with 1 M hydrochloric acid, aqueous sodium hydrogen carbonate, and water and dried. The solvent was removed, and the residue was purified by a silica gel column (4 g) with ethyl acetate–hexane (1:15, v/v) to give 31 mg (95%) of **10** as a syrup: $[\alpha]^{27}_D$ −335° (*c* 1.21, $CHCl_3$) [lit.[5] $[\alpha]^{28}_D$ −298° (*c* 0.37, $CHCl_3$)]; mass spectrum, calcd for $C_{23}H_{20}O_6$, *m/z* 392.1258, found, *m/z* 392.1256. The IR ($CHCl_3$), ^1H NMR ($CDCl_3$), and UV (C_2H_5OH) spectral data were identical with those described for the natural product.[5]

Selective Benzoylation of 9. To a stirred solution of **9** (66 mg, 0.27 mmol) in pyridine (3 mL) was added benzoyl chloride (60 μL, 0.51 mmol) in three portions at −5 °C during 30 min. TLC showed the formation of three components (R_f 0.62, 0.43, and 0.33), along with a trace of **9** (R_f 0.10) in ethyl acetate–hexane (1:2, v/v). The reaction mixture was processed in the usual way, and the products were fractionated by a silica gel column (6 g) with ethyl acetate–hexane (1:4, v/v). The first fraction gave 42 mg (35%) of **(2*R*)-*trans*-2,3-bis(benzoyloxy)-1-[(benzoyloxy)methyl]-cyclohexa-4,6-diene (11)** as a syrup: $[\alpha]^{25}_D$ −395° (*c* 0.88, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 8.07–7.96 (m, 6) and 7.55–7.32 (m, 9) (phenyl), 6.43–6.13 (m, 4, C_2 H, C_4 H, C_5 H, C_6 H), 5.87 (dd, 1, $J_{3,4}$ = 3.5, $J_{2,3}$ = 6.1 Hz, C_3 H), 5.00 (s, 2, CH_2OBz); mass spectrum (relative intensity), 332 (M^+ − $PhCO_2H$, 12), 122 ($PhCO_2H$, 7), 105 (PhCO, 100).

The second fraction gave 43 mg (46%) of **(2*R*)-*trans*-3-(benzoyloxy)-1-[(benzoyloxy)methyl]-2-hydroxycyclohexa-4,6-diene (13)** as needles (from benzene–hexane): mp 79.5–81 °C; $[\alpha]^{25}_D$ −297° (*c* 1.19, $CHCl_3$) [lit.[4] mp 90–91 °C; $[\alpha]^{25}_D$ −276° (*c* 0.145, $CHCl_3$)]. The ^1H NMR spectrum was superposable on that of the natural product.[4]

Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 71.70; H, 5.25.

The third fraction gave 8 mg (9%) of **(2*R*)-*trans*-2-(benzoyloxy)-1-[(benzoyloxy)methyl]-3-hydroxycyclohexa-4,6-diene (12)** as a syrup: $[\alpha]^{25}_D$ −119° (*c* 0.33, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 8.08–7.91 (m, 4) and 7.57–7.33 (m, 6) (phenyl), 6.33–6.04 (m, 3, C_4 H, C_5 H, C_6 H), 5.97 (d, 1, $J_{2,3}$ = 7.1 Hz, C_2 H), 4.97 (br s, 2, CH_2OBz), 4.63 (dd, 1, $J_{3,4}$ = 2.7 Hz, C_3 H), 2.37 (br s, 1, OH); mass spectrum (relative intensity), 332.1048 (M^+ − H_2O, 100) (calcd for $C_{21}H_{16}O_4$, 332.1047).

(1*R*)-1,2-Anhydro-4-*O*-benzoyl-(1,2,3/4)-2-*C*-[(benzoyloxy)methyl]-5-cyclohexene-1,2,3,4-tetrol [(+)-Pipoxide] (4). To a stirred mixture of **13** (43 mg, 0.12 mmol) in dichloromethane (1.5 mL) and phosphate buffer solution (pH 8) (2 mL) was added dropwise a solution of MCPBA (30 mg, 0.12 mmol, purity 70%) in dichloromethane (1 mL) at 0 °C, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was processed in the usual way to give 39 mg (87%) of **4** as needles (from benzene–hexane): mp 150–151 °C; $[\alpha]^{20}_D$ +48.6° (*c* 0.76, $CHCl_3$) [lit.[3] mp 152–154 °C; $[\alpha]^{20}_D$ +24.5° (*c* 0.20, $CHCl_3$); lit.[4] $[\alpha]^{20}_D$ +37.9° (*c* 0.16, $CHCl_3$); lit.[12] mp 152 °C, $[\alpha]^{23}_D$ +53° (*c* 0.02, $CHCl_3$)]; UV max (C_2H_5OH) 276 mm (ε 2340); IR (KBr) 3450 (OH), 1710 (ester C=O) cm^{-1}. The ^1H NMR spectrum was superposable on that of the natural product.[4]

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.57; H, 4.95. Found: C, 68.32; H, 5.04.

Acknowledgment. We express our sincere thanks to Saburo Nakada for elemental analyses. We also thank Drs. Shigeru Nishiyama and Kin-ichi Tadano for measurement of mass spectra. The ^1H NMR spectra of the natural products, **4**, **5**, **6**, **10**, and **13**, were kindly provided by Professor Yodhathai Thebtaranonth (Mahidol University, Thailand), to whom our thanks are due.

Registry No. (+)-**1**, 20421-13-0; (−)-**2**, 17550-38-8; (−)-**3**, 86702-28-5; (+)-**4**, 29399-87-9; (+)-**5**, 86747-02-6; **6**, 86782-19-6; **7**, 96247-02-8; **8**, 96247-03-9; **9**, 71481-04-4; **10**, 86702-29-6; **11**, 96247-04-0; **12**, 96247-05-1; **13**, 85966-24-1; (−)-**14**, 78804-17-8; **16**, 90695-19-5; **17**, 96291-84-8; **18**, 96291-85-9; **19**, 96291-86-0; (±)-**20**, 74766-83-9; **21**, 96291-87-1; **22**, 96291-88-2; **23**, 96291-89-3.

Synthesis of (20*R*,25*R*)-Cholest-5-ene-3β,26-diol and the Occurrence of Base-Catalyzed 1,5-Hydride Shift in a Steroidal 1,5-Ketol[1]

Arthur F. Kluge,* Michael L. Maddox, and Leslie G. Partridge

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

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Details are presented for the preparation of (20*R*,25*R*)-cholest-5-ene-3β,26-diol (**2**, "26-hydroxycholesterol"). Kryptogenin diacetate (**8**) was converted to **2** in 39% yield by successive removal of the C-16 and C-22 carbonyl functions (cycloethylene dithioketal formation followed by Raney nickel desulfurization). 22-Oxocholest-5-ene-3β,26-diol (**17**) was shown to be an intermediate in a previous preparation of **2**, and it was shown to be a source of C-25 epimerization and byproducts in that procedure. The products seen in the Wolff–Kishner reduction of **17** are explained by base-catalyzed equilibration of **17** with 26-oxocholest-5-ene-3β,22-diol (**23**). This equilibration by base-catalyzed 1,5-hydride shift was demonstrated by deuterium labeling. ^{13}C and ^1H NMR correlations were developed for the above compounds.

(20*R*,25*R*)-Cholest-5-ene-3β,26-diol, "26-hydroxycholesterol", an intermediate in bile acid biosynthesis, is a potentially important factor in the study of atherosclerosis. It is a potent inhibitor of cholesterol synthesis in vitro.[2] In human serum it is present in free and esterified form in both the low density (LDL) and high density lipoproteins (HDL). It is a constituent of human atherosclerotic plaque.[3] Because of these facts and because of the proposal that oxygenated sterols in LDL might be involved in the regulation of cholesterol synthesis through mediation of the binding of LDL to a cell surface receptor,[4] we decided to prepare 26-hydroxycholesterol for biological investigation.[5]

Microsomal hydroxylation at C-26 in cholesterol gives the 25*R* diastereoisomer,[6] and material isolated from hu-

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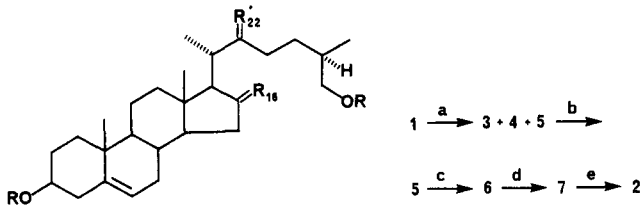
(2) Javitt, N. B.; Kok, E.; Burstein, S.; Cohen, B.; Kutscher, J. *J. Biol. Chem.* **1981**, *256*, 12644.
(3) Van Lier, J. E.; Smith, L. L. *Biochemistry* **1967**, *6*, 3269.
(4) Kandutsch, A. A.; Chen, H. H.; Heiniger, H. J. *Science (Washington, D.C.)* **1978**, *201*, 498.
(5) We thank Professor Norman B. Javitt, New York University Medical Center, for bringing this problem to our attention.

0022-3263/85/1950-2359$01.50/0

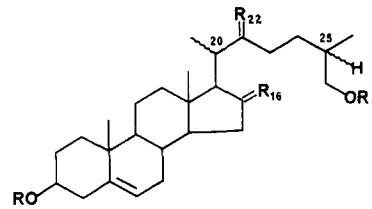
Scheme I. Preparation of 2 after Scheer et al.[8] [a]



1 : R=H; R_{16}=R_{22}=O

2 : R=H; R_{16}=R_{22}=H_2

7 : R=Ac; R_{16}=R_{22}=H_2



3 : R=H; R_{16}=O; R_{22}=H_2

4 : R=H; R_{16}=H_2; R_{22}=O

5 : R=H; R_{16}=R_{22}=H_2

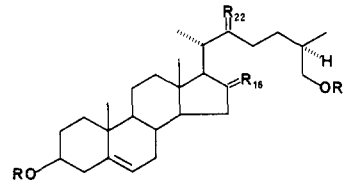
6 : R=Ac; R_{16}=R_{22}=H_2

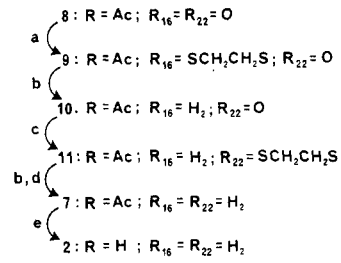
[a] (a) Ac_2O, pyridine; (b) flash chromatography (ref 36); (c) K_2CO_3, MeOH.

man atherosclerotic plaque has been shown to be largely (ca. 90%) the 25*R* diastereoisomer;[7] therefore, we decided to work first with the 25*R* material. The 25*R* diastereoisomer has been made from kryptogenin[8] and diosgenin.[9] The 25*S* diastereoisomer has been made by side-chain synthesis[10] and by microbial oxidation of cholesterol.[11]

(20*R*,25*R*)-Cholest-5-ene-3β,26-diol. Kryptogenin (1) is an appropriate starting material for **2** since it contains the required stereochemistry at C-20 and C-25, and it presents no more than the seemingly straightforward problem of reductive removal of its two ketone functions at C-16 and C-22. However, both the 1,4-arrangement of ketonic carbonyls and a 1,5-arrangement of a ketone and an alcohol in 1 place limitations on methods for reductive removal of carbonyl groups. Thus a direct Wolff–Kishner reduction of the C-16 and C-22 carbonyls is thwarted because the 1,4-diketone system combines with hydrazine to give a pyridazine.[12,13] Furthermore, exposure of such a 1,5-ketol to acidic conditions is known to lead to a reversible 1,5-hydride shift that creates a C-26 aldehyde function, which in turn activates the C-25 proton to acid-catalyzed epimerization, the so-called "iso reaction".[14,15]

Scheme II. Synthesis of (20*R*,25*R*)-Cholest-5-ene-3β,26-diol (2)[a]





[a] (a) $HSCH_2CH_2SH$, BF_3·Et_2O, HOAc; (b) RaNi, EtOH; (c) $HSCH_2CH_2SH$ (neat), BF_3·Et_2O; (d) flash chromatography (ref 36); (e) K_2CO_3, MeOH.

On repeating the literature preparation of 26-hydroxycholesterol from kryptogenin[8] (Scheme I) we noticed two significant points. Firstly, the mixture from the Clemmensen reduction contains the previously unreported 22-oxocholest-5-ene-3β,26-diol (**4**). Secondly, ^{13}C NMR examination of the crude acetylated product **6** showed the presence of the four possible C-20, C-25 epimeric diastereoisomers. Thus, the purification of **5** was difficult and we found that multiple recrystallizations led to material of only 90% to 95% purity. At this point the yield was variable: 23 ± 7% (n = 5). A pure product was obtained only after conversion to the 3,26-diacetate **6**, purification by chromatography, followed by hydrolysis, and recrystallization. The overall yield of **2** from **1** was ca. 17%.

The Clemmensen reduction was the principle weakness of Scheme I. It failed to go to completion (products **3** and **4**) and led to the epimerization of C-25 through the "iso reaction" and of C-20 via acid-catalized enolization. To circumvent the "iso-reaction" we acetylated the C-26 hydroxyl and then applied several variations of the Clemmensen reduction that utilize low-temperature condtions. Using the diacetate **8** we saw little reaction with zinc/HCl/diethyl ether/0 °C.[16,17] Reduction with active zinc/HCl/acetic anhydride/0 °C[18] did not give any of the desired product and led instead to very polar products.

At this point we adopted a strategy using dithioketal formation followed by Raney nickel desulfurization (Scheme II). Kryptogenin acetate (**8**) was converted selectively and quantitatively to the C-16 dithioketal **9** by using ethanedithiol/boron trifluoride etherate in acetic acid.[19] We were unable to convert **9** further into a C-16,C-22 bis-dithioketal by lengthening the reaction time and by increasing the concentrations of reagents. Compound **9** was desulfurized by using Raney nickel to give **10** in 85% yield. Efficient conversion of **10** to the C-22 dithioketal **11** required the use of neat ethane dithiol. These conditions led to partial epimerization at C-20: the ^1H NMR integrations of the C-21 methyl doublets showed

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Table I. ^{13}C Chemical Shifts[a]

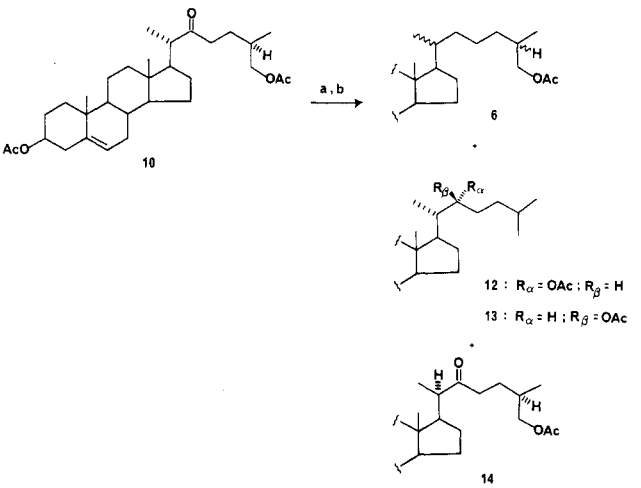
carbon	compound 8	9	10	14	12	13	7	17	6
1	37.2	36.9	37.0	37.0	37.1	37.0	37.0	37.3	37.0
2	27.7	27.7	27.8	27.8	27.8	27.8	27.8	31.6[b]	27.8
3	73.7	73.8	74.0	73.9	74.0	74.0	74.0	71.8	74.0
4	38.0	38.0	38.1	38.1	38.2	38.1	38.1	42.3	38.1
5	139.9	139.6	139.7	139.7	139.7	139.6	139.7	140.9	139.7
6	121.8	122.2	122.7	122.5	122.6	122.6	122.6	121.6	122.6
7	31.7	31.6	31.9	31.9	31.9	31.8	31.9	31.9[b]	31.9
8	30.9	30.6	31.8	31.8	31.9	31.9	31.9	31.9	31.9
9	49.6	49.5	50.0	50.0	50.1	50.1	50.0	50.1	50.1
10	36.7	36.5	36.6	36.6	36.6	36.6	36.6	36.5	36.6
11	20.5	20.9	21.0	20.9	21.1	21.1	21.0	21.0	21.0
12	39.7	39.6	30.6[b]	38.6[b]	39.8	39.7	39.7	39.7	39.7, 39.8
13	41.7	43.6	42.6	42.0	42.7	42.3	42.3	42.6	42.35, 42.39
14	51.2	54.3	56.0	56.1	56.4	56.6	56.7	56.1	56.7
15	36.7	37.3[b]	24.5	23.8	24.4	24.3	24.3	24.5	24.2, 24.3
16	217.9	71.6	27.6	26.9	27.2	28.1	28.3	27.5	28.0, 28.3
17	66.2	61.2	52.1	52.7	53.2	52.6	56.1	52.1	55.6, 55.8
18	13.0	13.1	12.1	12.6	11.9	11.7	11.9	12.1	11.9, 12.1
19	19.3	19.3	19.3	19.3	19.3	19.3	19.3	19.4	19.3
20	43.4	48.1	49.6	48.1	39.3	38.9	35.7	49.5	35.2, 35.7, 35.8
21	15.4	17.5	16.6[c]	17.1[c]	13.1	12.8	18.7	16.6	18.69, 18.72
22	213.2	211.4	214.1	214.8	77.1	76.6	36.1	215.5	35.6, 36.1, 36.2
23	38.6[b]	39.1[b]	38.7[b]	38.1[b]	25.0	30.0	23.3	39.1	23.3, 23.35, 23.38, 23.44
24	26.7	27.1	27.0	26.6	35.7	35.0	33.8	26.2	33.78, 33.84, 33.94
25	32.1	32.1	32.1	32.1	28.0	28.1	32.5	35.4	32.5, 32.6
26	69.0	69.1	68.9	69.0	22.4	22.4	69.6	67.5	69.5, 69.56, 69.62
27	16.8	16.8	16.7[c]	16.8[c]	22.9	22.7	16.8	16.6	16.8, 16.88, 17.0, 17.03
other	170.4	170.5	170.5	170.5	170.5	171.0	170.5		
	171.2	171.2	171.2	171.2	170.9		171.3		
	21.0	21.0	20.9	20.9	21.4	21.2	21.0		
	21.4	21.4	21.4	21.4		21.4	21.5		
		41.0[b]							
		53.3[b]							

[a] δ values in ppm, deuteriochloroform solutions. [b,c] Assignments in a column may be interchanged although these are preferred.

the 20S to 20R ratio was ca. 3:1. Desulfurization of **11** gave diacetate **7**. Hydrolysis of **7** gave pure (20R,25R)-cholest-5-ene-3β,25-diol (**2**) in 39% overall yield from kryptogenin acetate (**8**). The above procedure provided a higher yield of **2** than was obtained from the route of Scheme I. In addition, with the substitution of deuterated Raney nickel,[20] this route could be used to prepare [16,16,22,22-$^2H_4$]-**2**, which would be useful in measurement of serum levels of 26-hydroxycholesterol by the isotope dilution method.[2]

Base-Catalyzed 1,5-Ketol Rearrangement. The presence of the C-22 ketone **4** in the Clemmensen product mixture in Scheme I affected both the stereochemical purity of the final 26-hydroxycholesterol and the byproduct composition of the final crude product mixture. As shown in Scheme III compound **10** was committed to Wolff–Kishner reaction conditions. Acetylation of the crude Wolff–Kishner product mixture afforded **6** (34%), **12** (ca. 10%), **13** (9%), and **14** (4%). The formulation of **6** as a mixture of C-20,25 epimeric compounds was supported by ^1H and ^{13}C NMR evidence. The ^1H NMR spectrum contained three sets of doublets at δ 0.82,[21] 0.917, and 0.925, which represented the combined 21 and 27 methyls. By comparison, the 20R,25R reference compound **7** had coincident signals for the 21 and 27 methyls at δ 0.918. The spectrum of **6** also contained three singlets for the acetates and four sets of ABX patterns for the C-26 protons. The

Scheme III. Wolff-Kishner Reduction of 10[a]



[a] (a) KOH, N_2H_4, triethylene glycol, 165–195 °C; (b) Ac_2O, pyr.

^{13}C NMR spectrum (Table I) of **6** contained inter alia multiple resonances for side-chain and ring C and D carbons: two for carbons 12, 13, 15, 16, 17, 18, 21, and 25; three for carbons 20, 22, 24, and 26, and four for carbons 23 and 27. The assignments of configuration at C-22 in **12** and **13** were made primarily on the correlation of their ^{13}C NMR spectra with published values for 22(R)- and 22(S)-hydroxycholesterol 3-monobenzoates.[22] The melting point and $[\alpha]_D$ for **13** matched published values.[23] Com-

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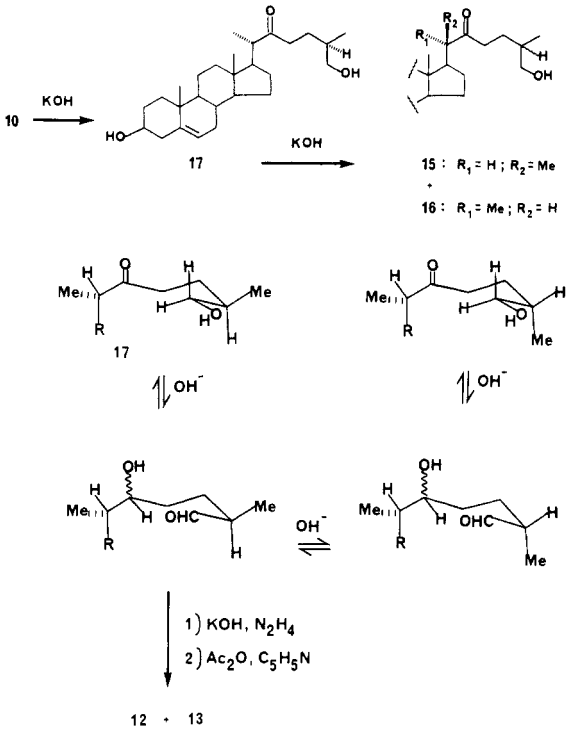
Scheme IV. Base-Catalyzed Epimerization of C-20 and C-25



pound **12** appeared to be a single compound on the basis of ^1H and ^{13}C NMR, TLC, and combustion analysis; however, its melting point and $[\alpha]_D$ (84–88 °C and −26°) were lower than literature values (101.5–103 °C and −32°).[23] These variances suggested the presence of an isomeric impurity, possibly one with 20*R* stereochemistry (vide infra). The evidence for the 20*R*,25*R* formulation for **14** came from a comparison of its NMR spectra with those of **10**. Relative shifts of +0.6, +0.5, −1.5, and +0.5 ppm were observed for carbons 17, 14, 20, and 21 of **14**, and the C-21 methyl protons of **14** were 0.1 ppm upfield of those in **10**.[21]

The key features of this Wolff–Kishner product mixture were the loss of oxygen functionality at C-26 and the epimerization of the C-25 proton. These changes could be rationalized (Scheme IV) by base-catalyzed 1,5-hydride shift from C-26 to C-22 to create a C-26 aldehyde functionality, which could be trapped by hydrazine and could also activate the C-25 proton for base-catalyzed exchange.

The base-catalyzed epimerization of stereocenters C-20 and C-25 shown in Scheme IV draws strong support from the demonstration that **6** is a mixture of all four possible C-20 and C-25 epimers. One would also expect to find a 25*S* counterpart to **14** as well as 20*R* counterparts to **12** and **13** in the reaction mixture. These other expected components of the equilibrium shown in Scheme IV might actually have been in the crude acetylated product mixture, whose TLC contained faint spots close in R_f to the spots for **12** and **14**.

A control experiment simulated the basic conditions of the Wolff–Kishner reduction of **10** and provided evidence for the equilibria described in Scheme IV. Heating **10** with potassium hydroxide in triethylene glycol at 160 °C for 1 h gave a mixture of C-20,25 epimeric 22-keto 26-ols **15** and **16** (ca. 100%). The ^1H NMR spectrum of **15** contained two doublets for the C-27 protons and two doublets for the C-26 protons, while the spectrum of **16** contained two sets

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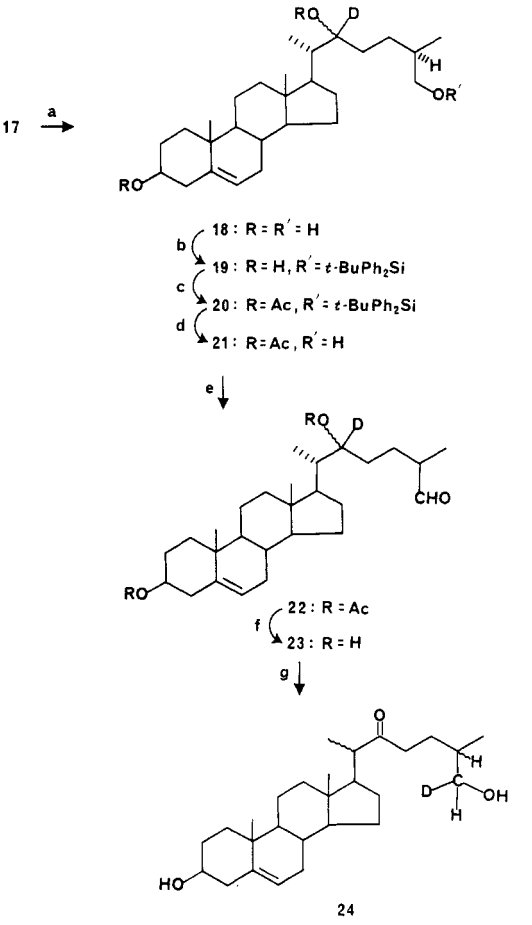
Scheme V. Base-Catalyzed 1,5-Deuteride Shift[a]



[a] (a) $NaBD_4$, EtOH; (b) *t*-$BuPh_2SiCl$, imidazole, DMF; (c) Ac_2O, pyridine; (d) $Bu_4^+F^-$, THF; (e) PCC; (f) K_2CO_3, MeOH; (g) KOH, triethylene glycol, 180 °C.

of doublets for both the 27- and 21-methyls. Compounds **15** and **16** were be assigned 20*R* and 20*S*, respectively, by the comparison of the ^1H NMR shifts of their 18- and 21-methyls to those of **17**. Comparison of the ^{13}C NMR spectra of **16** and **17** also supported the 20*S* formulation for **16**. We observed only **15** and **16** in the TLC of the reaction mixture, which strongly suggests that the base-catalyzed equilibrium in this 1,5-ketol system lies to the side of the 22-keto-26-hydroxy isomer.

Many precedents support the base-catalyzed 1,5-hydride shift proposed for our 1,5-ketol system. Such rearrangements have been described for alkaloids,[24-26] steroids,[27-29] and in the hydroxybicyclo[3.3.0]nonanone system.[30] In three cases the mechanism has been proven to be intramolecular through the demonstration of a 1,5-deuteride shift,[27,29,31] and therefore an intramolecular mechanism is likely in all cases.

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We used the deuterium-labeling experiment outlined in Scheme V to gather additional information on the equilibrium position of our sterol 1,5-ketol system and on the possible intramolecular nature of the proposed 1,5-ketol isomerization. Reduction of **17** with sodium borodeuteride gave triol **18**. C-22 appeared as two overlapping triplets in the proton-decoupled ^{13}C NMR of **18**, thereby confirming the presence of deuterium at C-22. The primary C-26 hydroxyl of **18** was differentiated from the remaining two secondary hydroxyls by selective protection with *tert*-butyldiphenylsilyl, acetylation, and deprotection with fluoride (**19** → **20** → **21**). The deuterium content of **21** was 95–97% $^2H_1$. Oxidation of **21** with pyridium chlorochromate followed by hydrolysis of the acetates afforded the 3,22-diol 26-aldehyde **23**.[32] ^1H NMR indicated that **23** was present as a mixture of the free aldehyde and tetrahydropyran forms. This compound, except for the deuterium at C-22, was the proposed intermediate that gave rise to the deoxygenated products **12** and **13** in the Wolff–Kishner reduction. Heating **23** with potassium hydroxide in triethylene glycol at 180 °C gave the 22-keto 26-ol **24** in 50% yield and with a deuterium incorporation of 95% $^2H_1$. TLC analysis showed that **24** was identical with the mixture of **15** and **16**. The ^1H and ^{13}C NMR spectra of **24** showed that the deuterium was at C-26. The C-26 proton was a complex multiplet at δ 3.38–3.48 with the same integration as the single proton at C-3 and also the single proton at C-6. In the proton-decoupled ^{13}C NMR spectrum C-26 appeared as two overlapping triplets (4 lines). All of the starting material was converted to **24** by heating with KOH, which indicated that the equilibrium favored the ketol isomer. Thus the characterization of the transformation of **23** to **24** provided both a convincing demonstration of the intramolecular mechanism of the base-catalyzed 1,5-ketol equilibration and the equilibrium position of the reaction.

In summary, the preceding experiments demonstrate that under strongly basic conditions the hydroxyl group and the carbonyl of a 1,5-ketol constitute a functional array that is linked in tandem in terms of potential chemical reactivity. This functional group linkage has been demonstrated to carry two important consequences. Firstly, the epimerization of C-25 as a consequence of intramolecular 1,5-ketol isomerization illustrates the potential for the loss of stereochemical integrity at a seemingly unactivated center. Secondly, a hydroxyl-bearing carbon might become a locus for ketonic reactivity.

Experimental Section

Measurements. ^1H NMR spectra were measured on a Bruker WM-300 spectrometer using a sweep width of 10 ppm, a flip angle of 30°, and an acquisition time of 5.47 s with a data table of 32K. The spectra were resolution enhanced by Gaussian multiplication when necessary to resolve closely spaced lines. ^{13}C NMR spectra were measured on either Bruker WH-90 or WM-300 instruments using a sweep width of 240 ppm, 35° flip angles, and 8K or 16K data tables, zero filled to 16K or 32K followed by a 1-Hz line-broadening function. The digital resolution in the frequency domain spectra was 0.03 ppm. Off-resonance and/or attached proton test techniques were used to establish the number of protons directly attached to carbon.[33] In all cases the spectra were referenced to internal tetramethylsilane. The assignments of the carbons of rings A, B, and C are in accord with literature values for cholesterol derivatives.[34] Melting points were recorded on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined in chloroform solutions on a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by the Syntex Analytical Research Services group. Mass spectra were obtained on a MAT CH-7 single focusing instrument.

(25R)-22-Oxocholest-5-ene-3β,26-diol 16,16-(Cycloethylene dithioketal) 3,26-Diacetate (9). A mixture of 2.57 g (5 mmol) of kryptogenin diacetate (**8**),[35] 1.16 g (12.3 mmol) of 1,2-dithioethane, 35 mL of acetic acid, and 15 drops of boron trifluoride etherate was set aside at room temperature for 1.5 h. The solid product was collected by filtration and the filtrate was poured into 300 mL of saturated sodium carbonate solution, and the solid that formed subsequently was collected by filtration. The combined precipitates were washed with saturated sodium carbonate solution and water. Upon drying there was obtained 2.95 g (100%) of white crystals, mp 171–172 °C: $[\alpha]_D$ −65° (*c* 1.02); ^1H NMR δ 0.70 (s, 3 H, 18-CH_3), 0.93 (d, *J* = 6.62 Hz, 3 H, 27-CH_3), 1.01 (s, 3 H, 19-CH_3), 1.12 (d, *J* = 6.99 Hz, 3 H, 21-CH_3), 2.03 (s, 3 H, CH_3CO), 2.05 (s, 3 H, CH_3CO), 3.90 (m, 2 H, CH_2O). Anal. Calcd for $C_{33}H_{50}O_5S_2$: C, 67.08; H, 8.53. Found: C, 67.04; H, 8.66.

(20RS,25R)-Cholest-5-ene-3β,26-diol 22,22-(Cycloethylene dithioketal) 3,26-Diacetate (11). A mixture of 0.78 g of **10** (1.56 mmol), 2.5 g of 1,2-dithioethane, and 20 drops of boron trifluoride etherate was left at 23 °C for 5 h. This material was poured onto excess 5% sodium bicarbonate and this mixture was extracted with diethyl ether. After evaporation and removal of the excess 1,2-dithioethane in vacuo, the residue was purifed by flash chromatography[36] to give 0.59 g (66%) of an oil: ^1H NMR δ 0.71 and 0.75 (two s, 3 H, 18-CH_3), 0.96 and 1.02 (two d, *J* = 6.5 Hz, 3 H, 27-CH_3), 1.01 (s, 3 H, 19-CH_3), 1.27 and 1.30 (two d, *J* = 6.8 Hz, 3 H, 21-CH_3), 2.03 (s, 3 H, 3-OAc), 2.06 and 2.07 (two s, 3 H, 26-OAc), 3.06–3.35 (m, 4 H, CH_2-5), 3.92 (m, 2 H, CH_2OAc). Anal. Calcd for $C_{33}H_{52}O_4S_2$: C, 68.70; H, 9.09. Found: C, 68.50; H, 9.33.

(20R,25R)-Cholest-5-ene-3β,26-diol 3,26-Diacetate (7) from 11. Raney nickel prepared from 15 g of alloy (see preparation of **10**) was stirred with 150 mL of absolute ethanol and to this mixture was added a solution of 0.4 g of **11** (0.69 mmol) in 50 mL of diethyl ether–ethanol (1:1). This mixture was heated at reflux for 3 h. The cooled mixture was filtered and the reside was rinsed with three 100-mL portions of ethanol. The filtrate was evaporated and the residue was purified by flash chromatography[36] (10% ethyl acetate–hexane) to give 0.25 g (74%) of **7** as white crystals, mp 117–120 °C. Recrystallization from methanol gave crystals, mp 128–129 °C, which were identical by mixture melting point with material that was prepared from kryptogenin by the method of Scheer[8] (vide post).

(20R,25R)-Cholest-5-ene-3β,26-diol (2). To a mixture of 250 mg (0.514 mmol) of **7** (mp 117–120 °C) in 5 mL of methanol was added 100 mg of potassium carbonate. This mixture was heated at reflux for 1 h. Water was added and crystals formed on cooling. After filtration and recrystallization from ethyl acetate there was obtained 198 mg (96%) of **2**, mp 178–179 °C (lit.[8] mp 177–178 °C): $[\alpha]_D$ −31.3° (*c* 0.575). Anal. Calcd for $C_{27}H_{46}O_2$: C, 81.34; H, 11.63. Found: C, 81.53; H, 11.68.

(20S,25R)-22-Oxocholest-5-ene-3β-26-diol 3,26-Diacetate (10). To a solution of 44.2 g of sodium hydroxide in 170 mL of water at 70 °C was added with stirring 34 g of Raney nickel alloy over a 0.5-h period. The resulting solid was rinsed with four 600-mL portions of water and two 600-mL portions of absolute ethanol. The washed Raney nickel was transferred into a 1000-mL round-bottomed flask along with 400 mL of ethanol. Dithioketal **9** (3.5 g, 5.92 mmol) was added and the contents were heated at reflux with stirring for 30 min. After being cooled to room temperature, the supernatant was isolated by filtration and the residue was rinsed with two 300-mL portions of ethanol. Evaporation of the filtrate left a crude product that was purified by flash chromatography[36] using 1% acetone–dichloromethane to give 2.52 of (85%) of white crystals, mp 117–118 °C (methanol): $[\alpha]_D$ −54° (*c* 0.548); ^1H NMR δ 0.70 (s, 3 H, 18-CH_3), 0.94 (d, *J* = 6.62 Hz, 3 H, 27-CH_3), 1.02 (s, 3 H, 19-CH_3), 1.11 (d, *J* = 6.99 Hz, 3 H, 21-CH_3), 2.03 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 3.86–3.97 (two q, 2 H, CH_2O). Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.06; H, 9.81.

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Wolff–Kishner Reduction of 10. A mixture of 1.8 g (3.6 mmol) of **10**, 3.6 mL of 85% hydrazine hydrate, 2.4 g (42.8 mmol) of potassium hydroxide, and 35 mL of triethylene glycol was heated at reflux for 0.5 h in a 165 °C oil bath. The condenser was removed and the bath temperature was raised to 195 °C and maintained at that point for 2 h. After being cooled to room temperature, the mixture was poured onto 200 mL of 0.5 N hydrochloric acid. The solid that separated (1.47 g) was collected by filtration. After drying this material was dissolved in 20 mL of pyridine and 10 mL of acetic anhydride and this mixture was poured onto a mixture of ice and excess concentrated hydrochloric acid. This mixture was extracted thoroughly with diethyl ether and the combined ether extract was washed with saturated sodium bicarbonate solution. Evaporation of the ether left a residue that was purified by flash chromatography[36] using 5% ethyl acetate–hexane to give in order of elution:

(a) (22*R*)-Cholest-5-ene-3β,22-diol 3,22-diacetate (12): 0.167 g (10%), mp 84–88 °C (methanol) (lit.[24] mp 101.5–103 °C); $[\alpha]_D$ −25° (*c* 0.007) (lit.[24] $[\alpha]_D$ −23°); ^{1}H NMR δ 0.67 (s, 3 H, 18-CH_3), 0.868 and 0.873 (two d, *J* = 6.62 Hz, 6 H, 26- and 27-CH_3), 0.92 (d, *J* = 6.80 Hz, 3 H, 21-CH_3), 1.01 (s, 3 H, 19-CH_3), 2.02 and 2.03 (two s, 6 H, CH_3CO), 4.83–4.90 (m, 1 H, 22-H). Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.38; H, 10.12.

(b) (22*S*)-Cholest-5-ene-3β,22-diol 3,26-diacetate (13): 0.15 g (9%), mp 145–146 °C (methanol) (lit.[23] mp 145–146 °C); $[\alpha]_D$ −57° (*c* 0.008) (lit.[23] $[\alpha]_D$ −56°); ^{1}H NMR δ 0.68 (s, 3 H, 18-CH_3), 0.87 (d, *J* = 6.62 Hz, 6 H, 26- and 27-CH_3), 0.97 (d, *J* = 6.80 Hz, 3 H, 21-CH_3), 1.02 (s, 3 H, 19-CH_3), 4.90–4.98 (m, 1 H, 22-H). Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.18; H, 10.20.

(c) (20*RS*,25*RS*)-Cholest-5-ene-3β,26-diol 3,26-diacetate (6): 0.6 g (34%), mp 45–65 °C; ^{1}H NMR δ 0.68 (s, 3 H, 18-CH_3), 0.82 (d, *J* = 6.55 Hz, 21-CH_3), 0.92 and 0.93 (two d, *J* = 6.70 and 6.71 Hz, 21- and 27-CH_3), 2.03, 2.057 and 2.059 (three s, 6 H, CH_3CO), 3.8–4.0 (m, 2 H, CH_2O). Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.44; H, 10.26.

(d) (20*R*,25*R*)-22-Oxocholest-5-ene-3β,26-diol 3,26-diacetate (14): 0.08 g (4%), mp 106–107 °C (methanol); $[\alpha]_D$ −54° (*c* 0.003); ^{1}H NMR δ 0.67 (s, 3 H, 18-CH_3), 0.94 (d, *J* = 6.68 Hz, 3 H, 27-CH_3), 1.00 (s, 3 H, 19-CH_3), 1.02 (s, *J* = 6.88 Hz, 21-CH_3), 2.03 and 2.06 (two s, 6 H, CH_3CO), 3.89 and 3.94 (two q, J_{AB} = 10.5 Hz, J_{AX} = 6.0 Hz, 2 H, CH_2O). Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.58; H, 9.78.

Base Treatment of 10. A mixture of 1.0 g of **10**, 0.5 g of potassium hydroxide, and 20 mL of triethylene gycol was heated at 160 °C under argon for 1 h. The mixture was cooled to room temperature and was poured into 150 mL of water. After acidification, the precipitate was collected by filtration. This solid was dissolved in 150 mL of ethyl acetate and this mixture was washed with water and dried over sodium sulfate. Evaporation afforded 0.83 g (ca. 100%) of a foam, which showed two components by TLC using 60% ethyl acetate–hexane (R_f 0.37 and 0.3). Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83 H, 10.64. Found: C, 78.00; H, 10.79. The two components were separated by flash chromatography[36] using ethyl acetate–hexane–acetic acid (65:35:1 by volume).

Component a, (20*S*,25*RS*)-22-oxocholest-5-ene-3β,26-diol (16): ^{1}H NMR δ 0.70 (s 3 H, 18-CH_3), 0.91 and 0.92 (two d, *J* = 6.63 Hz, 3 H, 27-CH_3), 1.01 (s, 3 H, 19-CH_3), 1.11 (d, *J* = 6.86 Hz, 3 H, 21-CH_3), 3.42 and 3.43 (two d, *J* = 5.86, 2 H, CH_2O).

Component b, (20*R*,25*RS*)-22-oxocholest-5-ene-3β,26-diol (15): ^{1}H NMR δ 0.67 (s, 3 H, 18-CH_3), 0.92 and 0.93 (two d, *J* = 6.63 Hz, 3 H, 27-CH_3), 0.99 (s, 3 H, 19-CH_3), 1.023 and 1.024 (two d, *J* = 6.86 Hz, 3 H, 21-CH_3), 3.45 (d, *J* = 5.75 Hz, CH_2O).

(20*R*,25*R*)-Cholest-5-ene-3β,26-diol 3,26-Diacetate (7). A solution of 1.9 g of **5**[8] (mp 175.5–177 °C), 4 mL of acetic anhydride, and 15 mL of pyridine was heated for 0.5 h on a 90 °C water bath. The solution was poured onto ice–hydrochloric acid, and the resulting mixture was extracted thoroughly with dichloromethane. The organic layer was extracted with saturated sodium bicarbonate solution. Evaporation of solvent and purification by flash chromatography[36] using 10% ethyl acetate–hexane gave 1.54g (67%); mp 128–129 °C (methanol) (lit.[8] mp 128–129 °C); $[\alpha]_D$ −40° (*c* 1); ^{1}H NMR δ 0.68 (s, 3 H, 18-CH_3), 0.92 (d, *J* = 6.62 Hz, 6 H, 21- and 27-CH_3), 1.00 (s, 3 H, 19-CH_3), 2.03 and 2.05 (two s, 6 H, CH_3CO), 3.84 (q, J_{AX} = 6.99 Hz, J_{AB} = 10.66 Hz, 1 H, CH_AH_BO), 3.94 (q, J_{BX} = 6.07 Hz, J_{BA} = 10.66 Hz, 1 H, CH_AH_BO). Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.83; H, 10.83.

(20*S*,25*R*)-22-Oxocholest-5-ene-3β,26-diol (17). A mixture of 0.84 g (1.68 mmol) of **10**, 0.1 g of potassium carbonate, and 15 mL of methanol was warmed at 60 °C for 40 min. Water was added and the resulting precipitate was collected by filtration. Recrystallization from ethyl acetate afforded 0.415 g; mp 149–152 °C; $[\alpha]_D$ −53° (*c* 1); ^{1}H NMR δ 0.70 (s, 3 H, 18-CH_3), 0.91 (d, *J* = 6.59 Hz, 3 H, 27-CH_3), 1.01 (s, 3 H, 19-CH_3), 1.11 (d, *J* = 6.84 Hz, 3 H, 21-CH_3), 3.43 (d, *J* = 5.86 Hz, 2 H, CH_2O). Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.61; H, 10.53.

[22-^{2}H$_1$]Cholest-5-ene-3β,22,26-triol (18). To a solution of 0.5 g (1.2 mmol) of **17** in 10 mL of ethanol was added 0.5 g of sodium borodeuteride (98% atom % D). After 24 h at 23 °C the solvent was removed in vacuo and the residue was treated with water and excess 1 N HCl. The resulting solid was collected by filtration, was washed with water, and was dried to yield 0.48 g of white crystals, mp 209–213 °C: ^{13}C NMR δ 11.6 and 12.4 (C-18), 72.0 (br, C-22).

[22-^{2}H$_1$]-26-Oxocholest-5-ene-3β,22-diol 3,22-Diacetate (22). To a solution of 0.48 g (1.15 mmol) of **18** in 5 mL of DMF plus 15 mL of dichloromehane were added 0.32 g (1.16 mmol) *tert*-butyldiphenylsilyl chloride and 0.4 g of imidazole. After 96 h at 23 °C TLC indicated that there was still a small amount of **18** present. An additional 0.1 g of *tert*-butyldiphenylsilyl chloride was added and the mixture was set aside at 23 °C for 48 h. Water (5 mL) was added and the mixture was stirred at 23 °C for 18 h. This mixture was mixed with 20 mL of dichloromethane and the resulting mixture was washed with 1 N HCl (2 × 20 mL) and water (2 × 20 mL). Evaporation gave a residue that was purified by flash chromatography[36] using 25% ethyl acetate–hexane to give 338 mg (ca. 44%) of **19**, a foam that was two components by TLC (30% ethyl acetate–hexane: R_f(a) 0.25, R_f(b) 0.2): ^{1}H NMR δ 0.683 and 0.695 (two s, 3 H, 18-CH_3) (Ratio of the two 18-CH_3 singlets = 2.6:1); ^{13}C NMR δ 11.82 and 11.89 (C-18), 16.83 and 17.02 (C-21), 73.5 (br, C-22).

To a solution of 338 mg of **19** in 2 mL of pyridine and 2 mL of dichloromethane were added 1 mL of acetic anhydride and 50 mg of 4-(dimethylamino)pyridine. After 18 h at 23 °C the mixture was diluted with 20 mL of dichloromethane and was washed successively with 1 N HCl, water, and 5% sodium bicarbonate. Evaporation gave 0.37 g of crude **20**. This was dissolved in 3 mL of THF to which was added 3 mL of 1 M tetrabutylammonium fluoride in THF. After 20 h at 23 °C TLC indicated complete conversion of **20** to a more polar spot. Water and dichloromethane were added and the organic layer was reserved and was dried over sodium sulfate. The residue obtained after evaporation was purified by flash chromatography[36] (30% ethyl acetate–hexane) to give 201 mg of **21** as a foam: ^{1}H NMR δ 0.682 (s, 3 H, 18-CH_3), 0.922 and 0.969 (two d, J_1 = 6.7 and J_2 = 6.8 Hz, 3 H, 21-CH_3), 2.033 (s, 3 H, 3-OAc), 2.044 and 2.046 (two s, 3 H, 22-OAc); MS, *m/z* 443 (P– HOAc) 443/442 = 95/5 to 97/3.

To a solution of 0.19 g of **21** in 5 mL of dichloromethane were added 0.5 g of $MgSO_4$ and 0.163 g of pyridium chlorochromate. The mixture was stirred at 23 °C for 2 h, at which time it was filtered through a short column containing 15 g of Florisil (250 mL of dichloromethane, then 250 mL of ethyl acetate). Evaporation followed by flash chromatography[36] (30% ethyl acetate–hexane) gave 101 mg of **22** as a white solid, mp 116–122 °C: ^{1}H NMR δ 0.681 (s, 3 H, 18-CH_3), 0.918 and 0.967 (two d, J_1 = 6.78 and J_2 = 6.74 Hz, 3 H, 21-CH_3), 1.11 (d, *J* = 7.04 Hz, 3 H, 2-CH_3), 2.032 (s, 3 H, 3-OAc), 2.053 and 2.057 (two s, 3 H, 21-OAc), 9.605 and 9.611 (two d, J_1 = 1.88 and J_2 = 1.91 Hz, 26-CHO); ^{13}C NMR δ 11.69 and 11.89 (C-18), 12.82 and 13.06 (C-21), 19.32 (C-27), 204.71 (C-26); MS, *m/z* 441 (P – HOAc) 441/440 = 97/3 to 98/2. Anal. Calcd for $C_{31}H_{47}DO_5$: C, 74.21; H, 9.85. Found: C, 74.46; H, 9.66.

[26-^{2}H]-22-Oxocholest-5-ene-3β,26-diol (24). A mixture of 90 mg (0.18 mmol) of **22**, 5 mL of methanol, and 100 mg of potassium carbonate was stirred at 23 °C for 22 h. The solvent was evaporated, water was then added to the residue, and the mixture was extracted throughly with dichloromethane. Evaporation of the combined extract and purification by flash chromatography[36] (5% methanol–dichlormethane) gave 55 mg of **23** as a foam. TLC (5% methanol–dichloromethane) indicated the presence of three components of nearly identical R_f (ca. 0.6): ^{1}H NMR δ 4.2–4.35 (m, OC*H*OH) and 9.605 (two d, 26-CHO); MS,

m/z 417 (P) 417/416 = 91/9, 399 (P - H_2O) 399/398 = 93/7.

To a solution of 50 mg (0.12 mmol) of **23** in 2 mL of triethylene glycol was added 20 mg of potassium hydroxide. This mixture was heated at 180 °C for 2.75 h under argon. After cooling the mixture was diluted with 30 mL of water and this mixture was made acidic with 1 N HCl. The mixture was extracted throughly with dichloromethane. The combined extract was evaporated to give a residue that was purified by flash chromatography[36] to give 25 mg of **24** as a foam: ^{1}H NMR δ 0.67 and 0.70 (two s, 3 H, 18-CH_3), 0.904, 0.908, 0.915, 0.927, 0.938, 0.968 (3 H, 27-CH_3), 1.01 and 0.985 (two s, 3 H, 19-CH_3), 1.033, 1.036, 1.096, 1.119 (3 H, 21-CH_3), 3.38–3.48 (m, 1 H, 26-C*H*DOH); ^{13}C NMR δ 66.8, 67.1, 67.4, 67.6 (overlapping triplets for C-26); MS, m/z 417 (P) 417/416 = 94/6, 399 (P - H_2O) 399/398 = 95/5. Anal. Calcd for $C_{27}H_{43}DO_3$: C, 77.65; H, 10.86. Found: C, 77.75; H, 10.55.

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Products of the Reaction of *N,N'*-Dibenzylethylenediamine and Glyoxal

Rodney L. Willer*† and Donald W. Moore

Chemistry Division, Research Department, Naval Weapons Center, China Lake, California 93555

David J. Vanderah‡

Department of Chemistry, Chatham College, Pittsburgh, Pennsylvania 15232

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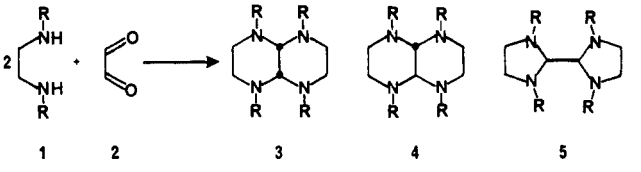
The reaction of *N,N'*-dibenzylethylenediamine with glyoxal in ethanol has been shown to give 1,1',3,3'-tetrabenzyl-2,2'-biimidazolidine (**5c**) and *trans*-1,4,5,8-tetrabenzyl-1,4,5,8-tetraazadecalin (**4c**) in a 60:40 ratio as the initial products. Compound **4c** has been shown to undergo a reversible isomerization to the corresponding cis isomer **3c** in $CDCl_3$ and the $\Delta G°_{333}$ for the isomerization has been determined to be <0.1 kcal/mol. Both **3c** and **4c** show dynamic behavior in their ^{1}H and ^{13}C NMR spectra. In **3c** this dynamic process has a $\Delta G^‡$ of 13.0 kcal/mol and is ascribed to a ring flip process. In **4c** the dynamic process has a $\Delta G^‡$ of 13.3 kcal/mol and is ascribed to slow nitrogen inversion. These results are compared and contrasted to the results obtained in the analogous methyl case.

The reaction of ethylenediamine or an N,N'-disubstituted ethylenediamine with glyoxal can produce three different 2:1 products, the *cis*- and *trans*-1,4,5,8-tetraazadecalins **3** and **4** and the biimidazolidine **5** as summarized in Scheme I.

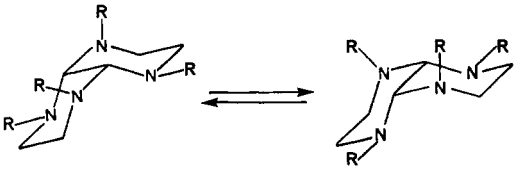
Previous work has established that with ethylenediamine (R = H) the sole product is the *trans*-1,4,5,8-tetraazadecalin **4a**.[1] With *N,N'*-dimethylethylenediamine considerable controversy existed about the structure of the products,[1,2] but it is now clear that the initial product is a mixture of *cis*- and *trans*-1,4,5,8-tetramethyl-1,4,5,8-tetraazadecalins (**3b** and **4b**) rich in the trans isomer.[3] Fuchs et al. were able to synthesize the pure trans isomer **4b** by careful reduction of *trans*-1,4,5,8-tetraethoxycarbonyl-1,4,5,8-tetraazadecalin[3] and observed that **4b** isomerized to the cis isomer **3b**, but because of decomposition of the products were unable to establish if this is a reversible isomerization or a one way process. Katritzky also established that both **3b** and **4b** showed dynamic behavior in their ^{1}H and ^{13}C NMR spectra.[2] The dynamic process in **3b** was ascribed to a ring reversal process between the two lowest energy conformers (see Scheme II). The energy barrier was determined to be 11.6 kcal/mole at 234 °K.

The dynamic process in **4b** was ascribed to *N*-methyl inversion which has a higher than normal energy barrier due to the fact that 1,8 or 4,5 N inversion must occur simultaneously, as summarized in Scheme III, in order to avoid severe peri interactions. This forces the methyl groups to approach very close to each other during the transition state. The barrier was measured to be 9.1 kcal/mol. An unanswered question from Katritzky's work on **4b** (R = CH_3) concerns the relative stability of its achiral (C_i) vs. chiral (C_2) forms of the trans isomer (see Scheme III).

Scheme I. Possible 2:1 Products from the Reaction of an N,N-Disubstituted Ethylenediamine and Glyoxal



Scheme II. Ring Inversion between the Two Lowest Energy Conformers of a *cis*-1,4,5,8-Tetrasubstituted-1,4,5,8-tetraazadecalin 3



Fuchs has reported that the reaction of *N,N'*-dibenzylethylenediamine, **1c**, with glyoxal gives a mixture of two crystalline products, mp 190 °C, one of which is the

†Current Address: Morton-Thiokol Inc., Elkton Division, Elkton, MD 21921.

‡1982 American Society for Engineering Education Summer Faculty Research Participant at the Naval Weapons Center.

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