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THE JOURNAL OF Organic Chemistry®

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1A

INTRODUCTION TO ORGANIC CHEMISTRY

by **Andrew Streitwieser, Jr.,** and **Clayton H. Heathcock,** both, University of California, Berkeley

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To achieve optimal teaching goals, the authors have departed somewhat from traditional organizational techniques by *diffusing theory, reaction mechanisms, and spectroscopy* throughout the text. The text begins with alkanes because they form the basis of nomenclature, and proceeds to halides, displacement reactions, alcohols, alkenes, alkynes, and carbonyl groups. After these important functional groups have been discussed, conjugated systems are treated; discussions of ring compounds and their conformations reinforce important reactions, and lead to an examination of glycols and hydroxy-carbonyl compounds as well as the cyclic chemistry of epoxides, hemiacetals, and lactones. This organization leads in a natural way to carbohydrates, which are followed by condensation reactions, amines, amino acids, proteins, aromatic chemistry, and heterocycles. The final chapters briefly survey additional topics, such as pericyclic reactions, and conclude with an examination of chemical literature.

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FEBRUARY 20, 1976

Stereochemistry, Conformations, and Carbon-13 Nuclear Magnetic Resonance Spectra of 9-Phenyl-9-phosphabicyclo[3.3.1]nonane Derivatives

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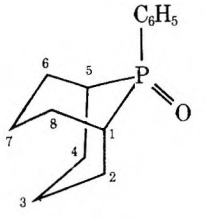
Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48104

Received July 8, 1975

Reaction of phenylphosphine with cycloocta-2,7-dienone followed by oxidation produces the syn (3) and anti (5) isomers of 9-phenyl-9-phosphabicyclo[3.3.1]nonan-3-one 9-oxide. Sodium borohydride reduction of 3 and 5 produces syn-endo alcohol 6 and anti alcohol 7, respectively. Reaction of 6 and 7 with concentrated hydrobromic acid gives syn and anti olefins 8 and 9. In a reaction with sulfuric acid, syn alcohol 6 is converted to anti olefin 9. Both 8 and 9 are reduced to 9-phenyl-9-phosphabicyclo[3.3.1]nonane 9-oxide (1) by catalytic hydrogenation. Stereochemical assignments for 8 and 9 (and the other compounds reported) are made based on (1) faster rate of catalytic hydrogenation of 8 over 9, (2) greater thermodynamic stability of 9 than 8 and (3) ^{13}C NMR spectra. Alcohol 6 is shown to have a chair–boat conformation which avoids interaction of the endo 3-hydroxyl group with carbon 7. The dependence of vicinal (three-bond) ^{13}C–^{31}P coupling constants upon dihedral angle is discussed.

Until recently polycyclic compounds containing phosphorus as a bridging[1] or a bridgehead[2] atom were rather uncommon. In connection with other studies we required 9-phenyl-9-phosphabicyclo[3.3.1]nonane 9-oxide (1). During the course of the synthesis of bridged phosphine oxide 1 we discovered some interesting chemistry pertaining to the stereochemistry about the phosphorus atom in various derivatives. In this report we describe some of our results and the stereochemical assignments in the 9-phosphabicyclo[3.3.1]nonane system.

Kashman and Benary have reported that treatment of cycloocta-2,7-dienone[3] with phenylphosphine gives the phosphinone 2.[4] The stereochemistry at the phosphorus atom was inferred from the similarity of the proton NMR spectra of phosphinone oxides 3 and 4,[5] the configuration of the latter having been established by an x-ray analysis.[6] We have confirmed the stereochemical assignment of 3, and we have isolated and characterized its isomer 5.



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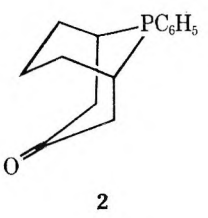

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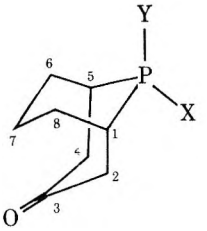
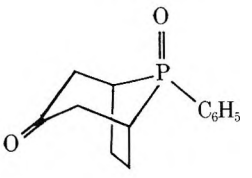


3, X = O; Y = C_6H_5
5, X = C_6H_5; Y = O



4

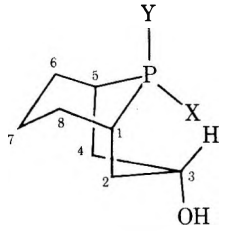
Results and Discussion

Synthesis and Chemistry. We utilized the double Michael addition procedure of Kashman[4] with the following results. Treatment of cycloocta-2,7-dienone[3] with 1 equiv of phenylphosphine afforded a white solid which was not purified, but oxidized directly with hydrogen peroxide. The oxidation product was shown to be a mixture of isomeric phosphine oxides 3 and 5 which could be separated by fractional crystallization. The first isomer to crystallize was the syn phosphinone oxide 3; the mother liquor contained mostly the anti isomer 5. Each isomer was purified by a subsequent recrystallization. The combined yield of purified 3 and 5 was approximately 50%, and the ratio of 3 to 5 was about 1:1.7. The infrared spectra of phosphinone oxides 3 and 5 are virtually identical, each displaying strong absorption bands at 1700 and 1160 cm^{-1} for the carbonyl and phosphonyl chromophores, respectively. The proton NMR spectra, however, are quite different. The NMR spectrum of 3 correlated well with the tabulated data of Kashman and Benary;[4] 5 has not been described previously. The melting point reported[4] for the syn isomer 3 is 250°, with decomposition. We found that 3 melts at 305–306°, with decomposition, and that 5 has a melting point of 201.5–204°. Because of the large discrepancy in the melting points found for 3, additional information was sought to support the structural assignments. Mass spectrometry and

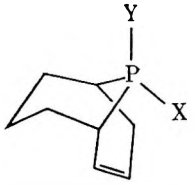
correct combustion analyses showed that **3** and **5** are isomeric and monomeric. The small ranges observed in the melting points of **3** and **5** indicated that they were isomerically pure, and the purity of each was substantiated by its ^{13}C NMR spectrum. Each spectrum was uncontaminated by signals from the other isomer. Furthermore, the gross structures of **3** and **5** were confirmed, since each spectrum displayed five signals for the five different types of nonaromatic carbon atoms in the 9-phosphabicyclo[3.3.1]nonan-3-one ring system. In addition, the ^{13}C NMR spectra indicated the syn and anti relationships of the phosphonyl and carbonyl oxygen atoms (see below).

The syn phosphinone oxide **3** and the anti phosphinone oxide **5** were each converted into the corresponding endo alcohols **6** and **7** by reduction with sodium borohydride in yields of 91 and 95%, respectively. Alternatively, the crude mixture of **3** and **5** was reduced, and the alcohols **6** and **7** were separated by fractional crystallization.

Ketones **3** and **5** should have double chair conformations and should be attacked by borohydride on the exo face. Therefore, alcohols **6** and **7** are assigned the endo configuration. The endo configuration of alcohol **6** was verified by ^{13}C NMR spectroscopy (see below). We were unable to obtain a ^{13}C NMR spectrum of **7** because it was not sufficiently soluble in the common organic solvents.



6, X = O; Y = C_6H_5
7, X = C_6H_5; Y = O

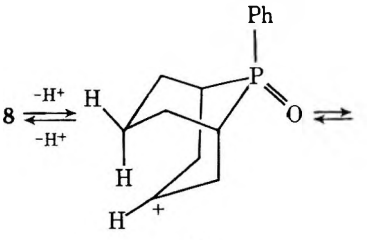


8, X = O; Y = C_6H_5
9, X = C_6H_5; Y = O

Alcohols **6** and **7** were dehydrated to olefins **8** and **9** in yields of 88 and 77%, respectively, by treatment with refluxing concentrated hydrobromic acid. The olefins **8** and **9** provided a chemical basis for the assignment of the syn and anti configurations at the phosphorus atom of all of the phosphine oxides prepared in the study. During attempts to convert **8** and **9** into 9-phenyl-9-phosphabicyclo-[3.3.1]nonane 9-oxide (**1**) by catalytic reduction at 1 atm using a platinum catalyst, one of the olefins was reduced only partially (about 50%) after 18 h, while the other alkene took up the theoretical volume of hydrogen by the end of 1 h. The *less* reactive isomer was assigned the anti structure **9**, since it should be somewhat resistant to hydrogenation owing to the steric bulk of the phenyl group which inhibits effective adsorption of the substrate onto the catalyst. Isomer **8** is not so hindered[7] and undergoes hydrogenation readily. The product of the reduction of **8** and **9** was phosphine oxide **1**. Subsequent experiments showed that the olefin **9** was quantitatively converted into **1** when the reduction was conducted at 4 atm pressure. Having determined the stereochemical configurations of the phosphorus substituents for the alkenes **8** and **9**, the configurations of the alcohols **6** and **7** and the ketones **3** and **5** are also established.

An interesting and useful result was observed during the scale-up of the synthesis of **1**. In the dehydration step, 57% sulfuric acid was substituted for the concentrated hydrobromic acid employed previously. As expected, alcohol **7** gave olefin **9**, but **6** also afforded olefin **9** in good yield. Evidently, olefin **9** must be more stable than **8** since **8** is converted into **9** under the reaction conditions. Inspection of molecular models reveals that **9** should be more stable than **8**. In the case of **8**, where the phenyl group is anti to the carbon double bond, the ortho hydrogens of the phenyl ring interact strongly with the axial hydrogens at carbons 6 and 8.[8] In olefin **9**, these interactions are diminished by removal of one of the hydrogens and flattening of the unsaturated bridge syn to the phenyl group. Thus, the dehydration experiment provides additional support for the configurational assignments made above.

The conversion of **8** into **9** could occur by either or both of the following pathways. Transannular hydride shifts are



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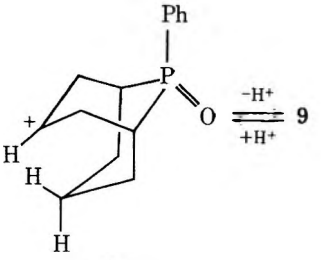
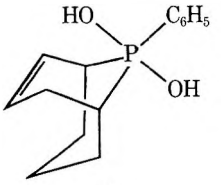


11

common in medium-sized rings[9] and have been observed to occur between the 3 and 7 positions of bicyclo[3.3.1]nonane derivatives.[10] Accordingly, such a shift, interconverting ions **10** and **11**, would account for the net transformation of **8** into **9**. Alternatively, the formation of **8** from **9** may be explained as an acid-catalyzed epimerization of the phosphorus atom via the pentacoordinate intermediate **12**. Wetzel and Kenyon[2b] have studied the acid-catalyzed oxygen exchange of phosphine oxides, including **13**. The rate con-



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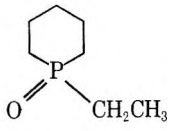

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stant[2b] for oxygen exchange of **13** in approximately 57% sulfuric acid is nearly large enough to account for the epimerization of the phosphorus atom of **8**, assuming that **8** would react at the same rate as **13**.

Finally, we briefly comment on the reaction of phosphine oxide **1** with methyllithium. The reaction was quenched with methyl iodide, and the ethyl derivative **14** was obtained in 77% yield. The mechanism depicted in Scheme I is proposed to account for this result. Such a mechanism is in accord with the results of Seyferth and co-workers.[11] A similar intermediate was invoked by Turnblom and Katz[1] with phenylphosphahomocubane oxide, phenylphosphahomocuneane oxide, and other phosphine oxides.

^{13}C NMR Spectra. Chemical Shifts. ^{13}C NMR spectroscopy provides additional evidence for the stereochemical assignments in the previous section. Table I records chemical shift data for the phosphine oxides **1**, **3**, **5**, and **6**; Table II contains ^{31}P–^{13}C coupling constants for these compounds. Assignments of shielding values (downfield from internal Me_4Si) of the wide-band proton noise de-

Table I
Chemical Shifts of 9-Phenyl-9-phosphabicyclo[3.3.1]nonane 9-Oxides

Compd	Aliphatic carbons[a]					Aromatic carbons			
	C-1	C-2	C-3	C-6	C-7	α	o	m	p
1	28.5	26.3	21.6	29.7	20.9	(130.5)[b]	129.6	128.9	131.4
3	30.8	42.8	208.3	29.1	17.1	(128.3)[c]	130.0	129.4	132.4
5	29.3	44.9	207.0	27.0	18.2	129.7	129.7	128.9	132.5
6	27.6	34.5	61.4	30.8	15.6	130.2	129.8	129.1	131.6

[a] See structural formulas for numbering of carbon atoms. [b] The α carbon resonates as a doublet due to coupling with phosphorus, but one of the peaks is obscured by the other aromatic signals. The value cited was calculated from the visible peak (132.3 ppm) assuming a P—C coupling constant of 96 Hz (Table II). [c] As in footnote *b*; the visible peak occurs at 126.4 ppm.

Scheme I

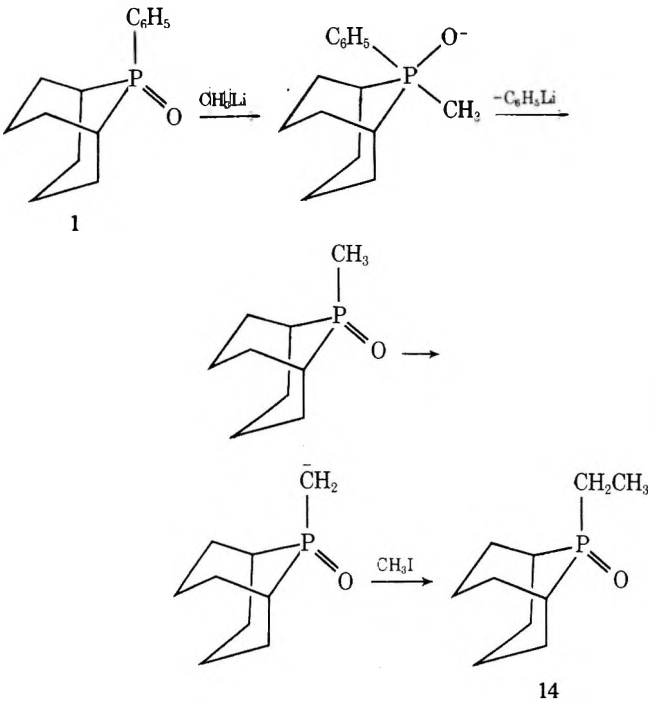


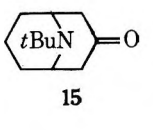
Table II
$^{31}P-^{13}C$ Coupling Constants of
9-Phenyl-9-phosphabicyclo[3.3.1]nonane 9-Oxides

Compd	C-1	C-3	C-7	α	o	m
1	60	8	6	*a*	8	10
3	62	7		*a*	9	12
5	62	7		95	*a*	*a*
6	63	20	7	96	9	12

[a] The coupling constant of phosphorus was obscured by the other aromatic resonance signals.

coupled spectra of ketones **3** and **5** were made as follows. The carbonyl carbons and those adjacent to the carbonyl group are readily recognized because of their characteristic shielding regions.[12] The bridgehead carbon signals are also easily discerned owing to the relatively large phosphorus–carbon coupling constants.[2a] Carbons 6(8) and 7 are assigned on the basis of relative peak heights and similar chemical shifts for other bicyclo[3.3.1]nonane compounds.[13] The aromatic carbons were assigned based upon the results of Gray and Cremer.[14] A particularly informative feature of the spectra of ketones **3** and **5** is the deshielding of carbons 2(4) and 6(8) when they are syn to the phenyl group. We have previously demonstrated that steric interactions between a methyl carbon and carbons 2(4) and 6(8) of 9-*tert*-butyl-9-azabicyclo[3.3.1]nonan-3-one (**15**) result in carbons 2(4) and 6(8) being deshielded by approximately 3 ppm.[15] In the case of the 3-keto phosphine oxides **3** and **5**, the ortho carbons of the phenyl groups interact sterically with the carbons 2 and 4 or 6 and 8 when they are in a syn relationship.[8] Thus, isomer **3** should have carbons 6 and 8 more deshielded than the corresponding carbons of **5**; and ketone **5** should have its carbons 2 and 4 more downfield than those of **3**. The δ steric shift is 2.1 ppm in each instance, and is in good agreement with our earlier observations[15] and those of others.[16] Coupling constants between the bridgehead protons and phosphorus atoms were found to be 18 Hz for both **3** and **5**. The coupling constants were determined after exchanging the protons adjacent to the carbonyl group for deuterium in order to simplify the spectra.

The carbons of alcohol **6** were assigned in the same manner as used with ketones **3** and **5**. Unfortunately, alcohol **7** was not sufficiently soluble in common organic solvents to permit obtaining its spectrum. The spectrum of **6** did allow us to assign unequivocally the endo configuration of the C-3 hydroxy group. We have shown by direct comparison of the ^{13}C NMR spectra of the *exo*- and *endo*-3-hydroxy-9-methyl-9-azabicyclo[3.3.1]nonanes (**16** and **17**) that in the endo isomer carbon atom 7 resonates at a rather high field (14.5 ppm) as a result of the gauche interactions brought about by the chair–boat conformation **18**,[15] which predominates over the chair–chair conformation in order to relieve transannular steric interactions.[17] Since carbon 7 of alcohol **6** is also quite shielded (15.6 ppm), we conclude that the C-3 hydroxy group is situated endo and that the predominant conformation of **6** in solution is the chair–boat.



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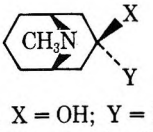
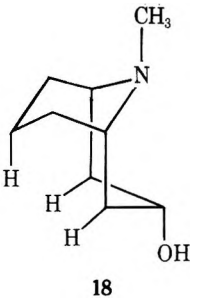


16, X = OH; Y = H
17, X = H; Y = OH



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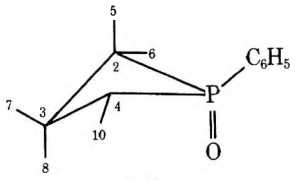
The carbon-13 chemical shifts of phosphine oxide **1** were assigned as follows. The bridgehead carbons were again readily assigned as a result of the large $^{31}P-^{13}C$ coupling constants. The remaining two most downfield aliphatic signals are attributed to carbons 2(4) and 6(8) based on the shieldings of ketones **3** and **5**. The most downfield signal is assigned to carbon 6(8) since it experiences the same steric interactions with the ortho carbons of the syn phenyl group that were observed with the ketones **3** and **5**. The two upfield signals are due to carbons 3 and 7. Based on the chemical shifts of carbons 7 for ketones **3** and **5**, the most shielded resonance of **1** is assigned to carbon 7.

Vicinal ^{13}C–^{31}P Coupling Constants. A large body of data exists on ^{13}C–^{31}P coupling constants,[12,14] but there are few examples where the angular dependence of the three-bond (vicinal) ^{13}C–^{31}P coupling constant has been examined in compounds with rigid and predictable geometries.[2a,14] Wetzel and Kenyon[2a] have pointed out that these coupling constants can be expected to show a dependence on dihedral angle similar to that observed in proton–proton[18] and ^{13}C–^{13}C vicinal coupling.[19] The ^{13}C–^{31}P coupling constant should be maximal when the dihedral angle formed by the bonds connecting the atoms is 0 or 180° and should be minimal when the dihedral angle is near 90°.

Gray and Cremer[14] have recorded the ^{13}C NMR spectra of an extensive series of polymethylphosphetane oxides, sulfides, and salts. Among these 1-phenyl-2,2,3,3,4-pentamethylphosphetane 1-oxide (**19**) is of interest because it



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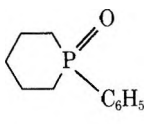

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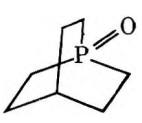
has a preferred conformation with C_7 equatorial and C_8 axial. The dihedral angle between the planes P–C_2–C_3 and C_2–C_3–C_7 is near 150° while the dihedral angle between planes P–C_2–C_3 and C_2–C_3–C_8 is near 100°. The ^{13}C–^{31}P coupling constants for C_7 and C_8 are 24.9 and 1.6 Hz, respectively. Six other pentamethylphosphetane oxides and salts differing in substituents on phosphorus show similar coupling constants of phosphorous to C_7 and C_8. In several other compounds which have greater conformational mobility the coupling constants for C_7 and/or C_8 are near an average value of 14–15 Hz.[14] Conformationally mobile phosphonium salts also have vicinal ^{13}C–^{31}P coupling constants of 12–15 Hz.[12] Compound **20** has a coupling constant of C_4 to P of 6.8 Hz;[14] the relevant dihedral angle along the C_2–C_3 bond is about 60°.

Bicyclic phosphine oxides **21** and **22**[2a] have unusually high coupling constants between the bridgehead carbon and phosphorus atoms of 47 and 35 Hz, respectively. These



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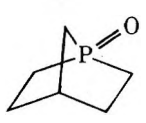

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rigid ring systems have fixed geometries with the dihedral angles of 0° along the C_2–C_3 bond. Each compound has three coupling paths linking the bridgehead atoms, two three-bond paths for **21** and two three-bond paths plus a two-bond path for **22**.[2a]

The three-bond ^{13}C–^{31}P coupling constants shown in Table II support the assignment of a chair–boat conformation for compound **6**. In compounds **1**, **3**, and **5**, which have double-chair conformations, the dihedral angle between the P–C_1–C_2 and C_1–C_2–C_3 planes is about 60°. In these compounds the three-bond ^{13}C–^{31}P coupling constants are 6–8 Hz, similar to that of **20**. In compound **6**, the relevant dihedral angle is close to 0° and the coupling constant is 20 Hz. Significantly, the coupling constant between C_7 and phosphorus in compound **6** is 7 Hz, showing that the unsubstituted ring remains in the chair form.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained on a Varian Associates T-60 instrument; ^{13}C magnetic resonance spectra were obtained on a JEOL JNM PS-100 spectrometer interfaced with a Digilab Nova 1200 computer. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Mass spectra were obtained on an Associated Electrical Industries MS-902. Vapor phase chromatographic analyses and collections were performed on a Varian Aerograph Model 90-P instrument. Elemental analyses were carried out by Spang Microanalytical Laboratory.

Unless specified otherwise, spectral data were obtained as follows: NMR, solutions in deuteriochloroform (units in parts per million downfield from internal Me_4Si); ir, solutions in chloroform (units in cm^{-1}); MS, 70 eV.

9-Phenyl-9-phosphabicyclo[3.3.1]nonane 9-Oxide (1). A mixture of alkenes **8** and **9** (6.96 g, 30.0 mmol) in 300 ml of methanol was hydrogenated over platinum (557 mg of PtO_2) at room temperature under 4 atm pressure on a Parr 22 apparatus. After 1 h the required amount of hydrogen had been taken up. The mixture was filtered through Celite and concentrated to afford 6.46 g (92%) of **1**, which was purified by crystallization (benzene–cyclohexane) and sublimination (175–178°, 0.015 Torr): mp 181–183°; ir, 3050, 1590, 1150, 1115 cm^{-1}; NMR 7.83–7.35 (5 H), 3.0–1.2 ppm (14 H).

Anal. Calcd for $C_{14}H_{19}OP$: C, 71.78; H, 8.17; P, 13.22. Found: C, 71.60; H, 8.26; P, 13.05.

***syn*-9-Phenyl-9-phosphabicyclo[3.3.1]nonan-3-one 9-Oxide (3) and *anti*-9-Phenyl-9-phosphabicyclo[3.3.1]nonan-3-one 9-Oxide (5).** The procedure of Kashman and Benary was used.[4] An equimolar solution of cycloocta-2,7-dienone[3] and phenylphosphine was heated under nitrogen at ~135° until the infrared spectrum showed the complete disappearance of the dienone carbonyl band. The reaction mixture was then cooled to room temperature, taken up in chloroform, cooled in an ice–water bath, and oxidized by the dropwise addition of excess aqueous 30% hydrogen peroxide solution. After stirring for an additional 3 h, the layers were separated; the aqueous layer was extracted with chloroform. The combined organic layers were washed once with half-saturated aqueous sodium bisulfite solution, dried (Na_2SO_4), and concentrated to provide a white solid. Crystallization from acetonitrile gave the syn isomer **3**; concentration of the mother liquor gave the anti isomer **5**. The ratio of **3** to **5** was 1:1.7 (one experiment), and the overall yield from the cycloocta-2,7-dienone was 48–59% (three experiments). The syn isomer **3** was purified by recrystallization from acetonitrile–benzene (mp 305–306° dec): ir 1700, 1590, 1160, 1115 cm^{-1}, NMR 8.0–7.3 (5 H), 3.8–1.3 ppm (12 H).

Anal. Calcd for $C_{14}H_{17}O_2P$: C, 67.73; H, 6.90; P, 12.48. Found: C, 67.74; H, 6.96; P, 12.36.

The anti isomer **5** was recrystallized from benzene–cyclohexane (mp 201.5–204°): ir 1700, 1590, 1160, 1120 cm^{-1}; NMR 8.0–7.3 (5 H), 3.2–1.4 ppm (12 H).

Anal. Calcd for $C_{14}H_{17}O_2P$: C, 67.73; H, 6.90; P, 12.48. Found: C, 67.85; H, 7.01; P, 12.47.

***syn*-2,2,4,4-Tetradeuterio-9-phenyl-9-phosphabicyclo-[3.3.1]nonan-3-one 9-Oxide (3-d_4).** A solution of 565 mg (2.3 mmol) of **3** in 20 ml of NaOD–D_2O solution (prepared from 20 ml of D_2O and 200 mg of Na) was heated on a steam bath under nitrogen for 6 h. After cooling, the aqueous solution was extracted with methylene chloride; the combined extracts were dried (Na_2SO_4) and concentrated to give 415 mg (74%) of **3**-d_4 (mp 290–293° dec). NMR indicated 96% exchange; ir 1700 cm^{-1}; NMR 2.88 (d, J_{P-H} = 18 Hz, 2 H), 2.3–1.3 ppm (6 H); MS *m/e* 254.

***anti*-2,2,4,4-Tetradeuterio-9-phenyl-9-phosphabicyclo-[3.3.1]nonan-3-one 9-Oxide (5-d_4).** The above procedure was used to prepare **5**-d_4 (mp 203–206° dec) in 96% yield. NMR indicated 96% exchange; ir 1695 cm^{-1}; NMR 3.1–1.4 ppm (8 H); MS *m/e* 254.

***endo*-3-Hydroxy-*syn*-9-phenyl-9-phosphabicyclo[3.3.1]nonane 9-Oxide (6) and *endo*-3-Hydroxy-*anti*-9-phenyl-9-phosphabicyclo[3.3.1]nonane 9-Oxide (7).** To a methanolic solution of the crude mixture of **3** and **5**, cooled in an ice–water bath, was added, in portions, an equal weight of sodium borohydride. After stirring for about 10 h, the reaction mixture was processed by extraction with methylene chloride, drying over sodium sulfate, and concentration to provide an 85% yield (two experiments) of a mixture of **6** and **7**. Crystallization of the crude mixture from methanol–ethyl acetate provided the anti isomer **7**; concentration of the mother liquor gave the syn isomer **6**. The anti isomer **7** was recrystallized from methanol–ethyl acetate (mp 303–306° dec): ir (KBr) 3250, 1140, 1100 cm^{-1}; NMR (TFA) 8.2–7.6 (5 H), 4.2–1.6 ppm (13 H).

Anal. Calcd for $C_{14}H_{19}O_2P$: C, 67.19; H, 7.65; P, 12.38. Found: C, 67.30; H, 7.74; P, 12.42.

The syn isomer **6** was purified by recrystallization from acetonitrile (mp 198–201°): ir (KBr) 3350, 1150, 1110 cm^{-1}; NMR (TFA) 8.1–7.6 (5 H), 5.3–4.7 (1 H), 3.6–1.4 ppm (12 H).

Anal. Calcd for $C_{14}H_{19}O_2P$: C, 67.19; H, 7.65; P, 12.38. Found: C, 67.36; H, 7.59; P, 12.21.

In separate experiments pure **3** was reduced to **6** (91% yield) and pure **5** was reduced to **7** (95% yield).

***syn*-9-Phenyl-9-phosphabicyclo[3.3.1]non-2-ene 9-Oxide (8).** A solution of 1.18 g (4.75 mmol) of syn-endo hydroxy oxide **6** in 60 ml of concentrated hydrobromic acid was refluxed for 6 h, then allowed to cool to room temperature overnight, cooled in an ice–salt bath, and basicified with 25% aqueous sodium hydroxide. The resulting solution was extracted with methylene chloride and the combined extracts were dried (Na_2SO_4) and concentrated to provide 0.96 g (88%) of **8** (mp 160–163°): ir 1640, 1590, 1160, 1120 cm^{-1}; NMR 8.0–7.3 (5 H), 6.4–5.3 (2 H), 3.4–1.2 ppm (10 H).

Anal. Calcd for $C_{14}H_{17}OP$: C, 72.40; H, 7.38; P, 13.34. Found: C, 72.35; H, 7.47; P, 13.13.

***anti*-9-Phenyl-9-phosphabicyclo[3.3.1]non-2-ene 9-Oxide (9).** The above procedure was employed to provide a 77% yield of **9** (mp 145–148°) from **7**: ir 1640, 1590, 1150, 1120 cm^{-1}; NMR 8.0–7.3 (5 H), 6.4–5.5 (2 H), 3.4–1.1 ppm (10 H).

Anal. Calcd for $C_{14}H_{17}OP$: C, 72.40; H, 7.38; P, 13.34. Found: C, 72.24; H, 7.26.

Dehydration of *endo-syn*-3-Hydroxy-9-phenyl-9-phosphabicyclo[3.3.1]nonane 9-Oxide (6) with Sulfuric Acid. A solution of 10.00 g (0.042 mol) of syn hydroxy phosphine oxide **6** in 57% sulfuric acid (prepared from 120 ml of water and 160 ml of concentrated sulfuric acid) was heated to boiling for 12 hr. The solution was cooled, saturated with sodium chloride, and extracted several times with dichloromethane. The dichloromethane extracts were combined and evaporated to yield 6.55 g (71% yield) of a slightly yellow solid. The NMR spectrum of the solid was identical with that of *anti*-9-phenyl-9-phosphabicyclo[3.3.1]non-2-ene 9-oxide (**9**) (see previous experiment).

In a similar experiment starting with 7.08 g of anti hydroxy phosphine oxide **7**, 4.025 g (61%) of olefin **9** was produced.

The acidic aqueous solutions from both of the above experiments were combined and extracted repeatedly with dichloromethane. Evaporation of the dichloromethane extracts yielded an additional 2.76 g of **9** bringing the combined yields for the two experiments to 84%.

9-Ethyl-9-phosphabicyclo[3.3.1]nonane 9-Oxide (14). To a mixture of 234 mg (1.0 mmol) of phosphine oxide **1** in 10 ml of ether (freshly distilled from lithium aluminum hydride) cooled in an ice bath was added 2 mmol of methyllithium in ether. After 15 min (during which time the solution became yellow), excess methyl iodide was added and the reaction mixture was allowed to warm to room temperature. The mixture was then poured into water, the layers were separated, and the aqueous layer was extracted with methylene chloride. The combined organic phases were dried (Na_2SO_4) and concentrated to give 143 mg of yellow solid material. Preparative VPC (4% SE-30 on Chromosorb G, 3 ft × 0.25 in.) afforded 30 mg of **14** (mp 131–133°): ir 1150 cm^{-1}; NMR 3.0–1.1 ppm; MS *m/e* 186.

Anal. Calcd for $C_{10}H_{19}OP$: C, 64.49; H, 10.28; P, 16.63. Found: C, 64.30; H, 10.28; P, 16.72.

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Registry No.—**1**, 57458-74-9; **3**, 37759-01-6; **3**-d_4, 57495-99-5; **5**, 57458-75-0; **5**-d_4, 57458-76-1; **6**, 37759-02-7; **7**, 57458-77-2; **8**, 57458-78-3; **9**, 57458-79-4; **14**, 57458-80-7.

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Potamogetonin, a New Furanoid Diterpene. Structural Assignment by Carbon-13 and Proton Magnetic Resonance

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Potamogetonin (1), a new furanoid diterpene with a labdane skeleton, has been isolated from seeds of *Potamogeton ferrugineus* Hagstr. The structure of 1 has been assigned on the basis of its spectral characteristics, particularly by nuclear magnetic resonance. The proton and carbon-13 chemical shifts of two related diterpenes of known structure, sciadin (3) and nepetaefuran (4), are correlated with shifts of 1.

We wish to report the isolation and structure of potamogetonin (1), a new member of the growing group of furanoid labdane derivatives.[1] Potamogetonin was isolated from seeds of *Potamogeton ferrugineus* (family Potamogetonaceae).[2] Gas–liquid phase chromatographic (GLC) analysis of the petroleum ether extract of these seeds revealed, in

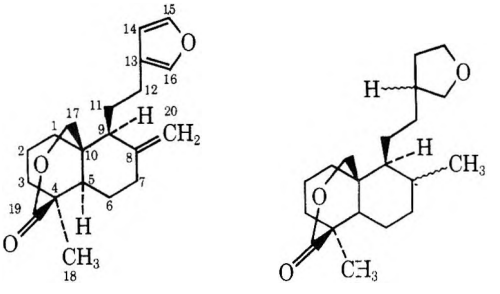
Table I
Selected Proton Chemical Shifts of Potamogetonin, Sciadin, and Nepetaefuran[a]

Protons	Potamogetonin (1)	Sciadin (3)	Nepetaefuran (4)
H-14	6.26, 1 H, dd ($J_{14,15}$ = 1.6, $J_{14,16}$ = 0.9)	6.43, 1 H, dd ($J_{14,15}$ = 1.8, $J_{14,16}$ = 0.9)	6.27, 1 H, dd ($J_{14,15}$ = 1.8, $J_{14,16}$ = 0.9)
H-15	7.33, 1 H, dd ($J_{14,15}$ = $J_{15,16}$ = 1.6)	7.38, 1 H, dd ($J_{14,15}$ = $J_{15,16}$ = 1.8)	7.38, 1 H, dd ($J_{14,15}$ = $J_{15,16}$ = 1.8)
H-16	7.18, 1 H, m	7.47, 1 H, m ($J_{12,16}$ = 0.9)	7.27, 1 H, m
H-17	3.95, 4.15, 2 H, AB q (J = 11)[b]	5.52, d, 1 H (J = 1.3)[c]	4.05, 5.02, 2 H, AB q (J = 12)[d]
H-18	0.87, 3 H, s	1.23, 3 H, s	1.12, 3 H, s
H-20	4.82, 4.94, 2 H, AB q (J = 1)	4.80, 5.05, 2 H, AB q (J = 1)	2.32, 2.70, 2 H, AB q (J = 14)

[a] Spectra were determined in $CDCl_3$. Chemical shifts (δ) are expressed in parts per million from tetramethylsilane and couplings (J) in hertz. Letters following the shifts indicate the multiplicities observed without decoupling. [b] The δ 4.15 doublet shows further splitting (J = 1.8 Hz). [c] Irradiation at δ 1.40 eliminates this coupling. [d] The δ 5.02 doublet shows further splitting (J = 1.7 Hz), decoupled by irradiation at δ 2.15.

addition to the expected triglycerides, 25% of an unfamiliar component (1) which subsequently was isolated by thin layer chromatography (TLC).

Scheme I



1 2

By high-resolution mass spectrometry, the empirical formula of 1 was established as $C_{20}H_{26}O_3$. The ^1H NMR spectrum of 1 indicated the presence of a β-substituted furan group (multiplets at δ 6.22, 7.18, and 7.30),[3] an exocyclic double bond (doublets at δ 4.82 and 4.94),[3] and a tertiary methyl group (singlet at δ 0.87). The uv spectrum exhibited a maximum at 201 nm (ϵ 8329), in accord with a furanoid structure.[3,4] The ir spectrum of 1 had maxima at 895 cm^{-1}, suggestive of an exocyclic double bond, and at 872 cm^{-1}, in harmony with a furan nucleus.[3] This ir spectrum also showed a peak at 1740 cm^{-1}, evidently due to an ester or δ-lactone grouping; no hydroxyl absorption was observed.

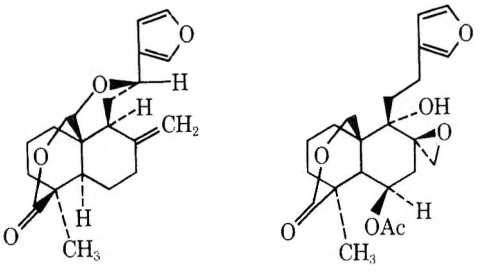
Catalytic hydrogenation of 1 provided a hexahydro derivative (2), $C_{20}H_{32}O_3$, and thus indicated that 1 probably contains three double bonds and four rings. In the ^1H NMR spectrum of 2, resonances at δ 4.82 and 4.94 were replaced by a doublet at δ 0.85, evidently associated with a new methyl substituent formed from the exocyclic methylene group. Low-field resonances attributable to a furan ring disappeared.

One of the three oxygens in 1 is allocated to a furan ring. Another oxygen must be in a carbonyl function; if this is assumed to be an ester or δ-lactone grouping, all three are accounted for. However, treatment with 0.5 M sodium methoxide in methanol followed by isolation under mild conditions left 1 unchanged, as did more rigorous reaction with 4 M potassium hydroxide. The new substance likewise was unaltered under conditions of acid-catalyzed methanolysis.

Additional chemical reactions on potamogetonin were precluded by our limited supply of plant material. However, as a working hypothesis, we adopted formula 1 for the constitution of potamogetonin on the basis of the spectral data and previously observed biogenetic patterns for furanoid labdane derivatives.[1] The apparent resistance of 1 to alkaline hydrolysis seemingly contradicts our proposed structure, since facile relactonization normally would be expected of a γ-lactone but not of a δ-lactone. Nevertheless, the chemistry of some related diterpenoid δ-lactones —derivatives of columbin,[5] nepetaefolin,[6] and nepetaefuran[6] (4)—provides parallels for the behavior of 1. In contrast, sciadin (3) can be saponified and isolated as a free acid;[7] perhaps its ether linkage makes the corresponding free acid relatively stable.

Structure 1 was validated by correlating its ^1H NMR and carbon-13 magnetic resonance (^{13}C NMR) spectra with those of two related furanoid diterpenes, sciadin (3) and nepetaefuran (4), which were selected as model compounds.[6,7] These correlations resulted in assignment of carbon-13 chemical shifts for 3 and 4, which had not been examined by ^{13}C NMR previously.

Scheme II



3 4

The ^1H NMR spectra of all three compounds (Table I) show similar signals for the furanoid protons at C-14, C-15, and C-16 as well as for the C-18 methyl group. The exocyclic methylene group at C-20 gives similar peaks in the spectra of 1 and 3. The AB quartet associated with the C-17 methylene group is comparable for 1 and 4, although one doublet of 1 is shifted downfield by about 1 ppm in 4 by the deshielding effect of the epoxy and 6β-acetoxy groups.

The ^{13}C NMR spectra of 1, 3, and 4 (Table II) provide strong support for both the aromatic and the alicyclic portions of the structure postulated for 1. Thus, for each of the furanoid peaks of 3 and 4, there is a corresponding peak in the spectrum of 1 within approximately 1 ppm. Inspection of the alicyclic portion of 1 suggests that C-1, C-2, and C-3 should have chemical shifts very similar to those of both 3 and 4, while carbons 6, 7, 8, 18, and 20 should have similar shifts in 1 and 3, for these carbon atoms are distant from

Table II
Carbon-13 Chemical Shifts of Potamogetonin, Sciadin, and Nepetaefuran[a]

Carbon	Potamogetonin (1)	Sciadin (3)	Nepetaefuran (4)
1	41.1 t	40.9 t	41.2 t
2	20.9 t	20.8 t	20.5 t
3	25.8 t	25.0 t	25.8 s/t
4	33.5 s	37.8 s	32.6 s
5	49.5 d	45.0 d	46.5 d
6	28.1 t	28.5 t	68.0 d
7	36.1 t	35.6 t	42.1 t
8	145.2 s	145.1 s	*b*
9	51.7 d	48.4 d	74.6 s
10	51.1 s	44.9 s	56.7 s/t
11	23.7 t	33.1 t	32.3
12	37.0 t	69.4 d	39.9 t
13	125.1 s	125.8 s	124.2 s
14	110.0 d	108.8 d	110.6 d
15	142.6 d	143.2 d	143.5 d
16	138.9 d	139.2 d	138.8 d
17	76.4 t	100.4 d	73.5 dd
18	23.7 q	22.3 q	22.4 q
19	173.0 s	174.4 s	*b*
20	108.3 t	110.0 t	46.8 t
Acetyl			170.5, 21.0 q

[a] Chemical shifts (δ) were measured in parts per million from tetramethylsilane in $CDCl_3$ solution. [b] Not observed.

sites that differ among the structures compared. Peaks with suitable shifts and off-resonance multiplicities are found for each of these carbon atoms. This correspondence of signals provides a satisfying demonstration of the power of ^{13}C NMR to elucidate structural features that are not otherwise readily accessible to spectroscopic examination.

Comparison of the ^{13}C NMR spectra of **1**, **3**, and **4** allows a reasonable assignment of the chemical shifts for all of the observed peaks, although the differentiation of some closely grouped peaks remains uncertain. Of the three high-field triplets allocated to C-1, C-2, and C-3 in each of the compounds, those at highest field are associated with C-2 because it has the fewest β substituents and should be shifted farther upfield by the C-17 and C-19 axial substituents.[8] They occur 1–2 ppm upfield from the C-2 of 10-methyl-*trans*-decalin.[9] Differentiation of the peaks for C-1 and C-3 is tentative and is based on assignments by Grover and Stothers[9] for *trans*-decalin systems.

Two singlets at high field, from C-4 and C-10, are anticipated in the spectrum of **4**. That of C-10 should be the lower of the two because of the larger number of β substituents. The same order can be retained for **1** and **3**, leading to the following correlations: the 6β-acetoxy group of **4** shifts C-4 slightly upfield by a gauche interaction, while the effect of the oxygen bridge of **3** upon C-9 affords an example of a heteroatom producing an upfield shift of a β-carbon atom.[10]

Only one high field doublet, due to C-5, is anticipated from **4**, but differentiation of the two doublets appropriate to C-5 and C-9 in **1** and **3** is difficult. The present assignments indicate a consistent effect of attaching the oxygen bridge to **3**, since each γ carbon is shifted upfield relative to the same carbons in **1** and **4**.[10]

The triplets at δ 28 and 36 can be grouped together because they occur in spectra of **1** and **3**, but not in that of **4**. Gauche interactions with C-17 and C-19 should shift the C-6 resonance upfield. Nepetaefuran's doublet at δ 68.0 is related to C-6, and it shows an appropriate downfield shift of 40 ppm under the influence of the acetoxyl substituent. Accordingly, we attribute the remaining upfield triplet for **4** to C-7.

In the spectra of **1** and **3**, assignment of the low-field singlet to C-8 is straightforward and agrees well with similar structures.[11] Two "midfield" singlets are expected for **4**, but only one is observed. In the trichothecanes, an epoxy carbon similar to C-8 has a chemical shift of δ 65.[12] Accordingly, the one observed singlet (δ 74.6) is allocated to C-9; the deshielding effect of the hydroxyl group is only 22–26 ppm.

After five of the six high-field triplets for **3** have been assigned, the remaining one must represent C-11. Of the two high-field triplets left in the spectrum of **1**, the more highly shielded one is assigned to C-11 in order to allow the following correlations: C-11 in **3** is shifted downfield appropriately from the corresponding signal for **1** owing to the influence of the oxygen bridge, and likewise in **4** as a result of deshielding by the hydroxyl at C-9.

The triplets associated with C-12 are similar for **1** and **4**. The only midfield doublet exhibited by **3** (δ 69.4) must be that of C-12, shifted downfield ca. 30 ppm by the oxygen bridge.

Assignment of the low-field signals generated by the furanoid system is straightforward. For all three compounds, a singlet must result from C-13 since it is quaternary. Of the three sets of doublets, those at highest field are assigned to C-14; the ones at lowest field are associated with C-15 because of substitution at C-13 that shields C-16 slightly.[13]

The only triplets at midfield in the spectra of potamogetonin and nepetaefuran are generated by C-17, as is a doublet for sciadin that is deshielded by the oxygen bridge and appears at lower field. The C-18 methyl group appears as a similar highfield quartet in each of the compounds, and the C-19 (lactone) carbonyl of **1** and **3** gives similarly placed singlets.

The only low-field triplet possible for **1** and **3** must represent C-20. The triplet near δ 48 in the spectrum in **4** is chosen for C-20 to correspond with shifts observed for the trichothecanes.[12]

Aside from establishing their empirical formulas, mass spectra of **1** and **2** did not lend themselves to interpretations that facilitated structural elucidation. Prominent peaks at *m/e* 94 ($C_6H_6O^+$) and 81 ($C_5H_5O^+$), probably from cleavages of the β-furylethyl side chain, occurred in the spectrum of **1**. The complexity of fragmentation of related diterpenoids in mass spectrometry has been noted previously.[14]

Our representation of **1** is intended to suggest only its relative stereochemistry. For convenience, we show the absolute stereochemistry that corresponds to lambertianic acid, although we have no basis for excluding the enantiomeric spatial arrangement of daniellic acid.[1,3] Inspection of a molecular model of potamogetonin emphasizes that C-17 and C-19 must be cis and diaxial, as in sciadin,[7,15] in order to accommodate the lactone ring without excessive strain. An A/B cis ring juncture, although sterically possible, is unlikely because of observed ^{13}C NMR resonances and biogenetic precedents. The β configuration chosen for C-9 may be somewhat arbitrary, but is consistent with ^{13}C NMR data.

On the basis of our ^{13}C NMR data, it appears that sciadin must have the *S* configuration at C-12 as indicated in the accompanying stereoformula. In the alternative *R* configuration, the β-furyl group of **3** would interact severely with the *exo*-methylene group so that C-8 and C-20 surely would be shielded much differently than they are in **1**.

Experimental Section[16]

General Techniques. ^1H NMR spectra were measured with a Varian HA-100 instrument. For ^{13}C NMR spectra, the instrument was a Varian XL-100 equipped with a Digi-Lab Fourier transform

accessory. Multiplicity of the various signals was determined by off-resonance decoupling. Exciting pulses at approximately 200 Hz below the frequency of tetramethylsilane were used, the free induction decay being sampled at 12 kHz, to fill an 8K data table, giving an effective resolution of 1.5 Hz. Typically, 70 000 FID's were collected overnight. Spectra were obtained using both a 30 and 90° (60 μs) pulse, the latter showing saturation effects for fully substituted carbon atoms. The multiplicity of high-field signals was confirmed by partially relaxed Fourier transform spectra using a 180°, 2 s, 90° sequence. Ir spectra were determined with a Perkin-Elmer Model 137 instrument. Low-resolution mass spectra were obtained with a Du Pont (CEC) 21-492-1 spectrometer, and corresponding high-resolution data with a Nuclide 12-90G spectrometer. A Beckman DK-2A spectrophotometer was used to record uv spectra. Analytical TLC was carried out on silica gel G F-254 plates (E. Merck, Darmstadt) with the solvent system hexane–ethyl ether–acetic acid (80:20:2). For preparative TLC, the same solvent was used with regular silica gel G plates of 1 mm thickness. Components were located under uv light after spraying with ethanolic dichlorofluorescein solution. GLC analyses were performed with a Hewlett-Packard Model 5750 instrument equipped with a 24 × 0.125 in. stainless steel column packed with 3% OV-1 on Gas-Chrom Q (100/200 mesh) (Applied Science Laboratories); column temperatures were programmed at 6°/min with an initial temperature of 160°. Equivalent chain length values for components separated by GLC were determined as described by Miwa and co-workers.[17]

Isolation of Potamogetonin (1). Ground seed of *Potamogeton ferrugineus* Hagstr. collected in Uruguay (28.3 g) was extracted for 8 h in a Soxhlet apparatus with petroleum ether and provided 2.6 g of oil after evaporation of solvent. TLC analyses of this oil revealed major components at R_f 0.63 (triglycerides), 0.15 (potamogetonin), and 0.08 (not characterized). GLC analyses revealed a component representing 25% of the oil and more volatile than triglycerides; this substance had equivalent chain length 21.4 (OV-1 column).[17] The R_f 0.15 component (1), a liquid, was isolated by preparative TLC and was shown to have these same GLC retention characteristics: ux max (cyclohexane) 201 nm (ε 8329); ir (CCl_4) 1745 (ester or δ-lactone), 1133, 1050, 1025, 900, 872 cm^{-1}; ORD $[\alpha]^{30}D$ −23, $[\alpha]_{400}$ −50, $[\alpha]_{300}$ −140, $[\alpha]_{250}$ −290, $[\alpha]_{230}$ −340° (*c* 0.48, CH_3OH);[18] ^1H NMR spectral data are in Table I and ^{13}C NMR data in Table II. Anal. Calcd for $C_{20}H_{26}O_3$: M^+, *m/e* 314.188. Found: M^+, *m/e* 314.188.

Compound 1 was resistant to hydrolysis (solvolysis) when treated with each of the following reagents: 5% methanolic hydrogen chloride (reflux), 0.5 M methanolic sodium methoxide (ambient temperature), and aqueous 4 N potassium hydroxide (reflux). In each case, the product was recovered by conventional procedures and was unaltered 1, as judged by GLC, TLC, ir, or ^1H NMR.

Hydrogenation of Potamogenin (1). A 16-mg portion of 1, dissolved in methanol, was hydrogenated with Adams catalyst for 4 h at ambient temperature and pressure. The product (2), mp 112–113° from hexane–chloroform, was isolated by filtration and evaporation of solvent: ir (CCl_4) 1735 (ester or δ-lactone), 1137, 908 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (dd, 1 H, *J* = 11, 1 Hz, part of C-17 methylene), 4.00 (d, 1 H, *J* = 11 Hz, part of C-17 methylene), 0.87 (s, 3 H, H-18), 0.85 (d, 3 H, *J* = 8 Hz, H-20), 1.0–2.4 and 3.0–3.8, complex multiplets.

Anal. Calcd for $C_{20}H_{32}O_3$: M^+, *m/e* 320.235. Found: M^+, *m/e* 320.234.

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Registry No.—1, 57459-42-4; 2, 57459-43-5; 3, 6813-08-7; 4, 29461-24-3.

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A Biomimetic Approach to the Synthesis of *Laurencia* Metabolites. Synthesis of 10-Bromo-α-chamigrene

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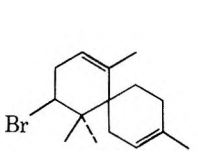
A number of halogenated sesquiterpenes based on the chamigrene skeleton have been isolated from red algae of the genus *Laurencia*. We have synthesized the simplest halogenated chamigrene, 10-bromo-α-chamigrene (**1**). The bromonium ion initiated cyclization of geranylacetone (**22**) gave the vinyl ether **23**, which underwent acid-catalyzed rearrangement to the bromo ketone **24**. The bromo ketone was converted into the vinyl alcohol **25**, which was cyclized under acidic conditions to obtain 10-bromo-α-chamigrene (**1**). We have studied the efficacy of various brominating reagents in the bromonium ion initiated cyclization of geranyl acetate (**15**).

An interesting group of halogenated sesquiterpenes whose structures are based on the chamigrene skeleton have been isolated from various species of red algae of the genus *Laurencia* (Rhodomalaceae, Rhodophyta).[1] Although several schemes for the biosynthesis of halogenated chamigrenes have been proposed,[2] they all involve a bromonium ion initiated cyclization of a suitable precursor. We wish to report an investigation of bromonium ion initiated cyclization reactions which has culminated in a synthesis of 10-bromo-α-chamigrene (**1**).

Although 10-bromo-α-chamigrene (**1**) has not been reported as a natural product, we believe that it may be regarded as the simplest bicyclic precursor to all other halogenated chamigrenes.[1,8] For example, 10-bromo-α-chamigrene (**1**) can be a precursor of both the epoxide **2**[3] and the dibromide **3**[4], as well as more complex chamigrenes such as prepacifenol (**4**)[5], pacifenol (**5**),[6] prepacifenol epoxide (**6**),[7] johnstonol (**7**),[8] elatol (**8**),[9] and acetoxyintracatol (**9**).[10]



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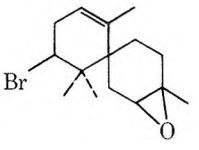

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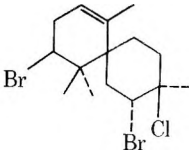

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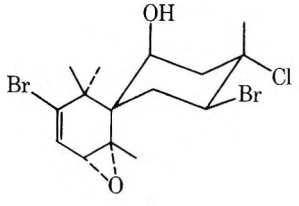

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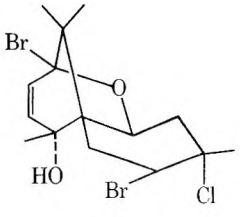

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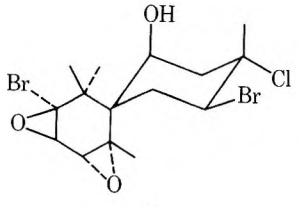

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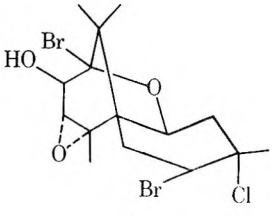

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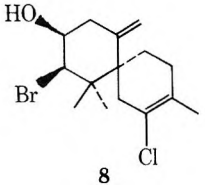

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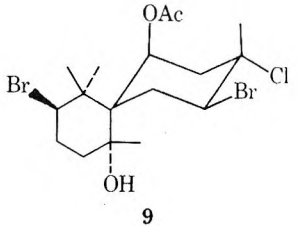

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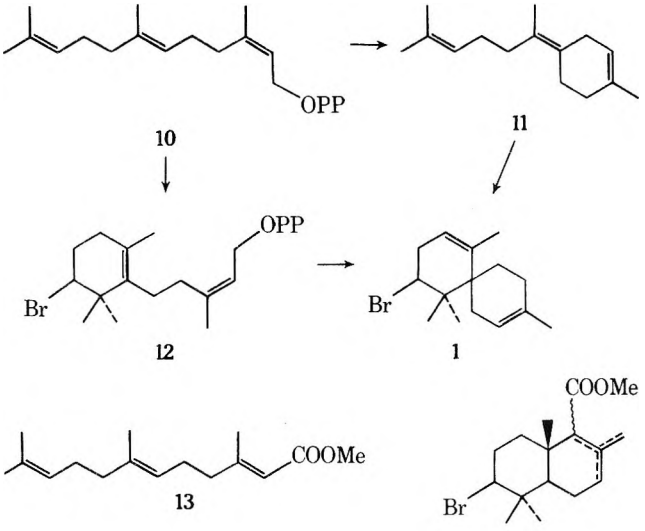
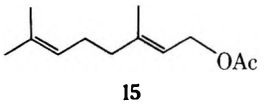
It is possible to envisage two distinct biosynthetic routes from farnesyl pyrophosphate (**10**) to 10-bromo-α-chamigrene (**1**) by way of either γ-bisabolene (**11**) or the brominated monocyclofarnesol (**12**). We have investigated synthetic routes which involve the use of both types of intermediate.



A bromonium ion induced cyclization was first observed by van Tamelen and Hessler,[11] who isolated bicyclic bromo esters **14** as a minor product from the treatment of methyl farnesoate (**13**) with *N*-bromosuccinimide in aqueous tetrahydrofuran. Sutherland et al.[12] have made use of the same reagent for the cyclization of humulene, a medium-ring sesquiterpene. The higher yields in the cyclization of medium-ring compounds were made possible by the close proximity of the participating olefinic bonds.

In order to compare the efficacy of various brominating reagents, we investigated the bromonium ion initiated cyclization of geranyl acetate. We were unable to obtain any trace of cyclized material by treatment of geranyl acetate (**15**) with *N*-bromosuccinimide in aqueous glyme. The intermediate bromonium ion **16** was quenched by water to give the bromohydrin **17** before cyclization could occur. We therefore investigated the use of reagent systems in which there were no nucleophiles present to trap the intermediate bromonium ion **16**. Treatment of geranyl acetate (>98% *E* isomer by vpc) (**15**) with 1 equiv each of bromine and stannic bromide in nitromethane at 0°C for 5 min gave, after work-up with sodium bicarbonate solution, a viscous oil from which crystals of the cyclized bromoacetate **19** were obtained in 16% yield after chromatography. The cyclized product **19** was shown by mass spectrometry to have the



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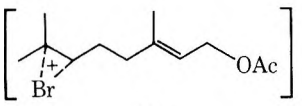

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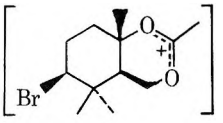

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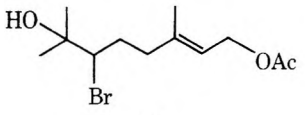

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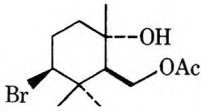

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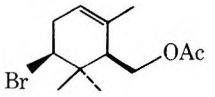

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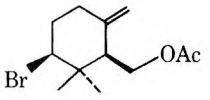

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molecular formula $C_{12}H_{21}O_3Br$, isomeric with the bromohydrin **17**. The chemical shifts of the three methyl singlets at δ 0.98, 1.15, and 1.22 ppm in the NMR spectrum of **19** clearly indicated that the methyl groups were no longer attached to olefinic carbon atoms. The NMR spectrum of **19** contained an acetoxy signal at 2.05 ppm and a double doublet at 4.00 ppm (J = 12 and 5 Hz) due to a proton α to bromine and a two-proton multiplet at 4.38 ppm due to the methylene group bearing the acetoxy group. Examination of the NMR spectra of *Laurencia* metabolites reveals that the double doublet signal at 4–5 ppm is characteristic of 1,1-disubstituted 2 (equatorial) bromocyclohexanes. Clearly, the expected cyclization had occurred.

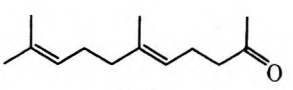
Since the bromoacetate **19** contained a tertiary alcohol functionality (ir 3480 cm^{-1}) and water had been rigorously excluded from the reaction mixture, we propose that the initial product was the bicyclic ion **18**, which was hydrolyzed during work-up. The stereochemistry shown for the bromoacetate **19** is an outcome of this reaction mechanism.

During the purification of the bromoacetate **19**, we had obtained fairly large quantities of materials having two bromine atoms, indicating normal bromine additions. We therefore attempted to remove bromide ion as it was produced. Treatment of geranyl acetate (**15**) with equimolar amounts of bromine and silver fluoroborate in nitromethane solution at 0°C resulted in an immediate precipitation of silver bromide. The bromoacetate **19** was obtained in 20% yield.

Treatment of the bromoacetate **19** with p-toluenesulfonic acid in refluxing benzene gave an inseparable mixture of dehydration products in 77% yield. The NMR spectrum of the mixture of olefins contained signals at δ 4.77 and 5.30 due to two methylene protons and at 5.35 ppm, indicative of a trisubstituted olefinic bond. The product was therefore a 2:1 mixture of the olefins **20** and **21**. At the time we considered this result to be a severe setback, since we required a tetrasubstituted olefinic bond for any synthesis of a spiro bicyclic system. Fortunately, application of the same series of reactions to geranylacetone gave the desired product.

Geranylacetone (**22**) was treated with 1 equiv each of bromine and silver fluoroborate in nitromethane at 0°C to obtain a bicyclic vinyl ether **23** in 20% yield. The NMR spectrum of the vinyl ether **23** contained four methyl singlets at δ 0.92, 1.05, 1.16, and 1.65, a double doublet at 4.00 ppm due to the proton α to bromine, and a triplet at 4.47 ppm due to the vinyl proton.

Rearrangement of the vinyl ether **23** using p-toluenesulfonic acid in benzene solution gave the desired ketone **24** (ir



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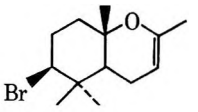

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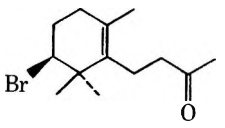

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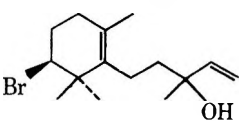

25

1725 cm^{-1}) in 73% yield. The NMR spectrum contained a six-proton singlet at δ 1.11, a vinyl methyl signal at 1.54 ppm, and an acetyl signal at 2.03 ppm but no trace of a vinyl proton signal. Thus the rearranged product must contain a tetrasubstituted olefinic bond.

The synthesis of a chamigrene required the addition of a two-carbon unit. The addition of vinylmagnesium bromide to the ketone **24** in tetrahydrofuran solution gave the vinyl alcohol **25** in 91% yield. For the purposes of the following reaction, the vinyl alcohol **25** may be regarded as equivalent to the monocyclofarnesol. The vinyl alcohol **25** was treated with p-toluenesulfonic acid in benzene solution for 15 min to obtain a mixture of brominated hydrocarbons. The major product was shown to be 10-bromo-α-chamigrene (**1**).

We have not been able to determine the stereochemistry of the 10-bromo-α-chamigrene (**1**) formed in the reaction. By analogy with spiro-cyclization reactions involving carbanions, we might expect the newly formed bond to be trans to the bromine. On the other hand, an x-ray crystallographic study of elatol (**8**) and acetoxyintracatol (**9**) indicated that the opposite stereochemical relationship might occur in the natural product. There is, however, no proof that all the natural bromochamigrenes have the same stereochemical relationship between the bromine on one ring and the bromine and chlorine on the second ring, or that the two hypothetical 10-bromo-α-chamigrenes are separable by VPC or can be distinguished by spectroscopic methods. Examination of combined gas chromatogram–mass spectrometer data suggested that the synthetic cyclization product contained only one isomer of 10-bromo-α-chamigrene and that the gas chromatographic retention times, mass spectral fragmentation pattern, and 220-MHz NMR spectrum were identical with those of a sample obtained by reductive dehalogenation of the *Laurencia* metabolite **3**.[13]

We have also investigated the bromocyclization reaction of (E)-γ-bisabolene (**11**), which had been prepared in this laboratory.[14] Although we investigated the use of several reagents, including bromine–stannic bromide and bromine–silver tetrafluoroborate, we were unable to detect any 10-bromo-α-chamigrene among the complex mixtures of products.

Because of the catalytic properties of enzymes, it is difficult to determine the biosynthetic significance of these experiments. We have shown that without the benefit of enzymes to direct the bromination to the correct olefinic bond and to control the stereochemistry of the substrate, the biosynthesis of the bromochamigrenes is more likely to occur through the intermediacy of a bromomonocyclofarnesol than via γ-bisabolene. The recent discovery of a brominated natural product having the carbon skeleton of monocyclofarnesol provides some support for this biosynthetic route.[15]

Experimental Section

Commercially available chemicals were used without further purification unless otherwise stated. All solvents were either analar grade or redistilled prior to use. Melting points were measured on

a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on Varian HR-220 or EM-360 spectrometers; chemical shifts are expressed as values in parts per million relative to tetramethylsilane (0). Infrared spectra were recorded on a Perkin-Elmer 700 spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard 402 instrument. Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass spectra were measured by Beth Irwin, Department of Chemistry, UCLA.

5-Bromo-1-acetoxymethyl-2,6,6-trimethyl-2-hydroxycyclohexane (19) (Procedure A). A 250-ml, three-necked, round-bottom flask equipped with a low-temperature thermometer, a magnetic stirrer, and a gas inlet tube was flushed with argon. A solution of *trans*-geranylacetate[16] (>98% *E* isomer) (5.88 g, 330 mmol) in anhydrous nitromethane (30 ml) was added via a syringe. The solution was cooled to −20° using a dry ice–carbon tetrachloride bath, and a nitromethane solution of tin(IV) bromide (13.14 g, 30 mmol) and bromine (30 ml, 1 M, 30 mmol) was added dropwise. The temperature was maintained below −10° during the addition. After 30 min, the solution was poured into sodium bicarbonate (100 ml) and ethyl ether (100 ml). The ether phase was separated and washed successively with saturated sodium bicarbonate solution and saturated brine. The ether phase was dried over anhydrous magnesium sulfate. Removal of the solvent by distillation under high vacuum afforded 11.18 g of a crude yellow oil. Thin layer chromatography on silica gel in 5% ethyl ether–petroleum ether (bp 30–60°) and 5:1 benzene–ethyl acetate showed the presence of many compounds. The 220-MHz NMR of this crude material showed several high-field methyl signals appropriate for a cyclic product. GLC analysis (6 ft, 2% SP2401 on Chromosorb W) showed many products, with one major product having a retention time of 6.8 min at 160°. The crude material was passed through a short Florisil column (6 × 2 in.) with ethyl ether to remove any tin compounds. The material collected from this column was carefully chromatographed on silica gel chromatography. Crude material (9.46 g) was placed on 100 g of silica gel (Grace Chemical) and eluted with a solvent gradient from petroleum ether to ethyl ether to chloroform and ethyl acetate. The majority of the material was found in two fractions. The less polar of the two fractions (R_f 0.90 in 50% ethyl ether–hexane) amounted to 1.2 g of a yellow oil. The 60-MHz NMR of this mixture indicated an acyclic compound. By mass spectrometry, this fraction was shown to contain dibrominated compounds. This fraction was disregarded. The second more polar fraction had R_f 0.20 in 50% ethyl ether–hexane. Upon standing, this fraction crystallized to give the desired bromoacetate **19**, which was recrystallized from petroleum ether: mp 73°; yield 1.4 g (16%); ir ($CHCl_3$) 3478, 1724, 1242 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 0.98 (s, 3 H), 1.15 (s, 3 H), 1.22 (s, 3 H), 2.04 (s, 3 H), 2.72 (s, broad, 1 H), 4.00 (dd, J = 12, 5 Hz, 1 H), 4.38 (dd, 2 H). Anal. Calcd for $C_{12}H_{21}BrO_3$: C, 49.15; H, 7.22; Br, 27.25. Found: C, 49.09; H, 7.31; Br, 27.14.

5-Bromo-1-acetoxymethyl-2,6,6-trimethyl-2-hydroxycyclohexane (19) (Procedure B). A 50-ml, three-neck, round-bottom flask, equipped with a magnetic stirrer, a low-temperature thermometer, and a gas inlet tube was flushed with argon. Silver tetrafluoroborate (197 mg, 1 mmol) was dissolved in anhydrous nitromethane (5 ml) and added to the reaction vessel. The mixture was cooled to 0° using an ice–methanol bath, following which a solution of bromine (1 ml, 1 mmol) in nitromethane was added. The resulting orange solution was stirred for 5 min. A nitromethane solution of geranylacetate (196 mg, 1 mmol) was added dropwise to obtain a precipitate of silver bromide. The reaction mixture was stirred for another 5 min at 0°, then quenched by addition of cold saturated sodium bicarbonate solution (50 ml) and extraction with ethyl ether (2 × 50 ml). The organic layer was dried and the solvent removed to yield a pale yellow oil. The GLC trace (2% SP2401 on Chromosorb G, 160°) showed two major peaks, one of which was the desired cyclic hydroxyacetate. This method gave a higher yield (judged by the GLC trace) than procedure A. The oil obtained was submitted to silica gel chromatography, to obtain the bromoacetate as white prisms, yield 58.4 mg (20%). All spectral properties were identical with those of the sample prepared by alternate route A.

Dehydration of Bromoacetate 19. Recrystallized bromoacetate **19** (20 mg, 0.7 mmol) was dissolved in anhydrous benzene (0.5 ml). A few crystals of *p*-toluenesulfonic acid monohydrate were added and the mixture was refluxed for 2 hr. The reaction was followed by thin layer silica gel chromatography (50% ethyl ether–petroleum ether). After 2 h, the purple-red solution was cooled and benzene (25 ml) was added. The mixture was carefully washed with sodium bicarbonate solution (2 × 50 ml). The benzene layer was then dried over anhydrous magnesium sulfate and the solvent removed under vacuum. This gave a mixture of dehydration products: yield 14 mg (77%). GLC analysis of the oil (6 ft Silar 10 CP glass column at 120°) showed two major peaks at retention times of approximately 10 min. It was assumed that these two products must be double bond isomers, since the mass spectra of the two peaks were almost identical. Ir (CCl_4) 1740, 1640 weak, 1240 cm^{-1}; NMR (220 MHz) δ 0.95 (s, 3 H), 1.15 (s, 3 H), 1.68 (s, 3 H), 2.02 (s, 3 H), 2.21 (m, 2 H), 2.59 (m, 2 H), 4.20 (m, 2 H), 4.44 (dd, 1 H), 5.35 (broad, 1 H). The NMR also contained what appeared to be two vinyl proton signals of an exocyclic double bond at δ 4.77 and 5.30. From the integration of the NMR and the GLC traces, it was concluded that the oil was an isomeric mixture of the two compounds 1-bromo-3-acetoxymethyl-2,2,4-trimethyl-4-cyclohexene (**20**) and 1-bromo-3-acetoxymethyl-2,2-dimethyl-4-methylenecyclohexane (**21**) in the ratio of 2:1.

6-Bromo-4a,5,6,7,8,8a-hexahydro-2,5,5,8a-tetramethyl-4*H*-1-benzopyran (23). A three-neck, 250-ml, round-bottom flask was equipped with a magnetic stirrer and a low-temperature thermometer. The apparatus was flushed with argon and a solution of silver tetrafluoroborate (10 g, 51 mmol) in anhydrous nitromethane was placed in the flask under argon. The solution was cooled to 0° and bromine (51 ml, 1 M Br_2 in CH_3NO_2, 51 mmol) was added dropwise with stirring. The resulting orange complex was then transferred under argon to an addition funnel. A solution of geranylacetone[17] (10.0 g, 51 mmol) in nitromethane was cooled to 0°, and the bromine–silver fluoroborate solution was added dropwise, with rapid stirring. The mixture was stirred for 20 min, then worked up by the addition of saturated sodium bicarbonate solution (100 ml) and extraction with ethyl ether. The ether phase was washed several times with brine solution and dried over anhydrous sodium sulfate. The solvent was removed under high vacuum (approximately 1 mm) at 30°. This left a clear yellow oil (14.9 g of crude material). Thin layer chromatography (TLC) on silica gel (50% ethyl ether–petroleum ether) showed two major spots. The oil was quickly filtered through a short Florisil column (6 × 2 in.). This oil was then submitted to a careful silica gel chromatography using a hexane–ethyl ether gradient. This enabled the isolation of two fractions, A and B, which corresponded to the two spots on the TLC. Fraction A (4.63 g) was the less polar material (R_f 0.5 in petroleum ether). GLC analysis on 6 ft × 2 mm glass column packed with 3% SP2401 on Chromosorb W showed several compounds. Fraction A was rechromatographed on silica gel with hexane to yield the desired cyclic vinyl ether **23**: yield 2.87 g (20%) of a clear pale-yellow oil; ir (CCl_4) 1660, 1375, 1140, 869 cm^{-1}; NMR (220 MHz, CCl_4) δ 0.92 (s, 3 H), 1.05 (s, 3 H), 1.16 (s, 3 H), 1.65 (s, 3 H), 1.82–2.27 (m, 7 H), 4.00 (dd, J = 12,4 Hz, 1 H), 4.47 (t, broad, 1 H); mass spectrum *m/e* (rel abundance) 274, 272 (M^+, 4), 256 (1), 193, 175 (15), 159 (13), 135 (44), 123 (73), 107 (100), 81 (73), 71 (89); high-resolution mass spectrum M^+ 272.0775 ($C_{13}H_{21}O^{79}Br$ requires 272.0776).

4-(5′-Bromo-2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)-2-butanone (24). Purified bromovinyl ether **23** (100 mg, 0.36 mmol) was dissolved in anhydrous benzene (26 ml). A crystal of recrystallized *p*-toluenesulfonic acid monohydrate was added and the solution was refluxed at 80° for 2 hr. Thin layer chromatography on silica gel (5% ethyl ether–petroleum ether) showed only one spot (R_f 0.5). The reaction mixture was cooled and benzene (10 ml) was added. The solution was carefully washed with sodium bicarbonate solution (2 × 50 ml) and the benzene layer was separated and dried over anhydrous magnesium sulfate. Removal of the solvent left a yellow oil (90 mg). Preparative thick layer chromatography of this oil on silica gel with 20% ethyl–petroleum ether as eluent yielded the desired 4-(5′-bromo-2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)-2-butanone: yield 70 mg (70%); ir (CCl_4) 1725 cm^{-1}; NMR (220 MHz, CCl_4) δ 1.11 (s, 6 H), 1.54 (s, 3 H), 2.03 (s, 3 H), 4.06 (dd, J = 10, 4 Hz, 1 H); mass spectrum (70 eV) *m/e* (rel abundance) 274, 272 (M^+, 1), 1.93 ($M - Br^+$, 2), 175 ($M - C_2H_4Br^+$, 4), 159 (4), 43 (100).

5-(5′-Bromo-2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)-3-hydroxy-3-methyl-1-pentene (25). Magnesium turnings (48 mg, 2 mg-atoms) were placed in a three-neck, round-bottom, 100-ml flask equipped with a dry ice condenser, a low-temperature thermometer, a serum cap, and a magnetic stirrer. The apparatus was set up and dried with a heat gun under an argon atmosphere. After the equipment was cool, anhydrous tetrahydrofuran (5 ml) was added and vinyl bromide (107 mg, 1 mmol) was quickly added through a syringe. The reaction mixture was stirred rapidly until all magnesium shavings had dissolved. The temperature was main-

tained below 35° throughout the reaction. The resulting brown solution was diluted with tetrahydrofuran (10 ml) and cooled to 0° in an ice bath. A tetrahydrofuran solution of the methyl ketone **24** (152 mg, 0.56 mmol) was added dropwise with stirring. The mixture was stirred for 15 min at 0°, and then saturated ammonium chloride solution (25 ml) was added slowly. The mixture was extracted with ethyl ether (2 × 25 ml). The ether phase was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the solvent left a yellow oil, which was immediately chromatographed on a thick layer silica gel plate, using 20% ether–petroleum ether as eluent (R_f 0.20). This gave 5-(5′-bromo-2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)-3-hydroxy-3-methyl-1-pentene: yield 154 mg (91%); ir ($CDCl_3$) 3550 sharp, 3420 broad, 1648, 1220, 910 cm^{-1}; NMR (220 MHz, CCl_4) δ 1.19 (s, 6 H), 1.30 (s, 3 H), 1.60 (s, 3 H), 4.22 (dd, J = 10, 4 Hz, 1 H), 5.02 (d, J = 11 Hz, 1 H), 5.18 (d, J = 18 Hz, 1 H), 5.85 (dd, J = 18, 11 Hz, 1 H); mass spectrum m/e (rel abundance) 302, 300 1:1 (M^+, 1.0) 284, 282 1:1 (2.0), 203 (10), 119 (100), 93 (83), 71 (89), 43 (89); high-resolution mass spectrum M^+ 300.1088 ($C_{15}H_{25}O^{79}Br$ requires 300.1089).

10-Bromo-α-chamigrene (1). The alcohol **25** (51 mg, 0.17 mmol) was dissolved in anhydrous benzene (10 ml). A few crystals of *p*-toluenesulfonic acid monohydrate were added and the mixture was heated to reflux for 15 min. Thin layer chromatography after this time showed no starting alcohol. The mixture was cooled and poured over saturated sodium carbonate (25 ml), then washed with saturated sodium chloride. The benzene layer was separated and dried over anhydrous magnesium sulfate. Most of the solvent was removed, and the black residue was put on a short silica gel column. Elution with ethyl ether gave 39 mg of a yellow oil. This material was purified by preparative thick layer chromatography on silica gel with hexane as an eluent to give a clear oil. The GLC on 3% SP2401 showed four components. The major component, with a retention time of 8.5 min, was 10-bromo-α-chamigrene, yield 26.5% (by GLC). The gas chromatograph–mass spectrum of this material was identical in every respect with that of another sample of 10-bromo-α-chamigrene prepared by an independent synthesis. Mass spectrum m/e (rel abundance) 284, 282 1:1 (M^+, 5.9) 216 (53), 214 (55), 203 (17), 202 (39), 187 (13), 173 (5.9), 161 (2.6), 159 (37.6), 147 (27), 145 (21), 135 (100), 119 (85), 105 (46), 91 (39), 81 (20), 79 (19), 77 (21), 69 (12), 67 (12), 45 (18), 43 (11); NMR (220 MHz, CCl_4) δ 0.95 (s, 3 H), 1.08 (s, 3 H), 1.65 (s, 6 H), 4.61 (dd, J = 4, 10 Hz, 1 H), 5.13 (broad, 1 H), 5.31 (broad, 1 H).

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Registry No.—**1**, 57473-87-7; **15**, 105-87-3; **19**, 57473-88-8; **20**, 57473-89-9; **21**, 57473-90-2; **22**, 3796-70-1; **23**, 57473-91-3; **24**, 57473-92-4; **25**, 57473-93-5.

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(18) **Note Added in Proof.** 10-Bromo-α-chamigrene (**1**) has recently been located in *Laurencia pacifica*.[15]

Nucleosides. XXXI.[1] Synthesis of 1-(2,6-Dideoxy-β-D-*arabino*-hexopyranosyl)cytosine, the Nucleoside Portion of Oxamicetin

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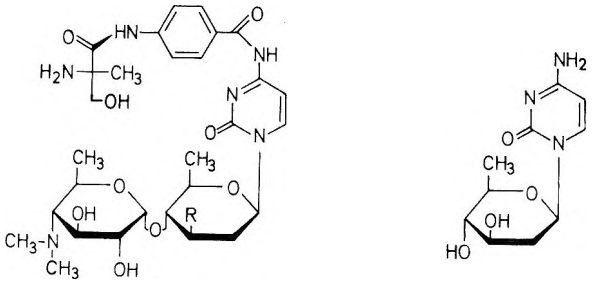
A synthesis of the nucleoside moiety of oxamicetin, 1-(2,6-dideoxy-β-D-*arabino*-hexosyl)cytosine (**3**), is described starting from the known 1-(2-deoxy-β-D-*arabino*-hexosyl)uracil (**7**). The synthetic sequence involved selective mesylation at the primary hydroxyl group, displacement by iodide, and reductive dehalogenation (**7** → **8** → **9** → **10**) followed by conversion of uracil nucleoside **10** into its cytosine analogue **3** by O-benzoylation, thiation, and ammonolysis. Structural and configurational assignments evolved from the mode of preparation as well as from spectroscopic data, a consideration of the circular dichroism Cotton effects indicating that the sugar-base conformation is strongly dependent on the nature of the 6′ substituent.

Oxamicetin (**1**), a new disaccharide nucleoside antibiotic isolated recently from the fermentation broth of *Arthrobacter oxamicetus*,[3,4] has been allotted[5] to the aminoacyl-4-aminohexosylcytosine group of protein biosynthesis inhibitors[6] on the basis of a close similarity to amicetin (**2**) in its gross antibacterial activity,[4] its inhibitory effect on the fragment reaction,[5] and its structural features,[7] differing from **2** only by an additional hydroxyl group in the disaccharide unit. The structural assignments within the nucleoside portion were mainly based on the isolation of 1-(2,6-dideoxy-β-D-*arabino*-hexopyranosyl)cytosine (**3**) on acid methanolysis, for which the alternate β-L-arabino configuration was excluded via the copper complex method.[7] This paper provides confirmatory evidence for the β-D-arabino configuration by an unequivocal synthesis of the nucleoside portion **3** and the proof of its identity with the oxamicetin derived product.

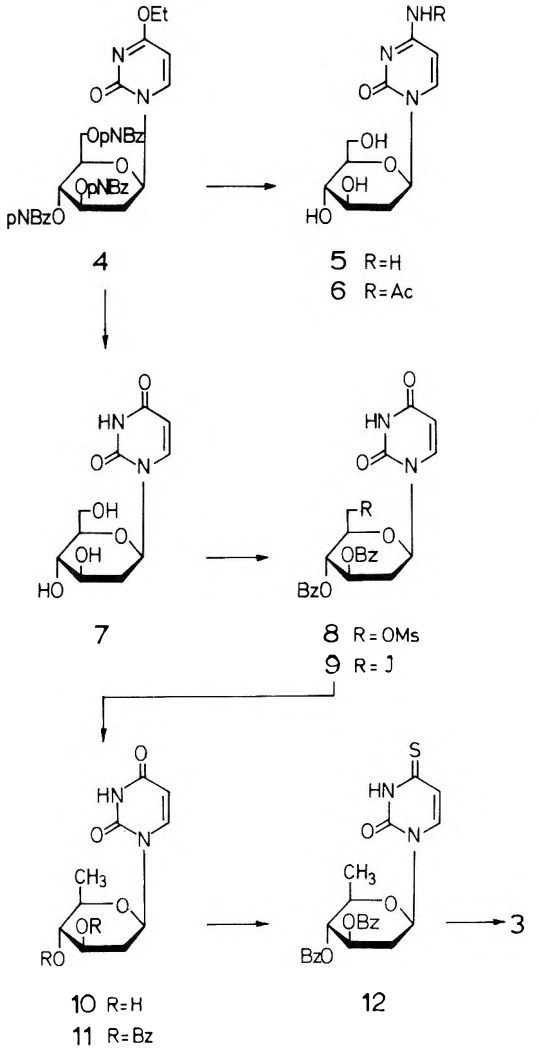
Of the several approaches conceivable for the synthesis of **3**, the utilization of the pyrimidinone nucleoside **4**, accessible from 3,4,6-tri-*O*-nitrobenzoyl-2-deoxy-α-D-*arabino*-hexosyl bromide and 2,4-diethoxypyrimidine in a remarkably stereoselective reaction,[8] was considered more propi-



1 R=OH
2 R=H

3

tious than starting from the parent sugar[9] whose N-glycosidation was surmised to proceed much less stereoselectively owing to the absence of a hydroxy function at C-6. For conversion of **4** into **3**, the replacement of the primary hydroxyl group in the respective cytosine nucleoside **5**[8] would be the most direct route, yet reactions of **5** or its *N*-acetate **6** with sulfuryl bromide–hexamethylphosphoric triamide,[10] Rydon reagent,[11] or with triphenylphosphine–*N*-bromosuccinimide[12] failed or resulted in multicomponent mixtures under conditions that converted cytidine into its 5′-halide in yields of 50–60%. Similar difficulties were encountered with the corresponding 4-ethoxypyrimidinone nucleoside (**4**, H instead of pNBz), obtainable from **4** by deacylation with barium hydroxide in 50% ethanol–water[13] in low yield and, as yet, impure form. Thus, a more conventional approach was followed comprising a two-step halogenation of the uracil nucleoside **7** with subsequent elaboration of the cytosine nucleobase.



4

5 R=H
6 R=Ac

7

8 R=OMs
9 R=J

10 R=H
11 R=Bz

12

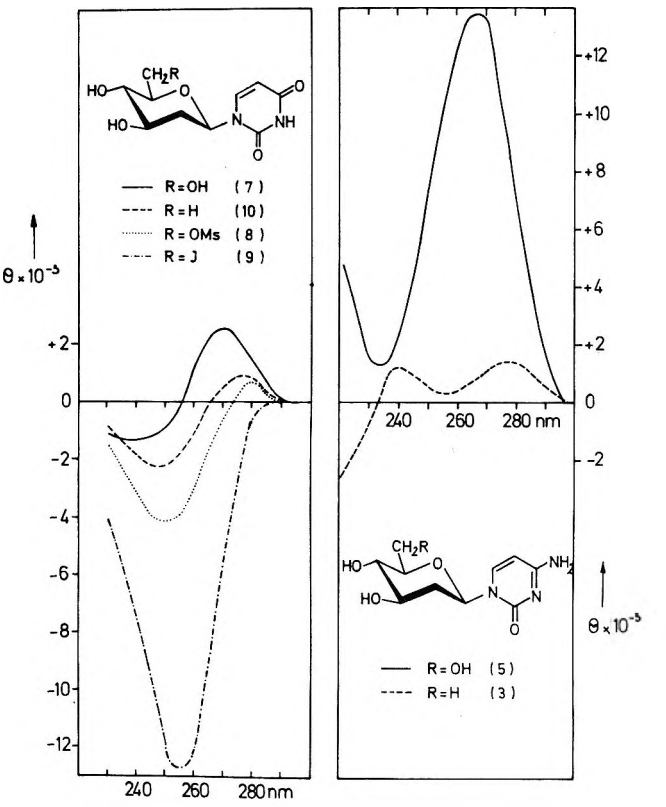


Figure 1. The circular dichroism curves of 1-(2-deoxy-β-D-*arabino*-hexopyranosyl)uracils **7**–**10** (left) and of cytosine analogues **3** and **5** (right) in water at pH 7.

The conversion of **4** into the uracil nucleoside **7**, previously effected by consecutive treatment with methanolic hydrogen chloride and sodium methoxide–methanol in 36% yield,[8] could readily be abridged into a single operation, stirring a suspension of **4** in aqueous barium hydroxide for 2 days, affording **7** in a yield of 85%. Subsequent selective mesylation of the primary hydroxyl group in **7** by treatment with methanesulfonyl chloride–pyridine yielded nucleoside **8** (51%). The primary mesyloxy group in **8** was then displaced with sodium iodide in dimethylformamide to give the corresponding 6′-iodonucleoside **9** (46%), which, in turn, was hydrogenated over 10% palladium on carbon, affording 1-(2,6-dideoxy-β-D-*arabino*-hexosyl)uracil (**10**) in 81% yield. The final transformation of the uracil moiety into the cytosine nucleobase (**10** → **3**) was effected in three steps, i.e., blocking of the hydroxyl groups in **10** by benzoylation to afford **11** (78%) followed by thiation with phosphorus pentasulfide–dioxane (58%) and subsequent treatment of the thionucleoside **12** with methanolic ammonia at 110° to give 1-(2,6-dideoxy-β-D-*arabino*-hexopyranosyl)cytosine (**3**) in 53% yield. All the physical constants of synthetic **3**, most notably the rotational and NMR spectroscopic data, were identical with those reported[7] for the oxamicetin derived **3**. Since well-defined synthetic procedures have been used throughout, structures and configurations of the newly synthesized nucleosides already followed from the mode of preparation. Sustaining evidence was furnished by NMR data exhibiting in all cases coupling patterns, particularly those arising from the 2′-CH_2 group, that are compatible with a $^4C_1$ conformation of the 2-deoxy sugar portion. The conformation of the planar pyrimidine ring with respect to the sugar, however, appears to be less uniform. As already indicated by the comparatively large differences in rotational values, e.g., −45.2° for the 6′-iodonucleoside **7** vs. +6.6° for the 6′-hydroxy analogue **5**, and more strikingly exposed in the circular dichroism spectra,

the conformation about the glycosidic bond is dependent on the nature of the 6′ substituent.

As in uridine [14a] the B_{2u} and B_{1u} Cotton effects for the uracil nucleosides **7** and **10** are resolved with positive and negative signs, respectively (cf. Figure 1). Although the magnitudes of the former are reduced by factors of 3 and 10 attributable to a less restricted rotation about the glycosidic bond, these data suggest that the main rotameric component is in the anti conformation. In the 6′-mesylate **8** the B_{2u} CD maximum is still smaller in magnitude with concurrent increase of the negative B_{1u} minimum, while in the 6′-iodonucleoside **9** only one intense negative Cotton effect at 255 nm is observed, seemingly the B_{1u} band. Although it is difficult to rationalize this result in geometrical terms, the CD behavior of **9** is reminiscent of that observed for 2′,3′-*O*-isopropylidene-O^2,5′-cyclouridine[14b] and, hence, may indicate a shift in the sugar–base rotameric equilibrium toward the syn conformation.

A similar dependence of sugar–base conformation on the nature of the 6′ substituent appears to be operative in the respective cytosine nucleosides, as clearly evidenced by the drastic change in CD behavior when replacing the 6′-hydroxyl group in **5** by hydrogen, i.e., **3** (cf. Figure 1).

Experimental Section

Melting points were determined on a Bock Monoskop, and are uncorrected. Spectra were recorded on Perkin-Elmer 125 (ir), 137 (uv), 141 (rotations), Jasco J-25 (CD), and Varian A-60A and XL-100 (NMR) instruments. Thin layer chromatography (TLC) on Merck plastic sheets of Kieselgel F_{254} and cellulose was used to monitor the reactions and to ascertain the purity of the products. Developers employed for silica gel plates: (A) ethyl acetate–benzene (3:2); (B) chloroform–methanol (7:3); for TLC on cellulose (C) ethyl acetate–2-propanol–water (3:3:4) and (D) 1-butanol–water (5:1). The spots were visualized by uv light. Preparative separations (PLC) were performed on 20 × 40 cm plates coated with 2 mm layers of silica gel $PF_{254+366}$ (Merck, Darmstadt) and activated at 120° overnight.

1-(3,4,6-Tri-*O*-*p*-nitrobenzoyl-2-deoxy-β-D-*arabino*-hexopyranosyl)-4-ethoxy-2(1*H*)-pyrimidinone (4). 3,4,6-Tri-*O*-benzoyl-2-deoxy-α-D-*arabino*-hexopyranosyl bromide was treated with 2,4-diethoxypyrimidine in three- to fivefold extensions of the procedure given by Zorbach et al.,[8] affording **4** of mp 273–274° and $[\alpha]^{20}D$ +12° (c 0.5, CH_2Cl_2) in yields of up to 65% [reported[8] mp 271–272.5°, $[\alpha]^{20}D$ −6.6° (c 0.5, CH_2Cl_2)].

1-(2-Deoxy-β-D-*arabino*-hexopyranosyl)-N^4-acetylcytosine (6). A solution of 154 mg (0.6 mmol) 1-(2-deoxy-β-D-*arabino*-hexosyl)cytosine (**5**)[8] in methanol (50 ml) containing 1 ml of acetic anhydride was refluxed for 3 h, followed by concentration to dryness. Purification of the residue over a silica gel column by elution with 3:2 chloroform–methanol and evaporation of the eluate to dryness gave a crystalline residue that was recrystallized from ethanol–ether: 125 mg (71%), mp 168–170°; uv (H_2O) λ_{max} 297 nm (ε 8100) and 249 (16 550), λ_{min} 273 (5300) and 228 (6600).

Anal. Calcd for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.73; N, 14.04. Found: C, 48.06; H, 5.65; N, 13.88.

1-(2-Deoxy-β-D-*arabino*-hexopyranosyl)uracil (7). To a solution of barium hydroxide (21 g) in water (400 ml) was added 12.0 g (16 mmol) of ethoxynucleoside **4** followed by stirring of the resulting suspension at room temperature for 48 h. The insoluble material (ca. 5 g) was filtered off and washed three times with 15 ml of $Ba(OH)_2$ solution. To the combined washings and filtrate was added dry ice (CO_2) with vigorous stirring to obtain pH 7. The neutral mixture was filtered and evaporated to dryness in vacuo to give a residue which was extracted twice with 600 ml of boiling ethanol. Standing of the combined extracts at 0° overnight was followed by filtration, evaporation to dryness in vacuo and recrystallization of the residue from methanol–ether: 3.6 g (85%) of **7**, mp 156–159°, suitable for ensuing conversions. The analytical sample was obtained by another recrystallization from ethanol–ether: mp 161–163°; $[\alpha]^{20}D$ +6.6° (c 0.5, water) [reported[8] mp 168–169° and 196–197.5°; $[\alpha]^{20}D$ +5.6° (c 0.45, water)]; uv (H_2O) λ_{max} 261 nm, λ_{min} 230; (pH 12) λ_{max} 261, λ_{min} 242; CD (H_2O) θ −1300 (239 nm), +2600 (270); NMR (D_2O) δ 7.81 and 5.88 (two 1 H d, $J_{5,6}$ = 8 Hz, H-6 and H-5), 5.77 (q, 1, $J_{1',2'a}$ = 10 and $J_{1',2'e}$ = 2 Hz, H-1′), 3.45 (broad m, 5, H-3′–H-6′), 2.22 (octet, 1, $J_{2'e,2'a}$ = 11, $J_{2'e,3'}$ = 4 Hz, H-2′e), 1.90 (quintet, 1, $J_{2'a,3'}$ = 10 Hz, H-2′a).

1-(6-*O*-Mesyl-2-deoxy-β-D-*arabino*-hexopyranosyl)uracil (8). To a solution of uracil nucleoside **7** (2.5 g, 9.6 mmol) in 100 ml of dry pyridine was added 0.5 ml of methanesulfonyl chloride at 0° followed by stirring at this temperature for 30 min. Ice (35 g) was subsequently added with vigorous stirring and the mixture was then evaporated to dryness in vacuo. The syrupy residue was dissolved in methanol (20 ml) deposited on eight PLC plates and developed thrice with 7:3 chloroform–methanol. The main zone was removed and eluted with methanol (500 ml), followed by evaporation to dryness and extraction of the residue with ethanol (300 ml). Charcoal treatment of the extract and concentration in vacuo gave a residue, that crystallized on trituration with small amounts of aqueous ethanol: 1.67 g (51%) of 6′-*O*-mesylate **8**; mp 109–111°; uv (CH_3OH) λ_{max} 259 nm (ε 9940), λ_{min} 232 (2350); CD (H_2O) θ −4100 (250 nm), +700 (281); NMR (Me_2SO-d_6) δ 7.70 and 5.64 (two 8-Hz d, H-6 and H-5), 5.70 (H-1′ signal, multiplicity obscured by H-5), 3.16 (3 H s, OMs).

Anal. Calcd for $C_{11}H_{16}N_2O_8S$: C, 39.28; H, 4.80; N, 8.33. Found: C, 39.13; H, 4.73; N, 8.16.

1-(2,6-Dideoxy-6-iodo-β-D-*arabino*-hexopyranosyl)uracil (9). To a solution of sodium iodide (10.3 g) in anhydrous dimethylformamide (75 ml) was added 1.5 g (4.5 mmol) of 6′-*O*-mesyl nucleoside **8** and the mixture was heated in an oil bath (140–150°) for 40 min, followed by evaporation to dryness in vacuo (1 Torr). The residue was purified by elution from a silica gel column (1.5 × 25 cm) with chloroform–methanol (4:1), followed by evaporation of the eluate and crystallization of the remaining syrup from acetone–methanol–ether: 0.74 g (46%) of **9** as needles: mp 213°; $[\alpha]^{20}D$ −45.2° (c 0.5, water); uv (H_2O) 259 nm (ε 13 020); λ_{min} 231 (3010); CD (H_2O) θ −12 700 (255 nm); NMR (Me_2SO-d_6) δ 7.61 and 5.64 (two 8-Hz d, H-6 and H-5), 5.73 (q, 1, $J_{1',2'a}$ = 10.5 and $J_{1',2'e}$ = 2.4 Hz, H-1′), 2.04 (octet, 1, $J_{2'e,2'a}$ = 12 and $J_{2'e,3'}$ = 4.8 Hz, H-2′e), 1.74 (quintet, 1, $J_{2'a,3'}$ = 10 Hz, H-2′a).

Anal. Calcd for $C_{10}H_{13}N_2O_5I$: C, 32.62; H, 3.56; N, 7.61. Found: C, 32.54; H, 3.45; N, 7.53.

1-(2,6-Dideoxy-β-D-*arabino*-hexopyranosyl)uracil (10). To the iodonucleoside **9** (0.75 g, 2.0 mmol) in 50% aqueous methanol (80 ml) was added 200 mg of 10% Pd/C catalyst, followed by vigorous agitation in an hydrogen atmosphere for 10 min at ambient temperature. Triethylamine (0.6 ml) was then added and agitation was continued for 2 h, whereafter TLC on cellulose (C) indicated absence of educt. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo to a syrup, which was purified over a small Dowex 2 (HCO_3^-) column by elution with water. Evaporation of the eluate to dryness, followed by reevaporations from acetone and crystallization from acetone–ether, afforded 390 mg (81%) of the 2′,6′-dideoxynucleoside **10**: mp 199–200°; uv (pH 2–7) λ_{max} 259 nm (ε 8870), λ_{min} 230 (2930); (pH 12) λ_{max} 259 (6650) λ_{min} 242 (5480); CD (H_2O) θ −2140 (248 nm), +860 (278); NMR (D_2O) δ 7.75 and 5.87 (two 8-Hz d, H-6 and H-5), 5.74 (q, 1, $J_{1',2'a}$ = 10.5 and $J_{1',2'e}$ = 2.5 Hz, H-1′), 1.32 (d, 3, 6′-CH_3).

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.50; H, 5.77; N, 11.47.

1-(3,4-Di-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)uracil (11). To a solution of nucleoside **10** (350 mg, 1.5 mmol) in 15 ml of anhydrous pyridine was added dropwise with efficient stirring 0.9 ml of benzoyl chloride. The reaction mixture was kept at 55–60° for 20 hr, whereafter TLC (silica gel, solvents A, B) showed disappearance of the starting material. The reaction mixture was concentrated in vacuo to half of the volume, applied to four PLC plates, and developed four times with chloroform followed by elution of the main band (R_f 0.50) with chloroform. The eluate was evaporated to dryness in vacuo, codistilled with ethanol for crystallization, and recrystallized from ethanol: 510 mg (79%) of **11** as long needles; mp 188–190°; uv (ethanol) λ_{max} 235 nm (ε 24 680), inflection at 252 (18 680). The product was used directly for thiation.

1-(3,4-Di-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-4-thiouracil (12). To a solution of 510 mg (0.9 mmol) of nucleoside **11** in dioxane (20 ml) was added 220 mg of phosphorus pentasulfide and the mixture was heated under reflux for 2.5 h. After concentration to about 5 ml, the suspension was filtered and the filtrate was applied to four PLC plates followed by development with chloroform–methanol (55:45). The main zone (R_f 0.43) was removed and eluted with chloroform, to give upon evaporation to dryness and trituration of the residue with ethanol 240 mg (58%), mp 220–222°, uv (ethanol) λ_{max} 328 nm (ε 8870).

Anal. Calcd for $C_{24}H_{22}O_6N_2S$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.65; H, 4.67; N, 5.95.

1-(2,6-Dideoxy-β-D-*arabino*-hexopyranosyl)cytosine (3). A solution of 175 mg (0.38 mmol) of thionucleoside **10** in anhydrous methanol (25 ml) was placed in a glass sealing tube (50 ml) an which after saturation with ammonia at 0° was sealed and heated at 110–120° for 20 h. The tube was cooled and opened and its contents were evaporated to dryness. The residue, already homogeneous by TLC in A and C, was purified by PLC on cellulose plates (Machery and Nagel 300–50 with 0.5-mm coatings) with 2-propanol–concentrated ammonia–water (7:1:2). Elution of the main zone (R_f 0.71) with water, evaporation of the eluate to dryness, and trituration with methanol–acetone afforded 51 mg (53%) of **3** as fine crystals of mp 135–140° after softening from 120° on and $[\alpha]^{25}D$ −4.3° (*c* 0.55, H_2O) [reported[7] mp 137–140° and $[\alpha]^{25}D$ −4° (*c* 0.38, H_2O)]; CD (H_2O) θ +1200 (240 nm), +1300 (278), cf. Figure 1. The uv data in 0.1 N HCl and 0.1 N NaOH were identical, i.e. ϵ_{max} (pH 13)/ϵ_{max} (pH 1) 0.68; the NMR spectrum in D_2O was superimposable on that reported[7] for oxamicetin derived **3**.

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Registry No.—**3**, 52598-18-2; **4**, 6067-28-3; **5**, 6027-64-1; **6**, 57459-51-5; **7**, 5139-56-0; **8**, 57459-52-6; **9**, 57459-53-7; **10**, 57459-54-8; **11**, 57459-55-9; **12**, 57459-56-0; acetic acid, 108-24-7; methanesulfonyl chloride, 124-63-0; benzoyl chloride, 98-88-4.

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Regiospecificity of the 1,4 Cycloaddition of 2-Methyl-1-penten-3-one to Methyl Crotonate and to Methyl Methacrylate

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The thermal cycloaddition of 2-methyl-1-penten-3-one (**6**) to methyl methacrylate (**2**) gave 3,6-dimethyl-2-ethyl-1-oxacyclohex-2-ene-6-carboxylic acid methyl ester (**12**), and subsequent reduction of the ester group and acid-catalyzed cyclization gave 1,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (**14**). In contrast to this result, the addition of **6** to methyl crotonate (**7**) gave 3,6-dimethyl-2-ethyl-1-oxacyclohex-2-ene-5-carboxylic acid methyl ester (**10**), and reduction and cyclization gave 3,7-dimethyl-1-ethyl-2,6-dioxabicyclo[2.2.2]octane (**11**). A dimer of **6**, 3,6-dimethyl-2-ethyl-6-propanoyl-1-oxacyclohex-2-ene (**16**), was formed in both thermal addition reactions, and the dimerization of **2** to yield 2-methyl-5-methylene-1,6-hexanedioic acid dimethyl ester (**18**) co-occurred with the addition of **6** to **2**.

Brevicomin (**5**),[1] frontalin (**4**),[2] and multistriatin (**9**)[3] are related bicyclic ketal structures that are components of the aggregation pheromones of three bark beetle species, *Dendroctonus brevicomis, Dendroctonus frontalis,* and *Scolytus multistriatus*. The aggregation pheromones of these insects are potentially useful agents for survey and control of insect populations. These compounds have been synthesized by different routes,[4–6] one of which utilized the cycloaddition of an α,β-unsaturated ketone to an α,β-unsaturated ester.[7]

Mundy and coworkers synthesized **4** via the cycloaddition of methyl vinyl ketone (**1**) to methyl methacrylate (**2**).[7] The cycloaddition product (**3**) was subsequently reduced and cyclized to yield **4**. One critical feature of this synthetic approach is the regiospecificity of the 1,4-cycloaddition reaction. Mundy's synthesis was based on earlier work of Smith and coworkers,[8] and in both studies addition proceeded via path a and not b. Furthermore, cycloadditions with dienophiles such as α,β-unsaturated nitriles, al-

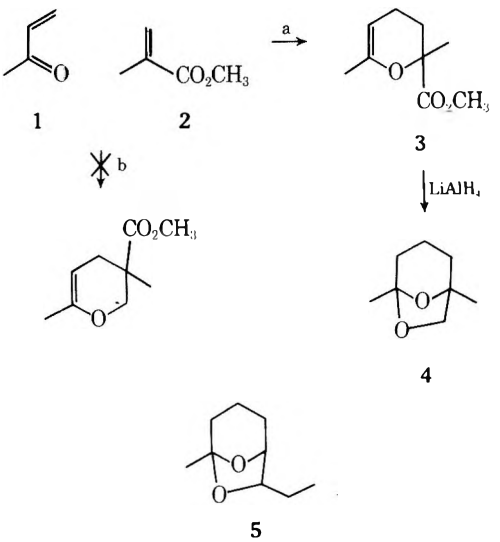


Table I
NMR Data for the 2-Oxacyclohexene Derivatives

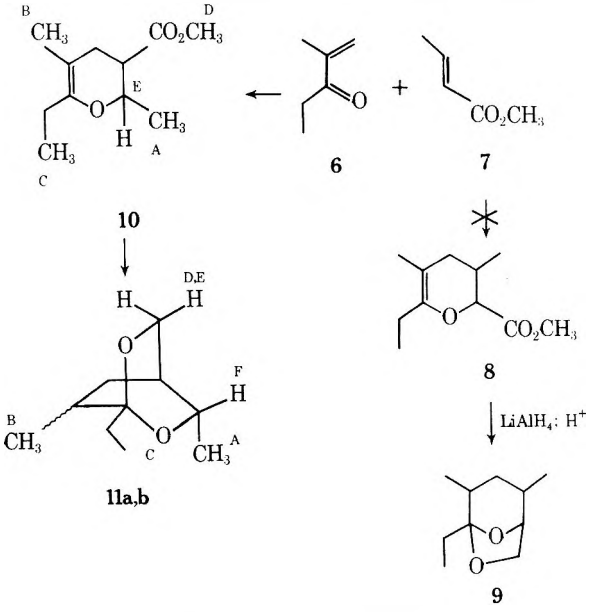
Compd	Chemical shifts,[a] δ, ppm				
	Protons				
	A	B	C	D	E
10	1.27 (3 H, d, J = 6.0)	1.62 (3 H, s)	1.02 (3 H, t, J = 7.5)	3.72 (3 H, s)	3.84 (1 H, m)
12	1.45 (3 H, s)	1.56 (3 H, s)	1.05 (3 H, t, J = 7.3)	3.70 (3 H, s)	
16	1.28 (3 H, s)	1.57 (3 H, s)	1.02 (3 H, t, J = 7.5)	1.09 (3 H, t, J = 6.5)	

[a] s = singlet, d = doublet, t = triplet, m = multiplet; J (observed splittings) in hertz.

dehydes, ketones, alcohols, and vinyl ethers, enamines, vinyl carbamates, and vinyl ureas have been reported; and in each case the 6-substituted 2-oxacyclohexene derivative was formed.[9,10]

Results and Discussion

We explored an analogous reaction pathway for the synthesis of **9**. This reaction sequence involved the addition of 2-methyl-1-penten-3-one (**6**) to methyl crotonate (**7**), which yielded a carbomethoxy 2-oxacyclohexene intermediate. In principle, intermediates **8** or **10** could result from the cycloaddition reaction. The reduction and cyclization of **8** would yield the desired ketal **9**; however, **10** would lead to 3,7-dimethyl-1-ethyl-2,6-dioxabicyclo[2.2.2]octane (**11**).



The ir and MS spectra provided evidence that a carbomethoxy 2-oxacyclohexene derivative (**10**) was formed from the thermal addition of **6** and **7**. The ir spectrum contained a strong carbonyl absorption at 1737 cm^{-1} and a vinyl ether absorption at 1686 cm^{-1}. The mass spectrum gave a molecular ion at m/e 198 and an M − CO_2CH_3 at 139. The NMR signals are assigned in Table I, and these data show that 3,6-dimethyl-2-ethyl-1-oxacyclohex-2-ene-5-carboxylic acid methyl ester (**10**), not the 6-carbomethoxy 2-oxacyclohexene derivative (**8**), was the reaction product. The NMR signals provided evidence for an ethyl group, a vinyl methyl group, a methyl group on a carbon atom α to an ether oxygen atom, and a methine proton α to an ether oxygen atom. The chemical shifts of the methyl group doublet at 1.27 ppm and the methine proton multiplet at 3.8 ppm are inconsistent with structure **8**. The methyl group at C-5 in **8** is on the carbon atom β to the ether oxygen atom and the carbomethoxy group, and the predicted chemical shift for this methyl group would be upfield from the observed value of 1.27 ppm. Also, the methine proton at C-6 in **8** is α to both the ether oxygen atom and the carbomethoxy group, and the signal should appear as a doublet at lower field than 3.8 ppm.

Reduction of **10** with lithium aluminum hydride and acid treatment yielded a mixture of two compounds (**11a** and **11b**, ~50:50) which were separated by GLC. As shown in Table II, the NMR, ir, and MS spectra of **11a** and **11b** were similar and indicated that both structures were 3,7-dimethyl-1-ethyl-2,6-dioxabicyclo[2.2.2]octanes. The mass spectra contained a molecular ion at m/e 170, and characteristic absorptions associated with CH, CC, and CO stretching and bending frequencies were observed in the ir spectra. Although some similarities were noted, the spectra of **11a** and **11b** were not identical with those recorded for any of the isomers of **9**.[11] Products **11a** and **11b** were stable in dilute CCl_4 and $CDCl_3$ solutions; however, neat samples appeared to be unstable. A related bicyclic acetal, 2,6-dioxabicyclo[2.2.2]octane, was previously described as "... hygroscopic and unstable toward oligomerization under ordinary conditions ...".[12]

The combined NMR, ir, and MS data and their mode of formation indicated that **11a** and **11b** were epimeric at C-7.[13] One of the characteristic differences between the isomers of **11** and the isomers of **9** was the presence of a doublet near 1.3 ppm in **11a** and **11b**. The methyl groups in **9** are on carbon atoms β to an oxygen atom, and the corresponding signals in the NMR occur at higher field than 1.3 ppm. The C-3 methyl group in **11** is on the carbon atom α to an oxygen atom, and a chemical shift of 1.3 ppm is consistent with that predicted.

The cycloaddition characteristics of the enone **6** were tested by the addition of **6** to a commonly used dienophile, methyl methacrylate (**2**). The addition occurred in the manner previously reported for the addition of acrolein[8] or methyl vinyl ketone[7] to **2**. 3,6-Dimethyl-2-ethyl-1-oxacyclohex-2-ene-6-carboxylic acid methyl ester (**12**) was identi-

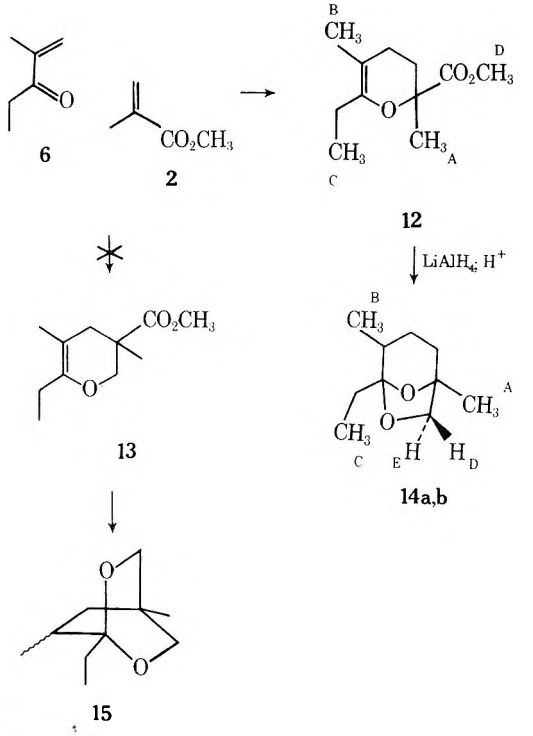


Table II
NMR Data for the Dioxabicyclooctanes

Compd	Chemical shifts,[a] δ, ppm					
	Protons					
	A	B	C	D	E	F
11a	1.27 (3 H, d, J = 6.5)	0.96 (3 H, d, J = 6.5)	0.89 (3 H, t, J = 7.5)	3.99 (2 H, m)		4.17 (1 H, m)
11b	1.26 (3 H, d, J = 6.5)	0.98 (3 H, d, J = 6.5)	0.88 (3 H, t, J = 8.0)	3.99 (2 H, m)		4.17 (1 H, m)
14a	1.31 (3 H, s)	0.83 (3 H, d, J = 6.2)	0.93 (3 H, t, J = 7.3)	3.41 (1 H, dd, J_1 = 6.8, J_2 = 1.0)	3.86 (1 H, d J = 6.6)	
14b	1.31 (3 H, s)	0.99 (3 H, d, J = 7.2)	0.92 (3 H, t, J = 7.3)	3.38 (1 H, dd, J_1 = 6.5, J_2 = 1.8)	3.88 (1 H, d, J = 6.7)	

[a] dd = doublet of doublets; J (observed splittings) in hertz.

fied as a reaction product, but the 5-carbomethoxy-2-oxacyclohexene derivative **13** was not found.

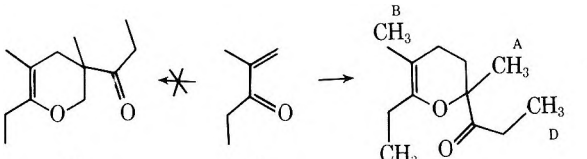
The structure of **12** is based on the NMR, ir, and MS spectra. The ir spectrum has characteristic absorptions for the vinyl ether and the ester group, and the mass spectrum has a molecular ion at *m/e* 198 and an M − CO_2CH_3 at 139. The NMR spectrum supports structure **12** but not **13.** The singlets at 1.56 and 1.45 ppm are assigned to the methyl groups at C-3 and C-6, respectively. The predicted high-field signals (1.2–1.3 ppm) for a C-5 methyl group and low-field signals (3.0–3.5 ppm) for C-6 methylene protons for **13** were not observed.

The $LiAlH_4$ reduction of **12** and subsequent acid-catalyzed cyclization yielded 1,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane diastereomers **14a** and **14b,** which were separated by GLC. Their MS and ir spectral characteristics and those of the isomeric bicyclic ketal **9** were similar;[11] the mass spectrum gave a molecular ion at *m/e* 170. The presence of the C-1 methyl group in **14a** and **14b** is clearly demonstrated by the presence of a singlet at 1.31 ppm in the NMR spectrum.

The relative stereochemistry at C-4 was assigned according to the relative chemical shifts observed for endo and exo methyl groups in the isomers **9**[11] in which the chemical shifts for the endo methyl groups were always upfield of the shifts for the exo methyl groups. Since the C-4 methyl group in **14a** is 0.09 ppm upfield of the corresponding methyl group in **14b,** the methyl group at C-4 is assigned the endo configuration in **14a** and the exo configuration in **14b.**

The NMR spectra precluded the possibility that structure **15** was formed and thereby supported the conclusion that **12** and not **13** was formed from the cycloaddition of **6** and **2.** The bicyclic ketal structure **15** contains four methylene protons α to oxygen atoms, but only two downfield methylene proton signals were observed in the NMR spectrum. Also, the bridgehead methyl group in **15** is on the carbon atom β to the oxygen atoms, and the predicted chemical shift for these protons would be upfield from the observed methyl group at 1.31 ppm.

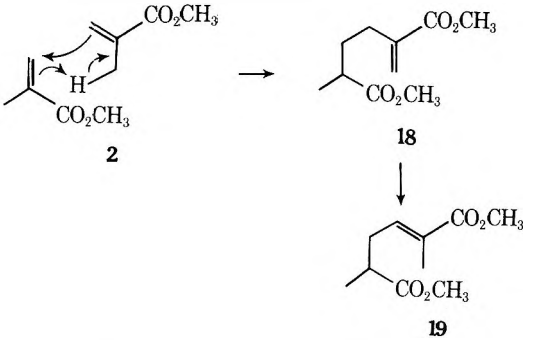
In the thermal addition reactions, where **6** was added to **2** and to **7,** the dimerization of **6** yielded an additional cycloaddition product, 3,6-dimethyl-2-ethyl-6-propanoyl-1-oxacyclohex-2-ene (**16**).[14] At lower temperature (210°) and with shorter heating periods (2 hr), **16** was the major product in the GLC chromatogram. A sample of **16** was isolated and purified by preparative GLC, and the identity of the



17 6 16

compound was established by spectrometric methods. The MS and ir spectra of **16** were related to those of **10** and **12.** The mass spectrum gave a molecular ion at *m/e* 196 and an M − CH_3CH_2CO peak at 139, and the ir spectrum contained carbonyl (1720 cm^{-1}) and vinyl ether (1685 cm^{-1}) peaks. The chemical shift assignments are consistent with structure **16.** Structure **17** would be expected to show a downfield absorption for the CH_2O group; these are not present in the spectrum.

In the reaction mixture of **6** and **2,** the tail-to-tail dimerization of **2** yielded 2-methyl-5-methylene-1,6-hexanedioic acid dimethyl ester (**18**). This structure was consistent with



2 18 19

the recorded spectral data. The mass spectrum gave a molecular ion (*m/e* 200) and M − CO_2CH_3 (141) and M − HCO_2CH_3 (140) peaks. The ir absorptions corresponded to ester groups (1735 and 1725 cm^{-1}) and to a terminal double bond (1628 and 945 cm^{-1}). In the NMR spectrum, signals were observed for the C-2 methyl group (1.17 ppm), the carbomethoxy groups (3.67 and 3.74 ppm), and the terminal olefinic protons (5.55 and 6.16 ppm).

The terminal dimerization of **2** in the absence of radical, cationic, or anionic catalysts has been investigated, and **19** and **18** were reported as major and minor products, respectively.[15] In the absence of catalysts the dimerization can proceed via the ene mechanism with one molecule of **2** acting as the ene component and a second acting as the eno-

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phile. The initial product, **18**, was the only product isolated under our conditions; however, the isomerization of **18** to **19** could occur with other reaction conditions.

Conclusions

Colonge and Descotes reviewed the 1,4-cycloaddition reactions of α,β-unsaturated carbonyl compounds with substituted olefins.[9] They observed that with terminally unsubstituted dienophiles the electronic nature of the functional group on th dienophile did not affect the direction of addition, but that high electron density on the dienophile did facilitate the addition. The dimerization of acrolein to yield 2-oxacyclohexene-6-carboxaldehyde is a typical example of this type of cycloaddition, and theoretical treatments have been provided by Devaquet and Salem[16] and by Alston and Shillady.[17]

Our observations that the addition of **6** and **2** yielded **12** and that the dimerization of **6** gave **16** are consistent with reported thermal cycloaddition reactions where enones such as acrolein and methyl vinyl ketone were added to isobutylene,[8,18] methyl acrylate,[8] and **2**.[7,8] Since in each case the 6-substituted 2-oxacyclohexene derivative was the only reported product, the methyl group and the carbomethoxy group apparently have the same net effect in controlling the regiospecificity of the reaction.

In the cycloaddition of **6** and **2**, the effects of the methyl group and the carbomethoxy group were in the same direction; however, the cycloaddition of **6** and **7** provided a novel situation where the directing effects of the methyl group were in opposition to those of the carbomethoxy group. In the latter case, the 5-carbomethoxy-2-oxacyclohexene derivative (**10**) was formed.

The cycloaddition of α,β-unsaturated aldehydes and ketones to substituted olefins represents a potential direct route to intermediates, which can be converted into dioxabicyclo[3.2.1]octanes; however, some characteristics of this reaction should be considered. The cycloaddition reaction may yield dimers such as **16** and **18** which complicate the purification scheme and reduce the yield of the substituted dihydropyran derivative. Furthermore, dienophile substituent effects can lead to 5-carbomethoxy-2-oxacyclohexene-intermediates, which give dioxabicyclo[2.2.2]octanes on reduction and cyclization.

Experimental Section

Mass spectra were recorded on an Hitachi RMU-6E; the ir spectra in carbon tetrachloride solution on a Perkin-Elmer 621; and the Fourier transform ^{1}H NMR spectra in deuteriochloroform solution on a Varian XL-100 as δ values with tetramethylsilane as an internal reference. Preparative GLC was performed with a Varian Aerograph Series 2700, and quantitative determinations were based on peak areas relative to an internal standard.

Addition of 2-Methyl-1-penten-3-one (6) to Methyl Crotonate (7). A solution of **6**[13] (0.98 g, 10 mmol), **7** (1.00 g, 10 mmol), and toluene (1% hydroquinone, 0.5 ml) was heated for 4 hr at 210°. The thermal additions were performed at autogenous pressure in glass tubes (6 mm × 60 cm, filled to ⅓ capacity), which were sealed under nitrogen and rocked continuously during the reaction. One product, 3,6-dimethyl-2-ethyl-6-propanoyl-1-oxacyclohex-2-ene (**16**), was isolated by GLC fractionation with a SE-30 column (5% on 60–80 AW DMCS Chromosorb G: silylated glass, 10 mm × 3.6 m; He, 100 ml/min; 190°) in 38% yield (by GLC peak area). A single peak with retention time (t_R) 10.0 min was collected for NMR, ir, MS, and elemental analysis. The GLC analysis indicated that **16** was the major product and that 3,6-dimethyl-2-ethyl-1-oxacyclohex-2-ene-5-carboxylic acid methyl ester (**10**) was not formed.

Infrared spectrum (CCl_4) 2995, 2930, 2890, 1720, 1685, 1450, 1370, 1160, 1138, 1100, 1063, 905 cm^{-1}; mass spectrum *m/e* (rel intensity) 27 (6), 29 (16), 41 (15), 43 (100), 57 (14), 69 (11), 81 (7), 95 (11), 121 (7), 139 (49), 196 (M^+, 11).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.46; H, 10.20. Found: C, 73.26; H, 10.35.

The reaction was repeated with **6** (1.96 g, 20 mmol) and **7** (10.0 g, 100 mmol), and toluene (1% hydroquinone, 10 ml) at 260–280°. The reaction mixture was fractionated by short-path distillation, and the volatile material was collected in two fractions: A, 37–42° (49 mm), and B, 79–85° (0.2 mm). Both fractions were analyzed by GLC, and A contained toluene and unreacted starting material. The SE-30 fractionation of B gave **10**, with t_R 10.8 min (90% of fraction B, 13% overall yield). The fraction collected from the SE-30 column gave a single peak, t_R 17.4 min, when rechromatographed on a Carbowax 20M column (5% on AW DMCS 60–80 Chromosorb G; silylated glass, 6 mm × 6 m; He, 60 ml/min; 160°), and samples were collected for NMR, ir, MS, and elemental analyses. A minor peak (<2%) with retention time corresponding to **16** was observed in the GLC chromatogram of B.

Infrared spectrum (CCl_4) 2985, 2960, 2945, 1737, 1686, 1435, 1385, 1367, 1112, 1088, 1062, 1030, 902 cm^{-1}; mass spectrum *m/e* (rel intensity) 27 (17), 29 (37), 39 (16), 41 (41), 43 (23), 57 (40), 69 (100), 99 (10), 100 (10), 109 (11), 123 (15), 139 (34), 198 (M^+, 19).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.66; H, 9.09. Found: C, 66.46, H, 9.17.

Addition of 2-Methyl-1-penten-3-one (6) to Methyl Methacrylate (2). A solution of **6** (1.96 g, 20 mmol) and **2** (10 g, 100 mmol) and toluene (1% hydroquinone, 10 ml) was heated at 260–280° for 4.5 hr. The resulting mixture was fractionated by short-path distillation, and the solvent and unreacted starting material were removed as fraction A at 32–35° (49 mm). Fraction B was collected at 75–84° (0.2 mm) and redistilled to yield two fractions: B1, 75–79° (0.2 mm), 0.45 g; B2, 79–83° (0.2 mm), 1.9 g. GLC analysis of B1 indicated that this fraction contained 65% 3,6-dimethyl-2-ethyl-1-oxacyclohex-2-ene-6-carboxylic acid methyl ester (**12**). B2 contained 90% 2-methyl-5-methylene 1,6-hexanedioic acid dimethyl ester (**18**). The overall yields of **12** and **18** were 8 and 18.5%, respectively. Both products **12** and **18** were purified by GLC chromatography; **12** and **18** had t_R 8.4 and 10.8 min, respectively, on the SE-30 column, and **12** had t_R 12.9 min on the Carbowax 20M column.

12: infrared spectrum (CCl_4) 2995, 2975, 2960, 2940, 1757, 1735, 1686, 1145, 1372, 1295, 1158, 1114 cm^{-1}; mass spectrum *m/e* (rel intensity) 27 (12), 29 (29), 39 (15), 41 (42), 42 (100), 53 (9), 55 (14), 57 (68), 59 (9), 67 (8), 69 (95), 70 (8), 79 (8), 81 (18), 83 (6), 85 (8), 88 (6), 95 (18), 96 (6), 97 (6), 98 (8), 99 (14), 100 (5), 101 (5), 109 (46), 110 (42), 111 (11), 121 (14), 123 (17), 127 (9), 137 (14), 138 (15), 139 (57), 140 (8), 141 (34), 142 (6), 166 (17), 169 (7), 198 (M^+, 46), 199 (6).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.66; H, 9.09. Found: C, 66.81; H, 9.16.

18: infrared (CCl_4) 3030, 2985, 2960, 2885, 1735, 1725, 1628, 1460, 1435, 1195, 1170, 1150, 1065, 945 cm^{-1}; mass spectrum *m/e* (rel intensity) 27 (25), 29 (16), 39 (29), 40 (22), 41 (44), 53 (26), 55 (25), 56 (30), 57 (30), 59 (45), 69 (28), 81 (78), 88 (100), 109 (35), 113 (27), 125 (26), 126 (58), 140 (44), 141 (25), 168 (33), 169 (30), 200 (M^+, 3); NMR spectrum δ 1.17 (3 H, d, J = 7.0 Hz), 3.67 (3 H, s), 3.74 (3 H, s), 6.16 (1 H, m), 5.55 (1 H, d, J = 1.3 Hz).

Anal. Calcd for $C_{10}H_{16}O_4$; C, 60.00; H, 8.00. Found: C, 60.21; H, 8.11.

3,7-Dimethyl-1-ethyl-2,6-dioxabicyclo[2.2.2]octane (11a,b). A GLC purified sample of **10** (11.3 mg, 0.057 mmol) in 1 ml of tetrahydrofuran (THF) was dried over 4Å sieves for 24 hr and stirred with lithium aluminum hydride (2.5 ml of a 0.029 *M* THF solution, 0.071 mmol) at 25° for 30 min. A sulfuric acid solution (1 *M*) was added dropwise until the solution was acidic to pH paper (about 150 μl), and the mixture was allowed to stand for 14 hr. The THF solution was separated from the gray precipitate and placed over anhydrous sodium carbonate for 6 hr, and the resulting neutral solution was dried over 4-Å sieves for 14 hr. GLC chromatography on the SE-30 column at 150° showed one peak (37% yield by peak area), t_R 20.0 min; however, fractionation with a Carbowax 20M column at 125° gave two peaks at approximately equal size with t_R 23.4 and 24.3 min. The two peaks were collected and designated **11a** and **11b**, respectively. Neat samples of **11a,b** were unstable and formed two phases on standing at room temperature.

11a: infrared spectrum (CCl_4) 2975, 2935, 2875, 1465, 1373, 1204, 1152, 1128, 1063, 937, 925 cm^{-1}; mass spectrum *m/e* (rel intensity) 27(10), 29 (18), 43 (15), 54 (8), 55 (26), 57 (100), 71 (10), 72 (3), 81 (5), 86 (6), 95 (10), 99 (4), 128 (9), 170 (M^+, 9).

11b: infrared spectrum (CCl_4) 2980, 2945, 2880, 1465, 1375, 1205, 1165, 1130, 1064, 927 cm^{-1}; mass spectrum *m/e* (rel intensity) 27 (10), 29 (28), 41 (16), 43 (11), 54 (13), 55 (20), 57 (100), 71 (12), 72 (4), 81 (6), 86 (8), 95 (4), 99 (7), 128 (10), 170 (M^+, 10).

1,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (14a,b).

A GLC purified sample of **12** (14.0 mg, 0.071 mmol) was reduced with $LiAlH_4$ (0.071 mmol) and worked up as in the preceding experiment. The SE-30 fractionation yielded one peak (49% yield), t_R 14.0 min, and the elemental analysis was obtained for this material. Chromatography with Carbowax 20M gave two peaks of approximately equal size, t_R 12.7 and 13.5 min, which were designated **14a** and **14b**, respectively.

14a: infrared spectrum (CCl_4) 2985, 2945, 2895, 1462, 1382, 1130, 1112, 1045, 1040, 925, 920, 900 cm^{-1}; mass spectrum *m/e* (rel intensity) 27 (11), 29 (32), 41 (11), 43 (15), 55 (14), 57 (100), 72 (31), 81 (7), 96 (4), 114 (10), 128 (6), 140 (4), 170 (M^+, 10).

14b: infrared spectrum (CCl_4) 2985, 2940, 2885, 1453, 1378, 1122, 1105, 1043, 1030, 913 cm^{-1}; mass spectrum *m/e* (rel intensity) 27 (12), 29 (26), 41 (12), 43 (16), 55 (14), 57 (100), 72 (31), 81 (7), 96 (4), 114 (11), 128 (5), 140 (4), 170 (M^+, 9).

Anal. Calcd for $C_{10}H_{18}O_2$; C, 70.66; H, 10.59. Found: C, 70.51; H, 10.78.

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Registry No.—**2**, 80-62-6; **6**, 25044-01-3; **7**, 18707-60-3; **10**, 57428-74-7; **11a**, 57428-75-8; **11b**, 57457-89-3; **12**, 57428-76-9; **14a**, 57428-77-0; **14b**, 57428-78-1; **16**, 57428-79-2; **18**, 4513-62-6.

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Mass Spectrometric Studies of the Dioxabicyclo[3.2.1]octanes Multistriatin, Frontalin, and Brevicomin

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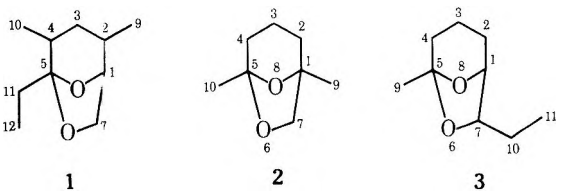
Mass spectra were recorded for three alkyl-substituted dioxabicyclo[3.2.1]octanes, 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (multistriatin), 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (frontalin), and 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane (*exo*-brevicomin), and for the corresponding deuterium-labeled compounds 4,11-11-trideuteriomultistriatin, 4,4,10,10,10-pentadeuteriofrontalin, and 4,4,9,9,9-pentadeuterio-*exo*-brevicomin, and structures were assigned for the characteristic ions. Where possible the relative abundances of the observed ions were related to the alkyl group substituents, and a general fragmentation pattern was proposed.

Multistriatin (**1**) was isolated and identified as one component of a three-component aggregation pheromone of the European elm bark beetle.[1] In the initial phase of the identification process, the mass spectrum exhibited several distinctive peaks, but this information did not provide definitive evidence for the bicyclic ketal ring system or the type of ring substitution.

After the structure of **1** was proved, the mass spectrum of **1** was compared with the reported spectra of known bicyclo[3.2.1]octane derivatives, including two insect pheromone components, frontalin (**2**)[2] and *exo*-brevicomin (**3**),[3] and to the known fragmentation patterns for cyclic ketals.[4] Inspection of the available data revealed that some ions were common to two or more of the bicyclic ketals. However, the identities of most of the ions were uncertain, and a fragmentation pattern for the substituted dioxabicyclo[3.2.1]octanes was not obvious.

We collected three types of data for the dioxabicyclo[3.2.1]octanes **12**, and **3**: (1) unit resolution electron impact (EI) mass spectra, (2) unit resolution EI spectra of deuterium labeled compounds, (3) high-resolution EI spectra of unlabeled compounds. The objective of these experiments was to determine the characteristic fragments of these dioxabicyclo[3.2.1]octanes and the effects of alkyl substituents on the fragmentation pattern.



1 **2** **3**

Results and Discussion

Multistriatin (**1**) exists as four diastereomers which have been synthesized and purified,[5] and the unit resolution spectrum of each isomer was recorded. Since no qualitative and only minor quantitative differences were observed in

Table I
Mass Spectral Data for α-Multistriatin (1)

Peak, m/e	Rel abundance (% of base peak)	Corresponding peak in 1′,[a] m/e	Formula[b]
27	11		
29	28		
39	9		
41	13		
43	6		
55	21	55	
57	100	59	
71	13	71	C_4H_7O
72	4		
81	10	82	C_6H_9
86	5		$C_5H_{10}O$
96	15	97	C_7H_{12}
99	3		
128	9	130	$C_7H_{12}O_2$
140	4		
170	4	173	$C_{10}H_{18}O_2$

[a] 1′ is multistriatin-d_3. [b] Formulas obtained from high-resolution MS data of 1.

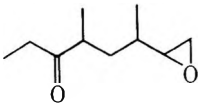
Table II
Mass Spectral Data for Frontalin (2)

Peak, m/e	Rel abundance (% of base peak)	Corresponding peak in 2′,[a] m/e	Formula[b]
27	8		
29	5		
39	10		
41	13		
43	100	46	
54	9		
55	8		
67	7		
69	5		
71	16	71	C_4H_7O
72	49	73	C_4H_8O
85	4		C_5H_9O
99	4		
100	23	103	$C_6H_{12}O$
112	6	117	$C_7H_{12}O$
142	9	147	$C_8H_{14}O_2$

[a] 2′ is frontalin-d_5. [b] Formulas obtained from high-resolution MS data of 2.

the four MS spectra, the data shown in Table I for the α isomer were regarded as representative of each of the multistriatin isomers. Similarly, no stereochemical effects were reported for *endo*- and *exo*-brevicomin,[6] and we have confined our experiments to the exo isomer, **3**. The compiled MS data for **2** and **3** are given in Tables II and III, respectively.

The mass spectra of the isomers of the precursor to **1**, 4,6-dimethyl-7,8-epoxy-3-octanone (**4**), were identical with



4

those recorded for **1**. Similar results have been observed in mass spectral studies,[7] and the conversion of a related keto epoxide to the bicyclic ketal structure has been reported.[8,9] The thermal conversion of **4** to **1** has been observed in this laboratory,[10] and this reaction could occur in the mass spectrometer inlet.

Acid-catalyzed D–H exchange at positions α to the ketal carbon atom occurred without decomposition of the bicyclic ketals,[5] and this method was used to prepare 4,11,11-trideuterio-α-multistriatin (**1′**), 4,4,10,10,10-pentadeuteriofrontalin (**2′**), and 4,4,9,9,9-pentadeuterio-*exo*-brevicomin (**3′**). The unit resolution MS for each compound was recorded, and the data for **1′**, **2′**, and **3′** are given in Tables I, II, and III, respectively.

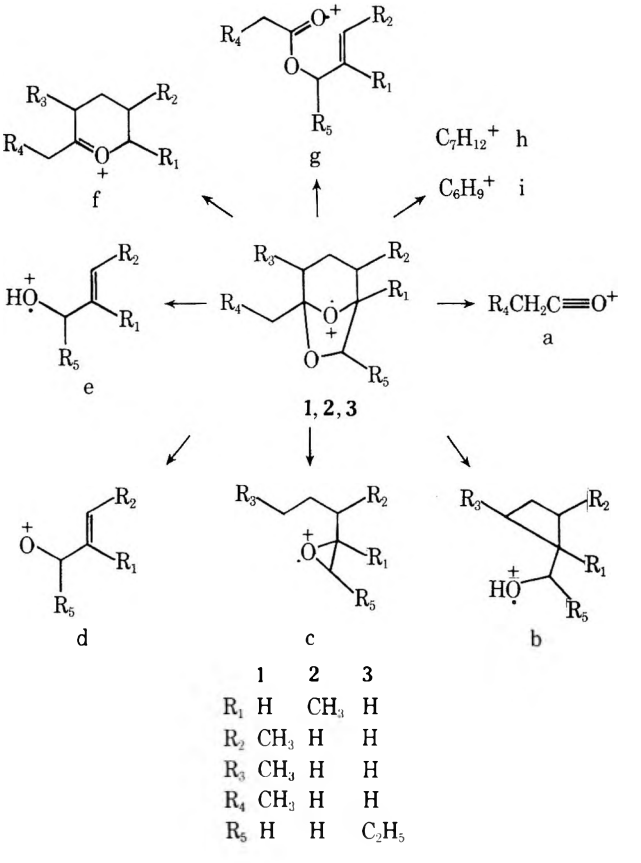
Table III
Mass Spectral Data for *exo*-Brevicomin (3)

Peak, m/e	Rel abundance (% of base peak)	Corresponding peak in 3′,[a] m/e	Formula[b]
27	13		
29	9		
39	8		
41	12		
43	100	46	
55	7		
57	9		
68	15	68	
71	8		C_4H_7O
72	4		C_4H_8O
85	29	85/86	C_5H_9O
86	11	87	$C_5H_{10}O$
98	13	103	$C_6H_{10}O$
99	5		$C_6H_{11}O$
114	26	117	$C_7H_{14}O$
127	4	132	$C_7H_{11}O_2$
156	4	161	$C_9H_{16}O_2$

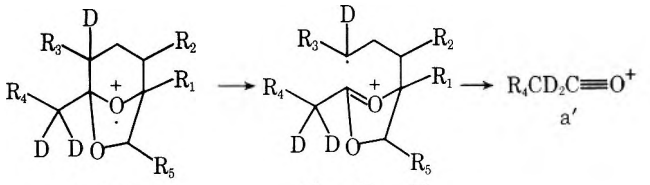
[a] 3′ is *exo*-brevicomin-d_5. [b] Formulas obtained from high-resolution MS data of 3.

The most abundant species observed for **1**, **2**, and **3** was the $R_4CH_2O^+$ ion. The retention of two D atoms in the *m/e* 59 ion in **1′** and three D atoms in the *m/e* 45 ions in **2′** and

Chart I
Mass Spectral Fragments from Multistriatin (1), Frontalin (2), and Brevicomin (3)



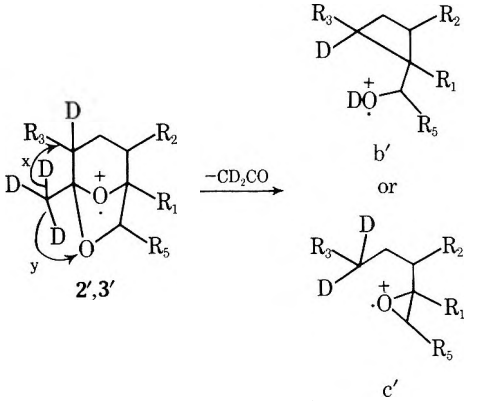
3′ supported the assignment of structure a′ for these ions and structure a for the corresponding ions *m/e* 57 in **1** and *m/e* 43 in **2** and **3**, as shown in Chart I. Fragment a was the predominant species observed for several other bicyclic ketals,[7,11] and a was also observed for the 2,2-dialkyldioxolanes.[4] The mode of formation of this ion in the bicyclic ketals was probably similar to that described for the cyclic ketals.[4] A possible mechanism for the formation of a′ (or a) is shown here.



1′, 2′, 3′

	1′	2′	3′
R_1	H	CH_3	H
R_2	CH_3	H	H
R_3	CH_3	D	D
R_4	CH_3	D	D
R_5	H	H	C_2H_5

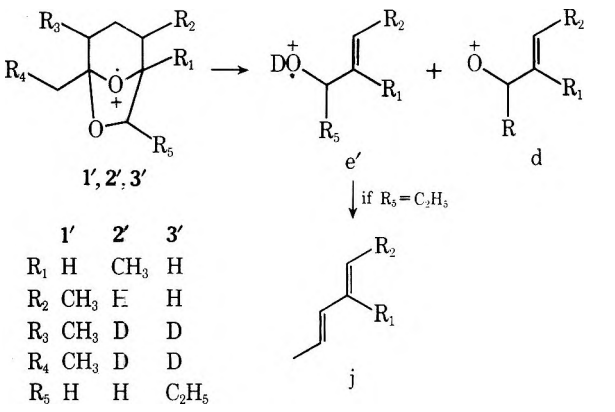
The loss of a related fragment with the formation of ions *m/e* 100 and 114 was observed in **2** and **3**, respectively. High-resolution data confirmed that CH_2CO was lost from the molecular ion, and deuterium labeling demonstrated that the intramolecular transfer of one D atom had occurred. A D shift from C-10 in 2′ or C-9 in 3′ to C-4 (path x) or to O-6 (path y) with the expulsion of CD_2CO could yield species c′ or b′, respectively. The corresponding M − CH_3CHCO peak in **1** was not observed.



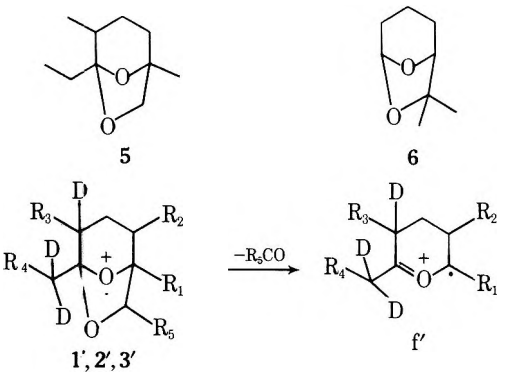
	2′	3′
R_1	CH_3	H
R_2	H	H
R_3	D	D
R_5	H	C_2H_5

The ions in **1** and **2** with *m/e* 71 ($C_4H_7O^+$) occurred with the *m/e* 72 ($C_4H_8O^{\cdot+}$) ions; and *m/e* 85 ($C_5H_9O^+$), 86 ($C_5H_{10}O^{\cdot+}$), and 68 ions were present in **3**. No D atoms were incorporated into the *m/e* 71, 85, or 68 ions, but one D atom was in the *m/e* 72 ions in 1′ and 2′ and the *m/e* 86 ion in 3′. This evidence indicated that the *m/e* 71 and 85 ions were derived from C-7, C-1, and C-2, the attached alkyl groups, and one of the oxygen atoms; and that *m/e* 72 and 86 ions were the protonated forms of these species. Structures d and e were consistent with these data, and the *m/e* 68 ion (j) in **3** and 3′ can result from the elimination of H_2O from fragment e or HDO from e′. The incorporation of one D atom into e′ supported the hypothesis that an intramolecular H shift from C-9 to one of the oxygen atoms occurred during fragmentation.

An interesting substituent effect was observed for fragments d and e. In **1** and **3**, d was the more abundant ion (d:e 13:4 in **1**; 29:11 in **3**), but e was the most abundant ion in **2** (d:e 16:49). The same pattern was observed in the spectrum of 1,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (**5**) (d:e = 7:31),[12] and this effect was attributed to the presence of an alkyl substituent at C1.

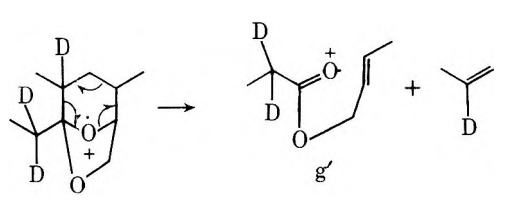


	1′	2′	3′
R_1	H	CH_3	H
R_2	CH_3	H	H
R_3	CH_3	D	D
R_4	CH_3	D	D
R_5	H	H	C_2H_5



The $C_6H_{10}O^{\cdot+}$ ion (*m/e* 98) in **3** retained all five D atoms in 3′ and was assigned structure f′. The corresponding ions which result from the loss of CH_2O were observed in the spectra of **1** and **2**, but the relative abundances were low. Substituent effects for alkyl groups at C-7 were important since the relative abundances of species f were 4, 6, and 13% in **1**, **2**, and **3**, respectively. Furthermore, in the reported MS data for the bicyclic acetal, 7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**6**),[11] f was the most abundant species.

A unique ion (*m/e* 128) which corresponded to M − CH_3CHCH_2 was present in the spectrum of **1**. The loss of C_3H_5D from 1′ with the retention of two deuterium atoms in the *m/e* 130 ion suggested that bonds C-2–C-3 and C-4–C-5 were broken. The formation of ion g or g′ via a retro-Diels–Alder process was consistent with the D labeling and the *m/e* data.



Once again, substituent effects were important since this species was observed for **1** but not for **2** and **3**. The C-2 methyl group in **1** could be related to the formation of this species; however, this possibility was precluded by the MS data obtained for **5**. This dioxabicyclo[3.2.1]octane did not contain a C-2 substituent, but the abundance of the M − CH_3CHCH_2 species was equal to that found in **1**.[12] These data did not exclude the possibility that the ethyl group at

C-5 in **1**, as opposed to the methyl groups in **2** and **3**, was related to this fragmentation pattern; however, the C-4 substituent was adjacent to the site of bond breaking and appeared to be the more important factor in this fragmentation pathway.

The loss of $CH_3CH_2CO_2H$ in **1** yielded a hydrocarbon fragment, $C_7H_{12}^+$ (h, *m/e* 96). One deuterium atom was retained in this ion and in the $C_6H_9^+$ ion (i, *m/e* 81), and the corresponding ions were not observed in **2** and **3**. The formation of h and i appeared to be a complex process, and neither the structure of the ions nor the substituent effects could be described with confidence.

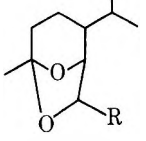
Conclusion

Ion species a–i, which are shown in Chart I, represent an ensemble of ions that appeared in the mass spectra of **1**, **2**, and **3**. The relative abundances of these ions for a given dioxabicyclo[3.2.1]octane reflected the location of ring substituents, and the *m/e* for a given species was related to the structure of the substituent. Substituents at C-1 and C-2 contributed to the *m/e* of ions d and e, and the presence of alkyl groups at C-1 can be determined on the basis of the relative abundances of d and e. The presence of groups at C-4 and C-5 was related to ions a, b or c, and g. Alkyl substitution at C-5 was apparent in ion a and ions b or c, and our evidence suggested that C-4 substituents can be detected in the ionic species g.

The MS data for **1**, **2**, and **3** and data obtained from literature[11] demonstrated that the relative abundance of f was determined by alkyl substituents at C-7. The elimination of water from e was possible when a C-7 alkyl substituent was present, and our data suggested that the e − H_2O peak was evidence for a C-7 substituent.

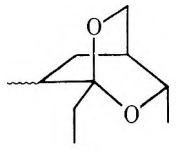
Ions a–g can be derived from the dioxabicyclo[3.2.1]octane ring system, and we have indicated how these ions can arise from **1**, **2**, and **3**. Compounds **1** and **4** give identical mass spectra, and our evidence suggests that **4** is converted to **1** and that **1** is the primary ion source for the mass spectrum of both compounds. In laboratory experiments the thermal conversion of **4** to **1** is facile and high yielding,[10] and the reversal of this reaction in the spectrometer inlet seems unlikely. However, acyclic intermediates similar to **4** may be involved in the ionization process.

A recent communication described three dioxabicyclo[3.2.1]octanes: 5-methyl-2-isopropyl-7-acetyl-6,8-dioxabicyclo[3.2.1]octane (**7**), 5-methyl-2-isopropyl-7-hydroxyethyl-6,8-dioxabicyclo[3.2.1]octane (**8**), and 5-methyl-2-isopropyl-7-(1-methylhydroxyethyl)-6, 8-dioxabicyclo [3. 2. 1]-octane (**9**).[7] A small M − CH_3CH_2 peak was observed for **3**, and prominent peaks corresponding to the loss of the C-7 substituent were reported for **7**, **8**, and **9**. A peak corresponding to a was the base peak for **7**, **8**, and **9**, but most of the remaining fragments did not correspond to ions b–i. These data suggested that complex substituents may make a significant contribution to the mass spectra of substituted dioxabicyclo[3.2.1]octanes.



7, R = $COCH_3$
8, R = $C(OH)HCH_3$
9. R = $C(OH)(CH_3)_2$

Mass spectral data can supply considerable information about the structure of the dioxabicyclo[3.2.1]octanes; however, some potential sources of difficulty should be noted. The mass spectrum of a related bicyclic ketal structure, 3,7-dimethyl-1-ethyl-2,6-dioxabicyclo[2.2.2]octane (**10**),[12]



10

was compared to the spectrum of **1**. Most of the spectral characteristics observed in **1** were present in **10**, thereby indicating that mass spectrometry was not the method of choice for distinguishing the two ring systems.

The M − CH_2CO peak (b, c) and the M − CH_3CHCH_2 peak g were coincident (P − 42) in **1**. This peak assignement problem can be solved by recording the spectrum of the D-labeled compound. Deuterium labeled compounds can also be utilized for the assignment of other peaks and for the determination of the number of substituents α to the ketal carbon atom.

Experimental Section

Preparation of Deuterium-Labeled Compounds. A sample of multistriatin (**1**, 50 mg) was refluxed in a mixture of 2.5 ml of 1 *M* deuteriophosphoric acid and 2.5 ml of THF for 48 hr.[5] The solution was saturated with NaCl, the THF layer was removed, and the water layer was extracted with 1 ml of fresh THF. The combined THF extracts were washed twice with 0.5-ml volumes of salt water. The THF solutions were dried initially over anhydrous potassium carbonate and then over 4-Å sieves. The products were separated by preparative GLC and the mass spectrum of each isomer fraction of **1** was recorded. The procedure was repeated for frontalin (**2**) and *exo*-brevicomin (**3**).

Mass Spectra. The unit resolution spectra were recorded on an Hitachi RMU-6E mass spectrometer at 70 eV ionization potential. The high-resolution spectra were recorded and empirical formulas were calculated with an AEI-9 computer–spectrometer system.

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Registry No.—**1**, 54815-06-4; **2**, 28401-39-0; **3**, 20290-99-7.

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Additions of Dihalocarbenes to Steroidal and Related Model Olefins. Studies in Carbenic Selectivity[1]

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CF_2 was added to trimethylethylene (**1**), cyclohexene (**2**), cyclohexen-4-one ethylene acetal (**3**), cyclohexen-3-one ethylene acetal (**4**), 2,2-ethylenedioxy-10-methyl-8-octalin (**5**), 2,2-ethylenedioxy-10-methyl-1(9)-octalin (**6**), 10-methyl-1(9)-octalin (**7**), and cholest-5-en-3-one 3-ethylene acetal (**8**). CCl_2 was also added to **5**, and CFCl to **8**. Stereoselectivities were determined for the various additions: (β/α) for CF_2 additions to **5**, **6**, and **7** were 250, 0.194, and 10.6, respectively. Only β addition could be detected for the addition of CF_2 or CFCl to **8**, and for the addition of CCl_2 to **5**. In the addition of CFCl to **8**, *endo*-F product exceeded *endo*-Cl product by a factor of ~ 3. Reactivities, relative to 2 (= 1.00) were determined for CF_2 additions (80°) to the various substrates: **1**, 49.5; **3**, 0.43; **4**, 0.018; **5**, 0.38; **6**, 0.12; **7**, 0.46. The significance of the quantitative data is discussed.

Reactions of carbenes with steroidal olefins have been of interest for more than a decade.[4-29] Carbenic species of particular interest included CBr_2,[5,8] CCl_2,[6,7,16-18] Simmons–Smith "CH_2",[4c,9-15] and CFCl.[16] Beyond this general concern, the medicinal potential of fluoro steroids has focused attention on the additions of fluorocarbenes to steroidal olefins.[4a,b,19,20] With a few exceptions,[21,22] most of this effort centered on CF_2 additions to ring A and ring B double bonds. Usually the stereoselectivity (α or β) of the difluorocyclopropanation was determined.[20,23-28] Key reports included those of Knox et al.,[27] and of Bond and Cornelia,[29] which indicated that normal steroids with $\Delta^{5,6}$ unsaturation afforded β-CF_2 adducts.

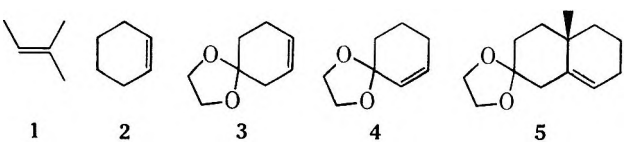
Given the variety and depth of interest, it was striking that systematic studies of carbenic selectivity toward steroidal substrates were nonexistent. Carbenic stereoselectivity has been discussed,[4a,b] but studies of the ability of, e.g., CF_2 to discriminate between different steroidal double bonds, and of how such discrimination related to the larger body of carbenic selectivity data,[30] were missing. Also sparse were discussions of the addition of unsymmetrical carbenes to steroidal olefins, and of the pertinent stereoselectivity,[31] subjects which have been extensively studied with nonsteroidal olefins.[32]

No doubt these lapses partially stemmed from anticipated analytical difficulties which could beset relative reactivity experiments with steroidal olefins. We therefore chose to examine CF_2 selectivities toward model olefins,[1] and then to extend aspects of these studies to steroidal substrates. In these initial efforts, we have restricted ourselves to Δ^4 and $\Delta^{5,6}$ AB model olefins and to a $\Delta^{5,6}$ steroidal olefin. Nevertheless, the results comprise the first integrated mechanistic study from the viewpoint of *carbenic reactivity*, deal with three kinds of carbenic selectivity, establish the utility of model studies in the $\Delta^{5,6}$ series, and should be of importance in future synthetic planning.

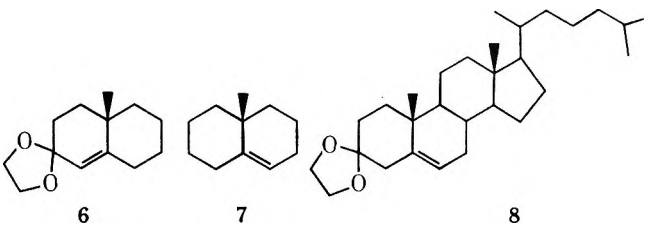
Results

Olefins. Primary substrates included olefins **1–8**. Olefin **3**[33] was prepared by the acid-catalyzed ketalization of 2-cyclohexen-1-one, whereas isomeric **4** was obtained from cyclohexanone ethylene acetal by the bromination–dehydrobromination method of Garbisch.[34]

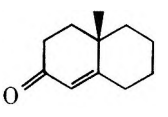
Bicyclic ketals **5** and **6** were both prepared from 10-methyl-1(9)-octal-2-one (**9**), which was itself obtained by condensation of 2-methylcyclohexanone and methyl vinyl ketone under either basic[35] or acidic[36] conditions. The latter procedure was simpler, and it gave a better yield. Conversion of **9** to **5** required ethylene glycol and a catalytic quantity of *p*-toluenesulfonic acid in refluxing benzene.[37] Under similar conditions, the use of adipic acid as the catalyst[38] converted (70%) **9** to a mixture of **6** (87%) and **5** (13%), which provided **6** upon fractional distillation. The isomers could easily be differentiated by NMR; in CCl_4, **6** had a vinyl resonance at δ 5.07 (broad singlet), whereas the vinyl resonance of **5** appeared as a multiplet centered at δ 5.23.[37]



1 2 3 4 5



6 7 8



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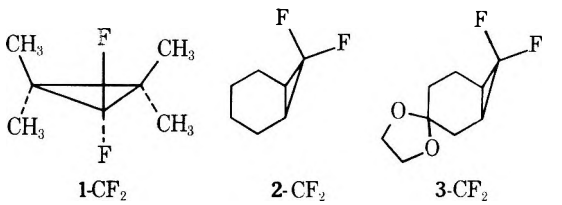
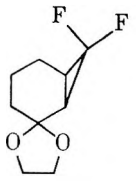
Octalin **7** was prepared from **9** by Marshall's sequence: reduction to the enol with $LiAlH_4$, acetylation with acetic anhydride, and removal of the acetoxyl group with Li–$C_2H_5NH_2$.[39] Finally, cholest-4-en-3-one was converted to **8** by treatment with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene.[40]

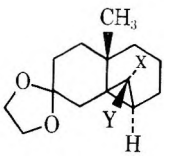
Dihalocarbene Additions. Adducts **1**-CF_2–**8**-CF_2 were obtained by the reaction, with substrates **1–8**, of CF_2 generated from $(CH_3)_3SnCF_3$ and NaI in refluxing 1,2-dimethoxyethane,[41] or from $C_6H_5HgCF_3$ and NaI in refluxing benzene,[42] whereas **5**-β-CCl_2 was prepared by treating **5** with chloroform and 50% aqueous NaOH in the presence of benzyltriethylammonium bromide.[18,43] Adducts **5**-β-CH_2, **5**-α-CH_2, **5**-β-*endo*-F-*exo*-Cl, and **5**-β-*endo*-Cl-*exo*-F were



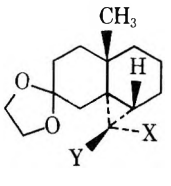
1-CF_2 **2**-CF_2 **3**-CF_2



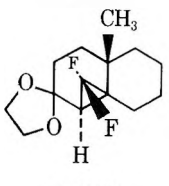
4-CF_2



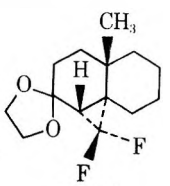
5-β-CF_2, X = Y = F
5-β-CCl_2, X = Y = Cl
5-β-CH_2, X = Y = H
5-β-*endo*-F-*exo*-Cl, X = F; Y = Cl
5-β-*endo*-Cl-*exo*-F, X = Cl; Y = F



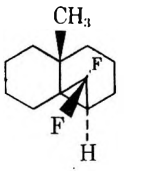
5-α-CF_2, X = Y = F
5-α-CH_2, X = Y = H



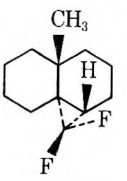
6-β-CF_2



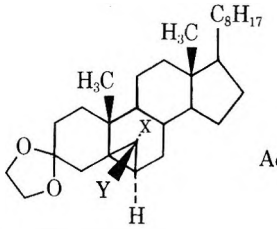
6-α-CF_2



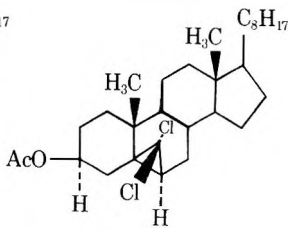
7-β-CF_2



7-α-CF_2



8-β-CF_2, X = Y = F
8-β-*endo*-F-*exo*-Cl, X = F; Y = Cl
8-β-*endo*-Cl-*exo*-F, X = Cl; Y = F



10-β-CCl_2

available from a previous study,[44] and 8-β-*endo*-F-*exo*-Cl and 8-β-*endo*-Cl-*exo*-F were prepared by the reaction of **8** with FCCl generated from $C_6H_5HgCFCl_2$ in refluxing benzene.[45]

The additions of CF_2 to **1** and **2** gave the known[46,47] difluorocyclopropanes in 80 and 70% yields. Ketal olefin **3** afforded **3**-CF_2 in 78% yield, but preparative scale CF_2 addition to **4** was complicated by NaI-catalyzed[48] isomerization of **4** to **3**, and subsequent difluorocyclopropanation of **3**. Adduct **4**-CF_2 was 20–30% of the product mixture and could be isolated by GC on a Carbowax column at 160°.

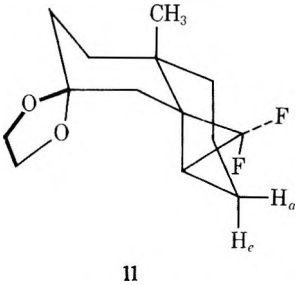
Difluorocyclopropanes **1**-CF_2–**4**-CF_2 were purified by GC (Carbowax), and their structures followed from consistent ir, ^1H and ^{19}F NMR spectra, mass spectral parent ions, and satisfactory elemental analyses. Significant NMR data appear in Table I.

The ^{19}F NMR spectra of **1**-CF_2–**4**-CF_2 are characterized by high-field doublets (*endo*-F), $J_{gem,F-F}$ = 130–150 Hz, and lower field signals for the *exo*-F atoms. The *exo*-F resonances show strong *vic*-H–F coupling to the (cis) cyclopropyl proton(s), $J_{vic,H-F}$ = 10–13 Hz, in addition to the major F–F coupling, and appear as either a doublet of doublets (**1**-CF_2) or a doublet of triplets (**2**-CF_2–**4**-CF_2). In fluorocyclopropanes, *trans*-*vic*-H–F coupling is substantially weaker than its cis counterpart, and the *endo*-F doublets are therefore not further split, although each component is clearly broadened ($W_{1/2} \sim 8$ Hz.)[49] All other CF_2 adducts prepared in this study exhibit ^{19}F NMR spectra similar to those of **1**-CF_2–**4**-CF_2.

Crucial to all structural assignments in this study were the carbene adducts of **5**. From CFCl and **5**, we isolated **5**-β-*endo*-F-*exo*-Cl and a minor isomer, which is now assigned as **5**-β-*endo*-Cl-*exo*-F (see below), in ratios ranging from 4:1 to 9:1.[44] The β configuration of the major adduct followed from its high-field (unsplit) ^{19}F NMR signal (*endo*-F), and from the ^1H NMR observation of long-range coupling (0.6 Hz) between F and the angular methyl protons (Table I). The latter observation is only consistent with a β-*endo*-F configuration: "long-range coupling between angular methyl protons and fluorine five or more σ-bonds apart may occur only when a vector directed along the C–F bond, and originating at the carbon atom converges upon and intersects a vector drawn along an angular methyl C–H bond in the direction of the proton and originating at the methyl carbon".[50] Of the four possible CFCl adducts of **5**, only **5**-β-*endo*-F-*exo*-Cl satisfies this requirement.[44] However, we noted that the extent of coupling was smaller than that usually observed in 5β,6β-difluorocyclopropyl steroids (1–3 Hz),[27] and that the model compound had probably assumed a conformation not well suited to the long-range coupling. This alternative conformation was unavailable to steroidal analogues. (See below.)

CF_2 and **5** gave 68% of **5**-β-CF_2 and **5**-α-CF_2 (ratio 250:1), separable by GC on a SE-30 column at 190°. Both adducts showed parent ions at *m/e* 258, and were void of olefinic protons (NMR). The major product was originally assigned the β configuration by analogy to the apparently exclusive β addition of CFCl to **5**, and because of the experimentally identical chemical shifts of the angular methyl resonances of **5**-β-*endo*-F-*exo*-Cl and the presumed **5**-β-CF_2 (Table I). In addition, calculations[51] of δ values for the angular methyls of **5**-β-CF_2 and **5**-α-CF_2, employing deshielding contributions of 5[27] and 17 Hz[29b] for the β and α CF_2 groups, respectively, indicated that the β adduct should have the higher field resonance.[52]

However, the calculated δ CH_3 values[52] were neither very accurate (cf. Table I) nor very different. Moreover, we could not resolve any long-range splitting of the angular methyl group of **5**-β-CF_2 on 60-, 90-, 100-, or 270-MHz spectrometers.[54] Therefore, crystalline **5**-β-CF_2 was subjected to x-ray analysis. The results not only definitively established the β configuration,[55] but, at least in the crystal, **5**-β-CF_2 was shown to adopt the "nonsteroid" conformation,[51,56] **11**. Were this conformation also preferred in



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solution, then long-range coupling of β-*endo*-F and CH_3 would not be expected; the appropriate vectors[50] do not intersect.[57,58]

Simmons–Smith methylenation of **5** gave **5**-β-CH_2 and **5**-α-CH_2 in a ratio of 45:55; the structures were assigned on the basis of their angular methyl chemical shifts.[44] Literature evidence strongly indicated that the higher field resonance had to belong to the β adduct.[14,29b]

Makosza addition of (excess) CCl_2[43] to **5** gave a single adduct, in nearly quantitative yield, to which we assigned the β configuration by analogy to the overwhelming β-addition preferences of CF_2 and CFCl toward **5**. In verification, re-

Table I
Selected NMR Data[a]

Adduct	^{19}F NMR, ϕ*[b]		^{1}H NMR, δ[c]	
	endo-F (J_{FF}, Hz)[d]	*exo*-F (J_{HF}, Hz)[e]	Ketal	Angular CH_3[f]
1-CF_2	150.4 (d, 134)	138.7 (dd, 10)		
2-CF_2	149.2 (d, 140)	127.5 (dt, 12)[g]		
3-CF_2	150.4 (d, 141)[h]	128.1 (dt, 12)[i]	3.86 (s)	
4-CF_2	148.2 (d, 146)	126.4 (dt, 13)	3.86 (br s)	
5-β-CF_2	146.1 (d, 142)	134.9 (dd, 12)[j]	3.84 (s)	1.13 (s, $W_{1/2}$ = 2)
5-α-CF_2	[k]		4.10 (s)	1.17 (s)
5-β-CCl_2			3.87 (s)	1.23 (s)
5-β-*endo*-F-*exo*-Cl	149.2 (s, $W_{1/2}$ = 8)		3.83 (s)	1.12 (d, J = 0.6)
5-β-*endo*-Cl-*exo*-F		129.8 (d, 20)[l]	3.83 (s)	1.20 (s)
5-β-CH_2			3.78 (s)	1.00 (s)
5-α-CH_2			3.78 (s)	1.11 (s)
6-β-CF_2	[k]		3.86 (s)	1.10 (s, $W_{1/2}$ = 8)
6-α-CF_2	145.6 (d, 144)	124.9 (dd, 13)	4.03 (m)	1.19 (s, $W_{1/2}$ = 2)
7-β-CF_2	143.7 (d, 143)	135.9 (dd, 14)[m]		1.10 (s)
7-α-CF_2	143.9 (d, 142)	133.0 (dd, 14)		1.12 (s)
8-β-CF_2	142.9 (d, 146)	129.8 (dd, 12)	3.88 (m)	1.02 (d, J = 1.5)
8-β-*endo*-F-*exo*-Cl	144.9 (s, $W_{1/2}$ = 10)		3.88 (m)	1.05 (d, J = 2.4)
8-β-*endo*-Cl-*exo*-F		123.4 (d, 17)	3.88 (m)	1.17 (s)
10-β-CCl_2				1.25 (s)[n]

[a] Additional NMR data appear in the Ph. D. Dissertation of D. J. Smudin, Rutgers University, New Brunswick, N.J., 1976. Abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, $W_{1/2}$ = width at half-height. [b] The solvent was CCl_4, containing 15% of $CFCl_3$ and 5% of c-C_4F_8 as internal standards. ϕ* in parts per million to high field of $CFCl_3$. [c] The solvent was CCl_4, with Me_4Si as internal standard. [d] Geminal F–F coupling; the equivalent coupling is not tabulated for the *exo*-F resonance. [e] *cis-vic*-H–F coupling involving the cyclopropyl proton(s). [f] At the A/B ring junction; splittings are due to long range β-*endo*-F–CH_3 coupling. [g] Further splitting (~2 Hz) was observed in the triplet components. [h] Further splitting (~2 Hz) was observed. [i] Further splitting (~3 Hz) was observed. [j] Long-range coupling (4.6 Hz) was also observed. [k] An insufficient quantity of this compound was available for determination of the ^{19}F NMR spectrum. [l] Long-range coupling (5.2 Hz) was also observed. [m] Long-range coupling (3 Hz) was also observed. [n] See ref 18.

duction of 5-β-CCl_2 with Na–NH_3 gave a single product, identical (ir and NMR) with 5-β-CH_2. It is interesting to note that, whereas the Simmons–Smith addition to **5** is nonstereoselective, the CCl_2 addition–reduction sequence is stereospecifically β.

The foregoing now permits the nearly certain designation of the minor adduct of CFCl and **5** as 5-β-*endo*-Cl-*exo*-F.[59] Thus, its angular CH_3 resonance (δ 1.20) is nearly identical with that of 5-β-CCl_2 (δ 1.23), and its *exo*-F ^{19}F NMR resonance exhibits long-range splitting similar to that of the exo-F resonance of 5-β-CF_2.[58] The *cis-vic*-H–F coupling of 5-β-*endo*-Cl-*exo*-F (20 Hz), although larger than those of the analogous CF_2 adducts, is similar in magnitude to the couplings of its steroidal analogue, 8-β-*endo*-Cl-*exo*-F (17 Hz), and to those of the *exo*-F CFCl and C_6H_5CF adducts of *cis*-butene (18 and 22 Hz, respectively).[49]

Addition of CF_2[42] to **6** was complicated by NaI-catalyzed[48] isomerization of **6** to **5**, and gave 23% of a mixture of 5-β-CF_2, 6-α-CF_2, and 6-β-CF_2 in a ratio of 18:5:1, respectively. Separation was achieved by GC on a SF-96 column at 178°. The β stereochemical assignment for the minor adduct of **6** rests upon its higher field angular methyl resonance, which was also broadened ($W_{1/2}$ = 8 Hz), relative to that of 6-α-CF_2 ($W_{1/2}$ = 2.2 Hz), presumably by long-range coupling[50] to the β-*endo*-F atom. The NMR assignments are buttressed by chemical evidence. Thus 6-α-CF_2 could be converted to the corresponding thioketal by acid-catalyzed transketalization with ethanedithiol in benzene, and thence to 7-α-CF_2 by Raney nickel desulfurization. The material thus obtained was insufficient for NMR characterization, but did have identical retention times with authentic 7-α-CF_2 (see below) on SF-96 and Carbowax 20M GC columns.

Addition of CF_2[42] to **7** afforded 90% of a mixture of 7-β-CF_2 and 7-α-CF_2 (ratio 10.6:1), separable by GC on a SF-96 column at 120°. Stereochemical assignments could not be made with confidence by NMR. Long-range CH_3–F coupling was not detectable in the isomer ultimately designated as 7-β-CF_2, and the chemical shift of its angular methyl group (albeit at higher field) was uncomfortably close to that of 7-α-CF_2 (cf. Table I). The *exo*-F atom of the likely 7-β-CF_2 did, however, exhibit the anticipated[58] long-range coupling (3 Hz).

Conclusive assignments were possible by chemical means. Adduct 5-β-CF_2, the structure of which was firm,[55] could be converted to authentic 7-$\beta$$CF_2$ by the ketal → thioketal interchange–Raney nickel desulfurization sequence. The material thus obtained was identical (ir and NMR) with the major (β) adduct of **7** and CF_2.

Addition of CF_2[42] to cholest-5-en-3-one ethylene acetal (**8**) gave 33% of purified 8-β-CF_2, the identity of which was established by elemental analysis and mass (M^+) and NMR spectroscopy. Its angular methyl resonance (δ 1.02) was a doublet (J = 1.5 Hz), indicating long-range coupling to the β-*endo*-F atom,[50] and securing the β stereochemistry. Apparently, CF_2 addition to **8** was highly β stereoselective; only the ^{19}F resonances of 8-β-CF_2 were observed in the NMR spectrum of the crude, concentrated reaction mixture.

Addition of CFCl[45] to **8** gave two products (ratio 3:1), as indicated by their ^{19}F NMR resonances, observable in the crude reaction mixture. Extensive purification (see Experimental Section) afforded a pure sample of the major product, 8-β-*endo*-F-*exo*-Cl, in 55% isolated yield. Of particular importance to the structural assignment were the high-field ^{19}F NMR "singlet" (*endo*-F, cf. 5-β-*endo*-F-*exo*-Cl) and the doublet (J = 2.4 Hz) angular methyl ^{1}H NMR resonance at δ 1.05. These features were only consistent with the β-*endo*-F-*exo*-Cl configuration.

The minor reaction product was isolated chromatographically, and can be most reasonably assigned as 8-β-*endo*-Cl-*exo*-F. Its ^{19}F NMR doublet at ϕ* 123.4 (J = 17 Hz) is consistent with this assignment (cf. 5-β-*endo*-Cl-*exo*-F, ϕ* 129.8, J = 20 Hz), as is its strongly deshielded singlet angu-

Table II
Empirical Relative Reactivities toward CF_2[a]

Case	Olefins A/B	Precursor[b]	Solvent	Temp, °C	GC analyt cond[c] Column	GC analyt cond[c] Temp, °C	k_A/k_B	a.d.$_n$, %[d]
1	1/2	Hg	C_6H_6	80	A	60–80	49.5	1.1_3
2	3/2	Hg	C_6H_6	80	A	83–150	0.43	
3	3/2	Hg	DME[e]	90	A	83–150	0.48	
4	3/2	Sn	DME	90	A	83–150	0.46	3.5_3
5	4/2	Sn	DME	90	A	83–150	0.020	9.1_2
6	4/2	Hg	C_6H_6	80	A	83–150	0.018	6.7_2
7	4/2	Hg	DME	90	A	83–150	0.020	
8	3/4	Sn	DME	90	A	158	25.6	3.5_3
9	3/4	Hg	C_6H_6	80	A	158	25.1	
10	5/4	Hg	C_6H_6	80	B	160–175	20.9	6.0_2
11	5/3	Hg	C_6H_6	80	B	160–175	0.933	
12	5/6[f]	Hg	C_6H_6	80	C	178	3.36	
13	6/4[f]	Hg	C_6H_6	80	C	178	6.74	
14	7/2[g]	Hg	C_6H_6	80	C	60–130	0.46	4.3_2

[a] Further details of each run, including initial reactant concentrations, reaction time, and thermal conductivity detector calibration coefficients, appear in the Ph.D. Dissertation of D.J.S. [b] Sn = [Me_3SnCF_3 + NaI],[41] Hg = [$C_6H_5HgCF_3$ + NaI].[42] [c] GC analyses were done on packed columns with injector and detector temperatures of 235 and 275°, respectively. Column temperatures were generally programmed between the indicated limits. Columns were: A, 12 ft × 0.25 in., 15% Carbowax 20M on 60/80 Gas-Chrom R; B, 20 ft × 0.25 in., 7% Carbowax 20M + 3% SF-96 on 60/80 Gas-Chrom R; C, 20 ft × 0.25 in., 10% SF-96 on 60/80 acid-washed, silylated Chromosorb W. Product peak integrals were determined by cut-and-weigh of Xerox copies, with a Disc integrator, or with a Varian Model 481 electronic integrator. [d] Percent average deviation of n experiments. [e] 1,2-Dimethoxyethane. [f] The isomerization of **6** to **5** was <20% under competition conditions, in which [NaI]/[6] was small. For relative reactivity calculations, the effective [6] was taken as the mean of its initial and final concentrations as determined by GC. The indicated reactivities are based on the *sum* of β and α CF_2 additions to **6**. [g] The indicated reactivity is based on the *sum* of β and α CF_2 additions to **7**.

lar methyl resonance at δ 1.17 (cf. the analogous resonance of **10**-β-CCl_2[18] at δ 1.25; the latter should be modified[53] to δ 1.22 if the 3β-acetate of **10**-β-CCl_2 were replaced by the 3-ethylene acetal function featured in the adducts of **8**). Careful ^{1}H NMR analysis of **8**-β-*endo*-Cl-*exo*-F failed to reveal vinylic or allylic resonances, thus excluding ring-opened, rearranged structures. Finally, in view of the very high preferences for β additions of CF_2[27] (see also above) and CCl_2[18] to $\Delta^{5,6}$ steroidal olefins, it seems unreasonable to entertain α-cyclopropyl formulations for the (**8** + CFCl) minor product.

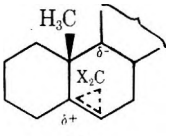
Relative Reactivity Studies. Relative reactivities of olefins **1**–**7** toward CF_2 were determined by the competition method,[30] in which pairs of olefins, present in excess, were permitted to compete for an insufficiency of CF_2. GC analysis of the crude product mixtures permitted calculation of the relative reactivities gathered in Table II. Inspection of the data shows that, within the indicated limits, the choice of carbene precursor, solvent, and reaction temperature had little effect on the olefinic reactivities. With the exception of case 5, reproducibility was within 7%.

Cross-check experiments[30] were performed. From cases 2 and 6, k_3/k_4 is calculated to be 23.9; the observed value (case 9) was 25.1 (deviation, 4.8%). From cases 10 and 11, k_3/k_4 is calculated to be 22.4 (deviation, based on case 9, 11%). From cases 4 and 5, k_3/k_4 is calculated to be 23.0; the observed value (case 8) was 25.6 (deviation, 10%). From cases 10 and 12, k_6/k_4 is calculated to be 6.22; the observed value (case 13) was 6.74 (deviation, 7.7%). The internal consistency of much of the reactivity data is thus verified. We consider the data to be accurate to <±10%. Though not spectacular, these limits are acceptable, especially considering the large spread of reactivities (k_1/k_4 = 2750, cases 1 and 6).

Discussion

Stereoselectivity. Table III summarizes pertinent stereoselectivity data. Patent is the overwhelming preference for β approach of CF_2, CFCl, and CCl_2 during additions at the $\Delta^{5,6}$ positions of both the model substrate **5** and its steroidal analogues **8** and **10**. This basic observation has precedent,[1,27,29,44,60] but there are additional points to be made.

Mechanistic analyses of the carbene–olefin addition reaction require that (1) there be maximum overlap of the carbene's vacant p orbital and an olefinic "p" orbital in the transition state (TS), and (2) that CX_2 approach the π bond in an highly unsymmetrical manner, such that, in the TS, the bulk of the positive charge resides on the carbon atom most capable of supporting it.[61] For a $\Delta^{5,6}$ substrate, (1) and (2) require *axial* attack of CX_2, through a partially charge-separated TS, in which β-attack biased toward C-6 (δ^+ at tertiary C-5), **12**, is energetically preferred to α-attack, biased toward C-5 (δ^+ at secondary C-6), **13**.



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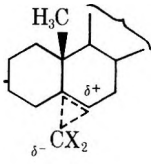

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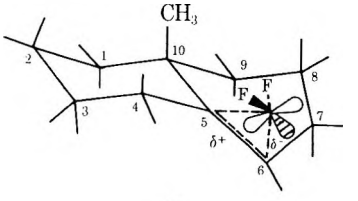
Model olefin **7** can be regarded as the parent $\Delta^{5,6}$ substrate. (For continuity, steroid numbering will be used with **7**.) Therefore, the observed CF_2 stereoselectivity (β/α = 10.6) demonstrates that the β > α preference is innate to the A/B ring system, and is directionally dependent neither on the presence of other substituents nor even of rings C and D of the full steroid. Dreiding models suggest **14** as the



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TS for β addition.[62] The β face of ring B "opens" so that β approach, biased toward C-6, appears to be sterically reasonable as well as electronically favored. Although β ap-

Table III
Stereoselectivies of the Carbene Additions[a]

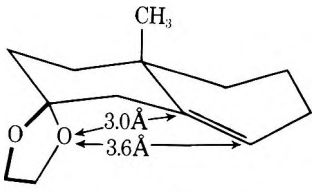
Carbene	Substrate	Stereoselectivity	
		β/α	*endo*-Cl/*endo*-F
CFCl	1		2.4[b]
CFCl	2		1.2–1.5[c]
CF_2	5	250	
CFCl	5	*d*	0.11–0.25[e]
CCl_2	5	*d*	
CF_2	6	0.194[f]	
CF_2	7	10.6[g]	
CF_2	8	*d*	
CFCl	8	*d*	0.33
CCl_2	10[h]	*d*	

[a] Reaction temperature was 80° unless otherwise noted. [b] Reference 49, Moss and Gerstl; temperature −10°. [c] W. Funasaka, T. Ando, H. Yamanaka, H. Kanehira, and Y. Shimokawa, Symposium on Organic Halogen Compounds, Tokyo, Japan, Nov. 29, 1967, Abstracts, p 25 ff; temperature, 35°. [d] Only β addition was detected. [e] Reference 44. The minor adduct (5-β-*endo*-Cl-*exo*-F) was relatively unstable. Presumably, the stereoselectivity is closer to 0.25, [f] Average of three runs; av dev ±0.007. [g] Average of two runs; av dev ±0.08. [h] Reference 18.

proach of CF_2 is opposed by the β angular methyl group, and by β H atoms at C-4 and C-8, α approach (biased toward C-6) appears to be opposed by the α-H atoms at carbons 1, 3, 7, and 9. The relative balance of steric hindrance permits the stereoelectronic preference for β addition to dominate.

Note, however, that peracid epoxidation of 7[39] and $\Delta^{5,6}$ steroidal olefins[63a] affords mainly the α epoxide. The loss of β stereoselectivity may reflect a lesser polarization of the TS for peracid epoxidation, vis-à-vis CF_2 addition, leading to a relaxation of the stereoelectronic control which dominates in the latter reaction. Combined with lower steric hindrance to α (rather than β) approach of the bulkier peracid, α-epoxidation would be expected to prevail. Loss of β stereoselectivity is also encountered in the Simmons–Smith methylenation of $\Delta^{5,6}$ steroidal olefins,[14] and can be similarly explained.

The β preference in CF_2 addition to **5** (β/α = 250) is 23.6 times more pronounced than in addition to **7**. We attribute the increased selectivity to specific deactivation of **5** at the α face of the $\Delta^{5,6}$ double bond by the 3α ketal oxygen, cf. **15**. This phenomenon is well precedented in various reac-



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tions of steroidal analogues,[63] and in the β-hydroboration of **5** itself.[37] In this regard, note that the very high β CF_2 stereoselectivity observed in addition to steroid **8** is not a function of the 3-ethylene acetal group. Steroids which lack this functionality also give highly β stereoselective additions of CF_2[27] (and of CCl_2[18]) at $\Delta^{5,6}$.

Originally, it was believed that CCl_2 could not add to $\Delta^{5,6}$ steroidal olefins.[27,29] Granted the necessity for β attack,[64] it was argued that only the smaller CF_2 could add; CCl_2 encountered insurmountable steric hindrance which originated at the 10β methyl group.[27] Although it is now clear that CCl_2 *can* add to both the model, **5**, and actual steroidal substrate, **10**,[18,65] the steric opposition of the 10β methyl to β carbene addition is real, and clearly evident in its effect on CFCl stereoselectivity (Table III). The β addition of CFCl to **5** and **8** occurs predominantly with *endo*-F-*exo*-Cl stereoselectivity, a preference opposite to that exhibited by CFCl with acyclic or simple cyclic alkenes such as **1** or **2** (Table III). There, favorable electrostatic interactions between the carbene's more polarizable Cl atom and the olefinic alkyl substituents (which become partially positive in the addition TS) outweigh any steric deficit due to chlorine's larger size; *endo*-Cl-*exo*-F stereoselectivity commonly results.[66] Note that, in both expressions of stereoselectivity, β/α and endo/exo, the model and steroidal olefins exhibit parallel behavior, underlining the value of the model studies.

Discussion of the α stereoselectivity observed for (CF_2 + **6**) will be considered below, but we note here that **6** can be formally derived from **7** by replacing the 3-allylic protons of the latter with the ethylene acetal function. Because (**7** + CF_2) exhibits β stereoselectivity, the ethylene acetal function of **6** must be responsible for the changeover to α stereoselectivity.

The stereoelectronic analysis developed to rationalize the β/α selectivity of CX_2 additions to $\Delta^{5,6}$ substrates is reasonably applicable at other sites of steroidal monoene and conjugated diene substrates,[4a,16,27,29,44,60,67] as long as principles 1 and 2 are strictly applied (see above), and due note is taken of any additional substituent-induced steric or electronic perturbations. However, a carbenic addition in which a strongly polarized TS is not involved is excluded from this analysis, and, in the absence of overwhelming steric or specific substituent directive effects, should not exhibit β stereoselectivity (e.g., Simmons–Smith methylenation at the $\Delta^{5,6}$ site[14]).

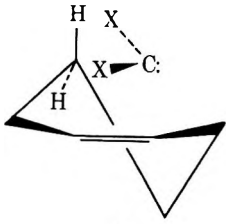
Relative Reactivities. From the empirical data of Table II, we construct a single set of relative reactivities, normalized to cyclohexene, and with CF_2 generated from ($C_6H_5HgCF_3$ + NaI) at 80° (cf. Table IV). In addition, employing the stereoselectivity data of Table III, we can partition the overall reactivities of **5**–**7** into β- and α-face reactivities.

Table IV
Relative Reactivities toward CF_2 (80°, Benzene[42])

Substrate	Overall rel reactivity	β-Face react.[a]	α-Face react.[a]
1	49.5		
2	1.00		
7	0.46	0.84	0.079
3	0.43		
5	0.38	0.76	0.0030
6	0.12	0.040	0.21
4	0.018		

[a] These values have been multiplied by 2; they are normalized to the cyclohexene scale.

Olefin **1** is 49 times more reactive than **2**. This is mainly due to electronic factors; **1** is trisubstituted whereas **2** is disubstituted, and it is well known that the electrophilic dihalocarbenes strongly discriminate in favor of more highly alkylated olefins.[30,68] For comparison, $(k_1/k_2)_{CCl_2} \sim 16$ (at 0°);[69] CF_2 is more selective than CCl_2, as anticipated.[46,68] The advantage **1** enjoys over **2** is not all electronic, however. Cyclohexene suffers from steric hindrance to addition, compared to acyclic alkenes. Toward CCl_2, for example, **2** is 1.68 times less reactive than *cis*-butene (at 0°);[69] steric interactions between the carbene's "endo" halogen atom and cyclohexene's pseudoaxial H atoms, **16**, probably account for the additional retardation.[70]



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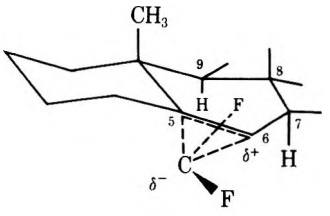
The β face of **7** is comparable in reactivity to **2**, but ought to react considerably faster because it is a trisubstituted "olefin". The problem is clearly steric, and originates at the β angular methyl group. Indeed, if we compare the two trisubstituted olefins, **1** and **7**-β, the reactivity ratio of ~59 can be largely attributed to the alteration of a methyl group in **1** to a *tert*-butyl group in **7**-β, cf. **17** and **18**. With

17 18

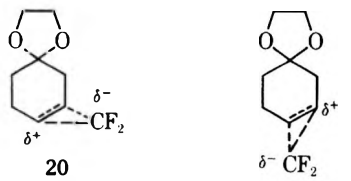
CCl_2, alteration of an ethyl group in 1-butene to a freely rotating *tert*-butyl group in 3,3-dimethyl-1-butene leads to a rate retardation of 34.5 (at −10°).[71] In **7**-β (**18**), the "*tert*-butyl moiety" is locked with a methyl group in the most disadvantageous orientation.

The α face of **7** is ~13 times less reactive than **2**. Axial attack[27,29] of CF_2 would here be biased toward C-5, **19**, placing most of the TS δ^+ on secondary C-6. This would make **7**-α and **2** electronically equivalent, but α approach of CF_2 to **7** (according to the Hoffmann model[62]) would encounter steric hindrance from α hydrogen atoms at C-7 and C-9 (as well as C-1 and C-3), cf. **19**. This hindrance would exceed that experienced by CF_2 in addition to **2**, cf. **16**.



19

Toward CF_2, olefin **3** is 0.43 times as reactive as **2**, demonstrating inductive deactivation by the ketal group. An identical deactivation was seen in CCl_2 additions to **3** (k_3/k_2 = 0.44 at 80°).[33] A "statistical" explanation was offered: **2** has two equivalent olefinic carbons, but **3** has one site for attack (**20**) which is electronically better than the other



20 20′

(**20′**), i.e., it effectively has one site for attack and should be ca. half as reactive as **2**.

The β-face reactivity of **5** resembles that of **7**; the modest (10%) decrease can be attributed to ketal inductive destabilization of the TS for **5**-β. Addition to the α face of **5** is the slowest process in the entire set, 16500 times slower than addition to **1**, and ~26 times slower than addition to **7**-α. Most of the latter retardation is attributable to specific steric hindrance provided by the 3α ketal oxygen atom, cf. **15**.[63]

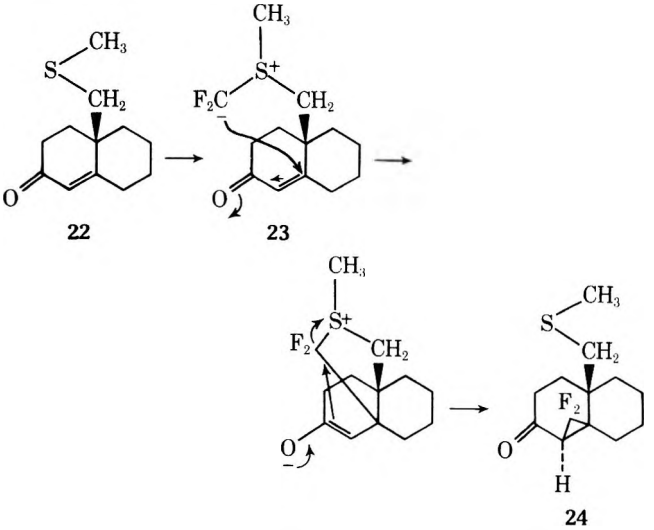
Substrate **4** is strongly deactivated toward CF_2 by its allylic ketal substituent, k_2/k_4 = 55.5 and k_3/k_4 = 23.9. The comparable ratios for CCl_2 additions are 83 and 38, respectively.[33] In additions of CX_2 to **4**, TS **21** is destabilized by

21 21′

the unfavorable inductive effect, whereas alternative **21′** suffers both from steric hindrance at the ketal-bearing carbon and from some inductive destabilization, cf. **20′**. That deactivation here is larger for CCl_2 than for the electronically more selective[68] CF_2 suggests that steric problems, which should be more serious with CCl_2, are quite important in this addition.

Bicyclic olefin **6** combines features of **4** and **7**; however, the ketal function is not tucked beneath ring A, as it is in **9**, but extends away from this ring. Both faces of **6** react with CF_2 more rapidly than does monocyclic analogue **4**, which (superficially) can be attributed to the more favorable trisubstituted alkylation pattern of **6**. However, the behavior of **6** is curious in comparison to that of **7**: $k_{7\text{-}\beta}/k_{6\text{-}\beta}$ = 21, whereas $k_{7\text{-}\alpha}/k_{6\text{-}\alpha} \sim 0.4$. That is, the α face of **6** appears *activated*, relative to **7**-α, although the reverse is true of the β faces. (The latter observation is readily attributed to ketal deactivation, cf. **21** and relevant discussion.) We dismiss two explanations for the α-face "activation": that ring A of **6** adopts a boat conformation, making **6**-α particularly accessible, and that there is ketal-mediated delivery of CF_2 to **6**-α. Inspection of Dreiding models lends no support to the former idea, and the latter is unpalatable in view of the absence of such synergistic dihalocarbene additions with related substrates.[33,61] We are frankly puzzled by the bizarre reactivity of **6**-α.

Because parent enone **9** did not react with CF_2, and **6** reacted with poor stereoselectivity and concomitant isomerization, we attempted the potentially stereospecific and synergistic transformation of **22** → **24**.



22 23 24

Substrate **22** was prepared as directed by Mathews and Meteyer, who have shown that the methylene ylide corresponding to **23** readily cyclopropanates the enone function from the β face.[72] However, reactions of **22** with CF_2 generated by pyrolysis of ClF_2COONa in glyme, diglyme, or Me_2SO, or from $C_6H_5HgCF_3$ + NaI in glyme, led mainly to the recovery of **22**.[73]

The foregoing results establish the utility of model stud-

ies for contemplated carbene–steroid addition reactions, and constitute the first quantitative study of this kind. These and similar results should prove useful in synthetic planning, as well as in our efforts to understand the selectivity of carbenes toward complicated substrates.

Experimental Section[74]

Olefins. Trimethylethylene (1) and **cyclohexene (2)** were obtained from Aldrich Chemical Co., and were percolated through a column of neutral alumina and Linde 4A molecular sieves before use. **Cyclohex-1-en-4-one ethylene acetal (3)** was prepared by the method of ref 33 in 97% purity.[75]

Cyclohex-1-en-3-one ethylene acetal (4) was prepared from cyclohexanone ethylene acetal by the method of Garbisch.[34] A pure sample was isolated by GC on column A[76] at 165°: NMR (CCl_4) δ 6.00–5.25 (m, 2 H, vinyl), 3.83 (s, 4 H, ketal), 2.71–1.84 (m, 2 H, allyl), 1.84–1.43 (m, 4 H, cyclohexyl).[77]

10-Methyl-1(9)-octal-2-one (9). This ketone was prepared either by the method of Marshall and Fanta[35] or, preferably, by the method of Heathcock and Ellis.[36] According to the latter, 44 g (0.39 mol) of 2-methylcyclohexanone, 41.3 g (0.59 mol) of methyl vinyl ketone, 100 ml of benzene, and 0.3 ml of concentrated H_2SO_4 were refluxed for 24 hr in a flask equipped with a water condenser, topped with a dry ice condenser. The reaction mixture was diluted with 400 ml of *n*-hexane, washed twice with 50-ml portions of 5% KOH solution, twice with 50-ml portions of water, dried over $MgSO_4$, and concentrated under reduced pressure. In our hands, the crude product thus obtained was 66% **9** and 33% uncyclized 2-methyl-2-(3-oxobutyl)cyclohexanone.[73] Therefore, the crude product in 25 ml of anhydrous ethanol was added slowly, with stirring, to 2.0 g of sodium ethoxide in 50 ml of anhydrous ethanol, maintained at 0°. After addition, the reaction temperature was raised to 25°, and stirring was continued for 3 hr. The reaction mixture was added to 250 ml of diethyl ether, washed 4 times with 30-ml portions of brine, dried over $MgSO_4$, and stripped of solvent. Distillation afforded 41 g of **9** (65%), bp 108–110° (3 Torr) [lit. bp[35] 82–83° (0.7 Torr)]. The ir spectrum[77] agreed with that reported by Marshall;[35] NMR (CCl_4) δ 5.23 (s, 1 H, vinyl), 2.67–2.00 (m, 4 H, allyl and CH_2CO), 2.00–1.37 (envelope, 8 H, ring), 1.25 (s, 3 H, methyl).

2,2-Ethylenedioxy-10-methyl-8-octalin (5) was prepared by the method of Marshall.[37]

2,2-Ethylenedioxy-10-methyl-1(9)-octalin (6). Ketone **9**, 10 g (61 mmol), 38 g (610 mmol) of ethylene glycol, and 2 g of adipic acid in 500 ml of benzene were refluxed in a flask equipped with a Dean-Stark trap and a condenser; water was azeotropically removed. The slow reaction was monitored by GC.[78] After 400 hr, about 70% of **9** had been converted to a mixture of **6** and **5**. The benzene phase of the product mixture was washed once with 50 ml of 5% $NaHCO_3$ solution and twice with 50-ml portions of water, and dried over Na_2SO_4. After filtration, solvent was stripped and the residue was chromatographed over neutral alumina, with elution by *n*-pentane. The oily product consisted of 87% of **6** and 13% of **5**.[78] Distillation over a 30-cm Vigreux column gave 4.5 g of 94% pure **6** (6% of **5** was present), bp 92–93° (0.9 Torr). A pure sample, obtained by GC on the SE-30 column,[78] had ir (neat) 1661 cm^{-1} (C=C);[77] NMR (CCl_4) δ 5.07 (broad s, 1 H, vinyl), 3.85 (s, 4 H, ketal), 2.23 –1.23 (envelope, 12 H, major absorption at 1.60, ring), and 1.08 (s, 3 H, methyl). M^+ was observed at *m/e* 208 in the mass spectrum.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.18; H, 9.67.

10-Methyl-1(9)-octalin (7) was prepared from **9** by the method of Marshall.[39]

Cholest-5-en-3-one 3-Ethylene Acetal (8). This olefin was prepared from cholest-4-en-3-one by the method of Antonucci et al.[40] Our material had mp 129–132° (from ether–methanol, lit. mp[40] 133.5–134.5°). NMR showed (CCl_4) 5.16 (broad s, 1 H, vinyl), 3.84 (s, 4 H, ketal), 1.02 (s, 3 H, C-19 methyl), 0.93 (d, J = 6 Hz, 3 H, C-21 methyl), 0.89 (d, J = 6 Hz, 6 H, C-26, C-27 methyls), 0.70 (s, 3 H, C-18 methyl).

Difluorocarbene Adducts.[79] Two procedures were used in CF_2 additions. (A) olefin (1.25 equiv), $(CH_3)_3SnCF_3$ (1 equiv),[41] NaI (1.1 equiv),[48] and 12 ml of 1,2-dimethoxyethane (distilled from sodium onto 3A sieves) were stirred and refluxed together for 16–20 hr under a N_2 atmosphere. The reaction mixture was cooled to 25°, and dry NH_3 was slowly passed in through a gas addition tube, precipitating the ammoniate of $(CH_3)_3SnI$. Filtration afforded a product solution which was worked up as described below. (B) Olefin (1 equiv), $C_6H_5HgCF_3$ (1 equiv),[42] NaI (2.5–3.0 equiv),[48] and 10–15 ml of C_5H_6 were stirred and refluxed together for 16–20 hr under a N_2 atmosphere. After cooling to 25°, the reaction mixture was filtered to remove C_6H_5HgI, NaF, and NaI, and the filtrate was processed as described below.

1,1-Difluoro-2,2,3-trimethylcyclopropane (1-CF_2)[46] was prepared from trimethylethylene by procedure A in 75–80% yield. A pure sample was isolated by preparative GC of the unconcentrated, crude reaction product on column A at 60°.[76] The ^1H NMR (CCl_4) showed multiplets centered at δ 1.20 (3 H) and 1.06 (7 H).

7,7-Difluoronorcarane (2-CF_2)[47] was prepared from cyclohexene in 65–70% yield by either procedure A or B. The pure material was obtained by careful fractional distillation of the crude reaction solution, bp 121–123°. The ir spectrum[77] agreed with that reported.[47] NMR showed (CCl_4) broad multiplets centered at δ 1.67 and 1.37.

7,7-Difluoronorcaran-4-one ethylene acetal (3-CF_2) was prepared from **3** by procedure A in ~78% yield. A pure sample was isolated by GC on column A at 160°.[76,77,80] The mass spectrum showed M^+ at *m/e* 190.

Anal. Calcd for $C_9H_{12}O_2F_2$: C, 56.83; H, 6.36; F, 19.98. Found: C, 57.06; H, 6.61; F, 20.01.

7,7-Difluoronorcaran-3-one ethylene acetal (4-CF_2) was prepared from **4** by either procedure A or B. The crude product mixture contained 20–30% of 4-CF_2, as well as 3-CF_2 (see above). The desired adduct was isolated by preparative GC on column A at 160°.[76,77,80]

Anal. Calcd for $C_9H_{12}O_2F_2$: C, 56.83; H, 6.36; F, 19.98. Found: C, 56.76; H, 6.38; F, 20.46.

8,9-Difluoromethylene-10-methyl-2-decalone 2-Ethylene Acetal (5-β-CF_2 and 5-α-CF_2). These compounds were prepared from **5** by either procedure A or B. They were isolated from the concentrated reaction mixture by GC on a 8 ft × 0.25 in., 20% SE-30 on 80/100 mesh Gas-Chrom RZ column at 190°. The average yield of 5-β-CF_2 (GC) was 68%; the ratio of 5-β-CF_2:5-α-CF_2 was 250:1. The β isomer had mp 51.5–53°.[77,80] The mass spectrum showed M^+ at *m/e* 258.

Anal. Calcd for $C_{14}H_{20}O_2F_2$: C, 65.10; H, 7.81. Found: C, 65.49; H, 7.67.

The α isomer[80] showed M^+ at *m/e* 258 in the mass spectrum.

1,9-Difluoromethylene-10-methyl-2-decalone 2-Ethylene Acetal (6-β-CF_2 and 6-α-CF_2). These compounds were prepared from **6** by procedure B. Because of isomerization of the substrate (see above), all four adducts of **5** and **6** were present in the concentrated reaction mixture. The overall yield was 23%, but the ratio of 5-β-CF_2:6-α-CF_2:6-β-CF_2 was 18:5:1, so that the yield of 6-α-CF_2 was only ~5%. It was isolated by preparative GC on column C at 178°,[76,77,80] and had mp 38–39°. The mass spectrum showed M^+ at *m/e* 258.

Anal. Calcd for $C_{14}H_{20}O_2F_2$: C, 65.10; H, 7.81. Found: C, 64.76; H, 7.92.

Minor adduct 6-β-CF_2 was similarly isolated,[80] and showed M^+ at *m/e* 258 in its mass spectrum.

1,9-Difluoromethylene-10-methyl-2-decalin (7-β-CF_2 and 7-α-CF_2) were prepared from **7** using procedure B in ~90% yield. The β/α ratio was 10.6, and the pure adducts could be isolated by GC on column C at 120°.[76] The β adduct had the shorter retention time, and showed M^+ at *m/e* 200 in its mass spectrum.[77,80]

Anal. Calcd for $C_{12}H_{18}F_2$: C, 71.97; H, 9.06. Found: C, 71.79; H, 9.07.

Adduct 7-α-CF_2[77,80] was subjected to mass spectral analysis.

Exact mass. Calcd for $C_{12}H_{18}F_2$: 200.1376. Found: 200.1355.

5β,6β-Difluoromethylenecholestan-3-one 3-ethylene acetal (8-β-CF_2) was prepared by procedure B, using 4.5 g (10.5 mmol) of **8**, 4.0 g (11.5 mmol) of $C_6H_5HgCF_3$, and 5.2 g (34.5 mmol) of NaI in 50 ml of benzene. After 24 hr of reflux, under N_2, filtration of the reaction mixture afforded a solution which, upon concentration, gave 1.6 g of recovered **8** (mp 132–133°), and a yellow oil. The oil was chromatographed over 80–200 mesh activity I alumina with benzene, benzene–methanol elution. The elutate was monitored by TLC on EM Laboratories F-254 0.25 mm silica gel plates ($CHCl_3$ eluent, visualization by uv or I_2 vapor). The desired product obtained from the column had (TLC) R_f 0.42 and could be crystallized from 95% ethanol.[81] Recrystallization gave 1.6 g (32%) of white needles of 8-β-CF_2, mp 51–53°, M^+ at *m/e* 478 and 479 (34.2% of 478).[80]

Anal. Calcd for $C_{30}H_{48}O_2F_2$: C, 75.27; H, 10.11, F, 7.94. Found: C, 75.07; H, 10.09; F, 7.26.

Other Carbene Adducts. 8,9-Dichloromethylene-10-methyl-2-decalone 2-Ethylene Acetal (5-β-CCl_2). Added to a Morton flask, fitted with a high-speed mechanical stirrer, dropping funnel,

and condenser, were 2.0 g (9.6 mmol) of **5**, 0.6 g of benzyltriethylammonium bromide, and 75 ml of chloroform. With vigorous stirring, 50 ml of 50% aqueous NaOH solution was added dropwise, over 1 hr. Stirring was continued at 25° for 100 hr. The reaction mixture was then diluted with 400 ml of water and extracted thrice with 200-ml portions of chloroform. The total chloroform extract was washed twice with 100-ml portions of water, dried over $MgSO_4$, filtered, and stripped. The residue was chromatographed over a column of neutral, activated alumina (packed in pentane). Elution with pentane, followed by pentane–chloroform, afforded 2.2 g (~78%) of crude 5-β-CCl_2,[82] which was distilled to afford a pure sample, bp 115° (0.04 Torr).[77,80] The mass spectrum showed M^+ at *m/e* 290 and 292 (68% of 290).

A satisfactory elemental analysis could not be obtained; the structure of 5-β-CCl_2 was therefore secured by reduction. Into a three-neck flask equipped with a dry ice condenser capped with a drying tube, dropping funnel, N_2 inlet, and magnetic stirring bar, there was condensed 100 ml of dry NH_3 at −78°. Then 2.6 g (113 mmol) of sodium was added, stirring commenced, and a solution of 1.1 g (3.8 mmol) of 5-β-CCl_2 in 25 ml of dry tetrahydrofuran (THF) was added over 1 hr. Stirring was continued at −78° for 5 hr after addition. Solid NH_4Cl was added to the reaction mixture until its blue color was discharged; stirring was then continued at 25° and the ammonia was allowed to evaporate. The semisolid residue was mixed with 50 ml of THF and filtered. The filtrate was concentrated, and the residue was dissolved in 300 ml of chloroform. This solution was washed thrice with 50-ml portions of $NaHCO_3$ solution and once with brine, and then dried over $MgSO_4$. Filtration and concentration afforded 0.7 g (83%) of an oil, shown by GC on an 8 ft × 0.25 in., 20% SE-30 column (190°) to contain a single product. The GC-purified material had ir and NMR spectra[77,80] identical with those of 5-β-CH_2 prepared from **5** by Simmons–Smith methylenation.[44]

5β,6β-Chlorofluoromethylenecholestan-3-one 3-Ethylene Acetal (8-β-*endo*-F-*exo*-Cl and 8-β-*endo*-Cl-*exo*-F). A solution of 2.0 g (4.67 mmol) of **8** and 2.7 g (7 mmol) of $C_6H_5HgCCl_2F$[45] in 10 ml of dry benzene was refluxed for 15 hr under N_2. Filtration and concentration gave an oil which exhibited two resonances (ϕ^* 144.9 s and 123.4 d, ratio 3:1, see above) in its ^{19}F NMR spectrum. The oil was dissolved in hot, 95% ethanol; cooling returned 0.31 g of substrate **8** (mp 130–133°). The filtrate was concentrated to an oil which was chromatographed on 80–200 mesh, activity I alumina. Elution was with benzene, benzene–chloroform, and chloroform–1% methanol. The initial material obtained from the column crystallized from 95% ethanol, and was shown to be 8-β-*endo*-F-*exo*-Cl, mp 94–95°, 1.26 g (55%), R_f 0.36.[83] In the mass spectrum, a parent ion series was seen at *m/e* 494 (10.6%), 495 (2.9%) and 496 (3.5%).[77,80] The base peak was observed at *m/e* 87.

Anal. Calcd for $C_{30}H_{48}O_2ClF$: C, 72.76; H, 9.77; Cl, 7.15. Found: C, 72.60; H, 9.88; Cl, 7.11.

Further elution of the column afforded a small amount of a product which could be crystallized from ethanol, and which was spectrally identical with the ketone obtained by treating 100 mg of separated this sample into two components. The one with the higher R_f was additional 8-β-*endo*-F-*exo*-Cl (NMR); the other component, 180 mg, was its isomer, 8-β-*endo*-Cl-*exo*-F, which was characterized by NMR (see Results).[80]

Further elution of the column afforded a small amount of a product which could be crystallized from ethanol, and which was spectrally identical with the ketone obtained by treating 100 mg of 8-β-*endo*-F-*exo*-Cl with 5 mg of *p*-toluenesulfonic acid in 0.1 ml of water and 5 ml of methanol, at reflux, for 1 day.[73] These materials were therefore 5β,6β-*endo*-fluoro-*exo*-chloromethylenecholestan-3-one. A pure sample had mp 153–154.5° (from 95% ethanol),[77] and key NMR features (CCl_4) δ 1.15 (d, J = 3.3 Hz, 3 H, C-19 methyl), 0.90 (d, J = 6.6 Hz, 3 H, C-21 methyl), 0.87 (d, J = 6.6 Hz, 6 H, C-26 and C-27 methyls), 0.67 (s, 3 H, C-18 methyl); ϕ^* ($CFCl_3$, CCl_4) 144.5 s. The mass spectrum revealed a parent ion series at *m/e* 450 (45.3%), 451 (14.6%), and 452 (15.3%). The base peak was observed at *m/e* 149.

Anal. Calcd for $C_{28}H_{44}OClF$: C, 74.55; H, 9.83; Cl, 7.85. Found: C, 74.35; H, 9.94; Cl, 8.02.[85]

Further elution of the column afforded 50 mg of an oil [shown by multiple development TLC (see above) to consist of additional 5β,6β-*endo*-fluoro-*exo*-chloromethylenecholestan-3-one and, perhaps, its β-*endo*-Cl-*exo*-F isomer] and, finally, 100 mg of cholest-4-en-3-one.

Conversion of 5-β-CF_2 to 7-β-CF_2. Heated to reflux for 20 hr, under stirring, were 0.15 g (0.58 mmol) of 5-β-CF_2, 0.11 g (1.16 mmol) of ethanedithiol, and 0.01 g of *p*-toluenesulfonic acid in 1 ml of benzene. The cooled reaction mixture was passed through a 3-cm column of 80–200 mesh, neutral activated alumina (packing and elution with benzene), affording 0.14 g of the thioketal analogous to 5-β-CF_2. The NMR spectrum showed the new compound to be ~95% pure, and featured (CCl_4) δ 3.15 (s, 4 H, thioketal) and 1.08 (s, 3 H, methyl).

The thioketal was then stirred with 8.5 g of W-2 Raney nickel[86] in 40 ml of methanol, under reflux for 8 hr. Filtration and concentration afforded 70 mg of an oil which was chromatographed (as above) to afford a product identical (ir, NMR, and retention time on column C[76] at 148°) with 7-β-CF_2.

Conversion of 6-α-CF_2 to 7-α-CF_2. Using an identical procedure, 10 mg (0.04 mmol) of 6-α-CF_2, 10 mg (0.1 mmol) of ethanedithiol, and 5 mg of *p*-toluenesulfonic acid in 1 ml of benzene afforded the thioketal analogue of 6-α-CF_2: NMR (CCl_4) δ 3.17 (m, 4 H, thioketal), 1.11 (s, 3 H, methyl). Again following the previous procedure, this material was treated with 4.3 g of W-2 Raney nickel[86] in 20 ml of methanol to afford, after work-up, 4 mg of an oil which had GC retention times identical with those of 7-α-CF_2 on columns A and C.[76]

Relative Reactivity Experiments. The carbene precursor (100–200 mg) and NaI (dried at 110°, 0.1 Torr, 24 hr, 1–1.1 equiv) were weighed (drybox) into a 10-ml flask which contained a magnetic stirring bar. A solution of olefin A and olefin B (each carefully weighed)[87] in several milliliters of benzene or 1,2-dimethoxyethane (distilled from Na)[79] was added, and the flask was fitted with a condenser which was topped with a N_2 inlet. A positive pressure N_2 atmosphere was maintained throughout the reaction. The flask was lowered into an oil bath, preheated to 80 or 90°, and stirring was begun. After reflux (4–23 hr), the reaction mixture was cooled and filtered through a glass wool plug. The filtrate was immediately assayed by GC.

The competitive cases, precursors, solvents, analytical conditions, and results are summarized in Table II. Relative reactivities were calculated from the standard expression, $k_A/k_B = (O_B/O_A)(P_A/P_B)$, in which O_i represents the initial molar quantity of olefin i, and P_i represents the integrated GC peak of the corresponding carbene adduct.[88]

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Registry No.—**1**, 513-35-9; 1-CF_2, 823-25-6; **2**, 110-83-8; 2-CF_2, 823-70-1; **3**, 7092-24-2; 3-CF_2, 54158-65-5; **4**, 1004-58-6; 4-CF_2, 54158-66-6; **5**, 3287-60-3; 5-β-CF_2, 54158-67-7; 5-β-CF_2 thioketal analogue, 57065-86-8; 5-α-CF_2, 54165-77-4; 5-β-CCl_2, 57065-87-9; 5-β-*endo*-F-*exo*-Cl, 28846-73-3; 5-β-*endo*-Cl-*exo*-F, 57128-63-9; 5-β-CH_2, 28846-74-4; 5-α-CH_2, 28846-75-5; **6**, 50900-97-5; 6-β-CF_2, 54158-68-8; 6-α-CF_2, 54165-78-5; 6-α-CF_2 thioketal analogue, 57065-88-0; **7**, 13943-77-6; 7-β-CF_2, 57065-89-1; 7-α-CF_2, 57128-64-0; **8**, 3496-88-6; 8-β-CF_2, 57090-63-8; 8-β-*endo*-F-*exo*-Cl, 57065-90-4; 8-β-*endo*-Cl-*exo*-F, 57065-91-5; **9**, 826-56-2; CF_2, 2154-59-8; CCl_2, 1605-72-7; CClF, 1691-88-9; ethylene glycol, 107-21-1; 5β,6β-*endo*-fluoro-*exo*-chloromethylenecholestan-3-one, 57065-92-6; ethanedithiol, 540-63-6.

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(58) The additional 4.6-Hz splitting observed in the *exo*-F ^{19}F NMR resonance of **5**-β-CF_2 is attributable to W-plan long-range coupling of *exo*-F and H_e on C-7, cf. **11**. Related long-range splittings were observed in monocyclic models **2**-CF_2 and **3**-CF_2 (see Table I). Dreiding models suggest that in the **5** (or **7**) series, the proper geometry for this coupling only obtains in the β adducts, and is specific to the *exo*-F atom.
(59) This assignment was previously unclear.[44]
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(65) CCl_2 generated from $Cl_3CCOONa$[27] or $C_6H_5HgCCl_3$[29] does not add to $\Delta^{5,6}$ steroidal olefins, but CCl_2 generated by the Makosza method[43] does add.[18] This curious contrast signals a prime topic for future research.
(66) See ref 4a for a review of carbenic stereoselectivity. For specific discussions of CFCl, see ref 49, Moss and Gerstl.
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(74) Ir spectra were recorded on a Perkin-Elmer Model 137 instrument; ^1H NMR spectra were generally recorded on either a Varian T-60 or a Jeolco JNM-MH-100 spectrometer. ^{19}F NMR spectra were recorded on the T-60 instrument (at 56.4 MHz). Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6L spectrometer. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.
(75) The balance was isomer **4**.
(76) Column identifications appear in footnote *c*, Table II.
(77) Complete ir descriptions of *all* compounds appear in the Thesis of D.J.S.[73]
(78) The analysis was by GC on a 12 ft × 0.25 in., 3% SE-30 on 80/100 Gas-Chrom RZ column at 150°.
(79) All olefins were purified just prior to use. They were percolated, in the reaction solvent, through a short column of 80–200 mesh, neutral, activated alumina and Linde 3A molecular sieves. Weighings were done in a N_2-filled drybox, relative humidity 4–5%.
(80) Key features of the NMR spectra of the adducts are described in Table I; additional details appear in the Thesis of D. J. S.[73]
(81) Further elution of the column with benzene–methanol gave 0.5 g of an oil, ir 1718 cm^{-1} (C=O), R_f (CCl_4) 0.20, which was shown to be the deketalized adduct. Control experiments showed that **8**-β-CF_2 partially deketalized during column chromatography, and that the ketone isolated from the reaction of **8** + CF_2 could be reketalized to **8**-β-CF_2. The ketone was not present in the crude reaction product (^{19}F NMR). It could be prepared from 8-β-CF_2 by deketalization.[73]
(82) Only a single angular methyl resonance (δ 1.23) could be observed in the NMR spectrum of the crude product.
(83) TLC conditions are described under **8**-β-CF_2.
(84) Phosphomolybdic acid was used for visualization.
(85) Control experiments showed that the ketone could be reketallzed to **8**-β-*endo*-F-*exo*-Cl, and that its origin was in alumina-induced deketalization of the latter during chromatography.[73]
(86) R. Mozingo, *Org. Synth.*, **21**, 15 (1941).
(87) The molar ratio of the more reactive olefin to carbene precursor was at least 3.3, and usually >5. The less reactive olefin was in excess of the more reactive olefin. Although the former ratio should ideally have been larger (>10), we were limited by substrate availability. The derived *k* values, however, appear to be acceptable; see Results.
(88) For a discussion of this method, see ref 30.

Periselective Addition of Nitrile Sulfides, Nitrile Oxides, and Diphenyldiazomethane to Tetracyanoethylene

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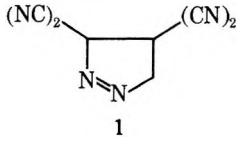
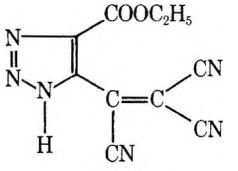
Nitrile sulfides and nitrile oxides underwent periselective 1,3-dipolar addition to the nitrile functions of tetracyanoethylene to form mono and bis thiadiazole and oxadiazole derivatives, respectively. Solvolysis reactions of the thiadiazoles and oxadiazoles were investigated. Diphenyldiazomethane added selectively to the carbon–carbon double bond of tetracyanoethylene to form 1,1-diphenyl-2,2,3,3-tetracyanocyclopropane in high yield.

The formation of Diels–Alder adducts from tetracyanoethylene (TCNE) and 1,3-dienes is a well-known reaction.[1] By contrast, 1,3-dipolar reactions of TCNE have been reported in only two cases. Diazomethane is claimed[2] to undergo exclusive addition to the double bond to yield a pyrazoline **1** which readily lost nitrogen to form 1,1,2,2-tetracyanocyclopropane. Ethyl diazoacetate, however, has been reported[3] to add to the nitrile function of TCNE. The unstable product was postulated to be 4-ethoxycarbonyl-5-tricyanovinyl-1,2,3-triazole (**2**) but was not fully characterized.



1



2

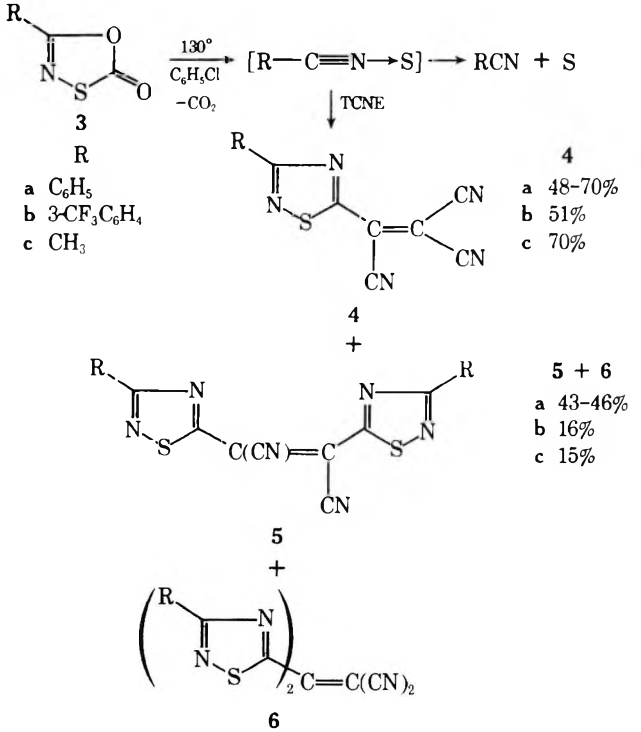
Related nitriles such as acrylonitrile,[4] cyanoacetylene,[5] and dicyanoacetylene[6,7] are reported to react at the unsaturated carbon–carbon bonds with various 1,3-dipoles.[8]

Since the factors which influence the mode of periselective addition of 1,3-dipoles to TCNE have not been studied, we have investigated this type of reaction in more detail.

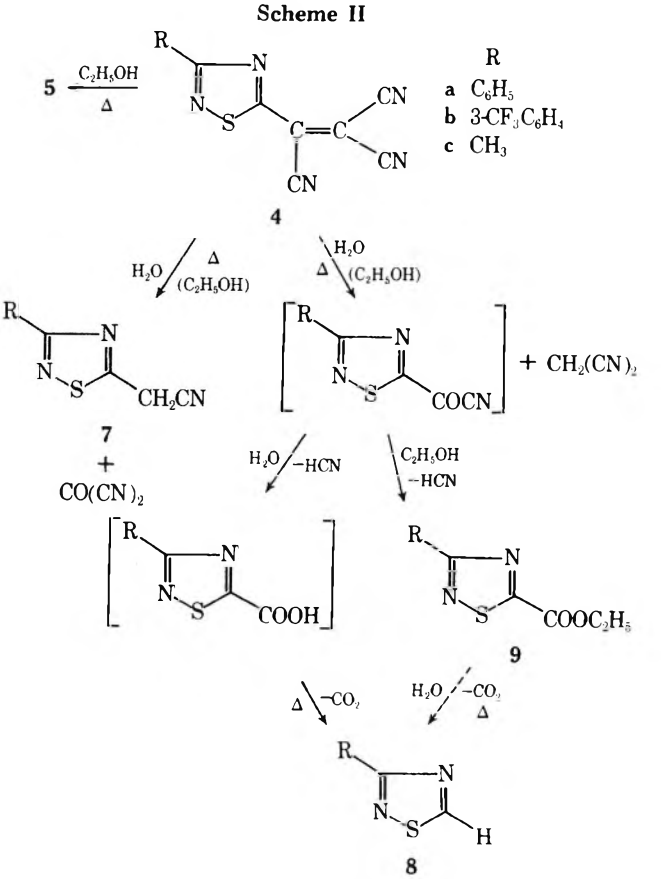
Benzonitrile sulfide,[9-11] obtained by the thermolysis of the oxathiazolone **3a**, reacted with TCNE at 130° to form benzonitrile, sulfur, tricyanoethylene **4a**, and a mixture of dicyanoethylene isomers **5a** (presumably cis and trans) and **6a** as indicated in Scheme I. The yields of dicyanoethylene isomers were substantially increased as the mole ratio of **3a** to TCNE was increased or when **3a** and **4a** were heated at 180°. Similar results were obtained with the oxathiazolone **3b** whereas **3c** produced **4c** and a single dicyanoethylene isomer (presumably trans) **5c**. There was no indication (ir, NMR, GC–mass spectra) that products arising from 1,3-dipolar addition to the carbon–carbon double bond of TCNE were present in significant amounts in any of these reaction mixtures. The major component of the dicyanoethylene mixture was easily separated by selective solvent extraction and is assumed to be the more thermodynamically stable trans isomer of **5**. The structures of **4** and **5** were supported by the elemental analyses, ir, NMR, and mass spectra. The structures of **4** were further supported by the chemical conversions outlined in Scheme II.

The major products **9** from solvolysis of **4** with 95% aqueous ethanol were identified by elemental analyses, spectral data (ir, NMR, mass), and, for **9a** and **9b**, comparison with authentic[11] materials. Malononitrile and the minor prod-

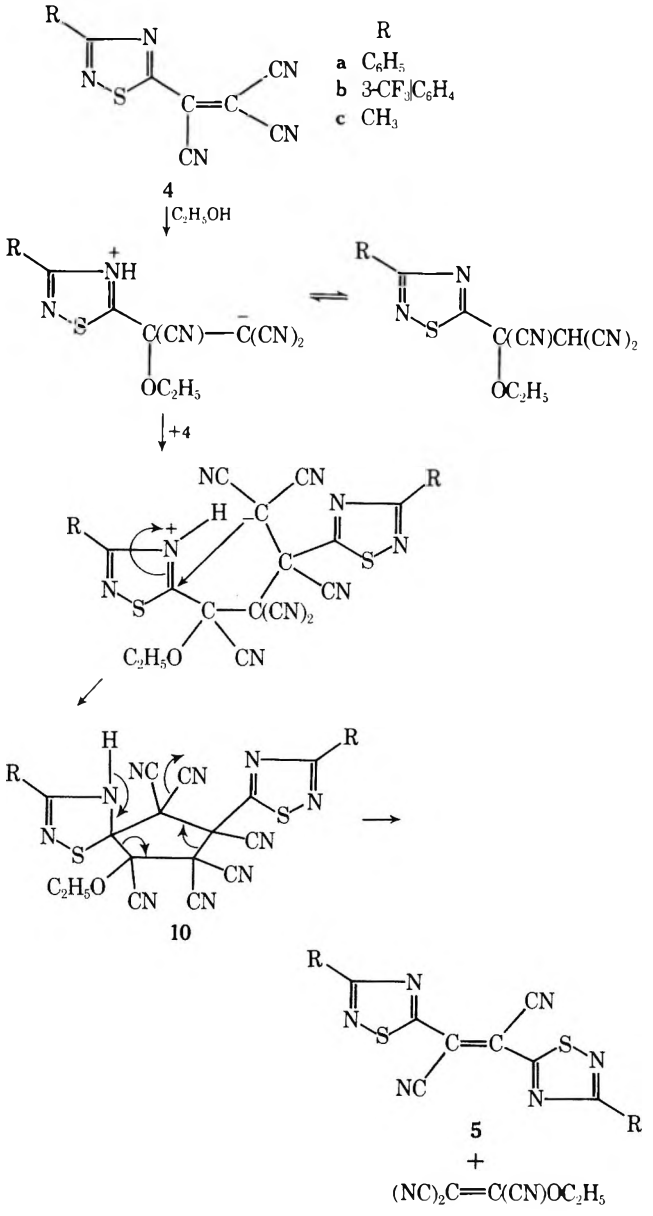
Scheme I



Scheme II



Scheme III

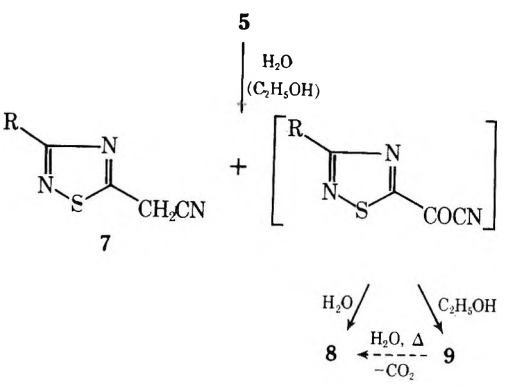


ucts **5**, **7**, and **8** were identified by ir and/or GC–mass spectra. The hydrolytic conversion of tricyanoethylenes to esters has been reported[12] previously. Although the mechanism of this reaction is not known, acyl cyanides[13a] appear to be plausible intermediates with suitable reaction characteristics.

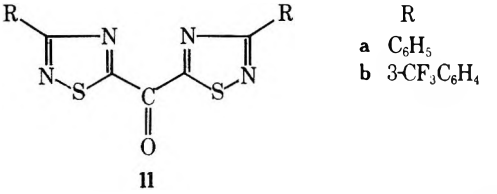
In contrast to 95% aqueous ethanol, dry alcohol converted **4** primarily to the dicyanoethylenes **5**. This unusual transformation is not a thermal reorganization since no change occurs when **4a** is heated in *o*-dichlorobenzene at reflux. Another possibility, the addition of the anion of **8a** to **4a** followed by elimination of cyanide, also did not occur in hot aprotic solvents. The reaction sequence illustrated in Scheme III involving an intermediate spiran **10** is one possible mechanism which is under investigation.[13b]

The hydrolysis of **5a** by 95% aqueous ethanol under various conditions was extremely slow owing to the insolubility of the starting material. The dicyanoethylenes **5b** and **5c**, however, were sufficiently soluble to undergo the expected conversions indicated in Scheme IV. Esters **9b** and **9c** and nitriles **7b** and **7c** were formed in approximately equivalent amounts as indicated by GC–mass spectral data. The thiadiazoles **8b** and **8c** were minor products formed by hydrolysis–decarboxylation of intermediate acyl cyanides

Scheme IV

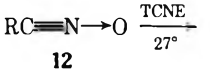


and/or esters **9** as indicated. Certain fractions consisting of mixtures of **5** and **6**, which were isolated from the hydrocarbon solvent of the TCNE reactions, were also sufficiently soluble in 95% aqueous ethanol to undergo solvolysis. Thus, the GC–mass spectrum of the solvolysis product of **5a** + **6a** indicated the presence of malononitrile, benzonitrile (7%), **7a** (27%), **8a** (9%), **9a** (45%), and bis(3-phenyl-1,2,4-thiadiazol-5-yl) ketone (**11a**, 12%). In a similar manner solvolysis of the mixture **5b** + **6b** yielded malononitrile, **7b** (17%), **8b** (2%), **9b** (24%), and bis[3-(3-trifluoromethylphenyl)-1,2,4-thiadiazol-5-yl)] ketone (**11b**, 54.5%). Product **11b** was iso-

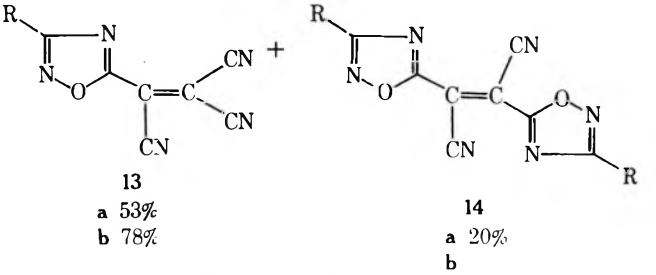


lated and further characterized by elemental analysis and the ir and NMR spectra.

In a manner similar to nitrile sulfides, benzonitrile oxide **12a** and mesitonitrile oxide **12b** reacted with TCNE at room temperature to yield the corresponding 1,2,4-oxadiazole adducts **13** and **14**. In each of these reactions only a



R
a C_6H_5
b 2,4,6-$(CH_3)_3C_6H_2$

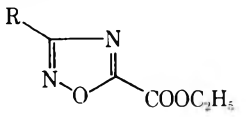


single dicyancethylene was formed and is assumed to be the trans isomer **14**. Product **14b** was initially obtained from the reaction mixture as a yellow powder. This product was converted to a more stable red crystalline form when it was dissolved in chloroform or heated in ether. Another product isolated from the mesitonitrile oxide reaction was an orange powder which had an elemental analysis, cryoscopic molecular weight, mass spectrum, and ir spectrum consistent for a TCNE π complex of **14b**. The orange powder also was formed in nearly quantitative yield when equimolar amounts of **14b** and TCNE were mixed in benzene at room temperature. The π complex could be recrystallized

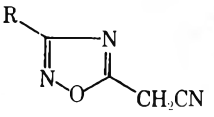
unchanged from benzene but was converted to **14b** by warm ethanol.

In analogy with the nitrile sulfide reactions, attempts to isolate or identify 1,3-dipolar adducts from nitrile oxides in which the carbon–carbon double bond of TCNE functions as an acceptor were not successful.

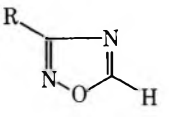
Dilute ethanol (95%) converted **13a** to a mixture of products containing ethyl carbamate, benzonitrile, malononitrile, ethyl ester **15a**, nitrile **16a**, and oxadiazole **17a**. The



15



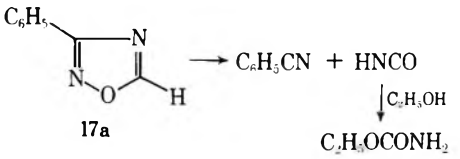
16



17

a C_6H_5
b $2,4,6\text{-}(CH_3)_3C_6H_2$

products were identified by their GC–mass spectra. The ester **15a** and nitrile **16a** were isolated by column chromatography, and **15a** was shown to be identical (GC retention time, ir spectrum, melting point, mixture melting point) with authentic material.[14] Apparently, benzonitrile and ethyl carbamate result from the ring degradation of **17a**.



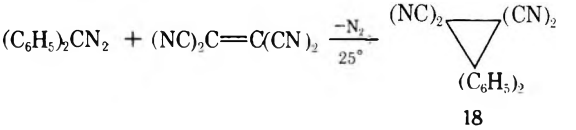
17a

During the solvolysis of **13a** the oxadiazole **17a** may be formed by the hydrolysis–decarboxylation of an intermediate acyl cyanide and/or **15a**. No reaction occurred when **15a** and 95% ethanol were heated at reflux for several hours. In the presence of a catalytic amount of potassium cyanide, however, **15a** was converted to a mixture of **17a**, benzonitrile, and ethyl carbamate. After a reflux period of 48 hr only the latter two components were present in the reaction solution. This result supports the view that ethyl carbamate and benzonitrile are derived from **17a** which in turn may be formed from **15a** during the solvolysis of **13a**. The mesityl analogue **13b** was hydrolyzed by 95% ethanol in a manner similar to the phenyl derivative **13a**. The ester **15b** was isolated and found to be identical with authentic material prepared from ethyl cyanoformate and mesitonitrile oxide. The nitrile **16b** was also isolated and identified by its ir, NMR, and mass spectra.

The 1,2,4-oxadiazolyltricyanoethylenes **13** were similar to the corresponding 1,2,4-thiadiazolyltricyanoethylenes **4** in their activity towards hot *absolute* ethanol. Thus, **13a** was readily converted to **14a** in 85% yield and **13b** yielded **14b** in 79% yield. A mechanism analogous to that outlined in Scheme III would account for these results. Finally, **14b**, like **5b**, was readily solvolyzed by hot 95% aqueous ethanol to yield a mixture of **15b** and **16b**.

Attempts to prepare nitrile imine adducts of TCNE were not successful. Irradiation of mixtures of TCNE and 3,5-diphenyl-1,3,4-oxadiazolin-2-one[15] at 2537 Å produced polymeric materials. Complex mixtures were also obtained when attempts were made to generate nitrile imines from α-halobenzaldehyde phenylhydrazones in the presence of TCNE.

The periselectivity of the TCNE reactions encountered in this work and in the literature may be due to electronic and/or steric factors. To assess the possibility that the contrasting mode of addition of diazomethane and ethyl diazoacetate to TCNE may be significantly influenced by steric effects, we investigated the nature of the diphenyldiazomethane reaction. In a mixed solvent at room temperature a rapid reaction occurred with liberation of nitrogen and precipitation of 1,1-diphenyl-2,2,3,3-tetracyanocyclopropane (**18**) in nearly quantitative yield. The structure of



18

product **18** was supported by the elemental analysis and the ir and mass spectra. The order of steric inhibition to formation of the pyrazoline transition state (i.e., addition to the carbon–carbon double bond of TCNE) is assumed to be in the order diphenyldiazomethane > ethyl diazoacetate > diazomethane. Since diazomethane and diphenyldiazomethane react readily at the double bond of TCNE in contrast to ethyl diazoacetate, however, it would appear that steric effects are somewhat less important than electronic factors in periselective additions of this type.

Our initial attempts to correlate the periselective nature of these diverse TCNE reactions by charge density considerations or frontier electron models have not been successful.

A study of the reactions of other 1,3-dipoles with TCNE is in progress. The reactions of adducts **4**, **5**, **13**, and **14** with a variety of reagents is also under investigation and will be reported at a later date.

Experimental Section

Melting points were taken in open capillaries in a Mel-Temp apparatus and are uncorrected. The tetracyanoethylene used in this work was Eastman white label grade. The 1,3,4-oxathiazol-2-ones were prepared from the corresponding acid amides and chlorocarbonylsulfenyl chloride according to reported procedures.[16] Benzonitrile oxide was prepared from α-chlorobenzaldehyde oxime[17] and mesitonitrile oxide was prepared by the method of Grundman and Dean.[18] Diphenyldiazomethane was prepared[19] by oxidation of benzophenone hydrazone. GC analyses were performed on an F and M Scientific 720 dual column programmed gas chromatograph using 2-ft columns packed with 10% SE-30 or OV-17. Programming was generally carried out from 50 to 300° at 15°/min.

Reaction of 5-Phenyl-1,3,4-oxathiazol-2-one (3a) and TCNE (1:1 Mole Ratio). A mixture of 18 g (0.10 mol) of 5-phenyl-1,3,4-oxathiazol-2-one (**3a**), 12.8 g (0.10 mol) of tetracyanoethylene, and 80 ml of dry chlorobenzene was heated at the reflux temperature (137°) for 16 hr with good agitation. The black reaction mixture was cooled to room temperature under dry nitrogen and diluted with ether and the precipitated solid was collected by filtration. The residue was washed with ether and air dried to yield 20.7 g of yellow powder, mp 200–204°. The ir spectrum indicated that the tricyanoethylene **4a** and the dicyanoethylenes **5a** and **6a** were the only materials present in significant amounts. The crude product (20 g) was extracted with 300 ml of warm tetrahydrofuran and the insoluble dicyanoethylenes (**5a** and **6a**) (1.1 g, 5.5%) collected by filtration. Pure 1,2-bis(3-phenyl-1,2,4-thiadiazol-5-yl)-1,2-ethenedicarbonitrile (**5a**) was partially separated from the mixture as a yellow powder, mp 290–293° dec, by repeated recrystallization from hot tetrahydrofuran: mass spectrum *m/e* (rel intensity, fragment) 398 (44, M^+), 295 (4, $M^+ - C_6H_5CN$), 263 (4, $M^+ - C_6H_5CNS$), 135 (100, $C_6H_5CNS^+$), 103 (36, $C_6H_5CN^+$); ir (Nujol) 4.5 (w), 6.25 (w), 8.85 (s), 11.75 (s), 12.6 (s), 14 μ (s). The ir spectrum of pure **5a** indicates that it is the major constituent of the dicyanoethylene mixture (which also shows weak absorption at 11.35, 11.9, 12.3, and 14.15 μ).

Anal. Calcd for $C_{20}H_{10}N_6S_2$: C, 60.28; H, 2.53; N, 21.09; S, 16.09. Found: C, 60.42; H, 2.54; N, 21.01; S, 16.22.

The tetrahydrofuran extract was concentrated to yield 18.5 g (70%) of tricyanoethylene **4a**. The ir spectrum indicated essentially pure product but the material contained a brown-colored impurity. The impurity was best removed by several recrystallizations from acetonitrile or by chromatography of the benzene solution through Florisil. Pure 2-(3-phenyl-1,2,4-thiadiazol-5-yl)-1,1,2-ethenetricarbonitrile (**4a**) was obtained as a bright yellow, crystalline solid: mp 210–211°; mass spectrum *m/e* (rel intensity, frag-

ment) 263 (58, M^+), 135 (100, $C_6H_5CNS^+$), 103 (50,$C_6H_5CN^+$), 77 (50, $C_6H_5^+$); ir (Nujol) 4.5 (w), 6.5 (w), 6.8 (s), 7.1 (s), 8.4 (s), 11.7 (s), 12.6 (s), 13.95 (s), 14.4 μ (s).

Anal. Calcd for $C_{13}H_5N_5S$: C, 59.30; H, 1.91; N, 26.60; S, 12.18; mol wt, 263.3. Found: C, 59.43; H, 1.81; N, 26.54; S, 12.31; mol wt (tetrahydrofuran), 284.

GC analysis of the chlorobenzene–ether filtrate indicated the presence of benzonitrile, sulfur, tetracyanoethylene, and tricyanoethylene **4a**. Concentration of the filtrate on a hot water bath at 20 mm gave 3.4 g of a mixture containing predominantly tetracyanoethylene, sulfur, and tricyanoethylene **4a**.

Reaction of 5-Phenyl-1,3,4-oxathiazol-2-one (3a) and TCNE (2:1 Mole Ratio). A mixture of 9 g (0.05 mol) of 5-phenyl-1,3,4-oxathiazol-2-one (**3a**), 3.2 g (0.025 mol) of TCNE, and 30 ml of dry chlorobenzene was heated at the reflux temperature (136–138°) for 15 hr. After being cooled to room temperature, the dark mixture was filtered and the residue washed several times with benzene and then ether. The yield of residual green powder was 3.9 g (39%). Gas chromatography and the ir spectrum indicated that the product was primarily a mixture (cis + trans?) of dicyanoethylenes **5a**. The benzene washes were concentrated at reduced pressure to yield 2.5 g of solid. By recrystallization from acetonitrile, the mixture was separated into 2.2 g (33%) of **4a** (mp 209–210°) and 0.4 g (4%) of dicyanoethylene mixture **5a**. The reaction filtrate was concentrated at reduced pressure on a hot water bath to remove solvent (C_6H_5Cl). The residue was washed with ether to yield 1.4 g of a mixture containing **4a**, **5a**, and **6a**. By extraction with acetonitrile the mixture was separated into 1 g (15%) of **4a** and 0.4 g (4%) of a mixture of **5a** and **6a**.

Reaction of 5-Phenyl-1,3,4-oxathiazol-2-one (3a) and 2-(3-Phenyl-1,2,4-thiadiazol-5-yl)-1,1,2-ethanecarbonitrile (4a). A mixture of 2.6 g (0.01 mol) of **4a** and 30 ml of *o*-dichlorobenzene was heated at the reflux temperature (179°) with good agitation under a nitrogen atmosphere. During intervals of 5 min, three 0.7-g portions (2.1 g, 0.012 mol) of **3a** were added to the hot solution. Heating was continued for 0.5 hr and then the mixture was cooled to room temperature. The precipitate (2.3 g, 58%) was collected by filtration and was washed with benzene and ether. The GC and ir spectrum [Nujol, 4.5 (w), 6.25 (w), 7.0 (m), 11.45 (w), 11.85 (s), 12.0 (m), 12.4 (w), 12.75 μ (s)] indicated predominantly a mixture of dicyanoethylenes **5a**. The reaction filtrate and benzene washes were combined and concentrated on a steam bath at 20 mm until most of the *o*-dichlorobenzene had been removed. The residue was washed with ether to yield 1.4 g (30%) of yellow-orange powder. GC analysis and the infrared spectrum [Nujol, 4.5 (w), 6.2 (w), 6.45 (w), 7 (s), 8.35 μ (m)] indicate that this material is predominantly a mixture of isomers **5a** and **6a** (see solvolysis data).

Reaction of 5-(3-Trifluoromethylphenyl-1,3,4-oxathiazol-2-one (3b) and TCNE. A mixture of 13.0 g (0.05 mol) of **3b**, 6.4 g (0.05 mol) of TCNE, 40 ml of dry chlorobenzene, and 20 ml of 1,2,4-trichlorobenzene was heated at the reflux temperature (146°) with stirring for 26 hr. After cooling to room temperature, the black mixture was filtered. The residue was washed with acetonitrile and ether to yield 0.5 g (4%) of **5b** as a yellow powder, mp 224–225°. After recrystallization from hot acetonitrile, 1,2-bis[3-(3-trifluoromethylphenyl)-1,2,4-thiadiazol-5-yl]-1,2-ethenedicarbonitrile (**5b**) was obtained as yellow needles: mp 222–223.5°; ir (Nujol) 4.5 (w), 6.22 (w), 7.6 (s), 8.5 (s), 8.65 (s), 8.85 (s), 8.92 (s), 13.55 (s), 14.4 μ (s); mass spectrum *m/e* (rel intensity, fragment) 534 (35, M^+), 515 (5, $M^+ - F$), 465 (37, $M^+ - CF_3$), 203 (100, $CF_3C_6H_4CNS^+$), 171 (15, $CF_3C_6H_4CN^+$), 145 (19, $CF_3C_6H_4^+$).

Anal. Calcd for $C_{22}H_8F_6N_6S_2$: C, 49.44; H, 1.51; N, 15.73; S, 12.00. Found: C, 49.52; H, 1.48; N, 15.69; S, 12.26.

The reaction filtrate was filtered through a short column of Florisil to remove a black impurity and the column was then washed with benzene. The combined eluate was concentrated at 100° (20 mm) to remove solvent and some unreacted TCNE. The orange residue was mixed with a large volume of petroleum ether and the precipitated powder collected by filtration. The yield of air-dried crude mono adduct was 13.8 g. The crude product (12 g) was heated with acetonitrile and then the mixture was cooled to room temperature and filtered. The residue (1.6 g, 12%) was a mixture of the bis adducts **5b** and **6b** as indicated by the ir spectrum [Nujol, 4.5 (w), 6.2 (w), 6.5 (w), 7.6 (s), 7.8 (m), 11.9 (m), 12.45 (m), 8.5 (s), 8.65 (s), 8.85 (s), 8.95 (s), 13.55 (s), 14.45 μ (s)] and solvolysis products (see solvolysis). The mixture of **5b** and **6b** was extracted with benzene and the benzene solution concentrated. The orange residue was extracted with ether to yield an insoluble orange powder, mp 212.5–216.5°. The ir spectrum [Nujol, 4.5 (w), 6.2 (w), 6.5 (w), 7.55 (s), 7.7 (s), 7.8 (s), 8.5 (s), 8.65 (s), 8.9 (s), 9.15 (s), 9.2 (s), 10.4 (m), 10.9 (s), 11.9 (s), 12.3 (s), 12.4 (s), 13.55 (s), 14.45 μ (s)] indicated primarily **6b**.

The acetonitrile solution was concentrated at reduced pressure. The residue was dissolved in benzene and chromatographed on Florisil. After removal of benzene from the eluate, the residue was agitated with petroleum ether and filtered. The yield of yellow mono adduct **4b** was 8.5 g (51%), mp 118.5–120.5° (sintered at 112° and resolidified). Analytically pure 2-[3-(3-trifluoromethylphenyl)-1,2,4-thiadiazol-5-yl]-1,1,2-ethenetricarbonitrile (**4b**), mp 119.5–121.5°, was obtained by recrystallization from heptane.

Anal. Calcd for $C_{14}H_4F_3N_5S$: C, 50.76; H, 1.22; N, 21.14; S, 9.68. Found: C, 50.83; H, 1.26; N, 20.88; S, 9.45.

The Nujol ir spectra and melting points of **4b** before and after recrystallization from heptane are slightly different. Since the solution ir spectra are the same, however, the differences are presumably due to different crystalline modifications. Ir ($CHCl_3$) 4.5 (m), 6.2 (m), 6.5 (w), 6.8 (m), 6.9 (m), 7.2 (s), 7.6 (s), 7.8 (s), 8.55 (s), 8.85 (s), 9.15 (s) 9.35 (s), 10 (m), 10.5 (m), 10.9 (s) 11.75 μ (s); mass spectrum *m/e* (rel intensity, fragment) 331 (4, M^+), 262 (9, $M^+ - CF_3$), 203 (12, $CF_3C_6H_4CNS^+$), 171 (3, $ArCN^+$), 145 (4, $CF_3C_6H_4^+$).

Reaction of 5-Methyl-1,3,4-oxathiazol-2-one (3c) and TCNE. A mixture of 2.95 g (0.025 mol) of **3c** and 3.2 g (0.025 mol) of TCNE in 25 ml of dry chlorobenzene was heated at 130° under nitrogen for 17 hr. Since some TCNE precipitated when the mixture was cooled to room temperature, an additional 2.95 g (0.025 mol) of **3c** was added and heating at 130° resumed for 24 hr. At the end of this time GC analysis indicated the absence of TCNE and substantial conversion to **4c**. After cooling to room temperature, the dark mixture was filtered to yield 0.6 g (9%) of the bis adduct **5c**. The chlorobenzene filtrate was concentrated on a steam bath at 20 mm and the residue extracted with several portions of hot petroleum ether to yield an additional 0.4 g (6%) of insoluble crude **5c**. Pure 1,2-bis(3-methyl-1,2,4-thiadiazol-5-yl)-1,2-ethenedicarbonitrile, mp 215–216.5°, was obtained by recrystallization of the crude products from tetrahydrofuran–ether: ir (Nujol) 4.5 (w), 6.05 (w), 6.8 (s), 7.0 (s), 7.1 (s), 10.0 (s), 12.0 μ (s); mass spectrum *m/e* (rel intensity, fragment) 274 (23, M^+), 247 (2, $M^+ - HCN$), 233 (12, $M^+ - CH_3CN$), 220 (2, $M^+ - 2HCN$), 192 (2, $M^+ - 2CH_3CN$), 73 (100, CH_3CNS^+), 41 (3, CH_3CN^+); NMR ($CDCl_3$) δ 2.85 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_6N_6S_2$: C, 43.78; H, 2.20; N, 30.64; S, 23.38. Found: C, 43.76; H, 2.12; N, 30.70; S, 23.26.

The petroleum ether extracts were concentrated to yield 4.4 g of a mixture containing predominantly **4c** and sulfur (~11%). An attempt to decolorize the mixture in benzene–hexane with decolorizing carbon was not successful. The recovered material was finally purified by several recrystallizations from methylcyclohexane to yield 2-(3-methyl-1,2,4-thiadiazol-5-yl)-1,1,2-ethenetricarbonitrile (**4c**) as a yellow, crystalline solid: mp 80–81°; ir (Nujol) 4.5 (w), 6.45 (w), 6.9 (s), 7.05 (s), 7.15 (s), 9.85 (s), 11.45 (s), 11.9 μ (s); mass spectrum *m/e* (rel intensity, fragment) 201 (18, M^+), 174 (1, $M^+ - HCN$), 102 [3, $C_2(CN)_3^+$], 76 (10, $C_2(CN)_2^+$), 73 (100, CH_3CNS^+), 41 (4, CH_3CN^+); NMR ($CDCl_3$) δ 2.90 (s, 3, CH_3).

Anal. Calcd for $C_8H_3N_5S$: C, 47.75; H, 1.50; N, 34.81; S, 15.94. Found: C, 47.79; H, 1.46; N, 34.74; S, 16.07.

Reaction of Benzonitrile Oxide (12a) with TCNE. To a cold (0–5°) stirred solution of 1.6 g (0.01 mol) of benzohydroxamyl chloride in 70 ml of ether was added in one portion a cold solution of 1.05 g (0.01 mol) of triethylamine in 5 ml of ether. The precipitated triethylamine hydrochloride (1.3 g) was removed by filtration and the filtrate added to a solution of 1.3 g (0.01 mol) of TCNE in a mixture of 20 ml of benzene and 5 ml of acetonitrile. After about 5 min a yellow precipitate began to form. The mixture was stirred at room temperature for 17 hr and then filtered. The yellow residue of **14a** (0.37 g, 20%), mp 285° dec, was washed with benzene and ether and air dried. An analytical sample of 1,2-bis(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2-ethenedicarbonitrile (**14a**), mp 285° dec, was prepared by recrystallization from *N,N*-dimethylacetamide–ether: ir (Nujol) 4.5 (w), 6.30 (w), 6.35 (w), 6.5 (m), 6.65 (m), 6.95 (s), 7.45 (s), 12.2 (s), 12.65 (s), 13.55 (s), 14.4 μ (s); mass spectrum *m/e* (rel intensity, fragment) 336 (37, M^+), 249 (31, $M^+ - C_6H_5CN_2$), 221 (3, $M^+ - C_6H_5C_2N_2O$), 145 (24, $C_6H_5C_2N_2O^+$), 119 (61, $C_6H_5CNO^+$), 117 (9, $C_6H_5CN_2^+$), 103 (64, $C_6H_5CN^+$), 77 (68, $C_6H_5^+$).

Anal. Calcd for $C_{20}H_{10}N_6O_2$: C, 65.57; H, 2.75; N, 22.94. Found: C, 65.69; H, 2.80; N, 22.98.

The reaction filtrate was concentrated at reduced pressure and the residue (2.25 g) extracted with 40 ml of benzene. GC analysis of the benzene solution using chlorobenzene as a standard indicated

the presence of 1.3 g (53%) of **13a**. The benzene solution was chromatographed on Florisil and the yellow eluate concentrated at reduced pressure. The residue was extracted with petroleum ether and the residue of **13a** (1.35 g) air dried. After recrystallization from acetonitrile, pure 2-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,1,2-ethenetricarbonitrile (**13a**), mp 176.5–178.5°, was obtained as yellow crystals: ir (Nujol) 4.45 (w), 6.25 (m), 6.35 (m), 6.42 (w), 6.6 (s), 6.92 (s), 9.3 (s), 11.3 (s), 12.6 (s), 13.45 (s), 14.2 (s), 14.45 μ (s); mass spectrum *m/e* (rel intensity, fragment) 247 (97, M^+), 221 (3, $M^+ - CN$), 145 (7, $C_6H_5C_2N_2O^+$), 130 (4, $M^+ - C_6H_5CN_2$), 119 (100, $C_6H_5CNO^+$), 117 (99, $C_6H_5CN_2^+$), 103 (39, $C_6H_5CN^+$), 77 (19, $C_6H_5^+$).

Anal. Calcd for $C_{13}H_5N_5O$: C, 63.16; H, 2.04; N, 28.33. Found: C, 63.33; H, 1.94; N, 28.53.

Reaction of Mesitonitrile Oxide (12b) with TCNE. To a solution of 1.2 g (0.0095 mol) of TCNE in 20 ml of benzene and 5 ml of acetonitrile was added a solution of 1.6 g (0.010 mol) of mesitonitrile oxide in 50 ml of ether. After stirring for 3 days at room temperature under dry conditions, the yellow-orange solution was concentrated at reduced pressure. The residue was triturated with petroleum ether to yield 2.4 g of insoluble solid. The crude product was extracted with ether and the insoluble orange powder (0.2 g) recrystallized from benzene to yield a TCNE π complex of **14b**: mp 185–187° dec; ir (Nujol) 4.45 (w), 6.2 (s), 6.5 (s), 6.65 (m), 7.5 (s), 9.15 (s), 11.7 (s), 12.3 μ (s); mass spectrum *m/e* (rel intensity, fragment) 450 (10, M^+), 291 [31, $M^+ - C_6H_2(CH_3)_3CN_2$], 263 [19, $M^+ - C_6H_2(CH_3)_3C_2N_2O$], 187 [20, $C_6H_2(CH_3)_3C_2O^+$], 161 [13, $C_6H_2(CH_3)_3CNO^+$], 159 [80, $C_6H_2(CH_3)_3CN_2^+$], 146 [14, $C_6H_2(CH_3)_3CNO^+-CH_3$], 145 [80, $C_6H_2(CH_3)_3CH^+$], 144 [70, $C_6H_2(CH_3)_3CN_2^+-CH_3$], 130 [100, $C_6H_2(CH_3)_3CN^+-CH_3$], 119 [9, $C_6H_2(CH_3)_3^+$].

Anal. Calcd for $C_{32}H_{22}N_{10}O_2$: C, 66.42; H, 3.84; N, 24.21. Found: C, 66.43; H, 3.82; N, 24.15.

Recrystallization of the π complex from ethanol produced 1,2-bis(3-mesityl-1,2,4-oxadiazol-5-yl)-1,2-ethenedicarbonitrile (**14b**), mp 177.5–178.5° dec, as red crystals: ir (Nujol) 4.5 (w), 6.2 (s), 6.4 (s), 6.65 (s), 11.2 (s), 11.8 μ (s); mass spectrum similar to that of the π complex with some relative intensity differences; NMR ($CDCl_3$) δ 2.28 (s, 12, $ArCH_3$-2), 2.33 (s, 6, $ArCH_3$-4), 6.97 (s, 4, ArH).

Anal. Calcd for $C_{26}H_{22}N_6O_2$: C, 69.31; H, 4.93; N, 18.66. Found: C, 69.43; H, 4.86; N, 18.69.

The orange π complex of **14b** was re-formed in almost quantitative yield when equimolar amounts of **14b** and TCNE were mixed in benzene.

The ether extract of the crude reaction product was concentrated at reduced pressure to yield 2.2 g (78%) of nearly pure **13b** as indicated by the ir spectrum. An analytical sample of 2-(3-mesityl-1,2,4-oxadiazol-5-yl)-1,1,2-ethenetricarbonitrile (**13b**), mp 130.5–131.5°, was prepared by two recrystallizations from heptane: ir (Nujol) 4.5 (w), 6.3 (m), 6.4 (m), 6.65 (s), 9.15 (s), 11.65 μ (s); mass spectrum *m/e* (rel intensity, fragment) 289 (40, M^+), 263 (7, $M^+ - CN$), 235 (37, $M^+ - 2HCN$), 187 (4, $ArC_2N_2O^+$), 159 (78, $ArCN_2^+$), 144 (100, $M^+ - ArCN$), 145 (24, $ArCN^+$), 128 (5, $M^+ - ArCNO$), 119 (2, Ar^+).

Anal. Calcd for $C_{16}H_{11}N_5O$: C, 66.42; H, 3.84; N, 24.21; mol wt, 289. Found: C, 66.23; H, 3.93; N, 23.96; mol wt (C_6H_6), 300.

From the petroleum ether extract of the crude reaction product there was recovered 0.5 g of a gum. Ether extraction of the gum yielded 0.2 g of a yellow powder, mp 187–190° dec. The yellow powder had ir and mass spectra similar to those **14b** and was converted to **14b** when refluxed in ether but was recovered unchanged from hot ethanol.

Solvolysis of 4a with 95% Ethanol. A mixture of 0.53 g (0.002 mol) of **4a** and 20 ml of 95% ethanol was heated with stirring at the reflux temperature for 17 hr. A small amount (0.003 g) of insoluble material was removed by filtration and the filtrate concentrated at reduced pressure. The ir spectrum of the residue (0.5 g) indicated the presence of malononitrile and ethyl ester **9a**. The crude product was dissolved in ether and washed with water and the ether layer was concentrated. The residue was extracted with methanol and the methanol solution concentrated to yield 0.4 g (85%) of nearly pure **9a** as indicated by the ir spectrum. After two recrystallizations from ethanol there was obtained 0.24 g (51%) of pure ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate (**9a**), mp 70.0–70.5°. The ir spectrum was identical with that of authentic material[11] and a mixture melting point (70.2–70.8°) was undepressed.

Solvolysis of 4a with Dry Ethanol. A mixture of 0.53 g (0.002 mol) of **4a** and 10 ml of dry ethanol was stirred under a Drierite column at the reflux temperature for 72 hr. After cooling to room temperature, the precipitated yellow solid was collected and washed with ether. The ir spectrum indicated that the product (0.31 g, 77.5%) was pure **5a**.

Solvolysis of 4b with 95% Ethanol. A mixture of 1.0 g (0.003 mol) of **4b** and 30 ml of 95% ethanol was stirred at the reflux temperature for 2 hr. After remaining overnight at room temperature, the solution was concentrated at reduced pressure to yield 1 g of light yellow solid. A GC–mass spectrum of the crude product indicated a mixture containing malononitrile (16%), 3-(3-trifluoromethylphenyl)-1,2,4-thiadiazole (**8b**, 5.5%) [*m/e* (rel intensity, fragment) 230 (73, M^+), 203 (100, $CF_3C_6H_4CNS^+$), 171 (16, $CF_3C_6H_4CN^+$), 145 (17, $CF_3C_6H_4^+$)], ethyl 3-(3-trifluoromethylphenyl)-1,2,4-thiadiazole-5-carboxylate (**9b**, 78%) [*m/e* (rel intensity, fragment) 302 (52, M^+), 283 (4, $M^+ - F$), 274 (2, $M^+ - C_2H_4$), 257 (4, $M^+ - OC_2H_5$), 203 (100, $CF_3C_6H_4CNS^+$)], and 3-(3-trifluoromethylphenyl)-5-cyanomethyl-1,2,4-thiadiazole (**7b** ~1%) [*m/e* (rel intensity, fragment) 269 (100, M^+), 250 (9, $M^+ - F$), 203 (100, $CF_3C_6H_4CNS^+$)].

A solution of the crude product (0.3 g) in benzene was chromatographed on Florisil. The benzene eluate was concentrated and the residue (0.16 g) recrystallized from heptane. The ester **9b**, mp 78–80°, was obtained as white plates and had an ir spectrum identical with that of authentic material[11] (mmp 79–80°).

Solvolysis of 5b with 95% Ethanol. A mixture of 0.1 g (0.0002 mol) of **5b** and 30 ml of 95% ethanol was heated at the reflux temperature with stirring for 6.5 hr. After the mixture cooled to room temperature, precipitated solid (0.01 g) was removed and the solution concentrated at reduced pressure. GC analysis of the viscous residue (0.12 g) indicated the presence of **8b** (3%), **9b** (46.5%), **7b** (46.5%), and starting material **5b** (2%).

Solvolysis of Mixture 5b + 6b with 95% Ethanol. A mixture of 0.2 g of **5b** + **6b** (isolated in the reaction of **3b** with TCNE) and 30 ml of 95% ethanol was stirred at the reflux temperature for 4 hr. After cooling to room temperature, the solution was concentrated at reduced pressure to yield 0.2 g of viscous yellow oil. GC analysis indicated a mixture containing **8b** (2%), **9b** (24%), **7b** (17%), the ketone **11** (54.5%), and starting material **5b** (2.5%). The crude product was extracted with hot hexane. Cooling the hexane extract resulted in a light yellow solid. After a second recrystallization from hexane, bis[3-(3-trifluoromethylphenyl)-1,2,4-thiadiazol-5-yl] ketone(**11**) mp 148.5–149.5°, was obtained as light yellow crystals: ir (Nujol) 5.98 (s), 7.55 (s), 8.4 (s), 8.55 (s), 8.9 (s), 9.3 (s), 10.45 (s), 13.55 (s), 14.45 μ (s); mass spectrum *m/e* (rel intensity, fragment) 486 (40, M^+), 467 (4, $M^+ - F$), 257 (2, $M^+ - CF_3C_6H_4C_2N_2S$), 203 (100, $CF_3C_6H_4CNS^+$), 171 (14, $CF_3C_6H_4CN^+$), 145 (11, $CF_3C_6H_4^+$).

Anal. Calcd for $C_{19}H_8N_4F_6OS_2$: C, 46.91; H, 1.66; N, 11.52. Found: C, 47.06; H, 1.60; N, 11.46.

Solvolysis of 5c with 95% Ethanol. A mixture of 0.15 g (0.005 mol) of **5c** and 10 ml of 95% ethanol was stirred at the reflux temperature for 2.5 days and was cooled to room temperature. A small amount of insoluble material was removed by filtration and the filtrate concentrated at reduced pressure. The residue was extracted with ether and the ether solution concentrated to yield 0.1 g of oil. GC–mass spectroscopy indicated two components in a 1:1 ratio with parent ions of *m/e* 172 and 139 consistent for ethyl 3-methyl-1,2,4-thiadiazole-5-carboxylate (**9c**) and 3-methyl-5-cyanomethyl-1,2,4-thiadiazole (**7c**).

Solvolysis of 5a + 6a with 95% Ethanol. A mixture of 0.3 g of **5a** + **6a**, prepared from **3a** and **4a** (fraction 2), and 30 ml of 95% ethanol was stirred at the reflux temperature for 24 hr. The mixture was filtered hot and the residue (0.18 g) washed with ethanol and ether. The ir spectrum of the yellow powder was similar to that of the starting mixture except for the absence of a band at 6.5 μ. The ethanol filtrate was concentrated at reduced pressure and the residue (0.15 g) extracted with ether. GC analysis of the ether extract indicated the presence of benzonitrile (7%), 3-phenyl-1,2,4-thiadiazole (**8a**, 9%), ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate (**9a**, 45%), 3-phenyl-5-cyanomethyl-1,2,4-thiadiazole (**7a**, 27%) and bis(3-phenyl-1,2,4-thiadiazol-5-yl) ketone (**11a**, 12%): mass spectrum *m/e* (rel intensity, fragment) **8a**, 162 (19, M^+) 135 (29, $C_6H_5CNS^+$), 103 (9, $C_6H_5CN^+$), 77 (11, $C_6H_5^+$); **9a**, 234 (46, M^+), 189 (4, $M^+ - OC_2H_5$), 161 (3, $M^+ - COOC_2H_5$), 135 (100, $C_6H_5CNS^+$), 103 (32, $C_6H_5CN^+$), 77 (16, $C_6H_5^+$); **7a**, 201 (69, M^+), 135 (100, $C_6H_5CNS^+$), 103 (18, $C_6H_5CN^+$), 77 (19, $C_6H_5^+$); **11a**, 350 (41, M^+), 189 (2, $M^+ - C_6H_5C_2N_2S$), 161 (2, $C_6H_5C_2N_2S^+$), 135 (100, $C_6H_5CNS^+$), 103 (31, $C_6H_5CN^+$), 91 (5, $C_6H_5N^+$), 77 (18, $C_6H_5^+$).

Solvolysis of 13a with Dry Ethanol. A mixture of 0.5 g (0.002

mol) of **13a** and 20 ml of dry ethanol was heated at the reflux temperature with stirring under anhydrous conditions for 20 hr and was cooled to room temperature. The resultant precipitate was collected by filtration, washed with ethanol and ether, and air dried. The yield of yellow powder was 0.31 g (85%). The ir spectrum of the product was identical with that of 1,2-bis(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2-ethenedicarbonitrile (**14a**) prepared previously. The ethanol filtrate was concentrated at reduced pressure to yield 0.2 g of brown oil. GC–mass spectroscopy indicated that the major constituents of the oil were malononitrile, **15a**, and **16a**.

Solvolysis of 13a with 95% Ethanol. A mixture of 0.45 g (0.002 mol) of **13a** and 20 ml of 95% ethanol was stirred at the reflux temperature for 20 hr. After being cooled to room temperature, the solution was concentrated at reduced pressure to yield 0.4 g of viscous oil. GC–mass spectral analysis indicated the presence of malononitrile, benzonitrile, ethyl carbamate, 3-phenyl-1,2,4-oxadiazole (**17a**), ethyl ester **15a**, and nitrile **16a**. A benzene solution of crude product (0.3 g) was chromatographed on Florisil. From the benzene eluate there was recovered 0.26 g of colorless oil. After being stored overnight under petroleum ether, the oil deposited white crystals of 3-phenyl-5-cyanomethyl-1,2,4-oxadiazole[20] (**16a**): mp 74.5–76.0°; ir (Nujol) 4.4 (w), 6.25 (s), 6.35 (m), 7.5 (s), 8.3 (s), 11.15 (s), 13.9 (s), 14.4 μ (m); NMR (CD_3CN) δ 4.4 (s, 2, $-CH_2CN$), 7.8–8.2 (m, 5, ArH); mass spectrum *m/e* (rel intensity, fragment) 185 (93, M^+), 145 (2, $M^+ - CH_2CN$), 119 (100, $C_6H_5CNO^+$), 103 (8, $C_6H_5CN^+$). A single sharp peak was observed on GC. The petroleum ether soluble product slowly crystallized at room temperature. The material was recrystallized from dilute ethanol to yield ethyl 3-phenyl-1,2,4-oxadiazole-5-carboxylate (**15a**), mp 54.5–55.0°, as white plates. The product gave a single sharp peak on GC. The ir spectrum was identical with that of authentic material[14] and the mixture melting point was undepressed.

Solvolysis of 15a with 95% Ethanol. A mixture of 0.22 g (0.001 mol) of **15a** and 10 ml of 95% ethanol was heated at the reflux temperature with stirring for 26 hr. GC analysis indicated that a reaction had not occurred. A catalytic quantity of potassium cyanide was added and heating resumed for 5 hr. GC analysis then indicated the emergence of small peaks due to benzonitrile and 3-phenyl-1,2,4-oxadiazole (**17a**) [ethyl carbamate was decomposed in the injector block (300°) during these analyses]. After the reaction mixture was held at the reflux temperature for 19 hr, the GC peak due to **15a** was greatly reduced and the peaks due to benzonitrile and **17a** proportionally increased. Finally, after the reaction mixture was heated at reflux for another 29 hr, the only component detected by GC was benzonitrile. After being cooled to room temperature, the ethanol solution was dried over magnesium sulfate and then concentrated at reduced pressure. The ir spectrum of the semisolid residue (0.15 g) indicated that benzonitrile and ethyl carbamate were the major components.

Solvolysis of 13b with Dry Ethanol. A mixture of 1 g (0.0034 mol) of **13b** and 10 ml of dry ethanol was stirred at the reflux temperature for 8 hr and was cooled to room temperature. The precipitate of red, crystalline **14b** (0.5 g, 65%) was collected, washed with ethanol and ether, and air dried. The ir spectrum of the product was identical with that of **14b** prepared previously from **12b** and TCNE.

Solvolysis of 13b with 95% Ethanol. A mixture of 0.5 g (0.002 mol) of **13b** and 20 ml of 95% ethanol was stirred at the reflux temperature for 1.5 hr. After being cooled to room temperature, the yellow solution was concentrated on a warm water bath at 20 mm. The residual yellow oil (0.55 g) was analyzed by GC–mass spectroscopy. Besides malononitrile and ethyl carbamate, the following products were detected [product, mass spectrum, *m/e* (rel intensity, fragment)]: mesityl isocyanate (2%), 161 (100, M^+), 146 (49, $M^+ - CH_3$), 133 (18, $M^+ - CO$), 132 (15, $M^+ - HCO$), 119 (8, $M^+ - NCO$); mesityl cyanide (20%), 145 (92, M^+), 130 (100, $M^+ - CH_3$), 115 (10, $M^+ - 2CH_3$); 3-mesityl-1,2,4-oxadiazole (**17b**, 1%), 188 (2, M^+), 161 (14, $M^+ - HCN$), 145 (85, $M^+ - HCNO$), 130 [100, $C_6H_2(CH_3)_3^+-CH_3$]; ethyl 3-mesityl-1,2,4-oxadiazole-5-carboxylate (**15b**, 35%), 260 (28, M^+), 187 (100, $M^+ - COOC_2H_5$), 161 (9, $M^+ - CNCOOC_2H_5$), 159 (47, $M^+ - COCOOC_2H_5$), 145 (28, $M^+ - CNOCOOC_2H_5$), 130 [18, $C_6H_2(CH_3)_3^+-CH_3$]; 3-mesityl-5-cyanomethyl-1,2,4-oxadiazole (**16b**, 42%), 227 (23, M^+), 187 (26, $M^+ - CH_2CN$), 161 [47, $M^+ - CH_2(CN)_2$], 159 (70, $M^+ - COCH_2CN$), 145 (100, $M^+ - CNOCH_2CN$), 130 [85, $C_6H_2(CH_3)_3^+-CH_3$].

Ethyl 3-Phenyl-1,2,4-oxadiazole-5-carboxylate (15a). The method of Huisgen et al.[14] was employed with slight modifications.

A solution of 1.5 ml (10.5 mmol) of triethylamine in 20 ml of ether was added with stirring to a mixture of 1.25 g (8 mmol) of phenyl hydroxamyl chloride[17] and 4 ml (20 mmol) of ethyl cyanoformate in a water bath. After 1 hr the precipitated triethylamine hydrochloride was removed by filtration and the ether solution was concentrated at reduced pressure. The residual yellow oil (1.7 g) was extracted with petroleum ether. From the extract there was recovered 1.5 g of oil which crystallized when seeded with **15a**. The crude product was recrystallized twice from ethanol to yield 0.9 g (52%) of white needles, mp 54–55.5° (lit. mp 53–54°).

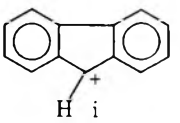
Ethyl 3-Mesityl-1,2,4-oxadiazole-5-carboxylate (15b). To a solution of 1.0 g (0.010 mol) of ethyl cyanoformate in 10 ml of dry ether was added 0.3 g (0.002 mol) of mesitonitrile oxide. The colorless solution was stirred at room temperature for 23 hr and then was concentrated at reduced pressure (0.5 mm) on a warm water bath. The residual oil (0.52 g, 100%) was essentially pure **15b** as indicated by the ir spectrum and a single peak eluting from the gas chromatogram.

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.59; H, 6.21; N, 10.76. Found: C, 64.71; H, 6.20; N, 10.74.

3-Mesityl-5-cyanomethyl-1,2,4-oxadiazole (16b). A solution of 1.3 g (0.02 mol) of malononitrile and 0.32 g (0.002 mol) of mesitonitrile oxide in 25 ml of dry ether was stirred at room temperature for 48 hr. The solution was then washed several times with water and finally dried over magnesium sulfate. After the ether was removed at reduced pressure, there was recovered 0.42 g (92%) of viscous oil. The product crystallized after a short time (mp 61–64°) and GC analysis indicated a single material: ir (Nujol) 4.42 (w), 6.2 (m), 6.3 (s), 7.6 (s), 9.2 (s), 11.35 (s), 11.8 μ (s); NMR (CD_3CN) δ 2.11 [s, 6, $Ar(CH_3)_2$-2,6] 2.27 (s, 3, $ArCH_3$-4), δ 4.27 (s, 2, $-CH_2CN$), 6.95 (s, 2, ArH).

Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.69; H, 5.78; N, 18.49. Found: C, 68.76; H, 5.76; N, 18.32.

1,1-Diphenyl-2,2,3,3-tetracyanocyclopropane (18). To a stirred solution of 1.3 g (0.01 mol) of TCNE in 20 ml of benzene and 5 ml of acetonitrile cooled in an ice bath was added dropwise a solution of 2 g (0.01 mol) of diphenyldiazomethane in 50 ml of ether. The purple color of the diazo compound disappeared immediately during addition and nitrogen was continuously liberated. Eventually a white precipitate began to form. After being stirred overnight at room temperature, the mixture was filtered and the residue (2.9 g, 100%), mp 274–276° dec, washed with ether: ir (Nujol) 4.45 (w), 6.3 (w), 6.75 (m), 13.05 (s), 13.37 (s), 14.1 (s), 14.4 μ (s); NMR (CD_3CN) δ 7.4 (m, 3, ArH), 7.8 (m, 2, ArH); mass spectrum *m/e* (rel intensity, fragment) 294 (69, M^+), 268 (36, $M^+ - CN$), 267 (65, $M^+ - HCN$), 241 (16, $M^+ - HCN - CN$), 230 [8, $M^+ - C(CN)_2$], 166 [29, $(C_6H_5)_2C^+$], 165 (100, i), 77 (18, $C_6H_5^+$). An



H i

analytical sample, mp 276–278° dec, was prepared by recrystallization from ethanol.

Anal. Calcd for $C_{19}H_{10}N_4$: C, 77.53; H, 3.43; N, 19.04. Found: C, 77.80; H, 3.62; N, 19.07.

Registry No.—**3a**, 5852-49-3; **3b**, 57459-15-1; **3c**, 17452-74-3; **4a**, 57459-16-2; **4b**, 57459-17-3; **4c**, 57459-18-4; *cis*-**5a**, 57459-19-5; *trans*-**5a**, 57459-20-8; *cis*-**5b**, 57459-21-9; *trans*-**5b**, 57459-22-0; **5c**, 57459-23-1; **6a**, 57459-24-2; **6b**, 57459-25-3; **7a**, 57459-26-4; **7b**, 57459-27-5; **8a**, 50483-82-4; **8b**, 57459-28-6; **9a**, 50483-79-9; **9b**, 50483-80-2; **11a**, 57459-29-7; **11b**, 57459-30-0; **12a**, 873-67-6; **12b**, 2904-57-6; **13a**, 57459-31-1; **13b**, 57459-32-2; **14a**, 57459-33-3; **14b**, 57459-34-4; **14b** TCNE π complex, 57474-16-5; **15a**, 37760-54-6; **15b**, 57459-35-5; **16a**, 57459-36-6; **16b**, 57459-37-7; **17b**, 57459-38-8; **18**, 57459-39-9; TCNE, 670-54-2; ethanol, 64-17-5; mesityl isocyanate, 2958-62-5; mesityl cyanide, 2571-52-0; ethyl cyanoformate, 623-49-4; malononitrile, 109-77-3; diphenyldiazemethane, 883-40-9.

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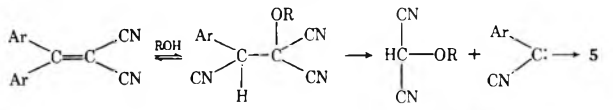

If one assumes that solvolysis of the carbene by ethanol is not a rapid reaction, this suggestion certainly appears feasible. Information to be presented in a future publication, however, will show that the formation of **5** is inhibited when a base is present in the reaction mixture.

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Electrochemical Reduction of Ethylene Trithiocarbonate. Reactions of Trithiocarbonyl Radical Anions

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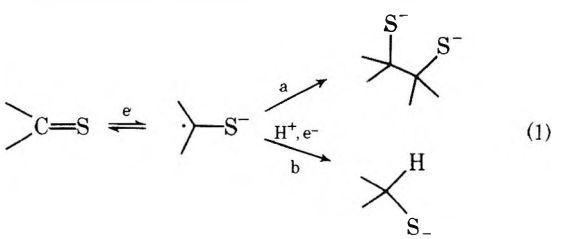
The electrochemical reduction of ethylene trithiocarbonate (**1**) has been studied in *N,N*-dimethylformamide–tetra-*n*-butylammonium bromide solutions at a platinum electrode. Reduction proceeds through the radical anion of **1** which reacts via anionic elimination of a molecule of ethylene. At potentials on the foot of the voltammetric wave the major electrolysis product is a bis(trithiocarbonate) dianion which was isolated as the methyl or ethyl ester after aklylation with the alkyl iodide. Alkylation with either 1,2-dibromoethane or 1,2-diiodoethane produced 1,4,6,9-tetrathiospiro[4.4]nonane as the major product. Reduction with sodium metal gives larger amounts of products derived from trithiocarbonate dianions. A mechanism is proposed for the reduction which accounts for the observed potential dependence of the electrolysis products.

Previous work in this laboratory has shown that several cyclic trithiocarbonates are electrochemically reduced under voltammetric conditions via an ECE pathway.[1] For ethylene trithiocarbonate cyclic voltammograms at fast sweep rates (ca. 75 V sec^{-1}) demonstrated the presence of a reversible one-electron couple in acetonitrile solutions at −1.76 V vs. a saturated calomel electrode (SCE). As the rate of the potential scan was decreased, the one-electron wave was transformed into an irreversible two-electron wave with a peak width of ca. 50 mV. This type of behavior has become familiar in recent years and is characteristic of an electrode process for which Nernstian electron transfer reactions are maintained and the irreversibility is caused by a chemical step involving the radical anion intermediate (an ECE pathway).[2]

By analogy to the well-studied electroreduction of carbonyl compounds, two possible pathways are suggested for the radical anion of thiocarbonyl groups: thiopinacol and mercaptan formation. In aqueous 2-propanol buffers two-



(1)

electron reductions of the thiocarbonyl group have been observed for a variety of thiones.[3] In nonaqueous solvents, however, the low proton availability would favor pathway a in eq 1 over b. In fact addition of proton donors such as phenol or water to DMF solutions did not appreciably decrease the lifetime of the radical anion in the voltammetric experiments,[1] a result which suggests pathway a. Further support for this pathway comes from work of Astruc et al.,[4] in which a dimeric product was obtained from the electroreduction of a 1,2-dithiole-3-thione.

The dimercaptide dianion which would result from the 2,2′ coupling of two ethylene trithiocarbonate radical anions represents a potentially useful synthetic intermediate as a ligand or a nucleophile for the preparation of new transition metal complexes or multisulfur heterocycles. Electrogenerated mecaptides have been used successfully for the preparation of compounds in the tetrathiofulvalene series[5] and it was our hope to carry out similar reactions using ethylene trithiocarbonate (**1**) instead of carbon disulfide. However, the radical anion of **1** was found to react by an unexpected pathway which is described below.

Results

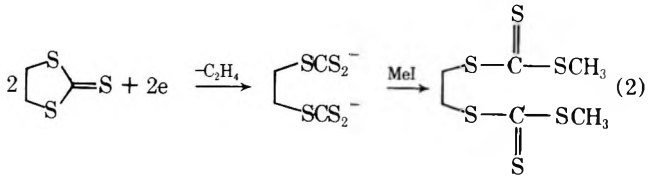
Alkylation with Alkyl Iodides. Electrolyses in DMF–TBABr solutions of ca. 1-g quantities of **1** at potentials between −1.4 and −1.6 V vs. SCE consumed an average of 0.98 F/mol of electricity. Usually the electrolysis was complete within 1 hr, at which point the solution had acquired a light brown color. Addition of an excess of alkylating agent, e.g., CH_3I, caused the color to change from brown to yellow. Product isolation gave yellow needles, mp 59.0–59.8°, in greater than 50% current yield (based on 1 F/mol) after two recrystallizations from acetonitrile. No attempt was made to maximize the yield of the major product. In

addition a yellow oil was isolated as a minor product after column chromatography on silica gel of the residue left after recrystallization.

The oil was shown to be dimethyl trithiocarbonate (2) by comparison of its ir and NMR spectra to that of an authentic sample and published spectra.[6,7] NMR spectra of the crude reaction product indicated that 2 was present at a concentration up to 40% of the major product in some electrolyses.

The analytical data on the solid product gave $C_6H_{10}S_6$ as the empirical formula, which implies the loss of an ethylene molecule for every two molecules of 1 in the reduction process. The loss of ethylene was verified by passing the effluent gas stream from a closed electrolysis cell through a solution of bromine in CH_2Cl_2. A substantial quantity of 1,2-dibromoethane was subsequently isolated from the CH_2Cl_2 solution and identified by its ir and NMR spectra.

The major product of the electrolysis was determined to be 1,2-ethanebis(methyl trithiocarbonate) (3), based on the



(2)

3

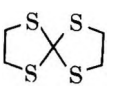
following spectral evidence. The NMR spectrum of 3 in deuteriochloroform contained two singlets at 3.67 and 2.78 ppm from Me_4Si with relative areas of 2.0–3.0. For comparison, the NMR spectrum of 2 exhibits a singlet at 2.73 ppm in CCl_4[6] and the value of 3.67 ppm for the methylene protons is consistent with NMR spectra of a variety of multisulfur heterocycles which contain $-SCH_2CH_2S-$ linkages.[8,9] Addition of a shift reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)europium(III), failed to resolve the singlets in deuteriobenzene. A ^{13}C NMR spectrum contained signals which could be assigned to the methyl and methylene carbon atoms in approximately a 1:1 ratio at 34.84 and 20.29 ppm from Me_4Si.

The presence of a trithiocarbonate group was clearly indicated by the strong absorption at 1050 cm^{-1} in the ir spectrum.[10] This functionality is also indicated by the uv spectrum of 3, which exhibits bands at 309 and 431 nm with molar absorptivities of 30 000 and 85 M^{-1} cm^{-1}, respectively. Furthermore, in accord with the bifunctionality of 3, these absorptivities are close to twice the values reported by Muller and Krebs for simple trithiocarbonates.[11] Cyclic voltammograms of 3 contained two irreversible reduction waves at −1.58 and −1.76 V vs. SCE (peak potentials). These waves had current functions and peak widths characteristic of successive reduction of the two trithiocarbonate groups in 3.

The mass spectrum of the electrolysis product showed the parent peak at *m/e* 274 and a fragmentation pattern consistent with the assigned structure (see Experimental Section).

Alkylation with ethyl iodide gave the 1,2-ethanebis(ethyl trithiocarbonate) as yellow, crystalline flakes, mp 34.5–35.5°. Details are given in the Experimental Section.

Alkylation with 1,2-Dibromo- or 1,2-Diiodoethane. The exhaustive reduction of ethylene trithiocarbonate followed by alkylation with either 1,2-dibromoethane or 1,2-diiodoethane produced three isolated compounds: a yellow, insoluble material (0.16 g per 0.75 g of 1 reduced), 1,4,6,9-tetrathiaspiro[4.4]nonane (4), and starting material. A yield of 4 based on isolated product was not determined,



4

but NMR spectra showed that 4 was present in twice the concentration of 1 in the crude product.

The yellow material precipitated from solution soon after the addition of the alkylating agent. It was found to be slightly soluble in hot DMF, but otherwise insoluble in 14 solvents that encompassed a wide range of polarity. Upon heating, the color gradually turned brown beginning at 90° and at 140° the material was tarlike.

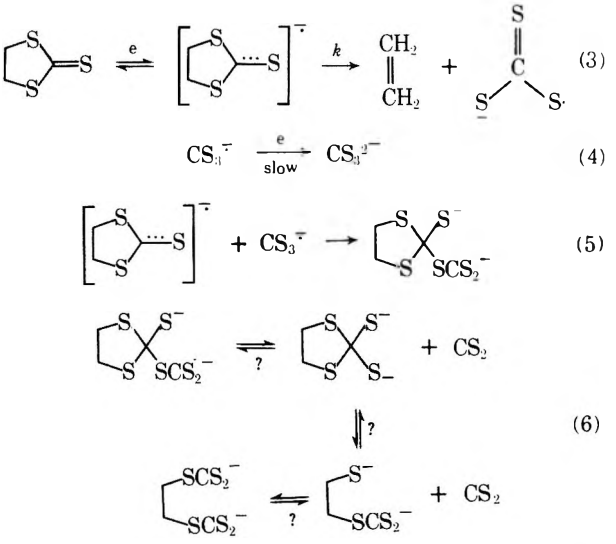
The ir spectrum, the uv spectrum, and cyclic voltammograms of the yellow material indicated the presence of trithiocarbonate groups. The indicators of this functionality were the strong ir band at 1055 cm^{-1}, the absorption bands at 312 and 430 nm in the electronic spectrum, and the peak voltammogram at −1.71 V vs. SCE.

The material may be a polymer with an ethylene trithiocarbonate repeating unit: $-CH_2CH_2SCS_2-_n$. The color, decomposition point, and ir spectrum are similar to those of pentamethylene and hexamethylene polytrithiocarbonates reported by Braun and Kiessel.[12]

The spiro compound, 4, was recrystallized from acetonitrile as a white, fluffy powder, mp 139–140°. The compound was identified by comparison of the mass, ir, and NMR spectra with the data reported by D'Amico and Campbell.[13]

Discussion

The above results can be accommodated by a relatively simple mechanism which is consistent with the voltammetric behavior of 1, eq 3–6. The key step in this mechanism



(3)

(4)

(5)

(6)

is the anionic elimination of ethylene from the radical anion of 1, eq 3. This reaction, which is suggested to be the chemical step which produces the ECE voltammetric behavior, has precedent in analogous oxygen compounds.[14] At potentials on the rising portion of the voltammetric wave, where the electrolyses were carried out, addition of an electron to $CS_3\cdot^-$ is slow and this species is viewed to couple with the radical anion of 1, eq 5. The mechanism is completed by a sequence of equilibria (eq 6) involving CS_2 additions which lead to the resonance stabilized bis(trithiocarbonate) dianion. The question marks under the equilibrium signs in eq 6 are meant to indicate that the reversibility of these steps has not been directly established in this study.

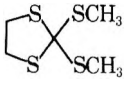
Reaction of the trithiocarbonate radical anion, $CS_3\cdot^-$, with 1 followed by an electron transfer is a possible alternative to the reaction in eq 5. Experimental evidence for or against the radical coupling reaction is lacking, since this step follows the irreversible fragmentation in the proposed mechanism. We favor the radical coupling reaction owing to the known propensity of electrogenerated radical anions to couple in DMF solutions.[15,16]

The effect of potential on the reduction process is readily rationalized by this scheme. Under voltammetric conditions the addition of a second electron to $CS_3\cdot^-$ is rapid in the region of the peak potential and a two-electron wave results. Sodium metal reduction of 1 in DMF followed by addition of CH_3I gave twice as much 2 as 3 based on NMR analysis of the crude mixture. Thus sodium, which is a powerful enough reducing agent to carry out eq 4, favors the voltammetric pathway to a greater extent than electrolysis on the foot of the wave.

In several control experiments potassium or sodium trithiocarbonate solutions in DMF were treated with excess 1 and allowed to stand overnight. Only methyl trithiocarbonate was recovered from the mixtures after addition of CH_3I. Thus reaction of 1 with CS_3^{2-} under electrolysis conditions is unlikely.

Several experiments were also carried out in which CS_2 was added to the solution after completion of the electrolysis and before addition of CH_3I. If CS_2 is involved in the equilibria of eq 6, then an increased yield of 3 could result by this procedure. Upon addition of CS_2 a transient red color developed in solution and an oxidation wave in the region of 0.0 V vs. SCE became less prominent in cyclic voltammograms of the solution, but no increase in yield of 3 appeared to result. It is likely that the equilibria in eq 6 lie in favor of the bis(trithiocarbonate) dianion and that the yield of 3 is determined by losses during the work-up.

Finally, it should be mentioned that, although the scheme rationalizes the presence of all the alkylated products, it also suggests the presence of several which were not found. In particular, compound 5 would be expected since



5

the dianion precursor was trapped by addition of the dihalogenoethane. Apparently this compound is either thermally unstable or, more likely, was lost in the work-up in the presence of excess 2 and 3.

Experimental Section

Chemicals. *N,N*-Dimethylformamide was purified by the procedure of Faulkner and Bard.[17] Tetra-*n*-butylammonium bromide (TBABr) was obtained from Eastman Kodak Co. and used as received. It was the electrolyte for all electrolyses of 1. Practical grade ethylene trithiocarbonate (Aldrich Chemical Co.) was recrystallized twice from acetonitrile. Methyl and ethyl iodide (Eastman), 1,2-dibromoethane (Fisher), and 1,2-diiodoethane (Aldrich) were used without further purification. Potassium trithiocarbonate (Alpha Inorganics) was also used as received. Sodium trithiocarbonate was synthesized by dissolving 0.23 g of reagent grade anhydrous sodium sulfide in 10 ml of DMF and adding 0.25 g of carbon disulfide. This solution was then used in subsequent experiments.

Procedures. Bulk electrolyses were performed in a three-compartment cell which was cooled with tap water. The cell was filled with 1 *M* TBABr in DMF and the platinum working electrode compartment (ca. 40 ml) was stirred with nitrogen gas throughout the experiment. After ca. 10 min of deaeration, between 0.5 and 1.5 g of 1 was added to the working electrode compartment. The working electrode potential was maintained between −1.4 and −1.6 V and the current averaged ca. 175 mA throughout most of the electrolyses. Usually electrolyses were terminated when the current dropped to less than 5 mA.

Product isolation was as follows. An excess of alkylating agent was added directly to the working electrode compartment. The solution was collected and poured into 500 ml of water and then extracted with ether which then was dried with anhydrous magnesium sulfate and evaporated on a rotoevaporator. Recrystallization of the resulting oil from acetonitrile gave the main product and the residue was separated by column chromatography on silica gel using hexane–methylene chloride mixtures as the eluent.

Voltammetric parameters of the isolated alkylated products were obtained in acetonitrile, 0.1 *M* tetraethylammonium perchlorate solutions using procedures given elsewhere.[1]

Physical Characteristics of Isolated Compounds. 1,2-Ethanebis(methyl trithiocarbonate). Most of the spectral parameters for 3 are given above. The ir spectrum (KBr) showed bands at the following frequencies: 820, 860, 960, 1050, 1135, 1205, 1385, 1410 cm^{-1}. The electron-impact mass spectrum at 20 eV gave the following major *m/e* peaks and assigned fragments: 274 (parent mass), 183 ($CH_3SCS_2CH_2CH_2S^+$), 138 ($CH_3SCS_2CH_3^+$), 136 ($CH_3SCS_2CH^+$), 91 ($SCSCH_3^+$), 76 (SCS^+, base peak), 60 ($SCH_2CH_2^+$), 59 ($SCHCH_2^+$), 47 (SCH_3^+), and 45 (SCH^+). All of these fragments are readily derived from the structure of 3 except for the peak at *m/e* 138, which may result from an impurity of 2 in the sample.

Anal. Calcd for $C_6H_{10}S_6$: C, 26.25; H, 3.67; S, 70.07. Found: C, 26.30; H, 3.66; S. 69.99.

1,2-Ethanebis(ethyl trithiocarbonate). The NMR spectrum of this compound in deuteriochloroform contains a singlet at 3.75 ppm, a quartet centered at 3.38 ppm, and a triplet centered at 1.38 ppm. Integration of the peak areas yielded a ratio of 2:2:3, respectively. The ir spectrum gave absorption bands at the following frequencies: 815, 1025, 1065, 1135, 1205, 1260, 1390, 1405, 1450 cm^{-1}. The uv spectrum in chloroform yielded wavelength maxima at 310 and 434 nm with corresponding molar absorptivities of 40 000 and 105 M^{-1} cm^{-1}. The mass spectrum at 10 eV gave the following major *m/e* peaks and assigned fragments: 302 (parent), 197 ($C_2H_5SCS_2CH_2CH_2S^+$, base peak), 168 ($SCS_2CH_2CH_2S^+$), 136 ($SCS_2CH_2CH_2^+$), 105 ($SCSCH_2CH_3^+$), 76 (SCS), and 61 ($SCH_2CH_3^+$). Cyclic voltammograms of the ethyl derivative showed two irreversible waves at −1.58 and −1.73 V vs. SCE.

1,4,6,9-Tetrathiaspiro[4.4]nonane:[13] NMR ($CDCl_3$) 3.40 ppm, singlet; ir (KBr) 1410, 1270, 965, 945, 845, 795, 755 cm^{-1}. The mass spectrum gave the parent mass at *m/e* 196. Cyclic voltammograms yielded two irreversible oxidation waves at 0.99 and 1.53 V vs. SCE.

Acknowledgment. We wish to thank the National Science Foundation for partial support of this research through Grant GP 31884.

Registry No.—1, 822-38-8; 3, 57443-63-7; 4, 13145-46-5; DMF, 68-12-2; TBABr, 1643-19-2; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; 1,2-dibromoethane, 106-93-4; 1,2-diiodoethane, 624-73-7; 1,2-ethanebis(ethyl trithiocarbonate), 57443-64-8.

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Chemistry of Diaminomaleonitrile. II. Preparation of the Open-Chain Adduct with Ketone in Phosphorus Pentoxide–Ethanol System[1]

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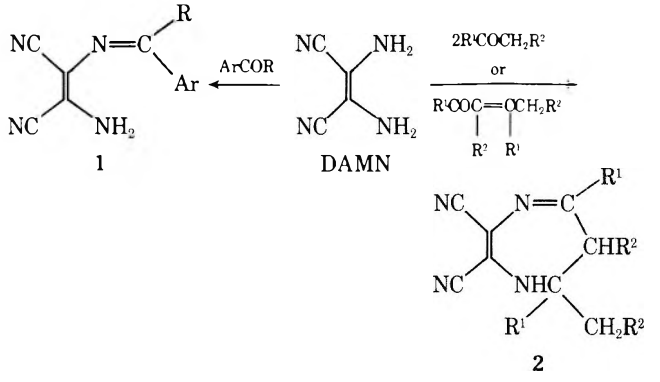
Condensations between diaminomaleonitrile (DAMN) and ketones in phosphorus pentoxide–ethanol gave the open-chain adducts. Aromatic α-ketones and acyl cyanides gave the Schiff bases (**1** and **5**), several of which were converted to alkyl DAMN (**3** and **7**), addition product with methyl vinyl ketone (**4**), and pyrazine derivatives (**6** and **8**). The condensation with β-keto esters and with β-diketones gave another type of adducts, enamines (**9** and **12**), which were converted to 2-substituted 4,5-dicyanoimidazoles (**10** and **11**) and the fragmentation products by α-C–C bond cleavage. Enamines **12** and phosphorus pentoxide in ethanol gave 1,4-diazepines **13**.

In recent years diaminomaleonitrile (DAMN) has received much interest as a source of nitrogen heterocycles.[1-4] The reactions most widely used in those syntheses are condensations with carbonyl compounds. The condensation of DAMN with aldehydes or amides gives Schiff bases, which can be cyclized to imidazoles.[2,5,6] Condensation of DAMN and ketones gives a greater variety of products. This reaction, however, is less clearly understood, since cyclic products are generally obtained in one step and the open-chain adducts have been isolated in few special instances.[2,7,8] Isolation of open-chain adducts and investigation of their chemical properties have now been carried out to extend the synthetic versatility of DAMN.

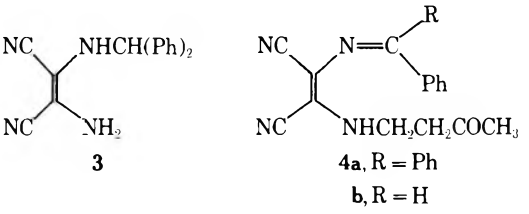
Schiff Bases of Diaminomaleonitrile and Ketones. From preliminary experiments, phosphorus pentoxide–ethanol was found to be an effective reagent for the condensation of DAMN and ketones under mild conditions. Using this system, condensations with a number of aromatic or heteroaromatic ketones were carried out and Schiff bases **1** were obtained. The results are summarized in Table I. The reaction with dialkyl ketones or α,β-unsaturated ketones under similar conditions gave dihydrodiazepines **2**.



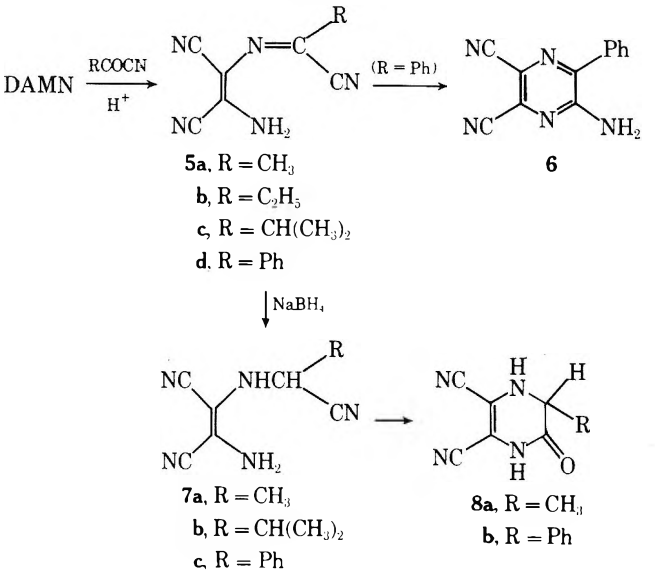
The condensation proceeded smoothly to give **1** as stable compounds. When a stronger acid ($POCl_3$) was used, it has been reported[2] that the condensation of ketones, including aromatic α-ketones, gave **2** exclusively, and that an isolated Schiff base (**1a**) hydrolyzed in moist air.

In the present reaction, the electron-deficient ketones condense readily with DAMN to give excellent yields of **1** (Table I). The reaction with *p*-methoxyacetophenone gave an 8% yield of **2** (R^1 = CH_3; R^2 = Ph-*p*-OCH_3) after 24 hr of refluxing in ethanol. The reaction failed with 2- and 4-acetylpyridine.

Reduction of the azomethine bond in **1d** (R = Ar = Ph) was carried out with sodium borohydride, giving **3** (Table II) under similar conditions to the reduction of the aldehyde Schiff bases.[2] Reaction of **1d** with methyl vinyl ketone afforded the N′-addition product **4a.** Similarly, treatment of benzylidene DAMN with methyl vinyl ketone gave **4b.**



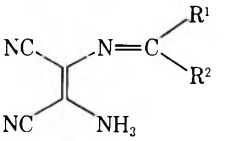
Condensation of acyl cyanides and DAMN gave the Schiff bases **5** (Table I). This reaction was catalyzed by acids, such as phosphorus pentoxide–alcohol, *p*-toluenesulfonic acid, or a trace of hydrogen bromide which was present in the crude acyl cyanide.



When **5d** (R = Ph) was refluxed in ethanol, aminopyrazine **6** was obtained; the other alkyl homologues, **5a–c**, were not cyclized by this treatment. Sodium borohydride reduction of **5a**, **5c**, and **5d** gave the corresponding aminonitriles **7a**, **7b**, and **7c** (Table II). Cyclization of **7a** or **7b** in refluxing ethanol gave tetrahydropyrazines **8a** and **8b**, respectively.

Enamine Derivative of Diaminomaleonitrile. Reaction of DAMN and ethyl acetoacetate with acid catalyst, phosphorus pentoxide–ethanol, or a drop of sulfuric acid gave an enamine **9a**. The structure was evidenced by the vinyl proton singlet at δ 4.43 (1 H), the NH_2 protons broad

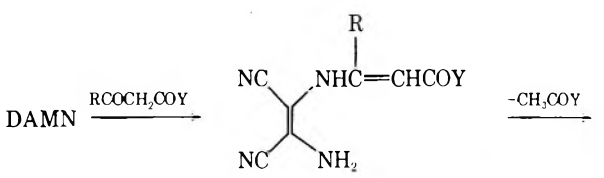
Table I[d]
Schiff Bases of Diaminomaleonitrile



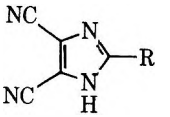
Compd[a] R¹	Compd[a] R²		Reaction conditions	Yield, %	Crystn solvent	Mp, °C	Appearance
CH_3	Ph	(1a)	1 hr, rt[b]	74	*i*-PrOH–acetone	122–123	
CH_3	*p*-NO_2Ph	(1b)	10 min, rt	98	EtOH–acetone	219–220	Orange needles
CH_3	*o*-OHPh	(1c)	46 hr, rt	34	*i*-PrOH	180–182	Yellow needles
Ph	Ph	(1d)	4 hr, rt	93	50% aq EtOH	167–168	Yellow needles
o-OHPh	*o*-OHPh	(1e)	24 hr, rt	60	*i*-PrOH	182–183 dec	Yellow crystals
CH_3	β-Naph	(1f)	30 min, rt	79	EtOH	187–188	Yellow needles
Ph	β-Naph	(1g)	37 hr, ref[c]	46	20% aq EtOH	179–181	Yellow powder
9-Fluorenylidene		(1h)	2.5 hr, ref[c]	68	Benzene	155–156	Red crystals
CH_3	2-Thienyl	(1i)	2 hr, rt	77	EtOH	177–178	Yellow plates
CH_3	2-Furyl	(1j)	1 hr, rt	73	EtOH	174–175	Yellow crystals
CH_3	3-Pyridyl	(1k)	1 hr, rt	82	EtOH	228–230	Yellow crystals
Ph	3-Pyridyl	(1l)	1 hr, ref[c]	71	EtOH	215–216 dec	Yellow crystals
CH_3	CN	(5a)	10 min, rt	41	aq MeOH	222–224	Colorless flakes
C_2H_5	CN	(5b)	10 min, rt	60	aq MeOH	198–199	Colorless needles
$CH(CH_3)_2$	CN	(5c)	10 min, rt	76	aq MeOH	150–152	Colorless flakes
Ph	CN	(5d)	15 min, rt	52	MeOH	184–185	Yellow powder

[a] The molecular structures are supported by spectroscopic data (ir, NMR, and MS) of each compound. [b] Excess of the ketone with several drops of ethanol was used as the medium (rt = room temperature). [c] Refluxed in ethanol. [d] Satisfactory analytical data (±0.2% for C, H, and N) for all compounds in this table and in Tables II and III were submitted for review. Ed.

singlet at δ 6.45 (2 H), and the NH proton singlet at δ 8.78 (1 H) in the NMR (in acetone-d_6 solution with Me_4Si) exhibited by the product.[9] Other enamines similarly prepared are given in Table III.

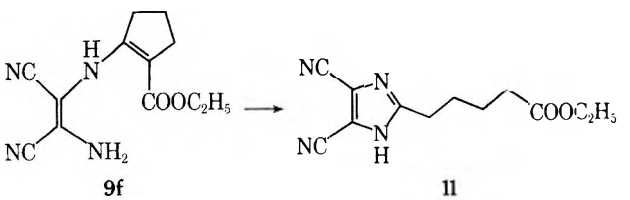


9a, R = CH_3; Y = OC_2H_5
b, R = CH_3; Y = morpholino
c, R = C_2H_5; Y = OC_2H_5
d, R = $CH(CH_3)_2$; Y = OC_2H_5
e, R = Ph; Y = OC_2H_5



10a, R = CH_3
b, R = C_2H_5
c, R = $CH(CH_3)_2$
d, R = Ph

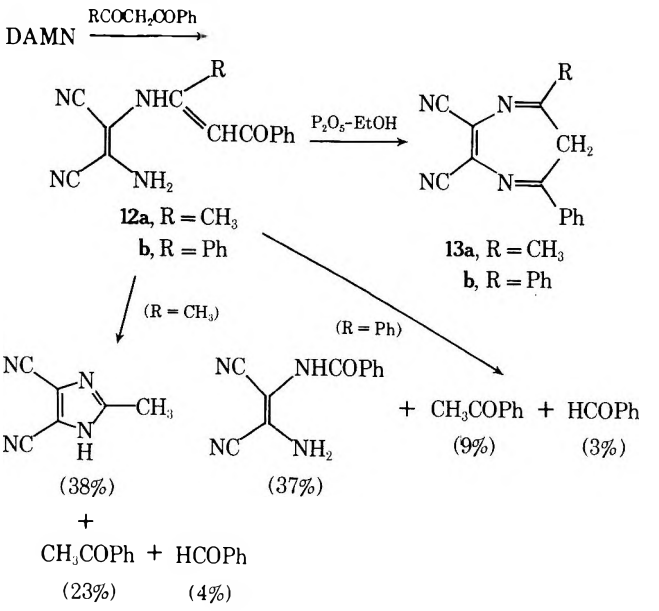
It was found that **9a–e** can be converted to the corresponding 4,5-dicyanoimidazoles (**10a–d**) by refluxing ethanol or butanol. Enamine **9f** gave the corresponding 2-valerate **11**. 4,5-Dicyanoimidazoles, **10** and **11**, are important intermediates for the synthesis of purine derivatives,[10] and



9f **11**

this reaction gives the pure products in good yield by a simple procedure. Similar reaction, a sort of reverse Claisen reaction, has been observed with several aromatic enamines.[11] A reaction of DAMN and ethyl acetoacetate with phosphorus oxychloride gives tetrahydro-6*H*-1,4-diazepine.[2]

Condensation of DAMN with benzoylacetone or dibenzoylmethane in phosphorus pentoxide–ethanol at room temperature gave enamines **12a** and **12b** (Table III), re-



12a, R = CH_3
b, R = Ph

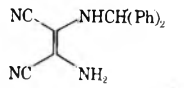
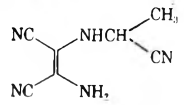
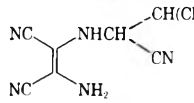
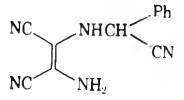
13a, R = CH_3
b, R = Ph

(38%) + CH_3COPh + HCOPh (23%) (4%)

(37%) + CH_3COPh + HCOPh (9%) (3%)

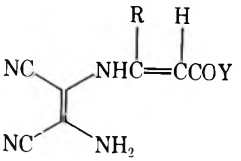
spectively. The structure of **12b**, for example, was evidenced by the vinyl proton singlet at δ 6.38 (1 H), the NH_2 protons broad singlet at δ 7.8 (2 H), and the NH proton singlet at δ 11.50 (1 H) in the NMR (in dimethyl sulfoxide-d_6 solution with Me_4Si). In chemical reactions, however, **12** showed rather ambiguous character. When **12a** or **12b** was heated with phosphorus pentoxide in ethanol 1,4-diazepine **13a** and **13b** were obtained, respectively. Upon heating **12a**

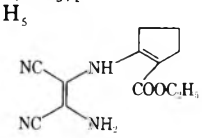
Table II
Alkyl Derivatives of Diaminomaleonitrile

Compd[a]	Starting compd	Yield, %	Mp, °C	Crystn solvent
 (3)	1d	93	217–219	EtOH
 (7a)	5a	54	224–226	aq MeOH
 (7b)	5c	68	229–231	aq MeOH
 (7c)	5d	59	203–204 dec	aq MeOH

[a] The molecular structures are supported by spectroscopic data (ir, NMR, and MS) of each compound.

Table III
Enamine Derivatives of Diaminomaleonitrile



Compd[a] R	Y	Reaction conditions	Yield, %	Crystn solvent	Mp, °C
CH_3	OC_2H_5 (9a)	1 hr, rt	97	*i*-PrOH	152–153
CH_3	 (9b)	5 min, rt	98	EtOH	167–168
C_2H_5	OC_2H_5 (9c)	4 hr, rt[b]	91	*i*-PrOH	133–134[c]
$CH(CH_3)_2$	OC_2H_5 (9d)	30 min, 40°C[b]	62	*i*-PrOH	134–136
C_6H_5	OC_2H_5 (9e)	1 hr, rt	94	*i*-PrOH	141–142
	(9f)	20 min, rt	79	EtOH	188–189
CH_3	C_6H_5 (12a)	1 hr, rt	87	*i*-PrOH	159–160
C_6H_5	C_6H_5 (12b)	1 hr, rt	86	EtOH	158–160

[a] The molecular structures are supported by spectroscopic data (ir, NMR, and MS) of each compound. [b] Neat reaction. [c] Crystal turns brown on standing in moist air.

in wet butanol,[12] 4,5-dicyano-2-methylimidazole (**10a**), acetophenone, and benzaldehyde were isolated. Similar treatment of **12b** gave benzoyl DAMN and hydrolyzed products. In the latter reactions, the process giving the different type of products is unclear, but both **12a** and **12b** undergo their C–C bond cleavage by the treatment.

Experimental Section

Infrared spectra were obtained with KBr disks on a Hitachi Model EPI-G3 spectrometer. NMR determinations were carried out either on a Hitachi Perkin-Elmer R-20B or on a Varian HA-100 spectrometer. The NH and NH_2 proton signals in the spectra were identified from the diminution of the intensity by addition of deuterium oxide. Mass spectra were determined at 70 eV on a Hitachi RMU-6E spectrometer using a solid sample inlet (at 100–150°C). Melting points were measured on a micro hot-stage apparatus and were corrected.

General Procedure of Condensation of Diaminomaleonitrile and Ketones with Phosphorus Pentoxide in Ethanol. Preparation of 1 (Table I), 9 and 12 (Table III). To a solution of DAMN (3.0 g) and the ketone (an equimolecular weight or an excess) in ethanol (80 ml) was added portionwise phosphorus pentoxide (1.3 g). After the reaction (listed in tables), the insoluble products were collected by filtration, washed with cold water, and dried. The soluble products were isolated after concentration of the reaction mixture by a rotary evaporator followed by treatment of the residue with ice–water (50–100 ml).

Preparation of Alkyl Diaminomaleonitrile (3 and 7a–c in Table II). Schiff bases (**1d, 5a, 5c,** and **5d**) were reduced by three equivalents of sodium borohydride in their solution in methanol–tetrahydrofuran mixtures.[2] After stirring at room temperature for 15 min, reaction mixtures were poured into ice–water, giving the corresponding products as fine crystals.

Reaction of Schiff Bases with Methyl Vinyl Ketone. *N*-Diphenylmethylene-*N'*-(3-oxobutyl)diaminomaleonitrile (4a). A mixture of **1d** (3.0 g), methyl vinyl ketone (70 ml), and phosphorus pentoxide (1.5 g) was stirred for 20 min at room temperature. The resulting semisolids were dissolved in ethyl ether (300 ml). The ether solution was washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The resulting oil was chromatographed by a column (silica gel–ether) to give yellow crystals, mp 151–153°C from 2-propanol, in 21% yield (0.8 g): NMR (Me_2SO-d_6) δ 2.11 (s, 3, CH_3), 2.72 (t, 2, CH_2), 3.58 (q, 2 CH_2), 7.2 and 7.5 (m, total 10, C_6H_5); ir 2215, 2180, 1718 cm^{-1}.

Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.66; H, 5.30; N, 16.36. Found: C, 73.39; H, 5.35; N, 16.14.

***N*-Benzylidene-*N'*-(3-oxobutyl)diaminomaleonitrile (4b)** was obtained similarly from benzylidene DAMN[13] (2.0 g), methyl

vinyl ketone (20 ml), and phosphorus pentoxide (0.5 g), as yellow needles: mp 156–157°C (from ethanol); yield 37% (1.0 g); NMR (Me_2SO-d_6) δ 2.15 (s, 3, CH_3), 2.88 (t, 2, CH_2), 3.60 (q, 2, CH_2), 7.44 and 7.94 (m, total 6. C_6H_5), 8.23 (s, 1, CH); ir 2230, 2220, 1740 cm^{-1}; MS *m/e* 266 (M^+, rel intensity 26), 223 (11), 209 (20), 208 (17).

Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.55; H, 5.30; N, 21.04. Found: C, 67.74; H, 5.32; N, 20.86.

Condensation of Diaminomaleonitrile with Acyl Cyanides[14] (Table I). α-Cyanoethylidenediaminomaleonitrile (5a). Method A. DAMN (10.8 g) and acetyl cyanide (10.0 g) were added successively to a solution of *p*-toluenesulfonic acid (1.9 g) in dry ether (100 ml). The resultant yellow solids were filtered and dried. The crude product was dissolved in acetone (600 ml) and undissolved solids were removed by filtration. Addition of water (900 ml) to the filtrate gave **5a**.

Method B. To a mixture of acetyl cyanide (22.1 g) and DAMN (16.3 g) was added dropwise a solution of phosphorus pentoxide (0.5 g) in ethanol (3 ml). The crude product was recrystallized from aqueous methanol to give **5a** in 26% yield (6.3 g). **5b** and **5c** were prepared by method B.

α-Cyanobenzylidenediaminomaleonitrile (5d). Benzoyl cyanide (10.8 g) and then DAMN (5.4 g) were added to a solution of phosphorus pentoxide (1.3 g) in methanol (50 ml). The resultant yellow crystals were filtered. Cooling the filtrate gave an additional crop.

2-Amino-5,6-dicyano-3-phenylpyrazine (6). 5d (1.5 g) was refluxed in ethanol (80 ml) for 19 hr and then concentrated. The residue was recrystallized from toluene to give colorless needles, mp 166–167°C, in almost quantitative yield: ir 3410, 3305, 3200, 2230, 1630, 1540, 1500 cm^{-1}; MS (150°C) *m/e* (rel intensity) 222 (9), 221 (M^+, 70), 220 (100).

Anal. Calcd for $C_{12}H_7N_5$: C, 65.15; H, 3.19; N, 31.66. Found: C, 65.17; H, 3.18; N, 31.72.

Cyclization of α-Cyanoalkyldiaminomaleonitrile (7a and 7d). 5,6-Dicyano-3-methyl-1,2,3,4-tetrahydropyrazin-2-one (8a). Phosphorus pentoxide (0.3 g) and **7a** (1.0 g) were refluxed in ethanol (30 ml) for 19 hr. Concentration of the mixture gave **8a** as a colorless powder: mp 241–243°C (from aqueous ethanol); yield 72%; ir 2210, 1700–1690, 1660, 1630 cm^{-1}; MS *m/e* 162 (M^+).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.37; N, 34.55. Found: C, 51.63; H, 3.78; N, 34.80.

5,6-Dicyano-3-phenyl-1,2,3,4-tetrahydropyrazin-2-one (8b) was obtained similarly from **7d** in 94% yield as a yellow-orange powder: mp 220–222°C (from aqueous methanol); NMR (Me_2SO-d_6) δ 5.08 (d, 1, CH), 7.35 (s, 5, C_6H_5), 8.31 (d, 1, NH), 10.94 (s, 1, NH).

Anal. Calcd for $C_{12}H_8N_4O$: C, 64.28; H, 3.59; N, 24.98. Found: C, 64.12; H, 3.60; N, 24.97.

Preparation of Imidazoles 10a–d and 11. General Method. The precipitate obtained from the reaction mixture of DAMN and ethyl acylacetates or *N*-acetoacetylmorpholine (see the preparation of 1) was washed with cold water and rapidly dried in vacuo. The solid thus obtained was almost pure compound **9** (Table III) and was refluxed in butanol (ca. 5 g/100 ml) for 24 hr. The reaction mixture was concentrated under reduced pressure.[15] *N*-Acetylmorpholine was removed at 60–80°C (2 mmHg). The resultant tan solid was washed with chloroform and recrystallized. **10a** (R = CH_3)[10e] was prepared in 83% yield from **9a** and in 92% yield from **9b**, the adduct of DAMN and *N*-acetoacetylmorpholine. **10b** (R = C_2H_5)[16] was prepared in 84% yield from **9c**, the adduct of DAMN and ethyl propionylacetate.[17] **4,5-Dicyano-2-isopropylimidazole [10c, R = $CH(CH_3)_2$]** was prepared in 33% yield from **9d**, the adduct of DAMN and ethyl γ-methyl-β-oxovalerate.[17] Recrystallization from water gave colorless flakes: mp 156–157°C; NMR (Me_2SO-d_6) δ 1.29 and 3.0 (total 7, isopropyl protons), 8.0 broad s, 1); MS (100°C) *m/e* (rel intensity) 160 (M^+, 20), 159 (12), 145 ([M − CH_3]$^+$, 100, M* 131.4).

Anal. Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 60.00; H, 4.87; N, 34.92.

10d (R = Ph)[13] was prepared in 77% yield from **9e**, the adduct of DAMN and ethyl benzoylacetate.

Ethyl 4,5-Dicyanoimidazole-2-valerate (11). 9f prepared from DAMN and 2-ethoxycarbonylcyclopentanone was refluxed in butanol. The evaporated residue was a syrup which was purified by a column (silica gel, benzene–ethyl acetate) to give a colorless oil in 46% yield. A 44% yield of **11** was estimated separately from its silver salt, which was obtained from a methanol solution of the crude syrup and aqueous silver nitrate. The silver salt is insoluble and can be purified by washing with hot ethanol. The ir spectum of the silver salt is similar to that of **11**. The silver salt was heated in an excess of trimethylsilyl chloride for 2 hr. Filtration and treatment of the evaporated filtrate with methanol gave **11** as a colorless liquid.

Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.75; H, 5.64; N, 22.88.

One-step preparations of imidazoles **10** from DAMN and acylacetates gave less satisfactory results. When a mixture of ethyl acetoacetate, DAMN, and phosphorus pentoxide was heated in ethanol without separation of **9a**, **10a** was obtained in a 38% yield. The yields by the treatment using other carbonyl compounds follow: 35% (**10a**) from *N*-acetoacetylmorpholine; 64% (**10b**) from ethyl propionylacetate; trace (**10c**) from ethyl γ-methyl-β-oxovalerate; 70% (**10d**) from ethyl benzoylacetate.

2,3-Dicyano-5-methyl-7-phenyl-1,4,6*H*-diazepine (13a). A mixture of **12a** (6.1 g), prepared from DAMN and benzoylacetone (Table III), and phosphorus pentoxide (1.3 g) in ethanol (100 ml) was refluxed for 16 hr and then evaporated. The residual brown syrup was treated with water and extracted with chloroform. The extract was dried with sodium sulfate and the solvent was removed. The residue was crystallized from a small quantity of 2-propanol to give light-tan crystals: yield 18% (1.2 g); mp 126–127°C (from 2-propanol); NMR (Me_2SO-d_6) δ 2.17 (s, 3), 7.5–7.7 and 8.1–8.3 (m, total 5); ir 3050, 2220, 1594, 1530 cm^{-1}; MS (100°C) *m/e* (rel intensity 234 (M^+, 100), 219 ([M − CH_3]$^+$, 76).

Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.54; H, 4.04; N, 23.84.

2,3-Dicyano-5,7-diphenyl-1,4,6*H*-diazepine (13b). A mixture of DAMN (24 g), dibenzoylmethane (50 g), and phosphorus pentoxide (10.5 g) in ethanol (700 ml) was stirred for 1 hr at room temperature. Additional phosphorus pentoxide (10.5 g) was added and the mixture was refluxed for 2 hr. The mixture was concentrated and cooled to give **13b** as crystals. Recrystallization from benzene or acetonitrile gave yellowish plates, mp 249–251°C, yield 73% (48 g). **13b** can be obtained also from **12b** (Table III) and phosphorus pentoxide: ir 3080, 2250, 1607, 1593, 1540, 1460, 1333, 1262, 1200 cm^{-1}; MS (100°C) *m/e* (rel intensity) 219 (11), 193 (3), 103 (100).

Anal. Calcd for $C_{19}H_{12}N_4$: C, 77.01; H, 4.08; N, 18.91. Found: C, 76.89; H, 3.87; N, 18.75.

Fragmentation Reaction of 12. One gram of **12a** or **12b** was refluxed in 20 ml of commercial butanol (containing water, ca. 0.5%) for 24 hr. The reaction mixtures were analyzed by GLC (2-m column Pora Pak Q, 225°C) and the presence of benzaldehyde and acetophenone was detected. Evaporation of the mixtures left solids, which were crystallized from water and identified as **10a** (from **12a**) and benzoyl DAMN (from **12b**) by comparison of spectroscopic data with authentic samples, respectively.

Acknowledgment. The author thanks Mrs. M. Aiba, K. Inoue, K. Eto, and M. Nagano for their help in carrying out some of the experiments.

Registry No.—**1a,** 51802-34-7; **1b,** 55752-07-3; **1c,** 55752-08-4; **1d,** 55752-09-5; **1e,** 57443-93-3; **1f,** 55752-10-8; **1g,** 55752-11-9; **1h,** 55752-12-0; **1i,** 55752-13-1; **1j,** 55752-14-2; **1k,** 55752-15-3; **1l,** 55752-16-4; **3,** 57443-94-4; **4a,** 57443-95-5; **4b,** 57443-96-6; **5a,** 57443-97-7; **5b,** 57443-98-8; **5c,** 57443-99-9; **5d,** 57444-00-5; **6,** 57444-01-6; **7a,** 57444-02-7; **7b,** 57444-03-8; **7c,** 57444-04-9; **8a,** 57444-05-0; **8b,** 57444-06-1; **9a,** 57444-07-2; **9b,** 57444-08-3; **9c,** 57484-04-5; **9d,** 57444-09-4; **9e,** 57444-10-7; **9f,** 57444-11-8; **10c,** 52685-70-8; **11,** 57444-12-9; **12a,** 57444-13-0; **12b,** 57444-14-1; **13a,** 56984-06-6; **13b,** 56984-07-7; DAMN, 1187-42-4; phosphorus pentoxide, 1314-56-3; acetophenone, 98-86-2; *p*-nitroacetophenone, 100-19-6; o-hydroxyacetophenone, 118-93-4; benzophenone, 119-61-9; 2,2′-dihydroxybenzophenone, 835-11-0; methyl β-naphthalenyl ketone, 941-98-0; phenyl β-naphthalenyl ketone, 642-29-5; 9*H*-fluoren-9-one, 486-25-9; methyl 2-thienyl ketone, 88-15-3; methyl 2-furyl ketone, 1192-62-7; methyl 3-pyridyl ketone, 350-03-8; phenyl 3-pyridyl ketone, 5424-19-1; acetyl cyanide, 631-57-2; 2-oxobutyronitrile, 4390-78-7; 3-methyl-2-oxobutyronitrile, 42867-39-0; benzoyl cyanide, 613-90-1; ethyl acetoacetate, 141-97-9; *N*-acetoacetylmorpholine, 16695-54-8; ethyl β-oxovalerate, 4949-44-4; ethyl γ-methyl-β-oxovalerate, 7152-15-0; ethyl 3-oxo-3-phenylpropionate, 94-02-0; benzoylacetone, 93-91-4; dibenzoylmethane, 120-46-7; methyl vinyl ketone, 78-94-4; 2-ethoxycarbonylcyclopentanone, 611-10-9.

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Contribution to the Chemistry of Indole. About the 5-(1-Indolyl)-2-pentanone System

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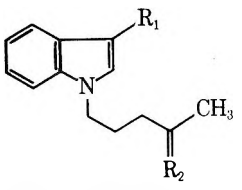
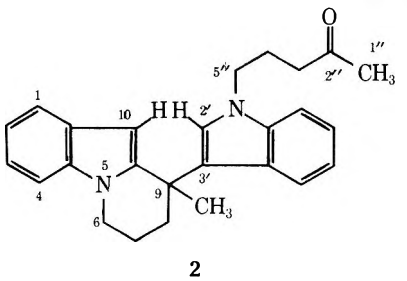
Alkylation of indole with 5-chloro-2-pentanone ethylene ketal gave **1a**. Attempts to hydrolyze the ketal gave **2** instead. The 3-substituted indoles **1b** and **1d** were hydrolyzed to the corresponding ketones **1c** and **1e**. Skatole was alkylated with the same alkylating agent to give **1f**. Hydrolysis gave the pyrido[1,2-*a*]indole **3**.

The alkylation of indole[1] on nitrogen is a well-documented reaction in organic chemistry. As a model for further studies we were interested in the preparation of 5-(1-indolyl)-2-pentanone. It was our intention to obtain this compound from the corresponding ethylene ketal via mild hydrolysis in acidic medium. For this purpose indole was treated with sodium hydride in absolute DMF followed by the addition of 5-chloro-2-pentanone ethylene ketal. The product of this alkylation, 5-(1-indolyl)-2-pentanone ethylene ketal (**1a**), was obtained in 98% yield and gave ir, NMR, and mass spectral data in agreement with the expected structure **1a**.

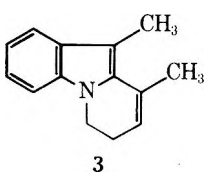
Chart I



1a, $R_1 = H$; $R_2 = OCH_2CH_2O$
b, $R_1 = COOMe$; $R_2 = OCH_2CH_2O$
c, $R_1 = COOMe$; $R_2 = O$
d, $R_1 = CH_2COOMe$; $R_2 = OCH_2CH_2O$
e, $R_1 = CH_2COOMe$; $R_2 = O$
f, $R_1 = CH_3$; $R_2 = OCH_2CH_2O$



2



3

Attempts to remove the protecting group in **1a** via hydrolysis in aqueous acetic acid did not yield the expected ketone. Instead compound **2** of the molecular composition $C_{26}H_{28}N_2O$ (*m/e* 384, M^+) was isolated in 63% yield. This formally represents a condensation between 2 mol of the product of the deketalization less 1 mol of water. One oxygen atom was retained as a saturated keto group as indicated by the presence of an ir band at 1713 cm^{-1} in the spectrum of **2** excluding the presence of an α,β-unsaturated ketone formed via an aldol condensation.

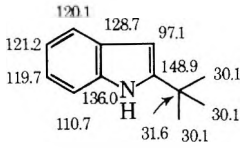
The ^1H NMR spectrum of **2** indicated ten aromatic protons and no vinylic protons, ruling out a double bond in the side chain and pointing to the structure **2**. This product was assumed to arise by intramolecular condensation of the carbonyl group liberated in the hydrolysis of **1a** at the indole 2 position followed by alkylation at C-3 of a second indole unit. Although electrophilic substitution should occur more readily in the β position of indole[1] and particularly of N-alkylated indoles, the ^1H NMR spectrum of **2** did not allow a definitive assignment of the position of the attachment of the second indole nucleus. Thus it was decided to study the ^{13}C NMR of **2** in the hope of establishing the substitution patterns of the two indole nuclei.

Discussion of the ^{13}C NMR Spectrum of 2. The fully proton decoupled spectrum of **2** gave a total of 26 peaks accounting for all the 26 carbon atoms of the product, indicating at the same time that the product on hand consisted of a single isomer.

Shift theory[2] and models from the literature[2a] (the compounds **1a**, **1f**, and **3**, see below, serving as additional models) were used for the calculations. Peaks at 126.7 and 97.7 ppm (see Experimental Section) were assigned to the carbon atoms at position 2′ and 10, respectively, based upon the following arguments. The chemical shift for C_2 of an unsubstituted indole[2a] is documented to occur at 125.2 ppm. Methyl substituents in positions 1 and 3 are known to shift the absorption by +4.1 and −2.5 ppm. This is in good agreement with the observed value of 126.7 ppm (calcd

126.8 ppm) which was assigned to the CH at position 2′ (see Chart I for numbering) of product **2**. Similar considerations regarding the chemical shift of the C_3 of the unsubstituted indole (102.6 ppm) lead to the assignment of the observed peak at 97.7 ppm to the carbon atom in position 10 of product **2** (calcd 99.1 ppm). The difference between observed and calculated values can be accounted for by assuming an upfield shift due to γ-shielding effects.[2b] Therefore 2- and 3-*tert*-butyl-*N*-methylindoles were selected as new models based upon the known chemical shifts of *tert*-butylbenzene relative to benzene and assuming that the observed difference of 20.5 ppm is also applicable in the case of indoles.

This approximation was put to test in the case of 2-*tert*-butylindole.[3] The following values were observed.



The chemical shifts for the phenyl ring were assigned in the same relative order as those documented for indole itself. More significantly, the measured values for the C_2 and C_3 carbons of the substituted indole show similar downfield and upfield shifts relative to indole as the corresponding phenyl carbons in *tert*-butylbenzene relative to benzene.

For 1-methyl-3-*tert*-butylindole the chemical shift for the C_2 was calculated to be 126.0 ppm while for the C_3 of 1-methyl-2-*tert*-butylindole a calculated value of 98.0 ppm was obtained. This is in good agreement with the values of 126.7 and 97.7 ppm as observed for compound **2**. (See above.)

For the C_3 of 1-methyl-3-*tert*-butylindole a value of 121.8 ppm was calculated. This is in agreement with the observed peak at 122.6 ppm of **2**, which is therefore assigned to the carbon atom in position 3′. In analogy the value for the C_2 of 1-methyl-2-*tert*-butylindole was estimated to be 149.8 ppm. The observed value of 145.0 ppm for **2** was assigned to the carbon atom 9a.

Single-frequency off-resonance decoupling (sford) experiments were used to assign the number of protons attached to each carbon atom. These experiments revealed the presence of two quartets allowing peaks 23 and 24 to be assigned to the two methyl groups and a singlet at 36.7 ppm to the fully substituted carbon atom 9. In summary these studies seem to establish the presence of *one* proton in an α position and *one* proton in a β position of two different indole nuclei. If *two* protons were present each in a β position as might be concluded from the ^1H NMR spectrum of **2**, this should give rise to two peaks near 100 ppm (both doublets in the sford experiment) in the ^{13}C NMR spectrum of **2** in place of the peaks observed at 97.7 and 126.7 ppm and to two peaks near 145 ppm (both singlets in the sford experiment) in place of the peaks observed at 122.6 and 145.0 ppm, respectively.

The two singlets at δ 6.32 and 6.38 indicate that the C-2′ proton is shielded (approximately 0.6 ppm) by the double bond of the other indole while the C-3 proton shows relatively little shielding effect. (The shifts[4] for the α and β protons of 3-*tert*-butylindole and 2-*tert*-butylindole are δ 6.83 and 6.13, respectively.)

Alkylation of 3-Substituted Indoles. Methyl indole-3-carboxylate[5] was alkylated with 5-chloro-2-pentanone ethylene ketal to the novel 5-(3-carbomethoxy-1-indolyl)-2-pentanone ethylene ketal (**1b**) and hydrolyzed under conditions similar to those employed above to yield 1-(3-carbomethoxyindolyl)-4-pentanone (**1c**) in good yield. That the difference in stability between compound **1c** and the product of deketalization of **1a** cannot be sought in the difference of reactivity of the corresponding indole double bond alone (in the presence of the carbomethoxy group the double bond may be regarded as part of the vinylogous amide or enamino ketone[6] with reduced reactivity rather than an enamine as in the case without the carbomethoxy group) became obvious when 1-(4-dioxolanyl)pentylindole-3-acetic acid methyl ester (**1d**) was treated with 80% aqueous acetic acid. The keto ester **1e** was isolated in 95% yield.

Contrary to the observations made with indoleacetic acid, skatole formed a dihydropyrido[1,2-*a*]indole **3**. Thus when 3-methylindole was alkylated under conditions similar to those described above the expected product **1f** was isolated in good yield. Under conditions favorable for the hydrolysis of the ketal (80% aqueous acetic acid at 80°) cyclization between the carbonyl carbon and position 2 of the indole with subsequent loss of water was observed. Pure compound **3** was isolated in 58% yield. The structural assignment was based on analytical and spectral data.

In the ^1H NMR spectrum of **1f** long-range coupling between the indole methyl group at δ 2.30 and the proton in position 2 of the indole was observed. In the spectrum of compound **3** the corresponding methyl group appeared as a sharp singlet at δ 2.42 indicating the replacement of the proton at position 2 with a carbon. The methyl group in position 9 gave rise to a broad signal at δ 2.14 which could be resolved to a quartet with the aid of the 100-MHz instrument. Decoupling experiments verified the presence of long-range coupling in **3** between the methyl group in position 9 and the vinyl proton. It also became clear that additional long-range coupling between the methyl group in position 9 and the protons in position 7 is present. Irradiation at δ 5.53 (vinyl proton) caused the multiplet at δ 2.14 to collapse to a triplet (J = 1.5 Hz).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. NMR spectra were measured on either a Varian A-60 or T-60 spectrometer and are recorded in δ values (parts per million) from Me_4Si as internal standard. The ^{13}C NMR spectra were measured on a Varian XL-100 spectrometer and are recorded in parts per million values from Me_4Si as internal standard. Ir spectra were taken on a Perkin-Elmer Model 257 or 457. Gas–liquid chromatography was carried out on a Hewlett-Packard 5750 chromatograph. Mass spectra were taken on a LKB 9000 mass spectrometer.

5-(1-Indolyl)-2-pentanone Ethylene Ketal (1a). To a mixture of 5.30 g (0.220 mol) of NaH in 50 ml of absolute DMF there was added a solution of 23.4 g (0.20 mol) of indole in 50 ml of DMF. After 2 h at room temperature 32.8 g (0.20 mol) of commercial 5-chloro-2-pentanone ethylene ketal was added slowly with an exothermic reaction taking place (~50°C). The mixture was stirred overnight at room temperature, the solvent removed in vacuo, and the residue extracted with ether and worked up in the usual way to yield 48.0 g (98%) of liquid **1a**. A sample was distilled in a Kugelrohr: bp 160° (0.2 mm); GLC 99% pure; *m/e* 245 (M^+); NMR ($CDCl_3$) δ 1.25 (s, 3, CH_3), 1.4–2.3 (m, 4, 2 CH_2), 3.82 (s, 4, OCH_2CH_2O), 4.03 (t, 2, J = 7.0 Hz, NCH_2), 6.43 (d, 1, J = 3 Hz, C_3H), 6.9–7.7 (m, 5, aromatic H); ir (film) 1620 cm^{-1} (weak). For ^{13}C NMR see Table I.

5-(3-Carbomethoxy-1-indolyl)-2-pentanone Ethylene Ketal (1b). From 17.5 g (0.1 mol) of methyl indole-3-carboxylate[5] and 16.5 g (0.1 mol) of 5-chloropentanone ethylene ketal in absolute DMF in the presence of 2.4 g (0.1 mol) of sodium hydride following the procedures described above there was obtained 25.0 g (83%) of **1b**: bp 160–180° (0.8 mm) (Kugelrohr); GLC one component; *m/e* 303 (M^+); NMR ($CDCl_3$) δ 1.27 (s, 3, CCH_3), 1.3–2.4 (m, 4, 2 CH_2), 3.9 (s) and 3.9–4.4 (m, 9, NCH_2 + OCH_3 + OCH_2CH_2O), 7.1–8.3 (m, 5, aromatic H); ir (film) 1698 cm^{-1} (ester). Anal. Calcd for $C_{17}H_{21}NO_4$ (303.4): C, 67.3; H, 7.0; N, 4.6. Found: C, 67.0; H, 6.9; N, 4.7.

5-(3-Carbomethoxy-1-indolyl)-2-pentanone (1c). Following the same procedures as described for the preparation of **2**, ketal **1b**

Table I

Peaks obsd, ppm	Rel intensity	Assignment
136.4	13	7a
129.0	36	3a
128.0	132	2
121.7	114	5
121.2	147	4
119.5	148	6
109.8	52	2′
109.7	149	7
101.3	108	3
64.6	214	OCH_2
46.2	164	5′
36.2	209	3′
24.8	215	4′
23.9	101	1′

Table II

Peaks obsd, ppm	Rel intensity	Assignment
136.8	9	7a
129.2	25	3a
125.7	93	2
121.6	97	5
119.3	76	4
118.8	97	6
110.3	22	3
109.9	50	2′
109.5	110	7
64.7	214	OCH_2
46.0	130	5′
36.4	121	3′
25.0	125	4′
23.9	80	1′
9.6	46	C_3CH_3

gave **1c** in yield of 93%: bp 180–200° (0.5 mm) (Kugelrohr); GLC one component; *m/e* 259 (M^+); NMR ($CDCl_3$) δ 2.05 (s) and 1.7–2.5 (m, 7, CCH_3 + $CH_2CH_2C{=}O$), 3.90 (s, 3, OCH_3), 4.08 (t, 2, *J* = 6.5 Hz, NCH_2), 7.0–8.3 (m, 5, aromatic H); ir (film) 1715 (ketone), 1698 cm^{-1} (ester). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.3): C, 69.5; H, 6.6; N, 5.4. Found: C, 69.4; H, 6.7; N, 5.4.

1-[3-(2-Methyl-2-dioxolanyl)propyl]indole-3-acetic Acid Methyl Ester (1d). Starting with 18.9 g (0.1 mol) of 3-indoleacetic acid methyl ester[7] and 16.5 g (0.1 mol) of 5-chloropentanone ethylene ketal in DMF in the presence of 2.9 g (0.1 mol) of NaH following the procedures described for the preparation of **1a** there was obtained after distillation 25.0 g (79%) of **1d**: bp 200° (0.7 mm) (Kugelrohr); GLC one component; *m/e* 317 (M^+); NMR ($CDCl_3$) δ 1.26 (s, 3, CCH_3), 1.3–2.1 (m, 4, 2 CH_2), 3.67 (s, 3, OCH_3), 3.75 (s, 2, CH_2COOMe), 3.85 (s, 4, OCH_2CH_2O), 4.03 (t, 2, *J* = 6.5 Hz, NCH_2), 6.9–7.7 (m, 5, aromatic H); ir (film) 1740 cm^{-1} (ester). Anal. Calcd for $C_{18}H_{23}NO_4$ (317.4): C, 68.1; H, 7.3; N, 4.4. Found: C, 68.4; H, 7.3; N, 4.7.

1-(4-Oxo-1-pentyl)indole-3-acetic Acid Methyl Ester (1e). Compound **1d** was hydrolyzed under the same conditions described for the preparation of **1c** to give **1e** in 95% yield: bp 200° (0.8 mm) (Kugelrohr); GLC one component; *m/e* 273 (M^+); NMR ($CDCl_3$) δ 2.03 (s, 3, $CH_3C{=}O$), 1.6–2.5 (m, 4, 2 CH_2), 3.68 (s, 3, OCH_3), 3.75 (s, 2, CH_2COOMe), 4.08 (t, 2, *J* = 6.5 Hz, NCH_2), 6.9–7.7 (m, 5, aromatic H); ir (film) 1745 (ester), 1720 cm^{-1} (C=O). Anal. Calcd for $C_{16}H_{19}NO_3$ (273.32): C, 70.3; H, 7.0, N, 5.1. Found: C, 70.4; H, 6.9; N, 5.3.

5-(3-Methyl-1-indolyl)-2-pentanone Ethylene Ketal (1f). Starting with 20.0 g (0.15 mol) of 3-methylindole and 26.3 g (0.16 mol) of 5-chloropentanone ethylene ketal in 200 ml of absolute DMF in the presence of 3.85 g (0.16 mol) of NaH following the procedures described for the preparation of **1a** there was obtained after distillation 31.1 g (80%) of **1f**: bp 140–160° (0.05 mm) (Kugelrohr); *m/e* 259 (M^+); NMR ($CDCl_3$) δ 1.27 (s, 3, $OCCH_3$), 1.4–2.2 (m, 4, 2 CH_2), 2.30 (d, 3, *J* = 1.0 Hz, indole CH_3), 3.85 (s, 4, OCH_2CH_2O), 4.00 (t, 2, *J* = 6.5 Hz, NCH_2), 6.80 (d, 1, *J* = 1.0 Hz, indole C_2 H), 6.9–7.6 (m, 4, aromatic); ir (CH_2Cl_2) 1620 cm^{-1} (weak). Anal. Calcd for $C_{16}H_{21}NO_2$ (259.3): C, 74.1; H, 8.2; N, 5.4. Found: C, 74.1; H, 8.4; N, 5.4. For ^{13}C NMR see Table II.

Table III

Peaks obsd, ppm	Rel intensity	Sford	Assignment
207	31	s	2″
145.0	44	s	9a
137.1	24	s	
135.9	19	s	
128.0	33	s	
126.7	181	d	2′
125.3	29	s	
122.6	34	s	3′
121.0	158		
120.7	172		
120.2	197		
119.9	166		
119.4	199		
118.4	170		
109.5	190	d	
108.9	129	d	
97.7	203	d	10
44.5	157	t	5″
42.0	190	t	6
39.6	205	t	3″
36.7	74	s	9
34.8	191	t	8
29.4	72	q	11
29.0	148	q	1″
23.7	149	t	7
19.6	197	t	4″

Table IV

Peaks obsd, ppm	Rel intensity	Assignment
136.4	7	4a
132.6	8	9a
129.9	14	9
129.3	18	10a
122.4	109	8
121.2	115	2
119.1	159	3
119.0	152	1
108.6	120	4
107.7	10	10
39.7	217	6
24.3	199	7
21.1	159	C_9CH_3
10.1	53	$C_{10}CH_3$

5-[3-(6,7,8,9-Tetrahydro-9-methylpyrido[1,2-*a*]indol-9-yl)]-1-indolyl-2-pentanone (2). A solution of 20.0 g (0.082 mol) of ketal **1a** in 65 ml of acetic acid and 15 ml of water was heated to reflux for 2 h. A liquid which separated from the cold solution crystallized after the addition of ether. There was obtained 9.8 g (63%) of **2**, mp 123–124°. The product was recrystallized from CH_2Cl_2–ether: mp 126–127°; *m/e* 384 (M^+); NMR ($CDCl_3$) δ 1.93 and 2.01 (2 s), 1.7–2.8 (m, total 14 H, 2 CH_3 + 4 CH_2), 3.7–4.4 (m, 4, 2 NCH_2), 6.32 (s, 1), 6.38 (s, 1), 6.9–7.7 (m, 8, 2 C_6H_4); ir (CH_2Cl_2) 1713 cm^{-1} (C=O). Anal. Calcd for $C_{26}H_{28}N_2O$ (384.5): C, 81.2; H, 7.3; N, 7.3. Found: C, 81.0; H, 7.6; N, 7.3. For ^{13}C NMR see Table III.

6,7-Dihydro-9,10-dimethylpyrido[1,2-*a*]indole (3). A solution of 5.2 g (0.02 mol) of **1f** in 20 ml of 80% aqueous acetic acid was warmed to 80°C for 1 h. Addition of water gave a solid which was filtered off and recrystallized from ethanol–water to give 2.3 g (58%) of pure **3**: mp 60–61°; *m/e* 197 (M^+); NMR ($CDCl_3$) δ 2.14 (q, 3, *J* = 1.5 Hz, C_9 CH_3), 2.42 (s, 3, C_{10} CH_3), 2.0–2.7 (m, 2, NCH_2CH_2), 3.82 (t, 2, *J* = 6.5 Hz, NCH_2), 5.53 (m, 1, vinyl H), 6.9–7.6 (m, 4, C_6H_4); ir (CH_2Cl_2) 1610 cm^{-1} (weak). Anal. Calcd for $C_{14}H_{15}N$ (197.3): C, 85.2, H, 7.7; N, 7.1. Found: C, 85.0; H, 7.7; N, 7.0. For ^{13}C NMR see Table IV.

Acknowledgment. The author would like to thank Dr. W. J. Houlihan for his interest and support, Dr. Renate Coombs for supplying the mass spectral data, and Dr. S. Barcza and his staff for recording the spectra and for helpful discussion in evaluating the data.

Registry No.—**1a,** 57512-87-5; **1b,** 57512-88-6; **1c,** 57512-89-7; **1d,** 57512-90-0; **1e,** 57512-91-1; **1f,** 57512-92-2; **2,** 57512-93-3; **3,** 57512-94-4; indole, 120-72-9; 5-chloro-2-pentanone ethylene ketal, 5978-08-5; methyl indole-3-carboxylate, 942-24-5; 3-indoleacetic acid methyl ester, 1912-33-0; 3-methylindole, 83-34-1.

References and Notes

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Preparation and Reactions of β-Chloro-α,β-Unsaturated Ketones[1]

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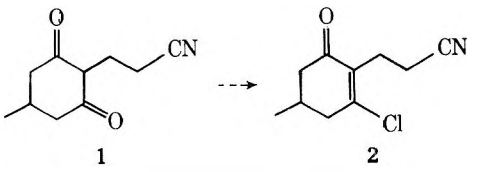
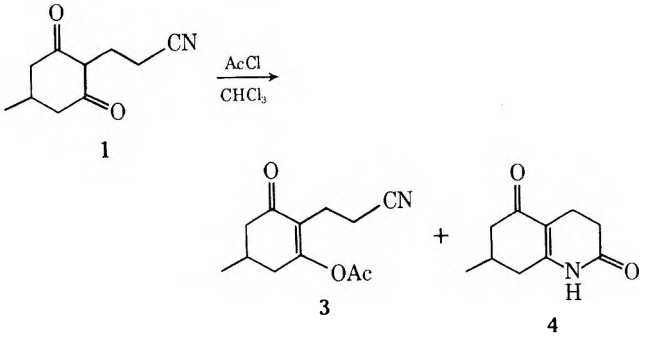
β-Chloro-α,β-unsaturated ketones are conveniently prepared by treating β-diketones or β-keto aldehydes with oxalyl chloride in an inert solvent such as benzene or chloroform. Symmetrical cyclic β-diketones and β-keto aldehydes afford a single β-chloroenone in good yield. Unsymmetrical cyclic β-diketones yield a mixture of isomeric β-chloroenones. Acyclic β-diketones yield a mixture of *E* and *Z* β-chloroenones. β-Keto esters do not afford β-chloro-α,β-unsaturated esters by this procedure; the only product produced is the enol chlorooxalate. The product β-chloroenones are smoothly dehalogenated by silver-zinc couple in methanol and readily couple with lithium dialkylcuprates. In contrast to β-alkoxy-α,β-unsaturated ketones, β-chloroenones do not undergo regiospecific base-catalyzed alkylation.

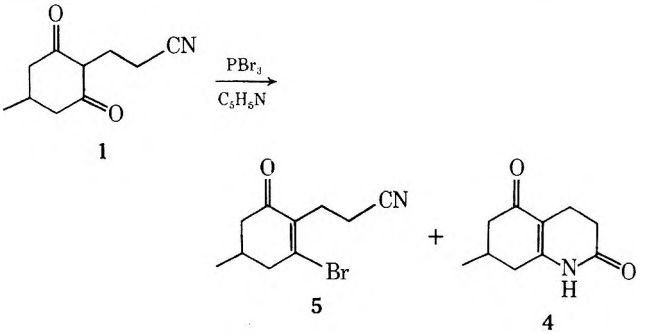
Preparation of β-Chloroenones. β-Chloro-α,β-unsaturated ketones have been prepared from β-diketones by reaction with phosphorus trichloride,[2-4] phosgene,[5] acetyl chloride,[6] thionyl chloride,[3] and phosphorus oxychloride.[2,7] Reported yields for this conversion are generally in the range 50–70%.[8]

In connection with a projected synthesis, we had occasion to prepare β-chloroenone **2** from cyanodione **1.** However, the presence of the nitrile function caused serious complications when we attempted to use standard methodology for this conversion. For example, treatment of **1** with acetyl chloride in chloroform[6] gives no β-chloroenone **2.** The only products obtained are acetate **3** (49–61%) and lactam **4** (29–39%).[9] Phosphorus trichloride does afford β-chloroenone **2** in 40–50% yield, but it is contaminated by substantial amounts of lactam **4.**



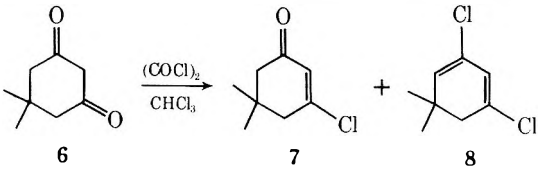


Similar difficulties were encountered when we attempted to transform dione **1** into β-bromoenone **5** using phosphorus tribromide in pyridine, a reagent often used to convert β-diketones into β-bromoenones.[2] In this case, β-bromoenone may be isolated in only 20% yield, and the major product appears to be lactam **4** (isolated in 20% yield).



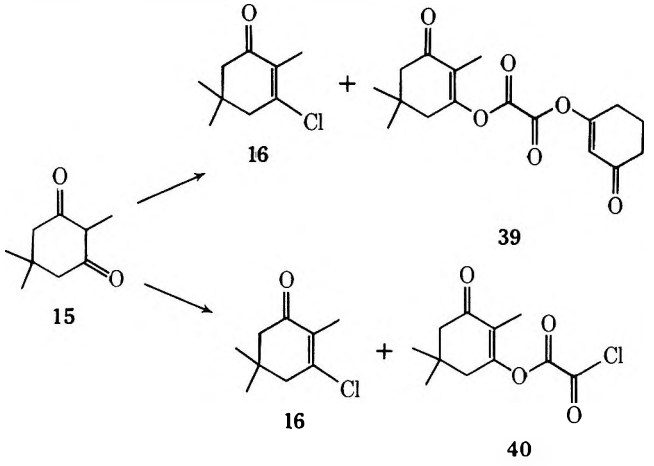
These difficulties led us to explore alternate methods for accomplishing the conversion of β-diketones to β-haloenones. In this paper, we report a successful solution to this problem, using a method which appears to be generally applicable and which, in many cases, gives higher yields than do the standard methods.[2-6]

Dimedone (**6**) reacts with oxalyl chloride (2.5 equiv) in refluxing chloroform to afford β-chloroenone **7** in 91% yield. The only side-product is a small amount of dichlorodiene **8** (ca. 2%), and the amount of this material may be suppressed by minimizing the reaction time. Application of

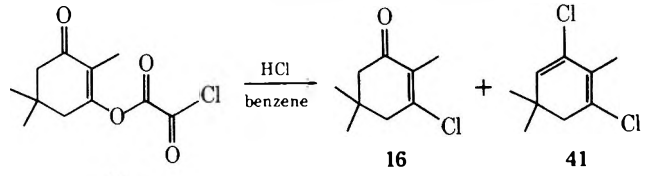


this method to dione 1 gave β-chloroenone in a distilled yield of 76%; none of the undesired lactam 4 was detected in the reaction product.

To test the generality of the procedure, we have carried out the reaction on a variety of other β-diketones and β-keto aldehydes. The results are summarized in Table I. Note that the procedure seems to be generally applicable for the conversion of cyclic β-diketones into β-chloroenones in good yield.[10] The sole cyclic β-diketone which has given us anomalous results is methyldimedone (15). Under our normal reaction conditions (2 equiv of oxalyl chloride, 180 min reflux, 5.7 mmol of 15 per ml of benzene), chloroenone 16 is produced in only 50% yield. The remainder of the product is the crystalline bisoxalate 39. Under more dilute conditions (2 mmol of 15 per milliliter of benzene), β-chloroenone 16 is produced in 34% yield, accompanied by the crystalline chlorooxalate 40. While one might reasonably



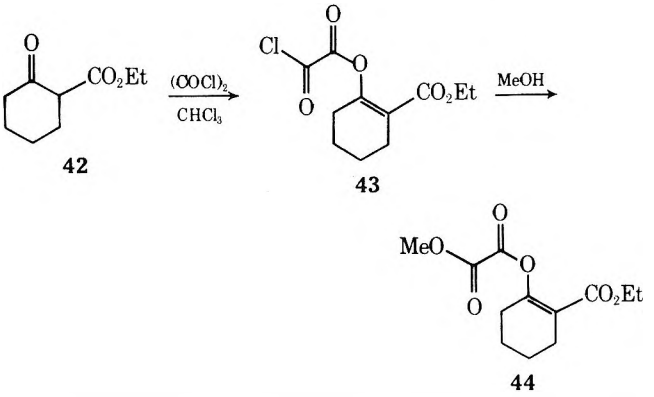
expect compounds 39 and/or 40 to be intermediates in the conversion of 15 into 16, their isolation and stability in this case is somewhat surprising. We have not encountered analogous products with any of the other β-diketones we have studied. Decomposition of 40 can be effected with HCl in benzene, but under these conditions chloroenone 16 is substantially converted into dichlorodiene 41.



The single acyclic β-diketone studied (29) afforded a 1:1 mixture of stereoisomeric β-chloroenones 30 and 31 in 50% yield. As a method for preparing 30 and 31, this procedure is competitive with Julia's method in which 2-chloropropene is treated with acetyl chloride and $AlCl_3$ (57%).[11] The structures of isomers 30 and 31 are readily assigned on the basis of their ^1H NMR spectra (see Experimental Section). Unsymmetrical β-diketones such as 19 and 26 give good yields of β-chloroenones, but the reaction is not regioselective.

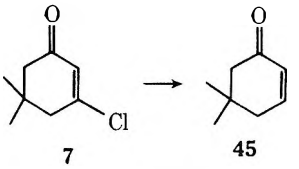
β-Keto aldehydes apparently react to yield a single β-chloroenone. The reaction is regiospecific *and* stereospecific. The chlorine appears to be cis to the carbonyl group in both examples we have studied (32 → 33, 34 → 35). The stereostructure shown in Table I was assigned on the basis of ^1H NMR arguments.[12]

So far, we have been unsuccessful in transforming β-keto esters into β-chloro-α,β-unsaturated esters with oxalyl chloride. Ethyl 2-oxocyclohexanecarboxylate (42) yields only the high-boiling chlorooxalate 43, which reacts with methanol to give the mixed oxalate diester 44. Attempts to

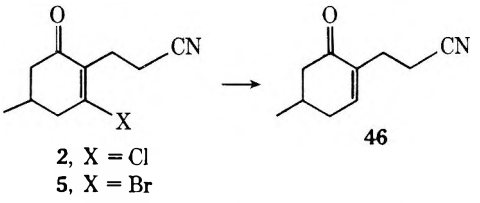


convert 43 into a vinyl chloride by reaction with anhydrous HCl in $CHCl_3$ were unsuccessful.

Reduction of β-Chloroenones. We have also studied the reduction of β-chloroenones to α,β-unsaturated ketones (e.g., 7 → 45). Crossley and Renouf reported in 1907 that



such reductions may be accomplished by utilizing acid-washed zinc dust in methanol.[18] Frank and Hall reported in 1950 that acceptable yields in this reduction are obtained only when potassium iodide is also added to the reaction mixture.[3] Thus, these workers reduced 7 to 45 by using 5 equiv of zinc dust and 1 equiv of KI in methanol. Using these conditions, we found that chloroenone 2 and bromoenone 5 are slowly reduced to enone 46 in yields of 40–50%. Conia's zinc–silver couple[19] gave comparable re-



sults—slow reduction, ca. 50% yield of 46. In contrast, we found that a zinc–silver couple prepared from acid-washed zinc *dust* causes a rapid reduction of 5, affording 46 in high yield (81% distilled).

In order to optimize the conditions for this reduction, a series of experiments were carried out on chloroenone 7. Reaction aliquots were analyzed by GLC, using peak areas to monitor the percent reduction as a function of reaction time. It was first established that potassium iodide is not necessary for facile reduction; in fact, reduction is somewhat more rapid in its absence. Secondly, it was established that the manner in which the zinc dust is washed with dilute acid is essential to the formation of an active couple. Optimum results are obtained when the zinc is treated with 10% aqueous HCl with occasional shaking for 4–5 min. Finally, the amount of silver used in preparing the couple is important. The couple is prepared by adding the acid-washed zinc dust to a hot solution of silver acetate in acetic acid, and the most effective reagent is obtained when 30–40 mg of silver acetate per gram of zinc dust is used (see Table II).

Using a zinc–silver couple prepared from 30 mg of AgOAc per gram of Zn, the reduction of 7 to 45 is effective-

Table I
Preparation of β-Chloroenones

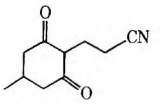
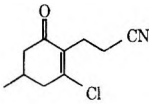
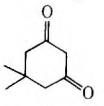
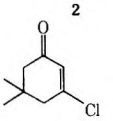
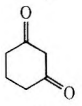
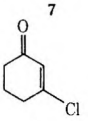
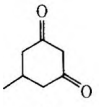
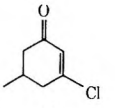
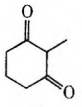
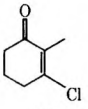
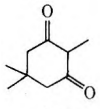
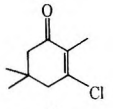
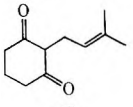
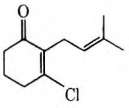
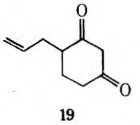
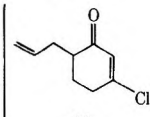
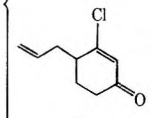
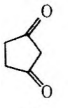
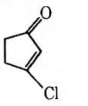
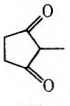
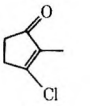
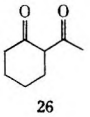
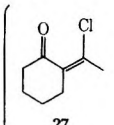
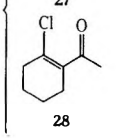
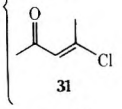
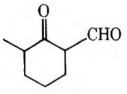
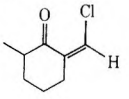
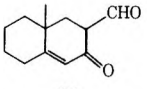
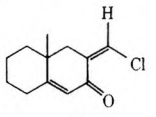
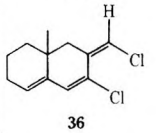
Starting β-dicarbonyl compd	Amount of $(COCl)_2$, equiv	Reaction time, min	Product	(% yield)[a]
 1	2.5[b]	60	 2	(76)
 6	2.0	20	 7	(91)
 9	2.5	13	 10	(78)
 11	2.5	120	 12	(92)
 13	2.5	60	 14	(87)
 15	2.0[b]	180	 16	(50)[c]
 17	2.0	15	 18	(62)
 19	2.0	15	 20	(51)
			 21	(22)
 22	2.0	15	 23	(78)
 24	2.0	15	 25	(73)
 26	2.0	15	 27	(51)
			 28	(27)

Table I
(Continued)

Starting β-dicarbonyl compd	Amount of $(COCl)_2$, equiv	Reaction time, min	Product	(% yield)[a]
 29	2.0	15	 30	(25)
			 31	(25)
 32	2.0	15	 33	(83)
 34	1.0	15	 35	(80)
			 36	(10)

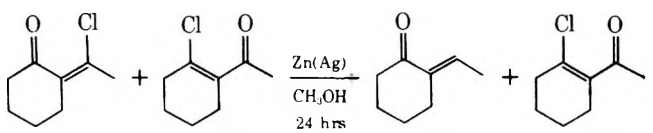
[a] Yields are distilled yields. [b] These reactions were carried out in benzene; all others were carried out in chloroform. [c] See text.

Table II
Reduction of β-Chloroenone 7

mg of AgOAc/g of Zn	% 45 in 5 min	mg of AgOAc/g of Zn	% 45 in 5 min
0	3	30	85
4	18	35	81
20	67	40	79
25	75		

ly quantitative in 15–20 min at room temperature. If acid-washed zinc dust is used, without being converted into the silver couple, the reduction requires more than 24 hr.

In order to explore the generality of the reduction procedure, a number of other β-chloroenones were reduced using the foregoing optimum conditions. Results are summarized in Table III. It is clear from Table III that this method of reductive removal of a halogen from a β-haloenone is widely applicable and constitutes a reliable synthetic method. Several generalizations may be made. β-Haloenones which have an alkyl group at the α position reduce much more slowly than those with hydrogen at this position. (**14** vs. **10**, **16** vs. **7**). β-Bromoenones reduce much more rapidly than β-chloroenones (**5** vs. **2**). In general, α-alkyl-β-chloroenones require on the order of 24 hr for complete reduction, while α-protio-β-chloroenones require only 15–60 min. One β-chloroenone, compound **28**, showed no signs of reducing at all, even after 24 hr. The reduction of this substance was actually carried out on a 2:1 mixture of **27** and **28**. After 24 hr, the reaction product consisted of a 2:1 mixture of **56** and **28**.

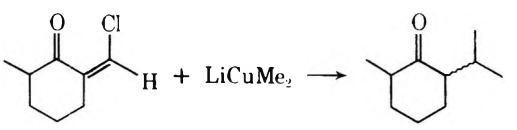


27 + **28** (2:1) → **56** + **28** (2:1)

Reduction of α-(chloromethylene)cyclohexanone (**33**) resulted in complete reduction to 2,6-dimethylcyclohexanone (**55**). Analysis by GLC showed that the product α-methylenecyclohexanone is reduced at a rate comparable to that for **33** itself.

It was found that dried zinc–silver couple is not nearly as effective as the freshly prepared couple. Furthermore, we noted that reduction of crude (undistilled) chloroenone results in substantial overreduction of the product enone, presumably owing to the acidity (HCl) of the undistilled chloroenone. We also investigated the Zn(Ag)–CH_3OH reduction of several other halides. *o*-Bromobenzoic acid, *p*-bromoethylbenzene, dichlorodiene **8**, and 1-chloro-4-methylcyclohexene were not reduced by the reagent in 24 hr.

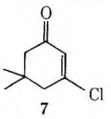
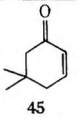
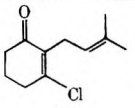
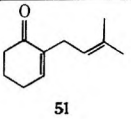
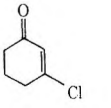
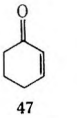
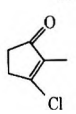
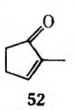
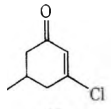
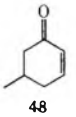
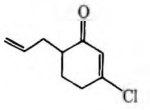
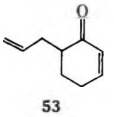
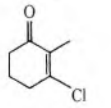
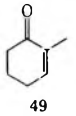
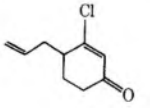
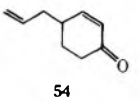
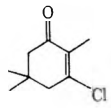
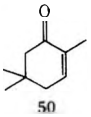
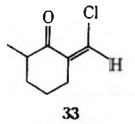
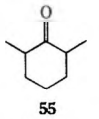
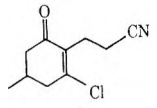
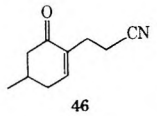
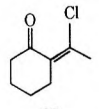
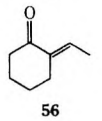
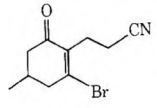
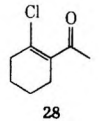
Reaction of β-Chloroenones with Organocuprates. Having a number of pure β-chloroenones in hand, we briefly investigated their reaction with lithium dimethylcuprate. Compound **33** reacts smoothly with 2 equiv of $LiCuMe_2$ to give 2-isopropyl-6-methylcyclohexanone (**57**) in 90% yield. Under the same conditions, the 2:1 mixture of **27**



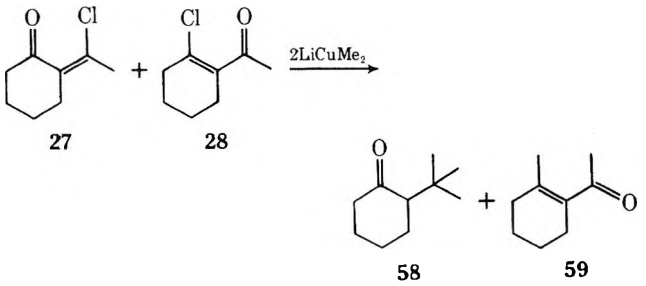
33 → **57**

and **28** affords a 2:1 mixture of 2-*tert*-butylcyclohexanone (**58**) and enone **59**.[20] A similar reaction with the α-(chloromethylene)octalone **35** resulted in exclusive alkylation of

Table III
Reduction of β-Chloroenones

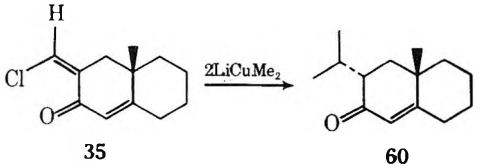
β-Chloroenone	Reaction time, min	Product	(% yield)[a]	β-Chloroenone	Reaction time, min	Product	(% yield)[a]
 7	20	 45	(81)	 18	1440	 51	(90)
 10	90[b]	 47	(75)	 25	1560	 52	(65)
 12	30	 48	(75)	 20	60	 53	(85)[d]
 14	2400	 49	(77)	 21	60	 54	(85)[d]
 16	2200	 50	(58)[c]	 33	60	 55	(80)
 2	1440	 46	(87, 81)	 27	1440	 56	*e*
 5	30			 28	1440		NR

[a] Isolated yield. [b] This reaction was carried out at 0° C. At room temperature, compound **10** reacts with methanol. [c] This reduction was incomplete after 37 hr; yield is by GLC. [d] Compounds **20** and **21** were reduced as a 70:30 mixture. The reduction products **53** and **54** were formed in 85% yield in a ratio of 70:30. [e] See text.



27 28 58 59

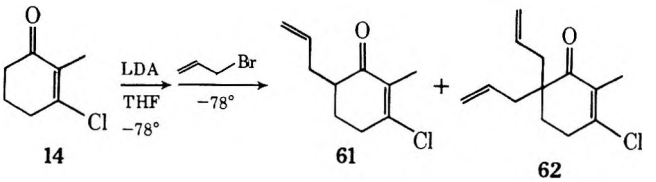
the double bond exocyclic to the ring, affording the isopropyl enone **60**. Similar alkylations of 1,3-dicarbonyl enol



35 60

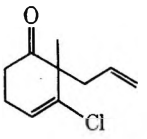
ethers,[22] enol sulfides,[22] and enol acetates[23] have been reported previously. However, alkoxyl (and presumably acyloxyl) groups cause the E_0 for an enone to be more negative,[21b] while halogens probably cause E_0 to be less negative.[24] Thus, in cases such as **35**, where there are two enone systems, greater selectivity is indicated.

Alkylation of β-Chloroenone Enolates. Finally, we have examined the kinetic alkylation of β-chloroenone **14**, in analogy to the kinetic alkylation of β-diketone enol ethers reported by Danheiser and Stork.[26] However, in the case of chloroenone **14**, we find proton transfer to compete very effectively with alkylation, even using allyl bromide as the electrophile. Thus, when **14** is converted into its kinetic enolate by lithium diiscpropylamide (LDA) in THF, followed by alkylation with allyl bromide at −78°, a mixture of monoalkylated and dialkylated chloroenones (**61** and **62**) and recovered **14** is produced in a ratio of 30:25:45. Using inverse addition of preformed enolate to allyl bromide at −78° gave slightly more monoalkylation (**61**:**62**:**14** 48:22:



14 61 62

30), but the results were still not satisfactory. When the alkylation is carried out at 0°, with HMPT as cosolvent, either normal or inverse addition gave mixtures of mono- and dialkylated products, also containing the product of thermodynamically controlled enolization, **63**. The rapid proton transfer observed with β-chloroenones, in contrast to the exclusive monoalkylation observed with analogous enol ethers,[26] is probably due to the greater acidity of the chloroenones.



63

Experimental Section

All melting and boiling points are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 spectrometer (in δ units with tetramethylsilane as internal reference). The infrared (ir) spectra were recorded on a Perkin-Elmer 137 infrared spectrophotometer. Mass spectra (MS) were obtained on a MS-12 mass spectrometer. Mass spectra are given as *m/e* with the relative intensity in parentheses. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, Calif. Preparative and analytical gas–liquid chromatography (GLC) was carried out on an Aerograph Model A 90-P3 gas chromatograph using the following stainless steel (10 ft × 0.25 in.) columns: column A, 15% NPGS: column B, 5% SE-30; column C, 10% NPGS; column D, 10% FFAP.

3-Acetoxy-2-(2-cyanoethyl)-5-methylcyclohex-2-en-1-one (3). Acetyl chloride (3.3 g, 42 mmol) was added to a suspension of dione 1[27] (5.0 g, 28 mmol) in chloroform (30 ml). The mixture was refluxed for 2 hr, evaporated, taken into ether, and filtered from a white solid. Evaporation of the ether filtrate gave 3.74 g (61%) of acetate **3** as a colorless oil: ir (film) 4.44, 5.67, 5.95, 8.40, 8.78, 9.52 μ; NMR (CCl_4) δ 1.08 (d, 3 H), 2.33 (s, 3 H), 2.00–2.60 (m, 9 H).

Anal. Calcd for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83. Found: C, 64.93; H, 6.97.

The white solid from above (1.44 g, 28.8%) was the known bicyclic lactam **4**.[28] Recrystallization from chloroform–petroleum ether gave light yellow needles, mp 191–193° (lit.[28] mp 198–199°): ir (Nujol) 5.91, 6.11 μ; NMR (pyridine) δ 0.85 (d, 3 H), 2.00–2.70 (m, 9 H).

3-Bromo-2-(2-cyanoethyl)-5-methylcyclohex-2-en-1-one (5). To a solution of diketone **1** (73.5 g, 410 mmol) in chloroform (700 ml) and lutidine (75 ml) was added phosphorus tribromide (62 ml, 660 mmol) and the resulting sclution was refluxed for 3 hr. Water was slowly added to the cooled solution, the chloroform layer was separated, and the aqueous layer was washed with ether. The combined organic layers were washed with water, dried, and evaporated to a half-solid residue. Trituration with ether gave 14.6 g (20%) of crystalline lactam **4**. The ether was evaporated and the residue distilled to give 19.4 g (20%) of bromoenone **5** (bath temperature 135°, 0.2 mm) as a colorless oil: ir (film) 4.50, 6.00, 6.19 μ; NMR (CCl_4) δ 1.05 (d, 3 H), 2.00–3.00 (m, 9 H).

Anal. Calcd for $C_{10}H_{12}ONBr$: C, 49.58; H, 4.96; N, 5.78; Br, 33.05. Found: C, 49.38; H, 4.93; N, 5.59, Br, 33.28.

General Procedure for the Synthesis of Chloroenones. 3-Chloro-5,5-dimethylcyclohex-2-en-1-one (7). To a suspension of dimedone **6** (15.0 g, 107 mmol) in chloroform[29] (40 ml) was added slowly oxalyl chloride (27.2 g, 214 mmol). The addition was accompanied by vigorous evolution of gas. After stirring at room temperature for 10 min, the slurry was refluxed for 20 min to give a yellow solution which was evaporated and distilled to give 15.7 g (92%) of chloroenone **7** as a colorless liquid, bp 72° (5 mm) [lit.[3] bp 105° (20 mm)]: ir (film) 5.95, 6.17 μ; NMR (CCl_4) δ 1.10 (s, 6 H), 2.20 (s, 2 H), 2.78 (d, 2 H), 6.13 (t, 1 H); MS *m/e* (rel intensity) 160 (6), 158 (19), 104 (32), 102 (100), 79 (17), 77 (11), 67 (48).

Anal. Calcd for $C_8H_{11}OCl$: C, 60.56; H, 6.94; Cl, 22.37. Found: C, 60.36; H, 6.79; Cl, 22.38.

3-Chloro-2-(2-cyanoethyl)-5-methylcyclohex-2-en-1-one (2). Dione **1** (35.0 g, 196 mmol) in benzene (100 ml) was treated with oxalyl chloride (62.5 g, 493 mmol) according to the general procedure described above. After a 60-min reflux, the solvent was evaporated and the residue was distilled to give 29.1 g (75.5%) of chloroenone **2** as a colorless oil, bp 152° (3 mm): ir (film) 4.46, 5.95, 6.17 μ; NMR (CCl_4) δ 1.05 (d, 3 H), 2.00–3.00 (m, 9 H); MS *m/e* (rel intensity) 199 (8), 197 (27), 172 (16), 162 (100), 115 (74).

Anal. Calcd for $C_{10}H_{12}ONCl$: C, 60.90; H, 6.09; N, 7.11; Cl, 18.05. Found: C, 60.77; H, 6.19; N, 7.06; Cl, 18.02.

Other β-chloroenones prepared using this general procedure had the following physical properties.[30]

3-Chlorocyclohex-2-en-1-one (10): bp 63° (4 mm) [lit. bp 78° (14 mm),[31] 104° (24 mm[32])].

3-Chloro-5-methylcyclohex-2-en-1-one (12): bp 52° (1.2 mm).

3-Chloro-2-methylcyclohex-2-en-1-one (14): bp 46° (0.6 mm), 62° (2 mm) [lit.[33] bp 84° (7 mm)].

3-Chloro-2-(3-methyl-2-butenyl)cyclohex-2-en-1-one (18): bp 110° (2.5 mm).

3-Chloro-4-(2-propenyl)cyclohex-2-en-1-one (21), 3-chloro-6-(2-propenyl)cyclohex-2-en-1-one (20): bp 85° (2 mm).

3-Chlorocyclopent-2-en-1-one (23): bp 35° (0.7 mm).

3-Chloro-2-methylcyclopent-2-en-1-one (25): bp 43° (1.6 mm).

(*Z*)-2-Chloroethylidinecyclohexanone (27), 1-acetyl-2-chlorocyclohexene (28): bp 80° (2 mm).

Reaction of Methyl Dimedone (15) with Oxalyl Chloride. Oxalyl chloride (56.0 g, 460 mmol) was added slowly to methyl dimedone (**15**,[34] 35.0 g, 227 mmol) in benzene (40 ml) and the resulting solution was refluxed for 3 hr. The solvent was evaporated and the residue distilled to give 19.5 g (50%) of chloroenone **16** as a colorless oil, bp 78° (2 mm) [lit.[35] bp 78° (2 mm)]: ir (film) 5.95, 6.11, 7.50, 7.7 μ; NMR (CCl_4) δ 1.33 (s, 6 H), 1.90 (t, 3 H), 2.28 (s, 2 H), 2.65 (q, 2 H); MS *m/e* (rel intensity) 174 (7), 172 (24), 118 (32), 116 (100).

Anal. Calcd for $C_9H_{13}OCl$: C, 62.61; H, 7.53; Cl, 20.55. Found: C, 62.64; H, 7.58; Cl, 20.29.

The crystalline pot residue from the distillation (10.0 g) was recrystallized from ethyl acetate to give the bisoxalate **39**, mp 159–161°: ir (Nujol) 5.62, 5.95, 6.80, 9.10 μ; NMR ($CDCl_3$) δ 1.16 (s, 12 H), 1.73 (t, 6 H) 2.38 (s, 4 H), 2.57 (q, 4 H).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.03; H, 7.27.

In a similar reaction of methyl dimedone (10.0 g, 65 mmol) and oxalyl chloride (20.6 g, 162 mmol) in benzene (30 ml), the higher boiling chlorooxalate **40** was obtained, bp 107° (1.2 mm): ir ($CHCl_3$) 5.37, 5.37, 5.95, 6.15 μ; NMR was identical with that of bisoxalate **39**.

(*Z*)-3-Chloropent-3-en-2-one (30) and (*E*)-3-Chloropent-3-en-2-one (31). Acetylacetone (**29**, 5.0 g, 50 mmol) in chloroform (15 ml) was treated with oxalyl chloride (12.7 g, 100 mmol) and the resulting solution was refluxed for 15 min. Evaporation of solvents and distillation gave 2.95 g (50%) of chloroenones **30** and **31**, bp 35° (6 mm) [lit.[11] bp 42° (11 mm)]. The two isomers were present in a 50:50 ratio by NMR analysis and were separated by preparative gas chromatography (column A, 140°). The *E* isomer **31** had retention time 2.2 min: NMR (CCl_4) δ 2.16 (s, 3 H), 2.33 (d, J = 1 Hz, 3 H), 6.43 (q, J = 1 Hz, 1 H). The *Z* isomer **30** had retention time 4.0 min: NMR (CCl_4) δ 2.08 (d, J = 1 Hz, 3 H), 2.30 (s, 3 H), 6.10 (q, J = 1 Hz, 1 H).

(*Z*)-2-Chloromethylene-6-methylcyclohexanone (33). A solution of 2-formyl-6-methylcyclohexanone (9.95 g, 71.7 mmol) in chloroform (40 ml) was treated with oxalyl chloride (13.6 g, 106 mmol) under the usual conditions to give 9.23 g (82.6%) of **33**, bp 60° (1.5 mm). Gas chromatography (column B, 150°) showed one component at retention time 4.0 min: ir (film) 5.92, 6.23, 6.40, 6.90, 7.75 μ; NMR (CCl_4) δ 1.10 (d, 3 H), 1.40–2.80 (m, 7 H), 6.96 (t, J = 3 Hz, 1 H).

Anal. Calcd for $C_8H_{11}OCl$: C, 60.57; H, 6.94; Cl, 22.40. Found: C, 60.78; H, 6.90; Cl, 22.18.

(*Z*)-2-Chloromethylene-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (35). Oxalyl chloride (2.41 g, 19 mmol) was slowly added to a cooled (10–15°) solution of formyl ketone **34** (3.58 g, 18.6 mmol) in chloroform (50 ml). After the addition was complete, the solution was stirred at room temperature for 15 min and then refluxed for 15 min. Evaporation and distillation gave 3.0 g of yellow oil, bp 125° (1.5 mm). NMR analysis showed a 9:1 mixture of chloroenone **35** and dichlorotriene **36**, which were separated by preparative gas chromatography (column C, 200°). Compound **36** had retention time 2.5 min: ir (film) 6.12, 6.20, 6.40, 9.80 μ; NMR (CCl_4) δ 1.00 (s, 3 H), 2.83 (d, 1 H), 5.53 (t, 1 H), 6.10 (s, 1 H), 6.56 (d, J = 2 Hz, 1 H); MS *m/e* (rel intensity) 232 (6), 230 (35), 228 (54), 195 (34), 193 (100), 165 (24), 157 (39).

Compound **35** had retention time 3.7 min: ir (film) 6.01, 6.20, 6.30, 7.65, 8.00 μ; NMR (CCl_4) δ 1.16 (s, 3 H), 2.93 (d, 1 H), 5.70 (t, 1 H), 7.05 (d, J = 2 Hz, 1 H); MS *m/e* (rel intensity) 212 (34), 210 (100), 195 (48), 175 (68), 105 (70).

Anal. Calcd for $C_{12}H_{15}OCl$: C, 68.41; H, 7.13. Found: C, 68.16; H, 7.23.

Under the usual conditions for formation of the β-chloroenone (2.0 equiv of $COCl_2$), compound **34** gave only dichlorotrienone **36** in good yield.

Reaction of Ethyl Cyclohexanone-2-carboxylate (42) with Oxalyl Chloride. To a solution of ethyl cyclohexanone-2-carboxylate (5.0 g, 29 mmol) in benzene (20 ml) was added oxalyl chloride

(7.9 g, 62 mmol). After 3.5 hr reflux, the mixture was evaporated and distilled to give 5.3 g of chlorooxalate **43** as a thick oil, bp 130° (1.5 mm): ir (film) 5.43, 5.56, 5.71, 5.80, 8.10 μ; NMR was virtually superimposable with that of the starting material.

When this material was refluxed in methanol, a colorless oil was obtained which was readily identifiable as the methyl oxalate **44**: ir (film) 5.68, 5.71 μ; NMR (CCl_4) δ 3.72 (s, 3 H).

General Procedure for the Reduction of β-Chloroenones. 5,5-Dimethylclohex-2-en-1-one (45). Aqueous 10% hydrochloric acid (10 ml) was added to zinc dust (Mallinckrodt analytical, 2.1 g, 31.5 mmol) and the resulting suspension was shaken periodically. After several minutes, the supernatant liquid was decanted and the zinc was washed with acetone (2 × 10 ml) and ether (10 ml). A suspension of silver acetate (60–70 mg) in boiling acetic acid (10 ml) was added. After the mixture was stirred for 1 min, the supernatant was decanted and the black zinc–silver couple was washed with acetic acid (5 ml), ether (4 × 10 ml), and methanol (10 ml). To the moist couple was added a solution of chloroenone **7** (1.0 g, 6.3 mmol) in methanol (3 ml). The reduction was exothermic, and GLC analysis (column A, 150°) showed it to be complete after stirring vigorously at room temperature for 10–20 min. The zinc was filtered off and washed with methanol. The filtrate was evaporated and the residue was partitioned between ether and 10% hydrochloric acid. The ether layer from five similar runs was dried and evaporated to yield 3.2 g (81%) of enone **45** as a colorless oil, bp 36° (1 mm): ir (film) 5.95 μ; NMR (CCl_4) δ 1.10 (s, 6 H), 2.30 (m, 4 H), 5.93 (m, 1 H), 6.80 (m, 1 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74; Found: C, 77.04; H, 10.09.

2-(2-Cyanoethyl)-5-methylcyclohex-2-en-1-one (46). Reduction of chloroenone **2** (27.6 g, 140 mmol) with the zinc–silver couple (63.0 g, 978 mmol) in methanol (120 ml) for 26 hr as above gave 19.5 g (86.5%) of enone **46** after distillation, bp 92° (0.3 mm): ir (film) 4.44, 5.97 μ; NMR (CCl_4) δ 1.10 (d, 3 H), 2.00–2.50 (m, 5 H), 2.46 (s, 4 H), 6.85 (d, 1 H).

Anal. Calcd for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.28; H, 8.13; N, 8.40.

2,6-Dimethylcyclohexanone (55). To the zinc–silver couple (5.2 g, 80 mmol) was added chloroenone **33** (2.5 g, 15.8 mmol) in methanol (10 ml). An exothermic reaction ensued which required mediation with an ice bath. GLC analysis (column B, 150°) showed the reaction to be complete in less than 5 min. The usual work-up gave 1.50 g (80%) of colorless oil which was identical (ir, NMR, GLC) with an authentic sample of 2,6-dimethylcyclohexanone.

Reduction of Chloroenones 27 and 28. A 2:1 mixture of chloroenones **27** and **28** (1.0 g, 6.4 mmol) in methanol (2 ml) was treated with the zinc–silver couple (1.25 g, 19 mmol) at room temperature for 20 hr. Work-up afforded 0.75 g of light red oil. GLC analysis (column B. 130°) showed two peaks at retention times of 4.8 and 6.6 min, in a 2:1 ratio. Both peaks were collected by preparative GLC and the major peak was (*E*)-2-ethylidinecyclohexanone (**56**): ir (CCl_4) 5.91, 6.19 μ; NMR (CCl_4) δ 1.68 (doublet of triplets, J = 7, 1 Hz, 3 H), 2.00–2.60 (m, 4 H), 6.55 (quartet of triplets, J = 7, 2 Hz, 1 H).[36]

The minor peak was chloroenone **28**: ir (CCl_4) 5.90, 6.20 μ; NMR (CCl_4) δ 1.53–1.90 (m, 4 H), 2.37 (s, 3 H), 2.00–2.60 (m, 4 H); MS *m/e* (rel intensity) 160 (8), 158 (24), 145 (22), 143 (69, loss of methyl, ^{35}Cl isomer).

Spectral[30] and physical properties of other enones prepared by this general method were in complete accord with the assigned structures. Furthermore, the synthetic samples of enones **45, 47, 48, 50,** and **54**[26] were identical with authentic samples of these materials.

Reaction of β-Chloroenones with Lithium Dimethylcopper. 2-Isopropyl-6-methylcyclohexanone (57). A solution of chloroenone **33** (5.0 g, 31.8 mmol) in ether was added to a −30° solution of lithium dimethylcopper (65 mmol) in ether (100 ml). The mixture was allowed to warm to room temperature, then was poured into aqueous ammonium hydroxide solution. Ether extraction gave 4.47 g (91.4%) of **57** as a light yellow oil: ir (film) 5.84, 6.89, 7.70 μ; NMR (CCl_4) δ 0.80–1.07 (overlapping methyl and isopropyl doublets from two isomers, 9 H), 1.07–2.40 (m, 9 H); MS *m/e* (rel intensity 154 (22).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.02; H, 11.93.

2-*tert*-Butylcyclohexanone (58) and 1-Acetyl-2-methylcyclohexene (59). An ether solution of chloroenones **27** and **28** (1.6 g, 10 mmol) was added to a −50° solution of lithium dimethylcopper (25 mmol) in ether (25 ml). The mixture was allowed to warm to room temperature and was poured into 10% aqueous hydrochloric acid and extracted with ether to give 1.7 g of yellow oil. GLC analysis (column B, 150°) showed two peaks at retention times 5.8 and 7.0 min, in a 65:35 ratio. Both components were collected and the major peak was 2-*tert*-butylcyclohexanone (**58**): ir (film) 5.83, 7.40, 7.65 μ; NMR (CCl_4) δ 0.96 (s, 9 H), 1.40–2.40 (m, 9 H).

The minor peak was the enone **59**: ir (film) 5.93, 6.20, 7.40 μ; NMR (CCl_4) δ 1.40–1.80 (m, 4 H), 1.82 (t, J = 1 Hz, 3 H), 2.10 (s, 3 H), 1.90–2.40 (m, 4 H).

3α-Isopropyl-4aβ-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (60). Reaction of choroenone **35** (2.2 g, 10.5 mmol) with lithium dimethylcopper (22 mmol), followed by aqueous ammonium hydroxide work-up, gave 1.9 g (88%) of the isopropyl enone **60** as a colorless oil. GLC analysis (column C, 200°) showed a single peak at retention time 6.1 min: ir (film) 6.00, 6.16 μ; NMR (CCl_4) δ 0.80 (d, J = 7 Hz, 3 H, nonequivalent isopropyl methyl), 0.93 (d, J = 7 Hz, 3 H), 1.25 (s, 3 H), 5.56 (s, 1 H).

Anal. Calcd for $C_{14}H_{22}O$: 206.1670. Found: 206.1675.

This material was unchanged upon prolonged treatment with sodium methoxide in methanol or *p*-toluenesulfonic acid in benzene.

3-Chloro-2-methyl-6-(2-propenyl)cyclohex-2-en-1-one (61) and 3-Chloro-2-methyl-6,6-di(2-propenyl)cyclohex-2-en-1-one (62). To a −78° solution of lithium diisopropylamide (16 mmol) in THF (3 ml) was added a solution of chloroenone **14** (2.0 g, 15.8 mmol) in THF (4 ml) dropwise over a 20-min period. After 10 min at −78°, the solution was treated with allyl bromide (2.1 g, 17.2 mmol) and allowed to warm to room temperature overnight. After dilution with ether, the solution was washed with water, 5% hydrochloric acid, and brine, dried, and evaporated to 2.62 g of reddish oil. GLC analysis (column D, 170°) showed three peaks at retention times 2, 3.7, and 6.2 min, in a ratio of about 45:30:25, respectively. Collection of individual peaks showed the first to be starting material **14**: MS *m/e* (rel intensity) 146 (13), 144 (41), 118 (32), 116 (100), 88 (66), 53 (64).

The second peak was the monoallylated chloroenone **61**: ir (film) 3.14 5.97, 6.11, 10.92 μ; NMR (CCl_4) δ 1.90 (t, J = 1 Hz, 3 H), 1.80–2.90 (m, 7 H), 4.80–6.00 (complex ABX, 3 H); MS *m/e* (rel intensity) 186 (12), 184 (39), 149 (19), 118 (33), 116 (100), 81 (50), 53 (68).

The third peak was the diallylated enone **62**: ir (film) 3.14, 5.97, 6.11, 10.93 μ; NMR (CCl_4) δ 1.90 (t, J = 1 Hz, 3 H), 1.80–2.90 (m, 8 H), 4.80–6.00 (complex ABX, 6 H); MS *m/e* (rel intensity) 226 (2), 224 (7), 183 (36), 155 (32), 118 (28), 116 (80), 93 (16), 91 (49), 42 (100).

Acknowledgments. We gratefully acknowledge Mr. Lee Kozar for his technical assistance in some aspects of this work, and the National Science Foundation for generous financial support under Grant GP-31321X.

Supplementary Material Available. NMR and infrared spectra for all new compounds (48 pages). Ordering information is given on any current masthead page.

Registry No.—**1,** 2172-73-8; **2,** 42747-36-4; **3,** 57428-51-0; **4,** 17812-55-4; **5,** 42747-37-5; **6,** 126-81-8; **7,** 17530-69-7; **9,** 504-02-9; **10,** 5682-75-7; **11,** 4341-24-6; **12,** 42747-34-2; **13,** 1193-55-1; **14,** 35155-66-9; **15,** 1125-11-7; **16,** 39776-34-6; **17,** 56946-66-8; **18,** 57428-52-1; **19,** 57428-53-2; **20,** 57428-54-3; **21,** 57428-55-4; **22,** 3859-41-4; **23,** 53102-14-0; **24,** 765-69-5; **25,** 35173-23-0; **26,** 874-23-7; **27,** 57428-56-5; **28,** 16111-92-5; **29,** 123-54-6; **30,** 49784-64-7; **31,** 49784-51-2; **32,** 1194-91-8; **33,** 57428-57-6; **34,** 57428-58-7; **35,** 57428-59-8; **36,** 57428-60-1; **39,** 57428-61-2; **40,** 51238-70-1; **42,** 1655-07-8; **43** (R = Me), 57428-62-3; **43** (R = Et), 57428-63-4; **44** (R = Me), 57428-64-5; **44** (R = Et), 57428-65-6; **45,** 4694-17-1; **46,** 42747-40-0; **47,** 930-68-7; **48,** 7214-50-8; **49,** 1121-18-2; **50,** 42747-41-1; **51,** 57428-66-7; **52,** 1120-73-6; **53,** 57428-67-8; **54,** 4166-61-4; **55,** 2816-57-1; **56,** 7417-55-2; **57,** 17781-07-6; **58,** 1728-46-7; **59,** 2047-97-4; **60,** 57428-68-9; **61,** 57428-69-0; **62,** 57428-70-3; acetyl chloride, 75-36-5; phosphorus tribromide, 7789-60-8; oxalyl chloride, 79-37-8.

References and Notes

(1) Portions of this work have appeared in preliminary form: R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **38**, 3658 (1973); *Synthesis*, **47** (1974).
(2) A Crossley and H. LeSeur, *J. Chem. Soc.*, **83**, 110 (1903).
(3) R. L. Frank and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **72**, 1645 (1950).
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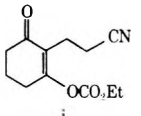
(5) M. Shemyakin et al., *Zh. Obshch. Khim.*, **30**, 542 (1960).
(6) W. Hückel and K. Thiele, *Chem. Ber.*, **94**, 96 (1961).
(7) W. Pfeiderer and K. Schundehütte, *Justus Liebigs Ann. Chem.*, **613**, 158 (1958).

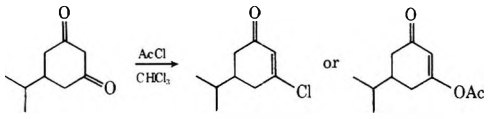
(8) It has recently been found that β-diketones react with triphenylphosphine dihalides to product β-halo-α,-β-unsaturated ketones. With chlorides and bromides, yields are excellent (90–97%). With iodides, the yields are lower, but respectable (71–83%): E. Piers and I. Nagakura, *Synth. Commun.*, **5**, 193 (1975).

(9) We also found that dione **1** reacts with ethyl chloroformate in chloroform to give the mixed carbonate i in 91% yield. These results lead us



i

to suspect that the reported conversion of dione ii into β-chloroenone iii[6] may be in error. Since no characterization of the alleged iii was reported, the reaction product may well be acetate iv.

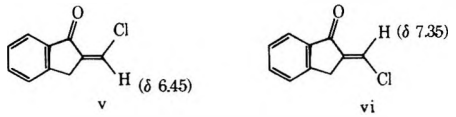


ii iii iv

(10) The reaction may also be carried out on the sodium salt of the β-diketone. Thus, the sodium salts of **1** and **11** reacted with oxalyl chloride in benzene to give **2** and **12**, in isolated yields of 46 and 56%, respectively. We have also briefly explored the analogous use of oxalyl bromide for the formation of β-bromoenones. Dione **6** reacts rapidly, giving the corresponding β-bromoenone in good yield. However, dione **1** was simply polymerized by treatment with oxalyl bromide.

(11) M. Julia, *Ann. Chim. (Paris)*, **5**, 595 (1950).

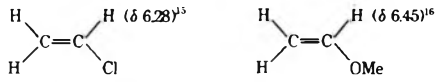
(12) Although several cyclic α-(chloromethylene) ketones have been reported,[13] no stereostructural assignments have been made except in the case of isomers v and vi,[14] and then on the basis of comparative chemical shifts. The general principle used in assigning structures to v



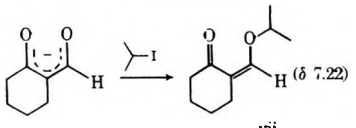
v vi

and vi is the empirical observation that olefinic β protons cis to the carbonyl group in enones resonate downfield from their trans counterparts.[14] However, in our case, only one isomer is in hand, and such comparative arguments may not be made.

Our assignment is based on the following argument: Protons α to the heteroatom in vinyl chloride and methyl vinyl ether resonate at δ 6.28 and δ 6.45, respectively. The enol ether vii, prepared by alkylation of an

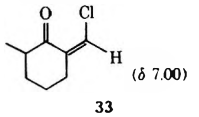


enolate of known geometry, almost certainly has the stereostructure indicated. The β-olefinic proton in this compound resonates at δ 7.22.[17]



vii

Compound **33** shows a β-olefinic proton resonance at δ 7.00 ppm.



33

Thus, it would appear that vii and **33** both have the same relative stereostructure, since the Δδ of 0.22 ppm observed is about the same as the Δδ of 0.17 ppm observed with vinyl chloride and methyl vinyl ether (vide supra). The cis and trans β-olefinic protons in α-methylenecyclohexanone resonate at δ 5.72 and 5.04, respectively. Thus, for vii and **33** to differ in stereostructure, their β-olefinic proton resonances should differ by about 1 ppm.

(13) (a) J. Wolinsky, D. Chan, and R. Novak, *Chem. Ind. (London)*, 720 (1965); (b) A. E. Pohland and W. R. Benson, *Chem. Rev.*, **66**, 161 (1966).

(14) L. M. Jackman and S. Sternhall, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Elmsford, N.Y., 1969, p 223.

(15) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).

(16) J. E. Sohn, unpublished spectrum.

(17) P. M. Wege, unpublished spectrum.

(18) A. Crossley and N. Renouf, *J. Chem. Soc.*, **91**, 63 (1907).

(19) J. M. Denis, C. Girard, and J. M. Conia, *Synthesis*, **5**, 549 (1972).

(20) Note that there is a large difference in reactivity between the presumed intermediate in the formation of **58** (enone viii) and enone **59**. By

viii

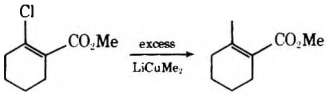
House's empirical rules for estimating standard reduction potentials for α,β-unsaturated carbonyl compounds, both viii and **59** should have E_0 vs. SCE of −2.3 V,[21] just on the borderline for reaction with lithium dimethylcuprate. However, these two enones may well differ in conformation, with **59** being *s*-trans and viii s-cis. This might well result in a less negative E_0 for viii, relative to **59**.

(21) (a) H. O. House and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 5495 (1972); (b) H. O. House, L. E. Huber, and M. J. Umen, *ibid.*, **94**, 8471 (1972).

(22) G. H. Posner and D. J. Brunelle, *J. Chem. Soc., Chem. Commun.*, 907 (1973).

(23) C. P. Casey, D. F. Marten, and R. A. Boggs, *Tetrahedron Lett.*, 2071 (1973).

(24) That halogens add a positive increment to the E_0 of an unsaturated carbonyl system is suggested by the rapid and quantitative conversion of chloro ester ix to unsaturated ester x.[25] By House's rules, compound ix



ix x

should have $E_0 = -2.4$ V ± the effect of the halogen. Since E_0 for $LiCuMe_2$ is estimated to be ca. −2.3 V, the β halogen probably contributes ≥ +0.1 V to E_0 for the system. Note that x, with a predicted E_0 of −2.5 V, does not react even though excess $LiCuMe_2$ is employed.

(25) C. H. Heathcock and J. Leong, unpublished results.

(26) R. L. Danheiser and G. Stork, *J. Org. Chem.*, **38**, 1775 (1973).

(27) C. A. Grob and H. R. Kiefer, *Helv. Chim. Acta*, **48**, 799 (1965).

(28) This lactam has been prepared in high yield by reaction of **1** with HCl: H. Dugas, M. E. Hazenberg, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 4931 (1967).

(29) Commercial chloroform was freed from ethanol by washing with dilute acid followed by drying over magnesium sulfate and distillation.

(30) See paragraph at end of paper regarding supplementary material.

(31) L. Bateman and F. W. Shipley, *J. Chem. Soc.*, 1996 (1955).

(32) A. Crossley and P. Haas, *J. Chem. Soc.*, **83**, 494 (1903).

(33) S. I. Zav'yalov and G. V. Kondrat'eva, *Zh. Obshch. Khim.*, **39**, 3975 (1961).

(34) R. D. Clark, J. E. Ellis, and C. H. Heathcock, *Synth. Commun.*, **3**, 347 (1973).

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(36) For NMR spectra of (*E*)-2-alkylidinecyclohexanones, see G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, *J. Am. Chem. Soc.*, **97**, 107 (1975), and references cited therein.

Ionic and Radical Addition of Methyl Hypochlorite to Dienes

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The products (chloro ethers and dichlorides) obtained from the reaction of butadiene (**1**), isoprene (**2**), and the 1,3-pentadienes, *cis*- (**3a**) and *trans*- (**3b**), with chlorine in methanol, methyl hypochlorite in methanol, and methyl hypochlorite under radical conditions are reported. Analysis of product compositions suggests that chlorine and methyl hypochlorite react via essentially identical carbonium ion intermediates in methanol and that in the absence of methanol, methyl hypochlorite reacts via a radical mechanism only. Ionic electrophilic attack by chlorine occurs only at the 1,2 bond in **2** and predominantly at the 1,2 bond in **3a,b**, suggesting that the transition states for the reactions are carbonium ion-like.

Alkyl hypochlorites (ROCl) have been utilized extensively[1] in radical reactions but their potential for ionic reactions has received limited attention. Reports in the literature[2] and observations of our own indicated that polar electrophilic additions of hypochlorites to alkenes apparently occurred in protic solvents (alcohols, carboxylic acids, and water). We decided to investigate the reaction of methyl hypochlorite with the conjugated dienes, butadiene (**1**), isoprene (**2**), *cis*-1,3-pentadiene (**3a**), and *trans*-1,3-pentadiene (**3b**) in methanol. Since earlier studies had made no clear distinction between ionic additions and possible radical reactions, we needed to clarify the conditions necessary for each mechanism. Our principal interest in studying the addition of methyl hypochlorite to dienes centered around the hope that this unsymmetrical electrophile would furnish insights into diene addition mechanisms which could not be obtained from symmetrical electrophiles such as bromine and chlorine. With methyl hypochlorite, the site of initial electrophilic attack on the diene is marked in the product with chlorine, permitting an assessment of the relative reactivities of the 1,2 vs. the 3,4 double bonds in **2, 3a,** and **3b.** The site of nucleophilic attack in the addition is confirmed by the position of the methoxyl group, which should afford an insight into the nature of the bonding in the intermediates.

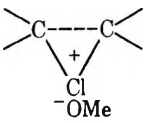
Results and Discussion

Table I shows the products which were obtained from the four dienes and the three reagents, chlorine (in methanol), methyl hypochlorite (in methanol), and methyl hypochlorite (radical addition).

Radical addition was accomplished simply by addition of the hypochlorite to the neat diene (or in solution at high diene concentration) where a molecule-induced homolysis occurred.

In dilute solution in methylene chloride (0.02 mol fraction in diene) the radical addition of methyl hypochlorite was greatly retarded and no reaction occurred in the presence of oxygen. In dilute methanol solution (0.02 mol fraction in diene) methyl hypochlorite reacted readily at 0°C, affording high yields of chloro ethers. The 1,2-chloro ethers exhibit the structure expected for Markownikoff addition of a positive halogen compound. Chlorination in methanol produced the same chloro ether products as methyl hypochlorite as well as relatively small amounts of dichlorides.

In considering the mechanistic implications of our results we were particularly interested in accounting for the role of the solvent methanol in promoting the ionic electrophilic addition of methyl hypochlorite. It seems to us that the inertness of methyl hypochlorite[6] toward alkenes in typical aprotic, nonnucleophilic solvents used for bromination and chlorination (i.e., CCl_4, CH_2Cl_2, hydrocarbons) could be due to the inability of methyl hypochlorite and an alkene to form an ion-pair intermediate (**27**). This could be



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related to the high basicity (and hence instability) of the methoxide ion. Scheme I presents two possible mechanisms which could account for the role of methanol and, therefore, circumvent the problem of the formation of the high-energy ion pair (**27**). Addition to the 1,3-pentadiene system is used as an example. Scheme I suggests that the diene reacts with hypochlorite in a fast, readily reversible step to produce charge-transfer (or π) complexes, **28** and **29.** Two mechanisms are then possible.[7] In mechanism i (ionization), a rate-determining ionization of the π complex occurs to yield the ion-pair intermediates, **30** and **31.** In this mechanism methanol is assigned the specific role of promoting ionization of the π complex by stabilizing the methoxide ion via hydrogen bonding.[8] Reaction of **30** and **31** with the nucleophiles methanol or methoxide ion takes place in a

Scheme I

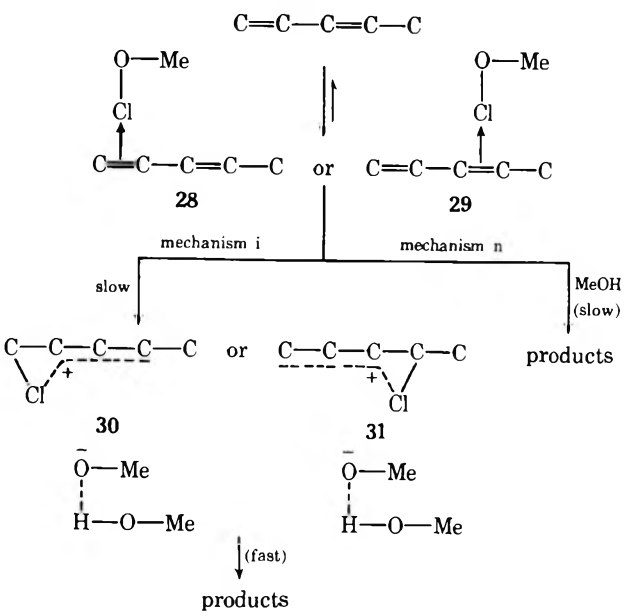
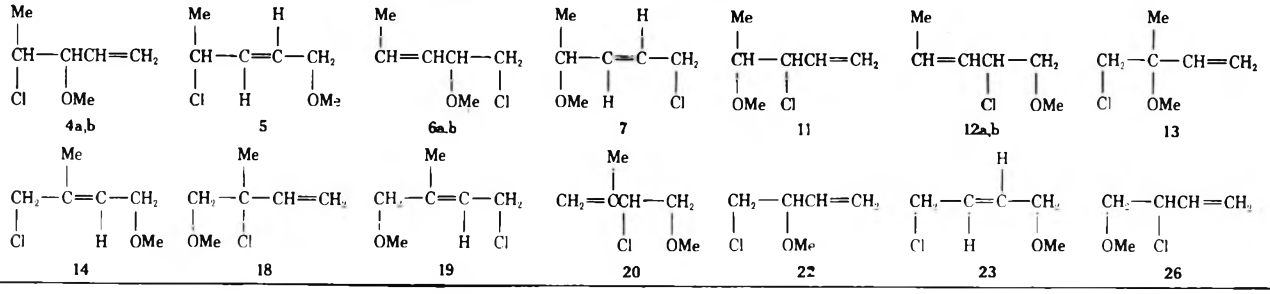


Table I
Reaction of Dienes with Methyl Hypochlorite and Chlorine



Reactants	Yield, %	Products, %[a] 4a,b[b]	5	6a,b[b]	7	11	12a,b[b]	Dichlorides
3a, MeOCl, MeOH	85	14	4	37	45			
3a, Cl_2, MeOH	70	27	7	22	29			14.5[c]
3b, MeOCl, MeOH	88	1.3	0.2	43	55			
3b, Cl_2, MeOH	62	6	1.5	28	45			20[c]
3a, MeOCl (radical)	84		37		44	2.5	15.5	
3b, MeOCl (radical)	96		30		54	4	12	

Reactants		13	14[d]		19[d]	18	20	Dichlorides
2, MeOCl, MeOH[e,f]	98	61	25					
2, Cl_2, MeOH[e-g]	70	59	18					14[c]
2, MeOCl (radical)[e]	98		9		80.5	4	3.5	

Reactants		22	23			26		Dichlorides
1, MeOCl MeOH	85	70	30					
1, Cl_2, MeOH	76	60.5	26					13.5[c]
1, MeOCl (radical)	86		86			14		

[a] The product percentages are normalized to 100%. [b] The products formed are, from 3a, *threo*-4-chloro-3-methoxypentene (4a), *cis*-5-chloro-4-methoxy-2-pentene (6a), *cis*-4-chloro-5-methoxy-2-pentene (12a), and from 3b, *erythro*-4-chloro-3-methoxypentene (4b), *trans*-5-chloro-4-methoxy-2-pentene (6b), and *trans*-4-chloro-5-methoxy-2-pentene (12b). [c] In the reactions with Cl_2 the following dichloride products are also formed: from 3a, 3,4-dichloropentene (8) (4.5%), 4,5-dichloro-2-pentene (9) (5%), 1,4-dichloro-*trans*-2-pentene (10) (5%); from 3b, 8 (3%), 9 (11%), 10 (6%); from 2, 3,4-dichloro-3-methylbutene (16) (6%) and 1,4-dichloro-2-methyl-*trans*-2-butene (17) (8%); from 1, 3,4-dichlorobutene (24) (7%) and 1,4-dichloro-*trans*-2-butene (25) (6.5%). [d] Compounds 14 and 19 are assigned the trans (*E*) configuration.[3,5] [e] 2-Chloromethyl-1,3-butadiene (15) was obtained in the reactions of 2: with MeOCl, MeOH, 14%; with Cl_2, MeOH, 8%; with MeOCl, radical, 3%. [f] A minor VPC peak of short retention time was observed (probably 1-chloro-2-methyl-1,3-butadiene, since this compound is reported[4b] in the chlorination of 2). [g] A compound, assigned the structure *cis*-1-chloro-2-methyl-4-methoxy-2-butene (21), was obtained in a quantity equal to 1.5% in this reaction.

fast step. In mechanism n (nucleophilic), the role of the methanol is to make a rate-determining nucleophilic attack on the π complexes **28** and **29**.[9] Considering the fact that chlorinations of alkenes[10] occur rapidly in aprotic nonnucleophilic solvents by mechanism i, it would seem highly unlikely that chlorinations in methanol would proceed by mechanism n where attack by methanol is rate determining. A sensitive test for similarity of reaction mechanisms between the two electrophiles is that if mechanism i is operative, then essentially identical intermediate cations (**30** and **31**) should be obtained. Therefore, the ratio of 1,2 to 1,4 methoxy chlorides obtained from electrophilic attack on a particular double bond of a diene should then be very similar for chlorine and methyl hypochlorite.

Analysis of the data on the ionic reactions (Table I) shows that product ratios from chlorine and methyl hypochlorite are strikingly similar. These are compared in Table II in terms of relative reactivities of double bonds and as the ratio of 1,2 to 1,4 products resulting from attack by chlorine at a particular carbon atom. In examining the data on relative reactivities of the double bonds in the unsymmetrical dienes, it is seen that in reaction with isoprene the only products detected result from attack at the methyl-substituted 1,2 bond.[11] The relative reactivities of the double bonds in the 1,3-pentadienes (**3a,b**) are shown in Table II. In each reaction the nonsubstituted (1,2) bond in **3a,b** is attacked to a greater extent than the methyl-substituted

Table II
Bond Reactivities and Ratios of 1,2 and 1,4 Adducts

Reactants	Reactivities of bonds in 3a and 3b (1,2/3,4)	Ratio[e] of chloromethoxy products (1,2 adduct/1,4 adduct) From attack on 1,2 bond	From attack on 3,4 bond
3a, MeOCl	4.6[a]	0.82	3.5
3a, Cl_2	1.45[b]	0.76	3.9
3b, MeOCl	65[c]	0.96	6.5
3b, Cl_2	8.0[d]	0.62	4.0
1, MeOCl		2.3	
1, Cl_2		2.3	
2, MeOCl		2.4	
2, Cl_2		3.2	

[a] (6a + 7)/(4a + 5). [b] (6a + 7 + 9)/(4a + 5 + 8). [c] (6b + 7)/(4b + 5). [d] (6b − 7 + 9)/(4b + 5 + 8). [e] E.g., for 3a (MeOCl), attack on 1,2 bond, 6a/7 = 0.82.

(3,4) bond. A clear difference between chlorine and methyl hypochlorite is also evident from this data.[12] The relative rates of attack at the 1,2 vs. the 3,4 bond in 3a and 3b is appreciably greater for methyl hypochlorite than for chlorine (4.6 vs. 1.5 for **3a** and 65 vs. 8 for **3b**).

The data on bond reactivities of the dienes would seem to be most easily explained by assuming that both reactions with chlorine and methyl hypochlorite proceed by

ionization mechanisms (mechanism i, Scheme I) in which appreciable carbonium ion character has developed in the transition state preceding the ion pair (**30, 31**).[13] Therefore the relative reactivities of the double bonds toward these electrophiles are a reflection of the stabilities of the allylic carbonium ions in ion pairs **30** and **31**. For example, the two possible allylic carbonium ions in ion pairs **30** and **31** from 1,3-pentadiene are shown in Scheme I. It is seen that the carbonium ion arising from bonding of chlorine to C_1 is a resonance hybrid of two contributing secondary ions but that bonding at C_4 gives a hybrid of a secondary and a primary ion. The fact that methyl hypochlorite gives an even larger percentage of attack at the 1,2 bond in **3a** and **3b** than does chlorine may be explained by taking into account that chlorine is far more reactive than methyl hypochlorite.[14] Greater reactivity implies that the transition state preceding intermediates (**30** and **31**) for ionization of the π complex (**28, 29**) in chlorination would be attained "earlier"—before as much carbonium ion character has developed—than would be true for the reaction with methyl hypochlorite.

Additional evidence that both methyl hypochlorite and chlorine react by similar carbonium ion mechanisms is obtained by comparing the relative amounts of 1,2 and 1,4 chloromethoxy product obtained from each of the dienes. These data are summarized in Table II. These data show that attack on a particular bond in any one of the dienes by either chlorine or methyl hypochlorite yields similar ratios of chloromethoxy products. The obvious explanation is that both chlorine and methyl hypochlorite yield essentially identical cationic intermediates which give products by reaction with methanol. The site of attack in the ionic intermediates by methanol apparently corresponds to the positions where the positive charge is most stable. That is, in the ionic intermediates which would be obtained from attack on dienes **1, 2,** and **3a,b** (3,4 bond intermediate **31**), where the 1,4 adduct would arise from attack by methanol at a primary carbon, the main product is the 1,2 adduct (1,2/1,4 ratios vary from 2.3 to 6.5). In the case where the 1,4 adduct is obtained by attack by methanol on a secondary carbon atom (initial attack on the 1,2 bond in **3a,b,** intermediate **30**) it is formed in larger amount than the 1,2 adduct (1,2/1,4, 0.62–0.96).

Turning attention to the principal aim of our investigation which concerns bond reactivities in unsymmetrical dienes, the data presented above seem to indicate that reactivities of the bonds in a diene toward an electrophile can be predicted on the basis of the carbonium ion stability of the intermediates. This conclusion differs from that which Poutsma[10] developed from extensive studies on the reactivities of monoalkenes (mostly acyclic, aliphatic) toward chlorine in aprotic solvents. He found that alkene reactivity toward chlorine depends upon the basicity or nucleophilicity of the π bond rather than upon the stability of the expected carbonium ion; the basicity of the alkene is related to the degree of alkyl substitution on the double bond. For example, the nearly equivalent reactivity of 2-butene and isobutylene is explained by assuming that the transition state for reaction of chlorine with these alkenes is reactant-like rather than intermediate-like, so that the potential for greater carbonium ion stabilization with isobutylene (tertiary vs. secondary) is not evident in the transition state.

Concerning the dienes included in the study, isoprene (**2**) would be expected to show greater reactivity at the 1,2 bond both on the basis of alkene basicity and carbonium ion stability, but in the case of the 1,3-pentadienes (**3a,b**) there is not a clear choice. For example, Poutsma's data on chlorination shows the relative reactivities of 1-butene, *cis*-2-butene, and *trans*-2-butene to be 1:63:50, respectively. On this basis we might expect the relative reactivities of the double bonds in the 1,3-pentadienes to be 1:63:50 for reaction at the 1,2, the cis 3,4, and the trans 3,4 bonds, respectively. In fact we find the relative reactivities to be 1:0.22:0.015 for reaction with methyl hypochlorite and 1:0.69:0.12 for reaction with chlorine.[15] Clearly, the effect of methyl substitution in the 1,3-pentadiene system is quite the contrary to what would be predicted on the basis of the monoalkenes. Reactivity is found to be much greater at the nonsubstituted bond. As we have stated above, the relative reactivities of the bonds in **3a,b** seem to be best interpreted from the viewpoint that the transition state for chlorination of conjugated dienes is quite different from that for monoalkenes, and is one in which significant carbonium ion character is developed. Another point of interest is that the substituted (3,4) bond (**3a,b**) in the cis diene is much more reactive than in the trans diene.[15]

Finally, we would like to comment briefly on the radical addition of methyl hypochlorite to the dienes. A common characteristic of the radical reactions is that the 1,4 adduct is produced in much larger amounts than in the ionic additions. In additions to the unsymmetrical dienes the relative bond reactivities are appreciably different than for ionic reactions. The 1,3-pentadienes exhibit far more attack at the methyl-substituted (3,4) bond than is noted in ionic addition; e.g., for ionic additions of methyl hypochlorite to **3a** and **3b,** the 1,2:3,4 bond reactivities (Table II) are 4.6 and 65, respectively, whereas, the relative reactivities in radical addition are 1.13 and 0.72 for addition to **3a** and **3b,** respectively. The radical reaction of methyl hypochlorite with isoprene (**2**) shows less discrimination than the ionic reaction, in that appreciable attack (12%) at the 3,4 bond is observed in the radical reaction.

Experimental Section

General. Dienes and solvents were obtained commercially in high purity. Methyl hypochlorite was prepared as a solution in methylene chloride by a modification of the method used by Jenner to prepare *n*-butyl hypochlorite.[16] NMR spectra were obtained on a Varian T-60A spectrometer and ir spectra on Beckman IR-10 or Perkin-Elmer 337 spectrophotometers. VPC analysis of products from **1** and **3a,b** was done on a Hewlett-Packard 5750 flame ionization chromatograph and from **2** on an Aerograph 90 P-3 thermal conductivity instrument.

Reaction Conditions. Ionic reactions were done at 0–2°C in methanol which had been previously saturated with oxygen gas. The diene was present in 0.02 mol fraction with respect to the methanol. Methyl hypochlorite and chlorine were added as ca. 1 M solutions (in methylene chloride and carbon tetrachloride, respectively) in amounts sufficient to consume 25% of the diene. Reactions of **2** and **3a,b** with methyl hypochlorite required about 1 h for completion. The reaction of **1** with methyl hypochlorite was much slower (30% complete, 1 h; 80% complete, 18 h). After completion, reaction mixtures were poured into ice water and the products isolated by extraction with pentane.

Experiments were done which showed that the dichlorides and methoxy chlorides formed in the above reactions did not react with solvent under the conditions used. For example, a mixture of the dichlorides from **2** (**16** and **17**) was allowed to stand in methanol for 1 h at 0°C and then poured into ice water and extracted into pentane. The ratio of dichlorides was unchanged and methoxy chlorides were not formed. The same experiment performed with the dichlorides of **3a** (**8, 9, 10**) and with the methoxy chlorides of **3a** (**6a** and **7**) showed that these compounds were likewise uneffected by the reaction conditions.[17]

Radical reactions were done as follows: methyl hypochlorite (ca. 1 M solution in methylene chloride) sufficient to consume 10% of the diene was added to the diene (0.5 mol fraction in CCl_4) at 0–5°C (−5 to −10°C for **1**). Reactions had a tendency to show induction periods and to proceed exothermically with dienes **2** and **3a,b** and were completed when addition of hypochlorite was fin-

ished. With **1** the reaction was considerably slower (50% complete, 30 min) so sun-lamp irradiation was employed to hasten the reaction.

Analysis Procedures. Mixtures of products were analyzed by VPC with the following columns: column A, 2.5% β,β-oxydipropionitrile, on 80–100 Chromosorb W (AW-DMCS), 4 ft × 0.25 in, SS; column B, 2.5% SE-30 on 80–100 Chromosorb W (AW-DMCS). VPC analysis is based on ratios of normalized peak areas. Peak areas were normalized by obtaining VPC response factors for each of the isolated compounds. This was done by analysis of standard mixtures of the pure compounds with an internal standard (the same internal standards were used to obtain yields in reactions).

Identification of Isomers. Assignment of structures to the compounds reported below is based on interpretation of NMR and ir spectra and on certain rearrangement experiments. Most of the isomers are readily distinguished by NMR and ir because of differences such as the number or location of vinyl hydrogens but certain of the isomers differ only in the positions of chlorine atoms and methoxyl groups. Such pairs of isomers are the following: **5,7; 6a,b, 12a,b; 13,18; 14,19; 22,26.** Structural distinctions between these isomers were made on the following basis.

(1) On the assumption that the reactions in methanol, Cl_2, and CH_3OCl are ionic and that the reaction of methyl hypochlorite at high diene concentration is radical, it would be expected that Markownikoff adducts would result from the former (**6a,b, 13,** and **22**) and non-Markownikoff adducts from the latter (**12a,b, 18,** and **26**), since in the former reactions chlorine would be the electrophile and in the latter reaction the methoxyl radical would be the chain carrier. It is also reasonable that the 1,4 adduct resulting from ionic addition to **2** should be **14** rather than **19** since the only 1,2 adduct observed is **13** (resulting from attack at the 3,4 bond). It is not unexpected that radical addition to **2** should occur primarily via attack by the methoxyl radical on the 3,4 bond and therefore result in **19.** A similar argument could be made for the structure of the principal 1,4 adduct from **3b** under ionic conditions. Since the overwhelming 1,2 adduct (**6a**) results from attack at the 1,2 bond, it is highly unlikely that the major 1,4 adduct would result from attack at the 3,4 bond (thus forming **5**).

(2) It is known that methine protons bonded to carbons bearing chlorine exhibit larger downfield chemical shifts than protons bonded to carbons bearing methoxyl groups.[5] The pairs of isomers assigned structures **5,7** and **22,26** exhibited chemical shifts for methine hydrogens in accordance with this principle, i.e., **5,** δ 4.5, and **7,** 3.7; **22,** 3.72, and **26,** 4.35. Compound **20** exhibited the methine absorption at δ 4.38, in close agreement with that in **26.**

(3) Observations on rearrangement of isomers provided additional evidence for structural assignments. Solutions of **13, 18,** and **20** in carbon tetrachloride to which anhydrous zinc chloride had been added were kept at 50° for several hours and analyzed at various times by NMR. Compound **18** had rearranged about 80% after 2 h to mainly the 1,4-methoxy chloride, **19.** After 18 h **20** had rearranged about 60% to mainly **14** and some **21** but in the same time **13** was essentially unchanged. The allylic chlorides **18** and **20** would be expected to rearrange to the 1,4-methoxy chlorides **19** and **14,** respectively, whereas **13,** in which the chlorine is not allylic, should be much more stable. When a mixture of mainly **7** and **12** in carbon tetrachloride was treated with anhydrous zinc chloride and allowed to stand at room temperature for 2 h, **12** rearranged to **5** (observed by NMR). It was also observed that when separations of mixtures containing **5, 7,** and **12** were attempted by large scale preparative VPC, samples of either **5** or **12** always contained both isomers. For example, **5** could be obtained free of **7** (and pure samples of **7** were readily obtained) but always contained appreciable **12** dispite the order of retention times, **12** < **7** < **5.** Isomers **5** and **12** can be interconverted by allylic rearrangement of the chloride.

Products from Butadiene (1). Products from **1** were analyzed on VPC columns A and B. On column A (50°), retention times (min) follow: **24,** 2.2; **22,** 2.2; **26,** 2.7; **23,** 8.2; **25,** 12.6. On column B (35°, 11 ft × 0.125 in.): **24,** 4.5; **22** and **26,** 5.0. Dichlorides **24** and **25** are known compounds.[4a] Methoxy chlorides were isolated from large-scale reactions by distillation and preparative VPC.

Summary of NMR spectra (parts per million downfield from Me_4Si, CCl_4): **22,** 3.25 (s, 3, CH_3O), 3.42 (m, 2, CH_2), 3.72 (m, 1, $CHOCH_3$), 5.08–5.49 (m, 2, CH_2=CH), 5.79 (m, 1, CH_2=C**H**); **23,** 3.26 (s, 3, CH_3O), 3.76–4.10 (m, 4, CH_2Cl and CH_2OCH_3), 5.69–5.90 (m, 2, CH=CH); **26,** 3.34 (s, 3, CH_3O), 3.47 (m, 2, CH_2), 4.35 (m, 1, CHCl), 5.04–5.50 (m, 2, CH_2=CH), 5.90 (ddd, 1, CH_2=C**H**, J = 9.4, J' = 6.9, J'' = 16.0 Hz).

Infrared absorptions (cm^{-1}, CCl_4): **22,** 3085 (C=CH), 2830 (CH_3O), 1640 (C=C), 1116 (CH_3O), 989 and 934 (CH=CH_2 bending); **23,** 3020 (C=CH), 2830 (CH_3O), 1120 (CH_3O), 965 (trans CH=CH); **26,** 3090 (C=CH), 2830 (CH_3O), 1645 (C=C), 1126 (CH_3O), 984 and 930 (CH=CH_2 bending).

Products from Isoprene (2). Products from **2** were analyzed by VPC on column A (60°), which gave the following retention times (min): **15,** 2.2; **18,** 3.0; **16,** 3.5; **13,** 4.8; **20,** 5.3; **21,** 10.9; **19,** 12.7; **14,** 15.0; and **17,** 20.7. All of the products from **2** were isolated by distillation of large-scale preparations followed by preparative VPC (the most generally useful column was 5% Silicone DC-550 on 80–100 Chromosorb W, AW-DMCS, 6 ft × 0.37 in., glass). Dichlorides **16** and **17** and the monochloride **15** have been previously identified.[4b]

NMR spectra (CCl_4): **13,** 1.31 (s, 3, CH_3), 3.15 (s, 3, CH_3O), 3.38 (s, 2, CH_2), 5.30–5.40 (m, 2, C**H**$_2$=CH), 5.53–6.04 (m, 1, CH_2=C**H**); **14,** 1.75 (d, 3, CH_3, J = 1.0 Hz), 3.24 (s, 3, CH_3O), 3.88 (d, 2, C**H**$_2$OCH$_3$, J_{34} = 6.0 Hz), 3.93 (s, 2, CH_2Cl), 5.62 (dt, 1, CH=C, J_{34} = 6.0, J = 1.0 Hz); **18,** 1.62 (s, 3, CH_3), 3.37 (s, 3, CH_3O), 3.43 (s, 2, CH_2), 5.08 [dd, 1, cis CH=C(H)**H**, J = 9.8, J' = 1.3 Hz], 5.27 [dd, 1, trans CH=C(H)**H**, J = 16.4, J' = 1.3 Hz], 6.00 (dd, 1, C**H**=CH_2, J = 16.4, J' = 9.8 Hz); **19,** 1.72 (s, 3, CH_3), 3.25 (s, 3, CH_3O), 3.77 (s, 2, C**H**$_2$OCH$_3$), 4.05 (d, 2, CH_2Cl, J_{34} = 7.2 Hz), 5.65 (t, 1, CH=C, J_{34} = 7.2 Hz); **20,** 1.80 (dd, 3, CH_3, J = 1.4, J' = 0.8 Hz), 3.33 (s, 3, CH_3O), 3.53 (m, 2, C**H**$_2$OCH$_3$), 4.38 (t, 1, CHCl, J_{34} = 6.8 Hz), 4.90 [q, 1, C=C(H)**H**, J = 1.4 Hz], 5.03 [q, 1, C=C(**H**)H, J = 0.8 Hz]; **21,** 1.87 (dd, 3, CH_3, J = 1.6 Hz), 3.27 (s, 3, CH_3O), 3.93 (d, 2, C**H**$_2$OCH$_3$, J_{34} = 6.8 Hz), 4.03 (s, 2, CH_2Cl), 5.48 (dt, 1, CH=C, J_{34} = 6.8, J = 1.6 Hz).

Infrared spectra (CCl_4): **13,** 3085 (C=CH), 2830 (CH_3O), 1640 (C=C), 1106 (ether), 995, 931 (CH=CH_2 bending); **14,** 2825 (CH_3O), 1120 (ether); **18,** 3080 (C=CH), 2820 (CH_3O), 1112 (ether), 988, 926 (CH=CH_2 bending); **19,** 2820 (CH_3O), 1660 (C=C), 1112 (ether); **20,** 3080 (C=CH), 2820 (CH_3O), 1128 (ether), 909 (C=CH_2 bending); **21,** 2825 (CH_3O), 1105 (ether).

Products from the 1,3-Pentadienes (3a,b). Products from **3a,b** were analyzed by VPC on columns A and B. On column A (60°) retention times (min) follow: **4a** and **4b,** 1.5; **8,** 2.0; **6b,** 2.9; **6a,** 3.3; **9,** 3.3; **7,** 4.2; **12a** and **12b,** 4.2; **5,** 6.2; **10,** 8.3. On column B (18 ft, 70°): **9,** 8.2; **6a,** 8.9; on column B (6 ft, 32°), **11,** 8.0; **12a,** 12.8; **12b,** 14.0; **7,** 14.8. Dichlorides **8, 9,** and **10** were identified previously.[18] Except for compounds **12a** and **12b,** identifications were made on pure samples of the isolated compounds obtained by preparative VPC. Columns used for preparative VPC were 5% DEGS, 15 ft × 0.5 in., steel and 5% Silicone DC-550, 6 ft × 0.37 in., glass.

Pure samples of **12** were not obtained because of the similar VPC retention time to **7** and because some rearrangement of **12** to **5** always occurred under the conditions used for preparative VPC collection. Identification of **12** was made on mixtures of **12** with **5** and **7.** Identification is based on the rearrangement observations described above and on the following NMR observations. Methoxyl and methyl absorptions for **12** occur separately from those for **5** and **7.** Decoupling experiments on the mixtures of **12** (with **5** and **7**) showed that irradiation at δ 5.7 caused decoupling of the methyl doublet of **12,** confirming that the methyl group was bonded to the vinyl group. Decoupling of the methyl doublets of **5** and **7** was accomplished by irradiation of their methine regions (δ 4.5 and 3.7, respectively). Isomers **4a** and **4b** were isolated from ionic reactions of **3a** and **3b,** respectively, and were found to be uncontaminated with each other. Assignment of the threo structure to **4a** and the erythro structure to **4b** is made on the assumption that the stereospecific addition of chlorine and methoxyl would be anti. Compound **11** was isolated from the reaction of **3b** with methyl hypochlorite. It apparently contained comparable amounts of the erythro and threo isomers which are responsible for the two methyl doublets (NMR).

NMR spectra (CCl_4): **4a,** 1.38 (d, 3, CH_3, J_{45} = 6.4 Hz), 3.28 (s, 3, CH_3O), 3.58 (dd, 1, C**H**OCH$_3$, J_{34} = 5.0, J_{23} = 5.0 Hz), 3.95 (dq, 1, CHCl, J_{45} = 6.4, J_{34} = 5.0 Hz), 5.03–5.43 (m, 2, CH=C**H**$_2$), 5.52–6.10 (m, 1, C**H**=CH_2); **4b,** 1.45 (d, 3, CH_3, J_{45} = 6.5 Hz), 3.28 (s, 3, CH_3O), 3.50 (dd, 1, C**H**OCH$_3$, J_{34} = 5.3, J_{23} = 5.3 Hz), 3.85 (dq, 1, CHCl, J_{45} = 6.5, J_{34} = 5.3 Hz), 4.93–5.40 (m, 2, CH=C**H**$_2$), 5.50–6.07 (m, 1, C**H**=CH_2); **5,** 1.58 (d, 3, CH_3, J_{45} = 6.8 Hz), 3.25 (s, 3, CH_3O), 3.73–3.95 (m, 2, CH_2), 4.22–4.72 (m, 1, CHCl), 5.45–5.88 (m, 2, CH=CH); **6a,** 1.72 (dd, 3, CH_3, J_{12} = 7.0, J_{13} = 1.5 Hz), 3.23, (s, 3, CH_3O), 3.23 [dd, 1, C(**H**)H, $J_{55'}$ = 10.5, J_{45} = 6.2 Hz], 3.47 [dd, 1 C(H)**H**, $J_{55'}$ = 10.5, $J_{45'}$ = 6.2 Hz], 4.07 (ddd, 1, C**H**OCH$_3$, J_{34} = 8.5, J_{45} = 6.2, $J_{45'}$ = 6.2 Hz), 5.15 (q of dd, 1, CH_3C**H**=C**H**, J_{23} = 11.0, J_{34} = 8.5, J_{13} = 1.5 Hz), 5.73 (dq, 1,

$CH_3CH{=}CH$, J_{23} = 11.0, J_{12} = 7.0 Hz); **6b,** 1.75 (dd, 3, CH_3, J_{12} = 6.2, J_{13} = 1.2 Hz), 3.27 (s, 3, CH_3O), 3.30 [dd, 1, CH(H), $J_{55'}$ = 11.0, J_{54} = 6.0 Hz], 3.44 [dd, 1, CH(H), $J_{55'}$ = 11.0, $J_{5'4}$ = 6.0 Hz], 3.61 (ddd, 1, $CHOCH_3$, J_{34} = 7.2, J_{45} = 6.0, $J_{45'}$ = 6.0 Hz), 5.30 (ddd, 1, $CH_3CH{=}CH$, J_{23} = 15.5, J_{34} = 7.2, J_{13} = 1.2 Hz), 5.75 (dq, 1, $CH_3CH{=}CH$, J_{23} = 15.5, J_{12} = 6.2 Hz); **7,** 1.18 (d, 3, CH_3, J_{45} = 6.6 Hz), 3.18 (s, 3, CH_3O), 3.43–3.90 (m, 1, CHCl), 3.90–4.07 (m, 2, CH_2), 5.53–5.77 (m, 2, CH=CH); **11,** 1.15 (d, CH_3, J_{45} = 6.0 Hz), 1.18 (d, CH_3, J_{45} = 6.2 Hz), 3.37 (s, 3, CH_3O), 3.20–3.60 (m, 1, $CHOCH_3$), 4.07–4.50 (m, 1, CHCl), 5.07–5.50 (m, 2, $CH{=}CH_2$), 5.63–6.32 (m, 1, $CH{=}CH_2$); **12a,** 1.73 (d, CH_3, J_{12} = 5.0 Hz), 3.33 (s, CH_3O); **12b,** 1.75 (d, CH_3, J_{12} = 5.2 Hz), 3.32 (s, CH_3O).

Infrared spectra (cm^{-1}): **4a** (liquid film), 3070 (C=CH), 2810 (CH_3O), 1075 (ether), 920 and 980 ($CH{=}CH_2$ bending); **4b** (CCl_4), 3080 (C=CH), 2825 (CH_3O), 1640 (C=C), 1095 (ether), 933 and 999 ($CH{=}CH_2$ bending); **5** (liquid film), 2820 (CH_3O), 1120 (ether), 960 (trans CH=CH); **6a** (liquid film), 2825 (CH_3O), 1655 (C=C), 1100 (ether), 750 (cis CH=CH bending); **6b** (liquid film), 2825 (CH_3O), 1095 and 1110 (ether), 965 (trans CH=CH bending); **7** (liquid film), 2820 (CH_3O), 1113 and 1090 (ether), 966 (trans CH=CH bending); **11** (CCl_4), 3080 (C=CH), 2825 (CH_3O), 1100 (ether), 986 and 928 ($CH{=}CH_2$ bending).

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Registry No.—**1,** 106-99-0; **2,** 78-79-5; **3a,** 1574-41-0; **3b,** 2004-70-8; **4a,** 57512-99-9; **4b,** 57513-00-5; **5,** 57513-01-6; **6a,** 57513-02-7; **6b,** 57513-03-8; **7,** 57513-04-9; *erythro*-**11,** 57513-05-0; *threo*-**11,** 57513-06-1; **12a,** 57513-07-2; **12b,** 57513-08-3; **13,** 57513-09-4; **14,** 57513-10-7; **18,** 57513-11-8; **19,** 57513-12-9; **20,** 6986-42-1; **21,** 57513-13-0; **22,** 7795-90-6; **23,** 57513-14-1; **26,** 57513-15-2; methyl hypochlorite, 593-78-2; chlorine, 7782-50-5.

References and Notes

(1) E. g., see W. A. Pryor, "Free Radicals", McGraw-Hill, New York, N.Y., 1966, pp 120, 167.
(2) W. Oroshnik and R. A. Mallory [*J. Am. Chem. Soc.*, **72,** 4608(1950)] have studied reactions of isoprene with *tert*-butyl hypochlorite; C. Walling and R. T. Clark [*J. Org. Chem.*, **39,** 1962 (1974)] report the reaction of *tert*-butyl hypochlorite with alkenes in alcohol, catalyzed by boron trifluoride.
(3) The trans (*E*) structure is assigned to **14** and **19** and the cis structure to **21** on the following basis. (1) Electrophilic additions to dienes (radical and ionic) are known to yield predominantly trans rather than cis 1,4 adducts (e.g., chlorination of butadiene[4a] and isoprene[4b]). (2) the NMR absorptions due to the methyl groups in **14, 19,** and **21** are consistent with the general finding[5] that cis allylic methyl groups exhibit higher field absorptions (δ 1.75 for **14** vs. 1.87 for **21**) and larger allylic coupling constants (**14,** 1.0 Hz; **21,** 1.6 Hz; **19,** < 0.5 Hz) than do corresponding trans methyls.
(4) (a) M. L. Poutsma, *J. Org. Chem.*, **31,** 4167 (1966); (b) G. D. Jones, N. B. Tefertiller, C. F. Raley, and J. R. Runyon, *ibid.*, **33,** 2946 (1968).
(5) E.g., L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Elmsford, N.Y., 1969, pp 164, 225, and 316.
(6) We have completed a study on the reaction of methyl hypochlorite with styrene in the aprotic solvents, nitrobenzene and acetonitrile. A manuscript describing the results of this study will be submitted to this journal in the near future.
(7) Mechanism i and mechanism n would be examples of two classes of electrophilic addition mechanisms designated Ad_EC_1 and Ad_EC_2, respectively; e.g., see F. Garnier and J. Dubois, *Bull. Soc. Chim. Fr.*, 3797 (1968).
(8) In a recent report [*J. Am. Chem. Soc.*, **97,** 1977 (1975)] J. E. DuBois and M. F. Ruasse have concluded from kinetic evidence that the bromination of alkenes in protic, nucleophilic solvents involves no nucleophilic contribution by the solvent in the transition state and that these solvents effect the rate by stabilization of the bromide ion.
(9) Mechanisms in which the rate-determining step is a nucleophilic attack have recently been proposed for some electrophilic addition reactions, e.g., bromination by Br_3^- [J. E. Dubois and X. Q. Huynh, *Tetrahedron Lett.*, 3369 (1971)] and certain electrophilic additions to 3-*tert*-butylcyclohexene [G. Bellucci, G. Ingrasso, R. Marioni, E. Mastrarilli, and I. Marelli, *J. Org. Chem.*, **39,** 2562 (1974)].
(10) E.g., see M. L. Poutsma, *J. Am. Chem. Soc.*, **87,** 4285 (1965).
(11) It is unlikely that significant amounts of products resulting from attack at the 3,4 bond in **2** were overlooked. All peaks appearing in the VPC of the ionic reaction products were collected and examined carefully by NMR. No evidence for the presence of 4-chloro-3-methoxy-2-methylbutene could be found. A VPC peak with the retention time of the 1,4 adduct (**19**) was observed in the product from chlorination of **2** (in methanol) in a quantity equal to ca. 0.5% of the total product.
(12) It is conceivable that methyl hypochlorite could react in methanol via decomposition to chlorine. The fact that methyl hypochlorite exhibits different relative reactivities toward the double bonds than chlorine does, as well as the fact that significant quantities of dichlorides are not obtained with methyl hypochlorite, is evidence that decomposition to chlorine does not occur.
(13) A reviewer has suggested that regiospecificity in addition to these dienes may be governed by relative stabilities (and hence concentrations) of the π complexes, i.e., **28** and **29.** Although this could well be a factor in determining relative reactivities of the double bonds, we do not see how the importance of this factor could be determined separately from that of the rate-determining ionization step.
(14) Although we have no quantitative data on the comparison between the rates of reaction of chlorine and methyl hypochlorite, qualitative observations (see Experimental Section) indicate that they probably differ in rate by several orders of magnitude.
(15) We do not mean to imply that the 1,2 double bonds in **3a** and **3b** are of equal reactivity. There are little data available on the relative reactivities of conjugated dienes among themselves or in comparison to nonconjugated alkenes. We hope to explore this problem in the near future.
(16) E. L. Jenner, *J. Org. Chem.*, **27,** 1031 (1962).
(17) The dichlorides (particularly **17** and **10** with two allylic halogens) would be expected to solvolyze at rates comparable to the most reactive of the methoxy chlorides, i.e., those containing allylic chloride. Small amounts of solvolysis of the dichlorides would have been detected by the formation of the known methoxy chlorides. The fact that the ratio of **6a** and **7** did not change also confirms stability to solvolysis since **7** is an allylic chloride but **6a** is not.
(18) A paper describing the chlorination of **3a,b** has been accepted for publication in this journal.

Acid-Catalyzed Hydration of Dienes. III. Effects of Ring Strain on Rate, Enthalpy, and Entropy for Hydration of 1,3-Cycloalkadienes

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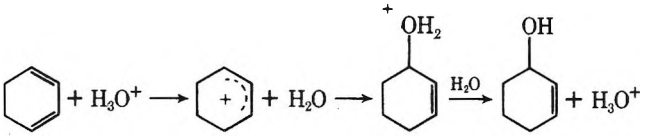
The effect of ring size on rate and equilibrium of hydration for 1,3-cycloalkadienes (C_5, C_6, C_7, C_8 dienes) in aqueous sulfuric acid is reported. Both rate and equilibrium changes are explained by 1,3-cycloalkadiene conjugative stabilization free energies; maximum estimates are 1.6, 0, 4.5, and 5.4 kcal mol^{-1} for C_5, C_6, C_7, and C_8 dienes, respectively. Maximum conjugative stabilization enthalpy is estimated at 2.5–3.5 kcal mol^{-1} for cyclooctadiene. Entropy changes augment enthalpy changes in rate differences, but compensate for enthalpy changes in equilibrium differences. An approximately linear inverse relationship between strain energy and log (rate of hydration) for olefins hydrating via a conjugated carbonium ion intermediate is reported; simple olefins fall orders of magnitude off the line. The solvent isotope effect for hydration of 1,3-cyclohexadiene is 2.2 (k_{H_2O}/k_{D_2O}). Conclusions reached are as follows. (1) Comparison of kinetic and/or equilibrium data obtained from reactions of alkenes with heats of hydrogenation is of dubious value, since entropy contributions do not necessarily parallel enthalpy contributions to free-energy changes. (2) A value of 3 kcal mol^{-1} seems a good estimate for conjugative stabilization enthalpy for 1,3-cyclooctadiene. The value for 1,3-cyclohexadiene appears near zero. Conjugative stabilization entropy is less certain, but may be comparable in size to enthalpy. (3) All data on olefin hydration may be accommodated by a single mechanism, provided conjugative interactions act to flatten the potential energy surface, giving rise to an "earlier" transition state.

In the first paper of this series[1] the mechanism of hydration of 1,3-cyclohexadiene in aqueous perchloric acid was elucidated. The simplest mechanism consistent with the evidence obtained was analogous to other alkene hydrations: rate-controlling proton transfer from hydronium ion to diene, producing a cyclic allylic carbonium ion which is rapidly attacked by water to produce product, 2-cyclohexenol (Scheme I).

Scheme I



In a recent study on conjugative interactions in cycloalkadienes it was concluded that 1,3-cyclohexadiene is rather different from the C_7 and C_8 analogues: 1,3-cyclohexadiene demonstrates little or no enhanced enthalpic stability attributable to conjugative stabilization arising from a 1,3 π system.[2] The present study compares reactions of 1,3-cycloalkadienes in aqueous sulfuric acid; our intent is to establish the effect of ring strain on rate-controlling proton transfer to olefinic carbon. If in fact there is little or no conjugative interaction in 1,3-cyclohexadiene relative to 1,3-cyclooctadiene or 1,3-cycloheptadiene, then considerable differences in rate should exist; it is important to establish the contribution of enthalpy and entropy to the free-energy difference.

Several previous studies are relevant: most recently it was observed that 1,3-cyclooctadien-2-yl triflate solvolyzes 3×10^3 faster than 1,3-cycloheptadien-2-yl triflate in 50% aqueous ethanol; presumably both reactions proceed via vinyl cationic intermediates.[3] This large difference in rate is not a strain effect per se, however, since cycloocten-1-yl triflate solvolyzes just ten times faster than cyclohepten-1-yl triflate[4] *and* cyclohepten-1-yl triflate solvolyzes at about the same rate as 1,3-cycloheptadien-2-yl triflate. Presumably the large difference of 3×10^3 arises from some allylic cation nature in the transition state of 1,3-cyclooctadien-2-yl triflate solvolysis, made possible by the greater flexibility of the larger eight-membered ring. A number of earlier reports examining the effect of ring strain on solvolysis rates have been reviewed,[5,6] based on pioneering work of Brown.[7] Typically, $C_4 < C_5 > C_6 < C_7 < C_8$, with overall rate changes of a few hundred (e.g., for cycloalkyl tosylates in acetic acid or aqueous ethanol, C_6:C_8 = 1:300).[5]

The effect of ring strain appears to be much smaller on electrophilic addition reactions than on solvolysis. This is of course a result of several factors: the limiting SN1 solvolyses just discussed involve changing a reactant state sp^3-hybridized carbon in a ring to a transition state hybridized carbon very nearly sp^2 in nature, whereas electrophilic additions involve changing a reactant state having two sp^2-hybridized carbons in a ring to a transition state having one of these carbons still sp^2 and the other intermediate between sp^2 and sp^3. For electrophilic additions (rate-controlling attack of electrophile) overall rate changes amount to about 10. For example, the acid-catalyzed hydration of 1-methylcyclopentene is about ten times faster than that of 1-methylcyclobutene;[8] 1,2-dihydrofuran is six times faster than 1,2-dihydropyran toward rate-controlling proton transfer (enol ether hydrolysis).[9] The BF_3 or $SnCl_4$ acid-catalyzed addition of acetic acid to cycloalkenes also shows small rate changes, overall about a factor of 2.5 (e.g., cycloheptene and cyclooctene are 2.5 and 2.0 times faster, respectively, than cyclopentene).[10] Although an attempt was made in this latter study to see if the effect was entropic or enthalpic in nature, the small rate changes masked any real differences in thermodynamic characteristics of the reactions. This latter point becomes more significant when it is realized that predicted orders are $C_4 > C_5 < C_6 > C_7 > C_8$, whereas these admittedly fragmented results are $C_4 < C_5 \geq C_6 > C_7 \leq C_8$. The tentative conclusion based on these reports of electrophilic addition reactions is that Brown's model of $sp^2 \rightarrow sp^3$ carbon within a ring[7] may be a poor one for reactions of cycloalkenes where at least one carbon within the ring retains sp^2 hybridization. Even accounting for possible "early" transition states, it is reasonable that rate-controlling attack of small electrophiles on cycloalkenes would relieve strain, although the net effect on reaction rate may be different from the case for reactions involving a change in ring carbon hybridization of all $sp^3 \rightarrow$ one sp^2 (solvolyses) or one $sp^2 \rightarrow$ all sp^3 (addition to carbonyl).

The results summarized above thus merit further study and we sought to attenuate the strain effect by studying

Table I
Values of k_{obsd} and Equilibrium Ratios ([Product]/[Reactant])[a]

	$10^4 k_{obsd}$, s^{-1}	[2-cycloalkenol]/[1,3-cycloalkadiene]	Temp., °C	$M_{H_2SO_4}$
	7.70	0.80	80	1.05
	2.34	3.43	50	1.05
	8.66	2.46	60	1.05
	25.0	2.65	70	1.05
	60.9 (40.9)[b]	2.56 (1.05)[b]	80	1.05
	311 (153)[b]	4.98 (2.57)[b]	80	2.56
	54.9	12.6	20	5.64
	148	13.7	30	5.64
	359	12.8	40	5.64
	0.140	1.39	80	1.05
	1.22	3.55	60	5.64
	2.90	4.29	70	5.64
	6.15	4.77	80	5.64

[a] Mean values measured at λ_{max} of 1,3-cycloalkadiene; average deviation of measurement $\leq \pm 5\%$. [b] Values in parentheses measured in D_2SO_4–D_2O.

rate-controlling electrophilic attack of the hydronium ion on 1,3-cycloalkadienes.

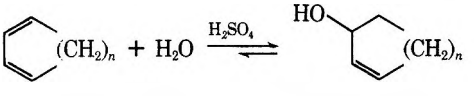
Experimental Section

Substrates were obtained from Aldrich Chemical Co. and were molecularly distilled prior to use. Deuteriosulfuric acid (99% D_2SO_4) and deuterium oxide (99.8%) were from Stohler Isotope Chemicals. Cyclopentadiene was obtained as the dimer and slow distillation of the monomer into ethanol yielded solutions of cyclopentadiene[11] which were stable for days at 0°; a fresh solution was prepared when the absorbance of cyclopentadiene (λ_{max} 238 nm)[12] in the stock solution decreased significantly. The general kinetic procedure is described elsewhere.[13]

Attempts to extend conditions (higher acidities and temperatures) reported in Table I for 1,3-cyclopentadiene and 1,3-cycloheptadiene failed because of the incursion of other, reactions: the kinetics were not pseudo-first-order but gave linear plots when treated as second order in 1,3-cycloalkadiene. Further discussion of these results is deferred to a time when reaction products can be characterized. *All* reaction conditions within Table I exhibited pseudo-first-order kinetics over 8–10 half-lives of reaction time reflecting clear hydration–dehydration; i.e., data reported in Table I are for eq 1.

Results

The reactions investigated are reversible and at equilibrium the product concentration is generally greater than that of reactant. Pseudo-first-order rate constants were ob-



1,3-cycloalkadiene 2-cycloalkenol (1)

tained in the traditional manner[1] by following decreasing absorbance at λ_{max} of cycloalkadiene; linear first-order kinetic plots were obtained for 3 half-lives (or longer) of reaction time. Rate constants and equilibrium ratios were calculated using equations below, as described elsewhere.[13]

$$\frac{[\text{2-cycloalkenol}]_e}{[\text{1,3-cycloalkadiene}]_e} = \frac{A_o - A_e}{A_e} \quad (2)$$

$$k_{obsd} = k_{hyd} + k_{dehyd} \quad (3)$$

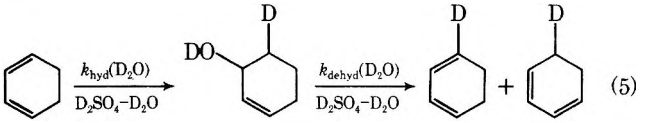
$$\frac{[\text{2-cycloalkenol}]_e}{[\text{1,3-cycloalkadiene}]_e} = \frac{k_{hyd}}{k_{dehyd}} \quad (4)$$

Table II
Solvent Isotope Effects on Hydration of 1,3-Cyclohexadiene in Aqueous Sulfuric Acid

$M_{H_2SO_4}$	$k_{hyd}(H_2O)/k_{hyd}(D_2O)$
1.05	2.1
2.56	2.3

In most instances the equilibrium ratio is considerably greater than unity and therefore k_{hyd} is more precisely defined than k_{dehyd} (i.e., k_{dehyd} is the small difference between the two larger rate constants, k_{obsd} and k_{hyd} in eq 3). As a result, this paper for the most part discusses effects of strain on rate constants for hydration, k_{hyd}.

Solvent Isotope Effect. k_{obsd} was determined in solutions of D_2SO_4 in D_2O. However, exchange of deuterium for hydrogen on the substrate occurs, since acid-catalyzed hydration is reversible to an appreciable extent. To ensure that k_{obsd} (D_2O) was measured prior to exchange becoming important, a computer program was developed[14] similar to the interative type provided by Wiberg.[15] Values of k_{obsd} (D_2O) so obtained were true constants over at least 2 half-lives of reaction time and are listed in Table I in parentheses. Values of A_e calculated by computer program were used to calculate the equilibrium ratio (eq 2). Rate and equilibrium measurements in D_2SO_4–D_2O, then, refer to the following reactions.



(5)

Ratios $k_{hyd}(H_2O)/k_{hyd}(D_2O)$ reflect both solvation and primary isotope effects,[16,17] whereas $k_{dehyd}(H_2O)/k_{dehyd}(D_2O)$ ratios reflect solvation and secondary isotope effects. The latter ratios cannot be discussed precisely because of their greater inherent error (eq 3 and 4 discussion); however, it is gratifying to note that they fall within 15–20% of unity, which is the magnitude expected for solvation plus secondary isotope effects for this type of reaction.[18] Solvent isotope effects given in Table II can thus be confidently discussed as isotope effects arising from solvation and primary isotope effects on the hydration of 1,3-cyclohexadiene in aqueous sulfuric acid. Regrettably, similar treatment of the data for 1,3-cyclocctadiene failed to yield separable constants: the equilibrium ratio under comparable conditions is much smaller for 1,3-cyclooctadiene, thus k_{dehyd} contributes much more to k_{obsd} (eq 3 and 4) and exchange of deuterium for hydrogen on the substrate becomes important within the first half-life of reaction time in D_2SO_4–D_2O. Qualitatively it can be said that the behavior of 1,3-cyclohexadiene in D_2SO_4–D_2O solutions is paralleled by the other cycloalkadienes studied; however, precise isotope effects could not be obtained in the latter cases and thus the value of $k_{hyd}(H_2O)/k_{hyd}(D_2O) \simeq 2$ for 1,3-cyclohexadiene is taken as typical of this class of alkene. This value is smaller than observed for styrene hydration (ca. 2–5)[18c] and larger than observed for isobutylene hydration (1.4).[19] Presumably the 1,3-cycloalkadienes are intermediate in kinetic basicity between styrenes and isobutylene; i.e., the extent of proton transfer in the transition state is intermediate.

Thermodynamic Parameters. Usual treatment of the dependence of k_{hyd} and equilibrium ratio on temperature affords $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and ΔH, ΔS, respectively.[13] Table III lists values resulting from a least-squares analysis of the data. Medium dependence of these quantities has been described[13] and in this paper comparison is made at the common acidity 5.64 M H_2SO_4. Medium effects can be safely

Table III
Effect of Ring Size on Hydration of 1,3-Cycloalkadienes

	k_{ref}[a]	$\Delta H^{\ddagger}$[b]	$\Delta S^{\ddagger}$[c]	$\left(\frac{[ROH]_e}{[D]_e}\right)_{rel}$	ΔH[e]	ΔS[f]
	200			1		
	2000	16.5	−12.9	3.2	0	5
	4			1.7		
	1	19.0	−20.6	(.25)	3.5	13

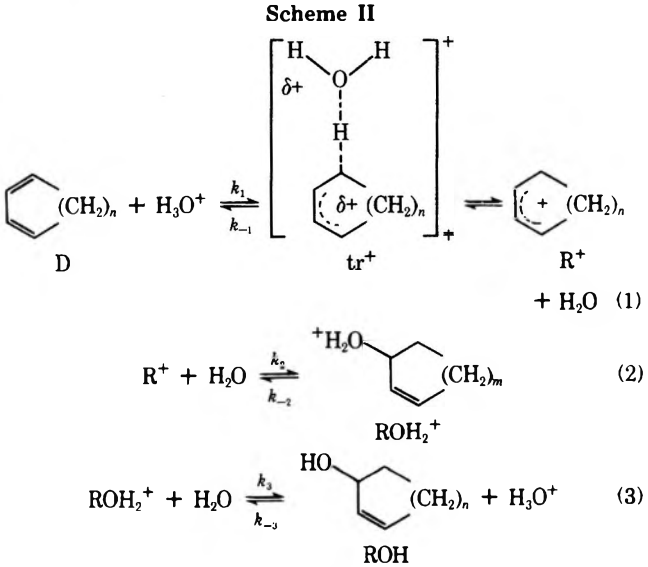
[a] Relative rates of hydration of 1,3-cycloalkadienes at 80° in 1.05 M H_2SO_4. Value for 1,3-cyclooctadiene is from data in ref 13 (extrapolation over 0.8 H_0 units). [b] Enthalpy of activation for hydration of 1,3-cycloalkadienes in 5.64 M H_2SO_4, kcal mol^{-1}. [c] Entropy of activation for hydration of 1,3-cycloalkadienes in 5.64 M H_2SO_4, cal deg^{-1} mol^{-1}. [d] Relative equilibrium ratios (eq 2, text) at 80° in 1.05 M H_2SO_4. Value for 1,3-cyclooctadiene is extrapolated from data in ref 13 in higher acidities; because of the nonlinear relationship between acidity and equilibrium ratio, this value is approximate [0.25 $\leq$ (value) $\leq$ 1]. [e] Enthalpy of hydration for 1,3-cycloalkadienes in 5.64 M H_2SO_4, kcal mol^{-1}. Calculated from the dependence of equilibrium ratio (eq 2, text) on temperature. [f] Entropy of hydration for 1,3-cycloalkadienes in 5.64 M H_2SO_4, cal deg^{-1} mol^{-1}. Calculated from the dependence of equilibrium ratios (eq 2, text) on temperature.

neglected when comparing thermodynamic data for C_6 and C_8 dienes;[13] the differences seen in Table III are thus due solely to effects of ring size.

Discussion

The mechanism of acid-catalyzed hydration of 1,3-cycloalkadienes is given in Scheme II, based largely on activation parameters, medium dependence, and solvent isotope effect.[1,13] Consistent with a solvent isotope effect of 2.2 (Table II) tr^+ is drawn showing significant, but not complete, proton transfer from hydronium ion to diene. The rate of hydration and the equilibrium ratio for hydration according to Scheme II are respectively

Scheme II



$$k_{hyd} = k_1 a_{H_3O^+} f_D / f_{tr^+} \quad (6)$$

$$[ROH]/[D] = \frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} a_w f_{ROH} / f_D \quad (7)$$

Table IV
Effect of Ring Size on Strain and Heats of Hydrogenation for 1,3-Cycloalkadienes

	Strain energy[a]	$-\Delta H_1$[b]	$-\Delta H_{total}$[c]
	0.8 (4.2)	24.0[21]	49.1[2,21]
	−1.2 (−0.3)	26.5[2,22]	53.6[2]
	1.4 (4.7)	24.1[2]	49.9[2]
	3.8 (5.2)	26.0[2]	49.0[2]

[a] Calculated by the method of ref 2, but anchored on the strain energies of cycloalkanes given by Eliel,[20] kcal mol^{-1}. Values in parentheses are strain energies of respective cycloalkenes, calculated in the same way. [b] Heat of hydrogenation of 1,3-cycloalkadiene to form cycloalkene, kcal mol^{-1}. [c] Heat of hydrogenation of 1,3-cycloalkadiene to form cycloalkane, kcal mol^{-1}. Value for 1,3-cyclopentadiene is corrected for acetic acid solvent effect; i.e., ΔH (given) = ΔH (gas phase) − 1.8, where 1.8 is the difference between the heats of hydrogenation of 1,3-cyclohexadiene in the gas phase and in acetic acid solution.[23]

Equation 7 is actually more complex than written because of significant concentrations of ROH_2^+ in acidities greater than 4–5 M H_2SO_4. This problem is discussed elsewhere[13] and for the present purpose no advantage exists in needlessly complicating eq 7: data to be discussed are in 1 or 5.6 M H_2SO_4, only in the latter case would protonation of ROH be significant, and even so it is almost certain that 2-cycloalkenols are similar in basicity (i.e., pK_a of ROH_2^+ is similar for 2-cyclohexenol and 2-cyclooctenol). Since (a) protonation of ROH is minor (i.e., [ROH] > [ROH_2^+] in acidities of this study) and (b) effects of protonation of ROH are likely to be similar for the 2-cycloalkenols (i.e., pK_a ROH_2^+ is not likely to depend significantly on ring size), equilibrium data will be discussed according to eq 7.

Table IV summarizes literature data relevant to strain in 1,3-cycloalkadienes, based solely on heats of hydrogenation and combustion. Equations 6 and 7 can be related to data in Table III only insofar as enthalpic and entropic contributions to free-energy changes can be separated. Table III summarizes data from the present study which afford such separation. We now wish to discuss effects of n = 1, 2, 3, or 4 (Scheme II) on rates of hydration (eq 6) and hydration equilibrium ratio (eq 7) emphasizing enthalpy (in comparison to Table IV data) and entropy terms.

Strain Effects on Rate. In Table IV, ΔH_1 is a measure of the relative enthalpic strain released on changing from four sp^2-hybridized carbon atoms to two in a carbocyclic ring. Clearly the changes in ΔH_1 with ring size do not parallel changes in relative rate recorded in Table III; strikingly, ΔH_1 is nearly the same (ca. 26 kcal mol^{-1}) for the two dienes differing in rate by >10^3. ΔH_{tot} is a measure of the strain released on changing from four sp^2-hybridized carbon atoms to all sp^3 in a carbocyclic ring. The kinetic data do not follow changes in ΔH_{tot} either. Close comparison of ΔH_1 and ΔH_{tot} *vs.* k_{rel} indicate that the greater the heat of hydrogenation, the faster hydration proceeds; i.e., k_{rel} appears to be related to total strain within diene. Strain energies have been calculated several ways for cycloalkanes and cycloalkenes; we have chosen to calculate strain energies for 1,3-cycloalkadienes in a manner consistent with Doering's recent study.[2] Clearly k_{rel} changes with ring size as strain energies do; the greater the strain energy, the *slower*

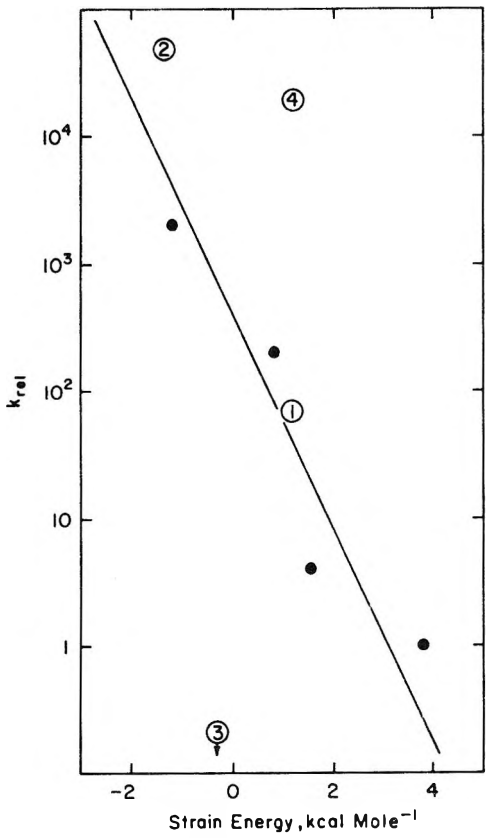


Figure 1. Plot of k_{rel} *vs.* strain energy (Tables III and IV) for 1,3-cycloalkadienes, slope −0.9. Points 1 and 2 are points for styrene[1] and 2-phenylpropene,[1] calculated on the same basis as 1,3-cycloalkadienes (see text), although the heat of hydrogenation[40] on which the strain energy of 2-phenylpropene is based was obtained in a different fashion and that point is not as precisely defined.[23] Point 3 represents the upper limit for cyclohexene hydration.[13] Point 4 is the point for 2,3-dimethyl-2-butene,[1] calculated on the same basis as 1,3-cycloalkadienes (see text) except the total strain was increased by 2 kcal mol^{-1} to help account for strain associated with methyl–methyl interactions in 2,3-dimethylbutane.

hydration proceeds. In fact, considering reasonable errors in values of ΔH used to calculate strain energies (±0.5 kcal mol^{-1} overall), the correlation is surprisingly linear with slope of −0.9 (Figure 1). The significance of this correlation is somewhat clouded by the uncertainty and interrelativity of strain energies; however, the correlation is real. Use of strain energies calculated by the single conformation increment provided by Schleyer[24] gives a plot at least as linear, but of slope −1.3. An interesting observation deserves mention. We have measured the hydration of styrene and 1,3-cyclohexadiene under comparable conditions in aqueous perchloric acid:[1] assuming the rate *difference* between these two compounds to be the same in 2.57 M $HClO_4$ at 50° as in 1.05 M H_2SO_4 at 80° (a reasonable assumption since $\Delta H^{\ddagger}$ values are nearly equal[1] and *differences* in $\Delta H^{\ddagger}$ do not seem to be very dependent on acidity[13]), styrene plots equally well on the line of Figure 1 as the cycloalkadienes. The strain energy for styrene (1.2) was calculated based on strain = 0 for ethylbenzene and heat of hydrogenation 28.6.[28] Similar calculations–extrapolations for 2,3-dimethylbutene and cyclohexene hydration gave points many orders of magnitude off the line in Figure 1. It is probably *not* coincidence that reactions proceeding via conjugated carbonium ions plot on the line and others do not. Data are much too scarce to allow more than just a report of this intriguing observation.

It is interesting that the rate order observed for hydration of 1,3-cycloalkadienes ($C_5 < C_6 > C_7 > C_8$) is exactly the same as for additions to cycloalkanones;[7] however, this order would not have been predicted based on consideration of strain energies and/or heats of hydrogenation using reasoning advanced in earlier studies.[6-8] That is, the fastest reacting diene ought to be the one undergoing the most favorable change in strain energy: using cycloalkadiene → cycloalkene as a model, column 1 of Table IV predicts the order $C_6 \geq C_8 > C_7 \sim C_5$. Thus our observed correlation between 1,3-cycloalkadiene strain energy and rate of hydration requires further analysis: it appears formally that tr^+ is more highly strained than diene, by an amount nearly proportional to the diene strain energy. The correlation may result from the following: (1) both rate and strain may be related to a common variable (e.g., conjugative interaction); (2) ring strain is enthalpic, entropy changes may override enthalpy giving rise to observed rate order; (3) a fortuitous interrelating of several factors (e.g., 1 and 2), which may themselves not be independent of each other, giving rise to what is in fact an artifact; (4) the model cycloalkadiene → cycloalkene may be inappropriate (certainly 2-methyl-1,3-cycloalkadiene → 3-methylenecycloalkene would be a useful model, but data are unavailable).

The term ring strain as applied to hydration of 1,3-cycloalkadienes is a composite of angle strain, eclipsing, and crowding interactions, part or all of which may be offset by conjugative interactions of the π system. These quantities have been amply defined by others,[2,24,25] but the present study affords a new and sensitive probe into their interrelationships. Supporting the importance of conjugative interaction (or lack of it in C_5 and C_6 cycloalkadienes) is that the rate difference we observe (overall $>10^3$) is at least an order of magnitude greater than that observed in other studies, *except* for a recent solvolysis study where conjugative stabilization was evident for C_8 ring dienyl cation but not for C_7.[3] In fact, other studies involving electrophilic attack on cycloalkenes[8-10] exhibited rate differences (overall) of <10. We see no other way to explain rate-controlling proton transfer to 1,3-cyclohexadiene being 2×10^3 faster than 1,3-cyclooctadiene except by invoking large differences in conjugative stabilization of the dienes.

It was observed above that our rate order parallels Brown's but that the order would not have been predicted based on similar consideration of strain energies and/or heats of hydrogenation. The reason lies in the overriding importance of the conjugative effect, both in reactant *and* transition states. Our discussion must be moderated by the rather ill-defined nature of the transition state, although for hydration of alkenes it is known to resemble a carbonium ion[1,13,18,19] (that is, tr^+ in Scheme II has considerable C–H bond formation and associated positive charge on carbon). The relative rates in Table III can be explained by differences in conjugative interaction in reactant states, augmented or moderated by associated changes in angle and/or eclipsing strain on going from diene to tr^+. Conjugative interaction in tr^+ is assumed to be comparable for C_5–C_8, and cycloalkenes are assumed to be good models for angle and/or eclipsing strain in tr^+ (column 1, Table III). Thus the summary below.

1,3-Cyclohexadiene: conjugative interaction is minimal (or nonexistent)[2] in diene; angle and eclipsing strain may be eased somewhat in tr^+.

1,3-Cyclopentadiene: conjugative interaction is minimal in diene; angle and/or eclipsing strain may be increased in tr^+.

1,3-Cycloheptadiene and 1,3-cyclooctadiene: considerable conjugative interaction ($C_8 > C_7$), angle and/or eclipsing strain is probably eased in tr^+.

Precedent for 1,3-cyclopentadiene conjugative interac-

tion is lacking; the factor of 10 observed ($C_5 < C_6$) could be due either to increased strain in tr^+ or to slightly greater conjugative interaction in C_5 diene than C_6. If the latter is true, the order of conjugative stabilization in 1,3-cycloalkadienes is $C_8 > C_7 > C_5 > C_6$. Assuming (a) zero conjugative stabilization for 1,3-cyclohexadiene[2] and (b) that differences in rate observed reflect differences *primarily* in conjugative interaction in dienes, produces the following maximum estimates of conjugative stabilization in 1,3-cycloalkadienes: 1,3-cyclopentadiene, 1.6 kcal mol^{-1}; 1,3-cyclohexadiene, 0 kcal mol^{-1}; 1,3-cycloheptadiene, 4.5 kcal mol^{-1}; 1,3-cyclooctadiene, 5.4 kcal mol^{-1}. These values, of course, are free energies of conjugative stabilization and may be greater or lesser than those calculated from enthalpy measurements, depending on entropy contributions. For 1,3-cyclooctadiene,[2] conjugative stabilization enthalpy has been estimated as about equal to that for 1,3-butadiene,[26] 3.6 kcal mol^{-1}. From Table III, the enthalpy estimate is 2.5 kcal mol^{-1}, in good agreement considering assumptions built into our calculation of conjugative stabilization energies.

Of considerable interest is the finding that only about *half* of the rate difference lies in the enthalpy term. The preceding discussion correlated free-energy differences (or relative rates) with known enthalpy differences because of the common effect of conjugative stabilization. Now, however, it has been demonstrated that enthalpy accounts for slightly less than half the free-energy difference. This means that relative rate data will not correlate with strain effects *unless* entropy changes parallel enthalpy changes (or happen to be negligible). The entropy of activation for hydration of 1,3-cyclohexadiene (−12.9 eu) is typical for olefin hydration, considering medium effects;[13] entropy of activation for a variety of olefins appears rather insensitive to relative changes in tr^+ (e.g., extent of proton transfer).[1] The entropy of activation for hydration of 1,3-cyclooctadiene thus appears "too negative" by about 8 eu. Knowing that (a) 1,3-cyclohexadiene is more nearly planar[27-29] than 1,3-cyclooctadiene,[2,30] (b) $\Delta S^{\ddagger}$ is relatively insensitive to changes in tr^+ arising from reasonably small differences in degree of proton transfer,[1] it can be concluded that the 8 eu arises from a transition state more nearly planar about sp^2-hybridized carbons than is the 1,3-cycloalkadiene (which is consistent with the inverse correlation of rate with strain). Thus, relative to 1,3-cyclohexadiene, 1,3-cyclooctadiene has greater conjugative stability (by ~4–5 kcal mol^{-1}), π–π dihedral bond[30] angle of ~30° (~15° for 1,3-cyclohexadiene),[28] and overall "loses" 8 eu on → tr^+. It is rather clear that 1,3-cyclohexadiene must be a much less flexible molecule than 1,3-cyclooctadiene, otherwise it (C_6) would achieve the conformation allowing significant π–π interaction, calling for ~30° π–π dihedral bond angle such as found in 1,3-cyclooctadiene. While the size (8 eu) seems rather large to be attributed solely to such an effect, our experimental error (±1–2 eu) does not justify further elaboration.

Strain Effects on Equilibrium. Enthalpic data in Table IV do not explain or correlate with the experimentally observed order of the equilibrium ratios in Table III. This is because of near cancellation of ΔH changes by ΔS. For example, the 3.5 kcal mol^{-1} enthalpy barrier for 1,3-cyclooctadiene relative to 1,3-cyclohexadiene is nearly cancelled by 2.8 kcal mol^{-1} (at 80°) entropy contribution. Presumably the other dienes exhibit comparable (but not equal) effects. The 3.5 kcal mol^{-1} enthalpy difference is close to the 3.6 kcal mol^{-1} conjugative stabilization enthalpy estimated earlier.[2] *However*, equilibrium ratios do not reflect this large difference because of compensating entropy contributions to free-energy differences. Differences in ΔH are thus explained totally on the basis of relative conjugative stabilization of 1,3-cycloalkadiene relative to 2-cycloalkenol.

Entropy differences (ΔS) between hydration of 1,3-cyclohexadiene and 1,3-cyclooctadiene probably reflect greater C_8 ring flexibility for diene → ene relative to C_6. Unfortunately, free-energy (and thus ΔS) data are not available from hydrogenation studies of 1,3-cycloalkadiene → cycloalkene; however, it is known that ΔS changes contribute significantly to free energies of hydrogenation.[31]

Though acyclic diene hydration would be of interest, our data indicate that studies of conjugated diene hydration are only possible insofar as mechanistic implications are possible from studies of 2-alkenol dehydration. That is, 1,3-cyclohexadiene is favorably hydrated because of lack of conjugative stabilization of diene, and 1,3-cyclooctadiene is hydrated measurably (but less than C_6) largely because of the large inherent strain[2] in the diene which partially compensates for conjugative stabilization.

Mechanistic Implications. Table V lists some intriguing relative rate data: replacing hydrogen by phenyl increases the rate of hydration by about the same amount as replacement by methyl (e.g., α-methylstyrene rate ~ isobutylene rate). Propenes and styrenes hydrate via carbonium ions and the reactions are subject to considerable substituent effects, ρ_m[33] ~ ρ_+[18] ~ ρ^*[34] = −(3–4). However, it has long been known that in limiting SN1 solvolyses, the rate enhancement of phenyl is comparable to *two* methyl groups.[35] This means that *phenyl* activates an alkyl halide much more than methyl toward a reaction proceeding via a carbonium ion, while *methyl* activates an alkene slightly more than phenyl toward a reaction proceeding via a carbonium ion. This rate effect is largely enthalpic (Table V) and is easily attributable to conjugative stabilization of the reactant state. The rate difference translates to about 5 kcal mol^{-1} at 25°,[36] which represents the maximum conjugative stabilization free energy for phenyl with an ethylenic group. In general terms, the similar reactivity of propene and styrene are probably not so much due to a less than expected stabilization of the transition state by phenyl (e.g., "early transition state") as to a conjugative stabilization of the reactant state. *However*, a simple application of the Hammond postulate[37] would lead to the conclusion that

Table V
Relative Rates of Hydration of Selected Alkenes[a]

Alkene	k_{rel}	$\Delta H^{\ddagger}$	Ref
	3×10^3	20.0	1
	1.3×10^3		32
	8×10^2	19.9	1, 32
	30	22.8	1
	1	24.2	1
	10^{-1}		32

[a] Rates from data in ref 33 normalized to conditions of ref 1, using mutually listed data for styrene and α-methylstyrene: 2.5 M $HClO_4$ and 30°.

the transition states for styrene hydrations occur comparable (e.g., α-methylstyrene) to or later (e.g., styrene) than for isobutylene and tetramethylethylene hydrations. This is contradictory to observed solvent isotope effects and general catalysis experiments: $k_{H_2O}/k_{D_2O} = 1.4$ for isobutylene hydration,[19] $k_{H_2O}/k_{D_2O} = 2$–4 for styrene hydrations[18] and general acid catalysis is easily observable for hydration of styrenes ($\alpha \simeq 0.8$),[18] but not for isobutylene[19,38] or tetramethylethylene. Thus the Hammond postulate suggests an earlier transition state for isobutylene and tetramethylethylene hydrations, whereas experimental data show that the reverse must be true. That is, both the low solvent isotope effect ($k_{H_2O}/k_{D_2O} = 1.4$) and the lack of observation of general catalysis ($\alpha = 0.85$, based on experiments in H_2O–D_2O mixtures)[19] indicate that proton transfer is nearly complete in the transition state for hydration of aliphatic alkenes. *However*, the above simple application of the Hammond postulate ignores a very basic assumption implicit in the postulate: not only must the reactant and intermediate states be considerably different in energy (certainly true for olefin hydration), *but* the general *shape* of the energy surface must not change. There are three ways in which the data for alkene hydration can be accommodated based on the two-dimensional energy surface describing proton transfer from acid, HA, to alkene. (1) The reactant state energy well may be broadened for aliphatic alkenes relative to conjugated alkenes. (2) The carbonium ion state energy well may be broadened for conjugated alkenes relative to aliphatic alkenes. (3) The shapes of the energy wells may be similar, but the energy maximum for conjugated alkenes may be truncated relative to that for aliphatic alkenes. Perhaps this rather complex situation is best viewed as resulting from the greater polarizability of conjugated π systems, resulting in a gradual flattening of the potential energy surface as the proton is in the intermediate stages of transfer. Thus contributions from 1 and 2 may be important, but perhaps the end result appears much as 3.

Thus the major role played by conjugative stabilization in diene hydration justifies differences in potential energy surfaces for simple alkene hydration and hydration of conjugated alkenes. This in turn accommodates all evidence accumulated to date on alkene hydration.

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Registry No.—1,3-Cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4; 1,3-cycloheptadiene, 4054-38-0; 1,3-cyclooctadiene, 1700-10-3; 2-cyclopentenol, 3212-60-0; 2-cyclohexenol, 822-67-3; 2-cycloheptenol, 4096-38-2; 2-cyclooctenol, 3212-75-7.

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gem-Diferrocenylalkane Derivatives. Acid-Catalyzed Condensation of Ferrocene with Methyl Levulinate and 5-Hydroxy-2-pentanone

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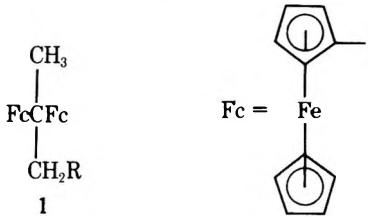
Ferrocene has been condensed with methyl levulinate in polyphosphoric acid to yield 4,4-diferrocenylpentanoate (**3**, 67% on reacted ferrocene), methyl 4-ferrocenylpentanoate (**5**, 1%) and 1,1′-bis[2-(2-ferrocenyl-4-carbomethoxy)butyl]ferrocene (**6**, 2%). Ferrocene condensed with 5-hydroxy-2-pentanone with trifluoroacetic acid catalyst to yield 4,4-diferrocenyl-1-pentanol (**6**, 70%), also prepared by lithium aluminum hydride reduction of ester **3**. Several 1-substituted 3,3-diferrocenylbutanes were synthesized in high yield including 4,4-diferrocenylpentanoic acid and 3,3-diferrocenylbutyl isocyanate. Proton and ^{13}C nuclear magnetic resonance spectra of new compounds are discussed in relation to structure.

The acid-catalyzed condensation of ferrocene with aldehydes and ketones is complex and leads to several types of compounds.[1-10] In the present study a convenient synthesis was sought for diferrocenylmethane derivatives **1**, in

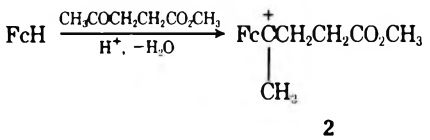


1

which R contains a reactive functional group. The acid-catalyzed ferrocene–ketone condensation, although presenting a potentially simple route to **1**, suffers the major disadvantage of providing very low yields under known reaction conditions. A major side reaction defeating the synthesis of **1** is the aldol self-condensation of reactant ketone, particularly under more vigorous conditions. The only reported synthesis of this type is the condensation of ferrocene with acetone (boron trifluoride, 25°) to produce 2,2-diferrocenylpropane (9% conversion, 31% yield based on reacted ferrocene).[1] Other ketones studied failed to produce diferrocenylmethane derivatives under a variety of conditions.[1,8,9]

This report describes reaction conditions for the acid-catalyzed condensation of ferrocene with methyl levulinate[11] and 5-hydroxy-2-pentanone providing good yields of the desired diferrocenylmethane derivatives. Few alternate methods of synthesis of *gem*-diferrocenylalkanes are available. No other synthetic routes are known leading to alkanes with *gem*-diferrocenyl substitution on quaternary carbon. 1,1-Diferrocenylethane is formed by reaction of ferrocene with 1,2-dichloroethane (aluminum chloride catalyst).[12]

A study was made of the condensation of ferrocene with levulinic acid and methyl levulinate employing polyphosphoric, phosphoric, sulfuric, and trifluoroacetic acid catalysts. Slow addition of an excess of methyl levulinate to ferrocene and polyphosphoric acid at temperatures below 80° favors a high conversion of ferrocene to methyl 4,4-diferrocenylpentanoate (**3**, 40% conversion, 67% yield based on reacted ferrocene). Methanol and cyclohexane in the reaction mixture speed the reaction and increase the yield of **3**.



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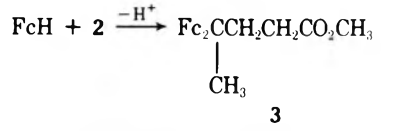
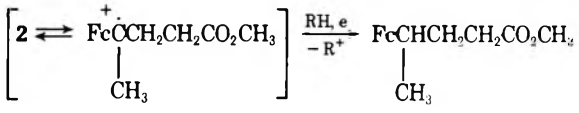


3

Substitution of sulfuric for polyphosphoric acid catalyst resulted in good yields of **3** but some ferrocene oxidation and much tar formation resulted. Trifluoroacetic acid alone failed to effect condensation of ferrocene with methyl levulinate or levulinic acid. Phosphoric, polyphosphoric, and trifluoroacetic acids have not been employed previously as catalysts in ferrocene–ketone or aldehyde condensations.[1-10]

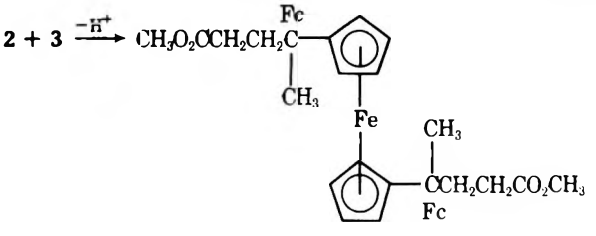
In addition to ester **3**, the condensation of ferrocene with methyl levulinate produced other esters. Two of these were isolated in a pure state. Liquid methyl 4-ferrocenylpentanoate (**5**) was obtained by distillation under reduced pressure (ca. 1% yield).



4 **5**

This 1:1 condensation product is believed to arise from **2** or a radical cation intermediate (**4**) by hydride transfer.[4,13] The identity of the reducing agent RH is unknown. The formation of **5** is favored by use of a large excess of methyl levulinate and its slow addition to the reaction mixture.

Separation of the ferrocene–methyl levulinate condensation products by dry-column chromatography permitted isolation of higher molecular weight esters. One of these (**6**) was obtained in crystalline form (mp 140–142°, 2% yield).



6

The formation of **6** is favored by use of a 1:1 molar ratio of ferrocene to methyl levulinate and by rapid addition of the methyl levulinate to the reaction mixture. Molecular formula and spectral data support the structure 1,1′-bis[2-ferrocenyl-4-carbomethoxy)butyl]ferrocene. The ^{13}C NMR spectrum reveals two narrowly separated ferrocenyl-substituted C-1 carbon signals (δ 99.69, 99.35) in agreement with a 1,1′-disubstituted ferrocene structure. The splitting

(0.3–0.4 ppm) of the ^{13}C NMR signals of the α (C-2 and C-5) carbon atoms of the cyclopentadienyl rings which are attached to chiral substituents is in agreement with observations of other workers.[14,15] Unresolved mixtures of oligomers related to 6 ($CH_2CH_2CO_2CH_3$ = CH_3; 1–7 monomer units) have been prepared from ferrocene and acetone (aluminum chloride catalyst).[9]

The condensation of ferrocene with 5-hydroxy-2-pentanone was effected in methylene chloride solvent with trifluoroacetic acid catalyst at ambient temperature to afford 4,4-diferrocenyl-1-pentanol (7, 44% conversion, 70% yield

$$2FcH + CH_3COCH_2CH_2CH_2OH \xrightarrow[-H_2O]{CF_3CO_2H,\ CH_2Cl_2} Fc_2CCH_2CH_2CH_2OH \xrightarrow[THF]{LiAlH_4} 3$$

(Fc = ferrocenyl; $Fc_2CCH_2CH_2CH_2OH$ bears a CH_3 substituent)

7

based on reacted ferrocene). As noted above, this procedure failed to produce ester 3 by condensation of methyl levulinate or levulinic acid with ferrocene under the same conditions. Alcohol 7 was also prepared by lithium aluminum hydride reduction of ester 3 in tetrahydrofuran solvent (94% yield).

4,4-Diferrocenylbutyl isocyanate and other derivatives of methyl 4,4-diferrocenylpentanoate (3) were prepared (8–12). Two methods of synthesis of isocyanate 11 were inves-

$Fc_2CCH_2CH_2X$ (CH_3)

8, X = CO_2H; 9, COCl; 10, CON_3; 11, NCO; 12, $CONHNH_2$

tigated. The best one proceeds from 4,4-diferrocenylpentanoic acid (8) in three steps (75–80% overall yield from ester 3).

Saponification of ester 3 gave 4,4-diferrocenylpentanoic acid (8) in quantitative yield. Acid chloride 9 (prepared in 97% yield) is unstable to heat and rapidly polymerizes, exothermically, with evolution of hydrogen chloride at 100–130°.[16] Its reaction with sodium azide occurs rapidly in aqueous tetrahydrofuran at 0–5° leading to acyl azide 10. In contrast to ferrocenoyl azide, acyl azide 10 is rather unstable.[17] In benzene solution azide 10 has a half-life of ca. 14 h at 25°. This stability is sufficient to permit rapid extraction of the crude azide with aqueous base to remove any 4,4-diferrocenylpentanoic acid impurity. The pure acyl azide 10 is converted in 90–98% yield into 3,3-diferrocenylbutyl isocyanate (11).

Carboxylic acids react with isocyanates to form relatively unstable carboxylic carbamic acid anhydrides.[18–21] Failure to remove 4,4-diferrocenylpentanoic acid from the reaction mixture after formation of the acyl azide results in reaction with isocyanate 11 as it forms to produce anhydride 13, characterized by a strong carbonyl doublet at 1770, 1740 cm^{-1}. The anhydride is cleaved rapidly by reaction with aqueous sodium hydroxide solution at 25°, regenerating the acid (after acidification of the salt) and the isocyanate.

$$8 + 9 \xrightarrow[\text{2. } H^+]{C_6H_6,\ 25^\circ;\ \text{1. NaOH}} Fc_2CCH_2CH_2CO_2CONHCH_2CH_2CFc_2$$

(CH_3 on each Fc)

13

A second route to 3,3-diferrocenylbutyl isocyanate (11) was investigated departing from 4,4-diferrocenylpentanohydrazide (12). Treatment of hydrazide 12 with nitrous acid in acidified aqueous tetrahydrofuran leads to acyl azide 10 (not isolated), which rearranges to the isocyanate in benzene solution. 3,3-Diferrocenylbutyl isocyanate reacts with water to produce *N,N'*-bis(3,3-diferrocenylbutyl)urea, with aniline to form *N*-(3,3-diferrocenylbutyl)-*N'*-phenylurea, and with methanol to form its methyl urethan derivative.

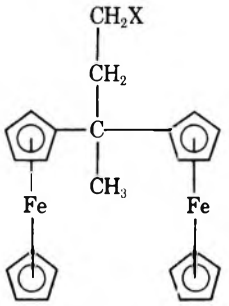
Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 137, ^1H NMR spectra on a Varian A-60 or XL-100, and ^{13}C NMR spectra on a Varian XL-100 spectrometer with Transform Technology TT-100 pulsed Fourier transform system. ^1H and ^{13}C chemical shift measurements were determined at ca. 30° and are referenced to tetramethylsilane internal standard. Melting points were determined on a Kofler hot stage and are corrected. Elemental analyses and molecular weights were determined by Galbraith Laboratories, Knoxville, Tenn.

Methyl 4,4-Diferrocenylpentanoate (3). Polyphosphoric acid was prepared by slowly adding phosphoric anhydride (125 g) to 85% phosphoric acid (125 g), followed by warming on the steam bath, with stirring, to obtain a solution. Methanol (140 ml) was added dropwise, with stirring, to the cooled acid and 150 ml of cyclohexane contained in a three-necked flask equipped with a constant-rate addition funnel, condenser, stirrer, thermometer, and nitrogen inlet, keeping the temperature below 60°. Ferrocene (93.0 g, 0.5 mol) was introduced into the flask all at once and the stirred mixture heated in an oil bath maintained at 98–100° throughout the reaction. Methyl levulinate[22,23] (97.5 g, 0.75 mol) was added dropwise with vigorous stirring during 24 h; ca. 0.2 mol was added during the first 2 h and the remainder at a constant rate until all added; temperature 76–78° within the mixture throughout the reaction. After cooling to 25°, the mixture was stirred with 100 ml each of water and benzene. The deep-orange upper layer was separated from the dark-green lower layer which was extracted twice with benzene. The combined organic solutions were washed successively with water, 10% aqueous sodium hydroxide solution, and water and dried. Concentration under reduced pressure on the steam bath gave 119.1 g of a mixture of oil and crystals. The mixture was heated in an oil bath for 2 h (bath temperature 115–130°, 1 mm) in a rotary evaporator provided with a 20 × 3 cm collection trap. The sublimate was washed thoroughly with water to yield recovered ferrocene (37.6 g, 40.5% recovery). The residue, a red grease (69.4 g), was distilled under nitrogen through a short stillhead (Woods metal bath held at 250–260°) as rapidly as possible to yield at ca. 0.1 mm fractions (1) bp 130–200°, 2.2 g, mainly methyl 4-ferrocenylpentanoate (ca. 1% yield); (2) bp 225–236°, 48.4 g (40% conversion, 67% yield based on reacted ferrocene) of methyl 4,4-diferrocenylpentanoate which crystallized on standing, mp 104–107°; and (3) 16.8 g of black, brittle solid residue. (A parallel run of doubled scale gave comparable results.) Crystallization of fraction 2 from hexane gave orange-yellow needles, mp 107–108° (ca. 80% recovery): ir (KBr) 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.08 (s, 18, Fc), 3.63 (s, 3, CH_3O), 2.22 (s, 4, CH_2CH_2), 1.62 (s, 3, CH_3C); ^{13}C NMR ($CDCl_3$) δ 174.5 (C=O), 99.5 (substituted ferrocenyl C-1), 68.5 (unsubstituted cyclopentadiene rings), 66.8, 66.2 (substituted ferrocenyl C-2, C-5), 66.8 (substituted ferrocenyl C-3, C-4), 51.5 (CH_3O), 38.4 (pentanoyl C-2, CH_2), 35.9 (pentanoyl C-4 quaternary), 30.1 (pentanoyl C-3, CH_2), 24.3 (pentanoyl C-5, CH_3); see Table I. Undistilled crude product ester crystallized with great difficulty and in poor yield from hexane or other solvents; it could be purified by dry-column chromatography on alumina (elution with benzene) after which it could be crystallized from hexane in high purity and yield. Small amounts of impurities in ester 3, as well as in the other ferrocene compounds encountered in the present work, vitiate purification by crystallization.

To maximize the conversion of ferrocene to product ester it was found desirable to employ a large excess of methyl levulinate; lower keto ester/ferrocene ratios gave much lower conversions. Slow addition of levulinate to the ferrocene also minimizes side reactions. It was found that concentrated sulfuric acid could be substituted for 100% phosphoric acid, but much tar formation resulted, the yield was lower, and the product was more difficult to purify. More dilute (85%) phosphoric acid gave lower yields. Levulinic acid substituted for its methyl ester also gave lower yields. To increase the reaction rate, cyclohexane was introduced as a cosolvent. Heptane and benzene were much less effective cosolvents for this purpose—both gave lower yields and benzene addition produced much tar. Maintenance of a reaction temperature below 80° within the reaction vessel (oil bath temperature below 100°) decreases tar formation. Small amounts of ferrocene (0.1–4%) could be recovered from the dark-green aqueous acid solutions remain-

Table I
1-Substituted 3,3-Diferrocenylbutanes



Registry no.	Compd	X	Mp, °C	Molecular formula[a]
56386-19-7	3	CO_2CH_3	107–108	$C_{26}H_{28}Fe_2O_2$
56386-21-1	8	CO_2H	195–199	$C_{25}H_{26}Fe_2O_2$
57458-81-8		$CONH_2$	149–150	$C_{25}H_{27}Fe_2NO$
57458-82-9	12	$CONHNH_2$	168–171	$C_{25}H_{28}Fe_2N_2O$
56386-20-0	7	CH_2OH	115–116	$C_{25}H_{28}Fe_2O$
56386-24-4	11	NCO	135–137	$C_{25}H_{25}Fe_2NO$
57458-83-0		$NHCO_2CH_3$	130–131	$C_{26}H_{29}Fe_2NO_2$
57458-84-1		$NHCONHC_6H_5$	182–183[b]	$C_{31}H_{32}Fe_2N_2O$

[a] Satisfactory analytical data (±0.3% for C, H, Fe, and N) and molecular weight data (±4%, by vapor osmometry in chloroform) for all compounds were submitted for review. [b] Previous melting at 124–129° (polymorph).

ing after removal of the water-insoluble organic products by addition of sodium sulfite or ascorbic acid. Methyl levulinate could be recovered (ca. 10–20%) from the volatile components distilled from the reaction mixture during work-up.

Methyl 4-Ferrocenylpentanoate (5). Fraction 1 in the above preparation of ester **3** was redistilled to yield a mobile red oil: bp 128° (0.05 mm); $n^{25}D$ 1.5693; ir (film) 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.05 (s, 5, unsubstituted cyclopentadienyl), 3.98 (s, 4, substituted cyclopentadienyl), 3.59 (s, 3, CH_3O), 2.1–2.7 (m, 1, CH), 1.5–2.7 (m, 4, CH_2CH_2), 1.22 (d, 3, J = 6.5 Hz, CH_3C).

Anal. Calcd for $C_{16}H_{20}FeO_2$: C, 64.02; H, 6.72; Fe, 18.60; mol wt, 300.2. Found: C, 64.30; H, 6.66; Fe, 18.40; mol wt, 296 ($CHCl_3$).

1,1′-Bis[2-ferrocenyl-4-carbomethoxy)butyl]ferrocene (6). Polyphosphoric acid was prepared by mixing 85% phosphoric acid (22.5 g) and phosphorus pentoxide (27.5 g). Methanol (25 ml), cyclohexane (30 ml), ferrocene (18.6 g, 0.1 mol), and methyl levulinate (13.0 g, 0.1 mol) were added to the acid all at once and the mixture stirred for 16 h while heating in an oil bath (bath temperature 95–98°, pot temperature 80–82°). The mixture was worked up as described above in the preparation of ester **3** to yield 2.5 g (13%) of recovered ferrocene and 18.6 g of product mixture not subliming at 130° (1 mm). The product mixture was fractionated by dry-column chromatography on alumina (elution with benzene) to yield as principal fractions 8.3 g (34% conversion, 41% yield) of methyl 4,4-diferrocenylpentanoate (**3**) and 2.2 g of a more slowly eluted fraction isolated as a dark red gum; crystallization of this material from hexane gave 0.53 g (2%) of diester **6** as orange crystals, mp 132–138°. Two recrystallizations from hexane gave flat, orange, hexagonal prisms: mp 140–142°; ir (KBr) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.8–4.2 (m, principal peak at δ 4.04, 26, Fc), 3.60 (s, 6, CH_3O), 2.14 (s, 8, CH_2CH_2), 1.53 (s, 6, CH_3C); ^{13}C NMR ($CDCl_3$) δ 174.7 (C=O), 99.7, 99.3 (substituted ferrocenyl C-1), 68.6 (unsubstituted cyclopentadienyl rings), 68.0, 67.6 (outer substituted ferrocenyl C-2, C-5), 67.1, 66.8 (inner substituted ferrocenyl C-2, C-5), 66.8 (outer substituted ferrocenyl C-3, C-4), 66.4 (inner substituted C-3, C-4), 51.5 (CH_3O), 38.7 (pentanoyl C-2, CH_2), 36.0 (pentanoyl C-4, quaternary), 30.1 (pentanoyl C-3, CH_2), 24.1 (pentanoyl C-5, CH_3).

Anal. Calcd for $C_{42}H_{46}Fe_3O_4$: C, 64.48; H, 5.92; Fe, 21.41; mol wt, 782.4. Found: C, 64.34; H, 5.88; Fe, 21.58; mol wt, 777 ($CHCl_3$).

4,4-Diferrocenyl-1-pentanol (7). A. From Methyl 4,4-Diferrocenylpentanoate (5). A solution of methyl 4,4-diferrocenylpentanoate (3.4 g, 7.0 mmol) in 15 ml of dry tetrahydrofuran was added dropwise with stirring during 15 min to a solution of 0.27 g (7.0 mmol) of lithium aluminum hydride in 25 ml of ether. The mixture was heated under reflux with stirring for 80 min. The mixture was chilled in an ice bath and stirred with an excess of 1 *N* hydrochloric acid until all aluminum salts were dissolved. The ether layer was separated, washed with water, and dried with magnesium sulfate. Concentration under reduced pressure gave 3.0 g (94% yield) of the alcohol, mp 104–111°; recrystallization from cyclohexane gave small prisms, 2.8 g, mp 110–111°. Recrystallization from benzene gave chunky prisms: mp 115–116°; ir (KBr) 3350 cm^{-1} (OH), carbonyl bands absent; ^1H NMR ($CDCl_3$) δ 4.12 (s, 18, Fc), 3.3–3.8 (m, 2, CH_2O), 1.2–2.2 (m, 4, CH_2CH_2), 1.65 (s, 3, CH_2); ^{13}C NMR ($CDCl_3$) δ 95.7 (substituted ferrocenyl C-1), 70.2 (unsubstituted cyclopentadienyl rings), 68.8 (substituted ferrocenyl C-2, C-5), 68.6 (substituted ferrocenyl C-3, C-4), 65.9 (CH_2OH), 47.1 (pentanol C-2, CH_2), 43.1 (pentanol C-4, quaternary), 37.8 (pentanol C-3, CH_2), 24.9 (pentanol C-5, CH_3); see Table I.

B. From Ferrocene and 5-Hydroxy-2-pentanone. Ferrocene (10.0 g, 0.054 mol) and 5-hydroxy-2-pentanone (1.02 g, 0.01 mol, from Aldrich Chemical Co.) were dissolved in 40 ml of methylene chloride. Trifluoroacetic acid (10 ml) was then added with stirring, causing the reaction mixture to darken and become slightly warm. The mixture was allowed to stand at ambient temperature for 2.3 h; water (50 ml) was then added with stirring. A blue color which had appeared in the aqueous phase was discharged with a small amount of ascorbic acid. The methylene chloride phase was separated and poured onto an activated alumina column (5 × 25 cm). Unreacted ferrocene (7.6 g, 76%) was eluted with methylene chloride. The next band appearing on the column was removed mechanically and the mixture of alumina and product was extracted with methanol. Removal of methanol from the extract gave 2.8 g of 4,4-diferrocenyl-1-pentanol; recrystallization from cyclohexane gave 2.0 g of pure product, red-brown crystals, mp 112–113° (44% conversion, 70% yield based on reacted ferrocene). The above procedure failed to effect condensation of ferrocene with methyl levulinate or levulinic acid; reactants were recovered.

4,4-Diferrocenylpentanoic Acid (8). A mixture of methyl 4,4-diferrocenylpentanoate (24.2 g, 0.05 mol) and potassium hydroxide (15 g, 85% assay) dissolved in a solution of 50 ml each of water, ethanol, and dioxane was heated on the steam bath (nitrogen atmosphere) for 3 h. The solution was concentrated to remove solvents; 50 ml of water and 100 ml of dioxane were added and the mixture warmed to dissolve the product. The cooled solution was acidified to pH 1 by addition of concentrated hydrochloric acid; the mixture was then warmed on the steam bath to dissolve all organic material. The solution was concentrated under reduced pressure on the steam bath to remove solvents and the residue treated with 500 ml of water; the solid was filtered and washed thoroughly with water. The dried solid was heated in boiling benzene (300 ml) to dissolve organic material and filtered hot to remove insoluble matter. The filtrate was concentrated to dryness and finally heated on the steam bath at 0.1 mm for 2 h to yield 23.3 g (99%) of the acid, mp 192–199°. Recrystallization from cyclohexane gave prisms: mp 195–199°; it is necessary to heat at 100° (0.1 mm) for 2 h to remove all cyclohexane solvent; ir (KBr) 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.98 (s, 18, Fc), 2.20 (s, 4, CH_2CH_2), 1.55 (s, 3, CH_3); see Table I.

4,4-Diferrocenylpentanohydrazide (12). A solution of methyl 4,4-diferrocenylpentanoate (2.42 g, 0.005 mol) and hydrazine hydrate (1.5 g, 0.015 mol) in 1-butanol (10 ml) was heated under reflux (nitrogen atmosphere) for 20 h. Concentration of the deep-red solution to dryness under reduced pressure gave 2.38 g (99%) of the hydrazide, mp 138–171°; recrystallization from 95% ethanol did not change the melting point; ir (KBr) 3200 (NH), 1640, 1620 cm^{-1} (C=O); see Table I.

4,4-Diferrocenylpentanoyl Chloride (9). 4,4-Diferrocenylpentanoic acid (23.5 g, 0.05 mol) dissolved in 500 ml of dry benzene containing pyridine (4.8 g, 0.06 mol) was treated with phosphorus trichloride (8.2 g, 0.06 mol). The mixture was heated in a nitrogen atmosphere on the steam bath from 25° to reflux during 15 min and at reflux for 30 min. The mixture was cooled to room temperature and the supernatant solution filtered by suction to separate it from insoluble material adhering to the flask; the solid residue was rinsed twice with dry benzene. The combined benzene solutions were concentrated under reduced pressure, *care being taken not to heat the flask contents above 25°. (Caution! The acid chloride decomposes rapidly, evolving hydrogen chloride when heated at 80–100°.)* The crude oily acid chloride revealed a strong carbonyl band at 1795 cm^{-1} and no other carbonyl absorption bands, yield 23.7 g (97%). The crude acid chloride was used immediately, without further treatment, for conversion to the acyl azide.

Prolonging the reaction time in refluxing benzene beyond 45 min to 2–6 h resulted in lowered yields of the acid chloride and formation of much benzene-insoluble material, as well as a carbonyl-containing impurity in the product (ν 1670 cm^{-1}). Heating the crude, neat acid chloride on the steam bath for a few minutes re-

sulted in rapid evolution of hydrogen chloride and formation of a black brittle solid having no acid chloride carbonyl absorption at 1795 cm^{-1} (hydroxyl absorption absent). Attempts to purify the crude acid chloride in benzene solution by washing with cold saturated sodium bicarbonate solution caused partial hydrolysis to the acid salt; severe emulsification resulted, making the extraction quite difficult.

4,4-Diferrocenylpentanoamide. A solution of 4,4-diferrocenylpentanoyl chloride (1.0 g, 2.04 mmol) in 5 ml of dry tetrahydrofuran was treated with 15 ml of a 3% ammonia solution in dry tetrahydrofuran. After standing protected from moisture for 4 days at ambient temperature the mixture, which contained a precipitate, was concentrated to dryness under reduced pressure. The residue was diluted with water and the mixture filtered and washed with water to yield 0.94 g (98%) of the amide, mp 148–150°; recrystallization from cyclohexane gave prisms, mp 149–150°; see Table I.

4,4-Diferrocenylpentanoyl Azide (10). 4,4-Diferrocenylpentanoyl chloride (24.4 g, ca. 0.05 mol of material prepared as described above) was dissolved in 100 ml of tetrahydrofuran and added dropwise with stirring to a solution of sodium azide (4.55 g, 0.07 mol) in 15 ml of water chilled to 3° in an ice bath, keeping the temperature below 5° during the addition (nitrogen atmosphere). Stirring was continued for 30 min at 3–4°. The infrared spectrum of an aliquot sample showed strong bands at 1710 (C=O) and 2130 cm^{-1} (N_3) characteristic of the acyl azide, and virtually no other components as indicated by the absence of other infrared bands, including those of the acid chloride or carboxylic acid. A trace of isocyanate was indicated by extremely weak absorption at 2270 cm^{-1}. *The following operations were performed as rapidly as possible owing to the short half-life of the acyl azide.* The mixture was concentrated under reduced pressure at 25° to remove tetrahydrofuran and the gummy residue diluted with 30 ml of cold water. Benzene (500 ml) was added and the mixture shaken vigorously to dissolve most of the residue; an emulsion results and some gummy solid remains undissolved in either the benzene or the water phase. The mixture was transferred to a separatory funnel and the aqueous layer (an emulsion containing some benzene and other material) drawn off and mixed with Celite and filtered; the filtrate (now a clear mixture of aqueous and benzene layers) was separated and the benzene layer added to the principal benzene extract. The combined benzene solutions were extracted twice with cold water and twice with cold 10% aqueous sodium hydroxide solution. As a result of these operations more insoluble gummy material precipitated. The combined aqueous layers (again an emulsion containing some benzene and other material, including the precipitate) were mixed with Celite and the mixture filtered through a Büchner funnel with suction. The clear filtrate (again a mixture of aqueous and benzene layers) was separated and the benzene layer combined with the principal benzene extract. The combined benzene solutions were washed twice with cold water and dried at 25° with anhydrous magnesium sulfate for ca. 1 h. The solution was filtered and concentrated under reduced pressure at 25° to remove benzene, leaving the crude acyl azide as a gummy solid, 19.8 g (85%), ir (film) 1710 (C=O), 2130 cm^{-1} (N_3). The crude azide was employed immediately for conversion into the corresponding isocyanate.

3,3-Diferrocenylbutyl Isocyanate (11). A. From 4,4-Diferrocenylpentanoyl Azide (10). The crude acyl azide (10) prepared above (19.8 g) was dissolved in 400 ml of dry benzene and stored over molecular sieves for 16 h at 25° in a flask having a calcium chloride tube attached. Nitrogen gas evolved slowly during this time; the reaction was completed by heating the solution under gentle reflux for 0.5 h. The benzene was removed under reduced pressure at 25° to yield 19.1 g of crude isocyanate as orange crystals, mp 132–135°; extraction with 500 ml of dry, refluxing cyclohexane, followed by cooling, filtration of insoluble material, and concentration of the filtrate, gave the pure isocyanate as orange crystals: 17.0 g (74% from ester 3), mp 135–137°; ir (KBr) 2270 cm^{-1} (NCO); ^1H NMR ($CDCl_3$) δ 3.92 (s, 18, Fc), 1.8–3.3 (complex A_2B_2 multiplet centered at 2.1 and 3.1, 4, CH_2CH_2), 1.54 (s, 3, CH_3); see Table I. The isocyanate is very sensitive to moisture and must be stored in a moisture-proof container in a dry atmosphere.

B. From 4,4-Diferrocenylpentanohydrazide (12). 4,4-Diferrocenylpentanohydrazide (0.97 g, 2.0 mmol) was dissolved by warming in 20 ml of tetrahydrofuran containing 0.40 ml of concentrated hydrochloric acid. The solution was cooled to 0–5° in an ice bath and treated with a solution of sodium nitrate (0.26 g, 0.0026 mol) in 0.5 ml of water. The solution was stirred at 0–5° for 45 min, then concentrated to near dryness at ambient temperature. The residue was extracted with benzene and the benzene extracts washed with 10% aqueous sodium hydroxide solution and water and dried; the infrared spectrum of an aliquot sample revealed a strong azide band at 2180 cm^{-1}. The dried extracts were concentrated after standing at 25° for 2 days to yield 0.38 g of a gummy product, a mixture by ir assay of ca. 1:1 3,3-diferrocenylbutyl isocyanate (21% yield, ν 2270 cm^{-1}) and unreacted hydrazide (ν 1670 cm^{-1}). Insoluble material remaining after the benzene extraction (0.35 g) was insoluble in water; it showed strong infrared bands at 3400 and 1640 cm^{-1} (mp above 230°).

***N*-(3,3-Diferrocenylbutyl)carbamic 4,4-Diferrocenylpentanoic Anhydride (13).** 3,3-Diferrocenylbutyl isocyanate and 4,4-diferrocenylpentanoic acid (0.47 g, 0.001 mol of each) were added to 15 ml of dry benzene and stored at 25° over molecular sieves. The insoluble acid dissolved after shaking for a few minutes and the isocyanate band at 2270 cm^{-1} and carboxyl band at 1690 cm^{-1} nearly disappeared (aliquot sample); there appeared a characteristic anhydride doublet at 1770, 1740 cm^{-1} and carbamoyl NH at 3400 cm^{-1}. Concentration under reduced pressure at 25° gave the crude anhydride 13 as an amorphous gum. The infrared spectrum of the material was virtually unchanged by heating in refluxing dry benzene for 1 h.

A benzene solution of the anhydride was extracted with 10% aqueous sodium hydroxide solution; sodium 4,4-diferrocenylpentanoate precipitated. The benzene solution was washed with water, dried, and concentrated to yield recovered 3,3-diferrocenylbutyl isocyanate (ν 2270 cm^{-1}). The sodium 4,4-diferrocenylpentanoate was separated and converted into 4,4-diferrocenylpentanoic acid by treatment with aqueous hydrochloric acid, mp 191–199°.

***N*-(3,3-Diferrocenylbutyl)-*N'*-phenylurea.** A solution of aniline (0.25 g, 2.7 mmol) and 3,3-diferrocenylbutyl isocyanate (0.85 g, 1.8 mmol) in 15 ml of dry benzene was heated under reflux for 45 min. Cooling deposited crystals of the urea derivative, 0.56 g, mp 118–125°. Recrystallization from benzene gave flat yellow prisms (0.46 g, 46%), mp 125–129°, changing on melting to small rectangular prisms, mp 182–183°; ir (KBr) 3300 (NH), 1630 cm^{-1} (C=O); see Table I.

Methyl 3,3-Diferrocenylbutyl Carbamate. To a solution of 3,3-diferrocenylbutyl isocyanate (0.23 g, 0.49 mmol) in 10 ml of dry tetrahydrofuran was added 1 ml of methanol. The mixture was heated under reflux on the steam bath for 16 h. Concentration of the solution to dryness gave 0.25 g (100%) of the urethane derivative, mp 128–131°; recrystallization from cyclohexane gave flat hexagonal prisms, mp 130–131°; see Table I.

***N,N'*-Bis(3,3-diferrocenylbutyl)urea.** A solution of 3,3-diferrocenylbutyl isocyanate (0.65 g, 1.4 mmol) in 25 ml of benzene and 0.1 ml of water was heated under reflux for 15 min. Cooling gave 0.48 g (74%) of the urea derivative as yellow prisms, mp 233–236°. Recrystallization from benzene gave needles: mp 240–241°; ir (KBr) 3400 (NH), 1620 cm^{-1} (C=O).

Anal. Calcd for $C_{49}H_{52}Fe_4N_2O$: C, 64.79; H, 5.77; N, 3.08; Fe, 24.59; mol wt, 908.4. Found: C, 64.71; H, 5.73; N, 3.15; Fe, 24.31; mol wt, 890 (osmometry, $CHCl_3$).

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Registry No.—**5**, 56411-04-2; **6**, 57458-85-2; **9**, 56386-22-2; **10**, 56386-23-3; **13**, 57458-86-3; ferrocene, 102-54-5; methyl levulinate, 624-45-3; 5-hydroxy-2-pentanone, 1071-73-4; *N,N'*-bis(3,3-diferrocenylbutyl)urea, 57484-07-8.

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Alkylations and Competing Rearrangements in the Aluminum Chloride Catalyzed Reactions of Secondary Alkyl Chlorides with Arenes[1]

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Aluminum chloride catalyzed alkylations of benzene and *p*-xylene by 2- and 3-chloropentane and 2- and 3-chlorohexane have been studied. The alkylations are accompanied by simultaneous isomerization of the chloroalkanes and rearrangement of the product arylalkanes. At 25°, rearrangement of the arylalkanes to an equilibrium composition is the dominant product-determining factor. At −20°, this rearrangement is minimized and product composition is determined by isomerization of the chloroalkanes and competitive alkylation by the isomeric chloroalkanes. The order of mixing the reactants affects the product composition at 0 and −20°. Rough kinetic analysis of alkylations of benzene and *p*-xylene by 2- and 3-chlorohexane indicates that the rates of isomerization and alkylation of the chloroalkanes are of the same order of magnitude. The rate of alkylation by 2-chlorohexane is estimated to be about 2–3 times the rate of alkylation by 3-chlorohexane. Alkylations with $AlCl_3$·CH_3NO_2 catalyst at 25° took place without product isomerization; rates of alkylation were reduced more than rates of chloroalkane isomerization. Comparison is made of the present results from chloroalkane alkylations and isomerizations with analogous reactions of alkenes.

There have been numerous reports of alkylations of arenes with secondary alkylating agents. However, because of the analytical methods employed in some of the older work, the analysis of isomeric phenylalkanes has led to some questionable and contradictory results.

Ipatieff, Pines, and Schmerling[2] alkylated benzene with both 1-pentene and 1-pentanol using 80% sulfuric acid as a catalyst. Their report of a 60% 2-phenylpentane and 40% 3-phenylpentane product was the first report of such a reaction mixture from this type of alkylation. Pines, Huntsman, and Ipatieff[3] reported 76% 2-phenylpentane and 24% 3-phenylpentane from the reaction of 3-pentanol and benzene in the presence of $AlCl_3$ at 25–35°. 2-Pentanol was reported to yield 60% 2-phenylpentane and 40% 3-phenylpentane. Streitweiser, Stevenson, and Schaeffer[4] studied the alkylations of benzene with isomeric pentanols using BF_3 catalyst. Both 2- and 3-pentanol gave identical product mixtures containing 65% 2-phenylpentane, 25% 3-phenylpentane, and 10% 2-methyl-2-phenylbutane. These workers suggested a carbonium ion type alkylating species and stated that the 2- and 3-phenylpentane ratio was probably determined by the rearrangement of the carbonium ion prior to alkylation.

Ipatieff, Pines, and Schmerling[2] reported a mixture containing 60% 2-phenylpentane and 40% 3-phenylpentane from the alkylation of benzene with 1-pentene and sulfuric acid. However, Axe[5] and Simons and Archer[6] reported 2-phenylpentane as the only reaction product from 2-pentene and BF_3 or HF. Olson[7] found 37% 2-phenylhexane and 63% 3-phenylhexane from benzene and 1-hexene with sulfuric acid, a complete reversal from the results from 1-pentene reported by Ipatieff et al.[2] Alul has studied the alkylation of benzene by 1-dodecene, *trans*-6-dodecene,[8,9] and 8-methyl-1-nonene[10] with various catalysts, and has discussed the influence of catalyst type and medium polarity on the distribution of products. A comparison of the alkene reactions with those of the chloroalkanes in this work will be given later.

Rearrangements of *sec*-phenylalkanes have also been previously investigated. Burwell and Shields[11] found that $AlCl_3$ caused complete racemization of optically active 2-phenylpentane after only 10 min at room temperature. No 3-phenylpentane was detected in the reaction mixture. They postulated that the racemization occurred via a rapid hydride ion transfer. The interconversion of 2- and 3-phenylpentane occurred more slowly and was ascribed to disproportionation to dipentylbenzene and benzene followed by the reverse of this reaction. However, Roberts and co-workers[12,13] have suggested that the rearrangements of 2- and 3-phenylpentane as well as the isotopic scrambling of 2-phenyl-2-^{14}C-butane occur via an intermediate phenylalkyl cation produced after hydride abstraction.

This paper is concerned with alkylations by 2- and 3-chloropentanes and 2- and 3-chlorohexanes and the relationship of the concomitant isomerizations of the chloroalkanes and the *sec*-phenylalkanes to the observed final compositions of the product mixtures.

Discussion

Alkylations of Benzene with 2- and 3-Chloropentane. Both 2- and 3-chloropentane isomerized rapidly in the presence of $AlCl_3$ at temperatures from −20 to 25° to a 64:36 equilibrium ratio (Table I). This 64:36 ratio very nearly represents a statistical distribution, since the chloropentanes have two carbon atoms to which chlorine may bond in the 2 position and one such carbon atom in the 3 position. When benzene was added to an isomerized chloropentane mixture at −20°, a very similar 66:34 distribution of 2-:3-phenylpentane resulted (run 6, Table II). The procedure of isomerizing a chloroalkane with $AlCl_3$, followed by addition of the arene, will be referred to as alkylation method B. When the order of addition of reactants was

Table I
Isomerization of 2- and 3-Chloroalkanes with Aluminum Chloride[a]

Starting chloroalkane	Temp, °C	Time, min	Product chloroalkanes[b] % 2-	% 3-
2-Chloropentane	25	2	64	36
	−20	1	64	36
	−20	25	65	35
3-Chloropentane	25	2	64	36
	−20	1	64	36
2-Chlorohexane	−20	1	53	47
	−20	10	52	48
3-Chlorohexane	−20	1	52	48
	−20	10	52	48

[a] Mole ratio, chloroalkane: $AlCl_3$ 10:1. [b] Relative percentages of chloroalkane isomers: by ir for chloropentanes; by GLC for chlorohexanes.

Table II
Alkylations of Benzene with 2- and 3-Chloropentane[a]

Method[b]	Chloropentane	Temp, °C	Time, min	Run no.	Product phenylalkane[c] % 2-	% 3-
A	2-Chloropentane	25	1	1	73	27
			155		74	26
		−20[d]	1	2	72	28
			5[e]		72	28
			20		73	27
A	3-Chloropentane	25	1	3	73	27
			155		74	26
		−20[d]	1	4	65	35
			5[e]		66	34
			155		68	32
			90[f]	5	72	28
			155[f]		74	26
B	2-Chloropentane	−20[d]	1	6	66	34
			120		65	35

[a] Mole ratio benzene: chloropentane: $AlCl_3$ 4:1:0.1. [b] Method A, $AlCl_3$ added to benzene plus chloropentane; method B, $AlCl_3$ added to chloropentane followed by addition of benzene. [c] Relative percentages determined by GLC. [d] Hexane added to reactions at −20° to prevent freezing. [e] Reaction >90% as measured by disappearance of chloropentane. [f] An additional quantity of $AlCl_3$ equal to original charge added after 45 min.

changed, different phenylalkane distributions resulted. Addition of $AlCl_3$ to a solution of chloroalkane and arene will be referred to as alkylation method A. Alkylation of benzene with either 2- or 3-chloropentane at 25° by method A yielded a 74:26 distribution of 2-:3-phenylpentane (runs 1 and 3, Table II). When the reaction temperature was reduced to −20°, 2-chloropentane gave the same distribution of 2-:3-phenylpentane (run 2, Table II); however, 3-chloropentane gave an initial distribution of 65:35, which changed to 68:32 upon standing for 2.5 h (run 4, Table II). When fresh catalyst was added to a 3-chloropentane alkylation reaction mixture after 45 min, the product distribution changed from 65:35 to 74:26 (run 5, Table II).

In order to determine the extent to which isomerization of the phenylalkane affects the final distribution of products from an alkylation reaction, alkylations of benzene with 2- and 3-chloropentane were carried out by method A but in the presence of 2- or 3-phenylhexane.[14] Reactions were carried out at 25, 0, and −20°. The results from the experiments at 0 and 25° are set out in Table III. It may be seen that a constant proportion of 2-:3-phenylpentane of 73:27 was reached in the first minute at 25°, and rearrangement to a constant proportion of 2-:3-phenylhexane of 63:37 was reached in 15 min. At 0° the constant proportion of 2-:3-phenylpentane was reached in ca. 15 min and the constant proportion of 2-:3-phenylhexane was reached in ca. 25 min when 2-phenylhexane was present at the start, and in ca. 60 min when 3-phenylhexane was present at the start. In the experiments carried out at −20°, a constant proportion of 2-:3-phenylpentane of 71:29 was reached in 5–10 min, and no rearrangement of 2- or 3-phenylhexane occurred in up to 2 h. Thus, with the reasonable assumption that the susceptibility toward rearrangement of 2- and 3-phenylpentane is essentially the same as that of 2- and 3-phenylhexane, one can conclude that the distribution of alkylation products from 2- and 3-chloropentane at −20° is determined in part by isomerization of the chloroalkanes preceding attachment to the benzene ring, but not by rearrangement of the phenylpentanes. The slightly higher proportion of 2-phenylpentane (73 ± 2% vs. 71 ± 2%) produced

Table III
Alkylations of Benzene with 2- and 3-Chloropentane in the Presence of 2- or 3-Phenylhexane[a]

Chloropentane	Phenylhexane	Temp, °C	Time, min	Phenylpentane % 2-	% 3-	Phenylhexane % 2-	% 3-
2-	2-	0	1	67	33	100	0
			15[b]	74	26	70	30
			25[b]	74	26	64	36
2-	3-	0	1	71	29	0	100
			15	74	26	27	73
			60[b]	74	24	62	38
3-	2-	0	1	70	30	100	0
			15	75	25	76	24
			25[b]	74	26	63	37
3-	3-	0	1	69	31	0	100
			15	75	25	27	73
			60	75	25	61	39
2-	2-	25	1	72	28	95	5
			15[b]	75	25	63	37
2-	3-	25	1	73	27	3	97
			15[b]	75	25	63	37
3-	2-	25	1	73	27	96	4
			15[b]	76	24	63	37
3-	3-	25	1	71	29	3	97
			15[b]	75	25	64	36

[a] Mole ratio benzene: chloropentane: phenylhexane: $AlCl_3$ 4:1:0.1:0.1. [b] No further change after 120 min. [c] No further change after 90 min.

Table IV
Alkylations of Benzene with 2- and 3-Chlorohexane[a]

Method[b]	Chlorohexane	Temp, °C	Time, min	Run no.	Percent reaction[c]	Recovered chlorohexane[d] % 2-	Recovered chlorohexane[d] % 3-	Product phenylhexane[d] % 2-	Product phenylhexane[d] % 3-
A	2-Chlorohexane	25	1	1				63	37
			120					60	40
		−20[e]	1	2	33	90	10	65	35
			3		71	51	49	65	35
			5		90–95	50	50	65	35
			20		100			64	36
			120					64	36
			240[f]					63	37
			240[g]					62	38
A	3-Chlorohexane	25	1	3				59	41
			120					61	39
		−20[e]	1	4	17	17	83	55	45
			3		29	22	78	55	45
			5		43	25	75	54	46
			20		94	50	50	55	45
			120		100			57	43
			240[f]	5				62	38
			240[g]					62	38
B	2-Chlorohexane	−20[e]	1	6				56	44
			120					57	43
B	3-Chlorohexane	−20[e]	1	7				56	44
			120					57	43

[a] Mole ratio benzene:chlorohexane:$AlCl_3$ 4:1:0.1. [b] Method A, $AlCl_3$ added to benzene plus chlorohexane; method B, $AlCl_3$ added to chlorohexane followed by benzene addition. [c] Determined by GLC from disappearance of chlorohexane. [d] Relative percentages determined by GLC. [e] Hexane added to reactions at −20° to prevent freezing. [f] An additional quantity of $AlCl_3$ equal to original charge added after 2 hr. [g] Reaction allowed to warm to 25° after 2 hr.

at 25° may be attributed to some rearrangement after attachment of the pentyl group to the ring, since rearrangement of the phenylhexanes obviously does occur under the reaction conditions. Another factor affecting the distribution of products of the alkylations is the relative rates at which the 2- and 3-chloropentanes react with benzene. This will be discussed in later sections.

Alkylations of Benzene with 2- and 3-Chlorohexane. When $AlCl_3$ was added to neat 2- or 3-chlorohexane, an equilibrium product distribution of 52:48 of 2-:3-chlorohexane resulted (Table I). This ratio is very near the 50:50 statistical distribution, since with the chlorohexanes there are an equal number of 2- and 3-carbon atoms to which chlorine can bond. When benzene was added to either 2- or 3-chlorohexane and $AlCl_3$ at −20° (alkylation method B, runs 6 and 7, Table IV), a 56:44 distribution of 2-:3-phenylhexane resulted. Alkylation by method A at 25° gave a product distribution of 61:39 of 2-:3-phenylhexane from either 2- or 3-chlorohexane (runs 1 and 3, Table IV). This higher 2-:3-phenylhexane product ratio may well be explained in terms of rearrangement of the phenylhexanes after attachment of the hexyl groups, as the data of Table III show that this occurs quite rapidly at 25°.

However, no phenylalkane rearrangement occurs at −20°, and it should be noted that the alkylations by both 2-chloropentane and 2-chlorohexane by method A at −20° also gave products higher in 2-phenylalkane content than either the equilibrium ratio of 2-:3-chloroalkanes (Table I) or the ratio of 2-:3-phenylalkanes produced by method B (compare runs 2 and 6, Table II, and runs 2 and 6 or 7, Table IV). The alkylations by both 3-chloropentane and 3-chlorohexane by method A at −20° gave product distributions lower in 2-phenylalkane content (run 4, Table II, and run 4, Table IV). These results are probably due to differences in *rates* of alkylation by 2- and 3-chloroalkanes in the reactions carried out by method A. Alul[9] has suggested that the 2 cation reacts faster than the 3 cation in dodecene alkylations of benzene catalyzed by $AlCl_3$ and $AlCl_3$–CH_3NO_2, and a more rapid alkylation by the 2 cation has also been proposed in alkylation of benzene by chloropentadecanes.[15,16]

Further information about the competitive reactions of alkylation and isomerization can be obtained by a rough kinetic analysis of the data in Table IV. On the basis of the results from the alkylations with 2- and 3-chloropentane in the presence of 2- or 3-phenylhexane at −20°, we can assume that no appreciable isomerization of the products occurs after alkylation by 2- and 3-chlorohexanes. In the experiments identified by runs 2 and 4 of Table IV, the amount and identity of the isomeric chlorohexanes remaining in the reaction mixtures were determined after various times, and the extent of the alkylation could thus be calculated. Using these data and the proportion of 2- and 3-phenylhexanes produced at the times samples were taken for GLC analysis, we can calculate approximate values for the competitive processes of isomerization of chlorohexanes and their simultaneous reactions with benzene, using the following expressions.

$$A_2 = \frac{R}{100} P_2$$

A_2 = mole percent of 2-chloroalkane which has alkylated benzene without isomerization at time t; R = mole percent reaction of 2-chloroalkane at time t, both alkylation and isomerization; P_2 = mole percent 2-phenylalkane produced at time t.

$$I_2 = \frac{(100 - R)}{100} C_3 + \frac{R}{100} P_3$$

I_2 = mole percent of 2-chloroalkane which has isomerized at time t (based on both recovered chloroalkane and phenylalkane resulting from alkylation by isomerized chloroalkane); C_3 = mole per cent 3-chloroalkane in remaining chloroalkane at time t; P_3 = mole percent 3-phenylalkane produced at time t.

Analogous expressions can be used to calculate A_3 and

Table V
Alkylation vs. Isomerization in Alkylations of Benzene[a] and p-Xylene[b] with 2- and 3-Chlorohexane at −20°

Arene	Rxn time, t, min	A_2[c]	I_2[d]	A_2/I_2	A_3[c]	I_3[d]	A_3/I_3	A_2/A_3
Benzene	1	21	18	1.2	7.7	23	0.33	2.8
	3	46	39	1.2	13	32	0.41	3.5
	5	60	37	1.6	20	37	0.54	3.0
p-Xylene	3	10	14	0.72	3.0	15	0.20	3.3
	10	23	27	0.85	7.5	28	0.27	3.1
	20	31	34	0.91	15	35	0.43	2.1

[a] Data for benzene calculations from Table IV. [b] Data for p-xylene calculations from Table VII. [c] Mole percent of chloroalkane which has alkylated without isomerization. [d] Mole percent of chloroalkane which has isomerized, including that which has alkylated benzene or p-xylene (see text).

I_3, and from these expressions, values of A_2/I_2 and A_3/I_3 can be calculated. A tabulation of these values for the reactions of 2- and 3-chlorohexane with benzene and $AlCl_3$ at −20° appears in the top part of Table V.

The values of A_2/I_2 at 1 and 3 min indicate that alkylation and isomerization take place at almost equal rates for 2-chlorohexane, whereas the values of A_3/I_3 at the same times show that the rate of alkylation by 3-chlorohexane is only 0.3–0.4 times the rate of its isomerization to 2-chlorohexane. Since the rates of isomerization are approximately equal ($I_2:I_3$ = 18:23 and 39:32), this means that the relative rates of alkylation by 2-chlorohexane and 3-chlorohexane are ca. 3:1 (A_2/A_3 = 2.8–3.5).

Alkylations of p-Xylene with 2- and 3-Chloropentane. The alkylation of p-xylene by method B at −20°, using either 2- or 3-chloropentane, gave a 62:38 distribution of 2-:3-p-xylylpentane (runs 5 and 6, Table VI). This is slightly different from the 64:36 distribution produced by equilibrating the neat chloropentanes (Table I), as was found in the case of method B alkylation of benzene, also.

The alkylation by method A at 0° using either 2- or 3-chloropentane gave a 75:25 distribution of 2-:3-p-xylylpentane (runs 1 and 3, Table VI). This distribution undoubtedly arises from product isomerizations, since the p-xylylpentanes do interconvert at 0° (Experimental Section). No p-xylene alkylations were run at temperatures above 0° because methyl reorientation to m-xylylpentanes becomes a competing process.

Alkylation at −20° using method A gave quite different results for 2-chloropentane and 3-chloropentane. 2-Chloropentane and p-xylene initially gave a 67:33 distribution of 2-:3-p-xylylpentane (run 2, Table VI); after 2 h this distribution was unchanged. 3-Chloropentane initially gave a 48:52 distribution of 2-:3-p-xylylpentane. After 2 h this distribution had changed to 64:36 (run 4, Table VI). Since no product isomerization occurs at −20°, there is clearly competition between alkylation and chloropentane isomerization prior to alkylation. The fact that there is initially a much higher 2-p-xylylpentane content produced from 2-chloropentane than 3-p-xylylpentane content produced from 3-chloropentane suggests that the 2-chloropentane alkylates faster than the 3-chloropentane in this system, too.

Alkylation of p-Xylene with 2- and 3-Chlorohexane. The alkylation of p-xylene with 2-chlorohexane at −20° using method B yielded a 53:47 distribution of 2-:3-p-xylylhexane (run 5, Table VII). This is very near the 52:48 equilibrium distribution for the neat chlorohexanes reported in Table I.

Competition between alkylation and isomerization of the chlorohexanes prior to alkylation is apparent with p-xylene at both 0° and −20°. Using method A and 2-chlorohexane at 0°, the product initially contained a 61:39 distribution of 2-:3-p-xylylhexane (run 1, Table VII); after 2 h this distribution was 66:34. However, with 3-chlorohexane, the product distribution was initially 46:54 (run 3, Table VII); after 2 h the distribution had changed to 65:35. At 0° there is apparently competition between isomerization of the chlorohexanes, alkylation, and isomerization of p-xylylhexanes. At −20°, where p-xylylhexane isomerization does not occur, the competition between alkylation and isomerization of chlorohexanes using method A is even more pronounced. 2-Chlorohexane initially yielded a 64:36 distribution of 2-:3-p-xylylhexane (run 2, Table VII); after 2 h this distribution was slightly reduced in 2 content to a 61:39 ratio. The results from 3-chlorohexane were dramatically different—initially the distribution of 2-:3-p-xylylhexane was 39:61 (run 4, Table VII); this changed to 53:47 after 2 h. The data in Table VII on the alkylations at −20° allow calculation of A_2/I_2, A_3/I_3, and A_2/A_3. The values for these quantities are presented in Table V, lower part. The values for A_2/I_2 indicate that in the p-xylene system, as in the benzene system, the rates of alkylation and isomerization of 2-chlorohexane are nearly equal. Significantly smaller values for A_3/I_3 suggest that alkylation by 3-chlorohexane is slower than its isomerization. Values for A_2/A_3 indicate that 2-chlorohexane alkylates p-xylene at −20° approximately three times faster than 3-chlorohexane. This rate difference is about the same as for alkylation of benzene at −20° by 2- and 3-chlorohexane. The calculated values for I_2 and I_3 in both p-xylene and benzene media are very nearly equal at a given time, indicating that the rates of interconversion of 2- and 3-chlorohexane are almost the same.

Table VI
Alkylations of p-Xylene with 2- and 3-Chloropentane[a]

Method[b]	Chloropentane	Temp, °C	Time, min	Run no.	Product p-xylylpentane[c] % 2-	% 3-
A	2-Chloropentane	0	15	1	75	25
			120		75	25
		−20[d]	1	2	67	33
			3		66	34
			5		65	35
			20		67	33
			120		67	33
A	3-Chloropentane	0	15	3	75	25
			120		75	25
		−20[d]	1	4	48	52
			3		50	50
			5		52	48
			20		57	43
			120		64	36
B	2-Chloropentane	−20[d]	1	5	61	39
			120		62	38
B	3-Chloropentane	−20[d]	1	6	62	38
			120		62	38

[a] Mole ratio p-xylene:chloropentane:$AlCl_3$ 4:1:0.1. [b] Method A, $AlCl_3$ added to p-xylene plus chloropentane; method B, $AlCl_3$ added to chloropentane followed by p-xylene addition. [c] Relative percentages determined by GLC. [d] Hexane added to reactions at −20° to prevent freezing.

Alkylations with Aluminum Chloride–Nitromethane Catalyst. The moderating effect of nitrobenzene and nitromethane upon aluminum chloride is well known. Alul reported that secondary dodecylbenzenes were not isomerized by $AlCl_3$·CH_3NO_2 even at the reflux temperature of benzene.[9] We found that 2- and 3-phenylpentane were not isomerized by this moderated catalyst at 25°. Thus we were

Table VII
Alkylations of *p*-Xylene with 2- and 3-Chlorohexane[a]

Method[b]	Chlorohexane	Temp, °C	Time, min	Run no.	Percent reaction[c]	Recovered chlorohexane[d] % 2-	Recovered chlorohexane[d] % 3-	Product *p*-xylylhexane[d] % 2-	Product *p*-xylylhexane[d] % 3-
A	2-Chlorohexane	0	1	1				61	39
			15					65	35
			120					66	34
		−20[e]	1	2				64	36
			3		16	90	10	65	35
			10		36	78	22	64	36
			20		50	70	30	61	39
			45		92	54	46	61	39
			120		100			61	39
A	3-Chlorohexane	0	1	3				46	54
			15					59	41
			120					65	35
		−20[e]	1	4				39	61
			3		5	14	86	39	61
			10		13	25	75	42	58
			20		26	33	67	44	56
			45		81	50	50	49	51
			120		100			53	47
B	2-Chlorohexane	−20[e]	1	5				53	47
			45					53	47

[a] The mole ratio *p*-xylene:chlorohexane:$AlCl_3$ 4:1:0.1. [b] Method A, $AlCl_3$ was added to *p*-xylene plus chlorohexane; Method B, $AlCl_3$ added to chlorohexane followed by addition of *p*-xylene. [c] Determined by GLC from disappearance of halide. [d] Relative percentages determined by GLC. [e] Hexane added to reactions at −20° to prevent freezing.

assured that we could eliminate the possibility of product isomerization by using $AlCl_3$-CH_3NO_2 catalyst at 25° for alkylations with chloropentanes and chlorohexanes, and thereby obtain an interesting comparison of the results with those from the alkylations in which unmoderated $AlCl_3$ was used at −20°. Table VIII presents the results of these alkylations with moderated catalyst.

In contrast to the alkylations of benzene with $AlCl_3$ at −20°, it made little difference whether method A or method B of mixing the reactants was used, or whether the 2- or 3-chloroalkane was the starting material. The products were 2- and 3-phenylpentane in a 74:26 ratio and 2- and 3-phenylhexane in a 66 ± 1:34 ± 1 ratio. These results indicate that adding nitromethane to aluminum chloride reduces the rate at which the chloroalkanes alkylate benzene much more than the rate at which they isomerize. Isomerization is therefore much faster than alkylation in the presence of the moderated catalyst, whereas the two processes are of comparable rate in the presence of unmoderated $AlCl_3$ (vide infra).

The alkylations of *p*-xylene in the presence of the moderated catalyst were more like those in which $AlCl_3$ alone was used; i.e., there was a difference in the product ratio depending on whether the 2- or 3-chloroalkane was the starting material in method A alkylations. This must mean that the alkylation of *p*-xylene competes more effectively than that of benzene with isomerization of the chloroalkanes in the presence of the moderated catalyst. In the alkylations of both benzene and *p*-xylene, the 2-chloroalkanes reacted more rapidly than the 3-chloroalkanes, as was the case with unmoderated $AlCl_3$ as catalyst.

In conclusion, we should like to comment briefly on the relationship of our findings to those of others. Alul found widely different phenyldodecane isomer distributions produced from 1-dodecene and *trans*-6-dodecene alkylations with $AlCl_3$·HCl catalyst under conditions that excluded product isomerization (0–5°), indicating that alkylation was much faster than isomerization of dodecenes or intermediate carbonium ions.[9] He also noted that alkylating in nitromethane solution slowed down alkylation more than isomerization. Geiseler et al.[17] reported that 1-heptene isomerized 3–7 times faster than it alkylated benzene when 100% H_2SO_4 was used as catalyst. Our results indicate that the rates at which 2- and 3-chloropentanes and 2- and 3-chlorohexanes isomerize and alkylate benzene and *p*-xylene in the presence of $AlCl_3$ are of the same order of magnitude; that is, they differ by no more than twofold or threefold. With $AlCl_3$-CH_3NO_2 catalyst, the rates of alkylation of benzene by the chloroalkanes are depressed much more than their rates of isomerization.

Table VIII
Alkylations with Aluminum Chloride–Nitromethane Catalyst[a] at 25°

Arene	Method[b]	Chloroalkane	Time, min	Product arylalkane % 2-	Product arylalkane % 3-
Benzene	A	2-Chloropentane	10	77	23
			45	74	26
	A	3-Chloropentane	10	72	28
			45	74	26
	B	3-Chloropentane	10	74	26
			30	74	26
	A	2-Chlorohexane	10	69	31
			45	67	33
	A	3-Chlorohexane	10	64	36
			45	65	35
	B	3-Chlorohexane	10	67	33
			30	67	33
p-Xylene	A	2-Chloropentane	15	71	29
			35	69	31
	A	3-Chloropentane	15	63	37
			35	61	39
	B	2-Chloropentane	10	68	32
			30	67	33
	A	2-Chlorohexane	10	67	33
			45	65	35
	A	3-Chlorohexane	10	54	46
			45	57	43
	B	2-Chlorohexane	10	60	40
			30	61	39

[a] Mole ratio arene:chloroalkane:$AlCl_3$:CH_3NO_2 4:1:0.1:1. [b] Method A: catalyst complex was added to arene and chloroalkane. Method B: catalyst complex was added to chloroalkane, stirred for 10 min, then arene was added.

One must conclude from the foregoing summary that it is not safe to generalize about the relative rates of competing reactions, such as alkylation and isomerization of "carbonium ions" without reference to their source (alkene, haloalkane, etc.), the generating catalyst or reactant, the arene substrate, and the solvent medium, since all of these factors may have a strong influence on the results.

Experimental Section

The structure and purity of all starting materials and products were checked by GLC, ir, and NMR analyses.[18]

A. Synthesis of Chloroalkanes. The method described by Vogel[19] was used for preparation of all chloroalkanes from the corresponding alcohols. 2-Pentanol was purchased commercially. 3-Pentanol was prepared from 3-pentanone by the method of Weinstock and Lewis.[20] 2-Hexanol was prepared from methylmagnesium iodide and *n*-valeraldehyde, 3-hexanol from ethylmagnesium bromide and *n*-butyraldehyde. A Carbowax 20M (30%) column (12 ft × 0.25 in.) was used for GLC analysis of the alcohols. A Bentone-34 (5%) silicone gum rubber SE-52 (5%) column (10 ft × 0.125 in.) was used for GLC analyses of the chloroalkanes.

B. Synthesis of Authentic Hydrocarbons. 1. Phenylalkanes. Standard methods were employed. Acetophenone or propiophenone was condensed with the appropriate alkylmagnesium halide.[21] The resulting carbinol was hydrogenated in glacial acetic acid using palladium on charcoal catalyst to yield the desired phenylalkane.[22] The resulting ir and NMR spectra were as expected.

2. *p*-Xylylalkanes. Standard methods were employed. Reaction of 2-bromo-*p*-xylene, magnesium turnings, and the appropriate ketone in anhydrous either gave the corresponding dialkyl-*p*-xylylcarbinol. Hydrogenation in glacial acetic acid using a palladium on charcoal catalyst gave the desired *p*-xylylalkane.[22] The resulting ir and NMR spectra were as expected.

C. Isomerizations of Chloroalkanes. The chloroalkane was placed in a flask equipped with a magnetic stirrer, a drying tube, and, for the chlorohexanes, a septum to allow aliquots to be removed with a hypodermic syringe. The reactions were run in a dry ice–ethanol bath to maintain −20° or stirred at room temperature for the 25° isomerizations. In the chloropentane isomerizations the reactants were hydrolyzed by pouring onto ice. The organic phase was separated, washed with saturated sodium bicarbonate and then with brine, and dried over calcium chloride. The chloropentanes were isolated by distillation and analyzed by infrared using a Beer's law plot. The values of 2-chloropentane were obtained from the absorption peak at 745 cm^{-1} and those of 3-chloropentane from that at 820 cm^{-1}. In the chlorohexane isomerizations a 0.25-ml aliquot was withdrawn after the desired time interval and quenched in a water-filled vial. The organic layer was analyzed directly by GLC without further purification. In all isomerizations the molar ratio of chloroalkane:catalyst was 10:1, the sample sizes of the chloroalkanes taken for isomerization were 0.05 or 0.1 mol. The results of these isomerizations are given in Table I.

Isomerizations of the chloroalkanes were also effected at 25° by $AlCl_3$-CH_3NO_2 (mole ratio chloroalkane:$AlCl_3$:CH_3NO_2 10:1:10). The equilibrium proportions of the isomeric chloroalkanes were the same (± 1%) as when unmoderated $AlCl_3$ was used.

D. Alkylations of Benzene and *p*-Xylene with 2- and 3-Chloropentane and 2- and 3-Chlorohexane. Aluminum Chloride Catalyst. Two different methods were used to carry out these alkylations. The difference involved changing the order of addition of reactants. In method A the aluminum chloride was added to a stirred solution of the chloroalkane and arene. In Method B the aluminum chloride was added to the stirred chloroalkane, followed by addition of the arene. Alkylation results are presented in Tables II, IV, VI, and VII. Overall yields of alkylarenes were in the 70–80% range.

1. Alkylation by Method A. The reactions were carried out in a flask equipped with a magnetic stirrer, a condenser with drying tube, and a septum to allow aliquots to be withdrawn by syringe. The arene and chloroalkane were stirred at the desired temperature (25, 0, or −20°), and the aluminum chloride was added in one lot to begin the reactions. In the alkylations carried out at 0 and −20°, it was necessary to add hexane (20–35 g) to prevent freezing. In all the alkylations the ratio of arene:halide:aluminum chloride was 4:1:0.1; 0.05-mol samples of chloroalkanes were used. At desired intervals 0.25-ml aliquots were withdrawn, quenched in water-filled vials, and analyzed directly by GLC.

The determination of percent reaction was based upon disappearance of the chloroalkane which was traced by GLC analyses. The recovered chlorohexanes were analyzed for isomer distribution using a Bentone-34 (5%), silicone gum rubber SE-52 (5%) column (10 ft × 0.125 in.). The aromatic hydrocarbon isomer distribution was determined by GLC using a similar column of 5 ft × 0.125 in. dimensions.

2. Alkylation by Method B. The reaction vessel used was the same as that described in method A. Aluminum chloride was added to the chloroalkane being stirred at −20°. After 3 min the arene dissolved in hexane (20–35 g) and cooled to −20° was quickly added to the stirred aluminum chloride–chloroalkane mixture and a timer was started. A considerable amount of hydrogen chloride gas was evolved even though the same reaction using method A gave a slower reaction. At various time intervals, 0.25-ml aliquots were withdrawn, quenched in a water-filled vial, and analyzed directly by GLC. In all the alkylations the ratio of arene:chloroalkane:aluminum chloride was 4:1:0.1; 0.05-mol samples of chloroalkanes were used. In some of the alkylations, method B was used with only one of the isomeric chloroalkanes. This was all that was necessary, since it had been shown (Table I) that the neat 2- or 3-chloroalkanes instantaneously isomerize to the same mixture even at −20°.

3. Alkylations of Benzene with 2- and 3-Chloropentane in the Presence of 2- or 3-Phenylhexane (Method A).[14] Benzene (15.6 g, 0.20 mol), 2- or 3-chloropentane (5.33 g, 0.050 mol), and 2- or 3-phenylhexane (0.60 g, 0.0050 mol) were stirred at 0 or 25°. In the reactions carried out at −20°, enough hexane was added to keep the benzene from freezing. Aluminum chloride (0.67 g, 0.0050 mol) was added, and at the time intervals stated in Table III, 1-ml aliquots of the reaction mixture were withdrawn, quenched, and analyzed as before, using a 6 ft × 0.25 in. 10% Ucon column at 140°. The results are presented in Table III.

E. Tests of Rearrangement of Xylylpentanes under Alkylation Conditions. 2- or 3-*p*-xylylpentane (4.4 g, 0.025 mol), isopropyl chloride (2.0 g, 0.025 mol), *p*-xylene (10.6 g, 0.100 mol), and aluminum chloride (0.33 g, 0.0025 mol) were stirred at 0 and at −20° for 2.5 hr. The reaction mixtures were decomposed and a 5 ft × 0.125 in. Bentone-34 (5%)–silicone gum rubber (5%) column was used to separate the xylylpropanes produced from the xylylpentanes remaining. In the reactions run at −20°, neither 2- or 3-*p*-xylylpentane showed any rearrangement. In the reactions run at 0°, 2-*p*-xylylpentane underwent 5% rearrangement to 3-*p*-xylylpentane, and 3-*p*-xylylpentane underwent 22% rearrangement to 2-*p*-xylylpentane.

F. Alkylations with Aluminum Chloride–Nitromethane Catalyst. These were carried out as in section D except that the aluminum chloride was dissolved in nitromethane before adding it to the reactants according to methods A and B. The mole ratios, conditions, and results are presented in Table VIII.

Registry No.—Benzene, 71-43-2; 2-chloropentane, 625-29-6; 3-chloropentane, 616-20-6; aluminum chloride, 7446-70-0; 2-chlorohexane, 638-28-8; 3-chlorohexane, 2346-81-8; 2-phenylhexane, 6031-02-3; 3-phenylhexane, 4468-42-2; *p*-xylene, 106-42-3; 2-*p*-xylylpentane, 942-08-5; 3-*p*-xylylpentane, 4465-85-4.

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od B does not seem valid, since equilibrium control implies reversibility of alkylation, and the lack of rearrangement of phenylhexanes present in the chloropentane alkylations at −20° appears to refute this possibility. Of course one must remember that the reaction mixtures produced by both methods A and B are heterogeneous, and the isomeric chloroalkanes, catalyst, arene, and solvent (hexane) may be distributed quite differently in the reaction medium when the order of addition is changed. It is conceivable that in the reactions carried out by method B either (1) equilibration of the product phenylalkanes *does* occur even at −20°, or (2) there is not the same difference in rates of alkylation by 2- and 3-chloroalkanes in the reaction medium of method B as in the reaction medium of method A.

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Transfer Hydrogenation and Transfer Hydrogenolysis. IX. Hydrogen Transfer from Organic Compounds to Aldehydes and Ketones Catalyzed by Dihydridotetrakis(triphenylphosphine)ruthenium(II)

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In the hydrogen transfer from organic compounds to aldehydes and ketones, $RuH_2(PPh_3)_4$ was found to have an excellent catalytic activity under mild conditions. Ethers, hydroaromatic compounds, tertiary amines, and alcohols showed hydrogen donating ability, and the ability decreased in the order 2,5-dihydrofuran > tri-*n*-propylamine > benzyl alcohol > cyclohexanol > ethyl alcohol > tetralin ≈ 1,2-dihydronaphthalene > dioxane. The mechanism of hydrogen transfer from alcohols to the aldehydes was investigated. The data of the reaction can be accommodated by the rate expression of the form rate = $k[D][Cat]_0/(1 + K[RCHO])$, where [D], $[Cat]_0$, and [RCHO] are alcohol, catalyst, and aldehyde concentration, respectively. The kinetic isotope effect, $R_H/R_D = 0.9$, and other data suggests that the rate-determining step of the reaction is the coordination of the alcohols to the complex. The process of the hydrogen transfer from alcohols to aldehydes on the metal is also proposed.

In catalytic hydrogenation using transition metal complexes as catalysts, olefins have been mainly used as hydrogen acceptors and the reduction of other functional groups has received little attention. As for the reduction of aldehydes and ketones by molecular hydrogen, it has been reported that several cobalt,[1] iridium,[2] and rhodium[3] complexes have activities as homogeneous catalysts. In the catalytic transfer hydrogenation of aldehydes and ketones to alcohols, only primary and secondary alcohols seem to have been used as hydrogen donors, and transition metal salts,[4] $CoH_3(PPh_3)_3$,[5] $RhCl(PPh_3)_3$,[6] $RuCl_2(PPh_3)_3$,[7] and $IrCl_3[P(OMe)_3]_3$,[8] have been reported to have activity as homogeneous transition metal catalysts. However, no detailed studies of the mechanism of the reaction, including that of heterogeneous systems, have yet been carried out.

This study was undertaken to examine the transfer hydrogenation of aldehydes and ketones in detail.

Results and Discussion

Catalytic Activity of Some Phosphine Complexes. The catalytic activity of some representative phosphine complexes for the reduction of *n*-hexaldehyde was investigated. When a catalyst (0.02 M), benzyl alcohol (2.0 M), and *n*-hexaldehyde (1.0 M) were heated in bromobenzene at 120° for 150 min, the yield of *n*-hexyl alcohol was given as follows: $RuH_2(PPh_3)_4$, 0.90 M; $RuH_2(CO)(PPh_3)_3$, 0.78 M; $RuCl_2(PPh_3)_3$, 0.43 M; $RhH(PPh_3)_4$, 0.02 M; and $RhCl(CO)(PPh_3)_2$, $CoH[P(OPh)_3]_3$, and $MCl_2(PPh_3)_2$ (M = Fe, Ni, Co, Pd, and Pt) had no catalytic activity under this condition. $RhCl(PPh_3)_3$ showed no catalytic activity, because the complex was transformed to $RhCl(CO)(PPh_3)_2$ by the reaction with aldehyde[9] which has no catalytic activity. $RuH_2(PPh_3)_4$ was found to have the highest activity among complexes tried in this transfer hydrogenation, and the complex catalyzed the hydrogen transfer even at room temperature. In this study, $RuH_2(PPh_3)_4$ was used as a catalyst.

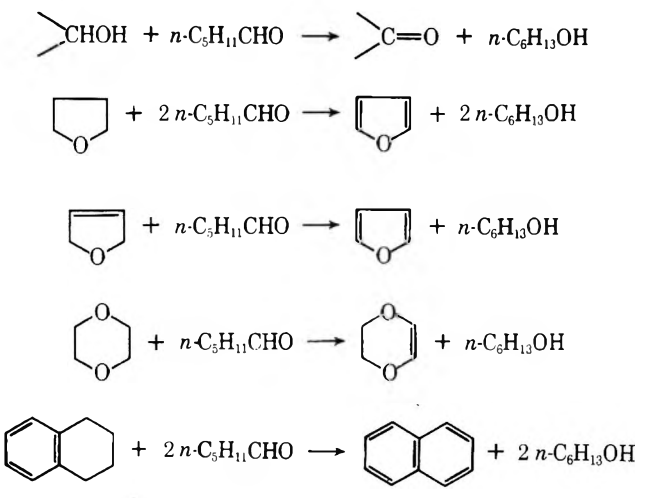
Hydrogen-Donating Ability of Some Organic Compounds. We have previously reported that cyclic ethers,[10] amines,[11] and alcohols[12] donate hydrogen to olefins in the presence of $RhCl(PPh_3)_3$, $RhH(PPh_3)_4$, or $RuH_2(PPh_3)_4$. The hydrogen-donating ability of some organic compounds to *n*-hexaldehyde was evaluated (Table I). 2,5-Dihydrofuran, benzyl alcohol, and cyclohexanol showed especially excellent hydrogen-donating abilities. Perhaps these compounds donate hydrogen rapidly and the resulted dehydrogenation products are relatively resistant to reduction. Other alcohols, hydroaromatic compounds, and ethers had almost the same hydrogen-donating abilities under the reaction condition. It is noteworthy that noncyclic ethers gave hydrogen in homogeneous catalysis, because such a phenomena seems not to be reported. When primary and secondary amines were used, *n*-hexyl alcohol was not detected and *n*-hexaldehyde disappeared. In the case of tertiary amines, the alcohol was obtained in good yield, but the amount of the surviving aldehyde was smaller than the theoretical one. These results show the existence of side reactions between the aldehyde and amines.

Analyses of the dehydrogenation products summarized in Table II clearly shows that the following reactions proceeded almost stoichiometrically without remarkable side reactions.

Table I
Transfer Hydrogenation of *n*-Hexaldehyde[a]

Registry no.	Hydrogen donor	Yield of *n*-hexyl alcohol, %	Dehydrogenation product
1708-29-8	2,5-Dihydrofuran	30	Furan
123-91-1	Dioxane	10	Dioxene
109-99-9	Tetrahydrofuran	9	Furan
111-43-3	Di-*n*-propyl ether	9	*b*
108-20-3	Diisopropyl ether	9	*b*
142-68-7	Tetrahydropyran	8	2,3-Dihydropyran
142-96-1	Di-*n*-butyl ether	7	*b*
628-81-9	Butyl ethyl ether	6	*b*
102-69-2	Tri-*n*-propylamine	25	*b*
1116-76-3	Tri-*n*-octylamine	11	*b*
100-51-6	Benzyl alcohol	23	Benzaldehyde
108-93-0	Cyclohexanol	19	Cyclohexanone
64-17-5	Ethyl alcohol	13	Acetaldehyde
67-63-0	Isopropyl alcohol	10	Acetone
119-64-2	Tetralin	11	1,2-Dihydronaphthalene Naphthalene
447-53-0	1,2-Dihydronaphthalene	11	Naphthalene
110-83-8	Cyclohexene	9	Benzene

[a] $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and the hydrogen donor (2.0 M) were heated in bromobenzene at 36.5 ± 0.5° for 72 h. [b] Dehydrogenation product was not identified.



When the reaction was carried out in alcohols, the produced alcohol was scarcely dehydrogenated to *n*-hexaldehyde and *n*-hexyl alcohol was obtained in good yield. In the case of 2,5-dihydrofuran, *n*-hexyl alcohol was obtained in the yield of 100%, partly because the dehydrogenation product, furan, is an aromatic compound and resists hydrogenation. Even when excess triphenylphosphine was added to 2-propanol solution, the yield of *n*-hexyl alcohol was about 100%. This fact suggests that the aldehyde has large coordinating ability to the complex.

Hydrogen Acceptor. Several aldehydes and ketones were examined as hydrogen acceptors (Table III). Aliphatic aldehydes were efficiently reduced. A more steric aldehyde was hydrogenated more easily than a less steric one. As a less steric aldehyde has strong coordinating ability, it may act as a poison of the catalyst and make the coordination of the hydrogen donor difficult. These results and reasoning are compatible with the dependence of the reaction rate on aldehyde concentration, as described later. Crotonaldehyde, which has two unsaturated bonds, C=C and C=O, was hydrogenated to *n*-butyraldehyde and *n*-butyl alcohol. As it has been reported that in the case of α,β-unsaturated carbonyl compounds only the C=C bond was hydrogenated,[13] this catalyst action seems to be a unique one. The low conversion of crotonaldehyde may be due to the stabilization by resonance between C=C and C=O bonds and/or to the coordination to the complex as bidentate ligand blocking the coordination of the hydrogen donor. Compared with aldehydes, ketones were relatively resistant to reduc-

Table II
Stoichiometric Relation of Transfer Hydrogenation[a]

Hydrogen donor	Yield of *n*-hexyl alcohol, M	Survived *n*-hexaldehyde, M	Dehydrogenation product, M
2,5-Dihydrofuran	1.00	0.00	Furan, 1.00
Isopropyl alcohol	1.00	0.00	Acetone, 1.00
Isopropyl alcohol[b]	0.99	Trace	Acetone, 1.00
Benzyl alcohol	0.97	0.03	Benzaldehyde, 0.97
Cyclohexanol	0.93	0.06	Cyclohexanone, 0.93
n-Propyl alcohol	0.88	0.11	Propionaldehyde, 0.86
Tetralin	0.29	0.70	1,2-Dihydronaphthalene, 0.10 Naphthalene, 0.09
Dioxane	0.29	0.70	Dioxene, 0.30
Tetrahydrofuran	0.10	0.88	Furan, 0.05

[a] $RuH_2(PPh_3)_4$ (0.02 M) and *n*-hexaldehyde (1.0 M) were heated at 140° for 2 h in the designated hydrogen donor. [b] 0.2 M of PPh_3 was added.

Table III
Transfer Hydrogenation of Aldehydes and Ketones[a]

Registry no.	Hydrogen acceptor	Yield of product, M
123-38-6	Propionaldehyde	*n*-Propyl alcohol, 0.22
123-72-8	*n*-Butyraldehyde	*n*-Butyl alcohol, 0.34
78-84-2	Isobutylaldehyde	Isobutyl alcohol, 0.50
110-62-3	*n*-Pentaldehyde	*n*-Pentyl alcohol, 0.40
66-25-1	*n*-Hexaldehyde	*n*-Hexyl alcohol, 0.42
111-71-7	*n*-Heptaldehyde	*n*-Heptyl alcohol, 0.44
124-13-0	*n*-Octaldehyde	*n*-Octyl alcohol, 0.48
123-05-7	2-Ethyl-1-hexaldehyde	2-Ethyl-1-hexyl alcohol, 0.49
4170-30-3	Crotonaldehyde	*n*-Butyl alcohol, 0.05 *n*-Butyraldehyde, 0.08
67-64-1	Acetone	Isopropyl alcohol, 0.18
96-22-0	Diethyl ketone	3-Pentanol, 0.09

[a] $RuH_2(PPh_3)_4$ (0.02 M), benzyl alcohol (2.0 M), and the hydrogen acceptor (1.0 M) were heated in bromobenzene at 100° for 1 hr.

Table IV
Solvent Effect in Transfer Hydrogenation[a]

Registry no.	Solvent	Rate, M min^{-1}	Registry no.	Solvent	Rate, M min^{-1}
67-68-5	Dimethyl sulfoxide	7.0×10^{-3}	110-54-3	*n*-Hexane	3.8×10^{-3}
98-95-3	Nitrobenzene	4.6×10^{-3}	108-90-7	Chlorobenzene	3.7×10^{-3}
140-11-4	Benzyl acetate	4.0×10^{-3}	1330-20-7	Xylene	3.5×10^{-3}
110-82-7	Cyclohexane	4.0×10^{-3}	150-76-5	Anisole	3.1×10^{-3}
108-86-1	Bromobenzene	3.8×10^{-3}	60-29-7	Diethyl ether	2.5×10^{-3}
71-43-2	Benzene	3.8×10^{-3}			

[a] $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and benzyl alcohol (2.0 M) were heated in the designated solvent at 80°.

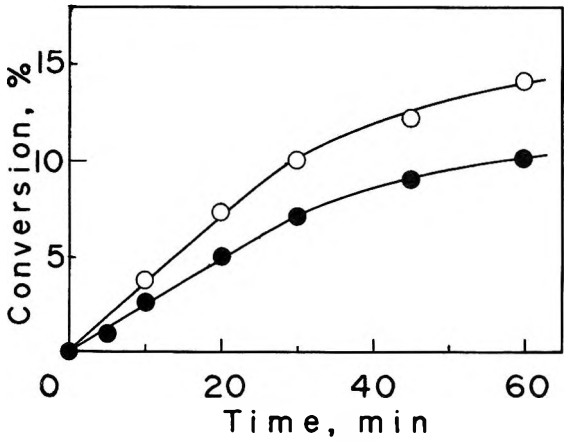


Figure 1. Plot of conversion vs. reaction time: $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and the hydrogen donor (2.0 M) were heated in bromobenzene at 80°. ○, benzyl alcohol; ●, isopropyl alcohol.

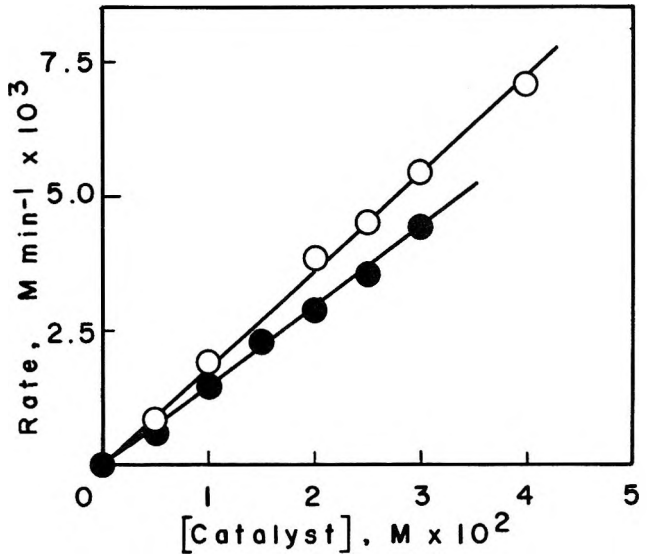


Figure 2. Dependence of rate of reduction of *n*-hexaldehyde on catalyst concentration: the catalyst, *n*-hexaldehyde (1.0 M), and the hydrogen donor (2.0 M) were heated in bromobenzene at 80°. ○, benzyl alcohol; ●, isopropyl alcohol.

tion. This may be explained by the fact that the formed secondary alcohols donate hydrogen more easily than primary alcohols, as shown in Table II. Nitrobenzene, benzonitrile, and acetonitrile were not reduced under the same condition. In this study, *n*-hexaldehyde was used as an acceptor because of the ease in GLC analysis.

Reaction Solvent. Initial rates of the transfer hydrogenation in several solvents were measured (Table IV). The catalyst dissolved well in these solvents at reaction temperature. The rate was not so varied by the kinds of solvents except for dimethyl sulfoxide and nitrobenzene. The fact

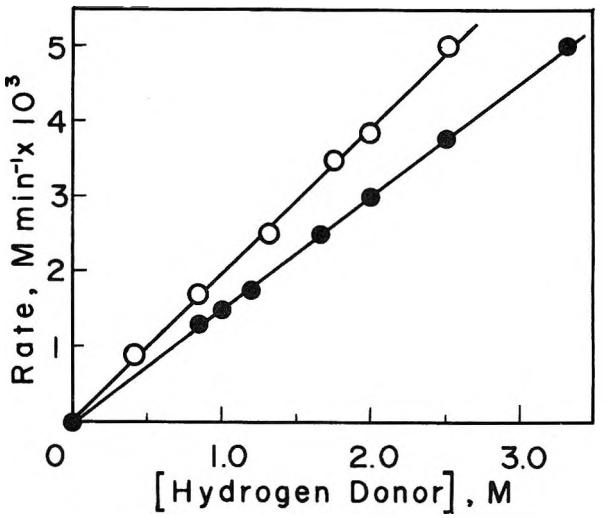


Figure 3. Dependence of rate of reduction of *n*-hexaldehyde on the hydrogen donor concentration: $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and the hydrogen donor were heated in bromobenzene at 80°. ○, benzyl alcohol; ●, isopropyl alcohol.

that the reduction of the aldehyde proceeded effectively in highly polar and coordinative solvents such as dimethyl sulfoxide and nitrobenzene suggests that the coordinating powers of alcohols and aldehydes are not so weak and strongly polar solvents promote the displacement of the dehydrogenation products by reactants. In this study, bromobenzene was used as a solvent because of convenience.

Measurement of Initial Rate. Figure 1 shows an example of the conversion of *n*-hexaldehyde to *n*-hexyl alcohol against reaction time. At the initial stage of the reaction, the conversion was proportional to the time. However, the linearity did not hold in the conversion more than 10% (benzyl alcohol) and 7% (isopropyl alcohol), perhaps because the produced *n*-hexyl alcohol itself was dehydrogenated to *n*-hexaldehyde and the dehydrogenated products, such as benzaldehyde and acetone, were hydrogenated to the original alcohols. The initial rate of the reaction (R) was derived from the linear part.

The initial rate of the reduction was found to be proportional to the concentration of the catalyst and hydrogen donors (Figures 2 and 3). This result indicates that either the coordination of the hydrogen donor takes place before the rate-determining step or this step is rate limiting.

The initial rate of the reduction decreased with the increase of aldehyde concentration, and the reciprocal of the rate against aldehyde concentration was linear with a positive intercept on the y axis (Figure 4). It is thought that the aldehyde has strong coordinating power and that a considerable amount of aldehyde complexes exists in the reaction system.

Dependence on Added Phosphine. In transfer hydrogenation of olefins,[11,12] except for the $RhCl(PPh_3)_3$–dioxane system,[10] the addition of triphenylphosphine decreased

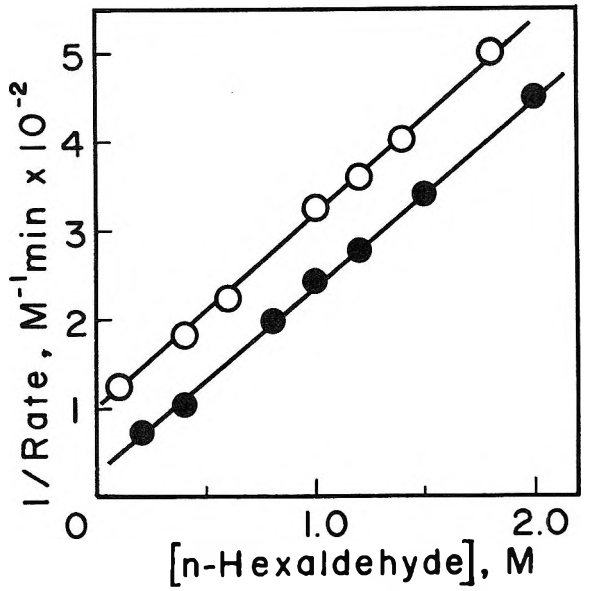


Figure 4. Dependence of rate of reduction of *n*-hexaldehyde on the aldehyde concentration: $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde, and the hydrogen donor (2.0 M) were heated in bromobenzene at 80°. ○, benzyl alcohol; ●, isopropyl alcohol.

the reaction rate. In contrast, the rate of the reduction of aldehyde was not decreased at all by the addition of the phosphine over the range of 0.02–0.2 M.

Dependence on Reaction Temperature. Initial rates were measured at 60, 70, 80, 90, 100, and 110°. Good linear plots of log R against $1/T$ were obtained in the case of benzyl alcohol and isopropyl alcohol, indicating that the kinetics of the reaction system are not so complicated. From the plots, activation energy, E_a, and activation enthalpy, $\Delta H^{\ddagger}$ are obtained (Table V), and activation entropy, $\Delta S^{\ddagger}$, is calculated with the observed rate constant (k'). The values of the corresponding parameters are almost equal in the reduction in bromobenzene, and this seems to show the similarity in the reaction mechanism. It is inferred that active intermediates are not ionized or strongly polarized and the coordination of bromobenzene occurs, because the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the reaction in bromobenzene are considerably lower than those in *n*-hexane. Further, the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the reduction of *n*-hexaldehyde are much lower than those in the case of cyclohexene. Perhaps this suggests that the nature of the rate-determining step is different in the two reactions and that active intermediates in the reduction of the aldehyde are more crowded or more ordered than in the reduction of cyclohexene.[14]

Isotopic Study. When isopropyl alcohol-d_8 (1.0 M) was used instead of isopropyl alcohol at 80°, the initial rate was 1.9×10^{-3} M min^{-1}, while in the case of isopropyl alcohol it was 1.7×10^{-3} M min^{-1}. The value of the kinetic isotope effect, $R_H/R_D = 0.9$, shows that a hydrogen transfer step is not rate limiting. In the transfer hydrogenation of olefins catalyzed by representative Rh(I) and Ru(II) complexes, the kinetic isotope effect of large values was observed, and the dehydrogenation of the hydrogen donor was considered to be rate limiting. The difference of the kinetic isotope effect in $RuH_2(PPh_3)_4$ catalysis indicates that the nature of reaction intermediates and the rate-determining step are different from one another. Other complexes shown in Table VI had no catalytic activity for the reduction of the aldehyde.

Dependence of the Rate on Hydrogen Donor. The initial rate of the hydrogenation of *n*-hexaldehyde was measured in the presence of several hydrogen donors (Table VII). The fact that aliphatic secondary alcohols, having a bulky branched chain, had less effective hydrogen-donating abilities suggests that the coordination of alcohols to the catalyst is an important reaction step. Benzyl alcohol and 2-phenylethyl alcohol showed more excellent hydrogen-donating abilities than aliphatic alcohols. Perhaps this fact may be rationalized by the stability of the formed carbonyl groups conjugated with benzene ring and/or by the promoting effect of benzene ring on the coordination of the hydrogen donors to the catalyst complex. The effective hydrogen-donating abilities of 2,5-dihydrofuran and tetralin may be due to aromatization.

Table V
Kinetic Parameters

Hydrogen donor	Solvent	E_a, kcal mol^{-1}	$\Delta H^{\ddagger}$ (80°), kcal mol^{-1}	$\Delta S^{\ddagger}$ (80°), eu
Benzyl alcohol[a]	Bromobenzene	10.3	9.6	−41.8
Benzyl alcohol[a]	*n*-Hexane	17.2	16.6	−17.0
Isopropyl alcohol[a]	Bromobenzene	11.0	10.3	−42.5
Isopropyl alcohol[b]	Toluene	31.4	30.7	20

[a] $RuH_2(PPh_3)_4$ (0.02 M) and *n*-hexaldehyde (1.0 M) were used. [b] $RuH_2(PPh_3)_4$ (0.01 M) and cyclohexene (0.5 M) were used.

Table VI
Kinetic Isotope Effect

Registry no.	Complex	Olefin[a] R_H/R_D	*n*-Hexaldehyde[b] R_H/R_D
14694-95-2	$RhCl(PPh_3)_3$	2.6 (180°)	Decarbonylation occurred
18284-36-1	$RhH(PPh_3)_4$	1.33 (80°)	*c*
15529-49-4	$RuCl_2(PPh_3)_3$	2.8 (180°)	*c*
19529-00-1	$RuH_2(PPh_3)_4$	2.7 (80°)	0.9

[a] The catalyst (0.01 M), isopropyl alcohol or isopropyl alcohol-d_8 (1.0 M), and cyclohexene (0.5 M) were heated in toluene. [b] The catalyst (0.02 M), isopropyl alcohol or isopropyl alcohol-d_8 (1.0 M), and *n*-hexaldehyde (1.0 M) were heated in bromobenzene. [c] The reduction of the aldehyde was very slow.

Spectrophotometric Study. The visible spectrum of $RuH_2(PPh_3)_4$ in chloroform showed an absorption peak at 650 nm (ϵ 10^3). The strength of the peak decreased gradually with time by addition of aldehydes. The initial rates of the decrease of the absorption peak were measured for several aldehydes (Table VIII). The rates of the decrease of branched aldehydes were smaller than those of straight-chain aldehydes, and this shows the existence of steric hindrance in the coordination of aldehyde to the complex. The appearance of the maximum value at *n*-hexaldehyde may be due to the optimum balance between the coordination of the aldehyde and the release of the resulting alcohol, which can reduce the Ru(0) complex to Ru(II) dihydrido complex. Besides, the decreasing order of rates is not parallel to that of the conversion of aldehydes to alcohols, and it may suggest that the hydrogen transfer from the complex to aldehydes is not the rate-determining step of the catalytic cycle. Accompanied with the decrease of the strength of the peak at 650 nm, the new absorption peak at 560 nm appeared. The peak was assignable to Ru(0) species on the following observations: (1) when *n*-hexaldehyde (0.1 M) and $RuH_2(PPh_3)_4$ (0.1 M) were heated in chloroform at 36.5° for 72 hr, 0.1 M of *n*-hexyl alcohol was obtained. In the reaction mixture, the absorption peak appeared at 560 nm and the one at 650 nm disappeared. (2) The ir spectrum of the chloroform solution showed no peaks assignable to the hydride ligands. Moreover, when the volatile compounds were evaporated from the solution in vacuo, the ir

Table VII
Rate of Transfer Hydrogenation of *n*-Hexaldehyde[a]

Hydrogen donor	Rate, M min^{-1}	Hydrogen donor	Rate, M min^{-1}
2,5-Dihydrofuran	15.5×10^{-3}	Ethyl alcohol	2.5×10^{-3}
Tetralin	4.2×10^{-3}	*sec*-Butyl alcohol	1.8×10^{-3}
Benzyl alcohol	3.8×10^{-3}	3-Pentyl alcohol	1.6×10^{-3}
Isopropyl alcohol	2.8×10^{-3}	4-Methyl-2-pentyl alcohol	1.5×10^{-3}
2-Phenylethyl alcohol	2.7×10^{-3}		

[a] $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and the hydrogen donor (2.0 M) were heated in bromobenzene at 80°.

Table VIII
The Rate of Spectral Change of the Catalyst[a]

Additive	Rate, M min^{-1}	Additive	Rate, M min^{-1}
Propionaldehyde	2.80×10^{-6}	*n*-Heptaldehyde	3.74×10^{-6}
n-Butyraldehyde	4.76×10^{-6}	*n*-Octaldehyde	3.10×10^{-6}
Isobutyraldehyde	2.00×10^{-6}	2-Ethyl-1-hexaldehyde	2.20×10^{-6}
n-Pentaldehyde	4.82×10^{-6}	Acetone	8.00×10^{-7}
n-Hexaldehyde	5.62×10^{-6}		

[a] $RuH_2(PPh_3)_4$, 5×10^{-4} mol l.$^{-1}$, additive; 5×10^{-2} mol l.$^{-1}$, temperature 20°, solvent chloroform.

spectrum of the residual solid was almost the same as that of the original complex, $RuH_2(PPh_3)_4$, except that the peak due to the hydride ligands had disappeared. (3) When $RuH_2(PPh_3)_4$ (0.10 M) and propionaldehyde (0.30 M) were heated in *n*-hexane at 60° for 5 hr, a yellow solid was obtained by evaporation of the volatile compounds from the solution. It was washed with *n*-hexane twice and dried in vacuo. The ir spectrum of the residual solid showed a peak at 1520 cm^{-1} which may be attributable to the coordinated carbonyl group of the aldehyde.[15] The NMR spectrum of the residual solid showed peaks at τ 8.9, 7.7, and 2.7 with 3:2:136 area in $CDCl_3$ with Me_4Si as an internal standard. The peak assignable to the aldehyde proton was not detected. The peak at τ 8.9 and 7.7 are assignable to the methyl and methylene group of the aldehyde, and the one at τ 2.7 is assignable to phenyl protons, respectively. From the ratio of the peak at τ 2.7 to the one at τ 8.9 or 7.7, the ratio of triphenylphosphine to propionaldehyde was found to be about 3. However, the elemental analysis did not agree with the reasonably presumed complex, $Ru(PPh_3)_3(CH_3CH_2CHO)$. (Calcd for an example: C, 72.37; H, 5.43. Found: C, 70.70; H, 5.62.) Moreover, the reproducibility of the elemental analysis was bad and the ratio of carbon gradually decreased by the storage of the sample. This suggests that the aldehyde complex is labile and the aldehyde is lost little by little.

From these results, it is inferred that the first step of the catalytic transfer hydrogenation is the transfer of hydride ligands of the complex to aldehydes, as shown in Scheme I.

Scheme I

$$RuH_2(PPh_3)_4 + RCHO \longrightarrow RuH_2(PPh_3)_3(RCHO) + PPh_3$$

$$RuH_2(PPh_3)_3(RCHO) \xrightarrow{S} Ru(PPh_3)_3S + RCH_2OH$$

S = solvent

Kinetic Discussion

The first step of this transfer hydrogenation was as shown in Scheme I. Based on the results described earlier and the comparison with the mechanism of transfer hydrogenation of olefins,[10-12] Scheme II is reasonably proposed as the catalytic cycle of transfer hydrogenation of the aldehyde.

From Scheme II, the rate is expressed as eq 1

$$R = \frac{(k_4K_1 + k_5K_2)[\text{RCHO}][\text{Cat}]_0[\text{D}]}{1 + K_1[\text{RCHO}] + K_2[\text{D}] + K_1K_3[\text{RCHO}]^2} \quad (1)$$

Scheme II

$$\begin{array}{ccccc} RuP_3 & \overset{K_1,\ \text{RCHO}}{\rightleftharpoons} & RuP_3(RCHO) & \overset{K_2,\ \text{RCHO}}{\rightleftharpoons} & RuP_3(RCHO)_2 \\ \text{I} & & \text{II} & & \text{IV} \\ {\scriptstyle K_2,\ \text{D}}\downarrow\uparrow & & {\scriptstyle \text{D}}\downarrow{\scriptstyle k_4} & & \\ RuP_3D & \xrightarrow[\text{RCHO}]{k_5} & RuP_3D(RCHO) & \xrightarrow{k_6} & RuP_3 + De + RCH_2OH \\ \text{III} & & \text{V} & & \end{array}$$

P = PPh_3, D = hydrogen donor,
De = dehydrogenation product of donor

where K_1, K_2, and K_3 are equilibrium constants and k_4, k_5, and k_6 are rate constants, and [D], [RCHO], and $[\text{Cat}]_0$ are the concentration of the hydrogen donor, the aldehyde, and added catalyst, respectively. In eq 1, the hydrogen transfer step in which V decomposes to the products may be reasonably assumed to proceed fast, because the kinetic isotope effect was negligible as described earlier.

As the reciprocal of the rate against aldehyde concentration gave the linear relationship, the following relation should be satisfied in the numerator of eq 1: $1 + K_2[\text{D}] \ll K_1[\text{RCHO}](1 + K_3[\text{RCHO}])$, that is, [I] + [III] $\ll$ [II] + [IV]. This relation requires that the coordination power of aldehydes is strong, and this is supported by the observations that the reduction rate was not decreased by the addition of acetone, triphenylphosphine, or olefins. Then, the rate expression is reduced to

$$R = \frac{k'[\text{D}][\text{Cat}]_0}{1 + K_3[\text{RCHO}]} \quad (2)$$

where k' is the observed rate constant, $(k_5K_2 + k_4K_1)/K_1$. This expression is found to accommodate all of the other experimental observations fairly well. When isopropyl alcohol was used as the hydrogen donor, the values of the constants in eq 2 are analyzed, that is, (a) the rate should be proportional to the catalyst concentration, and this agrees with the experimental result, as shown in Figure 2. From this figure, 7.5×10^{-2} min^{-1} was obtained as the value of $k'/(1 + K_3)$. (b) The rate should be in proportion to the donor concentration, and this agrees with the result in Figure 3. From this figure, the same value, 7.5×10^{-2} min^{-1}, was obtained as the value of $k'/(1 + K_3)$. (c) Equation 2 is rearranged as follows.

$$1/R = \frac{1}{k'[\text{D}][\text{Cat}]_0} + \frac{K_3}{k'[\text{D}][\text{Cat}]_0}[\text{RCHO}] \quad (3)$$

From Figure 4, the value for gradient, 2.2×10^2 mol^{-2} l.^{2} min, and the value for intercept, 10^2 mol^{-1} l. min, were obtained, respectively. By using these values, $k' = 0.25$ mol l.$^{-1}$ min^{-1} and $K_3 = 2.2$ mol^{-1} l. were obtained as the values at 80°. When these values are put to $k'/(1 + K_3)$, the value of 7.8×10^{-2} min^{-1} is given and fairly agrees with the one obtained from Figures 2 and 3. Therefore, when the reaction was carried out in bromobenzene at 80° with isopropyl alcohol as a hydrogen donor, the overall rate expression is formulated as follows.

$$R = \frac{0.25[\mathrm{D}][\mathrm{Cat}]_0}{1 + 2.2[\mathrm{RCHO}]} \quad (4)$$

Using a similar analytical method, the value for k', 1.0 mol l.$^{-1}$ min^{-1}, and the value for K_3, 9.0 mol^{-1} l., and rate expression, $R = [\mathrm{D}][\mathrm{Cat}]_0/(1 + 9[\mathrm{RCHO}])$, are obtained in the case of benzyl alcohol. From these results, the rate-determining step of the reduction seems to be the coordination of the hydrogen donor.

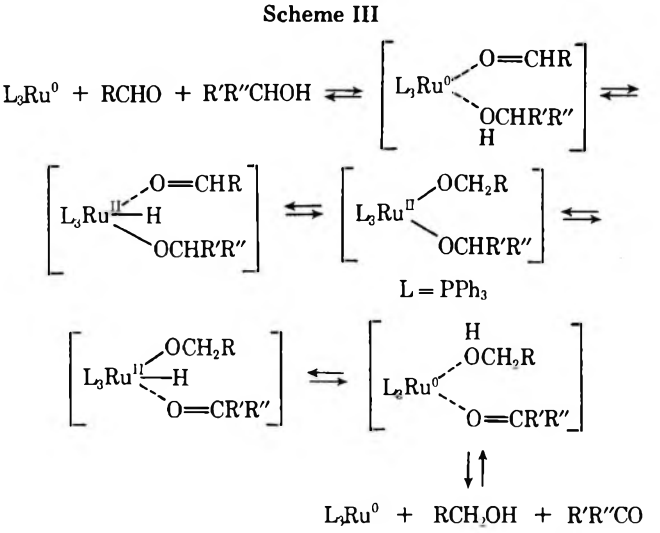
The hydrogen transfer from alcohol to aldehyde on the complex is thought to involve several steps. In the transfer hydrogenation of olefins, large R_H/R_D values were obtained as described earlier and the following reaction scheme has generally been shown

$$\mathrm{M} + \mathrm{D} \xrightarrow{-\mathrm{De}} \mathrm{MH_2} \xrightarrow{\text{olefin}} \mathrm{M} + \text{paraffin}$$

where M represents an active catalytic species. However, olefins were not reduced under the condition that aldehydes were effectively reduced, and the kinetic isotope effect in the reduction of aldehydes is negligible. In the hydrogen transfer from secondary alcohols to ketones catalyzed by $RuCl_2(PPh_3)_3$, a rather large kinetic isotope effect, $R_H/R_D = 1.68$, has been reported,[7] and Sasson et al. have proposed that $RuCl_2(PPh_3)_2$ is an active species and an alcohol coordinates to the complex in alkoxide form after a ketone has coordinated. Further, it has been reported that the dehydrogenation of alcohols via alkoxide complexes is generally promoted by the addition of basic compounds.[16] In the case of $RuH_2(PPh_3)_4$ catalysis, the hydride ligands rapidly transfer to aldehyde, and $Ru(PPh_3)_3S$ (S = solvent) is suitably considered as the main reaction intermediate. The rate of the reduction is not changed by the addition of triethylamine. These results suggest that in the transfer hydrogenation of aldehydes the mechanism of catalysis of $RuH_2(PPh_3)_4$ is greatly different from that of $RuCl_2(PPh_3)_3$ and that of any complex in the transfer hydrogenation of olefins. So we should like to propose that the hydrogen transfer from alcohols to aldehydes on the Ru(0) species may involve the following steps: (1) the oxidative addition of the Ru metal to the O–H bond of an alcohol to generate a monohydrido alkoxide complex and (2) the addition of the hydride ligand to the carbonyl group to give a dialkoxide complex, as shown in Scheme III.

According to Scheme III, the hydroxylic hydrogen transfers to the carbon atom of the carbonyl of aldehyde and the hydrogen atom attaching to the α carbon of the alcohol transfers to the oxygen atom of the aldehyde. This is supported by the following observations. In the presence of $RuH_2(PPh_3)_4$ (0.02 M), ethyl alcohol-d_1 (1.0 M) and propionaldehyde (1.0 M) were heated in benzene at 60° for 5 hr, and the NMR spectrum of the reaction mixture showed several peaks assignable to propionaldehyde, *n*-propyl alcohol, ethyl alcohol-d_1, and paraldehyde formed by trimerization of acetaldehyde. The peak attributable to a hydroxylic proton was found. The ir spectrum of the reaction mixture also showed peaks attributable to –OH and –CD bonds. The complex recovered after the reaction between $RuH_2(PPh_3)_4$ and isopropyl alcohol-d_8 in the absence of aldehydes had no peaks attributable to Ru–D and OH in the ir spectrum. This result indicates that no H–D exchange occurred between the alcohol and the hydride complex.

Scheme III



Experimental Section

Materials. Dihydridotetrakis(triphenylphosphine)ruthenium(II),[17] dihydridocarbonyltris(triphenylphosphine)ruthenium(II),[18] dichlorotris(triphenylphosphine)ruthenium(II),[19] hydridotetrakis(triphenylphosphine)rhodium(I),[17] chlorocarbonylbis(triphenylphosphine)rhodium(I),[20] chlorotris(triphenylphosphine)rhodium(I),[20] hydridotris(triphenyl phosphite)cobalt(I),[21] dichlorobis(triphenylphosphine)iron(II),[22] dichlorobis(triphenylphosphine)nickel(II),[23] dichlorobis(triphenylphosphine)cobalt(II),[24] dichlorobis(triphenylphosphine)palladium(II),[25] and dichlorobis(triphenylphosphine)platinum(II)[26] were prepared by methods reported in the literature. Alcohols and aldehydes were purified by distillation followed by dehydration with molecular sieves. Solvents were purified by distillation and degassed on a vacuum line with a liquid nitrogen bath before use.

An Example of Kinetic Runs. Reactions were carried out in a Pyrex glass tube. The sealed tube was prepared by the following procedure. Catalysts, hydrogen donors, and aldehydes were put into Pyrex glass tubes which had been sealed on one end. Into the mixture, solvent was added and the total volume of the solution was made 0.5 ml. The tube was sealed under vacuum after two freeze–pump–thaw cycles at 10^{-3} Torr on a vacuum line and liquid nitrogen bath. Five samples, prepared by the method described above, were heated in a polyethylene glycol bath kept at 80 ± 1° for 5, 10, 20, 30, and 45 min. The reaction mixture was submitted to GLC analysis which was performed at 120° using a 2 m × 6 mm stainless steel column packed with 20% of Carbowax (PEG) 20M on Celite 454 and 20 μl of benzene as an internal standard.

The other transfer hydrogenations were carried out in a similar way.

Spectrophotometric Measurement. The reactions of $RuH_2(PPh_3)_4$ and aldehydes have been studied using spectrophotometric techniques in the visible range. Oxygen was excluded from chloroform solvent by degassing on a vacuum line with a liquid nitrogen bath before use. However, the decreasing rate of the absorption peak was hardly affected by the existence of a small amount of oxygen. The reaction rates could be investigated by following the disappearance of the absorption peak with time: $RuH_2(PPh_3)_4$, λ_{max} 650 nm (ϵ 10^3). The measurement was made on a Shimazu double beam spectrophotometer.

Registry No.—*n*-Propyl alcohol, 71-23-8; toluene, 108-88-3; 4-methyl-2-pentyl alcohol, 108-11-2; 2-phenylethyl alcohol, 60-12-8; *sec*-butyl alcohol, 78-92-2; 3-pentyl alcohol, 584-02-1.

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Free-Radical and Hydrogen Bromide Inhibition in the Dark Reaction of Bromine with the 1,2-Dimethylcyclopropanes

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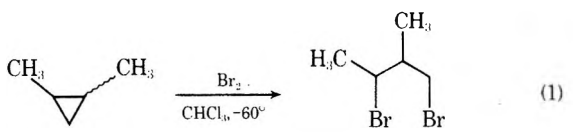
All detectable dibromide products and most of the tribromide products have been identified in the reaction of *cis*- and *trans*-1,2-dimethylcyclopropane with bromine in chloroform. The uncatalyzed reaction is close to 50% complete after 3 h at 0°. The addition of ferric bromide accelerates the reaction slightly but perturbs the product distribution to only a small extent, the main result being an increase in the proportion of the homovicinal dibromides (**6**) at the expense of some of the vicinal dibromides. Free-radical inhibition by either molecular oxygen or isoamyl nitrite has a similar effect on the product distribution. Suppression of the HBr in solution by the addition of NBS also enhances the proportion of the homovicinal dibromides. Some of the vicinal dibromides must therefore come from an addition–elimination–addition pathway, and the homovicinal dibromides **6** are indicated to be the primary electrophilic products. Nonstereospecific production of the homovicinal dibromides **6** in the identical ratio of 4:1 from both isomers is consistent with open carbonium ion intermediates.

Skell and co-workers[2] have recently found that a significant part of the products from the dark reaction of bromine with alkyl-substituted cyclopropanes results from attack by HBr rather than Br_2 on the ring. Opening of the ring by protonation, followed by loss of a proton, gives an alkene, which yields a vicinal dibromide on addition of Br_2. These authors found that this pathway may be suppressed by carrying out the reaction in the presence of *N*-bromosuccinimide.[2] We had previously reported that the major products from the uncatalyzed bromination of *cis*- and *trans*-1,2-dimethylcyclopropane included *threo*- and *erythro*-1,3-dibromo-2-methylbutane (eq 1).[3] The absence of ste-



(1)

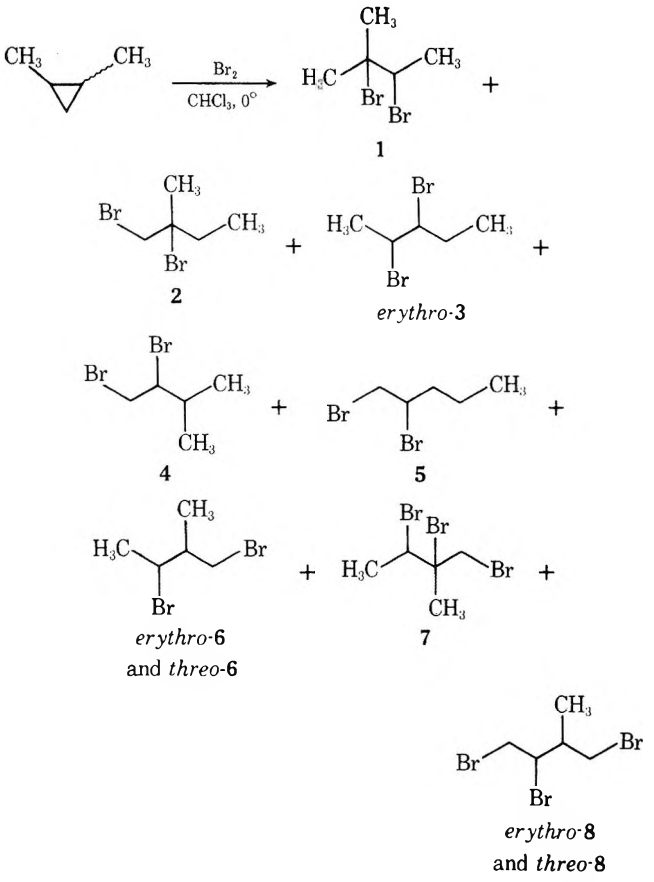
threo + erythro

reospecificity in the formation of these materials was interpreted in terms of open carbonium ion intermediates.[3] The reaction was carried out at low temperatures in the dark in order to minimize free-radical reactions. The conclusions reported previously would be unfounded if the products resulted either from a free-radical or an HBr-mediated pathway. The present paper is a report of the results of electrophilic catalysis (added ferric bromide), free-radical inhibition (molecular oxygen and isoamyl nitrite), and HBr inhibition (NBS) on the reaction of Br_2 with the dimethylcyclopropanes, in order to provide firm evidence for the electrophilic nature of the reaction and to determine which products arise from direct addition of Br_2 and which from the addition of Br_2 to alkenes that arose from initial attack of HBr. Absolute yields have been measured. We have been able to identify several more minor dibromide products, and the structures of two of the previously reported[3] minor dibromides are corrected. We have tentatively determined the structures of the major tribromide products. With the knowledge of the structures of essentially all dibromide and tribromide products and with the assurance that the reaction is indeed electrophilic in nature, we are able to construct a reasonable material balance of carbonium-ion pathways. The results of these experiments confirm the original conclusions regarding the mechanism of the addition of Br_2 to cyclopropanes.[3]

Results

The addition of bromine to *cis*- and *trans*-1,2-dimethylcyclopropane in chloroform was carried out at progressively higher temperatures beginning at −60°, always in the dark. The effect of temperature on the dibromide product distribution was found to be very small. Each dibromide product was collected by preparative gas chromatography and identified by comparison of its spectral and chromatographic properties with those of authentic materials. The tribromides were collected by gas chromatography and identified

Scheme I



by their spectroscopic properties. The structure proof of 8 is still considered tentative. The product identities are given in Scheme I (in order of increasing VPC retention time) and the product distributions in Table I. The extent of conversion was measured by direct examination of the NMR spectrum of the crude product mixture. The integral of the high-field cyclopropylmethylene resonances in the starting material was easily compared to that of the remainder of the spectrum. Conversion after 3 h reached about 50% at 0°. Two of the minor components were previously reported to be *meso*- and *dl*-2,4-dibromopentane,[3] by comparison of retention times only. Isolation of these components proved that the materials in fact were *erythro*-2,3-dibromopentane (*erythro*-**3**, coincident with the *dl* retention time) and 1,2-dibromopentane (**5**, coincident with the meso retention time). The retention time of *threo*-2,3-dibromopentane (*threo*-**3**) coincided with that of another product, 1,2-dibromo-3-methylbutane (**4**). Examination of the NMR spectrum of collected **4** revealed small resonances attributable to *threo*-**3**. The latter material therefore most likely comprises an additional, but very minor, product. The tribromide products were not observed in the original study,[3] since they do not survive Carbowax. The materials, however, were clearly evident on silicone columns. The reactions were all carried out at least three times with good reproducibility.

To promote the opening of the cyclopropane ring, ferric bromide was added to the reaction mixture as an electrophilic catalyst. To inhibit free-radical reactions, molecular oxygen and isoamyl nitrite were added in separate reactions. To decrease side reactions caused by the presence of HBr, the reaction was also carried out with added NBS.[2] The results of these studies are given in Table II for the trans isomer.[4]

Discussion

The question of the stereochemistry of the reaction has been dealt with in the previous paper.[3] The observation that both cyclopropanes give the same erythro/threo ratio of about 4/1 (the actual stereoisomers were not individually identified) indicates that the reaction must pass through the same open carbonium ion in both cases. The homobromonium ion would have led to opposite stereochemical results for the two isomers. These conclusions are further confirmed by the near constancy of the erythro/threo ratio when the reaction is carried out in the presence of the various additives (Table II).

The question of the polar or radical nature of the intermediates can be answered by examination of the effect on product distribution of added electrophilic catalysts and free-radical inhibitors. Ferric bromide accelerates the reaction slightly, but has little effect on the product distribution, the main result being an increase in the homovicinal dibromides (**6**) at the expense of certain vicinal dibromides (**3–5**). Introduction of molecular oxygen or isoamyl nitrite produces a similar result, but to a somewhat greater extent. The total amount of **6** (both isomers) increases from 50% without any additives to 63% in the presence of $FeBr_3$, and to 78% with oxygen. Thus 1,3-dibromo-2-methylbutane (**6**) in its two forms is clearly the predominant product of the

Table I
Normalized Product Distribution from the Bromination of Dimethylcyclopropane[a]

Isomer	1	2	*erythro*-3	4[b]	5	*erythro*-6[c]	*threo*-6	7	*erythro*-8[c]	*threo*-8	Other tribromides	Total convn
Trans	5	5	1	22	4	7	28	6	12	8	2	47
Cis	7	22	2	8	3	4	16	19	10	6	3	49

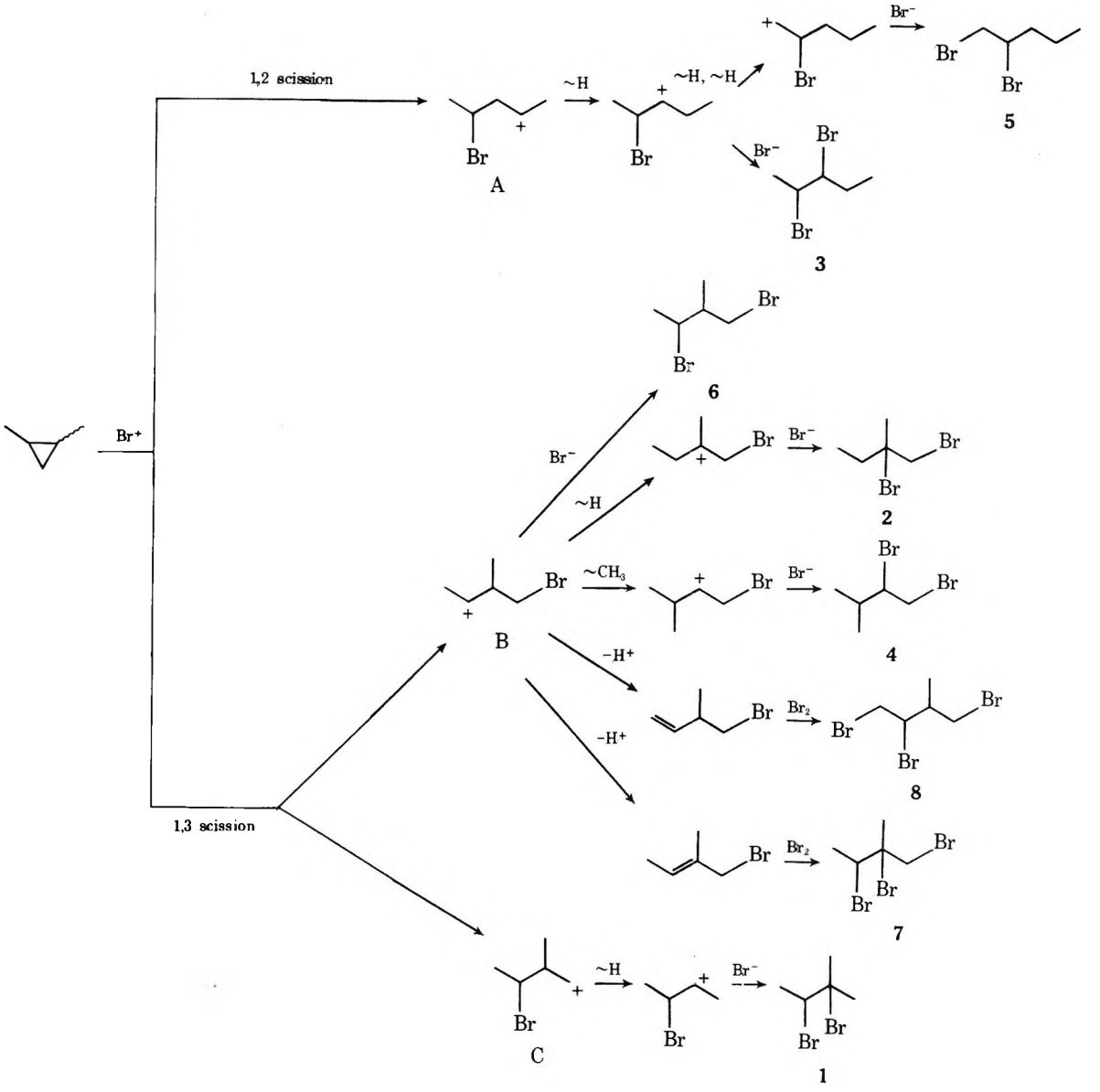
[a] At 0° for 3 h in $CHCl_3$; yields in percent. [b] Also includes a small amount of *threo*-3. [c] Isomers separated but not identified.

Table II
Normalized Yields of Dibromides from the Trans Isomer with Various Added Reagents[a]

Added reagent	1	2	*erythro*-3	4	5	*erythro*-6	*threo*-6
None	7	7	1	30	5	10	40
$FeBr_3$	7	10	–	17	3	16	47
NBS	4	8	1	20	3	13	51
O_2	–	6	–	9	7	21	57
i-AmONO	–	8	–	16	11	13	52

[a] At 0° for 3 h in $CHCl_3$; yields in percent.

Scheme II



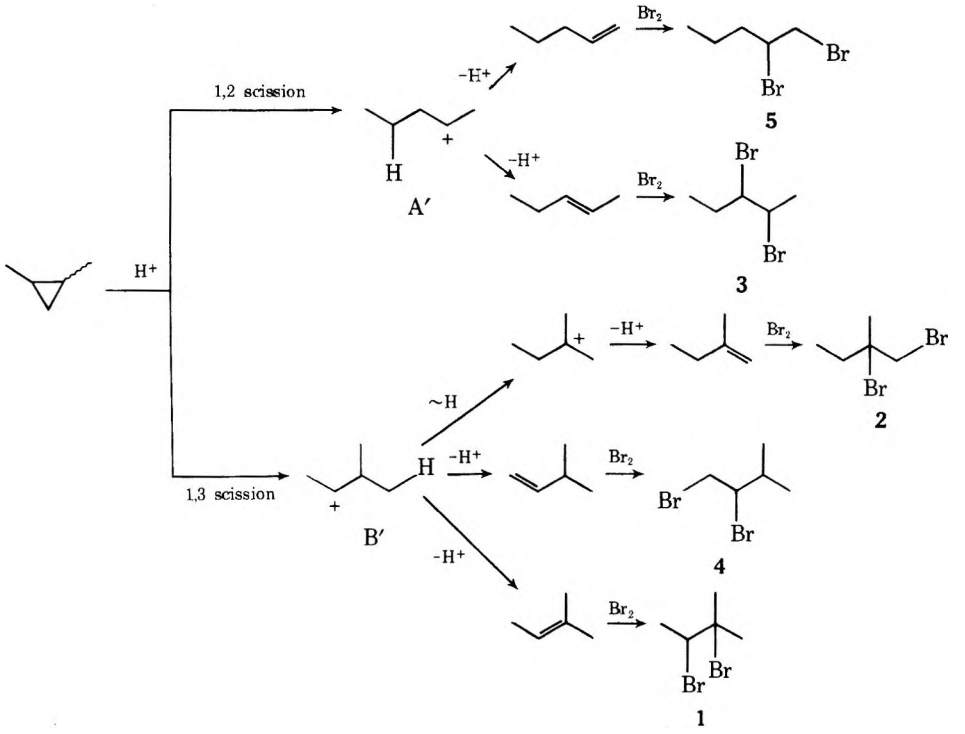
electrophilic pathway, so that the original stereochemical conclusions are indeed valid for the polar reaction. Scheme II depicts possible pathways for the production of all the observed materials, utilizing only open carbonium ions. The scheme is intended to be entirely illustrative, since it leaves out many important details, such as the collapse of α-bromocarbonium ions to three-membered bromonium ions. The tribromides are presumed to come from the addition of bromine to alkenes formed by loss of a proton from the initial bromocarbonium ion.[2]

As Skell et al. have pointed out,[2] there are several drawbacks to a scheme of this sort, e.g., the use of primary carbonium ions and methyl shifts. Thus, it is entirely unreasonable to expect that **5** could emanate from the indicated path in Scheme II. Although ion A is likely to undergo a hydride shift, the resulting cation probably collapses to a bromonium ion and ultimately gives **3**, rather than undergoing further hydride shifts to the primary carbonium ion that gives **5**. Likewise, **4** must come from ion B via a methyl shift, and **1** must result from ring opening to the primary carbonium ion C. Thus, although there are reasonable paths to **2**, **3**, and **6**, Scheme II is unlikely for **4** and not at all plausible for the production of **1** or **5**.

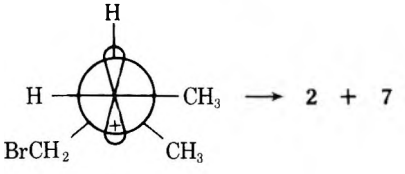
When alkenes are formed from the initial intermediates of Scheme II, a molecule of HBr is produced at the same time. As has been noted by Skell,[2] the HBr can protonate the starting cyclopropane to give a bromine-free carbonium ion. Attack of bromide on such an intermediate would produce a monobromide. A small amount (10% without NBS, a trace with NBS) has been found by Skell.[2b] The bromine-free carbonium ion, however, can also lose a proton to form an alkene, to which a molecule of Br_2 can add (Scheme III). The resulting dibromides have the same structures as those obtained from the direct pathway. Added *N*-bromosuccinimide reacts with any HBr formed and suppresses this pathway. The result of this experiment (Table II) is a decrease in the amounts of **1**, **4**, and **5**. These in fact are the products that must result from unfavorable pathways involving primary carbonium ions or methyl shifts in Scheme II. It is therefore likely that most, if not all, of these materials are formed via the HBr pathway of Scheme III, rather than from the direct Br_2 pathway. Our level of NBS was not sufficient to effect total suppression.

Because the amounts of **2** and **6** (and possibly **3**) increase or remain the same in the presence of NBS, we conclude that these materials are the result of initial ring opening by Br_2 rather than by HBr. Because there is still a very large amount of **4** remaining in the presence of NBS, some of this

Scheme III



material may indeed be formed from the methyl-shift pathway. The original attribution of the larger proportion of **2** in the reaction of the cis isomer than in that of the trans isomer to a steric effect on the hydride-shift process remains valid,[3] since **2** is a direct product. The conformation of the carbonium ion that leads to the hydride shift (**9**)



9

is obtained much more facilely from the cis than from the trans isomer.[3] It is interesting that this same ion can lead to the alkene that gives the tribromide **7**, which is also found in considerably larger amounts in the cis reaction mixture (Table I). The increased amounts of **2** and **7** bring about decreased amounts of the homovicinal dibromides **6** in the reaction of the cis isomer, since all three materials derive from the same initial carbonium ion, B (Scheme II).

In summary, the only products that are not suppressed by free-radical or HBr inhibitors are the homovicinal dibromides **6**, the vicinal dibromides **2** and **3**, and possibly some of **4**. These then are taken to be the primary products of the electrophilic addition reaction of Br_2. The identical erythro/threo ratio found for **6** in both the cis and the trans reaction mixtures substantiates the intermediacy of open carbonium ions.[3] The relative amounts of direct addition products (**6**) and rearrangement products (**2**) are controlled by conformational factors.[3] This result can be extended to the relative amounts of tribromide products (**7** vs. **8**). The presence of **3** and **5** indicates that there is possibly 5% of 1,2 scission, although the great predominance of the reaction mixture comes from 1,3 scission. No homovicinal dibromides are formed from 1,2 scission.

Experimental Section

Brominations. To a solution of 0.13 g (1.9 mmol) of 1,2-dimethylcyclopropane (Chemical Samples Co.) in 3 ml of $CHCl_3$, cooled to 0° in a dark room, was added a solution of 0.42 g (2.6 mmol) of Br_2 in 2 ml of $CHCl_3$. The reaction mixture was stirred for 3 h at 0° with the flask wrapped in aluminum foil. The reaction was stopped by the addition of dilute $Na_2S_2O_3$ solution. The organic layer was dried over $MgSO_4$, filtered, brought up to 10 ml in a volumetric flask, and analyzed by VPC on 11% Carbowax 20M on Chromosorb P (12 ft × 0.125 in.) at 110° with a flow rate of 40 ml/min. For the addition of molecular oxygen, the gas was bubbled into the solution by way of an inlet tube for 3 h at 0°. For the other additives, 0.102 g of NBS, 0.158 g of Fe, and the equivalent of 5% of isoamyl nitrite (based on Br_2) were used. For spectral and chromatographic comparisons, the vicinal dibromides **1–5** were prepared by the addition of bromine to the appropriate alkene. The homovicinal dibromides **6** were prepared as before.[3] Collection of all the dibromides was carried out on 10% Carbowax 20M on Chromosorb P 60–80 (12 ft × 0.25 in.) at 140° with a flow rate of 60 ml/min. Since tribromides were not observed under these conditions, they were collected using 4.8% Apiezon L on Chromosorb G 60–70 (6 ft × 0.25 in.) at 125° with a flow rate of 240 ml/min: NMR of **7** (CCl_4) δ 1.90 (d, 3 H), 1.97 (s, 3 H), 3.93 (s, 2 H), 4.54 (q, 1 H); NMR of **8** (first isomer) (CCl_4) δ 1.09 (d, 3 H), 2.49 (broad septet, 1 H), 3.39 (d, 2 H), 3.6–3.9 (m, 2 H), 4.65 (m, 1 H); NMR of **8** (second isomer) (CCl_4) δ 1.24 (d, 3 H), 2.53 (septet, 1 H), 3.48 (d, 2 H), 3.75–4.0 (m, 2 H), 4.27 (d of t, 1 H).

Acknowledgments. We are indebted to Professor P. S. Skell, The Pennsylvania State University, for valuable suggestions during the progress of this work.

Registry No.—**7**, 57513-16-3; *threo*-**8**, 57513-17-4; *erythro*-**8**, 57513-18-5; *cis*-1,2-dimethylcyclopropane, 930-18-7; *trans*-1,2-dimethylcyclopropane, 2402-06-4; Br_2, 7726-95-6; NBS, 128-08-5; O_2, 7782-44-7; *i*-AmONO, 110-46-3; $FeBr_3$, 10031-26-2.

References and Notes

(1) (a) This work was supported by the Chevron Research Co., by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Science Foundation (Grant MPS72-05006). (b) Petroleum Research Fund Postdoctoral Fellow, 1973–1974, on leave of absence from the University of Tokyo.
(2) (a) J. C. Day, K. J. Shea, and P. S. Skell, *J. Am. Chem. Soc.*, **95**, 5089 (1974); (b) P.S. Skell, J. C. Day, and K. J. Shea, *ibid.*, in press.
(3) J. B. Lambert and B. A. Iwanetz, *J. Org. Chem.*, **37**, 4082 (1972). We use the term "homovicinal" to describe these dibromides, since the carbon atoms bearing bromine are separated by one carbon atom.
(4) Parallel experiments were carried out on the previously studied[5] bromination of bicyclo[3.1.0]hexane. The main products of this reaction are 1,2-dibromocyclohexane and *cis*- and *trans*-1,3-dibromocyclohexane. The total conversion at 0° ranged from 20% (uncatalyzed) to 37%

(NBS). Conversion at −60° (uncatalyzed) was 10%. The effect of O_2, $FeBr_3$, *i*-AmONO, and NBS again was to depress the relative amount of the vicinal dibromide and to enhance the amount of the homovicinal dibromides slightly. The cis/trans ratio for the 1,3-dibromide remained constant at 2:3 under all conditions. We conclude that the reaction mechanism is not altered by free-radical or HBr inhibition or by electrophilic catalysis. The original conclusion that the reaction passes through open carbonium ions is not altered.[5]

(5) J. B. Lambert, R. D. H. Black, J. H. Shaw, and J. J. Papay, *J. Org. Chem.*, **35**, 3214 (1970).

Reaction of Tris(hydroxymethyl)phosphine with Substituted Ureas[1]

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The reaction of tris(hydroxymethyl)phosphine with monosubstituted and unsymmetrically disubstituted ureas has been shown to produce tris(4-substituted ureidomethyl)phosphine oxides. The products were characterized by ir spectra, NMR spectra, and elemental analyses. The NMR spectrum for tris(4-phenylureidomethyl)phosphine oxide showed a triplet for the NH attached to the phosphorus methylene, appearing at a higher field than the NH attached to the phenyl ring, which demonstrated that the reactive nitrogen of the urea was the unsubstituted nitrogen. Reactions of several monosubstituted ureas with tris(hydroxymethyl)phosphine oxide failed to give any of the tris(4-substituted ureidomethyl)phosphine oxides, indicating that oxidation of phosphorus occurred after formation of the P–C–N bond.

Hydroxymethylphosphorus compounds condense readily with amines, amides, ureas, and other nitrogen-containing compounds to yield linear and branched polymers which are useful in flame-retarding cotton cellulose.[3-6] Monomeric products have been obtained when secondary amines were allowed to react with hydroxymethylphosphonium salts or tris(hydroxymethyl)phosphine.[7-10] Our general interest in flame retardants and hydroxyalkylphosphorus chemistry, coupled with recent interest in reactions of phosphorus compounds with ureas in the presence of aldehydes,[11-13] has prompted us to report on the reactions of tris(hydroxymethyl)phosphine with partially substituted ureas.

Results and Discussion

Monomeric products have been obtained from the reaction of tris(hydroxymethyl)phosphine (THP) with several monosubstituted ureas according to eq 1.

$$R_1NR_2CONH_2 + (HOCH_2)_3P \longrightarrow (R_1NR_2CONHCH_2)_3P{=}O \quad (1)$$
$$R_1 = CH_3, CH_3CH_2, CH_3(CH_2)_{11}, (CH_3)_3C, C_6H_5;$$
$$R_2 = H, R_1 = R_2 = C_6H_5$$

Only the phosphine oxides were isolated as oxidation of the phosphorus occurred at some stage of reaction or work-up. A similar reaction occurred when 1,1-diphenylurea was combined with THP. Yields of crude product varied widely and are summarized in Table I (see Experimental Section). No products were isolated from the reactions of THP with acetylurea, benzoylurea, 1,3-dibenzylurea, and 1,1-dimethylurea; rather, 75, 100, 45, and 75% of the starting ureas, respectively, were recovered. If the concentration of the reactants (THP plus substituted urea) was too low in the refluxing ethanol, then the starting urea was recovered in the dodecylurea (88%) and 1,1-diphenylurea (95%) examples. In both examples, concentrations of 16–20% of reactants were necessary before any product could be isolated. A similar dependence on concentration was noted in the *tert*-butylurea reaction, where, with only 4% of reactants, a dark yellow, intractable oil resulted, whereas raising the reactants concentration to 17% caused product to precipitate after refluxing for 16 h. However, even at the higher concentration, several other substituted ureas produced intractable oils from which no solid material could be recovered; among these were 1,3-dimethylurea, 1,3-diethylurea, allylthiourea, and *N*-methylethyleneurea.

The purified products were characterized by ir spectroscopy, NMR spectroscopy, and elemental analysis. The bonding in tris(4-phenylureidomethyl)phosphine oxide (**5**) was readily deduced from its NMR spectrum (Figure 1), which shows a triplet at 6.56 ppm which is assigned to the CH_2NH and integrates for three protons. The singlet at 8.81 ppm is assigned to the C_6H_5NH proton because of the deshielding effect of the phenyl group and integrates for three protons. The triplet for the higher field signal shows that the NH group bonded to the phosphorus methylene is the unsubstituted nitrogen, rather than the phenyl-substituted nitrogen. Such bonding obviously must exist in tris(4,4-diphenylureidomethyl)phosphine oxide (**6**), since one of the nitrogens is fully substituted. Based on steric considerations, one would expect tris(4-dodecylureidomethyl)phosphine oxide (**3**) and tris(4-*tert*-butylureidomethyl)phosphine oxide (**4**) to show similar bonding, since both *tert*-butyl and dodecyl are larger than phenyl. However, the steric bulk of methyl and ethyl is such that one cannot rule out the possibility of reaction occurring at either nitrogen. In fact, it may well occur at both nitrogens, but the products isolated indicate the presence of only one isomer. Clear-cut evidence for which nitrogen is involved in bonding to the methylene was not possible for all samples because the NMR spectra were obtained in D_2O, but bonding similar to **5** would be expected.

The reaction of THP with secondary amines yields the tris(aminomethyl)phosphines,[7-10] but the reactions of THP with substituted ureas yields the tris(ureidomethyl)phosphine oxides. Monitoring of the THP–urea reactions by NMR indicated that some oxidation of THP was occurring, because the doublet due to the methylene protons of THP (D_2O, δ 4.1, J = 5 Hz) was overlapped by another doublet (D_2O, δ 4.2, J = 3 Hz) which we believed resulted from tris(hydroxymethyl)phosphine oxide (THPO). The use of ^{31}P NMR also indicated the presence of THPO; thus the reaction pathway might consist of oxidation of THP to THPO and subsequent reaction of THPO with the urea to form the tris(ureidomethyl)phosphine oxide. This mechanism would involve loss of formaldehyde from THPO by a

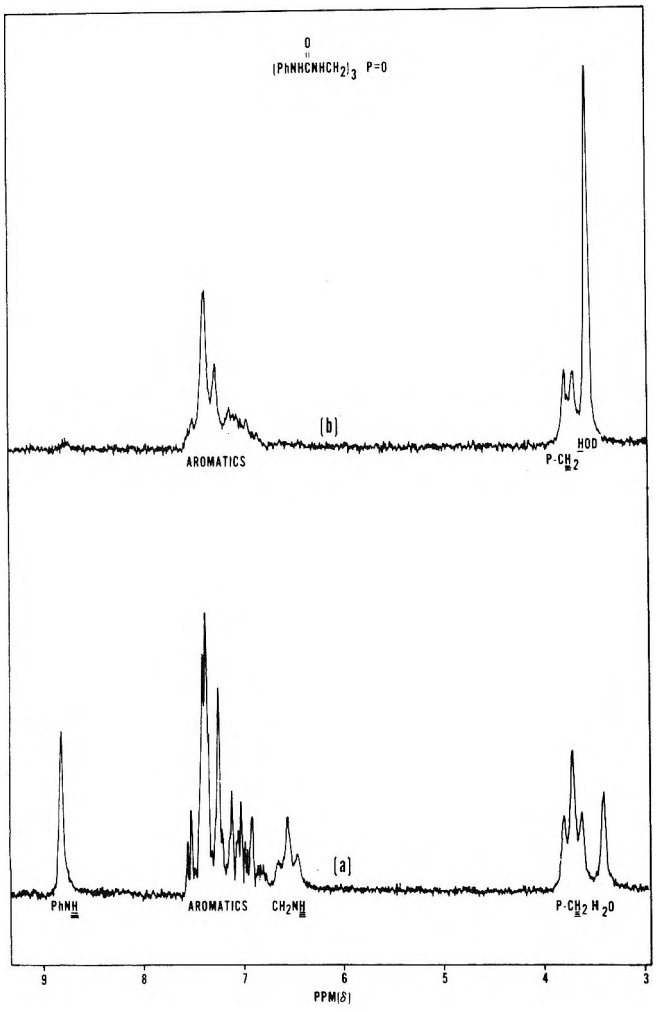

Figure 1. NMR spectrum of tris(4-phenylureidomethyl)phosphine oxide: (a) in Me_2SO-d_6; (b) after D_2O exchange.

mechanism similar to that recently proposed for the reaction of benzylbis(α-hydroxybenzyl)phosphine oxide with primary amines through loss of benzaldehyde.[14] THPO was prepared and refluxed in ethanol with methylurea, phenylurea, or *tert*-butylurea, respectively. No tris(ureidomethyl)phosphine oxide was obtained in any of these reactions. The starting ureas were recovered in 50–65% yield, the remainder of the reaction mixture being an intractable oil.

$$(HOCH_2)_3P{=}O + R_1R_2NCONH_2 \not\rightarrow (R_1R_2NCONHCH_2)_3P{=}O \quad (2)$$

This oil was water soluble in all three examples, whereas compounds **4** and **6** were water insoluble. Addition of acid or base and more vigorous reaction conditions (refluxing toluene) did not produce evidence that THPO reacted with the substituted ureas. Oxidation of THP to THPO prior to reaction with the urea is thus effectively eliminated as a possible mechanism for production of tris(ureidomethyl)phosphine oxides, as shown in eq 2. A likely mechanism for the reaction of THP with substituted ureas may involve nucleophilic attack by THP on the carbonium–immonium ion **7**, which is formed by reaction of the urea with formaldehyde and subsequent acid-catalyzed loss of water,[15] as shown in eq 3. Formaldehyde and traces of acid (a 1% solution of THP has a pH of 5.6–6.0) are present in the commercially supplied THP.

All the reactions of ureas with THP were complicated by formation of other products, probably some mono- and disubstituted ureidomethyl phosphine oxides and phosphorus-free products, such as methylenebisureas. Methylenebisureas were the predominant product when formaldehyde was added at an equimolar ratio to THP in the THP–urea reactions.

$$R_1R_2NCONH_2 + CH_2O \rightleftharpoons R_1R_2NCONHCH_2OH \xrightleftharpoons{H^+,\,-H_2O} \quad (3a)$$

$$R_1R_2NCONHCH_2^+ \longleftrightarrow R_1R_2\overset{+}{N}CONH{=}CH_2 \xrightarrow{P(CH_2OH)_3} \quad (3b)$$

7

$$R_1R_2NCONHCH_2\overset{+}{P}(CH_2OH)_3 \xrightarrow{-H^+,\,-CH_2O} R_1R_2NCONHCH_2P(CH_2OH)_2 \quad (3c)$$

$$\xrightarrow{\text{etc.}} (R_1R_2NCONHCH_2)_3P \xrightarrow{[O]} (R_1R_2NCONHCH_2)_3P{=}O \quad (3d)$$

8

The reaction of THP with formaldehyde and phenylurea was conducted, both at reflux and at ambient temperature, in ethanol with or without added acid. Yields of solid ranged from 30 to 60% (based on phenylurea) and were separated into two components, 20–40% of 1,1′-methylenebis(3-phenylurea) (**9**) and 10–20% of **5**.

$$(HOCH_2)_3P + CH_2O + C_6H_5NHCONH_2 \xrightarrow[\text{without } H^+]{\text{with or}} (C_6H_5NHCONH)_2CH_2 + (C_6H_5NHCONHCH_2)_3P{=}O \quad (4)$$

20–40% (**9**) 10–20% (**5**)

A similar reaction occurred when tetrakis(hydroxymethyl)phosphonium chloride (Thpc), neutralized with sodium hydroxide, was mixed with phenylurea to produce **9** in 26% yield. The neutralization of Thpc by sodium hydroxide has been shown by Vullo[16] to yield a mixture of THP, THPO, formaldehyde, and hemiacetals of THP and THPO. This complex mixture is referred to as THPOH.

$$THPOH + C_6H_5NHCONH_2 \longrightarrow (C_6H_5NHCONH)_2CH_2 \quad (5)$$

26% (**9**)

The reaction of 1,1-diphenylurea with Thpc in refluxing ethanol led to formation of 1,1′-methylenebis(3,3-diphenylurea) (**10**) in a 31% yield.

$$(HOCH_2)_4P^+Cl^- + (C_6H_5)_2NCONH_2 \longrightarrow [(C_6H_5)_2NCONH]_2CH_2 \quad (6)$$

31% (**10**)

When an equimolar (or greater) amount of formaldehyde is present, formation of the methylenebisureas is favored over formation of the tris(ureidomethyl)phosphine oxides.

Coupling of the ureas also occurred when sodium hydroxide equimolar to THPO was added during the reaction of THPO with phenylurea. Formation of the methylenebisurea (**9**) in 22% yield indicated that some decomposition of THPO occurred, yielding free formaldehyde.

$$(HOCH_2)_3PO + C_6H_5NHCONH_2 \xrightarrow{NaOH} (C_6H_5NHCONH)_2CH_2 \quad (7)$$

9

All of the reactions discussed above were conducted in a completely homogeneous system, because both the ureas and THP were readily soluble in hot ethanol. It was of interest to determine what course the reaction might take in another solvent system. THP has only a limited solubility in hot toluene (1–3%), whereas the substituted ureas vary from slightly soluble to soluble. The reactions of *tert*-butylurea, methylurea, dodecylurea, ethylurea, and phenyl-

Table I
Tris(4-substituted)ureidomethyl Phosphine Oxides $(R_1R_2NCONHCH_2)_3P{=}O$

Compd	R_1	R_2	Method	Crude yield, %	Recrystallizing solvent	Mp, °C
1	CH_3	H	A	15	Ethanol	233–234
			B	54		
2	C_2H_5	H	A	14	Ethanol–ethyl acetate	244
			B	97		
3	$CH_3(CH_2)_{11}$	H	A	94	Ethanol–ethyl acetate	170
			B	67		
4	$(CH_3)_3C$	H	A	61	Ethanol–water	220
			B	82		
5	C_6H_5	H	A	53	Dimethyl sulfoxide–water	263–264
			B	37		
6	C_6H_5	C_6H_5	A	38	Acetone	147–148

urea with THP in refluxing toluene proceeded readily, with water evolution being quantitative in 6–8 hr. The crude products were identified by ir spectroscopy as tris(ureidomethyl)phosphine oxides. Yields (37–97%) were generally better in the reactions conducted in toluene.

In contrast to reactions carried out in ethanol, the reaction of 1,1-diphenylurea with Thpc in refluxing toluene did not give either methylenebisurea or THPO. The ir spectra indicated a phosphonium salt, and the elemental analyses indicate that the product is tetrakis(4,4-diphenylureidomethyl)phosphonium chloride (**11**).

$$(HOCH_2)_4P^+Cl^- + (C_6H_5)_2NCONH_2 \xrightarrow{\text{toluene}} [(C_6H_5)_2NCONHCH_2]_4P^+Cl^- \quad (8)$$
14

A similar product has been found in the reactions of N-substituted carbamates with Thpc in refluxing toluene.[17] Reactions of Thpc with 1,1-dimethylurea, ethylurea, and phenylurea, however, all yielded intractable oils. Thus the reaction of THP with substituted ureas appear to be general, giving tris(ureidomethyl)phosphine oxides in two quite different solvents, ethanol and toluene. The reactions of Thpc with substituted ureas are not general and give mixtures of products under the different solvent conditions.

Experimental Section

Reagent grade chemicals were used without further purification. THP, supplied by American Cyanamid Co.,[2b] was shown by NMR to contain small amounts of THPO, methanol, formaldehyde, and other impurities. These contaminants were negligible in a freshly opened container of the solid, but increased on standing for 6 months to 5–10%. The formaldehyde used was a 37.4% aqueous solution from Fisher Scientific Co. The ir spectra were obtained on a Perkin-Elmer 137 with sodium chloride optics. Solid samples were run as KBr pellets containing about 0.3% of the sample. The ^1H NMR spectra were taken on a Varian A-60A and the ^{31}P NMR spectra were obtained on a JEOLCO CH-60. Elemental analyses and molecular weight determinations were performed by Enviro Analytical Laboratory,[2b] Knoxville, Tenn. All melting points are uncorrected.

Reaction of THP with Substituted Ureas. Method A consisted of mixing tris(hydroxymethyl)phosphine (0.015–0.1 mol) with the substituted urea (0.045–0.3 mol) in a 1:3 molar ratio in sufficient ethanol (75–200 ml) to produce a 16–20% weight concentration of reactants. The mixture was heated to reflux, and the water formed in the condensation reaction was removed by drying the distillate in a Soxhlet tube containing a corundum thimble filled with Linde molecular sieve 4A. Reaction was allowed to proceed for 1 week, or until a large amount of precipitate had formed. Work-up varied, depending on the original urea.

Method B consisted of mixing tris(hydroxymethyl)phosphine (0.004–0.02 mol) with the substituted urea (0.012–0.06 mol) in a 1:3 molar ratio in 50–75 ml of toluene. The heterogeneous mixture was heated to reflux, and the water formed in the condensation was collected in a Dean-Stark trap. Reflux was allowed to proceed until the evolution of water ceased or until theoretical water was collected (<8 h). The solid precipitated from the reaction mixture on cooling and was recrystallized from an appropriate solvent. Yields, recrystallizing solvents, and melting points of the compounds are summarized in Table I.

Tris(4-methylureidomethyl)phosphine Oxide (1). Method A afforded a 15% yield of white solid after a refluxing acetone trituration of the oil which remained after ethanol was removed from the reaction mixture.

Method B gave a 54% yield of white solid after a similar work-up. One recrystallization from ethanol gave the analytical sample, **1**: ir (KBr) 3.02 (NH), 3.3–3.5 (aliphatic CH), 6.1 and 6.32 (amide bands), 8.68 μ (P=O); NMR (D_2O) δ 2.7 (s, 9 H, CH_3), 3.77 (d, J = 4 Hz, 6 H, PCH_2).

Anal. Calcd for $C_9H_{21}N_6O_4P$: C, 35.06; H, 6.87; N, 27.26; P, 10.05. Found: C, 35.16; H, 6.96; N, 26.80; P, 9.91.

^1H and ^{31}P NMR Evidence for Oxidation of THP to THPO. A 10-ml aliquot of the reaction mixture of THP with methylurea was taken after 1 h reflux in ethanol. The solvent was removed by heating under vacuum, and the ^1H and ^{31}P NMR spectra were taken of the residual oil. Integration of the ^1H NMR spectrum was impossible because the signals of interest overlapped. However, in the ^{31}P NMR, there is a wide separation of signals due to phosphorus in different oxidation states since THP absorbs at +25 ppm relative to H_3PO_4, while THPO absorbs at −50 ppm. The ^{31}P NMR spectrum (D_2O, H_3PO_4 external reference) of the reaction mixture showed a signal at +25 ppm (THP, 62% of the integration) and one at −50 ppm (THPO, 32% of the integration). Thus considerable oxidation does occur, at least in the methylurea example.

Tris(4-ethylureidomethyl)phosphine Oxide (2). Method A gave a 14% yield of white solid after a refluxing acetone trituration of the oil which remained after removal of ethanol from the reaction mixture.

Method B gave a 97% yield of white solid. One recrystallization from an acetone–ethanol mixture, followed by a recrystallization from ethanol, yielded the analytical sample, **2**: ir (KBr) 2.98 (NH), 3.31–3.4 (aliphatic CH), 6.08 and 6.38 (amide bands), 8.64 μ (P=O); NMR (D_2O) δ 1.1 (t, J = 7 Hz, 9 H, CH_3CH_2), 3.2 (q, J = 7 Hz, 6 H, CH_3CH_2), 3.8 (d, J = 5 Hz, 6 H, PCH_2).

Anal. Calcd for $C_{12}H_{27}N_6O_4P$: C, 41.10; H, 7.77; N, 24.00; P, 8.84. Found: C, 41.24; H, 7.63; N, 24.18; P, 8.84.

Tris(4-dodecylureidomethyl)phosphine Oxide (3). Method A yielded 94% of white solid.

Method B gave a 67% yield of solid. The product proved difficult to recrystallize; only powders formed from a variety of solvents and solvent pairs. The analytical sample, **3**, was obtained after two recrystallizations from ethyl acetate–ethanol: ir (KBr) 2.99 (NH), 3.4 and 3.49 (aliphatic CH), 6.12 and 6.32 (amide bands), 8.7 μ (P=O). The solubility of **3** in common NMR solvents was too low to provide an interpretable spectrum.

Anal. Calcd for $C_{39}H_{87}N_6O_4P$: C, 64.25; H, 11.20; N, 11.53; P, 4.25. Found: C, 64.07; H, 10.97; N, 11.28; P, 4.10.

Tris(4-*tert*-butylureidomethyl)phosphine Oxide (4). Method A yielded 61% of white solid that precipitated after 3 days of reflux in ethanol.

Method B gave 82% of white solid. Recrystallization four times from ethanol–water gave a white, crystalline solid which softened at 132–138°, then resolidified and melted at 220–222°. The elemental analysis of this solid indicated a dihydrate of **4**.

After further recrystallization, some of this solid was dried in a vacuum oven at 140° until it had softened and resolidified. The melting point of the dried solid (**4d**) was 220°, whereas the undried solid (**4u**) exhibited both a low and a high melting point. The ir spectra of the two solids were identical, but the NMR spectra of **4u**

showed four protons from the water at δ 3.6, which **4d** did not. After D_2O exchange, the spectra were identical: ir (KBr) 2.96 (NH), 3.3–3.35 (aliphatic CH), 6.00 and 6.40 (amide bands), 8.6 μ (P=O); NMR (mixture of $CDCl_3$–Me_2SO-d_6) δ 1.3 [s, 27 H, $(CH_3)_3C$], 3.6 (**4u**, m, 10 H, PCH_2, 2 H_2O), 3.6 (**4d**, m, 6 H, PCH_2), 5.8 (broad s, 3 H, NH), 6.4 (broad s, 3 H, NH); after D_2O exchange δ 1.3 [s, 27 H, $(CH_3)_3C$], 3.65 (m, 6 H, PCH_2). The elemental analyses of **4d** and **4u** indicated that 2 mol of water was lost on drying.

Anal. Calcd for $C_{18}H_{39}N_6O_4P$: C, 49.75; H, 9.05; N, 19.34; P, 7.13. Found for **4d**: C, 49.71; H, 8.86; N, 19.17; P, 7.19.

Anal. Calcd for $C_{18}H_{39}N_6O_4P{\cdot}2H_2O$: C, 45.94; H, 9.21; N, 17.86; P, 6.58. Found for **4u**: C, 45.86; H, 9.12; N, 17.55; P, 6.57.

Tris(4-phenylureidomethyl)phosphine Oxide (5). Method A gave a 53% yield of white solid after only 48 h in refluxing ethanol.

Method B afforded a 37% yield of solid. Recrystallization from dimethyl sulfoxide–water gave the analytical sample, **5**: ir (KBr) 2.99 (NH), 3.25 (aromatic CH), 3.4 (aliphatic CH), 6.03, 6.24, 6.5, and 6.7 (overlapping amide bands and aromatic C=C), 8.59 μ (P=O); NMR (Me_2SO-d_6, 80°) δ 3.7 (d of d, $J_{PCH} = J_{NHCH} = 5$ Hz, 6 H, PCH_2), 6.56 (t, $J = 5$ Hz, 3 H, CH_2NH), 6.7–7.65 (m, 15 H, aromatics), 8.81 (s, 3 H, PhNH); after D_2O exchange, δ 3.74 (d, $J_{PCH} = 5$ Hz, 6 H, PCH_2), 6.7–7.65 (m, 15 H, aromatics).

Anal. Calcd for $C_{24}H_{27}N_6O_4P$: C, 58.29; H, 5.50; N, 17.00; P, 6.27. Found: C, 58.34; H, 5.60; N, 16.99; P, 6.28.

Tris(4,4-diphenylureidomethyl)phosphine Oxide (6). Method A yielded 38% of white solid after 10 days reflux. However, on cooling to ambient temperature, the first solid collected from the reaction mixture was diphenylurea. Addition of water to the ethanolic reaction mixture was necessary to precipitate **6**, which was recrystallized from acetone–ethanol and then from ethyl acetate–ethanol to yield the analytical sample, **6**: ir (KBr) 2.98 (NH), 3.24 (aromatic CH), 3.39 (aliphatic CH), 5.98 and 6.7 (amide bands), 8.65 μ (P=O); NMR ($CDCl_3$) δ 3.67 (m, 6 H, PCH_2), 5.6 (m, 3 H, NH), 7.23 (m, 30 H, aromatics); after D_2O exchange δ 3.73 (d, $J = 5$ Hz, 6 H, PCH_2), 7.23 (m, 30 H, aromatics). The elemental analysis indicated a dihydrate.

Anal. Calcd for $C_{42}H_{39}N_6O_4P{\cdot}2H_2O$: C, 66.48; H, 5.71; N, 11.08; P, 4.08. Found: C, 66.41; H, 5.61; N, 11.00; P, 4.17.

Tetrakis(4,4-diphenylureidomethyl)phosphonium Chloride (11). A mixture of 3.4 g (0.016 mol) of 1,1-diphenylurea, 0.76 g (0.004 mol) of Thpc, and 50 ml of toluene was refluxed for 4.5 h. The reaction mixture was allowed to cool, and the solid that formed was collected (2.0 g, 52% yield). This was recrystallized once from ethanol and twice from acetone–ethanol to yield the analytical sample, **11**: mp 246–247°; ir (KBr) 3.0 (NH), 3.25 (aromatic CH), 3.39 (aliphatic CH), 5.98, 6.27, and 6.7 μ (overlapping amide bands and aromatic C=C); NMR (mixture of $CDCl_3$–Me_2SO-d_6) δ 4.27 (m, 8 H, PCH_2), 6.75 (m, 4 H, NH), 7.3 (m, 40 H, aromatics); after D_2O exchange δ 4.3 (d, $J = 4$ Hz, 8 H, PCH_2), 7.3 (m, 40 H, aromatics).

Anal. Calcd for $C_{56}H_{52}N_8O_4PCl$: C, 69.52; H, 5.42; N, 11.58; P, 3.20; Cl, 3.67.

However, the elemental analyses indicate a monohydrate of **11**.

Anal. Calcd for $C_{56}H_{52}N_8O_4PCl{\cdot}H_2O$: C, 68.25; H, 5.52, N, 11.37; P, 3.14; Cl, 3.60. Found: C, 68.13; H, 5.45; N, 11.24; P, 3.20; Cl, 3.95.

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Registry No.—**1**, 57459-44-6; **2**, 57459-45-7; **3**, 57459-46-8; **4**, 57459-47-9; **5**, 57459-48-0; **6**, 57459-49-1; **11**, 57459-50-4; THP, 2767-80-8; methylurea, 598-50-5; ethylurea, 625-52-5; dodecylurea, 2158-09-0; *tert*-butylurea, 1118-12-3; phenylurea, 64-10-8; *N,N*-diphenylurea, 603-54-3; THPC, 124-64-1.

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Reaction of Picryl Azide with Aryloxyallenes[1]

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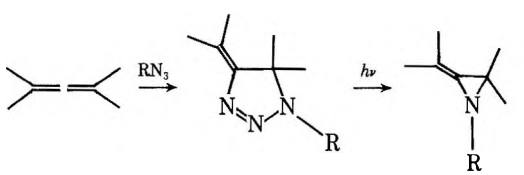
The reaction of aryloxyallenes with picryl azide gives two types of isolated adducts, **2** and **4**. The reaction is proposed to proceed via formation of the unisolated triazoline of type **5**. These compounds undergo an exceptionally facile Claisen rearrangement to yield the adducts of structure **4**, which unless blocked by a substituent at R_5 rapidly tautomerize to the isomeric adducts of type **2**.

As an extension of our work on allene oxides,[2] we have explored several potential synthetic routes to allenimines,[3] the nitrogen analogues of this strained small-ring heterocyclic system. One such approach[4] involves a 1,3-dipolar addition of organoazides to allenes, followed by photochemical expulsion of nitrogen from the adduct to give the desired allenimine (see eq 1). Bleiholder and Shechter[5] have earlier examined the reaction of several azides with alkyl-substituted allenes.[6] Although these authors were able to isolate the desired adducts in several instances,[7] these materials decomposed readily and the ring-contraction step of



(1)

eq 1 was not achieved. In the present study we utilized aryloxyallenes as substrates with the idea that these electron-rich allenes might undergo more facile cycloaddition reactions with azides. In fact, the observed products result from

an unanticipated rearrangement of these primary adducts which involves the activating aryloxy substituent.

The reaction of phenoxyallene (**1a**) with picryl azide at room temperature in chloroform gave a good yield of a yellow, crystalline solid subsequently identified as 4-(2-hydroxybenzyl)-1-picryl-1,2,3-triazole (**2a**). The presence of a phenol function in this product was indicated by its ir spectrum (bands at 3.0 and 8.1 μ), proton exchange with D_2O, and transformation to its acetate. The NMR spectrum of **2a** shows a two-proton singlet at δ 9.25 for the picryl-group protons, a sharp one-proton singlet at δ 8.39, four additional aromatic protons centered at about δ 6.8, and a two-proton singlet at δ 4.00. These data are best accommodated in terms of structure **2a**. In particular, the chemical shift of the downfield one-proton singlet is consistent only with a 4-substituted triazole.[8]

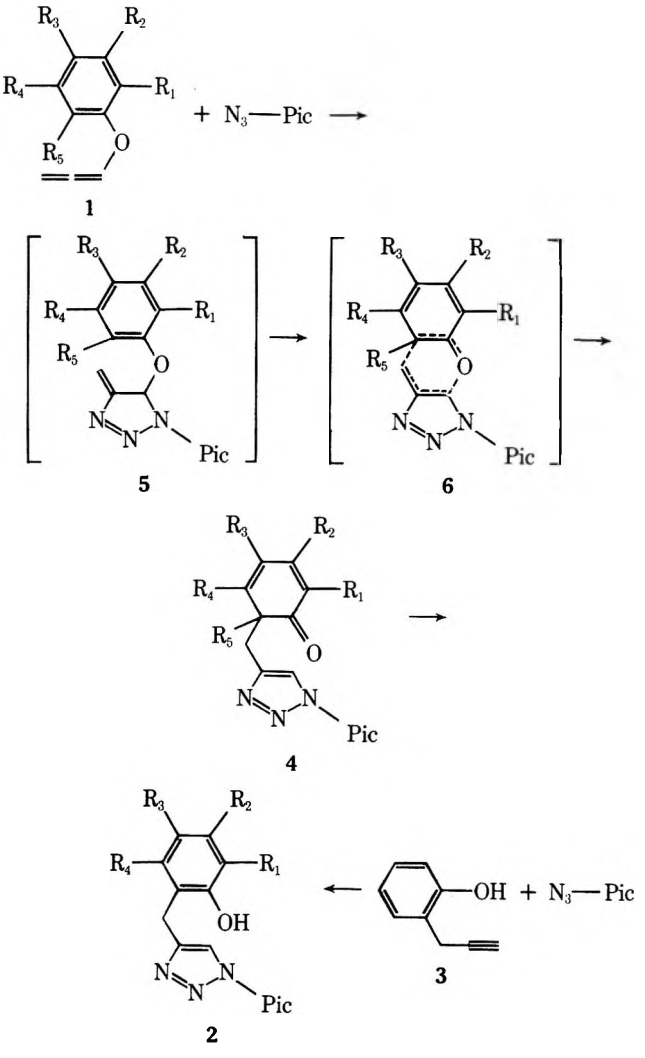
Confirmation of this structure was achieved by an alternate synthesis involving the cycloaddition of picryl azide to *o*-propargylphenol (**3**). Interestingly, only **2a** was observed in this reaction, whereas both regioisomers are usually formed in the addition of azides to terminal acetylenes.[9]

The generality of the reaction of aryloxyallenes with picryl azide was demonstrated by the formation of analogous adducts from allenes **1b** and **1c** in high yield. However, in the instances of **1d**, **1e**, and **1f**, whose aryl groups are blocked by substituents at both ortho positions, the isolated adducts are of the cyclohexadienone type **4**. The NMR spectra of these adducts show a downfield two-proton singlet for the picryl protons, a one-proton singlet appropriate for a C-5 triazole hydrogen, the expected number of olefinic protons for the respective compounds, and a two-proton AB pattern in the range 3.1–4.2 ppm. This latter feature results from the diastereotopic relationship of the benzylic protons owing to the adjacent chiral center. Compound **4f**, in particular, had ir, uv, and NMR spectra which correlated well with the data for model compounds in the literature.[10]

Supporting evidence for these structural assignments was provided by chemical correlation of the two types of adducts. Thus, reduction of the trichlorocyclohexadienone adduct **4d** with 1 equiv of tri-*n*-butyltin hydride[11] resulted in quantitative transformation to the dichloro adduct **2c** by selective removal of the R_5 chlorine substituent. The same adduct was obtained from picryl azide and 2,4-dichloroaryloxyallene (**1c**). Interestingly only the adduct **2c** was obtained in this reaction.

The most straightforward rationalization of the above results invokes a regiospecific 1,3 cycloaddition of the azide to the more electron-rich double bond of the allene to give triazoline **5** as an unisolated intermediate. This species undergoes Claisen rearrangement[12] to produce **4**. In those cases where the 2 and 6 positions of the original aryl group are blocked, the cyclohexadienone adducts **4** can be isolated; otherwise, tautomerization leads to the phenolic adducts **2** in a well-precedented manner.[12] Selective addition to the aryloxy-substituted double bond is expected[9] and the regiospecificity parallels that for the addition of azides to simple enol ethers.[13]

The surprising feature of this reaction is the unusual facility of the Claisen rearrangement of **5**, which proceeds readily at room temperature, rather than requiring the elevated temperatures typical of this type of transformation. However, the exceptional ease of this rearrangement is attributable to the generation of the aromatic[9] triazole system as the immediate product. Consequently, the aromatic character of the aryloxy moiety which is lost in achieving transition state **6** is largely compensated for by the developing aromatic stabilization of the triazole ring. This should result in a substantial lowering of the activation energy relative to a typical Claisen rearrangement.[12]



1 **5** **6** **4** **2** **3**

a, $R_1 = R_2 = R_3 = R_4 = R_5 = H$
b, $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = Cl$
c, $R_2 = R_4 = R_5 = H$; $R_1 = R_3 = Cl$
d, $R_2 = R_4 = H$; $R_1 = R_3 = R_5 = Cl$
e, $R_1 = R_2 = R_3 = R_4 = R_5 = Cl$
f, $R_2 = R_3 = R_4 = H$; $R_1 = R_5 = CH_3$

Attempts to effect the reaction of phenoxyallene with phenyl, *p*-nitrophenyl, *p*-toluenesulfonyl, and carbethoxy azides under similar reaction conditions were unsuccessful in our hands. Nor were products obtained from 1-methyl-1-phenoxyallene, methoxyallene, or 3,3-dimethyl-1-acetoxyallene, even with picryl azide.

Experimental Section

General. NMR spectra were recorded on Varian HR-220 and EM-360 spectrometers; chemical shifts are reported in parts per million downfield from internal Me_4Si. Ir spectra were obtained on KBr pellets or on neat samples using a Perkin-Elmer 137 Infracord. Mass spectra (70 eV) were obtained on Varian MAT CH-7 and AEI MS-9 spectrometers. Analyses were performed by Midwest Microlab, Inc. Anhydrous $MgSO_4$ was routinely used as a drying agent.

Preparation of Aryl Propargyl Ethers. To a solution of 1 equiv of the phenol in ethanol was added 1 equiv of sodium. After hydrogen evolution ceased, 1 equiv of propargyl bromide was added and the reaction mixture was refluxed for 3 hr. The mixture was poured into water and extracted with pentane. The pentane extract was washed with 10% NaOH solution and water, then dried and concentrated. The aryl propargyl ethers were purified by distillation or recrystallization from ethanol.

Phenyl propargyl ether:[14] bp 81–83° (15 mm); ir 3.02 and 4.70 μ; NMR (CCl_4) δ 2.34 (t, 1, J = 2 Hz), 4.52 (d, 2, J = 2 Hz), and 7.0 (m, 5).

4-Chlorophenyl propargyl ether: bp 62–64° (0.75 mm); ir 3.01

and 4.70 μ; NMR (CCl_4) δ 2.42 (t, 1, J = 2 Hz), 4.60 (d, 2, J = 2 Hz), and 7.05 (m, 4).

Exact mass. Calcd for C_9H_7ClO: 166.0186. Found: 166.019.

2,4-Dichlorophenyl propargyl ether: mp 45–46°; ir 3.05 and 4.72 μ; NMR ($CDCl_3$) δ 2.51 (t, 1, J = 2 Hz), 4.74 (d, 2, J = 2 Hz), and 7.2 (m, 3).

Anal. Calcd for $C_9H_6Cl_2O$: C, 53.77; H, 3.01. Found: C, 53.6; H, 3.3.

2,4,6-Trichlorophenyl propargyl ether: mp 99–100°; ir 3.03 μ; NMR ($CDCl_3$) δ 2.57 (t, 1, J = 2 Hz), 4.82 (d, 2, J = 2 Hz), and 7.37 (s, 2).

Anal. Calcd for $C_9H_5Cl_3O$: C, 45.90; H, 2.14. Found: C, 46.1; H, 2.4.

Pentachlorophenyl propargyl ether: mp 137–138°; ir 3.04 and 4.65 μ; NMR ($CDCl_3$) δ 2.59 (t, 1, J = 2 Hz) and 4.90 (d, 2, J = 2 Hz).

Anal. Calcd for $C_9H_3Cl_5O$: C, 35.51; H, 0.99. Found: C, 35.9; H, 1.3.

2,6-Dimethylphenyl propargyl ether: bp 63–64° (0.75 mm); ir 3.03 and 4.65 μ; NMR (CCl_4) δ 2.20 (s, 6), 2.35 (t, 1, J = 2 Hz), 4.35 (d, 2, J = 2 Hz), and 6.84 (s, 3).

Exact mass. Calcd for $C_{11}H_{12}O$: 160.0889. Found: 160.088.

Preparation of Aryloxyallenes. A solution of 50 mmol of the aryl propargyl ether and 2.0 g of potassium *tert*-butoxide in 120 ml of *tert*-butyl alcohol was refluxed for 1–3 h. The reaction mixture was cooled, poured into water, and extracted with pentane. The extract was washed several times with water, dried, and concentrated to give essentially pure allene, free from isomeric acetylene. Distillation of these materials caused decomposition, prompting their use as obtained.

Phenoxyallene:[14] ir 5.08 μ; NMR (CCl_4) δ 5.45 (d, 2, J = 6 Hz), 6.87 (t, 1, J = 6 Hz), and 7.1 (m, 5).

4-Chlorophenoxyallene: ir 5.08 μ; NMR (CCl_4) δ 5.45 (d, 2, J = 6 Hz), 6.82 (t, 1, J = 6 Hz), and 7.13 (m, 4).

Exact mass. Calcd for C_9H_7ClO: 166.0186. Found: 166.019.

2,4-Dichlorophenoxyallene: mp 31–32°; ir 5.10 μ; NMR (CCl_4) δ 5.43 (d, 2, J = 6 Hz), 6.83 (t, 1, J = 6 Hz), and 7.25 (m, 3).

Exact mass. Calcd for $C_9H_6Cl_2O$: 199.9796. Found: 199.980.

2,4,6-Trichlorophenoxyallene: mp 23–24°; ir 5.02 and 5.10 μ; NMR (CCl_4) δ 5.35 (d, 2, J = 6 Hz), 6.98 (t, 1, J = 6 Hz), and 7.34 (s, 2).

Exact mass. Calcd for $C_9H_5Cl_3O$: 233.9406. Found: 233.943.

Pentachlorophenoxyallene: mp 83–85°, ir 5.1 μ; NMR (CCl_4) 5.45 (d, 2, J = 6 Hz) and 7.08 (t, 1, J = 6 Hz).

Exact mass. Calcd for $C_9H_3Cl_5O$: 301.8627. Found: 301.864.

2,6-Dimethylphenoxyallene: ir 5.1 μ; NMR (CCl_4) δ 2.18 (s, 6), 5.18 (d, 2, J = 6 Hz), 6.30 (t, 1, J = 6 Hz), and 6.88 (s, 3).

Exact mass. Calcd for $C_{11}H_{12}O$: 160.0889. Found: 160.091

Reaction of Picryl Azide with Phenoxyallene. Stirring a solution of 1.3 g (5 mmol) of picryl azide and 0.7 g (10 mmol) of phenoxyallene in 40 ml of chloroform at room temperature resulted in finely divided yellow crystals. After 2 days the solid product was collected and washed with chloroform to yield 1.5 g (78%) of pure **2a**: mp 171–173°; ir 3.0, 6.19, 6.48, 7.50, 8.10, and 13.5 μ; NMR (Me_2SO-d_6) δ 4.00 (s, 2), 6.68 (t, 1, J = 7 Hz), 6.79 (d, 1, J = 7 Hz), 7.0 (m, 2), 8.39 (s, 1), and 9.25 (s, 2); mass spectrum *m/e* (rel intensity) 386 (29), 369 (25), 339 (16), 218 (15), 175 (100), 146 (30).

Anal. Calcd for $C_{15}H_{10}N_6O_7$: C, 46.62, H, 2.61; N, 21.77. Found: C, 46.3; H, 2.7, N, 21.7.

Acetylation of 2a. To a 400-mg sample of **2a** in benzene was added 0.8 g of acetyl chloride and 5 drops of pyridine. After refluxing for 1 hr the reaction mixture was poured into water and extracted with ether. The extract was dried and concentrated to give the crude acetate which was purified by recrystallization from methanol: mp 164–165°; ir 5.70, 6.20, 6.48, 7.48, 8.28, and 13.6 μ; NMR ($CDCl_3$) δ 2.23 (s, 3), 4.10 (s, 2), 7.20 (m, 4), 7.45 (s, 1), and 9.00 (s, 2); mass spectrum *m/e* (rel intensity) 428 (1), 386 (57), 131 (45), 119 (26), 118 (14), 107 (11), 91 (26), 43 (100).

Anal. Calcd for $C_{17}H_{12}N_6O_8$: C, 47.67; H, 2.82; N, 19.62. Found: C, 47.8; H, 2.8; N, 19.5.

Reaction of Picryl Azide with o-Propargylphenol.[15] A solution of 1.6 g of picryl azide and 0.8 g of *o*-propargylphenol in 30 ml of chloroform was stirred at room temperature for 3 weeks, after which 0.6 g (24%) of yellow, crystalline **2a** was collected, mp 171–172°, mmp 171–173°. This product was spectroscopically identical with the adduct obtained from the reaction of phenoxyallene with picryl azide.

Reaction of Picryl Azide with 4-Chlorophenoxyallene. Stirring a solution of 1.3 g (5 mmol) of picryl azide and 1.7 g (10 mmol) of 4-chlorophenoxyallene in 25 ml of chloroform for 1 day gave 1.4 g (67%) of **2b**: mp 161–163°; ir 3.22, 6.20, 6.47, 7.50, and 12.10 μ; NMR (Me_2SO-d_6) δ 4.00 (s, 2), 6.82 (d, 1, J = 10 Hz), 6.98 (s, 1), 7.05 (d, 1, J = 10 Hz), 8.47 (s, 1), and 9.25 (s, 2); mass spectrum *m/e* (rel intensity) 420 (4), 209 (46), 174 (89), 152 (21), 28 (100).

Anal. Calcd for $C_{15}H_9ClN_6O_7$: C, 42.82, H, 2.16. Found: C, 42.85, H, 2.16.

Reaction of Picryl Azide with 2,4-Dichlorophenoxyallene. Stirring a solution of 1.3 g (5 mmol) of picryl azide and 2.0 g (10 mmol) of 2,4-dichlorophenoxyallene in 30 ml of chloroform for 1 day at room temperature gave 1.8 g (79%) of **2c**, as finely divided yellow crystals: mp 199–200°; ir 3.25, 6.21, 6.50, and 7.50 μ; NMR (Me_2SO-d_6) δ 4.20 (s, 1), 7.08 (d, 1, J = 2 Hz), 7.26 (d, 1, J = 2 Hz), 8.34 (s, 1), and 9.30 (s, 2); mass spectrum *m/e* (rel intensity) 456 (6), 454 (9), 201 (37), 199 (68), 188 (29), 128 (100).

Anal. Calcd for $C_{15}H_8Cl_2N_6O_7$: C, 39.58; H, 1.77; N, 18.46. Found: C, 39.3; H, 1.7; N, 18.5.

Reaction of Picryl Azide with 2,4,6-Trichlorophenoxyallene. A solution of 0.6 g (2.5 mmol) of picryl azide and 1.2 g (5 mmol) of 2,4,6-trichlorophenoxyallene in 15 ml of chloroform was stirred at room temperature for 2 days. The light yellow precipitate was collected and washed with chloroform to give 0.8 g (66%) of **4d**: mp 165–166°; ir 3.21, 5.92, 6.20, 6.50, and 7.50 μ; NMR (acetone-d_6) δ 3.80 (AB q, 2, J = 14 Hz), 6.72 (d, 1, J = 2.5 Hz), 7.35 (d, 1, J = 2.5 Hz), 8.40 (s, 1), and 9.30 (s, 2); mass spectrum *m/e* (rel intensity) 490 (1), 488 (1), 247 (40), 109 (44), 30 (100).

Anal. Calcd for $C_{15}H_7Cl_3N_6O_7$: C, 36.80; H, 1.44; N, 17.16. Found: C, 37.0; H, 1.5; N, 16.7.

Reaction of 4d with Tri-*n*-butyltin Hydride. To a solution of 0.5 g of **4d** in 10 ml of acetone was slowly added 0.5 g of tri-*n*-butyltin hydride in 2 ml of acetone. The reaction mixture was stirred at room temperature for 2 hr, the solvent was removed, chloroform was added, and the resulting crystalline solid was collected and recrystallized from aqueous alcohol to give **2c**, mp 198–201°. The compound was spectroscopically identical with the adduct obtained from the reaction between 2,4-dichlorophenoxyallene and picryl azide in all respects.

Reaction of Picryl Azide with Pentachlorophenoxyallene. A solution of 0.13 g (0.5 mmol) of picryl azide and 0.31 g (1 mmol) of pentachlorophenoxyallene in 5 ml of chloroform was stirred at room temperature for 4 days. The light yellow precipitate was collected and washed with chloroform to give 0.2 g (72%) of **4e**: mp 202–203°; ir 3.23, 5.95, 6.21, 6.50, and 7.50 μ; NMR (acetone-d_6) δ 4.10 (AB q, 2, J = 14 Hz), 8.45 (s, 1), and 9.30 (s, 2); mass spectrum *m/e* (rel intensity) 558 (1), 556 (1), 494 (36), 269 (47), 256 (45), 36 (100).

Anal. Calcd for $C_{15}H_5Cl_5N_6O_7$: C, 32.26; H, 0.90; N, 15.05. Found: C, 31.98; H, 0.93; N, 14.85.

Reaction of Picryl Azide and 2,6-Dimethylphenoxyallene. A solution of 2.5 g (10 mmol) of picryl azide and 3.2 g (20 mmol) of 2,4-dimethylphenoxyallene in chloroform was stirred at room temperature for 1 day, after which the light yellow precipitate was collected and washed with chloroform to give 3.5 g (85%) of **4f**: mp 210–211°; uv λ_{max} 310 nm (ε 4500); ir 3.20, 6.08, 6.11, 6.18, 6.45, and 7.45 μ; NMR (Me_2SO-d_6) δ 1.16 (s, 3), 1.73 (s, 3), 3.05 (AB q, 2, J = 14 Hz), 6.07 (d of d, 1, J = 9 and 6 Hz), 6.25 (d, 1, J = 9 Hz), 6.80 (d, 1, J = 6 Hz), 8.20 (s, 1), and 9.20 (s, 2); mass spectrum *m/e* (rel intensity) 414 (25), 122 (100), 121 (61).

Anal. Calcd: C, 49.28; H, 3.41. Found: C, 48.9; H, 3.5.

Registry No.—**1a**, 1595-40-0; **1b**, 57444-41-4; **1c**, 57444-42-5; **1d**, 57444-43-6; **1e**, 57444-44-7; **1f**, 57444-45-8; **2a**, 57444-46-9; **2a** acetate, 57444-47-0; **2b**, 57444-48-1; **2c**, 57444-49-2; **3**, 39894-71-8; **4d**, 57444-50-5; **4e**, 57444-51-6; **4f**, 57444-52-7; propargyl bromide, 106-96-7; phenol, 108-95-2; 4-chlorophenol, 106-48-9; 2,4-dichlorophenol, 120-83-2; 2,4,6-trichlorophenol, 88-06-2; pentachlorophenol, 87-86-5; 2,6-dimethylphenol, 576-26-1; phenyl propargyl ether, 13610-02-1; 4-chlorophenyl propargyl ether, 19130-39-3; 2,4-dichlorophenyl propargyl ether, 17061-90-4; 2,4,6-trichlorophenyl propargyl ether, 17727-28-5; pentachlorophenyl propargyl ether, 19130-44-0; 2,6-dimethylphenyl propargyl ether, 21078-03-5; picryl azide, 1600-31-3; tri-*n*-butyltin hydride, 688-73-3.

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Solvolysis of Haloallenes. The Question of Nucleophilic Solvent Assistance

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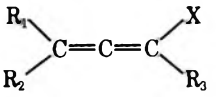
The solvolysis rates of 14 di- and trisubstituted bromoallenes are reported. Solvent effects in ethanol and trifluoroethanol, methyl/hydrogen ratios, and the effect of solvent nucleophilicity on relative rates and α- and β-secondary isotope effects are discussed. Increases in the magnitude of $(k_H/k_D)_\alpha$ and $(k_H/k_D)_\beta$ with decreasing solvent nucleophilicity are analogous to the behavior of highly hindered secondary brosylates. These data are interpreted in terms of a rate-limiting elimination step from an ion-pair intermediate. The relative rate of isomeric propargyl and allenyl systems is also discussed.

In earlier work we have reported that di- and trisubstituted chloro- and bromoallenes exhibit solvolytic behavior typical of an unimolecular bond heterolysis as the slow step.[1] These compounds exhibit m values between 0.80 and 1.06, k_{Br}/k_{Cl} leaving group ratios of 20–58, $\Delta S^{\ddagger}$ of −10 to +9.0 eu, ρ values for aryl-substituted chloroallenes of −2.0, CH_3/H rate ratios in 60E of $10^{4.5}$, and apparently "normal" α and β secondary isotope effects.

Since disubstituted haloallenes exhibit solvolytic reactivity in aqueous ethanol on the order of reactivity of secondary carbinyl systems, we were led to assess the possible involvement of nucleophilic solvent assistance in our system. To this end we have prepared the following substituted haloallenes, **1a–n**, and measured the rates of solvolysis in a



1

a, $R_1 = R_2 = t\text{-}C_4H_9$; $R_3 = H$; X = Br
b, $R_1 = R_2 = t\text{-}C_4H_9$; $R_3 = D$; X = Br
c, $R_1 = t\text{-}C_4H_9$; $R_2 = CH_3$; $R_3 = H$; X = Br
d, $R_1 = t\text{-}C_4H_9$; $R_2 = CH_3$; $R_3 = D$; X = Br
e, $R_1 = t\text{-}C_4H_9$; $R_2 = CD_3$; $R_3 = H$; X = Br
f, $R_1 = R_2 = CH_3$; $R_3 = H$; X = Br
g, $R_1 = R_2 = CH_3$; $R_3 = D$; X = Br
h, $R_1 = R_3 = CD_3$; $R_2 = H$; X = Br
i, $R_1 = R_3 = t\text{-}C_4H_9$; $R_2 = CH_3$; X = Cl
j, $R_1 = R_3 = t\text{-}C_4H_9$; $R_2 = CD_3$; X = Cl
k, $R_1 = R_3 = t\text{-}C_4H_9$; $R_2 = CH_3$; X = Br
l, $R_1 = R_3 = t\text{-}C_4H_9$; $R_2 = CD_3$; X = Br
m, $R_1 = R_3 = t\text{-}C_4H_9$; $R_2 = CH_3$; X = Br
n, $R_1 = t\text{-}C_4H_9$; $R_2 = R_3 = CH_3$; X = Br

variety of solvents. The results of this investigation are compiled in Table I. Tables II and III present the isotope effects based on the data in Table I and the isotopic purity of the deuterated samples. Deuterated and undeuterated compounds were solvolyzed in paired conductance cells. The bridge and digital clock were interfaced with a computer allowing no less than 100 points to be taken per cell. Rate constants were calculated using a nonlinear least-squares program. Each reaction exhibits excellent first-order behavior through better than 4 half-lives.

Results and Discussion

The question of nucleophilic solvent assistance has been approached through a study of the effect of solvent nucleophilicity on (a) α and β secondary isotope effects, (b) the CH_3/H ratio, (c) the relative rate of model compounds, and (d) the presence or absence of a rate–product correlation in the presence of azide ion.[2] In this paper we will focus only on the effect of changing solvent nucleophilicity on the reactivity of the haloallenes reported here. The effect of added salts on this reaction will be reported later.

Effect of Solvent Nucleophilicity on Rate. It has been suggested that in those systems where nucleophilic solvent assistance is important (such as secondary carbinyl derivatives) such assistance is manifested in markedly changing rate ratios between solvent assisted substrates and those incapable of assistance usually owing to steric inhibition.[3] An elegant example of this behavior was reported by Schleyer et al. These workers reported 2-propyl tosylate/2-adamantyl tosylate rate ratios which varied from $10^{-1.6}$ in TFA to 10^3 in 100E and interpreted this behavior as consistent with substantial solvent assistance in 2-propyl tosylate not present (or marginally present) in the weakly nucleophilic solvents. The 2-adamantyl tosylate shows no solvent assistance due to steric interactions and is therefore a good model of a nonassisted secondary carbinyl system. On the other hand, *tert*-alkyl halides exhibit a constant rate ratio over a variety of solvents. For example, the *t*-BuCl/1-adamantyl Br rate ratio remains constant throughout 19 solvents of widely varying polarity and nucleophilicity.[4]

Table I
Conductometric Rate Constants for Solvolysis of 1

Compd[a]	Temp, °C	Solvent[b]	10^4 k, sec^{-1} [c,d]
1a	74.37 ± 0.03	50E	0.276 ± 0.002
		70T	2.26 ± 0.02
1b		50E	0.219 ± 0.005
		70T	1.90 ± 0.01
1c	64.14 ± 0.02	97T	0.679 ± 0.006
	64.14 ± 0.02	60E	0.287 ± 0.008
	60.20 ± 0.01	70T	2.44 ± 0.001
	64.22 ± 0.02	50E	0.897 ± 0.009
1d	60.20 ± 0.01	70T	2.03 ± 0.007
	64.22 ± 0.02	50E	0.758 ± 0.007
1e	64.14 ± 0.02	97T	0.529 ± 0.003
	64.14 ± 0.02	60E	0.251 ± 0.006
	60.20 ± 0.01	70T	2.07 ± 0.03
	64.22 ± 0.02	50E	0.773 ± 0.005
1f	64.17 ± 0.02	97T	0.672 ± 0.009
	64.15 ± 0.02	60E	1.06 ± 0.02
	54.24 ± 0.01	70T	1.93 ± 0.01
	54.24 ± 0.01	50E	1.08 ± 0.01
1g	64.17 ± 0.02	97T	0.536 ± 0.020
	54.24 ± 0.01	70T	1.60 ± 0.02
	54.24 ± 0.01	50E	0.916 ± 0.009
1h	64.17 ± 0.02	97T	0.524 ± 0.007
	64.15 ± 0.02	60E	0.838 ± 0.009
	54.24 ± 0.01	70T	1.52 ± 0.007
	54.24 ± 0.01	50E	0.842 ± 0.002
1i	44.05	70E	0.440 ± 0.01
		60E	1.24 ± 0.01
		50E	3.94 ± 0.02
1j	15.3	97T	6.05 ± 0.03
	44.05	60E	1.105 ± 0.005
1m	24.63	80E	0.263 ± 0.003
		70E	0.970 ± 0.03
		60E	3.57 ± 0.10
	44.05	80E	3.16 ± 0.04
1n	24.62	80E	5.88 ± 0.08

[a] 2–5 × 10^{-4} *M*. [b] 50E represents 50:50 (v/v) ethanol–water; 70T represents 70:30 (w/w) trifluoroethanol–water; etc. [c] Average of triplicate determinations paired with appropriate deuterated compound. Occasionally quintuplicate determinations were performed. [d] Errors listed are standard deviations calculated in the usual manner for 95% confidence limits.

Table II
α Isotope Effects for Solvolysis of 1

	Temp, °C	Solvent	k_H/k_D[a,b]	$\Delta\Delta F^\ddagger/D$[a]
1a/1b	74.37	50E	1.28 ± 0.03	168
		70T	1.20 ± 0.01	126
1c/1d	64.22	50E	1.20 ± 0.01	121
	60.20	70T	1.218 ± 0.009	130
1f/1g	64.17	97T	1.28 ± 0.05	169
	54.24	70T	1.23 ± 0.02	136
	54.24	50E	1.20 ± 0.01	118

[a] Corrected to 100% deuteration at the temperature listed. [b] Errors listed are standard deviations for quotients calculated in the usual manner for 95% confidence limits. It should be noted that measured k_H/k_D values for each paired run were usually reproducible to better than 0.7% error, e.g., k_H/k_D = 1.20 ± 0.008.

Table III
β Isotope Effects for Solvolysis of 1

	Temp, °C	Solvent	$k_H k_{CD_3}$[a]	$\Delta\Delta F^\ddagger/CD_3$[d]
1c/1e	64.14	97T	1.33 ± 0.02[b]	192
	64.14	60E	1.17 ± 0.04[b]	103
	60.20	70T	1.21 ± 0.02[b]	125
	64.22	50E	1.18 ± 0.01[b]	114
1f/1h	64.17	97T	1.33 ± 0.02[c]	96
	64.15	60E	1.31 ± 0.04[c]	92
	54.24	70T	1.33 ± 0.01[c]	92
	54.24	50E	1.33 ± 0.04[c]	93
1i/1j	15.3	97T	1.121 ± 0.009[b]	72
	44.1	60E	1.13 ± 0.01[b]	80
1k/1l	24.62	60E	1.21 ± 0.03[b]	111
	45.30	80E	1.23 ± 0.02[b]	132

[a] See footnote *b*, Table II, for an explanation of errors. [b] Corrected to 100% deuteration, i.e., to three deuteriums/molecule. [c] Corrected to 100% deuteration, i.e., to six deuteriums/molecule. [d] Value listed is per *one* trideuteromethyl group at the temperature of the measurement.

The major exceptions to this behavior are the rates of 1-Adam Br solvolysis in aqueous TFE solutions, where consistently high rates (relative to *Y* values) are observed. These are apparently due to the greater electrostatic solvation or H bonding of the TFE to the leaving group. In the case of di- and trisubstituted haloallenes, protonation of the allene moiety precludes any solvolysis study in acidic solvents such as TFA. Nonetheless, within this constraint several trends are noticeable from a study of the solvent dependence of the rate. Table IV shows the steric dependence of the 97T/60E rate ratio (rate ratio at constant *Y* value) for several tri- and disubstituted haloallenes.[5]

Table V lists the relative rates for a variety of allenyl halides to allow comparison with saturated systems of comparable reactivity.

It should be noted that a marked change in this rate ratio between two compounds means also that the relative rate of solvolysis of these compounds changes with solvent. The compounds studied show substantial changes in 97T/60E rate ratios depending upon the steric size of the groups attached to the allene moiety, the 97T/60E rate ratio increasing with steric bulk, particularly at C-3. Within the series of trisubstituted chloroallenes studied the relative rates show a much steeper dependence on steric size of attached groups in 60E than in 97T. For example, the highly hindered compound tri-*tert*-butylchloroallene solvolyzes 1.7 times as slowly as 1,3-di-*tert*-butyl-3-methylchloroallene in 97T but nearly seven times as slowly in 60E. Disubstituted bromoallenes show an identical but somewhat muted behavior with the less hindered 3,3-dimethylbromoallene (**1f**), solvolyzing at the same rate as 3-methyl-3-*tert*-butylbromoallene (**1c**) in 97T but nearly four times faster in 60E. Such behavior may be interpreted as arising from increased nucleophilic solvent assistance in aqueous ethanol for less hindered substrates such as **1f**. The involvement of such assistance is clearly less important in the less nucleophilic TFE solutions. It is unlikely that such solvent assistance occurs by an in-plane route at C-1 owing to the lack of precedent for in-plane nucleophilic substitution in vinylic systems.[15] Thus, if a k_S process is involved, it probably occurs at the 3 position ("allylic position"). The question of direct displacement at C-1 is under investigation. Nucleophilic addition–elimination schemes are ruled out by the lack of dependence on pyridine concentration up to a fivefold excess and the observation of normal *m* values, e.g., **1f** and **1c** exhibit *m* = 0.88 and 0.90, respectively, in aqueous ethanol. In view of the "normal" behavior of these compounds with regard to classical SN1 criteria such as *m* values, $\Delta S^\ddagger$, CH_3/H ratios, k_{Br}/k_{Cl} ratios, and particularly the magnitude and solvent independence of the α and β secondary isotope effects (vide infra), it appears unlikely that the enhanced sensitivity of the rate of solvolysis to steric bulk in ethanol over TFE is due primarily to solvent assistance. Rappoport et al. have shown recently that vinylic substrates show unusual solvent effects in aqueous TFE, manifested as a nonlinear dependence of either log *k* vs. X_{H_2O} or log *k* vs. $Y_{t\text{-BuCl}}$.[16] These workers attribute the ob-

Table IV
$(TFE/E)_Y$ Ratios for $R_1R_2C{=}C{=}C(X)R_3$

Registry no.	R_1	R_2	R_3	X	Solvent	Rate ratio
37892-65-2	*t*-Bu	*t*-Bu	*t*-Bu	Cl	97T/60E	900
2115-12-0	*t*-Bu	Ph	*t*-Bu	Cl	97T/60E	280
	t-Bu	Me	*t*-Bu	Cl	97T/60E	12
	t-Bu	*t*-Bu	H	Br	70T/50E	8.2[a]
	t-Bu	Me	H	Br	97T/60E	2.4[b]
					70T/50E	3.7[b]
	Me	Me	H	Br	97T/60E	0.63[c]
					70T/50E	1.8[c]

[a] At 75°. [b] At 64°. [c] At 54°.

Table V
Relative Rates of Solvolysis of Saturated and Unsaturated Halides in 80% Ethanol at 25°

Compd	Rel rate	Ref
$(Ph)_2CHCl$	192	6
$(t\text{-Bu})(CH_3)C{=}C{=}C(CH_3)Br$	65	7
$(CH_3)_2CClC{\equiv}CCH_3$	60	8
$CH_3CH_2C{\equiv}CC(CH_3)_2Cl$	54	9
$(CH_3)_3CBr$	40	6
$(CH_3)_2CHC{\equiv}CC(CH_3)_2Cl$	38	9
$PhCH(CH_3)Br$	22	10
$(t\text{-Bu})(CH_3)C{=}C{=}C(t\text{-Bu})Br$	4.1	7
$CH_3CH_2C(CH_3)_2Cl$	1.8	11
$PhCH(CH_3)Cl$	1.2	10
$(CH_3)_3CCl$	1.0	5
$HC{\equiv}CC(CH_3)_2Br$	0.5	12
$HC{\equiv}CC(CH_3)_2Cl$	0.025	9
$(CH_3)_2C{=}C{=}C(H)Br$	0.011	7
$(CH_3)_2CHBr$	0.008	3
$(CH_3)_2CHCl$	2×10^{-4}	13
2-Adamantyl Br	1.2×10^{-5}	3
$CH_2{=}C{=}HBr$	4×10^{-7}	14

servation of high, low, or negative m values in TFE either to a balance between decreasing solvent electrophilicity and increasing dielectric constant with increasing X_{H_2O} or to an increase in the fraction of ion pairs leading to product forming dissociated ions with increasing H_2O content. In the present case **1c** and **1f** show a very steep dependence on $Y_{t\text{-BuCl}}$ in TFE. Even when compared against log $k_{Adam\text{-}Br}$[4] or log $k_{AnC(X){=}CMe_2}$[16] in aqueous TFE the resulting two-point solvent dependence is also steep. This suggests that unusual solvent effects in TFE may be operative in our system as well. In addition, a common ion rate depression has been observed in at least one chloroallene solvolysis, thus implicating ion pairs on these solvolysis. In the present case, a complete study of the effect of added salts, in particular the presence or absence of a rate–product correlation in the presence of added Nu^-, should provide substantial information in this area. Such a study is currently underway.

Finally, *tert*-butyl chloride exhibits rates of solvolysis in aqueous trifluoroethanol which are slower than expected when compared to the rate of 1-adamantyl bromide solvolysis. It has been suggested that this results from a shift to rate-limiting elimination in TFE.[2,4,5,16] The isotope effects reported here support such an explanation in this case as well.

Secondary Isotope Effects. Shiner et al. have suggested that the degree of solvent dependence of α and β secondary isotope effects is an excellent mechanistic probe for the involvement of k_S processes in solvolysis reactions.[2] Both *tert*-butyl chloride and α-phenylethyl chloride exhibit α and β isotope effects independent of the solvent nucleophilicity.[2] Shiner has reported also that the hindered secondary system 2-adamantyl tresylate exhibits α secondary isotope effects invariant (k_H/k_D = 1.225 ± 0.001) with solvent nucleophilicity.[17]

The isotope effects reported here are consistent with a limiting mechanism of solvolysis for disubstituted bromoallenes. The magnitudes of the α isotope effects (Table II) are the largest ever reported for halide leaving groups. They do not, however, approach the maximum value, k_H/k_D = 1.32, for an $sp^2 \rightarrow sp$ change estimated by the method of Shiner and Hartshorn.[18]

It must be noted that the use of the α secondary isotope effect in this system to assess the amount of k_S behavior is severely restricted since nucleophilic assistance at the 3 position results in increased s character in the C–H bond at the reaction center, thus increasing $(k_H/k_D)_\alpha$ while nucleophilic assistance at the 1 position, i.e., the reaction center, would lead to a lowered $(k_H/k_D)_\alpha$. While nucleophilic attack by solvent at C-1 may be unlikely on the neutral substrate, it is certainly possible in the tight ion pair where developing charge has been delocalized to both C-1 and C-3. β effects would then seem to be the probe of choice. The magnitude of the α effects observed rules out any carbene mechanism where proton loss is slow or where proton loss is a fast equilibrium step.[19]

The β effects (Table III) are remarkably constant from 50E to 97T, being somewhat smaller per CD_3 in the less hindered case, **1f/1h**, than in the hindered system **1c/1e**. Comparable behavior is observed in the solvolysis of several tertiary alkyl chlorides owing to a rather large fraction of olefin formation in the Me branch.[11] The increase in the β effect for **1c/1e** in 97T is analogous to the increase in β effect for *tert*-butyl chloride in 97T.[2,5,20] This has been explained as the result of increased involvement of rate-limiting elimination from an ion pair in this solvent and is manifested by an increased olefin fraction in 97T in this case as well. Reliable product studies are not yet available for our system. The β isotope effects observed in our system also preclude any mechanism involving removal of the terminal proton, since the base-assisted solvolysis of **1f** exhibits k_H/k_{d_6} = 1.15 in 80E.[19] Schleyer has suggested that variations in secondary isotope effects with solvent nucleophilicity may be too small to detect in certain cases, thus necessitating the very accurate measurement of rates, i.e., to a precision better than ±1%. The errors in the isotope effects reported here are calculated from the usual equation for the standard deviation of a quotient. In fact the measured k_H/k_D in each case of paired runs showed deviations usually one order of magnitude better than that reported.[22] It appears therefore that in spite of the low reactivity of 3,3-dimethylbromoallene, $k_{1f}/k_{i\text{-PrBr}}$ = 1.4 in 80E at 25°, a limiting mechanism of solvolysis is operative and supported by at least four commonly accepted mechanistic criteria. Work is now in progress to determine whether the limiting mechanism holds throughout the series $R_2C{=}C{=}C(R)Br$, $R_2C{=}C{=}CHBr$, $R(H)C{=}C{=}CHBr$, $CH_2{=}C{=}CHBr$.

Allenyl vs. Propargyl Halide Solvolysis. An interesting comparison is now possible between the reactivity of **1f** and 3-methyl-3-bromo-1-butyne. The propargyl isomer solvolyzes about 45 times faster than the allenyl isomer. Stang et al.[14] reported that propargyl bromide solvolyzed 4000 times as rapidly as allenyl bromide in 50E. They concluded that the difference in reactivity was due to the difference in ground-state energy as well as to differences in transition-state geometry. The smaller $k_{propargyl}/k_{allenyl}$ ratio observed here implies that the ground-state energy difference may be smaller than might be expected, since **1f** and 3-methyl-3-bromo-1-butyne both might be expected to rely heavily on the tertiary center for carbonium stabilization and thus have energetically similar transition states.

Experimental Section

Infrared spectra were obtained using a Perkin-Elmer Model 337 infrared spectrophotometer. Preparative gas–liquid chromatography was performed on a Hewlett-Packard chromatograph, Model 5750. The NMR spectra were run on an Hitachi Perkin-Elmer R-20B nuclear magnetic resonance spectrometer, 60 MHz. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga. Mass spectral analyses were performed by Professor Donald Hunt, University of Virginia.

Materials. 2,2,2-Trifluoroethanol (Halocarbon) was purified according to Shiner et al.[5] or Rappoport.[16] Ethanol was dried according to Wiberg.[23] 2,2,4,4-Tetramethyl-3-pentanone (Chemical Samples) was used without further purification. 3-Methyl-3-butyn-2-ol (Eastman) and 3,4,4-trimethyl-1-pentyn-3-ol (Farchan) were distilled prior to use.

3,3-Dimethyl-2-butanone-*1-d*$_3$ was prepared by three exchanges in 0.25 *M* NaOD–D_2O followed by pentane extraction and distillation. It was used without further purification, NMR (CCl_4) 1.1 ppm (s).

4,4-Dimethyl-3-*tert*-butyl-1-pentyn-3-ol was prepared using the procedure of Beumel and Harris[24] by adding 250 mmol of di-*tert*-butyl ketone dropwise to 25 g (250 mmol) of lithium acetylide–ethylenediamine in 250 ml of dry tetrahydrofuran in a flamed-out apparatus under dry N_2 at 35°C (maintained during addition by cooling). This mixture was allowed to react overnight with stirring and was then hydrolyzed with 100 ml of water. The contents were brought to a gentle boil for 1 hr, extracted with hexane, dried, and distilled: bp 85–90° (13 Torr); ir (neat) 3270 (C≡CH), 3500 (OH), 2090 cm^{-1} (w, C≡C).

1-Bromo-4,4-dimethyl-3-*tert*-butylpenta-1,2-diene (1a) was prepared using the procedure of Landor et al.[25] with the following proportions: 10.5 g (67 mmol) of 4,4-dimethyl-3-*tert*-butyl-1-pentyn-3-ol, 11.4 g of cuprous bromide, 6.1 g of ammonium bromide, 0.7 g of copper powder, 24 ml of 48% w/w HBr. The progress of the reaction was followed by watching the disappearance of the OH peak in the ir at 3500 cm^{-1}, which disappeared entirely after 5 days. The allene was then isolated and distilled: bp 89° (3.4 Torr) [lit. bp 80–81° (6 torr)];[25] ir (neat) 1920 cm^{-1} (C=C=C); NMR (CCl_4) 1.20 (s, 18), 5.80 ppm (s, 1). Anal. Calcd for $C_{11}H_{19}Br$: C, 57.14; H, 8.23; Br, 34.56. Found: C, 57.33; H, 8.34; Br, 34.29.

4,4-Dimethyl-3-*tert*-butyl-1-pentyn-3-ol-*1-d* was prepared by allowing 4.5 g of the undeuterated title compound to stir overnight in a 0.25 *M* NaOD–D_2O solution. This procedure was repeated three times and the recovered title alcohol was then distilled, yielding 2.4 g of the alcohol: bp 90–95° (12 Torr); ir (neat) 2555 cm^{-1} (C≡CD); NMR (CCl_4) 1.16 ppm (s).

1-Bromo-4,4-dimethyl-3-*tert*-butylpenta-1,2-diene-*1-d* (1b) was prepared identically with the undeuterated allene described above: bp 87° (3.4 Torr); ir (neat) 1900 cm^{-1} (C=C=C); NMR (CCl_4) 1.22 ppm (s). Mass spectral analysis yielded 0.95 D/molecule.

1-Bromo-3,4,4-trimethylpenta-1,2-diene (1c) was prepared by the procedure of Landor and Patel,[25] using 250 mol of 3,4,4-trimethyl-1-pentyn-3-ol: bp 55–58° (3.0 Torr) [lit. bp 57–61° (10 Torr)];[2] ir (neat) 1939 cm^{-1} (C=C=C); NMR (CCl_4) 5.68 (1, m), 1.85 ppm (9, s).

3,4,4-Trimethyl-1-pentyn-3-ol-*1-d* was prepared by allowing 13.4 g (116 mmol) of the undeuterated title compound to stir overnight in 0.25 *M* NaOD–D_2O solution prepared by adding 10 mmol (0.23 g) of sodium to 40 ml of D_2O. The alcohol was removed by syringe and the procedure repeated twice. The alcohol was then distilled: bp 72–73° (19 Torr); ir (neat) 3340 (OH), 2560 (C–D), 1980 cm^{-1} (C≡C); NMR (CCl_4) 1.03 (s, 9), 1.39 ppm (s, 3).

1-Bromo-3,4,4-trimethylpenta-1,2-diene-*1-d* (1d) was prepared by the following procedure of Landor et al.,[25] using the proportions 5.66 g of 3,4,4-trimethyl-1-pentyn-3-ol-*1-d*, 7.63 g of cuprous bromide, 3.8 g of ammonium bromide, 0.5 g of copper powder: bp 79–83° (6 Torr); ir (neat) 1933 (C=C=C), 2695 cm^{-1} (C–D); NMR (CCl_4) 5.72 (m, 1), 1.12 (s, 9), 1.83 ppm (d, 3). Mass spectral analysis gave 0.934 D/molecule.

3-Methyl-d_3-4,4-dimethyl-1-pentyn-3-ol was prepared by the method of Olah and Pittman:[26] bp 68–70° (20 Torr); ir (neat) 3400 (OH), 3260 cm^{-1} (≡CH), 3270 (C–D), 2090 cm^{-1} (C≡C); NMR (CCl_4) 1.03 (s, 9), 1.00 ppm (s, 1).

1-Bromo-3-methyl-d_3-4,4-dimethylpentadiene (1e) was prepared as described for **1c**: bp 56–57° (6 Torr); ir (neat) 3010 (=CH), 1925 cm^{-1} (C=C=C); NMR (CCl_4) 1.1 (s, 9), 5.73 ppm (s, 1). Mass spectral analysis gave 2.62 D/molecule.

1-Bromo-3-methylbuta-1,2-diene (1f) was prepared by the procedure of Landor and Patel:[25] bp 62–64° (38 Torr), [lit. bp 53–54° (60 Torr)];[2] ir (neat) 1958 cm^{-1} (s) (C=C=C); NMR (CCl_4) 1.80 (s, 9), 5.68 ppm (m, 1).

3-Methyl-1-butyn-3-ol-*1-d* was prepared by allowing 16.8 g (200 mmol) of the undeuterated title compound to stir overnight in a 0.25 *M* NaOD–D_2O solution. The solution was then extracted with 3 × 50 ml of ether, the ether evaporated, and the procedure repeated twice. Distillation yielded 5.5 g of alcohol: bp 100–102°; ir (neat) 1960 (C≡C), 2560 (C≡CD), 2470 cm^{-1} (OD); NMR (CCl_4) 1.5 ppm (s).

1-Bromo-3-methylbuta-1,2-diene-*1-d* (1g) was prepared using the procedure of Landor et al.,[25] using the proportions 5.5 g (66 mmol) of 3-methyl-1-butyn-3-ol-*1-d*, 3.3 g of cuprous bromide, 2.6 g of ammonium bromide, 0.13 g of copper powder, and 16 ml of 48% w/w HBr: bp 40–45° (47 Torr); ir (neat) 1920 (C=C=C), 2255 cm^{-1} (C=C=C–D); NMR (CCl_4) 1.84 ppm (s). Mass spectral analysis gave 0.894 D/molecule.

3-Methyl-d_3-butyn-3-ol-*4-d*$_3$ was prepared according to the method of Beumel and Harris.[24] Acetone-d_6 (Aldrich) (10 g, 16.2 mmol) was allowed to react with 17.2 g (17.2 mmol) of lithium acetylide ethylenediamine (Ventron) in THF. Work-up and distillation afforded a 62% yield of the title compound: bp 100–101°; ir (neat) 3250 (OH), 2200 (C–D), and 2090 cm^{-1} (C≡C); NMR (CCl_4) 2.27 (s) and 3.29 ppm (s).

1-Bromo-3-methyl-d_3-butadiene-*4-d*$_3$ (1h) was prepared as for **1f**. Preparative GC (10 ft × 0.5 in., SE-30 on Chromosorb W, 95°) afforded the title compound: ir (neat) 1940 cm^{-1} (C=C=C); NMR (CCl_4) 6.15 ppm (s). Analysis of CH_3 by NMR yielded 0.84 H/2CD_3. Mass spectral analysis gave 5.16 D/molecule.

2,2,3,6,6-Pentamethyl-4-heptyn-3-ol was prepared by the method of Olah and Pittman.[26] The product (24.8 g) was obtained in 90% yield: bp 73–76° (3 mm); ir (neat) 3470 (OH), 2240 cm^{-1} (C≡C); NMR (CCl_4) 0.99 (s, 9), 1.21 (s, 9), 1.33 (s, 3), 2.01 ppm (s, 1).

3-Chloro-2,2,5,6,6-pentamethyl-3,4-heptadiene (1i) was prepared by the method of Jacobs and Fenton.[27] 2,2,3,6,6-Pentamethyl-4-heptyn-3-ol (9.2 g, 50 mmol) was added to cold anhydrous ether. Thionyl chloride (3.6 ml, 5.9 g, 50 mmol) and 8.0 ml (7.9 g, 100 mmol) of pyridine in ether were quickly added with stirring, which was continued for 1 hr at 0°. The precipitate was filtered out of the reaction mixture and the organic layer washed three times with 100 ml of 5% sodium bicarbonate and twice with 50 ml of water. The organic layer was dried as above and vacuum distilled to give four fractions, 45–62°, 62–68°, 68–75°, 75–81° (4 mm). These fractions were found to contain varying proportions of the chloroallene and the ene-yne elimination product on the basis of ir and NMR spectra. Further separation was carried out using preparative gas chromotography: ir (neat) 1950 cm^{-1} (C=C=C); NMR (CCl_4) 1.07 (s, 9), 1.08 (s, 9), 1.11 (s, 9), 1.23 (s, 9), 1.74 (s, 3), 5.03 ppm (s, 2).

2,2,6,6-Tetramethyl-3-methyl-d_3-4-heptyn-3-ol was prepared by the method of Olah and Pittman.[26] Butyllithium in hexane (20%, 43 ml, 90 mmol) was chilled in an ice bath and 11.4 ml (7.7 g, 93 mmol) of *tert*-butylacetylene in 20 ml of hexane added dropwise. The solution was diluted with anhydrous diethyl ether, followed by slow addition of 9.1 g (90 mmol) of 3,3-dimethyl-*1-d*$_3$-2-butanone in anhydrous ether. The reaction mixture was gently refluxed for 2 hr and then cooled to 0° before addition of an excess of water to hydrolyze the lithium salt. After separation of the aqueous and organic layers, the latter was washed with two 50-ml portions of saturated sodium chloride solution, filtered through anhydrous magnesium sulfate, and stored over this drying agent overnight. Filtration followed by evaporation of solvent and vacuum distillation yielded 13.2 g (79%) of product: bp 73.5–75.5° (3 mm); ir (neat) 3470 (OH), 2250 (C≡C), 2080–2140 cm^{-1} (C–D), no residual ketone band; NMR (CCl_4) 0.98 (s, 9), 1.19 (s, 9), 1.83 ppm (s, 1).

3-Chloro-2,2,6,6-tetramethyl-5-methyl-d_3-3,4-heptadiene (1j) was prepared as described for the undeuterated compound, **1i**. Preparative GLC (10 ft × 0.5 in., SE-30 on Chromosorb W, 125°) afforded the title compound, ir (neat) 1960 cm^{-1} (C=C=C). Mass spectral analysis yielded 2.53 D/molecule.

3-Bromo-2,2,5,6,6-pentamethyl-3,4-heptadiene (1k) was prepared by adding 6.1 g (33 mmol) of 2,2,5,6,6-pentamethyl-3-heptyn-5-ol to a mixture of 5.7 g (40 mmol) of cuprous bromide, 2.8 g of ammonium bromide, 0.4 g of copper powder, and 12 ml of 48% w/w HBr warmed to 40°. The progress of the reaction was followed by watching the appearance of the 1940-cm^{-1} peak in the ir due to the allenyl stretch. After 3.5 hr the mixture was cooled and filtered and the residue washed with ether and extracted. The ether layer

was washed with 48% HBr until the lower layer showed no violet coloration. The ether layer was then filtered through $MgSO_4$–$NaHCO_3$ mixture and distilled: bp 78–79° (3.2 Torr); ir 1939 cm^{-1} (C=C=C); NMR (CCl_4) 1.07 (s, 9), 1.12 ppm (s, 9).

3-Bromo-2,2,6,6-tetramethyl-5-methyl-d_3-3,4-heptadiene (1l) was synthesized by the procedure of Marvel et al.[28] 2,2,6,6-Tetramethyl-3-methyl-d_3-4-heptyn-3-ol (5.7 g, 30 mmol) was dissolved in petroleum ether and 1.0 ml (2.85 g, 10 mmol) of phosphorus tribromide added. The reacting mixture was allowed to stir overnight, after which two layers were separated. The organic one was washed twice with 50 ml of saturated sodium bicarbonate and once with 100 ml of water. The organic solution was filtered through and dried over anhydrous magnesium sulfate. After filtering, the solvent was stripped by rotary evaporation. Vacuum distillation afforded 3.4 g (46%) of product: bp 80–84.5° (3 mm); ir (neat) 1947 (C=C=C), 2065–2140 cm^{-1} (C–D), no alcohol band; NMR (CCl_4) 1.09 (s, 9), 1.14 (s, 9), 1.74 ppm (m, 0.5). Anal. Calcd for $C_{12}H_{18}D_3Br$: C, 58.07; H and D, 8.56 (based on production of water); Br, 32.20. Found: C, 58.69; H, 8.64; Br, 32.16. Mass spectroscopic deuterium analysis yielded 2.50 D/molecule.

5,5-Dimethyl-4-*tert*-butyl-2-hexyn-4-ol was prepared by slowly bubbling propyne gas through 66 mmol (30 ml of 2.2 *M*) *n*-butyllithium in 120 ml of hexane with stirring under N_2 at room temperature. After 20 min 8.5 g (66 mmol) of di-*tert*-butyl ketone in 50 ml of diethyl ether was added dropwise and the mixture was refluxed for 30 min. After cooling, water was added dropwise to hydrolyze the mixture and the ether layer was washed with water and filtered through $MgSO_4$. The ether was then evaporated and the residue was distilled: bp 83–88° (3.1 Torr); ir (neat) 3470 (OH) and 2220 cm^{-1} (C≡C); NMR (CCl_4) 1.14 (s, 18), 1.83 ppm (s, 3).

2-Bromo-5,5-dimethyl-4-*tert*-butyl-2,3-hexadiene (1m) was prepared by adding 0.96 ml (2.73 g, 10.1 mmol) of PBr_3 to 5.5 g (30.2 mmol) of 5,5-dimethyl-4-*tert*-butyl-2-hexyn-4-ol in 75 ml of petroleum ether and allowing it to stir overnight in an ice bath. The mixture was then hydrolyzed with 40 ml of water. The ether layer was washed twice with 40 ml of saturated $NaHCO_3$ solution and then 30 ml of water and filtered through $MgSO_4$. The ether was evaporated and the residue distilled: bp 87–89° (2.9 Torr); ir (neat) 1940 cm^{-1} (C=C=C); NMR 1.24 (s, 18), 2.21 ppm (s, 3). Anal. Calcd for $C_{12}H_{21}Br$: C, 58.78; H, 8.63; Br, 32.59. Found: C, 59.48; H, 8.74; Br, 31.93.

4,5,5-Trimethyl-2-hexyn-4-ol was prepared by the method described for 5,5-dimethyl-4-*tert*-butyl-2-hexyn-4-ol using 66 mmol (30 ml of 2.2 *M*) of *n*-butyllithium and 6 g (60 mmol) of *tert*-butyl methyl ketone. The isolated alcohol was then distilled: bp 93° (18 Torr); ir (neat) 2220 (C≡C), 3420 cm^{-1} (OH); NMR (CCl_4) 0.97 (s, 9), 1.3 (s, 3), 1.8 ppm (s, 4).

2-Bromo-4,5,5-trimethylhexa-2,3-diene (1n) was prepared using the procedure of Landor et al.[25] using the following proportions: 3.4 g (24.3 mmol) of 5,5-dimethyl-2-hexyn-4-ol, 4.1 g of cuprous bromide, 2.0 g of ammonium bromide, 0.3 g of copper powder, and 8.7 ml of 48% w/w HBr. The reaction was kept at 30° for 1.5 hr. Distillation afforded the title compound, bp 78° (6 Torr). It was then purified by preparative GLC (SE-30 on Chromosorb W, 10 ft × 0.5 in., 155°), ir (neat) 1943 cm^{-1} (C=C=C). This compound decomposed rapidly (1 day) on standing at 0°.

Kinetic Studies. Kinetic solvents were prepared by weight from conductivity water and purified organic soolvents. Conductivity measurements were performed in paired cells using a Wayne Kerr autobalance universal bridge, B642, and a Chronolog Model 32001 digital clock interfaced with a Wang 600 advanced programable calculator. Solvent was allowed to equilibrate for 20 min in the conductance cells before initiating a kinetic run. From 0.5 to 1.3 μl of desired haloallene (preweighed syringe) was then introduced into the cell with stirring. Each kinetic sample was purified by preparative GLC on SE-30 (10 ft × 0.5 in.) prior to use. One hundred or more points were taken for each cell over 4–5 half-lives. Rate constants were obtained using an exponential least-squares program written in our laboratories for the Wang 600. In all other respects, rate constants were determined as described earlier.[1] Temperature control and measurement were accomplished using a PRT regulated proportional temperature controller and a Hewlett-Packard quartz thermometer.

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Registry No.—**1a**, 10575-75-4; **1b**, 57444-15-2; **1c**, 10575-72-1; **1d**, 57444-16-3; **1e**, 57444-17-4; **1f**, 6214-32-0; **1g**, 57444-18-5; **1h**, 57444-19-6; **1i**, 51211-93-9; **1j**, 57444-20-9; **1k**, 51038-84-7; **1l**, 57444-21-0; **1m**, 57444-22-1; **1n**, 57444-23-2; 2,2,2-trifluoroethanol, 75-89-8; ethanol, 64-17-5; 4,4-dimethyl-3-*tert*-butyl-1-pentyn-3-ol, 33420-19-8; 4,4-dimethyl-3-*tert*-butyl-1-pentyn-3-ol-*1-d*, 57444-24-3; 3,4,4-trimethyl-1-pentyn-3-ol-*1-d*, 57444-25-4; 3,4,4-trimethyl-1-pentyn-3-ol, 993-53-3; 3-methyl-d_3-4,4-dimethyl-1-pentyn-3-ol, 57444-26-5; 3-methyl-1-butyn-3-ol-*1-d*, 10313-04-9; 3-methyl-1-butyn-3-ol, 115-19-5; 3-methyl-d_3-butyn-3-ol-*4-d*$_3$, 57444-27-6; 2,2,3,6,6-pentamethyl-4-heptyn-3-ol, 36187-02-7; 2,2,6,6-tetramethyl-3-methyl-d_3-4-heptyn-3-ol, 57444-28-7; 5,5-dimethyl-4-*tert*-butyl-2-hexyn-4-ol, 57444-29-8; propyne, 74-99-7; di-*tert*-butyl ketone, 815-24-7; 4,5,5-trimethyl-2-hexyn-4-ol, 5187-21-3; *tert*-butyl methyl ketone, 75-97-8.

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$$k_H/k_D^2 = \frac{1}{k_D^2}\left[k_H^2 + (k_H/k_D)^2 k_D^2\right]$$

and assumes rate constants corresponding to $t_{1/2} \approx 100$ min and $k_H/k_D = 1.15$ then a precision of ±1% in rate constants yields a standard deviation in k_H/k_D of ±1.3% and a precision of ±0.5% in rate constants yields a standard deviation in k_H/k_D of ±0.65%. This strongly indicates the need for precise determination of rate constants and accurate reporting of *statistical* errors.
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The 4-Homoadamantyl Cation. III.[1] Sulfuric Acid Catalyzed Rearrangement of 4-Homoadamantanol-5-^{13}C

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The rearrangement–hydride transfer reduction of 4-homoadamantanol-5-^{13}C in concentrated sulfuric acid–pentane gave homoadamantane (2), 2-methyladamantane (3), and 4-homoisotwistane (4). The label was equilibrated over all ring carbons in each of the products but there was a small excess of the label located at the methyl group of 3. The results are interpreted in terms of a rapid degenerate rearrangement of the 4-homoadamantyl cation accompanied by rearrangements of this cation to the 2-homoadamantyl cation and an unsymmetrically bridged 2-adamantylcarbinyl cation. Therefore, 1,2-carbon shifts, 1,2-hydride shifts, and 1,3-hydride shifts are all involved.

The course of the rearrangement of the 4-homoadamantyl cation is highly dependent on the reaction conditions. Acetolysis and formolysis of 4-homoadamantyl tosylate yielded mixtures of the corresponding 4-homoadamantyl esters in addition to homoadamantene.[4,5] No product with the adamantane skeleton was formed. Experiments with isotopically labeled tosylate indicated the occurrence of both degenerate 1,2-carbon shifts and 1,2-hydride shifts. Thus, 4-homoadamantyl-4-^2H tosylate produced 4-homoadamantyl acetate with 38–45% of the label at the α position. If only 1,2-carbon shifts had been involved 50% of the label should have been located at this position.[5]

The reaction of homoadamantene with AlX_3 in carbon disulfide generated the 4-homoadamantyl cation, which yielded 20% of 2-methyladamantane.[1,6] Homoadamantene-4-^{13}C gave 2-methyladamantane with the majority of the label equally distributed between the α position and the methyl group, indicating that just the olefinic carbons were involved in this rearrangement.[1] Only a small amount of label was scrambled to the β and γ carbons relative to the methyl group. The degenerate homoadamantyl rearrangement (1,2-carbon shift) is retarded in such a low polar solvent as CS_2 presumably by intimate ion pairing. The suggested mechanism involves protonation of the olefinic bond by $AlX_3 \cdot H_2O$ to form the classical 4-homoadamantyl cation. This cation rearranges rapidly to an unsymmetrically bridged 2-adamantylcarbinyl cation[7] which then yields 2-methyladamantane by hydride abstraction.

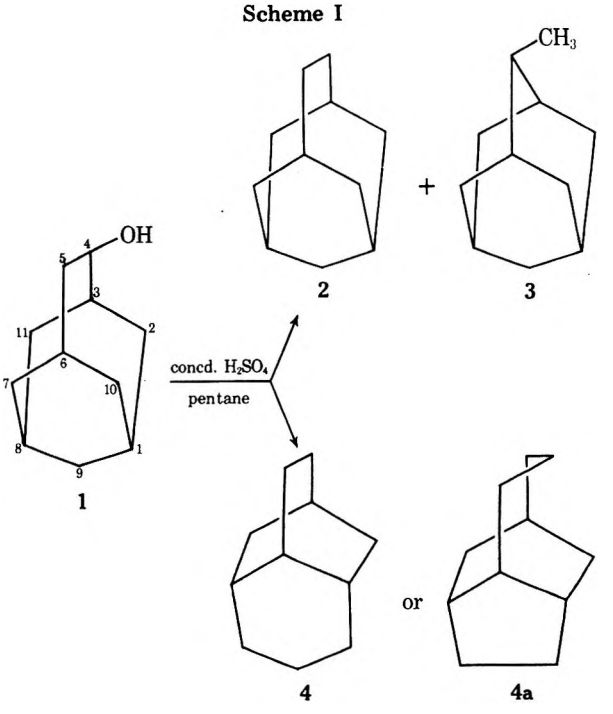
In this work we have studied the rearrangement of the 4-homoadamantyl cation in concentrated sulfuric acid[10] using ^{13}C labeling techniques. The 4-homoadamantyl cation was generated by protonation of 4-homoadamantanol-5-^{13}C.

Results

4-Homoadamantanol-5-^{13}C (**1b**) was obtained by $LiAlH_4$ reduction of 4-homoadamantanone-5-^{13}C.[11] Comparison of ^{13}C NMR spectra of the labeled (**1b**) and unlabeled (**1a**) 4-homoadamantanol, recorded under identical operating conditions, showed that no label scrambling had occurred during the synthesis of **1b**; the label was located exclusively at position 5. (The ^{13}C NMR spectrum of 4-homoadamantanol is discussed in detail in the Experimental Section.) Mass spectrometric analysis indicated a ^{13}C enrichment as 7.5 ± 1%.

Alcohol 1 was stirred with concentrated sulfuric acid in the presence of pentane for a few minutes at room temperature. The pentane layer was separated and the solvent evaporated to yield 40% of a crude product mixture which was analyzed by GLC. GLC analysis indicated the presence

Scheme I

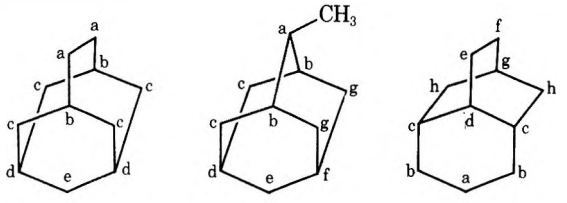


of three products in a ratio of 1:1:2 (Scheme I). The two minor products were identified as homoadamantane (**2**) and 2-methyladamantane (**3**) by ^{13}C NMR, ^1H NMR, ir, and mass spectra, and GLC comparison with authentic samples. The major product was also a tricyclic undecane but turned out not to be a diamonoid hydrocarbon! Its mass spectrum showed a molecular ion peak at *m/e* 150. ^1H NMR and ir spectra indicated the absence of unsaturation, cyclopropane rings, and alkyl groups, while its melting point (56–58°) was considerably lower than typical for diamonoid hydrocarbons. The ^{13}C NMR spectrum of this material showed eight signals (see Table I) corresponding to three different CH and five different CH_2 groups according to the proton off-resonance spectrum and the T_1 values. Such a ^{13}C NMR spectrum is only compatible with the two tricycloundecanes, **4** and **4a**, among all possible 11-carbon tricyclic hydrocarbons possessing all of the carbons in rings and having no three- or four-membered rings.[12] According to empirical force-field calculations, **4** is 9.5 kcal/mol less strained than its isomer **4a**.[13] The more stable isomer, **4** (tricyclo[5.3.1.$0^{3,8}$]undecane), is known[14,15] and has been conveniently named 4-homoisotwistane.[10] Ir, ^1H NMR, and ^{13}C NMR spectra of an authentic sample of this hydrocarbon were identical with those of the major

Table I
^{13}C NMR Signal Intensities of the Rearrangement–Hydride Transfer Products of 4-Homoadamantanol (1a) and 4-Homoadamantanol-5-^{13}C (1b) in Concentrated Sulfuric Acid at 22°

Product	Chemical shift[a]	Carbon[b]	T_1,[c] sec	Relative signal intensities[d] 1a[e]	1b[f]	x_i, %[g]
2	38.4	c	11.4	4.48	7.55	10
	36.5	e	11.5	1.14	1.66	7
	34.0	a	12.7	2.17	3.57	9
	32.1	b	19.7	2.16	3.55	9
	27.7	d	19.7	2.14	3.29	8
3	39.6	c	10.5	2.38	3.79	9
	39.2	a	19.5	1.10	1.73	8
	38.8	e	11.5	1.11	1.77	9
	34.0	b	17.5	2.19	3.37	8
	31.5	g	9.5	2.25	3.73	9
	28.7	d or f	16.5	1.06	1.67	8
	28.4	f or d	16.5	1.08	1.68	8
	19.0	CH_3	10.0	0.92	1.86	15
4	33.0	d	15.3	1.20	1.79	7
	32.2	b or h	8.9	2.39	3.81	9
	31.8	h or b	8.6	2.37	3.80	9
	30.8	c	15.3	2.15	3.53	9
	27.0	e or f	8.6	1.02	1.64	9
	26.2	f or e	9.0	1.06	1.73	9
	24.7	g	15.6	0.94	1.62	10
	15.2	a	8.2	0.97	1.68	10

[a] Relative to Me_4Si; solvent $CDCl_3$. [b] Description as indicated below.



[c] Measured in undegassed solutions. [d] The standard deviation of a single signal intensity was found to be less than 5% of the measured value for each signal of unlabeled and labeled 3. Since the sample concentrations and operating conditions were virtually equal for 2, 3, and 4, the uncertainties in signal intensities can also be expected to be the same. [e] The sum of the signal intensities was taken as 12.1 (the number of carbons multiplied by the natural abundance of ^{13}C); mean value of two measurements for 2 and 4, and five measurements for 3. [f] The sum of the signal intensities was taken as 19.6 (12.1 + 7.5, the percentage of the ^{13}C enrichment); mean value of two measurements for 2 and 4, and four measurements for 3. Relative signal intensities of 4 obtained from 1b at 0° were essentially the same: 1.77, 3.86, 3.75, 3.51, 1.70, 1.74, 1.64, and 1.65. [g] The amount of label per carbon atom calculated by using eq 1.

product from the rearrangement–hydride transfer reduction of 4-homoadamantanol in sulfuric acid.

The conversion of 4-homoadamantanol to 4-homoisotwistane in sulfuric acid is the first example of a skeletal rearrangement of homoadamantane to a nonadamantanoid structure. 4-Homoisotwistane appears to be one of the most stable tricycloundecanes.[13] Schleyer[16] and Inamoto[17] identified this hydrocarbon as an intermediate in the acid-catalyzed rearrangements of 2-hydroxymethyl-*exo*-2,3-trimethylenenorbornane, *exo*- and *endo*-2,3-tetramethylenenorbornane, and 2,3-trimethylenebicyclo[2.2.2]octane to methyladamantanes.

The products, homoadamantane (2), 2-methyladamantane (3), and 4-homoisotwistane (4), were stable under the used reaction conditions. Essentially no isomerization of 2 occurred in concentrated sulfuric acid–pentane even if an equivalent amount of 2-pentanol was present. Interestingly, the ratio of 2, 3, and 4 formed in the reaction of 4-homoadamantanol with sulfuric acid was found to depend on the reaction temperature. At room temperature (22°) the ratio 2:3:4 was 1:1:2, while at 0° it was 1:0.5:5.

The distribution of the ^{13}C label in the products was determined by quantitative ^{13}C NMR analysis. To eliminate the influence of the saturation effect a waiting time between successive pulses five times as long as the longest relaxation time was used. Dependence of signal intensities on their positions in the digital spectrum was avoided by using the narrowest possible sweep width (1250 Hz) and a mathematical filtering[1] which enhanced the signal-to-noise ratio and increased the signal width. By this procedure more than ten data points per signal were available. Nuclear Overhauser enhancements were not eliminated, since this would reduce the signal-to-noise ratio by a factor of up to three and the sample amounts were limited. The spectra of the labeled and unlabeled compounds were taken under precisely the same operating conditions. The relative signal intensities of homoadamantane (2), 2-methyladamantane (3), and 4-homoisotwistane (4) obtained from 4-homoadamantanol-5-^{13}C (1b) and those of unlabeled 2, 3, and 4 are shown in Table I.

The amount of label per carbon atom cannot be calculated directly from the normalized signal intensities of the labeled and unlabeled compounds. In undegassed solutions the contribution of dissolved oxygen to the total relaxation rate of carbon atoms with relaxation times greater than 10 sec is significant,[18a] so that nuclear Overhauser enhancements depend on the relaxation rates of the carbon atoms. A reduction of nuclear Overhauser effect is also expected for free rotating methyl groups.[18b] Since such effects lead to multiplicative errors in the signal intensities we calculated the amount of label per carbon atom (x_i) by

$$x_i = \frac{100}{x_{tot}}\left[\frac{I_i^*/I_i(1.11N + x_{tot})}{\Sigma_i n_i I_i^*/I_i} - 1.11\right] \quad (1)$$

where I_i^* and I_i are the measured intensities of the ith signal in the labeled and reference compound, respectively, N is the total number of carbon atoms, n_i the number of equivalent carbons corresponding to the signal i, and x_{tot} the total amount of label (7.5%). The results indicate that the label is essentially equilibrated over all carbons in the nucleus in 2, 3, and 4, but there is a small, statistically significant, excess of label located at the methyl group of 3.

Discussion

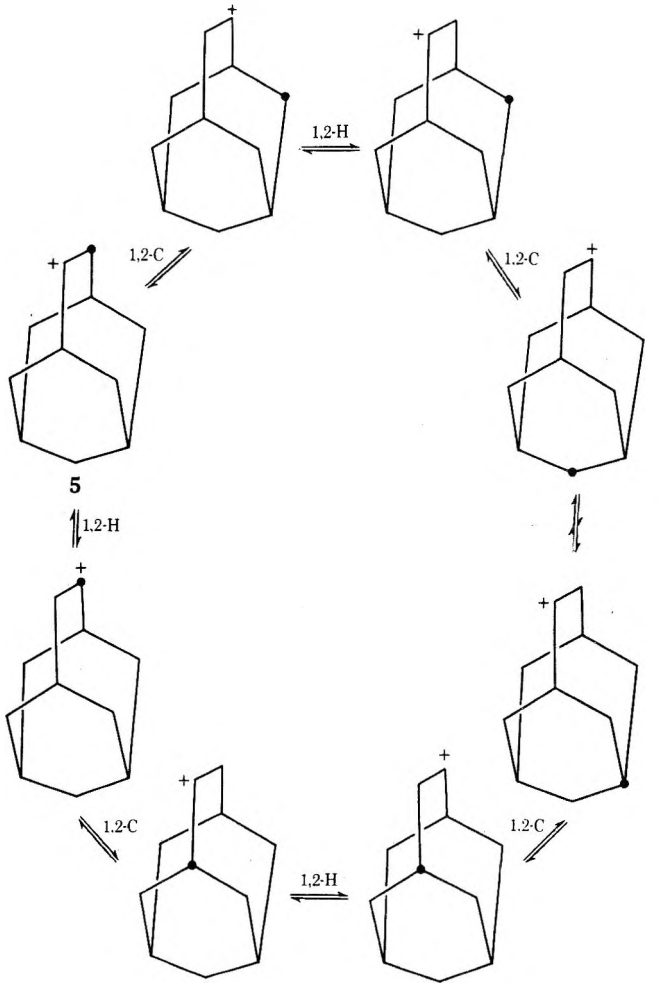
The sulfuric acid catalyzed conversion of 4-homoadamantanol to homoadamantane (2), 2-methyladamantane (3), and 4-homoisotwistane (4) undoubtedly involves protonation of the hydroxyl group followed by formation of the 4-homoadamantyl cation (5). This cation rearranges rapidly to other carbonium ions. The products 2, 3, and 4 are formed by the hydride-transfer reductions of the corresponding cations involving the solvent (pentane). The ^{13}C label in 2, 3, and 4 obtained from 4-homoadamantanol-5-^{13}C (1b) is completely scrambled over all ring carbons within experimental accuracy. However, there is a small but significant excess of label at the methyl group of 3.

The intermolecular hydride transfer from the products to pentyl cations (generated from the solvent) appears not to be an important process. If not, homoadamantane (2) should rearrange in the presence of pentyl cations, but essentially no rearrangement occurred when a mixture of 2 and 2-pentanol was subjected to the same reaction conditions as used for 4-homoadamantanol. A direct intermolec-

ular hydride transfer from one C_{11} tricyclic molecule to another one is even less probable, since in the reaction mixture pentane was present in large excess. Moreover, hydride abstraction from **2** should preferably produce the 3-homoadamantyl cation, which is less strained than other bridgehead homoadamantyl cations.[9b] This cation, under similar conditions, gives a considerable amount of 1-methyladamantane,[8] which in the reaction of 4-homoadamantanol with sulfuric acid is formed just in traces.

The high scrambling of the label in homoadamantane (**2**) can only be explained by essentially complete equilibration in the 4-homoadamantyl cation, i.e., by fast degenerate 1,2-carbon shifts accompanied by degenerate 1,2-hydride shifts. [If only 1,2-carbon shifts were involved the label in **2** would be located exclusively at positions a and c (see Table I, footnote *b*)]. In other words, the 4-homoadamantyl cation (**5**) formed directly from 4-homoadamantanol-5-^{13}C is in a fast equilibrium with the 4-homoadamantyl cations labeled at other positions (Scheme II). Since degeneracy is

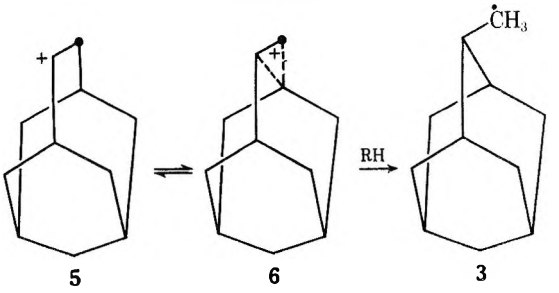
Scheme II



generally limited by bridging[19] the 4-homoadamantyl cations in the equilibrium should be classical. Carbonium ions in concentrated sulfuric acid are essentially free. However, the 4-homoadamantyl cation (**5**) formed in the reaction of homoadamantene with AlX_3 in CS_2 is probably paired with a gegenion and, consequently, the degenerate rearrangement of **5** is retarded in this medium.[1]

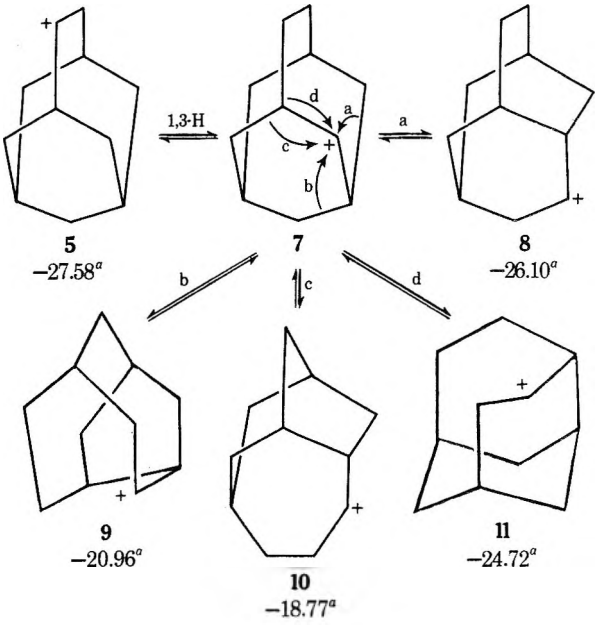
2-Methyladamantane (**3**) is probably formed by the hydride-transfer reduction of the unsymmetrically bridged 2-adamantylcarbinyl cation (**6**, Scheme III) as proposed for its formation in the Lewis acid catalyzed conversion of homoadamantene.[1] This cation can arise from any of the classical 4-homoadamantyl cations in the equilibrium. Since the ^{13}C label is equilibrated over all carbons in the 4-homoadamantyl cation, the label could be expected to be scrambled over all carbons in the derived bridged 2-adamantylcarbinyl cation and, therefore, 2-methyladamantane. The small excess of label found at the methyl group of **3** is consistent with the intermediacy of the bridged 2-adamantylcarbinyl cation. The formation of this cation is probably slightly faster than the degenerate rearrangement of the 4-homoadamantyl cation.[20]

Scheme III



The 1,2-carbon shifts and the 1,2-hydride shifts in the 4-homoadamantyl cation (**5**) lead either to another 4-homoadamantyl cation or to the bridged 2-adamantylcarbinyl cation (**6**). The other skeletal rearrangements can only be explained as proceeding through the 2-homoadamantyl cation (**7**), which can be formed from the 4-homoadamantyl cation by a 1,3-hydride shift.[21,22] Therefore, cation **7** is a precursor of 4-homoisotwistane. This cation can potentially rearrange by 1,2-carbon shifts to four different carbonium ions: **8**, **9**, **10**, and **11** (Scheme IV). Dihedral angles between

Scheme IV

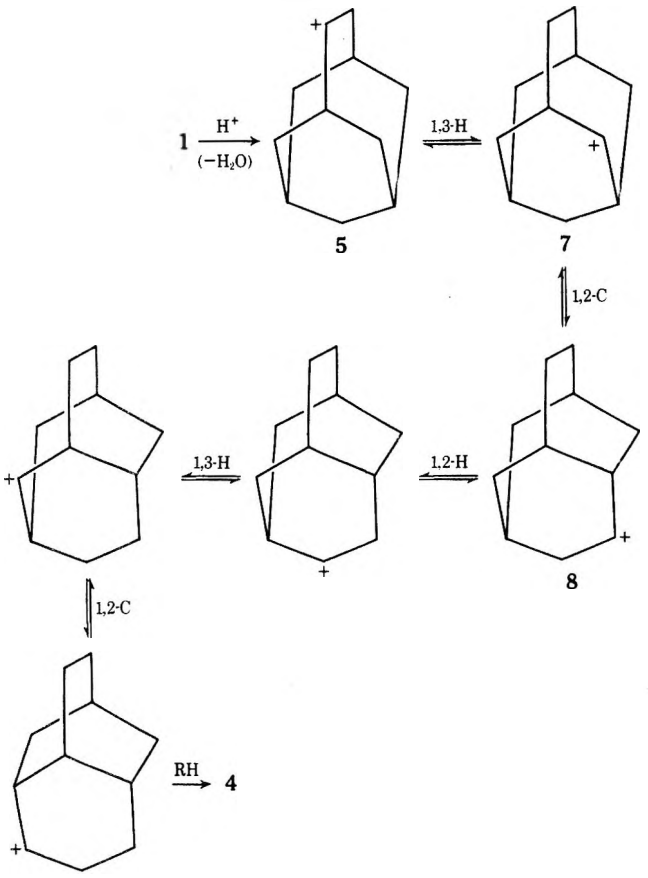


[a] Calculated heats of formation (kcal/mol) of the corresponding hydrocarbons.[13]

the 2-homoadamantyl cation empty p orbital and the migrating C–C bonds are similar in all four cases (20–40°). However, the calculated heats of formation (as well as strain energies) of the hydrocarbons corresponding to cations **8**, **9**, **10**, and **11** are significantly different.[13] Since all four cations (**8**–**11**) are secondary, the relative stabilities of these cations should roughly parallel to the relative stabilities of the corresponding hydrocarbons. Cation **8** appears to be the most stable, whereas cations **9** and **10** are considera-

bly less stable. For a similar reaction, isomerization of *exo*-1,2-trimethylenenorbornane to adamantane, it has been shown that the course of the reaction is governed by the relative thermodynamic stabilities of the possible products.[23] This indicates that the product-determining steps involve transition states closer to the products than to the initial cations. Using the same approach it can be predicted that rearrangement pathways b and c of the 2-homoadamantyl cation probably cannot compete successfully with pathways a and d (see Scheme IV). A reasonable mechanism of the conversion of the 4-homoadamantyl cation to 4-homoisotwistane via 8 is outlined in Scheme V. However, cation 11 is only about 2 kcal/mol less stable than cation 8 and cannot be excluded as a possible intermediate in the conversion of the 4-homoadamantyl cation to 4-homoisotwistane. There are a number of possible pathways for this conversion via cation 11 several of which involve only cationic intermediates with stabilities comparable to that of 8 and 11. However, these pathways are longer than that shown in Scheme V.

Scheme V



Our results demonstrate that the mechanism and, consequently, the product composition of the rearrangement–hydride transfer reduction of the 4-homoadamantyl cation depends highly on the reaction medium. The rearrangement in concentrated sulfuric acid involves 1,2-carbon shifts and both 1,2- and 1,3-hydride shifts, while the Lewis acid catalyzed rearrangement in nonpolar carbon disulfide[1] involves mainly the 1,2-carbon shift leading to the bridged 2-adamantylcarbinyl cation and 2-methyladamantane. The degenerate homoadamantyl rearrangement of the 4-homoadamantyl cation in the presence of AlX_3 in carbon disulfide is retarded by ion pairing.[1] However, this rearrangement is very rapid in concentrated sulfuric acid, where cationic intermediates are essentially free and probably live longer.

Experimental Section

^{13}C NMR spectra were taken at 22.628 MHz on a Bruker-Spectrospin HFX-90 spectrometer equipped with a B-SC-FFT-12 Fourier transform unit. Samples (40–50 mg) in $CDCl_3$ solutions (ca. 160 μl) were measured using a 5-mm cylindrical microcell. The deuterium signal of the solvent was used as the internal lock. The free induction decay spectra were accumulated in 8192 data points. Chemical shifts are given in parts per million relative to internal Me_4Si. Relaxation times (T_1) were measured in undegassed solutions. ^1H NMR spectra were recorded on a Varian A-60A spectrometer, ir spectra were taken on a Perkin-Elmer M-257 spectrophotometer, and mass spectra on a Varian CH-7 mass spectrometer. GLC analyses were carried out on a Varian Aerograph M-1800 gas chromatograph with a M-480 integrator.

4-Homoadamantanol-5-^{13}C (1b) was obtained in 92% yield by $LiAlH_4$ reduction of 4-homoadamantanone-5-^{13}C[1] using the standard procedure.

The proton decoupled ^{13}C NMR spectrum of 4-homoadamantanol shows 11 signals at 76.5 (6.6, d), 44.4 (4.0, t), 40.7 (t), 40.6 (d), 36.7 (3.5, t), 36.3 (3.8, t), 35.6 (3.7, t), 29.6 (d), 29.5 (t), 27.5 (6.3, d), and 27.1 ppm (6.8, d) (the data in parentheses indicate T_1 values in seconds and the multiplicity as determined by proton off-resonance decoupling). The T_1 values of the seven well-resolved signals are in accord with the results of the off-resonance decoupling. The signals at 29.5, 40.6, 76.5, 44.4, 29.6, and 35.6 ppm are assigned to carbons 2, 3, 4, 5, 6, and 11 (see Scheme I), respectively, on the basis of the proton off-resonance decoupling and estimated chemical shift values (28.2, 36.4, 76.0, 44.5, 28.4, and 34.7 ppm, respectively). These values were calculated using the chemical shifts of homoadamantane (see Table I) and the correction increments[24] for the introduction of the hydroxyl group. This procedure could not be used successfully to assign the signals of the δ carbons relative to the hydroxyl group. The estimated chemical shifts values were identical for carbons 7 and 10 (38.4 ppm) and 1 and 8 (27.7 ppm).

Reaction of 4-Homoadamantanol-5-^{13}C (1b) with Sulfuric Acid. To a mixture of 1 ml of concentrated H_2SO_4 and 2.5 ml of pentane vigorously stirred at room temperature (22°) 250 mg (1.5 mmol) of **1b** was added all at once. After 3 min 5 ml of pentane was added and the resulting mixture was poured on 100 ml of ice–water. The layers were separated and the aqueous one was extracted with pentane. The combined pentane extracts were washed with water and dried. The solvent was carefully removed through a Vigreux column to give 88 mg (39%) of the crude product. GLC analysis (SE-30, 80°) indicated the presence of three major products in a ratio of 1:1:2 and less than 1% of 1-methyladamantane. The major products were isolated by preparative GLC (SE-30, 120°) and identified as homoadamantane (**2**), 2-methyladamantane (**3**), and 4-homoisotwistane (**4**) by comparison of ^{13}C NMR, ^1H NMR, ir, and mass spectra with those of authentic samples.

The reaction of **1b** with concentrated H_2SO_4 in the presence of pentane was also carried out at 0° for 4 min. The work-up as described above gave **2**, **3**, and **4** in a ratio of 1:0.5:5, respectively.

Homoadamantane (**2**), 2-methyladamantane (**3**), and 4-homoisotwistane (**4**) were subjected to the same reaction conditions as used for 4-homoadamantanol (**1**). After 24 hr only traces of rearranged products were detected by GLC. A mixture of **2** (1.5 mmol) and 2-pentanol (1.5 mmol) was also subjected to the same reaction conditions as **1** and the mixture was worked up as described above. GLC analysis indicated the absence of 2-pentanol and essentially no isomerization of **2**.

The ^{13}C NMR spectrum of 2-methyladamantane (**3**) has been described in detail previously.[1,25] The spectrum of homoadamantane (**2**) shows five signals (Table I). The signals at 38.4 and 36.5 ppm are assigned to carbons c and e, respectively, on the basis of their relative intensities (see Table I, footnote *b*). The relaxation time T_1 corresponding to the signal at 34.0 ppm is considerably shorter than those corresponding to the signals at 32.1 and 27.7 ppm. Since relaxation times of CH_2 groups are generally shorter than those of CH groups, the signal at 34.0 ppm is assigned to the ethylene-bridge carbons (a). The chemical shift of the ethylene-bridge carbons in 2,6-bishomoadamantane is exactly the same.[26] In both homoadamantane and 2,6-bishomoadamantane the "ethylene" carbons are more shielded than the methylene ones. This is consistent with Grant's additivity rule for polycyclic hydrocarbons.[27] The bridgehead carbons in 2,6-bishomoadamantane, flanked by an "ethylene" group and two methylene groups, are less

shielded than those in adamantane which are flanked by three methylene groups. Consequently, the signals at 32.1 and 27.7 ppm in the spectrum of 2 are assigned to bridgehead carbons b and d, respectively.

The ^{13}C NMR spectrum of 4-homoisotwistane (4) is assigned by comparison of experimental and calculated chemical shifts. The spectrum shows eight signals (Table I). According to the proton off-resonance decoupling and the T_1 values the signals at 33.0, 30.8, and 24.7 ppm correspond to CH groups while those at 32.2, 31.8, 27.0, 26.2, and 15.2 ppm correspond to CH_2 groups. Grant's additivity rule[27] was used to calculate the shifts of carbons a and b (16.2 and 32.7, respectively). To calculate the chemical shifts of the other carbons the shifts of bicyclo[2.2.2]octane[28] were taken as the basis and the influence of the trimethylene bridge was estimated using the additivity increments. For carbons c, d, e, f, g, and h (see Table I, footnote *b*) the following values were obtained: 32.1, 33.9, 26.7, 26.7, 24.6, and 29.2 ppm, respectively. Therefore, the signals at 15.2, 30.8, 33.0, and 24.7 ppm are assigned to carbons a, c, d, and g, respectively, whereas the signals at 32.2 and 31.8 ppm, as well as the signals at 27.0 and 26.2 ppm, could not be assigned in this way.

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(7) Such a cation has also been suggested as one of the intermediates in the sulfuric acid catalyzed rearrangements of 1- and 3-homoadamantanols[8] and in the Lewis acid catalyzed rearrangement of homoadamantane.[9a]
(8) J. Janjatovic, D. Skare, and Z. Majerski, *J. Org. Chem.*, **39**, 651 (1974).
(9) (a) R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem., Forsch.*, **18**, 17 (1971); (b) *ibid.*, **18**, 71 (1971).
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(11) 4-Homoadamantanone-*5*-^{13}C was prepared[1] in 46% overall yield by the addition of $(CH_3)_3SI^{13}CN$ to adamantanone followed by $LiAlH_4$ reduction of the α-trimethylsilyloxy nitrile and Demjanow–Tiffeneau ring enlargement of the resulting α-aminomethyl alcohol. This synthetic procedure appears to be a general and convenient method for the preparation of ^{13}C-labeled ketones and their derivatives.
(12) Such a set of 11-carbon tricyclic structures has also been independently constructed by Osawa, Inamoto, Engler, and Schleyer.[13b]
(13) (a) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973); (b) P. v. R. Schleyer and E. Osawa, private communications.
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(19) For example, H. L. Goering and G. N. Fickes, *J. Am. Chem. Soc.*, **90**, 2848, 2856, 2862 (1968).
(20) On this basis a small excess of the label should also be expected at positions a, c, and g (see Table I, footnote *b*) in 3. However, this excess is probably too small to be detected, since it would be spread over five carbon atoms.
(21) The product mixture of the rearrangement–hydride transfer reduction of 2-homoadamantanol in sulfuric acid is essentially the same as that from 4-homoadamantanol: Z. Majerski, K. M. Majerski, and B. Goricnik, unpublished results.
(22) The formation of 4-homoisotwistane in CF_3SO_3H-catalyzed rearrangement of homoadamantane appears to proceed also via 7: Y. Inamoto, private communication.
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Tetrabutylammonium Borohydride. Borohydride Reductions in Dichloromethane

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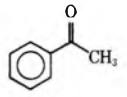
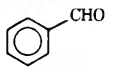
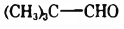
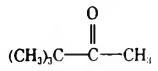
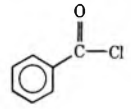
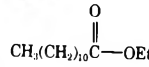
The utility of tetrabutylammonium borohydride as a reducing agent has been investigated. The high solubility of this reagent in dichloromethane permits reductions to be carried out in high yields in the absence of protic solvents. The selectivity of tetrabutylammonium borohydride in dichloromethane toward organic carbonyl compounds is similar to that exhibited by sodium borohydride in aqueous or alcoholic media. At room temperature acid chlorides are reduced extremely rapidly, aldehydes and ketones are reduced at convenient rates, and esters are reduced quite slowly. Synthetic procedures and results are reported for the reduction of a variety of aldehydes and ketones.

The preparation of quaternary ammonium borohydrides (tetramethylammonium, tetraethylammonium, and benzyltrimethylammonium borohydride) was reported by Banus, Bragdon, and Gibb in 1952.[1] The tetramethyl derivative exhibited solubilities similar to those of the alkali metal borohydrides, and consequently the quaternary ammonium derivatives did not appear to offer any advantages as synthetic reagents. Subsequently, Sullivan and Hinckley reported[2] the preparation of quaternary ammonium borohydrides which contained long chain alkyl groups: cetyltrimethylammonium borohydride and tricaprylmethylammonium borohydride. These compounds are soluble in

Table I
Reduction of Representative Carbonyl Compounds with Tetrabutylammonium Borohydride at 30°C

No.	Compd	1 equiv[a]		2 equiv[a]		4 equiv	
		$t_{1/2}$, min	Max %	$t_{1/2}$, min	Max %	$t_{1/2}$, min	Max %
1		2100	75	850	98	550	98
2		2600	69	1100	94	600	98
3		100	92	120[b]	92	40[b]	96
4		1250	94				
5		>10 000	40				
6		*c*	100				
7		*d*	25				

[a] This refers to the number of equivalents of reducing agent per mole of substrate; the concentration of the carbonyl compound was 1 M in each case. [b] $k \simeq 6 \times 10^{-3}$ l. mol^{-1} s^{-1}; none of the other substrates afforded a linear plot when the data were analyzed in terms of second-order kinetics (cf. ref 10c). Even benzaldehyde failed to follow second-order kinetics when only a single equivalent of reducing agent was used. [c] The reduction of benzoyl chloride was extremely rapid at room temperature and did not stop at the aldehyde state even at −78°C. [d] The reduction of ethyl laurate was followed for 96 h, at which time only 25% had been reduced.

nonpolar aprotic solvents such as benzene and hexane. In benzene, acid chlorides and aldehydes are reduced readily, "ketones only very slowly, even at elevated temperatures; and esters, not at all at room temperature and only slowly at higher temperatures".[2] Quaternary ammonium borohydrides have thus appeared to offer few advantages in organic synthesis; their utility has been restricted by the poor solubility of short-chain tetraalkylammonium derivatives in aprotic solvents and by the poor ability of the long-chain analogues to reduce ketones.

The ability to carry out borohydride reductions in nonhydroxylic solvents would nevertheless be quite useful. For instance, the reduction of aldehydes and ketones with sodium borohydride in the commonly employed aqueous or alcoholic solvents can be complicated by side reactions such as the formation of hydrates, acetals, ketals, or ethers.[3] In addition many organic compounds are not adequately soluble in those solvents. While borohydride reductions have been carried out in aprotic media, the available combinations of reagents and solvents have not been without disadvantages. For example, sodium borohydride shows very limited solubility[4] in ethereal solvents such as diethyl ether, tetrahydrofuran, and dimethoxyethane, and while it exhibits useful solubility[4] in diglyme and dimethylformamide, the water miscibility and high boiling points of the latter make work-up of reactions in these solvents quite inconvenient. Furthermore, Brown, Mead, and Subba Rao have shown[5a] that in diglyme sodium borohydride reduces ketones only very slowly, the reduction of acetone at 25°C being incomplete even after 96 h. Lithium borohydride is adequately soluble in many ethereal solvents, but its much greater reactivity decreases its synthetic utility; in contrast to sodium borohydride the lithium derivative readily reduces esters as well as aldehydes and ketones.[5]

Brändström, Junggren, and Lamm[6] recently prepared tetra-*n*-butylammonium borohydride and showed that it can be used to prepare solutions of diborane in dichloromethane by reaction with alkyl halides, but the reactions of tetrabutylammonium borohydride with carbonyl compounds were not reported. Our own use[7] of tetrabutylammonium borohydride as a mild and selective reagent for the reduction of oxonium ions indicated that this readily available[6] compound might be a versatile reagent for carrying out carbonyl reductions in aprotic solvents. Additional support for this idea was provided by the work of Hutchins, who found tetrabutylammonium cyanoborohydride to be an effective reducing agent in HMPA.[8]

We hoped that the high solubility of tetrabutylammonium borohydride in dichloromethane[6] would allow the use of that solvent for the reduction of aldehydes and ketones. Dichloromethane offers many advantages as a reaction medium: it is a powerful solvent for many organic compounds and (in contrast to many ethereal solvents) is relatively inexpensive; its low boiling point (41°C) and water immiscibility greatly facilitate the reaction work-up. We have therefore carried out an investigation of the reactions of a series of carbonyl compounds with tetrabutylammonium borohydride in dichloromethane.

Results and Discussion

Kinetic Studies. Our first goal was to determine the reactivity of dichloromethane solutions of tetra-*n*-butylammonium borohydride toward various types of carbonyl compounds, and this was done by monitoring the progress of the reactions by infrared spectroscopy. The changes in intensity in the carbonyl absorption of aliquots of reaction solutions permitted a quantitative measurement of the consumption of the substrate. The results are summarized in Table I and in Figures 1 and 2.

The data clearly demonstrate large differences in reactivity for the various classes of carbonyl derivatives as summarized by the following series (in order of decreasing reactivity): acid chlorides > aldehydes > ketones > esters. At one extreme, the reduction of benzoyl chloride (6) with tet-

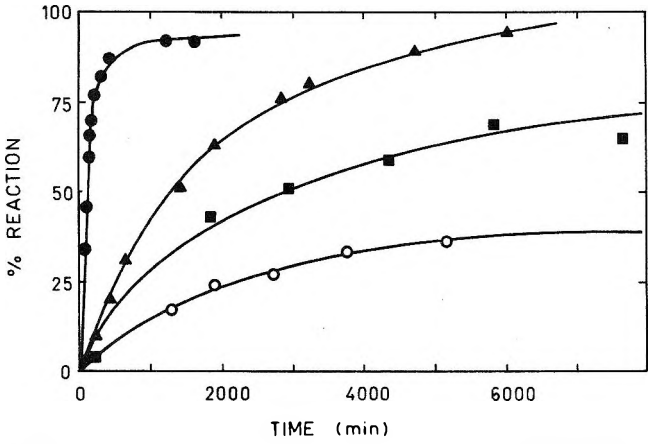


Figure 1. Rates of reduction of carbonyl compounds (●, benzaldehyde; ▲, acetophenone; ■, pivalaldehyde; ○, pinacolone) with tetrabutylammonium borohydride (1 equiv of reducing agent per mole of carbonyl compound) at 30°C in dichloromethane. The concentration of the carbonyl compound was 1 M in each case.

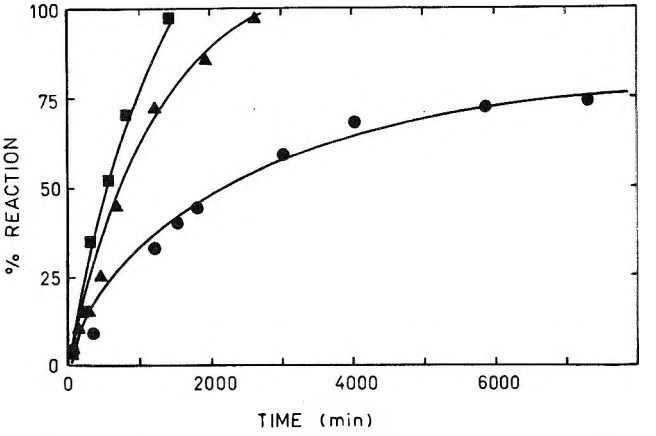


Figure 2. Rates of reduction of cyclohexanone (1 M) with tetrabutylammonium borohydride (■, 4 equiv; ▲, 2 equiv; ●, 1 equiv) at 30°C in dichloromethane.

rabutylammonium borohydride is essentially instantaneous; even at −78°C the reaction proceeds rapidly. The other extreme is represented by ethyl laurate (7): this ester is only 25% reduced after 4 days at 25°C. Both aldehydes and ketones undergo reduction at 25°C at rates which are useful for synthetic purposes.

Figure 1 shows that as expected the rate of reduction is highly dependent on the steric bulk of the substituents; thus replacement of a phenyl group by a *tert*-butyl group results in a substantial decrease in rate for both pinacolone (5) and pivalaldehyde (4) relative to acetophenone (2) and benzaldehyde (3), respectively. Similar effects have been found for other borohydride reductions.[9]

Figure 2 and Table I show the effects of variation of the concentration of borohydride relative to the concentration (1 M) of the carbonyl compound. As expected for a bimolecular process, the rate of reduction increases as the concentration of tetrabutylammonium borohydride is increased. Somewhat unexpected is the dependence of the total extent of reaction upon the concentration of borohydride relative to that of the carbonyl compound. Thus, while the reaction with aldehydes proceeds readily and nearly to completion with only 1 equiv of tetrabutylammonium borohydride, it is preferable to use 4 equiv of the reducing agent in the case of ketones; otherwise the reaction is inconveniently slow or does not proceed to completion.

Mechanistic Considerations. The reaction of borohydride ion with aldehydes and ketones in aqueous or alcoholic solutions is considered to proceed stepwise with successive replacement of each of the four hydrides with alkoxide groups generated by reduction of the carbonyl derivative (eq 1).[10] Under these conditions the reaction of bor-

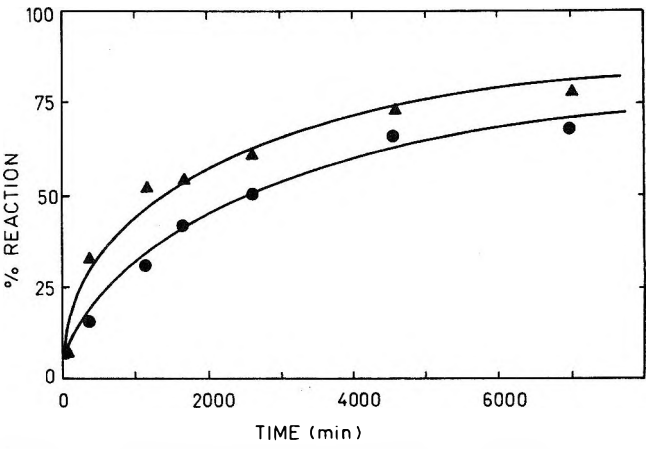


Figure 3. Rates of reduction of cyclohexanone (1 M) with tetrabutylammonium borohydride (1 M) (▲, in the presence of 1 molar equiv of ethanol; ●, in the absence of ethanol) at 30°C in dichloromethane.

$$BH_4^- \xrightarrow{R_2C=O} R_2CHOBH_2^- \xrightarrow{R_2C=O} (R_2CHO)_2BH_2^- \xrightarrow{R_2C=O}$$
$$(R_2CHO)_3BH^- \xrightarrow{R_2C=O} (R_2CHO)_4B^- \xrightarrow{\text{work-up}} R_2CHOH \quad (1)$$

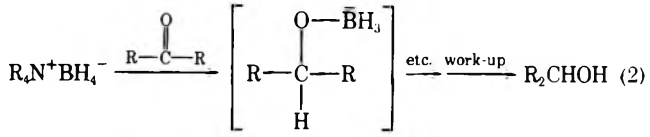
ohydride ion with aldehydes and ketones is rapid and exhibits clean second-order kinetics. This has been interpreted as evidence[10] that the first step of eq 1 is rate limiting; otherwise different kinetic behavior would be expected.

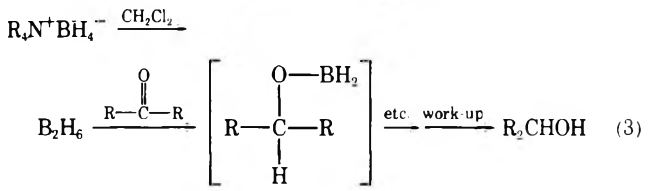
Studies of borohydride reductions in aprotic media have afforded additional mechanistic information. For example, the reactivities of borohydride salts in aprotic solvents are highly dependent on the nature of the cation. While lithium borohydride reduces ketones in anhydrous pyridine,[11] the sodium salt reduces them very slowly[12] or not at all.[11] This difference in reactivity could be a result of ion pairing effects as well as of electrophilic catalysis by lithium ions.[12,13] The importance of the former effect is suggested by the observation that lithium and sodium borohydride react with acetone at the same rate in aqueous solution[13] where the salts should be largely dissociated. In isopropyl alcohol (where more association of the ions would be expected) the lithium derivative reacts several times more rapidly.[13]

The importance of electrophilic catalysis is illustrated by the observation that the addition of lithium salts enhances the rate of reductions by sodium borohydride in nonaqueous solvents.[5,13] Similarly, the large rate difference in sodium borohydride reductions in aqueous or alcoholic solutions relative to reactions in aprotic media has been attributed to electrophilic catalysis by the hydroxylic solvent.[11,12] Our own work tends to support this interpretation. Thus, the overall rate of reaction of tetrabutylammonium borohydride with ketones and aldehydes in dichloromethane is much slower than comparable reductions with sodium borohydride in aqueous or alcoholic media. Figure 3 clearly shows that the addition of an equivalent amount of ethanol results in a substantial (ca. twofold) increase in the rate of reduction of cyclohexanone (1) by tetrabutylammonium borohydride in dichloromethane. Nevertheless, reduction does occur in the absence of ethanol, and one must conclude that electrophilic catalysis (by either protic solvent or metal ions) is not a prerequisite for reduction.

Earlier work has shown that sodium borohydride reduc-

tions of ketones in aprotic solvents are extremely slow. There was some initial confusion in the literature because rapid reduction can occur during aqueous work-up of aliquots of reaction mixtures.[11] Brown found essentially no reduction of acetone by sodium borohydride in diglyme, DMF, acetonitrile, or pyridine after 24 h at 0°C.[13] Similarly, Ritchie observed no reduction of cyclohexanone by sodium borohydride in pyridine after 72 h at room temperature. While the conditions used by those workers were not the same as those utilized by us, the earlier results concerning the reduction of ketones appear to be in sharp contrast with those summarized in Table I. The facile reduction of primary alkyl halides by tetrabutylammonium borohydride in dichloromethane[6] to liberate diborane suggested the possibility of a similar reaction between tetrabutylammonium borohydride and the solvent (dichloromethane).[14] The actual reducing agent in the ketone reductions of Table I might therefore be diborane (eq 3) rather than borohydride ion (eq 2). That diborane is indeed produced





by such a reaction was shown by the isolation of a moderate yield (50%) of cyclohexanol following oxidative work-up of a solution of cyclohexene and tetrabutylammonium borohydride in dichloromethane which had been maintained at room temperature for 40 h.

In order to ascertain whether or not the rate of production of diborane is sufficiently rapid to account for the reduction of ketones, several additional experiments were carried out. The rate of decomposition of tetrabutylammonium borohydride in dichloromethane at 30°C was determined by monitoring the 2240-cm^{-1} band[11] of aliquots of the solution; the decomposition followed first-order kinetics and exhibited a half-life of approximately 2300 min. We also found that the reduction of cyclohexanone (1) by diborane is quite rapid: the reaction of a dichloromethane solution of cyclohexanone (1 M) and diborane (0.5 M) is complete within 15 min at room temperature. On the other hand, only two of the three hydrides per boron exhibit this high reactivity. Thus when only an equivalent amount of diborane was employed (1 M cyclohexanone, 0.17 M B_2H_6) the reduction proceeded rapidly to ca. 67% completion; further reduction was extremely slow. Similar behavior was observed by Brown and Korytnyk for the reduction of cyclohexanone by borane in tetrahydrofuran.[15]

Comparison of the results of the borane reductions with the data in Figure 2 lead to the conclusion that diborane alone cannot be responsible for the reduction of cyclohexanone. Thus in 2300 min one-half of the original borohydride ion has been converted to diborane. In the case where 1 equiv (0.25 mol) of borohydride was employed this would correspond to the formation of 0.06 mol of diborane, which would account for only 37% reduction of cyclohexanone even if all three hydrides per boron were utilized. Since transfer of the third hydrogen is slow, 37% represents an upper limit. If transfer of that hydrogen were considered negligible, only 25% reduction would be expected. However, the actual reduction of cyclohexanone proceeded to greater

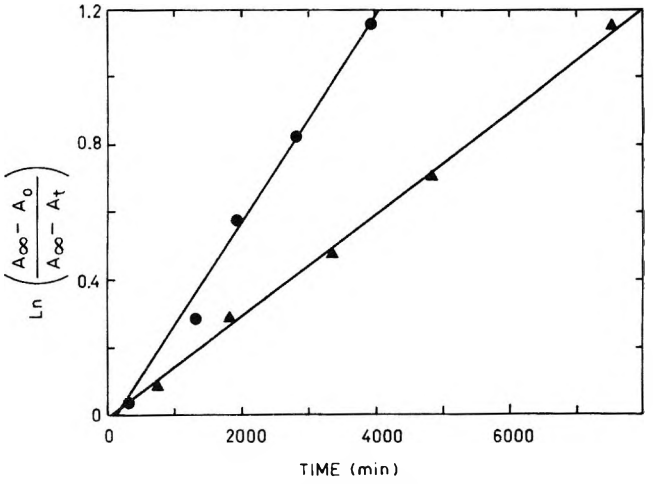


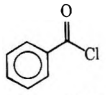
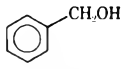
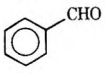
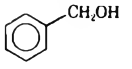
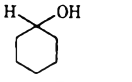
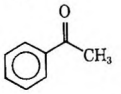
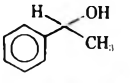
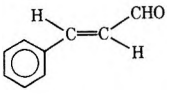
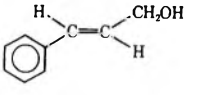
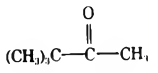
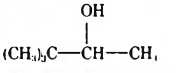
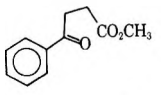
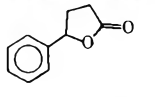
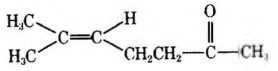
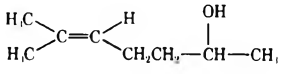
Figure 4. First-order decomposition of tetrabutylammonium borohydride at 30°C in dichloromethane [●, in the absence of ethanol, $k = (3.0 \pm 0.1) \times 10^{-4}$ s^{-1}; ▲, in the presence of 1 molar equiv of ethanol, $k = (1.52 \pm 0.03) \times 10^{-4}$ sec^{-1}]. The lines are least-squares fits of the experimental points.

than 50% within this time period, indicating that at least a substantial proportion of the reduction of cyclohexanone proceeds via direct reaction with borohydride ion (eq 2).

Thus, one must consider two alternative pathways for the initial reaction of the borohydride ion: direct hydride reduction of the carbonyl compound (eq 2) and initial reaction of the borohydride ion with solvent to give diborane as the reducing agent (eq 3).[16] Table I clearly shows that the reduction of aldehydes proceeds via eq 2 as the major pathway; these reactions are too fast to be reconciled with prior decomposition of tetrabutylammonium borohydride. On the other hand, the rates of ketone reductions are comparable to the rate of diborane production and eq 3 may represent a significant pathway in these cases. However, the addition of an equivalent amount of ethanol causes a substantial change in the reaction. Thus, while ethanol enhances the rate of cyclohexanone reduction (Figure 3), it actually decreases the rate of borohydride decomposition (Figure 4). Under these conditions the rate of borane production is much too slow to account for the reduction of cyclohexanone by the pathway of eq 3. Thus, the addition of protic solvent must result in electrophilic catalysis of the direct reduction of ketone by borohydride ion, and the pathway represented by eq 2 becomes increasingly important.

Synthetic Applications. The data in Table I suggested the general procedures to be followed for preparative reductions: Aldehydes (1 M) are reduced at a convenient rate with a single equivalent of borohydride; for preparative work we have used a 50% excess (1.5 equiv). Ketones (1 M) are reduced at a convenient rate only when a substantial excess of reducing agent is employed; for preparative reactions we have utilized 4 equiv of tetrabutylammonium borohydride. The results of a series of reductions are presented in Table II. Isolated yields and purities are consistently high, and the experimental procedure is straightforward. A typical reduction was accomplished by allowing a dichloromethane solution of the carbonyl derivative (1 M) and tetrabutylammonium borohydride to stand at room temperature for 0.25–48 h. The reaction mixture was then quenched by stirring with dilute alkaline hydrogen peroxide. The aqueous phase was extracted with dichloromethane, and the combined organic solutions were washed with saturated aqueous sodium sulfite, dried over sodium sulfate, and evaporated at reduced pressure. The crude product was taken up in diethyl ether and the insoluble ammonium salts were removed by filtration through a short col-

Table II
Reduction of Representative Carbonyl Compounds[a] with Tetrabutylammonium Borohydride

No.	Compd	Equiv[b]	Time, h	Product	% yield[c]	Purity,[d] %
6		4	0.25		98	99
3		1.5	24		91	99
1		4	24		86	99
2		4 4	45 2[e]		93 90	98 98
8		1.5	17		73	90
5		4 4	48 5.5[e]		82[d,f] 97	94
7	$CH_3(CH_2)_{10}CO_2Et$	4	96	$CH_3(CH_2)_{10}CH_2OH$	25[d,f]	
9		4	40		98	90
10		4	24		87	98

[a] The solutions were approximately 1 M in the carbonyl compound; reductions were carried out at room temperature. [b] This refers to the number of equivalents of reducing agent per mole of substrate. [c] Isolated yield after Kugelrohr distillation. [d] Estimated by GLC. [e] The reduction was performed in refluxing chloroform. [f] The major impurity was unreacted starting material.

umn of alumina. Kugelrohr distillation then afforded the final product.

The use of aqueous hydrogen peroxide in the work-up not only serves to destroy any unreacted hydride, but also facilitates the hydrolysis of the borate esters formed in the reduction.[17] If this step is omitted, much lower yields result. The dichloromethane solution was washed with aqueous sodium sulfite in order to destroy any peroxides in the organic phase prior to distillation.

Several entries in Table II require comment. As expected (Table I) only the keto group of methyl 3-benzoylpropionate (**9**) was reduced, and the lactone (which is formed spontaneously upon distillation) was obtained in excellent yield. The reduction of pinacolone (**5**) is extremely slow (Figure 1), and even after 48 h substantial amounts of unreduced ketone remained. However, when the reduction was conducted at higher temperatures (refluxing chloroform), a reaction time of 5.5 h provided pinacolyl alcohol in excellent yield. Reaction times necessary for reduction of other ketones can also be decreased by this procedure. For example, the reduction of acetophenone (**2**) in refluxing chloroform requires only 2 h for complete reaction. Although diborane is probably formed during the reduction of ketones, hydroboration of the carbon–carbon double bond in 6-methyl-5-hepten-2-one (**10**) did not compete with reduction of the keto group; the unsaturated alcohol was isolated in good yield. Although this may appear to contradict the relative reactivities of functional groups toward diborane reported by Brown,[15] hydroboration of olefins is known to take place very slowly in the absence of ethers.[18]

In conclusion, tetrabutylammonium borohydride is a mild and selective reagent for the reduction of organic compounds. It provides a useful complement to the variety of reducing agents which are already available: borohydride reductions can now be conveniently performed in dichloromethane thus avoiding difficulties which sometimes arise with aqueous or alcoholic media.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer; NMR spectra were recorded on a Varian A-60 spectrometer, and chemical shifts are reported in parts per million downfield from Me_4Si. Gas chromatographic analyses were performed on a Varian Model 2400 gas chromatograph equipped with flame ionization detectors and 5 ft × 0.125 in. (o.d.) columns packed with 10% Carbowax 20M on Chromosorb W.

Cyclohexanone, acetophenone, and 6-methyl-5-hepten-2-one were obtained from Aldrich Chemical Co. and were used without purification. Benzoyl chloride and ethyl laurate were obtained from Eastman Organic Chemicals and were used without purification. Pinacolone and cinnamaldehyde (Eastman Organic Chemicals) were distilled prior to use; benzaldehyde (Aldrich Chemical Co.) was washed with 1 M aqueous $KHCO_3$ and distilled prior to use. Pivalaldehyde was prepared via the reaction of *tert*-butylmagnesium chloride with ethyl formate.[19] Methyl 3-benzoylpropionate was prepared via esterification[20] of 3-benzoylpropionic acid.[21] Reagent grade dichloromethane was stored over Linde 4A molecular sieves and used without subsequent purification.

Tetrabutylammonium borohydride was prepared by the reaction between sodium borohydride and tetrabutylammonium chloride[6,22] and was purified by recrystallization from ethyl acetate followed by careful drying under vacuum at 50–60°C. Samples of tetrabutylammonium borohydride purified in this manner showed no loss of active hydrogen after storage at room temperature for more than 1 year. Nevertheless, we stored tetrabutylammonium borohydride at 6°C in a tightly stoppered bottle.

Kinetic Studies. Reductions with Tetrabutylammonium Borohydride. The following general procedure was employed for the reduction of cyclohexanone, acetophenone, pinacolone, benzoyl chloride, pivalaldehyde, and benzaldehyde.

In a 5-ml volumetric flask was placed either 5, 2.5, or 1.25 mmol

of tetrabutylammonium borohydride and approximately 3 ml of dichloromethane. To the resulting solution was added 5 mmol of the appropriate carbonyl compound followed by sufficient dichloromethane to bring the volume to 5 ml. The solution was then placed in a constant-temperature bath at 30.0°C. Aliquots (50 μl) were withdrawn periodically, diluted to 2 ml with dichloromethane, and analyzed by infrared spectroscopy. Matched sodium chloride cells (1 mm path length; the reference cell contained dichloromethane) were used to measure the intensity of the carbonyl absorption.

Beer's law plots of the carbonyl absorbance were found to be linear in the concentration range employed for all compounds except benzaldehyde. The concentrations of the benzaldehyde solutions were determined from a calibration curve.

Reduction of Cyclohexanone (1) with Diborane. A. Using 3 Equiv of Diborane. To a solution of 1.21 g (4.7 mmol) of tetrabutylammonium borohydride in 3 ml of dichloromethane was added dropwise with stirring 0.67 g (4.7 mmol) of methyl iodide. The resulting solution was allowed to stand at room temperature for 15 min and was then cooled in an ice bath while 0.46 g (4.7 mmol) of cyclohexanone was added dropwise. When the addition was complete, the solution was allowed to warm to room temperature and the volume was brought up to 5 ml with dichloromethane. The ir spectrum of an aliquot removed after a reaction time of 15 min showed no carbonyl absorbtion.

B. Using 1 Equiv of Diborane. To a solution of 0.46 g (4.7 mmol) of cyclohexanone in 3 ml of dichloromethane was added 0.40 g (1.6 mmol) of tetrabutylammonium borohydride. Sufficient dichloromethane was added to bring the total volume to 5 ml, and an aliquot of the resulting solution was removed for ir analysis. The reaction solution was cooled in an ice bath and 0.23 g (1.6 mmol) of methyl iodide was added. The reaction mixture was removed from the ice bath and aliquots were periodically removed for infrared analysis. The reaction had proceeded to the extent of ca. 66% after 15 min, and no further decrease of the carbonyl absorption was observed over a period of 24 h at room temperature.

Reduction of Ethyl Laurate (7) with Tetrabutylammonium Borohydride. To a solution of 1.15 g (5 mmol) of ethyl laurate in 5 ml of dichloromethane was added 1.3 g (5.1 mmol) of tetrabutylammonium borohydride. The solution was allowed to stand at room temperature for 96 h and was then quenched by the addition of 10 ml of 3% aqueous hydrogen peroxide and 5 ml of 10% aqueous sodium hydroxide. The mixture was stirred for 2 h, the layers were separated, and the aqueous phase was extracted with two 15-ml portions of dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated at reduced pressure. GLC analysis of the residue showed the presence of 25% lauryl alcohol and 75% unreacted ester.

Reduction of Cyclohexanone (1) with Tetrabutylammonium Borohydride in the Presence of Ethanol. To a solution of 0.92 g (9.4 mmol) of cyclohexanone in 8 ml of dichloromethane was added 0.44 g (9.6 mmol) of ethanol and 0.60 g (2.3 mmol) of tetrabutylammonium borohydride. Sufficient dichloromethane was added to bring the volume to 10 ml, and the general procedure was followed.

Decomposition of Tetrabutylammonium Borohydride. A solution of 0.64 g (10 mequiv) of tetrabutylammonium borohydride in 5 ml of dichloromethane was placed in a constant-temperature bath at 30.0°C. Aliquots (50 μl) were withdrawn periodically, diluted to 2 ml with dichloromethane, and analyzed by ir spectroscopy. The same procedure was followed for the decomposition of tetrabutylammonium borohydride in the presence of ethanol: 0.45 g (9.8 mequiv) or 0.23 g (5 mequiv) of ethanol was added to the reaction solutions immediately prior to placing it in the constant-temperature bath. The reaction with the lower concentration of ethanol exhibited behavior intermediate between that of the two cases illustrated in Figure 3.

Synthetic Studies. General Procedure. To a solution of tetrabutylammonium borohydride (15 mequiv for aldehydes, 40 mequiv for ketones) in 10 ml of dichloromethane was added in a single portion 10 mmol of the carbonyl compound. The reaction vessel was stoppered and the solution was allowed to stand for 0.25–48 h (Table II). The reaction was quenched by the addition of 20 ml of 3% hydrogen peroxide followed by 10 ml of 10% sodium hydroxide and the mixture was stirred for ca. 2 h. The layers were separated and the aqueous phase was extracted with three 30-ml portions of dichloromethane. The combined organic solutions were extracted with 20 ml of saturated sodium sulfite, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was taken up in anhydrous diethyl ether, the insoluble tetrabutylammonium salts were removed by filtration, and the ether solution was percolated through a short (ca. 3 cm) column of alumina. The solvent was evaporated under reduced pressure and the crude product was distilled (Kugelrohr).

Reduction of benzoyl chloride (6), benzaldehyde (3), cyclohexanone (1), acetophenone (2), and pinacolone (5) by this procedure afforded products in the yields and purities listed in Table II. The ir and NMR spectra of the products were in agreement with previously published spectra.[23]

Reduction of Benzoyl Chloride (6) at −78°. A solution of 1.0 g (7 mmol) of benzoyl chloride in 20 ml of dichloromethane was cooled to −78°C, and 1.8 g (7.0 mmol) of tetrabutylammonium borohydride in 10 ml of dichloromethane was added dropwise. The resulting solution was poured into ~50 ml of 1 N NaOH, and the layers were separated. The organic layer was washed with two 30-ml portions of 1 N NaOH and was dried over sodium sulfate. GLC analysis indicated a mixture of benzaldehyde and benzyl alcohol in a ratio of 1:15.

Reduction of Acetophenone (2) in Refluxing Chloroform. A solution of 1.1 g (4.3 mmol) of tetrabutylammonium borohydride and 0.50 g (4.2 mmol) of acetophenone in 5 ml of chloroform was heated at reflux for 2 h. Work-up according to the general procedure afforded 0.46 (90%) of 1-phenylethanol (98% pure by GLC).

Reduction of Cinnamaldehyde (8). To a solution of 1.0 g (15.6 mequiv) of tetrabutylammonium borohydride in 3 ml of dichloromethane cooled to 0°C was added slowly 1.32 g (10.0 mmol) of cinnamaldehyde in 10 ml of dichloromethane. The solution was allowed to warm slowly to room temperature (at which point the solution became red) and remain at room temperature for 17 h. Work-up as described in the general procedure (percolation through alumina was omitted) afforded 0.98 g (73%) of cinnamyl alcohol after Kugelrohr distillation (130–160°C, ~1 mm). The distilled product was 90% pure by GLC and exhibited ir and NMR spectra in agreement with those previously reported.[23]

Reduction of Methyl 3-Benzoylpropionate (9). To a solution of 1.4 g (5.4 mmol) of tetrabutylammonium borohydride in 5 ml of dichloromethane was added 1.0 g (5.2 mmol) of methyl 3-benzoylpropionate. The solution was allowed to stand at room temperature for 40 h and was then quenched by the addition of 10 ml of 3% hydrogen peroxide followed by 5 ml of 10% sodium hydroxide. The resulting mixture was stirred for 2 h and was then acidified with 3 M sulfuric acid. The layers were separated, and the aqueous phase was extracted with three 20-ml portions of diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate, and the solvent was evaporated at reduced pressure. Ammonium salts were removed by partitioning the crude product between diethyl ether (100 ml) and water (50 ml). The layers were separated and the aqueous phase was extracted with three 50-ml portions of diethyl ether. The combined ether extracts were dried over sodium sulfate and the solvent was evaporated at reduced pressure. The residue was distilled (Kugelrohr, 150–180°C, ~1 mm) to give 0.82 g (98%) of 4-phenylbutyrolactone. The lactone was 90% pure by GLC and exhibited ir and NMR spectra corresponding to those previously reported.[24] The major by-product was the uncyclized derivative, methyl 4-hydroxy-4-phenylbutyrate.

Reduction of Pinacolone (5) in Refluxing Chloroform. A solution of 2.6 g (10 mmol) of tetrabutylammonium borohydride and 1.0 g (10 mmol) of pinacolone in 10 ml of chloroform was heated at reflux for 5.5 h. The solution was allowed to cool to room temperature and was quenched by the addition of 20 ml of 3% hydrogen peroxide and 10 ml of 10% sodium hydroxide. The mixture was stirred at room temperature for 2.5 h. The layers were then separated, and the aqueous phase was extracted with three 30-ml portions of dichloromethane. The combined organic solutions were extracted with 10 ml of saturated sodium sulfite and dried over sodium sulfate. The solvent was distilled from the crude product through a 6-in. column packed with glass helices, and the residue was taken up in anhydrous diethyl ether. The resulting mixture was percolated through a 3-cm column of alumina and the solvent was distilled as above. The crude product was subjected to Kugelrohr distillation (170–180°C, 1 atm) to give 0.99 g (97%) of pinacolyl alcohol with a purity of 94% by GLC.

Reduction of 6-Methyl-5-hepten-2-one (11). The general procedure provided an 87% yield of 6-methyl-5-hepten-2-ol[25] with a purity of 98% by GLC after Kugelrohr distillation (100–105°C, ~8 mm): NMR ($CDCl_3$) δ 1.1 (d, J = 6 Hz, 3 H), 1.5 (s, 3 H), 1.6 (s, 3 H), 1.8–2.2 (m, 4 H), 3.2 (s, 1 H), 3.7 (m, 1 H), 5.0 (m, 1 H); ir (thin film) 3390, 1670 cm^{-1} (weak).

Hydroboration–Oxidation of Cyclohexene. To a solution of 1.0 g (12 mmol) of freshly distilled cyclohexene in 10 ml of dichlo-

romethane was added 3.2 g (12 mmol) of tetrabutylammonium borohydride. The solution was allowed to stand for 40 h and was then quenched by the addition of 3 ml of water and 3 ml of 3% hydrogen peroxide. Oxidation was effected by dropwise addition of 2 ml of 3 N sodium hydroxide and 3 ml of 30% hydrogen peroxide. The mixture was warmed to 40° for 30 min; it was then allowed to cool to room temperature and was stirred for an additional 1 h. Diethyl ether (100 ml) was added, and the layers were separated. The organic phase was extracted with three 50-ml portions of water, with 10 ml of saturated sodium sulfite, and with 50 ml of saturated sodium chloride. The organic solution was dried over sodium sulfate, percolated through a short column (~3 cm) of alumina, and concentrated at reduced pressure to afford 0.60 g (50%) of cyclohexanol (97% pure by GLC). The product was identical with an authentic sample of cyclohexanol by GLC and ir.

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Registry No.—**1**, 108-94-1; **2**, 98-86-2; **3**, 100-52-7; **4**, 630-19-3; **5**, 75-97-8; **6**, 98-88-4; **7**, 106-33-2; **8**, 104-55-2; **9**, 25333-24-8; **10**, 110-93-0; tetrabutylammonium borohydride, 33725-74-5; dichloromethane, 75-09-2.

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(14) Other mechanisms for the decomposition of tetrabutylammonium borohydride are possible, e.g., decomposition of a tetrabutylammonium borohydride ion pair to give tributylamine, butane, and borane:

$$(Bu)_4N^+BH_4^- \rightarrow (Bu)_3N + BuH + BH_3$$

However, we have not been able to isolate tributylamine from decomposing solutions of tetrabutylammonium borohydride in dichloromethane. Alternatively a radical process might be involved; cf. J. T. Groves and K. W. Ma, *J. Am. Chem. Soc.*, **96**, 6527 (1974).
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The Geometrical Isomers of γ-Bisabolene

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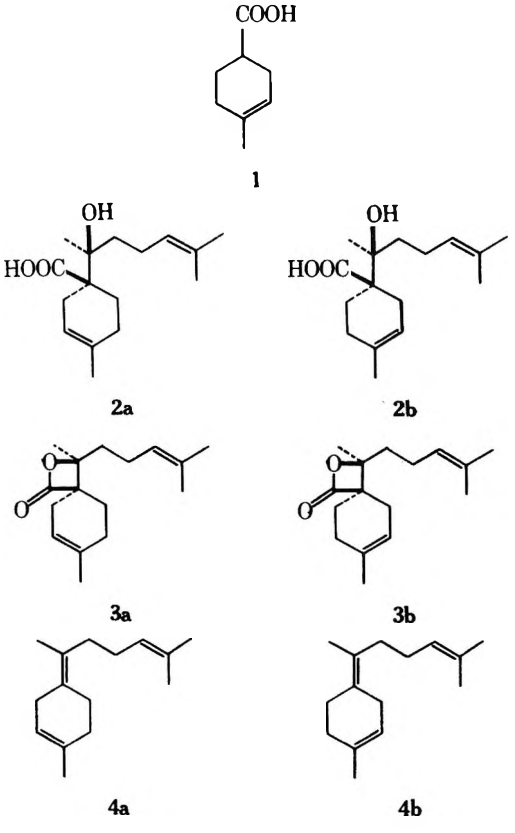
We have previously reported[2] a synthesis of γ-bisabolene which resulted in a mixture of two geometrical isomers about the tetrasubstituted olefinic bond. Although the isomers could be separated by GLC, we could find no way of determining the stereochemistry of the pure isomers from spectral data. We had determined that a red alga of the genus *Laurencia* contained only one isomer of γ-bisabolene, which must be identified before biosynthetic experiments can proceed. We wish to report a synthesis of γ-bisabolene which has allowed the separation and identification of the geometrical isomers.

There are relatively few methods available for the synthesis of tetrasubstituted olefinic bonds, and none of these could be used for a stereospecific synthesis of one isomer of γ-bisabolene. We chose to use the method of Krapcho and Jahngen,[3] since it offered the best opportunity for separating the two isomers at an intermediate stage.

The dilithium salt of 4-methyl-3-cyclohexenecarboxylic acid (1), which was obtained in 95% yield from the Diels–Alder reaction of isoprene with acrylic acid, was condensed with 6-methyl-5-hepten-2-one to prepare the diastereoisomeric β-hydroxy acids **2a,b**. The crude β-hydroxy acid mixture was obtained as a semisolid mass from which one diastereoisomer **2a** crystallized preferentially. Treatment of the crude β-hydroxy acids **2a,b** with *p*-toluenesulfonyl chloride in pyridine gave a mixture of two isomeric β-lactones **3a,b** (ir 1810 cm^{-1}), which was converted into a mixture of two isomeric γ-bisabolenes **4a,b** by decarboxylation at 140°C. The overall yield was 37% from the acid 1.



1 **2a** **2b** **3a** **3b** **4a** **4b**

During this reaction sequence on the mixture of diastereoisomers, we noticed only one differentiating spectral feature. The NMR spectrum of the mixture of β-lactones **3a,b** contained two methyl signals at δ 1.43 and 1.47 ppm for the methyl groups on the β-lactone rings. We assumed that the methyl group in the *E* isomer **3a** was situated in the shielding cone of the olefinic bond[4] in the cyclohexene ring. The β-lactone, prepared from the crystalline β-hydroxy acid **2a**, has the methyl signal at 1.43 ppm and was therefore the precursor of isomerically pure (*E*)γ-bisabolene.

The rather insecure assignment of stereochemistry was confirmed by a single-crystal x-ray diffraction analysis of the *p*-bromophenacyl ester of the β-hydroxy acid **2a**.

Crystals of the *p*-bromophenacyl derivative of hydroxy acid **2a** are orthorhombic and centrosymmetric. Systematic extinctions uniquely identify the space group as *Pccn*. The unit cell dimensions are $a = 24.929$ (2), $b = 16.615$ (1), and $c = 11.148$ (1) Å. A calculated density of 1.33 g/cm^3 indicated one molecule of composition $C_{24}H_{31}BrO_4$ per asymmetric unit. A total of 3504 reflections were measured on a Syntex P_{2_1} four-circle automated diffractometer using Cu Kα (λ 1.5418 Å) radiation and an ω-scan technique, with a minimum scan speed of 2°/min. Of these, 1953 reflections were judged observed ($F_o \geq 3\sigma(F_o)$).

A Patterson synthesis[5] was used to determine the bromine position and all other nonhydrogen atoms were located in the subsequent bromine-phased electron density synthesis and refined anisotropically until convergence was reached. The final residual index was 0.087 for the observed reflections. No hydrogens have been included in the current model. Bond distances and angles agree well with generally accepted values.[6] Figure 1 is a computer-generated drawing of the final x-ray model.

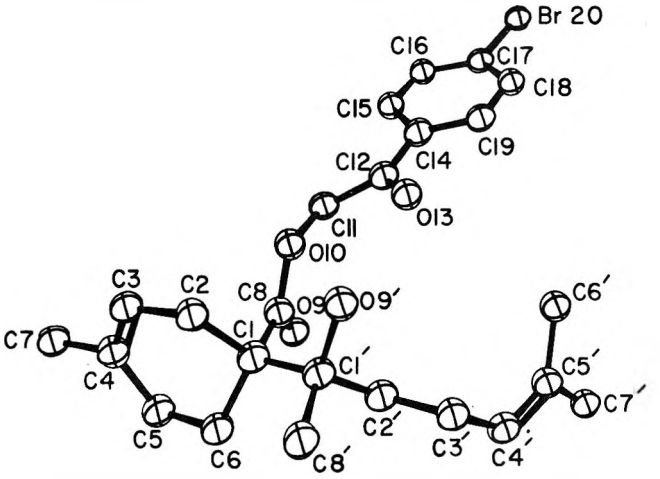


Figure 1. A computer-generated perspective drawing of the *p*-bromophenacyl derivative of hydroxy acid **2a**.

The GLC trace of a mixture of γ-bisabolene isomers

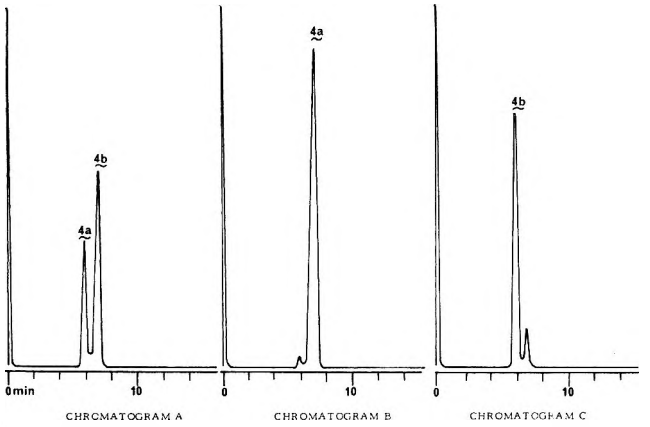


Figure 2. GLC traces of (a) a mixture of (*E*)- and (*Z*)-γ-bisabolene; (b) (*E*)-γ-bisabolene; (c) the purest sample of (*Z*)-γ-bisabolene obtained [2% Carbowax 20M on Chromosorb W (6 ft × 2 mm) at 100°C]. Retention time in minutes.

(Figure 2) contained two peaks at retention times of 5.8 and 6.5 min [2% Carbowax 20M on Chromosorb W (6 ft × 2 mm), 100°C]. On this and several other GLC systems,[7] the *Z* isomer always has the lower retention time. Thus we were able to determine that our previous synthetic route employing the Claisen rearrangement[2] gave a 60:40 ratio of (*E*)- and (Z)-γ-bisabolenes. We were able to determine that a species of *Laurencia* contained only the *E* isomer of γ-bisabolene and that a commercial sample of bisabolene[8] contained (*Z*)-γ-bisabolene as the major component. Commercial samples of Oil of Myrrh[8] and Oil of Lime[9] also contained only (*Z*)-γ-bisabolene.

Experimental Section

Commercially available chemicals were used without further purification unless otherwise stated. All solvents were either analar grade or redistilled prior to use. Melting points were measured on a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on Varian HR-220 or EM-360 spectrometers; chemical shifts are expressed as values in parts per million relative to tetramethylsilane (0). Infrared spectra were recorded on a Perkin-Elmer 700 spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard 402 instrument. Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass spectra were measured by Beth Irwin, Department of Chemistry, UCLA.

4-Methyl-3-cyclohexenecarboxylic Acid (1). Isoprene (27 g, 0.4 mol) and acrylic acid (28 g, 0.4 mol) were heated in a steel bomb at 100–110° for 24 h. After cooling, the 4-methyl-3-cyclohexenecarboxylic acid was obtained as a white solid: mp 94–96° (lit.[3] mp 99°); yield 54.0 g (96%); ir ($CHCl_3$) 3500–2900 (broad), 1700 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.68 (s, 3 H), 5.40 (broad, 1 H), 11.9 (s, 1 H).

1-(1′,5′-Dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic Acid (2a,b). A solution of lithium diisopropylamide was prepared by dissolving diisopropylamine (2.02 g, 20 mmol) in anhydrous tetrahydrofuran (50 ml) under an atmosphere of argon and adding *n*-butyllithium in hexane (Alpha) (10.9 ml, 20 mmol, 1.83 M) at −40°. The resulting solution was stirred for 20 min below 0° and then recooled to −40°. A solution of 4-methyl-3-cyclohexenecarboxylic acid (1.42 g, 10 mmol) in tetrahydrofuran (10 ml) was added dropwise with stirring. The temperature of reaction was maintained below −20° during the addition. The reaction mixture was heated to 50° for an additional 2 h. The resulting bright yellow solution was again cooled to −40°. 6-Methyl-5-hepten-2-one (1.26 g, 10 mmol) was added dropwise. The reaction mixture was stirred for 2 h at −40°, then poured over ice (100 g) and extracted with ethyl ether (4 × 50 ml). The aqueous phase was separated and acidified with 3 N hydrochloric acid (pH ≃ 3). The solution was again extracted with ethyl ether (4 × 50 ml). The organic layer was dried over anhydrous magnesium sulfate and solvent removed, to obtain (1-(1′,5′-dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic acid, a white solid, mp 129–133°, yield 2.10 g (80%). This solid was found to be a mixture of diastereoisomers. The mixture was separated by repeated fractional recrystallizations from chloroform. After four recrystallizations, white needles of one isomer were obtained, mp 149–150°. Data given were obtained for the pure isomer: ir ($CHCl_3$) 3500, 2950 (broad), 1240, 1690 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.23 (s, 3 H), 1.68 (s, 9 H), 5.18 (t, 1 H), 5.40 (broad, 2 H). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.18; H, 9.59.

1-(1′,5′-Dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic Acid β-Lactone (3a). 1-(1′,5′-Dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic acid (0.534 g, 2 mmol) was dissolved in anhydrous pyridine (20 ml). The resulting solution was cooled to −5° using an ice–methanol bath, after which *p*-toluenesulfonyl chloride (1.07 g, 6 mmol) was added with stirring. The mixture was stirred at 0° for 18 h. The red solution was then poured over ice (100 g) and extracted with ethyl ether (4 × 50 ml). The organic extract was washed repeatedly with saturated copper sulfate solution (3 × 50 ml) to remove the pyridine. This was followed by several washes with sodium bicarbonate (4 × 50 ml). The ether extract was dried over anhydrous magnesium sulfate. Removal of solvent gave 1-(1′,5′-dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic acid β-lactone: yield 0.429 g (84%) of a clear oil; ir (film) 1810 cm^{-1}; NMR (220 MHz, CCl_4) δ 1.43 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 6 H), 5.15 (t, 1 H), 5.39 (broad, 1 H); high-resolution mass spectrum M^+ 248.1777 ($C_{16}H_{24}O_2$ requires 248.1776). No attempt was made to purify this material.

(*E*)-γ-Bisabolene (4a). 1-(1′,5′-Dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic acid β-lactone (537 mg, 2.6 mmol) was heated to 140° under argon for 2 h (evolution of CO_2 was observed), then cooled. The brown oil obtained was vacuum distilled using a Kugelrohr oven to yield pure (*E*)-γ-bisabolene, bp 90–110° (0.75 mm), yield 468 mg (94%). This material had properties identical with those of another sample of γ-bisabolene prepared by an alternate synthesis involving the Claisen rearrangement[2] as shown by NMR, mass spectrum, and GLC: NMR (220 MHz, CCl_4) δ 1.54 (s, 3 H), 1.63 (s, 9 H), 2.70 (s, 2 H), 5.12 (t, broad, 1 H), 5.38 (broad, 1 H); mass spectrum *m/e* (rel intensity) 204 (23), 107 (100), 193 (34), 135 (52). The GLC (2% Carbowax 20M on Chromosorb W, 6 ft × 2 mm, at 100°) showed a single component. Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.09; H, 11.78.

(*Z*)-γ-Bisabolene (4b). The residue (11.5 g, 0.04 mol) from the first recrystallization of the β-hydroxy acid **2a** was converted to the corresponding β-lactone **3b** with *p*-toluenesulfonyl chloride (24.7 g, 0.13 mol) in anhydrous pyridine (150 ml) at 0° for 18 h. This gave, after work-up, a light brown oil (4.9 g). The NMR (220 MHz, CCl_4), δ 1.47 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 6 H), 5.15 (5, 1 H), 5.39 (broad, 1 H), confirmed the structure of the β-lactone **3b**. Thermolysis at 150°, under argon, yielded the (*Z*)-γ-bisabolene. GLC analysis on 2% Carbowax 20M showed this material to be 90% of the desired *Z* isomer and 10% of the *E* isomer.

***p*-Bromophenacyl Derivative for X-Ray Analysis (5).** Purified β-hydroxy acid **2a** (266 mg, 1 mmol) was suspended in approximately 1–2 ml of distilled water containing a small amount of phenolphthalein indicator. A 10% sodium hydroxide solution was added dropwise until all the acid was dissolved and the solution was very slightly pink. Sufficient 5% hydrochloric acid was added to discharge the pink color. *p*-Bromophenacyl bromide (249 mg, 0.9 mmol) was dissolved in 100% ethanol (5 ml) and added to the acid mixture. A fluffy white precipitate began to form immediately. The mixture was refluxed for 2 hr, then cooled. The precipitate was filtered and suspended in 5% aqueous sodium carbonate solution and filtered again. This was followed by several cold water washes. The white precipitate was dissolved in hot ethanol and filtered. Hot distilled water was then added until crystallization began. Upon cooling, white crystals of **5** were obtained: mp 120–121° (recrystallized from chloroform); yield 400 mg (86%); ir ($CHCl_3$) 3550, 2950, 1738, 1705, 1595 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.23 (s, 3 H), 1.68 (s, 9 H), 3.45 (s, broad, 1 H), 5.20 (broad, 1 H), 5.40 (s, 1 H), 7.67 (s, 2 H), 7.72 (s, 2 H); mass spectrum *m/e* 444, 446 (1:1) (M − 18).

Acknowledgments. This research was supported by a training grant (GM-01045-11) from the National Institutes of Health and by unrestricted grants from Abbott Laboratories and Hoffmann-La Roche.

Registry No.—**1**, 4342-60-3; **2a**, 57474-10-9; **2b**, 57474-11-0; **3a**, 57474-12-1; **4a**, 53585-13-0; **4b**, 13062-00-5; **5**, 57474-13-2; isoprene, 78-79-5; acrylic acid, 79-10-7; 6-methyl-5-hepten-2-one, 110-93-0.

Supplementary Material Available. A listing of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Camille and Henry Dreyfus Teacher–Scholar Grant Awardee, 1972–1977, and Fellow of the Alfred P. Sloan Foundation, 1973–1975.
(2) D. J. Faulkner and L. E. Wolinsky, *J. Org. Chem.*, **40**, 389 (1975).
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(5) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT, and FRIEDEL", USAEC Report IS-2625, Iowa State University, Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(6) See paragraph at end of paper regarding supplementary material.
(7) Two other GLC columns successfully used were 1% OV210 on Chromosorb G (6 ft × 2 mm), 100°C, and 2% SP2100 on Chromosorb W (6 ft × 2 mm), 150°C.

(8) We wish to thank Givaudan Corporation for generous gifts of bisabolene and Oil of Myrrh.
(9) We wish to thank Firtzsche, Dodge and Olcott for a generous gift of Oil of Lime.

A Short Synthesis of Camptothecin

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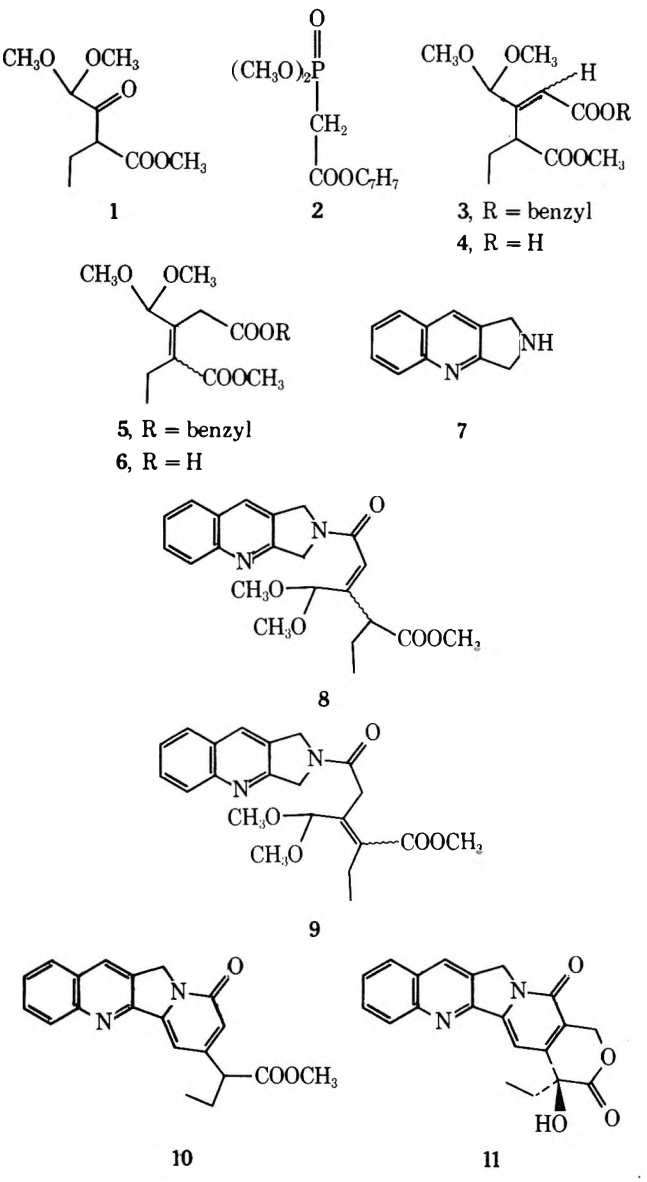
Camptothecin is an alkaloid first isolated from *Camptotheca acuminata*, a tree native to mainland China.[1] Structure **11** was established by x-ray crystallographic analysis of the iodoacetate.[2] Early clinical trials revealed promising antileukemic and antitumor properties causing many laboratories to commence work on total syntheses. Although subsequent testing uncovered the high toxicity of the compound, there is renewed interest in its inhibitory effect on macromolecular synthesis.[3] The first total synthesis of camptothecin (**11**) was completed in 1971[4] and since then a large number of successful approaches have been published.[5] All schemes thus far involve many steps and give low overall yields. In this note we describe another approach, although still not ideal, which does lead to intermediate **10** in five steps with an overall yield of 27%. This tetracyclic pyridone has previously been transformed to camptothecin (**11**) and the synthesis, owing to its convergent design, should be adaptable to the preparation of potentially more useful analogues.

The β-keto ester **1**,[6] readily available from methyl dimethoxyacetate and methyl butyrate, served as starting material. Wittig condensation with benzyl dimethylphosphonoacetate (**2**)[7] gave a mixture of *Z* and *E* benzyl esters **3** in 82% yield. Conversion to the carboxylic acids **4** was accomplished quantitatively and without disturbing the carbon–carbon double bond by hydrogenolysis over a 10% palladium on carbon catalyst in methanol. These sensitive acids were coupled without purification with the tricyclic amine **7**[8] by means of dicyclohexylcarbodiimide. The desired amides **8** were obtained in only 56% yield and we next explored the reactivity of the corresponding β,γ-unsaturated acids **6**. These were prepared by catalytic debenzylation of the tetrasubstituted unsaturated esters **5** available



in 96% yield by isomerization of the trisubstituted isomers **3** with potassium *tert*-butoxide in tetrahydrofuran. Dicyclohexylcarbodiimide promoted condensation of the diastereomeric mixture of these acids **6** with the tricyclic diamine **7** afforded the amides **9** (94%). Either isomers **8** or **9** could be converted to pyridone **10**[9] (41% yield) by treatment with boron trifluoride etherate followed by cyclization of the intermediate aldehydes in refluxing toluene containing a trace of trifluoroacetic acid. A sample of **10** recrystallized from ethyl acetate, mp 229–230°,[10] did not depress the melting point of authentic material, mp 228–230°, and infrared as well as ultraviolet spectra were superimposable. Nuclear magnetic resonance and mass spectra revealed a very minor but different impurity in each of the two samples of different derivation but otherwise confirmed identity. Furthermore, the compounds were indistinguishable by chromatographic techniques. Deoxycamptothecin accompanied by minor amounts of an isomer[11] has been prepared earlier in 35% yield by condensing the pyridone **10** with paraformaldehyde. The final conversion of deoxycamptothecin to *dl*-camptothecin (**11**) was accomplished in 55% yield by oxidation with hydrogen peroxide[9] or quantitatively by autoxidation in the presence of copper(II) species.[12]

Experimental Section

Microanalyses were performed by Midwest Microlab, Inc. Dry nitrogen was used in all reactions requiring an inert atmosphere.

Melting points were determined on a Kofler hot-stage microscope and are corrected, as are boiling points. Infrared (ir) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Ultraviolet (uv) spectra were measured on Perkin-Elmer 202 or Cary 14 instruments. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates T-60 instrument, and are given in parts per million (δ) downfield from an internal tetramethylsilane standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra were determined on Hitachi RMU-6D or RMU-6L instruments. The abbreviation M^+ refers to molecular ion. Gas chromatographic (GLC) analyses were done on either F & M 720 or Perkin-Elmer 990 instruments employing 6-ft 15% SE-30 or 3% OV-17 columns. Analytical thin layer chromatography (TLC) was done on Baker-flex silica gel IB-F sheets. Analtech silica gel GF plates (20 × 20 × 2 mm thick) were used for preparative separations. Merck PF_{254} or 0.05–0.2 mm silica gel and Fischer Florisil (100–200 mesh) were used for column chromatography.

Methyl 4,4-Dimethoxy-2-ethyl-3-oxobutyrate (1). This compound was prepared by the method of Royals[6] in 59% yield: bp 112–114° (11 mm); uv max (MeOH) 218 and 272 nm; ir (neat) 1750, 1730 cm^{-1}; NMR (CCl_4) δ 0.96 (t, 3, J = 7 Hz), 1.75 (m, 2), 3.37 (s, 6), 3.6 (m, 1), 3.67 (s, 3), 4.45 (s, 1).

Benzyl Bromoacetate (13). Bromoacetic acid (5.6 g, 0.04 mol) and benzyl alcohol (4.3 g, 0.04 mol) were added to a solution of 50 ml of benzene and 0.5 g of *p*-toluenesulfonic acid in a flask fitted with a Dean-Stark apparatus. The reaction mixture was heated to reflux for 2.5 hr and cooled to room temperature. After adding 100 ml of ether, the solution was extracted with two 25-ml portions of sodium bicarbonate solution, dried (Na_2SO_4), and concentrated, giving 8.1 g (96%) of benzyl bromoacetate (95% pure by GLC): ir (CCl_4) 1745 cm^{-1}; NMR (CCl_4) δ 3.70 (s, 2), 5.08 (s, 2), 7.28 (s, 5).

Benzyl Dimethylphosphonoacetate (2). Benzyl bromoacetate (35.0 g, 0.15 mol) was stirred in a flask with 30 ml of trimethyl phosphite and heated to 80°. After 48 hr, the contents were distilled giving 34.1 g (91%) of **2**: bp 148–150° (0.1 mm); ir (CCl_4) 1740 cm^{-1}; NMR (CCl_4) δ 2.91 (d, 2, J = 22 Hz), 3.67 (d, 6, J = 11 Hz), 5.09 (s, 2), 7.29 (s, 5).

(*Z*)- and (*E*)-Benzyl 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoate (3). Benzyl dimethylphosphonoacetate (**2**, 16.0 g, 0.06 mol) was added dropwise to a stirred suspension of sodium hydride (1.50 g, 0.062 mol) in 250 ml of dimethoxyethane. The reaction was stirred at 60° for 1 hr to ensure complete enolate formation. Then keto ester **1** (15.7 g, 0.077 mol) was added, and the reaction mixture was heated to reflux. After 24 hr the contents were concentrated to one-half volume, 100 ml of water was added, and the product was extracted with one portion of ether (subsequent extracts showed no desired product by GLC). The ether extract was dried (Na_2SO_4), concentrated, and distilled, giving 16.5 g (82%) of **3** (*Z* to *E* ratio 3:1 by GLC): bp 151–159° (0.1 mm); uv max (95% EtOH) 214 nm; ir ($CHCl_3$) 1725, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (t, 3, J = 7 Hz), 1.5–2.0 (m, 2), 3.3 (m, 1), 3.3–3.6 (m, 6), 3.7 (m, 3), 5.12 (s, 2), 5.92 (s, 1), 6.08 (s, 1), 7.33 (s, 5); mass spectrum (70 eV) *m/e* 336 (M^+).

(*Z*)- and (*E*)-4-Carbomethoxy-3-dimethoxymethyl-2-hexenoic Acid (4). Benzyl ester isomers **3** (3.36 g, 10 mmol) were added to a flask containing 100 ml of methanol and 440 mg of 10% palladium on carbon catalyst. After evacuating and flushing the flask with hydrogen several times, the reaction mixture was stirred under hydrogen at atmospheric pressure and room temperature. When the theoretical uptake (225 ml, 10 mmol) was observed, the reaction flask was removed, 40 ml of methylene chloride was added, and the catalyst was removed by filtration through Celite. The filtrate was concentrated in vacuo at a temperature not above 35°, giving 2.5 g (98%) of acid **4** (a mixture of *Z* and *E* isomers): ir (CCl_4) 3530, 1740, 1700, 1650 cm^{-1}; NMR (CCl_4) δ 0.94 (t, 3, J = 7 Hz); 1.67 (q, 2, J = 7 Hz), 3.2 (m, 1), 3.3–3.5 (m, 6), 3.64 (s, 3), 5.86 (s, 1), 5.99 (s, 1), 10.6 (s, 1).

(*Z*)- and (*E*)-Benzyl 4-Carbomethoxy-3-dimethoxymethyl-3-hexenoate (5). A solution of esters **3** (1.68 g, 5 mmol) in 10 ml of tetrahydrofuran was added slowly to a solution of potassium *tert*-butoxide (1.24 g, 11 mmol) in 15 ml of tetrahydrofuran at −65°. The resulting yellow solution was warmed gradually to −30°, water (10 ml) was added, and the solution was extracted with three 50-ml portions of ether. The combined and dried extracts gave 1.61 g (96%) of esters **5** as a mixture of *Z* and *E* isomers: uv max (95% EtOH) 214 nm; ir (CCl_4) 1745, 1730 cm^{-1}; NMR (CCl_4) δ 0.9–1.3 (m, 3), 2.2–2.7 (m, 2), 3.2–3.4 (m, 6), 3.4 (m, 2), 3.6–3.8 (m, 3), 4.6 (m, 1), 5.11 (m, 2), 7.24 (br s, 5); mass spectrum (70 eV) *m/e* 336 (M^+).

(*Z*)- and (*E*)-4-Carbomethoxy-3-dimethoxymethyl-3-hexenoic Acid (6). Benzyl ester isomers **5** (336 mg, 1 mmol) were added to a hydrogenation vessel containing 15 ml of methanol, 25 mg of 10% palladium on carbon catalyst, and 2 drops of triethylamine. After evacuating and flushing the flask with hydrogen several times, the reaction mixture was stirred under hydrogen at atomspheric pressure and room temperature. After 20 min, theoretical uptake (24 ml, 1 mmol) was observed, and the reaction mixture was removed, diluted with 10 ml of methylene chloride, and filtered through Celite. The filtrate was concentrated in vacuo at a temperature not above 35°, giving 248 mg (95%) of acid **6** (a mixture of *Z* and *E* isomers which was 95% pure by GLC): ir ($CHCl_3$) 3200, 1720, 1650 cm^{-1}; NMR (CCl_4) δ 1.01 (t, 3, J = 7 Hz), 2.31 (q, 2, J = 7 Hz), 3.1–3.4 (m, 8), 3.6–3.8 (m, 3), 5.0 (m, 1), 9.7 (br s, 1).

Amides 8. Freshly prepared carboxylic acid **4** (0.59 g, 2.4 mmol), dicyclohexylcarbodiimide (453 mg, 2.2 mmol), and tricyclic amine **7** (340 mg, 2 mmol) were combined in 25 ml of methylene chloride. This solution was stirred at room temperature for 12 hr, then filtered, concentrated, dissolved in 6 ml of methylene chloride, filtered again, and concentrated to an oil. The crude product was purified by preparative thin layer chromatography (silica gel GF, 8% methanol in ether) giving 450 mg (56%) of **8** (as a mixture of *Z* and *E* isomers). The product was further purified by recrystallization from methylene chloride–ether: mp 190–192°; uv max (95% EtOH) 234 nm (ϵ 40 400), 288 (4100), 294 (4300), 301 (4200), 307 (5600), 314 (4900), 321 (7700); ir ($CHCl_3$) 1730, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (t, 3, J = 7 Hz), 1.5–2.0 (m, 2), 2.2–2.5 (m, 1), 3.3–3.5 (m, 6), 3.6–3.8 (m, 3), 4.4 and 5.7 (2 m, total 1 H), 4.9–5.1 (br s, 4), 6.40 and 6.53 (2 s, total 1 H), 7.5–8.2 (m, 5); mass spectrum (70 eV) *m/e* 398 (M^+).

Amides 9. Carboxylic acid **6** (50 mg, 0.2 mmol), tricyclic amine **7** (32 mg, 0.2 mmol), and dicyclohexylcarbodiimide (43 mg, 0.21 mmol) were combined in 6 ml of methylene chloride. This solution was stirred at room temperature for 12 hr, then filtered and concentrated to a light solid. The crude product was purified by preparative thin layer chromatography (silica gel GF, 8% methanol in ether), giving 74 mg (93%) of **9** (as a mixture of *Z* and *E* isomers). The product was recrystallized from ether, giving colorless needles: mp 135–137°; uv max (95% EtOH) 232 nm (ϵ 48 200), 282 (4000), 288 (4200), 295 (4800), 301 (4900), 308 (6700), 314 (6000), 322 (9100); ir ($CHCl_3$) 1740, 1650, 1425 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, 3, J = 7 Hz), 2.3–2.8 (m, 2), 3.3–3.5 (m, 8), 3.7–3.9 (m, 3), 4.9–5.2 (m, 5), 7.5–8.2 (m, 5); mass spectrum (70 eV) *m/e* 398 (M^+).

Pyridone 10. Amide acetal **9** (300 mg, 0.75 mmol) was dissolved in 30 ml of methylene chloride and the resultant solution cooled to −65°. Boron trifluoride etherate (0.5 ml) was added, the cold bath was removed, and the reaction mixture was allowed to warm gradually to room temperature. After 20 min, 10 ml of water was added, and the two-phase system was stirred for 20 min, then brought to pH 5 with sodium bicarbonate solution. The methylene chloride layer was separated, dried (Na_2SO_4), and concentrated, giving 270 mg of crude aldehyde isomers: ir ($CHCl_3$) 1730, 1700, 1650 cm^{-1}. This mixture was dissolved in 20 ml of toluene with 6 μl of trifluoroacetic acid and the solution was heated to reflux. After 14 hr, the reaction mixture was filtered, diluted with 20 ml of methylene chloride, washed with dilute sodium bicarbonate solution, dried (K_2CO_3), and concentrated to an oil. Preparative thin layer chromatography (silica gel GF, 9% methanol in ether) afforded 105 mg (41%) of the pyridone **10**. One recrystallization from ethyl acetate gave plates: mp 229–230° (lit.[10] 228–230°); uv max (95% EtOH) 219 nm (ϵ 42 800), 249 (25 800), 254 (30 600), 287 (6100), 321 (7400), 366 (17 400); ir ($CHCl_3$) 1740, 1670, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (t, 3, J = 7 Hz), 1.8–2.2 (m, 2), 3.48 (t, 1, J = 7 Hz), 3.71 (s, 3), 5.22 (s, 2), 6.64 (m, 1), 7.30 (m, 1), 7.5–8.3 (m, 5); mass spectrum (70 eV) *m/e* 334 (M^+).

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.86; H, 5.39; N, 8.38. Found: C, 71.90; H, 5.43; N, 8.23.

Acknowledgment. This work was supported by the National Institutes of Health (GM 09868).

Registry No.—**1**, 57443-17-1; **2**, 57443-18-2; (*Z*)-**3**, 57443-19-3; (*E*)-**3**, 57443-20-6; (*Z*)-**4**, 57443-21-7; (*E*)-**4**, 57443-22-8; (*Z*)-**5**, 57443-23-9; (*E*)-**5**, 57443-24-0; (*Z*)-**6**, 57443-25-1; (*E*)-**6**, 57443-26-2; **7**, 34086-64-1; (*Z*)-**8**, 57443-27-3; (*E*)-**8**, 57443-28-4; (*Z*)-**9**, 57443-29-5; (*E*)-**9**, 57443-30-8; **10**, 34141-35-0; *dl*-**11**, 31456-25-4; **13**, 5437-45-6; bromoacetic acid, 79-08-3; benzyl alcohol, 100-51-6; trimethyl phosphite, 121-45-9.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXXIX. Apramycin—an Application of Amine Protonation Parameters[1]

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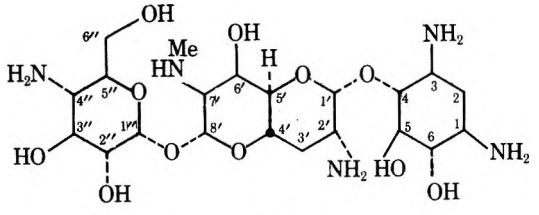
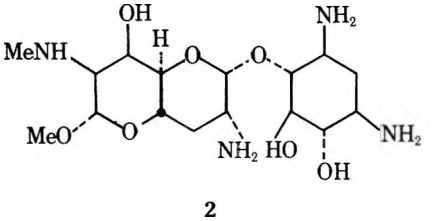
Received July 22, 1975

As part of a study of the structures of the nebramycin factors produced by *Streptomyces tenebrarius*[3] the ^{13}C NMR analysis of the kanamycin-like antibiotics has been investigated.[4] Alongside a structure determination of apramycin (1), the most complex of the nebramycin factors, by other physical and chemical means[5] the ^{13}C NMR analysis of this antibiotic was undertaken. In this connection recourse was taken to carbon shift perturbations induced by amine protonation, previously found to be an indicator of the substitution pattern in the proximity of the amino carbon.[4]



1

The ^{13}C NMR spectra of the antibiotic and two of its fragments, methyl β-aprosaminide (2)[5] and methyl 4-amino-4-deoxy-α-D-glucopyranoside (3), were run in aqueous solutions of pH less than 1 and more than 11 and the shift data of trehalose (4)[6] and of various compounds from earlier studies were used for the interpretation of the spectra. All chemical shifts are listed in Table I.

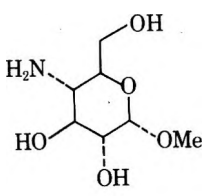


2

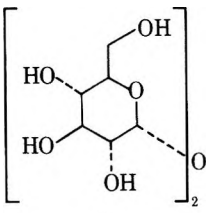
Table I
Carbon Chemical Shifts[a]

	1		2		3			
	>pH 11	<pH 1	>pH 11	<pH 1	>pH 11	<pH 1		4
C(1)	50.2	49.8	50.2	49.8				
C(2)	35.5	28.2	35.5	28.2				
C(3)	49.3	48.6	49.3	48.6				
C(4)	86.7	77.7	86.9	78.0				
C(5)	75.7	74.8	75.7	74.8				
C(6)	77.3	72.3	77.2	72.4				
C(1′)	100.4	94.9	100.5	95.1				
C(2′)	48.7	48.0	48.8	48.0				
C(3′)	32.0	26.8	32.1	26.9				
C(4′)	66.7[b]	65.7	66.3[c]	65.3				
C(5′)	69.8[b]	69.2	70.0[c]	69.4				
C(6′)	65.2	62.5	64.8	62.6				
C(7′)	61.2	59.3	61.8	60.2				
C(8′)	95.2	92.4	101.8	98.3				
C(1″)	94.1	94.1			99.1	98.9	92.9	
C(2″)	70.7	70.2			72.0	71.2	71.9	
C(3″)	73.0	68.9			72.9	68.9	72.5	
C(4″)	52.3	52.4			52.4	52.8	69.6	
C(5″)	72.4	68.4			71.4	67.4	70.9	
C(6″)	60.7	60.3			60.8	60.4	60.4	
NMe	32.0	30.4	32.1	30.5				
OMe			56.9	57.4	54.7	55.2		

[a] In parts per million downfield of Me_4Si; 1:1 D_2O–H_2O solutions with dioxane as internal reference. [b,c] The signals may be reversed. If so, they must be reversed at both pH values.



3

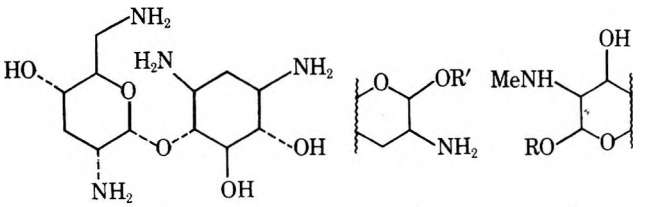


4

The δ values of all carbons of the monoglycoside model 3, except the anomeric carbon shift, are nearly identical with five of the carbons of the monosaccharide unit of the antibiotic, reflecting an α-anomeric attachment of the remainder of the skeleton to this moiety. Two of the three anomeric carbon signals move upfield on lowering of the pH. Since this behavior reflects the vicinality of amino groups to two anomeric carbon sites,[4] the anomeric carbon shift impervious to pH change must be that of the monoglycosyl fragment. The ca. 6 ppm shielding of the latter's anomeric carbon in the face of the normally invariant ca. 100 ppm α-glucopyranosyl anomeric carbon shift[4] implies the presence of a 1-*tert*-alkoxy substituent, e.g., as the fructosyl moiety in sucrose, or of a 1,1 linkage between the glucopyranosyl unit and another glycosyl function, as in trehalose (4). The latter molecular array in apramycin followed from further analysis (vide infra).

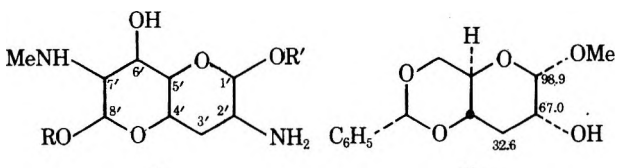
A comparison of the spectra of apramycin (1), methyl β-aprosaminide (2),[5] and neamine (5) reveals their common 2-deoxystreptamine unit. The identity of the six resonances of this ring in the three substances at high and low pH shows the attachment of the inosamine unit to be the same in all cases and hence to involve a C(4) ether linkage. The alternate C(6) oxygen attachment is precluded, since it introduces a different spatial environment around the amino groups of the deoxystreptamine moiety and its

neighboring ring and a consequent difference of conformation-dependent shift perturbation on acidification of the medium.[4] This argument establishes the liaison of the 2-deoxystreptamine unit to the anomeric site of a central saccharide moiety and the latter's α configuration.



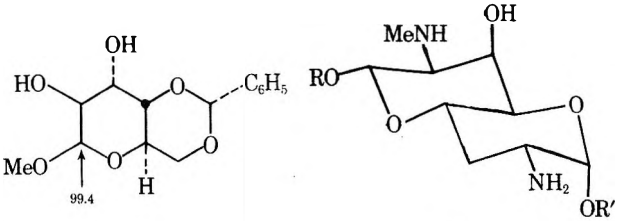
5 6 7

The remaining saccharide unit contains two amino groups, one primary and the other secondary. This difference of N substitution is recognizable easily by a strong shielding alteration of the β carbons ($\Delta\delta^{\beta}$ 4–6 ppm) of primary amines in acid solution and a reduced shielding disturbance ($\Delta\delta^{\beta}$ 2–3 ppm) for secondary amines.[4] Application of this diagnostic test to the N-methylated eight-carbon sugar moiety in apramycin (1) and methyl β-aprosaminide (2) reveals most of its structural detail. An anomeric carbon and the lone methylene group show $\Delta\delta$ values of 5.5 and 5.2 ppm, respectively, while the other anomeric center and an oxymethine exhibit shift differences of 2.8 and 2.7 ppm, respectively. These facts show six of the eight carbons to be contained in structural units 6 and 7 and yield their shift assignments. The remaining oxymethines can weld the two units to each other only in form 8. As a comparison of the anomeric carbon shifts of the antibiotic (1) and its degradation product 2 indicates, the removal of the aminoglucosyl unit leaves one anomeric carbon unfazed. Since the latter must be the site of attachment of the 2-deoxystreptamine moiety and since its $\Delta\delta^{\beta}$ value is 5.5 ppm, the inosamine-substituted anomeric site is vicinal to an amino, and not a methylamino, function. In view of R′ of 8 being the 2-deoxystreptamine unit the substituent R must be the aminoglucosyl residue, thus necessitating the involvement of the latter in a 1,1-disaccharide linkage. Since the ^{1}H NMR coupling characteristics of the anomeric hydrogens revealed the presence of one β and two α configurations in apramycin (1),[5] the aminoglucosyloxy moiety must be β oriented on the central saccharide fragment (8). Even though the 1,1 linkage in the antibiotic (1) differs stereochemically from that in trehalose (4), the anomeric carbon shift perturbation is similar in magnitude in both α–α and α–β relationships.



8 9

The stereochemistry of the ring juncture of the bicyclic saccharide (8) can be determined by comparison of the C(1′) and C(3′) shifts of methyl β-aprosaminide (2) with the shifts of the related carbons of a model, methyl 4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (9).[7] In view of the identity of the configuration of the C(1′) and C(2′) substituents of 2 with related carbons of 9 and of the β effect of an amino group at high pH with that of a hydroxy function[7] and in the face of the inosamine unit exerting the same effect as a methyl group on the anomeric site of the central ring system the nearly identical shifts of C(1′) and C(3′) of apramycin (1), 2, and the related carbons of model 9 reflect the identity of ring junctions.[8] Only the stereochemistry of the C(6′) and C(7′) substituents remains to be determined in view of the previous establishment of a β-anomeric C(8′) relationship. Two of the four possible configurations can be excluded. One possibility, a β-glucopyranosyl arrangement, is negated by a signal of C(8′) of methyl β-aprosaminide (2) appearing 2.5 ppm upfield of that of anomeric carbons of methyl β-glucopyranosides. While, in principle, the *N*-methyl group could exert a γ effect of such magnitude and field direction, ^{13}C NMR data from work on inositols[9,10] and inosamines[11] show such influence to be possible only in cases of methoxy or methylamino groups, respectively, being attached to carbons adjacent to axially substituted neighbors. The second possibility, a β-altropyranosyl arrangement, is untenable in view of the rigid model methyl 4,6-*O*-benzylidene-β-D-altropyranoside (10)[7] exhibiting an anomeric carbon signal 2.4 ppm upfield of the C(8′) resonance of 2. Thus the C(6′) and C(7′) substituents must have a cis relationship and be part of a β-allopyranosyl or β-mannopyranosyl configurational arrangement. The 8.5-Hz coupling visible in the H(8′) ^{1}H NMR signal and characteristic of a trans H(7′)–H(8′) relationship[5] shows the methylamino group to be equatorial and hence the ring to possess the stereochemistry of a β-allopyranoside as depicted in stereostructure 11 for saccharide 8. The full stereochemical details of apramycin are portrayed in structure 1.



10 11

Experimental Section

The ^{13}C NMR spectra of water solutions with the use of dioxane as internal reference [$\delta(Me_4Si) = \delta(C_4H_8O_2) - 66.3$ ppm] were recorded on Varian DP-60 and XL-100-15 spectrometers operating at 15.1 and 25.2 MHz in the Fourier transform mode, respectively. The chemical shifts in Table I and on formulas 9, 10, i, and ii are in parts per million downfield from Me_4Si.

Registry No.—1, 37321-09-8.

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(2) Address correspondence to Department of Chemistry, Rice University, Houston, Texas 77001.

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(8) Calculation of the C(2′) shift of 8 from the C(2) shift of 9 by the use of the 19.0 ppm C(2) shift difference between methyl α-D-glucopyranoside and methyl α-D-2-amino-2-deoxyglucopyranoside[4] yields a 48.0-ppm value, in close agreement with the observed shift and in support of identical C(2′) and C(4′) configurations in 8 and 9. Furthermore, the coupling characteristics of the C(3′) hydrogens in a ^{1}H NMR spectrum of 8[5] reveal an axial orientation for H(2′) and H(4′).

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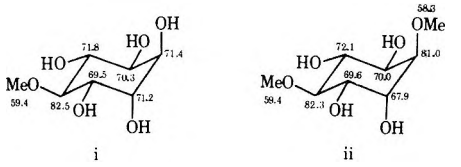
(10) Cf. also the shift data on pinitol (i) and pinpollitol (ii) [R. T. Gallagher, *Phytochemistry*, **14**, 755 (1975)]. (The authors acknowledge gratefully a gift of samples of these natural products.)



i ii

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Comparative Acidic Cleavage of Methoxybenzyl Protected Amides of Amino Acids[1]

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The use of 2,4-dimethoxybenzyl (Dmb) and *p*-methoxybenzyl (pmb) as amido protecting groups for conventional peptide synthesis has been previously reported.[3-5]

The possibility of using Dmb and pmb also in the solid-phase peptide synthesis[6] led us to study the relative stabilities of these groups in the acidic conditions normally associated with removal of the amino protecting groups.[7,8] For this purpose, cleavage of Dmb and pmb at 25° by 50% (v/v) trifluoroacetic acid in methylene chloride, 1 *N* HCl–acetic acid, and trifluoroacetic acid was investigated with the following protected amino acids: *N*-terbutyloxycarbonyl-N^{β}-*p*-methoxybenzyl and N^{3}-2,4-dimethoxybenzyl-L-asparagine [Boc-Asn(pmb)-OH and Boc-Asn(Dmb)-OH], *N*-*tert*-butyloxycarbonyl-N^{γ}-*p*-methoxybenzyl and N^{γ}-2,4-dimethoxybenzyl-L-glutamine [Boc-Gln(pmb)-OH and Boc-Gln(Dmb)-OH], and glycine-*p*-methoxybenzyl and 2,4-dimethoxybenzylamide (H-Gly-NHpmb and H-Gly-NHDmb). The removal of pmb and DMB was followed by thin layer chromatography. Partial cleavage of the amide protective groups was readily detected, since unchanged protected amides were well separated from L-asparagine, L-glutamine, and L-glycine amide resulting from cleavage.

In the case of H-Gly-NHpmb and H-Gly-NHDmb the removal of the protective groups was also checked by gas chromatography. Finally the action of liquid HF at 0° was examined[9] to ascertain whether pmb and Dmb had been removed under conditions where the side-chain protecting groups normally used in solid-phase peptide synthesis are cleaved.

This investigation has resulted in a method which is suitable to the quantitative determination of amino acid amides released during acidolysis of the corresponding *p*-methoxybenzyl or 2,4-dimethoxybenzyl amides. It should be noted that the results obtained by TLC are in good agreement with those obtained by GC (Table I).

The *p*-methoxybenzyl group was slightly affected by 1 *N* HCl–CH_3COOH under any conditions while prolonged exposure to this reagent caused partial cleavage of the 2,4-dimethoxybenzyl group (Table I).

Trifluoroacetic acid cleaved completely the 2,4-dimethoxybenzyl group after prolonged treatment (72 h), whereas the *p*-methoxybenzyl group was attacked partially only after 48 h (Table I).

2,4-Dimethoxybenzyl was completely removed by means of liquid HF; on the other hand, under these conditions the *p*-methoxybenzyl group was removed only partially. Boc-Gln(pmb)-OH, especially, has been shown to be sluggish to cleavage, confirming the work reported by Hruby et al.[10] Prolonged reaction times (12 h) were found necessary to complete removal.

These results demonstrate that 2,4-dimethoxybenzyl is suitable as an amido protecting group for asparagine and glutamine in solid-phase peptide synthesis and also indicate that *p*-methoxybenzyl is less promising in this connection.

Experimental Section

The Dmb derivatives were prepared as previously described.[5] The pmb derivatives were obtained in our laboratory as indicated below and their purity was checked by TLC using the following systems: A, benzene–ethyl acetate–petroleum ether (5:3:2 v/v); B, benzene–ethyl acetate–acetic acid–water (10:10:2:1 v/v); C, chloroform–methanol–acetic acid (15:3:2 v/v).

The removal of pmb and Dmb was followed by running chromatograms on Kieselgel G with 1-butanol–acetic acid–water (4:1:1 v/v); spots were detected with ninhydrin–cadmium acetate (0.2% v/v)[11] and evaluated by densitometry[12] using a chromoscan Zeiss double beam densitometer with thin layer attachment.

The gas chromatographic analysis was carried out using a Fractovap Model G.V. equipped with flame ionization detector. The

Table I
Stability[a] to Acidic Cleavages[b] of Dmb and pmb Amido Protecting Groups

Time, h	TLC/GC[c]		TLC			TLC		
	A	C	A	B	C	A	B	C
	H-Gly-NH-Dmb (35088-22-3)			Boc-Asn (Dmb)-OH (47553-91-3)			Boc-Gln (Dmb)-OH (31874-52-9)	
6	6/5	21/19		23	31		21	27
12	18/18.5	40/37		44	62		41	55
24	20/17.5	63/64	20	63	77	20	60	73
36	28/26	73.5/74	29	80	86	28	80	85
48	35/32	81/80	35	99	99	35	97	98
72	39.5/35	91/90	42	100	100	41	100	100
	H-Gly-NH-pmb (57459-57-1)			Boc-Asn (pmb)-OH (27482-66-2)			Boc-Gln (pmb)-OH (27482-68-4)	
48	3/2.6	26/28			13			15
72	6/5.5	35/35.5	5		20	3		21

[a] The percents of methoxybenzyl amides cleaved for different times are reported (mean of three independent determinations). [b] A, 1 N HCl–CH_3COOH; B, 50% CF_3COOH–CH_2Cl_2 (v/v); C, CF_3COOH. [c] Result of densitometric analysis/result of gas chromatographic analysis.

U-shaped glass column (2.5 mm × 2 m) was packed with 3% OV-101 on Gas-Chrom Q.

Nitrogen was used as carrier gas at a flow rate of 45 ml/min. Column temperature was kept constant at 210°.

***N*-*tert*-Butyloxycarbonyl-N^{β}-*p*-methoxybenzyl-L-asparagine Benzyl Ester [Boc-Asn(pmb)-OBzl].** This compound was prepared similarly to the Dmb analogue in 64% yield: mp 105–106° (from ethyl acetate); R_f(A) 0.74, R_f(B) 0.62.

Anal. Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.19; H, 6.87; N, 6.42.

***N*-*tert*-Butyloxycarbonyl-N^{β}-*p*-methoxybenzyl-L-asparagine [Boc-Asn(pmb)-OH].** Boc-Asn(pmb)-OBzl (2.21 g, 5 mmol) was hydrogenated in ethanol (50 ml) over 10% palladium on charcoal (0.6 g) for 10 h. The catalyst was then filtered off and the solvent evaporated. Crystallization from ethyl acetate gave the product (1.41 g, 80%): mp 132–133°; R_f(C) 0.71, R_f(B) 0.63; $[\alpha]^{20}D$ +9.92° (*c* 1.0, methanol).

Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86; N, 7.95. Found: C, 57.87; H, 6.84; N, 7.91.

***N*-*tert*-Butyloxycarbonyl-N^{γ}-*p*-methoxybenzyl-L-glutamine Benzyl Ester [Boc-Gln(pmb)-OBzl].** This compound was prepared similarly to the Dmb analogue in 88% yield: mp 108–109° (from ethyl acetate); R_f(A) 0.80, R_f(B) 0.59.

Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.13. Found: C, 65.64; H, 7.10; N, 6.12.

***N*-*tert*-Butyloxycarbonyl-N^{γ}-*p*-methoxybenzyl-L-glutamine [Boc-Gln(pmb)-OH].** This compound was prepared similarly to the asparagine analogue in 94% yield: mp 97–98° (from ethyl acetate); R_f(C) 0.80, R_f(B) 0.72; $[\alpha]^{20}D$ −2.66° (*c* 1.0, methanol).

Anal. Calcd for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.64. Found: C, 59.06; H, 7.13; N, 7.68.

Action of 1 N HCl–Acetic Acid. The protected amides (0.1 mmol) were placed in test tubes and treated with 1 N HCl in CH_3COOH (1.5 ml). The tubes were stoppered and kept in a desiccator and the reaction was allowed to proceed for the required time at 25°. Then the reagent was evaporated under nitrogen and the residue was dissolved in 1 N HCl (100 ml).

Action of 50% Trifluoroacetic Acid–Methylene Chloride and Trifluoroacetic Acid. The protected amides (0.1 mmol) were placed in test tubes and treated with 50% trifluoroacetic acid in methylene chloride (v/v) or trifluoroacetic acid (2 ml) in the presence of anisole (0.2 ml) for the desired time at 25°. After the evaporation under nitrogen of the reagent the residue was quantitatively transferred to a 25-ml funnel with 1 N HCl and extracted twice with ether (5 ml each). The solution was diluted with 1 N HCl to a constant volume (100 ml).

Action of Hydrofluoric Acid. The protected amides (0.1 mmol) were treated with HF and anisole[7] for 1 h at 0°. The HF was then evaporated under nitrogen within 1 h and the residue was quantitatively transferred to a 25-ml funnel with 1 N HCl (10 ml). The solution was extracted twice with ether (5 ml) and then brought to 100 ml with 1 N HCl.

Densitometry. The spots were scanned at 490 nm and the areas under the densitometric curve were measured by the relationship area = peak height × width at half height. By reading from standard graphs for glycine amide, L-asparagine, and L-glutamine, the areas were related to the amounts of amino acid amide present.

Acidolysis and Gas Chromatography. H-Gly-NHDmb or H-Gly-NHpmb (0.5 mmol) were treated with trifluoroacetic acid (18.5 ml) and anisole (1.5 ml) or with 1 N HCl–CH_3COOH (20 ml), respectively. At fixed times portions of the reaction mixture were evaporated under nitrogen. The residue was treated with trifluoroacetic anhydride (0.5 ml) and methylene chloride (2 ml) for 30 min at room temperature. The solution was evaporated under nitrogen and the residue dissolved in ethyl acetate (0.5 ml) containing 0.2 mg of methyl stearate as internal standard; 1 μl was injected in the gas chromatograph. The retention times relative to methyl stearate for N-TFA-Gly-NHDmb and N-TFA-Gly-NHpmb were 1.11 and 0.72, respectively. The peak areas were calculated as peak height × width at half height and corrected against the peak area of the internal standard. The values of these areas were then related to the amounts of glycine amide produced at time *t* using the relationship 100 − $(A_t/A_0)100$ where A_0 and A_t are the initial corrected area of N-TFA-Gly-NHDmb (or pmb) and that at time *t*, respectively.

Registry No.—Boc-Asn(pmb)-OBzl, 27482-84-4; Boc-Gln(pmb)-OBzl, 27482-67-3; HCl, 7647-01-0; acetic acid, 64-19-7; trifluoroacetic acid, 76-05-1; HF, 7664-39-3.

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Optically Active Amines. XXI.[1] Application of the Salicylidenimino Chirality Rule to Cyclic Steroidal Amines

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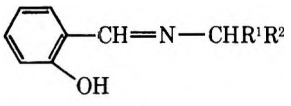
The salicylidenimino chirality rule[3] has been used to correlate the absolute configuration of *N*-salicylidenimino derivatives (1) of cyclic terpene amines (menthane, thujane,



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and fenchane ring systems) with the signs of the observed Cotton effects near 255 and 315 nm in their circular dichroism (CD) spectra.[1] The Cotton effects are generated by the coupled oscillator mechanism, demonstrated earlier to account for most of the observed optical activity in pyrimidine nucleosides.[4,5] For the *N*-salicylidene derivative the signs of the Cotton effects are determined by the chirality (right-handed screw for positive chirality) of vicinal carbon–carbon bonds and the attachment bond of the salicylidenimino chromophore.

We now apply similar consideration of a coupled oscillator mechanism to the interpretation of the CD spectra of the *N*-salicylidene derivatives of steroidal cyclic amines (Table I). These spectra were reported earlier,[6–9] but until now there has been no simple interpretation.

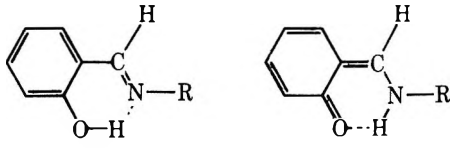
The electronic (isotropic) absorption (EA) spectra of *N*-salicylidene derivatives in hexane exhibit absorption bands at about 315 (log ϵ_{max} 3.68–3.73), 255 (log ϵ_{max} 4.12–4.21), and 215 nm (log ϵ_{max} 4.36–4.49),[1] designated as bands I, II, and III,[3] respectively, assigned to transitions of the intramolecularly hydrogen-bonded salicylidenimino chromophore[3] (2). In polar solvents such as dioxane, ethanol, and methanol a broad band at 400 nm (log ϵ_{max} 1.32–1.89 in dioxane[9] and log ϵ_{max} 3.06–3.38 in ethanol[9] and methanol[1]) and in ethanol a shoulder near 280 nm (log ϵ_{max} 3.49–3.67[9]) become evident, and the other three bands show a slight decrease in intensity.[1,9] The two additional bands are at-

Table I
Circular Dichroism for the *N*-Salicylidene Derivatives of Steroidal Cyclic Amines

Compd	*N*-Salicylidene derivative (solvent[b])	Circular dichroism maxima[a]			Coupled oscillator	
		Quinoid[c]	Band I	Band II[d]	Bond	Chirality
4	1α-Amino-5α-cholestane-2β,3β-diol (D, E)	+	+	+[e,f]	C(9)–C(10)	+
5	4β-Aminocholestan-5α-ol (D, M)		+[g]	+	C(5)–C(6)	+
6	4β-Aminocholestane-3β,5α-diol (D)		+	+	C(5)–C(6)	+
7	6α-Amino-5α-cholestane (D, E)	—	—	+, —	C(4)–C(5)	+
8	6β-Amino-3β-acetoxycholestan-5α-ol (D, E)	—	—	—[h]	C(4)–C(5)	—
9	6β-Amino-5α-cholestane-3β,7α-diol (D)		—	—[h]	C(4)–C(5)	—
10	7α-Amino-5α-cholestane-3β,6β-diol (D)		—	—	C(8)–C(14)	—
11	7β-Amino-5α-cholestane (E, I)	+	+	+, —[f]	C(8)–C(14)	+
12	11α-Amino-5β-pregnane-3α,20β-diol (D)		+	—, +[i]	C(9)–C(10)	—
13	12α-Amino-5β-cholane (D)		—	+	C(13)–C(17)	+
14	2β-Amino-5α-cholestane-1α,3β-diol (D)		—	—[h]	C(9)–C(10)	—
15	2β-Amino-5α-cholestan-3α-ol (D)		—	—	C(9)–C(10)	—
16	3α-Amino-5α-solanidane (D, E)	—	—[g,j]	—	C(5)–C(6)	—
17	3α-Amino-5α-cholestan-2β-ol (D, E)	+	—[g]	+[i]	C(5)–C(6)	—
18	3α-Amino-5α-pregnan-20α-ol (D)		—[k]		C(5)–C(6)	—
19	3β-Amino-5β-solanidane (D, E)	+	+[l]	+	C(5)–C(6)	+
20	3α-Amino-5β-solanidane (D, E)	—	—[g,j]	—	*m*	
21	3β-Amino-5α-solanidane (D, E)	+	+[n]	+	*m*	
22	Jurubidin (D)		+[o]		*m*	
23	Jurubin (D, E)	+	+[g,o]	+	*m*	
24	Solanocapsin (D, E)	+	+[l,p]	+	*m*	
25	5α-Aminocholestane-3β,6β-diol (D)		—	+	*m*	
26	3β-Dimethylamino-16α-amino-18,20(*R*)-epoxy-5α-pregnane (E)	+	+		*q*	
27	3β-Dimethylamino-16β-amino-18,20(*R*)-epoxy-5α-pregnane (D)		—[h]		*q*	
28	17α-Amino-5α-androstan-3β-ol (D)		—[k]		*q*	
29	17β-Amino-5α-androstan-3β-ol (D)		+[k]	—	*q*	
30	17β-Amino-5α-androstan-3α-ol-11-one (D)		+[k]	—	*q*	

[a] CD from ref 9, or as noted otherwise. [b] Solvents: D, dioxane; E, ethanol; M, methanol; I, isooctane. [c] Observed only in ethanol and methanol. [d] For S-shaped curves, the sign of the maximum at the longer wavelength is shown to the left. [e] A weak positive maximum at 246 nm in ethanol also reported. [f] A negative maximum at shorter wavelength in ethanol assigned to band III. [g] Only this band in dioxane reported. [h] Maximum in dioxane not reached. [i] A positive maximum at shorter wavelength assigned to band III. [j] CD in dioxane from ref 7. [k] CD from ref 6. [l] Two positive maxima in dioxane assigned to band II. [m] No obvious carbon–carbon bond as a single coupled oscillator. [n] A negative maximum near 275 nm in dioxane assigned to the quinoid tautomer. [o] CD in dioxane from ref 8. [p] A negative maximum near 275 nm assigned to the quinoid tantomer. [q] Cyclopentylamine system.

tributed to the presence of a quinoid tautomer (3) in the polar solvents.[10]



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For the *N*-salicylidene derivatives shown in Table I, corresponding CD maxima are reported[6–9] for bands I ($\Delta\epsilon_{max}$ ±0.13 to ±4.57) and II ($\Delta\epsilon_{max}$ ±0.9 to ±9.7) and for the band near 400 nm ($\Delta\epsilon_{max}$ ±0.05 to ±0.82) in ethanol and methanol. In dioxane a CD maximum near 400 nm was not detected,[9] and in all solvents the anisotropy factor ($\Delta\epsilon/\epsilon$) of band III is such that its CD maximum is difficult to measure and usually is not observed. The signs of the CD of bands I and II of a particular compound, however, remain unchanged with a change in solvent.

With the exception of **13**, when a single CD maximum is associated with band I and with band II, these maxima are of the same sign since the electronic transition moments of these two bands, although not coinciding exactly with each other, are almost parallel to the chromophore attachment bond.[3] In the case of **13**, the difference in sign is presumably due to the difference in orientation of these transition moments. For some of these compounds (**7**, **11**, and **12**), band II shows an S-shaped (double-humped[11]) CD curve. This may be the manifestation of the combined effect of an allowed progression of a totally symmetric vibrational mode and a forbidden progression of a possibly non-totally symmetric mode whose differential dichroic absorption maximum occurs at a shorter wavelength and borrows its intensity chiefly from band III.[12] An S-shaped CD curve for band II appears only when the two progressions have opposite signs and their rotational strengths are of approximately equal intensity. That the longer wavelength CD maximum for band II of **7** and **12** does not have the same sign as that of band I is also due to the slightly different orientation of the respective electronic transition moments.

Since in **4–19** the chromophore is symmetrically disposed with respect to the cyclohexane ring to which it is attached and the effect due to the polarizability of the carbon–hydrogen and carbon–oxygen bonds may be assumed to be small compared to a carbon–carbon bond,[4] only the carbon attachment bonds to the cyclohexane ring bearing the chromophore need be considered as inducing differential dichroic absorption. As shown in Table I for **4–13**, the sign of the CD maximum for band II (or the longer wavelength portion of band II) and with three exceptions for band I (**7**, **12**, and **13**) is the same as the chirality (right-handed screw for positive chirality) of the attachment bond of the salicylidenimino group and a carbon attachment bond to the cyclohexane ring vicinal to the chromophore. Assuming chair conformations for all cyclohexane rings, the dihedral angle for the two bonds is close to ±60°. The C(10)–C(19) bond in **4** and the C(13)–C(18) bond in **13** are essentially antiparallel to the chromophore attachment bond and have

little effect on the CD. For compounds with one hydroxyl group vicinal to the chromophore (**4, 5,** and **8–10**), the attachment bond of the hydroxyl group is nearly antiparallel to the chromophore attachment bond and has an insignificant effect on the CD. In **6** the vicinal C(5)–O bond is also antiparallel to the chromophore attachment bond, but the vicinal C(3)–O bond has a dihedral angle of about −60°. Nevertheless, the CD for both bands I and II is positive as a result of the positive chirality of the C(5)–C(6) bond.

As is also shown in Table I for **14–19**, the sign of the CD for bands I and II is determined also by the chirality of the attachment bond of the salicylidenimino group and a carbon attachment bond to the cyclohexane ring bearing the chromophore. This carbon–carbon bond and the chromophore attachment bond are separated from each other by two σ bonds and have a dihedral angle close to ±120°, again assuming chair conformations for all cyclohexane rings. The one exception is **17**, for which negative CD bands I and II are predicted. Since the C(2)–O bond in **17** is antiparallel to the chromophore attachment bond, and **16**, with an A/B ring system the same as that of **17**, shows the predicted negative CD for bands I and II, the CD of band II of **17** should be reexamined. In **14**, the vicinal C(1)–O bond is antiparallel to the chromophore attachment bond, but the vicinal C(3)–O bond has a dihedral angle of about +60°. The CD of bands I and II for **14**, however, is negative as a result of the negative chirality of the chromophore attachment bond and the C(9)–C(10) bond. In **14** and **15** the C(10)–C(19) bond is parallel with the chromophore attachment bond and will have little effect on the CD.

For **20–25**, the chromophore is 3α on a 5β ring system (**20**), 3β on a 5α ring system (**21–24**), or 5α (**25**), and in each there is no obvious single carbon–carbon bond as a coupled oscillator. Hence, no straightforward prediction as to the CD of bands I and II is possible. Also, the chromophore in **26–30** is attached to a cyclopentane ring which is not symmetrically disposed with respect to the chromophore attachment bond, and no simple interpretation of these CD spectra in terms of the coupled oscillator mechanism can be made.

Registry No.—**4**, 57525-86-7; **4** quinoid form, 57484-06-7; **5**, 57525-87-8; **6**, 57525-88-9; **7**, 57525-89-0; **7** quinoid form, 57474-17-6; **8**, 57525-90-3; **8** quinoid form, 57474-18-7; **9**, 57525-91-4; **10**, 57525-92-5; **11**, 57525-93-6; **11** quinoid form, 57474-19-8; **12**, 57525-94-7; **13**, 57526-20-2; **14**, 57572-73-3; **15**, 57525-95-8; **16**, 57525-96-9; **16** quinoid form, 57474-20-1; **17**, 57525-97-0; **17** quinoid form, 57474-21-2; **18**, 57474-22-3; **19**, 57525-98-1; **19** quinoid form, 57484-00-1; **20**, 57525-99-2; **20** quinoid form, 57474-23-4; **21**, 57526-00-8; **21** quinoid form, 57474-24-5; **22**, 57526-01-9; **23**, 57526-21-3; **23** quinoid form, 57484-08-9; **24**, 57526-02-0; **24** quinoid form, 57474-25-6; **25**, 57474-26-7; **26**, 57572-74-4; **26** quinoid form, 57474-27-8; **27**, 57526-03-1; **28**, 57526-04-2; **29**, 57526-05-3; **30**, 57474-28-9.

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A Novel Transformation of Chromone-3-carboxaldehyde to an o-Hydroxybenzophenone

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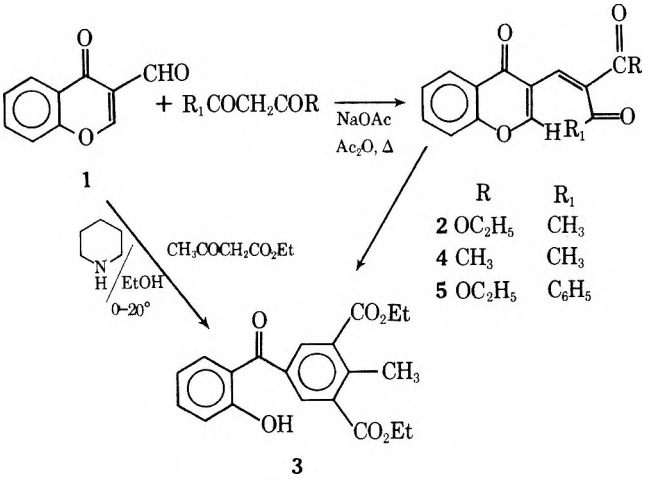
Recent publications[1–4] describing condensation reactions of 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (**1**) have prompted us to report a novel one-step transformation of **1** into an *o*-hydroxybenzophenone **3**.

Condensation of **1** with ethyl acetoacetate afforded **2** or **3** depending on reaction conditions. For example, reaction of



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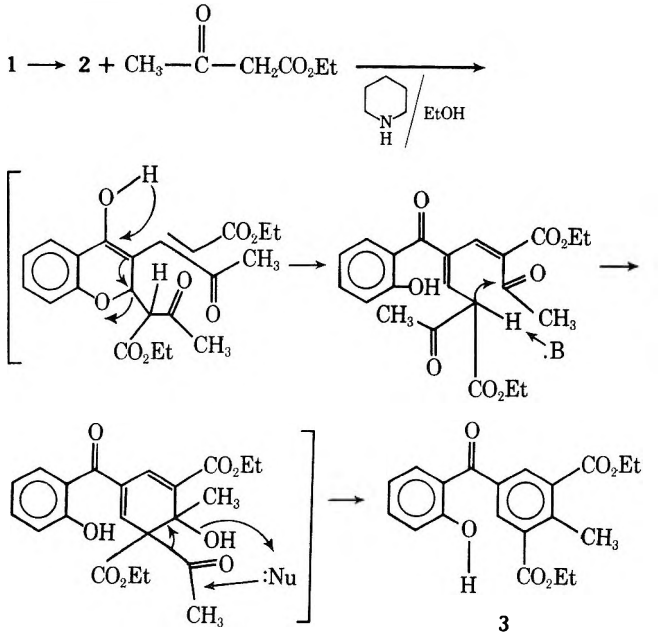
1 with ethyl acetoacetate in the presence of NaOAc–Ac_2O gave **2** in 62% crude yield. Similar condensations of **1** with 2,4-pentanedione and ethyl benzoylacetate gave **4** and **5** in 60 and 30% yield, respectively.

Reaction of **1** with excess ethyl acetoacetate in NaOAc–Ac_2O or pyridine–EtOH also gave **2**.

When the reaction was carried out in the presence of piperidine–EtOH the benzophenone **3** and a red oil were formed. This oil showed no trace of **3** on TLC (Et_2O–hexane, 1:1 silica gel). Upon prolonged standing it solidified. Examination of the solid by GC showed two components,



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compound 3, which comprised 80% of the mixture, and a second unidentified component, which was neither 1 nor 2.

A plausible mechanism for the formation of 3 involves initial condensation of 1 with ethyl acetoacetate followed by Michael addition of another molecule of ethyl acetoacetate and subsequent rearrangement. Evidence supporting this mechanism was the conversion of 2 with excess ethyl acetoacetate in piperidine–EtOH to 3 in 70% yield (NMR).

While 3 represents only one example of this synthesis, in principle it should be applicable to the preparation of other similarly substituted *o*-hydroxybenzophenones.

Experimental Section

General. Melting points were determined in open capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. The infrared and ultraviolet spectra were obtained on Perkin-Elmer 521 and Perkin-Elmer 350 recording spectrometers, respectively. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Mass spectra were obtained on a Finnigan 1015 quadrupole mass spectrometer. All compounds were analyzed for C and H and were within ±0.4% of the theoretical value.

3-(4-Oxo-4*H*-1-benzopyran-3-yl)-2-(1-oxoethyl)-2-propenoic Acid Ethyl Ester (2). Ethyl acetoacetate (13.0 g, 0.1 mol), NaOAc (8.2 g, 0.1 mol), and 1 (17.4 g, 0.1 mol) were heated and stirred in Ac_2O (50 ml) on the steam bath for 2 hr and diluted with H_2O (300 ml); the resulting tan solid was recrystallized from Et_2O to give 10.00 g of 2, mp 120–122°. Further concentration gave an additional 8.0 g, mp 95–100°. The first crop when recrystallized (EtOH–H_2O) gave tan needles of 2: mp 120–122°; ir (KBr) 1705, 1680, and 1650 cm^{-1} (ester, α,β-unsaturated ketone, and chromone carbonyl); NMR[3,5] ($CDCl_3$) δ 8.35 (s, 1 H, C_2 H), 8.18 (dd, 1, J = 7.0 Hz, benzene H_5), 7.28–8.05 (m, 4 H, benzene and olefinic), 4.3 (q, 2 H, J = 7.0 Hz, CH_2), 2 5 (s, 3 H, CH_3), 1.35 (t, 3 H, J = 7.0 Hz, CH_3); uv max (95% EtOH) 220 nm (ϵ 17 900). Anal. C, H.

5-(2-Hydroxybenzoyl)-2-methylbenzene-1,3-dicarboxylic Acid Diethyl Ester (3). To a stirred solution of 1 (26.2 g, 0.15 mol) and ethyl acetoacetate (35.4 g, 0.25 mol) in EtOH at 0–20° was added piperidine (10.0 ml). The resulting red solution was allowed to warm to room temperature over several hours, neutralized with HOAc, poured onto ice–H_2O (1 l.), and extracted with Et_2O (1 l.). The Et_2O layer was then washed with H_2O, 5% $NaHCO_3$, and brine and dried ($MgSO_4$). Concentration in vacuo gave a red oil. Boiling the oil with hexane followed by decantation gave, after cooling, 4.0 g of 3: mp 55–55.5°; ir (KBr) 1730 and 1630 cm^{-1} (ester and ketone carbonyl); NMR ($CDCl_3$) δ 8.3 (s, 2 H, H_4 and H_6), 7.8–6.8 (m, 4 H, aromatic) 4.5 (q, 4 H, J = 7.0 Hz, 2-CH_2), 2.8 (s, 3 H, CH_3), 1.35 (t, 6 H, J = 7.0 Hz, 2-CH_3); uv max 258 nm (ϵ 12 100); mass spectrum (70 eV) m/e 356 (P^+). Anal. C, H.

The residual red oil showed no trace of 3 by TLC (silica gel, Et_2O–hexane, 1:1). Attempts to crystallize it were unsuccessful. After prolonged standing it solidified to a waxy yellow solid yielding 18.5 g. GC analysis (2-ft 1% OV-22, 190°) showed that 80% of 3 was present.

3-[(4-Oxo-4*H*-1-benzopyran-3-yl)-methylene]-2,4-pentanedione (4). 2,4-Pentanedione (10.05 g, 0.1 mol), 1 (17.4 g, 0.1 mol), and NaOAc (8.2 g, 0.1 mol) were heated and stirred in Ac_2O (65.0 ml) for 3 h on the steam bath. The mixture was cooled and diluted with a two-phase CH_2Cl_2–H_2O mixture. The CH_2Cl_2 was separated, extracted with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and concentration in vacuo yielded a tan semisolid, which when recrystallized (EtOH, 300 ml) gave 5, 15.7 g (60%), mp 168–170°. Anal. C, H.

β-(Oxo-α-[(4-oxo-4*H*-1-benzopyran-3-yl)-methylene]benzenepropanoic Acid Ethyl Ester (5). Ethyl benzoylacetate (9.7 g, 0.05 mol), 1 (8.7 g, 0.05 mol), and NaOAc (4.2 g, 0.05 mol) were heated and stirred in Ac_2O (50 ml) for 4 h on the steam bath. Dilution with a two-phase CH_2Cl_2–H_2O solution and separation of the CH_2Cl_2 followed by drying ($MgSO_4$), filtration, and concentration in vacuo yielded an oily residue. Recrystallization (CH_2Cl_2–heptane) gave 5, 5.0 g (30%), mp 111–112°. Anal. C, H.

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Registry No.—1, 17422-74-1; 2, 57443-89-7; 3, 57443-90-0; 4, 57443-91-1; 5, 57443-92-2; ethyl acetoacetate, 141-97-9; 2,4-pentanedione, 123-54-6; ethyl benzoylacetate, 94-02-0.

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Total Synthesis of Steroids. XI.[1] Synthesis of Optically Active 11-Ketoestrane Derivatives

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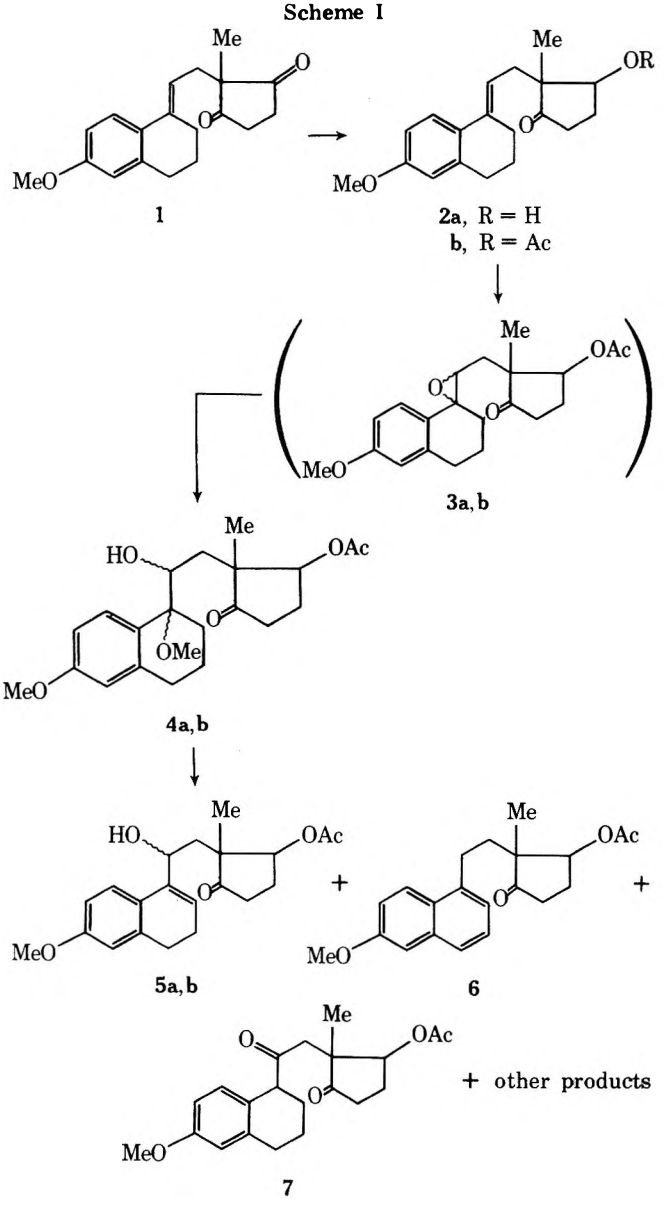
In addition to our work on the total synthesis of racemic 11-oxidized estrogens published recently,[2,3] we would like to report the total synthesis of optically active new estrane derivatives, which was based on the method applied to the synthesis of *rac*-14α-hydroxy-3-methoxy-8α-estra-1,3,5(10)-triene-11,17-dione.[2]

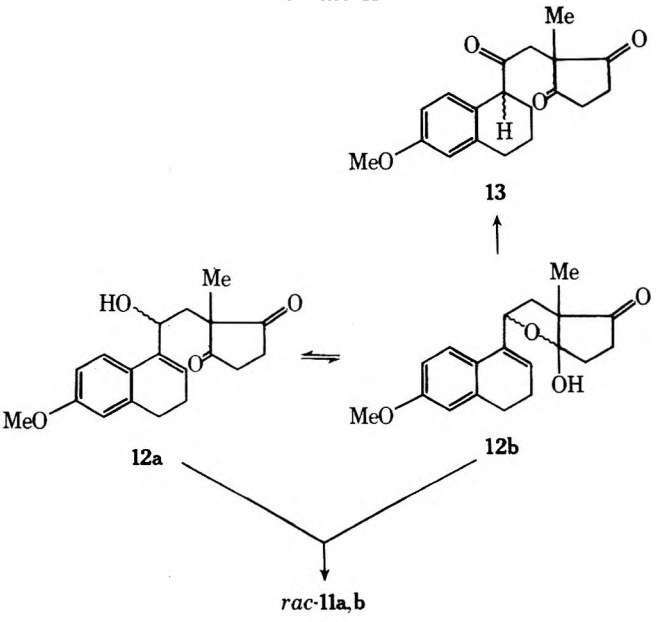
The Torgovs secodione 1[4] can be transformed easily by microbial reduction[5] to the secolone 2a. The latter has been used as the starting material in the present synthesis. The acetate of the secolone 2b obtained by standard method was subjected to the action of *m*-chloroperbenzoic acid (MCPBA) under the same conditions as we described earlier[6] for the secodione 1. Surprisingly, the reaction resulted in so many products that their separation was not rewarding, although some of them have been isolated and identified (5a,b, 6, and 7). In order to avoid the undesirable reactions we tried to carry out the oxidation in the presence of weak alkali and to vary the reaction solvent. The best results were obtained with methanol as solvent and pyridine *N*-oxide as weak base. Although it was not possible to prevent oxirane ring cleavage, the number of reaction products under these conditions was limited to only two, i.e., the methoxy alcohols 4a and 4b, obtained in ca. 90% yield. They could be separated very easily owing to their different polarities and they were reasonable stable. We suppose that they are formed by the cleavage of epoxides 3a and 3b with methyl alcohol; however, we were not able to assign an absolute configuration on the basis of our spectroanalytical data. One can conclude from the model studies that there is no special steric preference in formation of either of them, which also explains the 1:1 ratio of formation. These two products (4a,b) (Scheme I) proved to be very useful for further synthesis. Each of them undergoes in the presence of weak acid (acetic acid) in chloroform solution a methanol elimination to yield the allylic alcohols 5a and 5b, respectively; the more polar 4b looses methanol more easily and produces a small amount of 7, as by-product; the elimination of methanol from the less polar 4a is not accompanied by any side reaction. The elimination reaction can be also conducted on 4a,b mixture; however, the separation of the allylic alcohols is very difficult. Also in the case of the alcohols 5a and 5b we were not able to ascribe an absolute configuration to either of them.

Under the influence of strong acids at elevated temperature in benzene solution 5a and 5b undergo a rearrange-

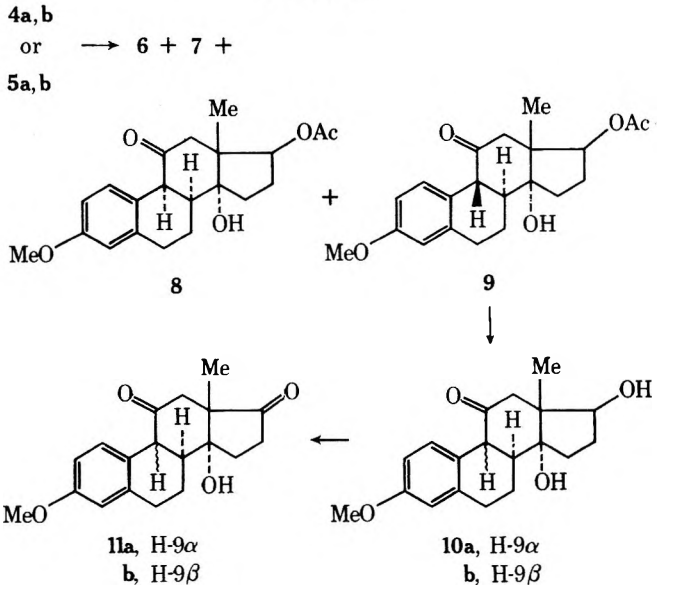
Scheme I



Scheme II



Scheme III



ment to a mixture of 6 and 7 (ratio ca. 1:1, checked by TLC). The racemic alcohols **12a,b** under similar conditions gave only the 17-keto analogue of 7, i.e., the triketone **13** (Scheme II). The cyclization of **4a,b** or **5a,b** with Meerwein reagent, i.e., $Et_3O^+BF_4^-$, gives four products: the desired tetracyclic compounds 8 and 9 and the two rearrangement products 6 and 7 in a ratio 3:5:5:5 (Scheme III). The yield of the tetracyclic compounds 8 and 9 is ca. 40%, i.e., only half of that obtained by the cyclization of **12a,b** in our previous work.[2] Apparently the allylic alcohols **5a** and **5b** underwent more easily the side reactions leading to 6 and 7 as compared with the racemic compounds **12a,b.** The mechanism of the cyclization is most probably the same as proposed before; the first step is the formation of 11-ethyl ether followed by nucleophilic attack of the double bond on the keto group, accompanied by proton elimination from C-11 and subsequent hydrolysis of the 11-enol ether grouping. The tetracyclic compound 9 has a trans B/C ring junction, which follows from the relatively large coupling constant $J_{9,8}$ = 10 Hz, whereas in the other isomer 8 the signals of H-9 and H-8 are coupled by J = 5 Hz (cis B/C junction). Compounds 8 and 9 can be interconverted in the presence of acids.

In order to prove the stereochemistry of all chiral centers in 8 or 9 we transformed them in a two-step reaction sequence (hydrolysis of the acetoxy group and Jones oxidation[7]) to diketone **11b.** The same diketone was obtained as a racemate by us before[2] and all uv, ir (in $CHCl_3$), and ^1H NMR data of the latter were in good agreement with the new optically active tetracyclic diketone **11b.** Since the absolute stereochemistry at the C-13 chiral center for the starting material **2a** is known and the reaction sequences described above do not involve any racemization reaction at this particular carbon atom, the absolute configuration of all new compounds must be as presented in all schemes.

Further transformations of **11** (in racemic form) have been reported earlier;[2,3] so the present work describes a facile, stereospecific synthesis of 11-ketoestrane derivatives from a known and easily accessible substrate **2a.**

Experimental Section[8]

17β-Acetoxy-3-methoxy-8,14-secoestra-1,3,5(10),9(11)-tetraen-14-one (2b). The secolone **2a** (5.1 g, 17.0 mmol) was acetylated with acetic anhydride–pyridine under standard conditions, yielding 5.7 g of **2b** (98%): ir 1740 and 1735 cm^{-1}; ^1H NMR 1.00 (s, 3, CH_3), 1.97 (s, 3, $OCOCH_3$), 3.70 (s, 3, OCH_3), 5.17 (t, 1, H-17), 5.64 (t, 1, H-11), 6.50 (m, 2, H-2 and H-4), 7.32 ppm (d, 1, $J_{1,2}$ = 10 Hz, H-1).

17β-Acetoxy-3,9ξ-dimethoxy-8,14-secoestra-1,3,5(10)-trien-11ξ-ol-14-one (4a and 4b). To a methanol (120 ml) solution of **2b** (5.7 g, 16.6 mmol) and pyridine *N*-oxide (9.51 g, 100 mmol), 88% MCPBA (6.55 g, 38.0 mmol) was added at room temperature. The reaction mixture was left for 3 h. One-half of the methanol was removed in vacuo at room temperature and the excess of MCPBA was destroyed with the 10% aqueous solution of Na_2SO_3. The products **4a,b** were extracted with 300 ml of benzene, and the benzene layer was shaken with saturated sodium hydrogen carbonate, dried over anhydrous Na_2SO_4, and evaporated in vacuo, giving 6.00 g (92.5%) of the oily mixture of **4a** and **4b**. This mixture (0.200 g) was separated by preparative TLC with benzene and acetone (9:1) as eluents yielding the oily, less polar **4a** (0.090 g): $[\alpha]D$ −55.4° (*c* 2.25, $CHCl_3$); uv max (95% EtOH) 229, 275, and 282 nm; ir 3500, 1740, and 1730 cm^{-1}; ^1H NMR 0.95 (s, 3, CH_3), 1.98 (s, 3, $OCOCH_3$), 3.09 (s, 3, OCH_3, at C-9), 3.72 (s, 3, OCH_3 at C-3), 4.78 (t, 1, H-17), 6.42 (d, 1, $J_{4,2}$ = 3 Hz, H-4), 6.65 (dd, 1, $J_{2,4}$ = 3, $J_{2,1}$ = 8 Hz, H-2), 7.45 ppm (d, 1, $J_{1,2}$ = 8 Hz, H-1).

The oily, more polar **4b** (0.095 g): $[\alpha]D$ +25.2° (*c* 2.62, $CHCl_3$); uv max (95% EtOH) 229, 275, and 282 nm; ir 3480, 1740, and 1720 cm^{-1}; ^1H NMR 0.91 (s, 3, CH_3), 1.95 (s, 3, $OCOCH_3$), 2.98 (s, 3, OCH_3 at C-9), 3.71 (s, 3, OCH_3 at C-3), 4.85 (t, 1, H-17), 6.42 (d, 1, $J_{4,2}$ = 3 Hz, H-4), 6.65 ppm (dd, 1, $J_{2,4}$ = 3, $J_{2,1}$ = 8 Hz, H-2).

17β-Acetoxy-11ξ-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),8-tetraen-14-one (5a and 5b). A chloroform solution of **4a** (0.12 g, 0.31 mmol) was refluxed with 1.5 ml of glacial acetic acid, and after 4 h worked up in the standard manner, giving 0.10 g (91%) of the oily, less polar **5a** which was purified by preparative TLC using benzene–acetone (9:1) as eluent. The product was crystallized from Et_2O, yielding 0.08 g of **5a** (72%): mp 110–113°; $[\alpha]D$ +24.3° (*c* 0.944, $CHCl_3$); uv max (95% EtOH) 219, 226, and 272 nm; ir 3450, 1740, and 1720 cm^{-1}; ^1H NMR 0.91 (s, 3, CH_3), 2.02 (s, 3, $OCOCH_3$), 3.75 (s, 3, OCH_3), 5.08 (m, 2, H-11 and H-17), 6.06 ppm (t, 1, H-8); *m/e* 358.

The same procedure was used for transformation of **4b** into **5b** and the crude product **5b** was separated by preparative TLC from the side product **7**, yielding 72% of **5b** and 14% of **7**.

5b: $[\alpha]D$ −0.136°, $[\alpha]_{578}$ −0.498°, $[\alpha]_{546}$ −0.908°, $[\alpha]_{436}$ −4.84° (*c* 2.21, $CHCl_3$); uv max (95% EtOH) 217, 226, and 272 nm; ir 3480, 1740, and 1720 cm^{-1}; ^1H NMR 1.05 (s, 3, CH_3), 1.98 (s, 3, $OCOCH_3$), 3.73 (s, 3, OCH_3), 4.98 (m, 2, H-11 and H-17), 6.01 ppm (t, 1, H-8); *m/e* 358.

17β-Acetoxy-3-methoxy-8,14-secoestra-1,3,5(10),6,8-pentaen-14-one (6) and 17β-Acetoxy-3-methoxy-8,14-secoestra-1,3,5(10)-triene-11,14-dione (7). A solution of **5a** (0.200 g, 0.56 mmol) in 20 ml of benzene was refluxed with *p*-TsOH (catalytic amount) for about 1 h. When **5a** completely disappeared the reaction mixture was worked up in the standard manner, yielding the mixture of **6** and **7**, which were separated by preparative TLC. The plates were developed five times with hexane–ethyl acetate (5:1) giving **6** and **7**.

6 (0.085 g, 44%): $[\alpha]D$ −13.0° (*c* 1.68, $CHCl_3$); uv max (95% EtOH) 230, 256, 278, 288, 317, 326, and 332 nm; ir 1748 cm^{-1}; ^1H NMR 1.05 (s, 3, CH_3), 2.05 (s, 3, $OCOCH_3$), 3.84 (s, 3, OCH_3), 5.37 (t, 1, H-17), 7.1 (m, 4, H in ring B), 7.42 (d, 1, H-2), 7.78 ppm (d, 1, $J_{1,2}$ = 9 Hz, H-1); *m/e* 340.

7 (0.090 g, 45%): $[\alpha]D$ −43.6° (*c* 2.51, $CHCl_3$); uv max (95% EtOH) 205, 224, 278, and 285 nm; ir 1750 and 1735 cm^{-1}; ^1H NMR 0.78 (s, 3, CH_3), 1.99 (s, 3, $OCOCH_3$), 3.70 (s, 3, OCH_3), 5.35 ppm (m, 1, H-17); *m/e* 358.

17β-Acetoxy-3-methoxy-8α-estra-1,3,5(10)-trien-14α-ol-11-one (8) and 17β-Acetoxy-3-methoxy-8α,9β-estra-1,3,5(10)-trien-14α-ol-11-one (9). To a solution of the mixture **4a,b** (5.00 g, 12.8 mmol) in 2.5 l. of acetone, $Et_3O^+BF_4^-$ (35 g, 184 mmol) was added in small portions and the solution was left overnight at room temperature. The solution was then refluxed for 45 min, the solvent was removed in vacuo, and the residue was dissolved in 250 ml of benzene, shaken with saturated sodium hydrogen carbonate, and dried over anhydrous Na_2SO_4. After evaporation of the solvents in vacuo the residue was washed with pentane (3 × 15 ml) and then hexane (3 × 15 ml) in order to remove the acetone condensation products. The remaining oil was chromatographed on 500 g of silica gel with benzene and acetone as eluents giving the mixture of both desired tetracyclic compounds **8** and **9** and the mixture of two rearrangement products **6** and **7**. The tetracyclic compounds **8** and **9** were separated by preparative TLC using hexane–ethyl acetate (2:1) as eluents. Elution from the plates with methanol gave **8** and **9**.

8 (0.70 g, 15%): mp 147–152° (from ethyl ether); $[\alpha]D$ +26.2° (*c* 1.197, $CHCl_3$); uv max (95% EtOH) 221 nm (ε 9200), 229 (6900), 278 (1610), and 285 (1430); ir 3550, 1740, and 1710 cm^{-1}; ^1H NMR 1.10 (s, 3, CH_3), 2.10 (s, 3, $OCOCH_3$), 3.75 (s, 3, OCH_3), 3.87 (d, 1, $J_{9,8}$ = 5 Hz, H-9), 4.88 (d, 1, H-17), 6.7 ppm (m, 3, H-1, H-2 and H-4).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.38; H, 7.43; *m/e* 358.

9 (1.25 g, 27%): mp 143–146° (from ethyl ether); $[\alpha]D$ −133.4° (*c* 1.140, $CHCl_3$); uv max (95% EtOH) 221 nm (ε 8400), 227 (7710), 278 (1690), and 285 (1600); ir 3450, 1735, and 1700 cm^{-1}; ^1H NMR 1.12 (s, 3, CH_3), 2.00 (s, 3, $OCOCH_3$), 3.72 (s, 3, OCH_3), 3.95 (d, 1, $J_{9,8}$ = 10 Hz, H-9), 4.65 (t, 1, H-17), 6.58 (m, 2, H-2 and H-4), 7.05 ppm (d, 1, H-1).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.49; H, 7.29; *m/e* 358.

The products **6** and **7** were separated on the preparative plates with hexane–ethyl acetate (5:1) as eluents, yielding 1.26 g (29%) of **6** and 1.25 g (27%) of **7**.

14α,17β-Dihydroxy-3-methoxy-8α-estra-1,3,5(10)-trien-11-one (10a) and 14α,17β-Dihydroxy-3-methoxy-8α,9β-estra-1,3,5(10)-trien-11-one (10b). To a methanol solution of the mixture **8** and **9** (0.150 g, 0.42 mmol) a methanol (2 ml) solution of KOH (0.023 g, 0.42 mmol) was added and left for 4 h at room temperature. The solution was then acidified with acetic acid, the solvent was evaporated in vacuo, and the products were extracted with chloroform. The extract was neutralized, dried over anhydrous Na_2SO_4, and evaporated in vacuo. After chromatography on one preparative plate with benzene–acetone (85:15) as developing solvent we obtained **10a** and **10b**.

10a: 0.011 g (8.3%); mp 167–172° (from ethyl ether); $[\alpha]D$ +37.4° (*c* 0.78, $CHCl_3$); uv max (95% EtOH) 223, 279, and 285 nm; ir 3420 and 1705 cm^{-1}; *m/e* 316.

10b: 0.105 g (79%); $[\alpha]D$ −105° (*c* 1.34, $CHCl_3$); uv max (95% EtOH) 227, 278, and 285 nm; ir 3500 and 1705 cm^{-1}; ^1H NMR 1.05 (s, 3, CH_3), 3.72 (s, 3, OCH_3), 4.02 (d, 1, $J_{9,8}$ = 11 Hz, H-9), 6.52 (d, 1, $J_{4,2}$ = 3 Hz, H-4), 6.65 (dd, 1, $J_{2,1}$ = 8.5, $J_{2,4}$ = 3 Hz, H-2), 6.97 ppm (d, 1, $J_{1,2}$ = 8.5 Hz, H-1); *m/e* 316.

The same procedure was used for the hydrolysis of **8** and **9** separately and in every case a mixture of **10a** and **10b** was obtained.

14α-Hydroxy-3-methoxy-8α,9β-estra-1,3,5(10)-triene-11,17-dione (11b). Oxidation of 0.050 g (0.158 mmol) of the mixture **10a** and **10b** with Jones reagent[7] under standard conditions yielded 0.037 g (74% yield) of the mixture **11a** and **11b**. The crystallization from ethyl ether yielded 0.020 g of **11b**: mp 154–156°; $[\alpha]D$ −116.5° (*c* 1.02, $CHCl_3$); uv max (95% EtOH) 276 and 283 nm; ir ($CHCl_3$) 3500, 1740, and 1720 cm^{-1}; ^1H NMR 1.18 (s, 3, CH_3), 3.73 (s, 3, OCH_3), 4.05 (d, 1, $J_{9,8}$ = 12 Hz, H-9), 6.53 (d, 1, $J_{4,2}$ = 2.5 Hz, H-4), 6.68 (dd, 1, $J_{2,1}$ = 8.7, $J_{2,4}$ = 2.5 Hz, H-2), 6.95 ppm (d, 1, $J_{1,2}$ = 8.7 Hz, H-1). Uv, ir ($CHCl_3$), and ^1H NMR data of the latter were in good agreement with the physical data obtained for the same racemic diketone.[2]

Conversion of the Diketone 7 into the Triketone 13. To a methanol solution of **7** (0.030 g, 0.084 mmol) a methanol solution of KOH (0.005 g, 0.09 mmol) was added and left for 2 h at room temperature. Standard work-up gave the crude product, which was oxidized with Jones reagent[7] under standard conditions yielding 0.017 g (65%) of the triketone **13**. The spectroanalytical data for this compound were the same as for the earlier obtained racemic triketone **13**.[6]

Acknowledgment. We are indebted to our technical assistant Mr. Jacek Kinowski for his skillful help in conducting some experiments.

Registry No.—**2a**, 6563-82-2; **2b**, 57549-39-0; **4a**, 57474-04-1; **5a**, 57474-05-2; **5b**, 57525-82-3; **6**, 57474-06-3; **7**, 57474-07-4; **8**, 57474-08-5; **9**, 57525-83-4; **10a**, 57474-09-6; **10b**, 57525-84-5; **11b**, 57525-85-6; acetic anhydride, 108-24-7.

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Stereochemistry of Bockmühl's Synthesis of Methadone

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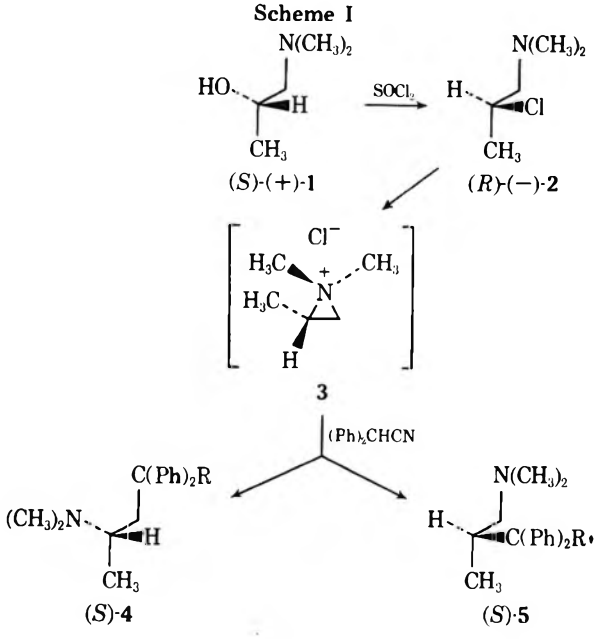
Methadone (**4b**) was first prepared in racemic form by Bockmühl and Erhardt[1] according to the approach outlined in Scheme I. The chloro amine **2** obtained from chlorination of (±)-1-dimethylamino-2-propanol (**1**) with thionyl chloride was treated with sodium diphenylacetonitrile to give a mixture of aminonitriles **4a** and **5a**. The aziridinium ion intermediate **3** has been proposed to account for the rearranged product **4a**.[2] Grignard reaction of **4a** with ethylmagnesium bromide followed by acid hydrolysis afforded methadone (**4b**). Similar treatment of **5a** gave rise to isomethadone (**5b**). More recently, amino alcohol (+)-**1** has been obtained from ethyl L-(−)-lactate (aminolysis, reduction) and thus assigned the (*S*)-(+) configuration.[3] The absolute configurations (shown in Scheme I) of the aminonitriles **4a**[4] and **5a**[5] and thus methadone and isomethadone have also been established. We have found that the conversion of **1** to **4a** and **5a** via **2** is stereospecific and proceeds with the stereochemistry as depicted in Scheme I.

Treatment of (*S*)-(+)-**1** with thionyl chloride in chloroform by the method of Schultz and Sprague[2] afforded (−)-1-dimethylamino-2-chloropropane (**2**) hydrochloride, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O), which was converted to the free base, $[\alpha]^{25}D$ −43.9° (*c* 2.55, $CHCl_3$), and treated with sodium diphenylacetonitrile in toluene essentially by the original procedure.[1] The mixture of aminonitriles thus obtained was separated by preparative thin layer chromatography on silica gel, affording substantially optically pure (*S*)-(+) ≡ L-(+)-**4a** and (*S*)-(+) ≡ D-(+)-**5a** by comparison of optical rotations with the literature values (see Experimental Section).

Scheme I



a, R = CN
b, R = COC_2H_5

The opposite configurations and identical optical purity of the nitriles **4a** and **5a** constitute compelling evidence that the aziridinium ion pathway is the exclusive mode of product formation in the alkylation step. It follows that unrearranged **5a** was formed with net retention of configuration (double inversion) while **4a** has the inverted configuration since the opening of the aziridinium ion **3** at the unsubstituted carbon would not alter the asymmetric center.[6] Thus the chloride **2** must have the (*R*)-(−) configuration and must have been obtained from **1** with inversion.

The present results clearly exclude the formation of an intermediate aziridine during chlorination of **1** and are best rationalized by SN2 displacement of the chlorosulfite ester of **1** hydrochloride. The high local concentration of chloride ion enforced by the internal ammonium ion of **1** should enhance the SN2 displacement process and may have been a factor in the high degree of stereospecificity observed in this case.[7]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Boiling points are uncorrected. Optical rotations were measured on a Rudolph polarimeter having a readability of ±0.01°, using a 1-dm tube. ^{1}H NMR spectra were obtained with Varian A-60 and T-60 instruments.

(−)-1-Dimethylamino-2-chloropropane Hydrochloride (2). To a solution of 3.77 g (0.0366 mol) of (*S*)-(+)-1-dimethylamino-2-propanol (**1**),[3] $[\alpha]^{25}D$ +24° (*c* 2.17, EtOH), in 10 ml of chloroform stirred and cooled in an ice–salt bath was slowly added 5.72 g (0.048 mol) of freshly distilled thionyl chloride in 2 ml of chloroform. When addition was complete a precipitate formed. The flask was allowed to warm to room temperature over 30 min, then heated to reflux for 30 min. The precipitated material redissolved on heating but the product crystallized from the boiling solvent shortly thereafter. The cooled mixture was diluted with ether and filtered. The crude product, 5.5 g (95%), was recrystallized from 2-propanol, giving 3.73 g (64%) of (−)-1-dimethylamino-2-chloropropane hydrochloride (**2**), mp 192–193°, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O) [lit.[2] mp for (±) hydrochloride 185–186°].

(−)-1-Dimethylamino-2-chloropropane (2). To a solution of 2.2 g of (−)-**2** hydrochloride in an equal volume of water was added 1.5 ml of 20% sodium hydroxide solution until the mixture was distinctly alkaline to pH paper. The free amine was extracted with two 5-ml portions of ether. The combined ether layers were dried over anhydrous potassium carbonate and distilled to give 0.8 g of (−)-1-dimethylamino-2-chloropropane (**2**): bp 115° [lit.[2] bp for (±) 62–63° (100–110 mmHg)]; $[\alpha]^{25}D$ −43.9° (*c* 2.55 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.5 (d, 3, J = 6 Hz, CCH_3), 2.28 (s, 6, NCH_3), 2.50 (m, 2), 4.07 (m, 1), identical with an authentic racemic sample.

Alkylation of Diphenylacetonitrile with (−)-2. A 1.0-g sample of the hydrochloride salt of (−)-**2**, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O), was converted to the base as previously described and treated with sodium diphenylacetonitrile by the Bockmühl procedure.[1] A 0.52-g portion of the crude mixture of aminonitriles was separated by preparative thin layer chromatography (silica gel, E. Merck, benzene–methanol 8:2) affording 145.7 mg of (*S*)-(+)-**4a**, recrystallized from petroleum ether, mp 100–101°, $[\alpha]^{25}D$ +49° (*c* 0.68, absolute EtOH) [lit.[8] mp 100–101°, $[\alpha]^{25}D$ +50° (*c* 1.5, absolute EtOH)], and 156.5 mg of (*S*)-(+)-**5a**, $[\alpha]^{25}D$ +70° (*c* 0.82, 95% EtOH) [lit.[8] $[\alpha]^{25}D$ +70° (*c* 1.5, USP EtOH].

Registry No.—(*S*)-(+)-**1**, 53636-15-0; (*R*)-(−)-**2**, 57496-00-1; (*R*)-(−)-**2** HCl, 57496-01-2; (*S*)-(+)-**4a**, 7576-08-1; (*S*)-(+)-**5a**, 6134-96-9; diphenylacetonitrile, 86-29-3.

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(4) A. H. Beckett and A. F. Casey, *J. Chem. Soc.*, 900 (1955).
(5) A. H. Beckett, G. Kirk, and R. Thomas, *Chem. Ind. (London)*, 1418 (1960).
(6) Inversion stereochemistry for the formation of aziridines and their ring opening by nucleophiles is well established. See O. C. Dermer and G. E. Ham, "Ethyleneimine and Other Aziridines," Academic Press, New York, N.Y., 1969, pp 26, 208, and references cited therein.
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Synthesis of 1,2,4-Triazoles from Tosylmethyl Isocyanide and Aryldiazonium Compounds[1]

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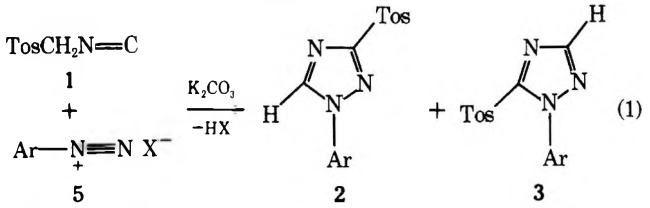
The coupling of diazonium salts and compounds XCH_2Y with an activated methylene group leads to formation of hydrazones. These reactions occur either without[3] or with loss (i.e. the Japp–Klingemann reaction)[4] of one of the activating functionalities X or Y. Ring-closed products are not usually formed in these processes.[3,4]

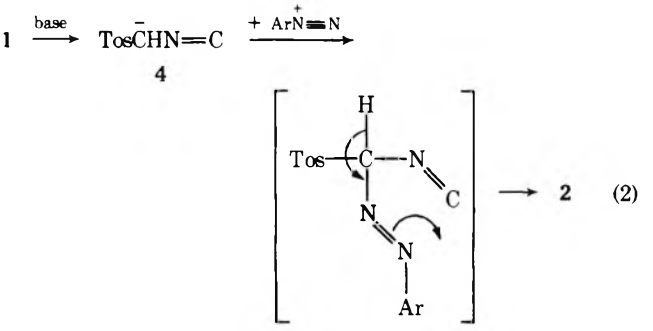
As a continuation of our work on synthetic applications of tosylmethyl isocyanide[5] (TosMIC, 1), we wish to report the synthesis of 1,2,4-triazoles from TosMIC and diazonium salts, according to eq 1. TosMIC accommodates, be-



sides an activated methylene, the isocyanide carbon as a second reactive site. This offers the opportunity to form cyclic products. Thus, a number of azoles (oxazoles,[5a] imidazoles,[5b] thiazoles,[5c] and pyrroles[5d]) has been synthesized previously from TosMIC and C=O, C=N, C=S, and C=C containing substrates.[6]

It now appears that the N≡N triple bond of diazonium salts also is capable of undergoing cycloadditions with TosMIC[23] to give 1-aryl-3-tosyl-1,2,4-triazoles (**2**), together with minor amounts of the isomeric 1-aryl-5-tosyl-1,2,4-triazoles (**3**). The construction of the 1,2,4-triazole nucleus by this method, i.e., by formation of the N_1–C_5 and N_2–C_3 bonds, has a precedent in the Einhorn–Brunner reaction of diacylamines and hydrazines.[7]

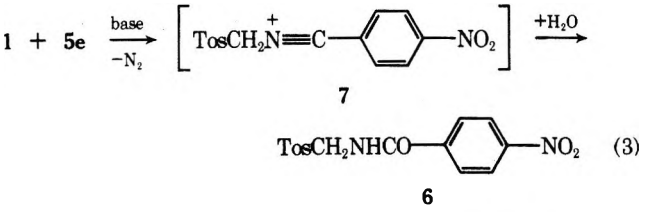
The formation of the main product **2** is explained by eq 2, in close analogy with mechanisms proposed for previous



TosMIC reactions.[8] TosMIC anion **4** is assumed to attack the electrophilic β nitrogen of the diazonium ion, followed by ring closure and a proton shift to give **2**.

Several pathways are conceivable for the formation of the isomeric side-product **3**. These include, as an initial step, attack of TosMIC anion **4** at N_α rather than N_β of the diazonium ion, or, alternatively, attack at N_β by **4** through its isocyano carbon. Reaction through a diazotate anion, which also is present in the basic medium,[9] seems less likely since no **2c** (or **3c**) was formed from benzenediazonium tetrafluoroborate at pH > 13.[10] In fact, the formation of the triazoles **3** is the first illustration of a reversed addition of TosMIC to an unsaturated substrate.[8]

The reactions of TosMIC were carried out with a series of para-substituted benzenediazonium compounds, as well as with 3-pyridinediazonium chloride and α-naphthalenediazonium tetrafluoroborate (eq 1). As appears from Table I, that the highest yields of **2** were obtained from benzenediazonium salts with electron-donating substituents. A completely different reaction was observed with *p*-nitrobenzenediazonium tetrafluoroborate (**5e**). Instead of triazoles, the only product isolated was *N*-tosylmethyl-*p*-nitrobenzamide (**6**, 39%), apparently formed by nucleophilic displacement of nitrogen and hydration of the nitrilium ion[11] **7** (eq 3). For structural proof, **6** was prepared inde-



pendently (62% yield) by a Mannich condensation of *p*-toluenesulfinic acid, formaldehyde, and *p*-nitrobenzamide.

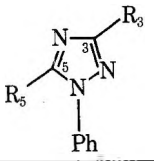
Structural Assignment of 2 and 3. The ^1H NMR, ir, and mass spectra of the isomers **2** and **3**, which were separable by preparative TLC, are consistent with the assigned structures (see Experimental Section). To differentiate between the substitution patterns in the isomeric triazoles,

Table I

		Compd 2		Compd 3	
Ar	X^-	% yield	Mp, °C	% yield	Mp, °C
a *p*-Dimethylaminophenyl	BF_4	94	177–178.5		
b *p*-Methoxyphenyl	Cl	80	144–145.5	12	141–142.5
c Phenyl	BF_4	40	120.5–122.5	18	112–114.5
d *p*-Acetylphenyl	BF_4	28	169–171.5	9	133.5–135.5
e *p*-Nitrophenyl[a]	BF_4				
f 3-Pyridyl	Cl	15	168.5–174[b]	3	127–128
g α-Naphthyl	BF_4	38	147.5–149.5		

[a] No triazole formed; see text and eq 3. [b] Dimorphous.

Table II
^{13}C NMR Data[a] of Triazoles 2c, 3c, and 8



			C_3			C_5		
Compd	R_3	R_5	δ	$^1J_{C-H}$[b]	$^3J_{C-H}$	δ	$^1J_{C-H}$[b]	$^3J_{C-H}$
8	H	H	151.8	208 (d)	12.5 (d)	140.3	212 (d)	7.5 (d)
2c	Tos	H	162.8		12.0 (d)	142.5	216 (d)	
3c	H	Tos	150.0	211 (d)		152.7		8.0 (d)

[a] Chemical shifts δ in parts per million downfield from Me_4Si; coupling constants J in hertz, multiplicity in parentheses. [b] For all other aromatic carbons $^1J_{C-H}$ is 165 ± 5 Hz.

the ^{13}C NMR spectra of **2c** and **3c** are compared with those of 1-phenyl-1,2,4-triazole (**8**, Table II). The ^{13}C NMR spectrum of **8**[12a] has not been reported previously; however, the signals at δ 151.8 and 140.3 can be assigned unambiguously to the heterocyclic ring carbons C_3 and C_5, respectively. This is based on (1) a large $^1J_{C-H}$ (>200 Hz);[13] (2) comparison with other 1-substituted 1,2,4-triazoles where C_3 is found at lower field than C_5.[13] By necessity, the structures of **2c** and **3c** are then as indicated. The tosyl substituent causes a considerable downfield shift (11–13 Hz) of the carbon to which it is attached directly, but it hardly affects the chemical shift of the other ring carbon.

The structural assignment of **2c** and **3c** is further supported by uv. The λ_{max} of **3c** shows a blue shift as compared with **2c**, since the N_1 phenyl (in **3c**) is twisted out of the plane of the triazole ring[14] because of the vicinal tosyl substituent. Also, the ^1H NMR signal of the N_1 phenyl in **3c** is almost a perfect singlet.[15]

Finally, the spectral evidence was corroborated by the following chemical conversions: (1) heating **2c** with a solid mixture of NaOH and KOH gave 3-hydroxy-1-phenyl-1,2,4-triazole (**9**, 37% yield), which was identical with an authentic sample; (2) similarly, **3c** gave in 40% yield the known 1-phenyl-Δ^2-1,2,4-triazolin-5-one (**10**); (3) compound **2c** was prepared recently in our laboratory by an independent route from N^1-phenyl-C-tosylformamidrazone and triethyl orthoformate.[16]

Experimental Section

The diazonium salts were prepared in the usual way.[17] Tosylmethyl isocyanide (TosMIC, **1**) was prepared by dehydration of N-tosylmethylformamide.[18] All compounds **2** and **3** showed the usual ^1H NMR signals for the tosyl protons at δ 2.4 (s, 3) and an AB q (4) at δ 7.3–8.2.

1-*p*-Dimethylaminophenyl-3-tosyl-1,2,4-triazole (2a). A solution of TosMIC (9.75 g, 50.0 mmol) and *p*-dimethylaminobenzenediazonium tetrafluoroborate (23.5 g, 100 mmol) in a mixture of Me_2SO (200 ml), MeOH (160 ml), and H_2O (80 ml) was cooled in ice–salt. To the stirred solution was added in 45 min a solution of K_2CO_3 (10.5 g, 76 mmol) in 100 ml of cold water. After stirring for another 10 min the reaction mixture was poured in 4 l. of ice–water, almost saturated with NaCl. The precipitate was collected, washed with water, and dried. Column chromatography (alumina, CH_2Cl_2–THF, 3:2) gave 16.0 g (94%) of **2a**, mp 172–175°. An analytically pure sample was obtained by preparative TLC (alumina, CH_2Cl_2), followed by crystallization from hot ethanol: mp 177–178.5°; ir (Nujol) 1335 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.44 (s, 1, H_5), 7.56, 7.41, 6.80, 6.66 (q, 4, J = 9 Hz), 3.00 (s, 6); mass spectrum M^+ m/e 342. Anal. Calcd for $C_{17}H_{18}N_4O_2S$: C, 59.63; H, 5.30; N, 16.35; S, 9.37. Found: C, 59.5; H, 5.3; N, 16.5; S, 9.5.

1-*p*-Methoxyphenyl-3-tosyl-1,2,4-triazole (2b) and 1-*p*-Methoxyphenyl-5-tosyl-1,2,4-triazole (3b). To a solution of TosMIC (683 mg, 3.50 mmol) in Me_2SO (11 ml), MeOH (16 ml), and H_2O (2 ml), cooled in ice–salt, was added K_2CO_3 (1.40 g, 10.1 mmol). After stirring for 15 min a diazonium chloride solution, obtained from *p*-methoxyaniline (0.51 g, 4.1 mmol) in 10.6 ml of 1 N HCl and $NaNO_2$ (0.31 g, 4.5 mmol) in 10 ml of water, was added in 30 min. The work-up, analogous to **2a**, resulted in the separation of **2b** and **3b** by preparative TLC on alumina, eluting successively with CH_2Cl_2–Et_2O–pentane (2:2:1) and CH_2Cl_2–Et_2O–MeOH (2:2:0.01 and 1:1:0.01). Compound **2b** was obtained as a pale yellow solid, 920 mg (80%), mp 142–145°. Crystallization from benzene gave an analytically pure sample: mp 144–145.5°; ir (Nujol) 1330 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.49 (s, 1, H_5), 7.68, 7.53, 7.09, 6.93 (q, 4, J = 9 Hz), 3.88 (s, 3); mass spectrum M^+ m/e 329. Anal. Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76; S, 9.74. Found: C, 58.3; H, 4.5; N, 12.7; S, 9.8. Furthermore, 140 mg (12%) of white **3b** was obtained after one crystallization from benzene–pentane, mp 138–140.5°. Another crystallization from benzene–pentane provided an analytically pure sample: mp 141–142.5°; ir (Nujol) 1330, 1160, and 1145 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.04 (s, 1, H_3), 7.58, 7.42, 7.11, 6.95 (q, 4, J = 9 Hz), 3.91 (s, 3); mass spectrum M^+ m/e 329. Anal. Calcd for $C_{16}H_{15}N_3O_3S$: see **2b**. Found: C, 58.4; H, 4.6; N, 12.7; S, 9.8.

1-Phenyl-3-tosyl-1,2,4-triazole (2c) and 1-phenyl-5-tosyl-1,2,4-triazole (3c) were prepared, analogously to **2a**, from TosMIC and benzenediazonium tetrafluoroborate. They were separated similarly to **2b** and **3b** by elution (twice) with CH_2Cl_2–Et_2O–pentane (1:2:2) to give the following. (1) **2c** (40%), mp 121–123° (from benzene–pentane). One more crystallization gave an analytically pure sample: mp 120.5–122.5°; ir (Nujol) 1330 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.58 (s, 1, H_5), 8.11–~7.3 (m, 9); mass spectrum M^+ m/e 299; uv (96% EtOH) λ_{max} 249 nm (log ε 4.32). Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.05; H, 4.38; N, 14.04; S, 10.71. Found: C, 60.1; H, 4.4; N, 14.2; S, 10.6. (2) **3c** (18%) (from MeOH–pentane), mp 119.5–121.5°. Further crystallization from MeOH–pentane and from Et_2O–pentane gave an analytically pure sample: mp 112–114.5°; ir (Nujol) 1325, 1165, and 1145 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.02 (s, 1, H_3), 7.56 (s, 5); mass spectrum M^+ m/e 299; uv (96% EtOH) λ_{max} 241 nm (log ε 4.24). Anal. Calcd for $C_{15}H_{13}N_3O_2S$: see **2c**. Found: C, 60.2; H, 4.4; N, 13.9; S, 10.6.

1-*p*-Acetylphenyl-3-tosyl-1,2,4-triazole (2d) and 1-*p*-acetylphenyl-5-tosyl-1,2,4-triazole (3d) were synthesized analogously to **2a**, from TosMIC and *p*-acetylbenzenediazonium tetrafluoroborate. The precipitate from the aqueous NaCl solution was washed with water, dried, and chromatographed over a column of alumina, containing 5% of activated carbon, using CH_2Cl_2–THF (10:1). The resulting solid was stirred with benzene–THF (2:1) to provide a first crop of near-white **2d**, mp 165–168° (22%). The concentrated mother liquor was chromatographed according to the procedure for **2b** and **3b**, using CH_2Cl_2–benzene (7:3). Obtained were the following. (1) A second crop of **2d**, mp 164–167° (6%, total yield 28%). Crystallization from EtOH and from THF provided an analytical sample: mp 169–171.5°; ir (Nujol) 1680 (C=O), 1335 and 1155 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.80 (s, 1, H_5), 8.22, 8.09, 7.92, 7.78 (q, 4, J = 8 Hz), 2.65 (s, 3); mass spectrum M^+ m/e 341. Anal. Calcd for $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31; S, 9.39. Found: C, 59.8; H, 4.6; N, 12.1; S, 9.4. (2) **3d**, 9% of a brown-white solid, mp 128–132°. Crystallization from EtOH and from Et_2O–THF (2:1) provided an analytically pure sample: mp 133.5–135.5°; ir (Nujol) 1680 (C=O), 1320, 1165, 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.25, 8.11, 7.85, 7.70 (q, 4, J = 8.5 Hz), 8.06 (s, 1, H_3), 2.68 (s, 3); mass spectrum M^+ m/e 341. Anal. Calcd for $C_{17}H_{15}N_3O_3S$: see **2d**. Found: C, 59.8; H, 4.5; N, 12.3; S, 9.4.

1-(3-Pyridyl)-3-tosyl-1,2,4-triazole (2f) and 1-(3-pyridyl)-

5-tosyl-1,2,4-triazole (3f) were prepared analogously to **2b** and **3b** from TosMIC and 3-pyridinediazonium chloride. No precipitate was formed by pouring the reaction mixture in the NaCl solution. Extraction with CH_2Cl_2 gave a black oil from which 20% of TosMIC was recovered by chromatography over a column of alumina with CH_2Cl_2. Continued chromatography with CH_2Cl_2 + 2% of MeOH gave a dark brown solid which was stirred with benzene to yield **2f**, mp 164–168° (11%). The mother liquor was concentrated and separated according to the procedure given for **2b** and **3b**, using CH_2Cl_2–Et_2O (1:1), giving the following. (1) A second crop of **2f**, mp 164–167° (4%, from benzene–pentane); the total yield of **2f** was 15% after correction for recovered TosMIC. Crystallization from EtOH gave an analytical sample: mp 168.5–174° (dimorphous); ir (Nujol) 1330 and 1145 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 9.07–8.97 (m, 1), 8.88–8.75 (m, 1), 8.72 (s, 1, H_5), 8.30–8.10 (m, 1), 7.70–~7.4 (m, 1); mass spectrum M^+ *m/e* 300. Anal. Calcd for $C_{14}H_{12}N_4O_2S$: C, 55.99; H, 4.03; N, 18.65; S, 10.67. Found: C, 55.8; H, 4.1; N, 18.4; S, 10.9. (2) **3f** (3%, based on recovered TosMIC), mp 124–127° (from benzene–pentane). An analytically pure sample was obtained after crystallization from benzene–pentane: mp 127–128°; ir (Nujol) 1340 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.99–8.72 (m, 2), 8.13–7.90 (m + s, 2, H_3), 7.66–~7.4 (m, 1); mass spectrum M^+ *m/e* 300. Anal. Calcd for $C_{14}H_{12}N_4O_2S$: see **2f**. Found: C, 55.8; H, 4.1; N, 18.7; S, 10.5.

1-(α-Naphthyl)-3-tosyl-1,2,4-triazole (2g) was prepared analogously to **2a** from TosMIC and α-naphthalenediazonium tetrafluoroborate. A readily solidifying black oil was obtained, which was chromatographed over a column of alumina (benzene). The resulting brown solid was crystallized from benzene–pentane to give **2g**, mp 144–146.5° (38%). Two more crystallizations from benzene–pentane gave an analytically pure sample: mp 147.5–149.5°; ir (Nujol) 1330 and 1145 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 8.51 (s, 1, H_5), ca. 8.2–7.88 (m, 2), 7.77–~7.5 (m, 5); mass spectrum M^+ *m/e* 349. Anal. Calcd for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.02; S, 9.18. Found: C, 65.0; H, 4.2; N, 12.2; S, 9.2.

***N*-Tosylmethyl-*p*-nitrobenzamide (6)** was prepared analogously to **2a** from TosMIC and *p*-nitrobenzenediazonium tetrafluoroborate. A dark brown solid was obtained, which was washed with CH_2Cl_2 and crystallized from acetone–pentane, yielding 39% of **6**, mp 211–213.5°. Further crystallization gave an analytical sample: mp 206.5–207° (slight dec); ir (Nujol) 1645 (C=O), 1545 and 1345 (NO_2), 1325 and 1130 cm^{-1} (SO_2); ^1H NMR (Me_2SO-d_6) δ ca. 10.0–9.7 (t, br, 1), 8.41, 8.26, 8.04, 7.90 (q, 4, J = 9 Hz), 4.94 (d, br, 2, J = 7 Hz); mass spectrum M^+ *m/e* 334. Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.22; N, 8.38; S, 9.59. Found: C, 53.8; H, 4.4; N, 8.4; S, 9.5. This compound was identical in all respects with a sample prepared independently by the procedure of Olijnsma et al.[19] for *N*-tosylmethylbenzamide; recrystallization of the crude product from acetone gave **6** in 62% yield, mp 203.5–204.5° (slight dec).

3-Hydroxy-1-phenyl-1,2,4-triazole (9). A powdered mixture of 1-phenyl-3-tosyl-1,2,4-triazole (**2c**, 450 mg, 1.51 mmol), NaOH (64 mg, 1.60 mmol), and KOH (136 mg, 2.43 mmol)[20] was heated for 10 min at 160°. The resulting brown solid was dissolved in 10 ml of an aqueous NaCl solution. After extraction with CH_2Cl_2 (10 ml), the solution was acidified to pH 1. The white precipitate was collected and stirred with CH_2Cl_2 (10 ml) to remove *p*-toluenesulfinic acid. The residual solid was collected, washed with water, and dried, yielding **9** (90 mg, 37%), mp 287° (subl). This compound was identical with an authentic sample, prepared by the method of Widman.[12a]

1-Phenyl-Δ²-1,2,4-triazolin-5-one (10) was prepared from **3c** analogously to the synthesis of **9**. The aqueous solution with the reaction product was neutralized with dilute sulfuric acid. Extraction with CH_2Cl_2 gave **10** as a white solid after removal of the solvent in 40% yield, after one recrystallization from Et_2O–pentane, mp 180.5–182.5°. Compound **10** has the same melting point (reported 182–184°,[21] 183–184° [22]) and the same characteristic ir and ^1H NMR data as reported previously.[22]

Registry No.—**1**, 39495-97-1; **2a**, 57428,35-0; **2b**, 57428-36-1; **2c**, 55860-44-1; **2d**, 57428-37-2; **2f**, 57428-38-3; **2g**, 57428-39-4; **3b**, 57428-40-7; **3c**, 57428-41-8; **3d**, 57428-42-9; **3f**, 57428-43-0; **5a**, 24564-52-1; **5b**, 4346-59-2; **5c**, 369-57-3; **5d**, 19262-73-8; **5e**, 456-27-9; **5f**, 35003-14-6; **5g**, 28912-93-8; **6**, 57428-44-1; **8**, 13423-60-4; **9**, 4231-68-9; **10**, 21434-16-2.

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Chemistry of Diaminomaleonitrile. I. Selective Preparations of Monoformyldiaminomaleonitrile and Imidazoles by Reaction with Formic Acid

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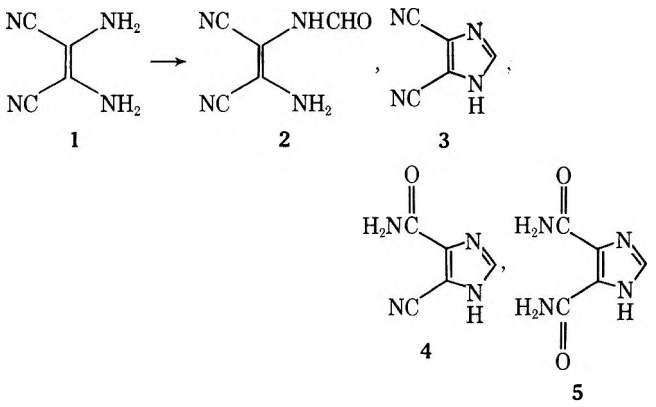
The reaction of diaminomaleonitrile (DAMN) and formic acid depends critically on the conditions under which the experiment is performed. Bredereck and Schmötzer[1] have reported the reaction of DAMN in anhydrous formic acid under mild conditions (<35°C, within 5 min) to give monoformyldiaminomaleonitrile in 50% yield. This reaction is accompanied by formation of tarry materials; an intractable black syrup is obtained after prolonged reaction times or at higher reaction temperatures. On the other hand, heating a heterogeneous mixture consisting of DAMN, formic acid, and xylene gives a fair yield (61%) of 4(5)-cyanoimidazole-5(4)-carboxamide (**4**)[2] with little tar formation.

We have examined the reaction in several solvents and found that monoformyldiaminomaleonitrile (**2**), 4,5-dicya-

noimidazole (3), 4(5)-cyanoimidazole-5(4)-carboxamide (4), and imidazole-4,5-dicarboxamide (5) can each be selectively prepared from DAMN (1) and formic acid by choice of reaction conditions.



Formic acid and 1 can be mixed at room temperature without tar formation as a stirred suspension in an inert medium. On heating the mixture in benzene, a 95% yield of crude 2 was obtained. Cyclohexane, carbon tetrachloride, and petroleum ether (immiscible with formic acid) can be used as the medium to give a similar result. The reaction was greatly retarded and a major part of 1 was recovered when solvents such as ethyl ether, ethanol, and chloroform (miscible with formic acid) were used.

Cyclization of 2 by heating in an inert medium appears to be a slow reaction. For example, refluxing 2 for 3 days in dry xylene with continuous separation of water gave only a 37% yield of 3. The presence of a small amount of water in the medium gave a mixture of 3 and 4. The reaction was facilitated in glycol ethers. Thus, 2 in diglyme gave 3 in 89% yield after 18 hr of refluxing. 3 was also prepared from 1 and formic acid in diglyme in 76% yield after 6 hr of refluxing. Similar results were obtained in diethyl carbitol. In glycol ethers, the presence of a small amount of water did not increase the formation of 4 and solvents can be used without any prior purifications to give a high selectivity for the formation of 3.

A one-step and selective preparation of 4 from 1 and formic acid[2] was reinvestigated at the temperatures between 115 (in toluene) and 170°C (in phenetol). 4 was obtained in 69–77% yield. When these reaction mixtures were heated at around 80°C, 2 was obtained. Refluxing 2 and formic acid in xylene gave a similar yield of 4 to that from 1 and formic acid, but 2 and other acids (*p*-toluenesulfonic acid, propionic acid, and sulfuric acid) gave considerable tar formations with small amounts of 3 and 4.

It was found that 5 was prepared directly either from 2 or from 1 and formic acid by heating in formamide at around 200°C for 1 hr in 65 or 90% yield, respectively. A brief examination using other high boiling point solvents gave unsuccessful results.

The present preparations are simpler and may be more economical than previous preparations of 3,[3,4] 4, and 5,[5] which are important intermediates for the synthesis of 4-amino-5-cyanoimidazole[5,6] or purine derivatives.[4,7] Typical experiments are shown in the Experimental Section.

Experimental Section

All compounds obtained here were identified from elemental analysis, mass spectra, and comparisons of their ir spectra with those of authentic samples prepared by known procedures.

Monoformyldiaminomaleonitrile (2). Anhydrous formic acid (16 ml) was added to a suspension of 1 (10 g) in dry benzene (200 ml). After stirring at room temperature for 30 min, the mixture was refluxed for 15 min. Filtration, washing with ethyl ether, and removal of volatile materials[8] gave brown crystals (12 g, 95% yield), of which the ir spectrum was almost identical with that of an authentic sample of 2.[1] Recrystallization from water gave a pure specimen, mp 182–184°C.[9]

4,5-Dicyanoimidazole (3). Method A. From 1 and Formic Acid. To a solution of 1 (2.8 g) in diglyme (120 ml) was added formic acid (4 ml). The mixture was stirred for 30 min at room temperature and then refluxed for 6 hr. The reaction mixture was evaporated under reduced pressure and the residual solids were dissolved in ethyl ether (150 ml). After separation of undissolved solids (a mixture of 1 and 2 identified from ir) by filtration, the ether solution was concentrated to give 3 (mp 176°C)[4] with 76% yield (2.2 g).[11]

Method B. From 2. 2 (2.0 g) was refluxed in dry diglyme (100 ml) for 18 hr and treated as above to give 89% yield of 3 (1.55 g). A small quantity of 2 was recovered as undissolved dark solids in ether.

4(5)-Cyanoimidazole-5(4)-carboxamide (4). Method A. From 1 and Formic Acid. A mixture of 1 (4 g), formic acid (4 ml), and xylene (150 ml) was stirred for 30 min at room temperature and then refluxed for 6 hr. The resulting dark solids (adhering to the walls of the vessel) were gathered, washed with ethyl ether, and extracted repeatedly with hot water. Concentration of the aqueous solution gave 4[5] (mp 273°C) with 77% yield (3.9 g). From the residue of the extraction, 5 was obtained (2.2%, yield, 0.12 g) by extraction with a larger quantity of water.

Method B. From 2. A mixture of 2 (1.36 g), formic acid (concentration 80%, 1.5 ml) and xylene (120 ml) was treated as in method A to give a 71% yield of 4 (0.97 g).

Imidazole-4,5-dicarboxamide (5). Method A. From 1 and Formic Acid. In an open vessel, 1 (4 g) and formic acid (5 ml, concentration 99%) in formamide (140 ml) were stirred for 30 min at room temperature and then heated at 200°C (bath temperature) for 1 hr. The reaction mixture was allowed to cool and the resulting solid (4.35 g) was separated by filtration. Another crop (1.25 g) was obtained by concentration of the filtrate under reduced pressure. The combined crude product was washed with ethanol and dissolved in hot 10% aqueous sodium carbonate. Charcoal treatment and neutralization with hydrochloric acid gave 5 (mp 300°C)[5] with 91% yield (5.2 g).

Method B. From 2. 2 (1.36 g) was heated at approximately 200°C for 2 hr in formamide (100 ml) as in method A, giving 5 in 65% yield (1.0 g). When 2 in formamide was heated at 180°C for 30 min, 4 was obtained with 42% yield.

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Registry No.—1, 1187-42-4; 2, 53144-01-7; 3, 1122-28-7; 4, 5372-23-6; 5, 83-39-6; formic acid, 64-18-6.

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(9) Aqueous solutions of pure 2 can be stored unchanged for several weeks. During this period aqueous solution of 1 results in the formation of black precipitates. 2 is more soluble in water (1.0% at 25°C) than 1 (0.6%) and the solubility increases in acid (1.5%, in 0.1 *N* HCl) or base (2.7% in 0.1 *N* NaOH, decomposition on standing). With aqueous cupric acetate, mercuric acetate, or silver nitrate, 2 gave insoluble precipitates. 2 is stable to uv light under the conditions where the cis–trans isomerization of 1 takes place.[10]
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Acyl Migration in 2-Hydroxylalkyl Aminimides

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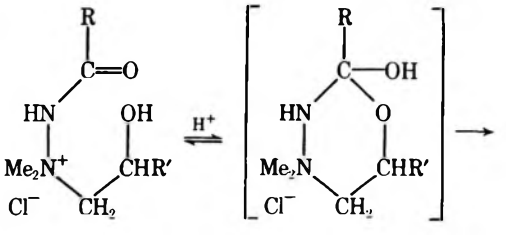
Since the discovery of a convenient and general one-step synthesis of 2-hydroxyalkyl dimethylaminimides $RCON^-N^+Me_2CH_2CH(R')OH$ from carboxylic esters, epoxides, and 1,1-dimethylhydrazine,[1] these compounds have been extensively evaluated.[2] The protonated aminimide of methacrylic acid (1c) was shown[3] to be a much more reactive monomer in radical polymerizations than the unprotonated derivative. Certain anomalies which were noted in the acid properties of this compound and its polymer and copolymers now appear to be the result of a facile, acid-catalyzed acyl migration.



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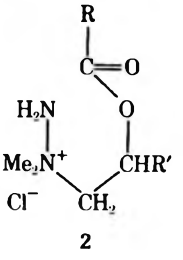

2

1a, R = *p*-tolyl; R′ = H

b, R = *trans*-CH=CH-(fumaroyl bis amide); R′ = CH_3

c, R = $-C(CH_3)CH{=}CH_2$; R′ = CH_3

The rearrangement products from the hydrochlorides of bis[1,1-dimethyl-1-(2-hydroxypropyl)amine]fumaroylbisimide and of 1,1-dimethyl-1-(2-hydroxyethyl)amine-*p*-toluylimide have been isolated and characterized. The assignment of structure 2 to these products was based on the following observations.

(a) The protonated aminimides 1 are acids which can be titrated with aqueous alkali (phenolphthalein) to a sharp end point. In contrast, the rearranged compounds are neutral. Argentometry indicates an unchanged equivalent weight.

(b) The rearranged compounds show a NH_2 band at 1615–1625 cm^{-1}, which is also displayed by trimethylhydrazinium chloride ($Me_3N^+NH_2Cl^-$), but which is absent in the protonated aminimides. The carbonyl band, which for aminimide salts approaches, but does not exceed, 1700 cm^{-1}, is shifted to around 1720 cm^{-1} after rearrangement, which is the range of ester carbonyl absorption.

(c) The relevant NMR signals before and after rearrangement were compared, and the recorded changes were consistent with structure 2.

The acyl migration is clearly acid catalyzed: protonated 1,1-dimethyl-1-(2-hydroxyethyl)amine-*p*-toluimide (1a) was rearranged more than 60% in a methanolic HCl solution at 60° in 3 hr, with negligible reaction in methanol alone after 28 hr. Acyl migration competes successfully with hydrolysis even in strong aqueous acids: the aminimide mentioned above rearranged completely in the course of 3 hr when dissolved in concentrated aqueous HCl; some hydrolysis to toluic acid became evident only after 12 hr. (See Experimental Section.)

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Experimental Section

Dimethylhydrazine was from F. M. C. Corp., propylene oxide from Jefferson, methyl *p*-toluylate from Hercules Inc., and dimethyl maleate from Eastman (Yellow Label). NMR spectra were recorded on a Varian A-60A 60-MHz instrument.

Bis[1,1-dimethyl-1-(2-hydroxypropyl)amine]fumaroylbisimide. Dimethyl maleate (144 g, 1 mol), 135 g (2.25 mol) of 1,1-dimethylhydrazine, 131 g (2.25 mol) of propylene oxide, and 250 ml of 2-propanol were stirred slowly under nitrogen in a 1-l. flask fitted with a thermometer, a dry ice–acetone cooler with a NaOH drying tube, and a nitrogen inlet. The temperature rose spontaneously to 65° in the course of 20 min (vigorous reflux) and was kept between 60 and 65° by intermittent cooling in ice–water. After about 1 hr, the reaction product began to precipitate. The temperature was held at 70° by gentle heating during the following 4 hr. The resulting thin slurry was then cooled to 15° and stirred for 1 hr. The precipitate was collected, washed with 2-propanol and then with acetone, and air dried. Bisaminimide was obtained as a white powder: mp 205–220° dec (239 g, 75% yield); equiv wt 161 (by titration with 0.1 *N* $HClO_4$ in acetic acid, crystal violet as the indicator) (calcd, 158); ir (KBr) 1580 (aminimide carbonyl)[2] and 970 cm^{-1} (trans CH=CH); NMR (D_2O) δ 3.43 [d, 6, $-N(CH_3)_2$], 3.5–4.65 [m, 3, $-N^+(Me)_2CH_2CH(Me)O-$], 6.62 (s, 2, vinylic H). After recrystallization from methanol–2-propanol the product was pure. Anal. Calcd for $C_{14}H_{28}O_4N_4$: C, 53.14; H, 8.92; N, 17.71. Found: C, 53.07; H, 9.09; N, 17.48.

From dimethyl fumarate, the same product is obtained, indicating cis–trans isomerization during the reaction of dimethyl maleate.

Bis[1,1-dimethyl-1-(2-hydroxylpropyl)amine]fumaroylbisimide Hydrochloride (1b). Bis[1,1-dimethyl-1-(2-hydroxypropylamine]fumaroylbisimide (22.1 g, 0.07 mol) was added to 40 ml of methanol containing 5.1 g (0.14 mol) of HCl. The resulting solution was filtered, cooled, and diluted with 400 ml of 2-propanol. After standing for 1 hr, the precipitate was collected, washed with 2-propanol and then with acetone, and air dried. Bishydrochloride was obtained as a white powder (23.1 g): mp 164–166° dec (85% yield); NMR (D_2O) δ 3.79 [d, 6, $-N(CH_3)_2$], 4.0–4.5 [m, 3, $-N^+(Me)_2CH_2CH(Me)O-$], 6.00 (s, 2, vinylic H); equiv wt (0.1 *N* aqueous NaOH, phenolphthalein) 197 (calcd, 194.5). Anal. Calcd: Cl^-, 18.25. Found: Cl^- (Volhard), 18.38. ir (KBr) 1695 cm^{-1} (aminimide salt carbonyl).[2]

Rearrangement. 1b, bis[1,1-dimethyl-1-(2-hydroxypropyl)-amine]fumaroylbisimide (31.6 g, 0.1 mol), was dissolved in 50 ml of methanol containing 11 g (0.3 mol) of HCl, and kept at 65° during 8 hr, with exclusion of moisture. Solvent was then removed by evaporation at 60° (20 mm). The residue, consisting of **2b,** crystallized on addition of 50 ml of 2-propanol. It was recrystallized from methanol–2-propanol, mp 235–245° dec. Anal. Calcd: Cl^-, 18.25. Found: Cl^-, 18.15. Ir (KBr) 1730 (ester carbonyl) and 1625 cm^{-1} ($-NH_2$) ($H_2N-N^+Me_3Cl^-$ has a band at 1630 cm^{-1}); NMR (D_2O) δ 3.48 [d, 6, $-N(CH_3)_2$], 5.4–5.9 [m, 1, $-CH(Me)O-$], 6.99 (s, 2, vinylic H).

1,1-Dimethyl-1(2-hydroxyethyl)amine-*p*-toluimide. A solution of 60 g (1.36 mol) of ethylene oxide in 150 ml of 2-propanol was added to 75 g (1.25 mol) of 1,1-dimethylhydrazine and 150 g (1 mol) of methyl *p*-toluate in 100 ml of 2-propanol, in a reaction vessel as for the preparation of the fumaroyl bisaminimide. The temperature rose slowly to 55° and was kept between 55 and 60° by cooling in ice–water. After 0.5 hr, cooling was interrupted, and the mixture kept at 70° during 4 hr under gentle heating.

Volatiles were removed at 50° (25 mm) and then at 1 mm in a rotatory evaporator. The very viscous, nearly colorless residue was diluted with 700 ml of ethyl acetate, and the mixture kept in ice–water during 2 hr. The precipitate was collected, washed with ice-cold ethyl acetate, and air dried. 1,1-Dimethyl-1-(2-hydroxyethyl)-amine-*p*-toluimide was obtained as a white powder (201 g): mp 123–125° (yield 90%); equiv wt (0.1 *N* $HClO_4$, see above) 224 (calcd, 222); NMR (D_2O) δ 3.46 [s, 6, $-N(CH_3)_2$], 3.6–4.3 [m, 4, $-N(Me)_2CH_2CH_2O-$].

1,1-Dimethyl-1-(2-hydroxyethyl)amine-*p*-toluimide Hydrochloride (1a). Treatment of 44.4 g (0.2 mol) **1a,** suspended in 50

ml of methanol, with a solution of 7.6 g (0.21 mol) of HCl in 25 ml of methanol gave a solution which was concentrated at 30° (20 mm) to a viscous syrup and then treated with 400 ml of ethyl acetate. The precipitate was collected after 2 hr, washed with ethyl acetate, and air dried, giving 50.0 g of the hydrochloride as a white powder (97% yield): mp 154–155° dec; equiv wt (0.1 *N* aqueous NaO, phenolphthalein) 262 (calcd, 258.5); ir (KBr) 1680 cm^{-1} (aminimide salt carbonyl);[2] NMR (D_2O) δ 4.00 [s, 6, $-N(CH_3)_2$], 4.1–4.6 [m, 4, $-N^+(Me)_2CH_2CH_2O-$].

Rearrangement. A solution of 4.44 g (20 mmol) of 1,1-dimethyl-1-(2-hydroxyethyl)amine-*p*-toluimide in 25 ml of ice-cooled 10 *N* aqueous HCl was kept at room temperature during 6 hr. The $-N^+(CH_3)_2$ singlet had by now completely shifted from δ 4.0 to 3.66 (see below). After evaporation in vacuo to dryness at room temperature (0.2 mm), the residue was dissolved in 15 ml of methanol, and the solvent evaporated again. The crystalline residue was recrystallized from 2-propanol–ethyl acetate and dried in vacuo over solid NaOH, giving 3.2 g **2a**, mp 154–156°. Anal. Calcd: Cl^-; 13.71. Found: Cl^-, 13.55. Ir (KBr) 1710 (ester carbonyl) and 1615 cm^{-1} ($-NH_2$); NMR (D_2O) δ 3.73 [s, 6, $-N(CH_3)_2$], 4.1–5.1 [d of m, 4, $-N^+(Me)_2CH_2CH_2O-$].

Kinetics by NMR. 1,1-Dimethyl-1-(2-hydroxyethyl)amine-*p*-toluimide (860 mg, 3.88 mmol) was dissolved under cooling in 5 ml of 10 *N* aqueous HCl, giving a 0.75 *M* solution. The solution was quickly brought to room temperature and was monitored by NMR, using the $-N^+(CH_3)_2$ singlet at δ 4.0 for unrearranged aminimide hydrochloride and at δ 3.66 for the rearranged product. The *p*-$CH_3C_6H_4$ singlet at δ 2.42 is a useful internal standard. Water of the aqueous acid does not interfere, since its signal is offset, and a spectrum can be recorded from 6 ppm upfield.

Acknowledgment. The author is indebted to Dr. P. J. Menardi of the Analytical Department (Ashland) for numerous NMR spectra and their interpretation.

Registry No.—**1a**, 57428-01-0; **1b**, 57428-02-1; **2a**, 57428-03-2; **2b**, 57428-04-3; bis[1,1-dimethyl-1-(2-hydroxypropyl)amine]fumaroylbisimide, 57428-05-4; dimethyl maleate, 624-48-6; 1,1-dimethylhydrazine, 57-14-7; propylene oxide, 75-56-9; dimethyl fumarate, 624-49-7; 1,1-dimethyl-1-(2-hydroxyethyl)amine-*p*-toluylimide, 57428-06-5; ethylene oxide, 75-21-8; methyl *p*-toluate, 99-75-2.

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Preparation and Condensations of 3-Lithiomethylquinoline

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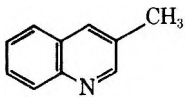
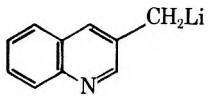
Received August 15, 1975

Though the chemical literature abounds with examples of metalation of 2- and 4-methylquinoline,[1] there appear to be no reports of similar reactions on 3-methylquinoline (I). This is perhaps not surprising when it is considered that, although the α carbanions from the 2- and 4-methyl isomers are stabilized by resonance directly involving the ring nitrogen atom, II from the 3-methyl isomer is incapable of



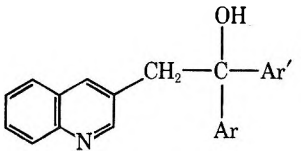
I



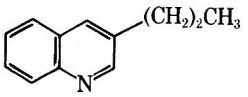
II

such stabilization. Also, the known propensity of quinoline rings unsubstituted at the 2 and/or 4 positions to undergo addition at these positions by bases strong enough to effect metalation[1a] has probably discouraged further investigation.

This note indicates that lateral metalation of 3-methylquinoline (I) to afford II can indeed be effected provided the proper choice of metalating agent is made. Thus, interaction of I with the strongly basic but weakly nucleophilic lithium diisopropylamide (LDIPA) in THF–HMPA at −78° gives a deep red solution which is apparently due to anion II since subsequent treatment with various electrophiles affords 3-substituted quinolines. For example, II and benzophenone afford III (61%). Similarly, the use of 4,4′-dimethylaminobenzophenone, *p*-chlorobenzophenone, and *p*-chlorobenzaldehyde yields IV (57%), V (36%), and VI (32%), respectively. Likewise, treatment of II with chalcone gives the 1,2-addition product VII (12%). Finally, II and ethyl bromide afford the alkylated product VIII (42%).



III, Ar = Ar′ = C_6H_5
IV, Ar = Ar′ = *p*-$(CH_3)_2NC_6H_4$
V, Ar = C_6H_5; Ar′ = *p*-ClC_6H_4
VI, Ar = *p*-ClC_6H_4; Ar′ = H
VII, Ar = C_6H_5; Ar′ = $CH{=}CHC_6H_5$



VIII

No attempt was made to maximize the conversion of I to II. However, a blank run using the mild conditions described (see Experimental Section) followed by the addition of deuterium oxide resulted in a 75% recovery of deuterated I; the remaining 25% of the material consisted of a tar. Likewise no attempt was made to maximize the yields of III–VIII. All the compounds except VIII are new; VIII was previously prepared (15%) by a Skraup synthesis.[2] Clearly, the preparation of this new organometallic derivative will allow facile synthesis of a variety of additional 3-substituted quinolines.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer and nuclear magnetic resonance spectra were obtained at 60 MHz on a Varian A-60 spectrophotometer using tetramethylsilane as an internal standard. 3-Methylquinoline was prepared by the method of Utermohlen.[3] *n*-Butyllithium was purchased from Apache Chemicals, Rockford, Ill. Commercial anhydrous tetrahydrofuran was distilled from solutions containing calcium hydride after preliminary drying over calcium oxide. Commercial anhydrous HMPA was distilled from solutions containing calcium hydride and stored in septum fitted dark bottles under a positive pressure of purified argon.

General Procedure for the Preparation of 3-Substituted Quinolines. To 0.71 g (0.007 mol) of diisopropylamine in 10 ml of THF at 0° under an argon atmosphere was added 4.4 ml (0.007 mol) of 1.6 *M* *n*-butyllithium in hexane followed, after 30 min, by 1.26 g (0.007 mol) of HMPA. Upon cooling to −78° with a dry ice–acetone bath, the solution was treated during 10 min with 1.0 g (0.007 mol) of 3-methylquinoline to afford a red solution which was stirred for 30 min. This solution was then treated during 5 min with 0.007 mol of an electrophile in 10 ml of THF at −78°. After 1 hr at −78°, the reaction mixture was poured into 100 ml of 10% hydrochloric acid, treated with 30 ml of ether, and made basic with potassium hydroxide pellets, and the product was extracted with three 20-ml portions of ethyl ether. The combined extracts were washed with water, dried (calcium chloride), and concentrated. Specific details follow.

A. Benzophenone. This ketone (1.27 g, 0.007 mol) gave a yellow solid which was recrystallized from aqueous ethanol to afford 1.4 g (61%) of 1,1-diphenyl-2-(3-quinolyl)ethanol (III): mp 178–180°; NMR ($CDCl_3$) δ 3.09–3.25 (s, 1, OH), 3.7 (s, 2, CH_2), 7.1–7.68 (m, 14, ArH), 7.75–8.35 (m, 2, ArH); ir (Nujol) 3200 cm^{-1} (OH).

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89. Found: C, 85.00; H, 6.07.

B. 4,4'-Dimethylaminobenzophenone. The use of 2.5 g (0.007 mol) of this ketone gave a white solid which was recrystallized from benzene to yield 2.0 g (57%) of 1,1-bis[4-(dimethylamino)phenyl]-2-(3-quinolyl)ethanol (IV): mp 196–197° dec; NMR ($CDCl_3$) δ 2.95 (s, 12, CH_3), 3.72 (s, 2, CH_2), 6.6–6.92 (m, 4, ArH), 7.2–7.73 (m, 9, ArH), 8.38 (m, 1, ArH); ir (Nujol) 3175 cm^{-1} (OH).

Anal. Calcd for $C_{27}H_{29}N_3O$: C, 78.80; H, 7.10. Found: C, 79.07; H, 7.15.

C. p-Chlorobenzophenone. This ketone (1.5 g, 0.007 mol) gave a yellow solid which was recrystallized from aqueous ethanol to yield 0.8 g (32%) of 1-(4-chlorophenyl)-1-phenyl-2-(3-quinolyl)ethanol (V): mp 192.5–193.5°; NMR ($CDCl_3$) δ 3.5 (s, 1, OH), 3.75 (s, 2, CH_2), 7.1–7.84 (m, 13, ArH), 7.9–8.38 (m, 2, ArH); ir (Nujol) 3100 cm^{-1} (OH).

Anal. Calcd for $C_{23}H_{18}ClNO$: C, 76.75; H, 5.04. Found: C, 76.64; H, 5.12.

D. p-Chlorobenzaldehyde. This aldehyde (0.98 g, 0.007 mol) afforded a yellow gum which was recrystallized from methanol to give 0.7 g (34%) of 1-(4-chlorophenyl)-2-(3-quinolyl)ethanol (VI): mp 170–171.5°; NMR (TFA) δ 3.09–3.34 (d, 2, CH_2), 4.85–5.09 (t, 1, CH), 6.93 (s, 4, ArH), 7.59–7.94 (m, 4, ArH), 8.35–8.7 (s, 2, ArH); ir (Nujol) 3215 cm^{-1} (OH).

E. Chalcone. This ketone (1.5 g, 0.007 mol) gave a yellow gum that was recrystallized from benzene–petroleum ether (bp 30–60°) to afford 0.3 g (12%) of 1,3-diphenyl-3-hydroxy-3-(3-quinolylmethyl)-1-propene (VII): mp 215–216°; NMR (Me_2SO) δ 6.9–7.55 (m, ArH); ir (Nujol) 3500 (OH), 1660 (C=C), 965 cm^{-1} (C=CH).

Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02. Found: C, 85.62; H, 6.21.

F. Ethyl Bromide. This alkyl halide (0.76 g, 0.007 mol) gave 0.5 g (42%) of 3-*n*-propylquinoline (VIII): bp 138–141° (11 mm) [lit.[2] bp 137–140° (11 mm)]; $n^{25}D$ 1.5921; picrate mp 173–174° (lit.[2] picrate mp 174–175°).

Registry No.—I, 612-58-8; II, 57443-81-9; III, 57443-82-0; IV, 57443-83-1; V, 57443-84-2; VI, 57443-85-3; VII, 57443-86-4; VIII, 20668-43-3; VIII picrate, 57443-87-5; LDIPA, 4111-54-0; benzophenone, 119-61-9; 4,4'-dimethylaminobenzophenone, 90-94-8; *p*-chlorobenzophenone, 134-85-0; *p*-chlorobenzaldehyde, 104-88-1; chalcone, 94-41-7; ethyl bromide, 74-96-4.

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Organometallic Chemistry. VIII.[1] Protonated Anisolechromium Tricarbonyl and Its Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study

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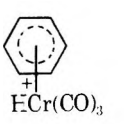
Received August 3, 1975

Arenechromium tricarbonyls undergo hydrogen–deuterium exchange in acid media, and it has been proposed that protonated species are intermediates in the reaction.[3] Protonated arenechromium tricarbonyls were first reported by Davison, McFarland, Pratt, and Wilkinson in 1962.[4] The hydrido hydrogen signals were observed at δ −3.5 to −4.0



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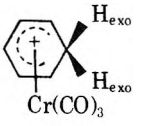


2

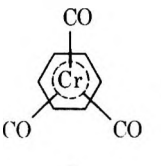
as singlets. Both metal-protonated 1 and ring-protonated 2 structures have been proposed. Based on the width of the hydride hydrogen absorption in comparison with the estimated $J_{exo,endo}$ coupling constants, a recent ^1H NMR study indicated that ring-protonated ion 2 cannot be the major species observed in solution.[5] Chromium protonated structure 1 is also indicated in protonated arenechromium triphenylphosphinedicarbonyls by the splitting of the signal corresponding to the hydrido hydrogen into a doublet due to a coupling with the ^{31}P nucleus.[6] We now report the preparation and carbon-13 NMR study of protonated anisolechromium tricarbonyl. We selected the methoxy substituent to enhance the ring π-donor ability of the system. Data obtained indicate that despite the powerful ring activating substituent the observed long-lived species contains the proton attached exclusively to the metal atom.

Results and Discussion

Anisolechromium tricarbonyl was protonated with FSO_3H in liquid SO_2 at −80° under nitrogen. The carbon-13 NMR spectral data of the protonated species as well of related model compounds are summarized in Table I.

Carbon-13 NMR spectroscopy seems to be a most suitable method for determining the structure of protonated arenechromium tricarbonyls. If protonation occurs on the aromatic ring, the ring carbons should exhibit characteristic shifts similar to areniumiron tricarbonyl cations.[7] The methylene carbon would show pronounced shielding in accordance with the transformation from aromatic sp^2 to aliphatic sp^3 hybridation upon protonation. Furthermore, the methylene carbon should appear as a triplet with J_{C-H} coupling corresponding to the sp^3 hybridization of the carbon. Based on the spectrum shown in Figure 1, the structure of protonated anisolechromium tricarbonyl is not consistent with formation of an arenium ion. If an arenium ion is formed, the C_2 and C_6 carbons should become most deshielded as in the case of the $C_6H_7Fe(CO)_3$ cation (Table I). The chemical shifts of all ring carbons are deshielded by about 8–17 ppm upon protonation, and the pattern of chemical shifts resemble that of the anisolemercurinium ion[14] (Table I), where the aromatic ring is complexed with electron-deficient metal. There is no chemical shift observed corresponding to an aliphatic methylene carbon which would result at the site of protonation due to a change from sp^2 to sp^3 hybridization. There is also no triplet absorption corresponding to a methylene carbon or doublet of doublets corresponding to proton exchange involving ring proton. The increase of J_{C-H} coupling constants of all ring carbons also rules out ring protonation.

The structure of arenechromium tricarbonyls is of considerable interest. Benzenechromium tricarbonyl shows structure 3 with the Cr–CO bonds directed toward the midpoints of the C–C bonds of the ring.[8] Monosubstituted derivatives adopt either an eclipsed configuration 4 or a staggered configuration 5.[9] The temperature dependence of



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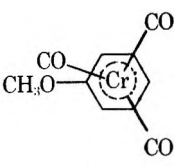

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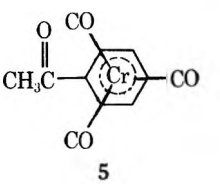

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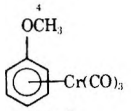
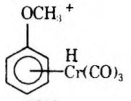
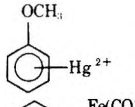
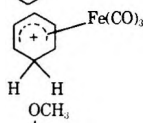
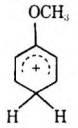
Table I
Carbon-13 NMR Parameters of Protonated Anisolechromium Tricarbonyl and Related Model Compounds[a]

Compd	C_1	C_2, C_6	C_3,C_5	C_4	OCH_3	CO	Ref
	159.47 (s)	113.57 (d, 159)	128.95 (d, 159)	120.22 (d, 162)	55.36 (q, 143)		c
	143.68 (s)	78.68 (d, 173)	95.71 (d, 177)	85.95 (d, 177)	55.67 (q, 145)	233.53 (s)	c
	151.24 (s)	95.69 (d, 183.4)	110.17 (d, 185.7)	100.12 (d, 184.4)	60.86 (q, 152.0)	224.26 (1)[b] (s) 220.42 (2) (s)	
	192.6	118.4	139.0	105.2	57.0		d
	99.43 (d, 179)	102.6 (d, 171)	92.58 (d, 162)	31.09 (t, 132)		208.12 (1)[b] (s) 198.36 (2) (s)	e
	192.9 (s)	122.3 (d) 128.5 (d)	168.7 (d) 175.5 (d)	41.9 (t)	54.4 (q)		f

[a] The spectra were obtained on a Varian XL-100 spectrometer. Chemical shifts in $\delta_{^{13}C}$ (parts per million) are referred to the external capillary. Coupling constants in hertz and the multiplicities are given in parentheses: s = singlet; d = doublet; t = triplet; q = quartet. [b] In a ratio 1:2. [c] G. Bodner and L. J. Todd, *Inorg. Chem.*, 13, 361 (1974). [d] Reference 14. [e] Reference 7a. [f] G. A. Olah and Y. K. Mo, *J. Org. Chem.*, 38 353 (1973).

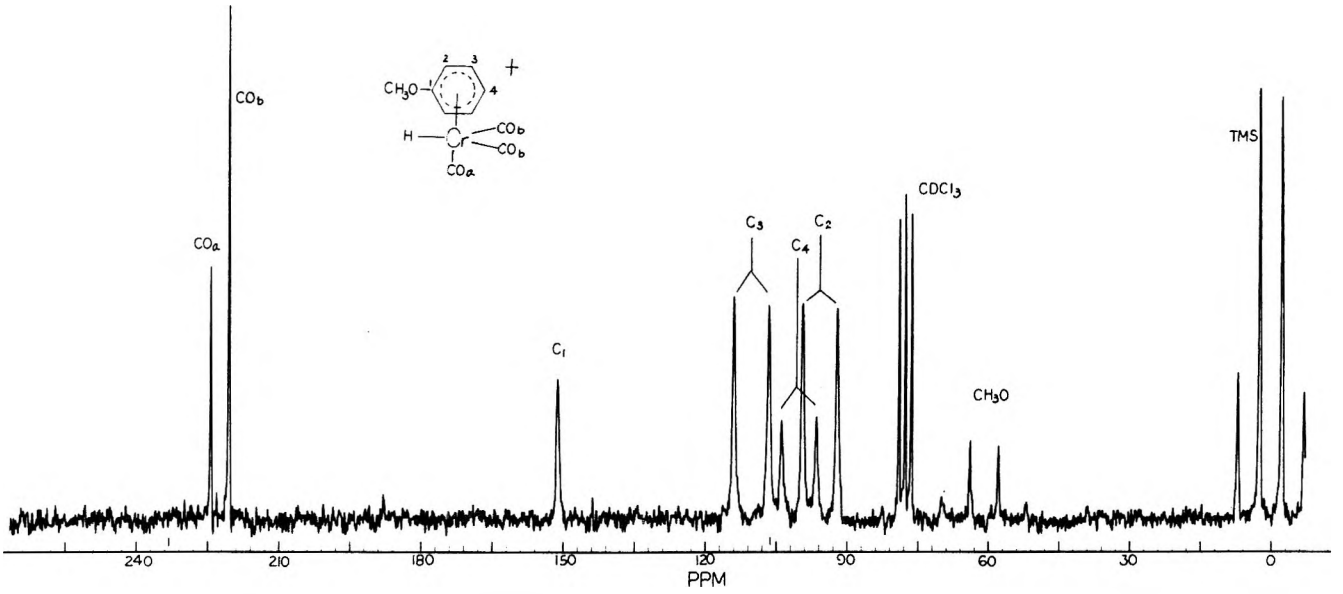


Figure 1. Proton coupled ^{13}C NMR spectrum of protonated anisolechromium tricarbonyl in SO_2 at −70°. (The structure shown is only one of the possible geometrical arrangements.)

the ^1H NMR spectra of arenechromium tricarbonyls has been proposed to be due to conformational equilibria indicating their fluxional nature in solution.[10,11] The rotation of the $Cr(CO)_3$ group relative to the arene ring is considered to be fast on the NMR time scale at all times. On the other hand, the resolution of two carbonyl resonances has been reported for cycloheptatriene–$Cr(CO)_3$ at −60° [12] and for norbornadiene–$Cr(CO)_4$ at room temperature.[13] The present observation of two separate carbonyl resonances in protonated anisolechromium tricarbonyl with a ratio 1:2 indicates a slow exchange process at −70° and at least *Cs* symmetry of the structure (as a consequence of either a conformational arrangement relating to the methoxy group or the arrangement of the carbonyls in the equatorial and axial positions). The deshielding of ring carbons of anisolechromium tricarbonyl upon protonation can also be attributed to the increase of σ forward donation in bonding. The electron density is transmitted to the metal atom via σ forward donation and counterbalances the positive charge on the metal atom. The pertinent increase in shielding of the carbonyl resonances upon protonation is also consistent with the increase of the positive charge on the metal atom and the extent of metal–carbonyl σ forward donation.[15] However, we cannot rule out other factors which might contribute to the change of chemical shifts upon protonation.[16]

Observation of exclusively metal protonated anisolechromium tricarbonyl in FSO_3H–SO_2 solution at −80°, under

so-called long-lived, stable ion conditions, does not necessarily exclude the possibility that in the kinetically controlled initial protonation of anisolechromium tricarbonyl ring (or carbonyl) protonation may compete with metal protonation. The former, however, then would rapidly reverse, whereas the latter would not. Under stable conditions generally the thermodynamically most stable forms are observed, if the energy barrier of interconversion is sufficiently low at the studied temperature.

Experimental Section

Anisolechromium tricarbonyl (Strem Chemical, Inc.) was used without further purification. Protonation was carried out by adding a cold $DCCl_3$ solution of anisolechromium tricarbonyl into excess FSO_3H–SO_2 at −80° under nitrogen, to obtain an about 10% solution of protonated anisolechromium tricarbonyl in FSO_3H–SO_2. Both solutions were purged with nitrogen before mixing. FT carbon-13 spectra were obtained on Varian XL-100 NMR spectrometer using external Me_4Si capillary as reference, under experimental details described previously.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—Protonated anisolechromium tricarbonyl, 57444-58-3.

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Carbon–Carbon Bond Formation via Organometallic Electrochemistry

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The use of electrochemistry for organic and organometallic synthesis is well documented in the literature. However, fewer studies have been conducted in which a deliberate attempt has been exerted to exploit organometallic electrochemistry for organic synthesis or more specifically for the formation of carbon–carbon bonds.[2] Further, published results suggest that transition metals in the lower valent states are probably responsible for promotion and/or catalysis of several organic reactions.[3] As a result of these two ideas, we have embarked on an investigation of the formation of carbon–carbon bonds from the electrochemical reduction of readily available transition metal complexes in the presence of organic substrates. In this paper we wish to report our preliminary results and emphasize the macroscale synthetic utility of this technique for organic chemistry.

Although there are several stable low-valent transition metal complexes such as the metal carbonyls, π-allylnickel,[4] and bis(cyclooctadienyl)nickel[5] which are isolable and have been used for organic synthesis, they have some disadvantages. For example, they are often sensitive to air, may require reasonably sophisticated techniques to incorporate them into reaction mixtures, and may be useful only in stoichiometric amounts owing to catalyst inactivation through reaction. This reported work emphasizes an approach which generates active but nonisolable catalysts and offers some advantages over the previously mentioned complexes. For example, the acetylacetonate complexes of many transition metals are soluble in organic solvents, easily prepared,[6] have reasonable air and thermal stability, and are convenient to incorporate into a reaction medium. Another potential advantage offered by the electrochemical system for generating chemically active metal complexes is the continuous recycling of the catalyst in the event it is inactivated by oxidation. Thus, the need for stoichiometric quantities of metal complex may be alleviated. One of the limitations of this technique is that one must choose the proper metal and substrate such that the reduction potentials allow for electrochemical reduction of the desired chemical components.

Description of Electrochemical Cell and Reaction Components. Several organic halides are presently under investigation, but this article shall deal only with aliphatic, benzylic, and aromatic halides. Data resulting from these substrates are shown in Tables I, II, and III.

Nickel and iron acetylacetonate were chosen as the starting metal complex because (a) they both have reported reduction potentials below the potentials of the substrate halides; and (b) they have isolable (Ni) and nonisolable (Fe) low-valent metal complexes which could be helpful later in the detailed investigations. There have only been a few σ-bonded aliphatic iron complexes isolated.[7] Since the metal complexes are being reduced to lower oxidation states, substances such as triphenylphosphine (Ph_3P), which are referred to in this paper as stabilizing ligands, were added to (a) modify the activity and (b) perhaps aid in the solubility of the reduced metal. In reactions run without Ph_3P, the solution becomes cloudy and the cathode develops a coating. However, neither of these two conditions appeared to adversely affect the product yields or distribution (Table II).

A diagram of the electrochemical cell used in this study is shown in Figure 1. Electrodes were made from sheet metal (Al, Cu, or Ni) which was cut to the dimensions of 45 × 45 × 0.90 mm and cleaned thoroughly just prior to use. In the cell these plates were placed parallel to one another with a 6–8-mm space between them. A potential was applied across the electrodes by a constant voltage power supply, which was automaatically regulated such that the potential on the cathode relative to SCE was more cathodic than the reduction potential of the metal complex [Fe(acac)$_3$[2] −0.82 V vs. SCE in THF; Ni(acac)$_2$[2] −1.5 V vs. SCE in DMF] and less cathodic than the reported substrate reduction potentials (aliphatic bromides[8] −2.2 V vs. SCE in DMF; bromobenzene[8] −2.3 V vs. SCE in DMF; benzyl bromide[8,9] −1.22 V vs. SCE in DMF). The standard calomel electrode was periodically inserted directly behind the cathode during the reaction to obtain an approximate

Table I
Aliphatic Bromides

Registry no.	Substrate	Metal acetyl-acetonate	Electrode[a]	Stabilizing ligand	Product	% yield[b]
109-65-9	1-Bromobutane[c]	Fe	Ni/Ni	Ph_3P	Octane	28
78-76-2	2-Bromobutane[c]	Fe	Ni/Ni	Ph_3P	3,4-Dimethyl-hexane	20
507-36-8	2-Bromo-2-methyl-butane[c]	Fe	Ni/Ni	Ph_3P	No coupled product	
111-83-1	1-Octyl bromide	Fe	Al/Al	Ph_3P	Hexadecane Octene Octane	72.3
	1-Octyl bromide	Fe	Al/Al		Hexadecane Octene Octane	93.9

[a] Cathode/anode. [b] Yield is based on GLC data gathered on starting halide and the total products. [c] Products other than coupled were not investigated.

check of its potential. Since this is not an ideal method for controlling the cell potential, and since organic halides are known to react by reduction[8] directly in electrochemical cells without metal complexes present, control reactions were run at the same applied potential without the metal complex present in the reaction medium. In all control experiments, only minimal current developed or flowed (<2 mA) and at best only trace amounts of products formed

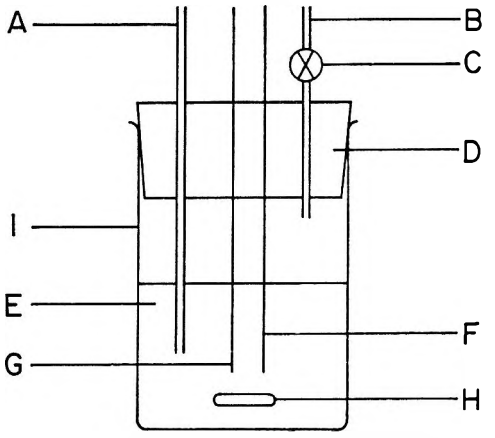

Figure 1. Electrolysis cell: (A) nitrogen inlet for purging the solution and maintaining a positive pressure; (B) gas outlet which is open during purging and closed during electrolysis; (C) stopcock for closing gas outlet; (D) rubber stopper; (E) electrolysis solution; (F) cathode; (G) anode; (H) magnetic stirring bar; (I) 100-ml Berzelius beaker.

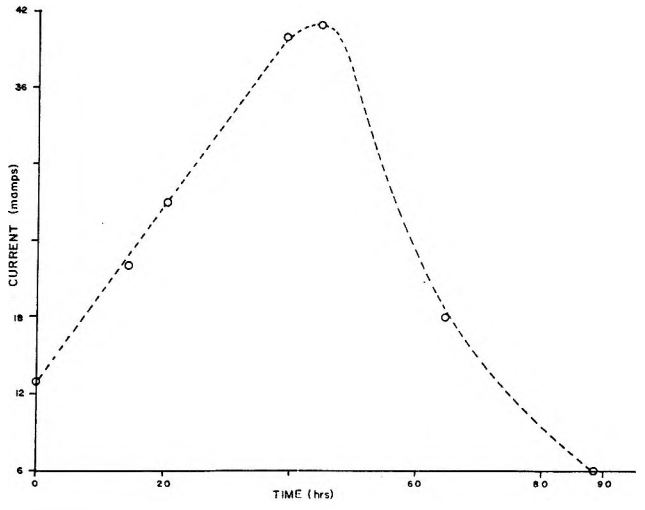

Figure 2.

Table II
Product Ratios and the Effect of Ph_3P

	Experiments	
	A	B
Catalysts	$Fe(acac)_3$	$Fe(acac)_3$
Octane, %	11.08	49.21
Octene, %	3.22	17.70
Hexadecane, %	32.26	30.71
Ane/ene	3.44	2.81
% reaction	72.3	93.9
Ligand	$+Ph_3P$	$-Ph_3P$
Electrodes	Al/Al	Al/Al

from 200 hr of electrolysis. In contrast, in a typical electrolysis experiment with metal acetylacetonate present, currents as high as 40–60 mA were observed with product formation completed after 50–90 hr. A typical current profile for the reaction of $Fe(acac)_3$ and 1-octyl bromide is shown in Figure 2.[10] This curve provides a useful measure of the reaction end point. For example, at 50 hr of electrolysis there was only 10% of the starting halide remaining in the reaction medium and by 70 hr there was only 3% of the starting material remaining.

Results and Discussion

From the fact that little or no product formed in absence of metal acetylacetonate, it is reasonable to conclude that direct electrolysis of the organic halides used in these studies at an applied potential of 1.3–1.8 V is negligible. Thus, it is then reasonable to suggest that the metal is being reduced first to a lower valent metal complex which then interacts with the organic halide substrate. Although somewhat indirect, the fact that metal carbonyls were generated when carbon monoxide is bubbled into the reaction medium during electrolysis strongly supports the assumption that the metal is reduced. Further, if octyl bromide is reduced in the system described in this note at an applied voltage of 2.0 V, only octane is obtained which obviously is a different product distribution than observed with metal complex present. It is also assumed without direct evidence, but with considerable literature precedence,[11] that interactions between the alkyl halide and reduced metal result in σ-bonded alkyl transition metal complex which decomposes by various pathways to products (vide infra).[12] By using a divided cell, it was ascertained that the reaction occurred only in the cathode compartment and that the anolytes are not needed for organic product formation. The anode dissolves presumably forming metallic halides or acetylacetonates which are complexed with the solvent dimethylformamide (DMF).[13]

Data in Table I show the overall yields and products

Table III

Registry no.	Substrate	Metal acetyl-acetonate	Electrode[a]	Stabilizing ligand	Product	% yield[b]
100-44-7	$PhCH_2Cl$	Ni	Cu/Ni	Ph_3P	Bibenzyl	87
100-39-0	$PhCH_2Br$	Ni	Cu/Ni	Ph_3P	Bibenzyl	85
108-86-1	PhBr	Ni	Cu/Ni	Ph_3P	Biphenyl	65

[a,b] See Table I.

using aliphatic bromides as substrates. It is apparent from these data that the butyl bromide isomers which are branched at the α carbon give lower amounts of coupled products than those that are not branched. This can be rationalized from at least two points of view. The first and most obvious rationale would be that the increased steric bulk lowers the yield of coupled product. A second explanation, which is probably complimenting the first explanation, is that more hydrogens located on the β carbons are present in tertiary butyl bromide than secondary or primary butyl bromides which may provide opportunity for additional reaction pathways to operate. The latter explanation is reasonable since σ-bonded aliphatic transition metal complexes are known to undergo a facile β-elimination of metal hydride.[12] Also from Table I, it can be seen that the overall yield from octyl bromide reactions is a function of the triphenylphosphine. The nature of this change in yield can readily be seen in Table II, which shows that in the absence of Ph_3P, both alkene and alkane production has increased. The origin of this effect will be the subject of a future publication.

Mechanistic Interpretation. At first, inspection of the data in Table II suggests that this reaction involves a free-radical mechanism which is consistent with other investigations. For example, Saito[14] had previously suggested that $Et_2Ni(bipy)$ decomposed from thermal conditions by a free-radical process to give butane, ethane, and ethene. Further, the product analyses of experiment A agreed quite well with results published by Kochi[15] on diacyl peroxide photodecomposition. For example, in the photodecomposition of di-*n*-butyl acyl peroxide, Kochi reports alkane:alkene:coupled product ratios of 0.09:0.03:0.38 in pentane solvent. The product ratios from experiment A are 0.11:0.03:0.32. However, in experiment B, which is comparable to A except that Ph_3P is absent, the relative product yields for alkane and alkene are significantly altered and more closely agree with Kochi's results in which the diacyl peroxide was decomposed in a more viscous solvent, decalin. Since the viscosity of DMF is not appreciably altered by either the presence or absence of Ph_3P, it is not readily apparent that free-radical processes are active in our electrolysis system. However, in experiments using cumene as a free-radical trapping reagent, the yield of coupled product was reduced. For example, a 32% reduction in the yield of coupled product was observed when a 1:1 mole ratio of cumene to 1-octyl bromide was used, a 45% reduction was observed from a reaction in which the mole ratio was 4.9:1, and a 60% reduction in coupled product yield resulted in a reaction having a 10:1 mole ratio. The dilution effect resulting from added cumene is accounted for in the above percentages.[16]

Thus it appears that the formation of coupled product occurs via free-radical processes, while the alkane–alkene product forming portion of the reaction is probably not occurring by free-radical processes. These latter results suggesting a non-free-radical pathway are consistent with observations made by both Whitesides[17] and Schwartz.[18] Whitesides has shown that di-*n*-butylbis(triphenylphosphine)platinum(II) does not decompose thermally by a free-radical process to produce butene and butane. Likewise, Schwartz has made the same observation using bis(triphenylphosphine)(carbonyl)-1-octyliridium(I) in which octane and octene are produced.

Other Substrates. In another series of experiments on different substrates designed to explore the useful breadth of this electrochemical technique, both benzylic and aromatic halides were briefly investigated (Table III).

One can readily see that the yields of coupled products from these substrates are improved over those of the aliphatic halides. While there may be some beneficial electronic factor inherently associated with the presence of the phenyl ring, we feel that one significant reason for the increased yields for the substrates listed in Table III is the lack of opportunity for alternative pathways of decomposition such as β-elimination.

Summary. This work has shown that readily available transition metal complexes such as $Ni(acac)_2$ and $Fe(acac)_3$ can be induced to react in an electrochemical system with alkyl halides to produce carbon–carbon bonds (coupled products). Presumably, low-valent metal complexes are prepared which react with alkyl halides to form σ-bonded alkyl transition metal intermediates which decompose by known pathways. The coupled products appear to arise from a free-radical pathway while the "disproportionation" products alkane and alkene may not be produced by a free-radical pathway. Organic halides having hydrogens on the carbon β to the halide atom tend to yield alkenes and alkanes in addition to coupled products.

Experimental Section

General. A Heathkit Regulated L.V. Power Supply Model IP-27 was used as a constant applied potential source for the electrochemistry. Reaction products and starting materials were analyzed via a Varian Aerograph Model 1740 gas chromatograph which was equipped with temperature program, flame detector, and a Varian CH-5 mass spectrometer. Peak areas of gas chromatographed samples were analyzed by mechanical integration which was referenced to hexane as an internal standard, and by mass spectral fragmentation patterns.

Dimethylformamide (DMF) was purchased from Baker Chemical Co. and purified by vacuum distillation at 0.50 mm and 30°C. It was stored under dried N_2 and over molecular sieves. All other reagents were purified by standard procedures. All materials used in the reaction were rigorously dried prior to electrolysis.

Tetraethylammonium Bromide (TEAB). An equal molar (1.5 *M*) mixture of triethylamine and ethyl bromide was refluxed for 24 hr. The ammonium salt which precipitated was filtered, washed with toluene, and recrystallized from a benzene–ethanol mixture. The resulting crystals were dried in a vacuum at 80°C and stored in a desiccator.

$Ni(acac)_2$ was prepared by adding an ammoniacal solution containing $NiCl_2$ (32.4 g, 0.25 mol), 150 ml of concentrated ammonia solution, and just enough H_2O to effect solution to another ammoniacal solution containing acetylacetone (55 ml, 0.535 mol) and concentrated ammonia (40 ml, 0.60 mol). The resulting thick blue mixture was vigorously stirred for 30 min, filtered, and air dried to give the diamine derivative of $Ni(acac)_2$. This derivative was boiled in toluene or, better, xylene to give the dark green solution of $Ni(acac)_2$. Hexane was added to precipitate $Ni(acac)_2$ which was filtered, washed with hexane, vacuum dried, and stored in a desiccator. An 80% yield of $Ni(acac)_2$ was obtained with mp 152–154°C.

$Fe(acac)_3$ was prepared by mixing stoichiometric amounts of

$FeCl_3$ and sodium acetylacetonate in a aqueous solution. The dark red product was extracted with $HCCl_3$. The extract was washed with H_2O three times and the solvent evaporated. The solid was then recrystallized from ethanol–water mixture which was vacuum dried. A 77% yield of $Fe(acac)_3$, mp 184°C dec, was obtained.

Electrodes. The nickel and copper electrodes were cleaned by thoroughly scouring them with steel wool and placing them in a solution of DMF and TEAB in which a potential of 5–10 V was applied across the electrodes for ≤1 min. After this procedure they were immediately transferred to the reaction flask. While all reactions followed a curve similar to that shown in Figure 2. cleaning the electrodes resulted in higher initial currents. Generally, currents ranged from 10 mA (initial) to as high as 80 mA (maximum) during the reaction.

The aluminum electrodes have, in more recent experiments, been cleaned by placing them in 3 *M* HCl for 15 min and rinsing thoroughly with H_2O and dried by rinsing them in organic solvents.

The standard calomel electrode which was periodically inserted into the reaction (≈1 min) to monitor the working electrode voltage probably led to some contamination by water. However, it did not affect product formation.

Since the anode dissolved during the reaction, current density measurements were not made. Likewise, electrochemical yields were not determined.

Electrolysis Reaction. In a typical reaction, to 60 ml of DMF in a 100-ml Berzelius beaker were added $Fe(acac)_3$ (4.4 g, 12.46 mmol), triphenylphosphine (1.5 g, 5.66 mmol), $Et_4N^+Br^-$ (0.802 g, 3.81 mmol), and 1-octyl bromide (8.6 ml, 49.78 mmol). A rubber stopper fitted with cleaned aluminum electrodes was used to seal the beaker. Nitrogen was bubbled through the stirred solution until solutes dissolved. An applied potential of 1.5 V was established and held until the current profile, as indicated in Figure 2, was completed.

Octane and octene were removed from the electrolyzed solution by vacuum distillation and analyzed by gas chromatography. An 8-ft column packed with 20% Carbowax 20M on 80–100 mesh Chromosorb W was used to separate octane from octene and a 6-ft column of 3% SE-30 80–100 mesh Chromosorb W was used to separate 1-octyl bromide from DMF.

The pot residue was treated with 100 ml of distilled H_2O and extracted with five 50-ml aliquots of ether. This ether solution was dried over anhydrous magnesium sulfate, filtered, and evaporated by rotoevaporator. Liquid chromatography on a 46 × 2 cm column of activated acidic aluminum oxide eluted with hexane was used to separate hexadecane and unreacted 1-octyl bromide from other residues contained in the ether extract. After solvent evaporation on a rotoevaporator, these products were analyzed by GLC on the same columns mentioned above.

The precent yields were based on the amount of 1-octyl bromide which had reacted and are reported in the text. The percent conversion (amount of product divided by amount of 1-octyl bromide) ranged from 70 to 98. The important factor in the percent conversion number is the concentration of starting halide or, more directly, the concentration of products. If the product concentration was too high, it began to oil out on the top of the DMF solution. This oil layer would then attract the 1-octyl bromide thereby reducing reactant in the bulk electrolysis solution. Thus it is essential for highest conversion to maintain a homogeneous solution.

Benzyl and Aryl Halides. While the general procedure for electrolysis with these substrates was identical with that described for the 1-octyl bromide, the work-up was slightly different. There was no vacuum distillation. The raw electrolysis mixture was diluted with 100 ml of water and extracted with five 50-ml aliquots of ether. The ether extract was dried, filtered, and reduced in volume by rotoevaporation. This material was then passed through an alumina column using hexane as the eluting solvent. The coupled products, bibenzyl or biphenyl, were thence isolated, sublimed, and weighed.

Divided Cell. An H cell design was used with a salt bridge mixture containing methyl cellulose (10.23 g), DMF (80 ml), and TEAB (4.4 g). Each half of the cell contained 60 ml of DMF, 0.8 g of TEAB, 1.50 g of Ph_3P, and 8.6 ml of 1-octyl bromide. The cathode compartment contained 4.4 g of $Fe(acac)_3$. After 366 hr, at an applied potential of 1.5 V and low currents (as expected), the reaction was stopped. Also the red color, due to $Fe(acac)_3$ diffusion, was hallfway across the salt bridge.

Although the yield was low owing to low currents, octane, octene, and hexadecane were isolated from the cathode compartment and analyzed by gas chromatography.

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Registry No.—$Fe(acac)_3$, 14024-18-1; $Ni(acac)_2$, 3264-82-2; $NiCl_2$, 7718-54-9; $FeCl_3$, 7705-08-0; acetylacetone, 123-54-6; sodium acetylacetonate, 15435-71-9.

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(10) It is not known why this curve is "bell" shaped at this time. However, it is felt that the initial rise in current flow could be due to (a) increased surface area on the electrodes owing to pitting and (b) also possibly from a drop in the cell resistance owing to an increase in ionic substances in solution. The latter part of the curve is more typical and is a function of $time^{-1}$.
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A New Stereospecific Synthesis of the *E* Isomers of 2-Phenyl-4-arylmethylene-2-oxazolin-5-ones*

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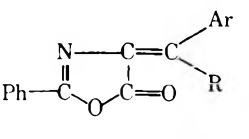
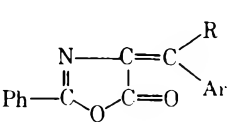
The Erlenmeyer azlactone synthesis,[1] a well-known reaction that is widely employed for the preparation of 2-aryl- (or alkyl-) 4-arylmethylene-2-oxazolin-5-ones, consists of heating aromatic aldehydes with hippuric or aceturic acids in the presence of acetic anhydride and sodium acetate and usually gives the thermodynamically stable isomers 1 (R = H).



1

(*Z*)



2

(*E*)

* Reactions in Polyphosphoric Acid. I.

Table I
Azlactones 2

Compd	R	Ar	Mp, °C	% yield	$\nu_{C=O}$ ($CHCl_3$)	τ ($CDCl_3$)	Formula	Anal., % Calcd C	Calcd H	Found C	Found H
2	H	C_6H_5	146–147	90[a]	1780	1.87 (m) 2.4–2.8 (m)					
5	H	4-ClC_6H_4	185	85	1790	1.65 (m) 2.4 (m)	$C_{16}H_{10}ClNO_2$	67.9	3.51	67.72	3.49
6	H	4-$CH_3OC_6H_4$	132	90	1780	1.7 (m) 2.4–2.8 (m) 6.1 (s)	$C_{17}H_{13}NO_3$	73.1	4.66	73.0	4.62
7	H	4-$CH_3C_6H_4$	117	80	1760	1.9 (m) 2.5–2.8 (m) 7.65 (s)	$C_{17}H_{13}NO_2$	77.5	4.95	77.2	4.9
8	H	3,4-$(MeO)_2C_6H_3$	141	82[a]	1775						
9	H	4-HOC_6H_4	109	80	1780		$C_{16}H_{11}NO_3$	72.5	4.15	72.3	4.1
10	H	2-HOC_6H_4	163	70	1720		$C_{16}H_{11}NO_3$	72.5	4.15	72.29	4.17
11	CH_3	C_6H_5	183	80	1770	1.87 (m) 2.4–2.8 (m) 7.4 (s)	$C_{17}H_{13}NO_2$	77.5	4.95	77.7	4.92
12	CH_3	4-ClC_6H_4	185	52	1780		$C_{17}H_{12}ClNO_2$	68.5	4.03	68.7	4.1
13	CH_3	4-$MeOC_6H_4$	169	50	1775	2.0 (m) 2.5–2.9 (m) 6.2 (m), 7.3 (s)	$C_{18}H_{15}NO_3$	73.7	5.09	73.8	5.1
14	CH_3	4-$O_2NC_6H_4$	180	88	1780		$C_{17}H_{12}N_2O_4$	66.4	3.9	66.5	3.87
15	CH_3	4-$CH_3C_6H_4$	160	70	1770	2.0 (m) 2.5–3.0 (m) 7.3 (s), 7.6 (s)	$C_{18}H_{15}NO_2$	78.0	5.4	78.2	5.3
16	H	4-$O_2NC_6H_4$	245	100	1795		$C_{16}H_{10}N_2O_4$	65.4	3.4	65.2	3.5
17	H	2,4-$Cl_2C_6H_3$	183	100	1790		$C_{16}H_9Cl_2NO_2$	60.2	2.82	60.3	2.79
18	H	2,6-$(MeO)_2C_6H_3$	168	100[a]	1780						
19	H	1-$C_{10}H_7$	160	100[a]	1775						
20	H	2-$CH_3OC_6H_4$	154	100[a]	1785						

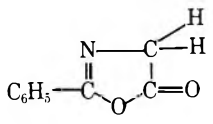
[a] Known compounds.

Although the existence of geometric isomers of azlactones with an exocyclic double bond in the 4 position had been predicted, it was through the pioneering work of Carter and co-workers[2] that the stable and labile isomers of 2-phenyl-4-ethylidene- and 2-phenyl-4-phenylmethylene-2-oxazolin-5-ones were prepared and characterized. Originally the Plöchl–Erlenmeyer azlactone,[3] **1** (Ar = Ph; R = H), had been assigned the *E* configuration[4] but recently it has been shown to have the *Z* configuration instead.[5] It is now generally accepted that *Z* isomers are obtained in Erlenmeyer synthesis.[4a] In a few cases the Erlenmeyer method does give a mixture of isomers,[6] which are separated by fractional crystallization. Niemann and co-workers[7] reported that the condensation of benzaldehyde with hippuric acid in 100% concentrated sulfuric acid gave a mixture of **1** and **2** (Ar = Ph; R = H) but the isomers could not be separated. In general, the *E* isomers **2** (R = H) are prepared by special methods,[2] by isomerization of the *Z* isomers in saturated hydrobromic acid,[4c,5c,8] by photochemical isomerization,[9] or from 2-phenyloxazolinonium perchlorate.[10] Of these, the hydrobromic acid method has been employed in the isomerization of a few azlactones [**1**, R = H; Ar = 1-$C_{10}H_7$, C_6H_5, 2-$CH_3OC_6H_4$, 2,6-$(CH_3O)_2C_6H_3$, 3,4-$(CH_3O)_2C_6H_3$] and has not worked in the case of others.[11] The photoisomerization method gives about 18% yield of the desired isomer. The perchlorate method of Boyd[10] was the first reported stereospecific synthesis of **2** (Ar = Ph; R = H) but the yield of **2** was low and the general applicability of the method has not been demonstrated.

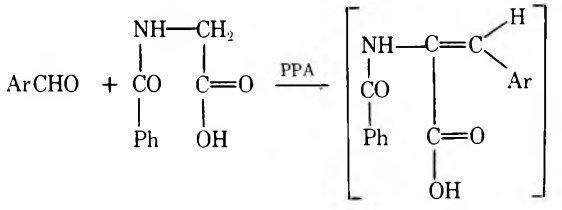
We now report here a new and simple method for the direct synthesis of the *E* isomers of azlactones. Aromatic aldehydes condense with hippuric acid when heated in polyphosphoric acid (PPA) at 80–100° to give 80–90% yields of **2**. One may alter this method by using the expedient of heating the stable isomers in polyphosphoric acid medium to get the same products (Table I). Polyphosphoric acid has been employed in a series of cyclodehydration reactions but not as a medium for the synthesis of azlactones from aldehydes and hippuric acid.[12] However, Kaneko and co-workers[12d] isomerized the azlactone of indole-3-aldehyde in PPA. By the PPA method, we have been able to synthesize some previously known *E* azlactones (**2**, R = H) and also some *E* isomers which had not previously been obtained. Salicylaldehyde and 4-hydroxybenzaldehyde, both of which give 4-(acetoxyphenyl)methylene oxazolones under Erlenmeyer conditions, condense with hippuric acid in PPA to give the corresponding hydroxy derivatives, **2** (Ar = 2-HOC_6H_4, 4-HOC_6H_4; R = H).[13] It is well known that ketones such as acetone, cyclohexanone, and fluorenone condense with hippuric acid to give the corresponding oxazolones.[14] Although Lure and co-workers[15] reported that 3- and 4-nitroacetophenononones condense with hippuric acid in the presence of anhydrous potassium carbonate to give α-arylethylidene azlactones in 13–28% yields, acetophenone and substituted acetophenones do not condense with hippuric acid. In PPA medium, these compounds react with hippuric acid to give α-arylethylidene azlactones **2** (R = CH_3) in good yields. Benzophenone does not, however, react under these conditions. The configuration of α-arylethylidene azlactones is tentatively assumed to be *E* at the present time, since our compounds differ in melting points from those prepared by Bernabe and co-workers[16a] by the C-alkylation of **1** (R = H) with diazomethane, products to which Burger and Pages[16b,c] assigned the *Z* structure. The configurations of the oxazolinones **2** (R = H), prepared by the PPA method, are shown to be *E* by spectral data and their ready conversion to the stable isomers by treatment with pyridine[2] or by melting and recrystalli-

zation of the molten products. In NMR spectra of these compounds, the ethylenic proton is masked by aromatic protons, whereas in the NMR spectra of the corresponding *Z* isomers, this proton appears as a singlet at τ 2.7–2.8.[5a,c,d,16d,18] These compounds show carbonyl absorption around 1770–1790 cm^{-1}.

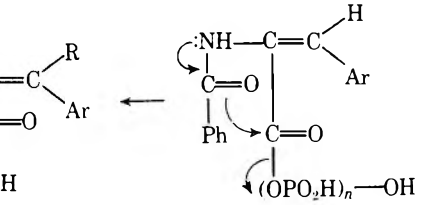
It is generally accepted that 2-phenyl-2-oxazolin-5-one (**3**) is an intermediate in the Erlenmeyer reaction[1c-e,17] and that **3** condenses with aldehydes to give **1**. It may be pointed out that hippuric acid is not converted to **3** in PPA but both the isomers of 2-benzamidocinnamic acids,[2c,5e,19] **4a** and **4b**, both of which are obtained by the alkaline hydrolysis of **1** and **2** (R = H; Ar = C_6H_5), respectively, and are hence assumed to have configurational identities, are converted to **2** (R = H; Ar = Ph) in PPA. Thus it is likely that aldehydes condense with hippuric acid in PPA to give **4b** which then cyclizes to give **2**. The following mechanism is suggested for the azlactone formation.



3



4b, Ar = C_6H_5



2, R = H

Other condensation reactions in PPA are currently under study and will be reported later.

Experimental Section

Melting points were determined on a Fisher-Johns block and are reported uncorrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer in $CHCl_3$ or CCl_4 solutions. NMR spectra were determined on a Varian A-60 instrument with tetramethylsilane as the internal standard with $CDCl_3$ as the solvent.

2-Phenyl-4-phenylmethylene-2-oxazolin-5-one (**2**). To a sample of polyphosphoric acid,[20] prepared from phosphoric acid (20 ml, d^{20} 1.7) and phosphoric anhydride (32 g), was added benzaldehyde (5.3 g, 50 mmol) and hippuric acid (8.95 g, 50 mmol). The mixture was then heated on a steam bath (80–95°) for 90 min and was then poured into water. The resultant solid product was collected and repeatedly washed with water. The oxazolone was recrystallized from a mixture of benzene–Skellysolve B: mp 146–147° (12.0 g, 90% yield); ir $\nu_{C=O}$ ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) τ 1.87 (4 ortho H), 2.4–2.8 (7 H).

Compounds **5–15** (Table I) were prepared by the condensation of the appropriate carbonyl compounds with hippuric acid in PPA.

Isomerization of 2-Phenyl-4-phenylmethylene-2-oxazolin-5-one (**1**). To a sample of **1** (Ar = Ph; R = H; 5 g) was added polyphosphoric acid (50 g). The mixture was heated on a steam bath for 90 min. The product was isolated as above, mp 146–147° (5.0 g). A mixture melting point with the above sample showed no depression.

Compounds **2**, **5–8**, and **16–20** were prepared similarly by isomerization of the stable isomer in PPA.

Conversion of 2 to 1 (Ar = Ph; R = H). A sample of **2** (1 g) was dissolved in 10 ml of pyridine at room temperature. After 5 min, the mixture was poured on excess concentrated hydrochloric acid on crushed ice. The precipitate was filtered, washed with water, and recrystallized from ethanol, mp 166° (yield 98%, 0.98 g).

Reaction of Hippuric Acid in PPA. Hippuric acid (1 g) in PPA (10 g) was heated for 90 min on a steam bath. The product was isolated as above, and turned out to be the starting material (yield 90%, 0.9 g, mp 189°).

Reaction of 2-Benzamidocinnamic Acid 4a.[5e] A sample of **4a**, mp 231–232° (1 g), was heated in 10 g of PPA on a steam bath for 90 min. The product isolated, as usual, turned out to be **2** (Ar = Ph; R = H), mp 147° (yield 97%, 0.97 g).

Reaction of 2-Benzamidocinnamic Acid 4b.[5e] A sample of **4b**, mp 201–202° (1 g), was treated as above. The final product **2** melted at 147°, identical in all respects with the *E* isomer above (yield 87%, 0.87 g).

Registry No.—**1** (R = H; Ar = C_6H_5), 17606-70-1; **1** (R = H; Ar = 4-ClC_6H_4), 57427-77-7; **1** (R = H; Ar = 4-$CH_3OC_6H_4$), 57427-78-8; **1** (R = H; Ar = 4-$CH_3C_6H_4$), 57427-79-9; **1** (R = H; Ar = 3,4-$(MeO)_2C_6H_3$), 25349-37-5; **1** (R = H; Ar = 4-$O_2NC_6H_4$), 57427-80-2; **1** (R = H; Ar = 2,4-$Cl_2C_6H_3$), 57427-81-3; **1** (R = H; Ar = 2,6-$(MeO)_2C_6H_3$), 57427-82-4; **1** (R = H; Ar = 1-$C_{10}H_7$), 57427-83-5; **1** (R = H; Ar = 2-$CH_3OC_6H_4$), 57427-84-6; **2**, 15732-43-1; **4a**, 26348-47-0; **4b**, 57427-85-7; **5**, 57427-86-8; **6**, 57427-87-9; **7**, 57427-88-0; **8**, 25349-38-6; **9**, 57427-89-1; **10**, 57427-90-4; **11**, 57427-91-5; **12**, 57427-92-6; **13**, 57427-93-7; **14**, 57427-94-8; **15**, 57427-95-9; **16**, 57427-96-0; **17**, 57427-97-1; **18**, 57427-98-2; **19**, 57427-99-3; **20**, 57428-00-9; hippuric acid, 495-69-2; polyphosphoric acid, 8017-16-1; benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1; 4-methoxybenzaldehyde, 123-11-5; 4-methylbenzaldehyde, 104-87-0; 3,4-dimethoxylbenzaldehyde, 120-14-9; 4-hydroxybenzaldehyde, 123-08-0; 2-hydroxybenzaldehyde, 90-02-8; acetophenone, 98-86-2; 4′-chloroacetophenone, 99-91-2; 4′-methoxyacetophenone, 100-06-1; 4′-nitroacetophenone, 100-19-6; 4′-methylacetophenone, 122-00-9.

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N-Methylation of Amides, Lactams, and Ureas

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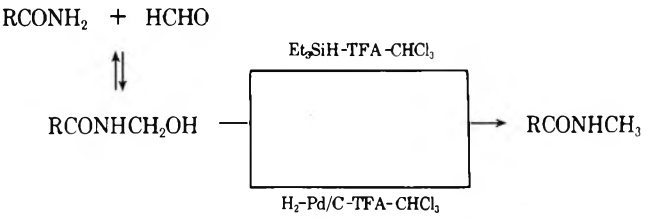
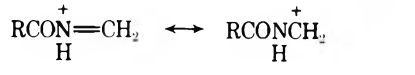
Few satisfactory methods are currently available for the N-methylation of amides and related compounds.[2] One of the more promising existing methods for amide alkylation was reported by Johnson and Crosby,[2c] who reduced a mixture of a primary amide and an acetal by catalytic hydrogenation in the presence of concentrated sulfuric acid. We now describe a milder and more versatile two-step procedure which consistently affords high isolated yields of mono-N-methylated products from the corresponding unsubstituted compounds.

Scheme I



It is well known[3] that various amides and related compounds react reversibly with formaldehyde, usually at neutral or slightly basic pH, to produce methylol derivatives (Scheme I). The equilibrium for this reaction lies to the methylol side at most pH's to the extent of about 5 kcal/mol. Many such methylols have been reported and usually are easily prepared and isolated. These methylols have found wide synthetic use in amidomethylation at carbon.[3] We have discovered that methylols derived from amides are reduced to the corresponding N-methylated product, usually at room temperature, by triethylsilane–trifluoroacetic acid, as well as by catalytic hydrogenation at atmospheric pressure in the presence of trifluoroacetic acid. A number of representative examples are shown in Table I.

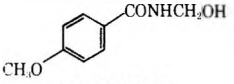
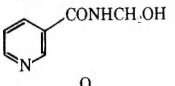
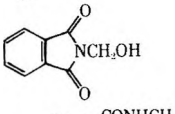
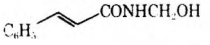
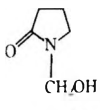
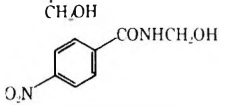
Triethylsilane has previously been shown to be effective for the reduction of many types of electrophilic species, particularly carbonium ions.[4] Treatment of an amide methylol with trifluoroacetic acid presumably produces an electrophilic acyliminium ion (1 ↔ 2)[3] which is then reduced to



1 2

the *N*-methyl compound by hydride transfer from silicon to carbon. It is likely that the catalytic reduction route, also utilizing trifluoroacetic acid, proceeds via the same acyliminium ion (1 ↔ 2).

Table I
Reduction of Methylols to *N*-Methyl Compounds

Registry no.	Methylol	Isolated yield of N-methylated product, %	
		Et_3SiH–TFA	H_2–5% Pd/C–TFA
57428-71-4	$C_5H_{11}CONHCH_2OH$	86	97
6282-02-6	$C_6H_5CONHCH_2OH$	94	97
57428-72-5		91	84
3569-99-1		88	93
118-29-6		No reaction[a]	No reaction
6043-65-8		85	79[b]
20779-63-9	$C_6H_5NHCONHCH_2OH$	85	80
57428-73-6	$(CH_3CH_2)_2NCONHCH_2OH$	57	65
15438-71-8		84	84
40478-12-4		92	66[c]

[a] No reduction product was observed upon prolonged heating. [b] The product is *N*-methylhydrocinnamamide. [c] The product is *p*-amino-*N*-methylbenzamide.

The catalytic hydrogenation method and the silane method complement each other nicely. Both procedures will provide *N*-methylamide from the corresponding methylol in excellent yield, but show different selectivities toward other functional groups in the same molecule.[4,5] This selectivity is exemplified by the reduction of cinnamamide methylol and *p*-nitrobenzamide methylol to different sets of products as shown in Table I. Both of these reduction methods can be used for lactam methylation as exemplified by reduction of *N*-methylolpyrrolidone to *N*-methylpyrrolidone. Imide methylols, on the other hand, appear to be inert to reduction, and phthalimide methylol was recovered unchanged in both experiments. This lack of reactivity is probably due to the inability of phthalamide methylol to form the corresponding less stable acylimidinium ion in trifluoroacetic acid.[6] Ureas can also be successfully methylated in this fashion, and in the two cases attempted (Table I) satisfactory yields were obtained using both reduction procedures.

Experimental Section

All methylols used in this study were prepared from the amide, urea, or lactam and 40% aqueous formaldehyde solution usually in the presence of potassium carbonate or sodium hydroxide using standard procedures previously described in detail.[3] Pyrrolidone methylol was purchased from K and K Laboratories. Trifluoroacetic acid was distilled from concentrated sulfuric acid before use.

General Procedure for Reduction of Methylols with Triethylsilane–Trifluoroacetic Acid. A solution containing 1 mmol of methylol, 1.14 g (10 mmol) of trifluoroacetic acid, 0.174 (1.5 mmol) of triethylsilane, and 10 ml of reagent grade chloroform was stirred for 1–4 hr at room temperature.[7] The mixture was diluted with ethyl acetate and washed with sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated to dryness, giving a nearly pure product which could be recrystallized or distilled if desired.

General Procedure for the Reduction of Methylols with Hydrogen–Pd/C–Trifluoroacetic Acid. A solution of 2 mmol of methylol, 2.28 g (20 mmol) of trifluoroacetic acid, and 200 mg of 5% Pd/C in 30 ml of reagent grade chlorofrrm was hydrogenated at room temperature and atmospheric pressure until the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and the organic phase was washed with saturated sodium chloride solution, washed with 15% sodium carbonate solution, dried ($MgSO_4$), and evaporated to afford an essentially pure product which could be purified further if desired.

Acknowledgment. We are indebted to the National Science Foundation (MPS 75-01558), National Institutes of Health (CA12568 and HL18450), and Eli Lilly & Co. for financial support.

Registry No.—Trifluoroacetic acid, 76-05-1; triethylsilane, 617-86-7; *N*-methylhexanamide, 3418-05-1; *N*-methylbenzamide, 613-93-4; 4-methoxy-*N*-methylbenzamide, 3400-22-4; *N*-methyl-3-pyridinecarboxamide, 114-33-0; *N*-methylhydrocinnamamide, 940-43-2; *N*-methyl-*N'*-phenylurea, 1007-36-9; *N,N*-diethyl-*N'*-methylurea, 39499-81-5; *N*-methylpyrrolidone, 872-50-4; *p*-amino-*N*-methylbenzamide, 6274-22-2.

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(1) (a) Postdoctoral Research Associate. (b) Fellow of the Alfred P. Sloan Foundation 1975–1977; recipient of an NIH Research Career Development Award, 1975–1980.
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(6) It has been shown that imide methylols will undergo amidomethylation at carbon if concentrated sulfuric acid is used as catalyst.[3]
(7) In the case of nicotinamide methylol, it was found best to reflux the reaction mixture for 2 hr.

Synthetic Applications of Phenylthio[(α-diethoxymethyl)vinyl]cuprate and (α-Diethoxymethyl)vinylcopper

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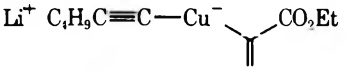
The utility of alkyl, alkenyl, and aryl organocuprate(I) reagents for the formation of carbon–carbon σ bonds via conjugate addition to α,β-unsaturated carbonyl compounds[2] and homoconjugate addition to cyclopropyl carbonyl compounds[3] has been demonstrated. Organocuprate (I) reagents have also been effectively used for selective substitution reactions with a wide variety of substrates[4]. Recently Marino[5] reported the preparation of α-carbethoxyvinylcuprate 1, which is specific for allyl halides. Alkyl



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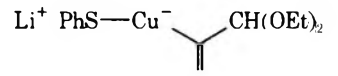

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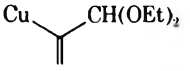
iodides, iodobenzene, 2-bromopropene, and benzyl bromide were unaffected under the reaction conditions employed with allyl halides. Furthermore, in direct contrast with lithium divinylcuprate, dialkylcuprates,[2] and mixed cuprate reagents,[6] the reaction of 1 with a series of α,β-unsaturated carbonyl compounds resulted in 1,2 addition to the carbonyl with the exception of methyl vinyl ketone.[7,8] In conjunction with our interest in functionalized nonterminal vinylcopper reagents,[9,10] we wish to communicate our results involving the mixed cuprate phenylthio[(α-diethoxymethyl)vinyl]cuprate (2) and (α-diethoxymethyl)vinylcopper (3).



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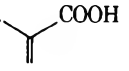

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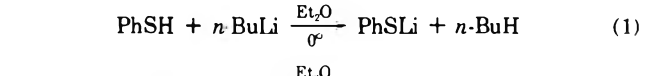
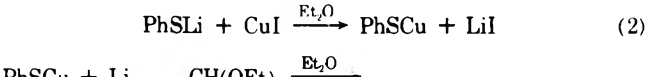
Our interest in reagents of type 2 stemmed from a need to construct a three-carbon unit fused to a carbon framework which would be equivalent to a 2-substituted propenoic acid derivative (e.g., 4). In this regard we wish to report the generation of the mixed organocuprate reagent 2, its reactivity toward allylic halides and α,β-unsaturated ketones, and its application to the synthesis of α-methylene lactones. In addition generation of the vinylcopper reagent 3 and its reactivity toward allylic halides is reported.

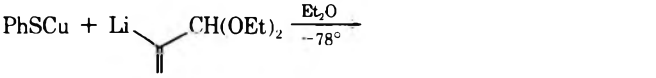
The mixed cuprate 2 was prepared according to eq 1–3. Thiophenol in anhydrous ether was treated with 1 equiv of



(1)



(2)



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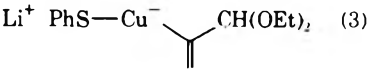
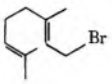
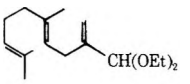
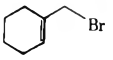
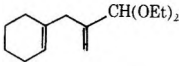
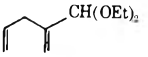
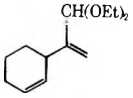
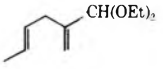
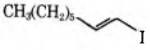


(3)

n-butyllithium. Addition of the lithium thiophenoxide to a suspension of cuprous iodide at room temperature in anhy-

Table I
Reaction of RX with Phenylthio[(α-diethoxymethyl)vinyl]cuprate (2) and (α-Diethoxymethyl)vinylcopper (3)

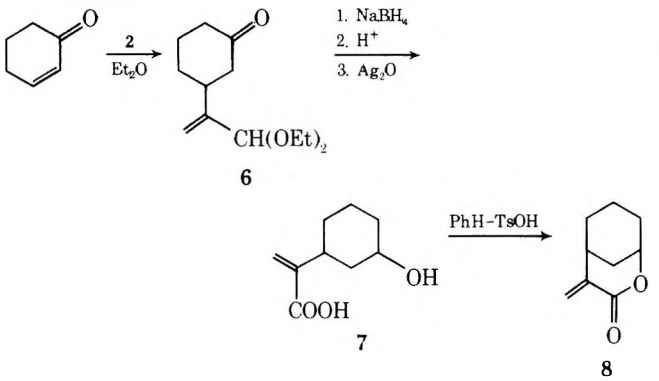
RX	Registry no.	Product	Registry no.	% yield[a] based on 2	% yield[a] based on 3
	25996-10-5		57428-07-6	85	90
	37677-17-1		57428-08-7	70	75
	106-95-6		57428-09-8	80	70
	1521-51-51-3		57428-10-1	76[b]	50[c]
	29576-14-5		57428-11-2	74	65
	42599-17-7			No reaction	
$PhCH_2Br$	100-39-0			No reaction	

[a] All yields are based on starting halide and on isolated chromatographically pure substances. In all experiments 2.0 equiv of reagent was employed and reactions were conducted at −78° (1 h) followed by warming to −40° (1 h) except where noted. [b] Reaction was carried out at −40° for 3 h. [c] Reaction was carried out at −40° for 2 h.

drous ether produced phenylthiocopper which was cooled to −78° and treated with the α-lithio derivative (**5**)[11] of the ethyl acetal of α-bromoacrolein. The reactivity of **2** at or below −40° with various halides revealed, as was the case with **1**, that mixed cuprate **2** allows for the economical selective transfer of a latent three-carbon propenoic acid chain and is highly specific for allylic halides. The results are summarized in Table I. As indicated in Table I, benzyl bromide[12] and 1-iodo-*trans*-oct-1-ene failed to undergo reaction under the conditions reported. Cyclohexene epoxide failed to react under similar conditions.

Recently new mixed cuprate(I) reagents for the selective transfer of vinyl[6] have been developed for 1,4-conjugate vinylation of cyclopentenones and cyclohexenones. The inability of the α-carbethoxyvinylcuprate reagent (**1**) to undergo conjugate addition is surprising and suggests that the ester moiety and the acetylenic ligand reduce the reagent's nucleophilicity. We have observed that the functionalized nonterminal mixed cuprate **2** undergoes smooth conjugate 1,4 addition to cyclohexenone, cyclopentenone, and methyl vinyl ketone in *diethyl ether*[13] at temperatures below −40° in 88, 50, and 50% yields, respectively.[14]

To illustrate the potential of this new reagent we have developed a route to an unreported class of δ-valerolactones[15] which employs the 1,4 addition of **2** to enones. The product **6** from addition to cyclohexenone was reduced



with sodium borohydride and smoothly converted to the hydroxypropenoic acid derivative **7** (82% overall yield). The unsaturated acid **7** was lactonized to the α-methylene-δ-valerolactone **8** in 60% yield.

During the course of this investigation we observed that the corresponding (α-diethoxymethyl)vinylcopper reagent **3** (generated from **5** and cuprous iodide in equimolar ratio) is highly specific for allylic halides and provides a stereospecific route to functionalized 1,4-dienes.[16] In contrast to the facile and efficient reactions with allylic halides, **3** did not react with benzyl bromide or 1-iodo-*trans*-oct-1-ene. Addition of cyclohexenone to **3** in diethyl ether resulted in a 90% isolated yield of only the 1,2-addition product.

The ability of phenylthio[(α-diethoxymethyl)vinyl]cuprate (**2**) to selectively transfer the nonterminal vinyl moiety to α,β-unsaturated enones and allylic halides provides a useful method for synthesizing a wide variety of 2-substituted propenoic acid derivatives.

Experimental Section

NMR spectra were obtained on Varian A-60 and T-60 spectrometers in CCl_4 or $CDCl_3$ solutions with Me_4Si as an internal standard. Infrared spectra (ir) were obtained on a Perkin-Elmer Model 247 infrared spectrophotometer as a liquid film or in $CHCl_3$ solution. Mass spectra (MS) were recorded on an LKB-9000 and a Varian MAT CH5-DF. Boiling points are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Anhydrous cuprous iodide was purchased from Alfa Inorganics, Inc., and used directly without further drying or purification. Diethyl ether was dried and kept over sodium prior to use. *n*-Butyllithium obtained from MCB was about 1.55 M in hexane solution.

General Procedure for Reaction for α,β-Unsaturated Ketones with Lithium Phenylthio[(α-diethoxymethyl)vinyl]cuprate. To a suspension of 381 mg (2.0 mmol) of cuprous iodide in 2.0 ml of anhydrous ether under nitrogen was added lithium thiophenoxide (2.0 mmol) [prepared by reaction of 1.29 ml (2.0 mmol) of *n*-butyllithinm and 220 mg (2.0 mmol) of thiophenol at 0° under nitrogen in 2.0 ml of anhydrous ether] in ether at room temperature. A yellow heterogeneous mixture was formed. After 5 min the mixture was cooled to −78° and a precooled (−78°) solution of 2-lithio-1,1-diethoxy-2-propene in ether [prepared[11] by reaction of 418 mg (2.0 mmol) of 1,1-diethoxy-2-bromo-2-propene with 1.29 ml (2.0 mmol) of *n*-butyllithium at −78° in 4.0 ml of anhydrous

ether (1 h)] was added. After 1 h at −78°, 96 mg (1.0 mmol) of cyclohexenone in 2.0 ml of dry ether was added. The reaction mixture was stirred at −78° for 1 h followed by warming to −40°. After 2 h at −40°, the reaction was quenched by the addition of 2.0 ml of saturated ammonium chloride solution. The yellow precipitate was removed by filtration through Celite and washed with ether. The combined ether layers were washed with saturated ammonium chloride and 5% sodium hydroxide and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 312 mg of crude product. Purification on 10.0 g of silica gel [elution with ether–hexanes (1:12)] gave 200 mg (88%) of pure 1,4-addition product **6**: ir ($CHCl_3$) 5.85 μ; NMR (CCl_4) δ 5.18 (s, 1 H), 4.98 (s, 1 H), 4.70 (s, 1 H), 3.40 (m, 4 H), 1.17 (t, 6 H); MS *m/e* 226. An analytical sample was prepared by distillation [45° (bath temperature) (0.25 mmHg)].

Anal. Calcd for $C_{13}H_{22}O_3$: 226.1569. Found: 226.1572.

2-(*cis*-3-Hydroxycyclohexyl)propenoic Acid Lactone (8). To a solution of sodium borohydride (46 mg, 0.92 mmol) in 10 ml of absolute ethanol was added a solution of ketone **6** (175 mg, 0.77 mmol) in 2 ml of absolute ethanol. After 1 h at room temperature, the solvent was removed under reduced pressure. The residue was taken up in ether and washed with saturated brine. The ether layer was dried (Na_2SO_4) and the solvent removed in vacuo to afford 171 mg (97%) of alcohol which was used directly in the next reaction.

A solution of the above alcohol (170 mg, 0.75 mmol) in 5 ml of tetrahydrofuran was added to 5 ml of 5% hydrochloric acid. The reaction mixture was stirred for 8 h at room temperature. Usual work-up with ether gave 113 mg (99%) of essentially pure aldehyde: ir (film) 2.95, 3.71, 5.95, 6.17 μ; NMR (CCl_4) δ 9.38 (s, 1 H), 6.22 (s, 1 H), 5.96 (s, 1 H).

The above aldehyde (113 mg, 0.73 mmol) in 5 ml of dioxane was added to a solution of silver nitrate (240 mg, 1.46 mmol) in 10 ml of water. The resultant solution was treated dropwise with 5% sodium hydroxide until pH 10 was reached. The mixture was heated at 80° for 1 hr. Additional sodium hydroxide was added to maintain the pH at 10. The reaction mixture was cooled, filtered, and extracted with ether. Acidification of the aqueous layer with hydrochloric acid followed by extraction with ethyl acetate gave, after drying ($MgSO_4$) and removal of the solvent in vacuo, 105 mg (85%) of hydroxycarboxylic acid **7**: ir ($CHCl_3$) 2.65–4.50 (broad), 5.91, 6.17 μ.

A solution of carboxylic acid **7** (105 mg, 0.61 mmol) in benzene (25 ml) containing *p*-toluenesulfonic acid (10 mg) was refluxed for 12 h employing a Dean-Stark apparatus. The cooled reaction mixture was extracted with sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave 71 mg of crude lactone. Purification on silica gel (10 g) [elution with ether–hexanes (1:2)] gave 55 mg (60%) of pure α-methylene lactone **8**: ir ($CHCl_3$) 5.85, 6.15 μ; NMR (CCl_4) δ 6.18 (d, J = 2 Hz, 1 H), 5.38 (d, J = 2 Hz, 1 H), 4.60 (bs, 1 H), 2.88 (bs, 1 H); MS *m/e* 152. An analytical sample was prepared by distillation [45° (bath temperature) (0.25 mmHg)].

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.95; H, 7.90.

General Procedure for Reaction of Phenylthio[(α-diethoxymethyl)vinyl]cuprate with Allylic Halides. To a suspension of phenylthiocopper (2.0 mmol) (prepared as described above) in anhydrous ether cooled to −78° was added a precooled (−78°) solution of 2-lithio-1,1-diethoxy-2-propene (2.0 mmol) in dry ether (prepared as described above). After 1 h at −78°, geranyl bromide (217 mg, 1.0 mmol) in 2.0 ml of ether was added. After stirring for 1 h at −78°, the temperature was warmed to −40° and stirring was continued for an additional 1 h. The reaction was quenched with saturated ammonium chloride solution (2.0 ml). The yellow precipitate was filtered and washed with ether. The combined ether layers were washed with saturated ammonium chloride, 5% aqueous sodium hydroxide, and brine. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure, affording 320 mg of crude product. Purification by passage through a silica gel column [10.0 g, elution with ether–hexanes (1:40)] gave 229 mg (85%) of pure compound: NMR (CCl_4) δ 4.8–5.3 (m, 4 H), 4.61 (s, 1 H), 3.45 (m, 4 H), 2.58 (d, 2 H), 2.05 (m, 4 H), 1.55 (bs, 3 H), 1.58 (bs, 6 H), 1.18 (t, 6 H); MS *m/e* 266. An analytical sample was prepared by distillation [50° (bath temperature) (0.3 mmHg)].

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.89; H, 11.50.

(α-Diethoxymethyl)vinylcopper. Preparation and Reaction with Allylic Halides. To a suspension of cuprous iodide (381 mg, 2.0 mmol) in 2.0 ml of anhydrous ether under nitrogen at −78° was added a precooled (−78°) solution of 2-lithio-1,1-diethoxy-2-propene (2.0 mmol) (prepared as described above) in anhydrous ether. After 1 h at −78°, a solution of cyclohexenyl bromide (161 mg, 1.0 mmol) in 2.0 ml of anhydrous ether was added. The reaction mixture was stirred at −40° for 2 h. The reaction was quenched with saturated ammonium chloride solution. The yellow precipitate was filtered through Celite and washed with ether. The combined ether fractions were washed with saturated ammonium chloride solution and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo afforded 339 mg of crude product. Purification on silica gel [10.0 g, elution with ether–hexanes (1:20)] gave 105 mg (50%) of pure product: NMR (CCl_4) δ 5.58 (m, 2 H), 5.20 (bs, 1 H), 4.98 (bs, 1 H), 4.71 (s, 1 H), 3.48 (m, 4 H); MS *m/e* 210. An analytical sample was prepared by distillation [40° (bath temperature (0.3 mmHg)].

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.98; H, 10.44.

Reaction of (α-Diethoxymethyl)vinylcopper with Cyclohexenone. To a suspension of cuprous idodide (381 mg, 2.0 mmol) in 2.0 ml of anhydrous ether under nitrogen at −78° was added a precooled (−78°) solution of 2-lithio-1,1-diethoxy-2-propene (2.0 mmol) (prepared as described above) in anhydrous ether. After 1 h at −78°, a solution of cyclohexenone (96 mg, 1.0 mmol) in 2.0 ml of anhydrous ether was added. The reaction mixture was stirred at −78° for 2 h. The reaction was quenched with saturated ammonium chloride solution. The yellow precipitate was filtered through Celite and washed with ether. The combined ether fractions were washed with saturated ammonium chloride solution and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo afforded 230 mg of crude product. Purification on silica gel [10.0 g, elution with ether–hexanes (1:4)] gave 203 mg (90%) of pure product [ir (neat) 2.89, 3.31, 6.13 μ; NMR (CCl_4) δ 5.7–5.5 (m, 2 H), 5.28 (bs, 1 H), 5.15 (bs, 1 H), 4.98 (s, 1 H), 3.7–3.2 (m, 4 H), 2.4–1.3 (m, 7 H), 1.18 (t, 6 H)] which was identical with a sample prepared by reaction of cyclohexenone with reagent **5**.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (CA 13689-04) from the National Cancer Institute.

Registry No.—**2**, 57428-24-7; **3**, 57428-12-3; **5**, 54780-30-2; **6**, 57428-13-4; **7**, 57428-14-5; **8**, 57428-15-6; cuprous iodide, 7681-65-4; lithium thiophenoxide, 2973-86-6; cyclohexenone, 930-68-7; 2-(*cis*-3-hydroxycyclohexyl)propenol diethyl acetal, 57428-16-7; 2-(*cis*-3-hydroxycyclohexyl)propenol, 57428-17-8.

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(11) The generation and use of 2-lithio-1,1-diethoxy-2-propene has been described by J. Ficini and J.-C. Depezay, *Tetrahedron Lett.*, 4797 (1969).
(12) Reaction of benzyl bromide with 2 at −40° for 4 h gave ca. 88% yield

of recovered benzyl bromide. At temperatures between −20 and 0° appreciable amounts of benzyl phenyl sulfide were isolated. At −40° <5% of benzyl phenyl sulfide could be detected.

(13) Posner[6c] has observed that lithium methyl(vinyl)cuprate in THF transfers the vinyl exclusively to C-3 of 2-cyclopentenone. When diethyl ether is employed instead of THF, the methyl and vinyl groups are both transferred to C-3 of 2-cyclopentenone. In our hands use of THF results in greatly diminished yields of 1,4-addition product.

(14) Yields are based on starting enone and on isolated chromatographically pure material. In general 2.0 equiv of **2** was employed and reactions were conducted at −78° (1 hr) followed by warming to −40° (2 hr).

(15) For an example of a δ-lactone fused 1,3 to the 14-membered cembrane ring system see M. B. Hossain and D. van der Helm, *Recl. Trav. Chim. Pays-Bas*, **88**, 1413 (1969).

(16) Similar selectivity has been observed in other organocopper(i) systems: (a) E. J. Corey and M. Jautelet, *Tetrahedron Lett.*, 5787 (1968); (b) E. J. Corey and I. Kuwajima, *ibid.*, 487 (1972); (c) I. Kuwajima and Y. Doi, *ibid.*, 1163 (1972).

Synthesis of α-Substituted Selenonesters

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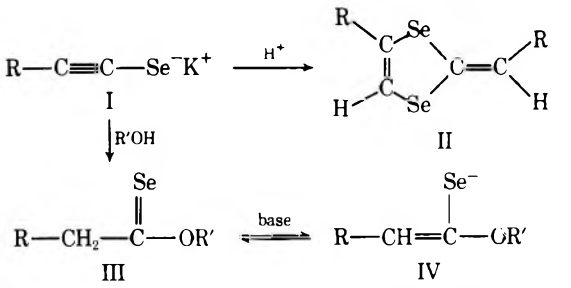
The syntheses of very few selenonesters have been reported[1]. We wish to report a new general synthesis of α-substituted selenonesters.

During our previous work we had observed that arylethynylselenolate salts (I), prepared from 4-aryl-1,2,3-selenadiazoles, dimerized to form 1,3-diselenafulvenes (II).[2] Raap[3] has reported that aryl- or alkylethynylthiolates under certain conditions react with alcohols to form thionesters. It appeared possible that in very dilute solutions the rate of the bimolecular step leading to the fulvene II should slow down and reaction of I with protic solvents should predominate.



When I (R = Ph) is added to ethanol in low concentrations, besides the appearance of the characteristic absorbance at 340 nm for the fulvene a new peak at 275 nm is formed. Upon basification, this absorbance is shifted to 325 nm with an increase in absorbance. By using a technique of slow addition to a slightly acidified solution, such that the concentration of I at any time remains below 10^{-5} *M*, the formation of the fulvene is minimized; the product is essentially the 275-nm compound. Purified by column chromatography, the light yellow liquid was identified by its NMR, MS, and ir spectra as *O*-ethylphenyl selenonacetate (III).

The bathochromic shift in the uv spectrum on addition of base is attributed to the formation of the enolate ion (IV). A similar enolization of thionesters could be observed under more strongly basic conditions. Evidence for thione–enethiol equilibrium has been reported using polarographic techniques[4].

The NMR spectrum of all the selenonester derivatives formed (Table I) showed a shift of the methylene as well as the protons of the alkyl group of the ester to a lower field than the corresponding oxygen and even slightly lower than the sulfur analogues.

Besides the derivatives shown in Table I, selenonesters of acetic and propionic acids were also prepared. However, owing to their volatility, they could not be isolated in pure form and were identified only through their characteristic uv spectra.

Table I
Chemical Shifts and Ultraviolet Spectral Data of Selenoesters and Comparison with Thione and Oxygen Esters

Ester	Registry no.	NMR,[a] δ, ppm	λ_{max}, nm (ε)
PhCH$_2$C(=Se)OMe	57444-30-1	3.95 (2 H, s), 4.13 (3 H, s), 7.2 (5 H, br s)	275 (6.7×10^3)[b]
PhCH$_2$C(=S)OMe	5873-85-8	3.95 (2 H, s), 3.94 (3 H, s), 7.2 (5 H, br s)	240 (7.1×10^3)[b]
PhCH$_2$C(=O)OMe	101-41-7	3.50 (3 H, s), 3.54 (2 H, s), 7.2 (5 H, br s)	214 (6.0×10^3)[b]
PhCH$_2$C(=Se)OEt	57444-31-2	1.40 (3 H, t), 3.95 (2 H, s), 4.60 (2 H, q), 7.2 (5 H, br s)	277 (7.7×10^3)[c]
PhCH$_2$C(=Se)O-*i*-Pr	57444-32-3	1.30 (6 H, d), 3.90 (2 H, s), 5.60 (1 H, m), 7.2 (5 H, br s)	282 (8.3×10^3)[d]
p-MeOPhCH$_2$C(=Se)OMe	57444-33-4	3.89 (2 H, s), 3.95 (2 H, s), 4.18 (3 H, s), 6.75 (2 H, d), 7.20 (2 H, d)	275 (7.6×10^3)[b]
p-ClPhCH$_2$C(=Se)OMe	57444-34-5	3.98 (2 H, s), 4.18 (3 H, s), 7.25 (4 H, br s)	275 (7.0×10^3)[b]
p-O$_2$NPhCH$_2$C(=Se)OMe	57444-35-6	4.0 (2 H, s), 4.16 (3 H, s), 7.4 (2 H, d), 8.1 (2 H, d)	275 (1.68×10^4)[b]
β-Naph-CH$_2$C(=Se)OMe	57444-36-7	4.20 (5 H, s), 7.6 (7 H, m)	276 (1.3×10^4)[b]

[a] In carbon tetrachloride with Me_4Si as internal reference. [b] In methanol. [c] In ethanol. [d] In 2-propanol.

The selenonesters were somewhat unstable at room temperature, slowly depositing red selenium, and were not sufficiently stable to permit shipment for analysis. At temperatures below 0° and in solution no changes could be observed after several weeks.

Experimental Section

NMR spectra were obtained on a Varian T-60; ir and uv spectra were determined on Pye-Unicam Models SP 1200 and 8000, respectively; mass spectra were taken on a Varian Model CH5 spectrometer.

General Method for the Preparation of Selenonesters. 1,2,3-Selenadiazole (150 mg) was added to a 100-ml solution of 0.01 *N* potassium *tert*-butoxide in *tert*-butyl alcohol. After the gas evolution ceased, the resulting solution of I was added slowly through a capillary tube, over 8–9 hr, to 500 ml of alcohol, to which enough acetic acid had been added to keep the solution slightly acidic throughout the reaction. After all of I had been added the alcohol was evaporated to near dryness on a rotary film evaporator at 40° bath temperature. The solid that separated (some fulvene and salts) was centrifuged and the supernatant liquid was chromatographed on 50 g of silica gel, using 10% chloroform in petroleum ether (bp 40–60°). The selenonesters moved as yellow bands, being eluted just behind the corresponding fulvenes. The yields depended on the speed of addition of I. Nearly quantitative yields could be obtained in very dilute solution, as judged by their absorbance in the uv. Yields of isolated pure esters, however, were about 50%.

Acknowledgment. This work was supported, in part, by the Ministery of Science and Higher Education of Iran.

Registry No.—I (R = Ph), 36928-61-7; I (R = *p*-MeO-Ph), 57444-37-8; I (R = *p*-Cl-Ph), 57444-38-9; I (R = *p*-O_2N-Ph), 57444-39-0; I (R = β-Naph), 57444-40-3; 4-phenyl-1,2,3-selenadiazole, 25660-64-4; 4-(*p*-methoxylphenyl)-1,2,3-selenadiazole, 27892-76-8; 4-(*p*-chlorophenyl)-1,2,3-selenadiazole, 27892-68-8; 4-(*p*-nitrophenyl)-1,2,3-selenadiazole, 27892-72-4; 4-β-naphthyl-1,2,3-selenadiazole, 52376-78-0; methanol, 67-56-1; ethanol, 64-17-5; isopropyl alcohol, 67-63-0.

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Organic Metals. A Novel Route to Cycloalkenotetrathiafulvalenes

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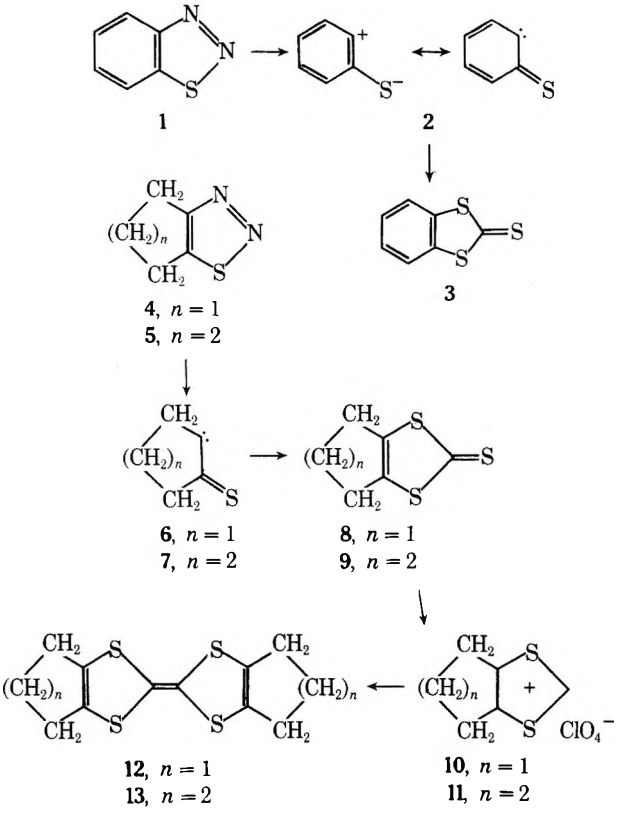
It has been known since 1961 that thermolysis of 1,2,3-benzothiadiazole (1) leads to the dipolar intermediate **2**, which can be efficiently intercepted by carbon disulfide to yield (84%) the benzotrithiocarbonate (**3**).[1] An attempt to carry out the analogous reaction with the parent 1,2,3-thiadiazole afforded only a 0.2% yield of vinylene trithiocarbonate.[1a] Since the poor result observed in the latter case may be attributed to the fragmentation of the thiocarbonyl carbene to sulfur and acetylene, we anticipated that cycloalkenothiocarbonyl carbenes, which could only fragment to give strained cyclic alkynes, would have a sufficient lifetime to be intercepted by carbon disulfide. This expectation has now been confirmed in the preparatively useful conversion of several cycloalkenothiadiazoles to the corresponding cycloalkenotrithiocarbonates, which in turn served as convenient precursors of the corresponding tetrathiafulvalenes.



Thus, cyclohexeno-1,2,3-thiadiazole (**5**), which is readily prepared by the thionyl chloride treatment of cyclohexanone tosylhydrazone,[2] was heated for 7 hr with carbon disulfide at 215° to give, in 42.6% yield, the trithiocarbonate **9**, identical with material prepared by the method of Fanghänel.[3] Thermolysis of cyclopenteno-1,2,3-thiadiazole (**4**) in carbon disulfide under similar conditions afforded, in 41.4% yield, the corresponding cyclopentenotrithiocarbonate (**8**), mp 105–108°. In either case, the reaction is assumed to proceed by way of a 1,3-dipolar addition of an intermediary thiocarbonyl carbene (**7** or **6**) to the thiocarbonyl group of carbon disulfide.[4]

A simple synthesis of the parent tetrathiafulvalene (TTF) consists of the peracid oxidation of vinylene trithiocarbonate to give the 1,3-dithiolium ion,[5] followed by treatment of the latter with triethylamine.[6] This procedure was readily applicable to the synthesis of the cycloalkeno TTF derivatives **12** and **13**. Thus, the cyclohexenotrithiocarbonate (**9**) was oxidized to the corresponding 1,3-dithiolium ion, isolated as the perchlorate **11**; triethylamine treatment of the latter afforded, in 73.8% overall yield from **9**, bis(cyclohexeno)tetrathiafulvalene (**13**), mp 247.6–248.2°. In a similar manner, the cyclopentenotrithiocarbonate (**8**) was converted, via the 1,3-dithiolium perchlorate **10**, into bis(cyclopenteno)tetrathiafulvalene (**12**), mp 244°, in 70% overall yield.

Charge transfer salts of **12** and **13** with the π acceptor TCNQ[7] were formed as the 1:1 TCNQ salts, **14**[8] and **15**, respectively. The four probe room temperature electrical

14, $12^{\cdot+}$ $TCNQ^{\cdot-}$
15, $13^{\cdot+}$ $TCNQ^{\cdot-}$

conductivities measured on compactions of **14** and **15** are 15 and 5 × 10^{-5} $(\Omega\ cm)^{-1}$, respectively [TTF–TCNQ: 25 $(\Omega\ cm)^{-1}$]. The wide difference in electrical behavior is likely associated with different crystallographic linear chain stacking of donors and acceptors in the two salts, segregated in **14** and alternating in **15**.[9]

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer and ultraviolet–visible spectra were determined on a Perkin-Elmer 202 spectrophotometer. Mass spectra were obtained on a Perkin-Elmer 270B mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Cyclopenteno-1,2,3-thiadiazole (4). Improving on the precedure of Meier,[2] 176.65 g (0.7 mol) of cyclopentanone tosylhydrazone was treated cautiously at 0° with 450 ml (6.2 mol) of thionyl chloride. The dark solution was stirred at room temperature for 3 h or until gas evolution ceased. The excess thionyl chloride was removed by rotary evaporation at 60°. The resulting residue was treated with 78.55 g (1.4 mol) of potassium hydroxide in 400 ml of water, warmed gently on a steam bath for 45 min, and filtered. The solution was extracted twice with ether, the ether layers being combined, dried over $MgSO_4$, and concentrated. The resulting dark oil was distilled at 60–62° (0.05 mm) to give 30.0 g (34%) of **4** as a slightly yellow liquid [lit.[2] bp 42–46° (0.01 mm)].

Cyclohexeno-1,2,3-thiadiazole (5) was prepared as described above for the preparation of **4** using 133.19 g (0.5 mol) of cyclohexanone tosylhydrazone, 320 ml of thionyl chloride, and 56.11 g of potassium hydroxide. The dark oil was distilled at 70–71° (0.05 mm) to give 63.7 g (91%) of **5** as a colorless liquid [lit.[2] bp 51–55° (0.01 mm)].

Cyclopentenotrithiocarbonate (8). A solution of 11.0 g of **4** in 60 ml of carbon disulfide was heated to 205° for 6 h in a glass-lined stainless steel autoclave. After cooling, the excess carbon disulfide was removed by rotary evaporation. The residue was dissolved in chloroform and filtered and the chloroform solution concentrated to a dark oil. The oil was chromatographed on silica gel using hexane as eluent. The highly colored impurities (<4.5%) were discarded and the remaining yellow fractions were combined and concentrated to a yellow solid. The solid was crystallized from hexane to give 6.29 g (41.4%) of **8** as long, yellow needles: mp 105–108°; ir (KBr) 1110 and 1040 cm^{-1}; λ_{max} (hexane) 232 nm (log ϵ 3.79), 268 (3.07), and 380 (4.02); mass spectrum *m/e* 174.

Anal. Calcd for $C_6H_6S_3$: C, 41.34; H, 3.47; S, 55.18. Found: C, 41.26; H, 3.56; S, 55.20.

Cyclohexenotrithiocarbonate (9). Following the above procedure for the preparation of **8**, a solution of 15 g of **5** in 60 ml of carbon disulfide was heated for 7 h at 215°. The dark oil was chromatographed using hexane–chloroform as eluent. The colorless fractions (<4%) were discarded and the remaining yellow fractions were combined and concentrated to a yellow solid. The solid was crystallized from hexane–chloroform to give 8.52 g (42.6%) of **9** as short, yellow needles: mp 81–82° (lit.[3] mp 82–83°); ir (KBr) 1055 and 899 cm^{-1}; λ_{max} (hexane) 234 nm (log ϵ 3.84), 273 (3.15), and 372 (4.072); mass spectrum *m/e* 188.

Bis(cyclopenteno)tetrathiafulvalene (12). *Caution should be exercised with perchlorate salts.*[10] A solution of 0.500 g (2.87 mmol) of **8** in 20 ml of acetone was cooled to 0°. A cold solution of 2.38 g (11.72 mmol) of *m*-chloroperbenzoic acid (85%) in 20 ml of acetone was added dropwise with stirring. After 30 min, no **8** could be detected by TLC (silica gel HF, chloroform, R_f 0.86). Perchloric acid (60–62%) (3 ml) was added to the dark solution precipitating the light tan perchlorate salt **10**. Further salt precipitated on addition of 200 ml of ether and the salt was filtered, washed with ether, and dried.[10] The perchlorate salt was directly dissolved in 20 ml of acetonitrile. The solution was degassed with argon and cooled to 5°. Triethylamine, 1.0 g, was added dropwise and immediately a solid formed. After stirring for 30 min, 20 ml of water was added and the solid filtered and dried. The crude product, mp 242–245°, was sublimed at 200° (0.05 mm) to give 0.284 g (70%) of **12** as a yellow-brown solid, crystallized from acetonitrile–trichlorobenzene: mp 244°; ir (KBr) 1450, 1325, and 769 cm^{-1}; λ_{max} (1,2-DCE) 307 nm (log ϵ 4.02), 327 sh (3.968), and 462 (2.248); mass spectrum *m/e* (rel intensity) 284 (M, 100), 142 (M/2, 17).

Anal. Calcd for $C_{12}H_{12}S_4$: C, 50.66; H, 4.26; S, 45.08. Found: C, 50.64; H, 4.13; S, 45.27.

Bis(cyclohexeno)tetrathiafulvalene (13). *Caution should be exercised with perchlorate salts.*[10] Following the above procedure for the preparation of **12**, 2.0 g of **9** was oxidized with 10.781 g of peracetic acid (30%) to give the hydrosulfate salt as a red oil. Treatment with 12 ml of perchloric acid (60–62%) gave the solid tan perchlorate salt **11**.[10] The perchlorate salt was directly dissolved in 30 ml of acetonitrile and treated with 1.51 g of triethylamine to give 1.49 g (90%) of **13** as a yellow solid, mp 245° dec, purified by sublimation at 190° (0.05 mm) to give **13** (82%) as a red-brown solid, crystallized from chlorobenzene: mp 247.6–248.2°; ir (KBr) 1448, 1340, and 779 cm^{-1}; λ_{max} (CH_3CN) 297 nm (log ϵ 4.025), 323 sh (3.98), and 472 (2.283); mass spectrum *m/e* (rel intensity) 312 (M, 100), 156 (M/2, 9).

Anal. Calcd for $C_{14}H_{16}S_4$: C, 53.80; H, 5.16; S, 41.04. Found: C, 53.86; H, 5.15; S, 41.30.

Bis(cycloalkeno)tetrathiafulvalene–tetracyanoquinodimethane (14 and 15). Charge transfer salts **14** and **15** were formed by the known procedure[7] using rigorously purified acetonitrile under an argon atmosphere. The two solutions were mixed, heated for an additional 15 min, and allowed to cool over several hours to yield the respective salts as black needles.

For **15**: Anal. Calcd for $C_{26}H_{20}N_4S_4$: C, 60.43; H, 3.91; N, 10.85; S, 24.82. Found: C, 59.37; H, 4.09; N, 10.60; S, 24.29.

For **14**:[8] Anal. Calcd for $C_{14}H_{16}N_4S_4$: C, 58.98; H, 3.31; N, 11.47; S, 26.24. Found: C, 59.05; H, 3.35; N, 11.46; S, 26.36.

Acknowledgments. This work was supported by the Advanced Research Projects Agency through Grant DAHC 15-72-C-0174 and the National Science Foundation through Grants MPS 74-03279 and GH-39303. The authors gratefully acknowledge Drs. L. B. Coleman and S. Khanna for aid in the conductivity measurements and Mr. P. J. Nigrey for sample handling.

Registry No.—**4**, 56382-73-1; **5**, 56382-72-0; **8**, 17534-29-1; **9**, 698-42-0; **12**, 57512-84-2; **13**, 35079-58-4; **14**, 57527-02-3; **15**, 57512-86-4; cyclopentanone tosylhydrazone, 17529-98-5; cyclohexanone tosylhydrazone, 4545-18-0; carbon disulfide, 75-15-0.

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Anodic Oxidation of Diphenylamine in the Presence of Methoxide Ion

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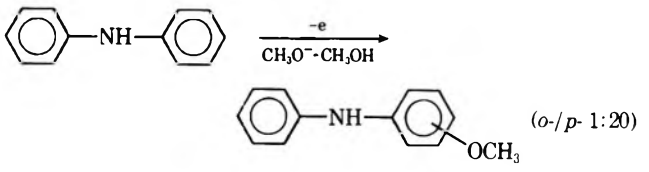
The electrochemical oxidation of diphenylamines produces the intermolecular and intramolecular coupling

Scheme I



products, *N,N'*-diphenylbenzidines and carbazoles, respectively.[1,2] If the anodic oxidation of diphenylamines is conducted under the cyanation conditions, the cyanide ion attacks the aromatic nucleus to yield *p*-cyanodiphenylamines[3] or the quinoneimine cyanohydrin methyl ether.[4] Since the aromatic substitution reaction of diphenylamines is uncommon, it was investigated if such a reaction takes place even when other nucleophiles such as acetate or methoxide ion are used.

The anodic oxidation of diphenylamine in methanol containing sodium methoxide was carried out with a constant current. A mixture of o- and *p*-methoxydiphenylamines was formed in 7.6% yield (based on unrecovered diphenylamine; o-:*p*- 1:20; conversion, 10%) (Scheme I) together with a considerable amount of tarry products.

With methanol containing salts of other anions such as perchlorate or tetrafluoroborate, a small amount of intermolecular coupling product, *N,N'*-diphenylbenzidine, was obtained along with a significant amount of tarry residue. Nuclear substitution product was not detected.

It is apparent from these results that nuclear methoxylation requires the presence of methoxide ion. Because a methoxy substituent lowers the oxidation potential of substrates, the methoxyamines formed are often much less resistant toward oxidation than the starting material, and, besides, the isomers might be oxidized at different rates. However, the isomer ratio did not change practically with the amount of passed electricity and the observed one would therefore represent a close approximation of the true isomer distribution. These orientations in the present methoxylation, para preponderance, are in accord with those in the cyanation.[3]

Anodic oxidation of diphenylamine in acetic acid containing sodium acetate affords brownish residue exclusively.

Experimental Section

Materials. Methanol was purified by fractional distillation from magnesium methoxide. Reagent grade sodium, sodium perchlorate, and sodium tetrafluoroborate were used.

Diphenylamine and *N,N'*-diphenylbenzidine were obtained commercially and the former substrate was purified by recrystallization. Preparation of *o*- and *p*-methoxydiphenylamines was as previously described.[3] *m*-Methoxydiphenylamine was prepared by the method of Dolman and Stewart.[5]

Anodic Oxidation of Diphenylamine in Methanolic Sodium Methoxide. The electrolysis was carried out nonpotentiostatically using a two-compartment cell under a nitrogen atmosphere as described previously.[6] The anolyte was made up of 0.85 g (5.0 mmol) of diphenylamine in methanol–sodium methoxide (50 ml, 1.0 M). The catholyte was a methanolic sodium methoxide solution. During the electrolysis, the solution was kept stirred magnetically and cooled externally with ice. The reaction was then run with a constant current of 0.05 A for 110 min. The electrolyzed mixture was treated as usual[3] and was analyzed by GLC (SE 30, 170°).

Anodic Oxidation in Methanolic Sodium Perchlorate. Diphenylamine (0.85 g, 5.0 mmol) was electrolyzed in methanol containing sodium perchlorate (50 ml, 1.0 M) at 0.05 A for 110 min. The organic material was chromatographed on silica gel using a 3:1 benzene–hexane mixture as an eluent. Unreacted starting material was first eluted, followed by *N,N'*-diphenylbenzidine (0.04 g, 0.12 mmol).

Registry No.—Diphenylamine, 122-39-4; methoxide ion, 3315-60-4.

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Nucleophilic Aromatic Substitution Reactions of Unactivated Aryl Chlorides with Methoxide Ion in Hexamethylphosphoramide

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It has previously been shown by other workers that metal alkoxides react with unactivated aryl halides to give aryl alkyl ethers.[1-5] Although some procedures gave good yields of products when aryl bromides or iodides were used, unactivated aryl chlorides gave poor yields of ethers.[1-3] In some procedures the aryl halides reacted by an aryne mechanism which led to an undesired mixture of isomeric products.[3-5] Recently it was shown that *o*-dichlorobenzene reacted by a bimolecular displacement mechanism with potassium methoxide complexed with a crown ether to give a 40–50% yield of *o*-chloroanisole.[6]

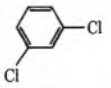
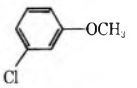
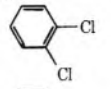
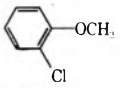
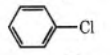
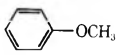
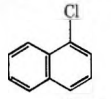
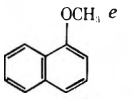
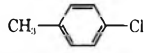
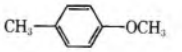
We wish to report that unactivated aryl chlorides react by a bimolecular displacement mechanism with sodium methoxide in hexamethylphosphoramide (HMPA) to give in most cases good yields of methyl aryl ethers. Various examples with reaction conditions and yields of products are shown in Table I. The variation in yields is consistent with the electronic effects of the substituents in the aryl chlorides.

The reactions are proceeding by a bimolecular displacement mechanism (SNAr)[7] rather than an aryne mechanism based on the products produced. The fact that the aryl chlorides give single products rather than mixtures of isomeric products indicates that an aryne mechanism is not operating. In the case of 1-chloronaphthalene an aryne mechanism may be operating to a slight extent, since a trace of 2-methoxynaphthalene was produced along with the 1-methoxy isomer. A radical-anion mechanism (SRN1) is not likely since there are no additional products where chloride is replaced by hydrogen[7] and also since addition of 0.1 molar equiv of *p*-dinitrobenzene, a radical inhibitor, had no effect on the yield of product in the reaction of *o*-dichlorobenzene.[8]

Experimental Section[9]

***m*-Chloroanisole.** A magnetically stirred mixture of 2.94 g (20 mmol) of *m*-dichlorobenzene, 1.30 g (24 mmol) of sodium methoxide, and 40 ml of dry HMPA was heated at 90° for 20 h in a flask equipped with a condenser and a drying tube. The mixture was then cooled and poured into 80 ml of water which was then extracted with two 75-ml portions of ether. The combined ether extract was washed with three 20-ml portions of water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to give 2.74 g of liquid. Analysis of the liquid by GLC (SE-30, 120°, or methyl silicone, 145°) revealed that it consisted only of *m*-chloroanisole and that the yield of *m*-chloroanisole was 87%. *o*-Chloroanisole and *p*-chloroanisole had retention times longer than that of *m*-chloroanisole and were completely absent. Product purified by GLC gave a refractive index of n^{20}D 1.5353 (lit.[10] n^{20}D 1.5362)

Table I
Reaction of Aryl Chlorides with Sodium Methoxide in HMPA

Registry no.	Aryl chloride	Reaction conditions: Temp, °C	Time, h	Molar/equiv[a] CH_3ONa	Product	Yield,[b] %	Registry no.
541-73-1		90 90	20 19	1.2 1.1[c]		87 79	2845-89-8
95-50-1		90	19.5	1.1		78[d]	766-51-8
108-90-7		120	18.5	1.5		50	100-66-3
90-13-1		120	19	1.5		54	2216-69-5
106-43-4		120	24	1.5		13	104-93-8

[a] Commercial sodium methoxide used in all cases except where noted. [b] Yields determined by GLC. [c] Sodium methoxide generated in reaction mixture from methanol and sodium hydride. [d] Addition of 0.1 molar equiv of *p*-dinitrobenzene had no effect on yield. [e] Trace of 2-methoxynaphthalene also present.

and an infrared spectrum identical with that of an authentic sample. An alternative procedure involved generation of sodium methoxide from methanol and sodium hydride. A mixture of 0.71 g (22 mmol) of methanol, 1.06 g of a 50% dispersion of sodium hydride in mineral oil (22 mmol), and 40 ml of dry HMPA was stirred at room temperature for 1.5 h before addition of 2.94 g (20 mmol) of *m*-dichlorobenzene and heating at 90° for 19 h. Completion of the reaction as in the above procedure gave a 79% yield of *m*-chloroanisole.

o-Chloroanisole. A magnetically stirred mixture of 2.94 g (20 mmol) of *o*-dichlorobenzene, 1.19 g (22 mmol) of sodium methoxide, and 40 ml of dry HMPA was heated at 90° for 19.5 h in a flask equipped with a condenser and drying tube. A work-up procedure the same as that described for *m*-chloroanisole gave 2.66 g of liquid. Analysis of the liquid by GLC (SE-30, 120°, or methyl silicone, 145°) revealed that it consisted of o-chloroanisole and a small amount of unreacted *o*-dichlorobenzene and that the yield of o-chloroanisole was 78%. *m*-Chloroanisole had a shorter retention time than *o*-chloroanisole and was completely absent. Product purified by GLC gave a refractive index of n^{20}D 1.5440 (lit.[10] n^{20}D 1.5445) and an infrared spectrum identical with that of an authentic sample. When the above reaction was run in exactly the same manner except that 0.34 g (2 mmol) of *p*-dinitrobenzene was also added, there was no change in the yield of o-chloroanisole.

Anisole. A magnetically stirred mixture of 2.25 g (20 mmol) of chlorobenzene, 1.62 g (30 mmol) of sodium methoxide, and 40 ml of dry HMPA was heated at 120° for 18.5 h in a flask equipped with a condenser and drying tube. A work-up procedure the same as that described for *m*-chloroanisole gave 1.71 g of liquid. Analysis of the liquid by GLC (methyl silicone, 127°) revealed that it consisted of anisole and unreacted chlorobenzene and that the yield of anisole was 50%. Product purified by GLC gave an infrared spectrum identical with that of an authentic sample.

1-Methoxynaphthalene. A magnetically stirred mixture of 3.25 g (20 mmol) of 1-chloronaphthalene, 1.62 g (30 mmol) of sodium methoxide, and 40 ml of dry HMPA was heated at 120° for 19 h in a flask equipped with a condenser and drying tube. A work-up procedure identical with that described for *m*-chloroanisole gave 2.80 g of liquid. Comparison of GLC (Carbowax 20M, 165°) retention times with those of authentic samples revealed that the liquid consisted of 1-methoxy- and 2-methoxynaphthalene (97:3 ratio), some unreacted 1-chloronaphthalene, and an unidentified product of short retention time. The yield of 1-methoxynaphthalene, which had only a slightly shorter retention time than the 2-methoxy isomer, was 54%. Product purified by GLC gave a refractive index of n^{20}D 1.6219 (lit.[10] n^{20}D 1.6220) and an infrared spectrum identical with that of an authentic sample of 1-methoxynaphthalene.

p-Methylanisole. A magnetically stirred mixture of 2.53 g (20 mmol) of *p*-chlorotoluene, 1.62 g (30 mmol) of sodium methoxide, and 40 ml of dry HMPA was heated at 120° for 24 h in a flask equipped with a condenser and drying tube. A work-up similar to that previously described for *m*-chloroanisole gave 1.98 g of liquid. Analysis of the liquid by GLC (SE-30, 122° or Carbowax 20M, 120°) revealed that it consisted of *p*-methylanisole and much unreacted *p*-chlorotoluene and that the yield of *p*-methylanisole was 13%. Product purified by GLC gave an infrared spectrum identical with that of an authentic sample.

Registry No.—HMPA, 680-31-9; methoxide ion, 3315-60-4.

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(9) HMPA was dried by distillation from sodium hydride at reduced pressure. Sodium methoxide (Matheson) was used from freshly opened bottles. Refractive indices were determined with a Bausch and Lomb refractometer (type 33-45-58). Infrared spectra were recorded with a Perkin-Elmer Model 237B or Beckman IR-33 spectrometer. Gas chromatography (GLC) was performed on a Hewlett-Packard 5750B or Perkin-Elmer Model 154D chromatograph employing helium as the carrier gas at 50 ml/min. The following 6 ft × 0.25 in. columns were used: 10% SE-30 on 60–80 mesh Chromosorb W (AW-DMCS); 10% methyl silicone oil (SF-96) on 60–80 mesh Chromosorb W; 10% Carbowax 20M on 60–80 mesh Chromosorb W (AW-DMCS).
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An Oxime to Nitro Conversion. A Superior Synthesis of Secondary Nitroparaffins

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We have devised a convenient oxime to nitro conversion which constitutes an improved synthesis of secondary ni-

Table I
Selective Reduction of *gem*-Chloronitro Compounds

Registry no.	Compd	Reagent	Yield, % of nitro compd
598-92-5	1-Chloro-1-nitroethane	$(Bu_3Sn)_2O$–PMS	50[a]
600-25-9	1-Chloro-1-nitropropane	Bu_3SnH	30[a]
		H_2–cat.	65[b] (28)[c]
594-71-8	2-Chloro-2-nitropropane	Bu_3SnH	56[a]
		H_2–cat.	50[b]
22236-53-9	2-Chloro-2-nitrobutane	Bu_3SnH	73[a]
		$NaBH_4$	0
873-92-7	1-Chloro-1-nitrocyclohexane	Bu_3SnH	67[d]
		H_2–cat.	65
		RaNi–NaOH–H_2O	50

[a] Identified by GC retention times. Yields based on GC analysis. [b] Water solvent. [c] Ethanol solvent. [d] Isolated yield 28%.

Table II
Preparation of Secondary Nitroparaffins, $RCH(NO_2)R'$

R	R'	Yields, %[a] This[b]	Direct oxidn[16]	Iffland[16]	Nitrite[16]	Registry no.
Me	Me	67		0	26	79-46-9
Me	Et	75	47			600-24-8
Me	*t*-Bu	37	0	30	0	599-02-0
Me	*n*-Hex	95		10	23	4609-91-0
Et	*n*-Am	77				4609-92-1
n-Pr	*n*-Bu	77				4609-93-2
$(CH_2)_4$		69	60	55	57	2562-38-1
$(CH_2)_5$		70	62	50	0	1122-60-7

[a] Yields are distilled product. [b] Products were identified by comparison of infrared spectra and/or index of refraction to those of authentic samples or published data (ref 5, 18, 19). Where spectra were not published, the spectra were consistent with assigned structure.

troparaffins. The method involves treatment of an oxime with chlorine to give chloronitroso compound; oxidation with ozone to the chloronitro compound; and, finally, catalytic hydrogenation in the presence of 2 equiv of sodium hydroxide to the nitro compound.

$$RCR' \overset{NOH}{\parallel} \xrightarrow{Cl_2\text{-}CH_2Cl_2} RC(Cl)(NO)R' \xrightarrow{O_3\text{-}CH_2Cl_2} RC(Cl)(NO_2)R' \xrightarrow[H_2O\text{-}Pd/C]{NaOH\text{-}H_2} RCH(NO_2)R'$$

The method is essentially a two-pot operation. It is carried out without purification of intermediates and the final product is easily isolated, usually in high purity.

Each of the individual steps was studied before arriving at the optimum conditions. The chlorination of oximes to *gem*-chloronitroso compounds is a well-known one and has been carried out by numerous reagents, using a variety of conditions and solvents.[1]

The most suitable reagent from the standpoints of expense, yield, and convenience was elemental chlorine with CH_2Cl_2 as solvent.[2,3]

It was felt initially that the oxidation step would be quite easily accomplished, since it had been described in several different places in the literature.[4] Those reagents that have been reported such as HNO_3–H_2O_2,[5] HNO_3,[6] or O_2 in the presence of illumination[7] gave, at best, only moderate yields and were contaminated with various unidentified side products. Other reagents such as *m*-chloroperbenzoic acid, peracetic acid, activated manganese dioxide, or nickel peroxide likewise either failed outright or did not give satisfactory yields.

It was finally found that treating a *gem*-chloronitroso compound in methylene chloride solvent with a stream of ozonized oxygen gave the corresponding chloronitro compound in quantitative yield free of side products. The only example of oxidation of a *gem*-chloronitroso compound with ozone was reported in a patent and then only in a poor yield.[8] This may have been due to the acetic acid solvent that was employed.

Several unsuccessful attempts to selectively reduce *gem*-chloronitro compounds to nitro compounds with various reagents such as sodium borohydride, chromous chloride, or "various catalytic procedures" have been noted in the literature.[9,10] We found only one successful example of such a reduction; in a study of the reduction of *gem*-chloronitro compounds to oximes, it was noted that nitrocyclohexane could be obtained on hydrogenation of 1,1-chloronitrocyclohexane in the presence of aqueous base, followed by acidification.[11] We verified this result and extended it to other compounds. This proved to be a convenient, effective method. Uptake of hydrogen ceases at the theoretical amount. The nitro compound is easily isolated by acidification of the aqueous solution with hydroxylamine hydrochloride and extraction with ether.[12]

Reducing agents that were less successful, but which could prove useful in special cases, were tributyltin hydride,[13] tributyltin oxide–polymethylhydrogen siloxane,[14] and Raney alloy in aqueous base. In these instances, isolation of product proved to be difficult. We also verified that sodium borohydride is ineffective in this reaction. The results of our reduction experiments are shown in Table I.

Having thus delineated optimum conditions for each step of the sequence, we applied it to a series of ketoximes. As can be seen in Table II, this method gives better yields than the other methods of synthesizing secondary nitroparaffins; these other methods are direct oxidation of ketoximes with trifluoroperacetic acid,[15] the Iffland oxidation of ketoximes,[5] and nitrite displacement reactions on secondary halides.[16]

Other advantages of this method are that work-ups are simpler, reagent costs are lower, scale-ups are easier, and by-products are virtually eliminated (e.g., nitrite esters). Disadvantages are that not all ketoximes will react with chlorine[17] and not all functionalities would survive the reaction conditions.

With minor modifications this sequence can be applied to aldoximes to yield primary nitro compounds. The chlorination of the aldoxime is carried out at −60° to prevent the chloronitroso compound from rearranging to the hydroximoyl chloride.[20] The ozonization is then carried out while allowing the solution to warm up gradually. The final hydrogenation step is carried out at slightly higher hydrogen pressure (3 vs. 2 atm) than is necessary to produce secondary nitro compounds.

In this manner yields of 1-nitrobutane, 1-nitroheptane, and phenylnitromethane were 50, 44, and 65%, respectively. However, as a method of synthesizing primary nitro compounds it must be pointed out that this method is probably inferior to the nitrite displacement of primary aliphatic halides.

Experimental Section

Boiling points are uncorrected. Ir spectra were determined using a Perkin-Elmer 421 instrument. GLC analyses were performed with a Beckman GC/2 instrument employing an SE-30 on Chromosorb W column.

Materials. The oximes employed except 3-octanone oxime and 4-octanone oxime were commercial materials and used without purification. 3-Octanone oxime and 4-octanone oxime were prepared by standard oximation of the corresponding ketones with hydroxylamine hydrochloride and excess sodium hydroxide in ethanol–water solvent. All other reagents used were commercial materials and used as received. The methylene chloride solvent was distilled before use.

General Procedure for Synthesis of Secondary Nitroparaffins. Nitrocyclopentane from Cyclopentanone Oxime. To a solution of 5.0 g (0.05 mol) of cyclopentanone oxime in 50 ml of methylene chloride cooled to 0–5° with an ice bath was added a slow stream of chlorine gas until the initially blue solution took on a distinct greenish cast.[21] This solution was then flushed with a stream of oxygen for approximately 15 min to remove excess chlorine and then was treated with an ozone–oxygen stream[22] until the blue color was completely discharged. The methylene chloride solvent was removed in vacuo on a rotary evaporator to leave a residue of 7.75 g (100%) of 1-chloro-1-nitrocyclopentane. The residue was added to a solution of 5.0 g of sodium hydroxide in 50 ml of water in a hydrogenation bottle. To this mixture was added 1.0 g of 5% palladium on charcoal catalyst. It was then hydrogenated on a Parr hydrogenation apparatus with an initial pressure of 26 psi until uptake of hydrogen ceased. The mixture was filtered to remove catalyst and then cooled to 0° and acidified at this temperature with 13 g (0.19 mol) of hydroxylamine hydrochloride. The mixture was allowed to stir overnight,[23] saturated with sodium chloride, and extracted with 3 × 50 ml of diethyl ether. The ether solution was dried over sodium sulfate, the ether removed in vacuo on a rotary evaporator, and the residue distilled to give 4.0 g (69%) of nitrocyclopentane, bp 82–84° (30 mm), n^{25}D 1.4525 [lit.[5] bp 90° (40 mm), n^{25}D 1.4518]. The infrared spectrum had bands at 1540 and 1370 cm^{-1} (RNO_2) and no other complicating features.

General Procedure for the Synthesis of Primary Nitroparaffins. 1-Nitroheptane from Heptaldoxime. To a solution of 5.0 g (0.038 mol) of heptaldoxime in 75 ml of methylene chloride cooled to −60° with a dry ice–acetone bath was added a slow stream of chlorine gas for approximately 5 min. At the end of this time the mixture was distinctly green. This solution was then flushed with a stream of oxygen for approximately 15 min at −60° and then was treated with an ozone–oxygen stream while allowing the mixture to warm up gradually to room temperature over a period of ca. 4 h. As the solution warmed up, the green color faded to yellow and then again turned to blue. When the blue color was completely discharged, the methylene chloride was removed in vacuo to leave a residue of 7.0 g (100%) of 1-chloro-1-nitroheptane. This residue was added to a solution of 5.0 g of sodium hydroxide in 50 ml of water and 1.0 g of 5% palladium on charcoal was then added. The mixture was then hydrogenated on a Parr hydrogenation apparatus with an initial pressure of 50 psi until uptake of hydrogen ceased. The solution was worked up as previously described to give 2.5 g (44%) of 1-nitroheptane, bp 42–45° (0.001 mm), n^{25}D 1.4310 [lit.[19] bp 66° (2 mm), n^{25}D 1.4285]. The infrared spectrum of the product was identical with that published for 1-nitroheptane.[19]

Tributyltin Hydride Reduction of 1-Chloro-1-nitrocyclohexane. Into a flask equipped with a reflux condenser, stopcock with septum inlet, nitrogen inlet, and magnetic stirrer were placed 5 g of 1-chloro-1-nitrocyclohexane and 50 mg of azobisisobutyronitrile. After flushing with prepurified nitrogen for 1 h, 9 g of tributyltin hydride (prepared from tributyltin chloride[13]) was added all at once through the septum, using a syringe. The mixture was heated at 90° until the Sn–H band at 1815 cm^{-1} disappeared and the nitro band shifted from 1570 cm^{-1} to 1540 cm^{-1} (ca. 2 h). Gas chromatographic analysis showed a 65% conversion to nitrocyclohexane. Distillation of the reaction mixture yielded 1.0 g (26%) of product, bp 106–108° (40 mm) [lit.[5] bp 106–108° (40 mm)].

Tributyltin Oxide–Polymethylhydrogen Siloxane Reduction of 1-Chloro-1-nitroethane. In a large Pyrex test tube were mixed successively 5 g (0.05 mol) of 1-chloro-1-nitroethane, 4.6 g (0.75 equiv) of polymethylhydrogen siloxane, and 22.8 g (0.038 equiv) of tributyltin oxide. On the addition of the tributyltin oxide, a red color developed. The tube was stoppered and the contents were photolyzed in a Hanovia photochemical reactor for 5 h total time. After 1 h the red color had disappeared and GLC analysis showed approximately 15% conversion. After 5 h, analysis showed approximately 50% conversion which did not increase with further irradiation. Attempted isolation by distillation failed to yield any 1-nitroethane.

Registry No.—Nitroethane, 79-24-3; 1-nitropropane, 108-03-2; 2-propanone oxime, 127-06-0; 2-butanone oxime, 96-29-7; 3,3-dimethyl-2-butanone oxime, 2475-93-6; 2-octanone oxime, 7207-49-0; 3-octanone oxime, 7207-50-3; 4-octanone oxime, 7207-51-4; cyclopentanone oxime, 1192-28-5; cyclohexanone oxime, 100-64-1; 2-chloro-2-nitrosopropane, 2421-26-3; 2-chloro-2-nitrosobutane, 681-01-6; 2-chloro-3,3-dimethyl-2-nitrosobutane, 677-58-7; 2-chloro-2-nitrosooctane, 690-91-5; 3-chloro-3-nitrosooctane, 57484-12-5; 4-chloro-4-nitrosooctane, 57484-13-6; 1-chloro-1-nitrosocyclopentane, 694-63-3; 1-chloro-1-nitrosocyclohexane, 695-64-7; 2-chloro-3,3-dimethyl-2-nitrobutane, 57484-14-7; 2-chloro-2-nitrooctane, 57484-15-8; 3-chloro-3-nitrooctane, 57484-09-0; 4-chloro-4-nitrooctane, 57484-10-3; 1-chloro-1-nitrocyclopentane, 931-93-1; methylene chloride, 75-09-2; 1-nitroheptane, 693-39-0; heptaldoxime, 629-31-2; 1-chloro-1-nitroheptane, 57484-11-4.

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(22) The concentration of ozone was not determined and is probably not important since the reaction can be followed by color change. We used a "homemade" electric discharge ozonator, but any commercial model should suffice.
(23) In some instances the regeneration of the nitro compound from the salt is very slow, as is the case for nitrocyclopentane. Other nitro compounds were usually generated more rapidly. This phenomenon has been noted elsewhere.[5]

Phase Transfer Catalyzed Reactions. II. Reactions of Methyl 3-Deoxy-3-nitro-β-D-hexopyranosides with Active Methylene Compounds

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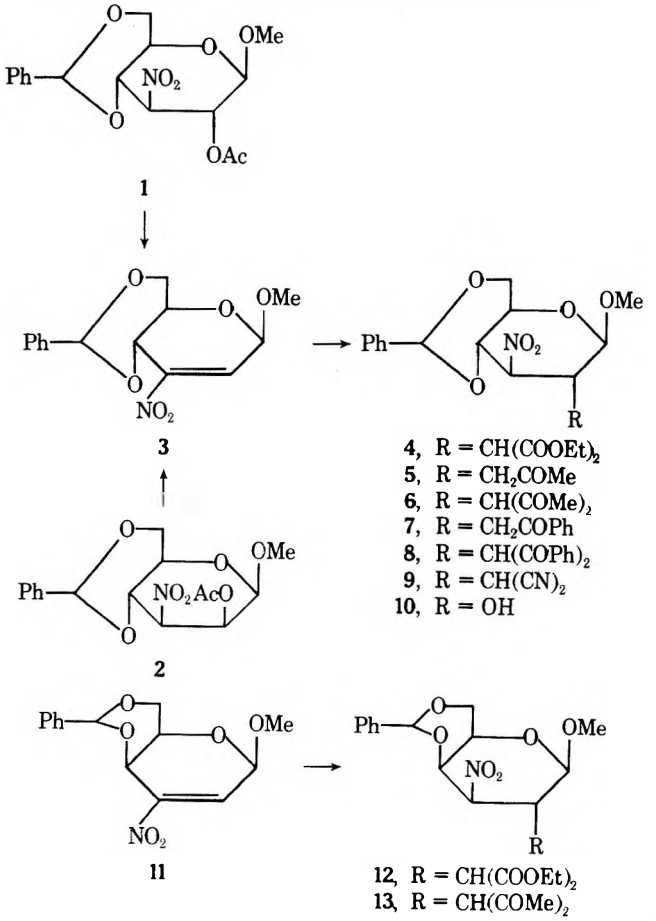
In recent years a considerable number of C-branched-chain sugars have been isolated as a component of natural sources, especially in antibiotics,[1] and synthetic studies on these sugars have been developed.[2] Some nitro sugars were shown to be useful intermediates for the purpose; they react with hydrogen cyanide[3-5] or active methylene compounds[6,7] to afford the corresponding C-branched-chain nitro sugars.

In a previous paper[8] we showed the usefulness of a phase transfer process for the selective preparation of 2-C-branched-chain nitro sugars having the thermodynamically less stable manno configuration; these were obtained from methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (the anomer of **3**) on treatment with some active methylene compounds. In the present paper we wish to describe some results on application of this phase transfer process to a β series of nitro sugars **1**, **2**, **3**, and **11**.



The reaction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**1**) with ethyl malonate in benzene–0.2 N sodium hydroxide in the presence of hexadecyltributylphosphonium bromide as a phase transfer catalyst afforded methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-β-D-glucopyranoside (**4**) in 75% yield. Similar reactions of the 2-*O*-acetylmannopyranoside (**2**) and nitro olefin **3** also gave **4** in good yield, showing that the reactions of **1** and **2** involve the nitro olefin intermediate **3**.

A similar reaction of **3** with acetylacetone afforded the 2-*C*-acetonyl glucopyranoside (**5**) with a release of an acetyl group, but this deacetylation was suppressed under milder conditions and the 2-*C*-(diacetyl)methyl derivative (**6**) was obtained in good yield. Similar results were observed in the reaction of **3** with dibenzoylmethane; the 2-C-benzoylmethylglucopyranoside (**7**) was formed under stronger conditions, and under the milder conditions, the 2-C-(dibenzoyl)methyl derivative (**8**) was isolated. Similarly treatment of **3** with malononitrile under the milder conditions gave the 2-*C*-(dicyano)methylglucopyranoside (**9**).

On similar treatment of **3** with acetone, however, instead of an acetonyl group a hydroxyl group was introduced at the C-2 position; this result may be rationalized by assuming that the ion pair formed between the phase transfer catalyst and the carbanion derived from acetone was too weak to go to the organic layer.

Structural assignments of these compounds were based on their NMR spectra (Table I); large values of coupling constants (≥8 Hz) of H^1–H^2 indicate their β-gluco configuration.

Treatment of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*threo*-hex-2-enopyranoside (**11**) with ethyl malonate and acetylacetone, under the conditions used for the preparation of **6**, gave galacto isomers **12** and **13**, respectively. The former product (**12**) was identical with an authentic sample prepared by the procedure of Baer et al.[6] The galacto configuration of **13** was deduced from its NMR spectrum: $J_{1,2}$ = 8.8, $J_{2,3}$ = 12.2, and $J_{3,4}$ = 3.8 Hz.

Experimental Section

All the melting points were determined in capillaries and are uncorrected. The NMR spectra were recorded at 100 MHz with a JNM-4H-100 (JEOL) spectrometer in chloroform-*d*, using tetramethylsilane as the internal standard. In this section the catalyst means hexadecyltributylphosphonium bromide.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-β-D-glucopyranoside (4). A. From Nitro Acetate 1. A mixture of **1**[9] (118 mg, 0.33 mmol), ethyl malonate (120 mg, 0.75 mmol), benzene (10 ml), and 1 N NaOH (1.25 ml) was stirred for 22 h at room temperature in the presence of the catalyst (12 mg) and then washed with water (3 × 5 ml). The benzene layer was evaporated in vacuo to give a residue (135 mg). Recrystallization from ethanol gave 113 mg (75%) of **4**, which was identi-

Table I
100-MHz NMR Spectra in $CDCl_3$ (Me_4Si as an Internal Standard)

Compd	Chemical shifts, δ						Coupling constants, Hz				
	H^1	H^2	H^3	H^4	PhCH	$H^{2'}$[a]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{2,8}$
6	5.15	2.82	4.90	4.15	5.52	3.58	8.1	11.6	10	8.8	3.8
7	4.82	2.68	5.23	4.18	5.53	3.24 3.07	8.4	11.6	10	8.8	4.4 4.4
8	5.36	3.11	5.27	4.08	5.49	?	8.1	11.3	9.7	8.8	3.4
13	4.87	3.25	5.04	4.53	5.51	3.98	8.8	12.2	3.8	≤1.5	3.1

[a] $H^{2'}$ means the acidic methine or methylene proton(s) of a chain moiety.

cal with an authentic sample prepared by the procedure of Baer et al.[6]

B. From Nitro Acetate 2. The same treatment of 2[10] with ethyl malonate gave **4** in 77% yield.

C. **From Nitro Olefin 3.** Under the same conditions described above except for the decreased amount of 1 N NaOH to 0.9 ml, reaction between 3[9] (98 mg) and ethyl malonate gave **4** in 77% yield. The yield was up to 87% when this reaction was carried out under the conditions described for preparation of **6**.

Methyl 2-*C*-Acetonyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (5). To a solution of **3** (98 mg, 0.33 mmol), acetylacetone (75 mg, 0.75 mmol), and the catalyst (12 mg) in benzene (10 ml) was added 1 N NaOH (0.9 ml). The mixture was stirred for 22 h and then evaporated in vacuo to afford a crystalline residue (108 mg), which was recrystallized from ethanol–acetone to afford 95 mg (81%) of **5**: mp 176–177 °C; $[\alpha]^{20}D$ −66.9° (*c* 1, MeOH); ir (KBr) 1715 (CO) and 1560 cm^{-1} (NO_2).

Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11, H, 6.02; N, 3.99. Found: C, 58.40; H, 6.04; N, 4.17.

The same product was also prepared in 80% yield by the similar reaction of **1** (236 mg, 0.67 mmol), acetylacetone (150 mg, 1.5 mmol), and the catalyst (60 mg) in benzene (20 ml)–0.5 N NaOH (5 ml) stirring for 23 h at room temperature.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(diacetyl)-methyl-3-nitro-β-D-glucopyranoside (6). To a solution of **3** (29.3 mg, 0.1 mmol), acetylacetone (18 mg, 0.18 mmol), and the catalyst (2 mg) in benzene (3 ml) was added 0.2 N NaOH (0.1 ml). The mixture was stirred for 1.5 h at room temperature and then washed with water (3 × 5 ml). The organic layer was evaporated to afford a NMR spectroscopically pure syrup (35 mg, 89%). The syrup (105 mg) was crystallized from ethanol to give **6** (83%): mp 110–111 °C; $[\alpha]^{20}D$ −153° (*c* 1, $CHCl_3$); ir (KBr) 1710 (CO) and 1560 cm^{-1} (NO_2).

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 57.72; H, 6.03; N, 3.72.

Methyl 2-*C*-Benzoylmethyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (7). To a solution of **3** (87.9 mg, 0.3 mmol), dibenzoylmethane (138 mg, ca. 0.4 mmol), and the catalyst (12 mg) in benzene (24 ml) was added 0.2 N NaOH (8 ml). The mixture was stirred for 18 h at room temperature and then evaporated in vacuo to give a crystalline residue. Recrystallization from ethanol gave 102 mg (83%) of **7**: mp 172–173 °C; $[\alpha]^{20}D$ −29° (*c* 1, $CHCl_3$); ir (KBr) 1680 (CO) and 1550 cm^{-1} (NO_2).

Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 64.20; H, 5.65; N, 3.39.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(dibenzoyl)-methyl-3-nitro-β-D-glucopyranoside (8). Treatment of **3** (58.6 mg, 0.2 mmol) with dibenzoylmethane (89.6 mg, ca. 0.28 mmol) under the conditions used to prepare **6** gave a pure syrup (90 mg, 91%). The syrup was chromatographed on silica gel (C-200, Wako-gel) with benzene. The eluate was evaporated in vacuo to give a syrup, which was crystallized from *n*-propyl alcohol: yield 81%; mp 102–103 °C; $[\alpha]^{20}D$ −194° (*c* 0.5, $CHCl_3$); ir (KBr) 1680 (CO) and 1550 cm^{-1} (NO_2).

Anal. Calcd for $C_{29}H_{27}NO_8$: C, 67.30; H, 5.26; N, 2.71. Found: C, 67.18; H, 5.38; N, 2.66.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(dicyano)-methyl-3-nitro-β-D-glucopyranoside (9). Treatment of **3** (147 mg, 0.5 mmol) with malononitrile (36.5 mg, 0.55 mmol) under the conditions used to prepare **6** gave a NMR spectroscopically pure crystalline residue (158 mg, 87.8%), which was recrystallized from ethanol to afford 146 mg (81%) of **9**: mp 177–178 °C; $[\alpha]^{20}D$ −40.2° (*c* 1, MeOH); ir (KBr) 1565 cm^{-1} (NO_2).

Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.70. Found: C, 56.92; H, 4.77; N, 11.58.

Methyl 4,6-*O*-Benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (10). Treatment of **3** (58.6 mg) with acetone (14.5 mg) under the conditions used to prepare **5** gave **10** in 73% yield, which was identical with an authentic sample.[9]

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-β-D-galactopyranoside (12). Treatment of 11[10] (58.6 mg) with ethyl malonate under the conditions used to prepare **6** gave a NMR spectroscopically pure residue of **12**, which was recrystallized from ethanol, yield 82%. It was identical with an authentic sample prepared by Baer et al.[6]

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(diacetyl)-methyl-3-nitro-β-D-galactopyranoside (13). Treatment of **11** (58.6 mg) with acetylacetone under the conditions used for the preparation of **6** afforded a syrup. Its NMR spectrum showed that it consisted of **13** and unknown compound in a ratio of ca. 3:1. Crystallization from ethanol gave 21.6 mg (55%) of **13**: mp 152.5–153.5 °C; $[\alpha]^{20}D$ −53.0° (*c* 1, $CHCl_3$); ir (KBr) 1700 (CO) and 1550 cm^{-1} (NO_2).

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 57.90; H, 5.74; N, 3.71.

Registry No.—**1**, 18604-56-3; **2**, 3650-61-1; **3**, 25541-58-6; **4**, 20777-18-8; **5**, 29847-30-1; **6**, 57559-94-1; **7**, 57559-95-2; **8**, 57559-96-3; **9**, 29847-31-2; **10**, 25541-57-5; **11**, 3650-62-2; **12**, 20777-19-9; **13**, 57559-97-4; ethyl malonate, 105-53-3; acetylacetone, 123-54-6; dibenzoylmethane, 120-46-7; malononitrile, 109-77-3.

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Quinazolines and 1,4-Benzodiazepines. LXXII.[1] Synthesis of Benzoxazinones from Anthranilic Acids. Revision of Structures Originally Described as 1,4-Benzodiazepines

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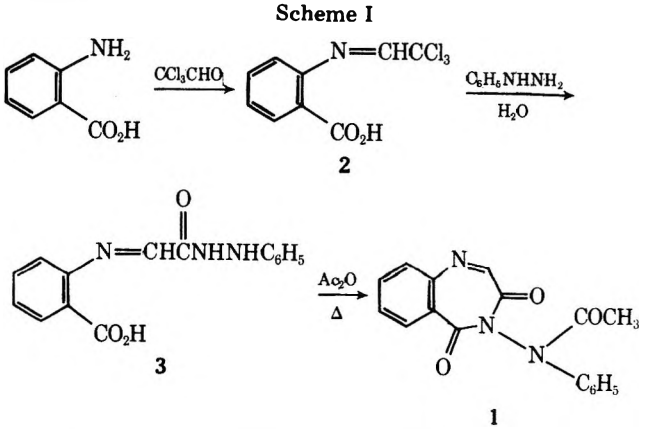
A report in the chemical literature[2] in 1904 described the preparation of a compound to which the 1,4-benzodiazepine structure **1** was assigned. The mechanism for the formation of **1** from anthranilic acid was reported as outlined in Scheme I.

Scheme I



Owing to our continuing interest in 1,4-benzodiazepines, we have repeated the original work and found that although the reactions proceed ostensibly as described, the structures previously assigned to compounds **1**, **2**, and **3** are incorrect. The final product **1** was found to have the benzoxazinone structure **6a** rather than the 1,4-benzodiazepine structure **1**. The revised pathway for the formation of **6a** from anthranilic acid is shown in Scheme II.

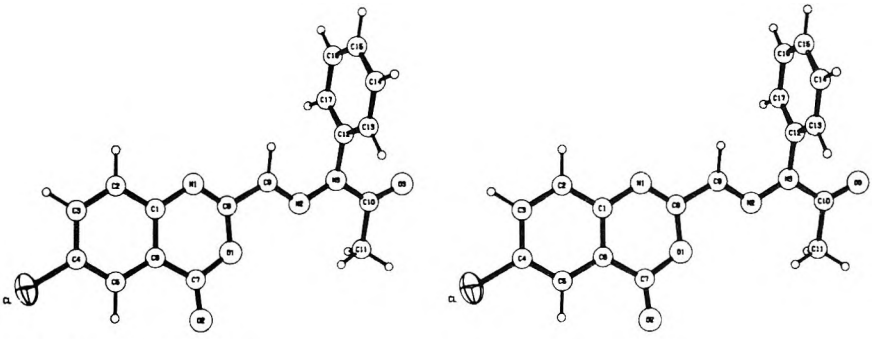
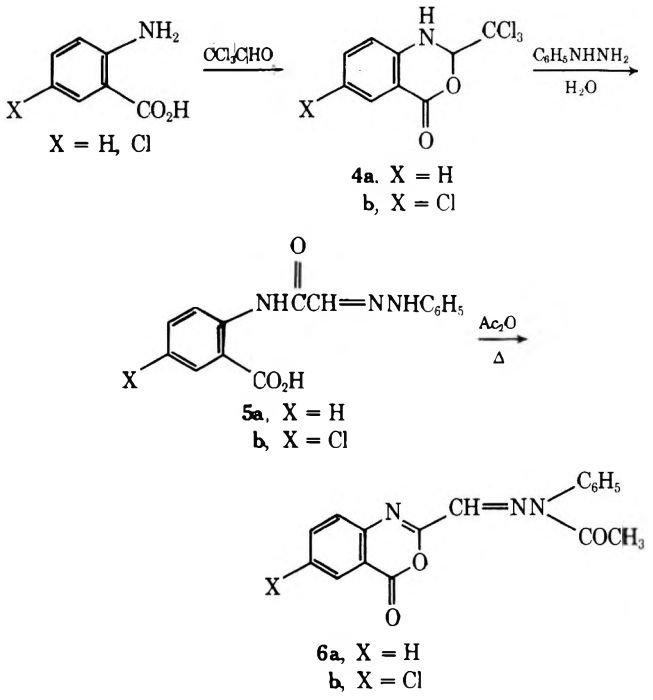


Figure 1. A stereodrawing of the structure of **6b**.

Scheme II



The NMR spectrum of **4a** (and **4b**) showed the presence of a NH proton (doublet, J = 4 Hz) and a methine proton (doublet, J = 4 Hz). The ir spectrum showed a NH band and a lactone absorption peak but no absorption due to an acid group. These data are consistent with **4a** (and **4b**) but not with **2**. The structures of **5a,b** were not proven conclusively but were assigned on the basis that the compounds **6a,b** were formed on acetylation rather than the 1,4-benzodiazepine **1**. Since an interpretation of the spectral data on the final product **6a** did not allow a definite assignment of structure, the chloro analogue **6b** was subjected to single-crystal x-ray analysis. The spectral data and physical properties (melting point, solubility, TLC behavior, etc.) of compounds **6a, 6b,** and intermediates were essentially identical, indicating that the chlorine substituent did not influence the course of the reactions.

Small acicular crystals of **6b** were obtained upon crystallization from CH_2Cl_2–hexane. Crystals of **6b** are triclinic, space group $P\bar{1}$, with a = 4.733 (2), b = 14.418 (5), c = 23.185 (10) Å, α = 91.59 (3), β = 93.45 (3), γ = 91.49 (3)°, and Z = 4. Intensity data were measured on a Hilger-Watts four-circle diffractometer (θ–2θ scans, Ni-filtered Cu Kα radiation; pulse height discrimination). The size of the crystal used for data collection was 0.04 × 0.05 × 0.55 mm; no absorption correction was made (μ = 23.4 cm^{-1}). Of the 4355 independent reflections measured, only 1441 had intensities which were greater than background.

The crystal structure was solved by a multiple solution procedure[3] and was refined by full-matrix least squares. In the final refinement anisotropic thermal parameters were used for the chlorine atoms and isotropic temperature factors were used for all other atoms. The positions of the hydrogen atoms were calculated and they were included in the structure factor calculations but were not refined. The final unweighted and weighted discrepancy indices are R = 0.096 and wR = 0.080 for the 1441 observed reflections. A difference map based on the final parameters has no features greater than 0.3 eA^{-3} in magnitude.

The unit cell contains two independent molecules. The conformations of the two independent molecules are similar and the bond lengths and angles in the two independent molecules are equivalent. A projection of the molecule is shown in Figure 1.

Experimental Section[4]

1,4-Dihydro-2-trichloromethyl-2*H*-3,1-benzoxazin-4-one (4a). A solution of 20 g (0.146 mol) of anthranilic acid and 22 g (0.15 mol) of chloral in 175 ml of benzene was refluxed for 4 h. The solution was filtered and the filtrate allowed to cool. Filtration gave 14.6 g (37%) of **4a** as colorless needles: mp 150–152°; ir (KBr) 3315, 3270 (NH), 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 6.00 (1 H, d, CH), 6.53–7.67 (4 H, m, C_6H_4), 8.25 (1 H, d, NH).

Anal. Calcd for $C_9H_6Cl_3NO_2$: C, 40.56; H, 2.27; N, 5.26. Found: C, 40.75; H, 2.22; N, 4.82.

6-Chloro-1,4-dihydro-2-trichloromethyl-2*H*-3,1-benzoxapin-4-one (4b). A mixture of 5-chloroanthranilic acid (1.72 g, 10 mmol) and 2 ml of chloral were ground together in a mortar heated on a steam bath. After the chloral had evaporated, 3 ml of chloral was added, followed by a last increment of 2 ml of chloral. The crude product was recrystallized from benzene to give 2.2 g (73%) of **4b** as colorless needles: mp 168–170.5°; ir (KBr) 3380, 3280 (NH), 1730 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 6.23 (1 H, d, CH), 7.07–7.70 (3 H, m, C_6H_3), 8.70 (1 H, d, NH).

Anal. Calcd for $C_9H_5Cl_4NO_2$: C, 35.92; H, 1.67; N, 4.65; Cl, 47.12. Found: C, 36.15; H, 1.65; N, 4.55; Cl, 46.93.

2-[1-(Phenylhydrazinyl-2-ylidene)acetylamino]benzoic Acid (5a). A cold solution of 2 g (19 mmol) of phenylhydrazine in 25 ml of H_2O and 15 ml of 3 N H_2SO_4 was added to a slurry of 5 g (19 mmol) of **4a** in 60 ml of EtOH. After stirring at room temperature overnight, the solution was refluxed for 1 h, cooled, and filtered to give 2.7 g (50%) of **5a**. The analytical sample was prepared by recrystallization from EtOH–H_2O: mp 235–237° (lit.[2] mp 243°); ir (KBr) 3300–2300 (CO_2H), 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.37; H, 4.51; N, 14.64.

2-[1-(Phenylhydrazinyl-2-ylidene)acetylamino]-5-chlorobenzoic Acid (5b). This compound was prepared in 76% yield in an analogous manner as that described for the preparation of **5a**. The analytical sample was prepared by recrystallization from EtOH–H_2O: mp 253–255; ir (KBr) 3275–2300 (CO_2H), 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{12}ClN_3O_3$: C, 56.70; H, 3.81; N, 13.23. Found: C, 56.52; H, 3.88; N, 13.19.

***N*-[(4-Oxo-4*H*-3,1-benzoxazin-2-yl)methyleneamino]-*N*-phenylacetamide (6a).** The following procedure is a modification of that described by Gärtner and although both methods gave the same product, the yields are greatly enhanced in the modified pro-

cedure. A mixture of 2.2 g (7.8 mmol) of **5a** and 10 ml of acetic anhydride was refluxed for 3.5 h. The solution was cooled and poured into 200 ml of ether and 200 ml of petroleum ether (bp 30–60°) and the resulting solid filtered to give 900 mg (37%) of **6a**. The filtrate was concentrated and the residue refluxed with 20 ml of acetic anhydride for 4 h to give an additional 800 mg (33%) of **6a**. The analytical sample was prepared by recrystallization from acetone–hexane: mp 267–268° (lit.[2] mp 260–262°); ir ($CHCl_3$) 1765, 1700 cm^{-1} (2 C=O).

Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.45; H, 4.26; N, 13.67. Found: C, 66.40; H, 4.36; N, 13.55.

***N*-[(6-Chloro-4-oxo-4*H*-3,1-benzoxazin-2-yl)methyleneamino]-*N*-phenylacetamide (6b).** A mixture of 1.6 g (5 mmol) of **5b** and 25 ml of acetic anhydride was refluxed for 3.5 h, cooled, and poured into ether–petroleum ether. Filtration gave 1.3 g (76%) of **6b**. The analytical sample was prepared by recrystallization from CH_2Cl_2–hexane to give **6b** as colorless needles: mp 266–267°; ir ($CHCl_3$) 1770, 1703 cm^{-1} (2 C=O).

Anal. Calcd for $C_{17}H_{12}ClN_3O_3$: C, 59.79; H, 3.54; N, 12.30. Found: C, 59.73; H, 3.33; N, 12.46.

Acknowledgment. The authors thank the following members of our Physical Chemistry Department, under the direction of Dr. R. P. W. Scott: Dr. F. Scheidl for elemental analyses, Dr. T. Williams for NMR spectra, and Mr. S. Traiman for ir spectra.

Registry No.—**4a**, 57527-44-3; **4b**, 57527-45-4; **5a**, 57527-46-5; **5b**, 57527-47-6; **6a**, 57527-48-7; **6b**, 57527-49-8; anthranilic acid, 118-92-3; chloral, 75-87-6; 5-chloroanthranilic acid, 635-21-2; phenylhydrazine, 100-63-0; acetic anhydride, 108-24-7.

Supplementary Material Available. Tables of the positional and thermal parameters for the structure of **6b** (2 pages). Ordering information is given on any current masthead page.

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An Electron Spin Resonance Study of Kinetics in the SRN1 Reaction of Aryl Halides with Potassium

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The reaction of aryl halides with alkali metals is known to be quite rapid,[1-3] with the anion radical of the aryl halide generally decomposing in less than 1 s, even at very low temperatures. The ESR signal normally obtained after the decomposition is that of the parent hydrocarbon anion radical. We have modified the usual reduction procedure[4] in order to observe the decay of the arene hydrocarbon anion radical in its electron exchange reaction with excess aryl halide (step 4 of Scheme II).

In this modification, a 10^{-3} M solution of the aryl halide in 2:1 THF–DME is only momentarily brought into contact with a potassium mirror at −135°. The solution (removed from contact with the metal) is immediately plunged into a precooled ESR cavity and the ubiquitous[5] arene hydrocarbon signal observed. Under these circumstances, the aryl halide is readily available for electron exchange with the small amount of freshly produced hydrocarbon anion radical.

With the biphenylyl halides what is actually observed then is the decay of the biphenyl anion radical, a special case of the SRN1 mechanism recently recognized by Bunnett et al.[6] and generalized in Scheme I.[7]

Scheme I

$$\text{electron donor} + \text{ArX} \longrightarrow (\text{ArX})\cdot^- \quad (1)$$

$$(\text{ArX})\cdot^- \longrightarrow \text{Ar}\cdot + \text{X}^- \quad (2)$$

$$\text{Ar}\cdot + \text{R}:^- \longrightarrow (\text{ArR})\cdot^- \quad (3)$$

$$(\text{ArR})\cdot^- + \text{ArX} \longrightarrow \text{ArR} + (\text{ArX})\cdot^- \quad (4)$$

The decay of the biphenyl anion radical signal in step 4 follows excellent first-order kinetics,[8] consistent with the SRN1 mechanism. The reaction steps of Scheme II follow the parallel paths of Scheme I, in which the solvent behaves as the "R" donor (steps 3).

Scheme II

$$\text{K}\cdot + \text{ArX} \longrightarrow (\text{ArX})\cdot^- + \text{K}^+ \quad (1)$$

$$(\text{ArX})\cdot^- \longrightarrow \text{Ar}\cdot + \text{X}^- \quad (2)$$

$$\text{Ar}\cdot + \text{solvent-H} \longrightarrow \text{ArH} \xrightarrow[\text{of K}\cdot]{\text{remaining traces}} (\text{ArH})\cdot^- \quad (3)$$

$$(\text{ArH})\cdot^- + \text{ArX} \longrightarrow \text{ArH} + (\text{ArX})\cdot^- \quad (4)$$

It must be noted that Scheme II requires one extra reduction as part of step 3 in which the remaining traces of solvated potassium are used up to produce more biphenyl anion radical. The chain proceeds until the ultimate product is unreduced biphenyl. If the final diamagnetic product is once again subjected to a somewhat longer reduction, the biphenyl signal is produced instantaneously and the signal does not decay.

Following the initial decay of the biphenyl signal from biphenylyl fluoride, a dimerization product, quaterphenyl anion radical, was observed to replace the biphenyl signal after some 90 min at −100°. The dimer probably arises from $2\text{Ar}\cdot \rightarrow$ Ar–Ar, followed by reduction via residual $\text{ArH}\cdot^-$ or K·. Since quaterphenyl was not observed in any of the other reactions, it is possible that a high initial concentration of Ar· from ArF could produce this unique result. The highly reactive ArF would give this high initial concentration.

As may be seen in Table I, we also attempted a similar reduction of 4-nitrilobiphenyl; however, owing to the stabilizing influence of the CN group, we succeeded in obtaining initially only the decay (first order) of the parent anion radical.[9] Upon subsequent reduction at −120°, only the biphenyl signal was found. Evidently, for this system step 2 is quite slow, using up all available solvated metal, and the reaction stops at the step 3 production of biphenyl (unreduced).

We measured the decomposition rates for three of the biphenylyl halides at two temperatures (Table I). Above

Table I
Pseudo-First-Order Kinetics in the Reaction of Biphenyl Radical Anion with Biphenyl 4-Halides

Registry no.	C_6H_5–C_6H_4X X =	Temp, °C	$k \times 10^4$, s^{-1}	ΔH, cal deg^{-1} mol^{-1}
324-74-3	F	−100	2.58 ± 0.5	
2051-62-9	Cl	−40	10.8 ± 0.9	15.4 ± 2.5
		−50	2.43 ± 0.5	
92-66-0	Br	−40	14.4 ± 0.9	22.8 ± 3.7
		−60	1.44 ± 0.5	
1591-31-7	I	−40	422. ± 10	17.8 ± 2.5
		−60	11.6 ± 1.0	
2920-38-9	CN	22	0.0362 ± 0.001	

−40° these materials were highly unstable, and below about −70° the reaction times were rather too long to measure accurately. From these measurements a very rough estimate of the activation energies may be calculated. The value obtained for 4-bromobiphenyl appears rather high, yet considering the error range, all three are somewhat similar. Nevertheless, the reaction rates of the halides Cl, Br, and I at −40° are sucessively more rapid. Since the reaction of 4-fluorobiphenyl with biphenyl·⁻ was too rapid to measure at temperatures higher than −100°, we were not able to attempt an activation energy calculation for it.[10]

We are presently investigating the corresponding naphthyl halide series, and expect to report on them in the near future.

Experimental Section

All compounds and solvents used in this study are available from Aldrich Chemical Co. and were used as purchased (with the exception of solvents—distilled and stored over Na metal). The glass reduction apparatus in its simplest form has been described earlier.[4] The EPR instrument used is a JES-ME-1X (Jeolco) with variable temperature accessory of the Universidad de Los Andes.

A typical kinetic run may be described as follows. The sample tube (in which the K mirror and the ca. 0.3 mg of aromatic compound in 1 ml of 2:1 THF–DME solution are maintained separately) was cooled in a bath consisting of a thick syrup of isopropyl alcohol and liquid nitrogen at −135°. The sample tube was tipped and the solution allowed to contact the metal mirror for almost 1 s. On righting the tube for insertion into the cavity, the solution was agitated a bit in a bulge provided on the tube for mixing. The tube was rapidly wiped of alcohol and inserted into the precooled cavity (−135°). By this time, however, the tube itself was usually ca. −100° (the lowest temperature available for measurement). As soon as an appropriate temperature was reached, the diminution of the nine-line biphenyl signal produced was followed in sweeps of approximately 2.0 min.

The initial intensities of all halides were ±10%, and were followed for ca. 10 min at −40° and ca. 50 min at −60° (six to ten points taken). At least three runs were made on each sample and the slopes of each run were within the error range of any single run. The results presented in Table I are the average results of the three runs.

Inasmuch as the error involved in the calculation of the activation energy puts all three halides (Cl, Br, and I) within the same range, we must consider these values as only approximate.

Registry No.—Biphenyl radical anion, 34509-93-8.

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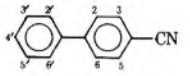
(8) Actually pseudo-first-order, inasmuch as the aryl halide is in large excess in the bimoiecular reaction of step 4.
(9) Splitting constants obtained from a McLachlan calculation and experimental values: $a^N_{CN} = 5.8$, $a_{3,5} = 2.8$, $a_{2,6} = 0.7$, $a_{2',4',6'} = 0.5$, $a_{3',5'} = 0.2$ G.



(10) Predicting the order of reactivity in various radical reactions of aryl halides has been a rather fruitless task: PhCN > PhI > PhBr (for e_{aq}) (ref 1); ArI < ArBr or ArCl (for KNH_2, NH_3) (ref 6). We too find the practice speculative, and prefer to offer for our system only the observations concerning the CN group and the order of reactivity of the halides at −40° as ArF ≫ ArI > ArBr > ArCl.

Synthesis of Cyanohydrins from Cyanides. Transition Metal Peroxide Reactions

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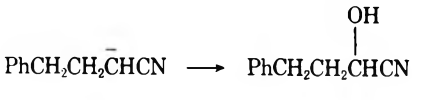
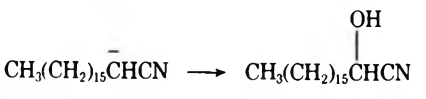
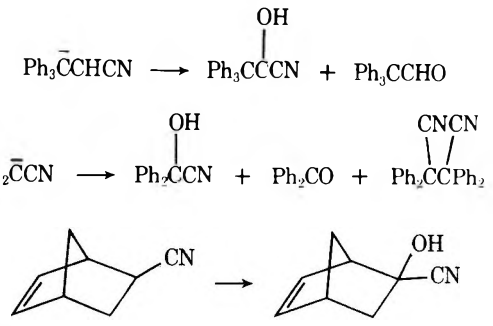
We have previously described the hydroxylation of enolates by the readily available molybdenum peroxide MoO_5·Py·HMPA (MoOPH).[1,2] In this paper, we report the analogous conversion of certain cyanide-stabilized anions to cyanohydrins.

Addition of a solution of 4-phenylbutyronitrile in dry THF to lithium diisopropylamide followed by reaction with MoOPH at −23° gives hydrocinnammaldehyde cyanohydrin in 57% yield (65%, considering recovered starting material) after aqueous work-up. Similarly, 5-cyanonorbornene is hydroxylated in 35–40% yield. Although the yield for this oxidation is poor, the procedure is simple and it becomes possible to convert the acrylonitrile–cyclopentadiene Diels–Alder adduct into an easily hydrolyzed derivative of the ketene–cyclopentadiene adduct.[3] The stereochemistry of the norbornenone cyanohydrin has not been determined, but the MoOPH product is identical with the cyanohydrin obtained by treating norbornenone with acetone cyanohydrin–KCN according to NMR evidence.

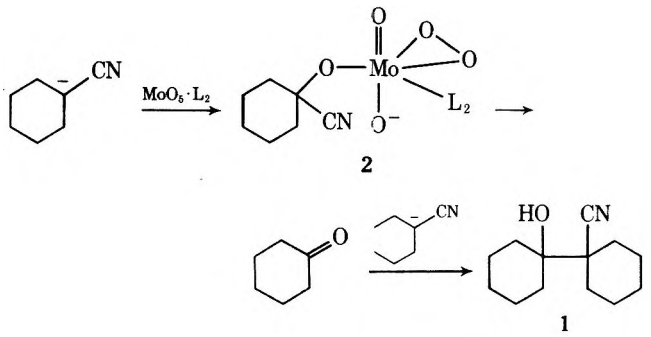
Under the usual conditions, stearonitrile affords the cyanohydrin in 55–60% yield and 3,3,3-triphenylpropanonitrile yields 55% cyanohydrin and 10% triphenylacetaldehyde (68 and 12.5%, respectively, considering unreacted starting material). The reaction of diphenylacetonitrile anion with MoOPH gives a mixture of comparable amounts of cyanohydrin and benzophenone in 71% yield (81% based on recovered nitrile) together with 11% of tetraphenylsuccinonitrile, apparently formed by dimerization of diphenylcyanomethyl radicals. Since radical coupling products are not formed in detectable amounts from other MoOPH hydroxylations, we prefer to rationalize cyanohydrin formation via carbanion attack at the peroxide O–O bond of the molybdenum reagent and not by an electron transfer mechanism.







Somewhat different results are obtained upon attempted hydroxylation of cyclohexyl cyanide. The major product from MoOPH oxidation is 1 (35%), identical with material prepared from cyclohexanone and cyclohexyl cyanide anion. Small amounts of the cyclohexanone cyanohydrin and cyclohexanone are also obtained (10–20% combined yield). Apparently an oxidation intermediate such as 2 is formed which fragments to cyclohexanone at a rate comparable to the rate of oxidation. Unreacted cyclohexyl cyanide anion then attacks the ketone in preference to the sparingly soluble MoOPH.



In general, moderate to good yields of cyanohydrins are expected from cyanides provided that the oxidation intermediates resist spontaneous fragmentation to the carbonyl compound. This condition is satisfied for typical aliphatic aldehyde cyanohydrins, but the behavior of ketone cyanohydrin precursors is unpredictable. A recent report describes a method for converting α-disubstituted cyanides into ketone cyanohydrins by oxygenation of $R_2\bar{C}CN$ to $R_2C(CN)OOH$, followed by reduction with stannous chloride.[4] This technique fails with α-monosubstituted cyanides RCH_2CN which are the preferred substrates for direct hydroxylation with MoOPH. Thus, anion oxygenation and MoOPH hydroxylation are complementary techniques which allow synthesis of ketone or aldehyde cyanohydrins, respectively.

Experimental Section

Oxodiperoxymolybdenum(hexamethylphosphoric triamide)(pyridine) (MoOPH). Oxodiperoxymolybdenum(hexamethylphosphoric triamide)[2,5] (18 g, 51.9 mmol) was dissolved in dry THF (40 ml) and pyridine (4.11 g, 51.9 mmol) was added with stirring. The product crystallized during addition. After filtering, washing thoroughly with ether, and vacuum drying over P_2O_5, yellow crystals (19.1 g, 85%) were obtained, identical with material prepared directly from MoO_5·HMPA·H_2O and pyridine.[2] The literature procedure[2] for preparation of MoOPH is less satisfactory because traces of hydrate may be present in the product.

Lithium Diisopropylamide (LDA). Purified (BaO distilled) diisopropylamine (2.18 ml, 15.6 mmol) was cooled to −80° and *n*-BuLi (8.0 ml, 13.1 mmol) in hexane was added dropwise under nitrogen. Dry THF was slowly added to a total volume of 16 ml and the mixture was brought to room temperature (nitrogen atmosphere throughout). The normality of the resulting LDA solution was calculated as being ca. 0.82 N. The LDA was prepared and stored under N_2 in a flask having no outlet other than a three-way stopcock. Aliquots were removed by syringe through the stopcock under nitrogen flow without disturbing the small amount of precipitate on the botton of the flask. With the stopcock closed, the LDA solution could be stored for several weeks at room temperature without apparent deterioration, and with no increase in the amount of precipitate.

Hydroxylation of 4-Phenylbutyronitrile. A solution of 4-phenylbutyronitrile (1.01 g, 6.95 mmol) in 15 ml of dry THF was added dropwise to LDA (8.6 mmol of 0.82 N solution in THF–hexane) at −78° under nitrogen. After 15 min at −78°, powdered MoOPH (3.90 g, 9.0 mmol) was added to the anion solution. The resulting mixture was stirred at −78° for 10 min and then at −23° for 40 min before being quenched with aqueous sodium bisulfite (25 ml). The mixture was stirred vigorously (ca. 5 min) at room temperature to extract molybdenum salts from the organic phase. The products were extracted with ether, and the ether layer was washed successively with 5% HCl, water, and brine, dried, evaporated, and separated by preparative layer chromatography over silica gel, using 1% methanol–CH_2Cl_2 to give recovered starting material (0.12 g, R_f 0.5–0.6) and dihydrocinnammaldehyde cyanohydrin (0.64 g, R_f 0.2–0.35).

Other cyanide hydroxylations were performed using an identical procedure, with appropriate modifications in the chromatographic separation technique.

Attempted Hydroxylation of Cyclohexyl Cyanide. A solution of 223 mg (2.04 mmol) of cyclohexanecarbonitrile in 4 ml of dry THF was added dropwise to 2.4 ml of 1.0 M LDA in THF–hexane at −78° under nitrogen. After 15 min at −78°, 1.130 g (2.6 mmol) of MoOPH was added to the vigorously stirred anion solution. The resulting red-brown mixture was maintained at −78° for 5 min and then allowed to warm to −23° for 10 min (light green solution). After addition of aqueous sodium bisulfite to the reaction mixture, the product was extracted with ether. The organic phase was washed successively with 5% HCl, water, and brine, dried, and evaporated to give a thick yellow oil.

The crude product, after addition of a few drops of pentane, deposited 72 mg (35%) of white crystals which were found to be identical with material obtained by quenching the anion of cyclohexanecarbonitrile with excess cyclohexanone at −70°. The hydroxynitriles produced by these two methods had mp and mmp 116–118° (from ether) and the same R_f by TLC (silica gel, 50% ether–hexane or methylene chloride containing a trace of methanol): *m/e* calcd for $C_{13}H_{21}NO$, 207.16220; found, 207.16231.

TLC analysis (same conditions as above) of the remaining oil showed starting material, cyclohexanone, and cyclohexanone cyanohydrin by comparison with authentic samples. Cyclohexanone was assayed by GLC on 5 ft × 0.25 in. SE-30–Chromosorb P at 120° (injection port at 220°), 10–20% yield. The cyclohexanone peak tailed somewhat, apparently due to on-column decomposition of cyclohexanone cyanohydrin. Authentic cyclohexanone cyanohydrin behaved similarly under these conditions.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—1, 57527-71-6; MoOPH, 23319-63-3; oxodiperoxymolybdenum(hexamethylphosphoric triamide), 25377-12-2; LDA, 4111-54-0; 4-phenylbutyronitrile anion, 57527-72-7; dihydrocinnamaldehyde cyanohydrin, 53279-92-8; cyclohexyl cyanide anion, 57527-73-8.

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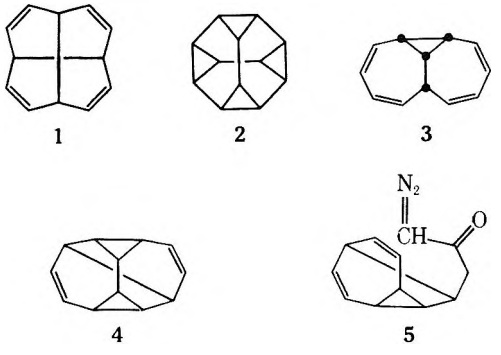
New $(CH)_{12}$ Hydrocarbons. Synthesis and Unusual Rearrangements

Summary: A synthesis of pentacyclo[5.5.0.0^{2,12}.0^{6,8}.0^{3,9}]dodeca-4,10-diene (**4**) is described, starting from bicyclo[4.2.1]nona-2,4,7-trien-9-one. Thermolysis of **4** above 160 °C gives benzene, but no products which might be derived from initial retro-Diels–Alder cleavage to tricyclo[5.5.0.0^{2,12}]dodeca-3,5,8,10-tetraene (**3**). Formation of benzene is explained by equilibration of **4** with tetracyclo[5.5.0.0^{2,4}.0^{3,10}]dodeca-5,8,11-triene (**9**) by an unusual 6-π electron reorganization. Retro-Diels–Alder cleavage of **9** would give bicyclo[6.4.0]dodeca-2,4,6,9,11-pentaene (**10**), which is known to fragment to benzene. Synthesis of **9** confirms this proposal because **9** rearranges to **4** above 120 °C, thereby demonstrating a low-energy pathway between the two isomers. Novel synthetic steps include (1) a procedure for conversion of α,β-unsaturated esters into α,β-saturated acids in the presence of other olefins via 1-pyrrazolin-3-one intermediates; and (2) conversion of tosylhydrazones into alkenes using lithium diisopropylamide at 0–25 °C.

The $(CH)_{12}$ isomer **1** is of interest as a potential photochemical precursor of the truncated tetrahedron **2**.[1] A possible approach to **1** involves the Cope rearrangement of a divinylcyclopropane **3** which in turn might be available by retro-Diels–Alder cleavage of **4**. In this paper we shall describe the synthesis of **4** and its thermal behavior.



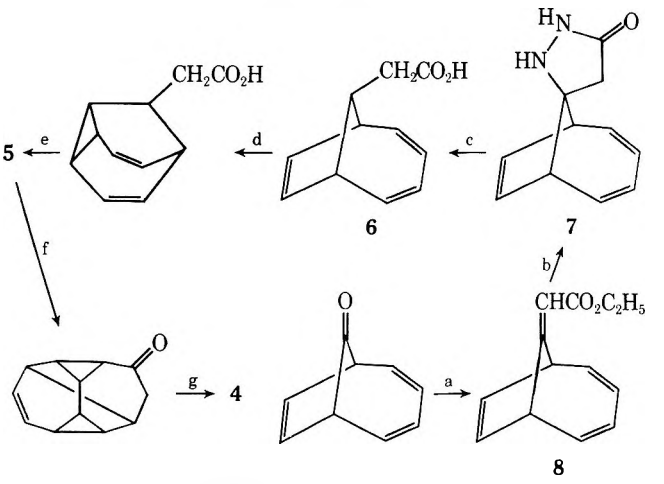
1 **2** **3**

4 **5**

Structure **4** can be recognized as a derivative of the barbaralane skeleton, accessible by internal ketocarbenoid addition to a double bond in the precursor **5**. A convenient sythesis of **4** and **5** is outlined in Scheme I starting from bicyclo[4.2.1]nona-2,4,7-trien-9-one.[2] The key steps in the scheme are the well-precedented di-π-methane rearrangement of **6**,[2,3] and conversion of **8** into **6**. The latter step is accomplished in 82% yield from **7** (57% overall from starting ketone) by oxidative fragmentation via a 1-pyrrazolin-3-one intermediate[4] (slow addition of *N*-chlorosuccinimide to **7** dissolved in H_2O–THF–KOH at −20 °C). Under carefully controlled conditions,[5] this reaction is an efficient general method for reduction of α,β-unsaturated esters.

Vapor phase pyrolysis of **4**[6] in a quartz reactor (stirred flow system)[7] does not give detectable amounts of any other $(CH)_{12}$ isomer. Instead, the starting material fragments to benzene at temperatures above 160 °C! This highly unusual (although perhaps not unexpected) rearrangement can be explained according to two categories of rationale. In the first category are numerous variations on the theme that some combination of electrocyclic steps will relate any $(CH)_{12}$ isomer having a continuous chain of all 12 carbons to 12-annulene. As demonstrated by Schröder et al., 12-annulene affords benzene via the valence bond tautomer **10** at 40 °C.[8] In a second category, we shall consider alternatives which do not require formation of a 12-annulene. The most reasonable of these mechanisms involves the novel 6-π electron transformation of **4** into **9**.[9] Retro-Diels–Alder cleavage of **9** to **10** would then be feasible,[10] and fragmentation to benzene would be the result.

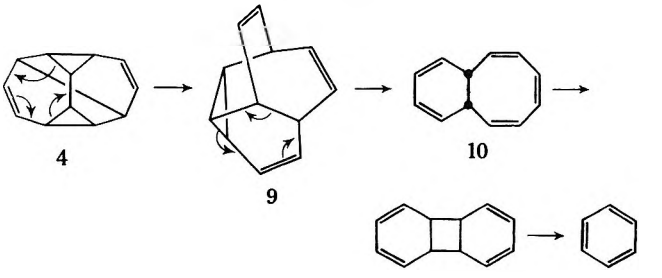
Scheme I[a]



[a] a, $(C_2H_5O)_2POCH_2CO_2C_2H_5$, NaH; b, $H_2NNH_2 \cdot H_2O$, C_2H_5OH, Δ; c, NCS, KOH, THF–H_2O, −20 °C; d, Ph_2CO, $h\nu$, C_6H_6; e, dicyclohexylamine, $(COCl_2)$, CH_2N_2; f, $CuSO_4$, 80 °C, C_6H_6; g, $TsNHNH_2$, $LiN(i\text{-}Pr)_2$, 25 °C.

To test the above proposition, we have prepared **9** by the route described in Scheme III. The nontrivial steps in this sequence are the carboxylation of bicyclo[3.2.2]nonatrienyl anion[11] and ring expansion of a cyclopropyl ketone **12**[12] by the excellent method of Taguchi, Yamamoto, and Nozaki.[13] The last step employs a variation of the tosylhydrazone olefin synthesis using lithium diisopropylamide (25 °C, 1–2 h) instead of the usual alkyllithium reagent.[14,15]

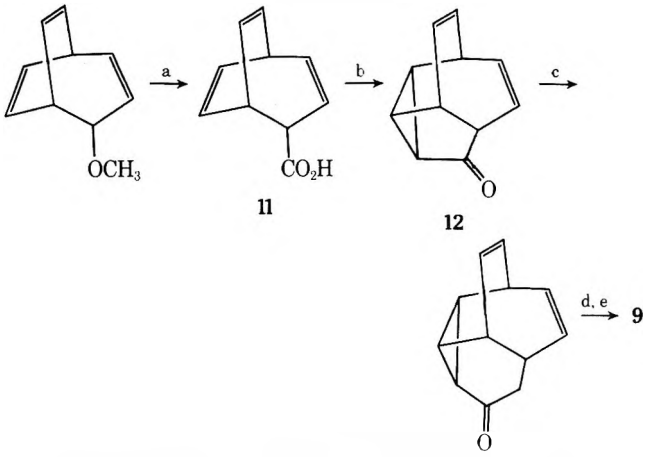
Scheme II



4 **9** **10**

Thermolysis of **9**[18] above 160 °C does indeed give benzene, but more significantly, reaction at temperatures between 120 and 150 °C results in complete rearrangement of **9** to **4**! Thus, a low-energy thermal pathway connects **4** and **9** and it is reasonable to invoke interconversion of the more stable isomer **4** with **9** at higher temperatures. This experiment provides strong support for the rationale given in Scheme II, and argues against mechanisms involving 12-annulenes. The experiment does not totally rule out the

Scheme III[a]



11 12

[a] a, Na/K, THF, CO_2 (58%); b, $(COCl)_2$, CH_2N_2, copper bronze, benzene, 80 °C (43% overall); c, $LiCHBr_2$, BuLi[13] (53% overall); d, $TsNHNH_2$, CH_3OH (62%); e, $LiN(i\text{-}Pr)_2$, THF, room temperature (60%).

possibility that **4** might also equilibrate with **3**, but this now appears to be a remote prospect.

Supplementary Material Available. Characterization of compounds **6** and **11**, together with the experimental details for preparation of these intermediates (4 pages). Ordering information is given on any current masthead page.

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(4) W. Nagata and S. Kamata, *J. Chem. Soc. C*, 540 (1970), were the first to report this reaction.
(5) As reported by Nagata and Kamata, attempted oxidative cleavage of **7** at higher temperatures results in thermal loss of CO and N_2 from the 1-pyrrazolin-3-one intermediate to form an olefin.[4]
(6) Characterization of **4**: NMR ($CDCl_3$) δ 5.8–5.9 (2 H, m), 2.24 (2 H, br s), 1.1–1.5 (4 H, m), 0.7–1.0 (2 H, m); *m/e* 156. The authors thank Dr. W. Wilber for performing the preparation and identification of **4**.
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(15) We have obtained excellent results using 2–4 mol of LDA for conversion of more typical tosylhydrazones into olefins at 0 °C in THF.[16] In one case, it has been reported that lithium 2,2,6,6-tetramethylpiperidide gives higher yields than LDA.[17] However, we find that LDA is entirely satisfactory for preparation of moderately strained or unstrained olefins.
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(18) Characterization of **9**: NMR ($CDCl_3$) δ 6.86 (1 H, dd, *J* = 8.2, 6.4 Hz), 6.24 (1 H, dd, *J* = 8.2, 6.4 Hz), 6.20 (1 H, dd, *J* = 9.0, 5.9 Hz), 6.06 (1 H, dd, *J* = 5.0, 6.8 Hz), 5.42 (1 H, dd, *J* = 9.9, 8.1 Hz), 5.30 (1 H, ddt, *J* = 9.9, 4.9, ca. 0.6 Hz), 3.15 (1 H, m), 2.71 (2 H, m), 1.4–1.8 (3 H, m); exact mass 156.09366 (calcd 156.09390).

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Reaction of 1,2- and 1,3-Dicarbonyl Compounds with Dimethyl β-Ketoglutarate. I. Synthesis of Methyl 5,6,7,8-Tetrahydro-5-oxocoumarin-$\Delta^{4(3H),\alpha}$-acetate

Summary: Reaction of dimethyl β-ketoglutarate (excess) and 1,3-cyclohexanedione in aqueous buffer (pH 6.8) yielded the product of 1:1 stoichiometry, methyl 5,6,7,8-tetrahydro-5-oxocoumarin-$\Delta^{4(3H),\alpha}$-acetate.

Sir: Reaction of dimethyl β-ketoglutarate **1** with 1,2-dicarbonyl compounds usually proceeds smoothly in aqueous solution (pH 6.8) at room temperature to furnish adducts formed from two molecules of **1** and one molecule of the carbonyl compound. Use of glyoxal (e.g.) yields tetramethyl bicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate.[1] Other 1,2-dicarbonyl compounds in general give analogous adducts,[1] while in a few cases more complex reaction products have been observed.[2] Cyclic 1,2 diketones yield tetramethyl propellanedione tetracarboxylates.[1,3] The tendency toward 2:1 stoichiometry in this reaction is marked;[1,3] in a few cases, however, 1:1 adducts have been isolated.[4]

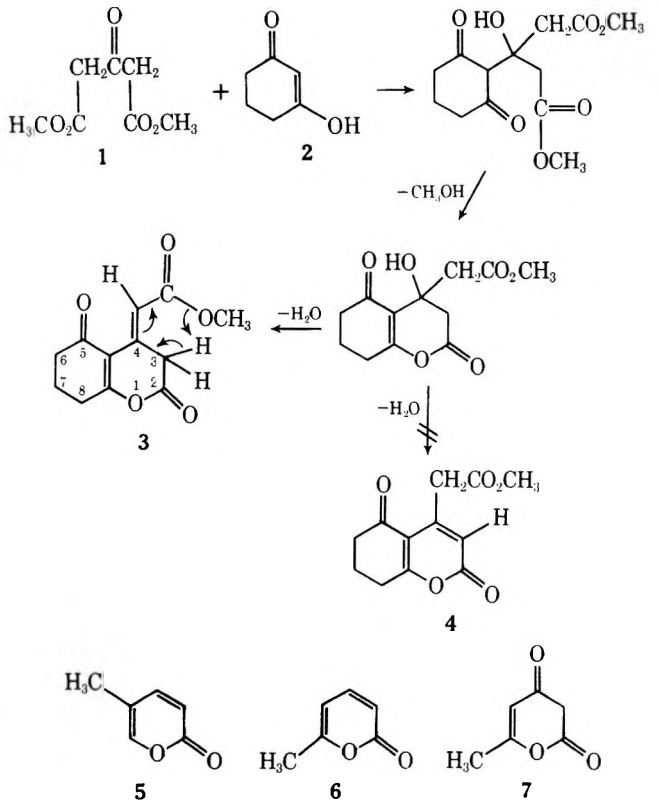
It seemed of interest to examine the analogous reaction between **1** and cyclic 1,3 diketones. We now wish to report on a compound obtained from **1** and 1,3-cyclohexanedione **2**.

When an aqueous solution of **1** (104.4 g, 0.60 mol) and **2** (22.4 g, 0.20 mol) in citrate/phosphate buffer (pH 6.8) was stirred for several days at room temperature, TLC indicated the presence of a single reaction product in addition to starting materials. Extraction with chloroform and concentration to small volume provided a 45% yield of a pure crystalline compound, mp 123–125°, not changed on recrystallization from chloroform. Elemental analysis and high-resolution mass spectrometry indicated that the new compound had the empirical formula $C_{12}H_{12}O_5$. In contrast to the results with 1,2 diketones, it is evidently produced by reaction of **1** and **2** in a 1:1 ratio with loss of one molecule each of water and methanol.

A plausible scheme leading to two alternative structures for $C_{12}H_{12}O_5$ can be easily written (Scheme I). Spectroscopic evidence is compatible with methyl 5,6,7,8-tetrahydro-5-oxocoumarin-$\Delta^{4(3H),\alpha}$-acetate **3** and not the α-pyrone **4**. The ultraviolet spectrum of **3** [λ_{max} 261 nm (log ε 4.06)] is different from those of the authentic α-pyrones **5** and **6** (λ_{max} 300[5] and 302[6] nm, respectively) but is similar to that of the ketolactone **7** (λ_{max} 271 nm).[5] In the NMR spectrum of **3**, two triplets representing the protons of C-6 (2 H) and C-8 (2 H) were observed at δ 2.60 and 2.90, respectively. The multiplet at δ 2.15 was assigned to the two protons of C-7. In addition three singlets were observed which were ascribed to the ester function (δ 3.71), the methylene protons of C-3 (3.81), and the vinyl proton (6.03).

Support for the stereochemical assignment of the exocyclic double bond as that depicted in **3** is obtained by close

Scheme I



examination of the mass spectrum. An intense peak (P − 32) was observed in the spectrum and corresponds to the loss of methanol from the parent ion. This process is known to proceed through a six-centered transition state involving a hydrogen atom γ to the ester group, as shown, and can only occur from **3**. The metastable ion for P → P − 32 was observed. Ample precedent for this process is available in the literature;[7] this fragmentation has also been observed repeatedly in the spectra of the tetramethyl propellanedione tetracarboxylate derivatives.[3] Dimedone reacted with **1** in the same fashion as **2** to provide the 7,7-dimethyl derivative of **3** (mp 115–116°C), although the yield of product was somewhat lower.

The obvious possibility for conversion of **3**[8] to α-pyrones, coumarins, and carbostyrils, etc., is at present under investigation in our laboratory; we are also studying analogous reactions of other 1,3-dicarbonyl compounds.

Acknowledgment. We wish to thank Dr. Ulrich Weiss (NIAMDD) for helpful discussions and Mr. William Comstock (NIH) for mass spectra.

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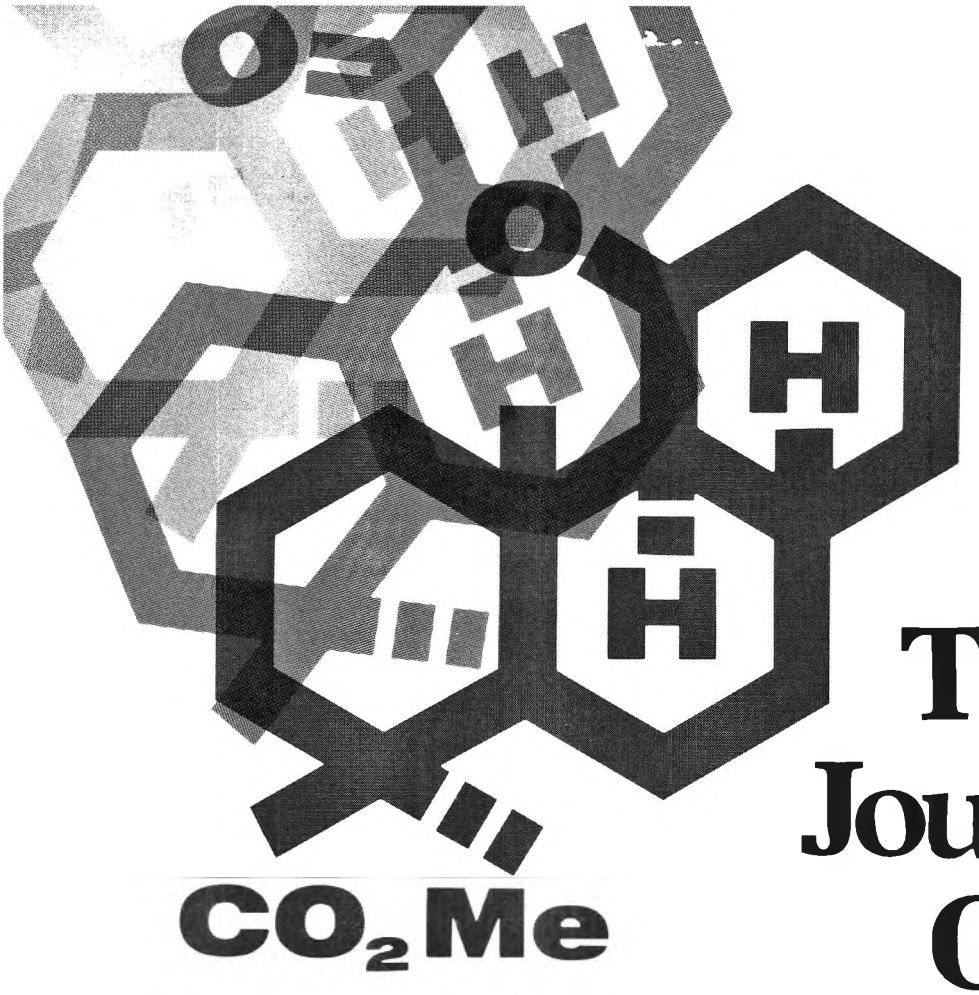

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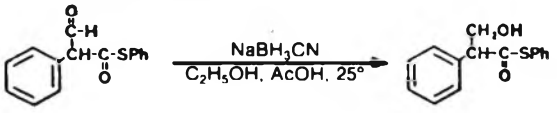
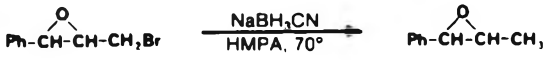
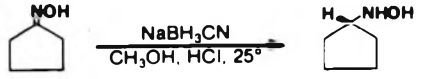


Reductive Displacement of Halides

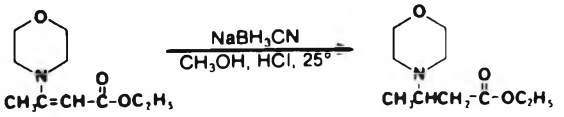


The most useful application of $NaBH_3CN$ is the selective reduction of the iminium ion ($\rangle C{=}\overset{+}{N}\langle$). The following are some specific reductions, all of which involve an intermediate iminium ion.

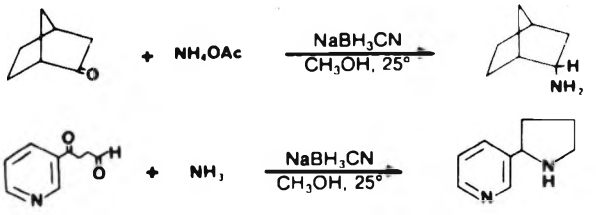
Reduction of Oximes

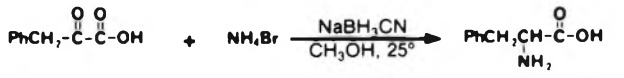


Reduction of Enamines

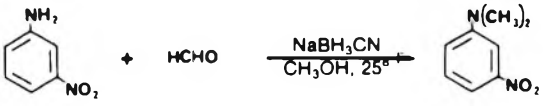


Reductive Amination

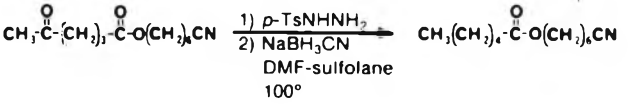




Reductive Alkylation



Deoxygenation (Modified Wolff-Kishner)



The stability and reactivity of the cyanoborohydride ion in aqueous systems at pH 6-8 indicate the potential for carrying out imine reductions and carbonyl aminations on complex biological systems. For example, the imino linkage between 11-*cis*-retinal and the lipoprotein, opsin, was recently reduced with $NaBH_3CN$ under mild conditions (aqueous, pH 5, 3°).

For a complete list of references, please send for a detailed technical information bulletin. The following are leading references:

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