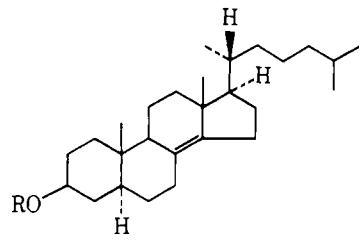
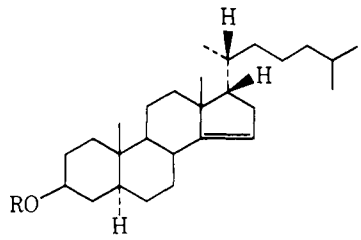
An Unusual Backbone Rearrangement. The Formation of 5α,17α-Cholest-14-en-3β-ol Acetate from 5α-Cholest-8(14)-en-3β-ol Acetate[1]

Summary: The acid-catalyzed isomerization of 5α-cholest-8(14)-en-3β-ol acetate (and 3β-benzoate) at −78° results in 5α,17α-cholest-14-en-3β-ol acetate (or 3β-benzoate); hydrogenation ($^1H_2$, $^2H_2$) gave a product which on the basis of ^{13}C NMR was tentatively assigned as 5α,14β,17α-cholestan-3β-ol.

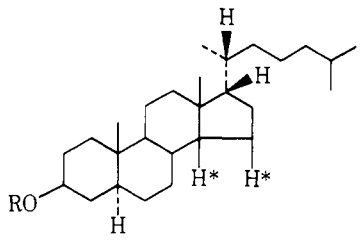
Sir: The preparation of 5α-cholest-14-en-3β-ol acetate (**1a**) requires the treatment of a chloroform solution of 5α-cholest-8(14)-en-3β-ol acetate (**2a**) first with a stream of dry HCl at −30° and then with aqueous $NaHCO_3$.[2] In our hands the obtained **1a** is usually accompanied by variable amounts of an unknown product, now characterized as **3a.**



2a, R = CH_3CO
b, R = C_6H_5CO



3a, R = CH_3CO
b, R = H
c, R = *p*-BrC_6H_4CO



4a, R = CH_3CO; H* = ^1H
b, R = CH_3CO; H* = ^2H
c, R = H; H* = ^1H
d, R = H; H* = ^2H

We present proof of structure and efficient methods of synthesis of the rather inaccessible 5α,17α-cholest-14-en-3β-ol acetate (**3a**) and 5α,14β,17α-cholestan-3β-ol acetate (**4a**). It is worthy of note that the unusual isomerization at C-17 occurred at a center remote from the reaction site.

When the reaction was carried out by treating a solution of **2a** (1500 mg) in dry chloroform (2 ml) with HCl at −78° for 7 hr, and then with aqueous $NaHCO_3$ for 8 hr, the main product (80–90% yield) was[3] **3a.** The mass spectrum [*m/e* 428 (M^+), −15, −60, −173, etc.] and NMR [δ 5.07 (m, 1 H, vinylic), 0.90 (s, 3 H, C-10 methyl), 1.13 (s, 3 H, C-13 methyl), 0.89 (d, *J* = 7 Hz, 9 H, C-25 and C-20 methyls] were consistent with a C_{27} structure having a trisubstituted double bond. Hydrogenation ($^1H_2$ or $^2H_2$) of **3a** gave saturated **4a** (^1H) or **4b** (^2H), which differed from cholestanol acetate (**5a**). These results were consistent with the hypothesis that **3a** was obtained via a structural rearrangement of the cholestenol skeleton, which very likely involved rings C and/or D.

The natural abundance, noise-decoupled ^{13}C NMR spectra of the 3β-hydroxy compounds [**1b, 3b, 4c** (^1H), **4d** (^2H), and **5b**] were obtained from dioxane solutions.[4] Each spectrum consisted of 27 peaks, clearly establishing the C_{27} nature of the unknown. Both **1b** and **3b** showed two peaks in the olefinic region, one carbinol peak, five methyl peaks, and peaks for two quaternary aliphatic carbons, presumably C-10 and C-13. The remaining peaks arose from secondary or tertiary carbons.

The mass spectrum of **3a** had pronounced peaks at *m/e* 255 [$M^+ - (C_8H_{17} + CH_3COOH)$] and 240 [$M^+ - (C_8H_{17} + CH_3COOH + CH_3)$]. These results were consistent with the view that **3a** has a tetracyclic steroidal structure with a C_8H_{17} moiety at C-17.[5] On this basis we assigned peaks corresponding to C-1 through C-10, C-19, and C-24 through C-27 in the ^{13}C spectrum of the 3β-hydroxy **3b.** The signals for these carbons in the spectrum of **3b** showed little displacement from the corresponding peaks in the spectrum of **1b.** This reinforced the view that **1b** and **3b** differ only in rings C and/or D.

The chemical shift of the protons of the C-10 methyl and the presence of a single vinylic *hydrogen* in the ^1H NMR spectrum of **3b** established that the double bond is trisubstituted and cannot be located in rings A or B or at C-9 (11). This, together with the mass spectral data narrowed the choice of the likely structures of **3** to the following: **a,** Δ^{12}-14β-methyl; **b,** 14ξ(H)-Δ^{16}; and **c,** Δ^{14}-17α side chain. The influence of the Δ^{14} on the chemical shifts of ^{13}C atoms of **5b** was deduced from a comparison of its spectrum with that of **1b.** The effects of epimerization at C-17 on the chemical shifts of ^{13}C atoms of the tetracyclic nucleus of **5b** were estimated from a comparison of the spectra of estra-1,3,5(10)-triene-3,17α-diol and estra-1,3,5(10)-triene-3,17β-diol.[6] Based on these considerations it was inferred that the most likely structure of **3b** is 5α,17α-cholest-14-en-3β-ol. This conclusion was confirmed by X-ray structure determination carried out on *p*-bromobenzoate (**3c**, mp 101.5–103.5°).

Cell dimensions of a small (0.3 mm on edge) crystal of the *p*-bromobenzoate derivative of the rearranged product (**3c**) were determined by a least-squares procedure of the 20 values of 15 well-centered reflections. Cell data: *a* = 22.125 Å, *b* = 51.859 Å, *c* = 11.072 Å, *V* = 12703 Å^3, orthorhombic, $P2_12_12_1$, *Z* = 16. Three-dimensional data were collected on an Enraf-Nonius Kappa automated diffractometer with Cu Kα radiation. Of the 11278 data collected, 3591 were classed as observed. The structure was solved by Patterson techniques and subsequent Fourier synthesis to an *R* factor of 25%. Least-squares refinement of the bromine positions with anisotropic thermal parameters and

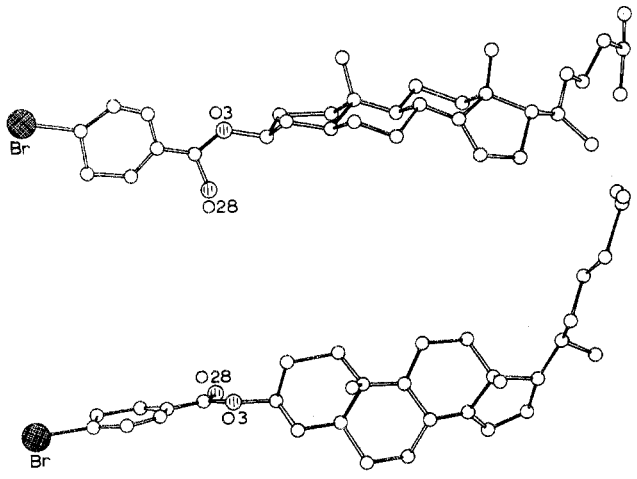


Figure 1.

the carbon and oxygen positions with isotropic thermal parameters is continuing. The R factor is 11.8% at the present time. The data revealed the presence of four crystallographically independent molecules of **3c** in the cell.[7] ORTEP views (50% probability thermal ellipsoids) of molecule 2 are seen in Figure 1. The structure of **3c** is unequivocally 5α,17α-cholest-14-en-3β-ol *p*-bromobenzoate. Molecules 1, 2, and 4 have the same D ring conformation, 17β envelope, and similar side chain orientation; C-21 is anti to C-13 and gauche to C-16. In molecule 3 tlhe D-ring conformation appears to be a 17α envelope and C-21 is gauche to C-13 and C-16. The end of the cholestane side chain, C-25, C-26, C-27, is probably disordered in at least two of the molecules. Other interesting conformational details which vary in the four molecules will be discussed in a future paper.

The saturated derivative 4 obtained by hydrogenation of **3** could have either the 14α or 14β stereochemistry. From ^{13}C NMR studies[4] of **4c** and **4d,** it was tentatively concluded that **4** is 5α,14β,17α-cholestan-3β-ol.

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Supplementary Material Available. Tables of ^{13}C chemical shifts and bond distances and angles will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2005.

References and Notes

(1) Professor A. Fiecchi and his associates at the University of Milano have obtained similar results. It was agreed to publish the results of both groups simultaneously.
(2) J. W. Cornforth, I. Y. Gore, and G. Popjak. *Biochem. J.*, **65,** 94 (1957). These authors have carried out the referred to transformation on the $\Delta^{8(14)}$-benzoate. We have carried out the reactions described in this communication on both $\Delta^{8(14)}$-acetate and the benzoate. In both instances analogous products were obtained which were interrelated as the free C-3 alcohol. At present we report the results for the acetate.
(3) All new compounds were fully characterized. ^1H NMR spectra were recorded on a Varian DA-60 instrument. ^{13}C NMR spectra were obtained on a Varian HA 100-15 instrument equipped with a Varian time-averaging computer (C-1024) and were recorded at 25.1 MHz. Mass spectra were obtained on a Du Pont 21-491 instrument.
(4) A table of ^{13}C chemical shifts of these compounds is published in the microfilm edition of the journal immediately following these pages.
(5) C. Djerassi, *Pure Appl. Chem.*, **21,** 205 (1970).
(6) T. A. Wittstruck and K. I. Williams, *J. Org. Chem.*, **38,** 1542 (1973).
(7) A table of bond distances and angles averaged over the four molecules is published in the microfilm edition of the journal immediately following these pages.
(8) (a) Worcester Foundation for Experimental Biology, Shrewsbury, Mass. 01545. (b) Medical Foundation of Buffalo Research Laboratories, Buffalo, N.Y. 14203. (c) Extracted in part from the Ph.D. Thesis of J. P. Moreau to be submitted to the University of Orleans, France.

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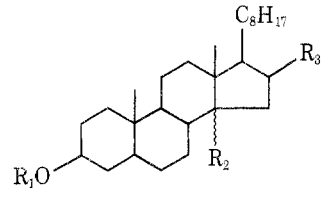
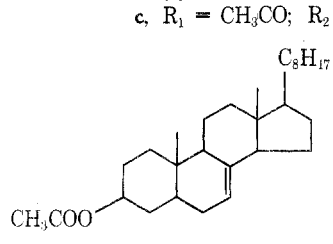
A Ready Synthesis of 17α Steroids[1,2]

Summary: Reaction of sterol acetates with a Δ^7, $\Delta^{8(14)}$, and Δ^{14} double bond with hydrogen chloride yields 3β-acetyloxy-14-chloro-5α,14β,17α-cholestane (structure determined by X-ray analysis), which is easily dehydrohalogenated to 3β-acetyloxy-5α,17α-cholest-14-ene.

Sir: Anhydrous hydrogen chloride in chloroform has been described to promote the isomerization of Δ^7, Δ^8, and $\Delta^{8(14)}$ double bonds to the 14 position in sterols.[3,4] Compound **1a** (mp 104–106°) was obtained as the single reaction product by bubbling hydrogen chloride for 3 hr at −60° in a 20–25 *mM* solution of 3β-acetyloxy-5α-cholest-7-ene (**2**) in diethyl ether. The ^1H NMR spectrum showed signals at δ



1a, $R_1 = CH_3CO$; $R_2 = \beta$-Cl; $R_3 = \beta$-H
b, $R_1 = C_6H_5CO$; $R_2 = \xi$-Cl; $R_3 = \alpha$-H
c, $R_1 = CH_3CO$; $R_2 = \xi$-Cl; $R_3 = \alpha$-H



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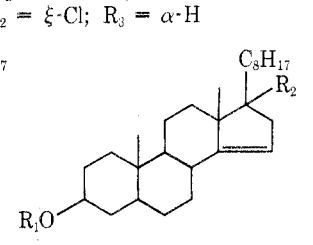
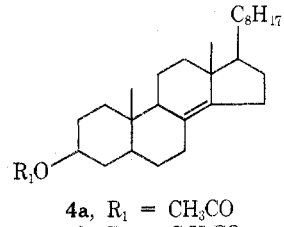
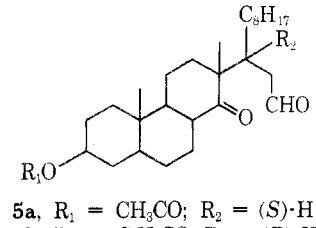


3a, $R_1 = CH_3CO$; $R_2 = \alpha$-H
b, $R_1 = C_6H_5CO$; $R_2 = \alpha$-H
c, $R_1 = CH_3CO$; $R_2 = \beta$-H
d, $R_1 = p$-BrC_6H_4CO; $R_2 = \beta$-H



4a, $R_1 = CH_3CO$
b, $R_1 = C_6H_5CO$



5a, $R_1 = CH_3CO$; $R_2 = (S)$-H
b, $R_1 = C_6H_5CO$; $R_2 = (R)$-H

$C_8H_{17}CH{=}CHCHO$

6