STEROIDS. PART V.*

Epoxidation of Pregnane Derivatives and Examination of the Epoxides

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The different epoxidation reactions of pregnadienolone acetate have been studied, the 5,6-epoxides of a number of 16-substituted pregnane derivatives prepared and the cleavage of these epoxides examined. The infrared spectrum of a series of pregnane epoxides has also been studied.

In recent years, various 6- and 16-substituted pregnane derivatives, respectively, with hormone activity, antiphlogistic effect, *etc.* have been prepared and reported (1). Especially significant are the 6-halogene compounds. These may be synthesized through the epoxidation of the 5,6-double bond and subsequent cleavage of the epoxide ring to halohydrine.

It has already been mentioned [2] that pregnadienolone acetate and a number of 16-substituted pregnane derivatives were epoxidated and their transformation to halohydrine, furthermore their infrared spectra studied. The present communication gives a more detailed description of these results.

It has been known that epoxidation of unsaturated steroids can be carried out in case of isolated double bond mainly with peracids, while in case of α,β-unsaturated ketones with alkaline hydrogen peroxide [3]. The hydrogen peroxide treatment, described at first by WEITZ and SCHEFFER [4], may be applied selectively even in that case, when besides the α, β-unsaturated ketone a conjugated diene system is also to be found in the molecule [5]. There are only sparse data in literature concerning the epoxidation with peracids of the 16,17-double bond, conjugated with ketone [6]. BERNSTEIN epoxidated $\Delta_{4,16}$-pregnadien-3,20-dione in the 20-ketal form with perbenzoic acid, thus breaking the ketone conjugation [7]. This way the 16,17-double bond of pregnadienolone acetate (I) could be epoxidated selectively with alkaline hydrogen peroxide to 3β-hydroxy-16,17α-epoxy-Δ_5-pregnene-20-one (II) [8, 9]. On the other hand, both the selective epoxidation of the 5,6-double bond (III) [10] and the preparation of the 5,6—16,17-diepoxide (IV) in two steps [11] can be achieved. In principle a similar method was followed in the present work, but the order of epoxidations was reversed and GRABER's [10] 4% peracetic acid was replaced by monoperphthalic acid (MPA). Thus the preparation of the 5,6-epoxide (III), the 5,6—16,17-diepoxide (IV), and the acetate of the latter (V) could be accomplished with appropriate yield.

* Part IV. M. HALMOS and É. PUSZTAY, *Steroids* **7**, 195 (1966).

Like pregnadienolone acetate, its 16β-methyl derivative, 3β-acetoxy-16β-methyl-$\Delta_{5,16}$-pregnadien-20-one (VI) could also be transformed selectively to the 16,17α-epoxide (VII) with alkaline hydrogen peroxide [12]. Both the latter and 3β-hydroxy-16,17α-epoxy-Δ_5-pregnene-20-one (II) were acetylated (VIII) (IX).

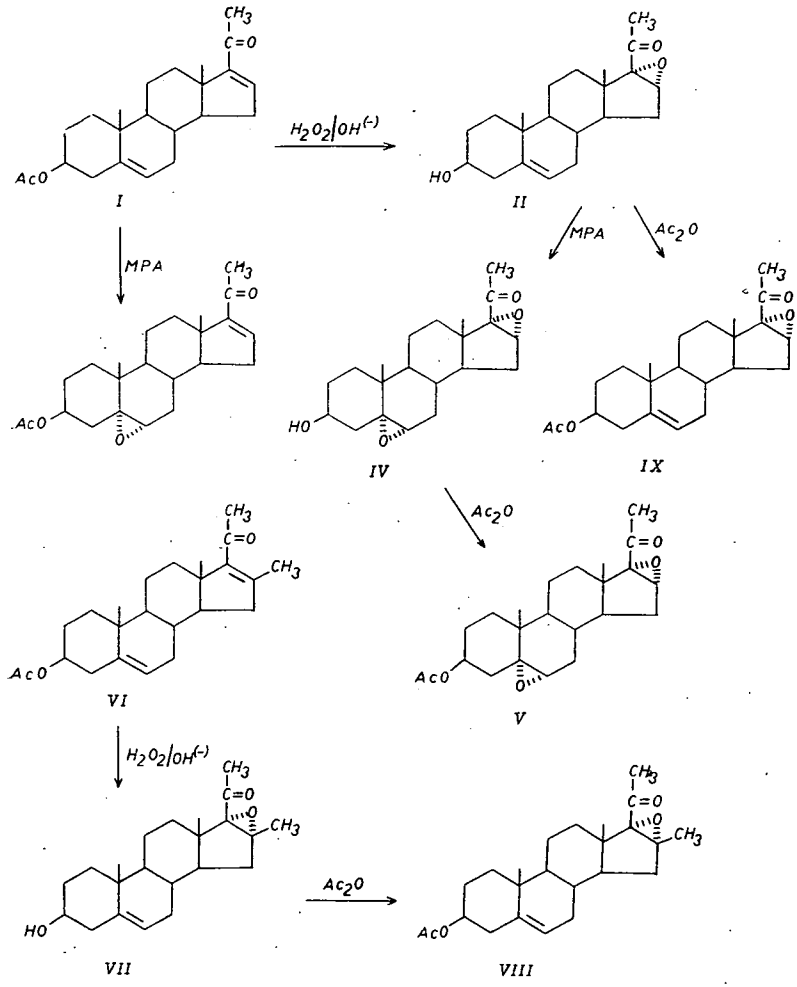


Fig. 1

The above described epoxidations with alkaline hydrogen peroxide were carried out in the presence of acetonitrile, as well. It was found that in the presence of that the epoxide forming reaction was faster and more unidirectional, which is in accordance with the observation of PAYNE and coworkers [13, 14] that at about pH 8 the interaction of hydrogen peroxide and nitrils results in the formation of

Table I

No	5,6-unsturated compound	Reference	Mark	Acetate (di- or triacetate)								5,6α-epoxide							
				Mark	m. p. °	$[\alpha]_D^{20}$	R_f	Anal. % calculated		Anal. % found		Mark	m. p. °	$[\alpha]_D^{20}$	R_f	Anal. % calculated		Anal. % found	
								C	H	C	H					C	H	C	H
1.	3β,20β-dihydroxy-16α-hydroxymethyl-Δ_5-pregnene	18	XIVd	XIVh	166—168	—69° ($CHCl_3$)	0,60	70,85	8,92	70,70	8,65	XVc	163—166	—57° ($CHCl_3$)	0,53	68,54	8,62	68,40	8,79
2.	3β,20β-dihydroxy-16β-hydroxymethyl-Δ_5-pregnene	18	XVIa	XVIb	167—169	—15° ($CHCl_3$)	0,62	70,85	8,92	70,76	8,99	XVII	148—151	—8° ($CHCl_3$)	0,56	68,54	8,62	68,61	8,80
3.	3β,20β-dihydroxy-16α-cyano-Δ_5-pregnene	18	XIVc	XIVg	212—214	—56° (dioxane)	0,58	73,03	8,72	73,12	8,79	XVb	161—165	—27° ($CHCl_3$)	0,51	70,39	8,40	70,30	8,42
4.	3β,20β-dihydroxy-16α-carboxy-Δ_5-pregnene	18	XIVb	XIVf	186—188	—52° (dioxane)	0,58	69,92	8,85	69,81	8,76	m i x t u r e							
5.	3β,20β-dihydroxy-16α-carbomethoxy-Δ_5-pregnene	18	XIVa	XIVe	189—190	—62° (dioxane)	0,62	70,40	8,75	70,22	8,68	XVa	199—207	—28° ($CHCl_3$)	0,51	68,04	8,46	67,78	8,57
6.	3β,20β-dihydroxy-16β-carboxy-Δ_5-pregnene-16,20-lactone	18	XVIIIa	XVIIIb	237—240	—36° (dioxane)	0,50	74,54	8,85	74,49	8,72	XIX	275—283	—32° ($CHCl_3$)	0,39	71,61	8,51	71,44	8,37
7.	3β-hydroxy-16α-cyano-Δ_5-pregnene-20-one	19	XXa	XXb	196—198	+16° ($CHCl_3$)	0,57	75,16	8,67	75,15	8,78	XXI	185—189	+27° ($CHCl_3$)	0,50	72,14	8,32	72,07	8,38
8.	3β-hydroxy-16,17α-carboxymethylene-Δ_5-pregnene-20-one	20	XXIIa	XXIIb	192—196	+33° ($CHCl_3$)	0,57	77,80	9,25	77,71	9,17	XXIII	183—185	+21° ($CHCl_3$)	0,48	74,57	8,86	74,18	8,76
9.	3β-hydroxy-16-exomethylene-17α-hydroxy-Δ_5-pregnene-20-one	12, 21	XXIVa	XXIVb	204—206	—148°* ($CHCl_3$)	0,54	74,57	8,86	74,55	8,71	XXV	231—235	—162° ($CHCl_3$)	0,47	70,24	8,16	69,84	7,97
10.	3β-hydroxy-16β-methyl-$\Delta_{5,16}$-pregnadien-20-one	22, 31	XXVIa	XXVIb	177—178	—83° (EtOH)	0,61	77,79	9,25	77,70	9,31	XXVII	193—198	—	0,55	74,57	8,86	74,38	8,78
11.	3β-hydroxy-16,17α-epoxy-16β-methyl-$\Delta_{5,16}$-pregnadien-20-one	12	XXVIIIa	XXVIIIb	179—181	—18° ($CHCl_3$)	0,52	74,57	8,86	74,50	8,92	XXIX	184—186	—25° ($CHCl_3$)	0,46	71,61	8,51	71,58	8,56
12.	3β-hydroxy-Δ_5-pregnene-20-one	23	XXXa	XXXb	145—146	+19° ($CHCl_3$)	0,60	77,05	9,56	76,86	9,47	XXXI	164—168	+13° ($CHCl_3$)	0,54	73,76	9,15	73,58	9,17

* mono-3-acetate

peroxycarboximidic acids, which are excellent epoxidating agents.

$$R-CN+H_2O_2 \xrightarrow[pH\ 8]{OH^-} R-C\begin{matrix}=NH\\ -OOH\end{matrix}$$

The transformation of the above epoxides to chlorohydrine was examined The epoxides were treated with dry hydrogen chloride gas in chloroform or according to the method of SCHWARZ and SYHORA [15] with aqueous acetone and hydrogen chloride, with the only modification that the solution had been saturated with $MgCl_2$, in order to prevent hydrolysis to diol. This technique, being known from analytical chemistry [16], was applied to increase chloride ion concentration. 3β-Acetoxy-16,17α-epoxy-Δ_5-pregnene-20-one (IX) and 3β-acetoxy-5,6α-16,17α-diepoxypregnane-20-one (V) afforded the corresponding mono- (X) and dichlorohydrine (XI), respectively, with hydrogen chloride gas in chloroform. 3β-Acetoxy-5,6α-epoxy-Δ_{16}-pregene-20-one (III) yielded a dihalogene derivative under identical conditions, which on basis of analytical data and of the disappearence of the IR band characteristic of conjugation may presumably be represented by structure XII. The addition of HCl is rendered probable by a number of similar known additions to the 16,17-α, β-conjugated unsaturated oxo-bond. With aqueous acetone and hydrogen chloride III gives the corresponding unsaturated chlorohydrine (XIII).

Further the epoxidation of pregnenolone and some $\Delta_{5,6}$-unsaturated pregnane derivatives were studied. Prior to epoxidation the free hydroxyl groups of these compounds were acetylated. The experimental results are shown by Table I.

It is to be noted that at the epoxidation of 3β,17α-diacetoxy-16-exomethylene-Δ_5-pregnene-20-one (XXIVb) the exomethylene bond does not react with monoperphthalic acid under the experimental conditions applied. It is proved by the

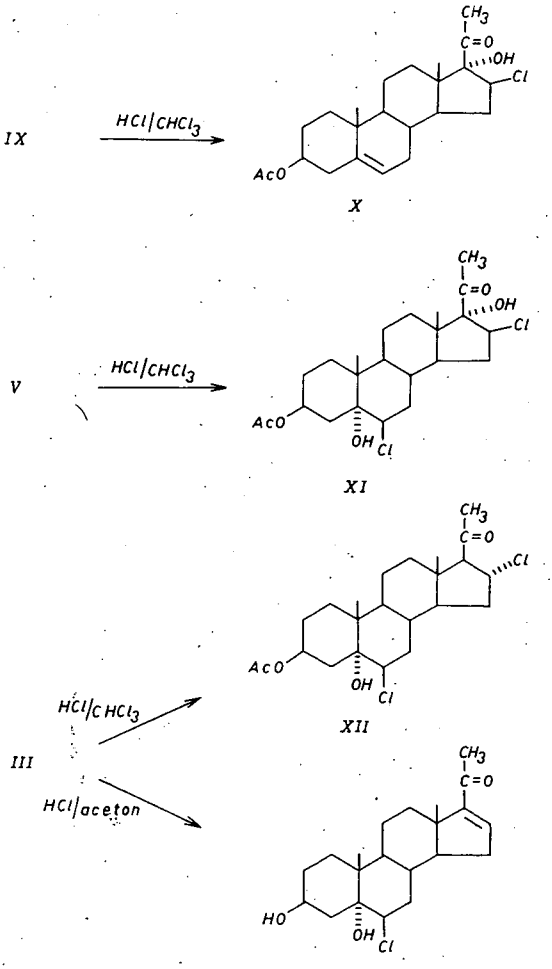
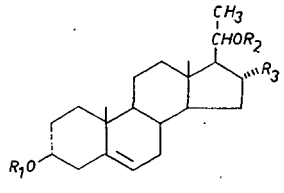


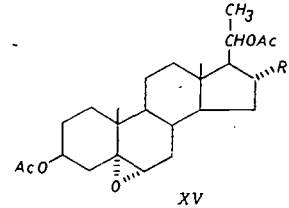
Fig. 2

IR spectrum of the epoxide obtained, in which the band at 1644 cm^{-1}, characteristic of exomethylene group, remains unchanged. According to literature, too, the epoxidation of steroid exomethylene groups goes extremely hard, it can be completed only under energetic conditions. TAUB and WENDLER [17] reported such an epoxidation, when treatment of the unsaturated compound with trifluoroperacetic acid gave a spiroepoxide. Of the epoxides 3β-acetoxy-5,6α-epoxy-16α-cyano-pregnane-20-one (XXI), 3β-acetoxy-20β-hydroxy-5,6α-epoxy-16β-carboxypregnane-16,20-lac-



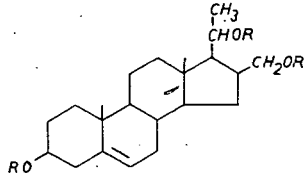
XIV

	R_1	R_2	R_3
a.	H	H	$COOCH_3$
b.	H	H	COOH
c.	H	H	CN
d.	H	H	CH_2OH
e.	Ac	Ac	$COOCH_3$
f.	Ac	Ac	COOH
g.	Ac	Ac	CN
h.	Ac	Ac	CH_2OAc



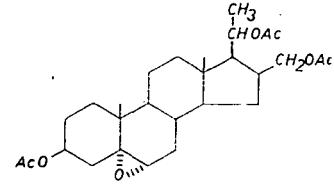
XV

	R
a.	$COOCH_3$
b.	CN
c.	CH_2OAc

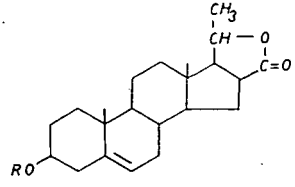


XVI

	R
a.	H
b.	Ac

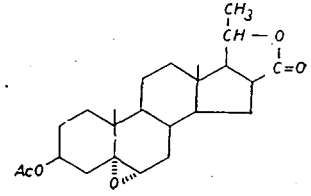


XVII



XVIII

	R
a.	H
b.	Ac



XIX

Fig. 3a

tone (XIX) and 3β-acetoxy-5,6α-epoxypregnane-20-one (XXXI) could be transformed to homogeneous chlorohydrine (XXXII, XXXIII, XXXIV) with the method of SCHWARTZ and SYHORA.

The epoxidation reactions may be detected well by thin-layer chromatography, using Kieselgel G. Merck and 5% ethanol in benzene, when the epoxide formed has always lower R_f value than the starting 5,6-unsatured compound (cf. Table I). In one case, with 3β, 20β-diacetoxy-16α-carboxy-Δ_5-pregnene (XIVf) the epoxidation gave two products, which is presumably due to the formation of the β-epoxide besides the main product α-isomer. According to literature [24, 25] the 5,6-double bond yields generally α-epoxides with peracids, since in case of trans anellation of the *A*/*B* rings the 10-angular methyl group shields the β-side, though due to the unsaturated character of the *B* ring it has only a "pseudo-axial" orientation, which,

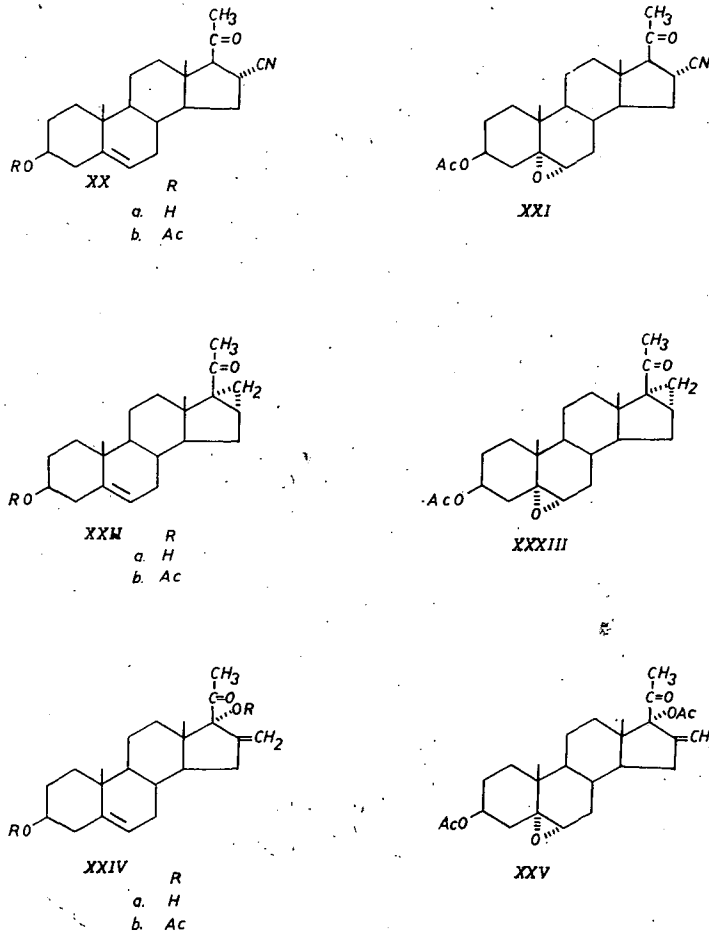


Fig. 3b

for a certain degree, makes possible the formation of β-epoxides, as well. For example, BERGSTROM and coworkers [26] reported the mixed formation of α and β epoxides (XXXVI, XXXVII) at the epoxidation of 17α,21-dihydroxy-Δ_5-pregnene-3,20-dione-21-acetate-3,20-*bis*-ethylene ketal (XXXV).

The trans-diaxial ring-cleavage to chlorohydrine [25, 27] of 5,6α-epoxides gave rise to 5α-hydroxy-6β-chloroderivatives (XXXII, XXXIII, XXXIV).

Infrared spectra of pregnane epoxides

It is well known that ethylene as the simplest epoxide possesses three characteristic bands in the infrared region, at 865, 1165 and 1250 cm^{-1}, respectively. The infrared spectrum of a steroid epoxide was mentioned first by GÜNTHARD [28].

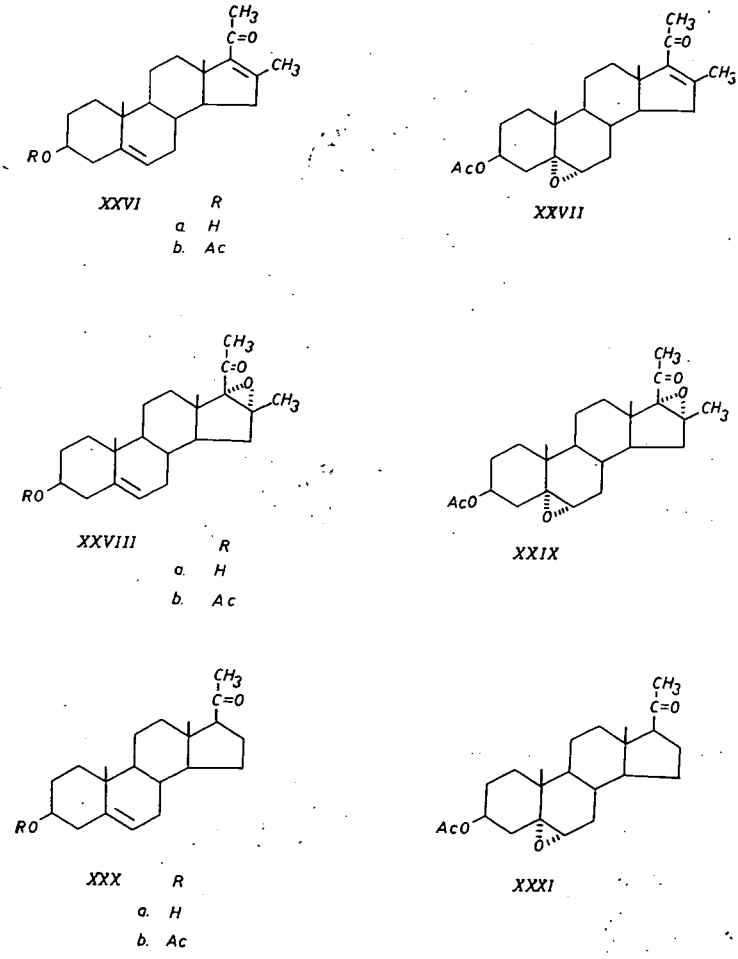
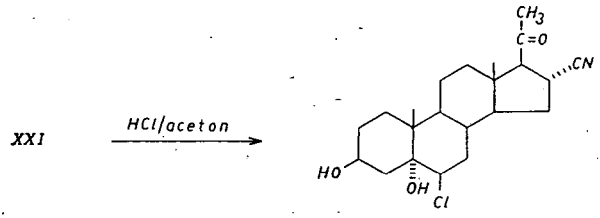
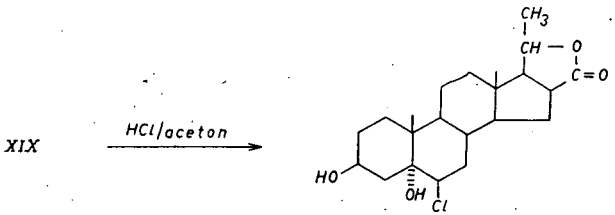


Fig. 3c

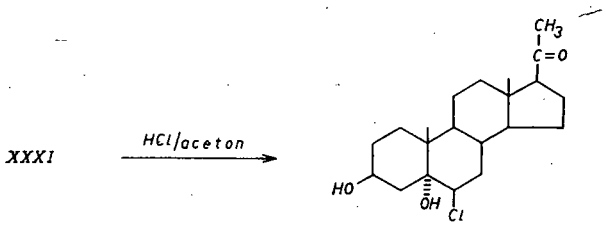


XXXII

Fig. 4



XXXIII



XXXIV

Fig. 5

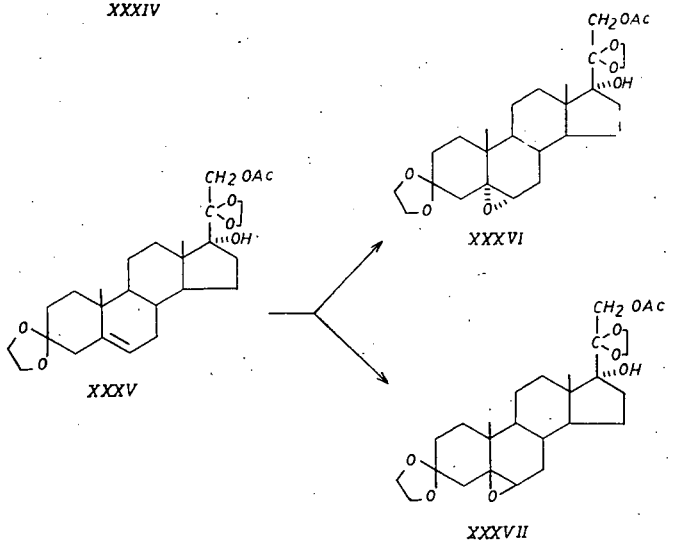


Table II[1]

No	Compound	Mark	1240-60 cm^{-1}	1150-60 cm^{-1}	850-900 cm^{-1}
1.	3β-acetoxy-$\Delta_{5,16}$-pregnadien-20-one	I	*1242*! (OAc)s!	1150 vw	888 vw, 860 vw
2.	3β-acetoxy-5,6α-epoxy-Δ_{16}-pregnene-20-one	III	*1242*! (OAc)s!	*1150* w	*878* s
3.	3β-acetoxy-16,17α-epoxy-Δ_5-pregnene-20-one	IX	*1242* (OAc)s!	1150 vw *1140* w	892 vw *860* s.
4.	3β-acetoxy-5α,6β-dihydroxy-Δ_{16}-pregnene-20-one		1245, 1236 (OAc)s!	1152 s	882 s 876 w
5.	3β-acetoxy-5α-hydroxy-6β-chloro-Δ_{16}-pregnene-20-one	XIII	*1236* (OAc) s!	1156 w	878 vw
6.	3β-acetoxy-16β-methyl-$\Delta_{5,16}$-pregnadien-20-one	XXVIb	*1242* (OAc) s!	1150 vw	888 vw 860 vw
7.	3β-acetoxy-16β-methyl-16,17α-epoxy-Δ_5-pregnene-20-one	XXVIIb	1236 (OAc) s!	*1150* w	*896* s
8.	3β, 17α-diacetoxy-16-exo-methylene-Δ_5-pregnene-20-one	XXIVb	1240 (OAc) s!!	1152 vvw	886 w, 870 w
9.	3β, 17α-diacetoxy-5,6α-epoxy-16-exomethylene-pregnane-20-one	XXV	1240 (OAc) s!!	*1162* w	*876* s
10.	3β, 20β-diacetoxy-16α-carbo-methoxy-Δ_5-pregnene	XIVe	1240 (OAc) s!!	1170 s, 1156 s	882 w
11.	3β, 20β-diacetoxy-5,6α-epoxy-16α-carbomethoxypregnane	XVa	1240 (OAc) s!!	1176 s *1160* s!	*880* s
12.	3β-acetoxy-20β-hydroxy-16β-carboxy-Δ_5-pregnene-16,20-lactone	XVIIIb	1238 (OAc) s!!	1152 vw	880 vw
13.	3β-acetoxy-20β-hydroxy-5,6α-epoxy-16β-carboxypregnane-16,20-lactone	XIX	1240 (OAc) s!!	*1160* w	*880* m
14.	3β-acetoxy-16,17α-cyclo-methylene-Δ_5-pregnene-20-one	XXIIb	1240 (OAc) s!!	*1152* m	888, 876 vw
15.	3β-acetoxy-5,6α-epoxy-16,17α-cyclomethylenepregnane-20-one	XXIII	1242 (OAc) s!!	*1156* s!	*880* m

[1] Unicam S.P. 200; 1,5 mg. substance in 300 mg. Merck uvasole KBr.

He exa mined different cholesterol 2,3-, 3,4- and 5,6-epoxides and found the bands at 1035—1050 cm^{-1} as characteristic of these derivatives. This region, however, may be covered by OH bands. JONES [29] and RAO [30] found the same bands as character istic of steroid epoxides. Actually, the above mentioned symmetric ethylene oxide eth er vibration band at 1250 cm^{-1} appears at steroids with decreased intensity, but in ca se of steroid acetates the so-called 8 microne acetate band (1240—1260 cm^{-1}) would c over it anyhow. Literature usually does not mention the 1165 cm^{-1} ethylene oxide band.

We have taken the infrared spectrum of a number of pregnane epoxide acetates; the band at 865 cm^{-1} could be observed in any case, as well as the characteristic acetate band at 1240—1260 cm^{-1}, and the ethylene oxide band at 1165 cm^{-1} appeared or its intensity increased to a multifold value as compared to that of the starting olefin. Therefore this band is also characteristic to the steroid epoxides investigated by us (Table II).

* * *

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Experimental

3β-hydroxy-16,17α-epoxy-Δ_5-pregnene-20-one (II)

a, 3 g pregnadienolone acetate (I) was dissolved in 200 ml. methanol, the solution cooled to 15°, 6 ml. 4 *N* NaOH added, and 12 ml. 30% H_2O_2 solution was added at 5°. The mixture was kept at 0° for 24 hours, then diluted with 800 ml. water. The material deposited was filtered, washed with water, dried and recrystallized from *abs.* methanol, to yield 1.7 g 3β-hydroxy-16,17α-epoxy-Δ_5-pregnene-20-one (II), m. p. 191—192°, $(\alpha)_D^{20} + 3°$ (c = 1, chloroform). Anal.: $C_{21}H_{30}O_3$ requires C 76,32; H 9,15. Found C 76,22; H 9,24%.

b, 1 g. pregnadienolone acetate (I) was dissolved in 120 ml. ethanol, 10 ml. acetonitrile was added and the mixture heated to 60°. 30 ml. 30% H_2O_2 solution was added at this temperature over a period of 2 hours, the pH being maintained at 9—10 with the simultaneous addition of 1 *N* NaOH solution. After cooling the reaction mixture was acidified with 5 *N* HCl, diluted with water and extracted with ethyl acetate. The combined extracts were washed with 5% Na_2CO_3 solution, with water and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue crystallized from methanol, to yield 0,72 g. 3 β-hydroxy-16,17α-epoxy-Δ_5-pregnene-20-one (II), m. p. 190—192°, $[\alpha]_D^{20} + 2°$ (c = 1, chloroform). Anal.: found C 76,18; H 9,12%.

3β-acetoxy-16,17α-epoxy-Δ_5-pregnene-20-one (IX)

1,1 g. 3β-hydroxy-16,17α-epoxy-Δ_5-pregnene-20-one (II) was dissolved in 10 ml. pyridine, 1 ml. acetic anhydride was added and the mixture kept overnight at room temperature. The mixture was diluted with water, the material precipitated was filtered, washed with water and dried. Crystallization from methanol gave 1 g. 3β-acetoxy-16,17α-epoxy-Δ_5-pregnene-20-one (IX), m.p. 152—4°, $(\alpha)_D^{20}$ -8° (c = 1, chloroform). Anal.: $C_{23}H_{32}O_4$ requires C 74,16; H 8,65. Found: C 74,07; H 8,67%.

3β-hydroxy-5,6α, 16,17α-diepoxypregnane-20-one (IV)

A solution of 3 g. 3β-hydroxy-16,17α-epoxy-Δ_5-pregnene-20-one (II) in 15 ml. chloroform was cooled to 0° and 50 ml. 5—6% ethereal monoperphthalic acid solution was added with stirring. The reaction mixture was kept overnight at room temperature, phthalic acid deposited was filtered off, and the solution was washed with $NaHCO_3$ solution and water and dried over anhydrous Na_2SO_4. The solvent

was removed *in vacuo* and the residue crystallized from methanol, to yield 2,1 g. 3β-hydroxy-5,6α, 16,17α-diepoxypregnane-20-one (IV), m. p. 189—191°, $(\alpha)_D^{20}$-21° (c = 1, chloroform). Anal.: $C_{21}H_{30}O_4$ requires C 72,80; H 8,73. Found C 72,76 H 8,91%.

3β-acetoxy-5,6α16,17α-diepoxypregnane-20-one (V)

1.8 g. 3β-hydroxy-5,6α,16,17α-diepoxypregnane-20-one (IV) was dissolved in 18 ml pyridine, 1.8 ml. acetic anhydride was added and the whole kept overnight at room temperature. The mixture was diluted with water, the material deposited was filtered, washed with water and dried. Recrystallization from methanol yielded 1,1 g. 3β-acetoxy-5,6α,16,17α-diepoxypregnene-20-one (V), m. p. 202—204°, $(\alpha)_D^{20}$-18° (c = 1, $CHCl_3$). Anal.: $C_{23}H_{32}O_5$ requires C 71,10; H 8,30. Found: C 71,02; H 8,51%.

3β-acetoxy-5,6α-epoxy-Δ_{16}pregnene-20-one (III)

60 ml. 5—6% ethereal monoperphthalic acid solution was added with stirring to a solution of 3 g. pregnadienolone acetate (I) in 50 ml. chloroform at 0°, the mixture kept overnight at room temperature and phthalic acid deposited was filtered off. The solution was washed with 5% Na_2CO_3 solution and water and dried over anhydrous Na_2SO_4. The dry solution was concentrated *in vacuo* and the residue crystallized from methanol, to yield 1,8 g. 3β-acetoxy-5,6α-epoxy-Δ_{16}-pregnene-20-one (III), m. p. 196—198°, $(\alpha)_D^{20}$ + 37°(c = 1, $CHCl_3$). Anal.: $C_{23}H_{32}O_4$ requires 74,16; H 8,66. Found: 74,08; H 8,52%.

3β-hydroxy-16β-methyl-16,17α-epoxy-Δ-pregnene-20-one (VII)

a, The compound obtained according to SYHORA (12) and crystallized from methanol melted at 191—193°, $(\alpha)_D^{20}$ − 20° (c = 1, $CHCl_3$). Anal.: $C_{22}H_{32}O_3$ requires C 76,70; H 9,36. Found: C 76,51; H 9,70%.

b, 3 g. 3β-acetoxy-16β-methyl-$\Delta_{5,16}$-pregnadien-20-one (VI) (22) was dissolved in a mixture of 200 ml. methanol and 30 ml. acetonitrile and 50 ml. 30% H_2O_2 solution was added over a period of 2 hours, the pH being maintained continuously at about 9 by the simultaneous addition of 1 *N* NaOH. After cooling the solution was acidified with 5 *N* HCl, diluted with water and extracted with ethyl acetate. The combined extracts were washed with 5% Na_2CO_3 and water and finally dried with Na_2SO_4. The solution was concentrated *in vacuo* and the residue crystallized from ethanol, to yield 2,6 g. 3β-hydroxy-16β-methyl-16,17α-epoxy-Δ_5-pregnene-20-one (VII), which was identical with the compound described above. M. p. 190—193°, $(\alpha)_D^{20}$ − 20° (c = 1, $CHCl_3$). Anal.: Found C 76,61; H 9,27%.

3β-acetoxy-16β-methyl-16,17α-epoxy-Δ_5-pregnene-20-one (VIII)

The compound was prepared according to SYHORA [12] from VII, and crystallized from methanol, m. p. 178—180°, $(\alpha)_D^{20}$ − 18° (c = 1, $CHCl_3$). Anal.: requires for $C_{24}H_{34}O_4$ C 74,57; H 8,86. Found: C 74,52; H 8,69%.

3β-acetoxy-16β-chloro-17α-hydroxy-Δ_5-pregnene-20-one (X)

1 g. 3β-acetoxy-16,17α-epoxy-Δ_5-pregnene-20-one (IX) was dissolved in 10 ml. chloroform and dry hydrogen chloride gas was passed through the solution for 3 hours, the temperature being maintained at 0°. The solution was washed with saturated aqueous $NaHCO_3$ solution and water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was crystallizedfro m a methanol-chloroform (3:1) mixture, to give 0,65 g. 3β-acetoxy-16β-chloro-17α-hydroxy-Δ_5-pregnene-20-one (X), m. p. 152—156°, $(\alpha)_D^{20} - 20°$ (c = 1, $CHCl_3$). Anal.: $C_{23}H_{33}O_4Cl$ requires C 67,54; H 8,13; Cl 8,67. Found: C 67,48; H 8,33; Cl 8,85%.

3β-acetoxy-5α,17α-dihydroxy-6β,16β-dichloropregnane-20-one (XI)

500 mg. 3β-acetoxy-5,6α,16,17α-diepoxypregnane-20-one was subjected to the same procedure as that described at X, when 320 mg. 3β-acetoxy-5α,17α-dihydroxy-6β,16β-dichloropregnane-20-one (VI) was obtained, m. p. 159—162°. Anal.: $C_{23}H_{34}O_5$ requires C 59,86; H 7,42; Cl 15,36. Found: C 59,70; H 7,47; Cl 15,91%.

3β-acetoxy-5α-hydroxy-6β,16β-dichloropregnane-20-one (XII)

By the same procedure 200 mg. 3β-acetoxy-5,6α-epoxy-Δ_{16}-pregnane-20-one (III) gave 165 mg. 3β-acetoxy-5α-hydroxy-6β,16α-dichloropregnane-20-one (XII), m. p. 244—248°. Anal.: $C_{23}H_{34}O_4Cl_2$ requires C 62,01; H 7,69; Cl 15,92. Found: C 61,91; H 7,85; Cl 15,21%.

3β,5α-dihydroxy-6β-chloro-Δ_{16}-pregnene-20-one (XIII)

500 mg. 3β-acetoxy-5,6α-epoxy-Δ_{16}-pregnene-20-one (III) was dissolved in 30 ml. acetone, 3 ml. concentrated hydrochloric acid was added, the solution was saturated with $MgCl_2$ and refluxed for 2 hours. The reaction mixture was heated with saturated Na_2CO_3 solution, the material deposited was filtered off, washed with water, dried and cristallized from ethanol, to yield 302 mg. 3β,5α-dihydroxy-6β-chloro-Δ_{16}-pregnene-20-one (XIII), m. p. 214—216°. Anal.: $C_{21}H_{31}O_3Cl$ requires C 68,74; H 8,51; Cl 9,66. Found: C 68,94; H 8,31; Cl 10,02%.

Acetylation of 16-substituted Δ_5-pregnene derivatives

500 mg. Δ_5-pregnene derivative was dissolved in 5 ml. pyridine, 5 ml. acetic anhydride was added and the mixture heated on a steam-bath for 30 minutes. After cooling the mixture was diluted with 20 ml. water and extracted with 3×50 ml. chloroform. The combined chloroform phases were washed with 2×25 ml. 5% HCl solution, with 2×25 ml. 5% Na_2CO_3 solution and finally with water, dried over anhydrous Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was crystallized from methanol and the homogeneity of the product controlled with thin-layer chromatography (using Kiesegel G. Merck, 5% ethanol in benzene; development with phosphoric acid). Data of the obtained acetates are shown by Table I.

Epoxidation of 16-substituted-Δ_5-pregnene acetates

2 ml. 5—6% ethereal monoperphthalic acid solution was added to a solution of 200 mg. 16-substituted Δ_5-pregnene acetate in 5 ml. chloroform at 0°, the mixture kept overnight and an aliquot of the clear supernatant subjected to thin-layer chromatography. (The thin-layer chromatography was carried out as above.) Whenever the epoxidation had not been completed a further 1 ml. 5—6% ethereal monoperphthalic acid solution was added. After the reaction had completed the phthalic acid deposited was filtered off, the solution washed twice with 5 ml. 5% $NaHCO_3$ solution and with 5 ml. water thrice, followed by drying the usual way. The dry solution was concentrated *in vacuo*, and the residue crystallized from methanol. Data of the epoxides are shown in Table I.

3β,5α-dihydroxy-6β-chloro-16α-cyanopregnane-20-one (XXXII)

50 mg. 3β-acetoxy-5,6α-epoxy-16α-cyanopregnane-20-one (XXI) was dissolved in 5 ml. acetone, 0.5 ml. concentrated hydrochloric acid was added, the solution heated with crystalline $MgCl_2$ and finally refluxed for two hours. After cooling the mixture was diluted with several volumes of water, extracted with ethyl acetate, the combined extracts were washed with water, dried in the usual way, evaporated to dryness and the residue was crystallized from methanol. The product melted at 198—200°. Anal.: $C_{22}H_{32}NCl$ requires C 67,07; H 8,18; Cl 9,00. Found: C 67,18; H 8,31; Cl 8,77%.

3β,5α,20β-trihydroxy-6β-chloro-16β-carboxy-pregnane-16,20-lactone (XXXIII)

50 mg. 3β-acetoxy-20β-hydroxy-5,6α-epoxy-16β-carboxypregnane-16,20-lactone (XIX) was treated with hydrogen chloride as described for the preparation of XXXII. The obtained 3β, 5α, 20β-trihydroxy-6β-chloro-16β-hydroxypregnane-16-20-lactone (XXXIII) was crystallized from methanol, m. p. 203—206°. Anal.: $C_{22}H_{33}Cl$ requires C 66,56; H 8,38; Cl 8,93. Found: C 66,18; H 8,29; Cl 8,75%.

3β,5α-dihydroxy-6β-chloropregnane-20-one (XXXIV)

50 mg. 3β-acetoxy-5,6α-epoxypregnan-20-one (XXXI) was treated with hydrochloric acid as described for the preparation of XXXII, the product was crystallized from methanol and melted at 164—166°, Anal.: $C_{21}H_{33}O_3Cl$ rquires C 68,36; H 9,01; Cl 9,61. Found: C 68,25; H 9,09; Cl 9,86%.

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ЭПОКСИДАЦИЯ ПРОЙЗВОДНЫХ ПРЕГНАНА И ИЗУЧЕНИЕ ОКИСЕЙ ДВУХАТОМНОГО РАДИКАЛА

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Авторами изучались различные реакции эпоксидации ацетата прегнадиэнолона. Приготовились 5,6-эпоксиды 16-замащенных производных прегнана и открытие этих окисей двухатомного радикала в галогидрины было также изучено. Исследовались инфракрасные спектры различных производных окисей двухатомного радикала прегнана.