Attempted Preparation of Bis[6-(hydroxymethyl)-2-pyridyl]acetylene (22). To a vigorously stirred, refluxing solution of potassium hydroxide in methanol was added **21** in ca. 50-mg quantities, and the mixture was then refluxed for 30 min. The mixture was concentrated in vacuo to give an off-white solid residue, which was slurried in ice–water, filtered, and recrystallized from ethyl acetate to give 59–72% of pure starting olefin **20**, mp 139–140 °C. No acetylenic proudcts were isolated from this reaction sequence.

1,2-Bis[6-(bromomethyl)-2-pyridyl]benzene (23). A stirred benzene (100 mL) solution of **12** (2.8 g, 10.7 mmol) and azobisisobutyronitrile (50 mg) was treated with *N*-bromosuccinimide (4.6 g, 26 mmol) and illuminated with a 150-W lamp. After the mixture was refluxed for 12 h, the red suspension was extracted with a 10% aqueous solution of sodium carbonate (100 mL) and water (100 mL) and then concentrated in vacuo to afford a red oily residue (5.21 g), which was column chromatographed (silica gel), eluting with ethyl acetate to afford a mixture, 3.81 g. Rechromatography (thick layer) of this mixture, eluting with ethyl acetate–cyclohexane (1:4), afforded two major fractions.

Fraction A gave 1-[6-(bromomethyl)-2-pyridyl]-2-[6-(dibromomethyl)-2-pyridyl]benzene (**24**) as a semisolid: 243 mg; NMR ($CDCl_3$) δ 4.39 (s, CH_2Br, 2 H), 6.48 (s, $CHBr_2$, 1 H), 7.05–7.80 (m, arom H, 10 H); mass spectrum (70 eV), *m/e* (relative intensity) 497 (M^+, 4.4), 417 ($M^+ - 80$, 70.6), 257 ($M^+ - 240$, 30.2), 217 ($M^+ - 280$, 100), 191 (26).

Fraction B afforded 1,2-bis[6-(bromomethyl)-2-pyridyl]benzene (**23**) as a sensitive semisolid: 297 mg (7%); NMR δ 4.39 (s, CH_2Br, 4 H), 6.95–7.80 (m, arom H, 10 H); mass spectrum (70 eV), *m/e* (relative intensity) 418 (M^+, 12), 339 ($M^+ - 79$, 98), 337 ($M^+ - 81$, 89), 218 ($M^+ - 200$, 100), 191 (23).

Preparation of Cyclophane 25. An ethanol (25 mL) solution of **23** (300 mg, 0.72 mmol) and an ethanol (25 mL) solution of sodium sulfide nanohydrate (173 mg, 0.72 mmol) were each added at an equimolar rate to a refluxing ethanol solution under nitrogen. After 22 h, the solution was concentrated in vacuo to afford a red solid residue, which was slurried in dichloromethane (20 mL) and filtered. The filtrate was concentrated to afford 233 mg of product which was chromatographed (thick layer), eluting three times with ethyl acetate–cyclohexane (1:4), to give two major fractions.

Fraction A gave the pyridinophane **25** as a colorless solid: 17 mg (8%); mp 162–166 °C dec; NMR δ 3.83 (s, CH_2S, 4 H), 7.03 (d, 5-H of pyr, *J* = 7 Hz, 2 H), 7.45–7.75 (m, arom H, 10 H); mass spectrum (70 eV), *m/e* (relative intensity) 290 (M^+, 23), 258 ($M^+ - 32$, 33), 257 ($M^+ - 33$, 100), 243 ($M^+ - 47$, 9), 242 ($M^+ - 48$, 12), 228 ($M^+ - 62$, 14), 217 (13.5), 204 (24), 182 (17), 149 (9), 128 (11).

Anal. Calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4,86; N, 9.65. Found: C, 74.18; H, 4.62; N, 9.61.

Fraction B afforded 1,2-bis[6-(mercaptomethyl)-2-pyridyl]benzene (**26**) as an air-sensitive solid: 18 mg (8%), mp 171–181 °C dec; NMR δ 2.25 (br s, exchanged with D_2O, SH, 2 H), 7.17 (d, 3-H of pyr, *J* = 2.0 Hz, 2 H), 7.40–7.85 (m, arom H, 6 H); mass spectrum (70 eV), *m/e* (relative intensity) 324 (M^+, 5.3), 322 ($M^+ - 2$, 38), 257 ($M^+ - 67$, 100), 243 ($M^+ - 81$, 12), 229 ($M^+ - 95$,19), 204 ($M^+ - 120$, 25), 191 (10), 128 (15).

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Registry No. 3, 74844-02-3; **5**, 35286-92-1; **6** (X = Y = CH), 74844-03-4; **6** (X = N; Y = CH), 74844-04-5; **7** (X = Y = CH), 74844-05-6; **8**, 74844-06-7; **9**, 42296-34-4; **10**, 2765-16-4; **11**, 74844-07-8; **12**, 74844-08-9; **13**, 73818-74-3; **14**, 74844-09-0; **15**, 74844-10-3; **16**, 74844-11-4; **17**, 74844-12-5; **18**, 74844-13-6; **20**, 74844-14-7; **21**, 74844-15-8; **23**, 74844-16-9; **24**, 74868-62-5; **25**, 74844-17-0; **26**, 74844-18-1; **30**, 74764-52-6; **31**, 74844-94-3; (3-methylphenyl)-methylenetriethoxyphosphorane, 74844-19-2; 3-methylbenzaldehyde, 620-23-5; α-pyrone, 504-31-4; lutidine, 27175-64-0; bis(2-pyridyl)-acetylene, 28790-65-0; cobalt chloride, 7646-79-9.

A One-Step Conversion of Cholest-4-en-3-one to 24-Hydroxychol-4-en-3-one

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Cholest-4-en-3-one has been converted in one step to 24-hydroxychol-4-en-3-one in 17% yield of crystalline material. The elimination of carbons 25–27 and the introduction of the primary alcohol group at C-24 are accomplished with $CF_3CO_3H–H_2SO_4$ at 0 °C.

The purpose of the present program is to selectively oxidize the saturated side chain of cholesterol, sitosterol, and campesterol. This would provide routes to steroids with modified side chains as well as routes to steroids of pharmaceutical value similar to the routes starting with deoxycholic acid, diosgenin, and stigmasterol.[1] The first success was the conversion of cholesterol to chol-5-ene-3β,24-diol in 14% yield in essentially three steps.[2] A further improvement is now reported.

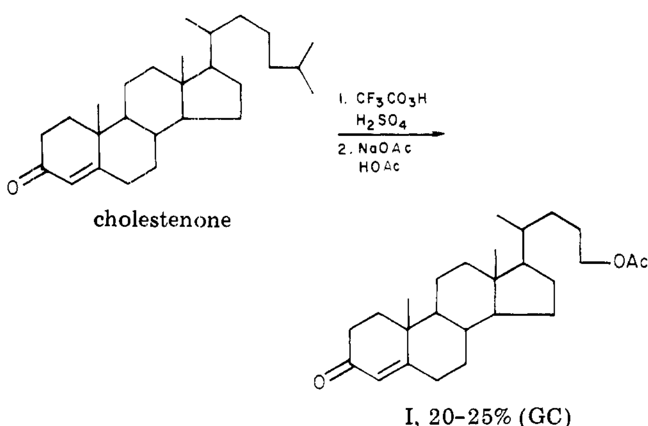
It would be desirable to eliminate protecting groups, and it has now been found possible to do this with cholestenone (cholest-4-en-3-one). The method depends on suppressing the reactivity of enone systems toward CF_3CO_3H by adding H_2SO_4. Model studies showed that $CF_3CO_3H–H_2SO_4$ oxidized isooctane faster than isophorone (3,5,5-trimethylcyclohex-2-en-1-one). However, 3-methylcyclohex-2-en-1-one and mesityl oxide (4-methylpent-3-en-2-one) reacted faster than isooctane despite the suppressing effect of the H_2SO_4. All three ketones reacted faster than isooctane in the absence of H_2SO_4. The H_2SO_4 is believed to act by a combination of protonation of the enone and hydrogen bonding of H_3O^+ to the enone. Both effects reduce the reactivity of the enone toward the electrophilic CF_3CO_3H. The oxidations with CF_3CO_3H exhibit acid catalysis, but it is not known how this affects relative rates.

The conversion shown in the following equation was accomplished in 20–25% yields as determined by GC (gas chromatography) analysis and in 17% yield as measured by the amount of pure crystalline material. This conversion is the most effective yet reported for selectively oxidizing the saturated side chain, and it achieves this without the use of protecting groups.

The side products are more polar than I. Hexane extracts of the diluted reaction mixture contained 0.5 g of material from 1.0 g of cholestenone and included all of I. Further extraction with diethyl ether gave an additional 0.2–0.3 g of material which was shown by NMR to contain

(1) (a) N. Applezweig, "Steroid Drugs", McGraw-Hill, New York, 1962, pp 41–83; (b) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, 1959, Chapter 19.
(2) N. Deno and M. D. Meyer, *J. Org. Chem.*, **44**, 3383 (1979).

0022-3263/80/1945-4385$01.00/0 © 1980 American Chemical Society



I, 20–25% (GC)

two acetoxy groups. These presumably arise by hydroxylation, dehydration, epoxidation, and hydrolysis to the glycol. This contrasts with the formation of I which involves hydroxylation, equilibration to a hydroperoxide, and Criegee rearrangement. This latter path is identical with the oxidation step in the conversion of cholesterol to chol-5-ene-3β,24-diol and the mechanism and intermediates have been discussed.[2] Although there was no evidence of products arising via secondary alcohols, it was noted that secondary alcohols are not stable to CF_3CO_3H–H_2SO_4 whereas they are stable to CF_3CO_3H alone.[3]

There are three major hazards in oxidizing cholestenone to I. Although they are avoided by the procedure described, small changes in the procedure can greatly reduce the yield of I so that the three hazards will be described in detail. First is the need for the added H_2SO_4. Without it, Baeyer–Villiger oxidation of the 3-one predominates. Second is oxidation of the 6-position. If a N_2 atomosphere is omitted or if peroxide is not destroyed before the sodium acetate treatment, cholest-4-ene-3,6-dione and 24-hydroxychol-4-ene-3,6-dione appear as products. The identification of cholest-4-ene-3,6-dione was based on a comparison of mass spectra (electron impact and chemical ionization) and GC retention times with those of an authentic sample.[4] The same properties were measured for 24-hydroxychol-4-ene-3,6-dione, but the identification is less secure because of the lack of an authentic sample.

The third hazard involves the discovery of a reaction which is new to steroid chemistry and which was briefly investigated. Addition of 100 mg of cholestenone to 5 g of CF_3COOH plus 5 g of 96% H_2SO_4 caused complete destruction of the cholestenone. About 60% was destroyed after 15 min at 0 °C, but this time is only qualitatively significant because the kinetics approximated those of an ionic chain reaction, with initiators and inhibitors causing major changes in rates as described below.

After 1.5 h, five products accounted for 80% of the GC peak areas and these had the same molecular weight as cholestenone, as shown by chemical-ionization mass spectra. Not only are they isomeric, but they are also closely related to cholestenone in other ways. The A and B rings and the 4-en-3-one system is the same as that in cholestenone. This was shown by each of the five isomers giving a major peak at m/e 124 in the electron-impact mass spectrum. This is diagnostic for 4-en-3-one steroids, and it originates by fission of the 6,7 and 9,10 allylic bonds with double hydrogen transfer to the charged fragment.[5] The NMR spectrum confirmed the 4-en-3-one and, in particular, the vinyl hydrogen at C-4 was identical in position and multiplicity with that in cholestenone. These similarities to cholestenone are reflected in the GC retention times being close (slightly less) to that of cholestenone. One isomer predominated and accounted for over half the GC peak areas. The stability of the enone system parallels that of simpler enones which can be dissolved in 50–96% H_2SO_4 and recovered unchanged.[6]

The isomerization occurs not at the enone "functional group" but at the C-17 alkyl side chain and possibly the D ring. The isomerization of such an alkane structural component must occur in a manner identical with the isomerization of simple alkanes. The mechanism is hydride abstraction (reversal effects epimerization), rearrangement of the alkyl cation, and replacement of hydride to reform the alkane.

Cholestenone was treated with CF_3COOH and H_2SO_4 as before, except that 1 mL of 96% HCOOH was added to test that this mechanism was the path for isomerization of cholestenone. The HCOOH is a hydride donor, and the intent was to have the HCOOH destroy adventitious alkyl cations and prevent initiation of the alkyl isomerization. This was successful and cholestenone showed no sign of change after 3 h at 25 °C. The reaction was divided into two equal parts and 5 mg of *tert*-butyl alcohol added to one part to complete the test and ensure that the inhibition was not a result of lowering the acidity level. After an additional hour, the original still showed no isomerization, whereas 7% of the cholestenone had isomerized in the sample initiated with the trace of *tert*-butyl alcohol. The above isomerizations are limited to positions remote from the enone group because electronegative groups such as enones strongly inhibit hydride abstraction.

Four minor products accounted for the remaining GC peak areas. These appeared at retention times significantly less than those of cholestenone and its isomers. The molecular weight values indicated that these four products arose from the loss of alkene fragments of 4, 5, 6, and 7 carbons. This type of reaction is the reverse of alkene plus alkane to form larger alkanes and is a common adjunct to alkane isomerizations.

When the mixture of cholestenone isomers was oxidized by CF_3CO_3H–H_2SO_4, the products consisted of I, two isomers of I (mol. wt. 400), several lower homologues of mol wt 386, and further lower homologues of mol wt 344 (two) and 330.

It is possible that addition of small amounts of HCOOH (before addition of H_2O_2) would be an advisable precaution in the preparation of I, but this has not been necessary with the present quality of reagents. Certainly any contamination of reagents by tertiary alcohols or branched alkenes is contraindicated.

Experimental Section

Instrumental Analysis. All melting points are uncorrected. Gas–liquid chromatography (GC) was conducted on a Barber-Coleman Model 5000 gas chromatograph using a flame-ionization detector. All separations were performed on a 6-ft column with a 3-mm i.d. containing 3% SE-30 on Gas Chrom Q (80–100 mesh) support (Applied Science, State College, PA). The operating temperature was 265 °C, and a N_2 carrier gas flow of 40 mL/min was used. NMR spectra were recorded on a Varian EM-360 spectrometer, using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Mass spectra were recorded on a Finnigan 3200 GC–MS instrument. IR spectra were recorded on a Perkin-Elmer Model 735 infrared spectrophotometer.

(3) N. Deno, E. J. Jedziniak, L. A. Messer, M. D. Meyer, S. G. Stroud, and E. S. Tomezsko, *Tetrahedron*, **33**, 2503 (1977).

(4) L. F. Fieser, "Organic Syntheses", Wiley, New York, 1963, Collect. Vol. 4, p 189.

(5) C. Djerrasi, *Pure Appl. Chem.*, **50**, 171 (1978).

(6) N. Deno, H. G. Richey, Jr., N. Friedman, J. D. Hodge, J. J. Houser, and C. U. Pittman, Jr., *J. Am. Chem. Soc.*, **85**, 2991 (1963).

Cholestenone. The literature method[7] was modified by using aluminum isopropoxide in place of aluminum *tert*-butoxide. A solution of 21 g of freshly distilled aluminum isopropoxide in 130 mL of benzene was added to a solution of 30 g of cholesterol in 350 mL of benzene and 250 mL of acetone. After the mixture was refluxed for 48 h, the product was isolated as described[7] to give 18 g of cholestenone, mp 80-81.5 °C (lit.[7] mp 78.5-80.5 °C). The filtrate was subjected to recycling which raised the overall yield to 85-90%.

24-Hydroxychol-4-en-3-one Acetate (I). Cholestenone (0.50 g) was dissolved at 0 °C in a solution of 19.5 mL of CF_3COOH, 10.5 mL of 96% H_2SO_4, and 1.0 mL of 50% aqueous H_2O_2. After being stirred for 4 h at 0 °C, the solution was quenched by slow addition to ice-water. A hexane extract was washed with 5% $NaHCO_3$ and dried over $MgSO_4$.

After removal of solvent in vacuo at 25 °C, the residue was dissolved in a solution of 50 mL of acetic acid, 2 mL of water, and 1.0 g of sodium acetate. The solution was refluxed for 18 h under N_2, cooled, and diluted with 100 mL of water. A hexane extract was washed with 5% Na_2CO_3 and dried over $MgSO_4$. Removal of solvent in vacuo at 25 °C gave 0.15 g of crystalline acetate (I). A GC analysis indicated that it was 70% pure with the remainder being unreacted cholestenone.

The impure I was chromatographed on 10 g of 28-200 mesh silica gel, using 65:35 hexane-ether. Cholestenone eluted before I. The purified I was recrystallized from methanol to give 0.087 g (17%) of white needles: mp 123-125 °C; NMR ($CDCl_3$) δ 0.68 (s, 3 H, CH_3 at C-18), 1.13 (s, 3 H, CH_3 at C-19), 2.03 (s, 3 H, acetate), 4.02 (m, 2 H, C-24 CH_2Oac), 5.67 (s, 1 H, vinyl H at C-4); IR (KBr) 1735 (s), 1675 (s), 1242 (s), 1030 (m); exact mass calcd for $C_{26}H_{40}O_3$ *m/e* 400.2976, found 400.2996.

24-Hydroxychol-4-en-3-one. A mixture of 0.089 g of I, 10 mL of 95% ethanol, and 0.60 g of KOH was stirred for 2 h at 25 °C under N_2 followed by addition to water. The ether extract was dried over $MgSO_4$ and the ether removed at 25 °C. Recrystallization from acetone gave 0.070 g (89%) of white needles of 24-hydroxychol-4-en-3-one, mp 131.5-133.5 °C (lit.[8] 131-132 °C).

Competition Reactions. A typical study involved addition of 2.2 mmol of isooctane and 2.2 mmol of the α,β-unsaturated ketone to a solution of 25 mL of CF_3COOH, 4 mL of 96% H_2SO_4, and 1.0 mL of 50% aqueous H_2O_2 at 0 °C. The progress of the reaction was monitored at 25 °C by NMR.

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Registry No. I, 74854-66-3; cholesterol, 57-88-5; cholestenone, 601-57-0; 24-hydroxychol-4-en-3-one, 17597-30-7.

(7) R. V. Oppenauer, "Organic Syntheses", Wiley, New York, 1955, Collect. Vol. 3, p 207.

(8) H. B. Henbest and W. R. Jackson, *J. Chem. Soc. C*, **22**, 2459 (1967).

Synthesis of Deoxyhalogeno Sugars. Displacement of the (Trifluoromethanesulfonyl)oxy (Triflyl) Group by Halide Ion[1]

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A new method for synthesis of deoxyhalogeno sugars is described. This reaction sequence consists of esterifying partially protected carbohydrates with trifluoromethanesulfonic (triflic) anhydride and reacting the resulting trifluoromethanesulfonates with tetrabutylammonium halides. This process for formation of halogenated carbohydrates is mild and convenient. It does not experience the difficulties, such as molecular rearrangement and lack of reactivity at secondary carbons, which sometimes are encountered in displacement reactions in carbohydrate systems.

Deoxyhalogeno sugars are among the most important and useful compounds in carbohydrate chemistry. They assume key roles in the syntheses of aminodeoxy, deoxy, and anhydro sugars; also, they serve as synthetic intermediates in the introduction of heteroatoms and unsaturation into carbohydrates and related structures. In addition to their synthetic importance, certain halogenated carbohydrates and nucleosides have biologically significant properties.[2]

The variety of functions for deoxyhalogeno sugars naturally has stimulated considerable interest in their syn-

(1) A portion of this research has been published in preliminary form: Binkley, R. W.; Hehemann, D. G. *J. Org. Chem.* **1978**, *43*, 3244.

(2) A number of excellent reviews of the chemistry and biochemistry of deoxyhalogeno sugars have been published. These include: (a) Szarek, W. A. *Adv. Carbohydr. Biochem.* **1973**, *28*, 225; (b) Barnett, J. E. G. *Adv. Carbohydr. Chem.* **1967**, *22*, 177; (c) Hanessian, S. Adv. *Chem. Ser.* **1968**, *74*, 159; (d) Haines, A. H. *Adv. Carbohydr. Biochem.* **1976**, *33*, 72.

(3) Pfanstiehl Laboratories, Inc., Waukegan, IL.

(4) Raymond, A. L.; Schroeder, E. F. *J. Am. Chem. Soc.* **1948**, **70**, 2785.

(5) Wolfrom, M. L.; Shafizadeh, F.; Armstrong, R. K.; Shen Han, T. M. *J. Am. Chem. Soc.* **1959**, *81*, 3716.

(6) Brady, R. F., Jr. *Carbohydr. Res.* **1970**, *15*, 35.

(7) Baker, D. C.; Horton, D.; Tindall, C. G., Jr. *Carbohydr. Res.* **1972**, *24*, 192.

(8) Slessor, K. N.; Tracey, A. S. *Can. J. Chem.* **1969**, *47*, 3989.

(9) Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem.* **1966**, *3*, 485.

(10) Reynolds, D. D.; Evans, W. L. "Organic Syntheses"; E. C. Horning, Ed.; Wiley: New York, 1955; Collect. Vol. III, p 432.

(11) Hall, L. D.; Miller, D. C. *Carbohydr. Res.* **1975**, *40*, C1; **1976**, *47*, 299.

(12) (a) Kunz, H.; Schmidt, P. *Tetrahedron Lett.* **1979**, 2123. (b) Garegg, P. G.; Samuelson, B. *J. Soc. Chem., Chem. Commun.* **1979**, 1978.

(13) Bell, R. H.; Horton, D.; Williams, D. M.; Winter-Mihaly, E. *Carbohydr. Res.* **1977**, *58*, 109.

(14) Haylock, C. R.; Melton, L. D.; Slessor, K. N.; Tracey, A. S. *Carbohydr. Res.* **1970**, *16*, 375.

(15) Schmidt, O. T.; Wernicke, E. *Justus Liebigs Ann. Chem.* **1947**, *558*, 70.

(16) James, K.; Angyal, S. J. *Aust. J. Chem.* **1972**, *25*, 1967.

(17) Brown, D. M.; Jones, G. H. *J. Chem. Soc. C* **1967**, 252; *Chem. Commun.* **1965**, 561.

(18) Slessor, K. N.; Tracey, A. S. *Can. J. Chem.* **1970**, *48*, 2900.

(19) Kissman, H. M.; Baker, B. R. *J. Am. Chem. Soc.* **1957**, *79*, 5534.

0022-3263/80/1945-4387$01.00/0 © 1980 American Chemical Society