Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Polycyclic δ-Lactones

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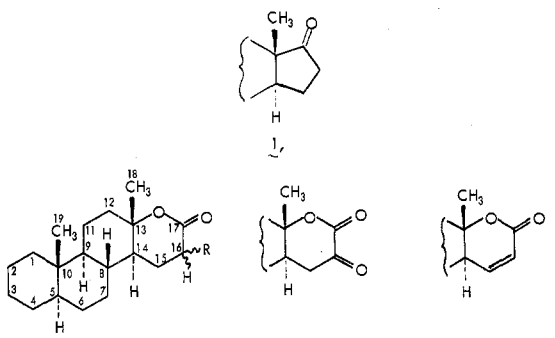
The ^{13}C NMR spectra of the steroidal and terpenoid δ-lactones, deoxyandrololactone and its C-16 epimeric acetoxy and hydroxy derivatives, and ambreinolide and its C-12 epimeric acetoxy derivatives, as well as their corresponding α,β-unsaturated derivatives, have been obtained by the Fourier transform technique at 25.03 MHz. The spectra are analyzed in terms of earlier investigations in the steroid and terpene series, using empirical correlations and single frequency off-resonance decoupling experiments. On the basis of chemical shift data, two conformations, the half-chair and twisted boat, may be proposed for the cited β- and α-oriented α-oxy-substituted δ-lactones, respectively.

Polycyclic natural products frequently contain a δ-lactone ring whose structural features sometimes remain insufficiently clarified. Although ^{13}C NMR spectroscopy is a powerful method for structural analysis, no systematic study of lactones by this method has yet been reported; however, the recent work by Carrol et al.[1] on the configuration and conformation of 3,5-dimethyl valerolactones has provided valuable spectral data for simple versions of such systems. Our earlier interest in δ-lactones[2,3] resulted in the preparation of a number of structurally related compounds which provided an opportunity to obtain basic information on factors affecting the chemical shift of carbons in lactones of more complex and rigid structure.

The assignment of individual resonances in compounds **1–4** (Table I) was made on the basis of earlier investigations in the steroid series,[4] empirical correlations, and single frequency off-resonance decoupling experiments.[5] As expected, the modification of ring D to a six-membered lactone ring does not alter the chemical shift of remote carbons (C-1 to C-6, C-10, C-11) relative to those in the parent steroid 5α-androstane derivative (**1**). The remaining carbons outside the lactone ring (C-7, C-8, C-9, and C-12) suffer minor changes of position of their respective resonances. As a consequence of ring D enlargement, C-7 is shifted upfield (1.1 ppm), probably from introduction of a new γ-H···H interaction[6] with the hydrogen at C-15. The same modification of ring D produces a decrease of steric interaction between the angular C-18 methyl group and axial hydrogen at C-8 and, therefore, must be partly responsible for the downfield shift of its resonance. Finally, the upfield shift of the highly hindered C-9 could not be attributed to any specific interaction but rather reflects a minor overall change in environment.

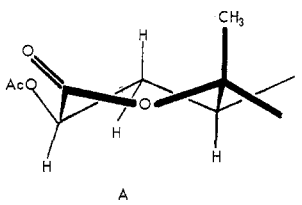


2a, R = H
b, R = β-OAc
c, R = α-OAc
d, R = β-OH
e, R = α-OH

The assignment of lactone ring carbons (C-13 to C-17) was easily achieved by empirical correlations throughout the series and by sford techniques; the recorded resonances are within the limits predicted by the chemical shift theory. The relatively high upfield position of both the C-17 carbonyl carbon and the C-16 α-methylene carbon in **2a** (C-13 and C-12 in **5a**, respectively) confirm the assumption that factors affecting the chemical shift of lactone ring carbons differ substantially from those determining the shielding of carbons in the corresponding cycloanones.[7]

The chemical shifts of carbons 14, 15, and 16 in the acetoxylated steroidal ring D lactones are interesting and may have some bearing on the conformation of the δ-lactone ring. First, it can be observed that the carbinyl carbon shieldings (C-16) in **2b** and **2c** reflect the configurational difference, as expected for different contributions of quasi-equatorial and quasi-axial acetoxy groups, respectively (Δδ 3.0 ppm).[9] The striking feature of the data is the magnitude of downfield shifts of neighboring C-15 carbons, which are not concomitant with recognized β effects of such isomeric acetoxy groups in chairlike conformations,[4a,10] the deshielding difference found being in favor of the quasi-axial epimer (Δδ 2.3 ppm). These seemingly contradictory findings, particularly in view of the absence of any γ effect at C-14 in either of the acetoxy epimers, can be accommodated by assuming different conformations for the two lactones **2b** and **2c**. Based on the earlier proposed coplanarity of the ethereal oxygen, the carbonyl group, and the two adjacent carbons,[8] two conformations may be proposed for lactones **2b** and **2c**, the half-chair A and the twisted boat B, respectively.

The proposed conformations A and B explain why introduction of an acetoxy group at C-16 does not result in a significant shielding γ effect at C-14 in either of the epimers **2b** or **2c**, relative to the unsubstituted lactone **2a**. Further-



A
2b, and 5b

Table I. Carbon-13 Chemical Shifts and Assignments for Steroidal δ-Lactones[a]

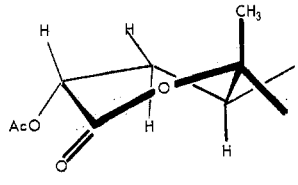
Carbon	1	2a	2b	2c	2d	2e	3	4
1	38.7	38.4	38.4	38.5	38.4	38.3	38.5*	38.4
2	22.1†	22.0	22.0	21.9	21.9	21.9	21.9	22.0
3	26.8	26.6	26.7‡	26.6	26.6	26.5	26.5	26.6
4	29.0*	28.7	28.7†	28.5	28.5*	28.6	28.4†	28.7*
5	47.0	46.4	46.3*	46.3	46.3	46.3	46.3	46.7
6	28.8*	28.7	28.5†	28.5	28.5*	28.6	28.6†	28.5*
7	31.7	30.6	30.6	30.5	30.7	30.7	30.2	30.4
8	35.1	37.9	37.2	38.5	37.1	38.6	38.5	35.2
9	54.9	53.5	53.4	53.2	53.5	53.0	52.8	54.2
10	36.4	36.2	36.2	36.2	36.2	36.1	36.2	36.4
11	21.8†	21.6	21.6	21.6	21.6	21.6	21.6	21.5
12	31.0	39.4	38.9	39.5	38.8	39.4	38.8*	38.4
13	47.7	83.1	85.4	84.4	86.3	85.1	84.7	83.3
14	51.6	46.4	46.7*	46.3	46.3	46.3	45.8	48.6
15	20.1	19.8	26.8‡	29.1	28.2*	30.5	38.1	145.4
16	35.8	28.7	68.6	65.6	68.3	64.5	190.3	121.6
17	220.7	170.9	168.5	168.3	174.8	174.8	157.4	163.7
18	13.8	20.1	20.7	19.5	21.1	19.3	20.6	18.5
19	12.2	12.0	12.0	12.0	12.1	12.0	12.0	12.0

[a] In parts per million downfield relative to Me_4Si. Solvent deuteriochloroform. The two carbon resonances at the acyl groups of **2b** and **2c** occur at 169.5 and 20.7 ppm. *,†,‡ Values within any vertical column may be interchanged.

Table II. Carbon-13 Chemical Shifts and Assignments for Terpenoid δ-Lactones[a]

Carbon	5a	5b	5c	6
1	39.2	39.3	38.8	38.6
2	18.4	18.4	18.2	18.1
3	41.8	41.8	41.7*	41.8
4	33.2	33.3	33.1	33.1
5	56.0	56.0	55.8	56.1
6	19.7	19.8	19.6	19.7
7	41.3	40.8	41.4*	39.8
8	83.5	85.8	84.9	84.0
9	53.7	53.5	53.1	55.4
10	37.2	37.4	37.3	36.5
11	15.8	24.0	24.6	145.4
12	29.0	69.1	65.5	122.2
13	171.2	168.5	168.4	163.9
17	22.9	23.5	22.7	21.0
18	33.3	33.3	33.3	33.1
19	21.5	21.3	21.5	21.4
20	15.1	15.7	14.4	17.0

[a] In parts per million downfield relative to Me_4Si. Solvent deuteriochloroform. The two carbon resonances of the acyl groups of **5b** and **5c** occur at 169.6 and 20.7 ppm. * Values within any vertical column may be interchanged.



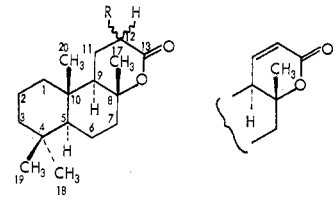
B

2c, and 5c

more, the twisted boat conformation B allows a substantial decrease in the C-18 methyl group eclipsing effect[11] at C-15, thus accounting for its greater relative deshielding in epimer **2c.** Finally, the greater shielding of the C-16 carbinyl carbon in lactone **2c** may be attributed to the eclipsing effect of the C-18 methyl group, i.e., to a greater steric congestion in the twisted boat form B. It should be noted that a similar conformational relationship for pairs of epimeric steroidal α-acetoxy ketones was proposed earlier by Johnson et al. on the basis of their proton NMR spectral data.[12]

The chemical shift of carbons in hydroxy lactones **2d** and **2e** follows the same general pattern, complementing both the assignments and the above arguments, the same being true for the remaining compounds **3** and **4** of the steroid series. However, the substituent-dependent variation of the C-17 lactone carbonyl carbon shielding over a range of ~17 ppm (Table I) should be noted. Although the interpretation of the apparent trend based solely on the electron-releasing properties of neighboring substituents is oversimplified, it seems still useful for a qualitative assessment of the degree of the carbonyl π-bond polarization toward oxygen.

The analysis of the terpene series (compounds **5–6,** Table II) was made on the basis of similar methods and also by correlation with relevant model systems such as the pimaradienes,[13] 9-methyldecalins, and perhydrophenanthrenes.[14] The results are in good agreement with those of



5a, R = H
b, R = β-OAc
c, R = α-OAc

6

the steroidal lactones. Again, introduction of an acetoxy group into the lactone ring (epimers **5b** and **5c**) does not lead to an upfield shift of the carbon in the γ position (C-9), indicating the same substituent-dependent conformational selectivity in α-acetoxylated δ-lactones, i.e., conformations A and B for lactones **5b** and **5c,** respectively. The conformational difference, however, between epimers **5b** and **5c** results in a reduced impact on the deshielding of C-11 in the latter when compared with the chemical shift difference of the corresponding C-15 carbon in the epimeric steroidal lactones **2b** and **2c.** The reduced deshielding of the C-11 carbon[11] neighboring the carbinyl carbon in **5c** is probably a result of the increased eclipsing effect of the C-20 methyl group. Thus, decreasing the C-17 methyl group eclipsing effect at C-11 through the twisted conformation B of **5c** is being partially replaced by this new inter-

action, the assumption being supported by an upfield shift of C-20 in **5c** by 1.3 ppm.

This initial effort in ^{13}C NMR analysis of complex lactone systems has supplied some rather interesting data; more basic information, particularly that pertaining to electric field effects in α-oxygenated carbonyl compounds, is needed before any generalizations can be drawn.

Experimental Section

Carbon-13 spectra were determined at 25.03 MHz in the Fourier mode using a JEOL-PFT-100 spectrometer in conjunction with an EC-100 20K memory computer. The spectrometer features a deuterium lock system, a JNM-SD-HC random noise (2500-Hz bandwidth) proton decoupler, and JNM-DP-1 digital pulse programmer. Spectra of the compounds were determined in ~0.5 M deuteriochloroform solution (which also provided the lock signal) with 5% Me_4Si added as internal reference. All samples were contained in precision ground 10 mm o.d. tubes. The spectrometer was used in the crosscoil configuration. On the average, a 12-μs pulse, corresponding to an approximate tilt angle of 45°, was employed. For the average spectral width of 5000 Hz the delay between pulses was 3 s.

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Registry No.—**1**, 963-74-6; **2a**, 2466-25-3; **2b**, 42516-17-6; **2c**, 42516-18-7; **2d**, 42516-15-4; **2e**, 42516-16-5; **3**, 42516-19-8; **4**, 57901-22-1; **5a**, 468-84-8; **5b**, 54632-03-0; **5c**, 54656-75-6; **6**, 52811-58-2.

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Synthesis and Characterization of Some Polycyclic Cyclobutanones

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A new stereospecific synthesis of 2,3-cis fused polycyclic cyclobutanone derivatives from readily available starting materials is described. The technique provides a valuable compliment to the use of dichloroketene in that it can be run on a large scale, makes efficient use of reagents, and in a number of cases (e.g., **16** and **22**) gives much higher yields of the ketone than the former technique. In addition, the complimentary endo isomers **18**, **20**, **24**, and **26** are formed in cases where dichloroketene has been demonstrated or predicted to occur stereospecifically to produce the exo isomers. The ultraviolet spectra of the ketones have been examined for evidence of nonconjugated chromophore interaction. The exo unsaturated derivative **22** shows a strong intensification of the $n \rightarrow \pi^*$ transition most reasonably described in terms of a geometric dependent interaction between the π orbitals of the double bond and those of the carbonyl group via the exo σ bond α to the carbonyl group.

The synthesis of fused ring and polycyclic cyclobutanones in preparatively useful yields has been a difficult problem. The most commonly used techniques have involved the thermal cycloaddition of ketene and alkyl and aryl substituted derivatives to olefins and dienes to yield cyclobutanones directly.[1] This technique has suffered from a lack of generality, and difficulty in large-scale preparations. The latter has been particularly obvious in cycloadditions involving ketene itself. The discovery that the highly reactive intermediate, dichloroketene, could be generated in situ and trapped by olefins and dienes has surmounted some of these difficulties.[2] This novel reagent allows the preparation of many cyclobutanone derivatives in good yield and exhibits high regio- and stereospecificity. Still some difficulties remain even with this reagent. For example, certain olefins and dienes give rather low yields of cycloaddition products[3] and with unreactive reagents, a relatively large excess of the ketenophile is generally necessary to produce useful quantities of product. Ironically, even the regio- and stereospecificity of the reagent can be a disadvantage if the isomeric derivative is the one desired. We have sought a reaction sequence which (1) makes efficient use of scarce reagents, (2) produces cyclobutanones in good yields where the dichloroketene method does not, and (3) is stereospecific but in a complimentary sense to dichloroketene. This paper describes a technique for the large-scale, stereospecific, and high-yield preparation of a number of fused ring and polycyclic cyclobutanones from readily available starting materials. The overall synthetic sequence is described in Scheme I.

Results and Discussion

The first step in the sequence involves the acyloin condensation of the corresponding diesters using the basic technique described by Bloomfield.[4] All of the acyloin condensations went smoothly and in good yield in spite of a potential complicating factor of having a strained double bond in close proximity to the reactive centers in **3**, **9**, and