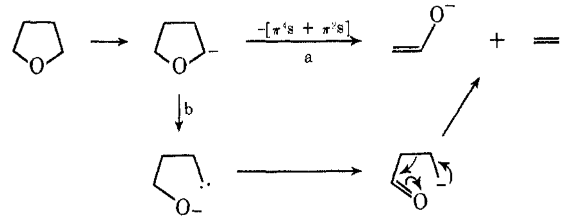
charge develops in the transition state on *two* electronegative atoms rather than one.



In certain reactions of epoxides with strong bases, α-proton abstraction is apparently followed by carbon-oxygen bond cleavage to a carbene, which gives rise to several products.[11] A carbene path in the current cleavages (path b above) is ruled out, at least in the 2-methyl- and 2-phenyltetrahydrofuran[2a] cases, by the cleavage products obtained; *e.g.*, the former gives propylene and the enolate of acetaldehyde rather than ethylene and the enolate of acetone. Relief of ring strain in the epoxide cases presumably aids considerably in the formation of the high-energy carbene intermediates.

The exclusion of path b leaves the much simpler, symmetry-allowed[12] $-[_{\pi}4_s + _{\pi}2_s]$ cycloreversion path a as most likely for these reactions. Honeycutt's finding[2d] that the rate of disappearance of butyllithium in THF is first order in butyllithium and *2.5* order in THF is understandable in terms of this mechanism, assuming 1.5 mol of THF on the average are necessary to solvate the lithium ions in the first step. In this connection, by increasing the butyllithium-THF ratio in a THF cleavage, we obtained a highly crystalline air-sensitive substance which appears to be lithium enolate of acetaldehyde·$^3/_2$ tetrahydrofuran.[8]

Registry No.—2,2,3,3-Tetramethylbutane-1,4-diol, 10519-69-4; lithium enolate of acetaldehyde, 2180-63-4; lithium enolate of propionaldehyde, 33020-96-1; lithium enolate of isobutyraldehyde, 32970-42-6; lithium enolate of crotonaldehyde, 32970-43-7.

Acknowledgment.—We are grateful to the Petroleum Research Fund, Ethyl Corporation, and National Science Foundation for financial support.

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[11] J. K. Crandall and L. H. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4526 (1967), and references cited therein.

[12] R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

The Crystal and Molecular Structure of 5′-Demethoxy-β-peltatin A Methyl Ether[1]

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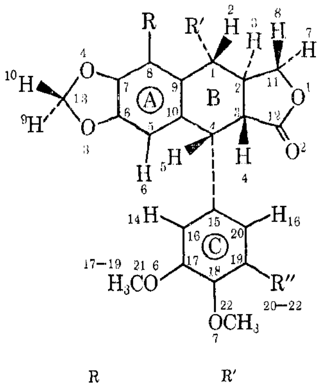
The constitution and relative configurations proposed for this natural antitumor agent by Bianchi, Sheth, and Cole were confirmed by an X-ray study on the polymorph with mp 142–143°, and the conformation was revealed for the first time. The C ring is rotated so that a methoxyl group lies above the A ring. The carbons in the methoxyls on the C ring lie in the plane of the C ring, as far from one another as possible. The carbon in the methoxyl attached to ring A is nearly as far from the plane of the A ring as possible, on the same side as the C ring. An attempt to confirm the absolute configuration using anomalous scattering by oxygen gave inconclusive results but seemed to favor the configuration opposite to that proposed earlier. The structure was solved by symbolic addition and refined to an *R* of 0.039.

Although the antitumor activity of podophyllotoxin (I) and several related lignans has long been known,[2]



	R	R′	R″
I	H	OH	OCH$_3$
II	5 14 11–13 OCH$_3$	1 H	15 H
III	OCH$_3$	H	OCH$_3$

no X-ray or other study showing their preferred conformation has been reported. 5′-Demethoxy-β-peltatin A methyl ether (II), one of the most active of these lignans, was recently isolated from a Mexican plant, *Bursera fagaroides*, and characterized by spectral comparisons with β-peltatin A methyl ether (III).[3] As a check on the proposed constitution and configurations, and to learn the conformational preferences of a lignan of this series, we undertook an X-ray study on this substance.

Experimental Section

Collection and Reduction of the Data.—A clear needle of dimensions 0.2 × 0.2 × 0.7 mm of 5′-demethoxy-β-peltatin A methyl ether (II), mp 142–143°, was mounted for rotation about the needle axis (*c*). Oscillation and Weissenberg photographs indicated space group $P2_12_12_1$ or $P2_12_12$; the former was later established by the full intensity data. The crystal was mounted on a Picker FACS-1 four-circle automated diffractometer set for graphite-monochromatized Cu Kα radiation, λ = 1.54051 Å. Unit cell dimensions, determined by least-squares refinement of the angular settings of seven reflections, were a = 9.174 (3), b = 27.628 (7), and c = 7.620 (1) Å.

For data collection, the 2θ scan technique using a basic 2° scan width modified for radiation dispersion was employed. After scanning at 2°/min, 10-sec background counts were taken at both ends of the scan. Three standard reflections were

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[1] This paper is based in part on the Ph.D. thesis of J. B. W., University of Arizona, 1971; some of the results were presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, ORGN 71.

[2] M. Belkin, *Proc. Soc. Exp. Biol. Med.*, **6**, 308 (1947); J. L. Hartwell and M. J. Shear, *Cancer Res.*, **7**, 716 (1947); M. G. Kelly and J. L. Hartwell, *J. Nat. Cancer Inst.*, **14**, 967 (1954).

[3] E. Bianchi, K. Sheth, and J. R. Cole, *Tetrahedron Lett.*, 2759 (1969).

TABLE I

ABSOLUTE CONFIGURATION RESULTS FROM PAIR MEASUREMENTS

h	k	l	D^a	I_{hkl}	$I_{\overline{hkl}}$	F_c+	F_c-	Configuration indication^b
1	6	6	4.9	128.6	124.8	46.1155	48.0222	−
4	5	1	2.8	44.1	40.2	11.4796	12.0651	−
2	8	2	1.2	144.2	145.1	29.4003	29.8750	+
4	6	1	1.1	46.3	45.3	17.0872	16.7117	+
5	10	1	1.1	12.7	14.7	14.1211	13.6527	−
6	4	1	1.0	166.6	160.9	45.3743	44.6065	+
6	1	3	0.9	30.0	27.4	19.6333	20.1580	−
3	14	1	0.9	142.5	147.2	38.8724	39.4858	+
1	9	3	0.8	424.5	426.7	52.2592	53.1525	+
4	4	2	0.8	189.0	192.2	38.3309	38.8640	+

[a] $D = [|F_c(hkl)| - |F_o(\overline{hkl})|]^2/\sigma^2|F_o(hkl)| \times 10^2$. [b] Plus means result agrees with literature absolute configuration.

measured 23 times during the data collection; there was no evidence for crystal decomposition. Of 1901 unique reflections measured up to $2\theta = 125°$, 1762 were judged to be statistically significant on the basis of $I \geq 2\sigma$.

Solution and Refinement.—The structure was solved by symbolic addition[4] using the MULTAN programs.[5] Given the top 207 E's, the program selected 1 6 0, 7 7 0, 0 16 5, and 0 5 7 as the origin- and enantiomorph-fixing reflections. From an E map using the set of phases having the highest figure of merit (1.03), and bond angles and distances between the top 51 peaks in this E map, all nonhydrogen atoms were found. After four cycles of isotropic refinement,[6] $R = \Sigma ||F_o| - |F_c||/\Sigma|F_o| = 0.16$ with C14 in a wrong position. A difference map showed the correct position of C14 and, after another refinement cycle, $R = 0.11$. After three anisotropic cycles, R was 0.076. All 22 hydrogens were found on the difference map used to find C14; three anisotropic cycles including hydrogens (which were given the same anisotropic temperature factors as the carbon to which they were attached) dropped R to its final value, 0.0394. No correction was made for extinction or absorption (μ 8.5 cm^{-1}).

An earlier partial solution had been obtained using the MAGIA programs with the starting set 1 7 0, 5 0 4, 0 24 5, and 2 15 0. An E map clearly showed a benzene ring with three substituents attached. Starting with these nine atoms, six F maps yielded positions for all the nonhydrogen atoms, but this solution would not refine below $R = 0.35$. At this time, the MULTAN programs gave the true solution, and it was discovered that the x and y coordinates for each atom in the partial solution were very close, but the z coordinates were displaced by about 0.8 Å. As partially correct structures of this type often result from direct methods, it seemed worth considering how the true structure might have been derived from the partial solution in this case. Accordingly, R's were calculated separately for the zero level data on the a, b, and c axes. The values obtained were 0.42, 0.52, and 0.22, respectively, providing strong evidence that the problem was with the z coordinates. By calculating R's for molecules shifted at regular intervals along the c axis, the true positions would presumably have been obtained.

Absolute Configuration.—R was 0.039529 when a value of $+0.04$ was used for $\Delta f_0''$ for oxygen and 0.039439 when a value of -0.04 was used. The R-factor ratio was thus 1.00228, and, according to Hamilton's test,[7] the absolute configuration with the higher R (the literature configuration, shown in the formula for II) can be rejected with 99.5% certainty.

To gain further evidence regarding the absolute configuration, the intensities of each of the ten reflections with the highest D values[8] and their negatives were each remeasured ten times, averaged, and corrected for background. The results are given in Table I.

TABLE II

FRACTIONAL COORDINATES AND ESTIMATED STANDARD DEVIATIONS

Atom	x/a	y/b	z/c
O1	0.2199 (3)	0.3694 (1)	−0.0713 (4)
O2	0.2147 (3)	0.3929 (1)	0.2101 (4)
O3	−0.5946 (3)	0.4989 (1)	0.1019 (3)
O4	−0.6192 (3)	0.4862 (1)	−0.1977 (3)
O5	−0.3976 (3)	0.4384 (1)	−0.4150 (3)
O6	−0.4102 (3)	0.2591 (1)	0.1592 (3)
O7	−0.2640 (3)	0.2279 (1)	0.4263 (3)
C1	−0.1412 (4)	0.4039 (1)	−0.2589 (5)
C2	−0.0268 (4)	0.3794 (1)	−0.1480 (5)
C3	0.0083 (4)	0.4104 (1)	0.0140 (5)
C4	−0.1214 (4)	0.4124 (1)	0.1391 (4)
C5	−0.3566 (4)	0.4577 (1)	0.1298 (5)
C6	−0.4743 (4)	0.4742 (1)	0.0405 (5)
C7	−0.4895 (4)	0.4671 (1)	−0.1407 (5)
C8	−0.3847 (4)	0.4439 (1)	−0.2331 (4)
C9	−0.2603 (4)	0.4271 (1)	−0.1485 (4)
C10	−0.2475 (4)	0.4336 (1)	0.0361 (4)
C11	0.1250 (5)	0.3723 (2)	−0.2245 (6)
C12	0.1549 (4)	0.3909 (1)	0.0704 (6)
C13	−0.6824 (5)	0.5095 (1)	−0.0479 (6)
C14	−0.4891 (6)	0.3992 (2)	−0.4637 (7)
C15	−0.1592 (4)	0.3628 (1)	0.2159 (4)
C16	−0.2724 (4)	0.3345 (1)	0.1501 (4)
C17	−0.3030 (4)	0.2897 (1)	0.2189 (4)
C18	−0.2228 (4)	0.2723 (1)	0.3629 (4)
C19	−0.1107 (4)	0.2997 (1)	0.4275 (5)
C20	−0.0793 (4)	0.3447 (1)	0.3545 (5)
C21	−0.4900 (6)	0.2732 (2)	0.0075 (7)
C22	−0.1925 (6)	0.2112 (2)	0.5809 (8)
H1	−0.197 (4)	0.379 (1)	−0.340 (5)
H2	−0.099 (4)	0.430 (1)	−0.334 (5)
H3	−0.062 (4)	0.340 (1)	−0.103 (4)
H4	0.034 (4)	0.448 (1)	−0.017 (5)
H5	−0.092 (4)	0.437 (1)	0.239 (4)
H6	−0.333 (4)	0.467 (1)	0.248 (4)
H7	0.131 (4)	0.334 (1)	−0.275 (5)
H8	0.162 (4)	0.401 (1)	−0.302 (5)
H9	−0.791 (4)	0.503 (1)	−0.024 (5)
H10	−0.682 (4)	0.549 (1)	−0.062 (5)
H11	−0.430 (4)	0.365 (2)	−0.411 (5)
H12	−0.580 (5)	0.400 (2)	−0.421 (6)
H13	−0.506 (5)	0.392 (1)	−0.587 (6)
H14	−0.339 (4)	0.348 (1)	0.071 (4)
H15	−0.047 (4)	0.288 (1)	0.517 (4)
H16	−0.003 (4)	0.363 (1)	0.395 (4)
H17	−0.555 (5)	0.237 (2)	−0.016 (6)
H18	−0.418 (5)	0.274 (2)	−0.086 (6)
H19	−0.547 (5)	0.309 (2)	0.028 (6)
H20	−0.234 (5)	0.177 (1)	0.591 (6)
H21	−0.082 (5)	0.207 (1)	0.556 (6)
H22	−0.213 (5)	0.235 (1)	0.676 (6)

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(4) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

(5) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).

(6) Refinements were by full-matrix least squares with the ORFLS program of W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-305, Oak Ridge National Laboratory, 1962. Unit weights were used. Form factors were obtained by graphical interpolation of those in the International Tables for X-ray Crystallography, Vol. III, Table 3.3.1A, except for hydrogen, for which the form factors of R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965), were used.

(7) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(8) H. Hope and U. de la Camp, *Nature (London)*, **221**, 54 (1969).

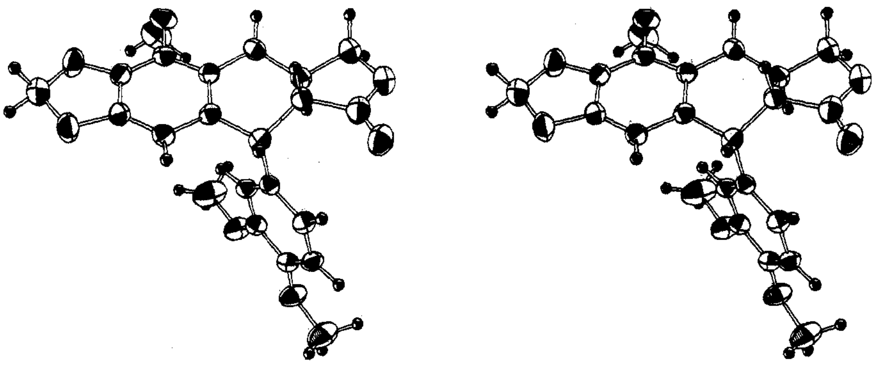

Figure 1.—Stereoscopic view of 5′-demethoxy-β-peltatin A methyl ether (II). Thermal ellipsoids enclose 50% probability.

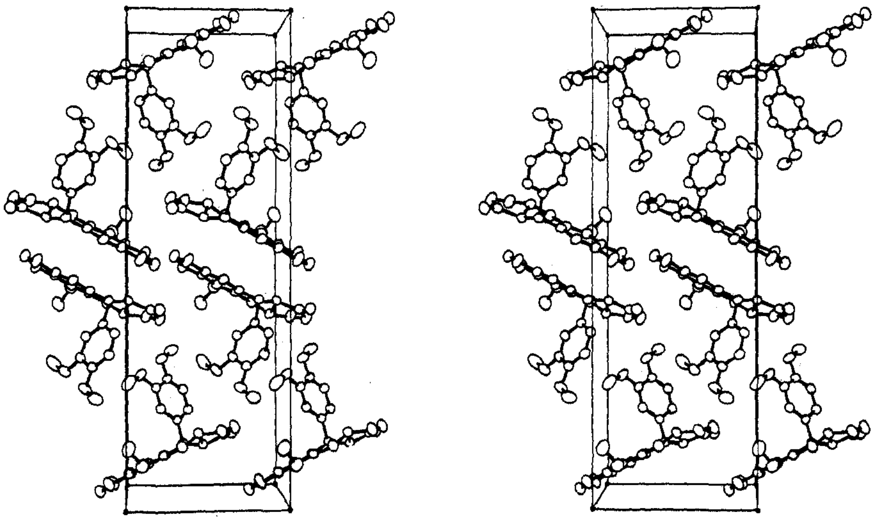

Figure 2.—Stereoscopic view of the unit cell, *c*-axis projection.

Results and Discussion

The final positional parameters are given in Table II. Temperature factors, bond angles, and distances were normal.[9] The average benzene bond lengths were 1.387 (5) Å for ring A and 1.385 (5) Å for ring C. The C–H distances ranged from 0.90 (4) to 1.19 (5) Å.

As can be seen from the ORTEP drawing in Figure 1, this study confirms the constitution and relative configurations proposed by Bianchi, Sheth, and Cole.[3] However, our attempts to verify the absolute configuration, while certainly not definitive, seem to provide weak evidence against the literature configuration. The significance test[7] on the *R* factor calculated for each enantiomer suggests a 99.5% probability that the literature configuration is wrong; however, as the general reflection data were not corrected for absorption or extinction, errors due to these may have been dominant in causing the difference in *R*'s. *D* values[8] were calculated for all of the reflections, and the reflections with the top ten *D* values and their negatives in 2θ were carefully measured; this technique minimizes absorption and extinction errors. As seen from Table I, six of ten values favor the literature configuration; however, the top two do not, and, as these two are much more sensitive than the others and should be weighted more heavily, the overall result seems to be "weakly against" the literature configuration. Anomalous scattering by oxygen was successfully used by Hope and de la Camp[8] on tartaric acid, which is 64% oxygen as compared to 28% in the current case. The absolute configurations of the lignans of this class rest on a 20-step sequence of chemical interconversions and rotation comparisons completed by Schrecker and Hartwell;[10] the current study casts a small measure of doubt on the result, and an independent check would seem worthwhile.

The C ring occupies a pseudoaxial position and is nearly at right angles (88.8°) to the A ring. It is rotated in such a way that C21 lies over the aromatic ring and H16 is only 2.58 (3) Å from O2.

C21 and C22 in methoxyl groups are only -0.15 and 0.17 Å out of the plane of ring C (the dihedral angles between C21–O6–C17 and ring C, and C22–O7–C18 and ring C are 4.3 and 5.8°, respectively), whereas C14 is almost as far as possible from the plane of the adjacent benzene ring (the angle between C14–O5–C8 and ring A is 80.2°). The coplanarity of the first two methoxyls permits overlap of a p orbital on oxygen with the p orbital on the adjacent ring carbon and gives relatively short bonds [both 1.373 (4) Å]. Nonbonded steric interactions with the adjacent ortho substituents presumably outweigh this resonance ef-

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[9] Tables of temperature factors, bond distances, bond angles, least-squares plane deviations, and structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $5.00 for photocopy or $2.00 for microfiche.

[10] J. L. Hartwell and A. W. Schrecker, *Fortschr. Chem. Org. Naturst.*, **15**, 115 (1958).

fect in the case of the third methoxyl group, and the C8–O5 bond is accordingly long [1.399 (4) Å]. All three methoxyl groups adopt staggered conformations about the methyl–oxygen bond.

A projection down the *c* axis (Figure 2; the *a* axis is horizontal and the *b* axis vertical) shows the molecular packing. The shortest intermolecular distance is 2.21 (5) Å, between H4 and H9. The shortest intermolecular distance between nonhydrogen atoms (O7 and C11) is 3.325 (5) Å.

Registry No.—5′-Demethoxy-β-peltatin A methyl ether, 32970-80-2.

Acknowledgments.—We thank Drs. E. Bianchi and J. R. Cole of our Pharmacy Department for providing crystals, Drs. L. L. Reed and Paul Johnson for helpful advice, the Computer Center of the University of Arizona for computer time, and the National Cancer Institute (CA-10944) and Sloan Foundation (fellowship to R. B. B.) for financial aid.

Reduction of α,β-Oxido Ketones with Chromous Acetate. Synthesis of 3β,5β,17β,19-Tetrahydroxy-5β-androstane, a Degradation Product of Strophanthidin[1,2]

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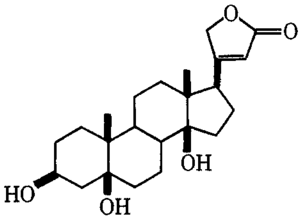
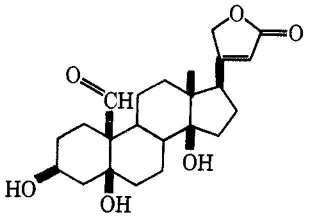
The reaction of steroidal α,β-oxido ketones with chromous acetate has been studied, using a variety of solvents, as a potential route to the A/B ring system of some cardiac-active steroids. These reductions generate β-hydroxy ketones with retention of configuration at the β-carbon atom, along with the corresponding α,β-unsaturated ketones. The β-hydroxy ketone formed in the reaction is stable to the reaction conditions. Steroidal 4β,5β-oxido-3 and 4α,5α-oxido-3 ketones give respectively 5β-hydroxy- and 5α-hydroxy-3-oxo steroids on reduction with chromous acetate, while 6α,7α-oxido-4-cholesten-3-one generates the biosynthetically interesting 7α-hydroxy-4-cholesten-3-one. Yields of β-hydroxy ketone are approximately 50% in the cases studied. The reaction has been used to prepare 3β,5β,17β,19-tetrahydroxy-5β-androstane, a degradation product of strophanthidin.

In a search for new ways to generate the 3β,5β-dihydroxy system found in cardiac-active steroids such as periplogenin (A) and strophanthidin (B), we considered the possibility of reduction of an α,β-oxido ketone (as C) with chromous ion. Cleavage of the C–O bond α to the ketone should occur, giving the required stereochemistry for the resulting tertiary hydroxyl group at the β carbon. Furthermore, α,β-oxido ketones are readily available by the action of alkaline hydrogen peroxide on the corresponding α,β-unsaturated ketones. If X were hydrogen or an oxygenated function, subsequent reduction of the carbonyl group in D to an axial alcohol would provide the required A/B ring system found in such compounds as periplogenin and strophanthidin.



A



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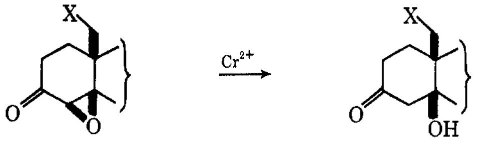

C　D

Numerous examples of the reaction of α,β-oxido ketones with chromous chloride can be found in the literature.[3,4] These reactions, however, invariably generate the α,β-unsaturated ketone in high yield, as illustrated[3a] by the conversion of 4,5β-oxidocholestan-3-one to 4-cholesten-3-one with chromous chloride. The conversions[5] of steroidal 16α,17α-oxido-20 ketones to the corresponding 16α-hydroxy-20 ketones using chromous acetate in acetic acid represent the only reported examples of β-hydroxy ketone formation from α,β-oxido ketone with chromous ion. These observations, coupled with the fact that the reported chromous chloride reactions all involve strongly acid solutions (which might convert any β-hydroxy ketone to the conjugated ketone), encouraged us to study reduction of the model compound 4β,5β-oxidocholestan-3-one (**1**) (Chart I) with chromous acetate.

Studies were carried out with a variety of solvents (dimethylformamide, *N*-methylpyrrolidinone, tetrahydrofuran, diglyme, ethanol, aqueous acetone, acetic acid–sodium acetate) at room temperature, under an atmosphere of carbon dioxide, using up to a tenfold excess of chromous acetate. Conversion of the oxido ketone **1** to the 5β-hydroxy ketone **2** was best effected (*ca.* 50% yield of isolated pure product) by use of a large excess (5–10 molar equiv) of freshly prepared chromous acetate in absolute ethanol or, better,

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[1] Abstract 158, 23rd International Congress of Pure and Applied Chemistry, Boston, Mass., July 1971.

[2] This work was supported, in part, by U. S. Public Health Service Grants HE-08913, AM-07422, and GM 16492.

(3) *Cf.* (a) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954); (b) D. Arigoni, D. H. R. Barton, E. J. Corey, and O. Jeger, *Experientia*, **16**, 41 (1960); (c) A. Akisanya, C. W. L. Bevan, T. G. Halsall, J. W. Powell, and D. A. H. Taylor, *J. Chem. Soc.*, 3705 (1961).

(4) For a recent review of reductions of organic compounds with chromous salts, see J. R. Hanson and E. Premuzic, *Angew. Chem., Int. Ed. Engl.*, **7**, 247 (1968).

(5) V. Schwarz, *Collect. Czech. Chem. Commun.*, **26**, 1207 (1961). See also R. Neher, P. Desaulles, E. Vischer, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1667 (1958), as well as ref 3 and 4.