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Reactions of 14β,15β-Epoxypregn-16-en-20-one with Nucleophiles[1]

Toshio Nambara, Shujiro Goya, Junichi Goto and Kazutake Shimada

Pharmaceutical Institute, Tohoku University School of Medicine[2]

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The reactivities of the nucleophilic reagents such as alcohol, cyanide and thiol toward the Δ^{16}-double bond of 3β-acetoxy-14β,15β-epoxy-5α-pregn-16-en-20-one (IV) have been investigated (Chart 1). All the nucleophiles showed the rear-side attack to provide the 16α-substituted derivatives. This result may be attributable to the characteristic feature of C/D-ring fusion, where ring D is less bent below than that of the ordinary 14β-steroid. Configuration of the 17-side chain of the adducts produced under the alkaline reaction conditions was found to be α. A possible explanation for the formation of the 16-cyano-14,16-diene (IX) from IV has also been described.

As a part of our program dealing with the synthesis of cardiotonic steroid analogs, the authors have attempted to explore the reactivities of nucleophilic reagents toward the Δ^{16}-double bond of the 14β,15β-epoxypregn-16-en-20-one in order to obtain the 14β-steroids having a large variety of 16-substituents. Numerous papers have already been published reporting additive condensation of the nucleophiles with the α,β-unsaturated ketone on the steroid nucleus. With respect to the Δ^{16}-20-ketone these works so far concern with the usual C/D-*trans* fused system, but not with C/D-*cis*, 14β-steroids.[3]

For this purpose 3β-acetoxy-14β,15β-epoxy-5α-pregn-16-en-20-one (IV) was prepared starting from 3β-acetoxy-5α-pregn-16-en-20-one (I). Bromination with N-bromosuccinimide gave the 15ξ-bromo derivative (II), which in turn was transformed into the pregna-14,16-diene (III) on treatment with sodium iodide.[4] Epoxidation of this product with perbenzoic acid furnished the desired 14β,15β-epoxypregn-16-en-20-one.

The initial project was directed to the studies on the reactions of the alcohols with the Δ^{16}-20-keto system. When IV was boiled under reflux in methanolic potassium hydroxide, the 16-methoxy derivative (Va) was provided in almost quantitative yield. Treatment with benzyl alcohol in the presence of alkali gave similarly 3β-hydroxy-14β,15β-epoxy-16-benzyloxy-5α-pregnan-20-one (VIa). Upon hydrogenolysis over palladium-on-charcoal VIa and VIb underwent debenzylation with ease yielding the 16-hydroxypregnan-20-one (VIc) and its 3-acetate (VId). As illustrated in Fig. 1, the optical rotatory dispersion curves of these new compounds showed the negative Cotton effect. It is sufficiently substantiated that the 17β-pregnan-20-one displays the positive Cotton effect, whereas the 17-epimer the negative sign.[5] Therefore the configuration of C-17-acetyl group in the 16-oxygenated products was established to be α. The nuclear magnetic resonance spectra showed a singlet

1) This paper constitutes Part I of the series entitled "Studies on Cardiotonic Steroid Analogs." A part of this work was presented at the 7th Annual Meeting of Tohoku Branch, Pharmaceutical Society of Japan, Sendai, October 1967.
2) Location: *Kita-4-bancho, Sendai.*
3) D.K. Fukushima and T.F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951); J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *ibid.*, **73**, 1528 (1951); H. Hirschmann, F.B. Hirschmann and M.A. Daus, *ibid.*, **74**, 539 (1952); J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 4961 (1951); A.S. Hoffman, H.M. Kissman and M.J. Weiss, *J. Med. Pharm. Chem.*, **5**, 962 (1962); L.L. Smith and D.M. Teller, *J. Med. Chem.*, **7**,531 (1964).
4) A.J. Solo and B. Singh, *J. Org. Chem.*, **30**, 1658 (1965).
5) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, 1960, p. 51; H. Mitsuhashi, T. Nomura and M. Fukuoka, *Steroids*, **4**, 483 (1964).

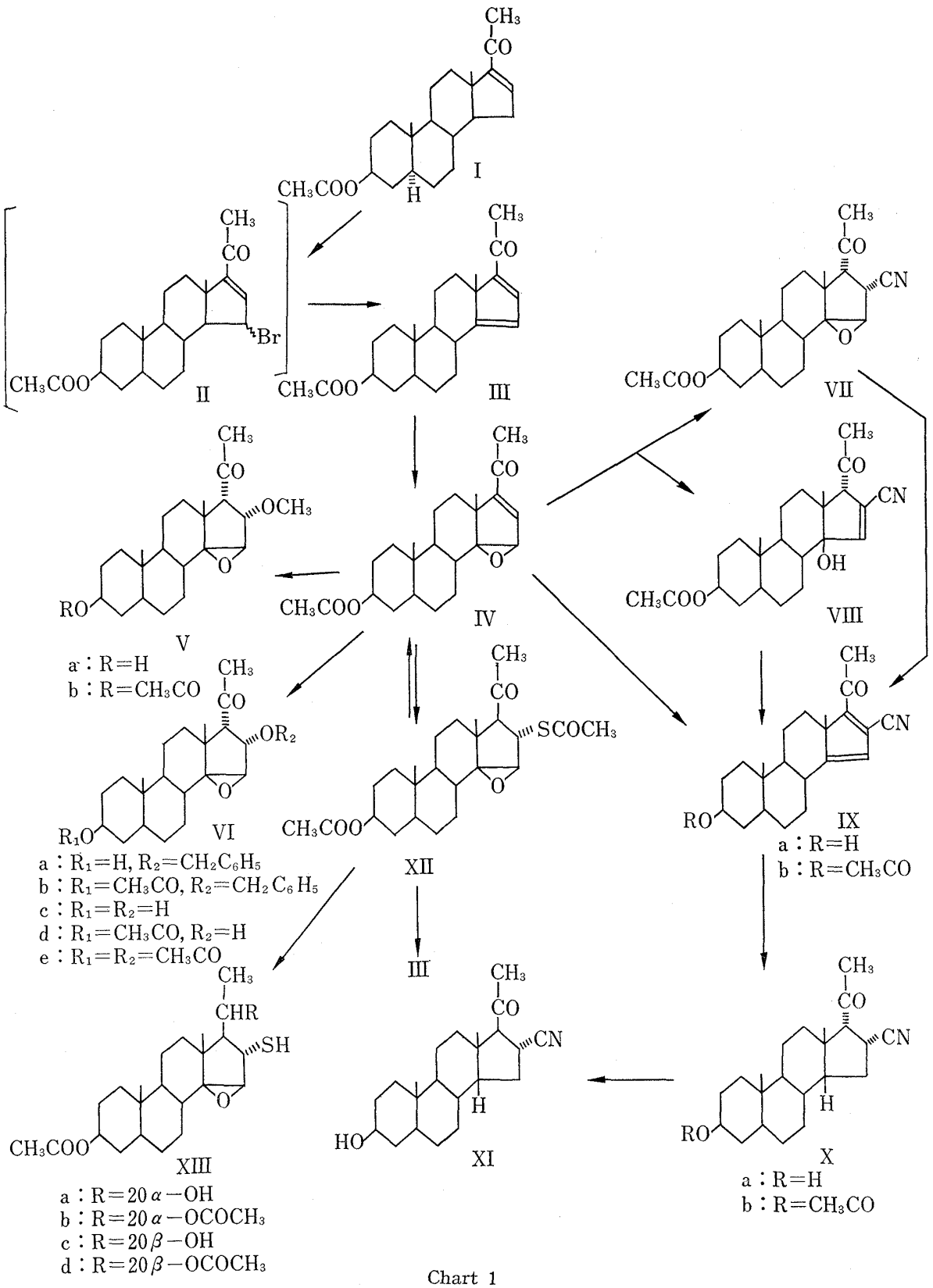


Chart 1

peak at about 3.5 ppm for the 15α-proton, which supported the *trans* arrangement of H15,16, that is, α-configuration of the newly introduced group into C-16 (See also TABLE I).

Next the reactions with the cyanide were performed under the different conditions. When IV was refluxed with sodium cyanide in aqueous ethanol, the crystalline product was solely provided. This substance (IXa) showed an absorption maximum at 325 mμ indicating

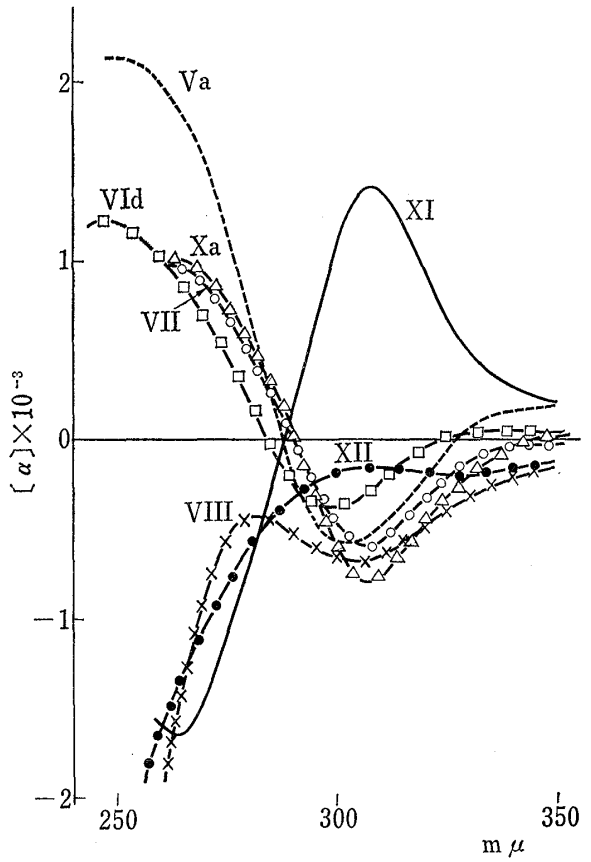


Fig. 1. Optical Rotatory Dispersion Curves of 16–Substituted 5α–Pregnan–20–ones in Methanol

the presence of the $\Delta^{14,16}$–dien–20–one. The structure was confirmed by further elaboration leading to the saturated compound. As was expected hydrogenation over palladium-on-charcoal took a normal course[6] to give 3β-hydroxy-16α-cyano-14β,17α-pregnan-20-one (Xa) and the 3-acetate (Xb). The configuration of the C–17–acetyl group in the reduction product followed readily from the rotatory dispersion spectra. Epimerization of the C–17–side chain was then undertaken with Xa. Upon prolonged adsorption on alumina 3β-hydroxy-16α-cyano-14β,17β-pregnan-20-one (XI) was afforded along with the unchanged material in a ratio of 5 to 1, which were efficiently separated by pre parative thin–layer chromatography. The positive Cotton effect and coupling constant value of H16,17 (J=5.5 cps) justified unequivocally the assignment of the structure of XI. It has already been reported that at equilibrium the presence of the 16α-methyl group in the 14β-pregnan-20-one favors exclusively the 17β-side chain, which is *trans* to C-16-substituent.[7] The ratio of the two 17-epimers of 16α-substituted 14β-pregnan-20-ones in the equilibrated state appears to depend on the size of the group at C–16.[8] On the other hand treatment with sodium cyanide in the presence of ammonium chloride at room temperature gave the different results. The reaction product was resolved into two components in a ratio of 6 to 1 by means of preparative thin–layer chromatography. Examination of the optical rotatory dispersion and nuclear magnetic resonance spectral data disclosed that the major one was 3β-acetoxy-14β,15β-epoxy-16α-cyano-5α,17α-pregnan-20-one (VII), while the minor 3β-acetoxy-14β-hydroxy-5α,17α-pregn-15-en-20-one (VIII). Being refluxed in ethanol containing sodium cyanide, these compounds were easily transformed into the same $\Delta^{14,16}$–dienes (IXa,b). This finding strongly suggested that both VII and VIII would be the intermediates leading to IXa. The reaction mechanism of the formation of the $\Delta^{14,16}$-diene can be explained as illustrated in Chart 2.

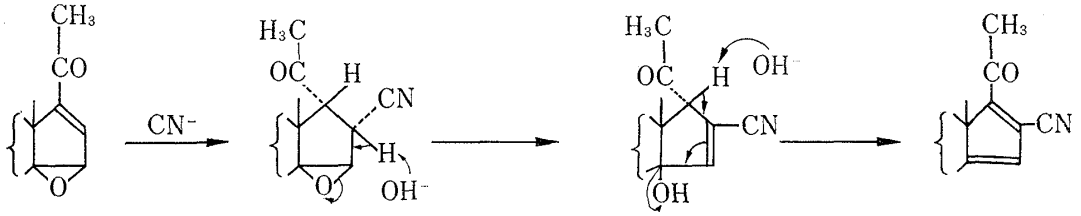
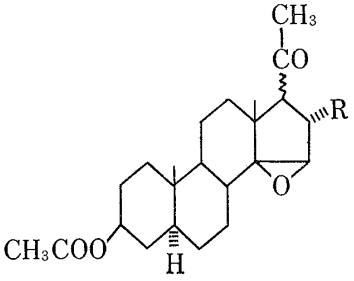


Chart 2

6) Pl.A. Plattner, H. Heusser and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).
7) R. Michova and K. Syhora, *Collection Czech. Chem. Commun.*, **30**, 2771 (1965).
8) The steric requirement of the cyano group is smaller than that of the methyl group.[9]

Condensation of thioacetic acid and IV was effected without catalyst to give the adduct (XII) in excellent yield. The orientation of the sulfur function introduced was formulated as α on the basis of the coupling constant of H15,16. The stereochemistry at C–17 was evident from the rotatory dispersion curve exhibiting the positive Cotton effect. With respect to the nuclear magnetic resonance spectra of this substance 18–methyl proton signal appeared at the higher field than those of the related 16α–substituted 17α–pregnan–20–ones as listed in Table I. These physical data together rationalized the assignment of β–configuration to the C–17–acetyl group in XII. The reaction with the sulfhydryl reagent appeared to offer a means of preparing the desired 14β,15β–epoxy–17β–pregnane derivatives, and therefore the chemistry of this adduct was further developed. On brief contact with alumina XII was backed again to the parent 16–dehydro–20–ketone (IV) with loss of thioacetic acid. Elimination of the 16–acetylthio function was found more facile than that of the 16–acetoxyl group. In addition an attempt for desulfurization with Raney nickel resulted in formation of the unexpected $\Delta^{14,16}$–diene (III). Reduction with potassium borohydride under the mild condition gave a pair of epimeric 3β–acetoxy–14β,15β–epoxy–16α–mercapto–5α,17β–pregnan–20–ols (XIIIa,c). Configuration of the 20–hydroxyl group was tentatively assigned on the basis of the increment of the molecular rotation for conversion of the 20–ol to the acetate (XIIIb,d).[10]

Table I. Chemical Shifts of C-18, C-19 and C-21 Protons in 16α-Substituted 14β,15β-Epoxy-5α-pregnan-20-ones



Compound			Chemical shift (δ) ppm[a]		
R	Configr. of C–17–$COCH_3$		18–H	19–H	21–H
OCH_3	α	Vb	1.35	0.86	2.18
$OCH_2C_6H_5$	α	VIb	1.33	0.83	2.11
OH	α	VId	1.35	0.83	2.16
$OCOCH_3$	α	VIe	1.37	0.93	2.15
CN	α	VII	1.33	0.86	2.20
$SCOCH_3$	β	XII	1.13	0.83	2.03

a) Tetramethylsilane was used as an internal standard.

It is of particular interest that all the nucleophiles so far examined exert the rear–side attack toward the Δ^{16}–20–ketone furnishing the 16α–substituted derivative as in usual 14α–ring system. This finding appears to be strange because the access of the reagent generally favors the β–side of the molecule in the 14β–steroids, where the ring D is bent below to form the cage–like structure. Inspection of the Dreiding model, however, shows that the C/D–ring juncture of the 14β,15β–epoxide seems to be more flat than that of the ordinary 14β–steroid and in consequence the α–side is less hindered. These characteristic features of the ring fusion

9) N.L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962); C. Djerassi, R.A. Schneider, H. Vorbruggen and N.L. Allinger, *ibid.*, **28**, 1632 (1963).
10) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publ., Co., New York, 1959, pp. 614—616.

may provide a possible explanation for the present observations.[11] In addition, with regard to the stereochemistry at C-17 orientation of hydrogen must be affected by equilibration under the alkaline reaction conditions and from the stability considerations may be expected to be β. In actuality this assumption has been demonstrated by characterizing the adducts derived from alcohols and cyanide. Nevertheless it should be now emphasized that of the nucleophiles only the sulfhydryl reagent reacts with the Δ^{16}-20-ketone without catalyst to form the 17β-pregnan-20-one derivative, although no plausible explanation is at present available.

Further studies on the reactivities of the nucleophiles toward the Δ^{16}-double bond of the usual 14β-pregn-16-en-20-one are being conducted in this laboratory, and the results will be reported in near future.

Experimental[12]

3β-Acetoxy-5α-pregna-14,16-dien-20-one (III)—A solution of 3β-acetoxy-5α-pregn-16-en-20-one (I) (1 g) in CCl_4 (25 ml) was concentrated to a volume of 15 ml by slow distillation to remove the moisture. To this solution were added N-bromosuccinimide (600 mg) and 2,2'-azobisisobutyronitrile (4 mg), and the solution was irradiated with two tungsten lamps (500 W) for 25 min under a stream of N_2. After removal of the precipitate by filtration, the filtrate was concentrated to give the 15ξ-bromo derivative (II) as an oily residue. The crude product was subjected to further step without purification. To a solution of this product in acetone (15 ml) was added NaI (900 mg) and refluxed for 3 hr under a stream of N_2. The reaction mixture was extracted with $CHCl_3$, washed with 5% $Na_2S_2O_3$, H_2O and dried over anhydrous Na_2SO_4. On usual work-up the residue obtained was chromatographed on Al_2O_3 (30 g). Elution with hexane-benzene (5:1) and recrystallization of the eluate from MeOH gave III (550 mg) as pale yellow prisms. mp 172—174°. Analytical sample melted at 180—182.5°. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.34; H, 8.96. UV λ_{max}^{EtOH} mμ (ε): 312 (13000). Tschesche, *et al.* prepared the same compound by the different method and reported it mp 181—182.5°.[13]

3β-Acetoxy-14β,15β-epoxy-5α-pregn-16-en-20-one (IV)——III (250 mg) was dissolved in $C_6H_5CO_3H$-$CHCl_3$ solution (0.046 M, 20 ml) and the solution was allowed to stand at room temperature for 43 hr. After usual work-up the crude product obtained was chromatographed on Al_2O_3 (8 g). Elution with hexane-benzene (4:1) and recrystallization of the eluate from MeOH gave IV (111 mg) as colorless plates. mp 194—195° (reported mp 194.5—195.5°).[14]

3β-Hydroxy-14β,15β-epoxy-16α-methoxy-5α,17α-pregnan-20-one (Va)——A 3% methanolic KOH solution (8 ml) of IV (80 mg) was refluxed for 1 hr. The resulting solution was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. Upon evaporation of solvent the colorless crystalline product was obtained. Recrystallization from MeOH gave Va (64 mg) as colorless needles. mp 257—260°. $[\alpha]_D^{21}$ +65.0° (c=0.28). *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.69; H, 9.49. NMR (4% solution in $CDCl_3$) δ: 0.83 (3H, s, 19-CH_3), 1.34 (3H, s, 18-CH_3), 2.18 (3H, s, 21-CH_3), 2.60 (1H, d, J=8 cps, 17β-H), 3.38 (3H, s, 16α-OCH_3), 3.55 (1H, s, 15α-H), 3.55 (1H, m, 3α-H), 4.23 (1H, d, J=8 cps, 16β-H). ORD (c=0.15, MeOH) $[\alpha]^{24}$ (mμ): +157° (350), 0° (327), −593° (302) (trough), 0° (288), +2133° (250) (peak).

3β-Acetoxy-14β,15β-epoxy-16α-methoxy-5α,17α-pregnan-20-one (Vb)——Usual treatment of Va with Ac_2O and pyridine and recrystallization from MeOH gave Vb as colorless needles. mp 193—194°. $[\alpha]_D^{21}$ +45.0° (c=0.17). *Anal.* Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 70.81; H, 8.82. NMR (4% solution in $CDCl_3$) δ: 0.86 (3H, s, 19-CH_3), 1.35 (3H, s, 18-CH_3), 2.03 (3H, s, 3β-$OCOCH_3$), 2.18 (3H, s, 21-CH_3), 2.64 (1H, d, J=8 cps, 17β-H), 3.40 (3H, s, 16α-OCH_3), 3.58 (1H, s, 15α-H), 4.23 (1H, d, J=8 cps, 16β-H), 4.70 (1H, m, 3α-H).

3β-Hydroxy-14β,15β-epoxy-16α-benzyloxy-5α,17α-pregnan-20-one (VIa)——To a solution of IV (340 mg) in benzyl alcohol (12 ml) was added pulverized KOH (300 mg), and the resulting solution was stirred at room temperature under a stream of N_2 for 11 hr. The reaction mixture was diluted with AcOEt, filtered and

11) As mentioned above the difference in ring fusion between these two C/D-*cis* steroids was also reflected on the prefered configuration of the 17-acetyl group in 16α-cyanopregnan-20-ones.

12) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in MeOH solution unless otherwise stated. Rotatory dispersion curves were obtained on Nihon-Bunko Model ORD/UV-5 rotatory dispersion recorder. Nuclear magnetic resonance spectra were obtained on Hitachi Model H-60 spectrometer at 60 Mc in $CDCl_3$ using tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet.

13) R. Tschesche, F. Riemhofer and G. Snatzke, *Chem. Ber.*, **98**, 1188, (1965).

14) Pl.A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947).

the filtrate was submitted to steam distillation. The residue thus obtained was extracted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up an oily residue obtained was subjected to preparative TLC on silica gel HF using benzene–AcOEt (11:2) as solvent. The adsorbent of the zone corresponding to *Rf* value 0.15 was eluted with AcOEt and recrystallization of the eluate from benzene–hexane gave VIa (200 mg) as colorless needles. mp 130.5—131.° $[\alpha]_D^{16}$ +36.4° (c=0.25). *Anal.* Calcd. for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.08; H, 8.61. NMR (4% solution in $CDCl_3$) δ: 0.80 (3H, s, 19–CH_3), 1.33 (3H, s, 18–CH_3), 2.11 (3H, s, 21–CH_3), 2.70 (1H, d, J=8.6 cps, 17β–H), 3.45 (1H, s, 15α–H), 3.55 (1H, m, 3α–H), 4.41 (1H, d, J=8.6 cps, 16β–H), 4.56 (2H, s, 16α–OCH_2–), 7.33(5H, s, –C_6H_5).

3β-Acetoxy-14β,15β-epoxy-16α-benzyloxy-5α,17α-pregnan-20-one (VIb)——Usual treatment of VIa with Ac_2O and pyridine and recrystallization from MeOH gave VIb as colorless plates. mp 146—147.5°. $[\alpha]_D^{16}$ +38.8° (c=0.30). *Anal.* Calcd. for $C_{30}H_{40}O_5$: C, 74.97; H, 8.39. Found: C, 74.58; H, 8.25. NMR (4% solution in $CDCl_3$) δ:0.83 (3H, s, 19–CH_3), 1.33 (3H, s, 18–CH_3), 2.00 (3H, s, 3β–$OCOCH_3$), 2.11 (3H, s, 21–CH_3), 2.70 (1H, d, J=8.6 cps, 17β–H), 3.45 (1H, s, 15α–H), 4.41 (1H, d, J=8.6 cps, 16β–H), 4.56 (2H, s, 16α–OCH_2–), 4.70 (1H, m, 3α–H), 7.33 (5H, s, –C_6H_5).

3β,16α-Dihydroxy-14β,15β-epoxy-5α,17α-pregnan-20-one (VIc)——A solution of VIa (50 mg) in EtOH (10 ml) was shaken with 10% Pd/C (20 mg) under a stream of H_2 at room temperature for 4 hr. After removal of catalyst by filtration, the filtrate was concentrated to give the crystalline product. Recrystallization from MeOH gave VIc (36 mg) as colorless needles. mp 257.5—259°. $[\alpha]_D^{16}$ +27.7° (c=0.10). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 71.88; H, 9.05. ORD (c=0.05, MeOH) $[\alpha]^{23}$ (mμ): +75° (400), 0° (342), −524° (303) (trough), 0° (286), +1405° (250) (peak).

3β,16α-Dihydroxy-14β,15β-epoxy-5α,17α-pregnan-20-one 3-Acetate (VId)——VIb (25 mg) was treated in the same manner as in VIc. Recrystallization from benzene–hexane gave VId (18 mg) as colorless needles. mp 210—212°. $[\alpha]_D^{16}$ +32.2° (c=0.16). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.85; H, 8.73. NMR (4% solution in $CDCl_3$) δ:0.83 (3H, s, 19–CH_3), 1.35 (3H, s, 18–CH_3), 2.00 (3H, s, 3β–$OCOCH_3$), 2.16 (3H, s, 21–CH_3), 2.50 (1H, d, J=8.4 cps, 17β–H), 3.48 (1H, s, 15α–H), 4.56 (1H, d, J=8.4 cps, 16β–H), 4.60 (1H, m, 3α–H). ORD (c=0.16, MeOH) $[\alpha]^{24}$ (mμ): +38° (400), 0° (323), −381° (299) (trough), 0° (284), +1212° (246) (peak).

3β,16α-Diacetoxy-14β,15β-epxoy-5α,17α-pregnan-20-one (VIe)——Usual treatment of VIc (or VId) with Ac_2O and pyridine and recrystallization from acetone gave VIe as colorless needles. mp 217—219°. $[\alpha]_D^{16}$ +57.2° (c=0.14). *Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.18; H, 8.24. NMR (4% solution in $CDCl_3$) δ:0.83 (3H, s, 19–CH_3), 1.37 (3H, s, 18–CH_3), 2.00, 2.04 (3H, s, 3β– and 16α–$OCOCH_3$), 2.15 (3H, s, 21–CH_3), 2.73 (1H, d, J=8.6 cps, 17β–H), 3.69 (1H, s, 15α–H), 4.60 (1H, m, 3α–H), 5.47 (1H, d, J=8.6 cps, 16β–H).

3β-Hydroxy-16-cyano-5α-pregna-14,16-dien-20-one (IXa)——To an ethanolic solution (64 ml) of IV (400 mg) was added aq. solution (16 ml) of NaCN (56 mg), and the resulting solution was refluxed for 50 min. The reaction mixture was extracted with $CHCl_3$, washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the residue obtained was chromatographed on silica gel (15 g). Elution with hexane–benzene (1:3) and recrystallization of the eluate from acetone–hexane gave IXa (290 mg) as colorless plates. mp 149—151°. $[\alpha]_D^{22}$ +399.5° (c=0.12). *Anal.* Calcd. for $C_{22}H_{29}O_2N$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.85; H, 8.60; N, 4.25. UV λ_{max}^{EtOH} mμ (ε): 325 (11400). IR ν_{max}^{KBr} cm^{-1}: 2208 (C≡N), 1642 (C=O), 1587 (C=C). NMR (4% solution in $CDCl_3$) δ:0.91 (3H, s, 19–CH_3), 1.20 (3H, s, 18–CH_3), 2.58 (3H, s, 21–CH_3), 3.50 (1H, m, 3α–H), 6.10 (1H, d, J=1.7 cps, 15–H).

3β–Acetoxy-16-cyano-5α-pregna-14,16-dien-20-one (IXb)——Usual treatment of IXa with Ac_2O and pyridine and recrystallization from MeOH gave IXb as colorless needles. mp 149—150°. $[\alpha]_D^{22}$ +375.0° (c=0.12). *Anal.* Calcd. for $C_{24}H_{31}O_3N$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.67; H, 7.88; N, 3.85. NMR (4% solution in $CDCl_3$) δ:0.95 (3H, s, 19–CH_3), 1.20 (3H, s, 18–CH_3), 2.01 (3H, s, 3β–$OCOCH_3$), 2.60 (3H, s, 21–CH_3), 4.65 (1H, m, 3α–H), 6.10 (1H, d, J=1.7 cps, 15–H).

3β-Hydroxy-16α-cyano-5α,14β,17α-pregnan-20-one (Xa)——A solution of IXa (100 mg) in MeOH (10 ml) was shaken with 10% Pd/C (30 mg) under a stream of H_2 at room temperature for 30 hr. After removal of catalyst by filtration, the filtrate was concentrated to give the semi-solid residue. The crude product was chromatographed on silica gel (3 g). Elution with benzene–ether (8:1) and recrystallization of the eluate from acetone–hexane gave Xa (75 mg) as colorless needles. mp 205—207°. $[\alpha]_D^{17}$ +23.7° (c=0.11). *Anal.* Calcd. for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.75; H, 9.72; N, 4.88. IR ν_{max}^{KBr} cm^{-1}: 2222 (C≡N), 1690 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.77 (3H, s, 19–CH_3), 1.20 (3H, s, 18–CH_3), 2.21 (3H, s, 21–CH_3), 2.76 (1H, d, J=9.4 cps, 17β–H), 3.10 (1H, q, J=8.6, 9.4 cps, 16β–H), 3.55 (1H, m, 3α–H). ORD (c=0.11, MeOH) $[\alpha]^{23}$ (mμ): +35° (400), 0° (346), −802° (308) (trough), 0° (291), +1004° (262) (peak).

3β-Acetoxy-16α-cyano-5α,14β,17α-pregnan-20-one (Xb)——Usual treatment of Xa with Ac_2O and pyridine and recrystallization from MeOH gave Xb as colorless needles. mp 204—206°. $[\alpha]_D^{16}$ +15.0° (c=0.20). *Anal.* Calcd. for $C_{24}H_{35}O_3N$: C, 74.76; H, 9.15; N, 3.63. Found: C, 74.48; H, 9.14; N, 3.58. NMR (4% solution in $CDCl_3$) δ:0.80 (3H, s, 19–CH_3), 1.20 (3H, s, 18–CH_3), 2.00 (3H, s, 3β–$OCOCH_3$), 2.22 (3H, s, 21–CH_3), 2.76 (1H,d, J=9.4 cps, 17β–H), 3.13 (1H, q, J=8.6, 9.4 cps, 16β–H), 4.60 (1H, m, 3α–H).

3β-Hydroxy-16α-cyano-5α,14β,17β-pregnan-20-one (XI)——Xa (68 mg) was adsorbed on Al_2O_3 (2 g) and allowed to stand for 3 days. Elution with AcOEt gave colorless oily substance. The crude product was submitted to preparative TLC on silica gel G using benzene–AcOEt (2:1) as solvent. The adsorbent of the zone corresponding to *Rf* value 0.51 was eluted with AcOEt. Recrystallization of the eluate from hexane–acetone gave XI (38 mg) as colorless needles. mp 170—172°. $[\alpha]_D^{17}$ +48.7° (c=0.20). *Anal.* Calcd. for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68; N, 4.08. Found: C, 77.09; H, 9.73; N, 4.14. IR ν_{max}^{KBr} cm^{-1}: 2230 (C≡N), 1712 (C=O). NMR (4% solution in $CDCl_3$) δ: 0.76 (3H, s, 19–CH_3), 0.98 (3H, s, 18–CH_3), 2.20 (3H, s, 21–CH_3), 3.00 (1H, d, J=5.5 cps, 17α–H), 3.27 (1H, q, J=2.6, 5.5 cps, 16β–H), 3.55 (1H, m, 3α–H). ORD (c=0.21, MeOH) $[\alpha]^{12}$ (mμ): +192° (400), +1414° (308) (peak), 0° (288), −1654° (263) (trough). The adsorbent of the zone corresponding to *Rf* value 0.46 was eluted with AcOEt. Recrystallization of the eluate from hexane–acetone gave the unchanged Xa (8 mg) as colorless needles.

3β-Acetoxy-16α-cyano-14β,15β-epoxy-5α,17α-pregnan-20-one (VII), 3β,14β-Dihydroxy-16-cyano-5α,17α-pregn-15-en-20-one 3-Acetate (VIII)——To an ethanolic solution (25 ml) of IV (100 mg) was added aq. solution (4 ml) of NaCN (25 mg) and NH_4Cl (30 mg), and the resulting solution was stirred at room temperature. Additional two portions of the same amount of NaCN and NH_4Cl were added after 18 hr and 42 hr, respectively. The reaction mixture was stirred for 66 hr, and then was extracted with CCl_4, washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from MeOH gave VII (62 mg) as colorless needles. mp 184.5—185°. $[\alpha]_D^{18}$ −26.0° (c=0.20). *Anal.* Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.42; H, 8.25; N, 3.52. IR ν_{max}^{KBr} cm^{-1}: 2235 (C≡N), 1736, 1709 (C=O). NMR (4% solution in $CDCl_3$) δ:0.86 (3H, s, 19–CH_3), 1.33 (3H, s, 18–CH_3), 1.99 (3H, s, 3β–$OCOCH_3$), 2.20 (3H, s, 21–CH_3), 2.63 (1H, d, J=8 cps, 17β–H), 3.34 (1H, d, J=8 cps, 16β–H), 3.69 (1H, s, 15α–H), 4.60 (1H, m, 3α–H). ORD (c=0.19, MeOH) $[\alpha]^{10}$ (mμ): −16° (400), −617° (307) (trough), 0° (290), +990° (264) (peak). After separation of VII the mother liquor was submitted to preparative TLC on silica gel G using hexane–AcOEt (5:2) as solvent. The adsorbent of the zone corresponding to *Rf* value 0.68 was eluted with acetone. Recrystallization of the eluate from MeOH gave additional 22 mg of VII as colorless needles. The adsorbent of the zone corresponding to *Rf* value 0.29 was eluted with acetone. Recrystallization of the eluate from acetone–hexane gave VIII (15 mg) as colorless needles. mp 185—186°. $[\alpha]_D^{17}$ −40.0° (c=0.08). *Anal.* Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51. Found: C, 71.89; H, 8.67; N, 3.62. UV λ_{max}^{MeOH} mμ (ε): 217 (6800). IR ν_{max}^{KBr} cm^{-1}: 2222 (C≡N), 1730, 1701 (C=O), 1660 (C=C). NMR (4% solution in $CDCl_3$) δ:0.79 (3H, s, 19–CH_3), 1.41 (3H, s, 18–CH_3), 1.99 (3H, s, 3β–$OCOCH_3$), 2.21 (3H, s, 21–CH_3), 3.98 (1H, d, J=3 cps, 17β–H), 4.60 (1H, m, 3α–H), 6.92 (1H, d, J=3 cps, 15–H). ORD (c=0.08, MeOH) $[\alpha]^{12}$ (mμ): −80° (400), −693° (304) (trough), −427° (280) (peak), −6200° (248) (trough).

A solution of VII (3 mg) in 95% EtOH (1 ml) containing NaCN (5 mg) was refluxed for 30 min. TLC of the reaction mixture showed that VII was entirely converted to IXa. Similar treatment of VIII for 5 min resulted in formation of IXa and IXb.

3β-Acetoxy-14β,15β-epoxy-16α-acetylthio-5α,17β-pregnan-20-one (XII)——A solution of IV (500 mg) in tetrahydrofuran (5 ml) containing AcSH (250 mg) was allowed to stand at room temperature for 6 hr. The reaction mixture was poured into ice–water and extracted with ether. Organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product was obtained. Recrystallization from MeOH gave XII (561 mg) as colorless needles. mp 124—126°. $[\alpha]_D^{18}$ −106.6° (c=0.16). *Anal.* Calcd. for $C_{25}H_{36}O_5S$: C, 66.94; H, 8.09. Found: C, 66.90; H, 8.01. NMR (4% solution in $CDCl_3$) δ:0.83 (3H, s, 19–CH_3), 1.13 (3H, s, 18–CH_3), 2.00 (3H, s, 3β–$OCOCH_3$), 2.03 (3H, s, 21–CH_3), 2.38 (3H, s, 16α–$SCOCH_3$), 3.05 (1H, d, J=6.9 cps, 17α–H), 3.39 (1H, s, 15α–H), 4.45 (1H, d, J=6.9 cps, 16β–H), 4.60 (1H, m, 3α–H). ORD (c=0.15, MeOH) $[\alpha]^{24}$ (mμ): −137° (350), −204° (330), −171° (306) (peak), −4010° (238) (trough).

Reduction of XII with Potassium Borohydride——To a solution of XII (200 mg) in MeOH (20 ml) was added a methanolic solution of KBH_4 (100 mg) dropwise under ice-cooling. The resulting solution was stirred for 2.5 hr. After addition of a few drops of AcOH the reaction mixture was poured into ice–water. The separated crystalline product was filtered and dried. The crude product was then submitted to preparative TLC on silica gel G using hexane–AcOEt (3:2) as solvent. The adsorbents of the zones corresponding to *Rf* values 0.25 and 0.24 were collected and eluted with MeOH, respectively. Recrystallization of the former eluate from hexane–acetone gave 14β,15β–epoxy–16α–mercapto–5α,17β–pregnane–3β,20α–diol 3–acetate (XIIIa) (100 mg) as colorless needles. mp 178—180°. $[\alpha]_D^{15}$ −65.1° (c=0.15). *Anal.* Calcd. for $C_{23}H_{36}O_4S$: C, 67.62; H, 8.88. Found: C, 67.36; H, 8.87. NMR (4% solution in $CDCl_3$) δ:0.75 (3H, s, 19–CH_3), 1.14 (3H, s, 18–CH_3), 1.41 (3H, d, J=5.5 cps, 21–CH_3), 1.99 (3H, s, 3β–$OCOCH_3$), 2.15 (1H, q, J=1.7, 4.3 cps, 17α–H), 3.16 (1H, d, J=1.7 cps, 16β–H), 3.18 (1H, s, 15α–H), 3.85 (1H, m, 20β–H), 4.60 (1H, m, 3α–H). Recrystallization of the latter eluate from hexane–acetone gave 14β,15β–epoxy–16α–mercapto–5α,17β–pregnane–3β,20β–diol 3–acetate (XIIIc) (60 mg) as colorless needles. mp 170—172°. $[\alpha]_D^{16}$ −136.4° (c=0.10). *Anal.* Calcd. for $C_{23}H_{36}O_4S$: C, 67.62; H, 8.88. Found: C, 67.97; H, 8.68.

14β,15β-Epoxy-16α-mercapto-5α,17β-pregnane-3β,20α-diol 3,20-Diacetate (XIIIb)——Treatment of XIIIa with Ac_2O and pyridine at room temperature overnight and recrystallization from hexane–acetone gave XIIIb as colorless plates. mp 190—191°. $[\alpha]_D^{15}$ −150.5° (c=0.10). ΔM_D (20α–OH→OAc) = −412.3°. *Anal.*

Calcd. for $C_{25}H_{38}O_5S$: C, 66.64; H, 8.50. Found: C, 66.95; H, 8.60. NMR (4% solution in $CDCl_3$) δ:0.75 (3H, s, 19-CH_3), 1.09 (3H, s, 18-CH_3), 1.42 (3H, d, J=5 cps, 21-CH_3), 2.00 (6H, s, 3β,20α-$OCOCH_3$), 3.10 (1H, d, J=1.7 cps, 16β-H), 3.12 (1H, s, 15α-H), 4.60 (1H, m, 3α-H), 5.00 (1H, m, 20β-H).

14β,15β-Epoxy-16α-mercapto-5α,17β-pregnane-3β,20β-diol 3,20-Diacetate (XIIId)——Similar treatment of XIIIc with Ac_2O and pyridine as in XIIIb and recrystallization from hexane–acetone gave XIIId as eolorless needles. mp 164—166°. $[\alpha]_D^{16}$ −75.0° (c=0.14). ΔM_D (20β-OH→OAc) = +219.2°. *Anal.* Calcd. for $C_{25}H_{38}O_5S$: C, 66.64; H, 8.50. Found: C, 66.99; H, 8.60. NMR (4% solution in $CDCl_3$) δ:0.75 (3H, s, 19-CH_3), 1.07 (3H, s, 18-CH_3), 1.31 (3H, d, J=6.5 cps, 21-CH_3), 1.99 (3H, s, 3β-$OCOCH_3$), 2.04 (3H, s, 20β-$OCOCH_3$), 3.14 (1H, d, J=5 cps, 15α-H), 3.38 (1H, q, J=3.8, 5 cps, 16β-H), 4.65 (1H, m, 3α-H), 5.00 (1H, m, 20α-H).

Desulfurization of XII with Raney Nickel——A solution of XII (40 mg) in EtOH (5 ml) was refluxed with Raney Ni (W2) (6 g) for 20 hr. During the continuation of the reaction Raney Ni was added portionwise every 3 hr. After removal of metal by filtration, the filtrate was concentrated and submitted to preparative TLC on silica gel G using hexane–AcOEt (4:1) as solvent. The adsorbent of the zone corresponding to *Rf* value 0.55 was eluted with MeOH. Recrystallization of the eluate from MeOH gave III (15 mg) as colorless needles. mp 180—182.5°. Mixed melting point on admixture with the authentic sample showed no depression.

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