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Received February 11, 1980

A series of quinazolone lactones were prepared and their structures analyzed by 360 MHz proton and carbon-13 nmr. It was found that the compound capable of lactonization to yield either a six or seven-membered ring forms only the six-membered system.

In a search for biologically active compounds, it was decided to prepare a series of lactone fused quinazolones. This project led to the synthesis of compounds 1 and 2.
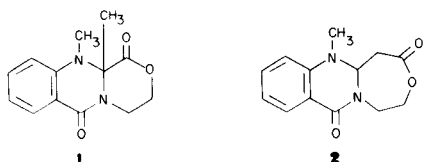

The first attempts at lactonization were *via* the ester-alcohol analogs of 1 and 2 by refluxing in xylene with and without a trace of methoxide. Since this process did not prove fruitful, the ring closure was performed using the corresponding acid-alcohols. The rate of reaction for the formation of 1 and 2 did not appear to be significantly different. Thus when material containing both potential modes of lactonization was prepared and subjected to very mild ring closure conditions, shown below, it was not clear, *a priori*; which of the ring systems would predominate (1).
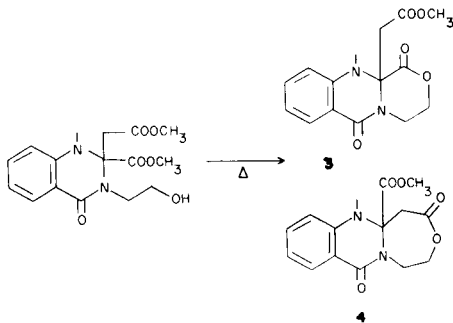
A study of molecular models of both the starting material and products did not reveal any striking differences in energetics or entropy factors. Surprisingly, only a single product, in high yield, was formed. It was not obvious from an inspection of routine spectra (ir, ms and 60 MHz proton nmr) which of the two possible structures was obtained. Looking at the molecular models of potential conformations of 3 and 4, it was decided that if the proton-proton coupling constants could be determined for the product, then by analogy with data obtained for 1 and 2 the structure could be solved. Thus 360 MHz spectra were obtained for compounds 1,2 and 3,4.

The first compound analyzed was 2. The most noticeable feature of the 360 MHz spectrum was that the lowest field aliphatic proton was adjacent to the nitrogen atom at C_4, its partner being ~1.8 ppm upfield as indicated below.
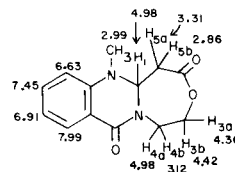

Coupling Constants in Hz

3a4a	=	4
3b4a	=	2.5
3a4b	=	2
3b4b	=	10
4a4b	=	15.5
5a5b	=	14.5
1,5b	=	10
1,5b	=	~0

The unusually lowfield nature of the H_{4b} chemical shift must arise from its colinear disposition towards the carbonyl (2). All of the other chemical shifts appeared quite normal. The protons on C_5 were the AB portion of an ABX spin system with a geminal coupling constant of 14.5 Hz. Proton H_{5b} was further split by H_1, while no coupling to H_{5a} was observed. Judging from the magnitude of the geminal H_{5a5b} coupling constant, the plane of the ester carbonyl group would form a dihedral angle of ~30° with H_{5a} as shown (3).
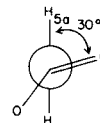

The lack of coupling between H_1 and H_{5a} indicates a dihedral angle of nearly 90° suggesting the following configuration.
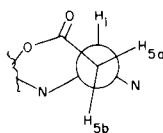
Due to the electronegative atoms, the Karplus method was deemed limited to discern the stereochemical nature of the H_3 and H_4 couplings. Although not tested for seven membered ring systems (4), it was decided to use Lambert's R value to calculate the dihedral arrangement (5). By using the method of Buys a quantitative measure of distortion can be obtained (6). Thus any XCH_2CH_2Y fragment can be analyzed, if R is known, by the following equation,

$$COS\ \psi\ =\ (3/2\ +\ 4R)^{1/2}$$

where ψ is the dihedral angle of the heteroatoms X and Y. Application of these equations to compound 2 led to an R value of 3.1 and $\psi = 63°$. Putting all of the above information together the lactone ring system 2 exists as a twist form as shown.
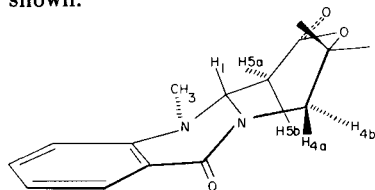
On the surface, the proton nmr of 1 at 360 MHz has a similar appearance to 2. In particular, the chemical shift for H_{4a} was observed at lower field than H_{3a} and H_{3b}, as indicated in the figure below. The R-value obtained for the ethyl fragment was 2.1 indicating a ψ-value of 57.5°, clearly distinguishing structure 2 from 1.
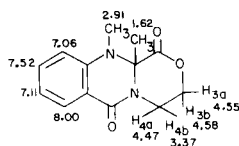
Coupling Constants in Hz

3a4a = 2
3b4a = 2
3a4b = 3.5
3b4b = 8.5
4a4b = 12.5

In addition, there are some differences in the aromatic proton chemical shifts. It was noticed that the shift of H_{13} in 1 was downfield of H_{13} in 2 by ~0.45 ppm as was H_{11}, ~0.20 ppm. The lower field nature of these chemical shifts suggest different degrees of nitrogen lone pair conjugation with the aromatic ring. This is most likely a consequence of the interactions between the N-methyl group and the ester carbonyl.

For both 1 and 2 the geminal coupling constant H_{3a3b}

was not readily obtainable due to the near chemical shift equivalence. In order to remove this near degeneracy, incremental portions of benzene were added to each sample and J_{3a3b} was revealed, being 11Hz for 1 and 14 Hz in 2. Interestingly, it was noticed that J_{3b4b} and J_{4a4b} in 1 were larger in benzene than in chloroform, increasing to 11 Hz and 14 Hz, respectively. This type of change has precedent in disubstituted ethanes (7) and would represent only a one-half degree change in the dihedral angle (5). This observation gives us yet another handle to distinguish compound 3 from 4.

The proton nmr of 3,4 was obtained and the chemical shifts and coupling constants are given in Table I. Looking first at the chemical shifts, it is readily apparent that the aromatic shifts for 3,4 are more similar to 1 than to 2. The coupling constants obtained for this system, due to deceptive simplicity (8), did not readily allow a structural assignment to be made. However, upon the addition of a small amount of benzene the shift degeneracy of H_{3a} and H_{3b} was removed and this resulted in the observed coupling constants of $J_{3a4b} = 3.5$ Hz and $J_{3b4b} = 11.5$ Hz. Also revealed was the J_{3a3b} coupling constant = 11.5 Hz. The coupling pattern now resembled 1 to a very high degree as shown in Figure 1. The R-value obtained for 3,4 was 2.1.

In addition, the partial ASIS shifts, given in Table II, were found to be more similar to 1 than to 2. To a high degree of probability the structure is compatible with the six-membered lactone 3.

The chemical shift of H_{4b} in 3 yields some insight into the overall geometry of the lactone ring. The shift of H_{4b} in 3 is more than 0.5 ppm to lower field than the analogous proton shift in 1. This shift must result as a consequence of the rotational preference of the ester carbonyl group and the relative conformation of the six-membered ring. In fact, this relationship can only occur in the chair-like structure shown below.
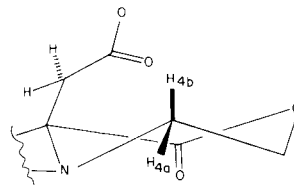
The above observations and conclusions not withstanding, it was decided to obtain an independent analysis of the problem using carbon-13 nmr data. Given in Table III are the carbon-13 chemical shift assignments for compounds 1,2 and 3,4. The shift assignments were determined in the usual manner employing fully coupled and single frequency off resonance decoupled spectra (9). The contiguous nature of the carbons assigned C_3 and C_4 was readily observed by this last technique (10). An interesting observation was made in the fully coupled spectrum for C_3. It would be expected, on first order principles, that C_3
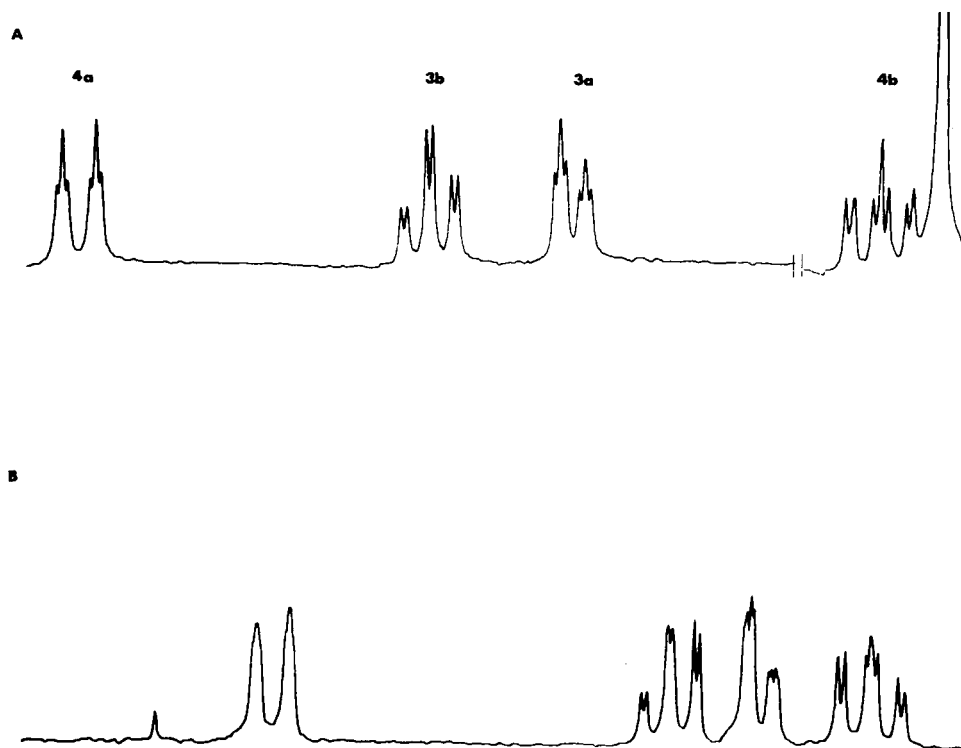
Figure 1. Benzene-induced ¹H nmr spectrum for A compound 1 and B 3,4.
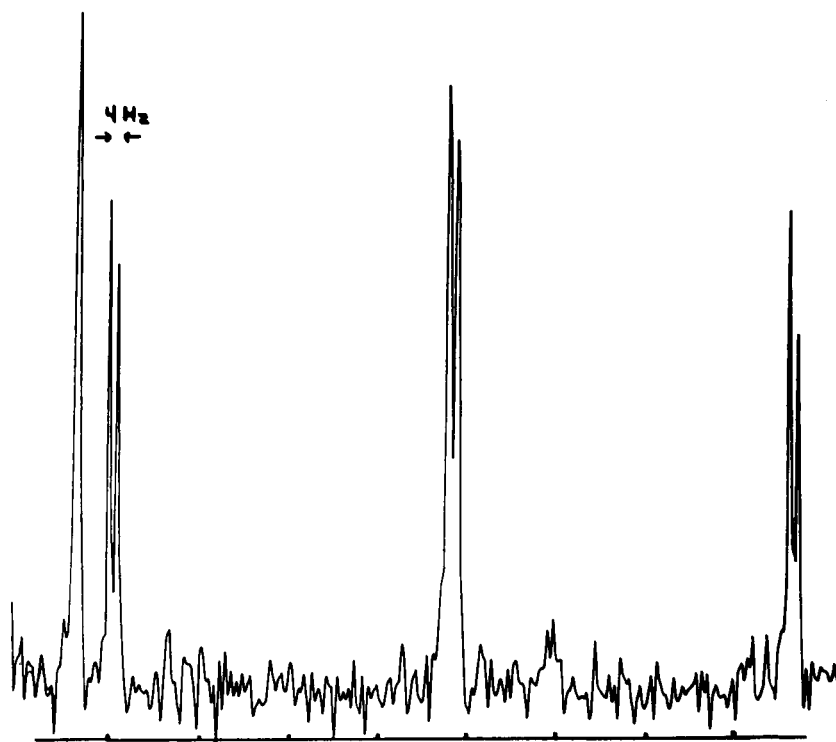
Figure 2. Proton-coupled carbon-13 spectrum for C_3 in compound 1.

Table I

Proton Nmr Chemical Shifts and Coupling Constants for **3,4**, in Deuteriochloroform

Proton	δ =	Coupling Constants in Hz	
3a	4.62	3a4a =	2
3b	4.62	3b4a =	2
4a	4.72	3a4b =	7.5
4b	3.90	3b4b =	7.5
5	3.23, 3.05	4a4b =	14
6	2.90	5a5b =	17
10	6.96		
11	7.50		
12	7.09		
13	7.99		

Table II

Partial Aromatic Solvent Induced Shifts (ASIS) for Compounds 1,2 and 3,4, in ppm

Proton	1	2	3,4
3a	−0.85	−0.61	−0.64
3b	−0.71	−0.58	−0.76
4a	−0.34	−0.34	−0.26
4b	−0.70	−0.66	−0.22
5	−0.32	−0.46, −0.69	−0.14, −0.15
6	−0.31	−0.64	−0.38
13	+0.11	+0.08	+0.10

Table III

Carbon-13 Chemical Shifts and Assignments for Compounds 1,2 and 3,4

Carbon	1	2	3,4
1	77.0	72.4	77.1
2	166.2	172.0	165.1
3	69.2	69.0	70.2
4	37.0	40.1	38.8
5	21.7	39.3	39.7
6	37.5	35.3	35.9
7	161.1	162.6	161.4
8	119.9	114.8	119.8
9	147.8	146.0	147.7
10	119.5	112.4	117.3
11	134.3	134.9	134.7
12	122.3	118.8	121.9
13	128.4	129.0	129.1
CO_2			171.0
OCH_3			52.1

should exhibit a large triplet further split by the adjacent methylene protons into smaller triplets. What is observed is shown in Figure 2. Each peak of the large triplet is split only into a doublet, necessitating that one of the two bond C-H couplings be near zero. At present it is not known which of the protons on C_4 has the near zero coupling with C_3, but by analogy with cyclopropane data the proton trans to an electronegative substituent has a smaller two bond C-H coupling than the cis proton (11). In the present instances, it is suggested that the proton having the near zero coupling constant is H_{4b}. Perhaps this observation, if it is general, will allow one to obtain nitrogen lone pair orientation in other ring sytems.

Looking at the shift data, it becomes apparent that there is more similarity for the aromatic carbon shifts of 1 and 3,4 than 2 and 3,4. The lower field shifts for C_8, C_{10} and C_{12} in 1 vs. 2 again must arise from a change in the degree of nitrogen lone pair conjugation with the aromatic ring. Compounds 1 and 2 were used as models for predict-

ing the carbon-13 chemical shifts of 3 and 4 by evaluating the substituent chemical shift of the CO_2CH_3 group. It was found that the α and β - effects of the carbomethoxy group are 17.4 and 2.8 ppm respectively (12). Using this data the following shifts are predicted for 3 and 4.
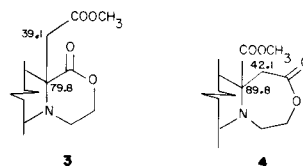
Judging from the predicted shifts, it is concluded that structure 3 is more compatible with the observed data. Thus we now have a convergence of the two NMR studies indicating structure 3 as the lactone formed.

EXPERIMENTAL

The synthesis of all compounds are reported elsewhere (1). Natural abundance ^{13}C nmr spectra were obtained at 25.2 MHz on a Varian XL-100-12 spectrometer system, equipped with a 620/L 16K computer, in the fourier transform mode with full proton decoupling. Off resonance spectra were obtained in the usual fashion. General spectral and instrumental parameters were internal deuterium lock to solvent; spectral width of 5000 Hz, a pulse width of 26 μs (45°), normal pulse amplifier and a pulse repetition of 1.8 seconds.

The 360 MHz proton nmr spectra were obtained on a Bruker system utilizing the solvent as deuterium lock. All coupling constants were measured from expanded spectra using first order-type approximations and are believed accurate to ±0.5 Hz.

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