Preparation of Vinylketene by 1,4-Elimination. Cycloaddition and Isomerization to Form α-Ethylidenecyclobutanones[1,2]

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Vinylketene (1) was shown to result from triethylamine initiated 1,4-dehydrochlorination of *trans*-2-butenoyl chloride. In the presence of 1,3-cyclopentadiene a $_{\pi}2 + _{\pi}2$ cycloaddition occurred to form adduct **2**. With a trace of excess triethylamine **2** isomerized chiefly to a 73:27 mixture of the *E* and *Z* isomers **3** and **4**, whose structures were securely assigned using lanthanide induced shift nuclear magnetic resonance techniques. The possible participation of ethylideneketene ($CH_3CH{=}C{=}C{=}O$) was judged remote since triethylamine, 3-butenoyl chloride, and 1,3-cyclopentadiene gave an identical reaction mixture. With either isomeric acid chloride if less than 1.0 molar equiv of triethylamine was used a 60:01:39 mixture of **2**:**3**:**4** was formed, which upon addition of triethylamine equilibrated to the 73:27 mixture of **3** and **4**.

Ketenes ($RR'C{=}C{=}O$) react with conjugated dienes in a highly perispecific and regiospecific manner to form 3-vinylcyclobutanones.[4] Since the olefinic component reacts suprafacially, the fusion geometry is consistently cis. When the two ketene substituents differ in steric bulk the larger one tends to assume the more hindered position in the product.[5,6] Ketene cycloadditions represent one of the few synthetic approaches to four-membered rings,[7] and also serve as sensitive mechanistic probes of the rare and difficult $_{\pi}2_s + _{\pi}2_a$ allowed concerted[8] pathway. A review of the available evidence[4] and recent theoretical analyses[9,10] indicate that both concerted and nonconcerted routes may be traversed, depending on the steric and electronic characteristics of ketene and ketenophile.

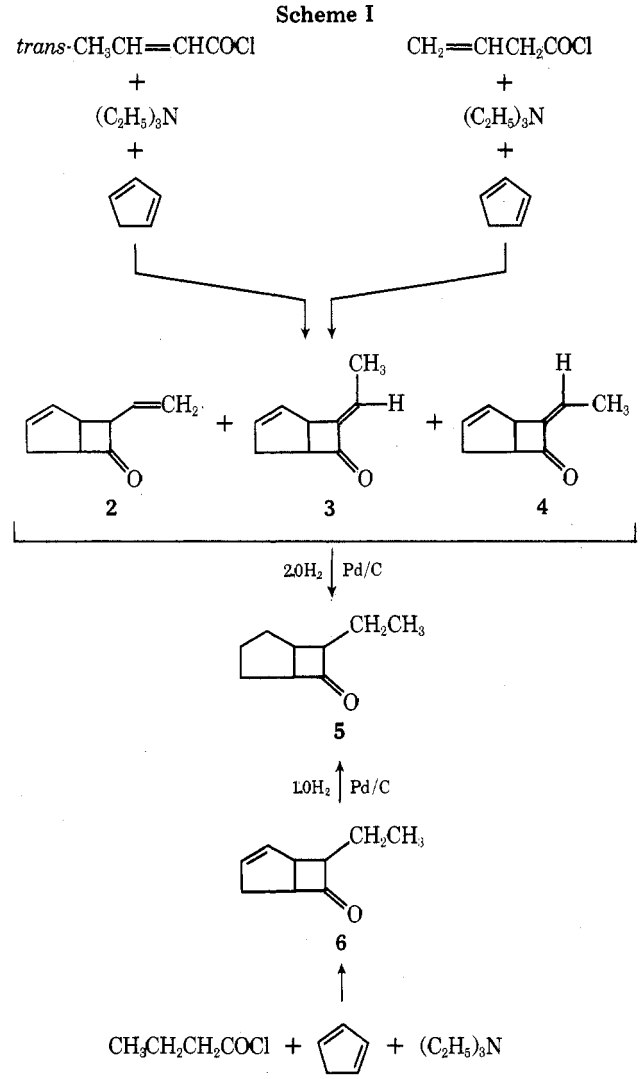
It is, therefore, of considerable synthetic importance and mechanistic interest to explore further the scope and nature of the ketene cycloaddition reaction. One approach is to study the reactions of especially unstable ketenes, such as the vinylketenes[11] and the alkylideneketenes ($RR'C{=}C{=}C{=}O$)[12,13] in which an additional carbon–carbon double bond is conjugated or cumulated with the ketene moiety. Although alkylideneketenes have been proposed as possible intermediates in the Einhorn reaction of α,β-unsaturated acid chlorides,[14-16] and may have been formed by dehydrochlorination of 3-methyl-2-butenoyl chloride,[17] the only unambiguous preparations involve photochemical[13] or flash vacuum pyrolytic[12] methods. Even with these techniques the simpler members of the class, such as the parent methyleneketene ($CH_2{=}C{=}C{=}O$) and ethylideneketene ($CH_3CH{=}C{=}C{=}O$), have not been detected.

We wish to describe our results involving a simple in situ preparation and subsequent cycloaddition of vinylketene (1), which acts as an ethylideneketene surrogate to afford cyclobutanones conveniently functionalized at the α position.

Results

When *trans*-2-butenoyl chloride was treated with 0.95 molar equiv of dry triethylamine in the presence of 6.0 molar equiv of 1,3-cyclopentadiene and worked up after 3 h a product mixture of 60% 7-vinylbicyclo[3.2.0]hept-2-en-6-one (**2**),[18] 1% (*E*)-7-ethylidenebicyclo[3.2.0]hept-2-en-6-one (**3**), and 39% (*Z*)-7-ethylidenebicyclo[3.2.0]hept-2-en-6-one (**4**) resulted (Scheme I). The adduct isomer **2** could be detected by NMR or rapid analytical vapor phase chromatography (VPC) at temperatures below 100 °C, but could not be isolated by preparative VPC since at temperatures above 100 °C or with long retention times it suffered apparent cyclorever-sion.[19] The entire adduct mixture, after purification by distillation in vacuo (yield 41%), took up 1.9 ± 0.1 molar equiv of H_2 over Pd/C to form only *endo*- and *exo*-7-ethylbicyclo[3.2.0]heptan-6-one (**5**), identified by independent synthesis (hydrogenation of the adducts of ethylketene and 1,3-cyclopentadiene; see Experimental Section).

Scheme I



The cycloaddition procedure was repeated with 3-butenoyl chloride replacing *trans*-2-butenoyl chloride and an identical adduct mixture was isolated (Scheme I).

When a trace of triethylamine was added to the above adduct mixtures before workup, equilibration occurred to give, ultimately, a mixture of 0.4% **2**, 63.7% **3**, 24.0% **4**, and two unidentified components (A, B). This isomerization is quite

complex, and we have not investigated it completely. The rate of equilibration seems to depend on surface effects, as well as the solvent and the particular equilibration catalyst present. We have established, however, that in pentane at 25 °C in the presence of triethylamine adduct **2** disappears very rapidly (half-life < 30 min) to form chiefly **4** with some **3** present.[22] The composition of this mixture continues to change for about 7 days, at the end of which time the 3:4 ratio has reached the equilibrium value of 72.6 ± 0.1:27.4 ± 0.1 (K_{eq} = 0.38, ΔG_{25} = +0.58 kcal/mol).

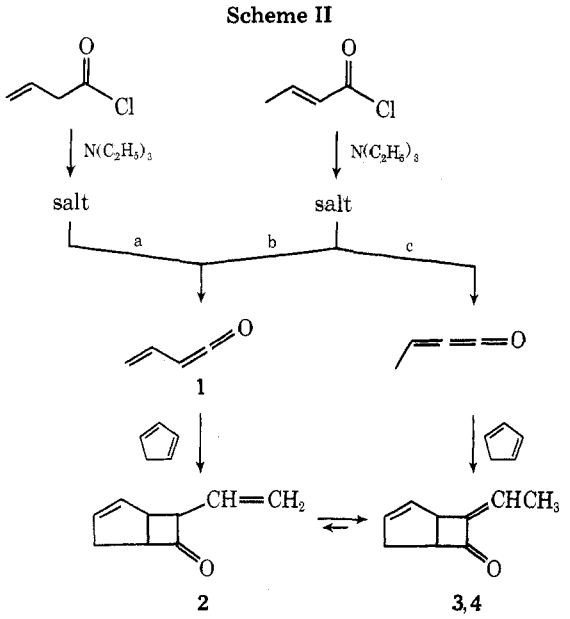
When a trace of triethylamine was added to pentane solutions of VPC-purified samples of **3** or **4** (vide infra) isomerization occurred at room temperature within 7 days to afford the same equilibrium mixture of the five components (**2, 3, 4,** A, B). When the entire cycloaddition was carried out beginning with either isomeric acid chloride and 1.05 molar equiv of triethylamine the relative amount of **2** in the mixture decreased with increasing reaction time. Delaying workup for 1 week or more (not an uncommon procedure with ketene cycloadditions[23]) again provided the equilibrium mixture.

Isomeric adducts **3** and **4** were obtained in >98% purity by preparative vpc; each gave an acceptable C, H analysis and each took up 2.0 ± 0.1 molar equiv of H_2 over Pd/C to give **5**. Mass, infrared (ir), nuclear magnetic resonance (NMR), and ultraviolet (uv) spectra confirmed the gross structural features of **3** and **4**. Lanthanide induced shift (LIS) NMR using a serial doping technique[24] and plots of shifts vs. added lanthanide reagents for H_8 and methyl (Table I) served to assign the exocyclic double bond geometry. It is noteworthy that these LIS–NMR studies support earlier assignments of double-bond geometry of α-ethylidene ketones made by comparisons of chemical shift data alone.[25,26]

Discussion

Although both mechanistic pathways b and c shown in Scheme II could operate when *trans*-2-butenoyl chloride

Scheme II

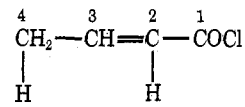


reacts with triethylamine and 1,3-cyclopentadiene, since the equilibrium between adduct **2** and the **3, 4** pair lies almost entirely toward the conjugated species[27] the ethylideneketene route c can at most be minor. Actually, no unambiguous evidence implicating the presence of this elusive alkylideneketene has been found in this work, and the evident failure to prepare it by flash-vacuum pyrolysis (a method successful for other alkylideneketenes)[12] indicates that its participation here is unlikely. All of our data are most economically explained as illustrated by routes b and c in which both *trans*-2- and -3-butenoyl chlorides react with triethylamine to form (presumably different) acylammonium salts,[29] which decompose by 1,4- and 1,2-elimination, respectively, to afford vinylketene (**1**). This species is trapped by 1,3-cyclopentadiene as adduct **2**, which subsequently provides **3** and **4** by isomerization.

Table I. NMR Chemical Shift Values for Ketones 3 and 4 Doped with Successive Amounts of Eu(fod)$_3$

Ratio of ketone:Eu(fod)$_3$	Ketone 3		Ketone 4	
	H_8	CH_3	H_8	CH_3
No doping	6.23	1.81	5.60	2.05
161.04:1.00	6.25	1.81	5.60	2.08
53.68:1.00	6.36	1.86	5.63	2.15
23.01:1.00	6.52	1.93	5.67	2.27
10.74:1.00	6.86	2.06	5.77	2.52
4.42:1.00	7.70	2.41	6.01	3.13

This view is supported by CNDO/2 charge density calculations for 2-butenoyl chloride,[33] which confirm the intuitive view of a much higher acidity for H_4 (lost in 1,4-elimination → vinylketene) than for H_2 (lost in 1,2-elimination → ethylideneketene):



CNDO/2 charge density + 0.0629 + 0.0306

We have devised no control experiment which can rule out the formal possibility that triethylamine catalyzes the equilibration of 3-butenoyl chloride and 2-butenoyl chloride prior to acylammonium salt formation. The known facility of the latter reaction, however,[29-32] and the slow isomerization of the corresponding esters[22] makes it a relatively unlikely mechanistic alternative.

In any case, owing to the facile isomerization subsequent to cycloaddition, vinylketene has been shown to be an effective ethylideneketene surrogate. When the reaction is carried out in the normal manner only adducts **3** and **4** are isolated. This reaction seems of some potential value, since (1) 1,4-dehydrochlorination of *trans*-2-butenoyl chloride represents a straightforward and economical route to vinylketene; and (2) cyclobutanones functionalized at the α carbon are obtained in moderate yields. Baeyer–Villager oxidation of species like **3** and **4** might provide a favorable synthetic approach to close analogues of α-methylene-γ-lactones,[34] some of which show antitumor activity.[35]

Experimental Section

Elemental analyses were performed by Ms. Ruby Ju of the University of New Mexico. Melting points are uncorrected. Mass spectra were measured[36] on a Du Pont Model 21-491 double focusing instrument at an ionizing voltage of 70 eV. Infrared (ir) spectra were recorded as thin films between NaCl plates on Perkin-Elmer 237, 337, or 521 spectrophotometers; all recorded absorptions were corrected by reference to polystyrene bands in the appropriate spectral regions. Nuclear magnetic resonance (NMR) spectra were obtained on Varian T-60, EM-360, or A-60 instruments. Ultraviolet (uv) measurements were made with a Perkin-Elmer Model 402 spectrophotometer. Preparative VPC separations were obtained with a Varian Aerograph Model 920 instrument equipped with a thermal conductivity detector with helium as the carrier gas. Analytical VPC determinations were measured using a Hewlett-Packard Model 5750 gas chromatograph equipped with flame ionization detector with nitrogen as the carrier gas. Quantitative VPC analyses resulted from automatic integration of peak areas by a Varian digital integrator Model 480 and calibration of detector response factors from known mixtures.[37,38] The VPC columns used are identified as column A, 10 ft × 0.25 in. 10% FFAP on 60–80 Chromosorb W; column B, 5 ft × 0.125 in. 4% FFAP on 100–120 Chromosorb P (AW, DMCS).

Analytical hydrogenations were carried out in ethyl acetate solutions over prereduced 10% Pd/C at atmospheric pressure. The volume H_2 adsorbed was compared with a control determination for cyclohexene + 1.0 H_2 → cyclohexane measured the same day. Thus for a typical determination 0.0408 g (4.967×10^{-4} mol) of cyclohexene adsorbed 13.40 ml of H_2. Immediately afterward 0.0318 g (2.370×10^{-4} mol) of VPC-purified 4 took up 13.35 ml of H_2. Adduct 4 thus has (4.967)(12.35)/(2.370)(13.40) = 1.93 double bonds. Repetitive determinations established a reproducibility estimated as ±0.1 double bond.

Reactions of *trans*-2-Butenoyl Chloride with Excess Triethylamine. Preparation of (*E*)-7-Ethylidenebicyclo[3.2.0]hept-2-en-6-one (3) and (*Z*)-7-Ethylidenebicyclo[3.2.0]hept-2-en-6-one (4). Under anhydrous conditions a solution of 15.25 g (0.15 mol) of dry (over KOH) triethylamine in 100 ml of low-boiling petroleum ether was added dropwise to a well-stirred mixture of 15.00 g (0.14 mol) of *trans*-2-butenoyl chloride, 57.11 g (0.86 mol) of freshly dedimerized 1,3-cyclopentadiene, and 600 ml of dry petroleum ether. Immediate formation of white solid was evident; the addition required 1.5 h, at the end of which time the mixture was brown in color and contained much solid. Stirring was continued for another 1.5 h, and the reaction mixture then sealed and allowed to stand at room temperature for 7 days. At the end of the time VPC analysis (column B, 95 °C) of the supernatant liquid showed (besides solvent and dicyclopentadiene) five components in the area ratio (order of elution times) 1.37:1.67:23.70:63.90:10.00.

Suction filtration afforded 9.1 g (46%) of triethylamine hydrochloride (mp 253–255 °C). The filtrate was washed with water, dried over $MgSO_4$, and concentrated to a brown oil by rotary evaporation. Distillation in vacuo resulted first in a large fraction of dicyclopentadiene and a second fraction of a pale yellow oil, 7.85 g (41%), bp 45–46 °C (0.1 mm). VPC analysis showed a small amount of dicyclopentadiene and the five components previously noted (area ratios essentially unchanged).

Preparative VPC (column A, 133 °C) resulted in isolation of the two major (third and fourth eluting) components in pure (>98% upon reinjection on column B) form. These were identified, respectively, as adducts 4 and 3 as described below. The second-eluting minor component had VPC retention time identical with adduct **2**, later identified by spectral analysis of an enriched mixture. The other two minor products remain unidentified.

(*Z*)-7-Ethylidenebicyclo[3.2.0]hept-2-en-6-one (4). The third-eluting component, which constituted 23.7% of the mixture, was assigned structure **4**: mass spectrum *m/e* (rel intensity) 134 (32), 106 (13), 105 (15), 91 (41), 69 (16), 68 (11), 66 (100), 65 (14), 51 (13), 41 (17), 40 (17), 39 (28); ir 3060, 2940, 2860, 1741, 1661, 1605, 1440, 1170, 1047, 896, 776, 741, 695 cm^{-1}; NMR (0.0392 g in 350 μl of $CDCl_3$) δ 5.8, m, 2 H (H_2, H_3); 5.60, q (J = 7 Hz) further split into a d (J = 1.5 Hz), 1 H (H_8); 3.8, m, 2 H; 2.6, m, 2 H; 2.05, d of d (J = 7.0, 1.5 Hz), 3 H ($-CH_3$). LIS NMR: to the above solution was added aliquots of a $CDCl_3$ solution of 0.0680 g (0.066 mmol) of Eu(fod)$_3$.[39] After each addition the NMR spectrum was run. Table I presents the chemical shifts of H_8 and $-CH_3$ as a function of the increasing Eu(fod)$_3$ concentration. The Δδ values extrapolated to a 1:1 molar ratio of **4**: Eu(fod)$_3$ are H_8 = 106 Hz, $-CH_3$ = 288 Hz. Taken with the complementary results of the other isomer these are sufficient to assign isomer 4 the *Z* configuration about the exocyclic double bond. Uv (95% ethanol) 209 nm (log ε 3.32), 238 (3.36).[40]

Reduction to 5. VPC-purified 4 (0.0318 g) took up 12.35 ml of H_2, thus having 1.9 ± 0.1 double bond. A larger sample of 0.40 g was hydrogenated in a Parr apparatus at 50 psi. After removal of the catalyst by suction filtration through sintered glass and concentration by rotary evaporation the residual oil showed by analytical VPC (column B, 135 °C) two components in a ratio (order of elution time) of 28.9:71.1. These were isolated by preparative VPC (column A, 130 °C) and had ir and NMR spectra congruent, respectively, with *exo*- and *endo*-7-ethylbicyclo[3.2.0]heptan-6-one (**5**), prepared and identified as described below.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.30; H, 7.43.

(*E*)-7-Ethylidenebicyclo[3.2.0]hept-2-en-6-one (3). The fourth-eluting component, which constituted 63.29% of the mixture, was assigned structure **3**: mass spectrum *m/e* (rel intensity) 134 (28), 106 (11), 105 (12), 91 (35), 78 (10), 69 (9), 68 (9), 67 (8), 66 (100), 65 (11), 51 (10), 41 (13), 40 (16), 39 (23); ir 3030, 2930, 2860, 1745, 1668, 1605, 1442, 1171, 1075, 793, 735, 690 cm^{-1}; NMR (0.0395 g in 350 μl of $CDCl_3$) δ 6.23, q (J = 7 Hz) further split into a doublet (J = 1.0 Hz), 1 H (H_8); 5.8, m, 2 H (H_2, H_3); 3.7, m, 2 H; 2.6, m, 2 H; 1.81, d of d (J = 7, 1.0 Hz), 3 H (CH_3). LIS NMR: sequential addition of a $CDCl_3$ solution of Eu(fod)$_3$[39] and spectral measurements were made as described above for isomer **4**. The results, presented in Table I, give shifts extrapolated to a 1:1 molar ratio of H_8 = 398 Hz, $-CH_3$ = 158 Hz. Taken with the complementary results of the other isomer these assign for adduct **3** the *E* configuration about the exocyclic double bond. Uv 223 nm (log ε 4.10).

Reduction to 5. VPC-purified **3** (0.0297 g, 2.214×10^{-4} mol) took up 12.10 ml of H_2, thus having 2.03 ± 0.1 double bond. A larger sample of 0.40 g was hydrogenated in a Parr apparatus at 50 psi. After removal of the catalyst by suction filtration through sintered glass and concentration by rotary evaporation the residual oil showed by analytical VPC (column B, 135 °C) two components in a ratio of 29.1:70.9. These were isolated by preparative VPC (column A, 130 °C) and had ir and NMR spectra congruent, respectively, with *exo*-**5** and *endo*-**5**, prepared and identified as described below.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.50; H, 7.64.

Reaction of *trans*-2-Butenoyl Chloride with Insufficient Triethylamine. Identification of 7-Vinylbicyclo[3.2.0]hept-2-en-6-one (2) in the Product Mixture. The reaction was carried out as described above except that 13.84 g (0.134 mol) of triethylamine was used, and workup was commenced after 3.0 h. Only 7.4 g (37%) of triethylamine hydrochloride (mp 252–254 °C) was obtained, and distillation afforded 2.5 g (13%) of pale yellow oil, bp 46–50 °C (0.1 mm). VPC (column B, 95 °C) showed evidence of some thermal decomposition (peak coincident with separately injected cyclopentadiene, polymer formation in injector sleeve), but eluted three components in the area ratio (order of elution times) 59.8:1.1:39.1. These corresponded (comparison of retention times) with the second-, third-, and fourth-eluting components, respectively, from the excess triethylamine cycloaddition. All attempts to isolate the major component of this mixture resulted either in irreversible cycloreversion (preparative VPC) or isomerization to **3** and **4** (column, thin layer, and high-pressure liquid chromatography). The identification of the first-eluting component as vinylketene adduct **2** was deduced from the following evidence. Ir: besides bands assigned previously to compound **4** there appeared absorptions at 1770, 1645, 970, and 930 cm^{-1}. NMR ($CDCl_3$): compatible with a 60:40 mixture of **2**:**4**. Subtracting the contributions of **4** the difference spectrum of **2** is δ 6.3, m, 1 H; 5.8, m, 2 H; 5.2, m, 2 H; 3.7, m, 2 H; 2.5, m, 3 H. The splitting pattern in the vinyl region is recognizably that of a $CH{=}CH_2$ moiety, but overlapping signals from minor component **4** preclude exact assignments.

Reduction to 5. The isomeric mixture (0.0513 g, 3.824×10^{-4} mol) absorbed 20.22 ml of H_2, thus indicating 1.96 ± 0.1 double bond. A larger sample of 0.40 g of the mixture was reduced in the Parr apparatus as described for isomers **3** and **4**. Workup provided a yellow oil which had VPC (column B, 135 °C) characteristic of 12.0% *exo*-**5** and 88.0% *endo*-**5**.[44] Ir and NMR spectra of VPC-collected samples (column A, 130 °C) were congruent with those of authentic material, prepared and identified as described below.

Anal. Calcd for $C_9H_{10}O$: C, 80.50; H, 7.51. Found: C, 80.27; H, 7.31.

Pyrolysis. Heating the mixture to 85 °C for 2.5 h resulted in formation of 1,3-cyclopentadiene and disappearance of the NMR signals assigned to adduct **2**. Analysis of VPC (column B, 95 °C) showed, besides cyclopentadiene and its dimer, the five previously observed components in the area ratio (order of elution times) 1.37 (unknown A):1.64 (component **2**):7.61 (component **4**):79.38 (component **3**):10.00 (unknown B).

Isomerization Experiments. A. 2 → 3 + 4. Addition of 2 μl of triethylamine to a $CDCl_3$ solution of 59.8% **2**, 1.1% **4**, and 39.1% **3** after 8 h resulted in the virtual disappearance of **2** as measured by NMR. VPC (column B, 95 °C) showed that the equilibrium mixture had been reached (1.37:1.65:23.70:63.29:10.00). Repetition of the experiment in a dry pentane solution afforded the same equilibrium mixture, but required nearly 7 days at room temperature before stabilization.

B. 3 → 3 + 4. Addition of 2 μl of triethylamine to a $CDCl_3$ solution of VPC-purified **3** resulted after less than 30 min in attainment of equilibrium between **3** and **4** (73:27 by NMR and VPC). Only trace amounts of the other three components were observed.

C. 4 → 3 + 4. Addition of 2 μl of triethylamine to a $CDCl_3$ solution of VPC-purified **4** resulted after less than 30 min in attainment of the **3**:**4** equilibrium (73:27). Again, only trace amounts of the other three components were detected.

Reaction of 3-Butenoyl Chloride with excess Triethylamine. Under anhydrous conditions a solution of 0.51 g (5.02 mmol) of dry triethylamine in 10 ml of low-boiling petroleum ether was added dropwise to a well-stirred mixture of 0.50 g (4.8 mmol) of 3-butenoyl chloride, 1.60 g (24.3 mmol) of freshly dedimerized 1,3-cyclopentadiene, and 50 ml of petroleum ether. A heavy, flocculent white solid

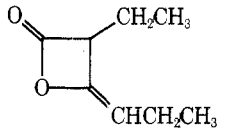
was formed immediately. Stirring was continued for 1.5 h, and then the mixture allowed to stand at room temperature for 7 days. VPC analysis (column B, 95 °C) of the supernatant liquid showed the five product components previously observed, in the area ratio (order of elution times) 1.38:1.62:23.71:63.29:10.00, and was virtually superimposable with that obtained from the analogous reaction of *trans*-2-butenoyl chloride with excess triethylamine.

Suction filtration provided 0.52 g (79%) of triethylamine hydrochloride (mp 251–255 °C). The filtrate was washed with water, dried over $MgSO_4$, and concentrated to an orange oil. Distillation in vacuo afforded 0.17 g (27%) of yellow oil, bp 46–55 °C (0.1 mm). Analysis by VPC showed no significant change in the area ratios of the five components due to fractionation during distillation.

Reaction of 3-Butenoyl Chloride with Insufficient Triethylamine. The reaction was carried out as described above except that 0.46 g (4.54 mmol) of triethylamine was used, and workup begun after 3.0 h. Filtration gave 0.45 g (68%) of triethylamine hydrochloride (mp 253–256 °C), and VPC analysis of the filtrate (column B, 95 °C) showed components **2**:**3**:**4** to be present in the area ratio 59.7:1.2:39.1. Concentration and distillation afforded 0.14 g (22%) of yellow oil, bp 45–55 °C (0.1 mm).

Preparation of 7-Ethylbicyclo[3.2.0]hept-2-en-6-one (6). Under anhydrous conditions a solution of 11.98 g (0.118 mol) of dry triethylamine was added dropwise to a well-stirred mixture of 11.30 g (0.106 mol) of butanoyl chloride, 19.44 g (0.294 mol) of freshly dedimerized cyclopentadiene, and 100 ml of dry benzene. There was immediate formation of a white precipitate, and the solution turned very dark. Addition required 20 min and stirring was continued for another 2.0 h. The reaction mixture was then allowed to stand for 42 h at room temperature.

Suction filtration afforded 14.75 g (100%) of triethylamine hydrochloride (mp 254–256 °C). The filtrate was concentrated by rotary evaporation to 14.20 g of dark oil, which was distilled in vacuo to provide 9.28 g (64%) of pale yellow oil, bp 30–145 °C (20 mm). The material was chromatographed on 34 g of silica gel using hexanes as eluent to remove 3.7 g of dicyclopentadiene. The remaining material was shown by VPC (column B, 135 °C) to be composed of three components in area ratio (order of elution times) 70.0:0.9:29.1. The first and third components were isolated by preparative VPC (column A, 130 °C) in >98% purity (checked by reinjection on column B) and assigned structures, respectively, as ethylketene β-lactone dimer **7**



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and *endo*-7-ethylbicyclo[3.2.0]hept-2-en-6-one (*endo*-**6**) on the basis of the following data.

Ethylketene β-Lactone Dimer (7): ir 2970, 2940, 2880, 1890, 1880, 1850, 1730, 1455, 1290, 1195, 938, 910, 845 cm^{-1}; NMR ($CDCl_3$) δ 4.72, d of t (J = 7.5, 1.5 Hz), 1 H; 3.91, broadened t (J = 7 Hz), 1 H; 2.4–1.6, m, 4 H; 1.06 and 1.03, overlapping triplets (J = 7.5, 7 Hz), 6 H.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.73; H, 8.70.

***endo*-7-Ethylbicyclo[3.2.0]hept-2-en-6-one (*endo*-6):** ir 3050, 2960, 2930, 2870, 1770, 1559, 795, 700 cm^{-1}; NMR ($CDCl_3$) δ 5.82, broad s, 2 H; 2.5, m, 3 H, 2.53, broad s, 2 H; 1.42, m, 2 H; 0.93, t (J = 7 Hz), 3 H ($-CH_3$).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.62; H, 9.07.

***exo*-7-Ethylbicyclo[3.2.0]hept-2-en-6-one (*exo*-6).** To a solution of 100.3 mg of VPC-purified *endo*-**6** in 10 drops of methanol was added 4 drops of 0.4 M sodium hydroxide in methanol. VPC analysis (column B, 100 °C) showed that after 2 days equilibration had occurred to form a 37.18:62.82 mixture of the second-eluting component from the cycloaddition described above and *endo*-**6**. The yellow solution was taken up in 8 ml of ether, washed with two 1-ml portions of water, dried over sodium sulfate, transferred by pipet, and concentrated by flash distillation to leave a cloudy, colorless oil, 99.3 mg. The minor, first-eluting component was isolated by preparative VPC (column A, 112 °C) and identified as *exo*-7-ethylbicyclo[3.2.0]hept-2-en-6-one (*exo*-**6**) from its method of preparation and on the basis of the following properties: ir 3070, 2980, 2945, 2890, 2865, 1780, 1603, 740, 720 cm^{-1}; NMR ($CDCl_3$) δ 5.77, broadened s, 2 H; 3.7, m, 1 H; 3.2, m, 1 H; 3.0–2.3, m, 3 H; 1.62, q (J = 6.5 Hz), 2 H; 1.00, t (J = 6.5 Hz), 3 H.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.08; H, 8.83.

***endo*-7-Ethylbicyclo[3.2.0]heptan-6-one (*endo*-5).** A mixture of 1.50 g of partially isomerized **6** (5% exo, 95% endo) was dissolved in 100 ml of 95% ethanol and hydrogenated in a Parr apparatus over 10% Pd/C at 45 psi. After 4.0 h a 0.8-psi pressure drop had occurred (ca. 1 molar equiv with this apparatus) and 1.51 g of yellow oil was isolated by suction filtration and rotary evaporation. VPC analysis (column B, 135 °C) showed two components in the area ratio (order of elution) 5:95. The larger, second-eluting component was isolated by preparative VPC (column A, 135 °C) and identified as *endo*-**5**: ir 2960, 2860, 1780 cm^{-1}; NMR ($CDCl_3$) δ 3.45, m, 1 H; 3.02, m, 2 H; 1.02–2.22, m, 8 H; 0.90, t (J = 6.5 Hz), 3 H.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.09; H, 10.11.

***exo*-7-Ethylbicyclo[3.2.0]heptan-6-one (*exo*-5).** To a solution of 95.0 mg of VPC-purified *endo*-**5** in 0.5 ml of methanol was added 5 drops of 0.4 M sodium hydroxide in methanol. After 4.0 h VPC analysis (column A, 135 °C) showed two components in the area ratio (order of elution times) 71.6:28.4. The latter component corresponded in retention time to reactant *endo*-**5**. The mixture was taken up in 5 ml of ether, washed with two 1-ml portions of water, dried over sodium sulfate, transferred by pipet, and concentrated by flash distillation to provide 85.0 mg of clear, colorless oil. The first-eluting, major component was isolated by preparative VPC (column A, 112 °C) and identified as *exo*-**5** from its method of preparation and on the basis of the following properties: ir 2955, 2865, 1770 cm^{-1}; NMR ($CDCl_3$) δ 3.42, broad s, 1 H; 2.52, m, 2 H; 2.4–1.3, m, 8 H; 0.98, t (J = 6.5 Hz), 3 H.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.49; H, 10.37.

Registry No.—**1**, 50888-73-8; **2**, 59796-68-8; **3**, 59796-69-9; **4**, 59796-70-2; *exo*-**5**, 54276-01-6; *endo*-**5**, 54235-96-0; *exo*-**6**, 54275-98-8; *endo*-**6**, 25975-87-5; **7**, 5659-15-4; *trans*-2-butenoyl chloride, 33603-82-6; 1,3-cyclopentadiene, 542-92-7; triethylamine hydrochloride, 554-68-7; 3-butenoyl chloride, 1470-91-3; butanoyl chloride, 141-75-3.

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(2) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, the University of New Mexico Research Allocations Committee, and the Vassar College Beadle Fund for the support of this research.
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Metalation Reactions. 18. Polymetalation Substituted Acetophenones

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The lithium enolates of methyl-substituted acetophenones are metalated further by butyllithium in the presence of TMEDA to di- and trilithium derivatives. The sequence of preferential proton abstraction is *o*-methyl > *o*-H > *p*-methyl > *m*-methyl. A second proton can also be abstracted from the carbon α to the carbonyl group. The compound dilithiated α to the carbonyl undergoes a lithium oxide elimination to yield an acetylene. Abstraction of two protons from two *o*-methyl groups, or from one *o*- and one *p*-methyl groups, or from one *o*-methyl group and the α-methylene group, was also observed. The directive effects in these metalations are discussed in terms of charge alternation.

A preferential proton abstraction by base in hexamethylphosphoric triamide from the *p*-methyl group in 4-methylacetophenone (I) was reported by Dubois.[1] On the other hand, abstraction of two protons from the methyl α to the carbonyl in 2,4,6-trimethylacetophenone (II) by butyllithium was claimed.[2] This last result was not entirely reliable, since it was proved only by the production of III, which contained two deuterium atoms in the acetyl group, as confirmed by the NMR spectrum. However, the second proton could have been exchanged during the deuteration.

Our interest in polymetalation[3] has prompted us to investigate the possibility of polymetalation of the substituted acetophenones. Several other ketones such as acetophenone (IV), 2- (V) and 3-methylacetophenone (VI) were studied in addition to I and II.

In order to avoid the attack of butyllithium on the carbonyl group, it was necessary (except in the case of 2,4,6-trimethylacetophenone, that was hindered enough to avoid addition of butyllithium to the carbonyl group) to carry out the abstraction of the first proton with a different base to form the enolate. The following procedure was adopted. The enolates, obtained by the action of sodium hydride or lithium diisopropylamide on the ketones, were converted into trimethylsilyl enol ethers. Addition of 1 equiv of butyllithium to a solution of these o ethers transformed them into lithium enolates.[4] Further metalation of these enolates was performed by an excess of butyllithium in the presence of TMEDA.

Results

Metalation of II with butyllithium in hexane–TMEDA and subsequent treatment with trimethylchlorosilane yielded the disilyl (VIIb) and two trisilyl (VIIIb and IXb) derivatives, that are the products of the reaction of the dilithium (VIIa) and the trilithium (VIIIa and IXa) intermediates. Hydrolysis of these derivatives gave the corresponding ketones Xb, XIb, and XIIb.

The metalation of II in ether made it possible to follow by NMR the transformation of II into XIIIa and, after the addition of TMEDA, the further lithiation to VIIa. In the first stage the signals of XIIIa appeared: aromatic at 6.63 (s), $=CH_2$ at 3.9 (s, 1 H) (the second vinylic proton was hidden by ether), the *o*-methyls at 2.24 (s), and the *p*-methyl at 2.07 ppm (s). These signals disappeared on further metalation, giveing place to two aromatic signals at 5.37 (s) for the proton para and at 59.97 ppm ortho to the CH_2Li. Meta coupling was observed by broadening of the singlets. The intensity of the *o*-methyls singlet was reduced and a new singlet for the CH_2Li appeared at 1.84 ppm. (s). Silylation of the ether solution led to VIIb. Similar results were obtained in THF (without TMEDA), but with an additional minor product XIVb formed by metalation of the *p*-methyl and subsequent silylation and hydrolysis of the enol ether.

The appearance of two aromatic signals in the product of dimetalation proved its structure VIIa, since ring metalation or at the *p*-methyl would have led to a product showing one aromatic signal only. Quenching of the enolate XIIIa with D_2O in our hands led to a mixture of mono-, di-, tri-, and undeuterated products in the α-methyl group as shown by he M^+ peaks obtained in the mass spectrum. In our conditions, the reported[2] dideuterated II was not the product of dimetalation, but an artifact of exchange.

Preferential ring metalation at the position ortho to the enolate group was obtained on metalation of XVb in hexane–TMEDA. Treatment of the product of metalation with trimethylchlorosilane yielded preponderantly XVIb and two products of dimetalation, XVIIb (9%) and XVIIIb (10%). A small amount of an unidentified product was also formed.

The metalation at the ortho position was proved by the NMR of the ketone, product of deuterolysis of the metalated mixture. Instead of the A_2B_2 pattern of the aromatic protons in I, there appeared one proton only at the ortho position in this product. Metalation of XVb with butyllithium in THF