by TLC. The mixture was chromatographed on a silica gel column (14 g).

*3*β,*6*β-*Diacetoxy-5,17*α-*dimethyl-5*β-*estr-9-ene-17*β-*diol* (**8**). Elution with a benzene–ether 1 : 1 mixture gave 200 mg (16%) of substance **8**, m.p. 193–196 °C (methanol), $[\alpha]_D$ –86° (*c* 0.54). Mass spectrum, *m/z* (%): 404 (M^+, $C_{24}H_{36}O_5$, 4.8), 389 (2.1), 386 (1.5), 371 (1.5), 344 (4.9), 326 (22.3), 311 (15.5), 284 (14.1), 266 (50.6), 251 (91.6), 162 (57.9), 147 (56.5), 133 (21.2), 123 (27.5), 119 (15.3), 105 (26.8), 95 (9.2), 91 (31.8), 79 (17.7), 67 (11.3), 55 (22.6), 43 (100), 41 (16.8). IR spectrum: 3 588, 3 479, 2 950, 2 862 (OH); 1 728 (CO); 1 252 (C–O); 1 030 (C–O). ^{1}H NMR spectrum: 0.95 s, 6 H (3 × H-18 and CH_3-17α); 1.13 s, 3 H (CH_3-5β); 2.03 s, 3 H (OAc-3); 2.07 s, 3 H (OAc-6); 4.77 t, 1 H, *J* = 2.6 (H-6); 5.20 m, 1 H, Σ*J* = 30 (H-3). For $C_{24}H_{36}O_5$ (404.6) calculated: 71.24% C, 8.99% H; found: 71.35% C, 9.20% H.

*6*β-*Acetamino-3*β-*acetoxy-5,17*α-*dimethyl-5*β-*estr-9-en-17*β-*ol* (**9**). Elution with a benzene–ether 1 : 1 mixture gave 70 mg (6%) of substance **9**, m.p. 229–233 °C (heptane–chloroform), $[\alpha]_D$ –71° (*c* 0.44). Mass spectrum, *m/z* (%): 403 (M^+, $C_{24}H_{37}NO_4$, 0.7), 385 (3.0), 326 (22.1), 310 (20.4), 266 (89.4), 251 (53.1), 224 (100), 164 (50.7), 135 (31.0), 122 (20.0), 117 (14.1), 105 (54.9), 95 (10.0), 91 (40.8), 79 (12.7), 72 (31.3), 43 (86.6), 41 (14.8). IR spectrum: 3 590 (OH); 3 462 (NH); 3 421 (OH); 2 951, 2 862 (CH); 1 720 (C–O, acetate); 1 671 (C–O, amide); 1 508 (C–N); 1 235 (C–O); 1 028 (C–O). ^{1}H NMR spectrum: 0.95 s, 6 H (3 × H-18 and CH_3-17α); 1.10 s, 3 H (CH_3-5β); 2.00 s, 3 H (NHAc); 2.02 s, 3 H (OAc); 3.08 s, 1 H (OH); 4.20 dd, 1 H, *J* = 2.4, 9.6 (H-6); 5.22 m, 1 H, Σ*J* = 30 (H-3); 5.72 d, 1 H, *J* = 9.6 (NH). For $C_{24}H_{37}NO_4$ (403.6) calculated: 71.41% C, 9.26% H, 3.47% N; found: 71.30% C, 9.41% H, 3.45% N.

Reaction of Epoxide **1** with Acetonitrile

Epoxide **1** (1 g, 2.6 mmol) was dissolved in acetonitrile (7.5 ml), 70% perchloric acid (4 drops) was added, and the whole was heated at 30–40 °C for 15 days. The reaction mixture was evaporated to dryness and the residue was dissolved in chloroform. The solution was treated conventionally to obtain 820 g of product, which was chromatographed on silica gel (30 g).

*21-Acetoxy-16*α,*17*α-*epoxy-5*α-*pregnane-3,6,20-trione* (**12**). Elution with a benzene–ether 1 : 1 mixture gave 40 mg (4%) of substance **12**, m.p. 195.5–197.5 °C (ethanol), $[\alpha]_D$ +46° (*c* 0.27). Mass spectrum, *m/z* (%): 402 (M^+, $C_{23}H_{30}O_6$, 0.4), 360 (3.5), 342 (1.5), 329 (4.3), 324 (2.2), 311 (2.3), 301 (3.0), 299 (4.1), 289 (2.8), 283 (3.0), 271 (1.6), 255 (0.9), 246 (2.3), 231 (1.4), 213 (1.3), 197 (1.1), 187 (1.6), 173 (2.4), 159 (3.0), 145 (5.9), 137 (4.9), 131 (5.0), 119 (12.9), 105 (12.9), 91 (20), 83 (45.7), 55 (37.0), 47 (18.6), 43 (100), 41 (18.3). IR spectrum: 2 951, 2 863 (CH); 1 719 (CO-20); 1 716 (CO-3); 1 231 (C–O); 1 044 (C–O). ^{1}H NMR spectrum: 0.97 s, 3 H (3 × H-19); 1.12 s, 3 H (3 × H-18); 2.16 s, 3 H (OAc); 3.83 s, 1 H (H-16); 4.60 and 4.70 AB system, 2 H, *J* = 17.3 (N-21). For $C_{23}H_{30}O_6$ (402.5) calculated: 68.62% C, 7.53% H; found: 68.76% C, 7.42% H.

16β,21-Epoxy-17α-hydroxypregn-4-ene-3,20-dione (**10**). Elution with ether gave 320 mg (36%) of substance **10**, m.p. 197–198 °C (ethanol), $[\alpha]_D$ –18° (*c* 0.54). Mass spectrum, *m/z* (%): 344 (M^+, $C_{21}H_{28}O_4$, 29.1), 329 (6.7), 313 (1.9), 311 (1.7), 302 (1.0), 297 (2.3), 286 (5.0), 271 (17.5), 245 (56.7), 244 (60.6), 230 (17.9), 229 (20.6), 187 (10.0), 173 (7.7), 159 (12.3), 149 (16.9), 133 (23.2), 121 (47.9), 115 (16.9), 105 (63.4), 91 (100), 79 (79.6), 67 (50.0), 55 (97.2), 43 (59.2), 41 (67.6). IR spectrum: 3 557 (OH); 2 945 (CH); 1 760 (CO-20); 1 667 (CO-3); 1 615 (C=C); 1 062 (C–O–C). ^{1}H NMR spectrum: 1.00 s, 3 H (3 × H-18); 1.21 s, 3 H (3 × H-19); 2.89 s, 1 H (OH); 4.16 and 4.23 AB system, 2 H, J = 18.1 (2 × H-21); 4.50 dd, 1 H, J = 3.6, J' = 6 (H-16); 5.75 s, 1 H (H-4). For $C_{21}H_{28}O_4$ (344.5) calculated: 73.21% C, 8.21% H; found: 72.99% C, 8.40% H.

16α,17α-Epoxy-21-hydroxypregn-4-ene-3,6,20-trione (**11**). Elution with an ether–acetone mixture gave 100 mg (11%) of substance **11**, m.p. >360 °C (ether), $[\alpha]_D$ +24° (*c* 0.19). Mass spectrum, *m/z* (%): 358 (M^+, $C_{21}H_{26}O_5$, 18.3), 340 (1.4), 327 (22.3), 311 (22.2), 299 (15.0), 281 (10.3), 271 (3.2), 253 (3.9), 239 (4.0), 227 (3.2), 217 (5.6), 21.1 (4.2), 197 (4.9), 189 (6.0), 171 (6.0), 159 (9.9), 147 (12.7), 143 (12.5), 137 (31.7), 128 (11.3), 121 (16.9), 115 (15.5), 105 (33.8), 91 (70.4), 79 (81.7), 77 (67.7), 55 (100), 43 (39.4), 41 (59.2). IR spectrum: 3 499 (OH); 2 950, 2 864 (CH); 1 710 (CO-20); 1 690 (CO-3 and CO-6); 1 605 (C–C); 1 087 (C–O). ^{1}H NMR spectrum: 1.20 s, 6 H (3 × H-18 and 3 × H-19); 2.64 d, 1 H, J = 11.5 (H-7); 2.93 t, 1 H, J = 4.8 (OH); 3.75 s, 1 H (H-16); 4.06 dd, 1 H, J = 19.6, J' = 4.8 (H-21); 4.38 dd, 1 H, J = 19.6, J' = 4.8 (H-21); 6.20 s, 1 H (H-4). For $C_{21}H_{26}O_5$ (358.5) calculated: 70.36% C, 7.33% H; found: 70.55% C, 7.21% H.

Reaction of Epoxide **1** with Perchloric Acid in Acetone

Epoxide **1** (450 mg, 1.2 mmol) was dissolved in acetone (15 ml), 70% perchloric acid (4 drops) was added, and the whole was heated at 40–50 °C for 7 days. The solvent was removed by evaporation, the residue was taken up in chloroform, and the solution was treated conventionally. The mixture was chromatographed on a silica gel column (20 g) using a benzene–ether 1 : 1 solvent mixture to obtain 110 mg (27%) of substance **10**, m.p. 196–199 °C.

Reaction of Substance **10** with Acetic Anhydride

Substance **10** (100 g, 0.29 mmol) was dissolved in acetic anhydride (10 ml) and the solution was allowed to stand at room temperature for 3 days. Since TLC revealed that substance **10** had not reacted at all, the mixture was refluxed for 5 h. The system was decomposed with ice, neutralized with 5% sodium carbonate, and extracted with ether. The ethereal solution was treated conventionally, and the residue was dissolved in chloroform and filtered through a layer of aluminium oxide to obtain 75 mg (67%) of substance **13**, m.p. 178–181 °C, $[\alpha]_D$ –38° (*c* 0.27). Mass spectrum, *m/z* (%): 386 (M^+, $C_{23}H_{30}O_5$, 0.3), 371 (0.1), 344 (0.5), 343 (0.5), 326 (8.7), 311 (76.1), 297 (3.0), 286 (3.5), 271 (5.9), 244 (3.5), 211 (1.4), 197 (1.4), 187 (3.5), 173 (4.2), 159 (7.0), 145 (8.4), 131 (11.3), 121 (15.5), 107 (22.5), 91 (32.4), 79 (29.6), 67 (15.5), 55 (29.6), 43 (100), 41 (19.3). IR spectrum: 2 957 (CH); 1 767 (CO-20); 1 737 (C–O, acetate); 1 665 (CO-3); 1 618 (C=C); 1 243 (C–O); 1 069 (C–O–C); 1 060 (C–O). ^{1}H NMR spectrum: 1.03 s, 3 H (3 × H-18); 1.51 s, 3 H (3 × H-19); 2.09 s, 3 H (OAc); 4.16 d, 1 H, J = 16.8 (H-21); 4.45 d, 1 H, J = 16.8 (H-21); 5.73 s, 1 H (H-4). For $C_{23}H_{30}O_5$ (386.5) calculated: 71.46% C, 7.84% H; found: 71.57% C, 8.00% H.

Reaction of Substance **10** with Acetic Anhydride in Pyridine

Substance **10** (20 mg, 0.06 mmol) was dissolved in pyridine (0.5 ml), acetic anhydride (0.5 ml) was added, and the whole was allowed to stand overnight at room temperature to obtain 15 mg (67%) of epoxide **1**, m.p. 161–166 °C (methanol). Mass spectrum, *m/z* (%): 386 (M^+, $C_{23}H_{30}O_5$, 0.8), 368

(2.1), 344 (14.9), 326 (3.5), 313 (6.5), 311 (6.2), 297 (3.4), 283 (5.4), 267 (8.0), 249 (2.3), 243 (4.9), 231 (2.7), 225 (4.1), 209 (2.3), 197 (2.5), 187 (4.1), 173 (4.2), 159 (7.6), 143 (10.7), 133 (9.2), 121 (10.6), 105 (17.6), 91 (26.4), 79 (21.1), 73 (10.0), 67 (10.0), 55 (26.8), 43 (100), 41 (15.5). IR spectrum: 2 942, 2 859 (CH); 1 748 (C–O, acetate); 1 725 (CO-20); 1 663 (CO-3); 1 615 (C=C); 1 221 (O–Ac); 1 057 (C–OAc). The two spectra were identical with those of the epoxide **1**.

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