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Alkyl Substituent Effects on the Photorearrangement of Cyclohex-2-en-1-ones to Lumiketones[1]

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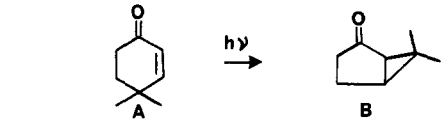
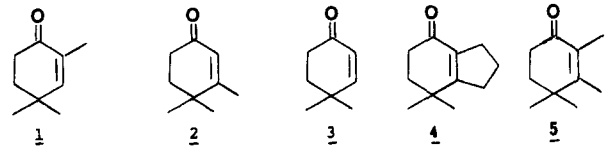
The effect of alkyl substitution on the photorearrangement of cyclohex-2-en-1-ones to bicyclo[3.1.0]hexan-2-ones (lumiketones) was investigated. Contrary to earlier reports, both 2,4,4- and 3,4,4-trimethylcyclohex-2-en-1-one undergo this rearrangement upon irradiation at 254 and 300 nm in *tert*-butyl alcohol, as does the analogous 2,3,4,4-tetramethyl derivative. The synthesis of the latter compound is described, starting from the 2,4,4-trimethyl enone, in four steps by conjugative methylation with lithium dimethylcuprate, silylation, bromination, and dehydrobromination. Structure assignments of the enones and lumiketones were based on spectroscopic data, including extensive use of ^{13}C NMR spectra. The results indicate that alkyl substitution on the C=C bond does not per se inhibit the lumiketone photorearrangement, as previously suggested, but lowers the quantium efficiency.

The photorearrangement of cyclohex-2-en-1-ones (A) to bicyclo[3.1.0]hexan-2-ones (lumiketones, B)[2] was reported





some time ago[3] to be extremely sensitive to the substitution pattern on the ring. Dialkyl or arylalkyl substitution at C-4 was concluded to be a necessary but not sufficient structural condition for the rearrangement, since both 2,4,4-trimethyl- and 3,4,4-trimethylcyclohex-2-en-1-ones (1 and 2, respectively) were reported not to undergo the rearrangement for which the parent compound 4,4-dimethylcyclohex-2-en-1-one (3) was a prototype.[4,5] These findings have been difficult to interpret in terms of an otherwise generally accepted mechanism[2,5] in which an enone triplet excited state, most likely a $^3\pi,\pi^*$ state, undergoes molecular distortion by twisting around the C=C bond, followed by more or less synchronous ring contraction and bonding between C-2 and C-4. This process has been found to be stereospecific,[5,6] with inversion of configuration at C-4 and retention at C-5,[7] in accord with an overall $_\sigma 2_a + _\pi 2_a$ process.[8] Some kind of inhibitory steric effect was suggested[3] for compounds 1 and 2, perhaps interfering with solvation of polar intermediates[9] along the reaction pathway, although ionic intermediates most likely play no significant role in this rearrangement in typical neutral organic solvents.[1,10]

Our interest in these early findings was stimulated by our recent discovery that the lumiketone rearrangement was completely inhibited (as predicted) on electronic excitation of the bicyclic enone 4,[11] which was attributed to the structural constraints provided by the fused five-

(1) Photochemistry of Ketones in Solution. 60. Part 59: Schuster, D. I.; Prabhu, K. V.; Smith, K. J.; van der Veen, J.; Fujiwara, H.; *Tetrahedron* **1980**, *36*, 3495.

(2) For a recent review, see: Schuster, D. I. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 3, p 167.

(3) Dauben, W. G.; Schaffer, G. W.; Vietmeyer, N. D. *J. Org. Chem.* **1968**, *33*, 4060.

(4) (a) Chapman, O. L.; Rettig, T. A.; Griswold, A. A.; Dutton, A. I.; Fitton, P. *Tetrahedron Lett.* **1963**, 2049. (b) Rettig, T. A. Ph.D. Dissertation, Iowa State University of Science and Technology, 1966.

(5) Schuster, D. I.; Brown, R. H.; Resnick, B. M. *J. Am. Chem. Soc.* **1978**, *100*, 4504.

(6) Chapman, O. L.; Sieja, J. B.; Welstead, W. J., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 161.

(7) Bellus, D.; Kearns, D. R.; Schaffner, K. *Helv. Chim. Acta* **1969**, *52*, 971.

(8) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie–Academic Press: Weinheim/Bergstr., Germany, 1970; especially pp 89–100.

(9) Polar intermediates in this reaction were postulated originally by Chapman in ref 4a and in: *Adv. Photochem.* **1963**, *1*, 323. These were excluded in subsequent studies reported by: Schuster, D. I.; Brizzolara, D. F. *J. Am. Chem. Soc.* **1970**, *92*, 4357.

(10) Photorearrangements of protonated 4,4-disubstituted cyclohexenones to protonated lumiketones have been observed at low temperatures in superacid solvents: Childs, R. F.; Hine, K. E.; Hung, F. A. *Can. J. Chem.* **1979**, *57*, 1442.

(11) Schuster, D. I.; Hussain, S. *J. Am. Chem. Soc.* **1980**, *102*, 409.

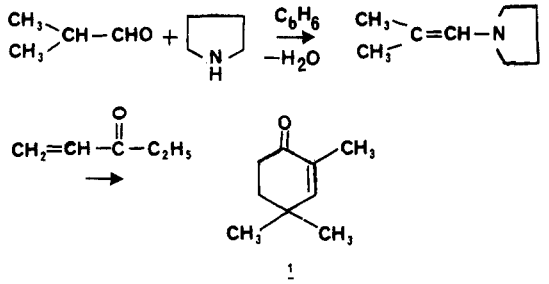
0022-3263/81/1946-1515$01.25/0

Table I. ^{13}C NMR Chemical Shifts of Cyclohex-2-en-1-ones in $CDCl_3$[a]

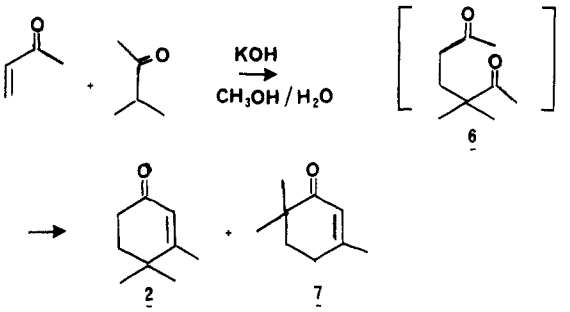
compd	chemical shifts[a]						
	C_1	C_2	C_3	C_4	C_5	C_6	methyls
3[b]	190.4	126.9	159.7	33.0	34.6	33.0	27.9
1	199.1	132.3	154.7	34.4	32.9	36.4	27.9 (C_4), 15.9 (C_2)
2	199.0	126.2	168.9	35.4	34.5	37.7	26.3 (C_4), 20.1 (C_3)
5	198.0	130.0	161.3	36.0	34.3	37.1	26.6 (C_4), 16.3 (C_3), 11.5 (C_2)
7	204	124.9	160.1	36.3	24.0	40.1	28.4 (C_6), 24.2 (C_3)

[a] In parts per million relative to Me_4Si. [b] Data obtained by I. Nuñez in this laboratory.

Scheme I



Scheme II



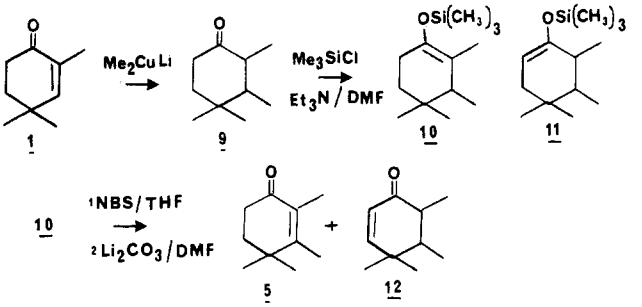
membered ring to twisting around the C=C bond, suggested to be a necessary stage in the lumiketone rearrangement.[5] The strength of this conclusion was mitigated by the reports on 1 and 2,[3,4b] since the inactivity of 4 toward rearrangement could be interpreted in terms of the above general (though vague) alkyl substituent effect, although the other observations on 4 (enhanced reactivity in H abstraction even in normally unreactive solvents such as acetone and *tert*-butyl alcohol and fluorescence in solution at room temperature)[11] were consistent with the operation of special structural factors in this case that are not operating for 1 and 2. The situation was further muddied by the discovery[12a,b] subsequent to the initial report on 2[3] that the material whose photochemistry was studied was not 2 but was 3,6,6-trimethylcyclohex-2-en-1-one (7; see Scheme II below), an enone that would not be expected to undergo the lumiketone photorearrangement since it lacks geminal substitution at C-4.

Therefore, in order to settle the question of the effects of alkyl substitution on the C=C bond of cyclohexenones on the lumiketone photorearrangement, we have investigated the photochemistry of 1,[2,5] 2,[3,12] and 2,3,4,4-tetramethylcyclohex-2-en-1-one (5) and can report that these enones do in fact rearrange to lumiketones on excitation in tert-butyl alcohol at 254 or 300 nm.[13] Extensive spectral data are provided for these ketones which should be of general interest in addition to their use in structural characterization in this study.

Results and Discussion

Synthesis. Compound 1 was prepared by the method employed earlier[4] involving the condensation of ethyl vinyl ketone with the pyrrolidine enamine of isobutyraldehyde, as shown in Scheme I. The isolated product had IR, UV, and ^1H NMR spectra identical with those reported previously, and ^{13}C NMR and mass spectral data are given in Table I and the Experimental Section. The synthesis of 2 is more problematical in that the route utilized here as well as previously,[3] involving the condensation of methyl vinyl ketone with 3-methylpropan-2-one (see Scheme II), gives a mixture of 2 and 3,6,6-trimethylcyclohex-2-en-1-one (7) in which 2 is the minor component.[12b,c] The IR, UV, and ^1H NMR data for the mixture of 7 and 2 do not differ greatly from those of the pure compounds isolated by preparative gas–liquid partition chromatography (GLC; see Experimental Section). The two isomers were distinguished previously by Cook and Waring[12b] on the basis of NMR solvent shifts and an independent synthesis of 2. We have found that a distinction between 2 and 7 could be made by using ^{13}C NMR and mass spectral data. The sp^3 carbon at lowest field should be that α to the carbonyl, which appears as a triplet at 37.67 ppm for 2 and as a singlet at 40.06 ppm for 7. Cyclohex-2-en-1-ones geminally substituted at C-4 show loss of ketene (M − 42) as the most favored primary fragmentation pathway on electron impact.[14] In accord with this, 2 shows a base peak in its mass spectrum at m/e 96, whereas 7 gives a base peak at m/e 82 attributable to expulsion of isobutene by a retro-Diels–Alder cleavage. Additional proof of 7 derives from catalytic hydrogenation to give 2,2,5-trimethylcyclo-

Scheme III



(12) (a) Correction given in: *J. Org. Chem.* **1970**, *35*, 4004; (b) Cook, K. L.; Waring, A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 529; (c) Conia, J. M.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1963**, 1925.

(13) Since for reasons already given Dauben et al.[3] did not actually investigate the photochemistry of 2, the major discrepancy between this study and earlier work concerns the photochemistry of 1, which has never been published other than in a doctoral dissertation.[4b] Side reactions which depend critically on enone concentration such as dimerization and polymerization occur on photoexcitation of enones[3] and can make comparison of irradiations carried out on the same compound in different laboratories particularly hazardous. However, since the enone concentrations in the current study (0.02 M) and in the earlier study (0.0145 M) are nearly identical and the reaction conditions otherwise are so similar, it would seem that the failure to observe rearrangement of 1 earlier[4b] must be ascribed to experimental error.

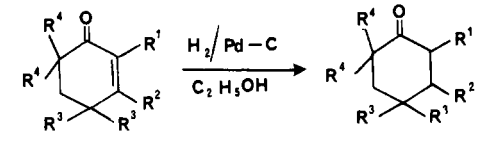
(14) (a) Harris, P. L. N.; Komitsky, F., Jr.; Djerassi, C. *J. Am. Chem. Soc.* **1967**, *89*, 4765. (b) Burlingame, A. L.; Fenselau, C.; Richter, W. J.; Dauben, W. G.; Shaffer, G. W.; Vietmeyer, N. D. *Ibid.* **1967**, *89*, 3346.

Table II. ^{13}C NMR Chemical Shifts of some Cyclohex-2-en-1-ones: Effect of Alkyl Substitution on Ring Carbons ($\Delta\delta$, ppm)

	cyclohex-2-en-1-one[a]			4,4-dimethylcyclohex-2-en-1-one[b]		
atom	2-methyl	3-methyl	2,3-dimethyl	2-methyl (1)	3-methyl (2)	2,3-dimethyl (5)
C_1	+0.5 (+0.4)[c]	+0.2 (−0.6)[c]	(−0.7)[c]	+8.6	+8.6	+7.6
C_2	+5.7 (+6.5)[c]	−3.1 (−2.8)[c]	(+1.6)[c]	+5.4	−0.7	+3.1
C_3	−5.3 (−5.2)[c]	+12 (+11.5)[c]	(+3.9)[c]	−5.0	+9.2	+1.6
C_4	+0.6	+5.2		+1.4	+2.4	+3.0
C_5	+0.9	−0.1		−1.7	−0.1	−0.3
C_6	+0.5	−1.1		+3.4	+4.7	+4.1

[a] Values reported in ref 19. [b] This work. [c] Values in parentheses reported in ref 20.

hexanone (8), in which the location of the *gem*-dimethyl group on carbon α to the carbonyl is indicated by a singlet at 44.43 ppm in the ^{13}C NMR spectrum.

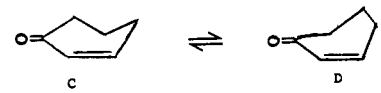


1 $R^1=R^3=CH_3$, $R^2=R^4=H$
2 $R^1=R^4=H$, $R^2=R^3=CH_3$
7 $R^1=R^3=H$, $R^2=R^4=CH_3$

13 $R^1=R^3=CH_3$, $R^2=R^4=H$
14 $R^1=R^4=H$, $R^2=R^3=CH_3$
8 $R^1=R^3=H$, $R^2=R^4=CH_3$

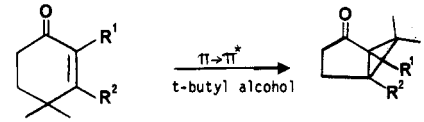
The synthetic route for 2,3,4,4-tetramethylcyclohex-2-en-1-one (5) is depicted in Scheme III. The alkylation of 1 with CH_3MgI alone or catalyzed by cuprous iodide not only proceeds sluggishly but also fails to give a single product. On the other hand, lithium dimethylcuprate reagent[15] brings about conjugative methylation to give a mixture of stereoisomeric 2,3,4,4-tetramethylcyclohexanones (9), the yield being dependent on reaction conditions.[15,16] No attempt has been made to separate the isomers of 9. Silylation[17] gave the two isomers 10 and 11 in approximately an 8:1 ratio, which were separated by column chromatography and identified spectroscopically. The bromination of 10 under the most favorable reaction conditions[18] gave a highly unstable yellow crystalline solid mixture which could not be analyzed further due to decomposition to give a dark brown oil. However, the IR spectrum of the crude product showed an absorption band at 1720 cm^{-1}, indicating the formation of α-bromo ketones. The dehydrobromination of the crude mixture gave admixed isomeric enones 5 and 12 which were separated by column chromatography and identified spectroscopically.

The ^{13}C NMR chemical shift assignments for enones 1, 2, and 5 were made on the basis of the multiplicities observed in SFORD spectra and also by comparison with data available on other methyl-substituted cyclohexenones, including 1.[19,20] Our ^{13}C data on compound 1 agree with those reported by Torri and Azzaro[19] except for the chemical shift of the carbonyl carbon. Values for carbonyl carbons in cyclohexenones reported by these authors[19] are invariably 5–8 ppm lower than values for the same compounds measured by Marr and Stothers.[20] The effect of methyl substitution on the chemical shifts of the ring carbons, as summarized in Table II, are not additive, although the trends observed are very similar for cyclohexenone itself and the corresponding 4,4-dimethyl enone. Comparison of the position of methyl resonances in compounds 1, 2, and 5 leads to the assignment of the quartets (SFORD spectra) downfield at 26.3–27.9 ppm to the *gem*-dimethyls, while the olefinic methyls are further upfield. In compound 5, the most upfield signal is due to the α-methyl, presumably because of electronic effects operating in the enones. The signal for the α-methyl in compound 5 lies farthest upfield of any olefinic methyl resonance in substituted cyclohex-2-en-1-ones studied to date. Steric effects of methyl groups in cyclohexenone rings are not well documented, except that a rapidly interconvertible equilibrium between conformations C and D (equal energy in the absence of substituents) was used to interpret the effect of substitution at C-3 and C-5 on ^{13}C resonances.[19]



C ⇌ D

Photochemistry. GLC analysis of the respective photolysates from irradiations of 2,4,4-trimethyl-, 3,4,4-trimethyl-, and 2,3,4,4-tetramethylcyclohex-2-en-1-ones (1, 2, and 5) in *tert*-butyl alcohol gave evidence of the formation of one major compound in each case besides some minor volatile products. Coinjection GLC analysis of the photolysate with the corresponding cyclohexanones 9, 13, and 14, obtained either by catalytic hydrogenation or during synthesis, showed the absence of products derived from photoreduction of the olefinic bond. In each case the photoproduct was isolated in a pure state, either by careful column chromatography or by preparative GLC. In all cases, the products had the same molecular weight as the starting enone, indicating that photorearrangement of the enones had occurred. The products were identified as the bicyclo[3.1.0]hexan-2-ones 15–17 on the basis of the spectral data presented below.



1 $R^1=CH_3$; $R^2=H$
2 $R^1=H$; $R^2=CH_3$
5 $R^1=R^2=CH_3$
3 $R^1=R^2=H$

15 $R^1=CH_3$; $R^2=H$
16 $R^1=H$; $R^2=CH_3$
17 $R^1=R^2=CH_3$
18 $R^1=R^2=H$

The compounds 15–17 all show a strong IR absorption band at 1710 cm^{-1} characteristic of this class of ketones.[3-7] The characteristic features of the ^1H NMR spectra are the absence of any resonance signals for olefinic protons and the appearance of closely spaced singlets for the methyl groups. The loss of magnetic equivalency of the *gem*-dimethyl groups is consistent with fixed endo and exo orientations in the lumiketones. This is further supported

(15) Posner, G. H. *Org. React.* **1975**, *19*, 1.
(16) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(17) House, H. O.; Fisher, W. F., Jr. *J. Org. Chem.* **1968**, *33*, 949.
(18) Blanco, L.; Arnice, P.; Conia, J. M. *Synthesis* **1976**, 194.
(19) Torri, J.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1974**, 1633.
(20) Marr, D. H.; Stothers, J. B. *Can. J. Chem.* **1965**, *43*, 596.

Table III. ^{13}C NMR Chemical Shifts of Lumiketones in $CDCl_3$[a]

compd	chemical shifts[a]						
	C_1	C_2	C_3	C_4	C_5	C_6	methyls
18[b]	41.3	214.9	37.9	19.7	35.6	26.1	27.3, 16.0
15	41.2	218.3	38.3	18.6	40.2	26.9	24.0, 17.1, 11.5
16	47.3	215.2	38.5	28.1	39.4	30.0	23.8, 18.7, 17.6
17	43.5	218.5	38.2	27.5	39.5	29.3	19.7, 18.5, 15.8, 8.2

[a] In parts per million relative to Me_4Si. [b] Data obtained by I. Nuñez in this laboratory.

Table IV. Relative Intensities of Mass Fragments on Primary Fragmentation of Enones and Lumiketones

mass peak	relative intensities, %					
	1	2	5	15	16	17
M^+	80	75	69	60	17	56
$M - CH_3$	31	12	50	20	6	32
M – CO	31	60	7.5	12.5	4	6
M – ketene	100	100	100	100	100	100

by the ^{13}C chemical shifts listed in Table III, where assignments are based on the multiplicity observed in SFORD spectra and comparison with the parent system (18).

We have also noticed an interesting correlation, which provides additional structural proof, in the mass spectra of enones 1, 2, and 5 and the corresponding lumiketones 15–17. The fragmentation pattern produced on electron impact (see Table IV) in both class of compounds bears very close resemblance. Notable among the primary fragmentation processes observed in the enones is the loss of ketene, for which two different pathways have been proposed.[14] One of them involves rearrangement of the molecular ion generated from the enone into a lumiketone ion radical, with subsequent loss of ketene from the latter.[14b] Since one has to deal with excited molecules in both electron impact and photochemical studies,[21] the occurrence of a common parent ion leading to loss of ketene in the mass spectra of these enones and their derived lumiketones can be invoked as additional proof for the structures assigned to the photoproducts.

Quantum yields for the formation of lumiketones from 2,4,4-trimethyl-, 3,4,4-trimethyl-, and 2,3,4,4-tetramethylcyclohex-2-en-1-ones (1, 2, and 5) were measured relative to the quantum yield of rearrangement of 4,4-dimethylcyclohex-2-en-1-one (3) in *tert*-butyl alcohol reported by Chapman[4] (6.5×10^{-3}). For this purpose, solutions of enones having the same optical density at 313 nm were irradiated simultaneously for the same length of time. Since the percent reaction was kept very small, any minor variations in optical density during reaction were assumed to be negligible. The quantity of lumiketone formed in each case was determined by GLC analysis using internal standards. The results of GLC analysis after irradiation for 80.25 h show that the amount of lumiketone formed could be determined in the cases of 4,4-dimethyl- and 3,4,4-trimethylcyclohex-2-en-1-ones (3 and 2). The quantity of lumiketone formed in the cases of 2,4,4-trimethyl- and 2,3,4,4-tetramethylcyclohex-2-en-1-ones (1 and 5) is less than the minimum detectable under the conditions of GLC analysis, and therefore the concentration of lumiketone in the photolysate was assumed to be less than or equal to the threshold limit necessary for detection. The results are summarized in Table V.

Mechanism. Sensitization and quenching experiments carried out earlier on enone 3 and other 4,4-disubstituted cyclohex-2-en-1-ones established that the lumiketone rearrangement proceeds from a triplet excited state.[2,5,7,22] The configuration of this state has been a matter of some controversy, as discussed at length in a recent review,[2] but it seems most likely at this time that the reactive state is a $^3\pi,\pi^*$ state which is usually the lowest triplet for this class of unsaturated ketones in polar solvents.[3,5,7,23-25] There is abundant evidence derived from flash excitation of enones[26] as well as studies with conjugated enones of larger ring size[27,28] that the reactive enone triplet undergoes substantial geometric distortion by twisting around the C=C bond in the excited state, which permits ready access to the ground-state potential surface connecting the enone and the lumiketone.[5] Partitioning between progress to product and return to enone upon crossover to this potential surface at or near its energy maximum has been postulated[5] to be the dominant factor controlling the quantum efficiency of the photoisomerization of cyclohexenones, which usually is on the order of 1% or less.[2] On the basis of this mechanistic description, steric effects on twisting should play a dominant role in determining the quantum yield of the photoisomerization.

The net influence of alkyl substitution on the C=C bond on twisting in the triplet enones is expected to be the resultant of two opposing steric effects. On the one hand, twisting increases the distance between the olefinic substituents and therefore should act to diminish any steric strain present in the cis olefin, which should be especially pronounced in enone 5 in this series. However, models indicate that twisting introduces nonbonded interactions between the olefinic substituents and one of the alkyl groups at C_4, which obviously is expected to worsen in severity as the size and number of substituents increase. In addition, it is difficult to predict the precise role of substituents in the twisted triplet state on the partitioning between formation of lumiketone product and return to starting enone, which should depend in a very sensitive

(21) There are several systems in addition to the cyclohexenones[14] where parallels exist between the pathways for photochemical and electron impact induced isomerization and fragmentation, the most noted being the correspondence of the Norrish Type II photochemical fragmentation and the McLafferty fragmentation of aliphatic and aromatic ketones: Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 1681; McLafferty, F. *Anal. Chem.* **1959**, *31*, 82.

(22) Zimmerman, H. E.; Lewis, R. G.; McCullough, J. J.; Padwa, A.; Staley, S. W.; Semmelhack, M. *J. Am. Chem. Soc.* **1966**, *88*, 1965.

(23) Dauben, W. G.; Spitzer, W. A.; Kellogg, M. S. *J. Am. Chem. Soc.* **1971**, *93*, 3674.

(24) Spectroscopic data which indicate that the lowest triplet of steroidal enones is $^3\pi,\pi^*$ have been reported by Kearns and co-workers: Kearns, D. R.; Marsh, G.; Schaffner, K. *J. Chem. Phys.* **1968**, *49*, 3316; Marsh, G.; Kearns, D. R.; Schaffner, K. *Helv. Chim. Acta* **1968**, *51*, 1890.

(25) More recent spectroscopic data on some enones from ref 24 taken at 4.2 K in single crystals confirm that the lowest triplet state is $^3\pi,\pi^*$ but indicate that under these conditions the triplet has the same planar geometry as in the ground state. It is suggested that geometry changes may occur at higher temperatures along pathways leading to products: Jones, C. R.; Kearns, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 344.

(26) Bonneau, R.; Fornier de Violet, P.; Joussot-Dubien, J. *Nouv. J. Chim.* **1977**, *1*, 31. Bonneau, R.; Fornier de Violet, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1977**, *284*, 631. Goldfarb, T. *J. Photochem.* **1978**, *8*, 29.

(27) Eaton, P. E. *J. Am. Chem. Soc.* **1964**, *86*, 2087; **1965**, *87*, 2052; *Acc. Chem. Res.* **1968**, *1*, 50.

(28) Corey, E. J.; Tada, M.; Le Mahieu, R.; Libit, L. *J. Am. Chem. Soc.* **1965**, *87*, 2051.

Table V. Relative Quantum Yield of Photorearrangement of Cyclohex-2-en-1-ones to Lumiketones

enone	IS[b]	oven temp, °C	% rel area of IS[b]	% rel area of lumiketone	[lumiketone] in photolysate, M	ϕ_{rel}
1	dodecane	110			$<5 \times 10^{-5}$[a]	<0.04[a]
2	cyclododecane	120	14.89	0.57	1.35×10^{-4}	0.11
3	dodecane	110	13.09	3.01	1.2×10^{-3}	1.0
5	cyclododecane	120			$<3 \times 10^{-5}$[a]	<0.02[a]

[a] Values were calculated from the minimum concentration of lumiketone present in the photolysate which can be detected under the conditions of GLC analysis utilized. [b] IS = internal standard.

way on the relative topology of the excited- and ground-state surfaces (i.e., the exact position along the reaction coordinate of the minimum in the triplet surface and the maximum in the ground-state surface) and any activation barriers which may exist on the latter between the geometry at the surface crossing and the final product. The effect of these should be reflected by the quantum efficiency of the photoisomerization. The relative quantum yields for the photoisomerization of the enones 1–3 and 5 show differences which suggest that alkyl substitution at C_2 has a greater inhibitory effect on conversion to lumiketone than substitution at C_3. This conclusion, however, must be considered tentative. A detailed analysis of structural influences on photochemical reactivity in this system must await similar data on many more substituted cyclohexenones.

These observations strengthen our previous contention that the abnormal photochemical behavior of the fused ring enone 4,[11] most significantly in the present context the absence of photoisomerization, is directly attributable to the constraints on twisting around the C=C bond provided by the fused five-membered ring. The effect on the photochemical behavior of 4,4-dialkylcyclohexenones caused by fusion to other rings at the olefinic bond is under study.

The most important consequence of the present investigation is clarification of the effect of alkyl substituents on the olefinic bond on the lumiketone photoisomerization of cyclohexenones. Rather than exertion of a rather mysterious inhibitory role on this process, as postulated some time ago,[3] the actual effect of such alkyl substitution is relatively insignificant. This removes a serious impediment to general applicability of the mechanism of this photochemical rearrangement as described by us previously[5] as well as in a recent theoretical analysis[29] which accounts for the observed stereospecificity of this triplet-derived isomerization in terms of a twisted triplet geometry.

Experimental Section

The irradiations were carried out in a Rayonet photochemical reactor with a cooling fan by using pretreated quartz tubes and employing 0.02 M solutions purged with nitrogen before photolysis. In the procedure used for cleaning the photolysis tubes, recommended by Professor H. Hellman, the tubes were washed with soap and water and then soaked in concentrated nitric acid for 1 h, followed by steaming for 2 h. They were then rinsed in distilled water and dried in an oven. Ultraviolet spectra were recorded on a Perkin-Elmer Coleman 124D double-beam spectrophotometer equipped with a digital display of absorbance or transmittance. Infrared spectra were recorded on a Perkin-Elmer Model 735 infrared spectrophotometer. A polystyrene film was used for calibration on all spectra. Proton magnetic resonance spectra were recorded on Hitachi Perkin-Elmer Model R-24 and R-20B high-resolution NMR spectrometers. Tetramethylsilane (Me_4Si) was used as an internal standard for all spectra. Carbon-13 magnetic resonance spectra were recorded on a Varian Associates Model XL-100 spectrometer equipped with a Nicolet Fourier transform accessory. Solutions in chloroform-*d* were used, and reported δ values are relative to Me_4Si. Mass spectra were recorded on a Varian Associates M-66, double-focusing, cycloidal-path mass spectrometer or a Du Pont Model 21-492B mass spectrometer.

Gas–Liquid Partition Chromatography. Analytical GLC analyses were carried out on a Hewlett-Packard Model 5710A gas chromatograph equipped with a Model 5702A oven temperature programmer, a strip-chart recorder (Model 7123A), and an electronic integrator (Model 3373B). Preparative separations were carried out by using a Varian Aerograph Model 920 chromatograph equipped with a thermal-conductivity detector. Sample collections were made in U-tubes submerged in dry ice–acetone. The 8 ft × $^1/_8$ in. and 13 ft × $^1/_4$ in. columns packed with 20% XE-60 on Chromosorb W were used for analytical and preparative GLC, respectively. All column chromatographic separations were done on silica gel (grade H, Davison Chemical Co.), and unless otherwise stated the eluent consists of a mixture of hexanes and ether in volume ratio of 10:1.

Hydrogenations were carried out in an all-glass apparatus at atmospheric pressure and room temperature. Palladium on carbon (5%) catalyst and absolute ethanol solvent were used, and the hydrogenation was terminated after the absorption of the calculated amount of hydrogen (1 equiv).

2,4,4-Trimethylcyclohex-2-en-1-one (1).[4b] The enamine formed by azeotropic removal of water from 7.5 g of pyrrolidine and 7.2 g (0.1 mol) of isobutyraldehyde in 400 mL of benzene was concentrated to 150 mL and added dropwise to a solution of 8.4 g (0.1 mol) of ethyl vinyl ketone in 10 mL of benzene kept at 5 °C. The mixture was stirred for 1 h at room temperature, heated at reflux for 17 h, and finally cooled. Hydrochloric acid (20%, 20 mL) was added to the reaction contents, which were heated under reflux for an additional 4 h. The reaction mixture was cooled and washed sequentially with water (4 × 50 mL), 5% HCl (6 × 30 mL), and water. The benzene layer was dried ($MgSO_4$) and concentrated, and the residue was distilled under vacuum. The fraction boiling in the range 54–55 °C (2.5 mm) contained 90% pure 2,4,4-trimethylcyclohex-2-en-1-one, which was further purified by column chromatography. The isolated yield was 2.5 g (20%). The IR and ^{1}H NMR spectra agreed with the data previously reported in a thesis[4b] but are given here for the published record: IR (neat) 1670 cm^{-1} with a shoulder at 1630 cm^{-1}; UV_{max} (cyclohexane) 230 nm (ϵ 11 600), 328 (29.8), 339 (29.5); 60-MHz ^{1}H NMR ($CHCl_3$) δ 1.12 (s, 6 H), 1.6–2.45 (A_2B_2 part of A_2B_2X system overlapping with a doublet at 1.63, J = 2 Hz, 7 H), 6.3 (br, 1 H); mass spectrum, m/e 138 (M^+), 123 ($M^+ - CH_3$), 110 ($M^+ - CO$), 97, 96 (100%, $M^+ - CH_2{=}C{=}O$), 95, 83, 82, 81 ($M^+ - CH_2{=}C{=}O - CH_3$), 79, 77, 67, 55, 54, 53.

3,4,4-Trimethylcyclohex-2-en-1-one (2). The reaction of 3-methylbutan-2-one with methyl vinyl ketone under the reaction conditions reported[3] gave a product mixture that contains at least 12 components (GLC, oven temperature 140 °C). The distillate [51–52 °C (1.5 mm)] containing the isomers 2 and 7 in the approximate relative ratio of 1:4 was subjected to preparatory GLC (oven temperature 185 °C, carrier gas flow rate 33 mL/min). The component with a retention time of 13.25 min is identified as 3,4,4-trimethylcyclohex-2-en-1-one: IR (neat) 1665, 1605 cm^{-1}; UV_{max} (ethanol) 236 nm (ϵ 14 600); 60-MHz ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 6 H), 1.6–2.6 (A_2B_2 part of an A_2B_2X system overlapping with a doublet at 1.8, J = 2 Hz, 7 H), 5.65 (m, 1 H); mass spectrum, m/e 138 (M^+), 123 ($M^+ - CH_3$), 111, 110 ($M^+ - CO$), 109, 97, 96 (100%, $M^+ - CH_2{=}C{=}O$), 95, 83, 82, 81 ($M^+ - CH_2{=}C{=}O - CH_3$), 79, 77, 67, 55, 54, 53. **3,6,6-Trimethylcyclox-2-en-1-one**

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(7) elutes at 10.5 min: IR (neat) 1660, 1630 cm^{-1}; UV_{max} (ethanol) 234 nm (ϵ 14100); 60-MHz ^1H NMR ($CDCl_3$) δ 1.02 (s, 6 H), 1.6–2.4 (A_2B_2 part of an A_2B_2X system overlapping with a doublet at 1.9, J = 2 Hz, 7 H), 5.6 (m, 1 H); mass spectrum, m/e 138 (M^+), 123, 110, 95, 83, 82 (100%), 79, 77, 67, 55, 54, 53.

2,3,4,4-Tetramethylcyclohexanone (9). A homogeneous solution of lithium dimethylcuprate reagent[15,16] in an argon atmosphere was prepared from 8.0 g (0.042 mol) of freshly purified cuprous iodide[30] and 50 mL of a 2.05 M solution of methyllithium–lithium bromide complex in ether. A solution of 5.52 g (0.04 mol) of 2,4,4-trimethylcyclohex-2-en-1-one in 165 mL of absolute ether was added dropwise over 15 min to the methylating agent, and the whole mixture was stirred for 1 h at 0 °C before the reaction temperature was slowly raised to reflux, and the system was then cooled immediately. The mixture was decomposed by addition to a vigorously stirred saturated ammonium chloride solution (200 mL), and the pH was adjusted to 8.0 with dilute ammonia. The ether extract was subjected to the usual workup, followed by column chromatography of the crude product to give 4.5 g of a 91% pure (GLC, oven temperature 120 °C, retention time 10 min) stereoisomeric mixture of 2,3,4,4-tetramethylcyclohexanones, which was further purified by repeat chromatography: yield 67%; IR (neat) 1710 cm^{-1}; mass spectrum, m/e 154 (M^+), 140, 139, 126, 125, 121, 111, 99, 98, 97, 96, 95, 85, 84, 83, 82, 81, 71, 70, 69, 67, 58, 57 (100%), 56, 55, 53; high-resolution mass spectrum, calcd for $C_{10}H_{16}O$ m/e 154.1358, found m/e 154.1290. The presence of more than one stereoisomer in the isolated product is indicated by the complex nature of the ^1H NMR spectrum. The methylene and methine protons appear in the range δ 1.2–2.7 and the methyls in the range 0.8–1.15 ppm. The proton decoupled ^{13}C NMR shows 18 signals, and not 9 signals as expected for one single configurational isomer.

2,3,4,4-Tetramethylcyclohex-1-en-1-yl Trimethylsilyl Ether (10). The silylation[17] of 3.08 g (0.02 mol) of **9** with chlorotrimethylsilane in the presence of triethylamine in DMF gave a mixture of isomeric ethers **10** and **11** in the relative ratio of 8:1 (GLC, oven temperature 120 °C). Column chromatography gave first 360 mg of slightly impure 4,4,5,6-tetramethylcyclohex-1-en-1-yl trimethylsilyl ether [GLC, oven temperature 120 °C, retention time 4.2 min; IR (neat) 1660 cm^{-1}] contaminated with starting material. The last fraction (retention time 5.0 min) obtained was 2,3,4,4-tetramethylcyclohex-1-en-1-yl trimethylsilyl ether (**10**): 2.3 g (51% yield); IR (neat) 1680 cm^{-1}; 60-MHz ^1H NMR (CCl_4) δ 0.15 (s, 9 H), 0.75–1.0 (unresolved, 11 H), 1.2–2.0 (unresolved, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.98 (s), 115.92 (s), 44.68 (d), 32.79 (t), 32.08 (s), 28.05 (q), 27.62 (t), 26.35 (q), 15.51 (q), 1.01 (q); mass spectrum, m/e 226 (M^+), 212, 211, 171, 170, 157, 156, 155 (100%), 75, 73.

2,3,4,4-Tetramethylcyclohex-2-en-1-one (5). A solution of 2.26 g (0.01 mol) of **10** in 100 mL of absolute THF was cooled to 0 °C, and 3.70 g of NBS was added. The reaction contents were stirred for 20 min at 0 °C and then poured into a mixture of 50 mL of saturated $NaHCO_3$ and 50 mL of saturated NaCl solutions. The organic layer was extracted with petroleum ether (bp 30–50 °C), and the extracts were dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum gave a yellow crystalline solid [IR ($CHCl_3$) 1720 cm^{-1}] which was rapidly transformed into a dark brown liquid on attempted isolation. This dark brown liquid was heated with 2.2 g of Li_2CO_3 in 6 mL of DMF for 135 min at 110–140 °C. The mixture was cooled at room temperature and extracted with hexanes, and the hexane extract was washed with water and dried (Na_2SO_4). The workup gave a mixture of isomeric enones from which the pure components were separated by column chromatography. The first fraction gave 350 mg (23%) of 4,4,5,6-tetramethylcyclohex-2-en-1-one: GLC retention time 11.64 min (oven temperature 120 °C); IR (neat) 1680 cm^{-1}; 60-MHz ^1H NMR (CCl_4) δ 0.7–2.6 (unresolved, 14 H), 5.76 (d, J = 5 Hz, 1 H), 6.57 (d, J = 5 Hz, 1 H); mass spectrum, m/e 152 (M^+), 138, 137 ($M^+ - CH_3$), 110, 109, 97, 96 (100%, $M - CH_2{=}C{=}O$), 95, 83, 82, 81, 69, 68, 67, 57. The last fraction gave 400 mg (26%) of 2,3,4,4-tetramethylcyclohex-2-en-1-one (**5**): GLC retention time 17.3 min; IR (neat) 1660 cm^{-1}; UV_{max} (cyclohexane) 327 nm (ϵ 34), 238 (13000); 60-MHz ^1H NMR ($CDCl_3$) δ 1.18 (s, 6 H), 1.5–2.0 (unresolved multiplets overlapping with broad singlets centered at 1.76 and 1.87, 8 H), 2.1–2.65 (unresolved multiplets, 2 H); mass spectrum, m/e 152 (M^+), 138, 137 ($M^+ - CH_3$), 124 ($M^+ - CO$), 123, 111, 110 (100%, $M^+ - CH_2{=}C{=}O$), 109, 107, 97, 96, 95 ($M^+ - CH_2{=}C{=}O - CH_3$), 93, 91, 86, 84, 82, 81, 79, 77, 69, 68, 67, 56, 55, 53; high-resolution mass spectrum, calcd for $C_{10}H_{16}O$ m/e 152.1201, found m/e 152.1160.

Irradiation of 2,4,4-Tetramethylcyclohex-2-en-1-one. The title compound (690 mg) was irradiated at 254 nm until the disappearance of 35% of the starting enone. GLC analysis showed one major product with a retention time of 10.4 min (7 ft × $^1/_8$ in. column packed with 10% Carbowax 20M on Chromosorb P, oven temperature 140 °C). Concentration and column chromatography of the crude photolysate first with pure hexanes and then with a mixture of hexanes and ether in volume ratio of 100:3 gave 60 mg of 1,6,6-trimethylbicyclo[3.1.0]hexan-2-one (**15**): IR (neat) 1710 cm^{-1}; UV_{max} (ethanol) 217.5 nm (ϵ 4000); 60-MHz ^1H NMR (CCl_4) three singlets centered at δ 1.03, 1.08, and 1.13 (9 H), 1.25–2.3 (unresolved multiplets, 5 H); mass spectrum, m/e 138 (M^+), 124, 123 ($M^+ - CH_3$), 110 ($M^+ - CO$), 100, 97, 96 (100%, $M^+ - CH_2{=}C{=}O$), 95, 83, 82, 81 ($M^+ - CH_2{=}C{=}O - CH_3$), 79, 73, 71, 69, 68, 67, 59, 58, 57, 56, 55, 54, 53; high-resolution mass spectrum, calcd for $C_9H_{14}O$ m/e 138.1045, found m/e 138.1047.

Irradiation of **1** in the Rayonet reactor using 3000-Å lamps under conditions otherwise identical with those of the above process proceeded much more slowly, and gave a photolysate that showed the same vapor chromatogram as that obtained above. The product of irradiation (**15**) was not isolated from the reaction mixture. Similar results were obtained when the other enones (see below) were irradiated with 3000-Å lamps. Thus, at least qualitatively, there is no wavelength dependence on the course of reaction of enones **1**, **2**, and **5** in *tert*-butyl alcohol.

Irradiation of 3,4,4-Trimethylcyclohex-2-en-1-one. The irradiation of 276 mg of the title compound for 30 h at 254 nm showed the presence of unreacted enone in trace amounts and the formation of a major compound: retention time of 6.5 min (oven temperature 140 °C). Preparative GLC (oven temperature 155 °C, helium flow rate 60 mL/min, retention time 10.5 min) gave pure 5,6,6-trimethylbicyclo[3.1.0]hexan-2-one (**16**): IR (neat) 1710 cm^{-1}; 60-MHz ^1H NMR (CCl_4) δ 1.1–1.5 (unresolved multiplets overlapping with 3 s centered at 1.17, 1.2, and 1.35, 11 H), 1.8–2.3 (unresolved multiplets, 3 H); mass spectrum, m/e 138 (M^+) 123 ($M^+ - CH_3$), 110 ($M^+ - CO$), 99, 97, 96 (100%, $M - CH_2{=}C{=}O$), 95, 93, 83, 82, 81, 80, 79, 77, 70, 68, 67, 65, 59, 56, 55, 54, 53; high-resolution mass spectrum, calcd for $C_9H_{14}O$ m/e 138.1045, found m/e 138.1043.

Irradiation of 2,3,4,4-Tetramethylcyclohex-2-en-1-one. The irradiation of 243 mg of **5** for 26 h at 254 nm and GLC analysis (oven temperature 140 °C) showed the formation of a product with a retention time of 5.8 min. Purification by column chromatography gave 10 mg of 1,5,6,6-tetramethylbicyclo[3.1.0]hexan-2-one (**17**): IR (neat) 1710 cm^{-1}; 100-MHz ^1H NMR ($CDCl_3$) four closely spaced singlets centered at δ 1.03, 1.06, 1.13, 1.16 (12 H), unresolved multiplets in the range 1.62–2.22 (4 H); mass spectrum, m/e 152 (M^+), 137 ($M^+ - CH_3$), 125, 124 ($M^+ - CO$), 123, 111, 110 (100%, $M - CH_2{=}C{=}O$), 109, 97, 96, 95, 93, 91, 83, 82, 81, 79, 77, 70, 69, 68, 67, 65, 57, 56, 55; high-resolution mass spectrum, calcd for $C_{10}H_{16}O$ m/e 152.1201, found m/e 152.1217.

Estimation of Relative Quantum Yields (ϕ_{rel}). Solutions of 4,4-dimethyl- (0.0353 M), 2,4,4-trimethyl- (0.02835 M), 3,4,4-trimethyl- (0.02016 M), and 2,3,4,4-tetramethylcyclohex-2-en-1-one (0.0189 M) in *tert*-butyl alcohol having the same optical density (1.006) at 313 nm were prepared. Equal volumes (2 mL) of the solutions of each enone in separate quartz tubes sealed with rubber septums were purged with nitrogen for 10 min and placed in a cell compartment which automatically brings each tube in the path of the beam periodically for a fixed time interval. The irradiations were carried out by using an Osram, 200-W, superhigh-pressure mercury lamp and a multicompartment quartz cell containing aqueous solutions of 15% w/v $KCrSO_4 \cdot 12H_2O$ (2 cm) and 0.25% w/v potassium hydrogenphthalate (2 cm) to cut off light below 300 nm and above 350 nm. After 321 h, during which time each enone was individually exposed to light for a total of 80.25 h, a 60-mL aliquot of a 0.1 M solution of the corresponding internal standard was added to the photolysate solution and then analyzed by GLC using a 6.75 ft × $^1/_8$ in. column of 20% XE-60

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on Chromosorb W. The response factors experimentally determined for enones were used in estimating the quantity of the corresponding lumiketone formed. Under an identical set of irradiation conditions the relative quantum yield (ϕ_{rel}) is related to the molar ratio of the amounts of lumiketone formed from the enone to the lumiketone formed from 4,4-dimethylcyclohex-2-en-1-one. The results are summarized in Table V.

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Registry No. 1, 13395-74-6; 2, 17299-41-1; 3, 1073-13-8; 5, 28354-98-5; 7, 23438-77-9; *cis*-9, 76514-89-1; *trans*-9, 76514-90-4; 10, 76514-91-5; 11, 76514-92-6; 12, 76514-93-7; 15, 76514-94-8; 16, 76514-95-9; 17, 76514-96-0; 18, 1846-48-6; 1-(2-methyl-1-propene)-pyrrolidine, 2403-57-8; ethyl vinyl ketone, 1629-58-9; 3-methylbutan-2-one, 563-80-4; methyl vinyl ketone, 78-94-4.

Structures of the Decomposition Products of Chlorozotocin: New Intramolecular Carbamates of 2-Amino-2-deoxyhexoses

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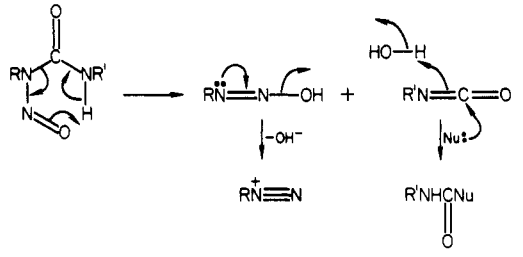
Six intramolecular five-membered-ring carbamate sugars were obtained from the decomposition of chlorozotocin (2-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-2-deoxy-D-glucose, **2**) in phosphate and triethylammonium bicarbonate buffers at pH 7.4. The structures were proven by spectroscopic methods and chemical inference to be 2-(carboxyamino)-2-deoxy-α-D-glucopyranose intramolecular 2,1-ester (**3**), 2-(carboxyamino)-2-deoxy-α-D-glucofuranose intramolecular 2,1-ester (**7**), "cis dimer" **11** (1*R*-[1α(1*S**,2*R**),5α,5aα,6α(1*S**,2*R**),10α,10aα]-5,10-dihydroxytetrahydro-1,6-bis[1,2,3-trihydroxypropyl]-1*H*,3*H*,5*H*,8*H*-dioxazolo[3,4-*a*:3′,4′-*d*]pyrazine-3,8-dione), "trans dimer" **12** (1*R*-[1α(1*S**,2*R**),5β,5aα,6α(1*S**,2*R**),10α,10aα]-5,10-dihydroxytetrahydro-1,6-bis[1,2,3-trihydroxypropyl]-1*H*,3*H*,8*H*-dioxazolo[3,4-*a*:3′,4′-*d*]pyrazine-3,8-dione), 2-(carboxyamino)-2-deoxy-α-D-mannofuranose intramolecular 2,3-ester (**13**), and the "monomer", which is either 2-(carboxyamino)-2-deoxy-D-glucopyranose intramolecular 2,3-ester (**15**) or its open-chain aldehyde hydrate **16**. It was shown that the latter "monomer" was in equilibrium with the "cis dimer" and "trans dimer" and was probably the precursor to **13**, whose formation by epimerization was catalyzed by silica gel. Acetate and *O*-trimethylsilyl derivatives were prepared of all compounds except the "monomer", which gave only "cis and trans dimer" derivatives. The acetate derivatives of compounds **7** and **11** have been found previously from the decomposition of the related streptozotocin (**1**).[30]

N-Nitrosoureas are believed to decompose in aqueous solution at pH 7–7.4 to produce diazo hydroxides and isocyanates.[2-8] These further react to form an active



alkylating agent and a carbamate or urea, depending on the nature of the nucleophile (Nu:). The alkylating side of the decomposition has been studied extensively by many research groups and is thought to be the cause of the antitumor activity of many of the *N*-nitrosoureas.[3,5,9-17] The ability of the presumed isocyanate to carbamoylate nucleophiles is determined in vitro by incubating the urea with radioactively labeled lysine.[18] An important biological role has been suggested for nitrosourea carbamoylating activity from data derived from in vitro studies. This includes the prolongation of the S phase of cell synthesis,[19] inhibition of repair X-irradiated and alkylated DNA,[20,21] inhibition of nucleolar and nucleoplasmic RNA,[22] and inhibition of DNA polymerase II.[23] The 2-amino-2-deoxy-D-glucose nitrosoureas streptozotocin (**1**) and chlorozotocin (**2**, 2-[[[(2-chloroethyl)nitrosoamino]carbonyl]-amino]-2-deoxy-D-glucose) show significantly reduced carbamoylating activity and bone marrow toxicity relative

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