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Katsumi Tanabe, Ryozo Hayashi, and Rinji Takasaki : Steroid Series. V.[1] Synthesis of B-Norsteroids. (1).

(*Takamine Laboratory, Sankyo Co., Ltd.*[*1])

The preparation of B-norcholesterol was first reported by Šorm and Dykova in 1948.[2] They described the successful isolation of a keto-acid, 3β-acetoxy-5-oxo-5,6-secocholestane-6-carboxylic acid (I), in crystalline form in 25~35% yield, by oxidation of cholesterol acetate (IVa) with chromium trioxide in acetic acid. This keto-acid (I) was converted, on treatment with benzoyl chloride in pyridine, into a lactone whose structure was incorrectly represented at that time as an enolic seven-membered lactone (II) but was later established as a β-lactone, 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid β-lactone[3] (XIa). This lactone was reported to lose carbon dioxide on heating it to its melting point and form B-norcholesterol acetate (VIIa) in a good yield. Various transformations of this modified steroid were carried out by Dauben and Fonken[4] not only to establish the fundamental structure but also to obtain information in regard to the stereochemistry of the compound prepared.

By application of the same sequence of reactions to 3β-acetoxyandrost-5-en-17-one (IVc), Šorm and his associates[5] recently reported the preparation of B-norandrostane derivatives, which were also prepared by Rull and Ourisson[6] by essentially the same method except that these workers had obtained the keto-acid (I) by a different procedure.

In a previous paper[7] of this series, it was shown that 3β-acetoxy-Δ^5-steroid (IV), on ozonization in the presence of formaldehyde and reduction of the product followed by chromatography on alumina, could be converted to 3β-acetoxy-5β-hydroxy-6β-formyl-B-norsteroid (V). In the present paper a convenient process is described for conversion of (V) into B-norcholest-4-en-3-one (IXa),[4] 17-hydroxy-B-norandrost-4-en-3-one (IXd),[5b] and hitherto unknown B-norpregn-4-ene-3,20-dione (IXb).

Treatment of 6β-formyl-B-nor-5β-cholestane-3β,5-diol 3-acetate (Va) with chromium trioxide in acetic acid afforded the corresponding carboxylic acid, 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (VIa) of m.p. 199~200°, $[\alpha]_D$ +31.3°. The methyl ester, m.p. 57~63°, of (VIa) was reduced with lithium aluminium hydride to a triol, 3β,5-dihydroxy-B-nor-5β-cholestane-6β-methanol (III; R=H) as an oily substance, which, on acetylation with acetic anhydride and pyridine, yielded a crystalline diacetate (III; R=Ac) of m.p. 105.5~106.5°.

The carboxylic acid (VIa) was found to liberate water and carbon dioxide when heated above its melting point or refluxed in acetic anhydride to give the known B-norcholesterol acetate (VIIa)[2,4] of m.p. 81.5~82.5°, $[\alpha]_D$ −89.2°. As was reported by Dauben, *et al.*,[4] (VIIa) was converted, after hydrolysis of the 3-acetoxyl group followed by Oppenauer oxidation, to B-norcholest-4-en-3-one (IXa).

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*1 Nishi-Shinagawa, Shinagawa-ku, Tokyo (田辺克巳, 林 了三, 高崎林治).

1) Part IV : This Bulletin, **9**, 7 (1961).
2) F. Šorm : Collection Czechoslov. Chem. Communs., **12**, 437 (1947); F. Šorm, H. Dykova : *Ibid.*, **13**, 407 (1948).
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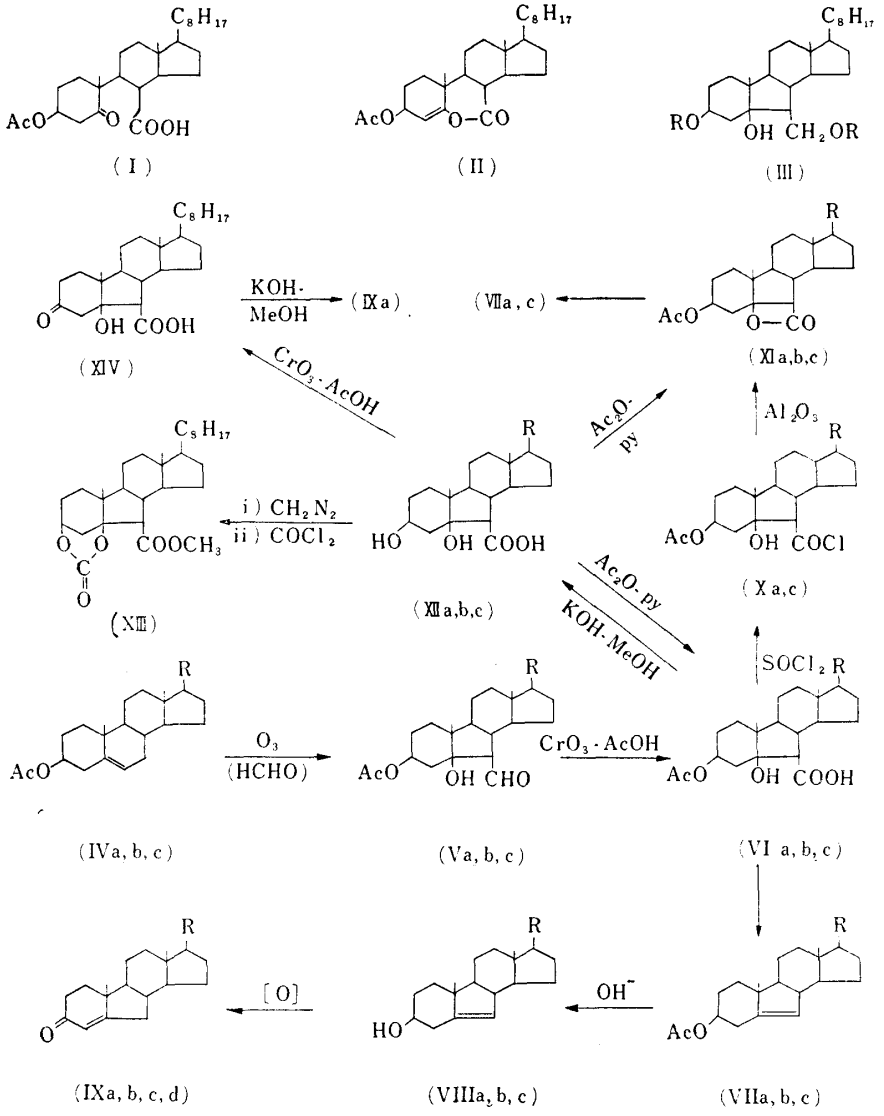
4) W.G. Dauben, G.J. Fonken : J. Am. Chem. Soc., **78**, 4736 (1956).
5) *a*) J. Joska, F. Šorm : Collection Czechoslov. Chem. Communs., **23**, 1377 (1958); *b*) J. Joska, J. Fajkos, F. Šorm : Chem. & Ind. (London), **1958**, 1665.
6) T. Rull, G. Ourisson : Bull. soc. chim. France, **1958**, 1581; H.B. Kagan, G. Jacques : *Ibid.*, **1958**, 1600.
7) Part III : This Bulletin, **9**, 1 (1961).



a; R=C_8H_{17}, b; R=$COCH_3$, c; R=O, d; R=OH

With the aim of eliminating 5β-hydroxyl group, (VIa) was treated with thionyl chloride in ether containing a small amount of pyridine at room temperature, but surprisingly afforded the corresponding acid chloride (Xa) melting at 114~114.5°, leaving the 5-hydroxyl group intact, and its structure was clearly indicated by its analytical values and infrared absorptions at 3525(OH), 1812(COCl), and 1718(AcO) cm^{-1}.

On passing a solution of (Xa) through a column of alumina, (Xa) was found to form the known 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid β-lactone (XIa) of m.p. 123.5~125°, $[\alpha]_D$ +54.9°, which displayed a characteristic absorption band for β-lactone at 1812 cm^{-1},[8] and its constants were also well in agreement with those reported.[2,4] Pyrolysis of (XIa), as shown in earlier reports,[2,4] produced B-norcholesterol acetate (VIIa).

Saponification of (VIa) with methanolic potassium hydroxide or ethanolic hydrogen chloride yielded 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylic acid (XIIa), m.p. 182~183°, which could also be obtained merely by shaking (VIa) in 2% sodium hydroxide solution at room temperature for several minutes. The ease with which the 3β-acetoxyl group

8) L. J. Bellamy: "The Infra-red Spectra of Complex Molecules," 2nd Ed., 178 (1958). Methuen & Co., Ltd., London.

was hydrolyzed should be noted.

When the dihydroxy-acid (XIIa) was allowed to react with acetic anhydride in pyridine, it furnished an acetylated carboxylic acid (VIa) as was expected, and, in addition, a neutral compound, which was identical in all respects with the β-lactone (XIa) obtained as above.

Oxidation of (XIIa) with chromium trioxide in acetic acid gave 3-oxo-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (XIV),[9] from which B-norcholest-4-en-3-one (IXa) also formed when heated in 3% methanolic potassium hydroxide.

Methyl 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylate prepared from (XIIa) with diazomethane was treated with phosgene and it afforded a carbonate, methyl 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylate 3,5-carbonate (XIII), m.p. 220~222°, whose infrared spectrum showed no hydroxyl but only a carbonyl band at 1725 cm^{-1}, indicating the structure assigned. In view of *a priori* β-configuration of 3-hydroxyl group and the formation of a 3,5-carbonate, it can be concluded that the 5-hydroxyl group in (XIIa) must be β-orientated.

The hydroxy-acids (VIa and XIIa) described above showed a tendency to lactonize readily between 5-hydroxyl and 6-carboxyl groups even under mild conditions. Such a lactonization, as indicated by Stuart Model, is possible only when the 6-carboxyl is in *cis* with respect to the 5β-hydroxy group. Thus, the β-configuration was assigned to the 6-carboxyl group.

All the reactions described above involve no reaction which might affect the carbon at 3, 5, and 6 positions. From these considerations the β-configuration was assigned to the substituents at these centers of all compounds in the B-norcholestane series, and by analogy of the mode of their preparation and similar behavior of the products, the same stereochemical assignments were also made for those in the B-norpregnane and B-norandrostane series.

By analogous series of reactions this work was extended to the preparation of B-norpregn-4-ene-3,20-dione (IXb) and 17β-hydroxy-B-norandrost-4-en-3-one (IXd).

Oxidation of 3β-acetoxy-5-hydroxy-6β-formyl-B-nor-5β-pregnan-20-one (Vb) with chromium trioxide afforded 3β-acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid (VIb), which readily gave 3β-acetoxypregn-5-en-20-one (VIIb) on heating in acetic anhydride. Alkaline hydrolysis of (VIIb) yielded 3β-hydroxy-B-norpregn-5-en-20-one (VIIIb), which was subjected to Oppenauer oxidation to give B-norpregn-4-ene-3,20-dione (IXb) of m.p. 145~146.5°, $[\alpha]_D$ +62.9°, exhibiting absorption bands in the infrared region at 1695 (20-CO), 1667, 1634 (Δ^4-3-CO) cm^{-1} and maximum absorption in the ultraviolet region at 240 mμ (ε 17,500).

The dihydroxy-acid, 3β,5-dihydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid (XIIb), obtained by alkaline hydrolysis of (VIb), was treated with acetic anhydride in pyridine and it afforded, in addition to the parent acid (VIb), a β-lactone, 3β-acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid β-lactone (XIb) as a neutral substance, whose structure was based on its composition and the infrared absorption bands at 1825 (β-lactone),[8] 1733 (AcO), and 1704 (20-CO) cm^{-1}.

3β-Acetoxy-5-hydroxy-6β-formyl-B-nor-5β-androstan-17-one (Vc) was oxidized with chromium trioxide into the corresponding carboxylic acid, 3β-acetoxy-5-hydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid (VIc), which was found to exist in two crystalline forms, e.g. prisms of m.p. 173~174° and plates of m.p. 162~163°. Refluxing of (VIc) in acetic anhydride afforded 3β-acetoxy-B-norandrost-5-en-17-one (VIIc) of m.p. 134~136°, which, on hydrolysis of the 3-acetoxyl group followed by Oppenauer oxidation, gave B-norandrost-4-ene-3,17-dione (IXc) melting at 142~143°, with absorption maximum in the ultraviolet at 239.5 mμ (ε 15,200). On sodium borohydride reduction of (IXc) in methanol at 0° to 2°, it

9) cf. Part VI of this series. This Bulletin, **9**, 20 (1961).

furnished 17β-hydroxy-B-norandrost-4-en-3-one (IXd) of m.p. 165~166° and λ_{max} 240 mμ (ε 15,300),[5b] together with a small amount of material of m.p. 136~142°, which showed no selective absorption in the ultraviolet region and was thus assumed to be B-norandrost-4-ene-3,17-diol.

When the hydroxy-acid (VIc) was treated with thionyl chloride, it gave, as in the cholestane series, the corresponding hydroxy-acid chloride (Xc), which was found so hygroscopic that it could not be purified. The chloride was therefore passed without purification through an alumina column and it was converted into 3β-acetoxy-5-hydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid β-lactone (XIc) with a characteristic β-lactone band at 1817 cm^{-1} in the infrared region.[8]

Saponification of (VIc) yielded 3β,5-dihydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid (XIIc), which, as in the other two series, could be converted to the parent acetylated acid (VIc) and also to the above-described β-lactone (XIc) on treatment with acetic anhydride in pyridine. The latter compound was then pyrolysed to afford 3β-acetoxy-androst-5-en-17-one (VIIc).

Experimental*2

B-Norcholestane Series

3β-Acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic Acid (VIa)—To a solution of 0.79 g. of 6β-formyl-B-nor-5β-cholestane-3β,5-diol 3-acetate (Va) in 18 cc. of 90% AcOH, a solution of 0.232 g. of CrO_3 in 6 cc. of 90% AcOH was added dropwise with shaking under cooling with ice. The mixture was allowed to stand for 5 hr. at room temperature, separating a crop of white needles. The excess reagent was decomposed with EtOH and 30 cc. of water was added to the solution. The precipitated crystals, after being separated by filtration, melted at 189~194°; yield, 0.79 g. Recrystallization from a mixture of petr. ether-Me_2CO gave 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (VIa) as silky needles, m.p. 199~200°, $[\alpha]_D^{26.5}$ +31.3° (c=0.95). *Anal.* Calcd. for $C_{29}H_{48}O_5$: C, 73.07; H, 10.15. Found: C, 72.86; H, 9.93. IR ν_{max}^{Nujol} cm^{-1}: 3615, 3150 (OH, COOH), 1736 (AcO), 1693 (COOH).

B-Norcholesterol Acetate (VIIa)—(i) A solution of 0.112 g. of 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (VIa) in 6 cc. of Ac_2O was refluxed for 2 hr. The solvent was removed under a reduced pressure. The crystalline residue was washed with a small amount of MeOH, leaving 0.072 g. (74%) of crude crystals melting at 73~78°, which were purified by chromatography on alumina. Elution with petr. ether-benzene (1:1), removal of the solvent, and recrystallization from Me_2CO-MeOH gave B-norcholesterol acetate (VIIa) of m.p. 81.5~82.5°, $[\alpha]_D^{27}$ −89.2° (c=1.01). (reported m.p. 78°, $[\alpha]_D^{20}$ −89°[2]; m.p. 78~79°, $[\alpha]_D^{25}$ −86.9°[4]). *Anal.* Calcd. for $C_{28}H_{46}O_2$: C, 81.11; H, 11.18. Found: C, 81.00; H, 11.21. IR ν_{max}^{EtOH} cm^{-1}: 1733 (AcO), 1636 (Δ^5).

(ii) A test tube containing 0.329 mg. of (VIa) was placed in an oil bath at 215~220° for 10 min. and at 240° for an additional 10 min. The product was chromatographed on alumina. Elution with petr. ether-benzene (4:1) gave 0.12 g. of (VIIa), which melted at 80.5~81° after recrystallization from a mixture of Me_2CO-MeOH, and undepressed on admixture with the sample obtained as above. The infrared spectra of the two compounds were identical.

B-Norcholesterol (VIIIa)—A solution of 0.5 g. of B-norcholesterol acetate (VIIa) in 20 cc. of 8% KOH-MeOH was refluxed for 1 hr. and after dilution with 50 cc. of water, the mixture was extracted with Et_2O. The extract was washed with water, dried, and the solvent was evaporated. The crystalline residue (0.43 g.) was recrystallized from MeOH to give B-norcholesterol (VIIIa) of m.p. 116~117°, $[\alpha]_D^{27}$ −89.5° (c=0.71) (reported m.p. 114°, $[\alpha]_D^{20}$ −90°[2]; m.p. 115.5~116.7°, $[\alpha]_D^{23}$ −89.8°[4]). *Anal.* Calcd. for $C_{26}H_{44}O$: C, 83.80; H, 11.90. Found: C, 83.66; H, 12.04.

B-Norcholest-4-en-3-one (IXa)—A solution of 0.3 g. of B-norcholesterol (VIIIa) in 35 cc. of anhyd. toluene containing 0.5 g. of $(iso\text{-}PrO)_3Al$ and 1 g. of cyclohexanone was refluxed for 2.5 hr. The solution was washed with three 20-cc. portions of 5% H_2SO_4 solution and then with water until neutral. The mixture was steam-distilled. The aqueous suspension was extracted with Et_2O, the extract was washed with water, dried, and the solvent was evaporated. The pale yellow residue was chromatographed on alumina. Elution with benzene afforded B-norcholest-4-en-3-one (IXa), m.p. 62~64°, $[\alpha]_D^{27}$ +3.5° (c=1.21), after recrystallization from MeOH. *Anal.* Calcd. for $C_{26}H_{42}O$: C, 84.26; H, 11.42. Found: C, 84.10; H, 11.31. UV: λ_{max}^{EtOH} 240 mμ (ε 16,500) (reported[4] m.p. 61.1~62.1°, $[\alpha]_D^{20}$ +30.2°; UV: $\lambda_{max}^{heptane}$ 235 mμ (ε 14,900)). IR: ν_{max}^{KBr} 1682 cm^{-1} (3-CO).

*2 All m.p.s are uncorrected. Rotations were measured in $CHCl_3$.

Methyl 3β-Acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylate—3β-Acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (VIa) was treated with CH_2N_2 in Et_2O solution. The methyl ester crystallized from MeOH to needles of m.p. 57~63°, $[\alpha]_D^{25}$ +35.4° (c=1.107). *Anal.* Calcd. for $C_{30}H_{50}O_5$: C, 73.43; H, 10.27. Found: C, 73.64; H, 10.43.

3β-Acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-methanol 6-Acetate (III; R=Ac)—To a suspension of 0.76 g of $LiAlH_4$ in 60 cc of dry Et_2O a solution of 0.713 g. of the methyl ester of (VIa) in 20 cc. of Et_2O was added dropwise under ice cooling and the mixture was gently refluxed for 2 hr. The excess reagent was decomposed by adding water-saturated Et_2O, the solution was acidified with *N* H_2SO_4, and extracted with Et_2O. The extract was washed successively with *N* H_2SO_4, water, 5% $NaHCO_3$, and water, and dried. Removal of the solvent afforded a colorless residue, which was chromatographed on alumina. Elution with a mixture of $CHCl_3$-MeOH (20:1) gave 0.5 g. of 3β,5-dihydroxy-B-nor-5β-cholestane-6β-methanol (III; R=H) as an oily material. Attempts to crystallize it from several kinds of solvents were without success. IR: ν_{max}^{Nujol} 3425 cm^{-1} (OH).

On acetylation of (III; R=H) with Ac_2O and pyridine at room temperature, it yielded a diacetate, 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-methanol 6-acetate (III; R=Ac), which recrystallized from MeOH to needles of m.p. 105.5~106.5°, $[\alpha]_D^{22}$ +56.8° (c=1.123). *Anal.* Calcd. for $C_{31}H_{52}O_5$: C, 73.76; H, 10.38. Found: C, 73.75, H, 10.34. IR ν_{max}^{Nujol} cm^{-1}: 3530 (OH), 1742 (AcO).

3β-Acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic Acid Chloride (Xa)—A solution of 0.164 g. of 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (VIa) in 25 cc. of dry Et_2O containing 0.2 g. of freshly distilled $SOCl_2$ and 4 drops of pyridine was allowed to stand for 15 hr. at room temperature. The solvent was then removed under a reduced pressure and the crystalline residue melting at 112~115° (decomp.) was recrystallized from petr. ether-Me_2CO to the acid chloride (Xa) as needles, m.p. 114~114.5°, $[\alpha]_D^{28.5}$ +35.7° (c=0.881). *Anal.* Calcd. for $C_{29}H_{47}O_4Cl$: C, 70.37; H, 9.57; Cl, 7.16. Found: C, 70.51; H, 9.51; Cl, 7.33. IR ν_{max}^{Nujol} cm^{-1}: 3525 (OH), 1812 (COCl), 1718 (AcO).

3β,5-Dihydroxy-B-nor-5β-cholestane-6β-carboxylic Acid (XIIa)—(i) A solution of 0.288 g. of 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (IVa) in 20 cc. of 0.5% KOH-MeOH was refluxed for 1 hr. The mixture was acidified with 2*N* HCl and extracted with Et_2O. The extract was washed with water, dried, and the solvent was evaporated. There was obtained 0.24 g. of crystalline residue melting at 165~180°, which was recrystallized from petr. ether-Me_2CO to 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylic acid (XIIa) as needles, m.p. 182~183°, $[\alpha]_D^{28}$ +46.1° (c=1.263). *Anal.* Calcd. for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67. Found: C, 74.91; H, 10.61. IR ν_{max}^{Nujol} cm^{-1}: 3525, 3200 (OH, COOH), 1737, 1712, (COOH).

(ii) A solution of 0.16 g. of (VIa) in 12 cc. of EtOH and 0.8 cc. of conc. HCl was set aside for 20 hr. at room temperature. The solvent was evaporated under a reduced pressure and a crystalline residue melting at 170~180° was recrystallized from petr. ether-Me_2CO to (XIIa) of m.p. 181~183°, undepressed on admixture with the sample obtained as above.

(iii) Crystals of (VIa) were dissolved in 2% NaOH solution. After several min. the yellowish green solution was acidified and extracted with Et_2O. The dried Et_2O was removed to leave a crystalline residue of (XIIa), which, after recrystallization from petr. ether-Me_2CO, melted at m.p. 182°, undepressed on admixture with the sample obtained as above.

3β-Acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic Acid β-Lactone (XIa)—(i) A solution of 0.05 g. of 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid chloride (Xa) in petr. ether-benzene (1:2) was passed through a column of 20 g. of alumina. The fraction eluted with the same mixture of solvents gave 0.01 g. of a crystalline residue melting at 123~124°, which was recrystallized from MeOH to give 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid β-lactone (XIa) as needles of m.p. 123.5~124°, $[\alpha]_D^{27}$ +54.9° (c=0.29) (reported m.p. 124~125°, $[\alpha]_D^{25}$ +59.6°[4]; m.p. 122°, $[\alpha]_D$ +60°[2]). *Anal.* Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 75.48; H, 10.49. IR ν_{max}^{Nujol} cm^{-1}: 1812 (β-lactone), 1735 (AcO).

(ii) A solution of 0.19 g. of 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylic acid (XIIa) in 3 cc. of pyridine and 1 cc. of Ac_2O was kept overnight at room temperature, acidified with 2*N* HCl, and extracted with Et_2O. The extract was washed with water and dried. Removal of the solvent afforded 0.19 g. of a crystalline residue (m.p. 140~180°), which was dissolved in benzene and chromatographed on alumina. The fraction eluted with benzene afforded 0.032 g. of needles (from MeOH), m.p. 123.5~125°, whose IR spectrum was completely identical with that of the β-lactone (XIa) obtained as above.

The fraction eluted with MeOH-AcOH (10:1) gave 0.03 g. of a crystalline residue, which was recrystallized from petr. ether-Me_2CO to fine needles of m.p. 198~200°. On admixture with (VIa) this showed no depression of m.p. and the infrared spectra of the two compounds were quite identical.

Pyrolysis of β-Lactone (XIa)—A test tube containing 11 mg. of 3β-acetoxy-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid β-lactone (XIa) was heated at 180° for 5 min. and at 190° for 10 min. The product was taken up in petr. ether (b.p. 60~80°) and chromatographed on alumina. Elution with petr. ether-benzene (4:1) afforded 5 mg. of crystals melting at 78~80°, whose infrared spectrum was completely identical with that of B-norcholesterol acetate (VIIa).

Methyl 3β,5-Dihydroxy-B-nor-5β-cholestane-6β-carboxylate (XIIa)—To a solution of 0.42 g. of 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylic acid (XIIa) in 30 cc. of Et_2O and 5 cc. of MeOH, a solution of CH_2N_2 in Et_2O was added and the mixture was kept in an ice-box overnight. After adding a few drops of AcOH, the solvent was evaporated to give an oily residue, which was chromatographed on 30 g. of alumina. The fractions eluted with $CHCl_3$ and $CHCl_3$-Me_2CO (1:1) afforded 0.433 g. of crystals, which were recrystallized from MeOH to give methyl 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylate as needles of m.p. 99~100°, $[\alpha]_D^{26}$ +35.1° (c=1.26). *Anal.* Calcd. for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 74.65; H, 10.11. IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 1736 (ester).

Methyl 3β,5-Dihydroxy-B-nor-5β-cholestane-6β-carboxylate 3,5-Carbonate (XIII)—To a solution of 0.313 g. of the methyl ester of (XIIa) in 23 cc. of EtOH-free $CHCl_3$ and 4.5 cc. of pyridine, 6 cc. of 14% $COCl_2$-toluene solution was added dropwise with shaking with chilling to −15°. A yellow substance deposited, which changed gradually to a brown, viscous oil. After standing at room temperature for 1.5 hr. with occasional shaking, the mixture was poured on ice, acidified with 2*N* HCl, and extracted three times with Et_2O. The combined extract was washed with water and 5% $NaHCO_3$ solution, and dried. Removal of the solvent gave 0.34 g. of a crystalline residue, which was chromatographed on alumina. The fractions eluted with Et_2O and Et_2O-$CHCl_3$ (1:1) gave 0.166 g. of a crystalline residue which was recrystallized from petr. ether-Me_2CO to a carbonate (XIII) as needles of m.p. 220~222°, $[\alpha]_D^{25}$ +62.6° (c=1.14). *Anal.* Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77; mol. wt., 474.66. Found: C, 73.45; H, 9.75; mol. wt. (Rast), 442. IR: ν_{max}^{Nujol} 1725 cm^{-1} (CO).

The fraction eluted with Me_2CO afforded 0.092 g. of residue, which was recrystallized from MeOH to give unchanged starting material of m.p. 96~98°, undepressed on admixture with the methyl ester of (XIIa).

3-Oxo-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic Acid (XIV)—To a solution of 87 mg. of 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylic acid (XIIa) in 20 cc. of 90% AcOH a solution of 27 mg. of CrO_3 in 2 cc. of 90% AcOH was added dropwise with shaking and ice-cooling. After standing at room temperature for 20 hr., the excess reagent was decomposed with EtOH and the mixture was evaporated to dryness under a reduced pressure. The residue was dissolved in Et_2O. The Et_2O solution was washed with water, dried, and the solvent was evaporated. The residue (88 mg.) melting at 170~174° was recrystallized from hydr. EtOH to give 3-oxo-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (XIV) as needles of m.p. 183~184° (decomp.), $[\alpha]_D^{26}$ +13.7° (c=0.84). *Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.80; H, 10.16. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1712 (3-CO), 1698 (COOH).

A solution of 65 mg. of (XIV) in 6 cc. of 3% KOH-MeOH was refluxed for 1 hr. The cooled solution was acidified with 2*N* HCl and extracted with Et_2O. The extract was washed with water and 2% $NaHCO_3$ solution, and dried. Removal of the solvent gave 58 mg. of a residue, which was chromatographed on alumina. Elution with benzene, removal of the solvent, and recrystallization of the product gave B-norcholest-4-en-3-one (IXa) of m.p. 61~64°. The identity with an authentic sample was confirmed by mixed m.p. determination and infrared spectra.

B-Norpregnane Series

3β-Acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic Acid (VIb)—A solution of 0.782 g. of CrO_3 in 20 cc. of 90% AcOH was added to a solution of 1.526 g. of 3β-acetoxy-5-hydroxy-6β-formyl-B-nor-5β-pregnan-20-one (Vb) in 30 cc. of 90% AcOH, and the solution was kept at room temperature for 4.5 hr. The excess reagent was decomposed with EtOH and 60 cc. of water was added to the solution. Et_2O extract was washed with water, dried, and the solvent was removed to give 1.337 g. (84.1%) of crystals melting at 184~188°, which were recrystallized from hexane-Me_2CO to 3β-acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid (VIb), needles of m.p. 191~192°, $[\alpha]_D^{26}$ +69.1° (c=0.796). *Anal.* Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.18; H, 8.60. IR ν_{max}^{Nujol} cm^{-1}: 3584, 3311 (OH, COOH), 1736, 1698 (CO).

The methyl ester was prepared from (VIb) with CH_2N_2 in Et_2O; m.p. 130.5~132° (from petr. ether-Me_2CO), $[\alpha]_D^{28.2}$ +68.9° (c=1.354). *Anal.* Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.64; H, 8.62. IR ν_{max}^{Nujol} cm^{-1}: 3571 (OH), 1725 (ester), 1708 (20-CO).

3β-Acetoxy-B-norpregn-5-en-20-one (VIIb)—A solution of 0.180 g. of 3β-acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid (VIb) in 7 cc. of Ac_2O was refluxed for 2 hr. Treatment as described for (VIa) gave 0.093 g. of crude crystals of m.p. 116~118°, which were recrystallized from MeOH to 3β-acetoxy-B-norpregn-5-en-20-one (VIIb) of m.p. 121~122°, $[\alpha]_D^{28}$ −26.2° (c=1.486). *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.76; H, 9.36. Found: C, 76.98; H, 9.58. IR ν_{max}^{Nujol} cm^{-1}: 1727 (AcO), 1704 (20-CO), 1639 (Δ^5).

3β-Hydroxy-B-norpregn-5-en-20-one (VIIIb)—A solution of 0.5 g. of 3β-acetoxy-B-norpregn-5-en-20-one (VIIb) in 20 cc. of 8% KOH-MeOH was refluxed for 1 hr., diluted with 50 cc. of water, and the mixture was kept in an ice-box. The crystals were collected by filtration, washed with a small amout of MeOH, and recrystallization from petr. ether-Me_2CO gave 3β-hydroxy-B-norpregn-5-en-

20-one (VIIIb) of m.p. 140~141°, $[\alpha]_D^{28.5}$ −32.8° (c=1.543). *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.39; H, 10.20.

B-Norpregn-4-ene-3,20-dione (IXb)—A solution of 0.6 g. of 3β-hydroxy-B-norpregn-5-en-20-one (VIIIb) in 70 cc. of dehyd. toluene containing 1.0 g. of $(iso\text{-}PrO)_3Al$ and 2.0 g. of cyclohexanone was treated as in the preceding experiment for (VIIIa) and there were obtained 0.38 g. of crude crystals melting at 140~144°, which were recrystallized from petr. ether (b.p. 60~80°) to B-norpregn-4-ene-3,20-dione (IXb) as plates of m.p. 145~146.5°, $[\alpha]_D^{28}$ +62.9° (c=1.042). *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.37. Found: C, 79.91; H, 9.31. IR ν_{max}^{Nujol} cm^{-1}: 1695 (20-CO), 1667, 1634 (Δ^4-3-CO). UV: λ_{max}^{EtOH} 240 mμ (ε 17,500).

3β,5-Dihydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic Acid (XIIb)—Treatment of 0.176 g. of 3β-acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid (VIb) in 20 cc. of 5% KOH-MeOH, as in the preceding experiment for (VIa) gave 0.157 g. of a crystalline residue, which was recrystallized from petr. ether-Me_2CO to give 3β,5-dihydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid (XIIb) as needles, m.p. 230~232° (decomp.), $[\alpha]_D^{28}$ +90.4° (c=0.714). *Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.08; H, 8.73. IR ν_{max}^{Nujol} cm^{-1}: 3521, 3165 (OH, COOH), 1730, 1684 (COOH, 20-CO).

The methyl ester was prepared from (XIIb) with CH_2N_2 in Et_2O, m.p. 66~69° (from petr. ether-Me_2CO), $[\alpha]_D^{29.2}$ +77.86° (c=1.057). *Anal.* Calcd. for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.00; H, 9.15. IR ν_{max}^{Nujol} cm^{-1}: 3425 (OH), 1732 (ester), 1693 (20-CO).

3β-Acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic Acid β-Lactone (XIb)—A solution of 0.113 g. of 3β,5-dihydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid (XIIb) in 3 cc. of pyridine and 0.2 cc. of Ac_2O was set aside at room temperature for 20 hr., poured on ice, acidified with 2*N* HCl, and extracted with Et_2O. The extract was washed successively with water, 5% $NaHCO_3$ solution, and water, and dried. Et_2O was evaporated to give 0.04 g. of a residue, which was recrystallized from petr. ether-Me_2CO to needles of 3β-acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid β-lactone (XIb), m.p. 162~163° (decomp.). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.51; H, 8.83. IR ν_{max}^{Nujol} cm^{-1}: 1825 (β-lactone), 1733 (AcO), 1704 (20-CO).

$NaHCO_3$ solution was acidified and there was obtained 0.06 g. of acidic substance, which, after recrystallization from petr. ether-Me_2CO, gave needles of 3β-acetoxy-5-hydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxylic acid (VIb), m.p. 190~191.5°, undepressed on admixture with an authentic sample.

B-Norandrostane Series

3β-Acetoxy-5-hydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic Acid (VIc)—Oxidation of 3β-acetoxy-5-hydroxy-6β-formyl-B-nor-5β-androstan-17-one (Vc; 0.343 g.) with CrO_3 (0.15 g.) in 90%-AcOH as in the preceding experiment for (Va) gave 0.268 g. (74.8%) of crude crystals of m.p. 172~174°, which after recrystallization from petr. ether-Me_2CO gave 3β-acetoxy-5-hydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid (VIc) as prisms of m.p. 173~174°, $[\alpha]_D^{30}$ +90.51° (c=1.62). *Anal.* Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.41; H, 7.82. IR ν_{max}^{Nujol} cm^{-1}: 3534, 3311 (OH, COOH), 1745, 1712 (CO).

(VIc) exists in two crystalline forms; the plates crystallized from the same mixture of solvents melted at 162~163°. IR ν_{max}^{Nujol} cm^{-1}: 3466 (OH, COOH), 1733, 1712, 1692 (CO). The infrared spectra of the two forms were quite identical in $CHCl_3$ solution; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1730 (broad; CO).

3β-Acetoxy-B-norandrost-5-en-17-one (VIIc)—Treatment of 0.192 g. of 3β-acetoxy-5-hydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid (VIc) in Ac_2O in the same manner for (VIa) gave crude crystals of m.p. 132~134°, which were recrystallized from MeOH to give 3β-acetoxy-B-norandrost-5-en-17-one (VIIc) of m.p. 134~136°, $[\alpha]_D^{30}$ −23.5° (c=0.832). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.99; H, 8.75. IR ν_{max}^{Nujol} cm^{-1}: 1745 (17-CO), 1739 (AcO).

3β-Hydroxy-B-norandrost-5-en-17-one (VIIIc)—A solution of 0.63 g. of 3β-acetoxy-B-norandrost-5-en-17-one (VIIc) in 22 cc. of 3% KOH-MeOH was refluxed for 1 hr., diluted with 30 cc. of water, and the mixture was extracted with Et_2O. The extract was washed with water, dried, and the solvent was evaporated. The residue (0.551 g.) was recrystallized from petr. ether-benzene to give 3β-hydroxy-B-norandrost-5-en-17-one (VIIIc) as needles of m.p. 140~140.5°, $[\alpha]_D^{28}$ −63.2° (c=1.422) (reported[5b] m.p. 140~141°, $[\alpha]_D^{20}$ −59°). *Anal.* Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.70; H, 9.48.

B-Norandrost-4-ene-3,17-dione (IXc)—A solution of 0.396 g. of 3β-hydroxy-B-norandrost-5-en-17-one (VIIIc) in 80 cc. of anhyd. toluene containing 0.5 g. of $(iso\text{-}PrO)_3Al$ and 3.9 cc. of cyclohexanone was treated as in the preceding experiment for (VIIIa). A crystalline residue obtained was chromatographed on alumina. Elution with a mixture of benzene-Et_2O (5:1 to 1:1) gave 0.329 g. of crystals melting at 140.5~142.5°, which were recrystallized from petr. ether (b.p. 60~80°) to needles of B-norandrost-4-ene-3,17-dione (IXc), m.p. 142~143°, $[\alpha]_D^{26}$ +61.0° (c=1.157) (reported[5b] m.p. 141~142°, $[\alpha]_D$ +73°). *Anal.* Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.18; H, 8.68. IR ν_{max}^{Nujol} cm^{-1}: 1742 (17-CO), 1656, 1639 (Δ^4-3-CO). UV: λ_{max}^{EtOH} 239.5 mμ (ε 15,200).

17β-Hydroxy-B-norandrost-4-en-3-one (IXd)—To a solution of 0.265 g. of B-norandrost-4-ene-3,17-dione (IXc) in 30 cc. of MeOH a solution of 0.058 g. of $NaBH_4$ in 10 cc. of MeOH was added drop-

wise with ice-cooling and stirring. After the addition was completed, stirring was continued for additional 1 hr. The excess reagent was then decomposed with 10% AcOH solution. The solvent was concentrated under a reduced pressure, poured into water, and the mixture was extracted with Et_2O. The extract was washed with water, dried, and the solvent was evaporated. The residue (0.3 g.) was chromatographed on alumina. The eluate with benzene-Et_2O (1:1) gave 0.183 g. of crystals melting at 146~164°, which were recrystallized from petr. ether (b.p. 60~80°) to needles of 17β-hydroxy-B-norandrost-4-en-3-one (IXd) of m.p. 165~166°, $[\alpha]_D^{24.2}$ −11.5° (c=1.441) (reported[54] m.p. 161~162°, $[\alpha]_D$ −16°). *Anal.* Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found : C, 78.51; H, 9.42. IR ν_{max}^{Nujol} cm^{-1} : 3425 (OH), 1656, 1637 (Δ^4-3-CO). UV : λ_{max}^{EtOH} 240 mμ (ε 15,300).

The eluate with $CHCl_3$ gave 0.043 g. of crude crystals, which were recrystallized from petr. ether-benzene to needles of m.p. 136~142°. This compound was assumed to be B-norandrost-4-ene-3,17-diol. *Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found : C, 78.31; H, 10.21. It exhibited no selective absorption in the ultraviolet region.

3β-Acetoxy-5-hydroxy-17-oxo-B-norandrostane-6β-carboxylic Acid Chloride (Xc)—A solution of 0.227 g. of 3β-acetoxy-5-hydroxy-17-oxo-B-norandrostane-6β-carboxylic acid (VIc) in 40 cc. of dehyd. benzene containing 0.5 cc. of $SOCl_2$ and a drop of pyridine was allowed to stand at room temperature for 60 hr., the solvent was then evaporated under a reduced pressure to leave a crystalline substance (Xc), which was very hygroscopic and changed to a viscous oil on standing. This was submitted to next chromatographic operation without purification.

3β,5-Dihydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic Acid (XIIc)—A solution of 0.127 g. of 3β-acetoxy-5-hydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid (VIc) in 15 cc. of 3% KOH-MeOH was treated as in the preceding way for (VIa), and there was obtained 0.117 g. of crystals of m.p. 163~166°, which were recrystallized from benzene to give 3β,5-dihydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid (XIIc) as needles of m.p. 167~168°, $[\alpha]_D^{28}$ +96.9° (c=0.832). *Anal.* Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found : C, 68.04; H, 8.29. IR ν_{max}^{Nujol} cm^{-1} : 3497, 3106 (OH, COOH), 1738, 1723, 1692 (CO).

3β-Acetoxy-5-hydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic Acid β-Lactone (XIc)—(i) The above-obtained acid chloride (Xc) was chromatographed on alumina. Elution with $CHCl_3$ gave 0.09 g. of a crystalline residue with m.p. 140~148° (decomp.), which was recrystallized from MeOH to give 3β-acetoxy-5-hydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid β-lactone (XIc) as needles of m.p. 155~156° (decomp.), $[\alpha]_D^{28}$ +128.8° (c=0.643). *Anal.* Calcd. for $C_{21}H_{28}O_5 \cdot H_2O$: C, 66.64; H, 7.99. Found : C, 66.31; H, 7.24. IR ν_{max}^{Nujol} cm^{-1} : 1817 (β-lactone), 1730 (17-CO).

(ii) A solution of 0.135 g. of 3β,5-dihydroxy-17-oxo-B-nor-5β-androstane-6β-carboxylic acid (XIIc) in 3 cc. of pyridine and 0.2 cc. of Ac_2O was treated as in the preceding experiment for (XIIa). As a neutral substance, there was obtained 0.09 g. of an oily residue, which was chromatographed on alumina. Elution with $CHCl_3$ afforded 0.03 g. of crystals melting at 155~156.5° with decomposition, whose infrared spectrum was identical with that of (XIc).

An acidic fraction (0.08 g.) was chromatographed on silica gel. Elution with $CHCl_3$-MeOH (10:1) gave 0.062 g. of an oily material, which, although failed to crystallize, showed infrared spectrum identical with that of (VIc).

Pyrolysis of β-Lactone (XIc)—A test tube containing 10 mg. of 3β-acetoxy-5-hydroxy-17-oxo-B-norandrostane-6β-carboxylic acid β-lactone (XIc) was heated at 190° for 15 min. The product dissolved in petr. ether (b.p. 60~80°) was chromatographed on alumina. The eluate with petr. ether-benzene (4:1) afforded 4 mg. of crystals melting at 121~128°, whose infrared spectrum was identical with that of 3β-acetoxy-B-norandrost-5-en-17-one (VIIc).

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Summary

3β-Acetoxy-5-hydroxy-6β-formyl-B-nor-5β-steroid (Va, b, c) was converted into the corresponding carboxylic acid (VIa, b, c), which was derived to Δ^5-B-norsteroid acetate (VIIa, b, c) on heating in acetic anhydride. (VIIa, b, c) was then transformed by hydrolysis of the 3β-acetoxyl group followed by Oppenauer oxidation into B-norcholest-4-en-3-one (IXa), B-norpregn-4-ene-3,20-dione (IXb), and B-norandrost-4-ene-3,17-dione (IXc). 17β-Hydroxy-B-norandrost-4-en-3-one (IXd) was prepared from (IXc) by selective reduction of 17-carbonyl group with sodium borohydride. The stereochemistry of the compounds prepared was also discussed.

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