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Studies on the Syntheses of Heterocyclic Compounds. 675.[1] A Facile Regiospecific and Stereocontrolled Synthesis of a Diterpene Alkaloid Intermediate from Benzocyclobutenes

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Abstract: Thermolysis of 1-cyano-4-methoxy-1-(4-methoxycarbonyl-4-vinyl)pentylbenzocyclobutene (**3**), derived from methyl methylacetoacetate (**7**) in five steps, gave (±)-4aα-cyano-1,2,3,4,4a,9,10,10aα-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (**19**) in a stereocontrolled manner, which was converted into the epimer (**26**) by oxidation, bromination, dehydrobromination, and hydrogenation. Catalytic reduction of **26** gave the lactam (**27**), whose reduction with lithium aluminum hydride afforded 16,17-imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene (**1**). The 5α-epimer (**22**) of **1** was also synthesized from **21.**

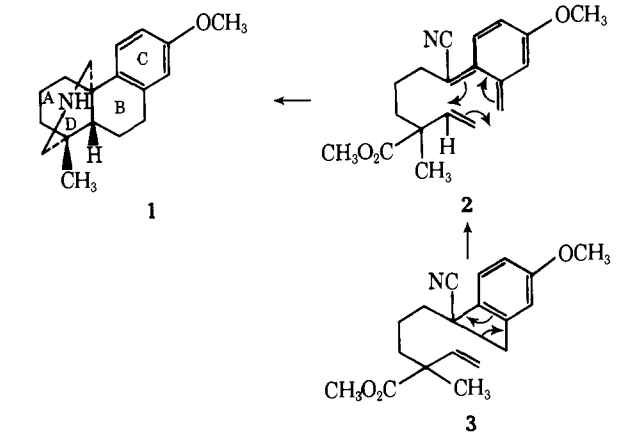
The synthetic challenge of diterpenes[2] and diterpene alkaloids[3,4] has attracted much attention by many investigators. A crucial step in the synthesis of these types of natural products is the introduction of a functionalized carbon unit at the C-4a angular position in combination with C-1 substituents with appropriate stereochemical control in the phenanthrene ring.[5] Hitherto, two general methods have been available; one is an introduction of a suitable group into the C-4a angular position of hydrophenanthrene,[6,7] and the other is a direct synthesis from β-tetralone derivatives having a functionalized group at the α position by Robinson annelation.[7,8]

Previously, we have reported a simple total synthesis of the isoquinoline alkaloids[9-13] by a regioselective electrocyclic reaction or cycloaddition of the cyanated *o*-quinodimethane to imines[14] and olefins.[15] In connection with our interest in a simple total synthesis of other types of natural products, we have investigated a new type of synthetic method of C-4a-substituted hydrophenanthrenes by our method. Herein, we wish to report an unusually simple and stereocontrolled synthesis of (±)-16,17-imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene (**1**),[4,5,7,15] which has already been correlated with atisine,[6,8] veatchine,[17] garryine,[16] and gibberellin A_{15}.[18] The method involves an intramolecular cycloaddition reaction of the *o*-quinodimethane derivative **2**[19] derived from the benzocyclobutene **3** as a key reaction (Scheme I).

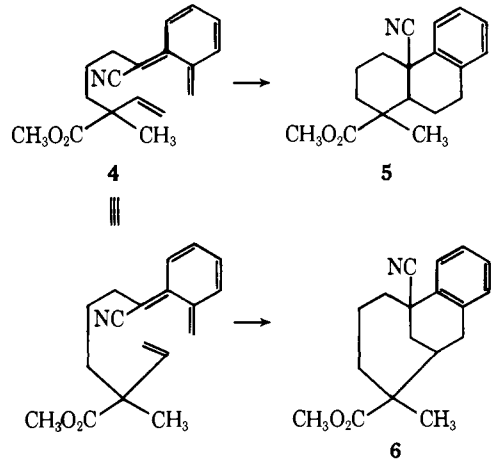
Our synthesis was designed on the basis of the idea that a hydrophenanthrene derivative which has two functional groups would be most effective for construction of the D ring of **1,** and that such an intermediate could be prepared in one step by an intramolecular cycloaddition reaction of an *o*-quinodimethane derivative. The benzocyclobutene **3** was chosen as a suitable starting material because this compound forms an *o*-quinodimethane on heating[19] and also has cyano and carbomethoxyl groups which are necessary for building up the D ring.

However, there are two regioselectively different routes for the intramolecular cycloaddition reaction of the *o*-quinodimethane **4** as shown in Scheme II. One is a formation of the

Scheme I



Scheme II



expected hydrophenanthrene **5,** and the other is that of bicyclo[4.3.1]decane (**6**). Therefore, we first investigated whether or not hydrophenanthrene would be formed by thermal decomposition of a benzocyclobutene by using the readily available benzocyclobutene **16** as a model experiment.

Model Experiment. As a key intermediate, benzocyclobutene derivative **16** was synthesized as follows.

Alkylation of methyl methylacetoacetate (**7**) with 1-bromo-3-chloropropane in the presence of sodium hydride in dimethylformamide gave the chloropropyl derivative **8** in 80–90% yield, which was reduced with sodium borohydride as usual to afford the secondary alcohol **9** in quantitative yield. Dehydration of **9** was carried out accordingly to the conventional method using phosphorous pentoxide and celite[20] at 120–160 °C to form, in 60% yield, the olefin **10** whose treatment with sodium iodide in boiling ethyl methyl ketone[21] furnished the unstable iodide **11.** This iodide, without purification, was condensed with 1-cyano-5-methoxybenzocyclobutene (**14**)[22] in the presence of sodium amide in liquid ammonia[23] to give the 1-cyano-1-(4-vinylpentyl)benzocyclobutene **16** in 70% yield from the chloride **10.** The product showed nitrile and ester groups at 2236 and 1720 cm^{-1} in the ir spectrum, respectively, and the NMR spectrum (δ in $CDCl_3$) revealed two protons on a cyclobutene ring at 3.08 and 3.58 as doublets having J value of 14 Hz in addition to vinyl protons showing a typical ABX pattern. Heating **16** in dry toluene at 180–230 °C in a sealed tube for 3 h afforded 4aα-cyano-1,2,3,4,4a,9,10,10a-octahydro-6-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (**18**) in 40–50% yield in a regiospecific and stereocontrolled manner in addition to starting material **16.** The NMR spectrum (δ in $CDCl_3$) of **18** showed three methyl resonances at 1.20, 3.69, and 3.76 as singlets but lacked the cyclobutene and olefinic proton resonances. At this stage, the structure of this product could not be determined, but was proved by conversion of this compound to the lactam **20.**[24] Thus, catalytic hydrogenation[25] of **18** was carried out on Raney nickel in ethanol at 80 °C under 115 atm of hydrogen to afford, in quantitative yield, the lactam **20,** mp 259–260 °C, which showed the amide group at 3410 and 1645 cm^{-1} in the ir spectrum. The NMR spectrum (δ in $CDCl_3$) revealed two methyl groups at 1.27 and 3.73 as singlets, methylene protons of C-17 at 3.36 and 3.77 as AB type doublets having J value of 11 Hz, and three aromatic protons at 6.53 (d, J = 2 Hz), 6.64 (dd, J = 2 and 8 Hz), and 6.98 (d, J = 8 Hz). This fact indicated a relative configuration between cyano and ester groups to be cis and also ruled out another possible structure, corresponding to **6,** in the thermolysis of **16,** because the bicyclo[4.3.1]decane type of compound could not form a lactam system from the stereochemical point of view. The stereochemistry of the hydrogen at C-5 in the lactam **20** also could not be determined in this series, but this was tentatively assigned as the α configuration because the protons at the C-17 position of the second lactam **21,** described later, resonated at 3.35 and 3.80 as AB type doublets which were very similar to those of **20,** but the third lactam **27**[6] having a β-hydrogen showed the proton resonance at 3.36 as a broad singlet.[25]

The stereocontrolled rearrangement of the benzocyclobutene **16** into the hydrophenanthrene **18** can be explained as follows. On thermolysis of **16,** which might be an epimeric mixture, the *o*-quinodimethanes are formed by an electrocyclic reaction of the cyclobutene ring.[26] Since a reversible conversion between cyclobutene and butadiene is possible, both epimers **16** would be transformed into the product **18** through the more stable intermediate **17.**

Since a simple regiospecific and stereocontrolled synthesis of 16,17-imino-16-oxopodocarpane-8,11,13-triene has been accomplished, we next investigated the synthesis of the key intermediates (**1** and **27**) used in the total synthesis of the diterpene alkaloids by Nagata[17,18] and Wiesner.[8]

Synthesis of 16,17-Imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene (1). An important precursor, the benzocyclobutene **15** was obtained by the usual method.[10-12] Decarboxylation of the α-cyanophenylpropionic acid **12**[28] at 170–180 °C in dimethylacetamide afforded, in 76% yield, the phenylpropiononitrile **13,** which was treated with an excess of sodium amide in liquid ammonia[29] to give the benzocyclobutene **15** in 64.5% yield.

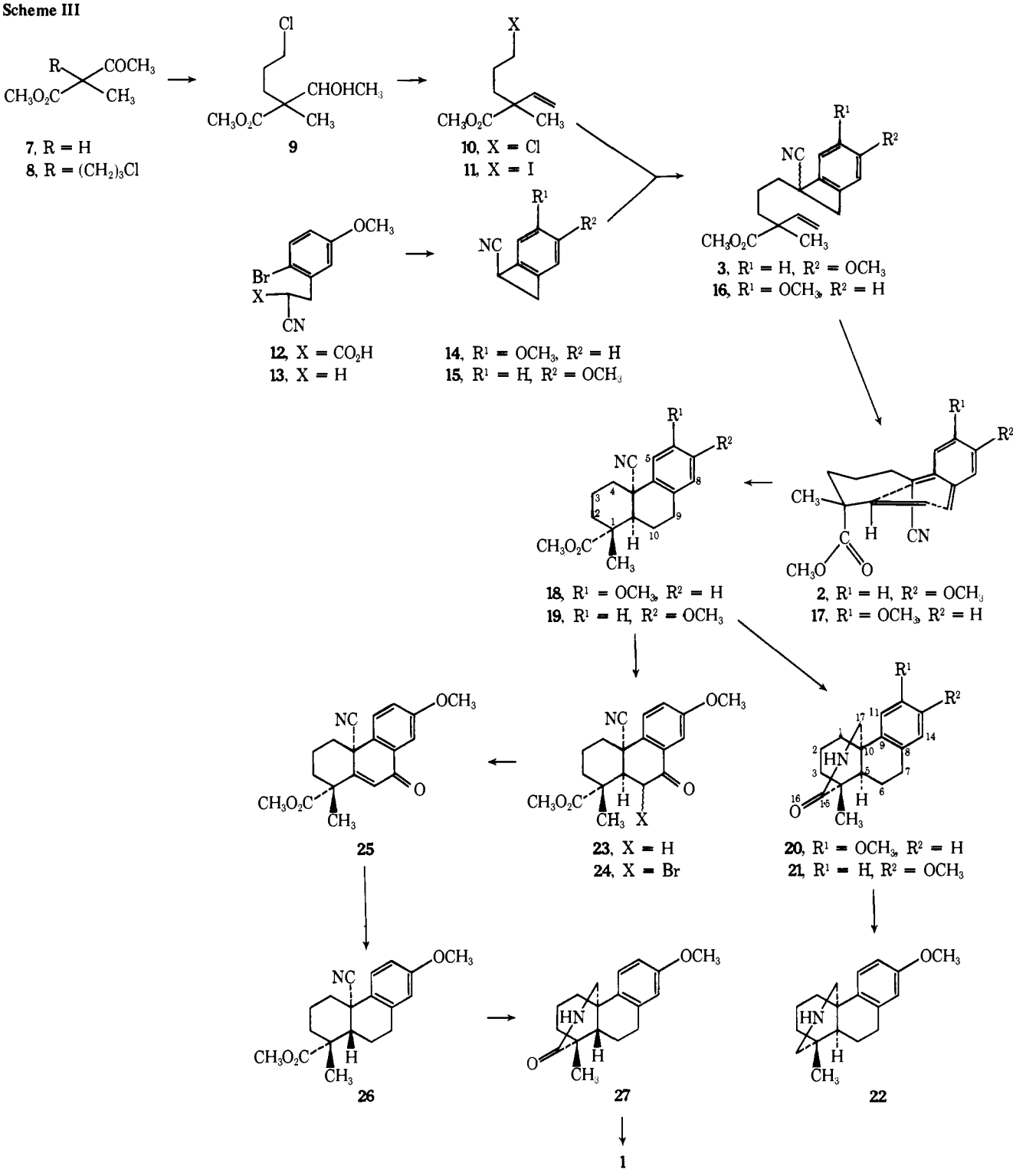
Condensation of 1-cyano-4-methoxybenzocyclobutene (**15**) with the iodide **11** afforded the second 1-cyano-1-(4-vinylpentyl)benzocyclobutene **3** in good yield. Thermolysis of **3** in toluene in a similar manner as above gave regiospecifically and stereoselectively the cycloaddition product **19,** mp 150–152 °C, in 52% yield, which was reduced on Raney nickel in ethanol under 110 atm of hydrogen at 80 °C to afford the lactam **21** [ν_{max} 3400 and 1645] in 80% yield. The NMR spectrum (δ in $CDCl_3$) of **21** showed methylene protons of C-17 position at 3.35 and 3.80 as doublets (J = 11 Hz), whose resonances were close to that of the first lactam **20.** Reduction of **21** with lithium aluminum hydride in boiling dioxane for 7 h furnished quantitatively 16,17-imino-13-methoxy-5α,10α-podocarpane-8,11,13-triene (**22**), characterized as its hydrochloride, mp 224–225 °C, which was also obtained directly from **19** by reduction with lithium aluminum hydride in moderate yield. The ir spectrum in chloroform of this product (**22**) is also very similar to that of **1,**[5] provided by Dr. Nagata, but many differences between both compounds (**22** and **1**) were found in the NMR ($CDCl_3$) and ir spectra in potassium bromide.

In order to obtain the trans fused octalin **26,** thermolysis of **3** was carried out by refluxing in triglyme in the presence of 10% palladium/carbon[30] for 6 h, but the cis fused octalin **19** was formed. Moreover, the direct epimerization of **19** into the trans fused octalin **26** by Pelletier's method was examined, and the starting octalin **19** was recovered. Therefore, an indirect conversion of **19** into **26** was investigated as follows. Oxidation of **19** with chromium trioxide in acetic acid for 16 h and then at 60 °C for 1 h[31] gave, in 45–50% yield, the ketone **23,** ν_{max} 1720 and 1680 cm^{-1}, which was treated with bromine in acetic acid at room temperature to produce the α-bromoketone **24,** in 98% yield, ν_{max} 1725 and 1685 cm^{-1}. Dehydrobromination of **24** was achieved by treatment with *N*-phenylbenzamidine[32] in boiling xylene for 3 h to give, in 90–95% yield, the α,β-unsaturated ketone **25,** ν_{max} 1725 and 1655 cm^{-1}, which was subjected to catalytic hydrogenation[33] on 10% palladium/carbon in ethanol to afford the expected 4aα-cyano-1,2,3,4,4a,9,10,10aβ-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (**26**), mp 157–158 °C. High-pressure reduction of **26** under the same conditions as the formation of **21** gave the lactam **27** in 80% yield, mp 239–240 °C (lit.[8] mp 240–241 °C), ν_{max} 3400 and 1645 cm^{-1}, whose NMR spectrum revealed the methylene protons of C-17 at 3.36 as a broad singlet.[25] Treatment of **26** with lithium aluminum hydride in boiling dioxane for 7 h afforded 16,17-imino-13-methoxy-5β,10α-podocarpene-8,11,13-triene (**1**), characterized as hydrochloride, mp 273.5–274 °C (lit.[6] mp 274–275 °C), which was identical with an authentic sample[6] by ir (KBr) spectral comparison and mixed melting point test. The lactam **27** has been transformed into atisine by Wiesner,[8] and the tetracyclic secondary amine **1** was also correlated to atisine,[6] garryine,[17] veatchine,[17] and gibberellin A_{15}.[18] Thus, we synthesized a key intermediate that has been used in the total synthesis of these substances.

Experimental Section

General. All melting points are uncorrected. Infrared spectra were recorded on a Hitachi EPI-3 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on JEOL JNM-PMX-60 and JNM-PS-100 spectrometers. Chemical shifts are reported as δ values relative to internal tetramethylsilane (Me_4Si). Mass spectra

Scheme III



were taken on a Hitachi RMU-7 spectrometer operating at an ionizing potential of 80 eV.

2-Bromo-5-methoxyphenylpropiononitrile (13). A suspension of 15.2 g (53.5 mmol) of α-cyanophenylpropionic acid (**12**) in 30 ml of *N,N*-dimethylacetamide was refluxed for 1 h. After cooling to room temperature, the reaction mixture was poured into 100 ml of water and extracted with 3 × 50 ml of ether. The ethereal layer was washed with 2 × 30 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a pale-yellow oil which was purified by distillation in vacuo to afford 9.7 g (75.8 %) of 2-bromo-5-methoxyphenylpropiononitrile (**13**): bp 158–160 °C (5 mm); ir ($CHCl_3$) 2240 cm^{-1}; NMR ($CDCl_3$) δ 2.50–3.18 (4 H, m, Ar-CH_2-CH_2-), 3.85 (3 H, s, OCH_3), 6.57–7.47 (3 H, m, Ar-H). Anal. ($C_{10}H_{10}NOBr$) C, H, N.

1-Cyano-4-methoxybenzocyclobutene (15). A solution of 9.7 g (40.4 mmol) of the above nitrile (**13**) and sodium amide (prepared from 5 g of sodium in liquid ammonia) in 500 ml of liquid ammonia was stirred for 2 h at −33 °C. After removal of the solvent, the residue was treated with an excess of crystalline ammonium chloride and diluted with 100 ml of saturated aqueous ammonium chloride solution. The mixture was extracted with 3 × 150 ml of chloroform, and the organic layer was washed with 2 × 50 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a reddish solid, which was recrystallized from ether to give 4.5 g (64.5%) of the cyclobutene **15** as colorless plates: mp 89–92 °C; ir ($CHCl_3$) 2240 cm^{-1}; NMR ($CDCl_3$) δ 3.52 (2 H, d, J = 3 Hz, Ar-CH_2-), 3.85 (3 H, s, OCH_3), 4.13 (1 H, t, J = 3 Hz, 1-H), 6.60–7.20 (3 H, m, Ar-H). Anal. ($C_{10}H_9NO$) C, H, N.

Methyl 2-Acetyl-5-chloro-2-methylvalerate (8). A solution of 8.7 g (67 mmol) of methyl α-methylacetoacetate (**7**) and 3.2 g (67 mmol)

of sodium hydride in 100 ml of dry *N,N*-dimethylformamide was stirred for 30 min at 0 °C, and then 10.5 g (67 mmol) of 1-bromo-3-chloropropane was added dropwise over a 30-min period. The resulting mixture was further stirred for 30 min at 60–70 °C and poured into 300 ml of ice-cold water. The mixture was extracted with 3 × 200 ml of ether, and the combined ethereal layer was washed with 2 × 100 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave 13.6 g of **8** as a pale-yellow oil which was purified by distillation to give 11.4 g (82%) of **8** as a colorless oil: bp 90 °C (3 mm); ir ($CHCl_3$) 1700 cm^{-1}; NMR (CCl_4) δ 1.38 (3 H, s, C-CH_3), 1.60–1.93 (4 H, m, -CH_2-CH_2-), 2.07 (3 H, s, $COCH_3$), 3.47 (2 H, t, J = 7.5 Hz, CH_2-CH_2-Cl), 3.68 (3 H, s, CO_2CH_3).

Methyl 5-Chloro-2-(1-hydroxyethyl)-2-methylvalerate (9). A solution of 8.7 g (42 mmol) of the keto ester **8** in 100 ml of methanol was stirred at 0 °C, while 3.18 g (84 mmol) of sodium borohydride was added in small portions over a 1-h period. After the continuous stirring for 1 h at 0 °C the solvent was evaporated in vacuo, and the residue was extracted with 3 × 100 ml of ether. The ethereal layer was washed with 2 × 50 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed to give 8.2 g (93.5%) of **9** as a colorless oil in sufficient purity to be used in the next step without further purification: ir ($CHCl_3$) 3470, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 4.5 Hz, CHCH_3), 1.08 (3 H, s, C-CH_3), 1.50–1.83 (4 H, m, -CH_2CH_2-), 3.52 (1 H, broad s, OH), 3.29–3.54 (2 H, m, CH_2Cl), 3.65 (3 H, s, CO_2CH_3).

Methyl 5-Chloro-2-methyl-2-vinylvalerate (10). A mixture of 5.5 g (26 mmol) of the alcohol **9**, 5.5 g of phosphorous pentoxide, and 2 g of celite was heated for 30 min at 100 °C in an oil bath. When the temperature of the oil bath had been raised to 160 °C, the mixture was distilled in vacuo (1 mm Hg) to give 3.0 g (60%) of the olefin **10** as a colorless oil: bp 100–103 °C (1 mm); ir 1715, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (3 H, s, C-CH_3), 1.75, 1.78 (4 H, each broad s, CH_2-CH_2-CH_2Cl), 3.36–3.60 (2 H, m, CH_2Cl), 3.65 (3 H, s, CO_2CH_3), 5.07 (1 H, dd, J = 2 and 16 Hz, H(H)C=C(H)-), 5.12 (1 H, dd, J = 2 and 16 Hz, H(H)C=C(H)-), 5.98 (1 H, dd, J = 11 and 16 Hz, CH=CH_2).

Methyl 4-Iodo-1-methyl-1-vinylvalerate (11). A solution of 2.3 g (12 mmol) of the chloride **10** and 5.4 g (36 mmol) of sodium iodide in 30 ml of ethyl methyl ketone was refluxed for 15 h. The reaction mixture was poured into 50 ml of water and extracted with 3 × 20 ml of ether. The combined ethereal layer was washed with 2 × 30 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded 3.2 g (94%) of the iodide **11** as a colorless oil, which was used for the next reaction without further purification: NMR (CCl_4) 1.23 (3 H, s, C-CH_3), 1.72 (4 H, broad s, $CH_2CH_2CH_2I$), 2.98–3.36 (2 H, m, CH_2I), 3.62 (3 H, s, CO_2CH_3), 5.03 (1 H, dd, J = 1.2 and 17 Hz, H(H)C=C(H)-), 5.05 (1 H, dd, J = 1.2 and 11 Hz, H(H)C=C(H)-), 5.27 (1 H, dd, J = 11 and 17 Hz, CH=CH_2).

1-Cyano-5-methoxy-1-(4-methoxycarbonyl-4-vinylpentyl)benzocyclobutene (16). To a stirred solution of 0.8 g (5 mmol) of the benzocyclobutene[22] **14** and sodium amide [prepared from 0.14 g (6 m atom) of sodium] in liquid ammonia was added 1.41 g (5 mmol) of the iodide **11** dropwise at −33 °C over a 10-min period. After stirring was continued for 1 h at the same temperature, the solvent was removed to give a reddish residue, which was treated with an excess of crystalline ammonium chloride and diluted with 20 ml of saturated aqueous ammonium chloride solution. The resulting mixture was extracted with 3 × 30 ml of ether, and the combined ethereal layer was washed with 2 × 20 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a reddish gum, which was purified by column chromatography on 30 g of silica gel utilizing benzene to afford 1.1 g (75%) of vinylbentylbenzocyclobutene derivative **16** as a colorless syrup: ir ($CHCl_3$) 2236, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (3 H, s, C-CH_3), 1.53–1.97 (6 H, m, 3 × CH_2), 3.08 (1 H, d, J = 14 Hz, ArCHH), 3.58 (1 H, d, J = 14 Hz, ArCHH), 3.61 (3 H, s, CO_2CH_3), 3.71 (3 H, s, OCH_3), 5.03 (1 H, dd, J = 1.2 and 16 Hz, H(H)C=C(H)-), 5.05 (1 H, dd, J = 1.2 and 10 Hz, H(H)C=C(H)-), 5.93 (1 H, dd, J = 10 and 16 Hz, CH=CH_2), 6.67 (1 H, d, J = 2 Hz, C_6-H), 6.75 (1 H, dd, J = 2 and 8 Hz, C_4-H), 6.95 (1 H, d, J = 8 Hz, C_3-H); mass m/e 313 (M^+). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

4aα-Cyano-1,2,3,4,4a,9,10,10a-octahydro-6-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (18). A solution of 1 g (3 mmol) of the vinylpentylbenzocyclobutene derivative **16** in 200 ml of dry toluene was heated in a sealed tube for 3 h at 180–230 °C. After cooling to room temperature, the solution was washed with 2 × 20 ml of water and dried over sodium sulfate, and the solvent was removed to give 0.95 g of a pale-reddish gum. Column chromatography on 40 g of silica gel with benzene provided the starting material (**16**) (0.4 g) from the first eluate and then 4aα-cyano-1,2,3,4,4a,9,10,10a-octahydro-6-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (**18**) as a colorless solid, whose recrystallization from *n*-hexane gave 0.49 g (49%) of **18** as colorless needles: mp 138–139 °C; ir ($CHCl_3$) 2230, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (3 H, s, C-CH_3), 3.69 (3 H, s, CO_2CH_3). 3.76 (3 H, s, OCH_3), 6.62 (1 H, dd, J = 2 and 8 Hz, C_{13}-H), 6.86 (1 H, d, J = 2 Hz, C_{14}-H), 6.87 (1 H, d, J = 8 Hz, C_{11}-H). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

16,17-Imino-12-methoxy-16-oxo-5α,10α-podocarpane-8,11,13-triene (20). A solution of 110 mg (0.38 mmol) of the cyano ester **18** in 30 ml of ethanol was hydrogenated in the presence of 0.5 g of Raney nickel at 80 °C under 115 atm of hydrogen until hydrogen uptake ceased. The mixture was filtered to remove an unsoluble material, and the filtrate was concentrated to give a colorless solid. Recrystallization from methanol afforded 93 mg (93%) of the lactam (**20**) as colorless needles: mp 259–260 °C; ir ($CHCl_3$) 3410, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (3 H, s, C-CH_3), 2.76 (2 H, t, J = 4 Hz, $ArCH_2$), 3.36 (1 H, d, J = 11 Hz, C_{17}-H), 3.73 (3 H, s, OCH_3), 3.77 (1 H, d, J = 11 Hz, C_{17}-H), 6.53 (1 H, d, J = 2 Hz, C_{11}-H), 6.63 (1 H, dd, J = 2 and 8 Hz, C_{13}-H), 6.98 (1 H, d, J = 8 Hz, C_{14}-H). Anal. ($C_{18}H_{23}NO_2 \cdot {}^1/_{10}H_2O$) C, H, N.

1-Cyano-4-methoxy-1-(4-methoxycarbonyl-4-vinylpentyl)benzocyclobutene (3). To a stirred solution of 0.8 g (5 mol) of the benzocyclobutene **15** and sodium amide [prepared from 0.14 g (6 m atom) of sodium] in liquid ammonia was added 1.41 g (0.005 mol) of the iodide **11** in portions at −33 °C over a 10-min period. After the stirring had been continued for 1 h at the same temperature, the solvent was removed to give a reddish residue, which was treated with an excess of crystalline ammonium chloride and diluted with 20 ml of saturated aqueous ammonium chloride solution. The resulting mixture was extracted with 3 × 30 ml of ether, and the combined ethereal layer was washed with 2 × 20 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a reddish gum, which was purified by column chromatography on 30 g of silica gel utilizing benzene to afford 1.2 g (76%) of the vinylpentylbenzocyclobutene derivative **3** as a syrup: ir ($CHCl_3$) 2230, 1700 cm^{-1}; NMR (CCl_4) δ 1.28 (3 H, s, C-CH_3), 1.45–2.03 (6 H, m, 3 × CH_2), 3.12 (1 H, d, J = 14 Hz, ArCHH), 3.63 (1 H, d, J = 14 Hz, ArCHH), 3.66 (3 H, s, CO_2CH_3), 3.75 (3 H, s, OCH_3), 5.05 (1 H, dd, J = 1.2 and 17 Hz, H(H)C=C(H)-), 5.09 (1 H, dd, J = 1.2 and 12 Hz, H(H)C=C(H)-), 5.98 (1 H, dd, J = 12 and 17 Hz, CH_2=CH), 6.67 (1 H, d, J = 2 Hz, C_3-H), 6.82 (1 H, dd, J = 2 and 8 Hz, C_5-H), 7.06 (1 H, d, J = 8 Hz, C_6-H). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

4aα-Cyano-1,2,3,4,4a,9,10,10a-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (19). a. Thermolysis in Toluene. A solution of 1 g (3 mmol) of the vinylpentylcyclobutene (**3**) in 200 ml of dry toluene was heated in a sealed tube for 3 h at 180–230 °C. After cooling to room temperature, the reaction mixture was washed with 2 × 20 ml of water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a pale-reddish gum which was purified by column chromatography on 40 g of silica gel utilizing benzene to give a colorless solid, whose recrystallization from *n*-hexane gave 0.52 g (52%) of the cyano ester **19** as colorless needles: mp 150–152 °C; ir 1720 cm^{-1}; NMR (CCl_4) δ 1.26 (3 H, s, C-CH_3), 2.63–3.03 (2 H, m, $ArCH_2$), 3.78 (3 H, s, CO_2CH_3), 3.80 (3 H, s, OCH_3), 6.6 (1 H, d, J = 3 Hz, C_8-H), 6.75 (1 H, dd, J = 3 and 9 Hz, C_6-H), 7.35 (1 H, d, J = 9 Hz, C_5-H). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

b. Thermolysis in Triglyme in the Presence of Palladium/Carbon. A solution of 1 g (3 mmol) of the vinylpentylcyclobutene **3** and 500 mg of 10% palladium/carbon in 100 ml of dry triglyme was heated in a sealed tube for 3 h at 180–220 °C. After cooling to room temperature, the solution was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a pale-reddish gum, which was purified by column chromatography on silica gel to give 550 mg of the cis-fused cyano ester **19**, which was identical with the authentic sample prepared by method a.

Trial of Epimerization of 19. A solution of 10 mg of the cyano ester **19** and 10 mg of 10% palladium/carbon in 10 ml of triglyme was refluxed for 5 h. After evaporation of the solvent, the residue was ex-

tracted with ether, and the ethereal layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave only starting material.

16,17-Imino-13-methoxy-16-oxo-5α,10α-podocarpane-8,11,13-triene (21). A solution of 270 mg (0.8 mmol) of the cyano ester **19** in 40 ml of ethanol was hydrogenated in the presence of 1 g of Raney nickel at 80 °C under 110 atm of hydrogen until hydrogen uptake ceased. The mixture was filtered to remove an unsoluble material, and the filtrate was concentrated to give a colorless solid, whose recrystallization from methanol afforded 202 mg (82%) of the lactam **21** as colorless needles: mp 217–218 °C; ir 3400, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (3 H, s, C-CH_3), 2.83 (2 H, distorted t, J = 4 Hz, $ArCH_2$), 3.35 (1 H, d, J = 11 Hz, C_{17}-H), 3.74 (3 H, s, OCH_3), 3.80 (1 H, d, J = 11 Hz, C_{17}-H), 6.56 (1 H, d, J = 2 Hz, C_8-H), 6.65 (1 H, dd, J = 2 and 8 Hz, C_6-H), 6.94 (1 H, d, J = 8 Hz, C_5-H). Anal. ($C_{18}H_{23}NO_2$) C, H, N.

16,17-Imino-13-methoxy-5α,10α-podocarpene-8,11,13-triene (22).

a. From the Lactam 21. To a stirred suspension of 10 ml of dry dioxane containing 100 mg of lithium aluminum hydride was added a solution of 108 mg (0.3 mmol) of lactam **21** in 10 ml of dry dioxane dropwise at room temperature over 30-min period. The reaction mixture was then refluxed for 7 h, and an excess of lithium aluminum hydride was decomposed by careful addition of 8 ml of water. The mixture was filtered on celite to remove an unsoluble material, and the filtrate was concentrated to dryness to give a colorless solid, whose hydrochloride was recrystallized from methanol to afford 92 mg (90%) of the hydrochloride of **22** as colorless needles: mp 224–225 °C; NMR ($CDCl_3$) δ 0.81 (3 H, s, C-CH_3), 3.74 (3 H, s, OCH_3); mass m/e 271 (M^+ − HCl). Anal. ($C_{18}H_{25}NO{\cdot}HCl{\cdot}\frac{1}{3}H_2O$) C, H, N.

b. From the Cyano Ester 19. A solution of 68 mg (0.1 mmol) of the cyano ester **19** and 100 mg of lithium aluminum hydride in 20 ml of dry dioxane was refluxed for 7 h, and an excess of lithium aluminum hydride was decomposed by carefully addition of 6 ml of water. The mixture was filtered on celite, and the filtrate was concentrated to dryness to give 22 mg of a colorless solid, which was identical with the product from **21.**

4aα-Cyano-1,2,3,4,4a,9,10,10a-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methyl-19-oxophenanthrene (23). To a stirred solution of 200 mg (0.6 mmol) of the cyano ester **19** in 2 ml of acetic acid was added 200 mg (20 mmol) of chromium trioxide in 4 ml of 80% acetic acid at room temperature over a 5-min period. After the continuous stirring for 16 h at the same temperature, the reaction mixture was heated at 60 °C for 1 h, and poured into ice-cold water. The resulting mixture was extracted with 2 × 10 ml of ether, and the combined ethereal layer was washed with 2 × 10 ml of 2% aqueous sodium hydroxide and 2 × 10 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a reddish gum, which was purified by alumina column chromatography. Elution with hexane–benzene (1:1) afforded a pale-yellow solid, whose recrystallization from ethanol gave 95 mg (45%) of the keto ester **23** as colorless needles: mp 181–184 °C; ir ($CHCl_3$) 2225, 1720, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (3 H, s, C-CH_3), 3.77 (3 H, s, CO_2CH_3), 3.87 (3 H, s, OCH_3), 7.20 (1 H, dd, J = 3 and 9 Hz, C_6-H), 7.50 (1 H, d, J = 3 Hz, C_8-H), 7.65 (1 H, d, J = 9 Hz, C_5-H). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

6-Bromo-4aα-cyano-1,2,3,4,4a,9,10,10a-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methyl-19-oxophenanthrene (24). To a solution of 40 mg (0.12 mmol) of the keto ester **23** in 1 ml of acetic acid was added two drops of acetic acid saturated with hydrogen bromide gas at room temperature with stirring to a mixture of which was added dropwise a solution of 29.3 mg (0.18 mmol) of bromine in 1 ml of acetic acid at room temperature with stirring. After continuous stirring for 2 h, the mixture was concentrated to give 50 mg (98%) of **24** as a pale-reddish gum, which was used in the following reaction without further purification: ir ($CHCl_3$) 2225, 1725, 1685 cm^{-1}; m/e 407, 405.

4aα-Cyano-1,2,3,4,4a,9-hexahydro-13-methoxy-1α-methoxycarbonyl-1β-methyl-9-oxophenanthrene (25). A solution of 820 mg (4.2 mmol) of N-phenylbenzamidine and 480 mg (1.19 mmol) of the bromide **24** in 20 ml of o-xylene was refluxed for 3 h. Removal of the solvent gave a reddish gum, which was acidified with 20 ml of 5% hydrochloric acid. The mixture was extracted with 3 × 20 ml of ether, and the ether layer was washed with 5% aqueous sodium carbonate solution and water and dried over anhydrous sodium sulfate. Removal of the solvent left a pale-yellow solid, which was recrystallized from ethanol to afford 365 mg (94%) of the enone **25**: mp 184–186 °C; ir ($CHCl_3$) 2230, 1725, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (3 H, s, C-CH_3), 3.72 (3 H, s, CO_2CH_3), 3.92 (3 H, s, OCH_3), 6.60 (1 H, s, C_{10}-H), 7.23 (1 H, dd, J = 2 and 8 Hz, C_6-H), 7.60 (1 H, d, J = 2 Hz, C_8-H), 7.65 (1 H, d, J = 8 Hz, C_5-H); mass m/e 325 (M^+). Anal. ($C_{19}H_{19}NO_4{\cdot}\frac{1}{3}H_2O$) C, H, N.

4aα-Cyano-1,2,3,4,4a,9,10,10aβ-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (26). A solution of 365 mg (1.12 mmol) of the enone **25** in 30 ml of ethanol was hydrogenated in the presence of 400 mg of 10% palladium/carbon until hydrogen uptake ceased. The mixture was filtered to remove an unsoluble material, and the filtrate was concentrated to give a pale-yellow gum, which was purified by alumina column chromatography. Elution with benzene afforded a colorless solid, which was recrystallized from methanol–n-hexane to give 52 mg (15%) of the trans-fused cyano ester **26**: mp 157–158 °C; ir ($CHCl_3$) 2230, 1720 cm^{-1}; NMR (CCl_4) δ 1.35 (3 H, s, C-CH_3), 2.70–3.06 (2 H, m, $ArCH_2$), 3.74 (3 H, s, CO_2CH_3), 3.78 (3 H, s, OCH_3), 6.57 (1 H, d, J = 3 Hz, C_8-H), 6.71 (1 H, dd, J = 3 and 8 Hz, C_6-H), 7.26 (1 H, d, J = 8 Hz, C_5-H). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

16,17-Imino-13-methoxy-16-oxo-5β,10α-podocarpane-8,11,13-triene (27). A solution of 37 mg (0.12 mmol) of the cyano ester **26** in 10 ml of ethanol was hydrogenated in the presence of 0.5 g of Raney nickel at 80 °C under 110 atm of hydrogen until hydrogen uptake ceased. The mixture was filtered to remove an unsoluble material, and the filtrate was concentrated to give a pale-yellow solid, which was recrystallized from methanol to afford 27 mg (80%) of the lactam **27**: mp 239–240 °C (lit.[8] mp 240–241 °C); ir ($CHCl_3$) 3400, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (3 H, s, C-CH_3), 3.36 (2 H, broad s, C_{17}-H) 3.77 (3 H, s, OCH_3), 6.63 (1 H, d, J = 2 Hz, C_{14}-H), 6.70 (1 H, dd, J = 2 and 8 Hz, C_{12}-H), 7.20 (1 H, d, J = 8 Hz, C_{11}-H).

(±)-16,17-Imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene (1). To a solution of 18 mg (0.063 mmol) of the lactam **27** in 5 ml of anhydrous dioxane was added 20 mg of lithium aluminum hydride, and the mixture was refluxed for 7 h with stirring in a current of nitrogen. The excess of the reagent was decomposed by dropwise addition of 1 ml of water under ice cooling, and the precipitate was filtered off and washed with 3 × 10 ml of ether. The filtrate was diluted with 20 ml of ether, and the ethereal layer was washed with 2 × 10 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a colorless gum which was characterized as hydrochloride. Recrystallization from methanol afforded 11.8 mg (70%) of **1** as colorless needles: mp 273.5–274 °C (lit.[6] 274–275 °C). Mixed melting point test showed both compounds to be identical. Its ir spectrum in KBr was superimposable with that of the authentic sample, and NMR spectrum of free base was also identical with that of the authentic specimen.

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Kinetic Studies on Diarylcarbenes[1]

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Abstract: Flash spectroscopic studies of diarylcarbenes have indicated optimal wavelength maxima for observation by kinetic spectrophotometry. In benzene solution at 25 °C, the second-order dimerization rate constants of diphenylcarbene, *p,p'*-dibromodiphenylcarbene, and *p,p'*-dimethyldiphenylcarbene were found to be 5.4, 3.5, and 1.1×10^9 M^{-1} s^{-1}, respectively. The absolute rate constants for reaction of 1,3-butadiene with the above carbenes are all 6.4×10^5 M^{-1} s^{-1}. The quotient of the absolute rate constant of reaction of singlet diphenylcarbene with methanol, k_{me}, and the singlet–triplet carbene equilibrium constant, K, has been determined to be $k_{me}/K = 6.8 \times 10^6$ M^{-1} s^{-1}. Steady-state competition experiments for the pairs oxygen–methanol, methanol–styrene, butadiene–styrene, and styrene–1,1-diphenylethylene were performed. These indicate the absolute rates of reaction of diphenylcarbene with styrene, 1,1-diphenylethylene, and oxygen to be 3.8×10^5, 4.8×10^5, and 1.0×10^9 M^{-1} s^{-1}, respectively. The results of the oxygen–methanol experiment, in conjunction with similar experiments performed under different conditions, suggest that k_{me} is near the diffusion limit. This fact, taken together with the experimental value of k_{me}/K, implies that $-\Delta H \approx 3$ kcal/mol, where $-\Delta H$ is the singlet–triplet energy splitting of diphenylcarbene.

During the last two decades much progress has been made in the chemistry of divalent carbon compounds. As an overview[3,4] of the literature will quickly show, most of the advances were made in the areas of structural information and in the exploration of new reactions involving carbenes. Despite the vast amount of data collected on relative reactivities of various carbenes with a great spectrum of substrates, relatively little quantitative kinetic information has been reported. To our knowledge not a single rate constant is known for a reaction of a carbene with an olefin in fluid solution, one of the most fundamental and useful carbene reactions.

Another topic of carbene chemistry that has drawn much attention follows from the close spacing of the lowest singlet and triplet states. Experimental efforts have been mostly directed toward establishing the spin multiplicity of the ground state of various substituted methylenes. Numerous theoretical calculations have reported energy differences for the spacing of the lowest states, but only few experiments[5-7] have been directed toward that problem. This information would be very useful because of relatively large discrepancies in the calculations for even the simple triatomic methylene, although recently the values tend to converge to 11 kcal.[8]

Of similar theoretical interest are the kinetics of interconversion between the triplet and singlet states of various carbenes. Indirect observations[9,10] made on several substituted methylenes point to a fast singlet–triplet intersystem crossing in both directions. For the case of diphenylmethylene it appears that the two states of different spin multiplicity convert so fast that they are in effective equilibrium during most reactions, thus preventing the separation of singlet and triplet chemistry. That this behavior is not characteristic for all carbenes has been demonstrated with fluorenylidene,[11,12] where slow reaction rates give predominantly triplet behavior, while in fast reactions the initially formed singlet state has a chance to compete.

To obtain better insight into the mechanistic detail of carbene reactions and to gather the facts necessary for answering some of the questions posed above, we decided to explore the feasibility of obtaining quantitative kinetic data of some simple carbene reactions in solution. In this paper we wish to report the results obtained from a flash photolysis study on some reactions of diphenylmethylene and some of its simple derivatives.[13] Although the reactions studied are by necessity simple and comprise only a tiny fraction of the known carbene reaction types, we believe the results when coupled with other data from relative rate measurements do enhance significantly our understanding of the chemistry of divalent carbon compounds. One other study of an arylmethylene by flash photolysis has been reported; however, no attempts were made to analyze the kinetics.[14]

Experimental Section

Flash Apparatus. The flash spectroscopic apparatus used was provided by Lehman and Berry.[15] Also modelled after their flash kinetic spectrophotometric apparatus, a similar device was built[16] with the following modifications. A Textronix RM503 oscilloscope, a Fairchild 453A oscilloscope recording camera using Polaroid type 47 film, a Beckman DU monochromator ($f/10$), and a Tobe Deutsch-