386, 358, 260, 245, 218, 217, 84, 77 (100%); *m/e* 401.1098 (calcd for $C_{24}H_{19}NO_3S$, 401.1086).

5,11-Dimethyl-6*H*-benzo[*b*]carbazole (22). To a magnetically stirred mixture of **19** (110 mg, 0.274 mmol) and sodium borohydride powder (34 mg, 0.90 mmol) in dry THF (5 mL) at 0–5 °C under N_2 was slowly added dropwise over 1.5 h a solution of trifluoroacetic acid (2.10 g) in dry THF (5 mL). The mixture was stirred at room temperature for 24 h. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The aqueous layer was treated with saturated aqueous sodium bicarbonate (100 mL) and further extracted with CH_2Cl_2. The combined organic portions were washed with 5% bicarbonate and worked up to give a tan residue. The mass spectrum of this crude material exhibited *m/e* 403 and 385, which were assigned as M^+ for **20** and **21**, respectively. This crude mixture was dissolved in THF (5 mL) and methanol (15 mL) and treated under N_2 with 2 N sodium hydroxide (5 mL). The mixture was refluxed for 6 h, treated with 50% aqueous sodium hydroxide (1 mL), and refluxed for another 24 h. The reaction mixture was cooled, treated with concentrated hydrochloric acid to pH 2, and stirred for 1.5 h at room temperature. The mixture was partitioned between saturated aqueous sodium bicarbonate and $CHCl_3$, and the aqueous portion was then further extracted with $CHCl_3$. The usual workup gave 66 mg (98%) of **22**, mp 190–192 °C, which showed one spot on TLC. Flash chromatography over silica gel with 1:2 cyclohexane–methylene chloride afforded 52 mg of pure **22** as a pale yellow solid: mp 208–209 °C (lit.[21] mp 211–213 °C); mass spectrum, *m/e* 245 (M^+, 100), 230, 215, 202, 149, 123; *m/e* 245.1192 (calcd for $C_{18}H_{15}N$, 245.1204).

6-(Phenylsulfonyl)-5,11-epoxy-5,11-dimethyl-5,11-dihydropyrido[4,3-*b*]carbazole (23a) and 10-(Phenylsulfonyl)-5,11-epoxy-5,11-dimethyl-5,11-dihydropyrido[3,4-*b*]carbazole (23b). To a magnetically stirred solution of **4** (1.00 g, 3.08 mmol) and 1-aminotriazolo[4,5-*c*]pyridine[25] (0.417 g, 3.09 mmol) in dry THF (30 mL) at 20 °C was added over 5 min via a solid addition funnel freshly recrystallized (HOAc) lead tetraacetate (1.37 g, 3.10 mmol). After 10 min, a second equivalent of lead tetraacetate (1.42 g, 3.20 mmol) was added in the same manner. The reaction was stirred at 20 °C for 3 h, the lead salts were removed by filtration, and the filtrate was concentrated in vacuo to give an amorphous solid. Flash chromatography with 1:4 ethyl acetate–methylene chloride gave 0.465 g (38%) of a mixture of **23a** and **23b** as an amorphous solid which was one spot by TLC (R_f 0.55, THF): UV (95% EtOH) λ_{max} 239, 221 nm; mass spectrum, *m/e* 402.1048 (M^+, calcd 402.1038).

Ellipticine (1a) and Isoellipticine (2a). A magnetically stirred solution of **23a** and **23b** (465 mg, 1.43 mmol) in THF (5 mL) was treated with methanol (15 mL), 50% sodium hydroxide (3 mL), H_2O (3 mL), and sodium borohydride (1 pellet, 0.3 g, 8 mmol) and was refluxed. After 1 h at reflux, more sodium borohydride (1 pellet, 0.3 g, 8 mmol) was added and the reaction was refluxed for an additional 16 h. The resulting yellow-orange fluorescent mixture was allowed to cool, poured into saturated sodium bicarbonate solution (100 mL), and extracted with $CHCl_3$ until the aqueous layer was not fluorescent. The usual workup gave 250 mg of a yellow solid. Flash chromatography with methylene chloride and then ethyl acetate gave 147 mg (52%) of a mixture of **1a** and **2a** as a yellow solid. Flash chromatography of the pure ellipticine–isoellipticine mixture with 9:1 ethyl acetate–triethyl amine afforded clean separation of **1a** and **2a** in a 45:55 ratio. Both were identical (IR, UV, TLC, mp) with authentic samples.

Acknowledgment. This investigation was supported by Grants CH-200 and CH-200A from the American Cancer Society, PHS Grant GM-30761 awarded by the National Institutes of Health, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We also thank Merck Sharp and Dohme Research Laboratories for general support and Dr. Catherine E. Costello (Massachusetts Institute of Technology) for the high-resolution mass spectra (NIH Resource Grant FR00317 from the Division of Research Facilities and Resources).

Registry No. **1a**, 519-23-3; **2a**, 13799-49-0; **4**, 89241-38-3; **6**, 1484-19-1; **7**, 77507-52-9; **8**, 92399-33-2; **9**, 92399-34-3; **10**, 92399-35-4; **11**, 92399-36-5; **12**, 487-89-8; **13**, 80360-20-9; **15**, 92399-37-6; **16**, 89241-39-4; **17**, 92399-38-7; **18a**, 92399-39-8; **18b**, 92470-57-0; **19**, 92399-40-1; **20**, 92399-41-2; **21**, 92399-42-3; **22**, 73326-97-3; **23a**, 92399-43-4; **23b**, 92399-44-5; benzenesulfonyl chloride, 98-09-9; acetaldehyde, 75-07-0; dimethyl acetylenedicarboxylate, 762-42-5; *N*-phenylmaleimide, 941-69-5; 2-bromofluorobenzene, 1072-85-1; 1-aminotriazolo[4,5-*c*]pyridine, 23589-45-9.

Photoisomerization of 4-Hydroxypyrylium Cations in Concentrated Sulfuric Acid

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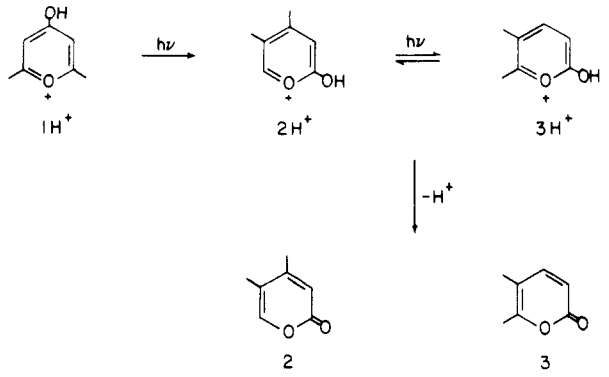
Irradiation of di-, tri-, and tetraalkyl-4-hydroxypyrylium cations in concentrated sulfuric acid leads to the formation of 2-hydroxypyrylium cations as phototransposition products and, in certain cases, to furyl cations by a photo-ring-contraction reaction. Product analysis by spectroscopic techniques, deuterium labeling, and unambiguous synthesis reveals that 2-hydroxypyrylium cations are formed by two distinct transposition patterns and accordingly, by two distinct mechanistic pathways. The bond-forming and -breaking requirements of the major transposition pattern, which constitutes approximately 95% of the reaction, are consistent with a mechanism initiated by 2,6-bridging in the first excited state of the 4-hydroxypyrylium cation. Similarly, the bond-formation and -breaking requirements of the minor pattern are consistent with a mechanism involving 2,5-bridging in the first excited state of the starting cation.

The photoisomerization of 2,6-dimethyl-4-hydroxypyrylium cation ($1H^+$) in concentrated sulfuric acid to yield 4,5-dimethyl-2-hydroxypyrylium cation ($2H^+$) was the first reported example of a 4-hydroxypyrylium cation photorearrangement.[1] The initially formed 2-hydroxypyrylium cation $2H^+$ was also observed to be in photoequilibrium with 5,6-dimethyl-2-hydroxypyrylium cation ($3H^+$). Thus,

(1) Pavlik, J. W.; Clennan, E. L. *J. Am. Chem. Soc.* **1973**, *95*, 1697.

0022-3263/84/1949-4523$01.50/0

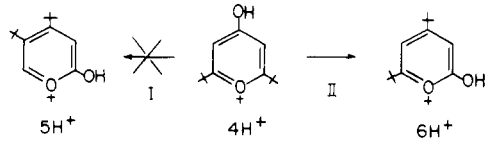


whereas continued irradiation with light of 254 nm resulted in essentially complete conversion of $2H^+$ to $3H^+$, the former cation can be regenerated by irradiation of $3H^+$ with light of 300 nm. Accordingly, neutralization of the acid solution of $1H^+$ that had been irradiated at 254 nm led to the isolation of 4,5-dimethyl-2-pyrone (**2**) and 5,6-dimethyl-2-pyrone (**3**) in a ratio dependent on the irradiation time.

The proposed mechanism for formation of $2H^+$ from $1H^+$ is shown in Scheme I. Thus, it was suggested[1] that 2,6-bridging, symmetry allowed in the first excited state of $1H^+$, leads to 4-hydroxyoxabicyclohexenyl cation **1a**. Subsequent ground-state epoxide ring migrations, which could involve oxaniabenzvalene intermediates, were then suggested to result in the formation of 2-hydroxyoxabicyclohexenyl cation **2a**, which collapses to the observed product $2H^+$.

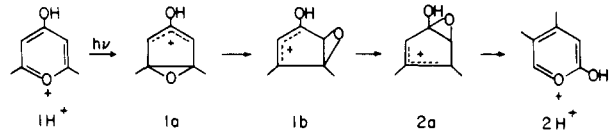
In order to rationalize the C_4–C_6 interchange by which $2H^+$ and $3H^+$ are interconverted, we evoked the intermediacy of the hydroxy-Dewar pyrylium cation **2b** (Scheme II), formed by 3,6-bridging in the first excited state of $2H^+$, which was suggested to be in equilibrium with the isomeric hydroxy-Dewar pyrylium cation **3a**. This latter ground-state isomerization requires only pivoting about the C_2–C_3 bond and could involve the intermediacy of the homoaromatic cyclobutenyl cation **2c**. Electronic rearrangement of either Dewar cation leads to either 2-hydroxypyrylium cation $2H^+$ or $3H^+$.

Although a variety of 4-hydroxypyrylium cations undergo photoisomerization according to pathway I, which places C_2 and C_6 of the reactant cation into positions 4 and 5 of the product, and can thus be rationalized by the 2,6-bridging mechanism shown in Scheme I,[2-5] later work in this laboratory revealed that irradiation of 2,6-di-*tert*-butyl-4-hydroxypyrylium cation ($4H^+$) does not result in the formation of 4,5-di-*tert*-butyl-2-hydroxypyrylium cation ($5H^+$), the product demanded by the 2,6-bridging mechanism (Scheme I, pathway I). Instead, $4H^+$ was observed to undergo photoisomerization to yield 4,6-di-*tert*-butyl-2-hydroxypyrylium cation ($6H^+$) (pathway II).[6]

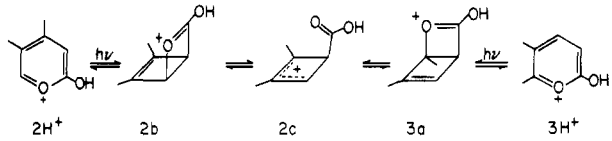


Since this product cannot arise via the 2,6-bridging mechanism, its formation was assumed to arise via hydroxy-Dewar pyrylium cation **4a** shown in Scheme III. Thus, it was suggested that when 2,6-bridging is sterically inhibited by bulky groups at the 2 and 6 positions, excitation leads to 2,5-bridging.[6] The resulting hydroxy-Dewar pyrylium cation **4a** was then suggested to undergo ground-state isomerization and electronic rearrangement, analogous to that shown in Scheme II, to yield $6H^+$.

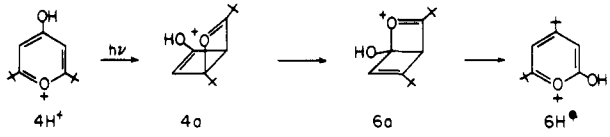
Scheme I



Scheme II

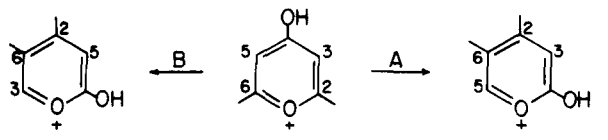


Scheme III



While the products from the photolysis of $1H^+$ or $4H^+$ can be rationalized by the mechanism in Scheme I or III, two questions remained. The first concerned whether pathway II, which places C_2 and C_6 of the starting cation into positions 4 and 6 of the product cation, is unique to the 2,6-di-*tert*-butyl cation $4H^+$ or whether it is general to all 4-hydroxypyrylium cation photorearrangements.

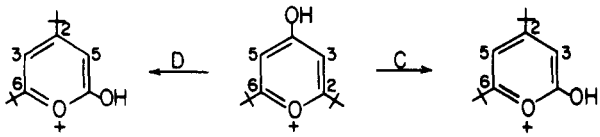
The second question is more mechanistic. Thus, the mechanisms for 4-hydroxypyrylium cation photoisomerizations shown in Schemes I and III place demands on the bond-breaking and bond-forming processes that are not completely substantiated by the experimental results. The 2,6-bridging mechanism in Scheme I requires bond formation between C_2 and C_6 (as in **1a**) and between the ring oxygen and C_3 and C_4 of the 4-hydroxypyrylium ring (as in **2a**) while bond breaking is demanded between the ring oxygen and C_2 and C_6 and also between C_4 and C_5. Significantly, the mechanism also requires that the C_2–C_3 and C_5–C_6 bonds remain intact during the photoisomerization. These requirements thus demand that pathway I photoisomerization occurs by transposition pattern A shown below. Because C_3 and C_5 of the reactant cannot be



distinguished in the product, this requirement cannot be substantiated. Indeed, the photorearrangement could have proceeded by the alternative transposition pattern B. This latter pattern would require C_2–C_3 and C_5–C_6 bond breaking and thus would be inconsistent with the proposed mechanism. Thus, although the two transposition patterns are mechanistically quite different, they cannot be distinguished in the present case because both lead to the same product.

A similar analysis of the conversion of $4H^+$ to $6H^+$ reveals an analogous ambiguity. Thus, this isomerization could occur by way of transposition patterns C or D requiring either C_4–C_5 or C_3–C_4 and C_5–C_6 bond breaking,

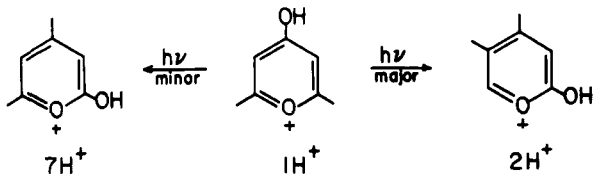
(2) Pavlik, J. W.; Kwong, J. *J. Am. Chem. Soc.* **1973**, *95*, 7914.
(3) Barltrop, J. A.; Day, A. C. *J. Chem. Soc., Chem. Commun.* **1975**, 177.
(4) Barltrop, J. A.; Carder, R.; Day, A. C.; Harding, J. R.; Samuel, C. *J. Chem. Soc., Chem. Commun.* **1975**, 729.
(5) Pavlik, J. W.; Bolin, D. R.; Bradford, K. C.; Anderson, W. G. *J. Am. Chem. Soc.* **1977**, *99*, 2816.
(6) Pavlik, J. W.; Dunn, R. M. *Tetrahedron Lett.* **1978**, 5071.



respectively. Again, although the mechanism shown in Scheme III is consistent with transposition pattern C, neither the two patterns nor their mechanistic consequences can be distinguished since they both lead to the same product.

Results and Discussion

If pathway II operates generally in 4-hydroxypyrylium cation photochemistry, then 4,6-dimethyl-2-hydroxypyrylium cation ($7H^+$) would be formed upon irradiation of $1H^+$. In order to rigorously establish the presence or absence of this product, the photochemistry of $1H^+$ was reinvestigated.

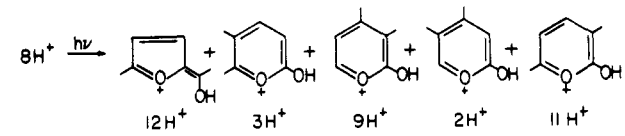


Although NMR monitoring of the photoreaction at room temperature did not reveal the formation of products other than $2H^+$ and $3H^+$,[1] rigorous gas chromatographic analysis of an ether extract of the neutralized irradiated solution did reveal that the peak due to **3** could be partially resolved into major and minor fractions. Furthermore, the partially resolved minor constituent was chromatographically identical with an authentic sample of 4,6-dimethyl-2-pyrone (**7**).[7] The NMR spectrum of these combined fractions, collected by gas chromatography after partial resolution by silica gel column chromatography, showed methyl singlets at δ 1.85 and 2.12 and two one-proton doublets at δ 5.85 and 6.88 as expected for the major constituent 5,6-dimethyl-2-pyrone (**3**). In addition, singlets of lesser intensity were clearly visible at δ 2.0 for the C-4 methyl group and at δ 5.63 for the nonresolvable C-3 and C-5 ring protons of **7**. The unequal area of the methyl singlets at δ 1.85 and 2.12 confirm that the C_6 methyl resonances for **3** and **7** overlap at δ 2.12. Furthermore, the signals at δ 2.12, 2.00, and 5.63 increased in intensity upon addition of authentic **7** to the NMR sample.

These chromatographic and spectroscopic observations confirm that **7** is present in the neutralized product mixture and that $7H^+$ is a minor product from the photoisomerization of $1H^+$. Accordingly, this shows that pathway II is not restricted to $4H^+$ but that it also operates as a minor pathway for $1H^+$ photorearrangement.

Although the specific transposition patterns for pathways I and II cannot be distinguished in the case of 2,6-disubstituted 4-hydroxypyrylium cations, the positions of the substituents in 2,3-dimethyl-4-hydroxypyrylium cation ($8H^+$) allow certain distinctions to be made. Thus, since C_3 and C_5 of the reactant can be distinguished in the product, the type A and B or C and D transposition patterns are no longer identical. Scheme IV shows the products possible by the two transposition patterns of each pathway.

Our original studies showed that $8H^+$ undergoes phototransposition to $3H^+$ and $9H^+$ as well as a novel photoring contraction leading to furyl cation $12H^+$.[5] Additional detailed gas chromatographic analyses employing coinjections with various authentic dimethyl-2-pyrones have also shown that small amounts of 3,6-dimethyl-2-pyrone (**11**) and 4,5-dimethyl-2-pyrone (**2**) are present in the neutralized extract revealing that cations $2H^+$ and $11H^+$ are also formed during the photolysis.



Although the ring contraction has been studied in greater depth and will be discussed in a subsequent paper, the observation of products $3H^+$ and $9H^+$ is significant since they were assumed to arise via the type A transposition pattern with initial 2,6-bridging and subsequent epoxide migrations either toward or away from the C-3 substituent. As Scheme IV shows, however, these products can also arise via the type C pattern and thus the 2,5-bridging mechanism. Accordingly, the original mechanistic conclusions[5] were not warranted and no direct conclusions regarding the origin of these products can be reached.

The formation of $2H^+$ and $11H^+$ would, however, seem to suggest that transposition D is in operation. It should be noted, however, that these cations are also the 4,6-interchange products expected from secondary photoisomerization of the two major primary 2-hydroxypyrylium cations $3H^+$ and $9H^+$. Indeed, upon continued photolysis, after NMR and GC analyses revealed complete consumption of the starting 4-hydroxypyrylium cation, the yields of $2H^+$ and $11H^+$ relative to $3H^+$ and $9H^+$ continued to increase confirming that they are formed in secondary reactions.[8]

Additional gas chromatographic coinjection studies with authentic 4,6-dimethyl-2-pyrone (**7**) revealed that this compound was not present in the neutralized mixture of photoproducts. Accordingly, $7H^+$ is not a product in this photoreaction. The absence of this cation is significant since it precludes operation of the type B transposition pattern in the photoisomerization of $8H^+$ and, by extrapolation, in the photorearrangements of other 4-hydroxypyrylium cations as well. This finding thus removes the ambiguity from the photoisomerization of $1H^+$. Having eliminated the type B pattern from consideration, it is now possible to conclude that the major product $2H^+$ is formed by the type A pattern of pathway I. Furthermore, it is also possible to conclude that $7H^+$, the minor photoproduct derived from $1H^+$, originated via the type C pattern of pathway II.

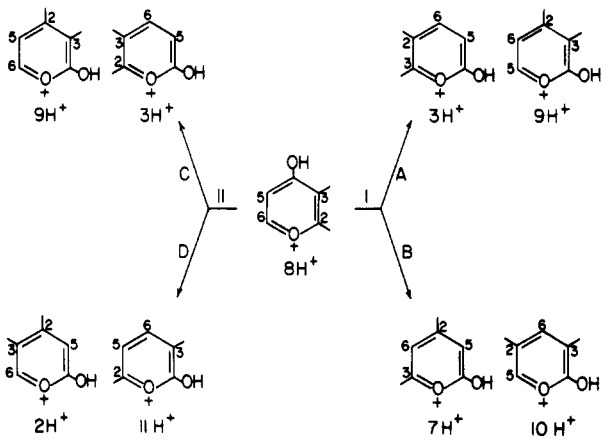
From these results it remains impossible, however, to distinguish whether $3H^+$ and $9H^+$, the major photoisomerization products from $8H^+$, are formed by the type A or type C patterns. At best, as in the photoisomerization of $1H^+$, it might be assumed that the type A pattern is the major pathway with only a small amount of $3H^+$ and $9H^+$ being formed by the type C pathway.

In order to remove this ambiguity, 2-methyl-3-ethyl-4-hydroxypyrylium cation ($13H^+$) was selected for study. Scheme V verifies that the type A and C patterns can be distinguished in this photoisomerization. Thus, although 4-methyl-3-ethyl-2-hydroxypyrylium cation ($14H^+$) is

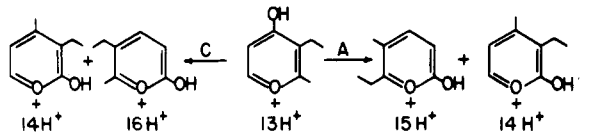
(7) Smith, N. R.; Wiley, R. H. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. 4, p 337, 549.

(8) At the point when the starting cation $8H^+$ is no longer detected in solution, GC analysis of the neutralized solution shows that **11** constitutes only 1% of the 2-pyrone mixture. Accordingly, although it is presumed that even this amount is formed in a secondary reaction, this does set an upper limit on the extent to which transposition pattern D can operate in this reaction.

Scheme IV

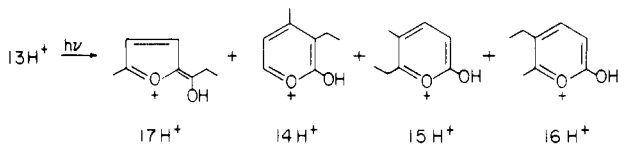


Scheme V



formed by both pathways, the type A pattern leads to 5-methyl-6-ethyl-2-hydroxypyrylium cation ($15H^+$) whereas formation of 6-methyl-5-ethyl-2-hydroxypyrylium cation ($16H^+$) would signal the type C pathway.

The photochemistry of $13H^+$ was found to be analogous to that of $8H^+$.[5] Thus, our original studies revealed that $13H^+$ undergoes photoring contraction to $17H^+$ and phototransposition to $14H^+$ and $15H^+$. These products were



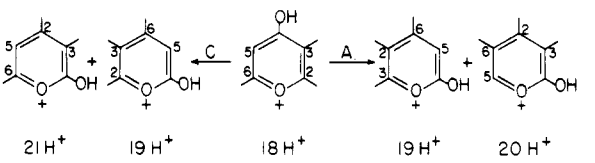
identified by their spectroscopic properties and, in the case of $17H^+$ and $15H^+$, by comparison of their isolated conjugate bases with 5-methyl-2-propanoylfuran (**17**) and 6-ethyl-5-methyl-2-pyrone (**15**) which were synthesized as described in the Experimental Section.

In addition to these products, subsequent gas chromatographic analysis of the neutralized photoproduct mixture allowed detection of a fourth product. Although the amount of this product was not sufficient for isolation, we have now shown that this additional product is chromatographically identical with an authentic sample of 5-methyl-6-ethyl-2-pyrone (**16**) which was synthesized in this laboratory. This confirms that $16H^+$ is also formed in the photoisomerization of $13H^+$. Furthermore, quantitative gas chromatography showed that 2-pyrone **16** accounted for only 2% of the 5,6-dialkyl-substituted 2-pyrone mixture.

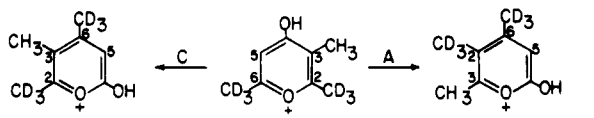
These results thus show that 98% of the phototransposition of $13H^+$ occurs via the type A pattern to yield $15H^+$ while 2% of the phototransposition follows the type C pattern to yield $16H^+$. These conclusions correspond well with the qualitative observation that photoisomerization of $1H^+$ occurs mainly by the type A pathway. Furthermore, these results lend credibility to the earlier suggestion that the type A pattern is also the major pathway in the photoisomerization of $8H^+$.

In order to further test the conclusions based on the photoisomerization of disubstituted 4-hydroxypyrylium cations, the photochemistry of more highly substituted 4-hydroxypyrylium cations was also studied.

Scheme VI



Scheme VII



Scheme VI shows the products expected from 2,3,6-trimethyl-4-hydroxypyrylium cation ($18H^+$) by the type A and C transposition patterns. Thus, although 4,5,6-trimethyl-2-hydroxypyrylium cation ($19H^+$) is common to both patterns, transposition pattern A is expected to lead to 3,4,5-trimethyl-2-hydroxypyrylium cation ($20H^+$) while 3,4,6-trimethyl-2-hydroxypyrylium cation ($21H^+$) would be formed via the C pathway.

Monitoring the photoreaction at room temperature by NMR showed that irradiation was accompanied by disappearance of the signals due to the starting cation and the concomitant formation of only one new ring proton signal at δ 6.9 and only three new methyl singlets upfield at δ 2.2, 2.4, and 2.6. Comparison of the NMR spectra of other 2-hydroxypyrylium cations shows that ring protons at C-4 and C-6 absorb close to δ 8.5 whereas those at the C-3 and C-5 ring positions resonate very close to δ 7.0. Accordingly, it appears that $18H^+$ has undergone photoisomerization to either 4,5,6-trimethyl-2-hydroxypyrylium cation ($19H^+$) or 3,4,6-trimethyl-2-hydroxypyrylium cation ($21H^+$).

Gas chromatographic analysis of an ethereal extract of the neutralized solution confirmed the regioselectivity of the photoisomerization since only a single product was observed and collected by preparative GC.

Mass[9] and infrared[10] spectral data provide excellent evidence that the neutralized photoproduct is a trimethyl-2-pyrone bearing one of the methyl groups in position 6 and a ring proton at either position 3 or 5. These spectral results are thus consistent with either 4,5,6-trimethyl-2-pyrone (**19**) or 3,4,6-trimethyl-2-pyrone (**21**). Since these two structures cannot be readily distinguished on the basis of spectral data, verification of the structure was firmly based by comparison of the isolated product with 4,5,6-trimethyl-2-pyrone, synthesized according to the method presented in the Experimental Section.

Although these results show that $18H^+$ undergoes regiospecific photoisomerization to $19H^+$, since this product can be formed by either the type A or type C pattern, its origin cannot be immediately determined. Examination of Scheme VI shows, however, that the type A and C 4,5,6-trimethyl-2-hydroxypyrylium cations are only superficially identical. Thus, in the type A product the C-2 and C-6 methyl groups of the starting cation are found at ring positions 5 and 4, respectively. In contrast, in the type C pathway, these methyl groups transpose to positions 6 and 4, respectively. Accordingly, Scheme VII confirms that labeling of these methyl groups allows distinction between these two pathways.

(9) Pirkle, W. H.; Dines, M. *J. Am. Chem. Soc.* **1968**, *90*, 2318.
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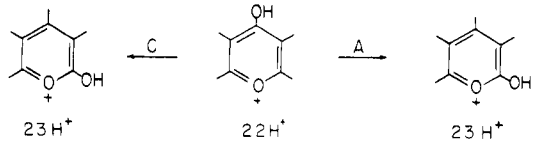
Scheme VIII



2,6-Di(methyl-d_3)-3-methyl-4-pyrone (**18**-d_6) was prepared by treatment of **18** with CH_3OD containing a trace of sodium methoxide. NMR analysis of the resulting 4-pyrone showed that 85% incorporation of deuterium into the C-2 and C-6 methyl groups had occurred.

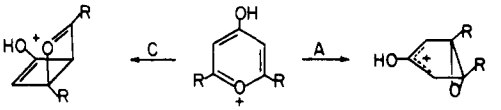
The NMR spectrum of **18H**$^+$-d_6 in concentrated H_2SO_4 showed the C-5 ring proton at δ 7.0, the undeuterated C-3 methyl group as a sharp singlet at δ 2.1, and a broad singlet of low intensity at δ 2.6 for the residual protons on the C-2 and C-6 methyl groups. After irradiation, subsequent spectra showed the disappearance of **18H**$^+$-d_6 and the appearance of the 2-hydroxypyrylium cation product with the undeuterated methyl signal at δ 2.6. This places the C-3 undeuterated methyl group of the reactant in the C-6 position of the product and confirms that photoisomerization has occurred mainly by the type A pattern.

More quantitative support for this conclusion was obtained by mass spectral studies of the neutralized photoproduct, isolated by preparative GC. Of particular importance is the m/e 43–46 portion of the spectrum. Thus, the appearance of an intense peak at m/e 43 due to the C-6 substituent, the C-6 ring carbon, and the ring oxygen, confirms that the C-3 nondeuterated methyl group of **18H**$^+$-d_6 has transposed to the C-6 position of the product as demanded by the type A pattern. Interestingly, the mass spectrum also exhibits a small peak at m/e 46. Since the spectrum of the nondeuterated 4,5,6-trimethyl-2-pyrone shows no signal at this position, this peak must be due to a CD_3CO fragment ion from a small amount of 4,6-di(methyl-d_3)-5-methyl-2-pyrone, the conjugate base of the type C product. The appearance of this peak thus indicates that, as in dimethyl-4-hydroxypyrylium cation photochemistry, transposition pattern C also operates as a minor pathway in this trimethyl-4-hydroxypyrylium cation photoisomerization. Indeed, direct comparison of the relative peak intensities for the m/e 43 and 46 fragment ions reveals that the type C pattern produces approximately 7% of the product whereas 93% of the photoisomerization occurs by transposition pattern A.

As shown in Scheme VIII, a single product, tetramethyl-2-hydroxypyrylium cation (**23H**$^+$), is expected from photoisomerization of tetramethyl-4-hydroxypyrylium cation (**22H**$^+$) via either the type A or C transposition pattern. Thus, as expected, irradiation of **22H**$^+$ in concentrated H_2SO_4 was accompanied by formation of a single product with methyl signals at δ 2.2 (6 H), 2.5 (3 H), and 2.6 (3 H) for the methyl groups at C_3 and C_5, C_4, and C_6, respectively of tetramethyl-2-hydroxypyrylium cation (**23H**$^+$). Furthermore, monitoring the photoisomerization of 2,6-di(methyl-d_3)-3,5-dimethyl-4-hydroxypyrylium cation (**22H**$^+$-d_6) by NMR and analysis of the resulting neutral deuterated tetramethyl-2-pyrone mixture by mass spectroscopy again revealed that 93% of the reaction occurred by way of the A pathway whereas only 7% of the product is formed by the alternative type C route.

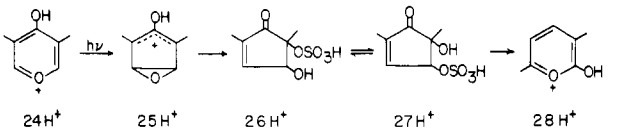
These experimental conclusions clearly show that methylated 4-hydroxypyrylium cations undergo photoisomerization to yield 2-hydroxypyrylium cations by two different transposition patterns and, accordingly, by two different mechanistic pathways. The major transposition pattern, first observed in the photoisomerization of 2,6-dimethyl-4-hydroxypyrylium cation (**1H**$^+$), is also identical with the P_4 permutation pattern observed by Barltrop, Day, and colleagues for the photoisomerization of three different dialkyl-4-hydroxypyrylium cations.[11] The minor pattern, the type C pathway, first observed in the photoisomerization of 2,6-di-*tert*-butyl-4-hydroxypyrylium cation (**4H**$^+$), is identical with the P_8 permutation pattern also observed by these workers.[11] Interestingly, although we have observed transposition pattern C as a general, although minor, pathway for all methylated-4-hydroxypyrylium cations studied, Barltrop and Day have reported that this pattern is limited to the photoisomerization of a single cation, 2,5-dimethyl-4-hydroxypyrylium cation.

The bond breaking and forming demanded by transpositions A and C are consistent with the mechanisms involving 2,6- and 2,5-bridging, respectively, as originally suggested in our earlier communications and illustrated in Schemes I and III. Whereas the relative yields of the type A and C products confirm that 2,6-bridging is a more facile process than 2,5-bridging, the former pathway is also more sensitive to the size of the substituents at C_2 and C_6.



Thus, since these groups move closer together during 2,6-bridging than during 2,5-bridging, the former pathway is inhibited by bulky groups at these positions. This inhibition is dramatically illustrated in the case of 2,6-di-*tert*-butyl-4-hydroxypyrylium cation (**4H**$^+$) which undergoes photoisomerization to yield 4,6-di-*tert*-butyl-2-hydroxypyrylium cation (**6H**$^+$), the product of 2,5-bridging.

Although the photoisomerization of 3,5-dimethyl-4-hydroxypyrylium cation (**24H**$^+$) to 3,6-dimethyl-2-hydroxypyrylium cation (**28H**$^+$) follows the type A pattern,



this rearrangement has been shown to proceed via a bisulfate adduct, **26H**$^+$ ⇄ **27H**$^+$, formed by reaction of the photochemically generated oxabicyclohexenyl cation **25H**$^+$ with H_2SO_4.[12] Although in this case the bisulfate adduct is readily observed by NMR, spectroscopic monitoring of the photoreactions currently under study failed to reveal any unambiguous evidence for the intervention of analogous intermediates. Accordingly, if such adducts are involved in the present photoisomerizations, they are transient in nature.

Alternatively, although oxabicyclohexenyl cation **25H**$^+$ undergoes efficient reaction with H_2SO_4 to yield **26H**$^+$, it seems plausible that the cations under current study might undergo intramolecular attack of the epoxide oxygen more rapidly than intermolecular trapping by the weakly nucleophilic solvent. Thus, although **25H**$^+$ is stabilized by methyl groups bonded to the oxyallyl system, lack of alkyl substitution at positions 2 and 6 of the original 4-pyrone ring should inhibit the rate of intramolecular epoxide ring migration since this rearrangement is accompanied by positive charge development at one of these latter carbons.

Conversely, due to the methyl substitution pattern, which destabilizes **1a** relative to **25H**$^+$, and which delocalizes the developing positive charge at C_2 or C_6, **1a** would

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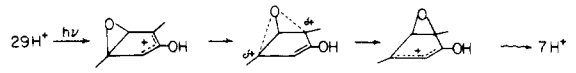
1a 25H$^+$

be expected to undergo more rapid intramolecular attack of the epoxide oxygen on the oxyallyl system. Similarly, with the exception of **22H$^+$**, all of the 4-hydroxypyrylium cations under current study bear at least one alkyl group at C_2 or C_6 and only one alkyl substituent at C_3 or C_5. As a consequence, all of the resulting oxabicyclohexenyl cations would be more susceptible to intramolecular ring migration than **25H$^+$**.

The direction of epoxide ring migration should also be influenced by the alkyl group substitution pattern. In the case of the oxabicyclohexenyl cation derived from 2,5-dimethyl-4-hydroxypyrylium cation (**29H$^+$**), for example, positive charge would not be equally distributed throughout the oxyallyl system but would be concentrated at the more highly substituted C_5 carbon. Accordingly, intramolecular attack by the epoxide oxygen should be preferred at that carbon. Indeed, Ishibe and colleagues have observed that the distribution of isomeric 2-pyrones obtained by photoisomerization of 4-pyrones is similarly sensitive to the electronic effects of the substituents at C_3 and C_5 of the 4-pyrone reactants.[13] Furthermore, as the epoxide oxygen–C_5 bond begins to form, the developing positive charge at C_2 would be stabilized by the methyl group at that position. In an identical manner, methyl



group stabilization of the developing positive charge has been shown to be important in controlling the direction of cyclopropane and aziridine migrations in photochemically generated bicyclohexenyl and azabicyclohexenyl cations.[14,15]

In view of these electronic effects, it is quite reasonable that upon irradiation of **29H$^+$** Barltrop and Day observed **7H$^+$**, the product of migration toward C_5, to predominate over the 3,5-dimethyl-2-hydroxy cation (**30H$^+$**) by a factor of almost 16.[11] Interestingly, according to our previous arguments, the methyl substitution pattern in 2,5-dimethyl-4-hydroxypyrylium cation should also enhance the rate of epoxide migration relative to solvent trapping. It is consistent, therefore, that a bisulfate adduct was not observed in this isomerization.

In the case of the 2,3-dimethyl-4-hydroxypyrylium cation (**8H$^+$**) the electronic effects of the ring methyl groups do not favor migration in a single direction. Thus, although substitution at the oxyallyl moiety favors bond formation between the epoxide oxygen and C_3 with eventual formation of the 5,6-dimethyl-2-hydroxypyrylium cation (**3H$^+$**), migration in the opposite direction to yield the isomeric 3,4-dimethyl cation **9H$^+$** is favored by the methyl group at C_3. Consistent with these opposing electronic effects, we have observed that 5,6-dimethyl-2-hydroxypyrylium cation formation is favored by a factor of only ~1.5.

Although these electronic effects are consistent with the formation of 4,5,6-trimethyl-2-hydroxypyrylium cation (**19H$^+$**) as the major product from photolysis of 2,3,6-trimethyl-4-hydroxypyrylium cation (**18H$^+$**), the apparent regiospecificity of the reaction is somewhat surprising and suggests that other factors are also important in controlling the direction of epoxide migration.

Experimental Section

General Procedures. Nuclear magnetic resonance spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer (PE) R-24B spectrometer. Unless otherwise stated, chemical shifts were measured relative to internal Me_4Si. Infrared spectra were recorded on a PE-397 spectrometer. Gas chromatography was performed on a PE-3920 FID instrument equipped with either 6 ft or 10 ft × $^1/_8$ in. (analytical) or 6 ft × $^1/_4$ in. (preparative) columns packed with 2% Carbowax 20M-TPA on Chromosorb G. Mass spectra were recorded on a Dupont 21-491 spectrometer. Elemental analyses were determined by MicAnal, Tucson, AZ.

Preparation of 4-Hydroxypyrylium Cations. All 4-hydroxypyrylium cations were prepared by dissolving the corresponding 4-pyrones in chilled AR grade concentrated H_2SO_4. For analytical reactions, 20 mg of the 4-pyrone was dissolved in 0.35 mL of H_2SO_4 while for preparative scale irradiations approximately 240 mg of the 4-pyrone was dissolved in 8.0 mL of H_2SO_4.

Preparation of 4-Pyrones. Whereas 2,6-dimethyl-4-pyrone (**1**) is commercially available, 2,3,6-trimethyl-4-pyrone (**18**) [mp 77–78 °C (lit.[16] mp 78 °C); IR (KBr) 1670, 1610, 1420, 1380, 1190, 1050 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.93 (s, 3 H), 2.26 (s, 3 H), 2.29 (s, 3 H), 6.03 (s, 1 H); mass spectrum, *m/e* (relative intensity) 138 (100), 110 (16), 109 (30), 95 (33), 85 (69), 69 (10), 43 (25)] and 2,3,4,6-tetramethyl-4-pyrone (**22**) [mp 92–93 °C (lit.[17] mp 92 °C); IR (KBr) 1665, 1600, 1430, 1390, 1380, 1190, 1040 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.97 (s, 6 H), 2.28 (s, 6 H); mass spectrum, *m/e* (relative intensity) 152 (100), 137 (15), 124 (33), 123 (37), 109 (89), 99 (87), 97 (8), 95 (5), 83 (15), 81 (11), 70 (12), 56 (7), 55 (10), 53 (28)] were prepared by condensing 2-butanone or 3-pentanone with acetic acid in the presence of polyphosphoric acid according to the procedure developed by Letsinger.[18] The syntheses of 2,3-dimethyl- and 2-methyl-3-ethyl-4-pyrones (**8** and **13**) are modifications of Dorman's synthesis of 2-methyl-4-pyrone.[19]

2,3-Dimethyl-4-pyrone (8). 3-Methyl-2,4-pentanedione (86 g, 0.75 mol, bp 168–170 °C, 70% yield from 2,4-pentanedione[20]) was ketalized by refluxing for 2.5 h with ethylene glycol (46 g, 0.75 mol), and a catalytic quantity of *p*-toluenesulfonic acid in 650 mL of benzene with continuous removal of water via a Dean–Stark trap. The resulting mixture was neutralized by addition to a rapidly stirred solution of 10% aqueous NaOH saturated with NaCl. The organic phase was washed with 4 × 100 mL water, dried over Na_2SO_4, and concentrated. Distillation provided 3-methyl-4,4-(ethylenedioxy)pentan-2-one as a colorless liquid [bp 49–52 °C (1 torr), yield 36 g (0.27 mol, 36%); IR (neat) 2850–3000, 1750, 1700, 1450, 1350 cm^{-1}; NMR (60 MHz, neat) δ 0.86 (d, 3 H, *J* = 7 Hz), 1.00 (s, 3 H), 1.97 (s, 3 H), 2.75 (q, 1 H, *J* = 7 Hz), 2.77 (m, 4 H)].

Acetylation at C-1 was accomplished by slowly adding a solution of ketal (30 g, 0.19 mol) and freshly distilled diethyl oxalate (28 g, 0.19 mol) in 200 mL of anhydrous methanol at 17–22 °C to a stirred solution of sodium methoxide (from 4.4 g sodium, 0.19 mol) in 150 mL of anhydrous methanol. The resulting solution was allowed to stir for 2 h at 17–22 °C and then overnight at room temperature. The solution was then neutralized by the addition of 5 mL of concentrated H_2SO_4 in 100 mL of water and extracted with 3 × 100 mL of $CHCl_3$ and 100 mL of benzene. The combined extracts were washed with 50 mL of water, dried over Na_2SO_4, and concentrated to leave 31 g of crude ethyl 2,4-diketo-5-methyl-6,6-(ethylenedioxy)heptanoate.

The ketal ester was hydrolyzed and cyclized by stirring at room temperature with 250 mL of 0.5 M HCl for 24 h followed by 2 h at reflux. Filtration of the cooled solution provided 3.1 g of a slightly yellow solid. Concentration of the aqueous acid solution provided an additional 7.7 g of the same material. Recrystalli-

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zation from acetone provided 2,3-dimethyl-4-pyrone-6-carboxylic acid as white needles: mp 237–238 °C dec; yield 10.8 g (0.064 mol, 33.8%); IR (KBr) 2250–3000, 1730, 1645, 1595, 1550, 1445, 1330, 1260, 1205, 1160, 930, 880, 780, 750 cm^{-1}; NMR (60 MHz; Me_2SO-d_6) δ 1.76 (s, 3 H), 2.25 (s, 3 H), 6.70 (2, 1 H). Anal. Calcd for $C_8H_8O_4$: C, 57.15; H, 4.80. Found: C, 57.28; H, 4.99.

2,3-Dimethyl-4-pyrone-6-carboxylic acid (1.0 g, 5.9 mmol) was decarboxylated at 240 °C and atmospheric pressure with a catalytic amount of copper powder in a Kugelröhr oven. A colorless liquid was collected which quickly solidified. Sublimation at 0.1 torr gave 2,3-dimethyl-4-pyrone as white crystals: mp 79–80 °C; yield 0.39 g (3.1 mmol, 53%); IR (CCl_4) 1665, 1640, 1430, 1355 cm^{-1}; NMR (60 MHz; CCl_4) δ 1.86 (s, 3 H), 2.25 (s, 3 H), 6.18 (d, 1 H, J = 5.4 Hz), 7.58 (d, 1 H, J = 5.4 Hz); mass spectrum, m/e (relative intensity) 124 (100), 95 (10), 71 (50), 43 (18.2). Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.76; H, 6.67.

2-Methyl-3-ethyl-4-pyrone (13). 3-Ethyl-2,4-pentanedione (bp 177–180 °C, 30% yield from 2,4-pentanedione[20]) was converted to 2-methyl-3-ethyl-4-pyrone-6-carboxylic acid by the procedures described for 2,3-dimethyl-4-pyrone-6-carboxylic acid. 2-Methyl-3-ethyl-4-pyrone-6-carboxylic acid was recrystallized from acetone to yield white needles: mp 210–212 °C dec; 69% yield from the ketal; IR (KBr) 2250–3000, 1730, 1640, 1595, 1545, 1440, 1340, 1255, 1155, 925, 880, 785, 735 cm^{-1}; NMR (60 MHz; Me_2SO-d_6) δ 0.90 (t, 3 H, J = 7.5 Hz), 2.30 (s, 3 H), 2.3 (q, 2 H, J = 7.5 Hz), 6.70 (s, 1 H). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.36; H, 5.70.

2-Methyl-3-ethyl-4-pyrone-6-carboxylic acid (0.60 g, 3.3 mmol) was decarboxylated at 220 °C and atmospheric pressure with a catalytic amount of copper powder in a Kugelröhr oven. A colorless liquid was collected which was redistilled (Kugelröhr) to give 2-methyl-3-ethyl-4-pyrone: bp 98–101 °C (0.4 torr); yield 0.32 g (2.3 mmol, 70%); IR (CCl_4) 2980, 2940, 1660, 1635 cm^{-1}; NMR (60 MHz; CCl_4) δ 0.90 (t, 3 H, J = 7.5 Hz), 2.17 (s, 3 H), 2.26 (q, 2 H, J = 7.5 Hz), 6.04 (d, 1 H, J = 6.0 Hz), 7.67 (d, 1 H, J = 6.0 Hz); mass spectrum, m/e (relative intensity) 138 (100), 137 (99), 123 (11.6), 110 (11.0), 71 (40.4), 69 (23.2), 67 (25.4), 53 (24.3), 52 (5.1), 51 (6.3), 50 (3.8), 43 (23.5). Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.27, H, 7.28.

2,6-Di(methyl-d_3)-3-methyl-4-pyrone (18-d_6). 2,3,6-Trimethyl-4-pyrone (0.10 g, 0.73 mmol) was dissolved in 2.0 mL of CH_3OD in which a small sliver of sodium had been dissolved. The solution was protected from light and allowed to stand at room temperature for 12 days. The CH_3OD was removed by rotary evaporation and the residue dissolved in CCl_4. Filtration and concentration left a white solid which was sublimed at 0.1 torr to give 91.4 mg of white crystals [mp 76–78 °C; NMR (60 MHz, CCl_4) δ 1.80 (s, 3 H), 5.83 (s, 1 H) and residual C_2 and C_6 methyl protons as a broad signal at δ 2.03].

2,6-Di(methyl-d_3)-3,5-dimethyl-4-pyrone (22-d_6). 2,3,5,6-Tetramethyl-4-pyrone (0.100 g, 0.658 mmol) was treated as above. Sublimation at 0.15 torr gave 89 mg of white crystals [mp 92–93 °C, NMR (60 MHz, CCl_4) δ 1.70 (s) and residual C_2 and C_6 methyl protons as a broad singlet at δ 2.03].

5,6-Dimethyl-2-pyrone (3). 4-Methyl-5-oxohexanoic acid[21] (10 g, 0.069 mol) was refluxed for 4 h in 25 mL of acetyl chloride. After standing at room temperature for 18 h, the acetyl chloride was removed at atmospheric pressure. Distillation of the residue gave 5,6-dimethyl-3,4-dihydro-2-pyrone as a colorless liquid: bp 90–91 °C (12 torr) (lit.[22] bp 90 °C at 15 torr); 6.6 g (0.052 mol, 75%); IR (neat) 2935, 1770, 1445, 1260, 1145, 870 cm^{-1}; NMR (60 MHz, neat) δ 1.70 (s, 3 H), 1.85 (s, 3 H), 2.2–2.7 (m, 4 H).

5,6-Dimethyl-3,4-dihydro-2-pyrone (8.5 g, 0.067 mol), N-bromosuccinimide (12.3 g, 0.069 mol), and benzoyl peroxide (0.35 g) in 225 mL of CCl_4 were refluxed for 1 h. The mixture was cooled and filtered. Most of the CCl_4 was removed by distillation, triethylamine (140 mL) was added, and the mixture heated under reflux for 0.5 h. Triethylamine was removed by distillation at atmospheric pressure. Distillation of the residue (115–125 °C at 8 torr) gave impure 5,6-dimethyl-2-pyrone which was purified by recrystallization from petroleum ether: mp 60–61 °C (lit.[22] mp 62–63 °C); 0.95 g (7.7 mmol, 11%); IR (CCl_4) 3040, 2940, 1750, 1650, 1450, 1295, 1085 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 2.00 (s, 3 H), 2.23 (s, 3 H), 6.15 (d, 1 H, J = 9.5 Hz), 7.20 (d, 1 H, J = 9.5 Hz); mass spectrum, m/e (relative intensity) 124 (100), 109 (16), 96 (78), 95 (26.5), 81 (34), 67 (15), 57 (12.5), 53 (59), 51 (15), 43 (73).

3,6-Dimethyl-2-pyrone (11). Ethanolic sodium ethoxide (0.5 mL, 10%) was added dropwise to a well-stirred solution of diethyl methylmalonate (62.6 g, 0.360 mol) and methyl vinyl ketone (23.8 g, 0.340 mol) in absolute methanol (100 mL). After the vigorous reaction subsided, stirring was continued for 2 h and the solution was then acidified with dilute HCl (60 mL) and extracted with 4 × 100 mL of ether. The combined ether extract was dried over $MgSO_4$ and concentrated. Distillation gave 5,5-dicarbethoxy-2-hexanone as a slightly yellow liquid: bp 128–131 °C (1.5 torr) (lit.[23] bp 114–116 °C at 0.4 torr); yield 62 g (0.25 mol, 73%); IR (neat) 1715, 1685, 1190 cm^{-1}; NMR (60 MHz) δ 1.1 (t, 6 H, J = 6 Hz), 1.2 (s, 3 H), 2.0 (s, 3 H), 2.3 (m, 4 H), 4.06 (q, 4 H, J = 6 Hz).

Saponification was accomplished by treating the diester (62 g, 0.25 mol) with hot ethanolic KOH. The resulting dipotassium salt [NMR (60 MHz, D_2O) δ 1.2 (s, 3 H), 2.3 (s, 3 H), 2.8–1.9 (m, 4 H)] was dissolved in water (300 mL), acidified, and extracted with ether. The latter was dried over $MgSO_4$ and concentrated to yield the dicarboxylic acid which was decarboxylated (130 °C, 3 h) to yield 5-oxo-2-methylhexanoic acid.[24] The crude acid was refluxed in acetic anhydride (100 mL) for 3 h and concentrated by distillation at atmospheric pressure. Distillation of the residue at reduced pressure gave 3,6-dimethyl-3,4-dihydro-2-pyrone as a colorless liquid: bp 99–101 °C (27 torr); 5.1 g (40 mmol, 16% from diester); IR (neat) 2950, 1775, 1450, 1400, 1300, 1150 cm^{-1}; NMR (60 MHz, CCl_4) δ 1.2 (d, 3 H, J = 7 Hz), 1.9 (s, 3 H), 2.4 (m, 3 H), 4.95 (m, 1 H).

3,6-Dimethyl-3,4-dihydro-2-pyrone (5.1 g, 40 mmol) was treated with N-bromosuccinimide followed by triethylamine as described earlier. Kugelröhr distillation gave 3,6-dimethyl-2-pyrone as a slightly yellow oil [bp 106–109 °C (25 torr), 2.1 g (17 mmol, 42%)] which was further purified by column chromatography (silica gel, 40% ether–hexane) to give white needles: mp 46–47 °C (lit.[25] mp 49–50 °C); IR (CCl_4) 1725, 1650 cm^{-1}; NMR (60 MHz, CCl_4) δ 2.0 (s, 3 H), 2.2 (s, 3 H), 5.75 (d, 1 H, J = 7 Hz), 6.92 (d, 1 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 124 (100), 109 (15), 97 (25), 96 (19), 95 (13), 94 (17), 82 (32), 69 (25), 68 (52), 67 (25), 57 (12), 56 (24), 55 (22), 53 (14), 45 (34), 43 (93).

5-Methyl-6-ethyl-2-pyrone (15). Methanolic KOH (10 mL, 30%) was added dropwise to a stirred mixture of 3-pentanone (550 mL, 5.21 mol) and acrylonitrile (34.0 mL, 0.516 mol) while the temperature was maintained below 30 °C. The mixture was stirred overnight at room temperature, acidified with dilute H_2SO_4, washed with saturated aqueous NaCl, and dried over $MgSO_4$. The unreacted reactants were removed by distillation at atmospheric pressure and the residue was distilled to provide 4-methyl-5-oxoheptanenitrile as a colorless liquid: bp 112–114 °C (8 torr); 25.7 g (0.185 mol, 36%); IR (neat) 2250, 1715 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.93 (t, 3 H, J = 7 Hz), 1.07 (d, 3 H, J = 7 Hz), 1.73 (m, 2 H), 2.33 (m, 5 H).

4-Methyl-5-oxoheptanenitrile (46.0 g, 0.331 mol) was hydrolyzed by refluxing in concentrated HCl (100 mL) for 4 h. The solution was neutralized with 40% aqueous NaOH, reacidified with dilute aqueous HCl, and extracted with 6 × 50 mL of ether. The combined ether extract was dried over $MgSO_4$ and concentrated. Distillation provided 4-methyl-5-oxoheptanoic acid as a pale-yellow liquid: bp 108–109 °C (0.25 torr); 37.5 g (0.237 mol, 72%); IR (neat) 3500–2500 br, 1740, 1710 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.97 (t, 3 H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz), 1.68 (m, 2 H), 2.32 (m, 5 H), 11.90 (s, 1 H).

Cyclodehydration was accomplished by refluxing 4-methyl-5-oxoheptanoic acid (36.0 g, 0.228 mol) in acetyl chloride (175 mL) for 4 h. After removal of the acetyl chloride at atmospheric pressure, distillation gave 3,4-dihydro-5-methyl-6-ethyl-2-pyrone as a colorless liquid: bp 106–108 °C (17 torr); 27.2 g (0.194 mol, 85%); IR (neat) 1765, 1700, 1150 cm^{-1}; NMR (60 MHz, CCl_4) δ

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1.03 (t, 3 H, J = 7 Hz), 1.67 (s, 3 H), 2.27 (m, 6 H).

3,4-Dihydro-5-methyl-6-ethyl-2-pyrone (27.2 g, 0.194 mol) was treated with N-bromosuccinimide followed by triethylamine as described earlier. The residue was distilled (8 torr) and the fraction boiling from 105–120 °C was collected as a yellow oil. Crystallization of a portion of this oil from petroleum ether gave 5-methyl-6-ethyl-2-pyrone as white crystals that were further purified by sublimation at 0.25 torr: mp 41.5–42 °C; IR (CCl_4) 2980, 2920, 1740, 1650, 1300 cm^{-1}; NMR (60 MHz, CCl_4) δ 1.17 (t, 3 H, J = 7 Hz), 1.90 (s, 3 H), 2.43 (q, 2 H, J = 7 Hz), 5.80 (d, 1 H, J = 9.5 Hz), 6.87 (d, 1 H, J = 9.5 Hz); mass spectrum, m/e (relative intensity) 138 (17), 124 (10), 123 (10), 109 (14), 110 (18), 95 (4), 81 (7), 67 (14), 53 (21), 43 (100).

6-Methyl-5-ethyl-2-pyrone (16). Starting with the monocyanoethylation of 2-pentanone, this was prepared by the analogous procedures used in the synthesis of 5-methyl-6-ethyl-2-pyrone. The intermediates and final product had the following characteristics.

4-Ethyl-5-oxohexanenitrile: colorless liquid; bp 126–127 °C (15 torr) (lit.[26] bp 115–116 °C, 10 torr); 37% yield; IR (neat) 2250, 1710 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.93 (t, 3 H, J = 7 Hz), 1.72 (m, 4 H), 2.13 (s, 3 H), 2.47 (m, 3 H).

4-Ethyl-5-oxohexanoic acid: colorless liquid; bp 104–105 °C (0.2 torr) (lit.[26] bp 151–152 °C, 5 torr); 51% yield; IR (neat) 3500–2500, 1740, 1710 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.73 (t, 3 H, J = 7 Hz), 1.70 (m, 4 H), 2.10 (s, 3 H), 2.23 (m, 3 H), 11.7 (s, 1 H).

3,4-Dihydro-6-methyl-5-ethyl-2-pyrone: colorless liquid; bp 95–97 °C (8 torr) (lit.[26] bp 94–96 °C, 8 torr); 91% yield; IR (neat) 1760, 1700, 1150 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.93 (t, 3 H, J = 7 Hz), 1.90 (s, 3 H), 2.12 (q, 2 H, J = 7 Hz), 2.40 (m, 4 H).

6-Methyl-5-ethyl-2-pyrone: colorless liquid: (lit.[27] bp 121–123 °C, 7 torr); preparative GC ($^1/_4$ in. × 6 ft column packed with 2% Carbowax 20 M on 60–80-mesh Chromasorb G at 190 °C); IR (CCl_4) 1745, 1650 cm^{-1}; NMR (60 MHz, CCl_4) δ 1.07 (t, 3 H, J = 7 Hz), 2.10 (s, 3 H), 2.23 (q, 2 H, J = 7 Hz), 5.83 (d, 1 H, J = 9.5 Hz), 6.97 (d, 1 H, J = 9.5 Hz); mass spectrum, m/e (relative intensity) 138 (31), 137 (21), 109 (35), 110 (24), 97 (57), 57 (10), 55 (100).

4,5,6-Trimethyl-2-pyrone (19). 3-Methyl-3-penten-2-one[28] (25.0 g, 0.255 mol) was added dropwise to a stirred solution of diethyl malonate (40.8 g, 0.255 mol) and sodium ethoxide (from 0.4 g sodium) in absolute ethanol (100 mL) at 0 °C, and the resulting solution was stored at 0 °C for 3 days. After acidification with dilute H_2SO_4, the ethanol was removed by rotary evaporation. The residue was extracted with 3 × 100 mL portions of ether, and the combined ether extracts were dried over $MgSO_4$ and concentrated. Distillation gave 5,5-dicarbethoxy-3,4-dimethyl-2-pentanone as a colorless liquid: bp 103–106 °C (0.2 torr); 42.0 g (0.163 mol, 64%); IR (neat) 1715, 1685, 1200 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.93 (d, 3 H, J = 6 Hz), 1.03 (d, 3 H, J = 6 Hz), 1.20 (t, 6 H, J = 7 Hz), 2.03 (s, 3 H), 2.43 (m, 2 H), 3.30 (d, 1 H, J = 6 Hz), 4.07 (q, 4 H, J = 7 Hz).

The above diester (5.0 g, 19 mmol) was dissolved in concentrated H_2SO_4 (15 mL) and added dropwise to boiling water (100 mL), and the resulting solution was allowed to reflux overnight. The cooled solution was extracted with 6 × 25 mL of ether and the combined ether extract was washed with aqueous sodium bicarbonate. The latter aqueous solution was acidified and extracted with 5 × 25 mL of ether and the ether was dried over $MgSO_4$ and concentrated. Distillation gave 3,4-dimethyl-5-oxohexanoic acid: bp 91–94 °C (13 torr); 2.2 g (14 mmol, 74%); IR (neat) 3400–2500, 1720, 1460 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.93 (d, 3 H, J = 6.5 Hz), 0.97 (d, 3 H, J = 6.5 Hz), 2.07 (s, 3 H), 2.35 (m, 4 H), 11.3 (s, 1 H).

3,4-Dimethyl-5-oxohexanoic acid (3.0 g, 19.0 mmol) in acetyl chloride (15 mL) was refluxed for 4 h. The acetyl chloride was removed at atmospheric pressure and the residue distilled to give 3,4-dihydro-4,5,6-trimethyl-2-pyrone as a colorless liquid: bp 93–95 °C (10 torr); 1.8 g (13 mmol, 66%); IR (neat) 1730, 1670, 1140, 1115 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.97 (d, 3 H, J = 7 Hz), 1.63 (s, 3 H), 1.77 (s, 3 H), 2.35 (m, 3 H).

3,4-Dihydro-4,5,6-trimethyl-2-pyrone (1.00 g, 7.14 mmol) was treated with N-bromosuccinimide followed by triethylamine as described earlier. The resulting residue was extracted with hexane (50 mL), and the hexane solution was filtered and concentrated. The residual brown oil was distilled (Kugelröhr) at 0.1 torr and the distillate collected up to 130 °C. This material was subjected to silica gel (40–140 mesh) column chromatography. The column was eluted with 50 mL of 20% ether in hexane, 25 mL of 30% ether in hexane, and 125 mL of 40% ether in hexane; 5-mL fractions were collected. On the basis of GC analysis, fractions 26–33 were combined and concentrated. The resulting white solid was recrystallized from hexane to give 4,5,6-trimethyl-2-pyrone as white needles: mp 72–73 °C; 0.11 g (0.80 mmol, 11%); IR (CCl_4) 1745, 1720, 1650 cm^{-1}; NMR (60 MHz, CCl_4) δ 1.87 (s, 3 H), 2.03 (s, 3 H), 2.17 (s, 3 H), 5.80 (s, 1 H); mass spectrum, m/e (relative intensity) 138 (39), 110 (100), 109 (37), 95 (52), 67 (95), 43 (57). Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.71; H, 7.14.

3,4,5,6-Tetramethyl-2-pyrone (23). This 2-pyrone was prepared starting with the Michael addition of diethyl methylmalonate to 3-methyl-3-penten-2-one[25] according to the procedure used in the synthesis of 4,5,6-trimethyl-2-pyrone. The intermediates and final product had the following properties.

5,5-Dicarbethoxy-3,4-dimethyl-2-hexanone: bp 102–104 °C (0.15 torr); 34% yield; IR (neat) 1730, 1250, 1100 cm^{-1}; NMR (60 MHz, CCl_4) δ 1.00 (d, 3 H, J = 7 Hz), 1.13 (d, 3 H, J = 7 Hz), 1.30 (t, 6 H, J = 7 Hz), 1.37 (s, 3 H), 2.13 (s, 3 H), 2.67 (m, 2 H), 4.13 (q, 4 H, J = 7 Hz).

2,3,4-Trimethyl-5-oxohexanoic acid [used without distillation]: 79% yield; IR (neat) 3400–2500, 1740, 1710 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.77 (d, 3 H, J = 7 Hz), 0.88 (d, 3 H, J = 7 Hz), 1.10 (d, 3 H, J = 7 Hz), 2.03 (s, 3 H), 2.37 (m, 3 H), 11.8 (s, 1 H).

3,4-Dihydro-3,4,5,6-tetramethyl-2-pyrone: bp 91–94 °C (11 torr); 85% yield; IR (neat) 1760, 1720, 1155 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.83 (d, 3 H, J = 7 Hz), 1.08 (d, 3 H, J = 7 Hz), 1.63 (s, 3 H), 1.77 (s, 3 H), 2.40 (m, 2 H).

3,4,5,6-Tetramethyl-2-pyrone: mp 49–49.7 °C (after sublimation at 0.15 torr); 6% yield; IR (CCl_4) 1713, 1650 cm^{-1}; NMR (60 MHz, CCl_4) δ 1.90 (s, 3 H), 1.93 (s, 3 H), 2.00 (s, 3 H), 2.17 (s, 3 H); mass spectrum, m/e (relative intensity) 152 (50), 125 (10), 124 (100), 123 (66), 110 (11), 109 (73), 81 (29), 79 (8), 77 (9), 43 (26). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.08; H, 7.93.

5-Methyl-2-acetylfuran (12). A mixture of 2-methylfuran (10 g, 0.12 mol), acetic anhydride (18 g, 0.18 mol), and H_3PO_4 (1.5 g, 85%) was heated (steam bath) for 2.5 h. The cooled solution was diluted with water and steam distilled. The distillate was extracted with 3 × 50 mL of ether and the ether extracts were dried over $MgSO_4$ and concentrated. Distillation gave 5-methyl-2-acetylfuran: bp 48–52 °C (4 torr) (lit.[29] bp 68–69 °C at 7 torr); 2.2 g (18 mmol, 15% yield). An analytically pure sample was collected by preparative GC: IR (CS_2) 1670, 1285, 1210, 1100, 1020, 920, 790 cm^{-1}; NMR (100 MHz, CCl_4) δ 2.31 (s, 3 H), 2.37 (d, 3 H, J = 1 Hz), 6.06 (d of q, 1 H, J = 4 Hz, 1 Hz), 6.92 (d, 1 H, J = 4 Hz); mass spectrum, m/e (relative intensity) 124 (100), 97 (41), 96 (36), 95 (18), 82 (13), 81 (16), 71 (49), 69 (18), 68 (38), 67 (25), 54 (21), 53 (26), 43 (49); 2,4-DNP, mp 210–11 °C (lit.[29] mp 210 °C).

5-Methyl-2-propionylfuran (17): prepared as above by heating 2-methylfuran (10 g, 0.12 mol), propionic anhydride (23 g, 0.18 mol), and H_3PO_4 (1.5 mL, 85%) for 3 h. After workup, distillation gave 5-methyl-2-propionylfuran: bp 72–74 °C (10 torr) (lit.[29] bp 100 °C at 22 torr); 6.6 g (48 mmol, 40% yield); IR (CS_2) 2985, 2945, 1670, 1250, 1200, 1110, 1010, 900, 780 cm^{-1}; NMR (100 MHz, CCl_4) δ 1.14 (t, 3 H, J = 7 Hz), 2.38 (s, 3 H), 2.73 (q, 2 H, J = 7 Hz), 6.08 (d of q, 1 H, J = 4 Hz, 1 Hz), 6.96 (d, 1 H, J = 4 Hz); mass spectrum, m/e (relative intensity) 138 (25), 110 (100), 53 (14).

Irradiation and Analyses Procedures. For analytical reactions, the acid solutions were irradiated in a quartz NMR tube while preparative-scale reactions were carried out in a 25 cm ×

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7 mm i.d. quartz tube. Either type of sample was placed in a water-jacketed quartz condenser and irradiated under a continuous fine stream of nitrogen using six 8-W low-pressure Hg lamps arranged in a circular array of diameter 1.5 in. around the condenser.

Samples were monitored by NMR analyses at ambient temperature. The chemical shifts (δ) are reported in ppm downfield from Me_4Si with methylene chloride (δ 5.30) as a secondary standard.

The irradiated mixtures were neutralized by dropwise addition to a rapidly stirred aqueous suspension of aqueous sodium bicarbonate and extracted with ether. GC analyses were carried out on the concentrated ether extracts by using the 10 ft × $^1/_8$ in. o.d. column described earlier. Preparative collections were accomplished by using the 6 ft × $^1/_4$ in. o.d. column.

2,6-Dimethyl-4-hydroxypyrylium Cation ($1H^+$). GC analysis at 140 °C of the neutralized ether extract exhibited three products. Retentions of 4,6-dimethyl-2-pyrone (**7**), 5,6-dimethyl-2-pyrone (**3**), and 4,5-dimethyl-2-pyrone (**2**) relative to 2,6-dimethyl-4-pyrone (**1**) are 0.76, 0.80, and 1.29, respectively.

2,3-Dimethyl-4-hydroxypyrylium Cation ($8H^+$). GC analysis at 140 °C of the neutralized ether extract exhibited five products. Retentions of 5-methyl-2-acetylfuran (**12**), 3,6-dimethyl-2-pyrone (**11**), 3,4-dimethyl-2-pyrone (**9**), 5,6-dimethyl-2-pyrone (**3**), and 4,5-dimethyl-2-pyrone (**2**) relative to 2,3-dimethyl-4-pyrone (**8**) are 0.23, 0.64, 0.94, 1.27, and 2.01, respectively.

2-Methyl-3-ethyl-4-hydroxypyrylium Cation ($13H^+$). GC analysis at 140 °C of the neutralized ether extract exhibited four products. Retentions of 5-methyl-2-propionylfuran (**17**), 4-methyl-3-ethyl-2-pyrone (**14**), 5-methyl-6-ethyl-2-pyrone (**15**), and 6-methyl-5-ethyl-2-pyrone (**16**) relative to 2-methyl-3-ethyl-4-pyrone (**13**) are 0.35, 1.08, 1.38, and 1.61, respectively.

2,3,6-Trimethyl-4-hydroxypyrylium Cation ($18H^+$). GC analysis at 170 °C of the neutralized ether extract exhibited one product. The retention of 4,5,6-trimethyl-2-pyrone (**19**) relative to 2,3,6-trimethyl-4-pyrone (**18**) is 2.1.

2,3,5,6-Tetramethyl-4-hydroxypyrylium Cation ($22H^+$). GC analysis at 170 °C of the neutralized ether extract exhibited one product. The retention of 3,4,5,6-tetramethyl-2-pyrone (**23**) relative to 2,3,5,6-tetramethyl-4-pyrone (**22**) is 2.4.

Registry No. **1**, 1004-36-0; $\mathbf{1H^+}$, 41463-78-9; **3**, 4209-44-3; **8**, 73761-48-5; $\mathbf{8H^+}$, 62968-76-7; **11**, 53034-20-1; **12**, 1193-79-9; **13**, 92490-73-8; $\mathbf{13H^+}$, 62968-77-8; **15**, 62968-85-8; **16**, 72185-13-8; **17**, 10599-69-6; **18**, 13519-43-2; **18**-d_6, 92490-77-2; $\mathbf{18H^+}$, 73761-43-0; **19**, 14818-31-6; **22**, 14901-87-2; **22**-d_6, 92490-78-3; $\mathbf{22H^+}$, 51595-74-5; **23**, 51595-76-7; $CH_3C(O)CH(CH_3)C(O)CH_3$, 815-57-6; $HO(CH_2)_2OH$, 107-21-1; $CH_3C(O)CH(Et)C(O)CH_3$, 1540-34-7; $CH_3C(O)CH(CH_3)(CH_2)CO_2H$, 6818-07-1; $CH_2{=}CHC(O)CH_3$, 78-94-4; $(EtOC(O))_2C(CH_3)(CH_2)_2C(O)CH_3$, 10433-88-2; $CH_3CH_2C(O)CH_2CH_3$, 1629-58-9; $CH_3CH_2C(O)CH(CH_3)(CH_2)_2C{\equiv}N$, 33739-94-5; $CH_3CH_2C(O)CH(CH_3)(CH_2)_2CO_2H$, 59627-89-3; $CH_3(CH_2)_2C(O)CH_3$, 107-87-9; $CH_3C(O)CH(Et)(CH_2)_2C{\equiv}N$, 10413-02-2; $CH_3C(O)CH(Et)(CH_2)_2CO_2H$, 39517-97-0; $CH_3CH{=}C(CH_3)C(O)CH_3$, 565-62-8; $(EtOC(O))_2CHCH(CH_3)CH(CH_3)C(O)CH_3$, 16728-78-2; $CH_3C(O)CH(CH_3)CH(CH_3)CH_2CO_2H$, 90113-51-2; $(EtOC(O))_2C(CH_3)CH(CH_3)CH(CH_3)C(O)CH_3$, 92490-80-7; $CH_3C(O)CH(CH_3)CH(CH_3)CH(CH_3)CO_2H$, 92490-81-8; 3-methyl-4,4-(ethylenedioxy)pentan-2-one, 6050-54-0; ethyl 2,4-dioxo-5-methyl-6,6-(ethylenedioxy)heptanoate, 92490-74-9; 2,3-dimethyl-4-pyrone-6-carboxylic acid, 92490-75-0; 2-methyl-3-ethyl-4-pyrone-6-carboxylic acid, 92490-76-1; 5,6-dimethyl-3,4-dihydro-2-pyrone, 4054-96-0; diethyl methylmalonate, 609-08-5; 3,6-dimethyl-3,4-dihydro-2-pyrone, 20155-55-9; acrylonitrile, 107-13-1; 3,4-dihydro-5-methyl-6-ethyl-2-pyrone, 59627-90-6; 3,4-dihydro-6-methyl-5-ethyl-2-pyrone, 4054-97-1; diethyl malonate, 105-53-3; 3,4-dihydro-4,5,6-trimethyl-2-pyrone, 92490-79-4; 3,4-dihydro-3,4,5,6-tetramethyl-2-pyrone, 92490-82-9.

Stereoelectronic Effects in the Hydrolysis of Ethyl and Methyl Ethylene Phosphates

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Ethyl and methyl ethylene phosphates **1** are shown to hydrolyze with complete endocyclic cleavage between pH 8 and 15 to yield ethyl and methyl 2-hydroxyethyl phosphates **3**, respectively. A much slower reaction involving recyclization of the methyl hydroxyethyl phosphate **3** to form ethylene phosphate **4**, which undergoes rapid further hydrolysis to 2-hydroxyethyl phosphate **5**, is conveniently monitored by ^{31}P NMR. The strained cyclic five-membered ring phosphate triester **1** reacts 10^8- to 10^{12}-fold faster than its strain-free initial diester product **3** via a common phosphorane intermediate/transition state **2**. When **1** is hydrolyzed in $H_2{}^{18}O$, only mono-^{18}O-labeled ester **3** is formed but no doubly ^{18}O-labeled **3** is detected. All reactions proceed with complete P–O cleavage as monitored by ^{18}O isotope shifts on the ^{31}P signals of the products. These results are consistent with the stereoelectronic effect, and a mechanism involving a hexacoordinate phosphorus intermediate can be ruled out.

The rate of hydrolysis of five-membered-ring cyclic phosphates such as methyl ethylene phosphate and ethylene phosphate is 10^6 to 10^8 times that of their acyclic analogues, trimethyl phosphate and dimethyl phosphate, respectively.[1] Westheimer and co-workers[1] proposed that this rate acceleration was due to relief of ring strain in the five-membered rings. However, as they later pointed out,[2] the energy released in a strained cyclic ester in going to a "strain-free" cyclic phosphorane transition state is insufficient to explain the total lowering of activation energy. We proposed,[3] based on molecular orbital calculations, that a significant fraction of this difference comes from orbital stereoelectronic effects in the tirgonal-bipyramid transition states. In this article we provide experimental support for the stereoelectronic effect in the hydrolysis of cyclic five-membered-ring phosphate esters. Preliminary communication of a portion of these studies has been made.[4]

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