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RUTHENIUM TETROXIDE OXIDATION IN NEUTRAL AND BASIC MEDIA[1]

H. GOPAL,* T. ADAMS† and R. M. MORIARTY‡

Department of Chemistry, The Catholic University of America, Washington, D.C. 20017

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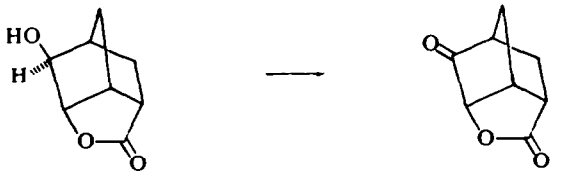
Abstract—Details are given on the use of sodium metaperiodate-ruthenium dioxide reagent for the oxidation of hydroxylactones to ketolactones under neutral conditions and the oxidation of lactones *via* γ or δ-hydroxycarboxylates to ketocarboxylates. The scope and limitations of the reaction are discussed.

OXIDATION OF SECONDARY ALCOHOLS under neutral conditions is an important synthetic step in organic chemistry. One frequently encounters situations in which acid sensitive groups are affected adversely by the acidic conditions used in many oxidation reactions. For example in our investigation[2a,b] of the solvolytic reactions of bridged bicyclic hydroxylactone derivatives it became necessary to synthesize the related ketolactones which were highly acid sensitive. Towards this end we examined the behavior of such hydroxy lactones towards several oxidizing agents.



I II

Previously all attempts to oxidize hydroxylactone I to ketolactone II with a number of oxidizing agents[3,4] were unsuccessful. Also, efforts to prepare bicyclic ketoacids by oxidation of corresponding hydroxyacids derived from γ and δ-lactones generally gave poor results. Such transformations with oxidizing agents in basic media such as $KMnO_4$ afforded fair yields,[5] but oxidations in acidic media (Jones reagent, CrO_3/HOAc, etc.) gave no detectable amounts of the respective ketoacids. This general behavior of hydroxylactones and hydroxyacids derived from lactones led to a search for a powerful, neutral oxidizing agent capable of accomplishing these conversions.

* Petroleum Research Fellow, 1967–68.

† US Steel Fellow, 1968–70.

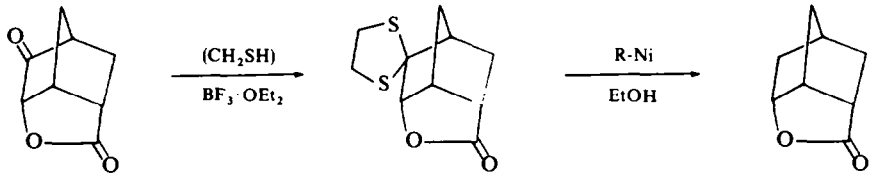
‡ Present address: Department of Chemistry, University of Illinois, Chicago Circle Campus, Chicago, Illinois, 60680, USA.

A reagent which meets the above requirements is ruthenium tetroxide. This oxidant has been shown[6] to be an excellent reagent for converting secondary alcohols to ketones under neutral conditions. We now wish to report on the application of ruthenium tetroxide to the oxidation of hydroxyacids and hydroxylactones.

Oxidation of hydroxylactones. After twenty attempts to prepare ketolactone II success was finally achieved by oxidation of hydroxylactone I with RuO_4 in a heterogeneous solvent system. A procedure has been adopted in which RuO_4 is generated *in situ* from a small amount of RuO_2 and at least one molar equivalent of $NaIO_4$ in a CCl_4–H_2O solvent system.[7,8,*] Thus a low concentration of RuO_4 is maintained and the reaction is easily controlled. Oxidation of hydroxylactone I under these conditions gives an 80% yield of ketolactone II.†

The product was identified by its high carbonyl stretching frequencies at 1795 and 1775 cm^{-1} and by its NMR spectrum which was as expected with the only downfield signal occurring for the 6-*exo*-proton at $\delta = 4{\cdot}4$ ppm.[9] The structure was further confirmed by systematic chemical degradation (Scheme I) and comparison of the product with a known sample of IV.

SCHEME I



II III IV

Under similar oxidation conditions hydroxylactones V, VII, and IX gave excellent yields of the corresponding ketolactones.

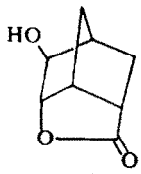
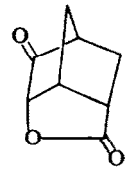
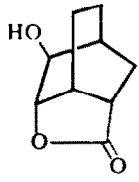
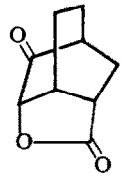
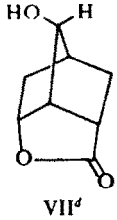
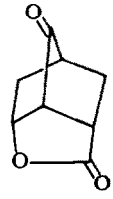
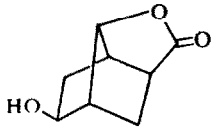
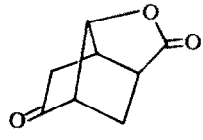
In the case of V and VII the carbonyl products were found to be identical to those formed in 10%[3] and 27%[9] yield by chromic acid oxidation. Ketolactone X is new; its structure accords with the IR spectrum which shows two carbonyl absorptions at 1795 and 1755 cm^{-1}. Also the structure is confirmed by elemental analysis.

To extend further the utility of this method compounds XI and XII were oxidized as above. However, in neither case was the ketone product obtained in any appreciable amounts (XII gave 10% of the corresponding ketoether XIIa). Since the only structural difference between XI and XII and the other hydroxy compounds is an

* Recently the use of NaOCl has been recommended as a convenient and useful reagent for the oxidation of RuO_2 to RuO_4 (private communication Prof. Saul Wolfe, Queens University). S. Wolfe, S. Hasan and J. Campbell, *Chem. Comm.* 1420 (1970)

† Ketolactone II could only be obtained in poor yield prior to this modified method[9]

TABLE 1. OXIDATION OF HYDROXYLACTONES[a]

Hydroxylactones	Ketolactones	Yields %
 I[b]	 II	80
 V[c]	 VI	87
 VII[d]	 VIII	76
 IX[e]	 X	88

[a] Oxidations accomplished by Procedure A (see experimental section:

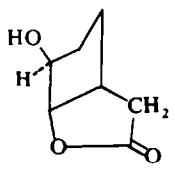
[b] H. B. Henbest and B. Nicholls, *J. Chem. Soc.* 221 (1959).

[c] Ref. 3.

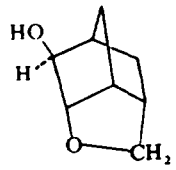
[d] The hydroxylactone VII was prepared by the base hydrolysis of the corresponding acetoxylactone: R. M. Moriarty, H. G. Walsh and H. Gopal, *Tetrahedron Letters* **36**, 4363 (1966).

[e] The hydroxylactone IX was obtained upon thermal lactonization of 2-*exo*-7-*anti*-dihydroxybicyclo[2.2.1]heptane-5-*exo*-carboxylic acid, R. M. Moriarty, H. Gopal and H. G. Walsh, *Tetrahedron Letters* **36**, 4369 (1966)

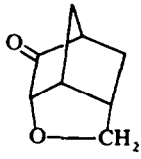
activated methylene group, it appears that RuO_4 attacks the methylene group adjacent to the lactone carbonyl in XI or the methylene adjacent to the oxygen in the cyclic ether (XII), thus causing undesired over-oxidation. Oxidation of a methylene group of the type present in XII is a complicating feature in this reaction.[10]



XI



XII

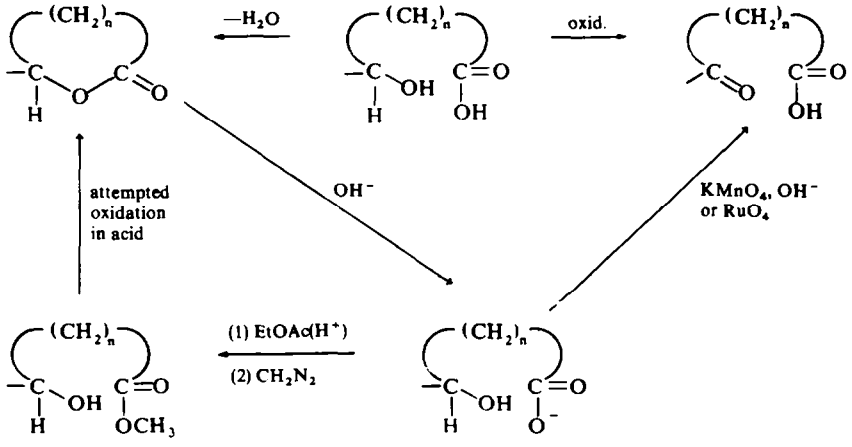


XIIa

In Wolff's synthesis of aldosterone a five-membered ether is oxidized to a lactone using RuO_4 in CCl_4.[10]

Oxidation of hydroxyacids. Initially we sought to prepare and isolate the hydroxy-acid from hydrolysis of the lactone, and in a second step oxidize it to the ketoacid under mild acidic or basic conditions. Thus lactones XIII and XV were treated with one molar equivalent of dilute base followed by careful acidification using one molar equivalent of dilute acid to generate the γ- and δ-hydroxy acids. However, upon isolation of the crude product only the lactones were detected (Scheme II). This result is not unexpected, since Brown *et al.*[11] have reported that in neutral media simple γ-hydroxyacids exist to a large extent in the lactone form at 25°. Since the hydroxyacids were unstable under neutral or acidic conditions, attempts were made

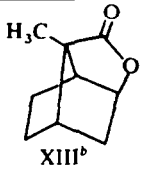
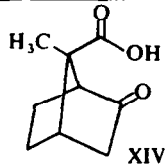
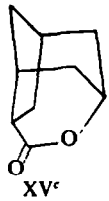
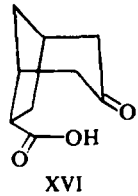
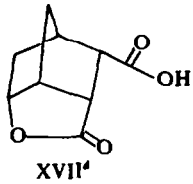
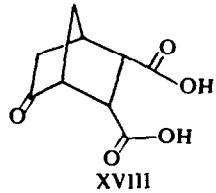
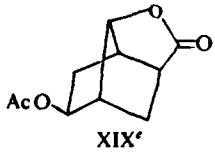
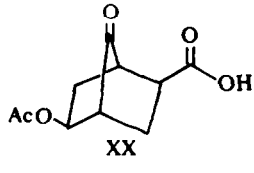
SCHEME II



n = 2 or 3

to prepare the corresponding hydroxyesters which could then be oxidized and hydrolyzed to ketoacids. For isolation of these esters a method was devised in which the carboxylate salt of a lactone such as XV was extracted with acidic EtOAc (containing 1 eq. of acid). The organic extracts were dried and immediately treated with CH_2N_2 to form the ester. In this manner the hydroxyester was isolated as a mixture with the lactone. Its presence was verified by spectral evidence. For example, in the case of XV, the hydroxyester the IR contained absorptions for OH (3600 cm^{-1}) and ester carbonyl (1725 cm^{-1}) and its NMR showed a Me resonance at δ 3·7 and a complex multiplet at δ 4·0 for the 3-*exo*-proton. However, attempted oxidation of these hydroxyesters under slightly acidic conditions (Jones Reagent) caused extensive lactonization before any oxidation occurred (Scheme II). From these observations our attention focused on an oxidizing agent stable in basic media and capable of

TABLE 2. OXIDATION OF LACTONES[a]

Lactones	Ketoacids	Yield %
 XIII[b]	 XIV	97
 XV[c]	 XVI	88
 XVII[d]	 XVIII	68
 XIX[e]	 XX	60

[a] Oxidations accomplished by Procedure B (see experimental section).
[b] Ref. 5.
[c] To be published.
[d] Ref. 3.
[e] Table 1.[e]

converting the hydroxycarboxylates directly to the ketoacids. Initially alkaline $KMnO_4$ was tried and gave poor to fair yields in the oxidation of XIII and XV. However, RuO_4 generated in H_2O proved to be extremely efficient for conversion of the hydroxycarboxylates to ketoacids (Scheme II).

The procedure involved treatment of the lactone with one molar equivalent of aqueous base (two molar equivalents in the case of XVII) in order to form the carboxylate anion. A small amount (0·02 molar equivalents) of RuO_2 was added and the aqueous solution stirred vigorously while $NaIO_4$ solution was added in small aliquots to generate RuO_4. The yellow color of the tetroxide persisted after addition of a slight molar excess of the periodate. The excess oxidant was then destroyed and the solution acidified to yield the respective ketoacid.

By this method ketoacids XIV, XVI, XVIII, and XX were prepared in excellent yields (Table 2). The products XIV and XVIII have been reported[3,5] and their m.ps agree with the literature values. The structures of lactone XV and corresponding ketoacid XVI have recently been verified by a lengthy degradation scheme* while the structure of XX is based on the IR carbonyl absorption at 1778 (C_7 carbonyl),[9] 1735 (ester carbonyl), and 1700 (acid carbonyl) cm^{-1} and the elemental analysis accords with the proposed structure.

In light of these results it appears that this oxidation method in neutral aqueous media can be extended to any lactone provided no other functional groups are present which are attacked by RuO_4[6f] such as —CH_2O—,[12] ethers,[10] aromatic rings,[12] olefins,[13] sulfides and sulfoxides.[12]

EXPERIMENTAL

All elemental analyses were performed by Mictro-Tech Laboratory, Skokie, Illinois. M.ps were determined either on a Kofler apparatus (corrected), or on a Thomas–Hoover capillary apparatus (uncorrected). IR spectra were recorded on a Perkin–Elmer 337 Infracord in the solvent indicated. NMR spectra were recorded on a Varian Associates Model A-60 spectrometer operating at 60 MHz. Samples were run as solutions in the solvent indicated using TMS as internal standard. Chemical shifts are recorded as parts per million downfield from TMS on the δ scale and coupling constants are given in hertz.

RuO_2 and $NaIO_4$ were purchased from K and K Chemical Company.

Oxidation of hydroxylactones (A)

In a typical procedure a solution containing 30 mmol of hydroxylactone in 25 ml of distilled H_2O was added to a suspension of 250 mg of RuO_2 in 25 ml of CCl_4. This heterogeneous mixture was cooled in an ice bath and stirred vigorously while 90 ml of a 10% solution of $NaIO_4$ (42 mmol) was added dropwise. When the yellow color of RuO_4 persisted for a few hr it was assumed that reaction was complete and excess RuO_4 was destroyed by addition of iso-PrOH. The solvent layers were separated and the aqueous layer was thoroughly extracted with EtOAc. The organic extracts and CCl_4 layer were combined, dried ($MgSO_4$), and the solvent removed *in vacuo* yielding the ketolactone.

Oxidation of lactones to the corresponding ketoacids (B)

In a typical procedure 26·3 mmol of the lactone was treated with a solution containing 26·3 mmol (53·0 ml of 0·498 N) of NaOH. The mixture was heated on a steam bath for 30 min in order to obtain a homogeneous solution. The solution was then cooled and a drop of phenolphthalein solution added and excess base neutralized with 0·60 N HCl. Usually no acid addition was required which indicated quantitative formation of the carboxylate salt. In all cases less than 1% of the initial amount of NaOH remained unreacted at the completion of the hydrolysis of lactone ring. To the neutral aqueous solution of

* To be published elsewhere.

sodium salt of the hydroxy-acid, was added 50 mg of RuO_2. The solution was cooled (~20°) and vigorously stirred while a solution containing approximately 10% of the stoichiometric amount (26·3 mmol) of $NaIO_4$ was added. The solution developed a yellow color indicating the presence of RuO_4. Upon appearance of the black RuO_2 precipitate another aliquot of $NaIO_4$ was added. Each successive addition required more time for the disappearance of the yellow color of tetroxide. After total addition of a slight excess (5 molar per cent) of periodate the tetroxide was destroyed with iso-PrOH. The solution was acidified and thoroughly extracted with five portions of EtOAc. The extracts were combined, dried ($MgSO_4$), and the solvent removed *in vacuo* yielding the ketoacid.

5-*Keto*-6-endo-*hydroxybicyclo*[2.2.1]*heptane*-2-endo-*carboxylic acid*-γ-*lactone* (II). 5-*exo*-*endo*-Dihydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid-γ-lactone (I) (5 g; 32·5 mmol) was oxidized according to Procedure A. A semisolid was obtained which was purified by crystallization with acetone–pentane and by sublimation (70–75° 0·5 mm) to yield 4·0 g (80%) of the ketolactone II; m.p. 202–203° (cor.); IR 1795 and 1770 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·4 (d, 1H, $J_{6\text{-}exo\text{-}1}$ = 5·2 Hz, 6-*exo*-proton), 3·6 (t, 1H, H_1), 2·83 (m, 2H), 2·67–1·73 (m, 4H); mass spectrum p *m/e* 152. (Calc. for $C_8H_8O_3$: C, 63·15; H, 5·30. Found: C, 62·95; H, 5·42%). Semicarbazone: m.p. 236–238° (uncor.); IR 3455, 3325 and 3180 (NH), 1755 (lactone C=O), 1660 (semicarbazone C=O) cm^{-1} (Nujol); NMR (DMSO) δ 4·9 (d, 1H, $J_{6\text{-}exo\text{-}1}$ = 5·5 Hz, 6-*exo*-proton) 6·24 (s, 2H, NH_2), 9·55 (s, 1H, —CO—NH—). (Calc. for $C_9H_{11}N_3O_3$: C, 51·70; H, 5·30; N, 20·05. Found: C, 51·57; H, 5·32; N, 20·28%).

Thioketal derivatives (III). The method described by Fieser[14] was used in which II (2·5 g, 16 mmol) was dissolved in 2·2 g (23 mmol) of ethanedithiol. The mixture was cooled in ice and ten drops of BF_3 etherate was added. After standing at room temp for 12 hr the solution was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with NH_4OH and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to yield 2·5 g of a thick oil. The oil was crystallized with acetone–pentane to yield 1·75 g (48%) of crystalline material, III; m.p. 111·5–112·5° (cor.); IR 1790 (lactone C=O) cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·75 (d, 1H, $J_{6\text{-}exo\text{-}1}$ = 5·2 Hz, 6-*exo*-proton), 3·32 (m, 5H, H_1 and —S—CH_2—CH_2—S—), 2·58 (broad m, 2H), 2·23–1·73 (m, 4H). (Calc. for $C_{10}H_{12}O_2S_2$: C, 52·60; H, 5·30. Found: C, 52·53; H, 5·28%).

Desulfurization of III. A sample of III (1 g, 4·4 mmol) was refluxed with excess W-2 Raney nickel in abs EtOH for 34 hr. The solution was filtered through celite and the EtOH removed *in vacuo* to yield 220 mg (36%) of an oil which was sublimed. The solid deposited had physical properties identical to those of 6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid-γ-lactone (IV).[5]

5-*Keto*-6-endo-*hydroxybicyclo*[2.2.2]*octane*-2-endo-*carboxylic acid*-γ-*lactone* (VI). According to procedure A, 12 mmol (2·0 g) of V was oxidized to yield a crude white solid which on crystallization with ether gave 1·75 g (87%) of a white powder: m.p. 218–219° (uncor.), [Lit[3] m.p. 213–215°]; IR 1790 and 1740 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·42 (d, 1H, $J_{6\text{-}exo\text{-}1}$ = 5·5 Hz, 6-*exo*-proton), 3·03 (m, 2H), 2·64 (broad S, 1H), 2·45–1·70 (m, 6H).

7-*Keto*-6-endo-*hydroxybicyclo*[2.2.1]*heptane*-2-endo-*carboxylic acid*-γ-*lactone* (VIII). In the same manner 3·08 mmol (475 mg) of hydroxylactone VII was oxidized to yield a crude white solid which was crystallized with acetone–pentane and vacuum sublimed to yield 360 mg (76%) of ketolactone VIII: m.p. 187–188° (uncor.), [Lit.[9] m.p. 193–194°]; IR 1775 cm^{-1} (both C=O) ($CHCl_3$).

5-*Keto*-7-syn-*hydroxybicyclo*[2.2.1]*heptane*-2-exo-*carboxylic acid*-γ-*lactone* (X). Procedure A was used without CCl_4. By this method 2·24 mmol (346 mg) of IX was oxidized over 14 hr. A white solid was again obtained which was crystallized with acetone–petroleum ether to yield 300 mg (88% 0 of ketolactone X: m.p. 186–187° (uncor.); IR 1795 (lactone C=O) and 1755 (ketone C=O) cm^{-1} ($CHCl_3$). (Calc. for $C_8H_8O_3$: C, 63·15; H, 5·30. Found: C, 62·91: H, 5·23%).

6-*Oxatricyclo*[3.2.2.1^{3,8}]*nonan*-4-*one* (XIIa). Under conditions of Procedure A or by a procedure formulated by Nakata[6b] 29 mmol (4 g) of hydroxyether XII was oxidized over a 4 hr period. This yielded 1·63 g of a thick brown oil which showed at least three components on TLC (EtOAc). The product was chromatographed on a 50 g silica gel column (63 × 2 cm) prepared in C_6H_6. Initial elution with C_6H_6 gave 472 mg of solid which was sublimed (27–35° 0·1 mm) to yield 400 mg (10%) of XIIa: m.p. 137–138° (uncor.); IR 1760 (C=O) cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) 4·18 (d, 1H, $J_{6\text{-}exo\text{-}1}$ = 4·0 Hz, 6-*exo*-proton), 3·78 (m, 2H, —CH_2—O—) 3·01 (t, 1H, H_1), 2·75–1·08 (m, 6H). (Calc. for $C_8H_{10}O_2$: C, 69·54; H, 7·30. Found: C, 69·44; H, 7·45%).

7-anti-*Methylbicyclo*[2.2.1]*heptane*-2-*one*-7-syn-*carboxylic acid* (XIV). Using procedure B, 19·4 mmol (2·98 g) of lactone XII was hydrolysed and then oxidized to ketoacid XIV. The crude dark solid was crystallized in acetone to yield 3·18 g (97%) of white plates: m.p. 207–209° (uncor.), [Lit.[6] m.p. 206–208°]; IR 1750 and 1700 cm^{-1} ($CHCl_3$).

5-Ketobicyclo[2.2.1]*heptane*-2-endo-3-endo-*dicarboxylic acid* (XVI). In an analogous manner 1·5 mmol (294 mg) of carboxylic acid lactone XV was oxidized to yield an oil which on crystallization with acetone–C_6H_6 gave 199 mg (68%) of XVI: m.p. 179–181° (uncor.), [Lit.[3] m.p. 182–184°].

3-Ketobicyclo[3.2.1]*octane*-6-endo-*carboxylic acid* (XVIII). A sample (26·3 mmol, 4·0 g) of 3-*endo*-hydroxybicyclo[3.2.1]octane-6-*endo*-carboxylic acid-δ-lactone XVII was oxidized according to procedure B. The resulting crude white solid was crystallized from acetone or $CHCl_3$ to give white plates; m.p. 179–180° (cor.) IR 1718 (both C=O) and 3500 (acid OH) cm^{-1} ($CHCl_3$), 1730 (ketone C=O) and 1685 (acid C=O) cm^{-1} (Nujol). (Calc. for $C_9H_{16}O_3$: C, 64·30; H, 7·15. Found: C, 64·39; H, 7·24%). DNP derivative: m.p. 235–236·5° (cor.). (Calc. for $C_{15}H_{16}O_6N_4$: C, 51·70; H, 4·65. Found: C, 51·80; H, 4·79%).

7-Keto-2-exo-acetoxybicyclo[2.2.1]*heptane*-5-exo-*carboxylic acid* (XX). As above 1. 13 mmol (242 mg) of acetoxylactone (XIX) was oxidized over 6 hr to yield a yellow oil. The oil was crystallized in ether–pentane to give 145 mg (60%) of crystals: m.p. 141–141·5° (uncor.); IR 1778 (ketone C=O), 1722 (ester C=O), 1706 (acid C=O) cm^{-1} ($CHCl_3$). (Calc. for $C_{10}H_{12}O_5$: C, 56·60; H, 5·70. Found: C, 56·84; H, 5·73%).

Methyl-3-endo-*hydroxybicyclo*[3.2.1]*octane*-6-endo-*carboxylate* (*Hydroxy ester derivative of* XV). To a solution containing 23·9 mmol of NaOH was added 8·13 mmol of lactone XV. The solution stood at room temp for 24 hr and was then titrated to its phenolphthalein endpoint with 15·39 mmol (15·39 ml of 1·0 N) of HCl. The 8·13 mmol of acid necessary to protonate the carboxylate salt was added to two 200 ml portions of EtOAc. The wet acidified EtOAc was used to extract the aqueous solution containing the carboxylate salt. After extraction the organic layers were combined, dried ($MgSO_4$), filtered, and cooled. An excess of freshly prepared CH_2N_2 was added to the cooled solution over a 10 min period. The EtOAc was removed at reduced pressure and at temperature between 30° and 40°. This yielded 1·40 g (94·5%) of yellow oil: IR 1725 and 3600 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) 4·0 (m, 1H, 3-*exo*-proton), 3·72 (s, 3H, Me), 3·05 (m, 2H); TLC showed presence of lactone XV besides a strong spot assumed to be the ester.

The crude oil (1·06 mmol) was dissolved in a solution of 2 ml of H_2O and 10 ml of acetone and stirred magnetically while 1·10 mmol (1·65 ml of 1N) CrO_3 was added dropwise over 5 min. After an additional 10 min isopropyl alcohol was added and most of the organic solvent was removed under reduced pressure. The remaining solution was extracted with three portions of ether. The extracts were combined and dried ($MgSO_4$) and the solvent was removed *in vacuo*. This yielded 0·160 g of a yellowish solid which was crystallized with acetone–pentane to yield white flakes which had physical properties identical to those of the lactone XV.

Note: The same general procedure and results were obtained for lactone XIII.

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