Molecular Design by Cycloaddition Reactions. XXV.[1] High Peri- and Regiospecificity of Phencyclone

Tadashi Sasaki,* Ken Kanematsu, and Kinji Iizuka

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464, Japan

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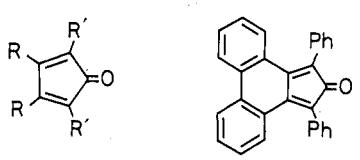
The cycloaddition reactions of phencyclone with electron-rich and -deficient olefins and seven-membered ring unsaturated polyenes are extensively investigated. The structural elucidations of these adducts were accomplished by spectral inspections. The high peri- and regiospecificity of phencyclone was observed. Some formation mechanisms for the adducts are discussed by the frontier orbital model.

It is well known that cyclopentadienone and its analogues (**1**) are reactive and versatile diene components in the Diels–Alder reactions.[2,3] We have described the cycloaddition reactions of cycloheptatriene with 2-pyrone derivatives to give novel bridged cage adducts.[4]

As a continuation of our previous work,[1] we now describe the cycloaddition reactions of phencyclone (**2**) with seven-membered ring unsaturated compounds and olefinic dienophiles; phencyclone (**2**) is known as a more reactive and stable diene compound than other cyclopentadienone derivatives.[5] However, no systematic study has been reported on its cycloaddition reactions.

Chart I



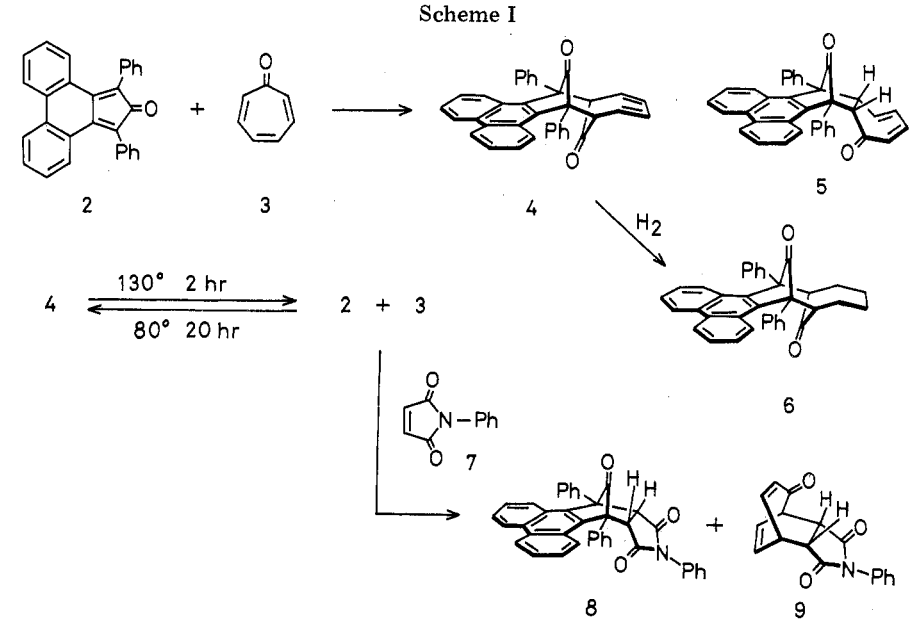
1 2

Results

Cycloaddition Reaction of Phencyclone with Seven-Membered Ring Polyenes. With Tropone. Reaction of phencyclone (**2**) with two equimolar amounts of tropone (**3**) in benzene at 80 °C for 20 h gave a 1:1 adduct **4** in 70% yield. The ir spectrum of **4** showed two characteristic bands at 1780 and 1725 cm^{-1} due to strained ring carbonyl and nonconjugated carbonyl groups, respectively. Furthermore, the NMR spectrum of **4** showed four vinyl protons as a multiplet centered at δ 6.17 and two bridgehead protons as a doublet at δ 4.60 suggesting a highly symmetrical structure,[6] and therefore, the structure of [4 + 2] adduct **5** could be ruled out. Catalytic hydrogenation of **4** over palladium on charcoal gave a tetrahydro compound **6** in quantitative yield, which showed two carbonyl bands at 1778 and 1718 cm^{-1} similar to that of compound **4** by the ir. From these data, the adduct **4** was suggested as a structure of the [6 + 4] adduct. Furthermore, the configuration of the [6 + 4] adduct could be determined to be exo, since the olefinic protons in the endo isomer might be shielded by the anisotropy of the phenanthrene moiety in comparison with the corresponding position in structure **54** (see Table VI). Pyrolysis of the adduct **4** in chlorobenzene at 130 °C for 2 h afforded the cycloreversion products, **2** and **3**, which was further confirmed by the formation of **8** and **9**[7] in the presence of *N*-phenylmaleimide (**7**) in the pyrolysis of **4** (Scheme I).

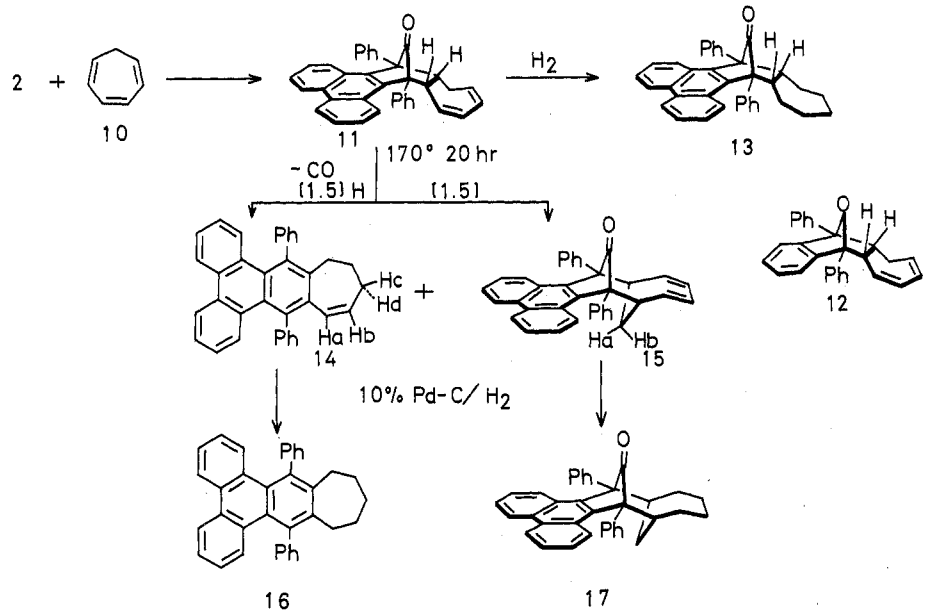
With Cycloheptatriene. A solution of **2** and an excess amount of cycloheptatriene (**10**) was heated in benzene at 80 °C for 16 h in a sealed tube under argon, and chromatographed on silica gel to give a 1:1 adduct **11** in 57% yield. The adduct **11** showed a characteristic band at 1790 cm^{-1} due to a strained carbonyl band by the ir, and methylene proton signals at δ 1.4–2.0 (m, 1 H) and 2.35–2.80 (m, 1 H), methine protons at δ 4.15 (m, 2 H), and olefinic protons at δ 5.2–6.3 (m, 4 H) by the NMR. The NMR spectral pattern of the cycloheptadiene moiety of **11** is very similar to that of an endo [4 + 2] adduct **12**[8] in the thermal cycloaddition of 1,3-diphenylisobenzofuran to cycloheptatriene (**10**). Catalytic hydrogenation of **11** over palladium on charcoal gave a tetrahydro compound **13** in quantitative yield. From

Scheme I

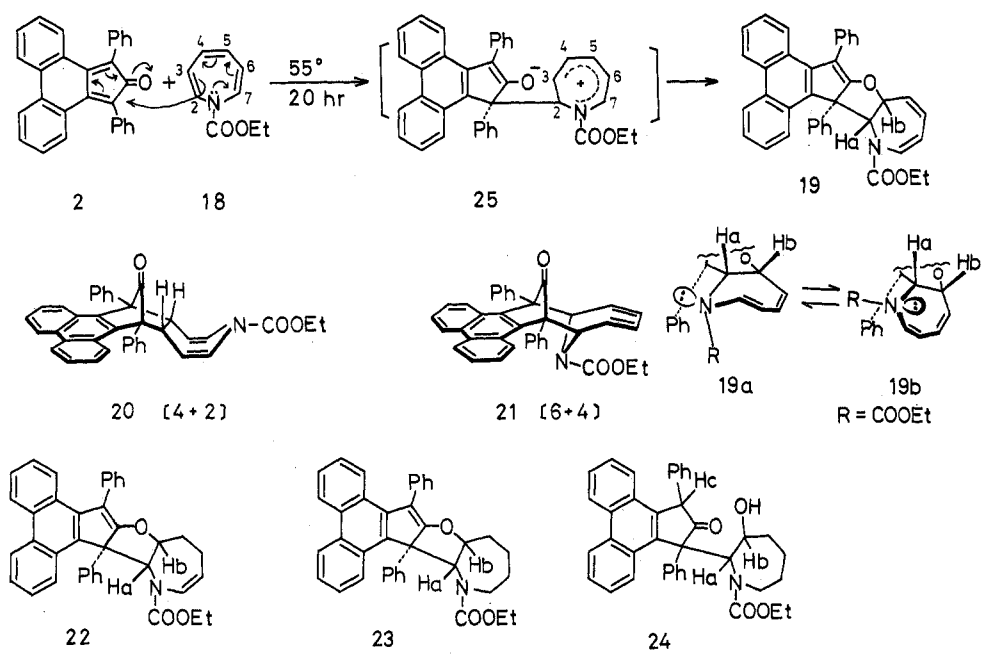


2 3 4 5 6 7 8 9

Scheme II



Scheme III



these data, the adduct **11** was assigned as a structure of the endo [4 + 2] compound. When the adduct **11** was heated in chlorobenzene at 170 °C for 20 h, the decarbonylated product **14** (34%) and the rearranged product **15** (47%) were obtained. The ir spectrum of **14** showed no carbonyl band, and the NMR spectrum displayed two benzylic protons at δ 2.68 as multiplets, four methylene protons at δ 2.20 as multiplets, and two olefinic protons at δ 6.0 (dd, J = 11.5 and 5.5 Hz) and 6.57 (d, J = 11.5 Hz). An appearance of a double doublet of one olefinic proton indicated that the dihedral angles between H_b and H_d are approximately 90° by a stereomodel inspection and, thus, only the protons in H_b and H_a, and H_b and H_c should be coupled. Catalytic hydrogenation of **14** over palladium on charcoal gave a dihydro compound **16** in quantitative yield. On the other hand, the ir spectrum of **15** showed a characteristic carbonyl band at 1768 cm^{-1} suggesting the presence of a bridged carbonyl group. The NMR spectrum of **15** showed two bridged methylene protons at δ 1.58 (m), two bridgehead protons at δ 4.05 (m), and four olefinic protons at δ 5.8–6.75 (m) suggesting a symmetrical structure of exo [6 + 4] adduct;[8] the lack of upfield shift of the methylene bridge protons could be explained by examination of a stereomodel showing that the protons are not closed to the phenanthrene moiety in comparison with that of compounds **33** and **35** (see later). By contrast, the methylene bridge protons in the endo isomer will be shifted strongly by the carbonyl anisotropy.[8] Similar catalytic hydrogenation of **15** gave a tetrahydro compound **17** in quantitative yield.

From the above data, the structures of **14** and **15** were assigned as depicted in Scheme II.

Thus, the formation of compound **14** might proceed initially producing a decarbonylated intermediate followed by successive 1,5-hydrogen shift, while the formation of compound **15** might proceed stereospecifically by the thermally allowed 1,5-sigmatropic shift, and also could arise from the endo [4 + 2] adduct **11**.

The NMR spectra of compounds **4**, **6**, **11**, and **13–17** are

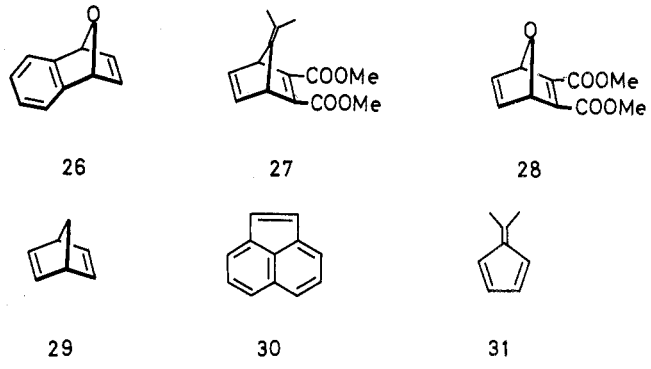
summarized in Table I (see paragraph at end of paper regarding supplementary material).

With *N*-Carbethoxyazepine. A solution of phencyclone (**2**) and equimolar amounts of *N*-carbethoxyazepine (**18**) in benzene was heated at 55 °C for 20 h (or at 100 °C for 3 h) under argon to give a 1:1 adduct **19** in quantitative yield. The adduct **19** exhibited ir bands at 1700 (urethane carbonyl) and 1640 cm^{-1} (olefinic band), and no absorption due to strained ring carbonyl.

The mass spectrum showed a characteristic molecular ion peak at *m/e* 547 and intense peaks at *m/e* 165, 92, and 65 due to characteristic fragmentation of *N*-carbethoxyazepine.

The NMR spectrum was complexed and not compatible with symmetrical structures such as [4 + 2] adduct **20** and [6 + 4] adduct **21;** it displayed methyl protons of the carbethoxy group as two kind of triplets centered at δ 0.85, and also signals at δ 3.3–4.0 (m, 3 H, CO_2CH_2– and H_a), 4.7–5.2 (m, 1 H, H_b), 5.3–5.85 (m, 2 H, olefinic H), and 6.4–8.1 (complex m, 20 H, aromatic and two olefinic H). Catalytic hydrogenation of the adduct **19** over 10% palladium on charcoal gave a mixture of dihydro (**22**) and tetrahydro compounds (**23**) in a ratio of 5:1. Similar catalytic hydrogenation of **19** over Adams catalyst in the presence of small amounts of acetic acid gave only tetrahydro compound **23** in quantitative yield. The NMR spectrum of **22** exhibited signals at δ 5.62 (m, 1 H) and 6.5–6.8 (m, 1 H) due to enamino olefins, while the NMR spectrum of **23** exhibited no olefinic proton signals. The NMR spectra of compounds **19** and **23** displayed the methyl proton signals of the carbethoxy group as a triplet at 120 °C (each δ 0.79, J = 7.5 Hz), but as a multiplet at 60 °C in pyridine-d_5 solution, respectively. This suggests that compounds **19, 22,** and **23** exist in an equilibrium of two kinds of conformational isomers **19a** and **19b** at room temperature as depicted in Scheme III. Compounds **19** and **23** were inert for reduction with sodium borohydride or for alkaline hydrolysis with methanolic potassium hydroxide. However, hydrolysis of compound **23** with hydrochloric acid in methanol gave compound **24;** its ir spectrum showed characteristic bands at 1745 (five-membered ring carbonyl) and 1680 cm^{-1} (urethane carbonyl). Thus, the formation of **24** might proceed by cleavage of a vinyl ether–carbon bond in compound **23.** Thus, compound **19** might be derived from initial attack at the C-2 position of *N*-carbethoxyazepine (**18**) followed by ring closure of an intermediate dipolar ion (**25**) to give a formal [6 + 2] adduct as shown in Scheme III. The NMR spectra of these compounds are summarized in Table II.

Chart II



26 27 28

29 30 31

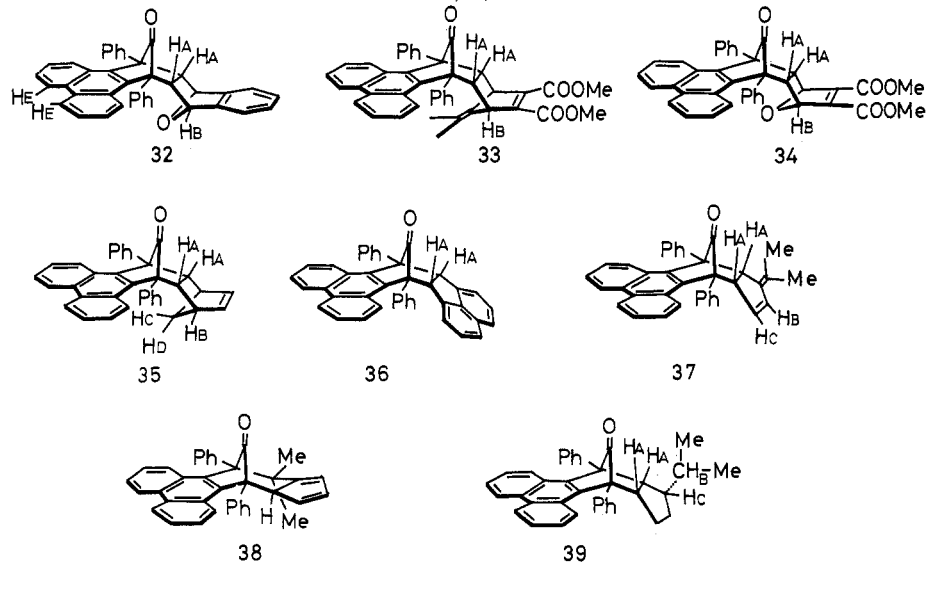
Cycloaddition Reactions of Phencyclone with Olefinic Dienophiles. In order to further investigate the reactivity of phencyclone (**2**), we attempted the thermal cycloaddition reactions of phencyclone (**2**) with a variety of electron-rich (**26–31**) and electron-deficient olefins (**7, 45–51**).

With Electron-Rich Olefins. Phencyclone (**2**) and equimolar amounts or an excess of the olefins (**26–31**) react to give 1:1 adducts (**32–37**) in high yields. The ir spectra of these adducts showed common characteristic bands at 1780–1800 cm^{-1} due to a strained ring carbonyl group. Interestingly, in the NMR spectra compounds **33** and **35** exhibited a very strong anisotropic effect of isopropylidene methyl signals as a singlet (δ −0.17), and bridged methylene proton signals as an AB quartet at δ 0.43 and −0.43 due to the phenanthrene ring current effect, suggesting strongly the structures of endo, exo [4 + 2] adducts. The NMR spectrum of **37** exhibited two olefinic proton signals as an AB quartet centered at δ 5.60 and 5.76, suggesting endo [4 + 2] adduct but no [6 + 4] adduct, since the [6 + 4] adduct **38** should display three olefinic proton signals. Catalytic hydrogenation of **37** over palladium on charcoal gave a tetrahydro compound **39** in quantitative yield. Thus, structural proofs of these adducts, **32–37,** were based on elemental analyses and spectroscopic data.

The reaction conditions for these addition reactions are summarized in Table III.

The NMR spectral data for these adducts are summarized in Table IV.

Chart III

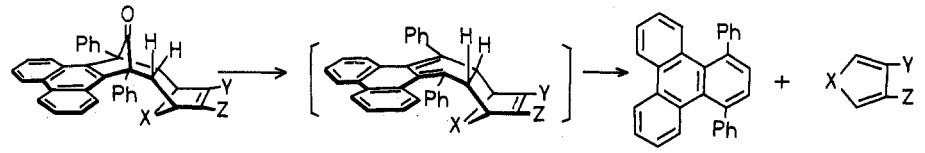


32 33 34

35 36 37

38 39

Scheme IV



32 X=O, YZ= 
33 X=C=CMe$_2$, Y=Z=COOMe
34 X=O, Y=Z=COOMe
35 X=CH$_2$, Y=Z=H

40

41

42

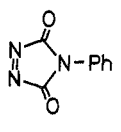
a X=O, YZ= 
b X=C=CMe$_2$, Y=Z=COOMe
c X=O, Y=Z=COOMe
d X=CH$_2$, Y=Z=H

On the other hand, when these adducts (**32–35**) were heated at 200 °C for 2 h, 1,4-diphenyltriphenylene (**41**) was produced by the retrogressive Diels–Alder reaction of the dihydroaromatic intermediates **40** derived by decarbonylation of the initially formed 1:1 adducts (Scheme IV).

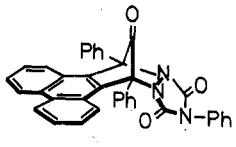
With Electron-Deficient Olefins. Recently, Ried et al.[9] reported that the cycloaddition of phencyclone (**2**) with a electron-deficient *N*-phenyltriazoline-3,5-dione (**43**) gave the endo [4 + 2] adduct **44** in quantitative yield. We have also investigated the cycloaddition of phencyclone (**2**) with electron-deficient olefins; equimolar amounts of **2** and **7** and **45–49** were treated to give the 1:1 adducts, **8** and **52–56**, in high yields. Similarly, equimolar amounts of **2** and **50** or **51** were treated to give the decarbonylated product **57** or **58**. The reaction conditions for these cycloadditions are summarized in Table V. The NMR spectral data are summarized in Table VI.

The adduct **52** is unstable since heating of **52** at below 65 °C afforded **2** and tetracyanoethylene (**45**) by the retro-

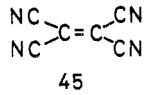
Chart IV



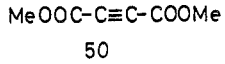
43



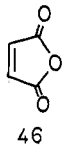
44



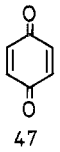
45



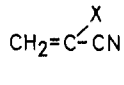
50



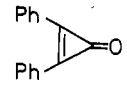
46



47



48 X=Cl
49 X=OAc



51

Diels–Alder reaction, but heating in the presence of methanol gave compound **59**, presumably via the initial zwitterionic intermediate **60** which was trapped with methanol to give **59**.

Hydrolysis of the adduct **55** with potassium hydroxide in Me_2SO gave compound **64** instead of an expected diketone

Table III. Reaction Conditions for the Cycloadditions of Phencyclone (2) with Electron-Rich Olefins

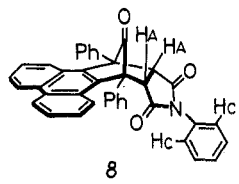
Olefins	Mole ratio (2:olefins)	Reaction conditions (in a sealed tube under argon)		Products (%)
26	1:1	130 °C	7 h	**32** (80)
27	1:1	100 °C	5 h	**33** (90)
28	1:1	80 °C	2 h	**34** (86)
29	1:2.5	80 °C	1.5 h	**35** (93)
30	1:1	80 °C	1 h	**36** (92)
31	1:1	110 °C	3 h	**37** (74)

Table V. Reaction Conditions for the Cycloadditions of Phencyclone (2) with Electron-Deficient Olefins

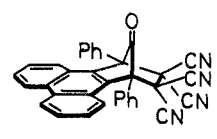
Olefins	Mole ratio (2: olefin)	Reaction conditions[a]		Product (%)
7	1:1	70 °C	10 min	**8** (91)
45	1:1	60 °C	30 min	**52** (87)
46	1:1	80 °C	20 min	**53** (90)[b]
47	1:1	80 °C	20 min	**54** (93)
48	1:1	80 °C	1.5 h	**55** (94)
49	1:1	80 °C	2.0 h	**56** (80)
50	1:1	90 °C	17 h	**57** (81)
51	1:1	150 °C	80 h	**58** (29)

[a] In sealed tube under argon. [b] The yield of 95% in benzene at room temperature for 3 h.

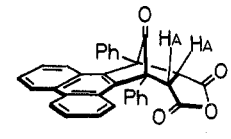
Chart V



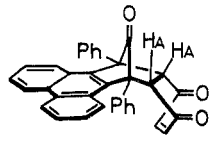
8



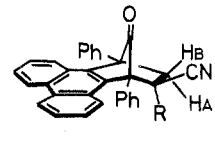
52



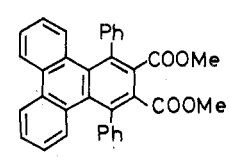
53



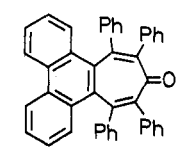
54



55 R=Cl
56 R=OAc

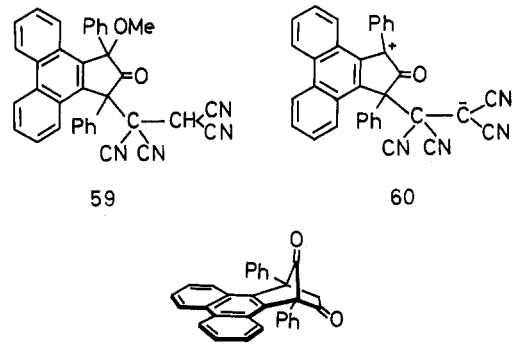


57



58

Chart VI



59 60 61

compound **61**. Similar hydrolysis of the adduct **56** gave also the same product **64**.

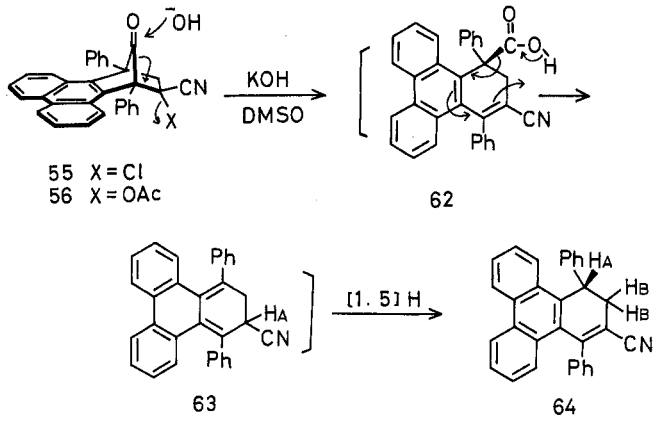
The ir spectrum of **64** showed a characteristic band at 2210 cm^{-1} due to a cyano group, but no carbonyl band. The NMR spectrum of **64** exhibited signals at δ 3.15 (m, 2 H, H_B) and 4.90 (dd, 1 H, J = 6.0 and 3.5 Hz, H_A). These results suggest that ring carbonyl groups of compounds **55** and **56** are very labile in alkaline hydrolysis and they are attacked by a hydroxide anion followed by elimination of leaving groups, i.e., chloro anion or acetoxy anion which locate a trans configuration for the ring carbonyl group.

Finally, an intermediate unstable quinodimethane (**63**) is rearranged by [1.5] hydrogen shifts, which are thermally allowed, to give resonance-stabilized product **64** (Scheme V).

The configurations of the adducts **8** and **52–58** were assigned by the NMR spectra as shown in Table VI.

The NMR spectrum showed the aromatic protons (H_C) at δ 5.87 for **8** and the olefinic protons at δ 5.77 for **54**, which might be shielded owing to lying over the phenanthrene ring.[10] Thus, it is concluded that both adducts **8** and **54** were assigned the endo configuration.

Scheme V



55 X = Cl
56 X = OAc

62 63 64

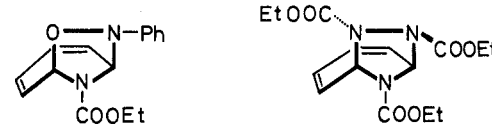
Discussion

It is well known[6,11] that 2,5-dimethyl-3,4-diphenylcyclopentadienone (**1**, R = Ph; R′ = Me) adds thermally to seven-membered ring unsaturated compounds, i.e., tropone, cycloheptatriene, and *N*-carbethoxyazepine, and some dienophiles to give [6 + 4] and [4 + 2] adducts followed by sigmatropic rearrangement products, respectively. However, many other cyclopentadienones, i.e., tetracyclone, acecyclone, indanocyclone, and phenalenocyclone, have not given any adducts with medium-membered ring unsaturated compounds in the cycloaddition reactions. Furthermore, these monomerous cyclopentadienones add to some olefinic dienophiles to give [4 + 2] adducts,[12] which are generally thermally unstable to give the decarbonylated products. However, as described above, phencyclone (**2**) is much more reactive than these cyclopentadienones in the cycloaddition reactions, and the adducts are relatively stable.

The cycloaddition of phencyclone (**2**) with tropone (**3**) gave the regio- and stereospecific exo [6 + 4] adduct **4**, which might be controlled by the secondary-orbital and the dipole–dipole interaction between the reactants in the transition state. On the other hand, the cycloaddition of **2** with cycloheptatriene (**10**) gave the regio- and stereospecific endo [4 + 2] adduct **11** under heating at 80 °C, while under heating at 170 °C for 20 h, the adduct **11** gave a mixture of a [1.5] sigmatropic rearrangement product (exo [6 + 4] adduct **15**) and a decarbonylated product **14**. However, any [3.3] sigmatropic rearrangement (Cope rearrangement) products were not detected in the cycloadditions of **2** with **3** or **10**. Such rearrangement in **4** and **11** might be energetically unfavorable because of destruction of the aromaticity in the fused phenanthrene ring.

On the other hand, the cycloaddition of phencyclone (**2**) to *N*-carbethoxyazepine (**18**) gave only a formal [6 + 2] adduct **19** without formation of an expected [4 + 2] adduct **20**. By contrast, nitrosobenzene is known to be susceptible to nucleophilic attack of the azepine (**18**) to give a formal [6 + 2] adduct **65**,[13] whereas reaction of *trans*-diethyl azodicarboxylate to the azepine (**18**) gave a formal [6 + 2] adduct **66**,[14] which has been explained to proceed via a nonconcerted fashion by influence of steric factors. Furthermore, high reactivity and stereospecificity were observed in the cycloaddition reactions of **2** with olefinic dienophiles.

Chart VII



65 66

In order to account for the formation of sterespecific endo [4 + 2] isomers in the cycloadditions of **2**, we have considered some common interactions such as secondary-orbital,[3] geometrical primary effect,[15] steric, and dipole–dipole interactions[16] between reactants.

It is clear that the secondary-orbital interactions would be favorable to endo addition in the transition state of the [4 + 2] cycloaddition, and the geometrical primary interactions would be also favorable to endo addition of monolefinic dienophiles like norbornyl compounds (**26–29**), in particular.

Similarly, the dipole–dipole interactions and the steric factors between the "X" portion of the dienophiles and the carbonyl group of **2** would be also favorable to endo approach ([B] and [C]) as depicted in Figure 1. In the absence of the dipole–dipole interactions, the secondary-orbital and steric effects controlled the stereospecificity. This was illustrated with *p*-benzoquinone where the endo adduct was the predominant product. Additionally, it is to be noted that phencyclone (**2**) reacted with both electron-rich and electron-deficient olefins in high yields. Furthermore, it is found that phencyclone was readily trapped by electron-deficient olefins rather than by electron-rich olefins in the Diels–Alder reactions as shown in Tables III and V. Houk et al.[17,18] have recently shown that consideration of frontier orbital analyses can provide a good rationalization of reactivity, regioselectivity, and periselectivity in a variety of cycloaddition reactions,[17] and also estimated frontier orbital energies and coefficients of cyclopentadienone as shown in

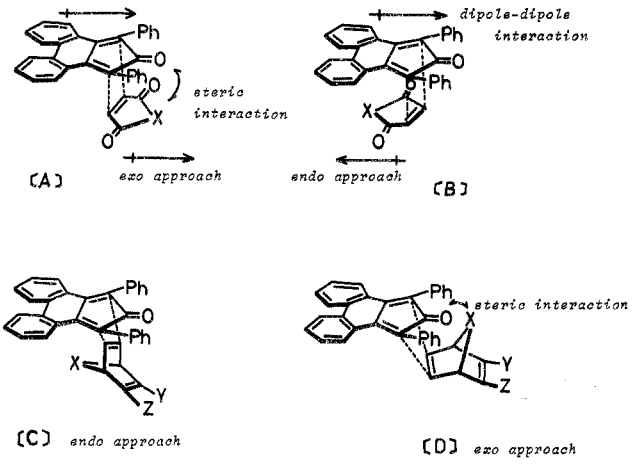


Figure 1.

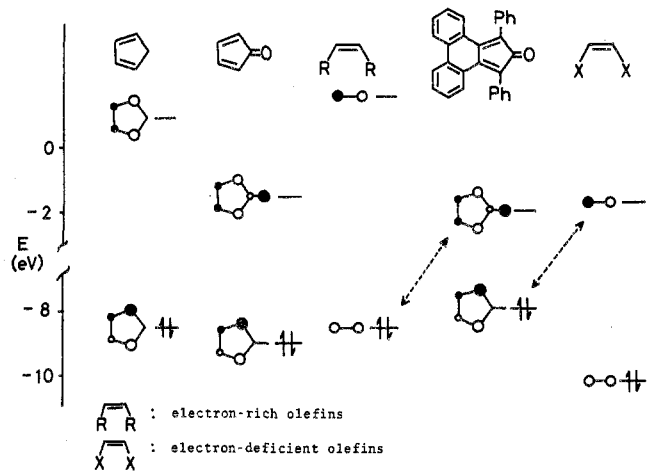


Figure 2. Estimated frontier orbital energies and coefficients for cyclopentadienone and related compounds, and olefins.

Figure 2.[18] In the light of these very low LUMO (lowest unoccupied molecular orbital) energies, cyclopentadienones should be more readily trapped by electron-rich dienophiles than by electron-deficient compounds.[17] However, it is also expected that phencyclone (2) has lower energy LUMO and higher energy HOMO (highest occupied molecular orbital), which has two phenyl groups and a fused phenanthrene ring.

In general, the electron-rich olefins have relatively higher LUMO and HOMO energy levels; on the contrary, the electron-deficient olefins have relatively lower LUMO and HOMO energy levels. Therefore, both interactions of phencyclone HOMO–electron-deficient olefin LUMO (phencyclone HO-controlled) and phencyclone LUMO–electron-rich olefin HOMO (phencyclone LU-controlled) are expected as depicted in Figure 2.

From our experimental results, it is suggested that the interaction between the phencyclone HOMO and electron-deficient olefin LUMO are stronger than the interaction between the phencyclone LUMO and electron-rich olefin HOMO. A more theoretical molecular orbital calculations for these compounds will be presented in the near future.

Experimental Section

The melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. The uv spectra were determined with a Jasco ORD-UV-5 spectrometer. The NMR spectra were taken with a JOEL C-60-XL spectrometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The ir spectra were taken with a Jasco Model IRA-1 grating infrared spectrophotometer. Mass spectra were obtained with a Hitachi RMU-D double-focusing spectrometer operating at an ionization potential of 70 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 100–150 °C.

Reaction of Phencyclone (2) with Tropone (3). A solution of **2** (1.91 g) and **3** (1.06 g) in benzene (20 ml) was heated at 80 °C under argon in a sealed tube for 20 h. The solution was diluted with methanol (10 ml) and the precipitated solids were filtered off and recrystallized from benzene–methanol to give **4** (1.71 g, 70%) as colorless cubics: mp 235–236 °C dec; ir (KBr) 1780, 1725, and 1605 cm^{-1}.

Anal. Calcd for $C_{36}H_{24}O_2 \cdot C_6H_6$: C, 89.0; H, 5.35. Found: C, 89.1; H, 5.5.

Hydrogenation of 4. A solution of **4** (0.2 g) in ethyl acetate (60 ml) was hydrogenated over 10% Pd/C (0.05 g) under atmospheric pressure to give the tetrahydro compound **6** (0.18 g) as leaflets: mp > 300 °C (chloroform–methanol); ir (KBr) 1778, 1718, and 1505 cm^{-1}.

Anal. Calcd for $C_{36}H_{28}O_2$: C, 87.75; H, 5.75. Found: C, 87.45; H, 5.6.

Reaction of 4 with *N*-Phenylmaleimide (7). A solution of **4** (0.12 g) and **7** (0.085 g) in chlorobenzene (5 ml) was heated at 130 °C under argon in a sealed tube for 2 h. The solution was then evaporated under reduced pressure and chromatographed on silica gel using chloroform as an eluent. The first fractions gave **8** (0.11 g, 80%) as colorless crystals: mp 295–297 °C dec (benzene–methanol); ir (KBr) 1800, 1705, 1600, and 1510 cm^{-1}.

Anal. Calcd for $C_{39}H_{25}O_3N$: C, 84.3; H, 4.55; N, 2.5. Found: C, 84.4; H, 4.75; N, 2.35.

The second fractions gave **9** (0.05 g, 75%) as colorless crystals, mp 235–236 °C (benzene–chloroform).

Reaction of 2 with Cycloheptatriene (10). A solution of **2** (1.91 g) and **10** (4.6 g, 10 mol) in benzene (20 ml) was heated at 80 °C under argon in a sealed tube for 16 h. The solvent was then evaporated under reduced pressure and the residue was chromatographed on silica gel using benzene to give **11** (1.34 g, 57%) as colorless crystals: mp 248–249 °C dec (chloroform–methanol); ir (KBr) 1790, 1600, and 1500 cm^{-1}.

Anal. Calcd for $C_{36}H_{26}O$; C, 91.1; H, 5.5. Found: C, 91.15; H, 5.55.

Hydrogenation of 11. A solution of **11** (0.2 g) in ethyl acetate (50 ml) was hydrogenated over 10% Pd/C (0.05 g) under atmospheric pressure to give the tetrahydro compound **13** (0.19 g) as colorless needles: mp 304–305 °C dec (chloroform–methanol); ir (KBr) 1790, 1605, 1505, and 1450 cm^{-1}.

Anal. Calcd for $C_{36}H_{30}O$: C, 90.35; H, 6.3. Found: C, 90.3; H, 6.35.

Pyrolysis of 11. A solution of **11** (0.15 g) in chlorobenzene (5 ml) was heated at 170 °C under argon in a sealed tube for 20 h. The solvent was then evaporated under reduced pressure and the residue was chromatographed on silica gel using *n*-hexane–benzene (4:1). The first fractions gave **14** (0.05 g, 34%) as colorless cubics: mp 221–222 °C (ether–methanol); ir (KBr) 1600, 1490, and 1440 cm^{-1}

Anal. Calcd for $C_{35}H_{26}$: C, 94.15; H, 5.85. Found: C, 93.9; H, 6.0.

The second fractions gave **15** (0.07 g, 47%) as colorless prisms: mp 274–275 °C dec (chloroform–methanol); ir (KBr) 1768, 1600, 1500, and 1448 cm^{-1}.

Anal. Calcd for $C_{36}H_{26}O$: C, 91.1; H, 5.5. Found: C, 91.2; H, 5.65.

Hydrogenation of 14. A solution of **14** (0.02 g) in ethyl acetate (20 ml) was hydrogenated over 10% Pd/C (0.01 g) under atmospheric pressure to give the dihydro compound **16** (0.02 g) as colorless needles: mp 191–192 °C (ether–methanol); ir (KBr) 1600, 1495, 1440 cm^{-1}.

Anal. Calcd for $C_{35}H_{28}$: C, 93.7; H, 6.3. Found: C, 93.6; H, 6.4.

Hydrogenation of 15. Similar hydrogenation of **15** gave the tetrahydro compound **17** (quantitative) as colorless leaflets: mp 305–307 °C (chloroform–methanol); ir (KBr) 1760, 1600, 1500, 1448 cm^{-1}.

Anal. Calcd for $C_{36}H_{30}O$: C, 90.35; H, 6.3. Found: C, 90.2; H, 6.5.

Reaction of 2 with *N*-Carbethoxyazepine (18). A solution of **2** (0.695 g) and **18** (0.3 g) in benzene (20 ml) was heated at 55 °C under argon in a sealed tube for 20 h, the deep-green color fading. The solvent was then evaporated under reduced pressure and the residue was recrystallized from chloroform–methanol to give the adduct **19** (0.94 g, quantitative) as colorless cubics: mp 251–252 °C; ir (KBr) 1700, 1640, 1600 cm^{-1}; *m/e* 547 (M^+), 382, 165, 92, 65.

Anal. Calcd for $C_{38}H_{29}O_3N$: C, 83.35; H, 5.35; N, 2.55. Found: C, 83.3; H, 5.5; N, 2.6.

Hydrogenation of 19. A. A solution of **19** (0.15 g) in ethyl acetate (50 ml) was hydrogenated over 10% Pd/C (0.05 g) under atmospheric pressure. The reaction mixture was separated by preparative thin layer chromatography on silica gel using chloroform to give the dihydro compound **22** (0.11 g, 73%) as colorless cubics, mp >300 °C (benzene–methanol), and the tetrahydro compound **23** (0.024 g, 15%) as colorless cubics, mp >300 °C (chloroform–methanol).

22: ir (KBr) 1690, 1635, 1600 cm^{-1}.

Anal. Calcd for $C_{38}H_{31}O_3N$: C, 83.05; H, 5.7; N, 2.55. Found: C, 82.8; H, 5.9; N, 2.55.

23: ir (KBr) 1685, 1635, 1600, 1490 cm^{-1}; *m/e* 551 (M^+), 384, 382.

Anal. Calcd for $C_{38}H_{33}O_3N$: C, 82.75; H, 6.05; N, 2.55. Found: C, 82.8; H, 6.15; N, 2.5.

B. A solution of **19** (0.15 g) in ethyl acetate (50 ml) containing acetic acid (1.5 ml) was hydrogenated over Adams catalyst under atmospheric pressure to give the tetrahydro compound **23** (0.15 g, quantitative).

Acid Hydrolysis of 23. To a suspension of **23** (0.15 g) in methanol (30 ml) was added concentrated hydrochloric acid (2 ml) and the solution was refluxed for 5 h. The solvent was then evaporated under reduced pressure and the residue was diluted with water and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, and then the residue was chromatographed on silica gel using benzene–chloroform (1:1) to give **24** (0.13 g, 83%) as a colorless, amorphous solid: ir (neat) 3400, 1745, 1680, and 1610 cm^{-1}.

Anal. Calcd for $C_{38}H_{35}O_4N$: C, 80.1; H, 6.2; N, 2.45. Found: C, 80.15; H, 6.45; N, 2.15.

Cycloaddition Reactions of Phencyclone (2) with Dienophiles. General Procedure for Cycloaddition. A solution of phencyclone (2) and an equimolar or excess amount of olefins was heated under argon in a sealed tube until the deep-green color had faded away. The cooled mixture was diluted with methanol and the precipitated solid was filtered off and purified by recrystallization.

With Oxabenzonorbornadiene (26). A solution of **2** (1.67 g) and **26** (0.63 g) in chlorobenzene (25 ml) was heated at 130 °C under argon in a sealed tube for 7 h. The cooled mixture was diluted with methanol and the precipitated solid was filtered off and recrystallized from chloroform–ethanol to give the adduct **32** (1.85 g, 80%) as colorless needles: mp 254–256 °C dec; ir (KBr) 1795, 1600, 1505, 1450 cm^{-1}.

Anal. Calcd for $C_{39}H_{26}O_2$: C, 88.95; H, 5.0. Found: C, 88.7; H, 5.25.

With Dimethyl 7-Isopropylidenenorbornadiene-1,2-dicarboxylate (27). A solution of **2** (0.382 g) and **27** (0.248 g) in chlorobenzene (10 ml) was heated at 100 °C under argon in a sealed tube for 5 h. Then work-up gave **33** (0.57 g, 90%) as colorless needles: mp 241–242 °C dec (benzene–methanol); ir (KBr) 1790, 1720, 1620, 1605 cm^{-1}.

Anal. Calcd for $C_{43}H_{34}O_5$: C, 81.9; H, 5.45. Found: C, 81.75; H, 5.6.

With Dimethyl 7-Oxanorbornadiene-1,2-dicarboxylate (28). A solution of **2** (1.53 g) and **28** (0.84 g) in chlorobenzene (20 ml) was heated at 80 °C under argon in a sealed tube for 2 h. Then work-up gave **34** (2.03 g, 86%) as colorless needles: mp 233–234 °C dec (ethyl acetate–chloroform); ir (KBr) 1800, 1720, 1710, 1630 cm^{-1}.

Anal. Calcd for $C_{39}H_{28}O_6$: C, 79.05; H, 4.75. Found: C, 79.3; H, 4.95.

With Norbornadiene (29). A solution of **2** (0.5 g) and **29** (0.3 g) in chlorobenzene (5 ml) was heated at 80 °C for 1.5 h. Work-up gave **35** (0.58 g, 93%) as colorless crystals: mp 233–234 °C dec (ethyl acetate–methanol); ir (KBr) 1795, 1610, 1510, 1445 cm^{-1}.

Anal. Calcd for $C_{36}H_{26}O$: C, 91.1; H, 5.5. Found: C, 91.25; H. 5.55.

With Acenaphthylene (30). A solution of **2** (0.955 g) and **30** (0.38 g) in toluene (15 ml) was heated at 80 °C for 1 h. Similar work-up gave **36** (1.23 g, 92%) as colorless needles: mp >300 °C (benzene–ethanol); ir (KBr) 1795, 1610, 1505 cm^{-1}.

Anal. Calcd for $C_{41}H_{26}O$: C, 92.1; H, 4.9. Found: C, 92.2; H, 5.15.

With 6,6-Dimethylfulvene (31). A solution of **2** (0.955 g) and **31** (0.265 g) in chlorobenzene (8 ml) was heated at 110 °C for 3 h. Similar work-up gave **37** (0.9 g, 74%) as colorless needles: mp 231–232 °C dec (benzene–methanol); ir (KBr) 1782, 1600, 1500, 1450 cm^{-1}.

Anal. Calcd for $C_{37}H_{28}O$: C, 90.95; H, 5.8. Found: , 91.0; H, 5.8.

With *N*-Phenylmaleimide (7). A solution of **2** (1.91 g) and **7** (0.865 g) in chlorobenzene (25 ml) was heated at 70 °C for 10 min. Similar work-up gave **8** (2.5 g, 91%) as colorless crystals, mp 295–297 °C dec (benzene–methanol).

With Tetracyanoethylene (45). A solution of **2** (0.955 g) and **45** (0.32 g) in benzene (8 ml) was heated at 60 °C for 30 min. Similar work-up gave **52** (1.15 g, 90%) as colorless prisms: mp 221–223 °C dec (benzene); ir (KBr) 2240, 1800, 1600, 1500, 1480 cm^{-1}.

Anal. Calcd for $C_{35}H_{18}ON_4 \cdot \frac{1}{2}C_6H_6$: C, 83.05; H, 3.85; N, 10.2. Found: C, 83.05; H, 4.1; N, 10.25.

On the other hand, the precipitated crystals **52** were recrystallized from methanol–ethyl acetate to give compound **59** (quantitative) as colorless needles: mp 240–242 °C dec; ir (KBr) 1730, 1505, 1450 cm^{-1}; NMR ($CDCl_3$) δ 3.17 (s, 3 H, OMe), 7.0–8.9 [m, 19 H, aromatic H and $CH(CN)_2$].

Anal. Calcd for $C_{36}H_{22}O_2N_4$: C, 79.7; H, 4.1; N, 10.35. Found: C, 79.45; H, 4.4; N, 10.2.

With Maleic Anhydride (46). A. A solution of **2** (1.19 g) and **46** (0.49 g) in benzene (20 ml) was heated at 80 °C for 20 min. Similar work-up gave **53** (2.21 g, 92%) as colorless needles: mp 296–298 °C dec (benzene–acetone); ir (KBr) 1865, 1790, 1758, 1605, 1500, 1455 cm^{-1}.

Anal. Calcd for $C_{33}H_{20}O_4$: C, 82.5; H, 4.2. Found: C, 82.6; H, 4.45.

B. A solution of **2** (0.955 g) and **46** (0.245 g) in benzene (20 ml) was stirred at room temperature for 3 h. Similar work-up gave **53** (1.2 g, quantitative).

With *p*-Benzoquinone (47). A solution of **2** (1.91 g) and **47** (0.54 g) in chlorobenzene (20 ml), was heated at 80 °C for 20 min. Similar work-up gave **54** (2.28 g, 93%) as colorless crystals: mp 272–273 °C dec (chloroform–methanol); ir (KBr) 1800, 1680, 1610, 1510, 1455 cm^{-1}.

Anal. Calcd for $C_{35}H_{22}O_3 \cdot \frac{1}{2}H_2O$; C, 84.15; H, 4.65. Found: C, 84.1; H, 4.8.

With 1-Chloroacrylonitrile (48). A solution of **2** (0.955 g) and **48** (0.22 g) in toluene (10 ml) was heated at 80 °C for 1.5 h. Similar work-up gave **55** (1.1 g, 94%) as colorless cubics: mp 176–178 °C dec (dichloromethane–methanol); ir (KBr) 1800, 1600, 1505, 1450, 1440 cm^{-1}.

Anal. Calcd for $C_{32}H_{20}ONCl \cdot \frac{1}{2}CH_2Cl_2$: C, 76.15; H, 4.15; N, 2.75. Found: C, 75.9; H, 4.3; N, 2.8.

With 1-Acetoxyacrylonitrile (49). A solution of **2** (1.91 g) and **49** (0.555 g) in chlorobenzene (18 ml) was heated at 80 °C for 2 h. Similar work-up gave **56** (1.97 g, 80%) as colorless needles: mp 258–260 °C dec (chloroform–methanol); ir KBr) 1800, 1760, 1600, 1500 cm^{-1}.

Anal. Calcd for $C_{34}H_{23}O_3N$: C, 82.75; H, 4.7; N, 2.85. Found: C, 82.95; H, 4.95; N, 2.85.

With Dimethyl Acetylenedicarboxylate (50). A solution of **2** (0.955 g) and **50** (0.355 g) in toluene (10 ml) was heated at 80 °C for 17 h. Similar work-up gave **57** (1.0 g, 81%) as light-green cubics: mp 272–273 °C (ethyl acetate–methanol); ir (KBr) 1750, 1740, 1600, 1500 cm^{-1}.

Anal. Calcd for $C_{34}H_{24}O_4$: C, 82.25; H, 4.85. Found: C, 81.95; H, 4.85.

With Diphenylcyclopropenone (51). A solution of **2** (0.955 g) and **51** (0.515 g) in chlorobenzene (18 ml) was heated at 150 °C for 80 h. Similar work-up gave **58** (0.4 g, 29%) as colorless needles: mp 264–265 °C (chloroform–methanol); ir (KBr) 1720, 1600, 1495, 1450 cm^{-1}.

Anal. Calcd for $C_{43}H_{28}O \cdot H_2O$: C, 89.25; H, 5.25. Found: C, 89.5; H, 5.3.

Hydrogenation of 37. A solution of **37** (0.17 g) in ethyl acetate (45 ml) was hydrogenated over 10% Pd/C (0.05 g) under atmospheric pressure to give the tetrahydro compound **39** (0.17 g) as colorless needles: mp 255–256 °C dec; ir (KBr) 1780, 1600, 1500, 1450 cm^{-1}; NMR ($CDCl_3$) δ 0.15 (d, 3 H, J = 7.0 Hz, CH_3), 1.14 (d, 3 H, J = 7.0 Hz, CH_3), 1.7–2.95 (m, 5 H, H_B and methylene H), 3.80 (m, 1 H, H_C), 4.4–4.92 (m, 2 H, H_A), 7.0–8.1 (m, 16 H, aromatic H), 8.72 (d, 2 H, J = 8.0 Hz, aromatic H).

Anal. Calcd for $C_{37}H_{32}O$: C, 90.2; H, 6.55. Found: C, 90.5; H, 6.35.

Pyrolysis of Compounds 32–35. General Procedure for Pyrolysis. An adduct was heated at 200 °C for 2 h without solvents and chromatographed on silica gel using *n*-hexane–benzene (3:1) as an eluent.

Pyrolysis of 32. The adduct **32** (0.15 g) was heated at 200 °C for 2 h. Work-up gave **41** (0.105 g, 97%) as colorless needles, mp 230–232 °C (lit.[5] 224–226 °C).

Pyrolysis of 33. The adduct **33** (0.1 g) was heated at 200 °C for 2 h. Work-up gave **41** (0.055 g, 91%) but not isolated compound **42b.**

Pyrolysis of 34. The adduct **34** (0.1 g) was heated at 200 °C for 2 h. Similar work-up gave **41** (0.058 g, 91%) and **42c** (0.015 g).

Hydrolysis of 55. To a solution of **55** (0.47 g) in Me_2SO (10 ml) was added a hot solution of KOH (0.17 g) in water (0.3 ml). The mixture was stirred at room temperature for 16 h, and the reaction mixture was then diluted with water (30 ml). The diluted solution was neutralized with dilute hydrochloric acid and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel using benzene to give **64** (0.2 g, 50%) as colorless leaflets: mp 235–237 °C (dichloromethane–methanol); ir (KBr) 2210, 1605, 1505, 1455 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (m, 2 H, H_B), 4.90 (dd, 1 H, J = 6.0 and 3.5 Hz, H_A), 7.1–8.1 (m, 16 H, aromatic H), 8.70 (d, 2 H, J = 8.5 Hz, aromatic H).

Anal. Calcd for $C_{31}H_{21}N$: C, 91.35; H, 5.2; N, 3.45. Found: C, 91.1; H, 5.05; N, 3.55.

Hydrolysis of 56. To a solution of **56** (0.493 g) in Me_2SO (10 ml) was added a hot solution of KOH (0.17 g) in water (0.3 ml). The mixture was stirred at room temperature for 16 h. Similar work-up gave **64** (0.16 g, 40%).

Supplementary Material Available. Tables I, II, IV, and VI of NMR spectra (4 pages). Ordering information is given on any current masthead page.

Registry No.—**2,** 5660-91-3; **3,** 539-80-0; **4,** 57969-45-6; **6,** 57969-46-7; **7,** 941-69-5; **8,** 58002-01-0; **9,** 58002-02-1; **10,** 544-25-2; **11,** 57969-47-8; **13,** 57969-48-9; **14,** 57969-49-0; **15,** 57969-50-3; **16,** 57969-51-4; **17,** 57969-52-4; **18,** 2955-79-5; **19,** 57969-53-6; **22,** 57969-54-7; **23,** 57969-55-8; **24,** 57969-56-9; **26,** 573-57-9; **27,** 19019-88-6; **28,** 1829-60-3; **29,** 121-46-0; **30,** 208-96-8; **31,** 2175-91-9; **32,** 57969-57-0; **33,** 57969-58-1; **34,** 57969-59-2; **35,** 57969-60-5; **36,** 57969-61-6; **37,** 57969-62-7; **39,** 57969-63-8; **41,** 57969-64-9; **42c,** 4282-33-1; **45,** 670-54-2; **46,** 108-31-6; **47,** 106-51-4; **48,** 920-37-6; **49,** 3061-65-2; **50,** 762-42-5; **51,** 886-38-4; **52,** 36428-90-7; **53,** 57969-65-0; **54,** 57969-66-1; **55,** 57969-67-2; **56,** 57969-68-3; **57,** 57969-69-4; **58,** 57969-70-7; **59,** 57969-71-8; **64,** 57969-72-9.

References and Notes

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Synthesis of β-Lactams via Cycloaddition of Iminodithiocarbonate Esters with Azidoketene[1]

Donald F. Sullivan,[2a] David I. C. Scopes,[2b] Arthur F. Kluge, and John A. Edwards*

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

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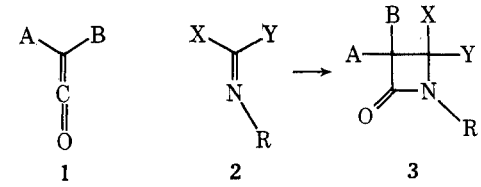
The reaction of iminodithiocarbonate esters with azidoketene afforded β-lactams containing an ortho ester functionality. The yield of cycloaddition is influenced by the steric and electronic nature of the imine substrate and by the order of addition of reagents. The 1,2-secopenam analogs **16b** and **25** were prepared through reaction of imines **15** and **22** with azidoacetyl chloride–triethylamine followed by transformation of the azide function to an acylamido function. Ring opening of the β-lactams was achieved under a variety of conditions: **7a** gave **11** with trifluoroacetic acid, **7b** gave **12** with hog pancreatic lipase, and **16b** and **25** were transformed to **17** and **26,** respectively, with silica gel.

Spurred by the importance of penicillins and cephalosporins to antibiotic therapy, synthetic chemists have devised numerous methods for the preparation of the natural β-lactams and related analogues.[3] One such route, the reaction of ketenes with imines, has proven a versatile method for the synthesis of medicinally important compounds.[4a–e]

We became interested in the ortho ester functionality which would result from the cycloaddition of a ketene with a bishetero-substituted imine (1 + 2 → 3). The use of azidoketene in a cycloaddition reaction with a bishetero-substituted imine, besides incorporating the ortho ester functionality, would permit the subsequent introduction of the biologically important *N*-acylamido moiety onto the resultant β-lactams (1 + 2 → 3; A = N_3; B = H). Suitable choice of the imine can yield β-lactams containing other functionalities important for biological activity (i.e., R = $CHR'CO_2R''$).



1 2 3

Several examples of β-lactams containing ortho ester functionality have been published. A Bayer group has described 41 β-lactams derived from the reaction of *N*-alkyliminodithiocarbonate dimethyl esters with various ketenes.[5] Bose has prepared the penicillin analogue **4** through the reaction of 2-methylthio-2-thiazoline with methoxyketene.[6] Bose has also described β-lactams of the general type **5** which were derived through the addition of various ketenes, including azidoketene, to N-acylated 2-methylthio-1,4,5,6-tetrahydropyrimidines.[7]