(43, loss of ethylene), 108 (80, a C_8H_{12} fragment), 91 (49, tropylium cation).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.81; H, 10.49.

5,10ξ-Epoxy-B(9a)-homo-5ξ-estran-17-one (12). A. By Epoxidation of B(9a)-Homo-5(10)-estren-17-one (8a).—*m*-Chloroperbenzoic acid (50 mg) was added to a solution of **8a** (100 mg) in chloroform (10 ml), and the mixture was allowed to stand at room temperature for 30 min. After the usual work-up, the residue was crystallized from CH_3OH to give **12**: mp 124–125°; $[\alpha]D$ +75.5°; nmr ($CDCl_3$) δ 0.97 (s, 3, C-18 CH_3).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.18; H, 9.68.

B. By Hydrogenation of 5,10ξ-Epoxy-B(9a)-homo-5ξ-estr-2-en-17-one (3).—A solution of **3** (50 mg) in EtOH (50 ml) was hydrogenated using Pd–C (5%) as a catalyst. After removal of solvent and catalyst, the residue was crystallized from CH_3OH to give **12**, mp 124–125°, identical in all respects (R_f, melting point, nmr, and ir) with the product described above.

Action of *m*-Chloroperbenzoic Acid on B(9a)-Homo-5α-estr-1(10)-en-17-one (9).—*m*-Chloroperbenzoic acid (400 mg) was added to a solution of **9** (400 mg) in chloroform (10 ml), and the mixture was allowed to stand at room temperature for 10 min. After the usual work-up the residue was chromatographed. Elution with petroleum ether–ether (9:1) (150 ml) yielded a crystalline solid (100 mg), identified as the α-epoxide **1α,10-epoxy-B(9a)-homo-5α-estran-17-one (10)**: mp 114–115° (from CH_3OH); $[\alpha]D$ +15.5°; nmr ($CDCl_3$) δ 3.30 (dd, 1, J = 4 cps, 1β proton), 0.85 (s, 3, C-18 CH_3); nmr (C_6D_6) δ 3.07 (dd, 1, J = 5 cps).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.17; H, 9.80.

Further elution with the same solvent system (600 ml) yielded a crystalline solid (200 mg) identified as the β-epoxide **1β,10-epoxy-B(9a)-homo-5α-estran-17-one (11)**: mp 140–142° (from CH_3OH); $[\alpha]D$ +32.5°; nmr ($CDCl_3$) δ 3.15 (d, 1, J = 6, 1α proton), 0.85 (s, 3, C-18 CH_3); nmr (C_6D_6) δ 2.95 (d, 1, J = 6 cps).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.15; H, 9.68.

Registry No.—**2a**, 22602-70-6; **3**, 24467-52-5; **4**, 24467-53-6; **5**, 24467-54-7; **6**, 22602-71-7; **7a**, 24467-56-9; **7b**, 24467-57-0; **8a**, 24467-58-1; **9**, 24467-59-2; **10**, 24467-60-5; **11**, 24467-61-6; **12**, 24467-62-7.

Acknowledgments.—The authors are grateful to Dr. P. Klimstra and G. D. Searle and Co. for the mass spectra.

Geminal Substitution *via* Steroidal 2- and 4-Cyano-3-ones

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The conversion of 3-cholestanone (**1**) into 2,2-dimethylcholestan-3-one (**15**) *via* 2β-cyano-2α-methylcholestan-3-one, to 2,2-dimethyl-5β-cholestan-3-one (**4**) *via* 2α-cyano-2β-methyl-5β-cholestan-3-one (**9**), and to 4,4-dimethylcholestan-3-one (**17**) *via* 4β-cyano-4α-methylcholestan-3-one (**13**) are reported as a model study of the site and stereoselectivity of alkylations. The assignments of the stereochemistry are made on the basis of nmr spectral correlations and chemical conversions. The preparation of 2,2-dimethyl-7-cholesten-3-one illustrates the conversion for an acid-sensitive compound. The syntheses of 4,4-dimethylcholestan-3β-ol-3,30-d_2 (**25**) and 4,4-dimethylcholestan-3-one-30-*d* (**26**) provide compounds for model-independent assignments of chemical shift for the axial and equatorial geminal methyls.

A key step in a number of terpene syntheses is the construction of a geminal center adjacent to the keto group on a cyclohexanone ring. A widely used method for carrying out this substitution, the carbon alkylation of enolate anions of β-keto esters, appears to give epimeric mixtures in most cases.[1,2] As part of a synthetic study designed to furnish labeled compounds for biosynthetic studies, we have carried out a model study of the site and stereoselectivity of carbon substitution in the methylation of potassium enolates of 2-cyanocholestan-3-one, 2-cyano-4-cholesten-3-one, 4-cyanocholestan-3-one, and 4-cyano-1-cholesten-3-one. Our results, which provide a route for control of the site of substitution of unsymmetrical ketones and give geminally substituted compounds which have stereochemistry not previously readily obtained, are reported herein.

2-Cyano ketones have been used occasionally in natural product synthesis.[3,4] The work of Kuehne[3,4] is especially pertinent since it suggests that alkylation of the cyanocholestanones may be stereospecific.

Results and Discussion

The synthesis of 2β-cyano-2α-methylcholestan-3-one (**4**) in 39% yield from cholestan-3-one (**1**) is outlined in Scheme I. Stereochemistry at C-2 is determined by the course of the methylation of the potassium enolate of **3**. The assignment of stereochemistry at the geminal center of **4** rests on spectral and chemical criteria (*vide infra*). The 2β-cyano-2α-methyl ketone **4** is accompanied by approximately 18% oxygen alkylated enol ether isomer. A careful search for the C-2 epimer of **4** led only to the estimate that, if present, this compound is formed in less than 5% yield. The conversion of **1** to **4** illustrates geminal substitution at the preferentially formylated α-methylene of an unsymmetrical cyclohexanone.

The effect of a Δ^4 double bond on the stereospecificity of the methylation is of interest for its potential in controlling stereoselectivity.[4] *A priori* it would be assumed that the flattening of the ring caused by the

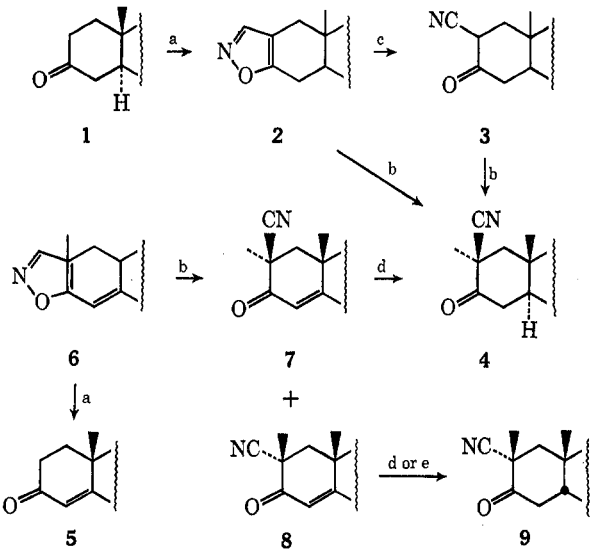
(1) (a) E. Wenkert, A. Afonso, J. Bredenberg, C. Kaneko, and A. Tahara, *J. Amer. Chem. Soc.*, **86**, 2038 (1964); (b) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. F. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); (c) R. E. Ireland and R. C. Kierstead, *ibid.*, **31**, 2543 (1966), and references cited therein.

(2) (a) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem. Int. Ed. Engl.*, **4**, 181 (1965); (b) J. Mathieu and J. Valls, *Chem. Weekbl.*, **63**, 21 (1967).

(3) (a) W. S. Johnson, J. W. Peterson, and C. D. Butsche, *J. Amer. Chem. Soc.*, **69**, 2942 (1947); (b) D. K. Banerjee, S. Chatterjee, C. N. Pillai, and M. V. Bhatt, *il id.*, **78**, 3769 (1956); (c) M. Kuehne, *ibid.*, **83**, 1492 (1961).

(4) After completion of our work we learned of similar studies by M. Kuehne [*J. Org. Chem.*, **35**, 171 (1970)] and M. Kuehne and J. A. Nelson [*ibid.*, **35**, 161 (1970)] on monocyclic, bicyclic, and tricyclic systems. The stereochemical results in that work and the present report are in agreement. We are grateful to Professor Kuehne for kindly providing prepublication copies of the manuscripts.

SCHEME I[a]

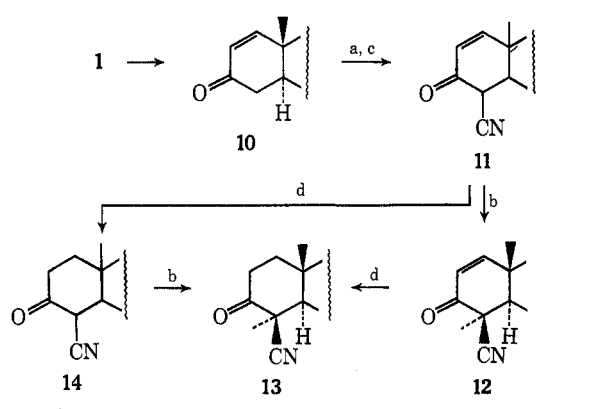


[a] a, $(C_2H_5)_2O$, CH_3ONa, $HCO_2C_2H_5$, $(CH_3)_3COH$, NH_3OHCl; b, $(CH_3)_3COH$, $(CH_3)_3COK$, CH_3I; c, CH_3OH, CH_3ONa; d, H_2, Pd-C; e, Li, NH_3, NH_4Cl.

double bond would lead to changes in 1,3-diaxial interactions between the 2 and 4 and 2 and 10 positions such that formation of both C-2 epimers might be observed. Methylation of the potassium enolate of 2-cyano-4-cholesten-3-one gives an equimolar mixture of 2β-cyano-2α-methyl-4-cholesten-3-one (**7**) and 2α-cyano-2β-methyl-4-cholesten-3-one (**8**) in 39% yield each from the enone **5** (Scheme I). The product of oxygen alkylation was not detected and it is estimated that considerably less than 10% was present. The structure of **7** is established by its catalytic reduction to **4** in 70% yield. However, **8** gives the A/B *cis* compound 2α-cyano-5β-cholestan-3-one (**9**) on catalytic reduction (68%) or on reduction with lithium in ammonia (97%).[5]

The use of a double bond as a blocking group (Scheme II) allows substitution at the C-4 position of cholestan-3-one (**1**). 1-Cholesten-3-one (**10**), prepared from **1** by

SCHEME II[a]

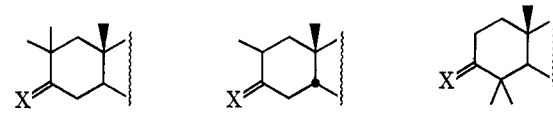


[a] See Scheme I, footnote *a* for a–d.

oxidation with 2,3-dicholoro-5,6-dicyano-1,4-benzoquinone, is readily converted (Scheme II) into 4-cyano-1-cholesten-3-one (**11**). Methylation of the potassium enolate of **11** gives 4β-cyano-4α-methyl-1-cholesten-3-one (**12**) in 68% yield from **10** and reduction of **12** produces 4β-cyano-4α-methylcholestan-3-one (**13**); **13** is also obtained if reduction to **14** precedes methylation. Attempts to find the C-4 epimer of **12** led only to the estimate that less than 5% is formed by either route. Oxygen methylation occurs to the extent of 10% in the alkylation of **11** and 27% in the alkylation of **14**. The fact that one epimer is produced in the carbon methylation of the enolate from 4-cyano-1-cholesten-3-one (**11**) while two are produced in the corresponding reaction of the enolate from 2-cyano-4-cholesten-3-one suggests that formally increasing steric hindrance to approach[7] of the alkylating agent favors the transition state which leads to the product with the nitrile in the more sterically hindered position.

The stereochemistry produced in alkylations of **12** and **14** is opposite to that observed for the major product from comparable keto esters;[1] thus, the two approaches provide reasonably efficient routes to different epimers at the 4 position. Control of the site of substitution of an unsymmetrical cyclohexanone by blocking of the favored site for formylation by a double bond introduced by dehydrogenation (*vide supra*) could prove useful for those cases in which formylation[8] and dehydrogenation[9] proceed at the same site.

The cyano group of the cyano ketones should be readily convertible to the acid, ester, aldehyde, methylenehydroxy, and methyl groups usually desired in terpenoid syntheses. By the procedures outlined in Scheme III, transformations of the cyano functions of **4**, **9**, and **13** to aldehydo and methyl groups have been achieved.[10] The geminal dimethyl ketones, 2,2-dimethylcholestan-3-one (**15**), 2,2-dimethyl-5β-cholestan-3-one (**16**), and 4,4-dimethylcholestan-3-one (**17**),



15, X = O **16**, X = O **17**, X = O
18, X = ···H, ◄OH **19**, X = ···H, ◄OH **20**, X = ···H, ◄OH

respectively, are produced in overall yields of *ca.* 30% *via* the corresponding alcohols **18**, **19**, and **20**. In addition to illustrating the conversions, this sequence provides structural confirmation by convergence with alcohols and ketones of established structure. The nonidentity of **15** and **16** supports the assignment of a *cis* A/B juncture for **9**.[11] A notable feature of this

(5) Production of a *cis* ring juncture in the lithium–ammonia reduction is in accord with the proposals of Stork and Darling,[6] provided that the relative energies of the transition states for hydrogen addition to the *cis* and *trans* conformations of the reduced anionic species from **8** are such that substituent interactions overcome the usual preference for a *trans* product. In the case of **8** the *trans* conformation of the reduced anionic intermediate has a severe 1,3-diaxial dimethyl interaction, and the *cis* conformation has a less demanding 1,3-diaxial cyano–C-9-proton interaction.

(6) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **82**, 1512 (1960).

(7) The formal difference between the two cases is an additional steric interaction involving the 6β hydrogen of the enolate of **11** and the alkylating species.

(8) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 267.

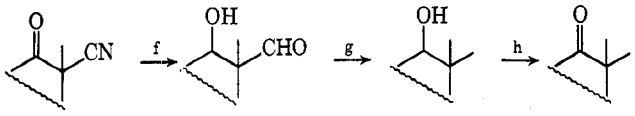
(9) L. M. Jackman, *Advan. Org. Chem.*, **2**, 329 (1960). Other methods of double-bond formation could also be used.

(10) E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).

(11) The half-height widths of the C-10 methyl groups in the nmr spectra of **9** and **4** are 0.4 and 1.0 Hz, respectively, in the same order as the values reported for a series of *cis* (0.36 ± 0.07 Hz) and *trans* (0.84 ± 0.03 Hz) steroids.[12] This assignment is in agreement with the criteria for stereochemistry suggested by Williamson, Howell, and Spencer,[13] provided that the 2β-cyano function in **9** causes the same type of line broadening as does a 2β-halogen function.

(12) D. J. Cram, M. R. V. Sahyan, and R. R. Knox, *J. Amer. Chem. Soc.*, **84**, 1734 (1962); H. H. Szmant and M. N. Roman, *ibid.*, **88**, 4034 (1966).

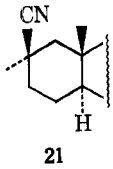
SCHEME III[a]



[a] f, $LiAlH_4$ or $LiAlH_2(OC_2H_5)_2$; H_3O^+; g, NH_2NH_2, KOH; or $HSCH_2CH_2SH$ $(C_2H_5)_2OBF_3$, RaNi; h, CrO_3–C_5H_5N or $Na_2Cr_2O_7$–H_2SO_4.

sequence is the effectiveness of the "low-temperature" Wolff–Kishner reduction[12] achieved without slow addition of the hydrazone, presumably because steric hindrance depresses the rate of competing azine formation.

Assignment of configurations of the geminal substituents of **4** and **13** is based on nmr spectroscopic and chemical correlations. The nmr chemical shifts of the C-10 methyl groups of **4** and **13** show downfield shifts of 0.25–0.36 ppm relative to cholestan-3-one (**1**) or its 2,2-dimethyl (**15**) or 4,4-dimethyl (**17**) derivatives. This deshielding is evidence for a 1,3-diaxial methyl–cyano interaction.[14,15] Reduction of the carbonyl groups of **4** and **13** of the ethane thioketal with Raney nickel produces 2β-cyano-2α-methylcholestane (**21**) and 4β-cyano-4α-methylcholestane (**22**), respectively.[17] The C-10 methyl resonances in the nmr spectra of **21** and **22** are deshielded by 0.32 and 0.34 ppm relative to cholestane. The C-10 methyl signal of **9** is within



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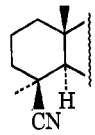

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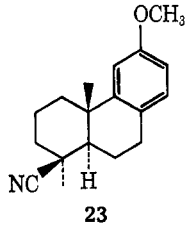
±0.04 ppm of the C-10 methyl signals in the nmr spectra of **1**, **15**, and **17** and, as expected, is not deshielded. The deshielding effect of the cyano group in the spectra of **4**, **13**, **21**, and **22** is opposite to the shielding of the C-10 methyl observed in the spectra of analogous esters and keto esters.[1b,14a] Both effects are in agreement with expectation based on the group magnetic susceptibilities of the nitrile[14b] and ester functions,[18] provided that the latter has a conformation which places the C-10 methyl in a shielding cone of the carbonyl group. Corroboration for the axial assignment for the functionality in **4** and **13** is the characteristic long-range splitting of 2 Hz observed between the 3α proton and the aldehydo proton of the 2β- and 4β-formyl groups[14a,19] in the aldehydo alcohols obtained on reduction of the nitriles (Scheme III).

Chemical evidence for the stereochemistry of the nitriles **4** and **13** is provided by a comparison of the hydrolytic characteristics of **21** and **22** with those of the models, O-methylpodocarponitrile (**23**), an axial nitrile, and dehydroabietonitrile (**24**), an equatorial nitrile.[20] Treatment of **21**, **22**, **23**, and **24** dissolved in ethylene glycol with aqueous potassium hydroxide at 150° for 24 hr gives complete hydrolysis of **24** and 85–91% recovery of unreacted **21**, **22**, and **23**. The



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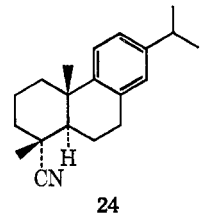

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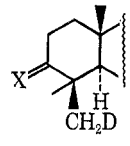
resistance to hydrolysis of the latter compounds is expected for these relatively hindered axial nitriles.[22,23]

Assignments of chemical shifts to the stereochemically different geminal C-4 methyl groups in the nmr spectra of 4,4-dimethyl-3-hydroxy sterols have been made on the basis of the expected similar response of the chemical shift of the 4β-methyl and C-10 methyl to 2β and 5α substituents.[24] These designations have been important in establishing that the methylation of 4-methyl-4-cholesten-3-one proceeds from the α side[25] and in determining the stereochemical course at C-4 of the enzymatic cyclization of squalene 2,3-oxide to lanosterol.[26] Nmr distinction between the 4,4-dimethyl groups has also been achieved for 3-keto-4,4-dimethyl steroids by use of model compounds and a solvent shift technique which shows that the equatorial methyl of steroidial 4,4-dimethyl-3-one shifts downfield and the axial methyl upfield when the solvent is changed from deuteriochloroform to benzene.[27] This synthetic sequence permits confirmation of the previous assignments without dependence on model compounds. The synthesis of 4,4-dimethylcholestan-3β-ol-3,30-d_2 (**25**) and 4,4-dimethylcholestan-3-one-30-*d* (**26**) was readily achieved by the previously discussed methods, with lithium aluminium deuteride being used for reduction of **13**. The nmr spectra of **25** contained a three-proton



25, X = D, OH
26, X = O

(13) K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).

(14) (a) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965); (b) A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.*, **85**, 3233 (1963); (c) J. Jacquesy, J. Lehn, and J. Levisalles, *Bull. Soc. Chim. Fr.*, 2444 (1961).

(15) The diamagnetic anistropy of the nitrile group also causes a large deshielding of the 4β proton in **4** (δ 2.91 ppm) and the 4α position in **9** (δ 3.37 ppm). These protons have a 1,3-diaxial location with respect to the nitrile. The assignments were confirmed by double-irradiation, "spin-tickling," and deuterium-exchange experiments. The Cotton effects of **4** and **9** confirm that ring A of these compounds has a chair conformation.[16]

(16) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(17) 2-Methylcholest-2-ene and 4-methylcholest-3-ene, respectively, are also produced in these reactions.

(18) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).

(19) M. Fetizon, G. Moreau, and N. Moreau, *Bull. Soc. Chim. Fr.*, 3295 (1968).

(20) The relative ease of hydrolysis of equatorial esters as contrasted with axial esters is an established method of determining stereochemistry in related systems.[1a,b,21]

(21) W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, **64**, 928 (1942); F. E. King, D. H. Godson, and T. J. King, *J. Chem. Soc.*, 1117 (1955); J. M. Beaton and F. S. Spring, *ibid.*, 3126 (1955).

(22) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958).

(23) M. R. Harnden, *J. Chem. Soc., C*, 960 (1969).

(24) F. Hemmert, A. Lablache-Combier, B. Lacoume, and J. Levisalles, *Bull. Soc. Chim. Fr.*, 982 (1966); F. Hemmert, B. Lacoume, J. Levisalles, and G. R. Pettit, *ibid.*, 967 (1966).

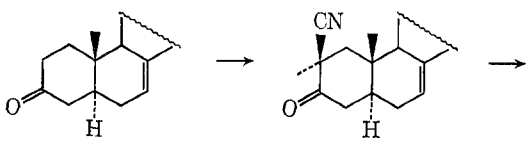
(25) D. Rosenthal, *J. Org. Chem.*, **32**, 4084 (1967).

(26) K. J. Stone, W. R. Roeske, R. B. Clayton, and E. E. van Tamelen, *Chem. Commun.*, 530 (1969).

(27) N. S. Bhacca and D. H. Williams, *Tetrahedron Lett.*, 3127 (1964); N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry, Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, pp 165–170.

methyl resonance at δ 0.96 ppm (equatorial CH_3) and a *ca.* two-proton signal at 0.78 ppm (axial CH_2D), in agreement with previous work.[24] The nmr spectra of **26** show a three-proton signal which undergoes a downfield shift of 0.09 ± 0.01 ppm (equatorial CH_3) and a broadened signal which has an upfield shift of 0.14 ± 0.02 ppm (axial CH_2D) on changing the solvent from deuteriochloroform to benzene.

The synthetic sequence outlined in Schemes I–III offers a convenient route for the stereoselective introduction of geminal substituents at either methylene group of an unsymmetrical cyclohexanone. The reaction conditions are sufficiently mild that sensitive groups can be present and unaffected by the conditions for the conversions. For example, 7-cholesten-3-one (**27**), containing the sensitive Δ^7 double bond,[28] can be converted to 2β-cyano-2α-methyl-7-cholesten-3-one (**28**) and subsequently to 2,2-dimethyl-7-cholesten-3-one (**29**), if the acid hydrolysis of the imine produced on reduction of the ketonitrile is carried out at pH 3-4.



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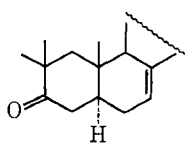

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Rationales for the stereochemistry of alkylation[2,4] in these and related systems should be constructed only in terms of the relative transition state energies[29] for the production of the epimeric products. Factors which should be considered in evaluation of alternative transition-state energies include electrophilicity of the alkylating agent, nucleophilicity of the enolate, steric hindrance and inductive effects of nonreacting groups in the molecule, effective sizes of the alkylating agent and groups on the enolate, the effect of the leaving group, bond distortion and torsional effects, the nature of the cation associated with the enolate, and the effect of ion aggregation. Differences in relative transition state energies of 1–2 kcal/mol could cause the differences in product ratios frequently observed in enolate alkylations; since any of the above factors could individually contribute this much difference, it may be that no broadly applicable yet unifying and rigorous analysis which has predictive value is possible.[30]

However, a useful simplifying assumption is that the same effects will be important in the different possible transition states. Kuehne and Nelson have recently analyzed the stereochemistry of methylation of enolates of 2-keto esters and 2-ketonitriles in carbocyclic six-membered rings in terms of the relative nucleophilicities of the enolates with attention given to steric hindrance, nonchair conformations, and cation chelation effects.[4] These rationales provide the best available correlation of previous results and should serve as the basis for further studies.

The stereochemistry of the alkylations of the enolates of cyanonitriles from **3**, **11**, and **14** can be rationalized in terms of twist boat productlike transition states which favor the smaller cyano group (*A* value, 0.2 kcal/mol)[31] in a sterically hindered position relative to the methyl group (*A* value, 1.7 kcal/mol),[31] with the alkylation of the enolate of 2-cyano-4-cholesten-3-one discussed in terms of reduced steric effects and flattening of ring A in the transition states for alkylation.

If different effects do have dominating significance in determining the relative energies of stereochemically different transition states for enolate alkylation, then fundamental understanding of these reactions may remain inextricable. Explanations will continue to be formulated *a posteriori*, with transition states being selected to accommodate the observed results.

In designing stereoselective alkylations of enolates at present, reliance must be placed primarily on previous experience whether stated as such or as a rationalization.

Experimental Section[32]

Materials.—Reagent grade anhydrous ether, absolute ethanol, methanol, methylene chloride, and chloroform were used without additional purification. Benzene, *t*-butyl alcohol, 1,4-dioxane, hexane, and diethylene glycol were distilled from metallic sodium. Dimethyl sulfoxide was percolated through molecular sieves and then distilled at reduced pressure. After preliminary drying over potassium carbonate, acetone was distilled from phosphorous pentoxide. Pyridine was stored over potassium hydroxide and was freshly distilled before use. The following reagents were obtained from the indicated suppliers and used without further purification: sodium methoxide and 99% hydrazine hydrate, Matheson Coleman and Bell; iodomethane, Eastman Organic Chemicals; potassium *t*-butoxide, Alfa Inorganics, Inc.; hydroxylamine hydrochloride, Mallinckrodt Chemical Works; lithium aluminum hydride and sodium borohydride, Ventron Corporation; 1,2-ethane dithiol and 2,3-dichloro-5,6-dicyano-1,5-benzoquinone (DDQ), Aldrich Chemical Co.; 10% palladium on charcoal, Engelhard Industries, Inc.; lithium aluminum deuteride, E. Merck Ag. Darmstadt (Germany); and chromium trioxide, Baker and Adamson Chemicals.

Product Isolation.—Reactions were cooled and then diluted with deionized water. The mixtures were neutralized, when necessary, and extracted at least five times with ether. The combined extracts were washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate prior to solvent removal by evaporation at reduced pressure. Products were purified by column chromatography on Brinkmann 0.05–0.20-mm silica gel, when necessary.

(28) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 259.

(29) D. Y. Curtin, *Rec. Chem. Progr.*, **15**, 111 (1954).

(30) Attempts to rationalize the stereochemistry of hydride reduction of ketones and alkylations of piperidines appear to have foundered on oversimplifications. See M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968), and D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hotley, *J. Chem. Soc., B*, 1184 (1962), for relevant discussions.

(31) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1966, p 44.

(32) Melting points were determined on a Reichert block equipped with thermometers accurate to ±1°, as determined by mixture melting points for appropriate standards. Ir spectra were measured on Perkin-Elmer Model 521 and Model 137 instruments with sodium chloride cells containing 10% chloroform solutions. Uv spectra were measured with a Perkin-Elmer Model 202 spectrophotometer and 1.0-cm matched silica cells. The pmr spectra were measured with Varian Associates A-60A, A-56/60, and HA-100 spectrometers with approximately 30% solutions in chloroform-*d* unless otherwise noted. Chemical shifts are reported in δ, parts per million relative to the internal standard TMS (δ 0.0). Mr. R. L. Thrift conducted the spin-decoupling experiments with a Varian Associates HA-100 instrument. The mass spectra were determined by Mr. J. Wrona on an Atlas Model CH4 instrument equipped with a solid inlet system. Microanalyses were performed by Mr. J. Nemeth and associates. The optical rotation measurements were determined on a Zeiss 0.01° polarimeter. The optical rotatory dispersion measurements were performed by Dr. R. W. Woody on a Jasco Model ORD/UV-5 instrument. All reactions were carried out in a nitrogen atmosphere.

2β-Cyano-2α-methylcholestan-3-one (**4**).—2-Hydroxymethylenecholestan-3-one (5.38 g, 13 mmol), prepared from cholestan-3-one by the method of Beton, Halsall, Jones, and Phillips,[8,33,34] dissolved in 200 ml of hot *t*-butyl alcohol, was allowed to react with 1.1 g (15 mmol) of hydroxylamine hydrochloride at reflux for 1 hr. Product isolation yielded 5.2 g (12.6 mmol, 97% yield) of isoxazole as a tan solid (mp 128–132°). Recrystallization from methanol yielded 4.6 g of product (85% yield, mp 137–139°) which was free from starting material according to tlc and a ferric chloride test. The product's ir spectrum had a weak absorption at 1644 cm^{-1} and the nmr spectrum was consistent with the assigned structure.

The isoxazole, 3.9 g (9.65 mmol), was dissolved in hot methanol and 540 mg (10 mmol) of sodium methoxide was added. After 18 hr at reflux, 3.78 g (9.2 mmol, 95% yield) of light tan 2-cyanocholestan-3-one (**3**) was isolated. Recrystallization from absolute ethanol produced 3.6 g of white solid (mp 176–178°) which gave a weak ferric chloride test; ir 2200 and 1730 cm^{-1}; the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{28}H_{45}NO$: C, 81.67; H, 11.04; N, 3.40. Found: C, 81.43; H, 11.09; N, 3.31.

Potassium *t*-butoxide (3 equiv, 1.5 g) was added to a solution of 1.83 g (4.46 mmol) of **3** (or the isoxazole) in *t*-butyl alcohol. A tan precipitate of the enolate formed while the solution was being heated at reflux for 10 min. Then 3 equiv of iodomethane was added and heating was continued for 45 min with repetitive additions of 1 equiv of iodomethane at 15-min intervals.

Extraction of the reaction mixture gave 1.9 g of white solid. Chromatography with 50% hexane–benzene (v/v) produced 15 mg of an unidentified oil and 1.2 g (59% yield, mp 187–190°) of 2β-cyano-2α-methylcholestan-3-one (**4**). 2-Cyano-3-methoxy-2-cholestene (505 mg, 27% yield, mp 184–187°) was then eluted. Further elution with benzene–ether gave 250 mg of an oil which appeared to be a mixture.

2β-Cyano-2α-methylcholestan-3-one (**4**) (905 mg, 48%, mp 194.5–196.0°) was obtained after two recrystallizations from ethanol: mass spectrum (14 eV) *m/e* 425; ir 2215 and 1720 cm^{-1}; the nmr spectrum contained 47 protons from δ 0.0–3.0 ppm with methyl singlets at δ 1.43, 1.34, and 0.68 ppm; ORD $[\alpha]^{24}D$ +104°, $[\alpha]_{316}^{max}$ +2616°, $[\alpha]_{270}^{min}$ −2642°, *A* +223° (*c* 0.422, $CHCl_3$).

Anal. Calcd for $C_{29}H_{47}NO$: C, 81.82; H, 11.13; N, 3.29. Found: C, 81.97; H, 11.20; N, 3.27.

After two recrystallizations from ethanol, 410 mg (22%, mp 190–191.5°) of 2-cyano-3-methoxy-2-cholestene was obtained: mass spectrum (14 eV) *m/e* 425; ir 2210 and 1640 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by a methyl singlet at δ 3.80 ($-OCH_3$); uv max (95% C_2H_5OH) 235 mμ (ε 1.2 × 10^4).

2α-Cyano-2β-methyl-5β-cholestan-3-one (**9**).—2-Hydroxymethylene-4-cholesten-3-one, 767 mg, prepared from 4-cholesten-3-one by the method of Beton, Halsall, Jones, and Phillips, was converted into the isoxazole derivative in 94% yield (724 mg, mp 105–110° after chromatography on silica gel with benzene) in the manner described above.

The isoxazole was quantitatively isomerized by basic methanol to 2-cyano-4-cholesten-3-one: mp 158–170°; ir 2230, 168, and 1610 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by a one-proton singlet at δ 5.77 ppm (C=CH). The structure of this product was confirmed by catalytic reduction with 10% palladium on charcoal in dioxane at 25° to a compound whose identity with **3** was demonstrated by melting point and mixture melting point (170–173°) and by nmr and ir spectral comparisons. In the same manner the unsaturated isoxazole was catalytically reduced to yield **2**, with identity established by mixture melting point and nmr and ir spectral criteria. These conversions establish that formylation had not proceeded at C-4 or C-6.

Alkylation with iodomethane of 2-cyano-4-cholesten-3-one, 8.35 g (or its isomeric isoxazole), by the above procedure yielded, after silical gel chromatography with 75% benzene–hexane (v/v), 3.76 g (0.89 mmol, 44%, mp 170–176°) of 2β-cyano-2α-methyl-4-cholesten-3-one (**7**) and 3.82 g (0.09 mmol, 44%, mp 111–118°) of 2α-cyano-2β-methyl-4-cholesten-3-one (**8**). These compounds were identified by ir spectra and by subsequent conversions.

2β-Cyano-2α-methyl-4-cholesten-3-one (**7**) (150 mg) was hydrogenated for 2 hr at room temperature and low pressure in absolute ethanol with 10% palladium on charcoal. After the catalyst had been separated by filtration, 140 mg of product was isolated (mp 180–189°). Two recrystallizations from absolute ethanol yielded 106 mg of **4** (mp 192–195°) which was identical with the previously prepared compound by nmr, ir, mass spectral, microanalytical, and mixture melting point comparisons.

Catalytic reduction of 1.12 g of **8** was achieved by the method described above. The product (1.02 g) was purified by silica gel chromatography with 50% benzene–hexane (v/v) as an elutent and recrystallization from absolute ethanol to yield 766 mg (68% yield) of 2α-cyano-2β-methyl-5β-cholestan-3-one (**9**): mp 140–141°; mass spectrum (14.5 eV) *m/e* 425; ir 2235 and 1725 cm^{-1}; the nmr spectrum was consistent with the assigned structure and contained methyl singlets at δ 1.44, 1.04, and 0.72 ppm; ORD $[\alpha]^{24}D$ −19°, $[\alpha]_{268}^{max}$ +2076°, $[\alpha]_{316}^{min}$ −1830°, *A* −165° (*c* 0.236, $CHCl_3$).

Anal. Calcd for $C_{29}H_{47}NO$: C, 81.82; H, 11.13; N, 3.29. Found: C, 81.72; H, 11.09; N, 3.33.

The reduction of **8** could be accomplished by condensation of 10 ml of ammonia into a stirred solution of 505 mg (1.2 mmol) of **8** in ether at −70° followed by the careful addition of 100 mg of lithium wire.[6] The reaction was maintained at the boiling point of ammonia for 1 hr and then the blue color was discharged by the addition of 2 g of ammonium chloride. After the ammonia had evaporated, wet ether was carefully added and extractive work-up produced a yellow oil which was chromatographed on silica gel with 50% benzene–hexane (v/v) to yield 493 mg (97% yield) of white solid identical with **9** by ir, melting point, and mixture melting point criteria.

1-Cholesten-3-one (**10**) was prepared[35,36] by treatment of 15.0 g (39 mmol) of **1** with 9.1 g (1.1 equiv) of DDQ at reflux in 250 ml of dioxane for 24 hr. The reaction mixture was filtered through 300 g of silica gel with methylene chloride, and evaporation of the solvent yielded 12.1 g of a mixture of cholestanone and 1-cholesten-3-one, which was purified by a modification of the procedure of Warnhoff.[37] The mixture was reduced with a large excess of sodium borohydride in methanol for 30 min at 25°. Extractive work-up yielded 12.2 g of the mixture of sterols which were oxidized[38] with 1.5 equiv of DDQ in 300 ml of *t*-butyl alcohol for 24 hr at 25°. After most of the solvent had been removed under reduced pressure and the residue had been filtered through 300 g of silica gel with methylene chloride, 7.3 g of 1-cholesten-3-one (mp 93–97°) was obtained. Two recrystallizations from absolute ethanol yielded **10**: 2.2 g; 15% yield; mp 100–101° (lit.[37] 101–102°); the nmr and ir spectra were consistent with the assigned structure.

4β-Cyano-4α-methylcholestan-3-one (**13**).—4-Hydroxymethylene-1-cholesten-3-one, prepared from 1.8 mmol of **10** by the method of Beton, Halsall, Jones, and Phillips,[33] was converted into the isoxazole derivative (602 mg, 81% overall yield, mp 107–112° after chromatography on silica gel with benzene) with hydroxylamine hydrochloride according to the above procedure. Recrystallization from absolute ethanol yielded an analytical sample with mp 111–114°; the nmr and ir spectra were consistent with the assigned structure.

Anal. Calcd for $C_{28}H_{43}NO$: C, 82.09; H, 10.58; N, 3.42. Found: C, 81.85; H, 10.56; N, 3.26.

This isoxazole was quantitatively isomerized to 4-cyano-1-cholesten-3-one (**11**) with sodium methoxide in methanol in the same way as previously described: mp 147–149°; ir 2250, 1680, and 1605 cm^{-1}; the nmr spectrum was consistent with the assigned structure including signals at δ 7.22 (d, 1, *J* = 10 Hz, CH=CH), 5.94 (d, 1, *J* = 10 Hz, CH=CH), 3.52 (d, 1, *J* = 13 Hz, −CHCN), 1.05 (s, 3, CH_3), and 0.70 (s, 3, CH_3). 4-Cyanocholestan-3-one (**14**) was obtained from the catalytic reduction (10% palladium on charcoal in 40 ml of dioxane at 25°) of 128 mg of **11** for 2 hr. Separation of the catalyst and removal of the solvent gave 128 mg of **14**: mp 184–186°; mass spectrum (9.5 eV) *m/e* 411, ir 2250 and 1720 cm^{-1}; the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{28}H_{45}NO$: C, 81.69; H, 11.02; N, 3.40. Found: C, 81.50; H, 10.97; N, 3.22.

(33) J. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J. Chem. Soc.*, 753 (1957).

(34) P. Morand, M. Flett, J. M. Lyall, and S. Stavric, *Steroids*, **8**, 679 (1966).

(35) A. B. Turner and H. J. Ringold, *J. Chem. Soc., C*, 1720 (1967).

(36) E. Caspi and P. J. Ramm, *Tetrahedron Lett.*, 181 (1969).

(37) E. W. Warnhoff, *J. Org. Chem.*, **27**, 4587 (1962).

(38) S. H. Burstein and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 4952 (1964).

Alkylation with iodomethane of 128 mg of 4-cyanocholestan-3-one (**14**) by the method described above yielded, after chromatography on silical gel with 30% hexane-benzene (v/v), 66 mg (50% yield) of **13** and 3 mg of a mixture tentatively identified as 4-cyano-2,4-dimethylcholestan-3-one and 4β-cyano-4α-methylcholestan-3-one (**13**) on the basis of ir (2250 and 1720 cm^{-1}) and mass spectral (*m/e* 439 and 425) evidence. The analytical sample of **13** was obtained in 30% yield after recrystallization from absolute ethanol: mp 138–139°; mass spectrum (15 eV) *m/e* 425; ir 2250 and 1720 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by methyl singlets at δ 1.48, 1.36, and 0.70 ppm.

Anal. Calcd for $C_{29}H_{47}NO$: C, 81.82; H, 11.13; N, 3.29. Found: C, 81.71; H, 11.25; N, 3.23.

Elution with hexane–benzene gave 35 mg (27% yield) of 4-cyano-3-methoxy-3-cholestene: mp 174–178°; ir 2200 and 1630 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by a methyl singlet at δ 3.80 ppm.

Alkylation with iodomethane of 574 mg of 4-cyano-1-cholestene-3-one (**11**) according to the procedure described above gave, after silica gel chromatography with 50% hexane–benzene (v/v), 511 mg (86% yield) of 4β-cyano-4α-methyl-1-cholesten-3-one (**12**) which was recrystallized from absolute ethanol: mp 147–149°; 40% yield; ir 2250, 1675, and 1605 cm^{-1}; the nmr spectrum was consistent with the assigned structure, including signals at δ 7.30 (d, 1, J = 10 Hz, CH=CH), 5.98 (d, 1, J = 10 Hz, CH=CH), 1.60 (s, 3, CH_3), 1.18 (s, 3, CH_3), 0.72 ppm (s, 3, CH_3). Further elution yielded 60 mg (10% yield) of 4-cyano-3-methoxy-1,3-cholestadiene which was recrystallized from absolute ethanol: mp 165–168°; ir 2200, 1640, and 1575 cm^{-1}. 4β-Cyano-4α-methyl-1-cholesten-3-one (**12**) (350 mg) was converted into **13** (350 mg, mp 125–130°) by catalytic reduction with 10% palladium on charcoal in dioxane which after recrystallization from absolute ethanol (55% yield) was identical with the previously prepared product according to melting point, mixture melting point (138–139°) and ir and nmr spectral criteria. Catalytic reduction of 60 mg of 4-cyano-3-methoxy-1,3-cholestadiene in dioxane with 10% palladium on charcoal yielded 57 mg of 4-cyano-3-methoxy-3-cholestene, whose identity with the previously prepared product was established by melting point, mixture melting point, and ir spectral criteria.

2,2-Dimethylcholestan-3-one (**15**).—To an ethereal solution of 690 mg (1.62 mmol) of **4** cooled to about 5° was added a slurry of 130 mg (3.42 mmol) of lithium aluminum hydride in ether. Stirring was continued for 15 min while the mixture was allowed to warm to room temperature. The excess reducing agent was destroyed with a paste of sodium sulfate and water. Excess 10% hydrochloric acid was added and the mixture was heated at reflux on a steam bath for 2 hr. Product isolation gave a solid in 51% yield (358 mg, 0.83 mmol, mp 119–126°). Recrystallization of 60 mg from ethanol yielded 29 mg of 2β-formyl-2α-methylcholestan-3β-ol: mp 125–127°; ir 3400, 2690, and 1710 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by signals at δ 9.59 (d, 1, J = 2 Hz, CHO) and 3.4 ppm (broad, 1, CHOH).

Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.82; H, 11.65.

To a solution of 294 mg (0.68 mmol) of 2β-formyl-2α-methylcholestan-3β-ol in 100 ml of diethylene glycol was added 15 ml of 99% hydrazine hydrate. The reaction mixture was maintained at 115° for 5 hr and then cooled. After the addition of 16 g of potassium hydroxide the reaction was heated to 160° for 6 hr. Extractive work-up of the cooled solution produced a gelatinous white material which was chromatographed on silica gel. From the benzene elutent, 2,2-dimethylcholestan-3β-ol was isolated in 62% yield (177 mg, mp 134–138°). Recrystallization from absolute ethanol gave 2,2-dimethylcholestan-3β-ol (43%, mp 142–144°). The acetate, prepared by the method of Mazur and Sondheimer,[39] melted at 127–129° (lit. sterol mp 116–118°,[39] 118–120°,[40] acetate mp 124–126°[39,40]).[41] The alcohol and its acetate showed undepressed mixture melting points and nmr spectra identical with those of the authentic compounds.[39]

A solution of 177 mg of 2,2-dimethylcholestan-3β-ol in 25 ml of benzene was added to 10 ml of a cold chromic acid solution prepared by dissolving 13.6 g of sodium dichromate in 60 ml of water, 18 ml of sulfuric acid, and 10 ml of acetic acid.[42] After the solution had been stirred at room temperature for 24 hr, the benzene layer was separated and the aqueous phase was extracted with benzene. After the combined organic phase had been washed twice with water, once with 5% sodium hydroxide, and twice more with water and dried over magnesium sulfate, the solvent was removed at reduced pressure. A 98% yield (172 mg, mp 95–99°) of 2,2-dimethylcholestan-3-one (**15**) was obtained which was recrystallized (75% yield) from absolute ethanol: mp 97–99° (lit.[43] mp 98–100°); mass spectrum (12.5 eV) *m/e* 414; ir (CS_2) 1702 cm^{-1} (C=O); the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.83; H, 11.94.

2β-Formyl-2α-methylcholestan-3β-ol (90 mg, 0.21 mmol) was dissolved in 50 ml of absolute ethanol containing 1 ml of triethylamine and 6 ml of 99% hydrazine hydrate. After the solution had been heated for 1 hr at reflux, it was poured into ether and washed with cold 10% hydrochloric acid until the amine odor was not detectable. The ethereal solution as dried over magnesium sulfate and evaporated to yield 79 mg (85% yield, mp 135–145°) of the hydrazone: ir 3400, 1640, and 1610 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by signals at δ 7.0 (s, 1, $-CH=NH_2$) and 5 ppm (broad, s, 2, NH_2). The crude hydrazone (30 mg in 0.5 ml of benzene) was added to 25 ml of dimethyl sulfoxide,[13] 200 mg of potassium *t*-butoxide, and 0.25 ml of *t*-butyl alcohol. The reaction was maintained at 70° for 30 min, after which time the product isolation produced 15 mg of oil. After silica gel chromatography with benzene, 9 mg of 2,2-dimethylcholestan-3β-ol was isolated (mp 139–142°, 32% yield, 27% yield from the aldehyde). Oxidation of this material (CrO_3) produced a ketone (mp 92–95°) which was identical with authentic 2,2-dimethylcholestan-3-one by mixture melting point and nmr and ir spectral criteria.

4,4-Dimethylcholestan-3-one (**17**).—4β-Cyano-4α-methylcholestan-3-one (**13**) (108 mg) was reduced with lithium aluminum hydride as described above. The isolated aldehyde (53 mg) was subjected to the Wolff–Kishner reduction and 4,4-dimethylcholestan-3β-ol (30 mg, 28% yield) was isolated after chromatography on silica gel with benzene: mp 152–155° (lit.[44] 156–157°), the ir and nmr spectra were consistent with the assigned structure. A partially reduced compound, 4β-cyano-4α-methylcholestan-3-ol, 9 mg, was recovered from the chromatography column.

4,4-Dimethylcholestan-3β-ol (30 mg) was oxidized with chromic acid as described above and 4,4-dimethylcholestan-3-one (**17**) (30 mg, mp 95–100°) was isolated after chromatography on silica gel with hexane–benzene. Recrystallization from absolute ethanol gave a 65% yield of **17**: mp 100–101° (different from 2,2-dimethylcholestan-3-one by mmp 59–76°); mass spectrum (14 eV) *m/e* 414; ir (CS_2) 1703 cm^{-1} (lit. mp[38] 100–101°; ir (CS_2)[40] 1703 cm^{-1}); the nmr spectrum was consistent with the assigned structure and showed three methyl singlets between δ 1.09 and 1.07 ppm in addition to the C-18 methyl singlet at 0.68 ppm.

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.15; H, 12.04.

2,2-Dimethyl-5β-cholestan-3-one (**16**).—2α-Cyano-2β-methyl-5β-cholestan-3-one (**9**, 766 mg, 1.8 mmol), dissolved in ether, was treated with excess lithium diethoxyaluminohydride[45] (from 1.38 g of lithium aluminum hydride and 4.23 ml of absolute ethanol) in ether. After the mixture had been stirred at room temperature for 1 hr, the reaction was quenched. The mixture was then acidified with 10% aqueous hydrochloric acid and hydrolyzed at 60° for 12 hr. Product isolation gave 445 mg of 2α-formyl-2β-methyl-5β-cholestan-3-ol, as evidenced by ir absorptions at 3600, 2750, and 1720 cm^{-1}. The aldehyde, 90 mg, was dissolved in 0.05 ml of ethanedithiol, 0.1 ml of 98% boron trifluoride etherate was added, and the solution was allowed to stand for 30 min at room temperature. The resulting solidified mass was filtered, washed with cold methanol, and then dissolved in absolute ethanol and refluxed for 5 min with 2 cm^3

(39) Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 5220 (1958).

(40) I. Malunowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **13**, 73 (1965).

(41) It has been found that at least one[40] of the previously reported 3β-sterols was impure and the corrected melting point is 143–144°: I. Malunowicz, personal communication, Feb 1968.

(42) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1943, p 139.

(43) F. Sondheimer, Y. Klibansky, Y. M. Y. Hadad, G. R. Summers, and W. Klyne, *J. Chem. Soc.*, 767 (1961).

(44) N. W. Atwater, *J. Amer. Chem. Soc.*, **82**, 2847 (1960).

(45) H. C. Brown and C. P. Garg, *ibid.*, **86**, 1085 (1964).

of W-2 Raney nickel.[46,47] After the catalyst had been separated by filtration and thoroughly washed with methylene chloride, the residue of 65 mg of material obtained by evaporation of the solvent was chromatographed on silica gel. Benzene elution gave a 2,2-dimethyl-5β-cholestan-3-ol (47 mg, mp 43–46°), which was not identical with 2,2-dimethylcholestan-3β-ol by tlc comparison. Chromic acid oxidation of 43 mg of the alcohol yielded 37 mg of 2,2-dimethyl-5β-cholestan-3-one (**16**), which was chromatographed on silica gel (31 mg isolated, 72% yield) and was not identical with 2,2-dimethylcholestan-3-one (**15**) by mixture melting point (52–79°) and tlc comparisons. 2,2-Dimethyl-5β-cholestan-3-one had mp 78–80°, mass spectrum (12.5 eV) *m/e* 414, ir 1700 cm^{-1}; the nmr spectrum was consistent with the assigned structure with methyl singlets at δ 1.24, 1.09, 1.04, and 0.72 ppm.

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.12; H, 11.93.

2β-Cyano-2α-methylcholestane (21).—To **4** (636 mg, 1.48 mmol) dissolved in 30 ml of glacial acetic acid and 1 ml of ethanedithiol was added 10 ml of 98% boron trifluoride etherate and the mixture, which solidified within 5 min, was allowed to stand overnight. The product, obtained by evaporation of the solvent after addition of methanol, filtration, and one wash with cold methanol, was purified by dissolution in chloroform and precipitation by the addition of methanol to yield 576 mg of white thioketal: mp 189–192°; ir 2225 cm^{-1}; mass spectrum (12.5 eV) *m/e* 501; the nmr spectrum was consistent with the assigned structure and was distinguished by a four-proton multiplet at δ 3.4 ppm ($-SC_2H_4S-$). The thioketal was dissolved in hot acetone, 8 cm^3 of Raney nickel[48] under a small amount of ethanol was added, and the mixture was heated at reflux for 10 min. The mixture was then rapidly filtered and the catalyst was washed thoroughly with methylene chloride. Evaporation of the filtrate produced 330 mg of solid which was chromatographed on silica gel.

Elution with hexane gave an oil (79 mg, 14%) which crystallized on standing (mp 97.5–98.5°) and was identified as 2-methyl-2-cholestene (lit.[49] mp 97–97.5°): mass spectrum (13 eV) *m/e* 384; the ir and nmr spectra were consistent with the assigned structure; the nmr spectrum included a broad one-proton singlet at 5.3 ppm (C=CH).[50]

A 50% hexane–benzene (v/v) mixture was used to elute 248 mg (48%) of 2β-cyano-2α-methylcholestane (**21**) (mp 170–177°). Recrystallization from absolute ethanol gave 115 mg (22%) of material: mp 178.5–180°; ir 2211 cm^{-1}; mass spectrum (14.5 eV) *m/e* 411; the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{29}H_{49}N$: C, 84.60; H, 12.00; N, 3.40. Found: C, 84.62; H, 11.93; N, 3.37.

4β-Cyano-4α-methylcholestane (22) was produced from 207 mg of 4β-cyano-4α-methylcholestan-3-one (**13**) by formation of the thioketal and reduction with Raney nickel according to the above procedure. Chromatography of the product on silica gel with hexane yielded 46 mg (23% yield) of 4-methyl-3-cholestene: mp 62–65°; mass spectrum (12.5 eV) *m/e* 384; the nmr and ir spectra were consistent with this assignment. Elution with hexane–benzene gave 52 mg (26% yield) of **22** (mp 115–130°). Two recrystallizations from absolute ethanol gave the analytical sample: mp 142–144°; 16% yield; mass spectrum (15 eV) *m/e* 411; ir 2230 cm^{-1}; the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{29}H_{49}N$: C, 84.60; H, 12.00; N, 3.40. Found: C, 84.59; H, 11.77; N, 3.29.

Comparative Hydrolysis Rates.—The following compounds were sealed in 5-ml ampoules containing a basic solution prepared from 5 g of potassium hydroxide, 3 ml of water, and 25 ml of ethylene glycol: O-methylpodocarponitrile (**23**),[3c] identified by melting point and nmr, ir, and mass spectral criteria; dehydroabietonitrile (**24**),[14a] identified by melting point and nmr, ir, and mass spectra; 2β-cyano-2α-methylcholestane (**21**); and 4β-cyano-4α-methylcholestane (**22**). The ampoules were heated to 150° for 24 hr and cooled and the contents were neutralized with 10% aqueous hydrochloric acid. Product isolation resulted in a 99–100% weight balance. Ir spectra of the product mixtures showed a small amount of carbonyl absorption in every case due to amide or acid functionalites. After hydrolysis of **24** no starting material was detected by ir or tlc and a 100% weight yield of an oily acid was extracted from hexane with 10% potassium hydroxide in methanol. The dehydroabietic acid was converted to its methyl ester with diazomethane and was characterized by its nmr spectrum. Silica gel chromatography of the product mixtures gave the results summarized in Table I.

TABLE I

Compound	Weight, mg	Basic solution, ml	Isolated starting material, %
21	21	2	86
22	24	1.5	91
23	13	1	85
24	13	1	0

4,4-Dimethylcholestan-3β-ol-3,30-d_2 (25).—This compound was synthesized by the procedure described above for 4,4-dimethylcholestan-3β-ol by substituting lithium aluminum deuteride for lithium aluminum hydride. The deuterated product **25** was isolated in 18% yield (mp 152–154°). After recrystallization from absolute ethanol, **25** melted from 154 to 155° (10% yield) and its nmr, ir, and mass spectra (*m/e* 418 at 12.5 eV) were consistent with the assigned structure. Oxidation with chromic acid by the previously described procedure gave 4,4-dimethylcholestan-3-one-30-*d*; ir, nmr, and mass spectra were consistent with the assigned structure.

2,2-Dimethyl-7-cholesten-3-one (27) was prepared from 7-cholesten-3-one in 5% yield by the procedures previously described exept that hydrolysis of the imine produced by reduction of the cyano ketone with lithium aluminum hydride was achieved by making the reaction mixture slightly acidic (pH 3–4) with 10% aqueous hydrochloric acid and stirring at room temperature for 15 hr. The resultant aldehyde was reduced in dimethyl sulfoxide as described above.

2β-Cyano-2α-methyl-7-cholesten-3-one (28) had mp 181.5–183.0°; mass spectrum (14 eV) *m/e* 423; ir 2215 and 1720 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by signals at δ 5.2 (broad, 1, CH=C), 1.43 (s, 3, CH_3), 1.33 (s, 3, CH_3), and 0.57 ppm (s, 3, CH_3).

Anal. Calcd for $C_{29}H_{45}NO$: C, 82.21; H, 10.71; N, 3.31. Found: C, 81.99; H, 10.47; N, 3.13.

2,2-Dimethyl-7-cholesten-3-one (29) had ir 1700 and 1605 cm^{-1}; mass spectrum (15.5 eV) *m/e* 412; the nmr spectrum was consistent with the assigned structure including signals at δ 5.2 (broad, 1, CH=C), 1.25 (s, 3, CH_3), 1.11 (s, 3, CH_3), 1.07 (s, 3, CH_3), and 0.68 ppm (s, 3, CH_3).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.10; H, 11.68.

Registry No.—**3**, 24164-61-2; **4**, 24164-62-3; **7**, 24164-63-4; **9**, 24164-64-5; **11**, 24215-74-5; **12**, 24164-65-6; **13**, 24164-66-7; **14**, 24164-67-8; **15**, 2542-57-6; **16**, 24164-69-0; **17**, 2097-85-0; **21**, 24164-90-7; **22**, 24164-91-8; **25**, 24164-92-9; **28**, 24164-93-0; **29**, 24164-94-1; isoxazole derivative of 4-hydroxymethylene-1-cholesten-3-one, 24164-95-2; 4-cyano-3-methoxy-1,3-cholestadiene, 24164-96-3; 2β-formyl-2α-methylcholestan-3β-ol, 24164-97-4; 2,2-dimethylcholestan-3β-ol, 2542-65-6; 2β-formyl-2α-methylcholestan-3β-ol hydrazone, 24164-99-6; 4-methyl-3-cholestene, 6785-18-8.

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Diborane Reductions of Oxygen Heterocycles. Synthesis of 3-Chromanols and 3-Chromanones

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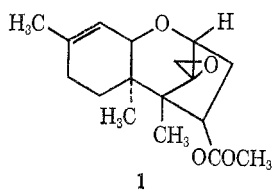
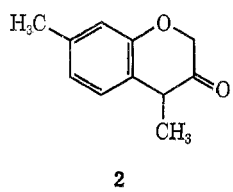
Hydroboration–oxidation of coumarin and 4,7-dimethylcoumarin affords 3-chromanol and 4,7-dimethyl-3-chromanol. Chrom-2-ene and chromone also afford 3-chromanol, and 3-methylcoumarin yields 3-methyl-4-chromanol. Oxidation of 4,7-dimethyl-3-chromanol with dicyclohexylcarbodiimide and dimethyl sulfoxide produces 4,7-dimethyl-3-chromanone, thus providing a quicker route to this type of ketone than previously reported methods. The three coumarins also yield as products of these reactions 3-(*o*-hydroxyphenyl)propane-1,2-diols. The specificity of these reactions in leading to the vicinal glycols is attributed to the effect of the phenolic oxygen. Reduction of flavone under these conditions leads to no cyclic product, but rather to a dibenzyl alcohol which results from the hydrogenolysis of a benzylic–allylic carbon–oxygen bond.

As part of a program directed toward the synthesis of trichodermin[1] (**1**) and related sesquiterpenes, we required 4,7-dimethyl-3-chromanone (**2**) as an intermediate. Previous syntheses reported for the 3-chromanone system have usually required the preparation of *o*-(carboxymethoxy)phenylacetic acids and their cyclization by either Dieckmann reaction of the corresponding diesters[2–4] or as in the original synthesis of 3-chromanone itself,[5] acetic anhydride catalyzed reaction of the diacid. In these syntheses, however, the particular 3-chromanone involved was generally the ultimate synthetic goal. Thus a lengthy route to a carboxymethylphenylacetic acid was a reasonable price to pay for obtaining the desired ketone. In our case such an expenditure of experimental effort in a multistep route to a synthetic intermediate was clearly undesirable, and we therefore sought a shorter route to **2** from readily available starting materials.



1

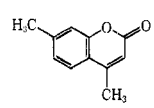
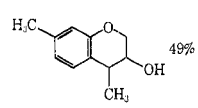
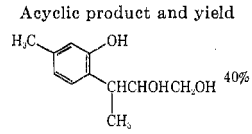
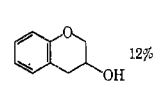
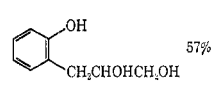
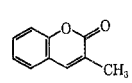
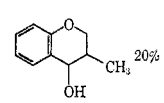
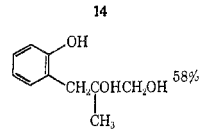
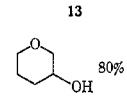
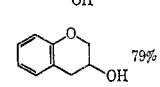
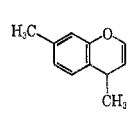
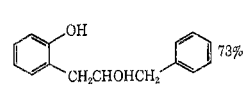


2

One such material is 4,7-dimethylcoumarin (**3**) (Table I), the Pechmann reaction product of *m*-cresol and acetoacetic ester. We have investigated a number of routes for the conversion of **3** to 3-oxygenated chroman systems, but one in particular, hydroboration–oxidation of **3**, has led directly to the desired structural type. Thus, continuous passage of externally generated diborane through a tetrahydrofuran solution of **3** followed by hydrogen peroxide oxidation of the intermediate alkylborane yielded 49% 4,7-dimethyl-3-chromanol (**4**). A second product, the triol **5**, obtained in 40% yield was readily separated from **4** by extraction of the reaction product mixture with aqueous base. The conversion of **4** to 4,7-dimethyl-3-chromanone (**2**) was then effected in 84% yield by Moffat oxidation[6] employing dicyclohexylcarbodiimide, dimethyl sulfoxide, and monophenyl phosphate.

TABLE I

HYDROBORATION–OXIDATION PRODUCTS OF OXYGEN HETEROCYCLES

Substrate	Cyclic product and yield	Acyclic product and yield
 **3**	 49% **4**	 40% **5**
Coumarin	 12%	 57% **14**
 **12**	 20% **13**	 58% **15**
Dihydropyran	 80%	
Chromone	 79%	
 **6**	**4** 88%	
Flavone		 73% **19**

The structural assignments of **4**, **5**, and **2** follow from their spectral characteristics. The nmr spectrum of **4**, for example, displays a two-proton multiplet at 3.71 ppm for the C_2-methylene group as well as a doublet for the C_4-methyl group at 1.12 ppm, and two one-proton multiplets at 2.53 and 3.43 ppm for the C_3

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