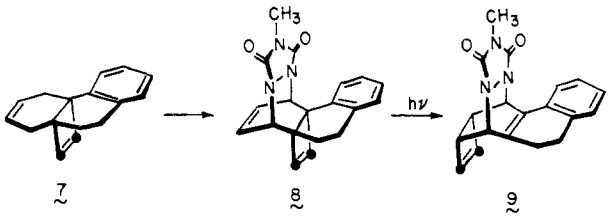
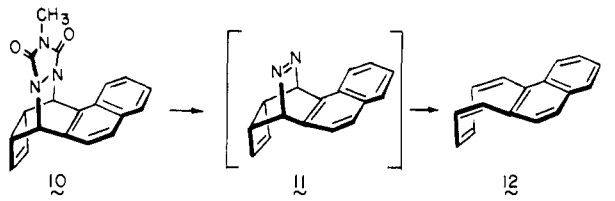
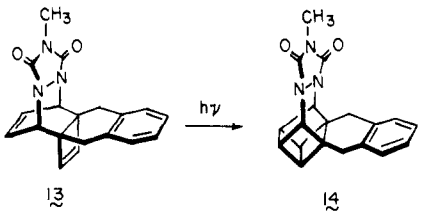
(NaOD, D_2O, dioxane) prior to Ramberg-Bäcklund rearrangement.[15] Subsequent elaboration of **8** resulted in introduction of the diagnostically useful isotopic labels into the cyclobutene sites. Photoisomerization of **8** provided **9** in addition to the anticipated bishomocubane-d_2. The ^1H NMR spectrum of **9** proved identical with that of **6** except that the two-proton olefinic absorption was now lacking and the multiplicities of the cyclobutyl protons were somewhat permuted. Unquestionably therefore, the trigonal cyclobutene carbons have formally maintained their integrity during the [3,3] shift.



When urazole **6** was irradiated with a tungsten lamp in the presence of *N*-bromosuccinimide (CH_2Cl_2 solution), HBr was lost spontaneously to give **10** directly (90%). Hydrolysis of **10** with boiling NaOH-*i*-PrOH under argon followed by MnO_2 oxidation of the resulting semicarbazide gave cyclooctatetraeno[*a*]naphthalene[16] (**12**, 70%), presumably via unstable azo compound **11**.



A hypothetical scheme for effecting the cleavage of **5** would involve homolytic rupture of that cubyl edge bond which gives rise in part to a benzylic free radical center.[17] Once this has occurred, introduction of the styrene and cyclobutene double bonds can result from cleavage of a second proximal strained bond. Alternatively, the ring opening may follow a concerted $[_\sigma 2_s + {}_\sigma 2_s]$ retrogression pathway. At the present time, no distinction can be made between these options. Notwithstanding, there are good reasons to believe that the ability to develop extended conjugation with the benzene ring at the transition state is a prerequisite for ring opening. For example, comparable irradiation of isomer **13** rapidly leads to **14** (93%),



but the latter is entirely stable even for extended reaction periods.[18] Therefore, in the absence of the special effects introduced by a properly positioned fused aryl substituent, the generally recognized photochemical inertness of the 1,8-bishomocubyl framework is restored.[19]

Supplementary Material Available: The crystallographic data for **6** (fractional coordinates (Table I), bond distances (Table II), and bond angles (Table III), together with observed and calculated structure factors (Table IV)) and a computer generated drawing of the final x-ray model (14 pages). Ordering information is available on any current masthead page.

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(2) See, for example, H. Musso, *Chem. Ber.*, **108**, 337 (1975); A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **31**, 1419 (1975); W. G. Dauben and L. N. Reitman, *J. Org. Chem.*, **40**, 841 (1975); R. Askani, I. Gurang, and W. Schwertfeger, *Tetrahedron Lett.*, 1315 (1975); R. D. Miller and D. L. Dolce, *ibid.*, 3813 (1974); E. Osawa, P. v. R. Schleyer, L. W. K. Chang, and V. V. Kane, *ibid.*, 4189 (1974).

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(11) $\delta_{Me_4Si}^{CDCl_3}$ 7.30–7.11 (m, 4), 5.40 (m, 1), 4.77 (m, 1), 3.63 (m, 2), 3.10–2.98 (m, 2), 3.02 (s, 3), 2.85–2.64 (m, 2), and 2.14–1.55 (m, 2).

(12) $\delta_{Me_4Si}^{CDCl_3}$ 7.32–7.07 (m, 4), 5.94 (m, 2), 5.42 (m, 1), 4.83 (m, 1), 3.36 (m, 2), 2.92–2.68 (m, 2), 2.92 (s, 3), and 2.52–2.17 (m, 2).

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(18) These data were first obtained in these laboratories by Dr. Tomas Kempe.

(19) This work was supported in part by a grant (CA-12115) from the National Institutes of Health.

(20) Camille and Henry Dreyfus Foundation Teacher-Scholar Grant Awardee, 1972–1977.

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Photoisomerization of 4-Hydroxypyrylium Cations. Furyl Cation Formation

Sir:

Previous reports have shown that 4-hydroxypyrylium cations undergo photoisomerization to 2-hydroxypyrylium cations.[1-4] We now wish to report that 2,3-dimethyl-4-hydroxypyrylium cation **1a** and 2-methyl-3-ethyl-4-hydroxypyrylium cation **1b** undergo photoisomerization to yield furyl cations **2a** and **2b**, respectively, as the major products. In these instances, 2-hydroxypyrylium cations **3a** and **4a** or **3b** and **4b** were observed as additional products.

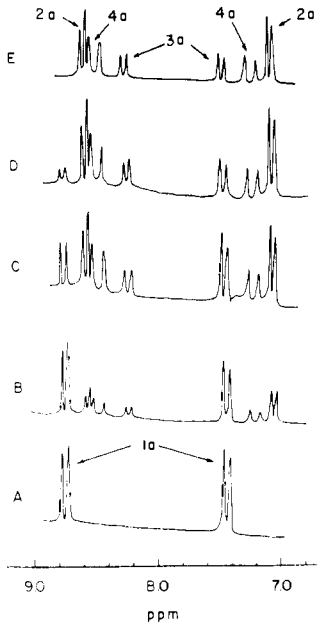
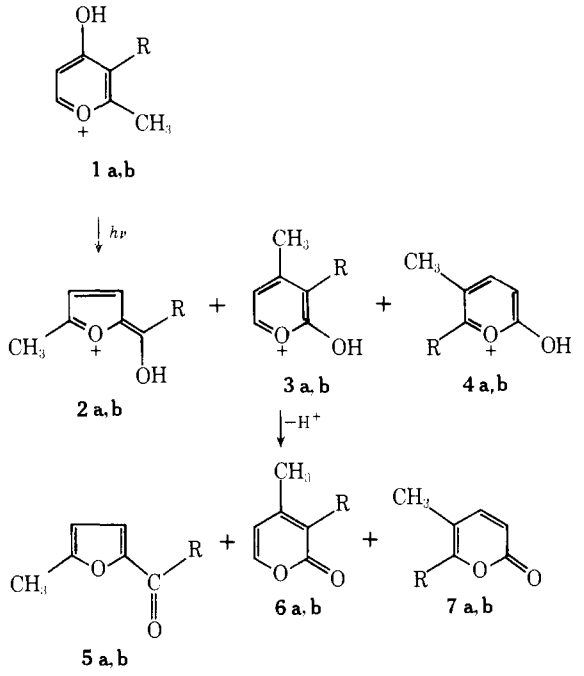


Figure 1. Partial NMR spectrum of **1a** in 96% H_2SO_4: A, before irradiation; B–E, after consecutive irradiations of 1 h each.

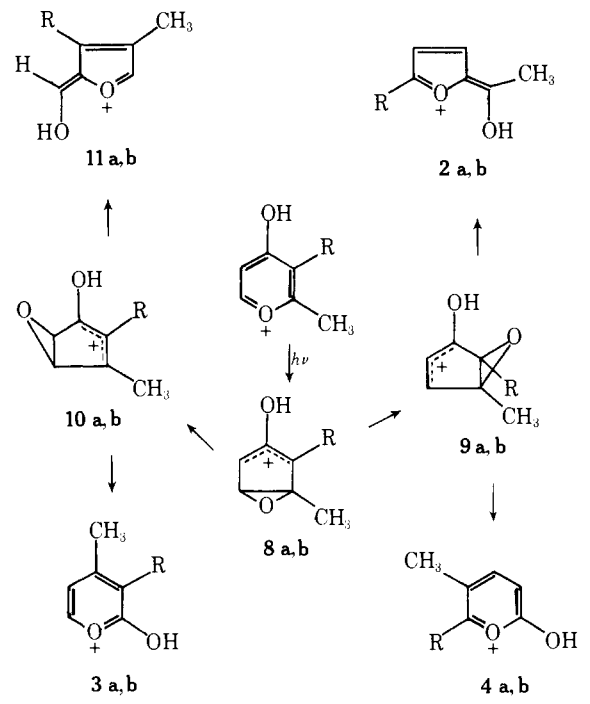


(a, R = CH_3; b, R = CH_3CH_2)

In 96% H_2SO_4, 2,3-dimethyl-4*H*-pyran-4-one gave a thermally stable solution of **1a** (λ_{max} 262 nm, ϵ 1.1 × 10^4; 100-MHz NMR δ 2.40 (s, 3 H), 2.88 (s, 3 H), 7.45 (d, J = 5 Hz, 1 H), 8.74 (d, J = 5 Hz, 1 H)). Figure 1 shows the δ 6.8–9.0 ppm portion of the 100-MHz spectrum of this cation before and after consecutive irradiations.[5] The spectra show the gradual disappearance of the vinyl protons of **1a** and the formation of three new pairs of vinyl doublets centered at δ 7.04 and 8.56 (J = 4.5 Hz), 7.43 and 8.22 (J = 5 Hz), and 7.20 and 8.46 ppm (J = 9 Hz), which were subsequently assigned to **2a, 3a,** and **4a** in relative yields of 47, 21, and 32%, respectively.[6] Consideration of these yields as a function of irradiation time indicates that none are intermediates in the formation of the others.

Neutralization and extraction of the irradiated solution yielded three products which were isolated by preparative gas

Scheme I



(a, R = CH_3; b, R = CH_3CH_2)

chromatography. The product eluting first (M^+ 124; IR (CS_2) 1670, 1285, 1210, 1100, 1020, 920, 790 cm^{-1}; 100-MHz NMR (CCl_4) δ 2.38 (d, $J \sim 1$ Hz, 3 H), 2.43 (s, 3 H), 6.17 (d of q, J = 4 Hz and ~1 Hz, 1 H), 7.12 (d, J = 4 Hz, 1 H); 2,4-DNP, MP 210–211 °C (lit.[7] 212 °C)) was assigned structure **5a** and was identical with an authentic sample of 2-methyl-5-acetylfuran.[8] The final product collected from the column (M^+ 124; IR (CCl_4) 3040, 2940, 1750, 1650, 1450, 1295, 1085 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.23 (s, 3 H), 6.15 (d, J = 9.5 Hz, 1 H), 7.20 (d, J = 9.5 Hz, 1 H)) was assigned structure **7a** on the basis of its chromatographic and spectroscopic identity with an authentic sample of 5,6-dimethyl-2*H*-pyran-2-one synthesized in this laboratory.[9] The spectroscopic properties of the product of intermediate retention time (M^+ 124; IR (CCl_4) 2950, 1720, 1440, 1350, 1130, 1035 cm^{-1}; 60-MHz NMR (CCl_4) δ 2.00 (s, 3 H), 2.08 (s, 3 H), 5.87 (d, J = 5 Hz, 1 H), 7.20 (d, J = 5 Hz, 1 H)) were consistent with a dimethyl-2-pyrone having adjacent ring protons isomeric with **7a.** Of the two remaining possible structures, viz., 3,4-dimethyl- and 3,6-dimethyl-2*H*-pyran-2-one, the observed coupling constant for these ring protons is more consistent with the assigned 3,4-dimethyl-2*H*-pyran-2-one structure, **6a.**[10] Furthermore, direct comparison confirmed that the isolated product is clearly different from an authentic sample of 3,6-dimethyl-2*H*-pyran-2-one.[11]

Redissolving **5a, 6a,** and **7a** in 96% H_2SO_4 resulted in thermally stable solutions of **2a, 3a,** and **4a** with combined NMR spectra identical with the spectrum observed upon photolysis of **1a.** This shows that no other unidentified products were formed in significant quantity and that neutralization of the photochemically generated cations was not accompanied by gross structural changes.

Photolysis of 4-hydroxypyrylium cation **1b** (λ_{max} 263 nm, ϵ 1.2 × 10^4; 100-MHz NMR δ 1.31 (t, J = 7 Hz, 3 H), 2.84 (q, J = 7 Hz, 2 H), 7.45 (d, J = 5 Hz, 1 H), 8.74 (d, J = 5 Hz, 1 H)) was accompanied by essentially identical changes in the vinyl region of the NMR spectrum to yield **2b, 3b,** and **4b** in relative yields of 61, 12, and 27%, respectively. Neutralization in this instance led to the isolation of **5b** and **7b,** which were identical with authentic samples of 2-methyl-5-propanoylfu-

ran[12] and 6-ethyl-5-methyl-2*H*-pyran-2-one,[13] respectively, and to **6b** which was identified as 3-ethyl-4-methyl-2*H*-pyran-2-one on the basis of its spectroscopic properties.[14]

2-Hydroxypyrylium cations **3a** and **4a** or **3b** and **4b** arising from irradiation of **1a** or **1b** can be adequately rationalized in terms of the mechanism previously suggested by us[1,2] and later by Barltrop and his colleagues,[3,4] which is outlined in Scheme I. Although the mechanistic details for the formation of furyl cations **2a** or **2b** are not clear, it seems likely that they arise from oxobicyclohexenyl cations **9a** or **9b** at the expense of **4a** or **4b**. This suggestion is consistent with the observation that the substituent at C-3 of **1a** or **1b** is found in the side chain of **2a** or **2b**. Failure to observe furyl cations of type **11** may indicate a reluctance of oxobiocyclohexenyl cations of type **10** to undergo this type of isomerization.[15] Alternatively, the known instability of furaldehydes in 96% H_2SO_4, even at 0 °C, may account for their absence.

Recently, Barltrop and his colleagues have shown that in certain cases 2-hydroxypyrylium cations arise via a sulfuric acid adduct, presumably formed by bisulfate anion trapping of a 4-hydroxyoxobicyclohexenyl cation of type **8**.[16] This type of intermediate is formed in particularly high yield and is readily observed upon photolysis of 3,5-dimethyl-4-hydroxypyrylium cation. Although we observe no such intermediates upon photolysis of **1a** or **1b** at room temperature, irradiation of **1a** at 0 °C was accompanied by the appearance of new methyl signals of low intensity in the NMR spectrum at δ 1.8, 1.9, and 2.1 ppm, similar in position to those observed upon photolysis of the 3,5-dimethyl-4-hydroxy cation.[16] Under these conditions, however, whereas the intensity of the NMR signals for furyl cation **2a** were not diminished, the formation of 2-hydroxypyrylium cations **3a** and **4a** was almost completely suppressed. The NMR signals due to these latter cations, however, increased at the expense of the new low intensity methyl signals after the irradiated solution was allowed to warm to room temperature. During these changes, however, no increase in the intensity of the furyl cation signals was observed. These observations indicate that whereas 2-hydroxypyrylium cations **3a** and **4a** may arise from a thermally labile bisulfate adduct, furyl cation **2a** is not formed from such an intermediate.

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(11) We are grateful to Mr. Martin Wai of Worcester Polytechnic Institute for the synthesis of this compound from 2-methyl-5-oxohexanoic acid. Cyclization in refluxing acetic anhydride gave 4,5-dihydro-3,6-dimethyl-2*H*-pyran-2-one which was converted to 3,6-dimethyl-2*H*-pyran-2-one by bromination (NBS) and dehydrobromination with triethylamine.
(12) Synthesized by treating 2-methylfuran with propanoic anhydride in the presence of phosphoric acid: 100-MHz NMR (CCl_4) δ 1.24 (t, J = 7.5 Hz, 3 H), 2.38 (d, J ~0.6 Hz, 3 H), 2.74 (q, J = 7.5 Hz, 2 H), 6.08 (d of q, J = 3 Hz and ~0.6 Hz, 1 H), 6.96 (d, J = 3 Hz, 1 H); IR (CCl_4) 2980, 2940, 1680, 1205, and 910 cm^{-1}.
(13) 6-Ethyl-5-methyl-2*H*-pyran-2-one was synthesized independently starting with the monocyanoethylation of 3-pentanone. See ref 9: 100-MHz NMR (CCl_4) δ 1.20 (t, J = 7.5 Hz, 3 H), 1.90 (s, 3 H), 2.44 (q, J = 7.5 Hz, 2 H), 5.92 (d, J = 9.6 Hz, 1 H), 6.92 (d, J = 9.6 Hz, 1 H); IR (CCl_4) 2980, 2940, 1735, 1642, and 1300 cm^{-1}.
(14) M^+ (124); IR (CCl_4) 2960, 1720, 1645 cm^{-1}; 100-MHz NMR (CCl_4) δ 1.08 (t, J = 7.5 Hz, 3 H), 2.10 (s, 3 H), 2.46 (q, J = 7.5 Hz, 2 H), 5.84 (d, J = 5.6 Hz, 1 H), 7.18 (d, J = 5.6 Hz, 1 H).
(15) Formation of furyl cations presumably involves ring opening of the oxobicyclohexenyl cation with considerable charge localization on C-6. In **9a** and **9b**, alkyl group substitution at C-6 would serve to stabilize this charge, while in **10a** and **10b**, positive charge would not be similarly stabilized. It also seems plausible that 3-hydroxypyrylium cations are transients in these isomerizations. Ring opening of such intermediates would be subject to identical substituent effects.
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(17) National Science Foundation Undergraduate Research Participant, June–Aug 1976.

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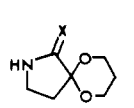
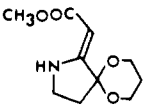
A Stereospecific Total Synthesis of *d,l*-Saxitoxin[1]

Sir:

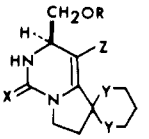
Saxitoxin is the neurotoxin isolated from Alaska butter clams (*Saxidomus giganteus*), toxic mussels (*Mytilus californianus*), and axenic cultures of *Gonyaulax catenella* and is one of the most toxic nonprotein substances known.[2] The structure of saxitoxin was established by x-ray crystallography.[3,4] The toxin was also found in aged extracts of scallops collected during a *Gonyaulax tamarensis* bloom.[2] Three new toxins in addition to saxitoxin were isolated from soft shell clams, *Mya arenaria*, collected during red tide blooms on the New England coast.[5] Two of the three new toxins were shown to be 11α- and 11β-hydroxysaxitoxins (gonyautoxin II and III).[6] In this communication we wish to report the first total synthesis of *d,l*-saxitoxin **13**.

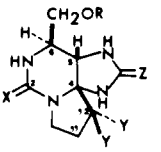


1 : X=O
2 : X=S



3





4 : X=S, Y=O, Z=CO_2CH_3, R=$CH_2C_6H_5$
5 : X=O, Y=O, Z=CO_2CH_3, R=$CH_2C_6H_5$
6 : X=S, Y=O, Z=$NHCONH_2$, R=$CH_2C_6H_5$
7 : X=S, Y=S, Z=$NHCONH_2$, R=$CH_2C_6H_5$

8 : X=S, Z=O, Y=$S(CH_2)_3S$, R=$CH_2C_6H_5$
10 : X=Z=NH, Y=$S(CH_2)_3S$, R=$CH_2C_6H_5$
11 : X=Z=NH, Y=$S(CH_2)_3S$, R=H
12 : X=Z=NH, Y=OH,OH, R=H
13 : Saxitoxin X=Z=NH, Y=OH,OH, R=$CONH_2$

Methyl 2-oxo-4-phthalimidobutyrate[7] was converted to the lactam **1**[8] (mp 104–105 °C) in two steps (1. $HO(CH_2)_3$-OH/*p*-TSA/$C_6H_5CH_3$/reflux, 2. $NH_2NH_2{\cdot}H_2O$/CH_3OH/reflux) in 74% yield. Phosphorus pentasulfide