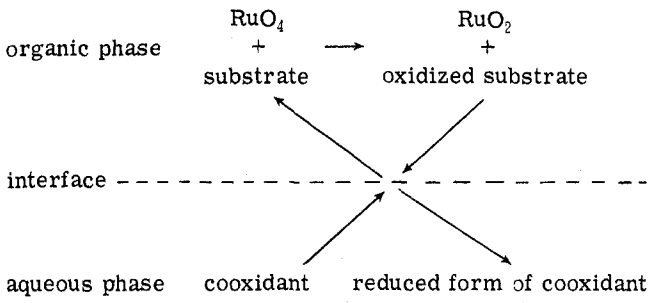
Table II
Relative Ratios for Reactions Involving Cycloalkanes

Reaction	Ring size 5	6	7	8
1. RuO_4 oxidation	1.5	1	2.5	8.7
2. Mn(VII) oxidation[b]	1.4	1	5.2	14.5
3. CrO_3 oxidation[c]	2.0	1	6.6	22.4
4. Acetolysis of tosylates[a,d]	14.0	1	25.3	191

[a] It has been proposed that these reactions proceed through carbonium ion intermediates. [b] Reference 10. [c] Reference 11. [d] Reference 9.

troxide by the cooxidant (which remains in the aqueous phase).

Scheme I



Consequently, it is likely that the organic substrates never come into direct contact with the cooxidant. The products (particularly if they are carboxylic acids) would, however, distribute between both phases and some second-stage oxidation could thus be the result of direct contact with the cooxidant. However, the fact that similar results were obtained when different cooxidants were used suggests that such reactions do not contribute significantly to the overall products obtained.

The results indicate that five- and six-membered rings have a greater tendency to undergo ring cleavage than the seven- and eight-membered rings. This may be due, at least in part, to the greater solubility of the corresponding cyclic ketones in aqueous solutions (where they would come into contact with cooxidant) or to the greater tendency for the smaller rings to undergo oxidative cleavage by ruthenium tetroxide. The reactions could be accelerated by working at a higher temperature, but because vigorous shaking is required to bring the two phases into contact, it is most convenient to work at room temperature. Despite the length of time required for a complete reaction, it would appear that this procedure compares favorably with other methods described in the literature for the oxidation of cyclic hydrocarbons.

Of particular interest is the observation that *trans*-decahydronaphthalene could be converted into *trans*-9-decahydronaphthol in about 60% yield. This suggests, as would be expected for an oxidative process, that tertiary carbon–hydrogen bonds are perferentially attacked.

In this work no solvent was used; however, an inert solvent such as carbon tetrachloride could be used if insufficient hydrocarbon was available.[7]

In a second series of experiments, the relative rates of reaction of cyclopentane, cyclohexane, cycloheptane, and cyclooctane were compared by subjecting all four compounds to oxidation under identical conditions and periodically determining the amount of unreduced cooxidant. In Table II, results of these experiments are described and compared with results that have been obtained from the oxidation of the same compounds by permanganate ion and hexavalent chromium. This comparison suggests that the mechanism is similar for all three oxidants and that the rate ratios are certainly different from those for the acetolysis of the corresponding tosylates. Since the latter reactions involve formation of carbonium ion intermediates,[8,9] it would appear that the oxidation reactions all proceed with homolytic carbon–hydrogen bond cleavage.

Acknowledgments. The authors are pleased to acknowledge the financial support of the National Research Council of Canada.

Registry No.—Ruthenium tetroxide, 20427-56-9.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXX. Griseofulvin[1]

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While the ^1H nuclear magnetic resonance spectra of griseofulvin (**1a**) and its derivatives have been known and used for some time[3,4,5] and their ^{13}C satellites exploited in an analysis of the path of ^{13}C-enriched acetate in griseofulvin biosynthesis,[6] no direct ^{13}C nuclear magnetic resonance data are available for this system. Accordingly a ^{13}C NMR investigation of the spirocyclic antibiotic and four of its derivatives, epigriseofulvin (**1b**), isogriseofulvin (**2a**), 4′-demethoxyisogriseofulvin (**2b**), and dehydrogriseofulvin (**3**), was undertaken.

Proton-decoupled and single-frequency, off-resonance decoupled spectra of compounds **1–3** in hexadeuteriodimethyl sulfoxide solution were recorded and the residual coupling information used for the differentiation of the various carbon types. The carbon shifts of the five compounds are listed in Table I.

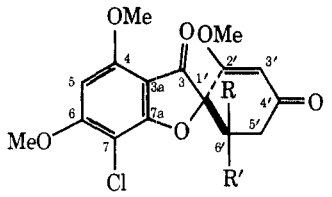
The *C*-methyl group is represented by the highest field signal in all spectra. The invariancy of the methyl shifts of the ring A methoxy groups permits assignment of the ring C methoxy shift by default. The ring A methoxy groups are distinguished from each other by the difference of the ef-

Table I
Carbon Chemical Shifts[a]

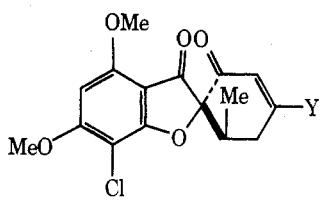
	1a	1b	2a[b]	2b	3
C(3)	191.2	192.3	190.3	189.4	188.0
C(3a)	104.1	105.1	104.0	103.8	103.5
C(4)	157.6	157.3	157.4	157.5	158.3
C(5)	91.2	91.2	90.8	91.1	91.7
C(6)	169.6	169.6	169.7	168.5	168.4
C(7)	95.3	95.6	95.1	95.1	95.8
C(7a)	164.5	164.2	164.0	164.1	164.8
C(1′)	90.1	89.4	94.3	95.1	88.2
C(2′)	170.3	167.9	188.0	189.4	167.5
C(3′)	104.7	105.8	99.2	125.8	103.5
C(4′)	195.6	195.7	178.8	154.1	185.6
C(5′)	39.5	40.1	32.3	30.6	128.9
C(6′)	35.4	34.2	34.3	36.1	146.8
Me	13.8	13.2	13.9	14.1	15.6
4-OMe	57.5	57.4	57.2	57.4	57.7
6-OMe	56.6	56.5	56.5	56.5	56.7
2′-OMe	57.1	56.8			56.7

[a] δ values in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [b] The 4′-OMe shift is 56.2 ppm.

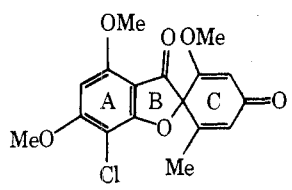
fect of *o*-chloro and *o*-acyl substituents. While ortho substituents have only a minimal influence on the methyl shift of ortho-substituted anisoles,[7] the similarity of the shift difference of the methyl groups of *o*-acetylanisole and *o*-chloroanisole in hexadeuteriodimethyl sulfoxide, depicted on formulas **4** and **5**, respectively, with that of the ring A methoxy groups of griseofulvin (**1a**) and its relatives points to the shifts of the latter methyl functions as designated.



1a, R = Me, R′ = H
b, R = H, R′ = Me



2a, Y = OMe
b, Y = H



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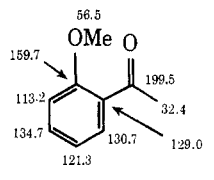

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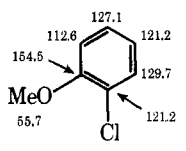

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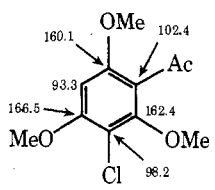
On the assumption of the carbonyl group of ring B being less affected by ring C changes than the ring C carbonyl group, carbon 3 can be assigned. The aromatic carbon shifts are derived from a calculated shift analysis of 3-chloro-2,4,6-trimethoxyacetophenone, an assumed model for ring A of the griseofulvin derivatives, based on the assumption that the additivity of individual substituent parameters holds even in a pentasubstituted aromatic system.[8] As the calculated shifts on formula **6** reveal, the δ values fall within 3 ppm of the experimental data for substances **1–3** despite the expected deviation from additivity



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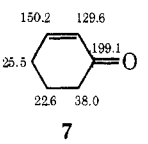

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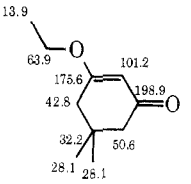

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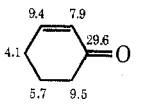
of substituent parameters within such a crowded ring system.

The tetrahedral ring C carbons of griseofulvin (**1a**), epigriseofulvin (**1b**), and isogriseofulvin (**2a**) are each unique in multiplicity and thus readily assigned. This is true also for the ring C, saturated carbons of compound **2b**, while the δ values of its ring C, trigonal carbons are based on those of the related centers in 2-cyclohexenone (**7**). Carbon 1′ is the sole ring C, nontrigonal site of dehydrogriseofulvin (**3**) and its C(5′) and C(6′) can be differentiated from the other, ring C olefinic centers by the difference of α and β effects of methyl and methoxy groups[8] and by the invariance of the C(3′) shift in **1a**, **1b**, **2a**, and **3**. Unambiguous shift assignment of C(2′) and C(4′) in these four substances requires a model study.

While a keto carbon can be expected to be downfield from an unsaturated, nonprotonated oxy carbon, even if the latter is β to the keto carbon and part of an α,β-unsaturated ketone system, this spectral relationship requires on examination of the C(2′) and C(4′) shifts of griseofulvin (**1a**) and isogriseofulvin (**2a**) that the C(1′) substituents exert a strongly shielding influence on C(2′). Since this is a most unusual β effect, verification of the C(2′) and C(4′) shift assignment is mandatory.[9] A ^{13}C NMR study of 5,5-dimethyl-3-ethoxy-2-cyclohexenone (dimedone ethyl ether) (**8**) including a $Eu(DPM)_3$ shift analysis was undertaken and paralleled by a similar investigation of 2-cyclohexenone (**7**)[11] in order to discount the effect of an europium contact shift component on the chemical shift difference of the carbonyl carbon.[12] The Δ_{Eu} values[12] of 2-cyclohexenone and the dimedone derivative, denoted on formulas **9** and **10**, respectively, verify the shift data indicated on



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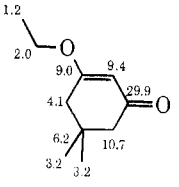

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7 and **8**, respectively, and, in turn, corroborate the initial view on the shifts of C(2′) and C(4′) of **1a**, **1b**, **2a**, and **3**.

Inversion of the ring C methoxyenone chromophore, i.e., comparison of **1a** or **1b** with **2a**, changes the C(5′) shift by ca. 7.5 ppm, a Δδ value similar to that of C(4) and C(6) of the dimedone derivative **8**. The same effect is dampened strongly in the heavily substituted C(1′). Introduction of a double bond in conjugation with an even already conjugated ketone, i.e., the **1a** or **1b** → **3** change, strongly shields the carbonyl group. Since the methyl group of griseofulvin (**1a**) is known to be equatorially oriented[5] and since the methyl and C(6′) shifts of the antibiotic and epigriseofulvin (**1b**) are similar, the latter probably also possesses an equatorial methyl substituent.

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian DP-60 spectrometer operating at 15.08 MHz in the Fourier transform mode. The δ values denoted on formulas **7** and **8** and the Δ_{Eu} values listed on **9** and **10** are for 0.5 *M* deuteriochloroform solutions [$\delta(Me_4Si)$ =

$\delta(CDCl_3)$ + 76.9 ppm]. The Δ_{Eu} values are $\Delta\delta$ values obtained by extrapolation to 1:1 molar ratio of ketone to $Eu(DPM)_3$ agent.

Registry No.—**1a**, 126-07-8; **1b**, 469-49-8; **2a**, 469-52-3; **2b**, 55658-69-0; **3**, 3573-90-8.

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Benzonorbornene-*endo*-2-carboxylic Acid and Its Methyl Ester[1]

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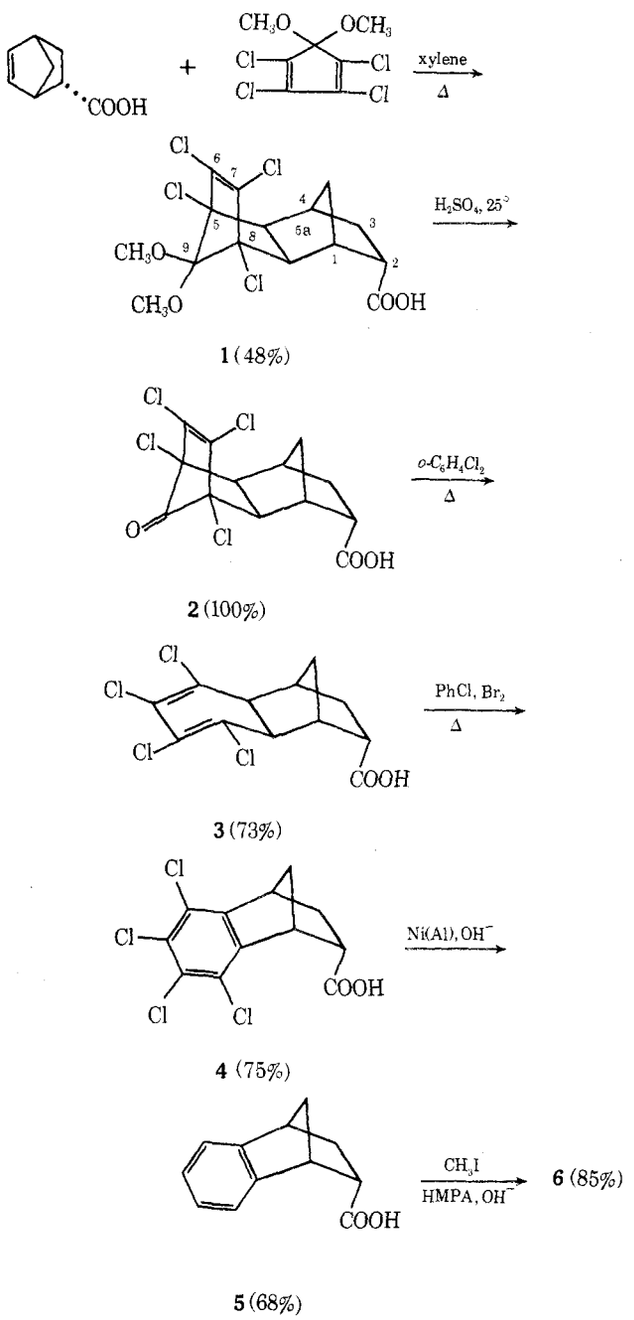
A need to confirm the structure of methyl benzonorbornene-*endo*-2-carboxylate (**6**) isolated in another study[2] led to the synthesis given in Scheme I. The sequence mirrors that used[3] to prepare the 1-carboxylic acid analog of **5** and requires no further discussion. However, the present use of the sequence involved an epimerizable acid function, in contrast to that earlier. The clean retention of configuration observed in **5** and **6**, with no trace of their exo epimers (both known[4]), shows that the sequence could have value as a general synthesis of ac-substituted benzonorbornenes of known stereochemistry, where ac = alicyclic in contrast to ar = aromatic.

Acid **5** was apparently unreported previous to our studies. However, two processes potentially capable of its synthesis have been reported. In the first, an ethyl ester possibly related to **6** was reported by Alder and Fremery,[5] but we have been unable to obtain **6** by their method (adduction of isoindene in situ with an acrylic ester). In the second, carbonation of the Grignard reagent obtained from *exo*-2-bromobenzonorbornene yielded only the exo 2 acid.[4]

Experimental Section

Melting points were taken on a calibrated Fisher-Johns block. Infrared spectra (ir) were determined on 1% KBr disks using a Perkin-Elmer Model 700 instrument. Only prominent or structurally significant absorptions are given (in microns). Nuclear magnetic resonance spectra (NMR) were taken in Me_2SO-d_6 solvent on a Varian A-60A spectrometer. Values are given in parts per million (δ) downfield from internal Me_4Si. Integration of signals agreed with the structural assignments. Mass spectra were taken on a Varian EM-600 instrument at 70 eV. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill.

Scheme I



5,6,7,8-Tetrachloro-9,9-dimethoxy-1,4:5,8-dimethano-1,2,3,4,5,5a,8,8a-octahydronaphthalene-*endo*-2-carboxylic Acid (1). A mixture of 5,5-dimethoxytetrachlorocyclopentadiene[6] (80.8 g, 0.306 mol) and norbornene-*endo*-2-carboxylic acid[7] (38.6 g, 0.263 mol) was refluxed in commercial xylene (150 ml) for 30 hr. Hexane (50 ml) was added and the solution was allowed to stand overnight. The precipitated material was collected and combined with some further material obtained by another treatment with hexane (100 ml): 53.5 g, 47.7%; mp 175–180°; ir 3.00–4.50, 5.88 (COOH), 6.24, 7.04, 7.69, 8.00, 8.40, 8.87, 9.52, 9.92, 10.38, 11.06, 13.15 μm; the compound was not soluble enough in the usual solvents to take a meaningful NMR spectrum. The analytical sample was obtained by recrystallization from xylene, mp 214–215°.

Anal. Calcd for $C_{15}H_{16}O_4Cl_4$: C, 44.80; H, 4.01. Found: C, 44.60; H, 4.01.

5,6,7,8-Tetrachloro-1,4-methano-1,2,3,4,5,5a,8,8a-octahydronaphthalene-*endo*-2-carboxylic Acid (3). Crude acid **1** (53.4 g, 0.133 mol) was added to concentrated sulfuric acid (250 ml) and stirred at 25° for 2 hr. The mixture then was poured over ice (625 g, the ratio of ice to sulfuric acid is critical, otherwise an oil results), stirred briefly, and filtered immediately. The solid so collected was crude keto acid **2** (47.3 g, quantitative yield) which was