to observe $T^{\pm}$, increases with *decreasing* basicity of the amine.

(2) Nucleophilic attack (k_1) is strongly affected by steric hindrance in the intermediate which, e.g., leads to the unusually large $k_1(Cl)/k_1(I)$ ratio of 24.5. It is shown that a possible alternative interpretation of this high ratio in terms of rate-limiting leaving-group departure is unattractive. It is also shown that the downward curvature in the plots of k_{obsd} vs amine concentration in the reactions of piperidine with **4-Cl** and **4-I** cannot possibly be due to the accumulation of an intermediate.

(3) β_{nuc} for piperidine and morpholine attack on **4-OMe** is 0.25, while for the intrinsic rate constant log $k_o \leq 0.87$ is estimated. This intrinsic rate constant is lower than log k_o for piperidine and morpholine addition to **4-H**, which is consistent with the loss of the resonance stabilization of **4-OMe** (8) being ahead of bond formation in the transition state.

(4) Among the kinetically equivalent competing pathways k_2, k_{2i}, and $K_a^{\pm}k_3^H$, the intramolecularly acid catalyzed leaving group departure from $T^{\pm}$ (k_{2i}) is shown to be dominant.

Experimental Section

Materials. **4-Cl**, **4-I**, and **4-OMe** were available from a previous study.[5] **4-SEt** was synthesized by adding 94 μL (1.27 mmol) of ethanethiol to a solution of 0.038 g (0.127 mmol) of **4-Cl** in 5 mL of acetonitrile. Upon addition of 177 μL (1.27 mmol) of triethylamine, a color change from pale yellow to bright yellow occurred. The solution was stirred for 1.5 h, poured into 25 mL of water, and extracted with 2 × 15 mL of dichloromethane. The dichloromethane layers were combined and washed with 5 × 25 mL water, dried over Na_2SO_4, and evaporated under reduced pressure. Recrystallization of the resulting yellow solid from 95% ethanol gave 7.7 mg (18%, first crop, mp 84–86 °C), 7.8 mg (18%, second crop, mp 84–87 °C): ^1H NMR (60 MHz, $CDCl_3$) δ 1.10 (t, 3 H, J = 7.2 Hz), 2.27 (q, 2 H, J = 7.2 Hz), 7.13 (s, 10 H); MS m/e 285 (M^+); UV/vis λ_{max} 365 nm (ε 1.08 × 10^4).

The piperidine and *n*-butylamine substitution products, **4-NRR′** were prepared as described by Rappoport and Topol.[2c] **4-Piperidine**: mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 1.70 (s, 6 H), 3.00 (s, 4 H), 7.17, 7.37, 7.53 (Ar-H, 10 H); MS m/e 308 (M^+); UV/vis λ_{max} 420 nm (ε 1.2 × 10^4). **4-*n*-BuNH$_2$**: mp 92–93 °C; ^1H NMR (CD_3CN) δ 0.79–0.84 (t, CH_3, 3 H), 1.24–1.33 (sextet, CH_3CH_2, 2 H), 1.47–1.56 (quintet, $CH_3CH_2CH_2$, 2 H), 3.08–3.10 (quartet, CH_2NH, 2 H); MS m/e 296 (M^+); UV/vis λ_{max} 368 nm (ε 2.17 × 10^4).

Piperidine, morpholine, pyrrolidine, *n*-butylamine, and triethylamine were refluxed over calcium hydride, distilled and stored at 4 °C in the dark. Dabco (1,4-diazabicyclooctane)[2.2.2] was recrystallized from hexane.

Kinetics. The fast rates were measured in a Durrum-Gibson stopped-flow spectrophotometer, the slow ones in a Perkin-Elmer 559A UV/vis spectrophotometer, both thermostatted and equipped with computerized data acquisition and analysis. The procedures, including the method of preparing solutions and pH measurements, were similar to the ones described in previous work.[30]

Acknowledgment. This research was supported by Grants CHE-8617370 and CHE-8921739 from the National Science Foundation (C.F.B.) and a grant from the US–Israel Binational Science Foundation, Jerusalem, Israel (Z.R.).

Registry No. **4-OMe**, 96746-56-4; **4-SET**, 85296-22-6; **4-Cl**, 57337-95-8; **4-I**, 55902-54-0; piperidine, 110-89-4; pyrrolidine, 123-75-1; morpholine, 110-91-8.

Supplementary Material Available: Tables S1–S4 listing kinetic data (10 pages). Ordering information is given on any current masthead page.

(30) Bernasconi, C. F.; Killion, R. B., Jr. *J. Org. Chem.* **1989**, *54*, 2878.

Pyrolysis of 9-Methylenespiro[3.5]nona-5,7-diene: A Route to Benzo-2-hexene-1,6-diyl, a Putative Intermediate in the Retro-Diels–Alder Reaction of Tetralin

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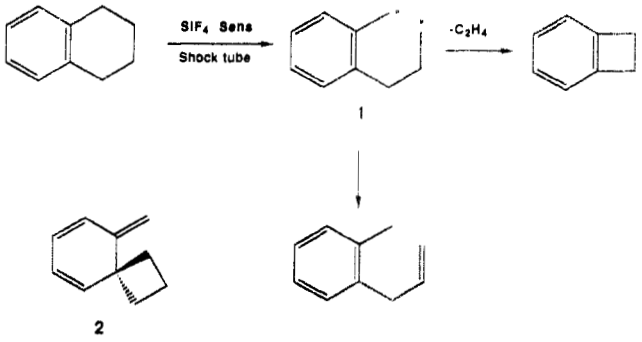
A precursor to the 1,6-biradical potentially formed in the retro-Diels–Alder reaction of tetralin, namely, 5-methylenespiro[bicyclo[2.2.1]hept-2-ene-6,1′-cyclobutan]-7-one (**9**) has been prepared and found to give tetralin and *o*-allyltoluene upon pyrolysis in solution below 100 °C and upon flash vacuum pyrolysis around 250 °C. The product ratio changes from 1:1 to 6:1 at higher temperatures. Rate-determining loss of CO from **9** to give 9-methylenespiro[3.5]nona-5,7-diene, **2**, has been demonstrated by trapping the triene with *N*-methyl- and *N*-phenyltriazolinedione in a reaction whose rate is independent of trapping agent concentration. The kinetics for loss of ketone, **9**, gave log k (s^{-1}) = 14.628 ± 0.038 − (30.554 ± 0.064)/2.3RT. Pyrolysis of *cis-syn*(to methylene)- and *trans*-1,2-dimethyl-9-methylenespiro[3.5]nona-5,7-diene gives the vinylcyclobutane rearrangement product, 2,3-dimetyltetralin, with a 4:1 and 2.7:1, respectively, preference for retention over inversion at the migrating carbon. Hydrogen shift products are also formed and by highly ordered transition states. One of these hydrogen shifts involves an unprecedented shift from the carbon remote from the vinyl group.

In tetralin pyrolyses, much attention has been focused on the intermediacy of the 1,6-biradical, **1**, that could result from benzylic C–C bond cleavage in tetralin. Thus, for example, in the SiF_4-sensitized laser pyrolysis of tetralin, benzocyclobutene and *o*-allyltoluene were observed as principal products.[1] Indene, styrene, and 1,2-dihydronaphthalene were also formed. The observation of *o*-allyltoluene and energetic considerations led authors to propose biradical **1** as an intermediate. Possible involve-

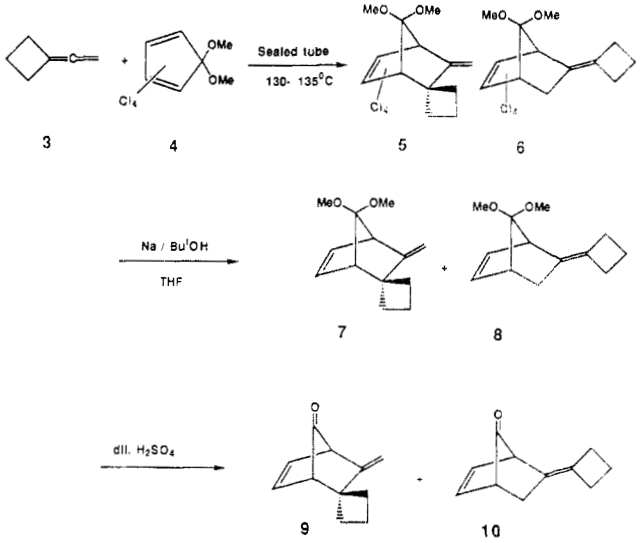
(1) Comita, P. B.; Berman, M. R.; Moore, C. B.; Bergman, R. G. *J. Phys. Chem.* **1981**, *85*, 3266.

0022-3263/90/1955-4575$02.50/0

Scheme I



Scheme II



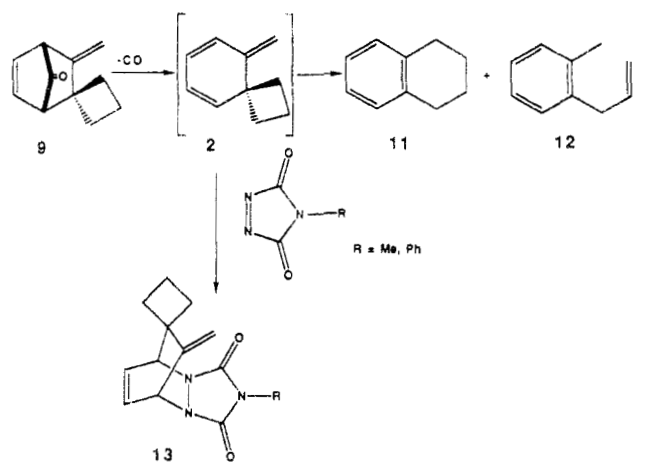
ment of **1** in the formation of 1,2-dihydronaphthalene was implicated. More recently, Tsang and Cui[2] have studied the decomposition of tetralin under shock tube conditions and have measured activation parameters for benzocyclobutene, *o*-allyltoluene, and styrene. These authors also propose **1** as an intermediate on the way to benzocyclobutene and o-allyltoluene (Scheme I). The question whether this biradical is involved and whether or not it might initiate radical reactions of tetralin has inspired us to look for an independent precursor which would generate **1**. To this end, the synthesis of and pyrolytic pathways available to spirotriene **2**, a potential precursor of **1**, are described.

Results

Synthesis of 5-Methylenespiro[bicyclo[2.2.1]hept-2-ene-6,1′-cyclobutan]-7-one (9). The norbornenone, **9**, a potential precursor of 9-methylenespiro[3.5]nona-**5,7-diene (2)**, was synthesized according to the reaction sequence shown in Scheme II. Reactions of vinylidenecyclobutane with 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene at 130–135 °C led to the regioisomeric cycloadducts **5** and **6** in nearly a 1:1 ratio. These cycloadducts were dechlorinated with sodium and *tert*-butyl alcohol in tetrahydrofuran to the corresponding ketals **7** and **8**, which could be hydrolyzed with 3 M H_2SO_4 to the respective ketones **9** and **10**. Pure samples of ketones **9** and **10** could be obtained by preparative GC separation of the precursor ketals **7** and **8** on a 12 ft (12 ft × $^1/_4$ in.) 20% OV 101 column on Chromosorb P. Spiro ketone **9** on both thermolysis and photolysis loses CO with production of tetralin

(2) Tsang, W.; Cui, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 1665.

Scheme III



Scheme IV

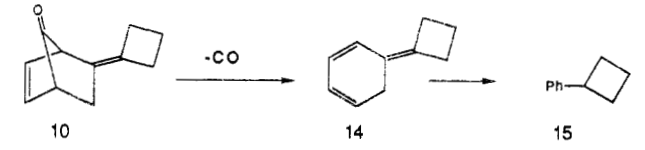


Table I. Kinetics of Decomposition of 9

temp, °C	k (s^{-1}) × 10^5
60.5	0.394 ± 0.021
80.0	5.292 ± 0.099
96.0	34.888 ± 0.597

E_a = 30.554 ± 0.064 kcal/mol
log A (s^{-1}) = 14.628 ± 0.038

(**11**) and *o*-allyltoluene (**12**). However, under no experimental conditions (including photolysis through Pyrex) could the desired spirotriene **2** be detected. However, pyrolysis of ketone **9** in degassed benzene-d_6 containing 2–3 molar excess of *N*-methyltriazolinedione (MTAD) at 80 °C under vacuum gave what appears from ^{1}H NMR and HRMS to be a Diels–Alder adduct, **13**. In a separate set of experiments, the rate of decomposition of the ketone was independent of the concentration of MTAD as long as the reagent was in excess. A similar adduct is formed when the pyrolysis of **9** was conducted in the presence of *N*-phenyltriazolinedione (Scheme III). In the presence of excess MTAD, no tetralin or *o*-allyltoluene was observed.

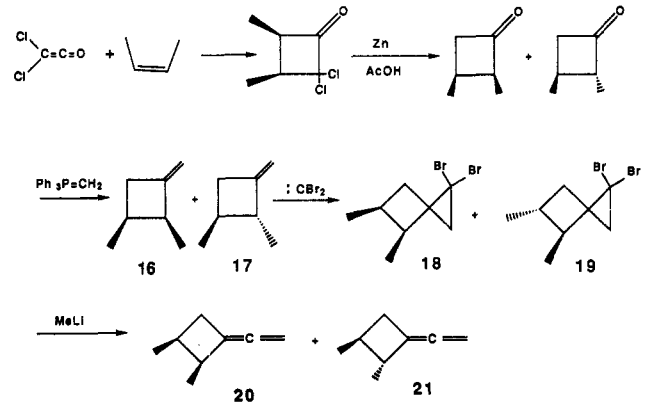
The tetralin–allyltoluene ratio from pyrolysis of **9** was found to be temperature dependent. Thus, flash vacuum pyrolysis (FVP) at 240 °C at 0.01 torr gave rise to tetralin and *o*-allyltoluene in a 5.6:1 ratio. This ratio changed to 1.3:1 at 96 °C and to 0.9:1 at 61 °C when the pyrolysis is carried out in CCl_4 solvent. This suggests that the formation of tetralin has an activation energy roughly 3 kcal/mol higher and a preexponential term roughly 100 times higher than that for formation of allyltoluene.

Kinetics of the decomposition of **9** were followed in CCl_4 in sealed NMR tubes at 60.5 °C, 80.0 °C, and at 96 °C, and activation parameters were determined (Table I).

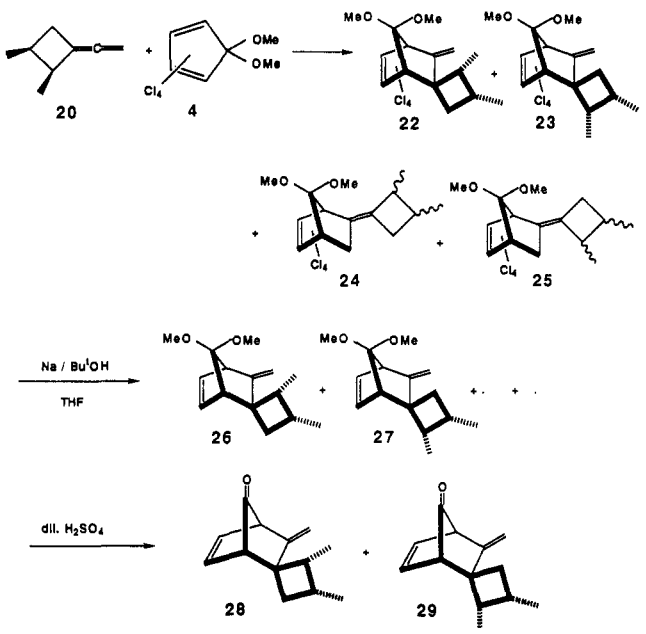
For comparison purpose, ketone **10** was thermolyzed in a sealed NMR tube at 79.6 °C, and the decomposition was monitored by ^{1}H NMR spectrometry. At short reaction times the product was the expected 5-cyclobutylidene-1,3-cyclohexadiene (**14**). However, at longer reaction times phenylcyclobutane (**15**) becomes the predominant product (Scheme IV).

Synthesis of 5-Methylenespiro[bicyclo[2.2.1]hept-2-ene-6,1′-(*cis*- and *trans*-2′,3′-dimethyl)cyclo-

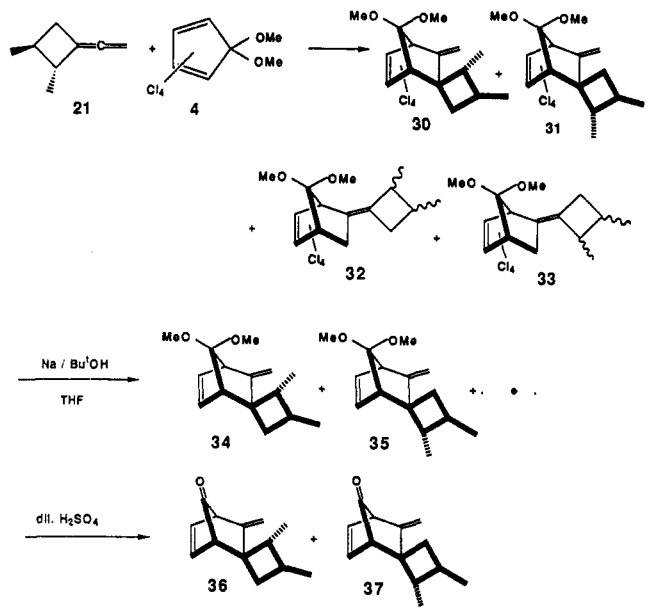
Scheme V



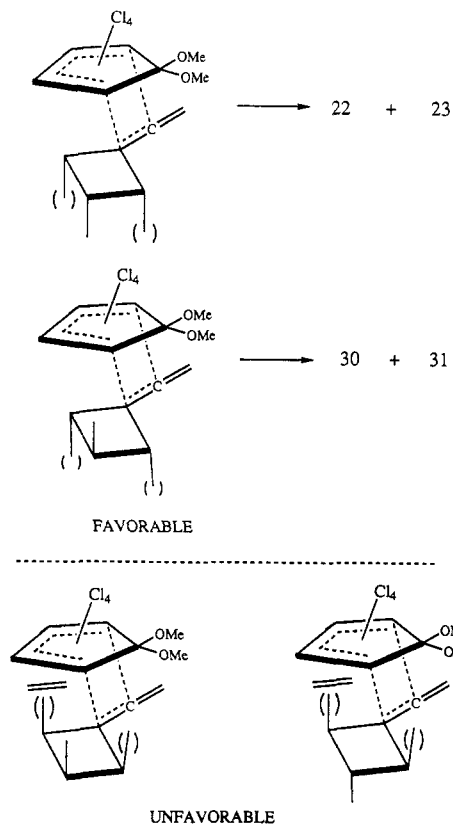
Scheme VI



Scheme VII



Scheme VIII



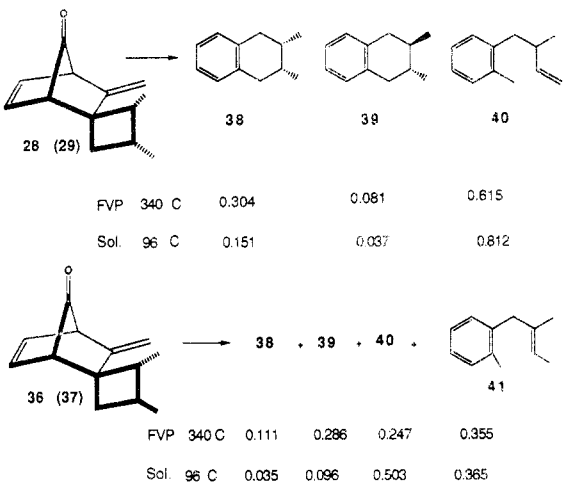
butan]-7-ones (28–29 and 36–37). To examine the stereochemistry of the formation of tetralin in the pyrolysis, 5-methylenespiro[bicyclo[2.2.1]hept-2-ene-6,1′-(*cis*- and *trans*-2′,3′-dimethyl)cyclobutan]-7-ones, **28–29** and **36–37**, respectively, were prepared. The precursor *cis*- and *trans*-dimethylvinylidenecyclobutanes, **20** and **21**, respectively, were prepared from 2-butene and dichloroketene by the sequence: reduction, Wittig methylenation, dibromocarbene addition, and treatment with methyllithium followed by GC separation (Scheme V).

Assignment of stereochemistry of **20** and **21** follows from the nearly 1 ppm upfield shift of the tertiary cyclobutyl protons in the trans isomer and the major products from use of *cis*-2-butene. Each allene was added to 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene at 130–135 °C, which led to only four isomers in each case: the two unnecessary cyclobutylidene materials and only two methylene spiro cycloadducts all in nearly equal amounts (Schemes VI and VII).

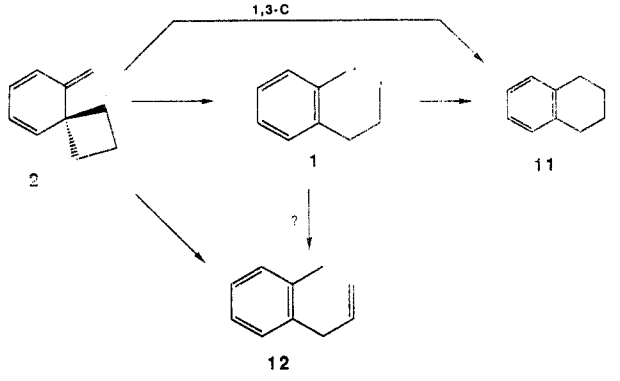
The formation of only two spiro cycloadducts in each case is consistent with steric effects in the transition state for the Diels–Alder addition (Scheme VIII), and it is on this basis that the stereochemistry of the methyls relative to the methylene is assigned. The rates of various hydrogen shift processes on pyrolysis (see Discussion) were also consistent with the stereochemistry assigned. Finally, the cycloadducts were dechlorinated with sodium and *tert*-butyl alcohol in tetrahydrofuran to the corresponding ketals which could be hydrolyzed with 3 M H_2SO_4 to the respective ketones.

Pyrolysis Studies. On flash vacuum pyrolysis or solution pyrolysis *cis*-spiro ketones **28–29** lose CO with formation of a 4:1 ratio of *cis*- to *trans*-2,3-dimethyltetralin, **38** and **39**, respectively, and a hydrogen shift product, **40**, which bears no relationship to *o*-allyltoluene (Scheme IX). On the other hand, *trans*-spiro ketones, **36–37** lose CO giving a 1:2.7 ratio of *cis*- to *trans*-2,3-dimethyltetralin and the same hydrogen shift product, **40**, formed from the cis isomer as well as nearly an equal amount of presumably (see Discussion) *E*-*o*-(2′-methyl-2′-butenyl-1′-yl)toluene,

Scheme IX



Scheme X



41 (Scheme IX). The stereochemistry of the 2,3-dimethyltetralins was established by comparisons of the ^1H NMR spectra of isolated material to those of the known materials.[3] The other potential vinylcyclobutane rearrangement product from either starting material, namely, 1,2-dimethyltetralin, is not detectable in the NMR spectrum of the reaction mixture.

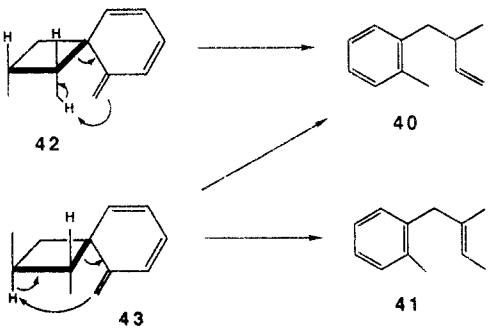
The tetralin-hydrogen shift product ratio from pyrolysis of both cis and trans isomers was found to be temperature dependent with the hydrogen shift products dominating at lower temperatures by factors of 4–8, respectively. Further, the rates of these rearrangements are similar to that of pyrolysis of the parent ketone, **9**.

Discussion

Though there is no direct spectroscopic evidence for formation of **2**, the kinetics, chemical trapping, and product formation are consistent with it being formed. Thus, for example, the kinetic parameters for loss of the ketone **9** are very similar to those for thermal extrusion of CO from similar compounds including that which gives 5-methylene-1,3-cyclohexadiene itself.[4] Furthermore, regioisomeric ketone **10** on thermolysis leads to **14** at nearly the same rate as that for loss of CO from **9**. Finally, evidence is also obtained from chemical trapping of **2** with *N*-methyl- and *N*-phenyltriazolinedione.

The striking temperature dependence of the tetralin: allyltoluene ratio from **2** suggests that the activation entropy for formation of tetralin is much higher than that

Scheme XI



for formation of allyltoluene. A mechanistic scheme (Scheme X) that is consistent with this involves two separate reaction channels for spirotriene, **2**: one is ring opening to a biradical like **1** or a concerted 1,3-carbon shift to give tetralin while the other path is a concerted 1,5-hydrogen shift from the remote carbon of the four-membered ring carbon to the exo methylene. The hydrogen shift process must have a lower activation energy and lower activation entropy than that for formation of tetralin. If the hydrogen shift were concerted, considerable restriction in the "flapping" of the four-membered ring is necessary to obtain extreme "pucker" to allow the hydrogen on the remote carbon to bond to the exomethylene. This hydrogen shift is unique in vinylcyclobutane rearrangements with no other examples reported, to our knowledge. Alternatively, to invoke a common biradical like **1** would require the partitioning of the biradical via two rotation-restricted transition states to have very different entropy demands.

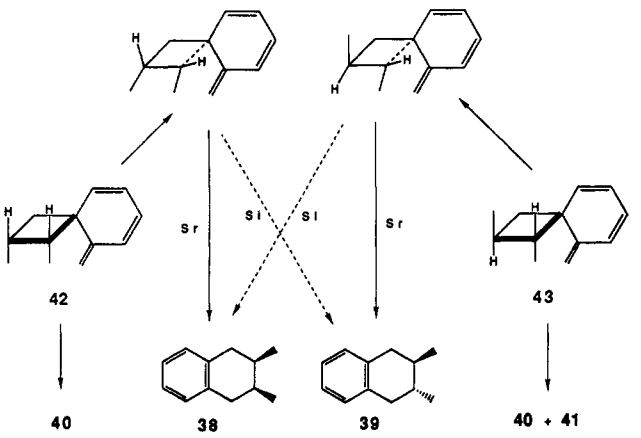
It would appear that the pathways involved in these experiments are not the same as those invoked by Tsang in the shock-tube pyrolysis of tetralin since allyltoluene is a diminishingly abundant product in the pyrolysis of spirotriene, **2**, at higher temperatures, but cleavage to benzocyclobutene and formation of allyl toluene are major pathways in the high-temperature pyrolysis of tetralin. There is the possibility described above that allyltoluene and tetralin seem to be formed by different reaction pathways from spirotriene, **2**, so that at higher temperatues, the species responsible for tetralin may also give some hydrogen shift product and may also give cleavage products whose absence is noteworthy in the pyrolysis of **2** at low temperatures.

The stereochemistry of the conversion of **2** to tetralin from **2** can provide evidence on the nature of the 1,3-carbon shift pathway. Thus, ketones **28–29** and **36–37** were prepared and pyrolyzed. The stereochemistry of the two methyls in **28–29** and **36–37** relative to one another on the four-membered ring of the ketones and on the six-membered ring of the tetralin product should be beyond reasonable doubt. However, the disposition of the methyls relative to the exo methylene is of concern. The stereopreference in the 4 + 2 addition of the allenes suggested the original assignment. In addition, the fact that no dimethyl-*o*-allyltoluene like product is formed from the cis material suggests that a methyl has replaced the hydrogen at C-2 syn to the methylene. The observation that little if any allyltoluene like product is formed from the cis material is also consistent with the process leading to allyltoluene in the parent spirotriene case being concerted since only the hydrogen syn to the exomethylene can transfer (Scheme XI). If that hydrogen transfer occurred via a biradical, then the anti hydrogen could also transfer. These observations also confirm the stereochemistry assigned to the methyls on the basis of steric effects in the

(3) (a) Peters, H.; Archer, R. A.; Mosher, H. S. *J. Org. Chem.* **1967**, *32*, 1382. (b) Morin, F. G.; Horton, N. J.; Grant, D. M.; Dalling, D. K.; Pugmire, R. J. *J. Am. Chem. Soc.* **1983**, *105*, 3992.

(4) Pryor, W. A.; Graham, W. D.; Green, J. G. *J. Org. Chem.* **1978**, *43*, 526.

Scheme XII



Diels–Alder addition (see Results). Further, the formation of both types of hydrogen shift product from the trans material supports the assignment of the methyl at C-1 being syn to the methylene and the methyl at C-2 being anti to the methylene (Scheme XI).

Mechanism of the Vinylcyclobutane Rearrangement. 1,3-Sigmatropic shifts of carbon have four possible stereochemical paths which can be disentangled only with stereochemical markers at both the migrating carbon and the two termini of the three-carbon unit. The current study has pursued just the stereochemistry at the migrating carbon and has found predominant, but not exclusive, retention of configuration. This rules out intervention of a biradical pathway in which the biradical is undergoing rapid rotation about bonds relative to the reclosure reaction. If the rearrangement were concerted, inversion might have been expected on the basis of the Woodward–Hoffmann rules[5] and on general experience with 1,3-shifts which prefer suprafacial-inversion stereochemistry perhaps even if the reaction is not concerted. However, retention of stereochemistry of the migrating carbon may result from a Woodward–Hoffmann "allowed" antarafacial-retention pathway, or, if subjacent orbital control is important as argued by Berson and Salem,[6] then a suprafacial-retention pathway might be involved (Scheme XII).

The preferred retention of configuration at the migrating carbon is reminiscent of Berson's observations with 1,3-shifts where the Woodward–Hoffmann "preferred" inversion pathway would place a substituent on the migrating carbon in a sterically destabilizing position in the transition state, and in these cases, dominant retention was observed.[6] The steric situation with the cis and trans materials used in the current study is similar to the Berson cases. The methyl group on the migrating carbon would be forced into the molecular system by a concerted suprafacial-inversion pathway. The surprise in this case and in Berson's cases is that the random biradical path is not the next most energetically attractive alternative and that a retention reaction (perhaps also mostly with suprafacial stereochemical use of the three carbon unit) is the next best alternative.

Conclusion

The formation of tetralin in the pyrolysis of spirotriene **2** appears to be the result of a partially concerted 1,3-carbon shift. It is unlikely that the reaction would occur with retention at the migrating group in the parent case, but it is also unlikely that a biradical pathway might be followed unless there is some other interaction favoring retention with methyls on the migrating center. Further, allyltoluene results from a concerted hydrogen shift pathway whose temperature dependence reduces the amount of allyltoluene formed by this pathway to diminishing amounts at the temperature at which tetralin could be formed. No loss of ethylene is observed in the pyrolysis of **2**. All of the pathways involved in the pyrolysis of spirotriene **2** appear to avoid a random 1,6-biradical. Whether or not that particular species is responsible for the high-temperature unimolecular chemistry of tetralin has yet to be determined, although Tsang's activation parameters for both the retro-Diels–Alder reaction and the hydrogen shift reaction suggest a more dissociative transition state as might be expected for rate-determining cleavage to a biradical.

Experimental Section

^{1}H NMR (360 MHz) spectra were recorded on a Nicolet Model NT-360 spectrometer. All chemical shifts were reported as parts per million (δ scale) from tetramethylsilane (TMS) and were taken in $CDCl_3$ solution unless otherwise indicated. Mass spectra (MS) were obtained on a Kratos MS-80 spectrometer. IR spectra were recorded on a Perkin-Elmer 298 spectrometer. Gas chromatographic (GC) analyses were performed on a Varian 3700 gas chromatograph equipped with flame-ionization detector.

Vinylidenecyclobutane. Methylenecyclobutane (Aldrich) was first converted to 1,1-dibromospiro[2.3]hexane (80–90% yield), which was then reacted with MeLi to give vinylidenecyclobutane (yield 63%) according to literature procedures.[7] ^{1}H NMR of 1,1-dibromospiro[2.3]hexane: 2.50–2.38 (m, 2 H), 2.30–1.96 (m, 4 H), 1.56 (s, 2 H). ^{1}H NMR of vinylidenecyclobutane: 4.67 (pent, 2 H), 2.90–2.78 (m, 4 H), 1.93 (pent, 2 H).

Reactions of Vinylidenecyclobutane (3) with 1,2,3,4-Tetrachloro-5,5-dimethoxycyclopentadiene (4). Vinylidenecyclobutane[7] (3.2 g, 0.04 mol) and diene **4** (15.84 g, 0.06 mol) taken in a thick-walled glass tube were degassed and sealed under vacuum. After heating the tube in a silicon oil bath at 130–135 °C for 16 h, the contents were transferred to a flask. Volatiles, if any, were removed under aspirator pressure. Fractional distillation of the residue gave cycloadducts **5** and **6** (55:45): 9.6 g (68%); bp 112–128 °C (~0.01 Torr). The boiling point of **5** (~110–114 °C at 0.01 Torr) is lower than that of **6**, but complete separation was not possible. ^{1}H NMR of **5**: 5.48 (d, 1 H, J = 0.72 Hz), 5.41 (d, 1 H, J = 0.72 Hz), 3.56 (s, 3 H), 3.47 (s, 3 H), 2.85–2.50 (m, 4 H), 2.10–1.85 (m, 2 H). MS: 309 (41), 307 (M^+ – Cl, 40), 279 (26), 261 (20), 233 (25), 198 (22), 170 (23), 109 (29), 59 (100). Calcd for $C_{13}H_{14}O_2Cl_3$ (MF-1 Cl) 307.0059, found 307.0037. ^{1}H NMR for **6**: 3.59 (s, 3 H), 3.57 (s, 3 H), 2.85–2.50 (m, (4 + 2)H), 2.10–1.95 (m, 2 H). MS: 307 (M^+ – Cl, 70), 271 (32), 233 (29), 196 (36), 170 (20), 59 (100).

5-Methylenespiro[bicyclo[2.2.1]hept-2-ene-6,1′-cyclobutan]-7-one Dimethyl Ketal (7) and 5-Cyclobutylidene-7,7-dimethoxy-2-norbornene (8). Compounds **5** and **6** together were dechlorinated with sodium and *tert*-butyl alcohol in THF under refluxing conditions following the literature procedure[8] to the respective ketals **7** and **8** in about 40% yield. Compounds **7** and **8** (bp 32–38 °C at 0.01 Torr) were separated by preparative GC on a 12 ft (12 ft × $^1/_4$ in.) 20% OV 101 column on Chromosorb P. ^{1}H NMR **7**: 6.24–6.19 (m, 1 H), 6.12–6.08 (m, 1 H), 5.04 (s, 1 H), 4.98 (s, 1 H), 3.25 (br s, 1 H), 3.18 (s, 3 H), 3.17 (s, 3 H), 2.97 (br s, 1 H), 2.31–2.26 (m, 2 H), 1.95–1.80 (m, 4 H). HRMS for $C_{13}H_{18}O_2$: calcd 206.1307, found 206.1347.

^{1}H NMR of **8**: 6.14–6.08 (m, 2 H), 3.21 (s, 3 H), 3.17 (s, 3 H), 3.20–3.16 (br s (under "Me" proton), 1 H), 2.93 (br s, 1 H),

(5) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970.
(6) Berson, J. A. *Acc. Chem. Res.* **1972**, *5*, 406.
(7) Suvorova, G. N.; Komendantov, M. I. *Zh. Org. Khim.* **1979**, *15*, 1435 (Eng 1280).
(8) Gassman, P. G; Marshall, J. L. *Org. Synth.* **1968**, *48*, 68. Recently better yields in similar reactions have been obtained using the Paddon-Row procedure: Lap, B. V.; Paddon-Row, M. N. *J. Org. Chem.* **1979**, *44*, 4979.

2.81–2.70 (m, 1 H), 2.70–2.57 (m, 2 H), 2.56–2.45 (m, 1 H), 2.33–2.24 (m, 1 H), 2.02–1.90 (m, 2 H), 1.56–1.50 (m, 1 H). HRMS for $C_{13}H_{18}O_2$: calcd 206.1307, found 206.1320.

5-Methylenespiro[bicyclo[2.2.1]hept-2-ene-6,1′-cyclobutan]-7-one (9). Hydrolysis of **7** with 3 M H_2SO_4 led to **9** in 70–80% yield. A typical procedure is as follows: 128 mg of **7** in acetone was treated with 3 M H_2SO_4 at room temperature for 10 h. The solution was diluted with water, and Et_2O was added. The acid can be neutralized with $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted twice with Et_2O. The combined organic phase was dried over anhydrous $MgSO_4$. Solvent and other more volatile components were separated under aspirator pressure, keeping the flask at 0–5 °C. Bulb-to-bulb vacuum distillation (0.01 Torr) of the residue at room temperature to a flask at −78 °C led to pure ketone **9** (70 mg, 70%). ^{1}H NMR of **9**: 6.56 (t, 2 H), 5.09 (s, 1 H), 5.07 (s, 1 H), 3.35 (br s, 1 H), 3.15 (br s, 1 H), 2.28–2.00 (m, 4 H), 1.95–1.85 (m, 2 H). IR 1784 cm^{-1} (C=O).

5-Cyclobutylidene-2-norbornenone (10). Ketal **8** was hydrolyzed to the ketone **10** by the procedure described above. ^{1}H NMR of **10**: 6.54 (t, 2 H), 3.26 (m, 1 H), 3.02 (m, 1 H), 2.80–2.60 (m, 2 H), 2.60–2.52 (m, 2 H), 2.52–2.40 (m (d of pent), 1 H), 2.06–1.94 (m, 2 H), 1.86–1.77 (m (d of t), 1 H). IR 1784 cm^{-1} (C=O).

Trapping Studies. Ketone **9** (7–8 μL) and 2–3 molar excess *N*-methyltriazolinedione was dissolved in a tube containing benzene-d_6 solvent. After degassing, the tube was sealed under vacuum and heated at 80 °C for 4–6 h. The solvent was removed, leaving a small amount of a gummy solid. ^{1}H NMR: 6.50–6.42 (d of t, 2 H), 5.31 (s, 1 H), 5.25 (s, 1 H), 5.04 (dd, 1 H), 4.91 (dd, 1 H), 3.01 (s, 3 H), 2.44–2.34 (m, 1 H), 2.28–2.15 (m, 1 H), 2.15–1.80 (m, 4 H). HRMS for $C_{13}H_{15}N_3O_2$: calcd 245.1160, found 245.1162. Similarly an *N*-phenyltriazolinedione adduct was obtained: ^{1}H NMR (C_6D_6): 7.60–7.10 (m, 5 H), 5.90–5.82 (m, 2 H), 4.93 (dd, 1 H), 4.85 (s, 1 H), 4.82 (s, 1 H), 4.75 (m, 1 H), 2.40–2.28 (m, 1 H), 2.07–1.95 (m, 1 H), 1.75–1.50 (m, 4 H).

Response to Concentration of MTAD. Seven microliters of ketone **9** was dissolved in 1 mL of benzene-d_6 in two separate NMR tubes, and 2.5 and 7 mg, respectively, of MTAD was added to each solution. After both tubes were sealed under vacuum and heated at 80 °C for 4 h, 51% and 55%, respectively, of **9** was left in each solution. Only cycloadduct was formed in the latter experiment while some tetralin and allyltoluene were formed in the former experiment.

Kinetic Studies. Samples were prepared by mixing **9** (8–9 μL), CCl_4 (~0.52 mL) and $CDCl_3$ (80 μL) in NMR tubes. Tubes were degassed and sealed under vacuum. Tubes were immersed in constant temperature baths ($CHCl_3$, C_6H_6, and 1-propanol), and NMR spectra were recorded at different periods of time. The ratio of integrals of the "2" vinyl protons of ketone **9** and of "8" (4 + 4) aromatic protons of *o*-allyltoluene and tetralin was measured in each run and was corrected. The rate constants were obtained from least-squares plots, and the Arrhenius parameters were evaluated (Table I).

***cis*- and *trans*-2,3-Dimethyl-1-vinylidenecyclobutanes (20 and 21).** Via the general procedure of Greenwald et al.,[9] a mixture of *cis*- and *trans*-2,3-dimethylcyclobutanones[10] were converted to *cis*- and *trans*-2,3-dimethyl-1-methylenecyclobutanes (**16** and **17**) in 65–78% yield. Compounds **16** and **17** were then reacted with dibromocarbene[7] to give 1,1-dibromo-4,5-dimethylspiro[2.3]hexanes **18** and **19** (yield 67%, bp 38–46 °C at ~0.3 Torr) as the only two identified products from GC and ^{1}H NMR spectroscopy. These spiro compounds were then treated with MeLi according to literature procedures[7] to afford vinylidenecyclobutanes **20** and **21** (bp 40–46 °C at 15–20 Torr) in about a 2:1 ratio. They were separated by preparative GC on a 12 ft (12 ft × $^1/_4$ in.) 20% OV 101 on Chromosorb P column.

^{1}H NMR of **16** and **17**: 4.64–4.54 (m, 4 H), 2.98–2.85 (m, 1 H), 2.76–2.66 (ddt, 1 H), 2.62–2.53 (m, 1 H), 2.38–2.25 (m, 2 H), 2.14–2.04 (ddt, 1 H), 2.00–1.92 (m, 1 H), 1.78–1.68 (pent, 1 H), 1.03–0.97 (2 d, 9 H), 0.88 (d, 3 H).

^{1}H NMR of **18** and **19**: 2.76–2.69 (br t, 1 H), 2.58–2.52 (m, 1 H), 2.18–2.12 (br t, 1 H), 2.06–2.02 (m, 1 H), 1.99–1.89 (m, 3 H), 1.67 (d, J = 7.56 Hz, 1 H), 1.66 (d, J = 7.56 Hz, 1 H), 1.43 (d, J = 7.56 Hz, 1 H), 1.42 (d, J = 7.56 Hz, 1 H), 1.56–1.51 (m, 1 H), 1.18 (d, J = 6.4 Hz, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 1.08 (d, J = 7.2 Hz, 3 H), 0.85 (d, J = 7.2 Hz, 3 H). MS: 268 (M^+ + 2, 1.8), 266 (M^+, 1.4), 253 (16), 189 (81), 187 (84), 161 (80), 159 (72), 155 (95), 127 (73), 97 (35), 87 (91), 69 (100), 68 (67).

^{1}H NMR of **20**: 4.78–4.68 (m, 2 H), 3.25–3.16 (m, 1 H), 3.02–2.91 (m, 1 H), 2.45–2.34 (m, 1 H), 2.32–2.22 (m, 1 H), 1.04 (d, 3 H), 1.02 (d, 3 H). IR: 1965 cm^{-1} (C=C=C). HRMS for C_8H_{12}: calcd 108.0939, found 108.0937.

^{1}H NMR of **21**: 4.76–4.70 (m, 2 H), 2.90–2.80 (m, 1 H), 2.70–2.60 (m, 1 H), 2.40–2.28 (m, 1 H), 2.02–1.88 (sept, 1 H), 1.14 (d, 3 H), 1.10 (d, 3 H). IR: 1965 cm^{-1} (C=C=C). HRMS for C_8H_{12}: calcd 108.0939, found 108.0935.

Reactions of Vinylidenecyclobutanes 20 and 21 with Dimethoxytetrachlorocyclopentadiene 4. *cis*-Dimethylvinylidenecyclobutane **20** (1.14 g) was treated with **4** (1.5 equiv) in a sealed tube at 130–134 °C for 16 h to give four cycloadducts **22–25** (2.84 g, 73%, bp 110–130 °C at ~0.01 Torr). These adducts were all formed in about equal amounts judging from the ^{1}H NMR integrations of the MeO protons and exomethylene protons. ^{1}H NMR of **22–25**: 5.60 (s, 1 H), 5.25 (s, 1 H), 5.51 (s, 1 H), 5.12 (s, 1 H), 3.59, 3.58, 3.56, 3.55, 3.54, 3.49, 3.47 and 3.45 (singlets, 24 H), 1.07, 1.01, 0.99, 0.98, 0.96, 0.95, 0.66 (doublets, 24 H), multiplets at 3.25–3.05, 2.94–2.70, 2.66–2.35, 1.85–1.62, and 1.55–1.30. HRMS for $C_{15}H_{18}O_2Cl_3$ (M − Cl): calcd 335.0346, found 335.0343.

Cycloadducts **22–25** were dechlorinated with sodium and *tert*-butyl alcohol to the respective ketals[8] (bp 40–55 °C at ~0.01 Torr). Fractionation afforded desired spiro ketals **26** and **27** as major products in the first fraction. ^{1}H NMR of **26** and **27**: 6.30–6.05 (m, 4 H), 5.07 (s, 1 H), 4.80 (s, 1 H), 5.03 (s, 1 H), 4.74 (s, 1 H), 3.24 (m, 2 H), 3.17 (s, 6 H), 3.15 (s, 6 H), 3.05–2.95 (m, 2 H), 2.56–2.20 (m, 4 H), 1.85–1.50 (m, 4 H), 1.08–0.90 (2 d, 9 H), 0.73 (d, 3 H). HRMS for $C_{15}H_{22}O_2$: calcd 234.1620, found 234.1624.

Treating *trans*-dimethylvinylidenecyclobutane **21** (0.740 g) with **4** (1.5 equiv) in a similar manner as described above led to four cycloadducts **30–33** (2.12 g, bp 110–130 °C at ~0.01 Torr) all in about equal amounts. This ratio was again judged on the basis of ^{1}H NMR integrations of exo metylene protons and MeO protons. ^{1}H NMR of **30–33**: 5.56 (s, 1 H), 5.29 (s, 1 H), 5.55 (s, 1 H), 5.23 (s, 1 H), several singlets at 3.59, 3.58, 3.56, 3.55, 3.54, 3.45, 3.43 (total 24 H), 2.65–1.62 (m, 16 H), 1.17–0.98 (several doublets, 18 H), 0.71 (d, 6 H). HRMS for $C_{15}H_{18}O_2Cl_4$: calcd 370.0061, found 370.0063.

Cycloadducts **30–33** were dechlorinated as above to the ketals (bp 38–55 °C at ~0.01 Torr). Fractionation afforded desired spiro ketals **34** and **35** as major products. ^{1}H NMR of **34** and **35**: 6.20–6.02 (m, 4 H), 5.09 (s, 1 H), 4.89 (s, 1 H), 5.07 (s, 1 H), 4.82 (s, 1 H), 3.23–3.18 (m, 2 H), singlets at 3.18, 3.15, and 3.13 (12 H), 2.80–2.74 (br d, 2 H), 2.45–2.34 (m, 2 H), 2.10–2.00 (m, 2 H), 1.90–1.74 (m, 4 H), 1.06–0.99 (2 doublets overlapped, 9 H), 0.76 (d, 3 H). HRMS for $C_{15}H_{22}O_2$: calcd 234.1620, found 234.1615.

Synthesis of 5-Methylenespiro[bicyclo[2.2.1]hept-2-ene-6,1′-2′,3′-*cis-syn* (to methylene)-dimethylcyclobutan]-7-ones (28 and 29). Hydrolysis of spiro ketals **26** and **27** with 3 M H_2SO_4 as described for compound **7** and trap-to-trap distillation led to spiro ketones **28** and **29**. ^{1}H NMR of mixture: 6.64–6.47 (m, 4 H), 5.17 (s, 1 H), 4.90 (s, 1 H), 5.12 (s, 1 H), 4.80 (s, 1 H), 3.35–3.27 (br m, 2 H), 3.13 (br s, 2 H), 2.64–2.20 (m, 4 H), 1.96–1.60 (m, 4 H), 0.96–0.89 (2 d, 9 H), 0.85 (d, 3 H). IR: (cm^{-1}) 1780 (C=O), 1690 (shoulder) and 1650 (C=C).

Synthesis of 5-Methylenespiro[bicyclo[2.2.1]hept-2-ene-6,1′-2′,3′-*trans*-dimethylcyclobutan]-7-ones (36 and 37). Hydrolysis of spiro ketals **34** and **35** with 3 M H_2SO_4 and bulb-to-bulb distillation as described above gave spiro ketones **36** and **37**. ^{1}H NMR of mixture: 6.56–6.40 (m, 4 H), 5.21 (s, 1 H), 4.99 (s, 1 H), 5.17 (s, 1 H), 4.91 (s, 1 H), 3.38–3.30 (m, 2 H), 3.00 (br s, 2 H), 2.30–1.95 (m, 4 H), 1.90–1.65 (m, 4 H), 1.06 (d, 6 H), 0.88 (d, 3 H), 0.81 (d, 3 H). IR: (cm^{-1}) 1790 (C=O), 1708, and 1650 (C=C).

(9) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128. Samuel, S. P.; Niu, T.-q.; Erickson, K. L. *J. Am. Chem. Soc.* **1989**, *111*, 1429.

(10) Depres, J.-P.; Coelho, F.; Greene, A. E. *J. Org. Chem.* **1985**, *50*, 1972 for dichloroketene additions; for the dimethylcyclobutanones, see: Gajewski, J. J.; Burka, L. T. *J. Am. Chem. Soc.* **1972**, *94*, 8865.

Characterization of 40 and 41. Compounds **40** and **41** were isolated from pyrolysate by preparative GC and are characterized. ^{1}H NMR of **40**: 7.16-7.06 (m, 4 H), 5.87-5.76 (m, 1 H), 4.98-4.91 (m, 2 H), 2.72-2.64 (m, 1 H), 2.56-2.48 (m, 1 H), 2.48-2.37 (m, 1 H), 2.31 (s, 3 H), 1.02 (d, 3 H). HRMS for $C_{12}H_{16}$: calcd 160.1251, found 160.1251. ^{1}H NMR of **41**: 7.15-7.06 (m, 4 H), 5.14-5.06 (m, 1 H), 3.27 (s, 2 H), 2.26 (s, 3 H), 1.60 (s), 1.585 (d overlapped, total 6 H). HRMS for $C_{12}H_{16}$: calcd for 160.1251, found 160.1255.

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Supplementary Material Available: ^{1}H NMR spectra of selected compounds (11 pages). Ordering information is given on any current masthead page.

Structural Elucidation and Independent Synthesis of the Radical-Radical Coupling Products of 3-Hydroxyanthranilic Acid with Tyrosine and Phenols

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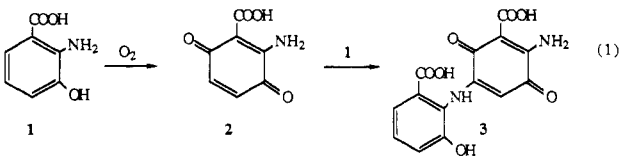
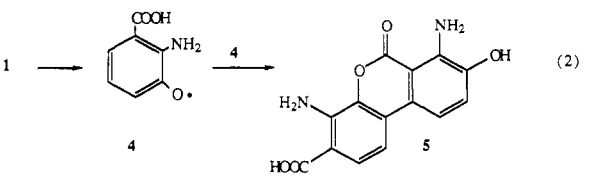
The autoxidation of 3-hydroxyanthranilic acid (3OHA) in the presence of tyrosine, *p*-cresol, or *p*-ethylphenol gives dibenzo[*b*,*d*]pyran-6-one products that arise from the coupling of the radical of 3OHA with that derived from the substituted phenol. As a proof of the structure of these adducts, they have been independently synthesized by employing a palladium(0)-catalyzed coupling of appropriately functionalized aryl boronic acids with methyl 6-bromo-3-methoxy-2-nitrobenzoate.

3-Hydroxyanthranilic acid (3OHA, 1) is a normal metabolite of the amino acid tryptophan and readily undergoes autoxidation. In a number of diseases, elevated levels of urinary tryptophan metabolites have been reported.[1,2] Patients with cancer of the bladder, for example, have been found to excrete increased amounts of 3OHA and 3-hydroxykynurenine.[2,3] Evidence that oxidation of 3OHA may be intimately associated with its carcinogenicity has come from studies which have shown a marked protective effect of simultaneously administered vitamin C.[4]

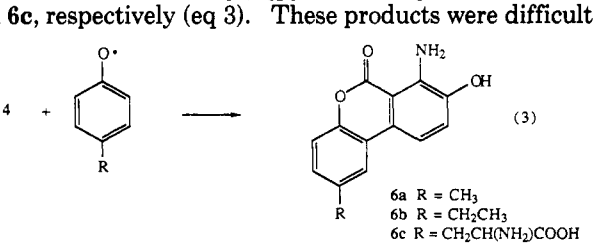
The autoxidation of 3OHA may result in the production of hydrogen peroxide,[5] superoxide radicals,[5] and, in the presence of trace amounts of iron, hydroxyl radicals.[6] Oxidized 3OHA intermediates are also very reactive and have been demonstrated to bind covalently to proteins.[7] 3OHA is thought to be responsible for the tanning of cocoon protein in some species of moths.[8]

Recent reports from our laboratories have described the products from the autoxidation of 3OHA in the presence and absence of amine nucleophiles.[9] Three dimeric products have been identified from the autoxidation of **1**, cinnabarinic acid,[9a] the *p*-quinone dimer **3**, formed via conjugate addition of **1** to **2** (eq 1), and the dibenzo[*b*,*d*]-pyran-6-one **5**,[9c] which presumably arises via an ortho,para radical-radical coupling reaction of phenoxy radical **4** (eq 2).





The extensively documented participation of tyrosine radicals in biochemical electron-transfer reactions[10] and the isolation of numerous fungal and bacterial metabolites which have arisen from radical dimerization of tyrosine[11] suggested that radical coupling products from tyrosine and 3OHA would be likely. In the event, autoxidation of 3OHA at pH 7 in the presence of tyrosine (4 molar equiv) or *p*-cresol or *p*-ethylphenol gave predominately cinnabarinic acid and the *p*-quinone dimer **3** along with a small quantity (0.5-1%) of the dibenzo[*b*,*d*]pyran-6-one products **6a**, **6b**, and **6c**, respectively (eq 3). These products were difficult



(1) Costa, C.; Angi, M. R.; De Cavli, M.; Vanzan, S.; Allegri, G. *Bull. Soc. It. Biol. Sper.* **1982**, *58*, 333-339.
(2) Boyland, E.; Williams, D. C. *Biochem. J.* **1956**, *64*, 578-582.
(3) Abul-Fadl, M. A. M.; Khalafallah, A. S. *Br. J. Cancer* **1961**, *15*, 479-484.
(4) Schegel, J. U.; Pipkin, G. E.; Nishimura, R.; Shultz, G. N. *J. Urol.* **1970**, *103*, 155-159.
(5) Ogawa, H.; Nagamure, Y.; Ishigure, I. *Hoppe-Seyler's Z. Physiol. Chem.* **1983**, *364*, 1507-1518.
(6) Iwahashi, H.; Ishii, T.; Sugata, R.; Kido, R. *Biochem. J.* **1988**, *251*, 893-899.
(7) (a) King, C. M.; Kriek, E. *Biochem. Biophys. Acta* **1965**, *111*, 147-153. (b) Truscott, R. J. W.; Martin, F. *Exp. Eye Res.* **1989**, *49*, 927-940.
(8) (a) Brunet, P. C. J. *Endeavour* **1976**, *26*, 68-74. (b) Nicholls, E. M.; Rienits, K. G. *Int. J. Biochem.* **1971**, *2*, 593.
(9) (a) Manthey, M. K.; Pyne, S. G.; Truscott, R. J. W. *J. Org. Chem.* **1988**, *53*, 1486-1489. (b) Manthey, M. K.; Pyne, S. G.; Truscott, R. J. W. *Tetrahedron* **1989**, *45*, 2803-2810. (c) Manthey, M. K.; Pyne, S. G.; Truscott, R. J. W. *Biochim. Biophys. Acta*, in press.
(10) For leading references, see: Prince R. C. *TIBS* **1988**, 286-288.
(11) (a) Fry, S. C. *Biochem. J.* **1982**, *204*, 449. (b) Tamai, S.; Kaneda, M.; Nakamura, S. R. *J. Antibiot.* **1982**, *35*, 1130-1136.

0022-3263/90/1955-4581$02.50/0