was treated with 0.1 M CH_3CO_2H. When analyzed by IR after 50 min, the C=O band of CH_3CO_2H (1710 cm^{-1}) was absent and the solution was water-white. After an additional 10 min, a white precipitate ($Ph_2BOCOCH_3$) formed. Two equivalents of MeOH (0.2 M) were added and the mixture was shaken. The white solid quickly dissolved. IR analysis of the resulting solution revealed a strong band at 1710 cm^{-1} (CH_3CO_2H) and a new strong band at 1325 cm^{-1} assigned to Ph_2BOMe. Proof that the white precipitate was the mixed anhydride, and not simply a TPB(MeOH) complex, was obtained by isolation of the white precipitate obtained in the reaction of 0.050 g of TPB (0.2 M) with 11.4 μL (0.2 M) of CH_3CO_2H in 1 cc of CCl_4. The KBr IR spectrum of the precipitate showed a weak broad band at 1720 cm^{-1}, assigned to the C=O group of $Ph_2BOCOCH_3$. The solvent was vacuum stripped and was analyzed by IR which showed peaks assigned to benzene (1475, 1805, 1950, 3015, and 3040 cm^{-1}), in addition to peaks from CCl_4 and a trace of CH_3CO_2H. The assignment of the structure $Ph_2BOCOCH_3$ for the white precipitate was also confirmed by ^1H NMR analysis. The aromatic protons (δ 7.75) and CH_3 protons (δ 2.2) gave an integral ratio 3.9/1 (theoretical 3.3). Finally, elemental analysis of the solid gave results more in agreement with the assigned mixed anhydride structure rather than a simple $TPB(CH_3CO_2H)$ complex. Anal. Calcd for $Ph_2BOCOCH_3$, $C_{14}H_{13}BO_2$: C, 75.00; H, 5.80. Found: C, 72.56 ± 1.23; H, 5.53 ± 0.12. Calcd for $TPB(CH_3CO_2H)$, $C_{20}H_{22}BO_2$: C, 78.69; H, 7.21.

Reaction of TPB with MeOH, Catalyzed by Metals and Metal Oxides. A stock solution was prepared which contained 0.2 M TPB and 0.2 M MeOH in CCl_4. Aliquots of 0.5 mL were placed in a series of small glass vials containing coils of metal wires, with diameters ranging from 0.05 mm to 0.25 mm, and of sufficient lengths to give surface areas of 0.4 cm^2. The wires included Al, Zn, Fe, Ni, and Cu. Analyses of the solutions by IR after 17 to 20 h showed that about 1% conversion of the MeOH per hour had taken place in the vials containing Al, Fe, and Ni wires as well as in the stock solution not exposed to metal. The solutions containing Zn and Cu metal, however, gave about 4% and 2% conversion per hour of MeOH. Very similar results were obtained when the experiments were repeated in toluene solvent. The percent MeOH conversions per hour were: Al (2%), Zn (3.5%), Fe (1.5%), Ni (2%), Cu (3.5%), and the control with no metal (2%). Possible catalysis by metal oxides was examined by repeating the experiments and using 0.01-g amounts of metal oxides in place of the metal wires. The percent MeOH conversions per hour were: Al_2O_3 (0%), Zn (1%), Fe_3O_4 (0%), NiO (0%), CuO (3%), and the control with no metal oxide (0%).

Computer Kinetic Model Calculation of $TPB(MeOH)_3$/TPB Ratios. The equations used to calculate rates of CF_3CO_2H methanolysis of TPB were also used to calculate percentages of $TPB(MeOH)_3$ and free TPB. For these cases, the irreversible rate constants k_1 and k_2 were set to zero. The three equilibrium rate constants for self-association of MeOH (K_1, K_2, and K_3) were set to 0.6, 3.8, and 28, respectively. The K_{equil} for $TPB(MeOH)_3$ formation was set to 316. For the ^{11}B NMR measurement conditions, with 0.32 M $[TPB]_{total}$ and 1.0 M $[MeOH]_{total}$ in Freon-11, the computer equilibrium ratio was 0.227 M $TPB(MeOH)_3$/0.0935 M TPB, or 70.8/29.2. For the ^{13}C NMR measurement conditions, with 0.20 M $[TPB]_{total}$ and 24.7 M $[MeOH]_{total}$ (neat MeOH), the computer equilibrium ratio was 0.199 M $TPB(MeOH)_3$/0.0017 M TPB, or 99.1/0.9.

Acknowledgment. Helpful discussions with Drs. F. A. VanCatledge and F. J. Weigert are gratefully acknowledged. ^{11}B NMR measurements were made by J. Chang.

Registry No. TPB, 960-71-4; $Ph_2B(MeO)$, 13471-36-8; $PhB(OMe)_2$, 13471-35-7; $Ph_2B(OEt)$, 43185-52-0; $PhB(OEt)_2$, 31044-59-4; $B(OMe)_3$, 121-43-7; $B(OEt)_3$, 150-46-9; MeOH, 67-56-1; EtOH, 64-17-5; *t*-BuOH, 75-65-0; $Ph_2B(O\text{-}t\text{-}Bu)$, 958-03-2; *i*-PrOH, 67-63-0; $Ph_2B(O\text{-}i\text{-}Pr)$, 69737-51-5; CF_3SO_3H, 1493-13-6; CF_3CO_2H, 76-05-1; CH_3CO_2H, 64-19-7; $Ph_2B(OCOCH_3)$, 93757-49-4; $Ph_2B(OCOCF_3)$, 3826-41-3; Zn, 7440-66-6; Cu, 7440-50-8.

Ene Reactions of Conjugated Dienes. 2. Dependence of Rate on Degree of Hydrogen Removed and s-Cis or s-Trans Diene Character

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The rates of the ene reactions between diethyl diazenedicarboxylate and a number of dienes have been measured and product structures determined. Accelerated reactions are observed with 1,3-cyclohexadienes but not with dienes held fixed in the s-trans form. Within the first set of systems tertiary hydrogens are much more reactive than secondary. Within the second set secondary are (in turn) more reactive than primary. There is no apparent correlation between the rate of the Diels–Alder reaction of the 1,3-cyclohexadienes with maleic anhydride and the rate of ene reaction with the diazenedicarboxylate.

Certain conjugated dienes have been observed to undergo facile ene reactions, even when the Diels–Alder reaction might well be expected to overwhelm them.[1] In an earlier paper,[2] acceleration of the ene reactions of dienes 1 and 2 was demonstrated, rather than a previously hypothesized slowing of the competing Diels–Alder process.[3] However, the generality of this was unclear. We have extended this earlier work, first to ascertain how general such acceleration is and then whether acceleration is a consequence of mere conjugation, of the endocyclic nature (i.e., s-cis conformation) of these dienes, or of the greater rigidity and likelihood of having an appropriately aligned hydrogen that results from placing the diene in a ring. It was also felt desirable to test the earlier inference that the observed transfer of hydrogen from the more substituted allylic position was to be expected in other cases[2] in contrast to the opposite preference found with simple alkenes.[4]

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[1] (a) Gillis, B. T.; Beck, P. E. *J. Org. Chem.* **1962**, *27*, 1947. (b) Lakeman, J.; Speckamp, W. N.; Huisman, H. O. *Tetrahedron* **1968**, *24*, 5151 and references therein. (c) Jones, D. N.; Greenhalgh, P. F.; Thomas, I. *Ibid.* **1968**, *24*, 5215. (d) Andrews, A. L.; Fort, R. C.; LeQuesne, P. W. *J. Org. Chem.* **1971**, *36*, 83. (e) Jacobson, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 2579. (f) Junek, H.; Uray, G.; Zuschnig, G. *Liebigs Ann. Chem.* **1983**, 154. (g) Paquette, L. A.; Charumilind, P.; Gallucci, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 7364.

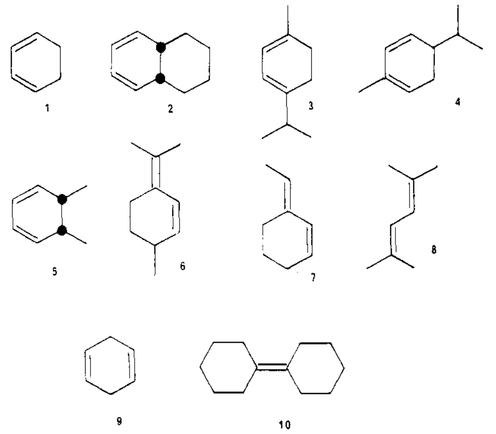
[2] Jacobson, B. M.; Feldstein, A. C.; Smallwood, J. I. *J. Org. Chem.* **1977**, *42*, 2849.

[3] Gillis, B. T. In "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1966; pp 147–148.

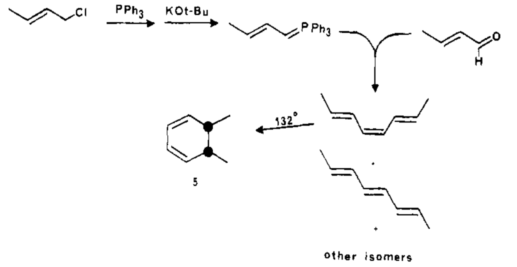
[4] (a) Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Thaler, W. A.; Franzus, B. *J. Org. Chem.* **1964**, *29*, 2226.

0022-3263/85/1950-0194$01.50/0

Chart I. Dienes Used



Scheme I



We now report that conjugation confers a noticeable acceleration to the ene reaction only for cisoid structures as in 1,3-cyclohexadiene systems. The preference for transfer of hydrogen in the order tertiary > secondary > primary seems to be more general, but does show exceptions.

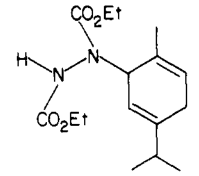
The dienes whose reactions we have studied are compounds **3**–**9** along with alkene **10** (Chart I). Of these, **3**, **4**, **8**, and **9** are commercially available, although the first two required purification by preparative VPC before either rate measurements or product studies could be done. Literature syntheses of **5**–**7** and **10** are known[5] and those for **6**, **7**, and **10** were adequate. The only preparative scale synthesis of **5** in the literature appears to be that of Marvell[5a] and is in six steps with very low overall yield. A rather simple four-step procedure was devized (Scheme I) that proved more satisfactory, though the yield was still modest. The 2,4,6-octatriene isomer mixture produced by the Wittig reaction consisted of approximately 50% trans–cis–trans isomer, 40% all-trans isomer, and 10% other isomers not identified. The mixture did not need to be separated before the next step because the desired cyclization product boiled a great deal lower than the octatrienes and could be removed afterward by fractional distillation even on a rather small scale. Final purification for use in kinetics was extremely easy by preparative VPC.

Of the eno(dieno-)philes used in our earlier work,[2] diethyl diazenedicarboxylate (DAZD, **11**) appeared to favor the ene reaction to the greatest extent and maleic anhydride did so the least, therefore these were chosen as the reagents most likely to give clear results when both ene and Diels–Alder reactions were conceivable.

Results

Adduct Structures. The maleic anhydride adducts of **1**–**4** have been reported previously[6] and in general were easily recognized from their NMR spectra. A mixture of adducts was produced with **5**, but although individual structures and properties were not determined, their Diels–Alder character was again clear from NMR. Dienes **6**–**9** and alkene **10** cannot give Diels–Alder adducts, of course, and no reaction to give ene adducts with maleic anhydride was observed at the temperature used for kinetics (25 °C). No attempt was made to obtain adducts at higher temperatures.

The DAZD ene adducts with **1** and **2** have been reported earlier.[2] Although 1,3-cyclohexadiene itself gives some 20% Diels–Alder adduct with DAZD,[1a,7] cyclohexadienes **2**–**5** give ene adducts exclusively, all in very high yields, though sometimes accompanied by a few percent of oxidation to an aromatic material and reduction of the DAZD to diethyl 1,2-hydrazinedicarboxylate. The single DAZD adducts with **3** and **4** were found to be identical by IR, NMR, and HPLC. This pointed to structure **12** rather than one of **13**–**15** since only **12** can be formed by concerted ene reaction from both dienes while the others require that one or both dienes react in a stepwise or forbidden manner. However, we did not feel this was sufficient for firm assignment. Detailed analysis of IR and NMR spectra was of little help, but because there was no UV maximum above 205 nm, **14** and **15** could be ruled out. The position of the hydrazine group on the ring was then determined by conversion of the adduct to the corresponding aromatic compound with tetrachloro-*o*-quinone and removal of the carbethoxy groups to give **16**. The latter is a known compound and a sample, prepared from 2-nitro-*p*-cymene,[8] was found to be identical by IR and NMR with the adduct derived material.



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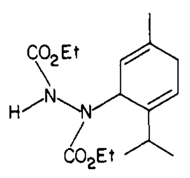

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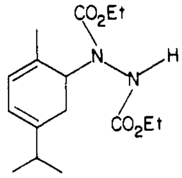

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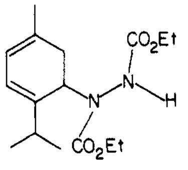

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A single adduct between **5** and DAZD was formed in quantitative yield. The similarity between its spectra and those of the adducts of **1** and **2** made the assignment of structure **17** straightforward.

It was initially difficult to obtain reproducible results with **6** because one or more minor impurities in it proved to be very much more reactive towards DAZD than was **6**. Sequential passage through two different preparative VPC columns was necessary before material pure enough (>99.8%) for either product or kinetic studies was obtained. Ironically, although **6** cannot give a Diels–Alder

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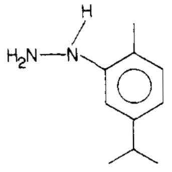
(5) (a) For **5**: Marvell, E. N.; Caple, G.; Schatz, B. *Tetrahedron Lett.* **1965**, 385. Marvell, E. N.; Caple, G.; Schatz, B.; Pippin, W. *Tetrahedron* **1973**, 29, 3781. (b) For **6** and **7**: Bank, S.; Rowe, C. A., Jr.; Schriescheim, A.; Naslund, L. A. *J. Org. Chem.* **1968**, *33*, 221. (c) For **10**: Bechara, J. H.; Wilson, T. *Ibid.* **1980**, *45*, 5261.

(6) (a) For **1** see ref 1b. (c) For **2** see ref 2. (c) For **3** as the diacid: Ipatieff, V. N.; Pines, H. *J. Am. Chem. Soc.* **1944**, *66*, 1120. (d) For **4**: Augestad, I. *Acta. Chem. Scand.* **1956**, *10*, 32. Diels, O.; Alder K. *Liebigs Ann. Chem.* **1928**, *460*, 98.

(7) (a) Although under some conditions larger amounts of Diels–Alder adduct are observed,[7b] our results match the 20% yields observed by Gillis[1a] and Franzus.[7c,d] (b) Cohen, S. G.: Zand, R. *J. Am. Chem. Soc.* **1962**, *84*, 586. (c) Franzus, B.; Surridge, J. H. *J. Org. Chem.* **1962**, *27*, 1951. (d) Franzus, B. *Ibid.* **1963**, *28*, 2954.

(8) Phillips, M. *J. Am. Chem. Soc.* **1923**, *45*, 1489. Wheeler, A. S. *Ibid.* **1929**, *51*, 3135.



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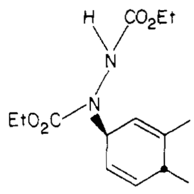

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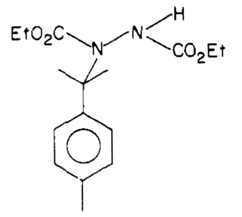

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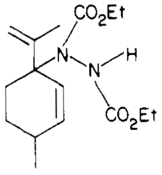
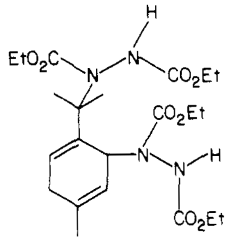


19

reaction, it was with this diene (and also **7**) that a multitude of products with DAZD was formed. There was one major product with **6** (60–70% of total adducts) which we have assigned as **20**, a 2:1 adduct. The proportion of this product decreased, but only slightly, when a large excess of diene over DAZD was used. Also isolated were 10–15% of an aromatic material which proved to be **18**, 8–10% of a 1:1 adduct which we have tentatively assigned as **19**, and small amounts of diethyl 1,2-hydrazinedicarboxylate (representing about 10–15% of the DAZD used). Very small amounts of five other peaks, all under 4% of total products, could be observed by HPLC but could not be isolated. A noteworthy and at first surprising aspect of **18** is that its NMR spectrum displays not two but three methyl singlets (at δ 1.60, 1.75 and 2.33). Also, although virtually all the DAZD ene adducts of **1–5** and **7–10** show small chemical shift differences between the two carbethoxy groups, typically just under 0.1 ppm for the CH_2's and 0.05 ppm for the CH_3's, **18** shows a difference of 0.3 ppm for the CH_2's and 0.33 ppm for the CH_3's with unusually high field positions for one of each (δ 3.95 and 0.96, respectively). As we were concerned that we might have an incorrect structure assignment, we prepared **18** by a different route, free radical addition of *p*-cymene to DAZD (dibenzoyl peroxide, 120 °C). The compounds were identical. Further, when cumene was used in place of *p*-cymene, there were two methyl signals (δ 1.60 and 1.75) and the carbethoxy groups showed the same large shift differences and higher field positions. Only with ethylbenzene in place of cymene did the shifts return to normal, but here both the CH_2 and CH_3 signals of one carbethoxy group were markedly broadened. Space filling models show extreme crowding around the carbon bearing the *gem*-dimethyl and nitrogen groups in **18**. It thus appears that crowding pushes one carbethoxy group out over the ring and either restricts rotation or forces the nitrogens to be nonplanar with slow inversion.[9] Heating the NMR samples to 85 °C (the limit of our apparatus) produced no broadening of the methyl signals.

The formation of **18** could be the result of either decomposition of **20**[10] or of oxidation of **21**. Direct oxidation of **2** to benzene by DAZD was observed by Franzus.[7d] On heating a sample of **20** to 115 °C, **18** plus diethyl 1,2-hydrazinedicarboxylate were formed, but the reaction had a half-life of several days. Exposure to air for several weeks also effected the conversion, but under the conditions used for the reaction of **6** and DAZD, **20** appears to be almost inert, so direct oxidation of **21** appears to dominate. Quite surprisingly, no adduct resulting from *initial* removal of the tertiary hydrogen (i.e., no **22**) could be detected. Although in theory **20** could also be formed from such an intermediate, we would not expect complete conversion under the reaction conditions nor the kinetic behavior observed (vide infra).



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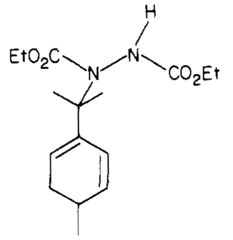

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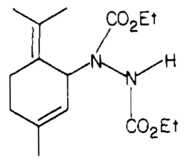

22

From the predominance of **20** and the pattern of rate constants discussed below, the major initial product of **6** and DAZD (and precursor to **20**) is the ene adduct **21**. This would be expected to have greater reactivity toward DAZD than does **6** (or **22**) but might be detectible if an overwhelming excess of **6** were present. To try to test this, a 15-fold excess of **6** was reacted with DAZD producing a small extra peak on the HPLC trace near **18** and **19**. The amounts of **18** and **20**, but not **19**, also seemed to decrease slightly. However, the uncertainty in the measurements is almost as large as the observed changes and it is possible the new peak is an artifact, a product from a trace but highly reactive impurity in the large amount of **6**. Isolation of the peak was not possible as it was very poorly separated from **18**.

The reaction of **7** with DAZD was quite similar to that of **6**. Two major products, accounting for 75% of total adducts, were produced in an approximately 2:1 ratio. Both proved to be 2:1 adducts. Both could be broken down, at 115 °C or on standing in air, to **23** and diethyl 1,2-hydrazinedicarboxylate, though under both conditions reaction was slower than with **20**. **23** was prepared independently by free radical addition of ethylbenzene to DAZD and based on this plus NMR and IR spectra, structures **24** and **25** were assigned as the major and minor isomers. Ten other products were present on the HPLC trace, but only **23** and diethyl 1,2-hydrazinedicarboxylate were present in amounts over 10% of that of the two major adducts. When a 15-fold excess of **7** over DAZD was used, the yield of 2:1 adducts dropped slightly but **23** was almost absent and a new peak representing about 13% of total products appeared. Although is was not possible to obtain this completely pure, centrifugally accelerated radial prep TLC afforded a few mg of material consistent (NMR and UV) with **26**. When mixed with additional DAZD, this material was completely converted into a product mixture identical with that obtained with 1:1 DAZD and **7** and at a rate estimated to be 10–20 times faster (fade time for the DAZD color) than the original reaction. The cis isomer of **7** (**27**) appeared to give the same products as did **7**. However, as we were unable to obtain **27** free of **7**, no kinetic measurements were made. Qualitatively, it appeared to be somewhat more reactive.

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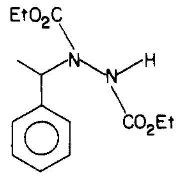
(9) There is evidence for nonplanarity of the nitrogens in some phenyl triazolinedione Diels-Alder adducts: Kaftory, M. *J. Am. Chem. Soc.* **1983**, *105*, 3832 and references therein.

(10) Jacobson, B. M.; Gerhard, D.; Jackson, C.; Smallwood, J. *J. Org. Chem.* **1980**, *45*, 3344.



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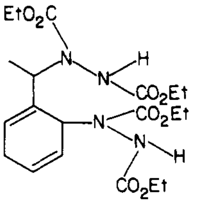

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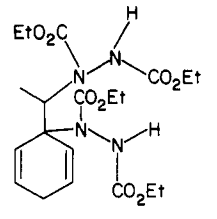

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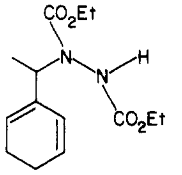

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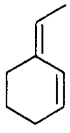

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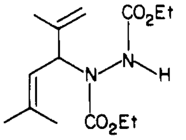
The reaction of **8** with DAZD has been examined qualitatively twice before,[1a,11] but our findings differ somewhat from both earlier reports. When a large excess of diene is used, the major adduct (93%) is **28**, in agreement with Gillis.[1a] However, at a ratio of diene to DAZD similar to those he reported, we found that the 2:1 adduct **29** was produced in nearly as large an amount.[12] A third, minor product (7%) present in constant ratio to **28** under all conditions does appear to match the structure **30** reported.[1a]

The reaction of **9** with DAZD was thoroughly investigated by Franzus[7c,d] and except for determination of the rate constant at 25 °C (the earlier work was done only at higher temperatures) we can add nothing.

To make comparisons of the rates of reaction more meaningful, the reaction of **10** was examined as a case where there is no second double bond at all to play a role in the reaction, but a cyclohexyl ring is still present. (Cyclohexene itself is not an appropriate model because it has been reported to react with DAZD via a free radical path, at least at elevated temperatures.[13] The reaction produced a single product, **31**, in quantitative yield. The presence of small amounts of 2,6-di-*tert*-butyl-4-methylphenol had no effect on the rate or product structure.



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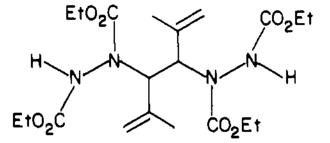

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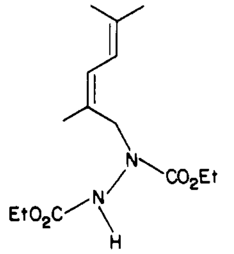

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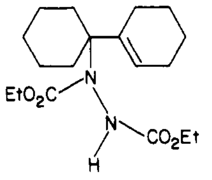

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Rate Measurements. The second-order rate constants for the overall reaction of dienes **1**–**9** and **10** with DAZD or maleic anhydride are listed in Table I along with partial rates per reactive hydrogen (for the ene reactions). A few conclusions seem warranted. Clearly, the cisoid character of dienes **1**–**5** produces a noticeable acceleration of the rate in every case. It is for this reason we are confident in assigning **21** as the unobserved intermediate in the reaction of **6** rather than **22**. As was actually observed with **26**, **21** should react far faster than **6** whereas **22** ought to survive at least in part. That **21** loses a tertiary hydrogen where **26** loses a secondary one makes it even more reactive (see below) and easy to understand why it could not be observed.

Table I. Second-Order Rate Constants for Ene and Diels–Alder Reactions

no.	10^7k (30 °C)[a] maleic anhydride	10^7k (25 °C)[a,b] DAZD	partial rates ene 10^7k (25 °C)[a,c]
1	1320[d]	760[e]	146 (2°)[e,f]
2	8.7[g]	11 500[g]	5750 (3°)
3	403	1150	575 (2°)
4	1730	27 500	27 500 (3°)
5	30	11 800	5900 (3°)
6		37	8.3 (2°)[h] 0.6 (1°)
7		128	32 (2°)[h]
8		8	0.64 (1°)[i]
9		32	5.6 (2°)[f]
10		153	19 (2°)

[a] In s^{-1} M^{-1} L. [b] Total rate of disappearance of DAZD. [c] Rate per reactive hydrogen and type, 1°, 2°, or 3°. [d] Sauer, J.; Lang, d.; Mielert, A. *Angew, Chem., Int. Ed. Engl.* **1962**, *1*, 268. [e] Reference 7d. [f] Corrected for Diels–Alder and direct oxidation reactions. [g] Reference 2. [h] Corrected for fast second step. [i] Radical pathway product excluded.

Two explanations for the faster reactions of the cisoid dienes can be suggested. Save possibly for **8**, the geometry of all the conjugated substrates used here have coplanar (or nearly coplanar, under 20° dihedral angle)[14] π-systems. Six-membered ring geometry also favors having at least some of the allylic hydrogens axial, and thus parallel to the π-orbitals, so that a concerted ene reaction is always possible. Indeed, except for **8**, the ene reactions all appear to be concerted, as there is no effect on the rate or products from the presence of 2,6-di-*tert*-butyl-4-methylphenol. (The reactivity of **8** is too low to use this phenol; although DAZD reacts very sluggishly with the latter, it is fast enough to interfere with rate measurements in this case.) The appearance of **30** suggests that **8** is reacting in part by a radical pathway while the presence of only products with migrated double bonds is by contrast added evidence for concert in the remaining reactions. It is conceivable that concerted ene reactions involve some loss of conjugation energy in the transition state when the product itself is no longer conjugated (as is the case for **1**–**5**). Is so, then since 1,3-cyclohexadiene is known to have a smaller than usual conjugation energy to begin with,[15] there would be a smaller loss with these dienes and hence a lower barrier. This would also explain why with **6** and **7** only the secondary hydrogens at the 4-position are reactive and not those at the 6-position, for the product can remain conjugated in the former case. However, if this were the entire explanation, why is not **9**, which should be *increasing* its conjugation energy in the transition state, albeit only slightly, more reactive than **1**? Why also would there be *no detectible reaction at all* at the tertiary hydrogen in **6** yet easily detectible reaction at the primary hydrogens (even taking into account the six to one statistical factor)

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(11) Levina, R. Y.; Skabarow, U. S.; Kuzmin, M. H. *Dokl. Akad. Nauk. SSSR* **1960**, *131*, 1080.

(12) It is possible that this is the third, minor component reported but not identified by Gillis.[1a]

(13) Huisgen, R.; Pohl, H. *Chem. Ber.* **1960**, *93*, 527.

(14) (a) Traetteberge, M. *Acta Chem. Scand.* **1968**, *22*, 2305. (b) Allinger, N. L.; Tai, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 4256 and references therein. (c) der Heyde, W. A.; Lüttke, W. *Chem. Ber.* **1978**, *111*, 2384.

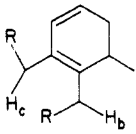
(15) Turner, R. B.; Mallon, B. J.; Tichy, M.; Doering, W. von E.; Roth, W. R.; Schröder, G. *J. Am. Chem. Soc.* **1973**, *95*, 8605.

for that is a consequence of the second conclusion easily drawn from the rate data.

In the absence of other differences, a 10- to 50-fold preference for tertiary over secondary and secondary over primary hydrogens seems to be general, with the reaction of **6** being the only odd case. (In **3**, the isopropyl group should be rotated for steric reasons, placing the tertiary hydrogen orthogonal to the π-system and rendering it unreactive. No such explanation can be made for **6**.) Given this, there ought to have been far more **22** than **19**. Why also, are the 1,3-cyclohexadienes more reactive than the simple alkenes such as **10** or others?[4b] From the results with the non-cisoid dienes, neither conjugation per se (with **6** and **7**) nor the gaining of it (with **9**) nor the losing of it (with **8** in the nonradical path) seems to make much difference in the rate of the ene reaction.

An alternative explanation would be that the cisoid geometry of the 1,3-cyclohexadienes allows for a secondary orbital interaction between the nominally uninvolved double bond of the diene (the bond that does not migrate) and a carbonyl of the DAZD. The observation that trans dienophiles make better enophiles than their cis isomers may be relevant.[3] From models, overlap of a carbonyl seems much more difficult to arrange with the extended geometry in **6**–**8** than for the cisoid dienes. (Models also seem to indicate that the trans nature of the DAZD should make the aziridinium imide approach of the type suggested by Greene[16] for *N*-phenyltriazolinedione ene reactions much more difficult, so that we have not considered it here.)

We hope to examine the question of enophile approach further by seeing what the selectivity for hydrogen transfer to DAZD will be among the three allylic positions in cisoid systems of type **32**. Again from models, secondary orbital interactions should be easiest to arrange during transfer of H_a, more difficult with H_b, and look impossible with H_c. Selection and synthesis of a set of appropriately substituted dienes in which other factors, particularly steric ones, will not distort the selectivity, or at least will let the effect of distortion be allowed for, is not a simple process, though work is underway.



The kinetic data also point to a third conclusion. Although the Diels–Alder and ene reactions are clearly closely parallel in their response to many changes in the structure of the dienophile (witness the appearance of both kinds of reactions in both the extremely rapid reaction of the "champion" dienophile *N*-phenyltriazolinedione and the slow reaction of fumaronitrile with **2**)[2] yet, relatively small changes in diene structure can cause a marked divergence. The Diels–Alder rates for reaction of maleic anhydride with **2**, **4**, and **5** cover a 200-fold range while the ene rate with DAZD varies by a factor of less than 3 (or about 5 if reactivity per hydrogen is used). Some of this difference is probably steric in origin, but what other factors are relevant remains uncertain.

Experimental Section

Capillary melting points (uncorrected) were taken on a Thomas-Hoover melting point apparatus. NMR spectra were obtained by using a Varian T-60 instrument. IR data were from a Perkin-Elmer Model 735B spectrometer. HPLC analyses were done with an RSil silica column (10μ, $^{1}/_{4}$ in. × 25 cm) and LDC refractive index detector. Where possible, refractive indices of isolated products were measured on a Bausch & Lomb refractometer to determine response factors for the HPLC detector. Preparative TLC was done on a Harrison Research centrifugally accelerated chromatograph ("Chromatotron"). Flash chromatography was performed according to the method reported by Still.[17] VPC was done on either an Aerograph A-90 or Gow-Mac 69-150 chromatograph with the following columns: (A) $^{3}/_{8}$ in. × 14 ft Carbowax 20 M, 15% on ChromosorbP; (B) $^{3}/_{8}$ in. × 14 ft Tris(cyanoethoxy)propane, 15% on Chromosorb P; (C) $^{3}/_{8}$ in. × 14 ft silicone rubber SE-30, 15% on Chromosorb P; (D) $^{3}/_{8}$ in. × 20 ft $\beta\beta'$-oxybis(propionitrile), 20% on Chromosorb P; (E) $^{1}/_{4}$ in. × 12 ft Carbowax 20 M, 10% on Chromosorb P; (F) $^{1}/_{8}$ in. × 14 ft Tris(cyanoethoxy)propane, 15% on Chromosorb P; all packings were 60/80 mesh. Analyses were done by Galbraith Laboratories, Knoxville, TN.

Materials and Purification Procedures. Cyclohexane was spectranalyzed grade from Fisher Scientific and a single bottle was used for all the kinetics. Before use in preparing diene solutions for kinetics, it was purged of air by nitrogen entrainment. *p*-Dioxane was filtered through grade I alumina, then distilled from $LiAlH_4$ under N_2 and stored under N_2 until used. Crotonaldehyde (Aldrich) was distilled before use, with a cut from 102.5–103.5 °C being taken. Tetrahydrofuran was transferred only by syringe or canula under N_2 (Aldrich Gold Seal). α-Terpinene and α-phellandrene, **3** and **4** (Pfalz & Bauer), were each purified by preparative VPC on column A at 135 °C and then stored in sealed ampules to prevent air oxidation. 2,5-Dimethyl-2,4-hexadiene (Aldrich) was distilled before use. Tetrachloro-*o*-benzoquinone (Aldrich), 2-nitro-*p*-cymene (Aldrich), crotyl chloride (Aldrich), 2,6-di-*tert*-butyl-4-methylphenol (Fisher), triphenylphosphine (Aldrich), cumene (Aldrich), *p*-cymene (Aldrich), and ethylbenzene (Aldrich) were used as received. Maleic anhydride and potassium *tert*-butoxide (both Aldrich) were sublimed before use. Ethyl acetate and hexane for HPLC were Fisher HPLC grade and degassed before use.

Cyclohexylidenecyclohexane, **10**, was prepared by the method of Bechara and Wilson[5c] except that prepared McMurry's reagent (Aldrich) was used and a recrystallization from methanol was found sufficient to produce VPC pure material. 1,4-Cyclohexadiene (Aldrich) was transferred to ampules and sealed under N_2 until needed. *trans*-3-Ethylidenecyclohexene, **7**, and 3-isopropylidenecyclohexene, **6**, were prepared by the method of Bank[5b] but purified after distillation by preparative VPC. For **6** this involved injection of 100 μL at a time on column B at 110 °C and then passing the collected material 70 μL at a time through column A at 120 °C. Material purified by a single pass through either column contained sufficient impurity to give strong curvature to all kinetic runs regardless of concentrations. For **7**, isolation of pure material required injection of 50-μL samples on column D after the cis–trans isomer pair has been collected from 250-μL injections on column C.[18]

Synthesis of *cis*-5,6-Dimethyl-1,3-cyclohexadiene, 5. Crotyl chloride (15 g) was refluxed with 20 g of triphenylphosphine in 30 mL of toluene overnight. The precipitated crystals were filtered, washed with toluene, and air dried. They were then placed over P_2O_5 in a vacuum desiccator overnight. This phosphonium salt (36 g) was placed in a 1-L three-necked flask under N_2, 500 mL of THF was added by canula, and 15 g of freshly sublimed potassium *tert*-butoxide was added. The deep red mixture was stirred for 2 h and then 7.1 g of crotonaldehyde in 40 mL of THF was added dropwise over a 1-h period. Stirring was continued under N_2 overnight. The light red mixture was then filtered, the collected solid washed with pentane, and the washings added to the first filtrate. The bulk of the solvent was distilled away through a $2^{1}/_{2}$-ft column of glass helices. The cooled residue was again filtered, the solids washed with pentane, and the combined filtrates chromatographed over 30 g of silica gel with pentane as the eluant. The eluate was distilled, with the fraction boiling from 140–155 °C being collected (2.3 g). VPC analysis on column F showed it to be 40% the all trans octatriene, 50% the trans–cis–trans isomer, and 10% a mixture of other isomers. Identi-

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[16] Seymour, C. A.; Greene, F. D. *J. Am. Chem. Soc.* **1980**, *102*, 6384.

[17] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[18] Dempster, C. J. Thesis, Harvard University, 1969, pp 88 and 90–92.

fication was made by NMR of small samples collected by using column B at 90 °C. Initially, a mixture of isomers collected by VPC was used in the next step, but later work showed that the same yields could be obtained with the crude distilled product. The octatriene isomers were placed in a tube with a few crystals of 2,6-di-*tert*-butyl-4-methylphenol to inhibit polymerization, degassed by freeze–pump–thaw cycling, and sealed up. After heating to 132 °C for 24 h, the cooled tube was opened and the contents distilled to yield 1 mL of crude diene boiling at 130–138 °C plus starting octatrienes boiling above 140 °C. Very pure diene could be obtained by preparative VPC with column C at 125 °C. The product has NMR absorbances identical with those reported by Marvell et al.[5a]

General Kinetics Procedures: Maleic Anhydride Runs. The diene was weighed into a 3- or 5-mL volumetric flask and purified *p*-dioxane was added to the mark and mixed. Freshly sublimed maleic anhydride and *m*-dinitrobenzene (as internal standard) were weighed into an NMR tube to which a ground joint had been fused. The diene solution (500 μL) was added by syringe and the tube immediately frozen in dry ice. The tube was attached to a vacuum line, degassed by freeze–pump–thaw cycling with minimal warming and sealed. The tube was then immersed in a water bath at 30 ± 0.02 °C. Periodically, it was removed and the NMR spectrum and integrals rapidly recorded. When points had to be taken for more than 12 h (but at less than 8-h intervals) the sample was frozen overnight at −78 °C and reimmersed in the morning. Best results were obtained by following the disappearance of the anhydride but the same rate constant, albeit with poorer statistics, was obtained by measuring adduct appearance. When the reaction was complete (over three half-lives) the height of the liquid in the tube was marked at 30 °C, the tube opened, and the contents removed. The volume of the solution at 30 °C was then determined by repeatedly weighing water into the tube to the mark.

General Kinetics Procedures: DAZD. For slow reactions (half-life over 6 h), redistilled DAZD was weighed into a 3-mL volumetric flask, approximately 2 mL of oxygen free cyclohexane was added carefully so as not to disturb the DAZD, and then the diene was weighed in. Working as rapidly as possible, the flask was filled to the mark and mixed rapidly and the solution was poured into a 10-mm pathlength UV cell equipped with a ground joint. The cell was attached to a vacuum line and frozen in dry ice. The cell was degassed by freeze–pump–thaw cycling and sealed. The reaction was monitored by placing the cell in the thermostated cavity of a Perkin-Elmer-Hitachi Model 200 spectrometer and recording the change in absorbance at 403 nm. When very slow reactions were run (over 24 h) or the reactions produced sufficient diethyl 1,2-hydrazinedicarboxylate to cause precipitation that might fog the glass, the cells were held inverted in a water bath at 25 ± 0.02 °C so that the solution was out of contact with the optical surfaces. Absorbance was then determined only periodically. The precipitated hydrazide generally formed as fine needles that clung to the glass in the inverted cell and careful righting returned clear solution to the optical part of the cell.

For rapid reactions (half-life under 6 h) separate cyclohexane solutions of diene and DAZD were prepared in small volumetric flasks. The solutions were pipeted into the UV cell, mixed rapidly, and placed in the spectrometer compartment. For both slow and fast runs, addition of a few crystals of 2,6-di-*tert*-butyl-2-methylphenol has no effect on the rate. A blank with just DAZD and the phenol in cyclohexane with both at concentrations comparable to the diene and DAZD concentrations used in the kinetics showed a very slow reactionbut with a rate constant smaller than those determined for all the dienes except **8**. In general, reactions using first a large excess (10-fold or more) and than a small excess (2-fold) of diene were run in duplicate at each concentration of diene. However, with **8** reactions were run only with a large excess both because they took excessively long otherwise and because here the product, **28**, appeared to be comparable to starting material in its reactivity. Reactions with **6** could not be run with more than a 5-fold excess of diene without introducing curvature to the second-order plots because of residual reactive impurities.

Isolation of Products and Structure Determination: Maleic Anhydride Adducts. For the Diels–Alder adducts of **3** and **4**, samples isolated by evaporation at reduced pressure at the end of kinetic runs were recrystallized from petroleum ether. Melting points matched literature values.[6c,d] With **5**, the Diels–Alder reaction produced a mixture of (at least) two isomers as an oily mass following evaporation. Hydrolysis with ethanolic NaOH gave fully crystalline material but with mp 133–141 °C. Recystallization from aqueous ethanol failed to give any separation of the isomers and nofurther attempt was made to determine which isomers among the exo, endo, syn, and anti combinations were present. The NMR spectrum of the isomer mixture (of acids) in acetone-d_6/D_2O showed signals at δ 6.2 (d of d, 2 H), 4.2 (HOD), 3.3 (t, 1 H), 3.1 (broad s, 1 H), 2.9 (m, 1 H), 2.6 (m, 1 H), 0.8 (d of d, 6 H). Anal. Calcd for $C_{14}H_{20}O_4$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.23.

DAZD Adduct with 3 and 4: Diethyl 1-(1-Isopropyl-4-methylcyclohexa-1,4-dien-3-yl)-1,2-hydrazinedicarboxylate, 12. From the kinetic runs of both **3** and **4** a single adduct was observed by HPLC and isolated by evaporation and Kugelrohr distillation at 120 °C (10^{-3} mm). Initially, the material was an extremely viscous colorless oil, but one sample crystallized on standing in a sealed tube after some weeks, mp 48–51 °C. On standing in air the adduct gradually decomposed to *p*-cymene and diethyl 1,2-hydrazinedicarboxylate. The oil could be purified further either by crystallization from ethanol or flash chromatography on silica gel with 3:1 hexane:ethyl acetate as eluant: NMR (CCl_4) δ 6.6 (broad, 1 H), 4.9–5.8 (m, 3 H), 4.15 (two interlaced q, J = 7 Hz, 4 H), 2.0–2.7 (m, 3 H), 1.7 (broad s, 3 H), 1.25 (two interlaced t, J = 7 hz, 6 H), 1.05 (d, J = 7.5 Hz, 6 H); IR (thin film) 3300, 3040, 2980, 2870, 1755, 1705 cm^{-1}.

Conversion of 12 into (2-Methyl-5-isopropylphenyl)-hydrazine, 16. To 6.2 g of **12** in 25 mL of benzene was added 4.7 g of tetrachloro-*o*-benzoquinone and the mixture refluxed for 6 h followed by overnight stirring at room temperature. A few drops of γ-terpinene were added to destroy any remaining quinone and petroleum ether was added giving an orange solution and a tarry red-brown precipitate. The solution was decanted and the precipitate refluxed with an additional 20 mL of petroleum ether. The combined petroleum ether solutions were extracted with 0.5 M NaOH (a troublesome dark green precipitate had to be filtered off at this stage). The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 3.2 g of orange oil that was used immediately in the next step. The aromatized material was refluxed with 25 mL of methanolic KOH for 2 h under N_2. The mixture was poured into 100 mL of water and acidified with 6 M HCl. The solution was extracted twice with 60 mL of ether. The yellow aqueous layer was made basic with NaOH and an orange oil separated. This was taken up in ether, dried over K_2CO_3, and evaporated. The NMR and IR spectra of the resulting oil were identical with those of a sample of 1-(2-methyl-5-isopropylphenyl)hydrazine prepared from 2-nitro-*p*-cymene.[8]

Adduct of DAZD and 5: Diethyl *cis*-(1,6-Dimethyl-1,4-cyclohexadien-3-yl)-1,2-hydrazinedicarboxylate, 17. The pooled solutions from the kinetic runs showed a single peak on HPLC. After evaporation to a small volume and flash chromatography on silica gel with 5:1 hexane:acetone as eluant, the product, a colorless oil, was placed in an ampule and pumped free of solvent at 10^{-3} mm: NMR (CCl_4) δ 6.9 (s, 1 H, moves on dilution), 5.1–5.9 (m, 4 H), 4.1 (interlaced q, J = 7 Hz, 4 H), 2.5 (m, 1 H), 1.8 (s, 3 H), 1.23 (interlaced t, J = 7 Hz, 6 H), 1.15 (d, J = 8 Hz, 3 H); IR (CCl_4) 3300, 3020 (sh), 2980, 2930, 2880, 1760, 1710 cm^{-1}. Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.39; H, 7.93; N, 10.01.

Adducts of DAZD and 6. After evaporation, 300 mg of oil accumulated from kinetics was dissolved in 1 mL of 3:1 hexane:ethyl acetate and applied to the Chromatotron. Elution with 4:1 hexane:ethyl acetate removed unreacted diene. Switching to 2:1 hexane:ethyl acetate eluted a mixture of **18**, **19**, and several minor products followed by **20**. The latter does not quench the fluorescent indicator on the plate and fractions must be monitored by HPLC. Evaporation of pure fractions of **20** at 10^{-3} mm yielded 120 mg of colorless oil that was almost solid: NMR ($CDCl_3$) δ 7.25 (m, 1 H), 6.5 (d of m, 1 H), 5.5 (m, 2 H), 4.1 (m, 8 H), 2.6 (m, 2 H), 1.70 and 1.75 (overlapping s and d, 6 H), 1.35 (s, 3 H) overlapped by 1.28, 1.25, 1.22 (three interlaced t, 12 H) [the signals at δ 7.25 and 6.4 move upon dilution]; IR (CCl_4) 3350, 3020 (sh), 2980, 2910, 2870, 1750, 1710 cm^{-1}; $n^{25}{}_D$ 1.4875. Anal. Calcd for $C_{22}H_{36}N_4O_8$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.38; H, 7.58;

N, 11.34. The impure mixture of **18** and **19** was concentrated and reapplied to the Chromatotron. 4:1 Hexane:ethyl acetate was used to elute the first band and then 7:3 hexane:ethyl acetate eluted the remaining bands. Several cuts were taken for each band and checked by HPLC. For the first band, evaporation of the purer cuts (>90% by HPLC) yielded 30 mg of **19** as a colorless oil: NMR (CCl_4) δ 6.6 (broad, 1 H, moves on dilution), 5.7 (m, 2 H), 4.8 (m, 2 H), 4.15 (two interlaced q, J = 7 Hz, 4 H), 1.5–2.5 (m, 5 H) overlapped by 1.75 (d, J = 3 Hz, 3 H), 1.25 (two interlaced t, J = 7 Hz, 6 H), 1.0 (d, J = 7.5 Hz, 3 H); IR (CCl_4) 3300, 3080, 3020 (sh), 2980, 2950, 2930, 2870, 1760, 1720, 1640 (w) cm^{-1}; $n^{25}{}_{D}$ 1.4949. The second band, on evaporation of the purer fractions, yielded fairly pure **18** with an IR and NMR identical, with the subtraction of a few blips in the latter, with those of the compound produced by free radical addition of *p*-cymene to DAZD (see below).

Pyrolysis of 20. A sample of 20 mg of **20** was dissolved in 0.1 mL of ethyl acetate, placed in a tube with a ground joint, degassed on a vacuum line, and sealed. After 10 days of heating to 115 °C the tube was opened. HPLC showed only **18** and diethyl 1,2-hydrazinedicarboxylate present. A second sample heated only two days showed only partial conversion. A sample left in the air for three weeks showed 50% conversion.

Adducts of DAZD and 7. Initially, a sample of products from a 1.3:1 mixture of DAZD and **7** was used. Elution of a 570-mg sample on the Chromatotron with 15:1 hexane:ethyl acetate afforded 140 mg recovered diene. Switching to 3:1 and then 2:1 hexane:ethyl acetate gave first 50 mg of a not very pure material (about 60% by HPLC, with one major but many minor peaks) followed by 225 mg of relatively pure **24** (95% by HPLC) and 100 mg of pure **25**. As was the case with **20**, neither of these two products quenched the fluorescent indicator on the plate and were found only with HPLC monitoring. Reapplication of the 50 mg of high R_f fraction and recycling the eluant five times with multiple development afforded 15 mg of fairly pure **23** with IR and NMR identical with those of material prepared by free radical addition of ethylbenzene to DAZD (see below). The major adducts, after removal of solvent at 10^{-3} mm, were frozen oils. For **24**: NMR (CCl_4) δ 7.5 (m, 2 H), 5.6–6.2 (m, 3 H), 5.2 (m, 1 H), 4.4 (m, 1 H), 4.1 (three interlaced q, J = 7 Hz, 8 H), 2.65 (m, 2 H), 1.25 (t, J = 7 Hz, overlapping a d, J = 7 Hz, 15 H) [the δ 7.5 signal moves upfield and splits into two bands on dilution]; IR (CCl_4) 3300, 3040, 2980, 2910, 2870, 1750, 1710 cm^{-1}; $n^{25}{}_{D}$ 1.4933. Anal. Calcd for $C_{20}H_{32}N_4O_8$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.58; H, 7.10; N, 12.09. For **25**: NMR ($CDCl_3$) δ 6.8 (broad, 1 H), 6.5 (broad, 1 H), 5.2–6.2 (m, 4 H), 4.9 (m, 1 H), 4.1 (three interlaced q, J = 7 Hz, 8 H), 2.65 (m, 2 H), 1.25 (t, J = 7 Hz, overlapping a d, J = 7 Hz, 15 H) [the first two signals move on dilution]; IR (CCl_4) 3300, 3030 (sh), 2980, 2930, 2910, 2870, 1760, 1715 cm^{-1}; $n^{25}{}_{D}$ 1.4930. Anal.[19] Found: C, 51.49; H, 7.05; N, 11.72. A sample of **7** and DAZD in which **7** was in 15-fold excess was also separated on the Chromatotron. The low R_f bands were unchanged, but from the mixture of high R_f bands treated in the earlier manner could be isolated 17 mg of a colorless oil with a purity of 95% (HPLC) that has tentatively been assigned structure **26**. The oil: UV (ethanol) λ_{max} 258 nm (ϵ = 4300); NMR ($CDCl_3$) δ 6.2 (m, 1 H), 5.9 (broad s, 2 H), 5.7 (m, 1 H), 4.8 (q, J = 6.5 Hz, 1 H), 4.2 (two interlaced q, J = 7 Hz, 4 H), 2.1 (broad s, 4 H), 1.2 (t, J = 7 Hz overlapping a d, J = 6.5 Hz, 9 H); IR (thin film) 3300, 3030, 2970, 2930, 2870, 2820, 1750, 1710 cm^{-1}; $n^{25}{}_{D}$ 1.4982. Anal.[19] Calcd for $C_{14}H_{22}N_2O_4$; C, 59.56; H, 7.87; N, 9.92. Found: C, 57.85; H, 7.77; N, 9.64. When **26** was mixed with additional DAZD and allowed to stand at room temperature, there was produced a mixture whose HPLC trace was identical with that of the crude product mix from the 1.3 : 1 mixture of **7** and DAZD save only that no starting **7** was present.

Pyrolysis of 24 and 25. Each compound (50 mg) was dissolved in 0.4 mL of CD_3CN in an NMR tube equipped with a ground joint. The solutions were degassed on a vacuum line and sealed. They were heated to 115 °C and periodically removed for monitoring. After 10 days both samples were approximately 50% converted to **23** and diethyl 1,2-hydrazinedicarboxylate. Exposure of other samples to the air for one month resulted in about 40% of the same conversion.

Reaction of Ethylbenzene and DAZD: Synthesis of Diethyl 1-(1-Phenylethyl)-1,2-hydrazinedicarboxylate, 23. To 25 mL of ethylbenzene was added 0.3 g of DAZD and 5 mg of dibenzoyl peroxide (DBPO). The solution was refluxed overnight, by which time it was nearly colorless. Unreacted ethylbenzene was removed by rotary evaporation and the 2 mL of residue transferred to a Kugelrohr. Heating to 80 °C (0.05 mm) distilled a colorless oil and left a residue of nearly pure **23**. Flash chromatography on silica gel with 3:1 hexane:ethyl acetate gave 400 mg of **23** (83%) as a nearly colorless oil: NMR ($CDCl_3$) δ 7.3 (s with attendant small peaks, 5 H), 7.0 (broad s, 1 H, shifts with dilution), 5.5 (q, J = 7.5 Hz, 1 H), 4.1 (two interlaced q, J = 7 Hz, 4 H), 1.5 (d, J = 7.5 Hz, 3 H), 1.2 (two interlaced t, J = 7 Hz, 6 H) [one of the q at 4.1 and one of the t as 1.2 are broadened]; IR (thin film) 3300, 3060, 3030, 2980, 2940, 2880, 1750, 1710 cm^{-1}; $n^{25}{}_{D}$ 1.5009.

Reaction of *p*-Cymene and DAZD: Synthesis of Diethyl 1-(1-*p*-Tolyl-1-methylethyl)-1,2-hydrazinedicarboxylate (18). To 17 g of *p*-cymene was added 0.42 g of DAZD and 5 mg of DBPO and the solution held with stirring at 120 °C overnight. The yellow color of the DAZD partially faded in the first few hours but the solution became a bright yellow again after further heating. The unreacted *p*-cymene was removed by distillation at 10 mm and further volatile material was removed on the Kugelrohr (80 °C (0.01 mm)) leaving 1 g of yellow oil. A 250-mg sample was applied to the Chromatotron and eluted in series with 5:1, 3:1, and 2:1 hexane:ethyl acetate mixtures, 50 mL each. 10 bands were visible under UV light but only three fractions yielded weighable quantities of material. The major fraction (4th band) gave 160 mg of **18** on evaporation: NMR ($CDCl_3$) δ 7.2 (AA′BB′ pattern, 4 H), 6.9 (s, broad, shifts with dilution, 1 H), 4.2 (q, J = 7.5 Hz, 2 H), 3.95 (q, J : 7.5 Hz, 2 H), 2.3 (s, 3 H), 1.75 (s, 3 H), 1.60 (s, 3 H), 1.30 (t, J = 7.5 Hz, 3 H), 0.96 (t, J = 7.5 Hz, 3 H); IR (thin film) 3300, 3050 (sh) 3020 (sh), 2980, 2930, 2870, 1760, 1710 cm^{-1}; $n^{25}{}_{D}$ 1.5062. Anal.[19] Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.08. Found: C, 61.47; H, 7.72; N, 8.83. A second cut eluted immediately after **18** gave 16 mg of diethyl 1-[(4-isopropylphenyl)methyl]-1,2-hydrazinedicarboxylate as a pale yellow oil: NMR ($CDCl_3$) δ 7.2 (s, 4 H), 6.5 (broad, 1 H, shifts on dilution), 4.7 (s, 2 H), 4.2 (two interlaced q, J = 7 Hz, 4 H), 2.9 (sept, J = 7 Hz, 1 H), 1.2 (two interlaced t, J = 7 Hz overlapping one d, J = 7 Hz, 12 H); IR (thin film) 3300, 3050 (sh), 2980, 2940, 2870, 1760, 1720 cm^{-1}.

Reaction of Cumene and DAZD: Synthesis of Diethyl 1-(1-Phenyl-1-methylethyl)-1,2-hydrazinedicarboxylate. To 25 mL of cumene was added 0.2 g of DAZD and 8 mg of DBPO. The solution was held with stirring under N_2 at 120 °C for 3 h by which time the color of the DAZD had completely faded. Unreacted cumene was removed by evaporation at 60 °C (10 mm). About 1.5 g of dicumyl was removed on the Kugelrohr at 70 °C (10^{-3} mm). The 0.4 g of residue was flash chromatographed on silica gel wiith 3:1 hexane:ethyl acetate eluant. Evaporation at 10^{-2} mm gave 250 mg of HPLC pure product as an almost colorless oil: NMR ($CDCl_3$) 7.0–7.5 (m, 6 H), 4.25 (q, J = 7 Hz, 2 H), 3.93 (q, J = 7 Hz, 2 H), 1.75 (s, 3 H), 1.60 (s, 3 H), 1.30 (t, J = 7 Hz, 3 H), 0.93 (t, J = 7 Hz, 3 H); IR (thin film) 3300, 3090, 3050, 2980, 2910, 1760, 1720 cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 60.62; H, 7.47; N, 9.48.

Adducts of 8 and DAZD. The major adduct, **28** was isolated by flash chromatography on silica gel with 3:1 hexane:ethyl acetate. Its NMR spectrum was consistent with the structure assigned by Gillis.[1a] A later cut from the chromatography was found to be a 1:1 mixture of **28** and **30**. Pure **30** was isolated by application of this mixture to the Chromatotron and elution with two recyclings with 4:1 hexane:ethyl acetate. From an original 1 g of crude adducts was isolated 30 mg of **30** which by HPLC was 90% pure. A UV spectrum had λ_{max} 240 nm (ϵ 17000) (lit.[1a] 240 nm (21000)). The NMR spectrum was somewhat odd, with one of the three methyl groups quite shielded: (CCl_4) δ 7.0 (m, 1 H), 6.0 (broad, 2 H), 4.1 (two interlaced q, J = 8 Hz, 4 H), 4.0 (m, overlapping previous signal, 2 H), 1.75 (overlapping s and d, J = 2 Hz), 1.25

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[19] We note that the values for carbon in compounds **18**, **25**, **26**, and **31** are slightly low. As indicated, we could not get **26**, an oil, entirely pure. Further, not only are the others also oils, but as solvent is pumped away from **25** and **31** they become virtually frozen (**25** does not flow detectibly in a week). It is probable that small amounts of ethyl acetate and CCl_4 remain trapped in the oils. The amounts of C, H, and N found show similar percentage errors (2–3% low) though the H and N values are generally within acceptable ranges.

(t, J = 8 Hz, overlapping a s, total 9 H); IR (CCl_4) 3300, 3070, 2960, 2900, 1740, 1695 cm^{-1}; n^{25}_D 1.4734 (lit.[1a] n^{25}_D 1.4712). When the DAZD and diene were reacted in comparable concentrations a third compound was isolated from the chromatography after the first two had eluted. On brief standing it crystallized. Recrystallization from hexane gave pure **29**: mp 89–90 °C; NMR (CCl_4) δ 6.8 (broad, 2 H), 4.7–5.1 (m, 6 H), 4.15 (m, 8 H), 1.9 (s, broad, 6 H), 1.25 (t, J = 7 Hz, 12 H); IR (CCl_4) 3300, 3020, 2900, 2850, 1750, 1700, 1640 cm^{-1}. Anal. Calcd for $C_{20}H_{34}N_4O_8$: C, 52.39; H, 7.47; N, 12.22. Found: C, 52.46; H, 7.45; N, 12.24.

Reaction of 10 and DAZD: Diethyl 1-[1-(1-Cyclohexen-1-yl)cyclohexyl]-1,2-hydrazinedicarboxylate (31). After evaporation of the samples of **10** and DAZD used for kinetics there was isolated 130 mg of a colorless oil. Flash chromatography on silica gel with 3:1 hexane:ethyl acetate gave after evaporation at 10^{-2} mm 122 mg of **31** as a viscous colorless oil: NMR ($CDCl_3$) δ 6.3 (s, 1 H, shifts on dilution), 5.7 (m, 1 H), 4.2 (two interlaced q, J = 7 Hz, 4 H), 1.8–2.4 (m, 8 H), 1.3–1.7 (m, 10 H) overlapped by 1.2 (two interlaced t, J = 7 Hz, 6 H); IR (thin film) 3300, 3050, 2970, 2930, 2850, 1760, 1710 cm^{-1}. Anal.[19] Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.94; N, 8.28. Found: C, 62.44; H, 8.59; N, 8.02.

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An Oxyanionic [3,3]-Sigmatropic Approach to the Ophiobolin Ring System

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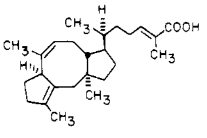
The addition of 1-cyclopentenyllithiums to (7R*)-7-methyl-7-vinylbicyclo[3.2.0]hept-2-en-6-ones results in spontaneous oxyanionic Cope rearrangement. Addition of methyl iodide traps the resulting regiospecifically positioned enolates to provide highly functionalized *all-cis*-dicyclopenta[*a*,*d*]cyclooctane products such as **5**, **8**, and **11**. Hydride reduction of these ketones proceeds regiospecifically with formation of secondary alcohols which have proven to be exceptionally prone to transannular bond formation. The preparation of **12a–c** is exemplary. Attempts to fully deoxygenate either the ketones or the alcohols were unsuccessful. Epimerization α to the carbonyl group in **5** could be achieved via the silyl enol ether and this stereoisomer (**19**) was found to be susceptible to acid-catalyzed rearrangement.

The dicyclopenta[*a*,*d*]cyclooctane ring system constitutes the fundamental structural element of a large family of diterpenes and sesterterpenes which possess significant, wide-ranging biological activity. Ceroplastols typified by albolic acid (1)[1] and fusicoccins such as cotylenol (2)[2] are representative. The ophiobolins comprise the most prevalent subgroup. Ophiobolin F (**3**), a prototypical example, features the characteristic angularly fused 5-8-5 molecular backbone.[3,4] The stereochemical and functional group differences that distinguish these natural products provide structural arrays that are architecturally novel and attractive. Although several approaches to this class of substances have been reported,[5-8] no successful de novo synthesis of any member has yet been achieved.



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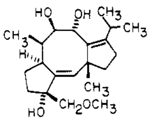

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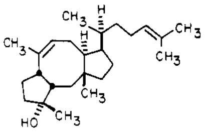
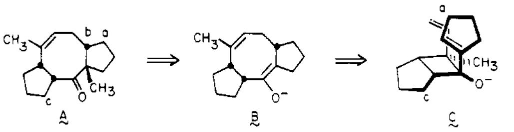


3

Two prime considerations behind any strategic planning involving the ophiobolins should be rapid construction of the tricyclic nucleus and appropriate control of those six chiral centers that find themselves clustered in two groups of three about the central cyclooctyl ring. To resolve the first of these issues, we envisioned an anionic rearrangement/ring enlargement sequence that would simultaneously introduce an appropriately positioned cyclooctenyl double bond and associated methyl group. Although the C → B transformation gives rise to an *all-cis* arrangement of tertiary hydrogens, the enolate anion is suitably disposed for methylation and the resulting carbonyl group allows for additional chemical manipulation in that sector of the molecule. Moreover, suitable placement of functionality



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