Effect of Polar Attraction on the Equilibria of Rigid Tetracyclic Hemiacetals

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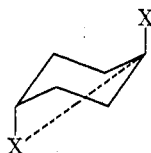
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Tetracylic hemiacetals 14–24 were synthesized and their isomeric equilibria in DMSO-d_6 at 50° were studied by nmr techniques. Substitution of polar groups at the C_9-exo position caused the equilibrium to shift toward the lesser stable β isomer. This shift is interpreted on the basis of a stabilization of the β isomer through polar attraction between the electropositive carbon, C_9, and the electronegative oxygen of the nearby hydroxyl group. Halogen or mesyl substituents at C_9 cause a stabilization of 0.4–0.5 kcal/mol while hydroxyl imparts about 0.2-kcal/mol stabilization. These results are significant in understanding the forces responsible for hemiacetal and conformational equilibria.

Recent evidence has clearly shown that the position of conformational equilibria of pyranose derivatives and multisubstituted cyclohexanes cannot be predicted reliably on the basis of additive conformational free energies and anomeric effects. Pyranose derivatives substituted at C_1 with negative substituents, such as acetate, benzoate, and especially halogen, invariably prefer that conformation in which the C_1 substituent is axial, regardless of the fact that this often forces substituents at the other positions into axial conformations.[1-3] An extreme situation is encountered in the case of tri-O-acetyl- and tri-O-benzoyl-β-D-xylopyranosyl chloride, which at equilibrium contains 80 and 98%, respectively, of the *1C* conformer in which the three acetate (benzoate) groups, as well as the chlorine at C_1, are all axial.[3] According to Durette and Horton,[3] this would not have been predicted on the basis of conformational free energies[4,5] and the anomeric effect of the chloro group.[6]

In the case of trifluoroacetoxycyclohexane the equilibrium is 80% in favor of the equatorial conformer, but, with two such substituents situated 1,4-trans, the equilibrium is only 55% in favor of the diequatorial conformer.[7] Stabilization of the diaxial conformer through polar attraction between an electropositive carbon and the electronegative substituent at the C_4 axial position as shown was suggested to account for this phenomenon.[7] The substantial stability of diaxial conformers of trans-1,2 and trans-1,4 disubstituted cyclohexanes is further confirmation of the complexity of the interactions involved.[8] Under circumstances where several interacting groups are present, predic-

tions of the conformational preferences become hazardous.

It is the purpose of this paper to present equilibria studies of hemiacetals of some rigid tetracyclic ring systems in which the stereochemistry and the polar interactions are strictly controlled. These results will then be interpreted to indicate the magnitude of the polar forces between a halogen substituted carbon and an electronegative hemiacetal hydroxyl group. With appropriate corrections for the distances involved in the interactions it is suggested that these results provide a further parameter for predicting, or justifying, the position of hemiacetal and conformational equilibria.

Results

Synthesis and Characterization of Tetracyclic Lactones.—Trichloromethyl lactols **1** and **2** were starting materials for the preparation of lactones **3–13**. Lac-

3, X = H	**9**, X = H
4, X = Cl	**10**, X = Cl
5, X = Br	**11**, X = Br
6, X = I	**12**, X = I
7, X = OH	**13**, X = OH
8, X = OMs	

tols **1** and **2** were prepared through the reaction of sodium trichloroacetate with the Diels–Alder adducts of cyclopentadiene and 1,3-cyclohexadiene with maleic anhydride.[9,10]

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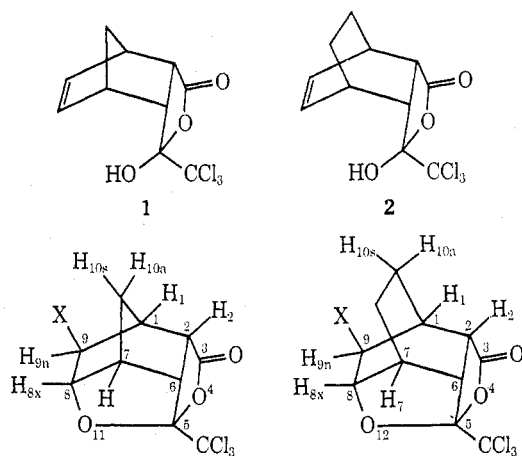(7) G. Wood, E. P. Woo, and M. H. Miskow, *Can. J. Chem.*, **47**, 426 (1969).

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Lactones **3** and **9** were prepared by a reaction of the lactols **1** and **2** with concentrated sulfuric acid as reported previously for the synthesis of lactone **3**.[11] The 9-halo lactones **4–6**, reported previously,[12] and **10–12** were prepared by the reactions of lactols **1** and **2** with the appropriate halogen in aqueous sodium carbonate in the presence of the corresponding potassium halide. The 9-hydroxy lactones **7**[12] and **13** were prepared by treatment of lactols **1** and **2** with peracetic acid. The mesyl lactone **8** was prepared from hydroxy lactone **7** by treatment with methanesulfonyl chloride in pyridine.

Significant nmr lines for lactones **3–13** are reported in Table I. Chemical shifts and coupling assignments

14, X = H
15, X = Cl
16, X = Br
17, X = I
18, X = OH
19, X = OMs

20, X = H
21, X = Cl
22, X = Br
23, X = I
24, X = OH

TABLE I

NMR DATA FOR TETRACYCLIC LACTONES

| Compd	Solvent	Chemical shifts, τ		Coupling constants, Hz		
		H_{8x}	H_{9n} (multiplicities)	$J_{7,8x}$	$J_{9n,10}$	$J_{1,9n}$
3	DMSO-d_6	5.10 (m)	a			
4	DMSO-d_6	5.10 (d)	5.98 (d)	5.0	2.5	
5	DMSO-d_6	4.91 (d)	5.95 (d)	5.0	2.5	
6	DMSO-d_6	4.78 (d)	6.04 (d)	5.0	2.5	
7	DMSO-d_6	5.57 (d)		5.0		
8	DMSO-d_6	5.02 (d)	5.51 (s)	5.0		
9	CDCl$_3$	5.35 (t)	a	5.0		
10	CDCl$_3$	5.45 (d)	5.82 (d)	5.0		4.0
11	CDCl$_3$	5.22 (d)	5.73 (d)	5.0		4.0
12	CDCl$_3$	5.01 (d)	5.62 (d)	5.0		4.0
13	CDCl$_3$	5.70 (d)	5.94 (d)	5.0		4.0

a Concealed in upfield multiplet.

of Table I are based in part upon a detailed nmr analysis of a structure closely analogous to the present series.[13] For lactones **4–8** and **10–13**, the H_{8x} protons are clearly evident as doublets ($J = 5$ Hz) coupled with the bridgehead protons H_7. The failure to observe coupling between H_{8x} and H_{9n} can reasonably be attributed to a dihedral angle close to 90°, caused by distortion of the bicyclic ring by the oxygen bridge. Similar lack of coupling of vicinal trans protons has been reported for other strained cyclic and bicyclic systems.[13,14] For lactones **4**, **5**, and **6**, H_{9n} appears as doublets ($J = 2.5$ Hz) through W coupling[15] with H_{10a}. For lactones **10–13** H_{9n} also appears as doublets of $J = 4$ Hz, which is a somewhat larger value than is ordinarily observed in W coupling. Examination of molecular models reveals that the dihedral angle between H_{9n} and H_1 changes from about 80° for the bicyclo[2.2.1]heptane series to about 50° for the bicyclo[2.2.2]octane series **9–13**. Hence, in the case of lactones **9–13**, it would seem more reasonable to assign the source of these doublets to coupling between the H_{9n} and H_1 rather than to W coupling with H_{10a}.

Synthesis, Characterization, and Equilibration of the Tetracyclo Hemiacetals.—The tetracyclic lactones were smoothly converted into the corresponding hemiacetals **14–24** by reduction with sodium borohydride. Even
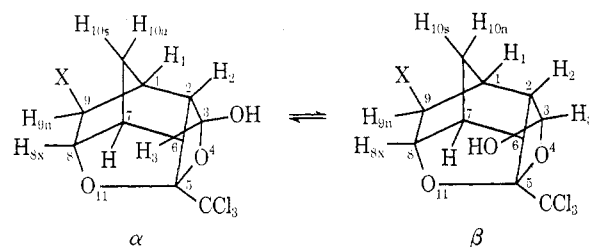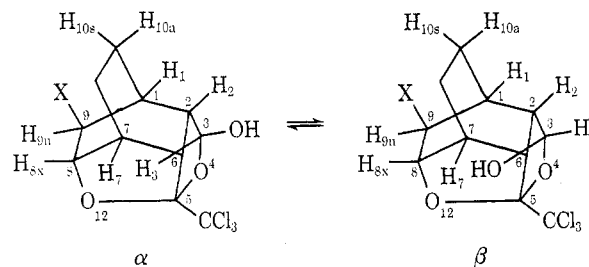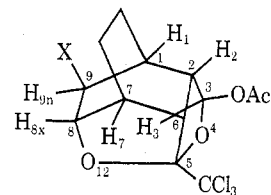
though excess sodium borohydride was often used, opening of the cyclic hemiacetal with further reduction of the aldehyde was never observed. The acetates **25** and **26** were prepared from hemiacetal **20** and **21** by treatment with acetic anhydride in pyridine.

25, X = H
26, X = Cl

The α–β equilibria of hemiacetals **14–24** are clearly revealed by their nmr spectra using DMSO-d_6 as solvent. Although the equilibria could also be detected using pyridine-d_5 and other solvents, DMSO-d_6 was the ideal choice, not only because of the good solubility of the compounds, but also because the C$_3$ hydroxyl protons appear far downfield and exhibit good splitting patterns.[16–18] The most significant feature is the doublet–triplet combination shown schematically in Figure 1 and listed in detail for each hemiacetal in Table II. Acetates **25** and **26**, which do not undergo equilibration, are also included in the table for comparison.

The origin of these lines and their assignments to particular protons of the two isomeric hemiacetals can

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TABLE II

NMR DATA FOR TETRACYCLIC HEMIACETALS AND
DERIVATIVES IN DMSO-d_6

Compd	OH-β (d)	OH-α (d)	H$_3$-β (t)	H$_3$-α (d)
	Chemical shift, τ^a			
14	2.90	3.34	4.33	4.58
15	2.48	3.12	4.30	4.37
16	2.49	3.11	4.33	4.38
17	2.51	3.14	4.35	4.38
18	2.76	3.27	4.37	4.52
19	2.47	3.07	4.31	4.32
20	3.00	3.45	4.38	4.70
21	2.47	3.13	4.32	4.46
22	2.51	3.19	4.31	4.46
23	2.51	3.18	4.31	4.52
24	2.86	3.41	4.42	4.65
25				3.86[b]
26				3.66[b]

^{a} Coupling constants, $J(\text{OH},\text{H}_3) = 5$ Hz; $J(\text{H}_3,\text{H}_2) = 5$ Hz. ^{b} Singlet.

Figure 1.—General appearance of the downfield nmr lines of hemiacetals 14–24.

be established by area ratios, spin decoupling, and splitting patterns. The two isomers have been arbitrarily designated α and β as shown in the structural drawings for compounds 14–26. Referring to Figure 1, integration of the lines revealed that, in those cases in which the upfield triplet–doublet pair was sufficintly separated for measurement, the areas of A were always equivalent to the areas of C. Similarly, the areas B and D were always equivalent. In every case the total area of A and B was the same as the total area of C and D. These results indicate that lines A and C arise from one of the two isomers, while B and D are from the other. This idea was confirmed by spin decoupling. Irradiation of the doublet A caused triplet C to collapse to a doublet, while irradiation of triplet C caused doublet A to become a singlet. Similarly, irradiation of either of the doublets B or D caused the other to collapse to a singlet.

The lines can be assigned to a particular isomer, α or β, by analysis of the splitting pattern. The C$_3$-OH protons appear as doublets in both isomers as a result of coupling with H$_3$. Protons H$_3$ are correspondingly split by the OH protons. In the case of the β isomer, H$_3$ is again split by H$_2$, giving rise to the triplet C. For the α isomer, further splitting by H$_2$ is at a minimum due to a dihedral angle close to 90°. Hence, H$_3$ for the α isomer appears only as the doublet. Thus, doublet A and triplet C (Figure 1) arise respectively from the OH proton and H$_3$ of the β isomer, while doublets B and D are from the corresponding protons of the α isomer. For acetates 25 and 26, which cannot undergo equilibration, only singlets were observed for H$_3$, characteristic of the α form. Only the α isomers of acetates 25 and 26 were ever isolated in the preparation. The β isomers, if they formed at all, were in low concentration and were not detected.

The presence of two isomeric hemiacetals in solution is undoubtedly a result of equilibration *after* formation of the hemiacetal by sodium borohydride reduction. Reduction by borohydride, being a kinetically controlled process, would be expected to occur by an approach of the reagent from the less hindered, convex, face of the tetracyclic lactone to form exclusively the β isomer as the kinetic product. Equilibration would normally be expected to occur during the isolation and purification procedures. If the conditions of the re-
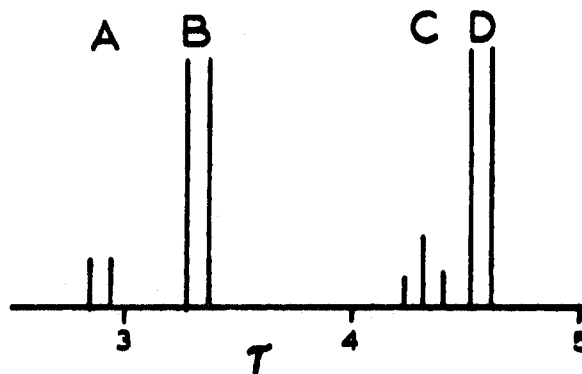
duction and the isolation of the product are carefully controlled, a single isomer can be obtained. The pure β isomer of 19 was prepared by reduction of the lactone 8 in dioxane at 0°. Recrystallization from nonprotonic solvents at low temperatures produced a product, the nmr spectrum of which exhibited only the doublet–triplet combination of the β isomer. After 10 min at ambient temperatures (37°) in the nmr spectrometer the spectrum was still unchanged, indicating that under these conditions equilibration is reasonably slow. After heating the same sample for 10 min at 50° in the nmr tube the pair of doublets characteristic of the α isomer had appeared.

A pure α isomer was also isolated by slow crystallization of hemiacetal 16 over a period of 2 months. The initial nmr spectrum of a sample of this material showed only the pair of doublets of the α isomer, but, after heating at 50°, lines for both isomers were then present.

The hemiacetals 14–24 were allowed to equilibrate in DMSO-d_6 at 50° and the nmr spectra were recorded periodically at ambient temperatures (37°) until no further changes in the line intensities could be noted (about 72 hr). The relative concentrations of the isomers were measured by integration of the sharp, well-resolved OH doublets (lines A and B in Figure 1). Each spectrum was integrated five times and the average values were taken. Deviations from the average were not greater than ±5%. The equilibrium constants and the $\Delta G°$ values at 50° are reported in Table III.

TABLE III

EQUILIBRIUM CONSTANTS AND FREE ENERGY VALUES FOR THE
α–β EQUILIBRIA OF HEMIACETALS
AT 50° IN DMSO-d_6

Compd	X	$K_{eq}{}^a$	$\Delta G°$, kcal/mol
14	H	0.23	0.97
15	Cl	0.58	0.36
16	Br	0.67	0.25
17	I	0.61	0.34
18	OH	0.30	0.75
19	OMs	0.63	0.29
20	H	0.38	0.62
21	Cl	0.85	0.10
22	Br	0.88	0.08
23	I	0.84	0.11
24	OH	0.52	0.42

^{a} $K_{eq} = [\beta]/[\alpha]$.
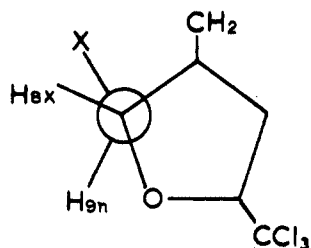
Figure 2.—Newman projection of the tetracyclic system showing the conformation about C_8 and C_9.

Figure 3.—Conformations of α and β isomers of tetracyclic hemiacetals.

Discussion

Equilibria and thermodynamic data, Table III, clearly reveal that in every case the position of the α–β equilibrium is in favor of the α isomer. This is understandable since it is in this form that the C_3 hydroxyl group is directed away from the ring toward an area of relatively lower steric crowding. The position of the equilibrium, however, varies appreciably with the nature of the substituent at the C_9-exo site. Taking compounds **14** and **20** (X = H) as the standard, the β isomers show a marked increase in stability when X is changed to halogen or O-mesyl. A considerable, but somewhat lesser stability, is imparted to the β isomer by the hydroxyl group at C_9-exo. To arrive at a reasonable interpretation of these results requires a consideration of both steric and electronic factors.

The presence of bulky groups at the C_9-exo position should have little effect on the steric environment of the C_3 hydroxyl group of the β isomer. The lack of coupling between H_{8x} and H_{9n} indicates that the corresponding dihedral angle approaches $90°$.[12–14] This would mean that the C_9-exo substituent is directed upward and situated in a slightly staggered conformation with respect to the H_{8x} substituents, Figure 2. Rotation about the C_8–C_9 bond in the other direction is not only sterically unfavorable due to the rigidity of the tetracyclic ring system, but is also contrary to the nmr results. If this were the case, the dihedral angle between H_{8x} and H_{9n} would have to approach $180°$, and in such a situation coupling should have been observed. Also, since the steric requirements of the hydroxyl group and the O-mesyl group are about the same, the great difference in the equilibrium constants of hemiacetals **18** and **19** cannot be justified on steric grounds. It is thus clearly apparent that, in general, steric effects arising from C_9-exo substituents cannot be regarded as providing a significant contribution to stabilization of the β isomer.

On the other hand, consideration of polar effects provides a quite reasonable interpretation. The presence of an electronegative group at the C_9-exo position would induce a net positive charge on C_9. Attraction between positive C_9 and the nearby negative oxygen of the β isomer would provide a clear justification for the greater stability of the β isomer. Comparing **18** (X = OH) with **19** (X = OMs) the electronegativity of the oxygen at C_9-exo is increased substantially on converting the hydroxyl group to the O-mesyl group, thus increasing the induced positive charge at C_9 and resulting in a stronger attractive force between C_9 and the β-C_3 hydroxyl group.

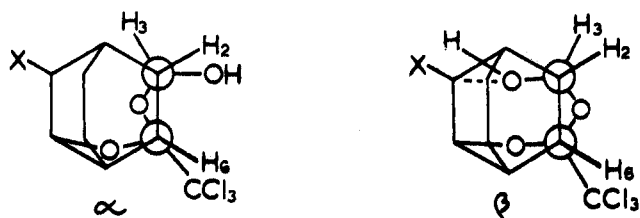The increased stabilization of the unfavorable β isomer through substitution at C_9 is of the order of

0.4–0.5 kcal/mol for halogen and O-mesyl and 0.2 kcal/mol for hydroxyl. Although the equilibrium constants and $\Delta G°$ values may change somewhat for solvents other than DMSO, as it is well known that the nature of the solvent does influence hemiacetal equilibria;[18] nevertheless, the results clearly establish the existence of polar attractive forces. Appropriate application of these concepts to polysubstituted cyclohexanes, pyranoses, and other systems may well lead to a better understanding of the parameters involved in conformational preferences. For example, in the case of *trans*-1,4-bis(trifluoroacetoxy)cyclohexane, the conformational $\Delta G°$ value was found to be only 0.077 kcal/mol, whereas on the basis of additive conformational free energies it should have been 0.970 kcal/mol, based on 0.485 kcal/mol for each trifluoroacetoxy group.[7] The difference of 0.9 kcal can be accounted for on the basis of two polar attractive forces of 0.45 kcal each, clearly of the same magnitude as the energies found here for such attraction. Recently quantitative theoretical support for attractive nonbonded interactions has been provided[19] to account for various conformational populations, with particular reference to the "anomeric effect."[20] On this basis the involvement of longer range attractive forces in conformation and hemiacetal equilibria appears quite reasonable.

The nmr spectra also give information concerning the precise conformation of the hemiacetal ring system. In the α form the apparent lack of coupling between H_3 and H_2 would indicate that these protons lie at a dihedral angle close to $90°$, and that the conformation approaches that of Figure 3, α. In the β form the 5-Hz coupling between H_3 and H_2 would indicate a dihedral angle of 20–$30°$. Since there is polar attraction between C_9 and the C_3-OH group, the most likely conformation would be represented as shown in Figure 3, β.

In comparing the two hemiacetal systems with each other we find that for series **14–19** the equilibrium constants indicate an energy consistently lower by about 0.2 kcal/mol than series **20–24**. This result can be accounted for by subtle steric differences in the positions of the protons H_{9n} in the two cases. Molecular models show that H_{9n} of **14–19**, derived from the bicyclo[2.2.1] system, is located somewhat further under the ring and closer to the C_3-β-hydroxyl group than H_{9n} of **20–24**, derived from the bicyclo[2.2.2] system. The C_3-β hydroxyl group of the bicyclo[2.2.1] series would appear to experience a greater

(19) S. Wolfe and A. Rauk, *J. Chem. Soc. B*, 136 (1971); S. Wolfe, *Accounts Chem. Res.*, **5**, 102 (1972).

(20) R. U. Lemieux and N. J. Chü, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, 31N; N. J. Chü, Ph.D. Thesis, Department of Chemistry, University of Ottawa, 1959.

steric crowding from H_{9n} than the corresponding hydroxyl group of the bicyclo[2.2.2] series and thus justify the generally lower stability of the β isomers of the [2.2.1] series.

Experimental Section

Melting points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were measured with the Beckman IR-8 spectrophotometer. Nmr spectra were recorded on the Varian T-60 and A-60 spectrometers, using TMS as internal standard. Yields, melting points, and ir carbonyl absorptions are given in Table IV.

TABLE IV

EXPERIMENTAL DATA FOR NEW COMPOUNDS[a]

Compd	Yield, %	Mp, °C	Ir, cm^{-1}, C=O (KBr)
2	25	175–176	1785[b]
8	98	140–141	1793
9	85	139–140	1794
10	94	134–135	1795
11	97	148–149	1790
12	97	197–198	1787
13	99	205–206	1787
14	72	185–186	
15	52	183–184	
16	61	192–193	
17	90	223–224	
18	73	216–217	
19	70	200–201	
20	45	152–153	
21	50	181–182	
22	46	184–185	
23	65	214–215	
24	63	229–230	
25	64	138–139	1744
26	42	151–152	1757

[a] Satisfactory analytical data were reported for all compounds listed: Ed. [b] CHCl₃.

endo-cis-Trichloroacetylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid lactol (1) was prepared from the reaction of sodium trichloroacetate with *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride in dimethoxyethane.[9] Lactone 3 was prepared by the action of concentrated sulfuric acid on lactol 1.[11] The *exo*-9-chloro, -bromo, and -iodo lactones 4, 5, and 6 were prepared by the action of the appropriate halogen on lactol 1 in the presence of the corresponding potassium halide in aqueous sodium carbonate.[12] The *exo*-9-hydroxy lactone 7 was prepared by the action of peracetic acid on lactol 1.[12]

5-Hydroxy-5-trichloromethyl-4-oxatricyclo[5.2.2.0²,⁶]undec-8-en-3-one (2).—A solution of 17.8 g (0.1 mol) of *endo-cis*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride in 100 ml of anhydrous dimethoxyethane was stirred at 25° while 18.5 g (0.1 mol) of anhydrous sodium trichloroacetate was added in one portion. The resulting white slurry was stirred for 2 days at 25–30°. The solvent was removed *in vacuo* below 40°, and the solid product, 32.5 g, was pulverized and triturated with 400 ml of cold water for 0.5 hr. The insoluble solid was collected, washed with water, and dried to give 17.1 g crude product, mp 157–170°, 8.0 g after crystallizations from benzene–heptane.

exo-9-Mesyloxy-5-trichloromethyl-4,11-dioxatetracyclo[5.2.1.-1⁵,⁸.0²,⁶]undecan-3-one (8).—A solution of 2.00 g (6.7 mmol) of hydroxy lactone 7 in 24 ml of dry pyridine was stirred at room temperature while 0.51 g (13.4 mmol) of mesyl chloride was

slowly added. The mixture was warmed on the steam bath until dissolution was complete, and then the reaction mixture was allowed to stand at room temperature for 3 days. White crystals formed immediately upon the addition of 70 g of ice and water. The crystals were collected and the filtrate was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and then evaporated. The residue was combined with the collected crystals, and the entire product was treated with decolorizing carbon in ether. Recrystallization from ether–pentane afforded 2.48 g (6.55 mmol) of 9-*exo*-mesyl lactone 8.

5-Trichloromethyl-4,12-dioxatetracyclo[5.2.2.1⁵,⁸.0²,⁶]dodecan-3-one (9).—Concentrated sulfuric acid (30 ml) was added to 5.00 g (16.8 mmol) of lactol 2 over a period of 10 min with stirring. The lactol dissolved rapidly to give a straw-colored solution and the reaction was only slightly exothermic. The acid solution was chilled in an ice bath while 150 ml of cold water was added slowly, causing the precipitation of a white solid. After stirring 15 min the solid was collected, washed with water, and dried *in vacuo* at 60° for 3 hr to give 4.89 g of impure lactone 9. Crystallization from heptane–CCl₄ gave 4.24 g of pure lactone 9.

Preparation of exo-9-Chloro- (10), -9-Bromo- (11), -9-Iodo- (12), and -9-Hydroxy-5-trichloromethyl-4,12-dioxatetracyclo[5.2.2.-1⁵,⁸.0²,⁶]dodecan-3-one (13).—These compounds were prepared by treating the trichloromethyl lactol with chlorine, bromine, iodine, and peracetic acid, respectively, according to the methods presented in a previous publication.[12]

Preparation of Hemiacetals 14–24 through Sodium Borohydride Reduction of the Corresponding Lactones.—A solution of 6.00 mmol of lactone, dissolved in the minimum amount of 95% ethanol or anhydrous isopropyl alcohol (100–150 ml), was stirred at room temperature while 7.00 mmol of solid sodium borohydride was slowly added. Stirring was continued for 18–24 hr after which glacial acetic acid was added until effervescence ceased. After 15 min of additional stirring, 20 ml of water was added and the solution was evaporated to a small volume leaving a white crystalline solid suspended in acetic acid–water. The solid was collected, washed well with water, and dried *in vacuo* at 50°. The solid was then recrystallized from carbon tetrachloride, cyclohexane, or dimethoxyethane.

Preparation of Acetyl Derivatives 25 and 26 through Acetylation of Hemiacetals 20 and 21.—Acetic anhydride (1.2 ml) was added slowly with swirling to 1.14 mmol of hemiacetal 20 or 25 in 2 ml of pyridine with cooling. The flask was stoppered and allowed to stand in the ice bath for 8 hr. The cold solution was poured over 50 g of crushed ice, and the precipitated solid was stirred for 0.5 hr before filtering. The products were purified by crystallization from heptane.