# The Rearrangement of 20-Substituted Bisnorallocholanes and Derivatives[1]

F. KOHEN, R. A. MALLORY, AND I. SCHEER*

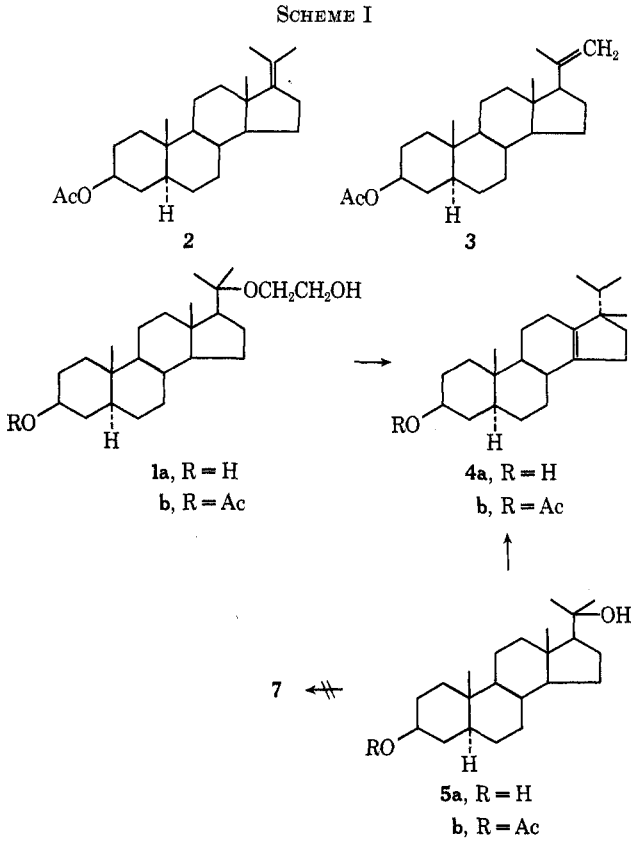
*Division of Organic Chemistry, Ortho Research Foundation, Raritan, New Jersey 08869*

*Received July 8, 1970*

Dehydration of bisnorallocholane-3β-20-diol (**5a**) in refluxing acetic acid solution containing a catalytic amount of iodine or acid cleavage of 20-(2-hydroxyethoxy)bisnorallocholan-3β-ol (**1a**) gave a rearranged product which was shown to be 18-nor-17β-methyl-17α-isopropylandrost-13(14)-en-3β-ol (**4a**). On the other hand, dehydration of the *D*-homo alcohol **6** afforded two *D*-homo products, **8b** and **7**. Chemical degradation and mass spectral analysis confirmed the proposed structures.

The rearrangement of 17-deoxy 20-substituted steroids under acidic conditions is of interest both from a mechanistic viewpoint and as a pathway to structurally modified steroid hormones. Previous studies have indicated that the products formed upon dehydration depend largely on the reaction conditions and the substituents at the 3 position. For example, dehydration of bisnorallocholane-3β,20-diol (**5a**) in acetic acid, followed by acetylation of the reaction product, afforded three isomeric rearranged products. The major product was identified as the isopropylidene derivative **2**, one of the minor products as the isopropenyl derivative **3**, while the other minor product remained unidentified (Scheme I).[2] However, dehydration of **5b** in acetic acid gave mainly **3**.[3] On the other hand, Uskoković, *et al.*, carried out the dehydration of **5a** in refluxing acetic acid containing a catalytic amount of iodine and obtained a product, in nearly quantitative yield, which they formulated as the *D*-homo derivative **8a**.[4] In the same work the dehydration of the *D*-homo alcohol **6** with acetic acid containing a catalytic amount of *p*-toluenesulfonic acid was also reported to give **8b**[4] which upon hydrolysis afforded **8a**.

SCHEME I




In the course of studies on the synthesis of tertiary glycol ethers[5] from the corresponding ketals, we examined the dehydration products of 20-(2-hydroxyethoxy)bisnorallocholan-3β-ol (**1a**) and the corresponding 5,6-unsaturated derivative (**12**). Refluxing a solution of **1a** in acetic acid containing a catalytic amount of iodine gave after chromatography only one rearranged product (*ca.* 80% yield), with the empirical formula $C_{22}H_{36}O$, which was identical in all respects (melting point, specific rotation, infrared comparison, and $R_f$ values) with the product obtained under the same conditions by the dehydration of **5a** and formulated as **8a** by Uskoković, *et al.*[4] (Scheme II).

We sought further evidence for the postulated structure **8a** by nmr examination of the rearranged product. Structure **8a** would require the presence of two vinyl methyl groups near δ 1.7. The nmr spectrum of the rearranged product showed the presence of four methyl groups between the region of δ 0.75 and 0.99, two of them being secondary and attributable to an isopropyl group, the remaining two being tertiary. There was no indication of the presence of vinyl methyl groups. The postulated *D*-homo system (**8a**) is consequently untenable, and we suggest the structure **4a**, an 18-nor-17α-isopropyl-17β-methyl-13-androstene system, which may be envisaged as formed by a hydride shift from C-17 to the initially formed C-20 carbonium ion, followed by a 1,2 shift of the C-18 methyl group to C-17, and loss of a proton at C-14. The nmr signals at δ 0.75 ($J$ = 7.5 cps) and 0.85 ($J$ = 6.5 cps) are attributable to the methyl protons on the isopropyl group at C-17. The remaining singlets at δ 0.81 and 0.99 are assigned to the C-19 and C-17 methyl protons, respectively. Structure **4a** was further substantiated by mass spectral analysis. The spectrum exhibited the proper molecular ion peak at $m/e$ 316, loss of methyl ($m/e$ 301), and an intense fragment at $m/e$ 273 due to the loss of 43 mass units ($C_3H_7$) attributable to the removal of the isopropyl group at C-17.[6]

Since the *D*-homo alcohol **6** was also reported to give the *D*-homo product **8b**,[4] we reexamined this re-

(1) A preliminary account of this work has appeared: F. Kohen, R. A. Mallory, and I. Scheer, *Chem. Commun.*, 1019 (1967).

(2) A. Butenandt and H. Cobler, *Z. Physiol. Chim.*, **234**, 218 (1935).

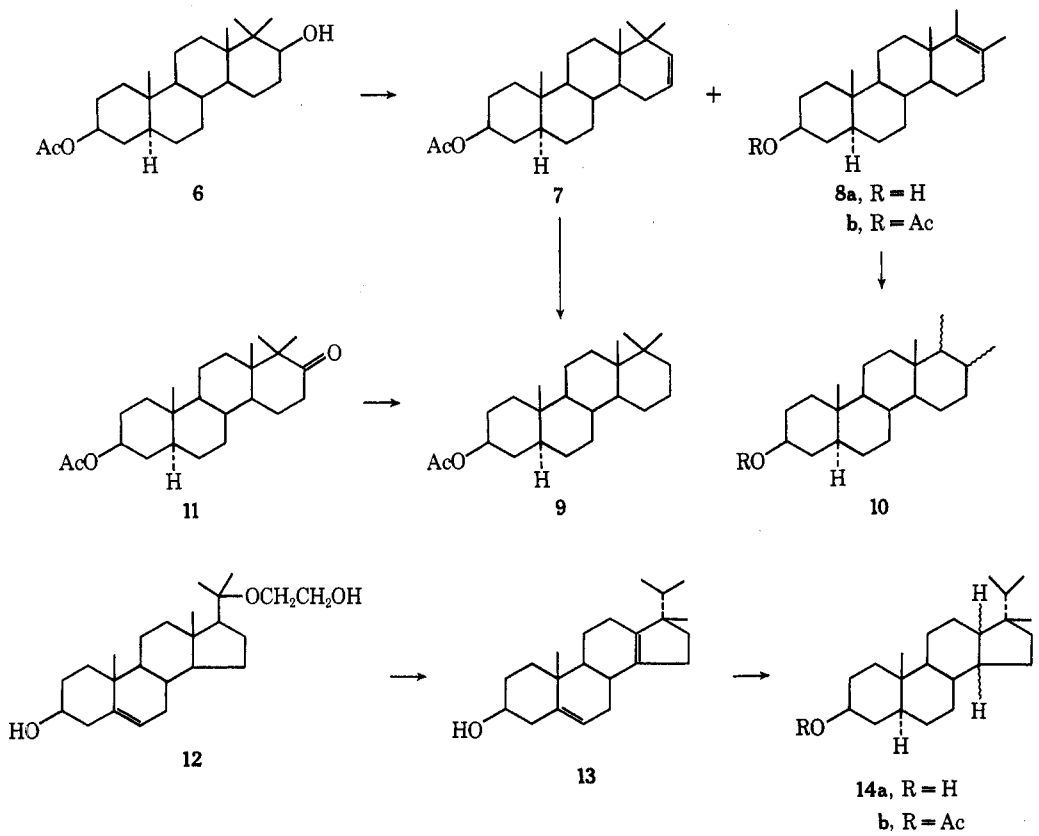
(3) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

(4) M. Uskoković, M. Gut, and R. I. Dorfman, *J. Amer. Chem. Soc.*, **82**, 3668 (1960).

(5) R. A. Mallory, S. Rovinski, F. Kohen, and I. Scheer, *J. Org. Chem.*, **32**, 1417 (1967).

(6) Similar rearrangements have been reported recently by B. Krieger and E. Kaspar [*Chem. Ber.*, **100**, 1169 (1967)], and by H. Laurent, H. Muller, and R. Wiechert [*ibid.*, **99**, 3836 (1966)].

SCHEME II




action. Reduction of the *D*-homo ketone **11** with LiAlH(*tert*-OBut)$_3$ gave the corresponding axial alcohol **6**, since attack from the less hindered $\alpha$ side is expected. Dehydration of **6** in acetic acid containing *p*-toluenesulfonic acid gave an oil which upon chromatography afforded a crystalline solid, mp 84–86°. However, the complexity of the methyl region in the nmr indicated that this product was a mixture. This was further substantiated by tlc examination on silica gel G impregnated with $AgNO_3$. Two spots of equal intensity were observed. Separation of this mixture was achieved by chromatography on silicic acid impregnated with $AgNO_3$. In this way, two isomeric olefinic products, **7** and **8b**, were obtained.

The more mobile component **8b**, mp 122–123°, $[\alpha]D$ +35.7°, analyzed for $C_{24}H_{38}O_2$ and displayed two vinyl methyl peaks at $\delta$ 1.55 in the nmr. The C-18 and C-19 methyl groups appeared at $\delta$ 0.87 and 0.82, respectively. The absence of vinyl protons in the nmr indicated that the double bond formed upon dehydration was tetrasubstituted. Structure **8b** was readily assigned to this product, and this was further confirmed by chemical transformation. Hydrogenation of **8b** gave the dihydro derivative **10** whose nmr spectrum showed the presence of two secondary methyl peaks at $\delta$ 0.92 and 0.90 in addition to the C-18 and C-19 methyl peaks. The formation of **8b** can be viewed as a 1,2 shift of one of the methyl groups at C-17a to the initially formed carbonium ion at C-17 followed by a loss of proton at C-17.

The more polar component **7**, mp 134–135°, $[\alpha]D$ −66°, also analyzed for $C_{24}H_{38}O_2$. The nmr spectrum showed two vinyl protons at $\delta$ 5.40, attributable to C-16 and C-17 protons. The C-17a methyl groups appeared at $\delta$ 0.94 and 0.82. The peaks at $\delta$ 0.87 and 0.82 were attributed to C-18 and C-19, respectively. The correctness of the assignment of structure **7** to this product was further confirmed by chemical reduction. Hydrogenation of **7** gave the dihydro derivative **9**, identical in all respects with the product obtained by Wolff–Kishner reduction, followed by acetylation, of the *D*-homo ketone **11**.

In the 20-(2-hydroxyethoxy)bisnorchol-5-en-3$\beta$-ol (**12**) series, we found that the action of acetic acid containing a catalytic amount of iodine resulted in the formation of 18-nor-17$\beta$-methyl-17$\alpha$-isopropylandrosta-5,13(14)-dien-3$\beta$-ol (**13**), with appropriate nmr signals at $\delta$ 0.74 (doublet, $J$ = 7 cps), 0.86 (doublet, $J$ = 7 cps) (the isopropyl protons at C-17), and 1.00 (the C-19 and C-17 methyl protons).

Hydrogenation of **13** with platinum oxide in acetic acid resulted in an uptake of 2 mol of hydrogen with formation of the tetrahydro derivative **14a**, with unassigned configuration at C-13 and C-14. A mixture of geometrical isomers may be present in this compound. Mass spectral examination of **14a** revealed the presence of a molecular ion peak at *m/e* 318, a peak at *m/e* 303, due to the loss of a methyl group, and an intense fragment at *m/e* 275, due to the removal of the isopropyl group at C-17.

## Experimental Section[7]

**18-Nor-17$\beta$-methyl-17$\alpha$-isopropylandrost-13(14)-en-3$\beta$-ol (4a). A.**—A solution of 20-(2-hydroxyethoxy)bisnorallocholan-3$\beta$-ol

(7) Specific rotations were determined in $CHCl_3$ solution at a concentration of approximately 1%. All melting points were determined using a Fisher-Johns melting point apparatus. Nmr spectra were determined using a Varian A-60 spectrophotometer. Mass spectra were carried out by Morgan-Schaffer Corporation in Montreal, Canada. Petroleum ether refers to the fraction of bp 30–60°.

(1a, 0.8 g) in HAc (50 ml) was refluxed with a catalytic amount of $I_2$ (7 mg) for 30 min. After cooling the solution, the $I_2$ was reduced with saturated $NaHSO_3$ solution, and a large amount of $H_2O$ was added. The mixture was extracted with $CHCl_3$, and the extract was washed with $NaHCO_3$, $H_2O$, dried ($MgSO_4$), and evaporated. The dark red residue (0.7 g) was chromatographed on Woelm neutral $Al_2O_3$ (activity II). Elution with benzene gave **4a**[8] (550 mg, 82% yield): mp 144.5–146° (from acetone); $[\alpha]D$ −64° (lit.[4] mp 144.5–145.5°); nmr ($CDCl_3$) $\delta$ 0.75 (d, 3, $J$ = 7.5 cps, a methyl group at C-20), 0.85 (d, 3, $J$ = 6.5 cps, a methyl group at C-20), 0.81 (s, 3, C-19 $CH_3$), and 0.99 (s, 3, C-17 $CH_3$); mass spectrum (70 eV) $m/e$ (rel intensity) 316 (4) ($M^+$), 301 (6) (M − 15), 273 (98) (M − 43, loss of the ispropyl chain), and 255 (83) (M − 43 and loss of $H_2O$).

*Anal.* Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.36; H, 11.18.

Acetylation with pyridine and $Ac_2O$ gave the **acetate 4b**, mp 70–71° (from $CH_3OH$), $[\alpha]D$ −57° (lit.[4] mp 62–64°, $[\alpha]D$ −58°).

*Anal.* Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.27; H, 10.59.

**B.**—A solution of bisnorallocholane-3$\beta$,20-diol[4] (**5a**, mp 182–183°) (3.0 g) in HAc (150 ml) was refluxed with a catalytic amount of $I_2$ (15 mg) for 30 min and worked up as in A above. The product thus obtained was recrystallized from acetone to give **4a**, 2.2 g, mp 143–145°. This material was identical in all respects (melting point, ir, nmr, and $R_f$) with that obtained in A above.[9]

**17a,17a-Dimethyl-*D*-homoandrostane-3$\beta$,17$\beta$-diol 3-Acetate (6).**—To a solution of the *D*-homo ketone **11**[10] (1 g) in dry THF (50 ml) was added LiAlH(*tert*-OBut)$_3$ (3 g), and the reaction mixture was stirred overnight. Dilute HCl was then added, and the organic phase separated, dried, and evaporated. Recrystallization from $CH_3OH$ gave **6** (0.8 g): mp 194–195°; $[\alpha]D$ 0.0° (lit.[4] mp 193–195°; $[\alpha]D$ −13.9°); nmr ($CDCl_3$) $\delta$ 0.83 (s, 3, C-19 $CH_3$), 0.88 (s, 3, C-18 $CH_3$), 0.97 (s, 3, C-17a $CH_3$), and 1.1 (s, 3, C-17a $CH_3$).

**Dehydration of 17a,17a-Dimethyl-*D*-homoandrostane-3$\beta$,17$\beta$-diol 3-Acetate.**—A solution of **6** (0.5 g) in HAc (25 ml) was refluxed with *p*-toluenesulfonic acid (25 mg) for 1 hr. The reaction mixture was poured into a large excess of $H_2O$, the mixture extracted with $CHCl_3$, and the extract washed with $NaHCO_3$ solution, $H_2O$, dried ($MgSO_4$), and evaporated. The residue (0.4 g) was first chromatographed on Woelm neutral $Al_2O_3$ (activity II). Elution with hexane–chloroform gave a solid (0.4 g), mp 84–85° (from methanol). However, the complexity of the methyl region in the nmr indicated that this product was a mixture. Furthermore, tlc examination of this product on silica gel G impregnated with $AgNO_3$ showed the presence of two spots of $R_f$ 0.2 and 0.34, respectively, benzene being used as a developing solvent. This mixture was then rechromatographed on silicic acid (Mallinckrodt) impregnated with 5% $AgNO_3$.

Elution with hexane–benzene (9:1) (100 ml) gave **17,17a-dimethyl-*D*-homoandrost-17(17a)-en-3$\beta$-ol 3-acetate (8b)** (100 mg): mp 122–123° (from $CH_3OH$); $[\alpha]D$ +35.7°; nmr ($CDCl_3$) $\delta$ 0.82 (s, 3, C-19 $CH_3$), 0.87 (s, 3, C-18 $CH_3$), and 1.55 (s, 6, vinyl methyl groups at C-17 and C-17a).

*Anal.* Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.15; H, 10.48.

Further elution with the same solvent system (400 ml) gave a mixture of **7** and **8b** (200 mg). Elution with hexane–benzene (1:1) (100 ml) gave **17a,17a-dimethyl-*D*-homoandrost-16(17)-en-3$\beta$-ol 3-acetate (7)** (55 mg): mp (from $CH_3OH$) 134–135°; $[\alpha]D$ −66°; nmr ($CDCl_3$) $\delta$ 0.82 (s, 6, C-19 $CH_3$ and a methyl group at C-17a), 0.87 (s, 3, C-18 $CH_3$), and 0.94 (s, 3, C-17a $CH_3$).

*Anal.* Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.25; H, 10.59.

**17$\xi$,17a$\xi$-Dimethyl-*D*-homoandrostan-3$\beta$-ol 3-Acetate (10).**—A solution of **8a** (80 mg) in HAc (50 ml) was hydrogenated using $PtO_2$ as catalyst. After hydrogen uptake had ceased, the catalyst was filtered, and the filtrate was poured into a large excess of $H_2O$, and the product was filtered and crystallized from $CH_3OH$ to give **10** (60 mg): mp 110–111°; $[\alpha]D$ 0°; nmr ($CDCl_3$) $\delta$ 0.90 (d, 3, $J$ = 6 cps, C-17a $CH_3$) and 0.92 (d, 3, $J$ = 6 cps, C-17 $CH_3$).

*Anal.* Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 80.02; H, 11.22.

**17a,17a-Dimethyl-*D*-homoandrostan-3$\beta$-ol 3-Acetate (9). A.**—A solution of **7** (40 mg): in HAc (25 ml) was hydrogenated using $PtO_2$ as catalyst and worked up as above. Recrystallization from $CH_3OH$ gave **9**: mp 180–181°; $[\alpha]D$ −21°; nmr ($CDCl_3$) $\delta$ 0.78 (s, 6, C-18 $CH_3$ and C-17a $CH_3$), 0.83 (s, 3, C-19 $CH_3$), and 0.94 (s, 3, C-17a $CH_3$).

*Anal.* Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.89; H, 11.09.

**B.**—A mixture of the *D*-homo ketone **11** (200 mg), 99% hydrazine hydrate (2 ml), and diethylene glycol (15 ml) was heated at 150° for 10 min, KOH (2 g) then added, and heating continued at 150° for 45 min. Solvent was then distilled off until a solution temperature of 210° was reached, and the mixture was refluxed for a further 6 hr, cooled, poured into $H_2O$, and extracted with $CHCl_3$. The washed and dried extract was evaporated, and the residue was acetylated with pyridine and acetic anhydride. After the usual work-up, the product was crystallized from $CH_3OH$ to give **9** (100 mg) identical in all respects with that obtained in A above.

**18-Nor-17$\beta$-methyl-17$\alpha$-isopropylandrost-5,13(14)-dien-3$\beta$-ol (13).**—A solution of 20-(2-hydroxyethoxy)bisnorchol-5-en-3$\beta$-ol[5] (**12**, mp 190–192°, 3.0 g) in HAc (150 ml) was refluxed with a catalytic amount of $I_2$ (15 mg) for 0.5 hr and worked up in the usual way. The red oily residue was chromatographed on Woelm neutral $Al_2O_3$ (activity II). Elution with benzene (600 ml) afforded **13** (2.1 g) which crystallized from $CH_2Cl_2$–petroleum ether as needles: mp 134–135°; $[\alpha]D$ −197°; nmr ($CDCl_3$) $\delta$ 0.74 (d, 3, $J$ = 7 cps, one of the methyl groups at C-20), 0.86 (d, 3, $J$ = 7 cps, a methyl group at C-20), and 1.00 (s, 6, C-19 and C-17 methyl protons).

*Anal.* Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 83.91; H, 10.73.

**Hydrogenation of 18-Nor-17$\beta$-methyl-17$\alpha$-isopropylandrost-5,13(14)-dien-3$\beta$-ol.**—A solution of **13** (500 mg) in HAc (75 ml) was hydrogenated using $PtO_2$ (100 mg) as catalyst. When $H_2$ uptake ceased (80 ml, 2 hr), the catalyst was removed by filtration, and a large volume of $H_2O$ was added to the filtrate. The resultant white precipitate (350 mg) was filtered off and recrystallized from acetone to afford the tetrahydro derivative **14a** as prisms: mp 115–117°; $[\alpha]D$ +8.8°; nmr ($CDCl_3$) $\delta$ 0.80, 0.84, and 0.95 (methyl groups); mass spectrum (70 eV) $m/e$ (rel intensity) 318 (5) (M), 303 (7) (M − 15), 275 (97) (M − 43, loss of the isopropyl side chain), and 257 (90) (M − 43 and loss of $H_2O$).

*Anal.* Calcd for $C_{22}H_{38}O$: C, 82.95; H, 12.03. Found: C, 83.09; H, 12.00.

Acetylation with acetic anhydride and pyridine gave the derived acetate **14b** which crystallized from acetone–water as needles, mp 75–76°, $[\alpha]D$ −1°.

*Anal.* Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.98; H, 11.27.

**Registry No.**—**4a**, 27390-93-8; **6**, 27390-94-9; **7**, 27390-95-0; **8b**, 27390-96-1; **9**, 27390-97-2; **10**, 27390-98-3; **13**, 27390-99-4; **14a**, 27391-00-0; **14b**, 27391-01-1.

**Acknowledgment.**—The authors wish to acknowledge the experimental assistance of Mr. S. Rovinski. We are indebted to Mrs. E. Kaffitz for the determination of the nmr spectra. We would also like to thank Dr. G. Karmas for his valuable suggestions.

(8) The homogeneity of this compound was confirmed by tlc on silica gel G impregnated with $AgNO_3$, a method that is commonly used for the separation of double bond isomers. Only one spot was observed with different developing solvents.

(9) We wish to thank Dr. Marcel Gut of the Worcester Foundation for Experimental Biology for supplying us with a sample of material obtained from the dehydration of **5a**.

(10) M. Uskoković, M. Gut, and R. I. Dorfman, *J. Amer. Chem. Soc.*, **81**, 4561 (1959).