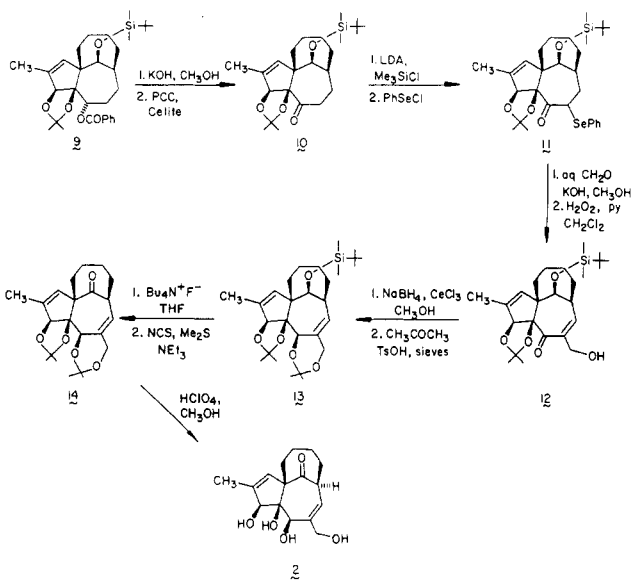
Scheme II



to be more prone to 1,4-reduction than expected. However, recourse to $LiAlH_4$ in toluene at −78 °C[9,10] did provide **5** in 65% yield alongside 4% of the epimer and 22% of the saturated ketone. The stereochemistry of the hydroxyl group in **5**, established by a comparative lanthanide shift ^1H NMR study of the two alcohols,[11] provided an additional clue[5] that delivery of reagents from the α surface might be generally favored kinetically.

To arrive at **6**, it was necessary to override this tendency and advantage was taken of the Sharpless epoxidation.[12,13] Introduction of the double bond in ring A was most expeditiously accomplished at this juncture. Subsequent to Cr(VI) oxidation of **6**, the ketone was converted into its silyl enol ether.[14] Of the several oxidation schemes applied to this intermediate, the combination of NBS[15] and DBU[16] was most accommodating, leading to **7** in 70% overall yield from **6**. Low-temperature hydride reduction of **7** then gave **8**.

Heightened functionalization of ring B was next initiated by titanium isopropoxide induced opening of the epoxy alcohol in the presence of ammonium benzoate.[17] Ensuing acetonide formation delivered **9** (91% for the two steps) and made possible chemospecific manipulation of the benzoyloxy group. To this end, saponification and oxidation of **9** with PCC on Celite[18] led to **10** (95%, Scheme II). For the purpose of introducing an oxygenated carbon α to its carbonyl group, the enolate of **10** was prepared and condensed with benzyl chloromethyl ether. However, complex mixtures and low yields were invariably seen. Recourse to SEMCl fared better at this stage, but the blocking group could not subsequently be disengaged. Accordingly, the enol silyl ether of **10** was reacted with benzeneselenenyl chloride[19] to give **11** (90%). Although the ^1H and ^{13}C NMR spectra of **11** revealed it to be a single stereoisomer, the relative orientation of the C–Se bond was not determined. Activation of the system in this manner permitted direct base-promoted condensation with aqueous formaldehyde[20] and caused oxidative elimination[21] within the single carbinol so produced to proceed more efficaciously than when alkylation preceded selenation. Noteworthy here is that no protection of the primary hydroxyl proved necessary during introduction of the final carbon center.

With **12** in hand, it remained to adjust the oxidation level at two key sites. As expected, reduction with $CeCl_3$-doped $NaBH_4$[22] proceeded exclusively to afford the 5-β-ol, nicely setting the stage for the subsequent elaboration of **13** (99% overall). Cleavage of the silyl ether with n-$Bu_4N^+F^-$ followed by Corey–Kim oxidation[23] resulted in smooth conversion to **14** (75%). Unmasking of the four hydroxyl groups merely required stirring **14** at 20 °C with 7% perchloric acid in methanol.[24,25]

As in the case of **1**, it has proven possible to acylate **2** regiospecifically at C-3 and to prepare 3,5-diesters. The 3-palmitate, in particular, carries all of the functional groups presently known to be required for cocarcinogenic activity.[26] However, a major distinction with 3-*O*-palmitoylingenol is the level of inherent strain energy. What is the relationship between ring strain and the potential to serve as tumor promoter? How necessary are the additional four carbons attached to ring C for hydrophilicity? We plan to respond to these questions and to report on a total synthesis of **1** at a future date.[27]

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(25) All new compounds exhibited compatible infrared, proton/carbon magnetic resonance, and mass spectrometric or combustion analysis data. Yields refer to isolated chromatographically homogeneous materials. For **2**: mp 173–176 °C; IR (thin film, cm^{-1}) 3700–3100 (br), 2940, 2860, 1675, 1455, 1435, 1380, 1370, 1330, 1280, 1220, 1115, 1055, 1025, 1005, 970, 925, 875, 845; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (s, 1 H), 5.26 (s, 1 H), 4.61 (s, 1 H), 4.58 (s, 1 H), 4.56 (br s, 1 H, OH), 4.47 (br d, J = 11 Hz, 1 H), 4.12 (d, J = 11 Hz, 1 H), 3.79 (br s, 1 H, OH), 3.53 (s, 1 H), 3.41 (br s, 1 H, OH), 3.17 (br s, 1 H, OH), 2.23 (dd, J = 14.9, 11.7 Hz, 1 H), 2.00–1.92 (m, 1 H), 1.81 (s, 3 H), 1.80–1.50 (m, 5 H), 1.07 (qt, J = 12 Hz, 1 H); MS, m/z (M^+) calcd 294.1467, obsd 294.1449.
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(27) This work was supported by the National Cancer Institute through Grant CA-12115.

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Thermal and Photochemical Reactions of Bicyclic Azoalkanes in Concentrated Sulfuric Acid

Summary: Thermolysis of bicyclic azo compounds **1a–d** in concentrated sulfuric acid affords ethylene (trapped as ethyl sulfate) and pyrazoles **3** in marked contrast to thermolysis of the nonprotonated azoalkanes, for which only loss of nitrogen (N_2) is observed.

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Sir: A most pronounced diversity in the thermal and photochemical behavior of the azoalkane 7,7-dimethyl-2,3-diazabicyclo[2.2.1]heptene (**1a**) was observed in concentrated sulfuric acid versus under more normal reaction conditions (Scheme I).

Depending on the mode of activation and the type of medium, either the dimethylene bridge (cleavage a) was eliminated in the form of ethylene to afford the protonated 3,4-dimethylpyrazole (**3a**), the isopropylidene bridge (cleavage b) was opened, leading to the protonated 3-isopropylpyridazine (**4a**), or the much precedented[2] diazene bridge (cleavage c) was expelled in the form of molecular nitrogen to generate a mixture of 5,5-dimethylbicyclo[2.1.0]pentane (**5a**) and 2,3-dimethylcyclopentene (**6a**). Thus, at will one can manipulate the fragmentation pattern of this azoalkane.

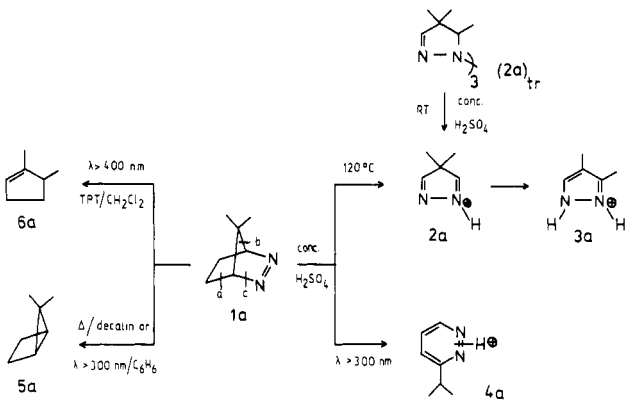
Although the protonation of the azo linkage in strong acid media is well established,[3] little chemistry of such protonated azoalkanes has been documented.[4] For example, protonated bicyclic azoalkanes which cannot tautomerize easily (Bredt's rule) to their hydrazones act as potent dienophiles in Diels–Alder cycloadditions.[4] In view of the established Wagner–Meerwein-type rearrangements of nitrenium ions,[5] extensive skeletal migrations of protonated bicyclic azoalkanes were expected, in view of their α-amino nitrenium resonance form. It was, therefore, our interest to investigate the thermolysis and photolysis of the diazanorbornenes **1** in concentrated sulfuric acid as medium and contrast this chemistry with that under the more conventional conditions[2] or with the very recently reported[6] SET photolysis using triphenylpyrylium tetrafluoroborate (TPT).

Indeed, dissolution of azoalkane **1a** in concentrated H_2SO_4 produced its protonated form **1a**-H^+, easily recognized by its characteristic ^1H and ^{13}C NMR spectra.[7] Heating to 120 °C led within ca. 1 h to the protonated pyrazole **3a** and ethyl sulfate (trapping product of ethylene), demonstrated by passing a stream of the olefin into concentrated H_2SO_4, as confirmed by ^1H and ^{13}C NMR.[8] The spectrum of the protonated species **3a** could be readily generated by dissolution of the trimer of 4,4-dimethyl-4*H*-pyrazole ($[\mathbf{2a}]_{tr}$)[9] in concentrated H_2SO_4 and heating at 120 °C; however, at room temperature (ca. 20 °C), first the protonated species **2a** was observed.[10]

On prolonged heating (ca. 4 h) of **1a**-H^+ in concentrated H_2SO_4 at 120 °C, the spectrum of **3a** remained unchanged, but that of ethyl sulfate was converted into that of isethionic acid.[11] Quantitative NMR analysis (CH_3SO_3H as internal standard and D_2SO_4 as lock) revealed that the conversion **1a** → **3a** was ca. 100%!

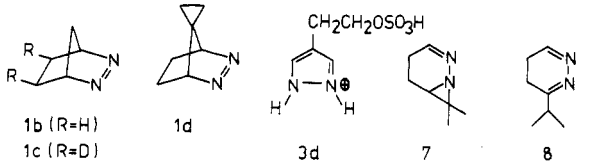
Irradiation of the solution of azoalkane **1a** in concentrated H_2SO_4 at $\lambda > 300$ nm (Hanau TQ 150 lamp) in a NMR tube at 15 °C led to the protonated 3-isopropylpyridazine (**4a**).[12] The latter was identified by means of its characteristic ^1H and ^{13}C NMR spectra.[13]

Scheme I



In contrast, the photolysis of azoalkane **1a** in benzene-d_6 (medium-pressure mercury lamp, NMR tube) at room temperature gave exclusively the 5,5-dimethylbicyclo[2.1.0]pentane (**5a**). This was also the product in the thermolysis of azoalkane **1a** in refluxing decalin.[14] However, the 2,3-dimethylcyclopentene (**6a**) was the predominant product under single-electron-transfer (SET) photolysis conditions.[6] Thus, TPT-sensitized irradiations of azoalkane **1a** in CH_2Cl_2 at $\lambda > 400$ nm (Hanau TQ 150 lamp source, UVW-55 filter) gave a 53:47 mixture of **5a** and **6a** in 46% yield (quantitative capillary GC; 50-m OV-101 column).

Similar chemistry is observed for the parent diazanorbornene **1b** and its dideuterio and spirocyclopropane derivatives **1c** and **1d**, respectively. Thus, both azoalkanes **1b,c** afforded the protonated parent pyrazole **3b** quantitatively when heated in concentrated H_2SO_4 at ca. 120 °C for 1 h. In concentrated D_2SO_4 the pyrazole **3b** exhibited extensive hydrogen–deuterium exchange at the 4-position[15] and, of course, complete exchange of the protons in ethyl sulfate and isethionic acid. The azoalkane **1d** gave essentially quantitatively 2-(4-pyrazolyl)ethyl sulfate (**3d**). Unfortunately, both azoalkanes **1b** and **1d** proved photostable on irradiation at $\lambda > 300$ nm (Hanau TQ 150 lamp, NMR tube) in concentrated H_2SO_4 even for prolonged times (ca. 48 h).



Instead of the expected nitrenium ion chemistry,[5] the course of thermolysis and photolysis of protonated bicyclic azoalkanes such as the diazanorbornene **1a** entailed

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(7) ^1H NMR (H_2SO_4, 400 MHz) δ 5.38 (s, 2 H), 2.33 (m, 2 H), 1.37 (m, 2 H), 1.18 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (H_2SO_4, 100.6 MHz) δ 87.0 (d), 62.3 (s), 22.0 (dd), 18.0 (q), 17.0 (q).

(8) ^1H NMR (H_2SO_4, 400 MHz) δ 7.77 (s, 1 H), 4.53 (q, J = 7.0 Hz, 2 H), 2.40 (s, 3 H), 2.12 (s, 3 H), 1.47 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (H_2SO_4, 100.6 MHz) δ 146.1 (s), 134.1 (d), 118.4 (s), 73.4 (t), 14.0 (q), 8.9 (q), 7.0 (q).

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(11) ^1H NMR (H_2SO_4, 400 MHz) δ 4.78 (t, J = 5.0 Hz, 2 H), 3.73 (t, J = 5.0 Hz, 2 H); ^{13}C NMR (H_2SO_4, 100.6 MHz) δ 66.0 (t), 50.9 (t). Wooton, D. L.; Lloyd, W. G. *J. Org. Chem.* **1974**, *39*, 2112.

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cleavage of the [2.2.1]skeleton with retention of the diazenyl moiety (Scheme I). In contrast, the neutral azoalkane **1a** exclusively extruded the diazenyl group in form of molecular nitrogen on thermal activation and photochemical excitation.

The novel thermal fragmentation of the protonated azoalkanes **1** observed here in concentrated H_2SO_4 can be readily rationalized in terms of a Diels–Alder retrocyclization (bond a cleavage; Scheme I). The driving force for this process presumably derives from tautomerization of the initially produced protonated 4*H*-pyrazole **2** to its aromatic 1*H*-pyrazole **3** form.[16] Furthermore, it has been shown[9] that the equilibrium of the acid-catalyzed reaction of nonisomerizable 4*H*-pyrazoles with alkenes lies on the side of the adduct. Consequently, the complex set of possible reaction intermediates derived from the protonated azoalkanes **1** are irreversibly and essentially quantitatively displaced toward the protonated 1*H*-pyrazoles as final products.

The unusual photochemistry of the protonated azoalkane **1a** leading to the protonated pyridazine **4** is more difficult to explain. Clearly, it involves bond b cleavage (Scheme I) and resembles the β-cleavage process observed in the benzophenone-sensitized photolysis of certain azoalkanes.[17] Thus, a likely intermediate product in the complex transformation **1a**-H^+ → **4a** would be the azirane **7**. In view of the labile nature of such aziranes toward acids,[17a] rearrangement of **7** into the azine **8** and subsequent oxidation to **4a** in concentrated H_2SO_4 is proposed.

Whatever the mechanistic details, the present observations underscore that the thermal and photochemical behavior of protonated substrates differs significantly from that of the neutral species.[18] That well-defined and novel chemistry can be promoted in concentrated H_2SO_4 should be apparent from the results reported here for the protonated azoalkanes **1**.

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Additions and Corrections

Vol. 51, 1986

Carlos Jaime, Rosa M. Ortuño, and José Font*. Di- and Trisubstituted γ-Lactones. Conformational Study by Molecular Mechanics Calculations and Coupling Constant Analysis.

Page 3948, Chart I. Entries **8t** and **9t** should read as follows:

8t	H	H	H	Me	Me	H
9t	H	H	H	OH	Me	H

Page 3949, Table II. The order of the two values within each entry in columns 3, 6, and 8 should be reversed for **8c** and **9c**.

Page 3949, column 2, lines 17–20 should read having C_4-methyl in axial and C_3-methyl in equatorial positions (Table II).

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John Wityak, Steven J. Gould, Scott J. Hein, and Douglas A. Keszler*. A 1,3-Dipolar Cycloaddition Route to the 3(*R*)- and 3(*S*)-Hydroxy-(2*S*)-arginines.

Page 2183, the **Acknowledgment** should have included the following: D.A.K. acknowledges the support provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society.