H), 2.88 (tt, J = 7, 7 Hz, 1 H), 3.98 (s, 4 H), 4.28 (d, J = 7 Hz, 2 H); mass spectrum, m/e (relative intensity) 157 (10), 100 (4), 99 (21), 88 (5), 87 (100), 85 (3), 71 (4), 55 (15), 53 (4). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.72; H, 7.04.

Ruthenium-Catalyzed Reaction of Aldehydes with Alcohols (General Procedure). A mixture of aldehyde (2.0 mmol), alcohol (2.0 mmol), and $RuH_2(PPh_3)_4$ (0.1 mmol) in dry toluene (1.0 mL) was heated at 180 °C for 24 h in a sealed Pyrex tube (180 × 18 mm) under argon. Short column chromatography (SiO_2, elution with ether–hexane) gave ester. The product was identified by comparison of the spectral data with that of the ester prepared by the catalytic esterification of alcohols described above. GLC analysis of the reaction mixture using an appropriate internal standard gave the conversion of aldehyde and the yield of ester (see Table V).

Ruthenium-Catalyzed Reaction of Benzaldehyde with 1-Octanol. Preparative TLC (SiO_2, ether/hexane = 1/5) afforded **5** (0.054 g, 21%) (R_f 0.76), **10** (0.036 g, 15%) (R_f 0.68), **11** (0.055 g, 24%) (R_f 0.62), and benzyl benzoate (0.041 g, 19%) (R_f 0.53).

Methyl Octanoate (29). A mixture of octanal (0.128 g, 1.00 mmol), methanol (0.638 g, 19.9 mmol), mesityl oxide (0.498 g, 5.07 mmol), and $RuH_2(PPh_3)_4$ (0.115 g, 0.10 mmol) in dry toluene (0.5 mL) was heated at 140 °C for 4 days under argon. Column chromatography (5 g of SiO_2, elution with pentane) afforded yellow oil **29** (0.104 g, 66%): IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.87 (t, J = 5.0 Hz, 3 H), 1.10–1.87 (m, 10 H), 2.30 (t, J = 7.0 Hz, 2 H), 3.63 (s, 3 H); mass spectrum, m/e (relative intensity) 127 ($M^+ - OCH_3$, 3), 115 (4), 101 (4), 87 (32), 74 (100), 69 (5), 59 (14), 57 (18), 55 (19). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.51; H, 11.51.

General Procedure for the Ruthenium-Catalyzed Reaction of Aldehydes with Water. The reaction of butanal with water is representative. **(A) In the Presence of a Hydrogen Acceptor.** A mixture of butanal (0.216 g, 3.00 mmol), water (0.108 g, 5.99 mmol), benzalacetone (0.439 g, 3.00 mmol), and $RuH_2(PPh_3)_4$ (0.104 g, 0.09 mmol) in 1,2-dimethoxyethane (0.5 mL) was heated at 180 °C for 24 h in a sealed Pyrex tube (180 × 18 mm) under argon. Short column chromatography (SiO_2) of the reaction mixture gave butyric acid (**30**) (0.224 g, 85%) along with the trace amount of butyl butanoate (**31**). **(B) In the Absence of a Hydrogen Acceptor.** The same reaction was carried out in the absence of benzalacetone. Short column chromatography (SiO_2) gave ester **31** (0.132 g, 59%) along with carboxylic acid **30** (0.027 g, 10%).

Reaction of Crotonaldehyde with Water. A mixture of crotonaldehyde (0.216 g, 3.08 mmol), water (0.113 g, 6.27 mmol), and $RuH_2(PPh_3)_4$ (0.104 g, 0.09 mmol) in 1,2-dimethoxyethane (0.5 mL) was heated at 180 °C for 48 h in a sealed Pyrex tube (180 × 18 mm) under argon. Short column chromatography (SiO_2) of the reaction mixture gave **30** (0.163 g, 60%). GLC analysis of the reaction mixture showed that acid **30**, 1-butanol, and ester **31** were obtained in 68%, 2%, and 8% yields, respectively (conversion of aldehyde 91%).

Registry No. **2**, 6378-65-0; **3**, 33673-65-3; **4**, 112-58-3; **5**, 2306-88-9; **6**, 3234-85-3; **7**, 2445-78-5; **8**, 90397-38-9; **9**, 659-70-1; **10**, 102-20-5; **11**, 2611-02-1; **12**, 64945-70-6; **13**, 94-50-8; **14**, 10276-85-4; **15**, 6939-71-5; **16**, 87-41-2; **17**, 518-86-5; **18**, 119-84-6; **19**, 20721-78-2; **20**, 74786-83-7; **21**, 81683-97-8; **22**, 80880-36-0; **23**, 104-50-7; **24**, 27345-71-7; **25**, 81683-96-7; **27**, 109908-74-9; **28**, 109908-75-0; **29**, 111-11-5; **30**, 107-92-6; **31**, 109-21-7; $RuH_2(PPh_3)_4$, 19529-00-1; $RuH_2(CO)(PPh_3)_3$, 25360-32-1; $RuCl_2(PPh_3)_3$, 15529-49-4; $RuCl_3$, 10049-08-8; $Ru_3(CO)_{12}$, 15243-33-1; $Ru(OCOF_3)_2(CO)(PPh_3)_2$, 65912-34-7; $PdCl_2$, 7647-10-1; $RhH(PPh_3)_4$, 18284-36-1; $RhCl_3$, 10049-07-7; $RhCl(PPh_3)_3$, 14694-95-2; C_4H_3OH, 71-36-3; $C_6H_{13}OH$, 111-27-3; $C_8H_{17}OH$, 111-87-5; $C_{14}H_{29}OH$, 112-72-1; $PhCH_2OH$, 100-51-6; $C_2H_5CH(CH_3)CH_2OH$, 137-32-6; $C_3H_7CH(CH_3)CH_2OH$, 105-30-6; $(CH_3)_2CHCH_2CH_2OH$, 123-51-3; $PhCH_2CH_2OH$, 60-12-8; $C_6H_{11}CH_2OH$, 100-49-2; $(CH_3)_2NCH_2OH$, 108-01-0; $PhCO_2CH$[2Ph, 120-51-4; $PhNO_2$, 98-95-3; CH_2=CH-$COCH_3$, 78-94-4; $CH_3CH_2COCH_3$, 78-93-3; HO-$CH_{24}OH$, 110-63-4; $HOCH_2$-o-$C_6H_4CH_2OH$, 612-14-6; HO-o-$C_6H_4(CH_2)_3OH$, 1481-92-1; $HOCH_2CH_2NMeCH_2CH_2OH$, 105-59-9; $C_5H_{11}CHO$, 66-25-1; $C_7H_{15}CHO$, 124-13-0; PhCHO, 100-52-7; $C_2H_{11}CO_2H$, 142-62-1; $C_7H_{15}CO_2H$, 124-07-2; $PhCO_2H$, 65-85-0; 1,4-octanediol, 51916-47-3; *trans*-2-(2-hydroxyethyl)cyclohexanol, 27345-72-8; 1,2,6-hexanetriol, 106-69-4; diphenylacetylene, 501-65-5; γ-butyrolactone, 96-48-0; *cis*-2-butene-1,4-diol, 6117-80-2; acetonitrile, 75-05-8; methanol, 67-56-1; mesityl oxide, 141-79-7; acetone, 67-64-1; benzalacetone, 122-57-6; 1,5-pentanediol, 111-29-5; butanal, 123-72-8; tetrahydropyran-2-one, 542-28-9; *cis*-1,2-bis(hydroxymethyl)cyclohexane, 15753-50-1; 1,8-bis(hydroxymethyl)-naphthalene, 2026-08-6; 4-(2-hydroxymethyl)-5-(hydroxymethyl)benzodioxole, 81683-95-6; crotonaldehyde, 4170-30-3; *p*-benzoquinone, 106-51-4.

Supplementary Material Available: Spectral data of compounds **5–7** (Table II), **16**, **18** (Table IV), and **23** (2 pages). Ordering information is given on any current masthead page.

Cycloaddition Reactions of a Bisisobenzofuran Leading to Linear Polyacenequinones and a Quadruply Bridged Cyclophane

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Received March 6, 1987

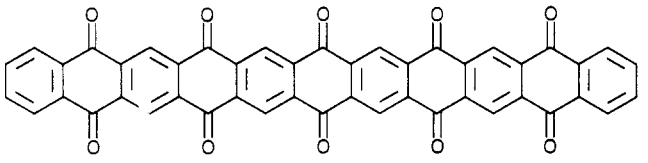
The bisisobenzofuran 1,3,7,9-tetrakis(4-*tert*-butylphenyl)anthra[2,3-*c*:6,7-*c*']difuran-5,11 dione (**3**) was reacted with dienophiles. Maleic anhydride and *N*-methylmaleimide produced bis adducts that were the syn and anti isomers resulting from endo additions. The relative rates of the first and second additions were measured by time-resolved NMR for the reaction of **3** with *N*-methylmaleimide. Reaction of **3** with the longer dienophile *N*-(4-*tert*-butylphenyl)maleimide gave only the anti-bis-endo adduct. All three bis adducts were cleanly aromatized by dehydration to form soluble pentacenequinone derivatives. Reaction of **3** with the bis dienophile 1,4-*N*,*N*'-dimaleimidobenzene gave a 1:1 adduct, which is an unusual quadruply bridged cyclophane.

We have become interested in the synthesis of long, rigid molecules with delocalized π-systems, and recently we have reported the preparation of polyacenequinones **1** and **2**.[1,2] Although the length of the undecacenepentaquinone (**1**) suggests that it should have unusual properties, it is extremely insoluble, making it difficult to purify or to study. For this reason Dr. W. Christopfel, in this laboratory, has developed a scheme to prepare soluble compounds of this type.[2] His synthesis hinges on the bisisobenzofuran **3**, which has *p*-*tert*-butylphenyl groups attached for solubility. Compound **3** should be useful for elongation

(1) Miller, L. L.; Thomas, A. D. *J. Org. Chem.* **1986**, *51*, 4160.
(2) Christopfel, W. C.; Miller, L. L. *J. Org. Chem.* **1986**, *51*, 4169.

0022-3263/87/1952-4327$01.50/0

through the use of a pair of cycloaddition reactions. In this paper we describe such reactions in some detail using maleate derivatives. These particular reactions are of interest because they lead to derivatized polyacenequinones like 7 which can be used for the formation of soluble, oligomeric, rigid-rod polyimides. In addition to answering stereochemical questions, and identifying an unexpected cyclophane product, we also report on the relative rates of the first and second Diels–Alder additions to 3 and the dehydrative aromatization of the bis adducts. Spectroscopic and electrochemical studies of the aromatized bis adducts are underway and will be reported in the context of a broader investigation.



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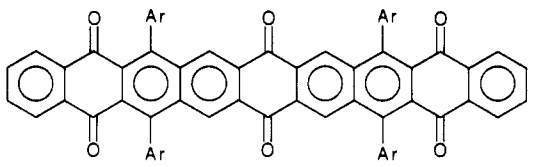
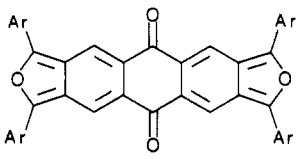


2

Ar = $(CH_3)_3C$–



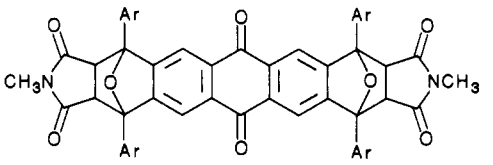
3

Results and Discussion

Diels–Alder Additions. Consider first the reaction of 3 with excess *N*-methylmaleimide. In contrast to the reaction of 3 with naphthoquinone, acid catalysis was not required. The reaction at room temperature produced an excellent yield of the thermally unstable bis adduct 4 as identified by NMR. ^1H NMR suggested that 4 was a mixture of two stereoisomers, present in a ratio of 1:1.3. Note that there are six isomers possible because of exo–endo and syn–anti relationships. The 300-MHz spectrum could, however, be completely assigned as arising from the syn, endo and anti, endo species **4a**, **b**. The N-methyl protons of the stereo-isomers are observed at 2.44 and 2.33 ppm, significantly upfield of the N-methyl protons of *N*-methylsuccinimide (2.99 ppm)[3] or *N*-methylmaleimide (3.01 ppm). Molecular models show the N-methyl protons of endo adducts to lie in the shielding regions of the aromatic rings of the central anthraquinone unit suggesting that both stereoisomers are formed by endo addition of *N*-methyl-maleimide to 3. Also in agreement, with this assignment, the aliphatic hydrogens α to the imide carbonyls are not shifted upfield as they might be for exo isomers. The specific formation of endo products is expected, since quite favorable secondary orbital interactions are available between dienophile and isobenzofuran.

Reaction of 3 with maleic anhydride also proceeded at room temperature to produce bis adducts. In this case, 300-MHz ^1H NMR did not clearly resolve the isomers; however, the spectrum was in agreement with structure 5.

Aromatization of the adducts 4 and 5 with trimethylsilyl triflate, used successfully for the preparation of 2,[2] was unsuccessful; however, concentrated sulfuric acid proved to be a most effective catalyst for these reactions and 4 was converted to 6, in 90% yield, by shaking a chloroform



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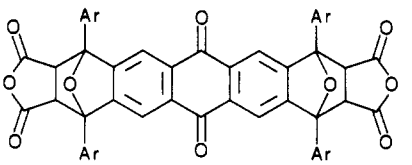

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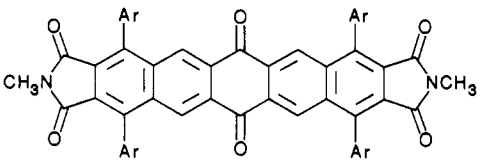

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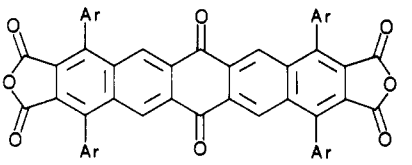


7

Ar = $(CH_3)_3CC_6H_4$

solution of 4 with sulfuric acid for 15 min. The corresponding reaction with 5 was much slower and the product 7 was formed in 70% yield only after more than 5 h of vigorous agitation. It is thought that the dehydration takes place in the concentrated sulfuric acid and that the differences in reactivity between the two adducts reflects differences in their solubilities in sulfuric acid. We note that, as expected, NMR shows the two isomers **4a**,**b** form one product, 6, and that the N-methyl peaks of 6 (3.09 ppm) are downfield from those in **4a**,**b**.

The linear, aromatized compounds 6 and 7 are soluble in common organic solvents, illustrating the effectiveness of the *p-tert*-butylphenyl groups. These phenyl groups are twisted out of the plane of the pentacenequinone and along with the butyl groups prevent the close packing of the molecules required for crystallization.

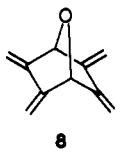
The next goal was to observe a mono adduct from the reaction of 3 with a dienophile and to measure the relative rates of the first and second Diels–Alder addition reactions on 3. In the case of bis diene 8, Vogel and co-workers found that the first Diels-Alder addition went substantially faster than the second.[4] This provides an important synthetic advantage, because unsymmetrical bis adducts can be formed by the sequential addition of two different dienophiles.

For our study, *N*-methylmaleimide was chosen as the dienophile. It was especially useful because the methyl provided an NMR probe. Time-resolved ^1H NMR allowed

(3) Sadtler NMR Spectrum 16338, Sadtler Research Laboratories, Philadelphia, 1973.

(4) Pilet, O.; Vogel, P. *Helv. Chim. Acta* 1981, *64*, 2583.

detection of mono adduct **9** as well as the bis adducts **4a,b**.



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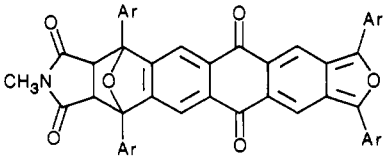


9

To observe the mono adduct **9**, 1.00 equiv of *N*-methylmaleimide was added to a solution of **3** in deuteriochloroform and the ^1H NMR spectrum of the reaction mixture was recorded as a function of time until the reaction was observed to be essentially complete (110 min). The process was then repeated with further additions of *N*-methylmaleimide at 134 min (0.40 equiv) and 265 min (1.40 equiv).

From a spectrum taken 7 min after the start of the experiment, the signals due to **9** can be seen at 8.89, 8.00, 4.19, and 2.44 ppm (Figure 1). Note that the singlet due to **3** appears to be slightly broadened. The chemical shift of this resonance moves slightly downfield with decreasing concentration and the broadening is a consequence of concentration change during the sampling period.

Forty-seven minutes after the second addition of *N*-methylmaleimide, **3** can still be observed but significant amounts of **4a,b** have already formed (Figure 1). Interestingly, the N-methyl resonance of one of the stereoisomers coincides with that of **9**, so as the reaction progresses, a steady increase in the integrated intensity of the singlet at 2.32 ppm relative to that of the singlet at 2.44 ppm is observed.

Finally, 242 min after the third addition of *N*-methylmaleimide and 507 min after the start of the experiment, the only species to be observed in the reaction mixture are the excess *N*-methylmaleimide and **4a,b** (Figure 1). Clearly the reaction is extremely clean.

In order to quantify the relative reactivities of **3** and **9** as Diels–Alder dienes, a solution of **3** was mixed with 2.75 equiv of *N*-methylmaleimide and the progress of the reaction was monitored as before by ^1H NMR. The concentrations of species in solution can be computed from the integrated intensities of selected resonances relative to the integrated intensity of the reference resonance (dioxane, 3.70 ppm). Figure 2 shows the result. Reactant **3** smoothly disappears over a period of about 50 min. Mono adduct **9** waxes and wanes with a maximum yield of about 65% at about 25 min.

The data taken at 25 min, where $d[\mathbf{9}]/dt = 0$ can be used to estimate that the rate constant ratio $k_1/k_2 = 5$, where k_1 and k_2 are for the first and second Diels–Alder additions. Since **3** has a statistical advantage of two, the ratio of reactivities of a single diene of **3** and **9** is 2.5. Since **3** and **9** react at such similar rates, it may prove difficult to isolate unsymmetrical adducts by sequential addition of two different dienophiles.

The observation of a pair of endo products, e.g. **4a,b**, from Diels–Alder additions to **3** and the similarity of their properties made us chary of attempting to isolate single compounds from these adduct mixtures. It seemed, however, that if one used a longer and sterically more demanding dienophile, it would block the formation of the syn-bis-endo product and only the anti would result. This prediction was realized by reaction of *N*-(4-*tert*-butylphenyl)maleimide with **3**. A bis adduct (**10**) could be isolated in 62% yield. Its ^1H NMR spectrum was consistent with spectra from the other adducts, and there was no evidence for the presence of two isomers. Predictably,

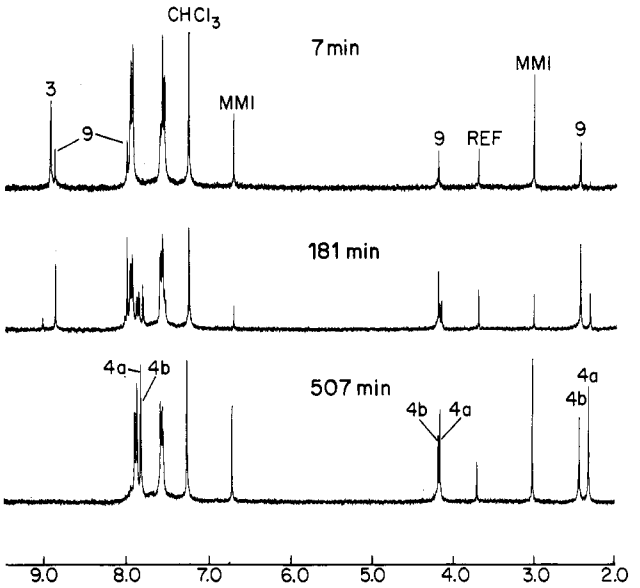


Figure 1. Time-resolved ^1H NMR study of the reaction of **3** with *N*-methyl-maleimide. Resonances labeled MMI and REF are due to the *N*-methylmaleimide and the intensity reference dioxane.

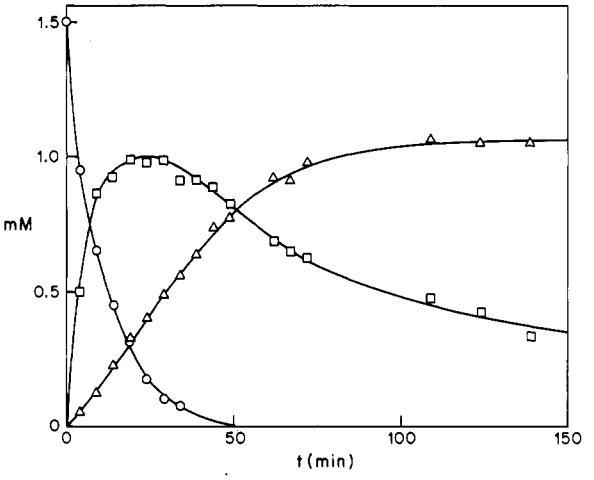
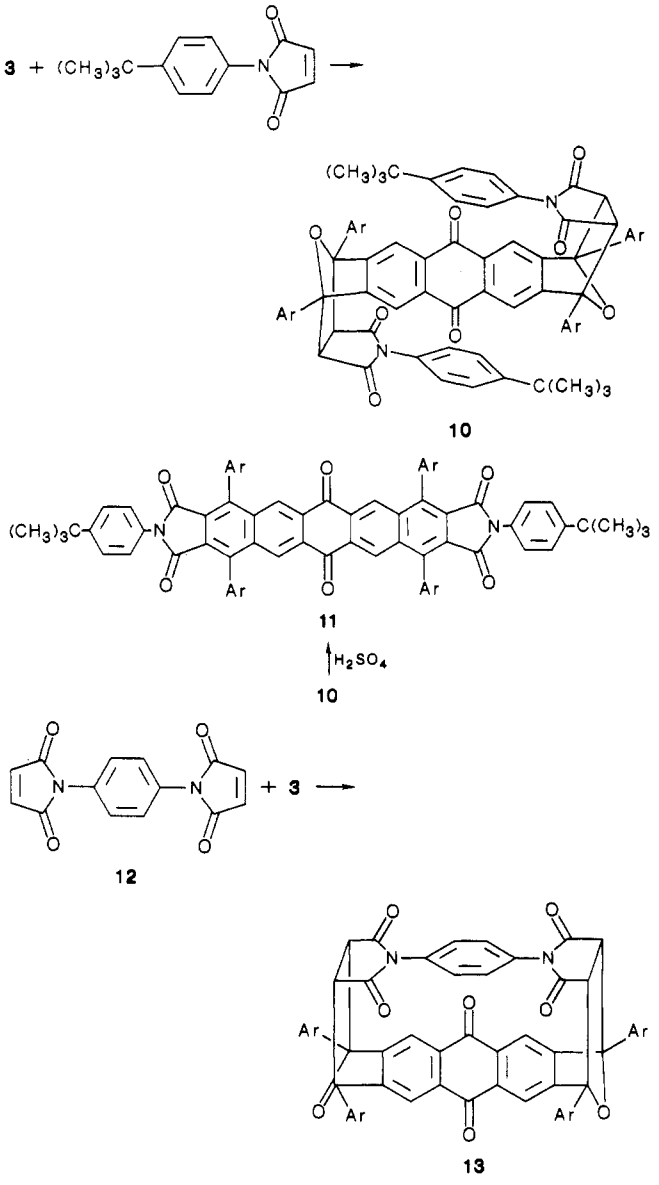


Figure 2. Concentrations of **3** (○), **4** (△), and **9** (□) measured by ^1H NMR as a function of time for the reaction of **3** with *N*-methylmaleimide.

aromatization of **10** with H_2SO_4 proceeded smoothly to give **11**. We suggest that **10** is the anti-bis-endo isomer.

Cyclophane Formation. With the intention of building an oligomeric rod, it was anticipated that reaction of excess **12** with **3** would give a bis adduct that could again be used as a bis dienophile. Reaction of **12** with **3** was quite clean but produced a product which could not be aromatized with concentrated H_2SO_4. The mass spectrum and ^1H and ^{13}C NMR spectra of the product indicated that it was a symmetrical 1:1 adduct with structure **13**. Predictably, the base peak (*m/e* 817) in the FAB mass spectrum of **13** corresponds to retro-Diels-Alder cleavage of the protonated molecular ion. The ^1H NMR spectrum showed the four ring hydrogens of the nitrogen-substituted ring at 7.18 ppm. This is substantially downfield from the signal due to the ring hydrogens ortho to nitrogen of **10** which appear at 6.35 ppm.

In restrospect the formation of **13** is not surprising, considering that initial Diels-Alder addition gives an endo adduct; this places the second diene and dienophile within easy striking distance. Models indicate that there is not too much strain in this very rigid (still soluble) product. The UV spectrum of **13** (λ_{max} 322) is quite similar to that



of anthraquinone (λ_{max} 332 nm).

Experimental Section

General Methods. Melting points were determined on a Mel-Temp capillary melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer 7100 Fourier transform instrument and were calibrated with the 1601.8-cm^{-1} absorption of polystyrene. ^1H NMR spectra were measured at 200 MHz on an IBM-NR-200-AF instrument and at 300 MHz on either a Nicolet NT-300-WB instrument or an IBM-NR-300-AF instrument. ^{13}C NMR spectra were measured on an IBM-NR-300-AF instrument at 75.4 MHz. Chemical shifts are reported in δ units relative to internal Me_4Si. Fast atom bombardment (FAB) mass spectra were recorded at the University of Minnesota on a high resolution VG-7070E-HF instrument using an ONPOE matrix. High resolution FAB peak matching data were obtained at University of Minnesota. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Absorption spectra were recorded on a Varian/Cary products Model 17D spectrophotometer system.

Materials. The bisisobenzofuran **3** was prepared as described previously[2] and in the synthetic work was used without further purification. Material for the time-resolved ^1H NMR experiments was purified by flash chromatography (silica gel, 230–400 mesh, chloroform). Maleic anhydride was recrystallized (chloroform) and sublimed. *N*-(4-*tert*-Butylphenyl)maleimide, mp 95 °C (lit.[5] mp 95–99 °C), was prepared from 4-*tert*-butylaniline and maleic anhydride by using the literature[6] procedure for the analogous *N*-phenylmaleimide and gave satisfactory spectroscopic data. *N*-Methylmaleimide, 1,4-dimaleimidobenzene and 4-(*tert*-butyl)aniline were commercial products (Aldrich) and were used without further purification.

Bis *N*-Methylimide 6. A freshly prepared sample of **3** (approximately 110 mg, 0.135 mmol) was stirred in chloroform (20 mL) with *N*-methylmaleimide (210 mg, 1.89 mmol) for 20 h, under nitrogen and in the absence of light. The reaction mixture was diluted with chloroform (10 mL) and was shaken with concentrated sulfuric acid (25 mL) for 15 min in a separatory funnel. Ice and water was added cautiously to the reaction mixture. When dilution of the sulfuric acid was complete, the mixture was extracted with chloroform (30 mL) and reextracted with more chloroform (50 mL). The chloroform extracts were washed with brine, combined, and dried with sodium sulfate. The chloroform was removed and the yellow solid which remained was washed into a centrifuge tube with diethyl ether. The product was spun down and the ether was discarded. The washing procedure was repeated two more times.

The yellow solid thus obtained (122 mg, 90%) was found to be reasonably pure by TLC and ^1H NMR. The crude product was purified by dissolving it in hot chloroform/ether and cooling. A bright, golden yellow solid and was obtained (80 mg, 59%). The mother liquor was evaporated to dryness and the residue was purified by flash chromatography (silica gel, chloroform) to give a bright golden, yellow product (24 mg, 18%): mp >360 °C, no darkening observed; ^1H NMR ($CDCl_3$) 8.91 (s, 4 H), 7.61 (d, J = 8.4 Hz, H), 7.37 (d, J = 8.4 Hz, 8 H), 3.09 (s, 6 H), 1.45 (s, 36 H); ^{13}C NMR ($CDCl_3$) 182.0 (no H), 166.5 (no H), 152.2 (no H), 141.3 (no H), 138.2 (no H), 131.6 (no H), 130.3 (1H), 130.2 (no H), 129.7 (1H), 126.8 (no H), 125.4 (1H), 34.9 (no H), 31.4 (3H), 24.2 (3H); IR (KBr) cm^{-1} 2964, 1772, 1717, 1688, 1591, 1369, 1258, 1095, 992, 902, 834, 765, 743, 564; high resolution mass spectrum (FAB) 1003.4739 corresponding to protonated molecular ion (calcd for $C_{68}H_{63}N_2O_6$, 1003.4686). *Anal.* Calcd for $C_{68}H_{62}N_2O_6$: C, 81.41; H, 6.23; N, 2.79. Found: C, 81.24; H, 6.30; N, 2.58.

Bis Anhydride 7. A freshly prepared sample of **3** (approximately 120 mg, 0.147 mmol) was stirred in chloroform (16 mL) with maleic anhydride (388 mg, 3.96 mmol, sublimed) for 19 h, under nitrogen and in the absence of light. The reaction mixture was transferred to a 100 mL recovery flask and concentrated sulfuric acid (45 mL) was added. The flask was securely stoppered and agitated vigorously using a vortex mixer until ^1H NMR showed the reaction to be complete (about 5 h).

The reaction mixture was extracted with chloroform (50 mL) and the sulfuric acid layer was reextracted three times with chloroform (50 mL). The chloroform extracts were washed with brine, combined, and dried with magnesium sulfate. The chloroform was removed to give a yellow solid (101 mg, 70%) which appeared to be quite pure by TLC and ^1H NMR. The product was purified by dissolving it in hot chloroform/ether and then cooling it. The 33 mg of crude gave 27 mg (82% recovery) of a bright, golden yellow solid (mp > 360 °C, no darkening observed): ^1H NMR ($CDCl_3$) 9.03 (s, 4 H), 7.63 (d, J = 8.3 Hz, 8 H), 7.39 (d, J = 8.3 Hz, 8 H), 1.45 (s, 36 H); ^{13}C NMR ($CDCl_3$) 181.6 (no H), 161.0 (no H), 153.0 (no H), 144.6 (no H), 136.6 (no H), 132.2 (no H), 130.9 (1 H), 129.7 (1 H), 129.0 (no H), 125.8 (1 H), 125.2 (no H), 35.0 (no H), 31.4 (3 H); IR (KBr) cm^{-1} 2962, 1854, 1826, 1782, 1686, 1614, 1267, 1201, 1133, 921; high res mass spec (FAB), 977.4039 corresponding to protonated molecular ion (calcd for $C_{66}H_{57}O_8$ = 977.4053). *Anal.* Calcd for $C_{66}H_{58}O_8$: C, 81.12; H, 5.78. Found: C, 80.91; H, 5.78.

Time-Resolved ^1H NMR Experiments. The solvent used in these experiments was deuteriochloroform to which a small quantity of dioxane had been added as an intensity reference. In the first experiment a solution of the bisisobenzofuran, **3**, was prepared and 1.0 equiv of *N*-methylmaleimide (disolved in the same solvent) was added. The ^1H NMR spectrum of the sample was recorded as a function of time. Further additions of *N*-methylmaleimide were made at 134 min (0.4 equiv) and 265 min (1.4 equiv), and the progress of the reaction was monitored as

(5) Fletcher, H. R.; Little, J. R. U.S. Patent 3 153 014, 1964.

(6) Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. J. *Org. Synth.* **1973**, *5*, 944.

before until only the resonances due to the stereoisomeric bis adducts and the unreacted *N*-methylmaleimide could be observed. ^{1}H NMR spectral data for the mono adduct **9** and bis adducts **4a,b** are given below.

9: 8.89 (s), 8.00 (s), 7.8 (d, J = 9 Hz), 7.95 (d, J = 8.7 Hz), 7.60 (d with J = 9 Hz assumed), 7.59 (d with J = 9 Hz assumed), 4.19 (s), 2.44 (s), 1.41 (s), 1.39 (s).

Major bis adduct **4a:** = 7.88 (d, J = 8.5 Hz), 7.82 (s), 7.56 (d, J 8.5 Hz), 4.15 (s), 2.32 (s), 1.39 (s).

Minor bis adduct **4b:** 7.87 (d, J = 8.4 Hz), 7.81 (s), 7.55 (d, J = 8.4 Hz), 4.17 (s), 2.44 (s), 1.37 (s). Stereoisomeric ratio = 1.3:1

In a second experiment, an estimate for k_1/k_2 was obtained. Solutions of the bisisobenzofuran and *N*-methylmaleimide were mixed and the ^{1}H NMR spectrum was recorded as a function of time. Concentrations of the two reactants immediately after mixing were 1.5 mM **3** and 4.2 mM *N*-methylmaleimide. The ratio k_1/k_2 is given by the ratio of the maximum mono adduct concentration to the bisisobenzofuran concentration at the time corresponding to the maximum mono adduct concentration.

Bis *N*-(4-*tert*-Butylphenyl)maleimide Derivative 11. A freshly prepared sample of **3** (56 mg, 0.069 mmol) was stirred in chloroform (15 mL) with *N*-(4-*tert*-butylphenyl)maleimide (53.7 mg, 0.234 mmol) for 18 h under nitrogen and in the absence of light. The reaction mixture was filtered to give **10** as a white solid (43 mg, 49%) which was essentially pure by ^{1}H NMR and TLC. The solvent was removed from the filtrate, and the resulting product was purified by flash chromatography (silica gel, chloroform) to give more of the previously obtained white solid (11 mg, 13%): mp, some decomposition evident at 135 °C; ^{1}H NMR ($CDCl_3$) 7.95 (d, J = 8.4 Hz, 8 H), 7.93 (s, 4 H), 7,58 (d, J = 8.4 Hz, 8 H), 7.10 (d, J = 8.6 Hz, 4 H), 6.35 (d, J = 8.6 Hz, 4 H), 4.28 (s, 4 H), 1.39 (s, 36 H), 1.15 (s, 18 H); IR cm^{-1} (KBr disk) 2963, 1779, 1716, 1678, 1517, 1366, 1176, 832.

The adduct **10** (21 mg, 0.016 mmol) was stirred with concentrated sulfuric acid (8 mL) for 5 h. The reaction mixture was then poured onto crushed ice and then extracted with chloroform (3 × 40 cm^3). The solvent was removed to give **11** as a bright golden-yellow solid (20 mg, 98%) which was pure by TLC: mp >360 °C, slight darkening observed: ^{1}H NMR 8.99 (s, 4 H), 7.58 (d, J = 8.4 Hz, 8 H), 7.41 (d, J = 8.4 Hz, 8 H), 7.40 (d, J = 8.6 Hz, 4 H), 7.24 (d, J = 8.6 Hz), 1.42 (s, 36 H), 1.26 (s, 18 H); ^{13}C NMR 182.0 (no H), 165.6 (no H), 152.1 (no H), 151.5 (no H), 142.0 (no H), 138.4 (no H), 131.7 (no H), 130.4 (no H), 130.1 (no H), 129.8 (1 H), 128.6 (no H), 126.48 (no H), 126.45 (1 H), 125.9 (1 H), 125.4 (1 H), 34.9 (no H), 34.7 (no H), 31.4 (3 H), 31.2 (3 H); IR cm^{-1} (KBr disk) 2963, 1772, 1724, 1688, 1365, 1265, 806; high resolution mass spectrum (FAB), 1239.6277 corresponding to protonated molecular ion, calcd for $C_{86}H_{83}N_2O_6$ 1239.6251.

Cyclophane 13. A 15-mL $CHCl_3$ solution containing approximately 0.1 mmol of **3** (unpurified) was added dropwise over a 30-min period to a refluxing solution of dimaleimidobenzene (**12**) (268 mg, 1.0 mmol) in 30 mL of dry $CHCl_3$. The purple color disappeared rapidly, but the refluxing and stirring were continued for 17 h.

The reaction mixture was allowed to cool, upon which the filtrate was concentrated to 7 mL. The resulting insoluble mass was removed again by filtration, and the product was collected from the filtrate and purified by column chromatography (silica gel, CH_2Cl_2). A white solid was obtained (56 mg, 52%): ^{1}H NMR ($CDCl_3$) 1.41 (s, 36 H), 4.14 (s, 4 H), 7.18 (s, 4 H), 7.60 (d, J = 8 Hz, 4 H), 7.66 (s, 4 H), 7.95 (d, J = 8 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) carbons with 0 or 2 protons attached 34.9, 92.0, 131.0, 131.5, 135.3, 148.8, 152.6, 172.7, 183.7; carbons with 1 or 3 protons attached 31.4, 52.9, 119.8, 121.0, 126.0, 127.1; IR (KBr) 2967, 1780, 1718, 1679, 1605 cm^{-1}; mass spectrum (FAB), m/e 1085.4 (protonated parent ion), 817.3 (base); absorption spectrum (CH_3CN) λ_{max} 253 nm (ϵ 68 650), 322 (6050). Anal calcd for $C_{72}H_{64}O_8N_2$: C, 79.68; H, 5.94; N, 2.58. Found: C, 79.55; H, 6.05; N, 2.47.

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Studies in Biomimetic Alkaloid Syntheses. 16. Syntheses of D/E Trans and Cis Desethylvincadifformines[1] and of the C16 Epimeric Carbomethoxydesethyldihydrocleavamines and Their Isolable Piperidine Ring Conformational Isomers[†]

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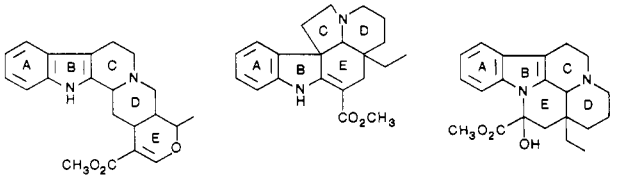
Generation of *D*-secodesethylvincadifformine intermediate **18** allowed its conversion to D/E trans and D/E cis desethylvincadifformine (**10** and **19**) as well as to two C-16 epimeric carbomethoxydesethyldihydrocleavamines, each of the latter selectively obtained in two isolable conformational forms: **26** vs. **20** and **28** vs. **21**. Corresponding conformation inversion energies were determined to be about $\Delta G^{\ddagger}$ = 28 kcal/mol and 23 kcal/mol, respectively.

Confronted with a quarter century challenge of providing syntheses of the clinically used "dimeric" indole–indoline alkaloids of the vinblastine class, the chemical community had, until completion of the present sudies (see following paper and its ref 5b), furnished only one method of coupling of monomeric precursor units,[6-8] which provides the crucial C10 to C16′ linkage of the two halves in the stereochemical sense essential for antineoplastic activity,[9] i.e., with a C16′ to C14′ priority antireflective (parf) relative stereochemistry.[10] This biomimetic[11,12] coupling of catharanthine *N*-oxide (**1**) and vindoline (**2**), followed

[†]Dedicated to Professor Gibert Stork on occasion of his 65th birthday by representatives of two chemical generations, who benefited from his wise tutelage.

(1) For ring labeling (ABCDE) of the vincadifformine type compounds we adopt a pattern that parallels the commonly used biogenetic numbering system[2] and that differs from one we and others used previously,[3,4] but which has also been used elsewhere.[5]



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