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Chemistry

06073	**Allyltrimethylsilane** purum >97%(GLC); BP 83-85°		1 lt ≈ 0.72 kg	10 ml	sFr. 15.—	us$ 7.50

$CH_2:CHCH_2Si(CH_3)_3$ $C_6H_{14}Si$ MW 114.27

	50 ml	sFr. 63.— us$ 31.50

Reagent for the allylation of carbon electrophiles (carbonyl compounds, acyl halides etc.): I. Ojima et al., Tetrahedron Lett. **(1977)** 1385 (and references cited therein); A. Hosomi, H. Sakurai, Tetrahedron Lett. **(1977)** 4041 (and references cited therein); β-acylcarbanion equivalent: D. Ayalon-Chass et al., J. Chem. Soc. Chem. Comm. **(1977)** 772 (and references cited therein)

03155	**2-Bromo-1-ethylpyridinium tetrafluoroborate** purum MP 102-104°; very sensitive to moisture		10 g	sFr. 20.—	us$ 10.00

$CH:CHCH:CHC(Br):NC_2H_5(BF_4)$ $C_7H_9BBrF_4N$ MW 273.86

50 g	sFr. 85.— us$ 42.50

A new and efficient coupling reagent for the preparation of carboxylic esters under mild conditions: K. Saigo, M. Usui, K. Kikuchi, E. Shimada, T. Mukaiyama, Bull. Chem. Soc. Jap. **(1977)** *50*, 1563; T. Mukaiyama, M. Usui, E. Shimada, K. Saigo, Chem. Lett. **(1975)** 1045; T. Mukaiyama, H. Toda, S. Kobayashi, Chem. Lett. **(1976)** 13
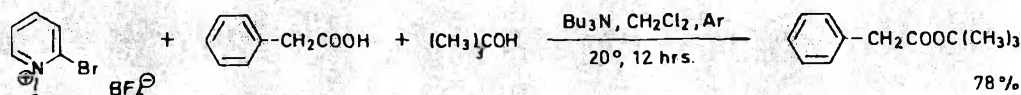
37360	**3,4-Dihydro-2H-pyrido[1,2-a]pyrimidin-2-one** purum MP 185-187°		10 g	sFr. 14.—	us$ 7.00

$C_8H_8N_2O$ MW 148.16

50 g	sFr. 60.— us$ 30.00

A very effective non-basic hydrogen halide captor in various condensation reactions: T. Mukaiyama, H. Toda, S. Kobayashi, Chem. Lett. **(1976)** 13; T. Mukaiyama, Y. Aikawa, S. Kobayashi, Chem. Lett. **(1976)** 57; T. Mukaiyama, Heterocycles **(1977)** *6*, 1509
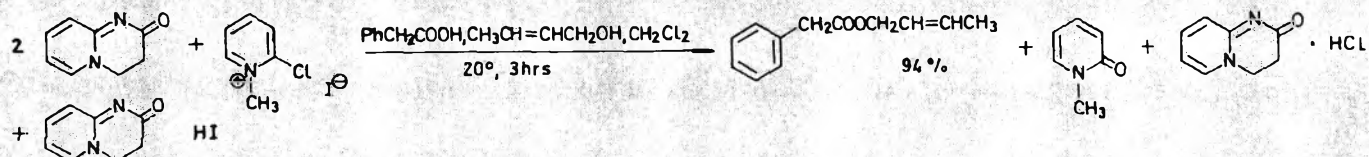
55510	**N-Hydroxymaleimide** purum MP 124-126°		1 g	sFr. 35.—	us$ 17.50

$HONCOCH:CHCO$ $C_4H_3NO_3$ MW 113.08

5 g	sFr. 145.— us$ 72.50

Reagent for the preparation of N-hydroxysuccinimide ester polymers via polymerizable active esters: M. Akiyama, K. Shimizu, M. Narita, Tetrahedron Lett. **(1976)** 1015

28380	**2,4-Pentadienenitrile** purum >98%(GLC); BP₁₀30-33° (1-Cyano-1,3-butadiene) light sensitive, stabilized with 0.2% DBPC		1 lt ≈ 0.86 kg	5 ml	sFr. 20.— us$ 10.00

$CH_2:CHCH:CH_2CN$ C_5H_5N MW 79.10

25 ml	sFr. 85.— us$ 42.50

Intermediate, reactive diene: R. Huisgen, A. Ohta, J. Geittner, Chem. Pharm. Bull. **(1975)** *23*, 2735

90550	**Triethylsilane** purum ~99%(GLC); BP 107-109°; n²⁰_D 1.4122		1 lt ≈ 0.73 kg	10 ml	sFr. 14.— us$ 7.00

$(C_2H_5)_3SiH$ $C_6H_{16}Si$ MW 116.28

50 ml	sFr. 60.— us$ 30.00

Reagent for the reduction of different functional groups (e.g. acyl halides to aldehydes, alkyl halides and secondary alcohols to hydrocarbons): L. Fieser, M. Fieser: "Reagents for Organic Synthesis", *1*, 1218, *2*, 433, *3*, 304, *4*, 530, *5*, 694; John Wiley and Sons Inc.; M. P. Doyle et al., J. Org. Chem. **(1976)** *41*, 1393; M. P. Doyle et al., J. Organomet. Chem. **(1976)** *117*, 129; M. G. Adlington et al., Tetrahedron Lett. **(1976)** 2955; J. L. Fry et al., J. Org. Chem. **(1978)** *43*, 374

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AUTHOR INDEX

Some Deoxygenation Reactions with Low-Valent Titanium (TiCl₃/LiAlH₄)

John E. McMurry,* Michael G. Silvestri, Michael P. Fleming, Tova Hoz, and Michael W. Grayston

Thimann Laboratories, University of California, Santa Cruz, California 95064

Received March 15, 1978

A low-valent titanium reagent prepared by treating anhydrous $TiCl_3$ with 0.25 molar equiv of $LiAlH_4$ is capable of carrying out reductions on numerous types of organic systems: epoxides are deoxygenated nonstereospecifically to olefins (nine examples); bromohydrins are reduced nonstereospecifically to olefins (seven examples); allylic and benzylic alcohols are reductively coupled to hydrocarbons, although intramolecular coupling is not possible; certain α-hydroxy ketones are deoxygenated to ketones; and cyanohydrins are deoxygenated in low yield to nitriles. Mechanisms are proposed to account for the observed results.

Several years ago, we observed[1] that ketones could be deoxygenatively dimerized to olefins on treatment with a reagent prepared by reacting a tetrahydrofuran (THF) solution of anhydrous $TiCl_3$ with 0.5 molar equiv of $LiAlH_4$. Subsequent to our initial disclosure, however, we found the ketone coupling reaction to give variable results depending on the exact batches of reagents used. After considerable experimentation, we developed an improved carbonyl coupling procedure based on the use of highly active titanium metal,[2] and we did not further pursue the use of $LiAlH_4/TiCl_3$ for carbonyl coupling. We did, however, find that the $LiAlH_4/TiCl_3$ reagent effects a variety of other organic reductions reproducibly and in good yield. Our investigations of these reductions form the basis of this paper.

Reduction of Epoxides. The deoxygenation of epoxides to olefins is a transformation which can be effected by numerous reagents, including strongly reducing metals or metal salts such as chromium atoms,[3] zinc,[4] magnesium amalgam,[5] zinc–copper couple,[6] chromous ion,[7] low-valent tungsten complexes,[8] and $FeCl_3$-BuLi.[9] We have found that $TiCl_3/LiAlH_4$ is also capable of carrying out this reaction.[10] Operating on the assumption that a Ti(II) species is the active reducing agent formed on reduction of $TiCl_3$, we carried out our reactions using the exact molar ratio of $TiCl_3/LiAlH_4$ necessary for stoichiometric formation of Ti(II), i.e., 4:1. Optimum reaction conditions were established in a study of the reduction of 1,2-epoxydecane (Table I). We found that heating of the reaction is required and that a 4:1:2 ratio of $TiCl_3/LiAlH_4$/epoxide is necessary.

Our results on the reduction of some representative epoxides are given in Table II.

With the exceptions of α-methylstyrene oxide and α-pinene oxide, these deoxygenations take place cleanly and in acceptable yields. We suspect that the two epoxides which reduce poorly suffer competing side reactions from carbonium ion rearrangements since both would be expected to be highly acid sensitive.

The mechanism of this reduction is probably similar to that postulated by Kochi for the related chromous ion reduction.[7]
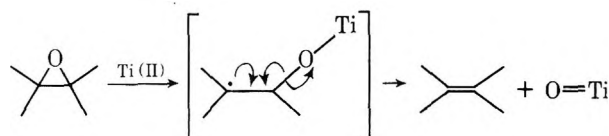
This mechanism, in which stepwise deoxygenation through an intermediate radical occurs, would explain the lack of stereospecificity observed in the cis- and trans-5-decene epoxide reductions.

If this mechanism is correct, it suggests that low-valent titanium-induced deoxygenation should be a general reaction for structures of type A → B where the group X neighboring
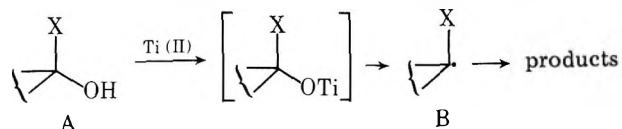
the oxygen can either stabilize a radical center or undergo further reaction.

For example, if in structure A the group X = C–Br, then deoxygenated radical intermediate B can lose Br by a low energy pathway. Thus, we predict that bromohydrins should reduce to give olefins. Similarly, if X = CN, deoxygenation of cyanohydrins to nitriles might occur [one would expect B (X = CN) to add a further electron to give a nitrile anion]. Similarly also, α-hydroxy ketones should reduce to ketones and allylic and benzylic alcohols should deoxygenate. All of these possibilities have been realized, and we now discuss them.

Reduction of Bromohydrins. There have been relatively few direct methods reported for reducing bromohydrins to olefins. As shown in Table III, however, the $TiCl_3/LiAlH_4$ reagent is most effective for this reduction.[11]

Synthetically, this reaction has several things to recommend it. All substrates tried reduce in good yield, and the conditions are nonacidic in contrast to the normal zinc–acetic acid method.[12] The reduction, however, is not stereospecific as shown from reactions of threo- and erythro-5-decene bromohydrins. In this respect, the results are similar to those obtained both with zinc[12] and with chromous ion.[13]

Table I. Deoxygenation of 1,2-Epoxydecane with TiCl₃/LiAlH₄

$$CH_3(CH_2)_7CHCH_2 \xrightarrow[\text{THF}]{\text{TiCl}_3/\text{LiAlH}_4} CH_3(CH_2)_7CH{=}CH_2$$

Trial	Rxn time, h	Rxn temperature, °C	Reagent ratio[a]	Yield,[b] %
1	4	20	4:1:2	Low
2	16	20	4:1:2	21
3	3	65	4:1:2	68
4	17	65	4:1:2	65
5	16	65	4:1:4	38

[a] The ratio represents molar equivalents of TiCl₃/LiAlH₄/epoxide. [b] Yield determined by GLC with an internal standard.

Table II. Deoxygenation of Some Epoxides with TiCl₃/LiAlH₄

Reactant	Registry no.	Product	Yield,[b] %
Cyclohexene oxide	286-20-4	Cyclohexene	69
Cyclooctene oxide	286-62-4	Cyclooctene	53
α-Methylstyrene oxide	2085-88-3	α-Methylstyrene	36
5α,6α-Epoxycholestan-3β-ol	1250-95-9	Cholesterol	79
1,2-Epoxydecane	2404-44-6	1-Decene	67
1,2-Epoxydodecane	2855-19-8	1-Dodecene	68
α-Pinene oxide	1686-14-2	α-Pinene	11
cis-5,6-Epoxydecane	36229-64-8	5-Decene (21:79 cis/trans)[c]	70
trans-5,6-Epoxydecane	2165-61-9	5-Decene (18:82 cis/trans)[c]	70

[a] A molar ratio of 4:1:2 TiCl₃/LiAlH₄/epoxide was used. [b] With the exception of cholesterol, yields were determined by GLC using an internal standard. [c] Registry no.: cis-5-decene, 7433-78-5; trans-5-decene, 7433-56-9.

Mechanistically, we view the process as occurring by a pathway analogous to that proposed for the related chromous ion reduction in which an intermediate radical species is produced. An alternative concerted path is ruled out by the lack of stereospecificity observed in the reactions of the 5-decene bromohydrins.
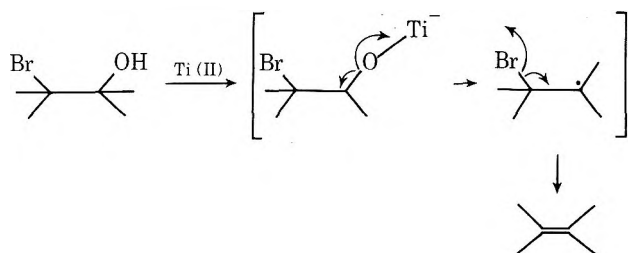
Coupling of Allylic and Benzylic Alcohols. The titanium-induced coupling of allylic and benzylic alcohols was first observed by van Tamelen and Schwartz in 1965.[14] These workers found that when 2 equiv of alkoxide was added to TiCl₄ and the resulting dichlorotitanium(IV) dialkoxide was

$$2RO^- + TiCl_4 \longrightarrow TiCl_2(OR)_2 \xrightarrow{K} Ti(OR)_2$$

$$R{-}R \longleftarrow 2R\cdot + TiO_2$$
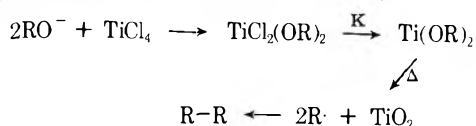
Table III. Reductions of Bromohydrins with TiCl₃/LiAlH₄

Substrate	Registry no.	Product	Yield, %
	1502-14-3	Cyclooctene	96
	56804-70-7	Indene	93
	1857-83-6	Cholesterol	79
2-Bromo-1-decanol	39579-74-3	1-Decene	74
2-Bromo-1-dodecanol	56804-71-8	1-Dodecene	91
erythro-5-Bromo-6-decanol	56804-72-9	5-Decene (80:20 trans/cis)	91
threo-5-Bromo-6-decanol	56804-73-0	5-Decene (70:30 trans/cis)	82

Table IV. Reductive Coupling of Alcohols with TiCl₃/LiAlH₄

Alcohol	Registry no.	Product	Yield, %
n-Decanol		No reaction	
Cholesterol		No reaction	
PhCH₂OH	100-51-6	PhCH₂CH₂Ph	78
PhCH(OH)CH₃	98-85-1	PhCH(CH₃)CH(CH₃)Ph	68
PhC(OH)(CH₃)₂	617-94-7	PhC(CH₃)₂C(CH₃)₂Ph	95
	4096-38-2		87
	4602-84-0	**1** + **2** + **3** + **4**	33 15 13 8

reduced with molten potassium in refluxing benzene, coupling to dimeric hydrocarbon was observed. Benzyl alcohol, for example, coupled to bibenzyl in 51% yield.

Subsequently, a modification based on the use of TiCl₃ and CH₃Li was introduced, simplifying the procedure.[15] We have

Scheme I

Table V. Attempted Intramolecular Diol Coupling with TiCl₃/LiAlH₄

Diol	Product	Yield, %
10	+ isomers	80
13	+ isomers	100
14	No reaction	
15	No reaction	
16		
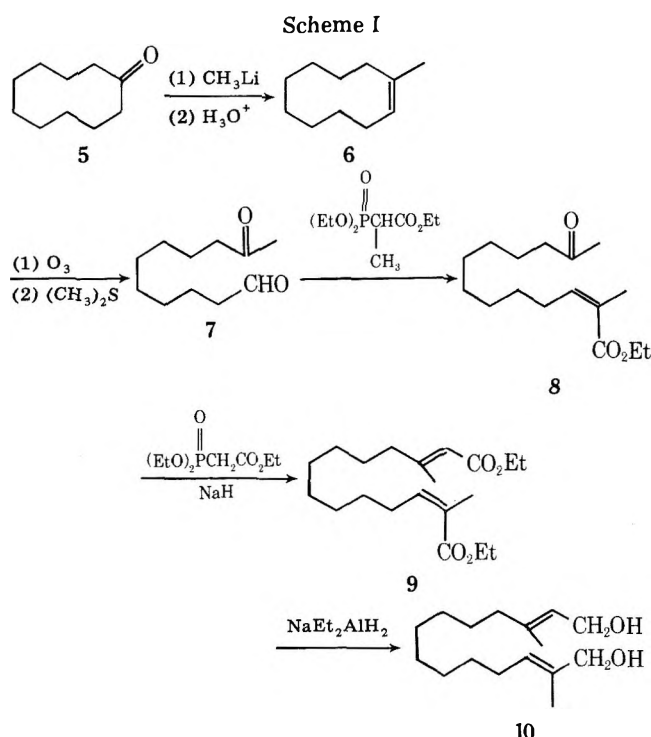
found that direct treatment of allylic or benzylic alcohols with TiCl₃/LiAlH₄ results in a high yield of coupled dimer.[16] Some of our results are given in Table IV.

Both allylic and benzylic alcohols couple in good yield, and steric hindrance to the coupling of tertiary alcohols is not observed. There are, however, several drawbacks to the reaction. Nonallylic alcohols (n-decanol, cholesterol) do not couple. This is presumably due to the greater strength of the nonallylic C–O bond vs. the allylic C–O bond. A further drawback is that when unsymmetrical alcohols such as farnesol are reduced, coupling can occur with allylic rearrangement, leading to product mixtures. Finally, we have also observed that hydrogenolysis of the hydroxyl occurs as a competing reaction in some cases (for example, farnesol). We ascribe this hydrogenolysis to hydrogen atom abstraction from solvent dimethoxyethane by the intermediate alkyl radical. Recently, both Fujimoto[17] and Baumstark[18] have reported that hydrogenolysis product is found exclusively when a large excess of LiAlH₄ is employed in conjunction with TiCl₄. Under our conditions, however, in which there is no excess hydride and in which the amount of hydrogenolysis product is solvent dependent (THF and dioxane favor hydrogenolysis relative to dimethoxyethane), we favor solvent donation of a hydrogen atom.

It was clear to us from the outset that this coupling reaction would be much more valuable synthetically if it could be used intramolecularly to form rings. In particular, a number of 14-membered ring diterpenes known as cembranolides have been isolated recently from natural sources. Cembrene itself is a 14-membered ring hydrocarbon first isolated from the Japanese black pine (*Pinus thunbergii*). Cembrene has been synthesized by Dauben by the nickel carbonyl catalyzed intramolecular coupling of a bis(allylic bromide).[19] We were intrigued by the possibility of cembranolide synthesis via titanium-induced intramolecular bis(allylic alcohol) coupling. We therefore synthesized the model diol **10** by the route shown in Scheme I.

Similarly, it might also prove possible to synthesize both *elemane* sesquiterpenes (1,2-divinylcyclohexanes) and germacrane sesquiterpenes (cyclodecadienes) by appropriate intramolecular couplings. We therefore synthesized bis(allylic diol) **13** as a model by the route shown in Scheme II.

Unfortunately, neither **10** nor **13** gave any detectable
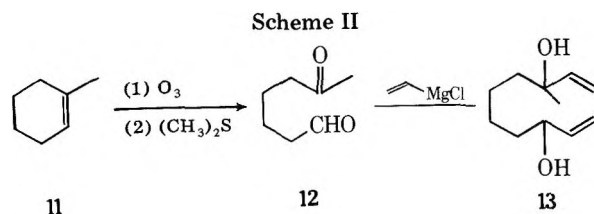
amount of cyclization product when treated with TiCl₃/LiAlH₄. Treatment of **10** with TiCl₃/LiAlH₄ gave a mixture of four products in 80% yield. Analysis by GC/MS clearly showed that all four were isomeric hydrogenolysis products. When **13** was treated with TiCl₃ and LiAlH₄, a mixture of four hydrogenolysis products was again formed in quantitative yield. These and other attempted intramolecular coupling reactions are presented in Table V. In no case was any cyclization product obtained.[20]

Reduction of Cyanohydrins. If cyanohydrins were to undergo deoxygenation by the general mechanism postulated above, one would expect nitriles to result, and the net effect would be a one-carbon chain extension.
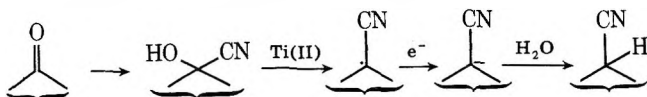
To investigate this possibility, we prepared benzaldehyde cyanohydrin and attempted its reduction with TiCl₃/LiAlH₄. We observed a *complex mixture* of products from which phenylacetonitrile could be isolated in 20% yield. In addition, cyanostilbene was produced (30%). The cyanostilbene presumably arises by condensation of phenylacetonitrile anion with benzaldehyde formed by the reversal of cyanohydrin formation. This loss of HCN was the sole mode of reaction

Scheme II
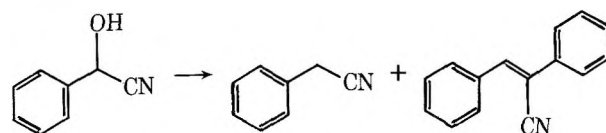
Table VI. Reduction of α-Hydroxy Ketones with TiCl₄/Zn

α-Hydroxy Ketone		Product (yield)

a Registry no.: 28925-00-0. *b* Registry no.: 63662-71-5.

when cyclohexanone cyanohydrin was subjected to reduction conditions, and no cyclohexanecarbonitrile was formed. We conclude therefore that mechanistically, cyanohydrin reduction is a feasible process. In practice, however, side reactions render the reaction of no synthetic value.

Reduction of α-Hydroxy Ketones. Analogous to the reduction of cyanohydrins, one might also expect α-hydroxy ketones to undergo direct deoxygenation on treatment with TiCl₃/LiAlH₄. We are aware of no other direct one-step methods for accomplishing this transformation, and the successful reaction should therefore prove valuable. The reaction does in fact take place as expected, although TiCl₃/
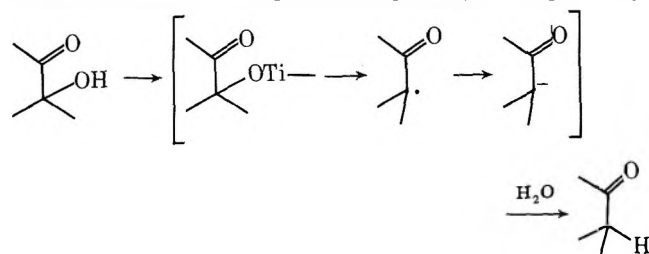
LiAlH₄ generally gives rather low yields of product. We found, however, that the low-valent species produced by reducing TiCl₄ with zinc[21] was quite effective and gave good yields in a number of cases. Some of our results are shown in Table VI.

As Table VI shows quite clearly, the deoxygenation of α-hydroxy ketones with TiCl₄/Zn is of limited synthetic use due to the fact that rearrangements often occur. 1-Acetylcyclododecanol, for example, ring expands at approximately the same rate at which reduction occurs. By adding a large excess of reducing agent this problem can be suppressed but not

entirely eliminated. 17-Hydroxy-20-keto steroids also give D-homo rearrangement products in competition with simple deoxygenation. Only in the case of acetylcyclohexanols (where rearrangement to a cycloheptane is unfavorable) does reduction occur smoothly and in good yield. For these cases, however, the reaction is an excellent one. The direct product of the ketol deoxygenation is, presumably, an enolate ion, and the trapping of this ion by electrophiles would effect a net
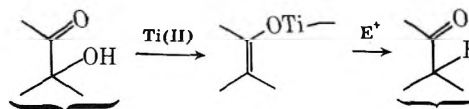
replacement of hydroxyl by carbon. All attempts at trapping the enolate were unsuccessful, however, presumably due to the unusually high strength and low reactivity of the Ti–O bond.

Summary

We have demonstrated that the TiCl₃/LiAlH₄ reagent is effective for carrying out a number of useful reduction procedures. In particular, most epoxides and bromohydrins reduce cleanly to olefins, allylic and benzylic alcohols couple smoothly to dimeric hydrocarbons, and acylcyclohexanols deoxygenate to acylcyclohexanes. These reactions, along with the carbonyl coupling procedure employing active titanium metal,[22] demonstrate the versatility and power of low-valent titanium species as deoxygenating agents in organic chemistry.

Experimental Section

General. Melting points were obtained on a Thomas-Hoover unimelt apparatus. Proton NMR spectra were recorded on a Varian A56/60A (60 MHz) or a Jeolco Minimar (60 MHz) instrument. Chemical shifts are reported in δ (ppm) downfield from internal tetramethylsilane. IR spectra were recorded on Perkin-Elmer 237 or 337 grating spectrophotometers. Gas chromatography/mass spectroscopy was performed on a Finnigan Model 4000 instrument operating at a 70 eV ionization potential and employing a 3% OV-1 on Chromosorb W glass column (4 ft × 0.25 in). TiCl₃ was obtained from Alfa Inorganics and was transferred under an inert atmosphere in a glovebag or a Schlenk apparatus.

The phrase "usual workup procedure" used below means that the reaction mixture was cooled to room temperature, diluted with water, and extracted several times with ether. The combined ether extracts were washed with saturated brine, dried (MgSO₄), and concentrated by solvent removal at the rotary evaporator.

General Procedure for Preparation of Epoxides. A solution of 85% m-chloroperbenzoic acid (0.850 g, 4.20 mmol) in 10 mL of dichloromethane was added dropwise to a stirred solution of olefin (4.0 mmol) in 30 mL of dichloromethane under a nitrogen atmosphere. After stirring for 15 h at room temperature, the reaction mixture was washed with 20% aqueous sodium sulfite and 5% aqueous sodium bicarbonate and then dried (MgSO₄) and concentrated at the rotary evaporator to yield the epoxide product.

General Reaction Procedure for Epoxide Reduction. Lithium aluminum hydride (0.20 g, 5.0 mmol) was added in small portions to a stirred slurry of TiCl₃ (3.08 g, 20.0 mmol) in 60 mL of dry THF under a nitrogen atmosphere at room temperature. Hydrogen evolution was immediate, and the resulting fine black suspension was stirred for 15 min. A solution of epoxide (10 mmol) in 10 mL of dry THF was added in one portion, and the reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction was worked up in the usual way. In this manner, the following reactions were carried out.

1-Decene from 1,2-Epoxydecane. A 65% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using cyclooctene as an internal standard.

Cyclohexene from Cyclohexene Oxide. A 69% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using cyclooctene as an internal standard.

Cyclooctene from Cyclooctene Oxide. A 53% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-decene as an internal standard.

α-Methylstyrene from α-Methylstyrene Oxide. A 36% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1,5-cyclooctadiene as an internal standard.

1-Dodecene from 1,2-Epoxydodecene. A 69% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-decene as an internal standard.

α-Pinene from α-Pinene Oxide. An 11% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-decene as an internal standard.

Cholesterol from 5α,6α-Epoxycholestan-3β-ol. A 75% yield was *determined by isolation and crystallization of the product, mp* 148 °C.

cis-**5-Decene.** A mixture of 5-decyne (2.00 g, 14.5 mmol) and Lindlar catalyst (0.14 g) in 60 mL of petroleum ether was stirred under 1 atm of hydrogen pressure. Hydrogen uptake (300 mL) ceased abruptly after 1 h. Filtration and solvent removal gave *cis*-5-decene (1.95 g, 96%), pure by GLC (20% SF-96 on GC-22 "Super Support"): NMR (CCl$_4$) δ 0.7–1.7 (m, 14 H), 1.7–2.3 (m, 4 H), 5.15–5.35 (m, 2 H).

trans-**5-Decene.** A solution of sodium (1.50 g, 65.4 mmol) in 80 mL of liquid ammonia at −78 °C was prepared, and 5-decyne (3.00 g, 18.5 mmol) was added over 20 min. After stirring for 1.75 h, excess sodium was destroyed by cautious addition of aqueous NH$_4$OH. Ammonia was evaporated, and the reaction was worked up in the usual way to give *trans*-5-decene (2.071 g, 68%): NMR (CCl$_4$) δ 0.7–1.7 (m, 14 H), 1.7–2.2 (m, 4 H), 5.20–5.45 (m, 2 H).

Deoxygenation of *cis*-**5,6-Epoxydecene.** A 70% yield of 5-decene was obtained as determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-dodecene as an internal standard. The cis/trans ratio of the product could not be determined directly since the isomeric 5-decenes were inseparable by GLC under all conditions tried. We therefore analyzed the product mixture in the following way.

The olefin product mixture was dissolved in 30 mL of dichloromethane and epoxidized with *m*-chloroperbenzoic acid using the general reaction conditions discussed above. After workup, the mixture of *cis*- and *trans*-5-decene oxides was analyzed by GLC (10% Carbowax 20M on GC-22 "Super Support"; 12 ft × 0.25 in). In this manner, a ratio of 21% of *cis*-5-decene to 79% of *trans*-5-decene was determined. The validity of this analytical method was determined by carrying out the appropriate control reaction on a mixture of known composition.

Deoxygenation of *trans*-**5,6-Epoxydecane.** A 70% yield of 5-decene was obtained. Analysis of the cis/trans product ratio by the method outlined above indicated a ratio of 22% of *cis*-5-decene to 78% of *trans*-5-decene.

General Reaction Procedure for Bromohydrin Preparation. The olefins to be used as substrates were epoxidized according to the general procedure outlined above. A solution of epoxide (4.0 mmol) in 60 mL of CCl$_4$ was exposed to a slow stream of gaseous HBr for 2 h at room temperature. After washing the reaction mixture with 5% aqueous sodium bicarbonate, the solution was dried (MgSO$_4$) and concentrated at the rotary evaporator to yield the bromohydrins.

General Procedure for Bromohydrin Reduction. LiAlH$_4$ (0.142 g, 3.75 mmol) was added to a stirred slurry of TiCl$_3$ (2.3 g, 15 mmol) in 70 mL of dry THF under a nitrogen atmosphere. Hydrogen evolution commenced, and the resulting black suspension was stirred for 10 min before use. The bromohydrin (5.0 mmol) in 10 mL of THF was added, and the reaction mixture was refluxed for 16 h. After cooling to room temperature, the reaction was worked up in the usual way. In this manner, the following reactions were carried out.

Cyclooctene from *trans*-**2-Bromo-1-cyclooctanol.** A 96% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using 1-decene as an internal standard.

Indene from *trans*-**1-Bromo-2-hydroxyindane.** A 93% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using 1-dodecene as an internal standard.

Cholesterol from 6β-Bromo-3β,5α-hydroxycholestane. A 79% yield was determined by isolation and crystallization, mp 148 °C.

1-Decene from 2-Bromo-1-decanol. A 74% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using cyclooctene as an internal standard.

1-Dodecene from 2-Bromo-1-dodecanol. A 91% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using indene as an internal standard.

5-Decene from *erythro*-**5-Bromo-6-decanol.** A 91% yield was determined by GLC analysis (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using cyclooctene as an internal standard. Analysis of the cis/trans ratio by the epoxide method outlined above showed a ratio of 20% of *cis*-5-decene to 80% of *trans*-5-decene.

5-Decene from *threo*-**5-Bromo-6-decanol.** An 82% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using cyclooctene as an internal standard. The cis/trans ratio was 30% of *cis*-5-decene to 70% of *trans*-5-decene.

General Reaction Procedure for Alcohol Coupling. LiAlH$_4$ (0.190 g, 5.0 mmol) was added to a stirred slurry of TiCl$_3$ (2.3 g, 15.0 mmol) in 70 mL of dry dimethoxyethane under a nitrogen atmosphere. The resulting black suspension was stirred for 10 min before use. The substrate alcohol (5.0 mmol) in 10 mL of dry DME was added, and the reaction mixture was refluxed for 16 h. After cooling to room temperature, the reaction was worked up in the usual way. In this manner, the following reactions were carried out.

1,2-Diphenylethane from Benzyl Alcohol. A 78% yield was determined by isolation and crystallization of the product, mp 51–52 °C (lit.[23] mp 52 °C).

2,3-Diphenylbutane from α-Phenethyl Alcohol. A liquid mixture of meso and *dl* products was isolated in 68% yield. Anal. Calcd for C$_{16}$H$_{18}$: C, 91.37; H, 8.63. Found: C, 91.59; H, 8.67.

2,3-Dimethyl-2,3-diphenylbutane from 2-Phenyl-2-propanol. A 95% yield was determined by isolation and crystallization, mp 117–118 °C (lit.[24] mp 118–119 °C).

3-(2-Cycloheptenyl)cycloheptene from 2-Cycloheptenol. An 82% yield was determined by chromatographic isolation. Anal. Calcd for C$_{14}$H$_{22}$: C, 88.35; H, 11.65. Found: C, 88.14; H, 11.76.

Farnesol coupling gave a mixture of products which was separated by high-pressure liquid chromatography on Porosil A (16 ft × 0.25 in) using petroleum ether as eluent.

Fraction 1 (13%) was assigned structure **3** based on spectroscopic data: IR (CCl$_4$) 990 and 905 cm^{-1}; mass spectrum, *m/e* 206 (M$^+$); NMR (CDCl$_3$) δ 5.84 (m, 1 H), 5.14 (m, 4 H), 2.05 (m, 7 H), 1.72 and 1.67 (2 singlets, 9 H), 1.31 (m, 2 H), 1.05 (d, 3 H, J = 7 Hz).

Fraction 2 (8%) was assigned structure **4** based on spectroscopic data: IR (CCl$_4$) 1445 and 1365 cm^{-1}; mass spectrum, *m/e* 206 (M$^+$); NMR (CDCl$_3$) δ 5.10 (m, 3 H), 2.00 (m, 8 H), 1.73 and 1.60 (2 singlets, 15 H).

Fraction 3 (48%) was obtained as an inseparable mixture of **1** and **2**: mass spectrum, *m/e* 410 (M$^+$). Although squalene itself shows only a single broad vinyl proton absorption center at δ 5.2, careful examination of the NMR spectrum of fraction 3 indicated the presence of an extra ABX vinyl spin system attributed to the monosubstituted double bond in **2**. Careful integration indicated a 2:1 ratio of **1** and **2**.

1-Methylcyclodecene (6). Cyclodecanone (1.0 g, 6.48 mmol) in 5 mL of ether was added to 40 mL of methyllithium solution (1.5 M) under nitrogen. The mixture was stirred overnight at room temperature and then worked up in the usual way. The crude alcohol product was dissolved in 45 mL of hexane and stirred for 16 h at room temperature with 45 mL of 50% aqueous sulfuric acid. The hexane layer was drawn off, dried (MgSO$_4$), and concentrated to yield **6** (0.99 g, 100%): NMR (CDCl$_3$) δ 5.14 (t, 1 H, J = 8 Hz), 2.24 (m, 4 H), 1.68 (s, 3 H), 1.43 (m, 12 H).

10-Oxoundecanal (7). 1-Methylcyclodecene (0.31 g, 2.04 mmol) was dissolved in 25 mL of methylene chloride and cooled to −78 °C. Ozone (Welsbach ozone generator) was bubbled through the solution until a blue color persisted. Nitrogen gas was then bubbled through the solution for 30 min, and dimethyl sulfide (0.2 g, 3.1 mmol) was added. After stirring at room temperature overnight, the reaction was worked up in the usual way to give 0.34 g (91%) of keto aldehyde **7** as a light oil: IR (neat) 1725 cm^{-1}; NMR (CDCl$_3$) δ 9.80 (t, 1 H, J = 2 Hz), 2.45 (broad t, 4 H, J = 6 Hz), 2.15 (s, 3 H), 1.33 (m, 12 H).

Keto Ester 8. Sodium hydride (0.07 g of a 57% mineral oil suspension; 1.59 mmol) was degreased by pentane washings and slurried in 10 mL of DME. Ethyl α-diethylphosphonopropionate (0.36 g, 1.5 mmol) was dissolved in 5 mL of dry DME and added to the NaH suspension. After stirring for 30 min at room temperature, the solution was taken up in a dry syringe and added to a solution of keto aldehyde **7** (0.23 g, 1.27 mmol) in 5 mL of DME. The reaction was stirred for 16 h at room temperature and then refluxed for 1 h. After cooling to room temperature, the reaction was worked up in the usual way to give crude keto ester **8**. Chromatography on silica gel (elution with 10% ethyl acetate–90% pentane) gave 74 mg (22%) of pure **8**: IR (neat) 1710 (broad) and 1650 cm^{-1}; NMR (CDCl$_3$) δ 6.75 (t, 1 H, J = 7 Hz), 4.18 (q, 2 H, J = 7 Hz), 2.41 (t, 2 H, J = 7 Hz), 2.12 (s, 3 H), 1.82 (s, 3 H), 1.29 (s, 3 H, J = 7 Hz).

Diester 9. Sodium hydride (0.14 g of a 57% mineral oil dispersion; 3.31 mmol) was washed with pentane and slurried in 5 mL of DME under a nitrogen atmosphere. Ethyl diethylphosphonoacetate (0.74 g, 3.2 mmol) dissolved in 5 mL of DME was added, and the reaction was stirred for 1 h at room temperature. The resultant solution was drawn into a dry syringe and added to a solution of keto ester **8** (74 mg, 0.28 mmol) in 3 mL of DME. After stirring for 12 h at 85 °C, the reaction mixture was cooled and worked up in the usual way. The crude material was chromatographed on silica gel to give 48 mg (52%) of pure diester **9**: IR (neat) 1700 and 1650 cm^{-1}; NMR (CDCl$_3$) δ 6.75 (t, 1 H, J = 7 Hz), 5.67 (s, 1 H), 4.18 and 4.14 (2 quartets, 4 H, J = 7

Hz), 2.16 (s, 3 H), 1.34 and 1.33 (2 triplets, 6 H, *J* = 7 Hz).

Bis(allylic diol) 10. Diester 9 (48 mg, 0.14 mmol) was dissolved in 3 mL of ether and cooled to 0 °C under nitrogen. Sodium diethylaluminum dihydride (0.3 mL of a 2.0 M solution in toluene) was added, and the reaction was stirred for 2 h at 0 °C. After workup in the usual way, the crude product was chromatographed on Florisil to give the desired diol 10 (28 mg, 93%): NMR (CDCl$_3$) δ 5.41 (t, 2 H, *J* = 7 Hz), 4.14 (d, 2 H, *J* = 6 Hz), 3.99 (s, 2 H), 2.02 (m, 4 H), 1.66 (s, 6 H).

Attempted Intramolecular Cyclization of 10. A solution of titanium reagent was prepared as detailed above by mixing TiCl$_3$ (0.13 g, 0.84 mmol) and LiAlH$_4$ (0.01 g, 0.28 mmol) in 20 mL of DME. Diol 10 (28 mg, 0.13 mmol) was added, and the mixture was refluxed for 17 h. After workup in the usual manner, the crude product was chromatographed on Florisil to give 19 mg (80%) of a hydrocarbon fraction. Analysis by GC/MS indicated four major components in the product mixture. These components were isomeric and all showed *m/e* 222 (M$^+$) corresponding to hydrogenolysis products. No material with *m/e* 220 (M$^+$) corresponding to cyclized material, was observed (<1%).

6-Oxoheptanal (12). Methylcyclohexene (1.0 g, 10.4 mmol) was dissolved in 70 mL of methylene chloride and cooled to −78 °C. A stream of ozone was bubbled through the solution until a blue color persisted. A stream of nitrogen was then bubbled through to remove excess ozone, and dimethyl sulfide (1.0 g, 16 mmol) was added. After stirring for 16 h at room temperature, the reaction was worked up in the usual way to give keto aldehyde 12 (1.09 g, 82%) as an oil: IR (neat) 1720 cm^{-1}; NMR (CDCl$_3$) δ 9.74 (t, 1 H, *J* = 2 Hz), 2.48 (m, 4 H), 2.15 (s, 3 H).

Bis(allylic alcohol) 13. Keto aldehyde 12 (1.09 g, 8.50 mmol) was dissolved in 60 mL of ether under nitrogen, and vinylmagnesium chloride (18.2 mL of a 2.8 M solution) was added. The reaction was stirred for 16 h at room temperature and then worked up in the usual way to give diol 13 (1.50 g, 96%): IR (neat) 3365, 1650, 995, 920 cm^{-1}; NMR (CDCl$_3$) δ 5.89 (m, 2 H), 5.12 (m, 4 H), 4.08 (d, 1 H, *J* = 6 Hz), 2.43 (s, 2 H), 1.25 (s, 3 H).

Attempted Intramolecular Cyclization of 13. A solution of titanium reagent was prepared as detailed above by mixing TiCl$_3$ (3.26 g, 21.1 mmol) with LiAlH$_4$ (0.27 g, 7.0 mmol) in 70 mL of DME. Diol 13 (0.65 g, 3.5 mmol) in 40 mL of DME was added, and the reaction was refluxed for 16 h. After workup in the usual way, the crude product was chromatographed on silica gel to give 0.31 g (60%) of a hydrocarbon product. Analysis by GC/MS indicated four major components. These components were isomeric with *m/e* 152 (M$^+$), corresponding to uncyclized hydrogenolysis products. No material with *m/e* 150 (M$^+$), corresponding to cyclized product, was observed (<1%).

Reduction of Benzaldehyde Cyanohydrin. A slurry of TiCl$_3$ (1.56 g, 10 mmol) in 50 mL of DME was treated with LiAlH$_4$ (0.13 g, 3.8 mmol), and the resulting black suspension was stirred for 10 min at room temperature under a nitrogen atmosphere. Benzaldehyde cyanohydrin (0.417 g, 3.1 mmol) in 10 mL of DME was added, and the reaction was refluxed for 16 h. After workup in the usual manner, the crude product was chromatographed on silica gel to give phenylacetonitrile (55 mg, 15%), identified by comparison with an authentic sample, and 2,3-diphenylacrylonitrile (195 mg, 61%), mp 88 °C (lit.[25] mp 88 °C).

1-Acetylcyclododecanol (17) was prepared by the general procedure of Baldwin.[26] Thus ethyl vinyl ether (7.38 g, 0.10 mol) was dissolved in 10 mL of dry THF at −78 °C under a nitrogen atmosphere, and *t*-BuLi (35 mL of a 1.6 M solution in pentane) was slowly added over 10 min. The reaction was warmed to room temperature for 0.5 h and then again cooled to −78 °C. A solution of cyclododecanone (9.10 g, 0.050 mol) in 10 mL of THF was added, and the solution was warmed to room temperature for 0.5 h. The reaction was then quenched by addition of aqueous 1.5 N HCl until the water layer remained acidic. Workup in the usual way then provided the crude product which was purified by Kugelrohr distillation (75 °C, 0.05 mm) to give 9.50 g (84%) of impure 17, mp 55–75 °C. Several recrystallizations from pentane provided the pure material (3.6 g, 32%): mp 82–84.5 °C; IR (CHCl$_3$) 3500 and 1700 cm^{-1}; NMR (CCl$_4$) δ 2.15 (s, 3 H), 1.50 (s, 22 H).

Acetyladamantanol (24). Ethyl vinyl ether[26] (7.58 g, 0.105 mol) was dissolved in 10 mL of THF at −78 °C under nitrogen, and *t*-BuLi (35 mL of a 1.6 M solution) was added slowly by syringe. The reaction was warmed to room temperature for 0.5 h and then again cooled to −78 °C. A solution of adamantanone (6.0 g, 0.04 mol) in 25 mL of THF was slowly added, and the solution was warmed to room temperature for 1 h. The solution was then cautiously acidified with 1.5 N HCl and worked up in the usual way. Crystallization of the residue gave 3.5 g (45%): mp 86.5–88 °C; IR (CHCl$_3$) 3600 and 1705 cm^{-1}; NMR (CCl$_4$)

δ 2.10 (s, 3 H); mass spectrum, *m/e* (relative intensity) 194 (M$^+$, 1), 151 (100).

General Reaction Procedure for Reducing α-Hydroxy Ketones. TiCl$_4$ (1.6 g, 8.2 mmol) was dissolved in 2 mL of benzene under a nitrogen atmosphere, and 20 mL of DME was slowly added. Zinc dust (0.39 g, 6.0 mmol) was added, and the mixture was stirred for 45 min at room temperature. The substrate ketol (5.0 mmol) in 2 mL of DME was added, and the reaction was refluxed for 4 h. Workup in the usual way gave the product. In this way, the following reductions were carried out.

Acetyladamantane from Acetyladamantanol. An 80% yield was determined by isolation and crystallization, mp 29.5–31.0 °C.

Acetylcyclohexane from 1-Acetylcyclohexanol.[26] An 84% yield was isolated as the 2,4-DNP, mp 140 °C (lit.[27] mp 140 °C).

Reduction of 1-Acetylcyclododecanol. The product mixture (70%) was found by GLC (15% XF-1150 on Chromosorb W; 5 ft × 0.25 in) to be a mixture of two products. The major product (58%) was identified as acetylcyclododecane: IR (CHCl$_3$) 1700 cm^{-1}; NMR (CDCl$_3$) δ 2.08 (s, 3 H); mass spectrum, *m/e* (relative intensity) 210 (M$^+$, 100), 195 (20), 43 (90). The minor product (12%) was identified as 2-methylcyclotridecanone: IR 1700 cm^{-1}; NMR (CDCl$_3$) δ 1.25 (s, 20 H), 1.03 (d, 3 H, *J* = 7 Hz); mass spectrum, *m/e* (relative intensity) 210 (M$^+$, 80), 195 (2), 99 (100).

2,6-Dimethylcyclohexanone from 2-Hydroxy-2,6-dimethylcyclohexanone. A 20% yield was determined by chromatographic isolation and comparison with an authentic sample.

Reduction of 3β,17α-Dihydroxy-20-ketopregn-5-ene (21).[28] The product mixture was separated by column chromatography. The minor product (32%) was identified as 3β-hydroxy-20-ketopregn-5-ene (22) by comparison with an authentic sample. The major product (50%) was assigned structure 23, the D-homo rearrangement product, although we were unable to carry out a complete characterization.

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Titanium-Induced Reductive Coupling of Carbonyls to Olefins

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Active titanium metal, produced in a finely divided form by reduction of $TiCl_3$ with either potassium or lithium, will reductively couple ketones and aldehydes to olefins. Although the intermolecular coupling works best when two identical carbonyls are coupled to a symmetrical product, unsymmetrical couplings can also be carried out in certain cases. The unsymmetrical coupling of a diaryl ketone with another partner is particularly efficient, and a mechanism to account for this is proposed. Intramolecular dicarbonyl coupling to form rings is also possible, and the combination $TiCl_3/Zn–Cu$ works best. Rings of size 4–16 and 22 are prepared in high yield. The nature of the active titanium metal is studied by scanning electron microscopy, and a mechanistic proposal accounting for all observed results is presented. It is believed that the coupling reaction occurs on the surface of the active titanium particle.

Recently, three separate research groups independently observed that low-valent titanium reagents ($TiCl_4/Zn$,[1] $TiCl_3/Mg$,[2] $TiCl_3/LiAlH_4$[3]) would reductively dimerize ketones and aldehydes to olefins. Two of these reagent systems[1,2] were reported to be effective only for aryl ketones, while our $TiCl_3/LiAlH_4$ reagent gave excellent yields in both aryl and alkyl cases.[3] Subsequently, a number of research groups used our method to prepare a variety of interesting olefins,[4–9] but, as we have reported,[10] the $TiCl_3/LiAlH_4$ reagent gives capricious results depending on the exact batches of reagents used. Although we have been unable to discover the reason for these capricious coupling results, we have found that the $TiCl_3/LiAlH_4$ reagent does reproducibly effect numerous other organic reductions.[11] We have also found that the carbonyl coupling reaction can be reproducibly carried out using active titanium metal prepared by reducing $TiCl_3$ with 3 equiv of potassium.[10] The results of our study of this Ti^0-induced coupling reaction are presented herein.

Intermolecular Carbonyl Couplings. Significant developments have occurred recently in the preparation of metals in highly active forms.[12,13] Rieke and co-workers, for example, have described a general method for the preparation of highly active metals in finely divided form by reduction of the metal halide with potassium in tetrahydrofuran (THF). Magnesium prepared by this method shows extraordinary reactivity in Grignard reagent formation.[14] We therefore reduced a slurry of $TiCl_3$ in THF with 3 equiv of potassium and observed that the resultant black slurry reductively coupled carbonyl compounds to olefins in high yield. Since the reaction is a heterogeneous one, excess titanium reagent is required and we therefore optimized conditions to find the most efficient procedure. Our results using cyclododecanone as substrate are shown in Table I.

As can be seen in the table (run 2 vs. run 1), heating the reaction for prolonged periods did not increase the yield. The use of either 1 equiv of potassium per $TiCl_3$ (run 4) or 2 (run 3) rather than the theoretical 3 gave markedly lower yields of product. Use of dimethoxyethane (DME) as solvent rather than THF had little effect. Addition of KI to the mixture[14] prior to reduction had little effect. The optimum ratio of $TiCl_3/K/ketone$ was 1:3.5:0.25. It became clear in the course

of these optimization experiments that material was being lost during aqueous workup, and we therefore developed a nonaqueous filtration procedure for workup (run 13; see Experimental Section). This modification allowed us to isolate excellent yields (90%) reproducibly.

With optimum conditions established, the coupling of other aliphatic ketones and aldehydes was examined and our results are given in Table II. The coupling reaction is general for aliphatic ketones and aldehydes, and good yields of products are usually obtained. Cycloalkanones of varying ring sizes couple well, and highly hindered olefins (tetraisopropylethylene) can be made in modest yields. The one obvious problem revealed by the results in Table II is that diaryl ketones (fluorenone, benzophenone) couple well, but the products do not survive. The tetraarylethylenes produced reduce further to tetraarylethanes.

It is clear that this Ti^0-induced coupling procedure is an effective one, but the use of potassium to reduce the metal halide, as recommended by Rieke, is a potentially hazardous process. We therefore examined the use of other less reactive alkali metals and were surprised to discover that lithium metal proved as effective as potassium even at temperatures far below its melting point. Thus, heating a slurry of $TiCl_3$ and 3 equiv of Li in DME for 1 h produced a black slurry which effectively coupled carbonyl compounds to olefins. This is a most surprising result for several reasons. In the first place, one would expect the solid lithium pieces to become coated on the surface and rapidly inactivated. This does not appear to happen, however, perhaps due to mechanical agitation by the stirrer. More surprising is the fact that, although the reduction of $TiCl_3$ to Ti^0 is incomplete (much unreacted lithium is recovered), the coupling still proceeds well. We do not know whether lithium is recovered because the $TiCl_3$ is reduced only to Ti(II) rather than Ti^0 or if Ti^0 is actually produced. Considering, however, both the fact that Ti(II) ($TiCl_3$ + 1 equiv of K; run 4, Table II) does not effectively couple alkyl ketones and the fact that Li is a stronger reducing agent than K, we feel that Ti^0 is probably the active species in the $TiCl_3/Li$ reduction. When we investigated the reactivity of $TiCl_3/Li$ for carbonyl coupling, we found that it was generally as effective as $TiCl_3/K$ but was somewhat less reactive in that diaryl ke-

Table I. Reductive Coupling of Cyclododecanone

run	molar ratio TiCl₃/ K/ketone	solvent	time,[a] h	yield,[b] %
1	1:3:0.5	THF	18	59
2	1:3:0.5	THF	40	56
3	1:2:0.5	THF	16	38
4	1:1:0.5	THF	16	28
5	1:3:0.5	THF	15	64
6	1:3:0.5	DME	15	49
7	1:3:0.25	THF	16	67
8	1:3.5:0.25	THF	17	76
9	1:4.7:0.25	THF	13	71
10	1:3:0.25	THF[c]	15	77
11	1:3:0.25[d]	THF	16	67
12	1:3:0.25[e]	THF	16	68
13	1:3:0.25	THF	16	90[f]

[a] Heating at reflux subsequent to addition of ketone. [b] Isolated yield after aqueous workup and column chromatography. [c] Solvent deoxygenated prior to reaction. [d] KI (0.25 equiv) added prior to potassium. [e] AlCl₃ (1.0 equiv) added prior to potassium. [f] Isolated yield after nonaqueous workup and column chromatography.

tones gave good yields of olefin without over reduction. Some results are shown in Table III.

Both the TiCl₃/K procedure and the TiCl₃/Li procedure are effective. We did however examine several other possibilities. Neither Al⁰, Fe⁰, V⁰, Cr⁰, Zn⁰ (all prepared by potassium reduction of their chlorides), nor commercial titanium powder had any activity. Of the systems we examined, active Ti⁰ was unique.

Mixed Couplings. Thus far, we have considered only the symmetrical coupling of two identical ketones. From a synthesis point of view, it would of course be more useful to be able to effect a mixed coupling of two different ketones, yielding an unsymmetrical olefin. In practice, this mixed coupling reaction is unlikely to be successful unless certain conditions are met. We have already demonstrated that the carbonyl coupling proceeds through an intermediate pinacol dimerization,[3,10] and it is generally accepted that pinacol dimerization occurs via anion radicals.[15] The synthesis of unsymmetrical olefins by our method would therefore require a mixed pinacol reaction. Although little literature is available on mixed pinacol couplings, it appears that one generally obtains a nearly statistical mixture of the three possible products.[16-20] It was therefore our expectation that a mixed carbonyl coupling reaction could probably be carried out in a synthetically useful manner only when one carbonyl component was used in excess and when the olefin dimer of that

component could be readily removed from the product mixture. Acetone is the obvious choice as the component to be used in excess, and the results of some mixed couplings between acetone and other ketones are shown in Table IV.[21]

In all cases examined, the isopropylidene products could be isolated in synthetically useful yields, and since the isopropylidenecycloalkane functionality is commonly found among sesquiterpenes, this mixed coupling reaction may prove quite useful. Further, the synthesis and spectroscopic study of *vic*-diisopropylidene compounds such as that derived from pulegone (entry 12, Table IV) has been an active field recently,[22] and the present synthesis is efficient.

Careful examination of the results in Table IV reveals an interesting fact. Although dialkyl ketones and monoaryl ketones give an approximately statistical ratio of products, the diaryl ketones benzophenone and fluorenone give only cross coupled products. This is surprising when one considers that the reduction potentials of both benzophenone and fluorenone are 1.0–1.5 V less negative than that of acetone.[23] One would therefore expect their anion radicals to form more rapidly than that of acetone, leading predominantly to symmetrical coupling. Since this is not the case, we believe it unlikely that the mixed pinacol coupling of acetone with diaryl ketones is a radical process.

An alternative mechanistic hypothesis is to assume that the initially formed diaryl ketyl further reduces to a dianion and the dianion effects a nucleophilic addition to acetone. Support for this hypothesis comes from the fact that the second reduction potential of benzophenone and fluorenone to give dianions is less negative than the first reduction potential of acetone.[23]

$$Ar_2C{=}O \xrightarrow{2e^-} Ar_2\overset{-}{C}{-}O^- \xrightarrow{CH_3CCH_3} Ar_2\overset{O^-}{\underset{|}{C}}{-}\overset{O^-}{\underset{|}{C}}(CH_3)_2$$
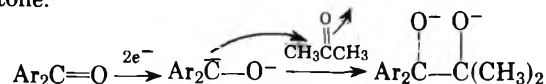
If this suggestion is correct, then the mixed pinacol coupling of diaryl ketones with other ketones should be a general process, not limited to cases where one inexpensive component is used in excess. We should be able to obtain good yields of mixed coupled product whenever one component of the reaction reduces to a dianion before the other component reduces to a radical anion. We have carried out several such reactions successfully, and our results are given in Table V.

The problem of mixed couplings thus remains only partially solved. A procedure is still not available to cleanly couple any desired pair of carbonyl compounds.

Intramolecular Couplings. Another type of unsymmetrical couplings which might have great synthetic potential is the intramolecular coupling of a dicarbonyl compound to form a cycloalkene. Such a procedure, were it to be successful, might be considered the formal reverse of a double bond ozonolysis.

Table II. Coupling of Carbonyl Compounds with TiCl₃/K

entry	registry no.	carbonyl	$\xrightarrow{TiCl_3/3K}$ product	registry no.	yield,[a] %
1	110-62-3	Valeraldehyde	5-Decene (70% trans/30% cis)		77
2	112-31-2	Decanal	10-Eicosene	66587-45-9	60
3	120-92-3	Cyclopentanone	Cyclopentylidenecyclopentane		40
4	108-94-1	Cyclohexanone	Cyclohecylidenecyclohexane		85
5	502-42-1	Cycloheptanone	Cycloheptylidenecycloheptane		86
6	502-49-8	Cyclooctanone	Cyclooctylidenecyclooctane		70
7	700-58-3	Adamantanone	Adamantylideneadamantane		91
8	565-80-0	Diisopropyl ketone	Tetraisopropylethylene		37
9	830-13-7	Cyclododecanone	Cyclododecylidenecyclododecane	53416-00-5	90
10	566-88-1	Cholestanone	Cholesterylidenecholestane	66673-25-4	85
11	486-25-9	Fluorenone	9,9'-Bifluorene		85
12	119-61-9	Benzophenone	Tetraphenylethane		80
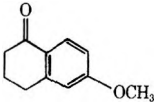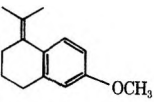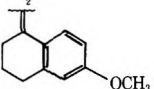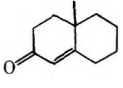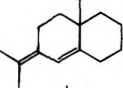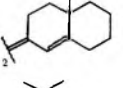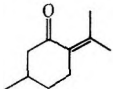
[a] Isolated yield.

Table III. Coupling of Carbonyl Compounds with TiCl₃/Li

entry	carbonyl[b] $\xrightarrow{\text{TiCl}_3/3\text{Li}}$	product[c]	yield,[a] %
1	Cyclohexanone	Cyclohexylidenecyclohexane	79
2	Cycloheptanone	Cycloheptylidenecycloheptane	85
3	Cyclododecanone	Cyclododecylidenecyclododecane	65
4	Adamantanone	Adamantylideneadamantane	82
5	Benzaldehyde	Stilbene	97
6	Acetophenone	2,3-Diphenyl-2-butene (10% cis/90% trans)	94
7	Benzophenone	Tetraphenylethylene	96
8	Retinal	β-Carotene	95

[a] Isolated yield after column chromatography. [b] Registry no.: benzaldehyde, 100-52-7; acetophenone, 98-86-2; retinal, 116-31-4. [c] Registry no.: *cis*-2,3-diphenyl-2-butene, 782-05-8; *trans*-2,3-diphenyl-2-butene, 782-06-9.

Table IV. Mixed Coupling Between Acetone and Other Ketones (Acetone/Ketone = 4:1)

entry	registry no.	ketone $\xrightarrow{\text{TiCl}_3/3\text{Li}}$	products	registry no.	yield,[a] %
1		Adamantanone	Isopropylideneadamantane	20441-18-3	63
			Adamantylideneadamantane		12
2	98-53-3	4-tert-Butylcyclohexanone	4-tert-Butylisopropylidenecyclohexane	14033-75-1	55
			Bi-4-*tert*-butylcyclohexylidene		22
3		Cycloheptanone	Isopropylidenecycloheptane	7087-36-7	50
			Cycloheptylidenecycloheptane		26
4		3-Cholestanone	3-Isopropylidenecholestane	1176-53-0	54
			3-Cholesterylidenecholestane		29
5	83-33-0	1-Indanone	1-Isopropylideneindane	61370-23-8	71
			1-Indanylidene-1-indane		24
6		Acetophenone	2-Methyl-3-phenyl-2-butene	769-57-3	65
			2,3-Diphenyl-2-butene		16
7		Benzophenone	1,1-Diphenyl-2-methylpropene	781-33-9	94
			Tetraphenylethylene		Trace
8		Fluorenone	Isopropylidenefluorene	19326-47-7	84
			Bifluorenylidene		0
9	1078-19-9			61370-24-9	85
			+		9
10	826-56-2			61370-26-1	67
			+		26
11	78-59-1			50523-39-2	63
12	89-82-7			66587-46-0	55

[a] Isolated yield after column chromatography.
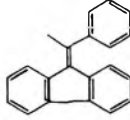
We have reported in a preliminary communication[24] that the intramolecular dicarbonyl coupling is in fact successful, and our results are given in Table VI.

Our initial results in attempting intramolecular dicarbonyl coupling were discouraging in that rather low yields of cycloalkenes were produced under conditions that worked well for intermolecular couplings. We discovered, however, that when high dilution conditions were used (36-h addition of dicarbonyl to TiCl₃/Zn–Cu via syringe pump) much better yields were obtained. We also discovered that, although the coupling could be carried out with TiCl₃/Li, better yields were obtained when zinc–copper couple was used as the reducing agent. This reagent is readily and safely prepared (see Experimental Section), and we now prefer it for all carbonyl couplings, both intermolecular and intramolecular.

As can be seen from Table VI, the cyclization is general for

Table V. Mixed Carbonyl Coupling of Diaryl Ketones with Other Partners (Ratio of Ketones 1:1)

entry	registry no.	ketones	$\xrightarrow{\text{TiCl}_3/3\text{Li}}$ products		registry no.	yield,[a] %
1		Benzophenone	1,1-Diphenyl-2-methylpropene			81
		Acetone	Tetraphenylethylene			14
2		Benzophenone	Cyclohexylidenediphenylmethane		30125-24-7	78
		Cyclohexanone	Tetraphenylethylene			19
			Cyclohexylidenecyclohexane			6
3		Benzophenone	1,1-Diphenyl-1-heptene		1530-20-7	84
	66-25-1	Hexanal	Tetraphenylethylene			9
			6-Dodecene			8
4		Benzophenone	3-Cholesterylidenediphenylmethane		66673-26-5	82
		3-Cholestanone	Tetraphenylethylene			14
			3-Cholesterylidene-3-cholestane			15
5		Benzophenone	Tetraphenylethylene			90
	815-24-7	Di-*tert*-butyl ketone				
6		Fluorenone	Isopropylidenefluorene			74
		Acetone	Bifluorenylidene			8
7		Fluorenone	Cycloheptylidenefluorene		61370-29-4	77
		Cycloheptanone	Bifluorenylidene			7
			Cycloheptylidenecycloheptane			17
8		Fluorenone				
		Acetophenone			61370-30-7	70
			2,3-Diphenyl-2-butene			15
			Bifluorenylidene			8

[a] Isolated yield after column chromatography.

both aldehydes and ketones. Most remarkable, however, is the fact that excellent yields of cycloalkene are obtained for all ring sizes, including the difficult medium size rings and the very large 22-membered ring. To compare the titanium dicarbonyl cyclization to other methods,[25] the Thorpe–Ziegler dinitrile cyclization[26] is reported to fail for ring sizes 9–13. The acyloin cyclization of diesters is much better,[27] but it shows a dip in yield for ring sizes 9–11.

As an example of the potential utility of the method, we undertook a synthesis of the natural product civetone (6), a 17-membered ring olefinic ketone. Civetone has been synthesized several times previously[28] by other workers, but it nevertheless appeared to be a good target for synthesis by our reaction. The route used is shown in Scheme I.

We were surprised to learn that the key coupling step occurred with partial removal of the ketal protecting group during the reaction. The ethylene ketal, in particular, was almost totally removed, and we therefore resorted to use of the somewhat more stable catechol ketal 3. This proved more stable, and civetone ketal 5 was isolated in 70% yield. This compares favorably with the yield reported for civetone synthesis by the acyloin reaction.[28]

Reduction of 1,2-Diols. The deoxygenation of 1,2-diols to olefins is a useful synthetic transformation which can be carried out by various methods.[29] Since the carbonyl coupling reaction proceeds through the intermediacy of a pinacol dianion, we examined the reaction of diols with active Ti⁰. The deoxygenation is quite successful,[10] and our attempts at optimizing reaction yields are given in Table VII. Some results on different diols are given in Table VIII.

There are several interesting features of the reaction displayed in these tables. The use of 3 equiv of potassium to reduce the diol (runs 4 and 5, Table VII) led to considerably lower yields of product than did the use of 4.5 equiv. We assume that this is due to the necessity of first removing the acidic hydroxyl protons to form the pinacol dianion. A further point is that both cyclic and acyclic diols reduced in good yield, including the trans diaxial glycol $2\beta,3\alpha$-dihydroxy-3β-

methyl-5α-cholestane (entry 2, Table VIII). *trans*-9,10-Decalindiol (entry 7, Table VIII), however, did not reduce. From a synthetic point of view, the good yields and generality observed make this reaction a potentially useful one. From the mechanistic point of view, these results have clear implications as to the exact nature of the carbonyl coupling process.
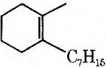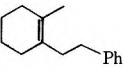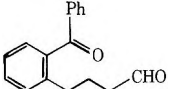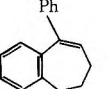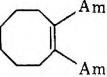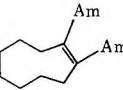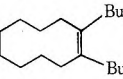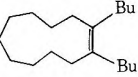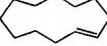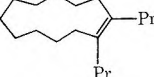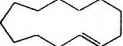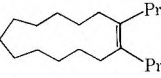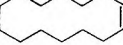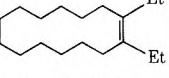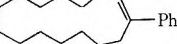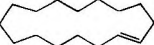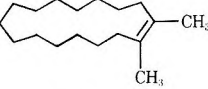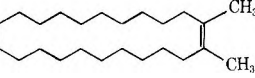
Mechanism of the Titanium-Induced Carbonyl Coupling. One can conceive of many possible mechanisms to account for the carbonyl coupling reaction, and we depict four such likely possibilities in Scheme II.

The intermediate pinacol can reduce in one of several ways, and it should be possible, by a proper choice of experiments, to distinguish between them. In path A, we assume that the pinacol forms a five-membered ring intermediate with both oxygens bound to the same titanium atom [presumably Ti(II)]. This intermediate can further react either by a concerted path A_1, giving olefin and TiO_2, or it can react by a nonconcerted path A_2, in which the two C–O bonds are broken at different times. It should be possible to distinguish between these by looking at the reduction of a diol of known stereochemistry, and entries 4 and 5 in Table VIII do just this. When both *meso*- and *dl*-5,6-dihydroxydecane were reduced with $TiCl_3/K$, mixtures of *cis*- and *trans*-5-decene were produced, indicating the nonconcerted nature of the reaction. It was rather surprising to us that a different mixture was observed in the two cases, indicating perhaps that the reaction lies on the borderline of being concerted. We have, however, verified the results and carried out a control experiment, showing that both *cis*- and *trans*-5-decene are stable to reaction conditions.

An alternative explanation accounting for the observed mixture of cis and trans products would be to postulate that our starting diols were undergoing isomerization by reverse pinacol reaction prior to deoxygenation. Such reverse pinacol reactions have been reported,[30-31] and it is possible that such a process is occurring here and thus hiding a concerted deoxygenation.

Table VI. Intramolecular Dicarbonyl Coupling

entry	registry no.	dicarbonyl	$\xrightarrow{\text{TiCl}_3/\text{Zn–Cu}}$ product		registry no.	yield,[a] %
1	495-71-6	$PhCO(CH_2)_2COPh$				87
2	6303-82-8	$CH_3CO(CH_2)_3COPh$				70
3	66587-47-1	$CH_3CO(CH_2)_4COC_7H_{15}$			66587-48-2	79
4	3375-38-0	$PhCO(CH_2)_4COPh$				95
5	63521-73-3	$CH_3CO(CH_2)_4COCH_2CH_2Ph$			63521-79-9	50
6	63521-74-4				21855-89-0	80
7	31335-02-1	$AmCO(CH_2)_6COAm$			66587-49-3	67
8	31335-05-4	$AmCO(CH_2)_7COAm$			66587-50-6	68
9	31335-01-1	$BuCO(CH_2)_8COBu$			63521-82-4	75
10	63521-75-5	$BuCO(CH_2)_9COBu$			63521-83-5	76
11	38279-34-4	$CHO(CH_2)_{10}CHO$			1501-82-2	76
12	7029-25-6	$PrCO(CH_2)_{10}COPr$			66587-35-7	71
13	63521-76-6	$CHO(CH_2)_{11}CHO$			6573-70-2	52
14	31335-04-3	$PrCO(CH_2)_{11}COPr$			66587-36-8	65
15	63521-77-7	$CHO(CH_2)_{12}CHO$			6568-33-8	71
16	31335-00-9	$EtCO(CH_2)_{12}COEt$			66587-37-9	75
17	63521-78-8	$CHO(CH_2)_{13}COPh$			63521-84-6	80
18	6812-43-7	$CHO(CH_2)_{14}CHO$			6568-44-1	85
19	34959-20-1	$CH_3CO(CH_2)_{14}COCH_3$			66587-38-0	90
20	34689-16-2	$CH_3CO(CH_2)_{20}COCH_3$			66587-39-1	83

[a] Isolated yield.

This is clearly not the case, however. We have shown conclusively in other studies[32] that the pinacol coupling of simple aliphatic carbonyl compounds is not readily reversible, and we have also run the *meso*- and *dl*-5,6-dihydroxydecane reductions to partial completion and examined the recovered diols. The recovered diols showed no isomerization. We feel

Table VII. Deoxygenation of Bicyclohexyl-1,1'-diol to Cyclohexylidenecyclohexane with TiCl$_3$/K
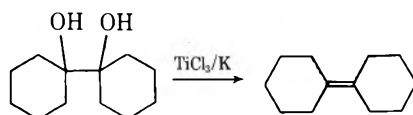
run	molar ratio TiCl$_3$/K/diol	rxn temp, °C	rxn time, h	diol recovered,[a]	olefin,[a] %
1	1:4.5:0.25	65	16	0	85
2	1:4.5:0.25	65	1.25	61	24
3	1:4.5:0.25	20	16	78	14
4	1:3.0:0.25	65	17	28	59
5	1:3.0:0.125	65	18	37	49
6	1:3.1:0.25[b]	65	13	46	43

[a] Isolated yield after column chromatography. [b] Diol added as dipotassium salt.

Scheme I. Synthesis of Civetone (6)

Scheme II

6) proceeds smoothly to yield the expected 1,2,3,4,5,6,7,8-octahydronapthalene. Reaction of the isomeric *trans*-9,10-decalindiol under identical conditions, however, gives no
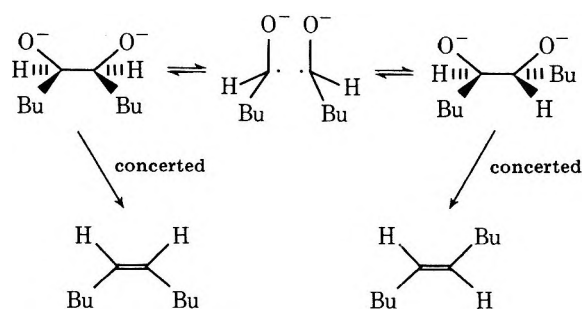
olefinic product. The only obvious difference between the two diol substrates is that in the cis isomer the oxygen atoms can

that these results rule out path A$_1$ as a possible deoxygenation mechanism.

Path B differs from path A in that a five-membered ring is not present and the two oxygens are bound to different titanium atoms. The path B intermediate would presumably further react, giving olefin by a nonconcerted path. Entries 6 and 7 (Table VIII) were designed to distinguish between path A$_2$ and path B. Reduction of *cis*-9,10-decalindiol (entry

Table VIII. Reduction of Some Diols with TiCl₃/K

entry	registry no.	diol	product	yield, %
1	2888-11-1			85
2	28809-87-2			80[a]
3	13553-19-0			55[b]
4	3266-25-9	*meso*-BuCH(OH)CH(OH)Bu	5-Decene (40% cis/60% trans)	75[b]
5	59367-33-8	*dl*-BuCH(OH)CH(OH)Bu	5-Decene (9% cis/91% trans)	80[b]
6	28795-95-1			80[b]
7			No reaction	
8		 **7**		78[b]
9		 **8** **9**		60[b]

[a] Isolated yield after column chromatography. [b] GLC yield relative to internal standard.

both bond to a common surface or single titanium atom while in the trans isomer this is not possible. We conclude therefore that path B does not represent a viable choice of reaction mechanism.
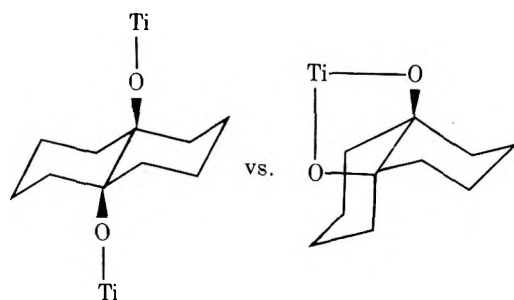
At first glance, one might consider it surprising that a trans diaxial glycol such as the 2α,3β-dihydroxy steroid in entry 2 of Table VIII reacts so readily since in the chair conformer the oxygens can not bond to a common point. The logical explanation of this reduction, however, is that reaction occurs through the A ring boat conformer.

The final mechanistic possibility we would like to consider is path C of Scheme II. This is rather poorly defined in comparison to paths A and B, but we would like to consider the chance that the deoxygenation reaction may actually be occurring on the surface of an active titanium particle in a heterogeneous process. Such a process would be analogous to the acyloin condensation which is thought to occur on the surface of molten sodium droplets.[27] Path C differs from path A in
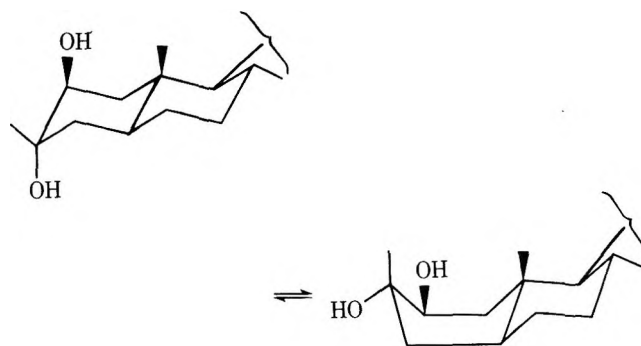
that the two oxygens bond to a common surface rather than to a common atom, and both are compatible with the results of the isomeric decalindiol reactions. Paths A₂ and C should be distinguishable, however, by employing a classic test for the presence or absence of a five-membered ring intermediate. Entries 8 and 9 of Table VIII accomplish this.

Previous studies have shown a large difference in the reaction rates of cis diol **7** and trans diols **8** and **9** with various reagents assumed to form five-membered ring intermediates. For example, cis glycol **7** undergoes cleavage with lead tetraacetate at 20 °C very quickly (second order rate constant $k = 2.5 \times 10^4$ mol⁻¹ L min⁻¹) in contrast to the reaction with trans diols **8** and **9**, which proceeded too slowly at 20 °C to be measured ($k = 0.38$ mol⁻¹ L min⁻¹ at 50 °C.[33] The explanation for this difference is that the cis diol can easily form a five-membered ring lead alkoxide while the trans diols have their hydroxyls rigidly held too far apart to accommodate a five-
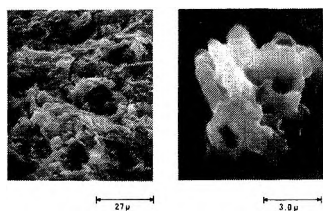
Figure 1. The surface of the active titanium reagent as examined by scanning electron microscopy.

Table IX. Deoxygenation of *cis*- and *trans*-Camphanediols with TiCl₃/K in THF

run	time, h	% yield[a] from cis diol 7	% yield[a] from trans diols 8,9
1	0.5	51	29
2	1	76	33
3	5	81	60

[a] GLC yield determined relative to internal standard.

membered ring. If the titanium deoxygenation reaction also proceeds through a five-membered ring (path A), we would expect cis diol 7 to reduce at a much faster rate than trans diols 8 and 9. If, however, the hydroxyls need only approach a common broad surface (path C), both cis and trans diols should reduce. Treatment of cis diol 7 and a 70:30 mixture of trans diols 8 and 9 in side by side experiments gave the results shown in Table IX.

Aliquots were periodically removed, and yields of 2-bornene were determined by GLC. The table clearly shows that both *cis*- and *trans*-camphanediols were reduced at approximately the same rate and were complete after 5 h. These results strongly suggest to us that the deoxygenation of diols does not require the formation of a five-membered ring intermediate. We therefore conclude that the reaction occurs by the route shown in path C of Scheme II; i.e., the deoxygenation of diols occurs in a heterogeneous process on the surface of an active titanium particle (see Scheme III).

Nature of the Titanium Reagent. With the knowledge that the carbonyl coupling reaction is occurring on the active titanium surface, we were curious as to the nature of the particles. We therefore prepared the active reagent and examined it by scanning electron microscopy. The results are shown in

Scheme III

Figure 1. The titanium evidently forms aggregates of widely varying shapes and sizes. A highly pebbled "Swiss cheese" type of surface is present giving what must certainly be an extremely high surface-to-mass ratio. The wide variation in particle shape and size, however, makes a simple calculation of surface area impossible.

Reaction of Ti⁰ with Other Functional Groups. We have spent considerable time investigating the reactions of other functional groups with Ti⁰, but to date our efforts have not been fruitful. One can imagine, for example, that Ti⁰ might react with esters to give an acyloin reaction, and the product enediolate might then deoxygenate, yielding an acetylene.[34]

$$RCO_2R' \xrightarrow{Ti^0} R\overset{O^-}{\underset{|}{C}}=\overset{O^-}{\underset{|}{C}}R \longrightarrow RC{\equiv}CR$$
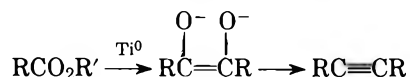
We found, however, that treatment of esters with Ti⁰ led only to complex mixtures of products containing only small (2–3%) amounts of acetylene. Ethyl valerate, for example, gave only about 2% of 5-decyne along with 5-decene and various oxygen-containing products. Attempted acyloin-type cyclization of a 1,16-diester gave none of the desired cyclohexadecyne, but rather a mixture containing cyclohexadecene, cyclohexadecane, cyclohexadecanol, 2-hydroxycyclohexadecanone, and other products.

In similar reactions, we have also treated acids, acid chlorides, α-bromo ketone enolates, α-phenylsulfenyl ketone enolates, and α-diketones with Ti⁰, but in no case were useful results obtained. A control experiment in which 5-decyne was treated with Ti⁰ established that acetylenes are slowly reduced. A successful acetylene synthesis is therefore unlikely unless its rate is rapid.

Table X reports the results of some other reactions with Ti⁰. Saturated alcohols do not react with Ti⁰, and imines (entries 3 and 5) react poorly. Thioketones (entry 6) react well, as might be expected, and surprisingly, a free aliphatic acyloin (entry 7) also reacts cleanly, although the product is, unexpectedly, the dimer resulting from coupling of cyclotetradecanone.

Summary

It is clear from the results presented that active titanium metal is an efficient reagent for coupling ketones and aldehydes to olefins. The reactions work well both inter- and intramolecularly. In special cases, even mixed couplings can be carried out in good yield. Ti⁰ will also reduce diols to olefins, and we believe the reaction occurs on the surface of active metal particles. Unfortunately, however, Ti⁰ does not react cleanly with other reducible functional groups and it therefore appears that its use is limited to cases where functional groups other than alcohols, ethers, and olefins are not present.

Experimental Section

General. Melting points were obtained on a Thomas-Hoover unimelt apparatus. Proton NMR spectra were recorded on a Varian A56/60A (60 MHz) or a Jeolco Minimar (60 MHz) instrument. Chemical shifts are reported in δ (ppm) downfield from internal tetramethylsilane. IR spectra were recorded on Perkin-Elmer 237 or 337

Table X. Reaction of Some Functional Groups with TiCl₃/Li

entry	registry no.	starting material	product	yield, %
1		Cholesterol	No reaction	
2			No reaction	
3			No reaction	
4	19813-45-7		Mixture	
5	66587-40-4			14
6	1450-31-3		Tetraphenylethylene	90
7	54561-32-9			80

grating spectrophotometers. Gas chromatography/mass spectroscopy was performed on a Finnigan Model 4000 instrument operating at a 70 eV ionization potential and employing a 3% OV-1 on Chromosorb W glass column (4 ft × 0.25 in). TiCl₃ was obtained from Alfa Inorganics and was transferred under an inert atmosphere in a glovebag or a Schlenk apparatus.

The phrase "usual workup procedure" used below means that the reaction mixture was cooled to room temperature, diluted with water, and extracted several times with ether. The combined ether extracts were washed with saturated brine, dried (MgSO₄), and concentrated by solvent removal at the rotary evaporator.

General Procedure for Intermolecular Coupling Using TiCl₃/K. Potassium metal (1.92 g, 49 mmol) was washed with hexane to remove oil and was added to a stirred slurry of TiCl₃ (2.15 g, 14 mmol) in 75 mL of dry tetrahydrofuran (THF) at room temperature under an inert atmosphere. After refluxing for 40 min, the black mixture was cooled and a solution of ketone or aldehyde (3.5 mmol) in 5 mL of THF was added. After a further 16 h at reflux, the reaction mixture was cooled to room temperature and transferred by syringe to a sintered glass filtration tube (medium frit) under an inert atmosphere. The mixture was vacuum filtered, and the filter cake was washed with hexane. The filtrate was then concentrated by solvent removal at the rotary evaporator to yield the crude product. The black filter cake was carefully quenched by the slow dropwise addition of methanol and was allowed to stand until gas evolution ceased. This must be done with caution under an inert atmosphere since the filter cake is pyrophoric when exposed to air. In this manner, the following reactions were carried out.

5-Decene from Valeraldehyde. A 77% yield was obtained as determined by GLC analysis (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-dodecene as an internal standard. The cis/trans ratio of the product was determined by the method outlined in the accompanying paper[11] and was found to be approximately 70% trans to 30% cis.

10-Eicosene[35] from Decanal. A 60% yield was obtained by column chromatographic isolation: NMR (CDCl₃) δ 5.3 (m, 2 H), 2.0 (m, 4 H), 0.8–1.5 (m, 34 H); mass spectrum, *m/e* (relative intensity) 280 (M⁺, 100).

Cyclopentylidenecyclopentane from Cyclopentanone. A 40% yield was isolated as an oil by column chromatography: mass spectrum, *m/e* 136 (M⁺); NMR spectrum corresponds to that reported.[36]

Cyclohexylidenecyclohexane from Cyclohexanone. An 85% yield was isolated by column chromatography, mp 52–53 °C (lit.[37] mp 53.5–54.5 °C).

Cycloheptylidenecycloheptane from Cycloheptanone. An 86% yield was isolated as an oil by column chromatography: mass spectrum, *m/e* 192 (M⁺); NMR spectrum corresponds to that reported.[36]

Cyclooctylidenecyclooctane from Cyclooctanone. A 70% yield was isolated by column chromatography, mp 39–40 °C (lit.[36] mp 39–41 °C).

Adamantylideneadamantane from Adamantanone. A 91% yield was isolated by column chromatography, mp 183–185 °C (lit.[38] mp 184–187 °C).

Tetraisopropylethylene from Diisopropyl Ketone. A 37% yield was isolated by chromatography, mp 118–120 °C (lit.[5] mp 116–117 °C).

Cyclododecylidenecyclododecane from Cyclododecanone. A 90% yield was isolated by column chromatography: mp 150–152 °C; NMR (CDCl₃) δ 1.8–2.3 (m, 8 H), 1.2–1.6 (m, 36 H); mass spectrum, *m/e* (relative intensity) 332 (M⁺, 100). Anal. Calcd for C₂₄H₄₄: C, 86.67; H, 13.33. Found: C, 86.53; H, 13.45.

3-Cholesterylidene-3-cholestane from 3-Cholestanone. An 85% yield was isolated by column chromatography: mp, decomposition at ca. 310 °C. Anal. Calcd for C₅₄H₉₂: C, 87.49; H, 12.51. Found: C, 87.66; H, 12.75.

9,9'-Bifluorene from Fluorenone. An 85% yield was isolated by column chromatography, mp 244–246 °C (lit.[39] mp 246 °C).

Tetraphenylethane from Benzophenone. An 80% yield was isolated by column chromatography, mp 207–209 °C (lit.[40] mp 209–210 °C).

General Procedure for Intermolecular Coupling Using TiCl₃/Li. Lithium wire (0.328 g, 47.3 mmol) and TiCl₃ (2.405 g, 15.6 mmol) were slurried in 40 mL of dry dimethoxyethane (DME) under an argon atmosphere, and the mixture was refluxed for 1 h. After cooling, a solution of ketone in 10 mL of DME was added. After a further 16 h at reflux, the reaction mixture was cooled to room temperature, diluted with petroleum ether, and filtered through a small pad of Florisil on a sintered glass filter. The residue was cautiously quenched by the slow addition of methanol. The filtrate was concentrated by removal of solvent at the rotary evaporator to yield the crude product. In this manner, the following reactions were carried out.

Cyclohexylidenecyclohexane from Cyclohexanone. A 79% yield was isolated by column chromatography. The product was identified by comparison with the sample prepared above.

Cycloheptylidenecycloheptane from Cycloheptanone. An 85% yield was isolated by column chromatography. The product was identified by comparison with the sample prepared above.

Cyclododecylidenecyclododecane from Cyclododecanone. A 65% yield was isolated by column chromatography. The product was identified by comparison with the sample prepared above.

Adamantylideneadamantane from Adamantanone. An 82% yield was isolated by column chromatography. The product was identified by comparison with the sample prepared above.

Stilbene from Benzaldehyde. A 97% yield was isolated by column chromatography. The product (trans) was identified by comparison with an authentic sample.

2,3-Diphenyl-2-butene from Acetophenone. A 94% yield was isolated by column chromatography. NMR spectroscopy of the resulting oil showed it to be a 90:10 mixture of isomers. The major isomer showed an NMR methyl absorption at δ 2.14 while the minor isomer had a methyl absorption at δ 1.87. According to the literature

assignments[41] therefore, our mixture is 90% Z and 10% E. We believe, however, that these assignments are almost certainly wrong and should be reversed since analogous compounds (stilbene and stilbestrol) are known to prefer an E geometry.

Tetraphenylethylene from Benzophenone. A 96% yield was isolated by column chromatography, mp 221–222 °C (lit.[42] mp 222 °C).

β-Carotene from Retinal. A 95% yield of crude material was isolated by column chromatography. This dark red solid was homogeneous by TLC, but by comparison with published UV spectra[43] it was shown to be a mixture of double-bond isomers.

General Reaction Procedure for Mixed Carbonyl Coupling Using TiCl₃/Li. Lithium wire (0.45 g, 65 mmol) was added to a stirred slurry of TiCl₃ (2.87 g, 18.6 mmol) in 30 mL of DME under an argon atmosphere, and the mixture was refluxed for 1 h. The black slurry was then cooled to room temperature, and the two carbonyl components (4.65 mmol total) in 5 mL of DME were added. The mixture was stirred for 2 h at room temperature and then refluxed for 16 h. After cooling to room temperature, the reaction was diluted with pentane and filtered through a small pad of Florisil. Evaporation of solvent from the filtrate gave the crude product. In this manner, the following reactions were carried out.

Adamantanone with 4 equiv of acetone gave isopropylideneadamantane[44] as an oil (63%): NMR (CCl₄) δ 2.87 (m, 2 H), 1.77 (m, 12 H), 1.63 (s, 6 H); mass spectrum, *m/e* 176 (M⁺).

4-tert-Butylcyclohexanone with 4 equiv of acetone gave isopropylidene-4-*tert*-butylcyclohexane[45] as an oil (55%): NMR (CCl₄) δ 2.83–2.53 (2 H), 1.95–1.0 (7 H), 1.63 (s, 6 H), 0.87 (s, 9 H); mass spectrum, *m/e* 180 (M⁺).

Cycloheptanone with 4 equiv of acetone gave isopropylidenecycloheptane[46] as an oil (50%): NMR (CCl₄) δ 2.22 (m, 4 H), 1.65 (s, 6 H), 1.52 (m, 8 H); mass spectrum, *m/e* 138 (M⁺).

Cholestanone with 4 equiv of acetone gave 3-isopropylidenecholestane as white crystals (54%): mp 94–96 °C (lit.[47] mp 95–97 °C); mass spectrum, *m/e* 412 (M⁺).

1-Indanone with 4 equiv of acetone gave 1-isopropylideneindane[48] as an oil (71%): NMR (CCl₄) δ 7.4 (m, 1 H), 7.05 (m, 3 H), 2.77 (m, 4 H), 2.02 (s, 3 H), 1.83 (s, 3 H); mass spectrum, *m/e* 158 (M⁺).

Acetophenone with 4 equiv of acetone gave 2-methyl-3-phenyl-2-butene[49] as an oil (65%): NMR (CCl₄) δ 7.13 (m, 5 H), 1.95 (m, 3 H), 1.82 (s, 3 H), 1.58 (m, 3 H); mass spectrum, *m/e* 146 (M⁺).

Benzophenone plus acetone gave 1,1-diphenyl-2-methyl-1-propene[50] as an oil (94%): NMR (CCl₄) δ 7.12 (s, 10 H), 1.78 (s, 6 H); mass spectrum, *m/e* 208 (M⁺).

Fluorenone plus acetone gave isopropylidenefluorene[51] as an oil (84%): NMR (CCl₄) δ 7.6 (m, 4 H), 7.13 (m, 4 H), 2.40 (s, 6 H).

6-Methoxy-1-tetralone with 4 equiv of acetone gave 1-isopropylidene-6-methoxytetralin as an oil (85%): NMR (CCl₄) δ 7.08 (m, 1 H), 6.55 (m, 2 H), 3.72 (s, 3 H), 2.47 (m, 4 H), 1.88 (s, 3 H), 1.78 (s, 3 H), 1.68 (m, 2 H); mass spectrum, *m/e* 202 (M⁺).

4a-Methyl-4,4a,5,6,7,8-hexahydronapthalen-2(3H)-one with 4 equiv of acetone gave 2-isopropylidene-4a-methyl-2,3,4,4a,5,6,7,8-octahydronapthalene as an oil (67%): NMR (CCl₄) δ 6.0 (m, 1 H), 2.2 (m, 4 H), 1.7 (s, 6 H), 1.5 (m, 8 H), 1.07 (s, 3 H); mass spectrum, *m/e* 190 (M⁺).

Pulegone with 4 equiv of acetone gave 1,2-diisopropylidene-4-methylcyclohexane as an oil (55%): NMR (CCl₄) δ 2.6 (m, 2 H), 2.1–1.2 (3 H), 1.68 (s, 6 H), 1.50 (s, 6 H), 0.9 (m, 5 H); mass spectrum, *m/e* 178 (M⁺).

Isophorone with 4 equiv of acetone gave isopropylidene-3,5,5-trimethyl-2-cyclohexene[52] as an oil (63%): NMR (CCl₄) δ 6.1 (m, 1 H), 1.95 (m, 2 H), 1.73 (m, 9 H), 1.17 (m, 2 H), 0.88 (s, 6 H); mass spectrum, *m/e* 164 (M⁺).

Benzophenone with cyclohexanone gave cyclohexylidenediphenylmethane (78%): mp 83–84 °C (lit.[53] mp 83–83.5 °C); NMR (CCl₄) δ 7.13 (10 H), 2.23 (m, 4 H), 1.58 (m, 6 H); mass spectrum, *m/e* 248 (M⁺).

Benzophenone with hexanal gave 1,1-diphenyl-1-heptene[54] as an oil (84%): NMR (CCl₄) δ 7.17 (s, 10 H), 6.03 (t, 1 H, *J* = 7 Hz), 2.1 (m, 2 H), 1.7–0.65 (9 H); mass spectrum, *m/e* 250 (M⁺).

Benzophenone with 3-cholestanone gave 3-cholesterylidenediphenylmethane (82%): mp 106–109 °C; NMR (CCl₄) δ 7.12 (m, 10 H), 0.93 (s), 0.83 (s), 0.67 (s); mass spectrum, *m/e* 536 (M⁺).

Fluorenone plus cycloheptanone gave cycloheptylidenefluorene (77%): mp 123.5–124.5 °C; NMR (CCl₄) δ 7.67 (m, 4 H), 7.23 (m, 4 H), 3.05 (m, 4 H), 1.72 (m, 8 H); mass spectrum, *m/e* 260 (M⁺).

Fluorenone plus acetophenone gave fluorenylidene-1-phenylethane (70%): mp 112–113.5 °C; NMR (CCl₄ Δ —/]9–6/67 (7 H), 7.43 (s, 5 H), 6.23 (d, 1 H, *J* = 8 Hz), 2.72 (s, 3 H); mass spectrum, *m/e* 268 (M⁺).

General Procedure for Intramolecular Dicarbonyl Coupling with TiCl₃/Zn–Cu. The Zn–Cu couple was prepared by adding zinc dust (9.81 g, 150 mmol) to 40 mL of deoxygenated water and adding CuSO₄ (0.75 g, 4.7 mmol). The black suspension was agitated by purging with a stream of N₂ gas for 10 min and was then filtered under N₂. After washing with deoxygenated water, acetone, and ether, the couple was dried under vacuum and then stored under an inert atmosphere.

A stirred slurry of TiCl₃ (1.03 g, 6.7 mmol) and Zn–Cu (1.0 g, 15.4 mmol) in 20 mL of DME was refluxed under argon for 1 h. The dicarbonyl compound (0.30 mmol) in 20 mL of DME was added by a motor driven syringe pump over 9 h, and the reaction was further refluxed for 12 h. An additional 0.30 mmol (0.60 mmol total) of dicarbonyl compound in 20 mL of DME was added over 9 h followed by a further 12-h period of reflux. The reaction mixture was then cooled to room temperature and filtered through a Florisil pad. Concentration by solvent removal at the rotary evaporator gave the crude product. In this manner, the following reactions were carried out.

1,2-Diphenylcyclobutene from 1,4-Diphenylbutane-1,4-dione. An 87% yield was isolated by column chromatography, mp 49–50.5 °C (lit.[55] mp 50.5–52 °C).

1-Methyl-2-phenylcyclopentene from 1-Phenylhexane-1,5-dione. A 70% yield was isolated by distillation, bp 53–58 °C (0.14 mm) [lit.[56] bp 66–67 °C (2 mm)].

1-Methyl-2-heptylcyclohexene from Tetradecane-2,7-dione. A 79% yield was isolated by distillation: bp 37 ° (0.26 mm) [lit.[57] bp 78–80 °C (1.8 mm)]; mass spectrum, *m/e* 194 (M⁺).

1,2-Diphenylcyclohexene from 1,6-Diphenylhexane-1,6-dione. A 95% yield was isolated by distillation, mp 46–47 °C (lit.[7] mp 48–48.5 °C).

1-Methyl-2-(2-phenylethyl)cyclohexene from 1-Phenylnonane-3,8-dione. A 50% yield was isolated by Kugelrohr distillation: bp 75–80 °C (0.1 mm); mass spectrum, *m/e* 200 (M⁺).

3-Phenylbenzocyclohept-3-ene was isolated from the corresponding keto aldehyde in 80% yield by Kugelrohr distillation: bp 110–115 °C (0.6 mm) [lit.[58] bp 182 °C (15 mm)]; mass spectrum, *m/e* 220 (M⁺).

1,2-Diamylcyclooctene from Octadecane-6,13-dione. A 67% yield was isolated by distillation: bp 70–75 °C (0.15 mm); mass spectrum, *m/e* 250 (M⁺).

1,2-Diamylcyclononene from Nonadecane-6,14-dione. A 68% yield was isolated by distillation: bp 70–74 °C (0.25 mm); mass spectrum, *m/e* 264 (M⁺).

1,2-Dibutylcyclodecene from Octadecane-5,14-dione. A 75% yield was isolated by distillation: bp 61–63 ° (0.25 mm); mass spectrum, *m/e* 250 (M⁺).

1,2-Dibutylcycloundecene from Nonadecene-5,15-dione. A 76% yield was isolated by distillation: mp 80.5–82.5 °C; mass spectrum, *m/e* 264 (M⁺).

Cyclododecene from Dodecanedialdehyde. A 76% yield was isolated by distillation: bp 50–55 °C (0.25 mm) [lit.[59] bp 76 °C (4 mm)]; mass spectrum, *m/e* 166 (M⁺).

1,2-Dipropylcyclododecene from Octadecane-4,15-dione. A 71% yield was isolated by distillation: bp 71–74 °C (0.7 mm); mass spectrum, *m/e* 250 (M⁺).

Cyclotridecene from Tridecanedialdehyde. A 52% yield was isolated by distillation: bp 50–53 °C (0.1 mm) [lit.[60] bp 122–126 °C (10 mm)]; mass spectrum, *m/e* 180 (M⁺).

1,2-Dipropylcyclotridecene from Nonadecane-4,16-dione. A 65% yield was isolated by distillation: bp 65–68 °C (0.12 mm); mass spectrum, *m/e* 264 (M⁺).

Cyclotetradecene from Tetradecanedialdehyde. A 71% yield was isolated by distillation: bp 55–60 °C (0.05 mm) [lit.[61] bp 136–138 °C (13 mm)]; mass spectrum, *m/e* 194 (M⁺).

1,2-Diethylcyclotetradecene from Octadecane-3,16-dione. A 75% yield was isolated by distillation: bp 63 °C (0.1 mm); mass spectrum, *m/e* 250 (M⁺).

1-Phenylcyclopentadecene from 1-Phenylpentadecane-1,15-dione. An 80% yield was isolated by Kugelrohr distillation: bp 121–128 °C (0.15 mm); mass spectrum, *m/e* 284 (M⁺).

Cyclohexadecene from Hexadecanedialdehyde. An 85% yield was isolated by Kugelrohr distillation: bp 110–115 °C (0.25 mm) [lit.[60] bp 105 °C (0.15 mm)]; mp 49–50.5 °C; mass spectrum, *m/e* 222 (M⁺).

1,2-Dimethylcyclohexadecene from Octadecane-2,17-dione. A 90% yield was isolated by distillation: bp 66–68 °C (0.1 mm); mass spectrum, *m/e* 250 (M⁺).

1,2-Dimethylcyclodocosane from Tetracosane-2,23-dione. An 83% yield was isolated by distillation: bp 125–128 °C (0.15 mm); mass

spectrum, m/e 334 (M+).

Ketone 2. Methyl oleate (30.0 g, 100 mmol) was dissolved in 180 mL of dry DME and added to NaH (7 g of a 57% dispersion in mineral oil; 166 mmol). The mixture was refluxed for 20 h under an inert atmosphere and then acidified with dilute HCl. Workup in the usual way gave the β-keto ester product (22.3 g, 80%): IR (film) 1750 and 1715 cm⁻¹; NMR (CDCl₃) δ 0.86 (t, 3 H), 1.92 (m, 8 H), 2.45 (m, 2 H), 3.37 (m, 1 H), 3.63 (s, 3 H), 5.27 (t, 4 H).

This β-keto ester was decarbomethoxylated[62] without further purification. The crude β-keto ester (22.3 g, 40 mmol) was added to a solution of NaCl (2.3 g, 40 mmol) and 2.1 mL of water in 30 mL of Me₂SO. The solution was heated to 145 °C under an inert atmosphere for 8 h and then cooled to room temperature. Workup in the usual way gave ketone 2 (19 g, 95%), homogeneous by TLC: IR (film) 1725 cm⁻¹; NMR (CCl₄) δ 0.86 (m, 6 H), 1.26 (CH₂ envelope, 44 H), 1.80–2.46 (m, 12 H), 5.22 (t, 4 H).

Ketal Dialdehyde 4. Ketone 2 (2 g, 4 mmol) and catechol (1.76 g, 16 mmol) were combined with triethyl orthoformate (6 mmol) in 20 mL of benzene. A small amount of p-toluenesulfonic acid catalyst was added, and the reaction was stirred for 16 h at room temperature. After quenching with NaHCO₃, the reaction was worked up in the usual way to give ketal 3 (75%): NMR (CCl₄) δ 0.86 (m, 6 H), 1.26 (CH₂ envelope, 48 H), 1.66–2.33 (m, 8 H), 5.22 (t, 4 H), 6.53 (s, 4 H).

Ketal 3 (1.78 g, 3.0 mmol) was dissolved in 25 mL of dichloromethane at −78 °C, and a dilute stream of ozone (Welsbach ozonator) was passed through. The reaction was monitored by TLC, and when starting material was consumed excess ozone was removed by purging with nitrogen. The solution was warmed to room temperature, and NaBH₄ (0.76 g, 20 mmol) in 10 mL of 50% aqueous ethanol was added. The reaction was stirred overnight at room temperature and then acidified and worked up in the usual way. Column chromatography on silica gel gave a dihydroxy ketal (340 mg, 30%). This material was dissolved in 5 mL of dichloromethane and added to a solution of pyridinium chlorochromate (700 mg, 3.3 mmol) in 5 mL of dichloromethane. After stirring for 2 h at room temperature under an inert atmosphere, the reaction mixture was worked up in the usual way to provide ketal dialdehyde 4 (236 mg, 75%) as an oil: IR (film) 2720 and 1715 cm⁻¹; NMR (CDCl₃) δ 1.29 (CH₂ envelope, 24 H), 2.37 (t, 4 H), 6.71 (s, 4 H), 9.70 (t, 2 H).

Civetone (6). Ketal dialdehyde 4 (236 mg, 0.63 mmol) was dissolved in 40 mL of DME. Half of this solution was added via a motor driven syringe pump over a 9-h period to a refluxing slurry of TiCl₃ (1.3 g, 8.4 mmol) and Zn–Cu (1.1 g, 16.2 mmol) in 15 mL of DME. After addition was complete, the reaction was refluxed for 12 h, and the remaining half of the dialdehyde solution was added over a further 9-h period. After dialdehyde addition was complete, the reaction was refluxed for 12 h and then cooled to room temperature and filtered through a Florisil pad. Concentration gave 195 mg of crude product which was deketalized by acid treatment. This crude cyclization product, levulinic acid (3 mL), and 0.3 mL of 1 N HCl were dissolved in 3 mL of chloroform and heated to 70 °C for 72 h. Workup in the usual way and column chromatography on neutral alumina gave civetone[63] as a mixture of cis and trans isomers (33%): IR (film) 1705 cm⁻¹; NMR (CDCl₃) δ 5.4 (m, 2 H); mass spectrum, m/e 250.

meso-5,6-Decanediol. A solution of cis-5-decene (0.269 g, 1.92 mmol) and osmium tetroxide (0.5 g, 1.97 mmol) in 15 mL of pyridine was stirred at room temperature for 2 h. A solution of sodium sulfite (0.9 g) in 17 mL of 14% aqueous pyridine was added, and the reaction was stirred for an additional 45 min. The mixture was diluted with chloroform, and the organic layer was drawn off and concentrated. The residue was taken up in ether and washed with aqueous cupric sulfate to remove residual pyridine. After drying (K₂CO₃), removal of solvent gave the product (0.25 g, 76%), pure by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in), mp 134–135.5 °C (lit.[64] mp 130–132 °C).

dl-5,6-Decanediol. A solution of 85% m-chloroperbenzoic acid (2.03 g, 10.1 mmol) in 20 mL of dichloromethane was added dropwise to cis-5-decene (1.34 g, 9.6 mmol) in 50 mL of dichloromethane at room temperature. After stirring for 16 h, the mixture was washed with 10% aqueous sodium sulfite and 10% aqueous potassium carbonate and then dried (MgSO₄) and concentrated. The crude epoxide was stirred in 50 mL of 70% aqueous THF containing 2 drops of sulfuric acid at 60 °C for 4 h. Workup in the usual way gave the diol (1.28 g, 77%); mp 49–51 °C; NMR (CDCl₃) δ 2.3 (s, 2 H), 3.7–4.0 (m, 2 H); IR (neat) 3350 cm⁻¹; mass spectrum, m/e (relative intensity) 174 (M+, 1), 117 (100). Anal. Calcd for C₁₀H₂₂O₂: C, 68.92; H, 12.72. Found: C, 68.73; H, 12.95.

2-exo,3-exo-Camphanediol (7). The method of Robertson[65] was used. Camphorquinone (2.0 g, 12.0 mmol) in 20 mL of ether was added dropwise over 15 min to a stirred solution of LiAlH₄ (0.49 g, 13.0

mmol) in 30 mL of ether at room temperature. After refluxing for 1.5 h, the reaction was cooled to room temperature and cautiously quenched by the addition of wet ether. The mixture was then filtered, and the filtrate was dried (MgSO₄) and concentrated. Chromatography on 60 g of Florisil gave product 7 (1.40 g, 68%): mp 257–259 °C (lit.[66] mp 259–261 °C); NMR spectrum was in agreement with published data.[66]

2-exo,3-endo-Camphanediol (8). A solution of borane in THF (50 mL of a 1 M solution; 50 mmol) was added dropwise over 30 min to a solution of camphor enol silyl ether[67] (11.2 g, 50.0 mmol) in 50 mL of dry THF. The reaction was stirred for 2 h at 0 °C and then at 35 °C for 2 h. After cooling at 0 °C, 16 mL of 30% hydrogen peroxide and 16 mL of 3 N sodium hydroxide were added. The reaction was warmed to 35 °C for 1.5 h and then cooled to room temperature and worked up in the usual way. The product consisted of a 70:30 mixture (NMR integration) of two diols whose spectral properties corresponded to those reported[66] for 9 and 8. We believe, however, based on our method of synthesis in which camphor enol silyl ether should be hydroborated from the less hindered endo face, that the literature assignments should be reversed and that the major product (70%) is the 2-exo,3-endo diol 8 while the minor product is the 2-endo, 3-exo diol 9.

General Reaction Procedure for the Reduction of Diols Using TiCl₃/K. A stirred slurry of TiCl₃ (1.103 g, 7.15 mmol) in 40 mL of dry THF was refluxed for 1.5 h with potassium (1.3 g, 33.2 mmol) under an inert atmosphere. The black suspension was then cooled slightly, and diol (1.8 mmol) in 5 mL of THF was added. After a further 16 h at reflux, the reaction mixture was cooled and quenched by the slow addition of methanol. The quenched mixture was diluted with water, extracted with ether, and worked up in the usual way. In this manner, the following reactions were carried out.

Cyclohexylidenecyclohexane from Bicyclohexyl-1,1′-diol.[68] An 85% yield of product was isolated by column chromatography. The product was identified by comparison with an authentic sample obtained above.

Cycloheptene from trans-Cycloheptane-1,2-diol. A 55% yield of product was obtained as judged by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using cyclooctene as an internal standard.

3-Methylcholest-2-ene from 3β-Methylcholestane-2β,3α-diol. An 80% yield of product was isolated by column chromatography. Identification was made by comparison with an authentic sample.

5-Decene from dl-5,6-Dihydroxydecane. An 80% yield of 5-decene was obtained as judged by GLC (5% Carbowax 20M on Chromosorb P; 4 ft × 0.25 in) using 1-dodecene as an internal standard. The cis/trans product ratio was determined by the method described in the accompanying paper[11] and was found to be 9% cis to 91% trans.

5-Decene from meso-5,6-Dihydroxydecane. A 75% yield of 5-decene was obtained as judged by GLC (5% Carbowax 20M on Chromosorb P; 4 ft × 0.25 in) using 1-dodecene as an internal standard. The cis/trans product ratio was determined by the method described in the accompanying paper,[11] and was found to be 40% cis to 60% trans.

1,2,3,4,5,6,7,8-Tetrahydronaphthalene from cis-9,10-Dihydroxydecalin.[69] An 80% yield of product was determined as isolated by column chromatography. Identification was made by comparison with an authentic sample.

2-Bornene from 2-exo,3-exo-Camphanediol (7). This reduction was carried out on 0.335 g (1.97 mmol) of diol in the presence of 0.340 g of 1-decene, serving as an internal GLC standard. An 81% yield of product was obtained after a 5-h reaction time. The reaction was followed by withdrawing aliquots at given intervals and analyzing by GLC.

2-Bornene from 2-exo,3-endo-Camphanediol (8) and 2-endo,3-exo-Camphanediol (9). This reduction was carried out in the same manner as the previous one, and its course was followed by removing aliquots at intervals. After 5 h, a 60% yield was obtained.

Registry No.—1, 112-62-9; **2**, 504-54-1; **3**, 66587-41-5; **4**, 66587-42-6; cis-**5**, 66587-43-7; trans-**5**, 66652-56-0; cis-**6**, 542-46-1; trans-**6**, 1502-37-0; **7**, 56614-57-4; **8**, 56614-58-5; **9**, 13837-85-9; cis-5-decene, 7433-78-5; camphorquinone, 465-29-2; camphor enol silyl ether,

56613-17-3; acetone, 67-64-1; (Z,Z)-2-(7-hexadecenyl)-11-eicosenoic acid methyl ester, 66587-44-8.

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Role of Silver(II) in Silver-Catalyzed Oxidations by Peroxydisulfate[1]

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In Ag^+-catalyzed oxidations of organic substrates by peroxydisulfate, both $SO_4^-\cdot$ and Ag(II) are present as oxidants and may show quite different selectivity patterns, yielding quite different products. Ag(II) is shown to oxidize alcohols to alkoxy radicals, but at a slower rate than its known decarboxylation of acids. Contrary to some previous reports, rates of acid decarboxylation appear quite sensitive to acid structure and also to pH. In the oxidation by Ag(II) of aromatic molecules with side-chain –OH or –COOH functions, reaction may involve either side-chain attack or ring oxidation to a radical cation, the relative importance of the two paths depending on structure. The contribution of Ag(II) to the overall oxidation is shown to increase with the Ag/substrate ratio and to vary inversely with the rate of the $SO_4^-\cdot$ substrate reaction. The rate of the reaction $SO_4^-\cdot + Ag^+ \rightarrow SO_4^{2-} + Ag(II)$ is estimated as $\sim 3 \times 10^9$.

Silver ion is a well-known catalyst for peroxydisulfate ($S_2O_8^{2-}$) oxidations, the first report being by Marshall in 1900,[2] and a number of reviews covering earlier work are available.[3–5] The initial steps usually postulated for such oxidations are the one-electron redox processes

$$S_2O_8^{2-} + Ag^+ \rightarrow SO_4^{2-} + SO_4^-\cdot + Ag(II) \quad (1)$$

$$SO_4^-\cdot + RH \rightarrow SO_4^{2-} + R\cdot + H^+ \quad (2)$$

$$SO_4^-\cdot + Ag^+ \rightarrow SO_4^{2-} + Ag(II) \quad (3)$$
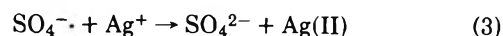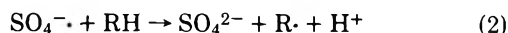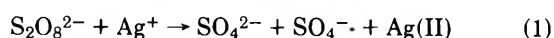
although in some interpretations Ag(III) has also been proposed as an intermediate. Reactions 1 and 2 are quite analogous to the initial steps in the Fenton's reagent oxidation of organic substrates by Fe^{2+}–H_2O_2 or Fe^{2+}–$S_2O_8^{2-}$ [6] but differ in that while Fe^{3+} is able to oxidize intermediate substrate radicals, Ag(II) is a considerably stronger oxidizing agent and capable of oxidizing suitable substrates as well. As a conse-

Table I. Oxidation of 2-Methyl-2-butanol[f]

| | Products, % | | |
Conditions[a]	2-Methyl-2,3-butanediol	Acetone	Ethanol
Fe[b,c]	45, 48	3, 6	2
60 °C	48, 38	0, 5	5, 2
60 °C, 10^{-4} M Ag$^+$	16	23	2
60 °C, 10^{-3} M Ag$^+$	6	35	2
Fe,[b] H$_2$O$_2$[d]	54	0	e
Fe,[b,c] H$_2$O$_2$[d]	38	2	e

[a] All experiments used ~1 M substrate, ~0.04 M $S_2O_8^{2-}$ (or H$_2$O$_2$), and 0.1 M Cu^{2+}. [b] Fe^{2+} initiation in 0.1 M HClO$_4$ at room temperature. [c] "Inverse addition," Fe^{2+} was added slowly to the system. [d] H$_2$O$_2$ was used in place of $S_2O_8^{2-}$. [e] Other diols were present (~10%). [f] Registry no.: 2-methyl-2-butanol, 75-85-4.

quence, it is rapidly reduced back to Ag$^+$ to reenter the cycle, thus accounting for the catalytic effect of traces of Ag$^+$ on the overall oxidation rate.

Since a different oxidant is present in the Ag$^+$-catalyzed reactions, different products might be expected. The first clearly documented case of such a difference is in the oxidation of glycols, where in 1954 Greenspan and Woodburn[7] reported that 1,2-diols are cleaved in good yield by Ag$^+$–$S_2O_8^{2-}$ but not by $S_2O_8^{2-}$ alone. Subsequently, Anderson and Kochi[8] have shown that Ag$^+$ also changes the course of $S_2O_8^{2-}$ oxidation of aliphatic acids, leading to smooth decarboxylation (eq 4), while SO$_4^-$· radicals from peroxydisulfate alone predominantly attack C–H bonds in the rest of the molecule.

$$RCOOH + Ag(II) \rightarrow R\cdot + CO_2 + Ag^+ + H^+ \qquad (4)$$
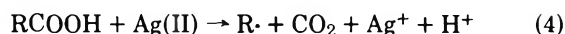
The thermal oxidation of alcohols by $S_2O_8^{2-}$ is consistent with a chain reaction involving the propagation steps[9]

$$SO_4^-\cdot + R_2CHOH \rightarrow SO_4^{2-} + R_2\dot{C}OH \qquad (5)$$

$$R_2\dot{C}OH + S_2O_8^{2-} \rightarrow R_2C\!\!=\!\!O + SO_4^-\cdot + SO_4^{2-} + H^+ \qquad (6)$$
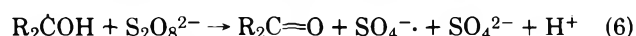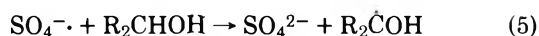
Reaction 6 is relatively slow, and in Fe^{2+}–$S_2O_8^{2-}$ systems it is replaced[6] by

$$R_2\dot{C}OH + Fe^{3+} \rightarrow R_2C\!\!=\!\!O + Fe^{2+} + H^+ \qquad (7)$$
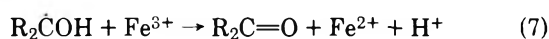
or if Cu^{2+} is present by

$$R_2\dot{C}OH + Cu^{2+} \rightarrow R_2C\!\!=\!\!O + Cu^+ + H^+ \qquad (8)$$
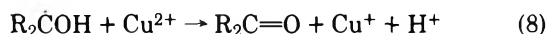
Our interest in the problem was aroused by the report by Ledwith[10] that he had been able to trap alkoxy radicals in the oxidation of alcohols by $S_2O_8^{2-}$, both in the presence and absence of Ag$^+$, a result quite at variance with the above formulation. We find that typical reactions of alkoxy radicals are indeed observed during the oxidation of alcohols by $S_2O_8^{2-}$, *but they are important only in the presence of Ag$^+$*, indicating that alcohols react with Ag(II) in the same manner as do carboxylic acids.

$$ROH + Ag(II) \rightarrow RO\cdot + Ag^+ + H^+ \qquad (9)$$
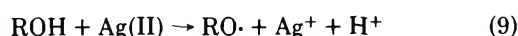
While this work was in progress,[11] a similar conclusion was reported by Caronna et al. using quite a different technique.[12] This paper presents our findings together with some results on the oxidation of carboxylic acids and aromatic molecules which provide a more comprehensive view of Ag$^+$-catalyzed $S_2O_8^{2-}$ oxidations and the relative rates of reaction of Ag(II) with different functional groups.

Results

Alcohol Oxidations. Our initial experiments were carried out with 2-methyl-2-butanol, using Cu^{2+} as an oxidant for intermediate radicals, with conditions under which O–H and

C–H attack should lead to clearly different products as shown.

$$X = SO_4^-\cdot \text{ or } Ag(II) \qquad (10)$$
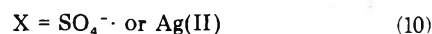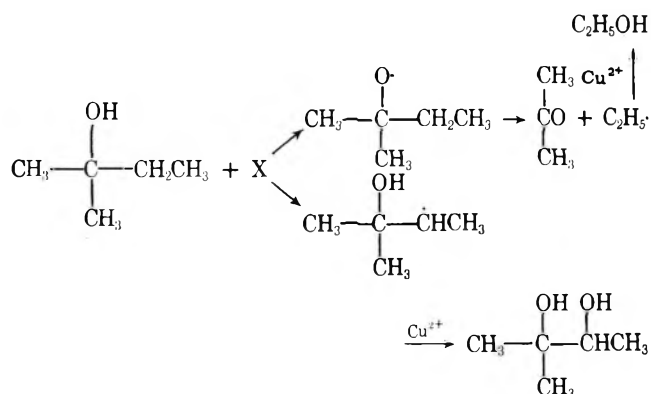
The oxidation of the β-hydroxyalkyl radical shown probably leads initially to an epoxide,[13] which, however, rapidly opens to a diol in acid solution. Results with several oxidizing systems are listed in Table I which clearly show the large effect of Ag$^+$ on product distribution. In the presence of Ag$^+$, acetone is the predominant product, consistent with reaction 9. The small yield of diol probably results either from some attack by SO$_4^-$·, reaction 2, or attack by an intermediate alkoxy radical on another molecule of alcohol. With $S_2O_8^{2-}$ in the absence of Ag$^+$, the chief product is 2-methyl-2,3-butanediol, while with H$_2$O$_2$ some isomeric diols are also formed by attack on CH$_3$ groups by the less selective HO· radical. Interestingly, small yields of acetone are also observed in the absence of Ag$^+$, pointing to detectable O–H attack even by SO$_4^-$· and HO·.

Differentiation between C–H and O–H attack is more difficult with primary and secondary alcohols because of the facile interconversion

$$R_2CHO\cdot + R_2CHOH \rightarrow R_2CHOH + R_2\dot{C}OH \qquad (11)$$

Here, advantage can be taken of the even more facile intramolecular abstraction of δ hydrogens by long chain alkoxy radicals, as in the Barton reaction, intramolecular chlorination with hypochlorites, and lead tetraacetate oxidations, which in the presence of a suitable oxidant lead to tetrahydrofurans.[14]
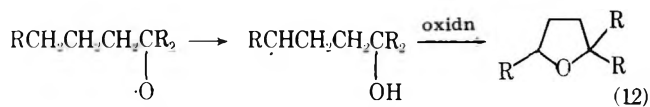
Results on the oxidation of 1- and 2-pentanol appear in Table II, employing thermal $S_2O_8^{2-}$ oxidations in the presence of Cu^{2+} with and without Ag$^+$. With 1-pentanol and no Ag$^+$ the product is chiefly pentanal, although a small amount of 2-methyltetrahydrofuran is also formed. With increasing Ag$^+$ the furan yield rises substantially. Similar results are obtained with 2-pentanol, except that here intramolecular reaction requires attack on a primary C–H bond and is slower, so β scission to acetaldehyde (and presumably an n-propyl radical) takes place as well.

Aliphatic Acids. Since the decarboxylation of carboxylic acids by Ag(II) is well established, our chief interest was in comparing the rates of reaction of Ag(II) with acids and alcohols. To this end, products (CO$_2$ and acetone) were determined for the oxidation of mixtures of 2-methyl-2-butanol and three aliphatic acids. Results, expressed as $k_{CO_2}/k_{acetone}$ (i.e., the ratio of CO$_2$ to acetone formed corrected for the concentrations of acid and alcohol present), are listed in Table III. While the results are reproducible and consistent (see Experimental Section), yields of CO$_2$ from acid oxidations are in general higher than those of acetone from the alcohol. Ac-

Table II. Oxidation of Pentanols[a]

Substrate	Registry no.	[Ag+], M	Products, %		
			Pentan-al	2-Pent-a-none	2-Me-THF
1-Pentanol (4)	71-41-0	0	42 ± 2		9.8 ± 0.5
1-Pentanol (2)		0.01	16 ± 2		40 ± 2
1-Pentanol (2)		0.05	9.7 ± 2		55 ± 3
2-Pentanol (2)	6032-29-7	0		92 ± 4	2.2 ± 0.1
2-Pentanol (2)		0.05		26 ± 1	17[b] ± 1

[a] Conditions for all runs: 3–6 h at 60 °C; [ROH] = 0.5 M; [S$_2$O$_8$$^{2-}$] = 0.05 M; [Cu^{2+}] = 0.05 M; in 26% by volume acetonitrile (1-pentanol) or 20% (2-pentanol). The indicated uncertainty is the standard deviation of the mean of the number of runs indicated in parentheses. [b] Plus 37% of acetaldehyde.

Table III. Competitive Oxidations of Acids and 2-Methyl-2-butanol[a]

Acid	Registry no.	pH	$k_{CO_2}/k_{acetone}$	
n-Butyric	107-92-6	1.0	1.42 ± 0.13	(2)
n-Butyric		2.7	2.63 ± 0.04	(4)
n-Butyric		4.7	3.96 ± 0.05	(2)
Isobutyric	79-31-2	1.0	5.13 ± 0.08	(2)
Isobutyric		2.7	12.2 ± 0.05	(2)
Pivalic	75-98-9	1.0	196 ± 16	(6)

[a] Conditions for all experiments: 4 h at 60 °C; [S$_2$O$_8$$^{2-}$] = 0.05 M; [Cu^{2+}] = 0.05 M; [Ag$^+$] = 0.01 M. The indicated uncertainty is the standard deviation of the mean of the number of runs indicated in parentheses.
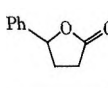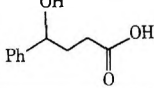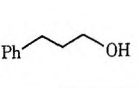
cordingly, the actual relative rates of oxidation of acid to alcohol could be smaller by a factor of as much as 2. Nevertheless, their variations with conditions and acid structure should be significant.

The most notable feature of the table is the large change in reactivity with acid structure in the order butyric < isobutyric < pivalic. This is in marked contrast to Anderson and Kochi's[8] finding for the same acids. Second, relative reactivities are evidently pH dependent, with the relative reactivity of the acid increasing as the acidity decreases. The results are qualitative only, since the table reports initial pH, and additional acid is generated during reaction (cf. eq 4). However, it seems likely that the change is in the rate of reaction of Ag(II) with the acid (see below).

Because of the difference between Anderson and Kochi's findings and our own, we also carried out direct competitive oxidations of pivalic and butyric acids in the presence of Cu^{2+} and 0.1 M HClO$_4$, analyzing the reaction mixtures for CO$_2$, propene and *tert*-butyl alcohol. (Any isobutene formed would be hydrated in the acid medium.) Four experiments at average butyric/pivalic acid ratios of 14.3 gave 87 ± 2% of CO$_2$, 8.2 ± 0.5% of propene, and 66 ± 3% of *tert*-butyl alcohol. The *tert*-butyl alcohol/propene ratio corresponds to a relative reactivity for pivalic/butyric acids of 115 compared with 138 from the data of Table III.

Aromatic Substrates. As we have discussed in detail elsewhere,[15,16] the major path by which SO$_4$$^-$· attacks aromatic molecules is by oxidizing them to radical cations which can either react with water to yield hydroxycyclohexadienyl radicals (capable of subsequent oxidation to phenols) or undergo some species of side-chain fragmentation, giving side-chain oxidation products.

Table IV. Oxidation of γ-Phenylbutyric Acid[a]

[Ag^3], M	Yield, %			
	Ph—⟨lactone⟩=O	Ph—CH(OH)CH$_2$CH$_2$C(=O)OH	Ph—CH$_2$CH$_2$CH$_2$OH	Ph—CH(OH)CH$_3$
0 (2)	46.1 ± 2	5.1 ± 0.2	12.5 ± 0.2	2.9 ± 0.2
1 × 10^{-3} (2)	38.3 ± 2	5.2 ± 0.6	17 ± 0.2	3.2 ± 1
1 × 10^{-2} (5)	14.2 ± 1.4	2.2 ± 0.5	24.0 ± 0.6	1.4 ± 0.2
5 × 10^{-2} (4)	7.7 ± 1.4	1.5 ± 0.4	33.5 ± 2.4	3.3 ± 1

[a] Conditions for all experiments: [phenylbutyric acid] = 0.1 M; [Cu^{2+}] = 0.05 M; [S$_2$O$_8$$^{2-}$] = 0.01 M; [H$^+$] = 0.1 M; CH$_3$CN, 20–30 vol %; T = 60 °C (90 °C without Ag$^+$). Experimental errors are the standard deviations of the mean of the number of experiments shown in parentheses. Registry no.: γ-phenylbutyric acid, 1821-12-1.

$$ (13) $$

fragmentation → side-chain oxidation products
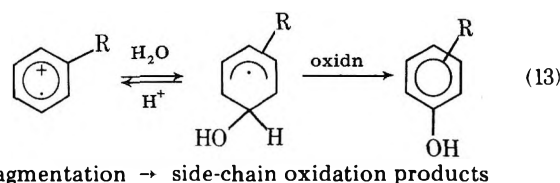
Simple aromatics are apparently also oxidized to radical cations by Ag(II)[17] and should yield similar products. However, when the aromatics contain side-chain –OH or –COOH groups, attack may occur there as well, and the problem is to choose molecules where the two paths predict significantly different products.

Table IV shows results with γ-phenylbutyric acid, carried out in the presence of Cu^{2+} to efficiently trap radical intermediates and 0.1 M acid to suppress the formation of phenolic products.[6,16] A complex mixture of products is obtained, but one which plainly varies with the concentration of Ag$^+$.

In the absence of Ag$^+$, the major reaction path is evidently fragmented by loss of a benzylic proton.

$$ (14) $$
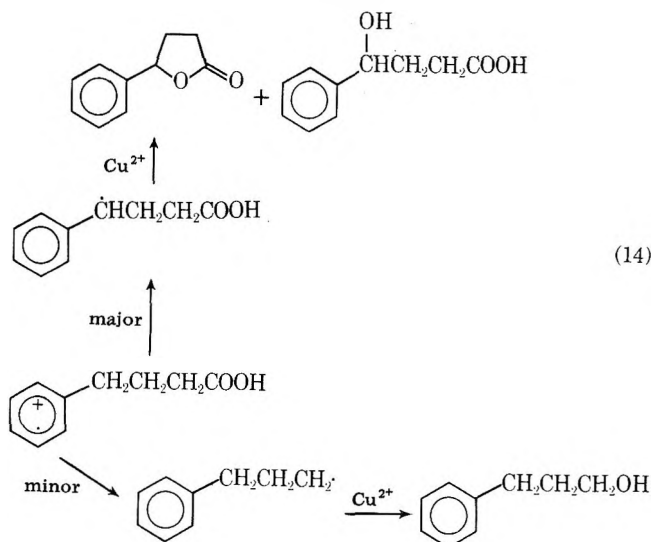
With increasing Ag$^+$, the yields of products expected from 3-phenylpropyl radicals increase. If at 0.05 M Ag$^+$ all oxidation is occurring through Ag(II), some 75% of its reaction with phenylbutyric acid must be by decarboxylation.

A similar case is provided by 1-phenylpropanol (Table V). Here data in the absence of Ag$^+$ indicates that the radical cation fragments by two paths to give propiophenone and benzaldehyde, as had been previously reported by Snook and Hamilton.[18]

Table V. Oxidation of 1-Phenylpropanol[a]

[Ag+], M	[Cu²⁺], M	Yield, % Benzaldehyde	Propiophenone
0 (2)	0.01	30.3 ± 0.5	65.9 ± 0.4
0.001 (2)	0.01	31.5 ± 1.4	56.9 ± 0.6
0.01 (2)	0.01	45.7 ± 1.8	38.0 ± 2.7
0.1 (2)	0.01	64.8 ± 0.1	27.7 ± 0.1
0	0	28.7	64.5
0.1 (4)	0	88.0 ± 15	44.5 ± 8
0.2 (2)	0	91.5 ± 5	39.2 ± 24

[a] In all runs $[S_2O_8^{2-}]$ = 0.01 M, [phenylpropanol] = 0.1 M, and CH_3CN = 30 vol % at T = 60 °C. Experimental errors are the standard deviations of the mean of the number of experiments shown in parentheses. Registry no.: 1-phenylpropanol, 93-54-9.

$$\xrightarrow{\text{oxidn}} \quad (15)$$
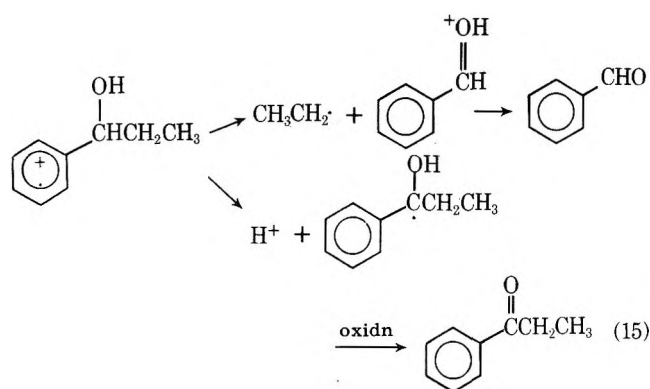
In the presence of Ag⁺ the yield of benzaldehyde rises, suggesting that –OH attack is now important.

$$(16)$$
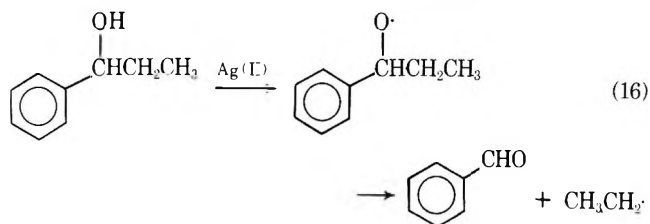
The cleanest experiments are those in the presence of Cu^{2+}, which efficiently oxidizes intermediate radicals. Assigning "excess" benzaldehyde yield to reaction 16 and assuming that at the highest Ag⁺ concentration the reaction is going entirely through Ag(II), we calculate that 56% of the reaction is via reaction 16. Analysis of the data in the absence of Cu^{2+} leads to a similar result. Here it will be noted that at high Ag⁺ concentrations the total product yields (calculated on the basis of 1 mol of product/mol of $S_2O_8^{2-}$) exceed 100%. This is stoichiometrically acceptable if some ethyl radicals escape further oxidation.

Agreement between the phenylpropanol and phenylbutyric acid systems is plausible. Somewhat more side-chain attack occurs with the acid, consistent with the indications of Table III.

With some substrates side-chain cleavage of the radical cation and initial side-chain attack lead to the same products. Here we might expect to determine the reaction path by carrying out oxidations under conditions (high Cu^{2+} and low acid) where the radical cations give substantial yields of phenols. Phenylacetic acid and 2-phenylethanol are two such examples. Tables VI and VII show that phenol yields are significantly reduced in the presence of Ag⁺, implying chiefly side-chain attack on –COOH or –OH. However, the results are a bit equivocal since blank experiments show that phenols are rapidly oxidized further by Ag^+–$S_2O_8^{2-}$ at high Ag⁺ levels, a previously known reaction;[19] so phenols are probably lost.

Table VI. Oxidation of Phenylacetic Acid[a]

[Ag+], M	Yield, % Benzyl alcohol	Phenols (o–m–p)
0	42	21 (36–25–39)
5.9 × 10⁻⁴	48	20 (36–24–40)
3.5 × 10⁻³	47	12 (35–25–40)
6.1 × 10⁻³	49	9 (33–26–41)
1.4 × 10⁻²	47	4 (32–26–42)

[a] All runs used [phenylacetic acid] = 0.06 M and $[Cu^{2+}]$ = 0.20 M at T = 60 °C. Registry no.: phenylacetic acid, 103-82-2.

Table VII. Oxidation of 2-Phenylethanol[a]

[Ag+], M	Yield, % Benzyl alcohol	Phenols (o–m–p)
0	17	38 (40–15–45)
3.6 × 10⁻³	16	31 (42–15–45)
3.5 × 10⁻²	16	6 (53–16–31)
7.6 × 10⁻⁴ᵇ	32	19 (49–18–33)
3.6 × 10⁻² ᵇ	27	3

[a] All runs used [phenylethanol] = 0.08 M and $[Cu^{2+}]$ = 0.24 M at T = 60 °C. Styrene glycol (1–3%) was also detected in the products. Registry no.: 2-phenylethanol, 60-12-8. ᵇ $HClO_4$ (0.05 M).

Discussion

In planning and interpreting our experiments, we have assumed that SO_4^-· and Ag(II) are the two species involved in the initial attack on substrates in our systems, but other intermediates have been proposed in the past and we should give our reasons for discarding them. Hydroxyl radicals, formed by oxidation of water by either Ag(II)[20] or Ag(III),[21] have been proposed as the intermediates which actually attack substrates. However, the marked difference in products found in Ag^+–$S_2O_8^{2-}$ and HO· radical systems and the fast bimolecular reactions observed between Ag(II) and typical substrates (see below) make their role here unlikely.

The possible intervention of Ag(III) is more complicated, and the problem has been clearly discussed by Wilmarth and Haim.[4] There is evidence that the equilibrium

$$2Ag(II) \rightleftharpoons Ag^+ + Ag(III) \qquad (17)$$
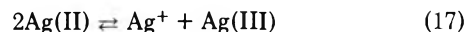
is fast but lies far to the left and also that Ag(III) may be involved in the oxidation of water by higher valence Ag. The role of Ag(III) has usually been invoked in order to account for the complex overall kinetics of Ag^+–$S_2O_8^{2-}$ oxidations.[22] Perhaps the best reason to exclude it is the observation that the kinetics of those Ag(II)–substrate reactions which have been studied[23] appear to be cleanly second order, inconsistent with Ag(III) being the active oxidant if equilibrium 17 is in fact rapid and unfavorable.

Our conclusion that alkoxy radicals are the major products in the oxidation of alcohols by Ag(II) is consistent not only with the results of Caronna et al.[12] (who employed protonated quinoline as a trapping agent for cleavage products) but also with earlier reports of cleavage products from *tert*-butyl alcohol[24] and 1,3-diols.[25] The possibility that oxidation and β scission might be concerted so that alkoxy radicals do not in fact exist as discrete intermediates seems ruled out by the formation of tetrahydrofurans from long-chain alcohols (cf. Table II) and Carona et al.'s trapping of intermediate δ-hydroxyalkyl radicals.

With these observations it seems likely that the better-known cleavage of 1,2-diols should also be formulated as a stepwise process,

$$\underset{R_2C-CR_2}{\overset{OH\ \ OH}{|\ \ \ \ |}} + Ag(II) \longrightarrow Ag^+ + \underset{R_2C-CR_2}{\overset{O\cdot\ \ \ OH}{|\ \ \ \ |}} \qquad (18)$$

$$\longrightarrow R_2C=O + R_2COH \xrightarrow{\ S_2O_8{}^{2-}\ } R_2C=O$$
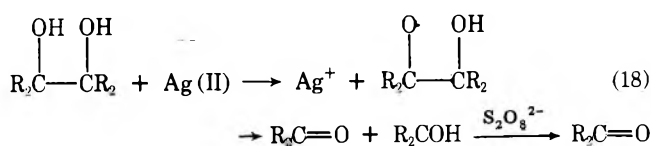
particularly since *cis-* and *trans-*cyclohexanediols[7] and *cis-* and *trans-*cyclopentanediols[26] behave very similarly. Taken overall, our results suggest that Ag^+–$S_2O_8{}^{2-}$ may provide a convenient route for generating alkoxy radicals to bring about the cleavage of C–C bonds or the formation of tetrahydrofurans, particularly since the reactions occur smoothly in H_2O–acetonitrile mixtures for substrates of low water solubility.

Three conclusions of interest emerge from our results with carboxylic acids. First, contrary to Anderson and Kochi's report[8] but consistent with direct measurement of carboxylic acid oxidations by Ag(II),[23] rates vary with acid structure, consistent with rapid reversible complex formation followed by slow concerted oxidation and R–CO2 bond scission,

$$RCOOH + Ag(II) \rightleftarrows RCOOH\cdot Ag(II)$$

$$\longrightarrow R\cdot + CO_2 + Ag^+ + H^+ \quad (19)$$
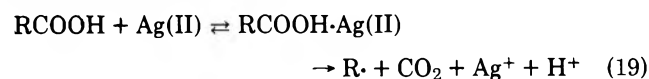
paralleling the behavior of Pb(IV), Co(III), and Mn(III).[27] If so, the discrepancy with Anderson and Kochi's results could arise because in their much less aqueous medium the first step in eq 19 is less completely reversible. Second, the rate of decarboxylation is apparently pH dependent. This has been discussed by Mentasti et al.[23] in terms of the $Ag^{2+} \rightleftarrows AgOH^+$ equilibrium,[28] but it could also arise from a series of complexes, e.g.,

$$RCOOH + Ag(II) \rightleftarrows RCOOH\cdot Ag(II)$$

$$\rightleftarrows RCOO^-\cdot Ag(II) + H^+ \quad (20)$$
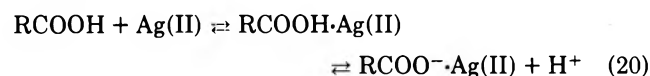
Third, our competitive experiments indicate that at low acidities even unreactive straight-chain acids react more readily with Ag(II) than do alcohols, implying that in the oxidation of complex molecules containing –OH and –COOH groups preferential decarboxylation by Ag^+–$S_2O_8{}^{2-}$ can be achieved.

Our results with aromatic systems are complex, but in general they show that Ag(II) oxidations occur by two competing paths: oxidation of the ring to a radical cation and attack on side-chain –OH or –COOH groups. The balance evidently depends on the particular structure involved, but both processes must be taken into consideration in accounting for product distributions.

The oxidation of γ-phenylbutyric acid with and without Ag^+ has also been examined by Clerici, Minisci, and Porta[29] with results qualitatively similar to our own. However, in the absence of Cu^{2+} and at relatively low substrate/$S_2O_8{}^{2-}$ ratios, benzaldehyde was reported as a major product and attributed to β scission of 3-phenylpropyl radicals. We also obtained benzaldehyde under these conditions, but since we find no benzyl alcohol or bibenzyl we suggest that it arises instead from further oxidation of 1-phenylpropanol (cf. Table V).

A further consideration is the point at which substrate oxidation by Ag(II) takes over in Ag^+–$S_2O_8{}^{2-}$ systems. This obviously depends upon the relative rates of reaction of $SO_4{}^-\cdot$ with Ag^+ and substrate, reactions 2 and 3. As far as we are aware of, the rate constant for reaction 3 has not been reported, but it can be estimated from our data. From the yields of acetaldehyde plus 2-methyltetrahydrofuran and 2-pentanone from 2-pentanol (Table II), $k_3/k_2 \cong 21$. Taking k_2 the same as for 2-propanol (8.5×10^7)[29] gives $k_3 = 1.8 \times 10^9$. A similar calculation for the two pieces of data on 1-pentanol, taking $k_2 = 4.8 \times 10^7$, the same as for 1-propanol,[29] gives $k_3 = 3$ and 6×10^9. The geometric mean of the three would be 3

$\times 10^9$ and indicates that reaction 3 is close to a diffusion-controlled process. Since rates of reaction of primary and secondary alcohols with $SO_4{}^-\cdot$ in general lie between 10^7 and 10^8, oxidation by Ag(II) becomes the dominant process at Ag^+/substrate ratios greater than 10^{-2}, but with tertiary alcohols even lower ratios should be effective. Relatively low concentrations of Ag^+ should also be effective in decarboxylating acids (k_2 for acetic acid is 8.8×10^4,[30] and we obtain 85–90% of CO_2 at Ag^+/substrate = 0.01). On the other hand, k_2 for $SO_4{}^-\cdot$ attack on aromatics is in general greater than 10^9.[31] From Tables IV and V, Ag^+/substrate ratios approaching unity are necessary to insure that almost all of the reaction involves Ag(II).

Finally, we can comment briefly on the overall rate of oxidation in Ag^+–$S_2O_8{}^{2-}$ systems, a topic discussed at length by Wilmarth and Haim, but where the various steps involved are now better understood. The slow thermal decomposition of $S_2O_8{}^{2-}$ is accelerated by reaction 1, the Ag(II) returning to Ag^+ by oxidation of water or attack on substrates. If intermediate radicals do not participate in the chain processes, substrates should have little further effect on the rate of $S_2O_8{}^{2-}$ decomposition. If substrates yield radicals capable of attacking $S_2O_8{}^{2-}$ (alcohols provide the best studied case, cf. reactions 5 and 6, but the range of substrates participating in such chains is not well defined at present), a chain decomposition of $S_2O_8{}^{2-}$ is superimposed on reaction 1. However, the situation is complicated since Ag(II) can also provide a termination step by oxidizing radical intermediates to stable products or by generating different intermediates, e.g., alkoxy radicals in the case of alcohols. It is not surprising that such systems have not proved very amenable to purely kinetic analysis.

The addition of Cu^{2+} ion has been sometimes observed to produce a further acceleration of $S_2O_8{}^{2-}$ consumption, and here it is plausible that an alternate chain process is introduced.

$$R\cdot + Cu^{2+} \rightarrow product + Cu^+ \qquad (21)$$

$$Cu^+ + S_2O_8{}^{2-} \rightarrow Cu^{2+} + SO_4{}^{2-} + SO_4{}^-\cdot \qquad (22)$$
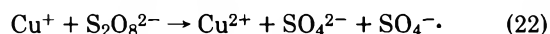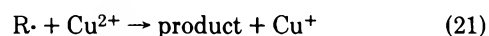
Since reaction 21 occurs readily with most carbon radicals, such induced chains should be quite general in Cu^{2+}–Ag^+–$S_2O_8{}^{2-}$ systems.

Experimental Section

Reagents. Potassium peroxydisulfate was recrystallized from water, purity by titration >98%. Reagent grade perchloric acid, cupric perchlorate, ferrous perchlorate, cupric sulfate, and silver nitrate were used as received. The purity of organic reagents was checked by gas–liquid chromatography (GLC), and they were distilled or sublimed if necessary. 1-Phenylpropanol was synthesized from phenylmagnesium bromide and propionaldehyde. Reference compounds were either purchased or synthesized by known methods.

Reactions. Thermal reactions were carried out in stoppered flasks by mixing standard solutions, flushing the mixtures with N_2, and placing the flasks in a thermostat. In experiments where CO_2 was determined, the flasks containing weighed amounts of $K_2S_2O_8$ were closed with a serum cap and evacuated through a syringe needle, N_2-flushed solutions of other reagents were added via syringes, and the mixtures were stirred to solution and placed in the bath. Reactions employing ferrous ion were carried out by the dropwise addition of peroxydisulfate or ferrous ion solution to the other components of the system as described previously.[16]

Analyses of reaction mixtures were by GLC, using previously calibrated internal standards and reference materials. For CO_2 and propene, ethane, introduced via syringe after the reaction was complete, was used as an internal standard. The CO_2 that dissolved in the aqueous phase was corrected for using Henry's Law using a constant measured on similar reaction mixtures containing known amounts of CO_2. In determining aromatic acids and phenols, products were silylated as described previously.[16]

References and Notes

(1) Taken from the Ph.D. Dissertation of Donald M. Camaioni, University of Utah, 1978. Support cf this work by a grant from the National Science Foundation is gratefully acknowledged.
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Thermolysis of *tert*-Butyl Cubanepercarboxylate. The Cubyl Radical

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The rate and activation parameters for the thermal decomposition of *tert*-butyl cubanepercarboxylate have been measured in cumene. The cubyl radical is formed about 4600-fold less rapidly than the *tert*-butyl radical under the same conditions. The selectivity of the cubyl radical in halogen atom abstraction reactions has also been investigated. The competition constant, r, for the reactions of the radical with bromotrichloromethane and carbon tetrachloride is 80. This value is larger than the competition constants of other bridgehead radicals. These results may be rationalized on the basis of the novel hybridization of the carbon atoms of cubane.

The stereochemistry of tricoordinate carbon radicals has been actively investigated for some time.[1] Recent studies indicate that simple alkyl radicals are not strictly planar and that *tert*-butyl radicals are distinctly pyramidal.[2–5] However, the energy difference between the planar and pyramidal forms of the simple carbon free radicals is apparently quite small.[5]

Bridgehead radicals can neither undergo inversion nor become planar. The radicals of this class are readily formed and their chemistry has also been actively investigated. Two lines of investigation, the thermal decomposition of the peresters[6–9] and the selectivity of the radicals in halogen atom abstractions,[9–11] have received special attention. The rates of decomposition of the peresters depend on the structure of the radical importantly with norbornyl radical formed about 1000-fold less rapidly than the *tert*-butyl radical.[6–9] The selectivity of the bridgehead radicals in reactions with carbon tetrachloride and bromotrichloromethane at 80 °C decrease in the order: 3-homocubyl > 1-bicyclo[2.2.1]heptyl > 1-bicyclo[2.2.2]octyl > 1-adamantyl.[9–11] We have undertaken a complementary investigation of the related reactions of the more highly strained cubane derivatives.

Results and Discussion

Cubanecarboxylic acid was prepared by a well known procedure.[12,13] The acid was converted to the perester through reaction of the acid chloride with *tert*-butyl hydroperoxide. The *tert*-butyl perester of adamantane carboxylic acid was also prepared for study of the procedures used in this work.

Kinetic Observations. The rates of decomposition of the peresters of adamantane and cubane are presented in Table I.

First-order reactions were observed in all the kinetic experiments. The rate constant for the decomposition of adamantane is within experimental error of the constants reported in prior work.[6–9] The relative rates and activation parameters for the *tertiary* acyclic and bridgehead peresters are summarized in Table II.

Analyses of the data for the homolytic decomposition reactions of peresters indicate that such reactions occur by several different mechanisms which range from simple oxygen–oxygen bond homolysis to two-bond fragmentation reactions with varying degrees of polar character. Several experimental approaches have been used to distinguish between these two extremes. The entropy of activation has frequently been used as one of these criteria.[15] Generally, two-bond concerted decomposition reactions which proceed with rotational restriction exhibit more positive entropies of activation. From this viewpoint, the results presented in Table II suggest that the thermolysis of the bridgehead peresters may not all occur by the same mechanism. However, the experimental errors are relatively large and the reaction solvents differ. Further, Traylor and his students investigated the decomposition of 1-bicyclo[2.2.1]heptanecarboxy, cubanecarboxy, and 4-homocubanecarboxy radical in hydrocarbon solvents.[16] They report that even the relative rates of decarboxylation are immeasurably fast and that there is a quantitative evolution of carbon dioxide. These results do not require that the thermolysis reactions of the peresters proceed by two-bond fragmentation processes. However, these observations and

Table I. Rates of Thermal Decomposition of *tert*-Butyl Peresters in Cumene

perester	registry no.	temp, °C	$k_1 \times 10^5$, s^{-1}
adamantyl[a]	66769-98-0	80	75.0 ± 0.3
cubyl[a]	21245-43-2	80	0.262 ± 0.019
		100	2.29 ± 0.10
		110	7.35 ± 0.26

[a] Concentration: 0.02 to 0.04 M.

Table II. Relative Rates and Activation Parameters for the Thermal Decomposition of *tert*-Butyl Peresters in Cumene

perester	rel rate, 80 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
tert-butyl[a,b]	1.0	25.5	−2.9, 3.6
1-adamantyl[a-c,f]	1.4	27.6	3.7
1-bicyclo[2.2.2]octyl[a,c]	0.1	28.7	2.2
1-bicyclo[3.2.1]octyl[d,e]	0.05	31.9	10
1-bicyclo[2.2.1]heptyl[a,c]	1.6×10^{-3}	35.9	14.8
9-triptycyl[d,e]	5.9×10^{-4}	34.6	10
3-homocubyl[d,e]	5.9×10^{-3}	35.6	17
cubyl[f]	4.6×10^{-3}	30.2 ± 1.5	1.0 ± 2.0

[a] Reference 7. [b] Reference 6. [c] Reference 8. [d] Reference 9. [e] In ethylbenzene. [f] This study.

the finding that the decomposition rates depend importantly on the structure of the alkyl group indicate that the reactions all proceed by mechanism in which carbon–carbon bond cleavage has a major influence on the energy requirements.

The relative rate data suggest that two factors, the hybridization of the exocyclic bonding orbital of the bridgehead carbon atom and the polar character of the endocyclic carbon–carbon bonding orbitals, are dominant. The compounds with high s character in the exocyclic bonding orbital, for example, the bicyclo[2.2.1]heptane, the homocubane, and the cubane, are all about 1000-fold less reactive than the adamantane or butane derivatives and the compound with the additional features of polar endocyclic carbon–carbon bonds, the triptycene, is the least reactive molecule of the series. We infer that the slow decomposition rates arise from the stronger carbon–carbon bonds in the molecules with greater s character and from the depressed opportunity for the development to polar character in the transition state in the reactions of such radicals. These experimental results do not require an interpretation based on the idea that bridgehead radicals are inherently unstable.

There are subtle variations in the rate data which suggest that other, probably less important factors also influence the reaction. Indeed, we recently proposed that rehybridization may influence the chemistry of cubane derivatives. Specifically, we suggested that the cubyl anion may undergo rehybridization to enhance s character of the exocyclic carbon orbital to bring the interorbital angles into better accord with the internuclear angles and thereby to relieve strain and stabilize the anion.[17] This idea can be extended to the radical to account for the greater rate of decomposition of the cubyl and homocubyl peresters compared to the bicyclo[2.2.1]heptyl perester.

Selectivity Measurements. The selectivity of the cubyl radical was determined by the study of the product distribution obtained in the Hunsdiecker reaction of the carboxylic acid in carbon tetrachloride[18] and in the decomposition of the *tert*-butyl perester in a solution of bromotrichloromethane and carbon tetrachloride.[9]

Table III. Bridgehead Radical Selectivity in Halogen Atom Abstraction Reactions

radical	Hunsdiecker reaction, 80 °C, [RBr]/[RCl]	perester dec, 80 °C, r
1-adamantyl	0.14[a,b]	29,[c] 30[a]
1-bicyclo[2.2.2]octyl	0.48[b,d]	59[c]
9-triptycyl		32[c]
1-bicyclo[3.2.1]octyl		56[c]
1-bicyclo[2.2.1]heptyl	0.50[b]	47[c]
3-homocubyl	1.00[b,e]	75[c]
cubyl	1.05[a]	80[a]

[a] This study. [b] Reference 11. [c] Reference 9. [d] Reference 10. [e] Reference 19.

$$RCO_2H \xrightarrow[CCl_4, 78\ °C]{HgO, Br_2} RBr + RCl$$
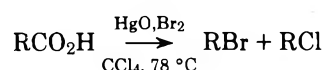
In the Hunsdiecker reaction, the selectivity is measured by the cubyl bromide to cubyl chloride ratio. In the perester decomposition reaction, the selectivity is measured by the

$$RCO_3Bu \longrightarrow R\cdot \begin{cases} \xrightarrow{BrCCl_3}_{k_{Br}} RBr \\ \xrightarrow{ClCCl_3}_{k_{Cl}} RCl \end{cases}$$
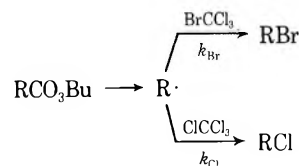
competition constant, r, which depends on the initial concentration of the halocarbons as well as the product ratio.

$$r = \frac{k_{Br}}{k_{Cl}} = \frac{[RBr][CCl_4]_i}{[RCl][CBrCl_3]_i}$$

The experimental observations for several bridgehead radicals are presented in Table III.

The results obtained in the Hunsdiecker reaction parallel the data obtained in the perester decomposition reaction. The most remarkable feature of these data is the fact that the bridgehead radicals are much less selective in halogen atom abstraction reactions than other aliphatic radicals. Giese has recently shown that the r values for primary, secondary, and tertiary radicals are all about 2000 at about 60 °C.[20,21] It is not yet clear whether or not the bridgehead radicals exhibit an isoselective temperature as do the other alkyl and aryl radicals.[22] The r values for 1-adamantyl radical are 24, 29, and 25 at 90, 80, and 62 °C, respectively.[9] The r values for the 1-bicyclo[3.2.1]octyl radical are equally insensitive to temperature.[9] However, preliminary results for the 1-bicyclo[2.2.1]-heptyl radical suggest that the r value for this radical is much more temperature dependent.[22] Thus, the r values for the bridgehead radicals may or may not converge to an isoselective temperature. In any event, the most striking feature of the results for cubane and the other bridgehead radicals is the large decrease in selectivity compared to other acyclic and monocyclic aliphatic radicals. Rüchardt and his students have commented on this aspect of the chemistry. They noted that the decreased steric requirement of the bridgehead radicals is one of the key factors in the lessened selectivity of these substances.[9] Giese also pointed out that the less sterically crowded radicals are generally less selective.[21] Hence, the finding that the bridgehead radicals are, as a group, unselective is not surprising. It is, however, somewhat surprising to find that the least hindered radicals of this group are the most selective. Such results, if not controverted by new data on radical selectivity at low temperature, suggest that the greater
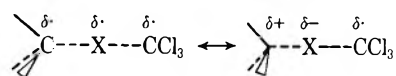
selectivity of the least hindered cubyl radical may originate in variations in the polar character of the transition state for the halogen with this character less developed in the halogen atom abstraction reaction of the cubane than for the adamantane.

Experimental Section[23]

***tert*-Butyl Cubanepercarboxylate.** Cubanecarboxylic acid[12,13] (200 mg, 1.35 mmol) and freshly purified thionyl chloride (5 mL) were refluxed for 1.5 h. The excess thionyl chloride was removed in vacuo to afford the acid chloride in satisfactory quality for the next reaction. It was dissolved in ether (10 mL) and cooled to 0 °C. Pyridine (0.5 mL) and *tert*-butyl hydroperoxide (500 mg, 5.56 mmol) were added in that order. Pyridine hydrochloride precipitated immediately. The cold bath was removed and the cloudy mixture was stirred for 2 h. The pyridine salt was collected. The filtrate was washed with three portions (10 mL each) of cold aqueous sulfuric acid (5%), three portions of aqueous sodium carbonate solution (5%), and finally with ice cold water. The organic phase was dried over sodium sulfate and then evaporated in vacuo to dryness. The white solid was taken up in petroleum ether (20 mL) and chromatographed on silica gel (5 g). The column was flushed with additional petroleum ether (20 mL). The total eluent was evaporated in vacuo. Crystallization of the colorless residue from hexane gave *tert*-butyl cubanepercarboxylate as light colorless feathers (260 mg, 87%, mp 62–63.5 °C). The NMR spectrum, δ 4.12 (m, 7 H), and 1.30 (s, 9 H), and the infrared spectrum, (CCl_4) 1760 and 1350 cm^{-1}, are in accord with the assigned structure. Anal. Calcd for $C_{13}H_{16}O_3$: C, 65.43; H, 7.28. Found: C, 65.37; H, 7.39.

***tert*-Butyl Adamantanepercarboxylate.** *tert*-Butyl adamantanepercarboxylate was prepared in the manner described above. Adamantane carboxylic acid (360 mg, 2 mmol) was transformed into *tert*-butyl adamantane percarboxylate (250 mg, 50%). The product was an oil which solidified in the refrigerator (4 °C) but liquified again at room temperature.[8]

General Procedure for the Study of the Thermal Decomposition of the Peresters in Cumene. A solution of the perester and cumene was transferred into six or eight ampules which were then degassed and thermostated. At intervals, the ampules were removed from the bath and the reaction was quenched by immersion of the ampules in a −10 °C bath. When all of the samples for one run had been obtained, they were warmed to room temperature and the concentration of the perester was measured by infrared spectroscopy. All determinations were made on a Beckman IR-7 infrared spectrophotometer using the perester carbonyl absorption near 1760 cm^{-1}. Preliminary study established that this absorption obeyed Beer's law over the concentration range used in this work. The concentration of the perester in the ampule withdrawn from the bath after 2 min was adopted as the zero value. All the rate constants were assessed from a plot of log (A_0/A_t) versus *t* in the usual way. Work with *tert*-butyl adamantylpercarboxylate verified the accuracy of this procedure. The results are summarized in Table I.

Selectivity Study. The Hunsdiecker Reactions. Equal molar quantities of mercuric oxide and the carboxylic acid were mixed in a 100-fold molar quantity of purified carbon tetrachloride. The suspension was heated to reflux (78 °C). An equivalent amount of bromine was added dropwise to the mixture and the mixture was refluxed for 1 h. The cooled solution was filtered to remove any solid residues. The filtrate was analyzed by gas chromatography. The products were identified by spectroscopic methods following their isolation by preparative VPC and comparison with authentic materials. A typical experiment for cubanecarboxylic acid is summarized.

Cubanecarboxylic acid (148 mg, 1 mmol) was mixed with red mercuric oxide (216 mg, 1 mmol) and carbon tetrachloride (15.4 g, 0.1

mol). The slurry was heated to reflux (78 °C). Bromine (160 mg, 1 mmol) was added dropwise to the mixture and the mixture was refluxed for 1 h. The cooled solution with filtered and the filtrate was analyzed as described above. Bromocubane (67 mg, 31%) was isolated; this product was identical in every respect with that prepared by other methods.[14] Chlorocubane (41 mg, 30%) was isolated as a colorless liquid which solidified below 4 °C, *m/e* 140.0201, 138.0233 (parent peaks), 103.0543 (base peak). Anal. Calcd for C_8H_7Cl: C, 69.40; H, 5.09; Cl, 25.51. Found: C, 69.28; H, 5.18; Cl, 25.41.

Selectivity Study. The Thermal Decomposition of *tert*-Butyl Peresters in Halocarbon Solvents. A solution of the *tert*-butyl perester and triphenylmethane in bromotrichloromethane and carbon tetrachloride was immersed in a constant temperature bath at 80 °C for several hours. The cooled solution was analyzed by VPC as described for the Hunsdiecker reaction. A typical experiment for the decomposition of *tert*-butyl cubanepercarboxylate is described.

tert-Butyl cubanepercarboxylate (118 mg, 0.5 mmol), bromotrichloromethane (510 mg, 2.5 mmol), and triphenylmethane (610 mg, 2.5 mmol) were dissolved in carbon tetrachloride (7.7 g, 0.05 mol). The reaction mixture was immersed in a thermostat at 80 °C for 100 h. Analysis of the cooled solution indicated that chlorocubane and bromocubane were produced in 13 and 50%, respectively, on the basis of the starting material consumed.

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Acetolysis of Dibenzonorbornadienyl-1-carbinyl Trifluoromethanesulfonate and Comparison with the Norbornyl-1-carbinyl System and Its Unsaturated Analogues

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The preparation of dibenzonorbornadienyl-1-carbinyl derivatives (5) is described. The acetolysis of the trifluoromethanesulfonic acid ester (triflate, 5-OTf) gives the acetate with retention of configuration and the internally returned dibenzobicyclo[2.2.2]octadien-1-yl triflate (13). The acetolysis of the benzonorbornadienyl-1-carbinyl system (4) previously reported is reinvestigated using the triflate and shown to proceed by a similar pathway. The acetolysis of dibenzobicyclo[2.2.2]octadienyl-1-carbinyl triflate (6-OTf) gives only the ring-enlarged dibenzobicyclo[3.2.2]nonadien-1-yl acetate (14). These rates and products are compared with those reported in acetolyses of norbornyl-1-carbinyl (1), norbornenyl-1-carbinyl (2), and benzonorbornenyl-1-carbinyl (3) arenesulfonates. The absence of the unsaturated bridge-migrated products is established. The dissociation constants of the corresponding bridgehead acids are determined in 50% aqueous ethanol. A linear relation is found between the logarithms of the acetolysis rates and the dissociation constants. Therefore, evidence for anchimeric assistance by the unsaturated linkage in these systems is not found; rather the inductive effect of these bonds accounts for the results observed.

Solvolysis of bicyclic bridgehead neopentyl systems proceeds with ready rearrangements forming bridgehead substituted products.[1] A representative example is the acetolysis of norbornyl-1-carbinyl tosylate (1-OTs) which produced bicyclo[2.2.2]octyl-1-yl acetate in 85% yield.[2] Effects of unsaturation in the [2.2.1] system have been investigated by Wilt, Bly, and their co-workers with norbornenyl-1-carbinyl tosylate (2)[3,4] and benzonorbornenyl-1-carbinyl tosylate (3).[5] Of particular interest are the absence of etheno (or benzo) bridge-migrated products and the formation of considerable amounts of unrearranged products. Introduction of additional unsaturation has been investigated by Chenire et al.[6] with benzonorbornadienyl-1-carbinyl tosylate (4). A major path of this acetolysis proceeds without accompanying rearrangement. Interest in the changes of the rearrangement manner with unsaturation led us to undertake a study of the dibenzonorbornadienyl-1-carbinyl system (5) and, in addition, the

Scheme I

Scheme II
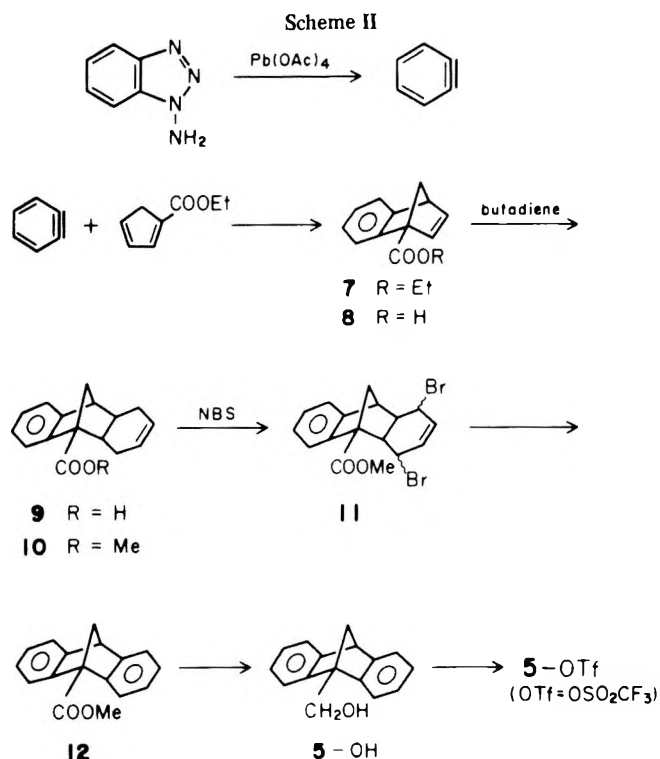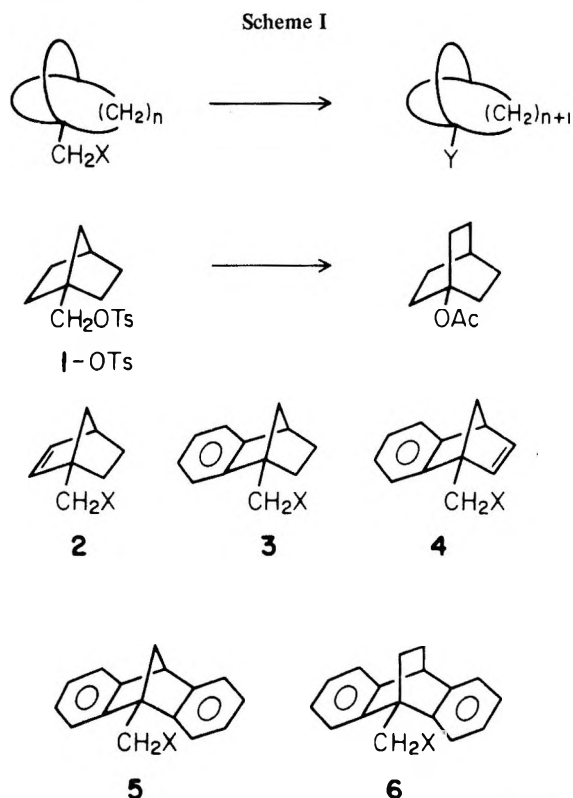
dibenzobicyclo[2.2.2]octadienyl-1-carbinyl system (6). With these present results the solvolytic behavior of bicyclo[2.2.1] bridgehead neopentyl systems will be complete.

Results

Preparation. 1-Bromobenzonorbornadiene was previously prepared by Wilt and Chenier[7,8] starting from benzonorbornadiene via a relatively long reaction sequence. Benzyne, generated by thermal decomposition of 1,2,3-benzothiadiazole 1,1-dioxide, was added to methyl cyclopentadienyl-1-carboxylate affording methyl benzonorbornadienyl-1-carboxylate (7, R = Me) in a yield of 30% (based on o-nitrobenzenesulfinic acid the benzyne precursor was prepared from).[9] Since dimerization of cyclopentadienyl-1-carboxylate is very facile at 10 °C–room temperature which is necessary for the thermal decomposition,[10] we considered that a benzyne generation at a much lower temperature might give a better result and, in this respect, adapted treatment of 1-aminobenzotriazole with lead tetraacetate.[11] The benzyne thus generated

Table I. Acetolysis Rates of Bridgehead Carbinyl Triflates

triflate system	registry no.	temp, °C	k_1, s^{-1}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, cal/deg	rel rate at 100 °C
benzonorbornadienyl 4	66687-87-4	75.0	1.05×10^{-4}	20.3	−18.8	
		100.0	8.01×10^{-4}			6.4
dibenzonorbonadienyl 5	66687-88-5	100.0	1.25×10^{-4}	25.8	−7.6	1
		125.0	11.9×10^{-4}			
neopentyl[a]	66687-89-6	50.0	1.05×10^{-4}	25.0	0.58	
		75.0	18.6×10^{-4}			
		25.0[b]	3.68×10^{-6}			
		100.0[b]	2.25×10^{-2}			180
dibenzobicyclo[2.2.2]octadienyl 6	66687-90-9	75.0	0.452×10^{-4}	27.7	0.9	
		100.0	7.10×10^{-4}			5.7
norbornyl 1[c]	66687-91-0	100.0	1.59×10^{-1}			1272
norbonenyl 2[d]	66687-92-1	100.0	4.21×10^{-2}			337
benzonorbornenyl 3[e]	66687-93-2	100.0	4.34×10^{-3}			35

[a] For the tosylate, the literature data[12] determined at uniform and comparable concentration (0.0796 M of tosylate) are 8.32×10^{-8} s^{-1} at 74.71 °C and 1.60×10^{-6} s^{-1} at 99.58 °C. Calculation by a FACOM computer gives the rates 5.25×10^{11} s^{-1} at 25.0 °C and 1.68×10^{-6} s^{-1} at 100.0 °C. [b] The rates of triflate at 25.0 and 100.0 °C are calculated from those observed at 50 and 75 °C. Comparison between the rates of triflate and tosylate gives the OTf/OTs rate ratios as 7.01×10^4 at 25 °C and 1.34×10^4 at 100 °C. [c] For the tosylate, the literature data[5] are 1.13×10^{-5} s^{-1} at 99.5 °C and 2.70×10^{-4} s^{-1} at 133.0 °C. Calculation gives 1.19×10^{-5} s^{-1} at 100.0 °C. The OTf/OTs ratio at 100 °C (footnote b) gives the listed rate. [d] A rate of the brosylate was reported as 9.98×10^{-7} s^{-1} at 80 °C.[4b] A rate of the tosylate was reported as 7.3×10^{-5} s^{-1} at 132.5 °C (ref 6). With the OBs/OTs rate ratio of 3, a rate of the tosylate at 100 °C is calculated as 3.14×10^{-6} s^{-1}. [e] For the tosylate, the literature[5] indicates 1.02×10^{-6} s^{-1} at 110.0 °C, 5.53×10^{-6} s^{-1} at 131.0 °C, and 55.7×10^{-6} s^{-1} at 154.0 °C. Calculation gives 3.24×10^{-7} s^{-1} at 100 °C and the listed rate is obtained from the OTf/OTs ratio in footnote b.

at −60 °C in methylene dichloride was successfully added to ethyl cyclopentadienyl-1-carboxylate giving 7 in about 85% yield. This ester was hydrolyzed by aqueous sodium hydroxide to the acid 8, which was heated with a benzene solution of 1,3-butadiene in a Diels–Alder reaction. The adduct (9) was transformed into a methyl ester (10) by warming it in methanol containing a trace of sulfuric acid. Treatment with *N*-bromosuccinimide in the presence of a catalytic amount of azobis(isobutyronitrile) gave dibromide 11, which was refluxed in *o*-dichlorobenzene in the presence of sodium carbonate to eliminate HBr. The yield from 10 to 12 was 42–48%. Reduction of 12 with lithium aluminum hydride gave carbinol 5-OH, which was esterified to trifluoro methanesulfonate (triflate) 5-OTf.

As reference compounds, neopentyl triflate and dibenzobicyclo[2.2.2]octadieny_-1-carbinyl triflate (6-OTf) were prepared from the corresponding carbinols.

Acetolysis. The acetolyses of 5-OTf, neopentyl triflate, and 6-OTf were performed in glacial acetic acid with 0.02 M triflate, 0.022 M sodium acetate buffer, and 1% acetic anhydride. The acetolysis of 4-OTf was also carried out for comparison with the data reported on the corresponding tosylate.[6] The rate data are listed in Table I and the reactivities are compared at 100 °C. The acetolysis rates of neopentyl tosylate reported[12] were extrapolated to 25 and 100 °C. Comparison of rates of the triflate gave the triflate/tosylate rate ratios as 7.01×10^4 at 25 °C and 1.34×10^4 at 100 °C. The remarkably constant ratios which are in a range of $10^{4.3}$–$10^{5.3}$ at 25 °C have been found in a variety of systems.[13] The present ratio is not exceptional. Reported rates of the related systems 1–3, which were determined using tosylates or brosylates,[3–5] were thus converted into rates of the triflates and compared.

Products from the acetolysis of 5-OTf were the acetate (5-OAc) of retained configuration, dibenzobicyclo[2.2.2]octadien-1-yl triflate (13) via internal return, and no other detectable compound. For the product 13, the possibility of a dibenzobicyclo[3.2.1]octadien-2-yl structure was excluded by ^{1}H and ^{13}C NMR spectra. The products composition varied with the reaction temperature and the added sodium acetate buffer. The varying yields of 5-OAc and 13 were determined by VPC and are shown in Table II as normalized values.

The acetolysis of 6-OTf gave the ring-enlarged dibenzobi-

Table II. Dependence of Yield of 5-OAc[b] and 13[c] upon Reaction Temperature and Added Sodium Acetate[a]

temp, °C	[CH₃COONa], M	5-OAc, %	13, %
100	0	54.3	45.7
	0.02	55.4	44.6
	0.04	58.6	41.4
	0.20	67.2	32.8
125	0	39.5	60.5
	0.02	40.4	59.6
	0.20	58.1	41.9

[a] The acetolyses were performed with a 0.02 M solution of 5-OTs in glacial acetic acid containing 1% acetic anhydride. Yields were determined by VPC, normalized, and based on theory. [b] Registry no. 66687-94-3. [s] Registry no. 66687-95-4.

cyclo[3.2.2]nonadien-1-yl acetate (14) in a nearly quantitative yield. Acetolysis of system 4 was reinvestigated at 100 °C using the triflate. The retained acetate (4-OAc) was obtained in 80% yield and benzobicyclo[2.2.2]octadien-1-yl triflate by internal return in 20% yield. Therefore, the occurrence of a similar type of rearrangement in both systems (4 and 5) was confirmed.

Acidity Constants. In order to obtain information on the inductive effects of the aromatic rings and the double bonds in the present systems, the pK_a of the bridgehead carboxylic acids and benzoic acid were determined in 50% ethanol–water. The results are listed in Table III, which shows the similar effects of the homoallylically positioned vinyl and aromatic functionalities, ca. a 0.4–0.5 pK_a unit decrease compared to the saturated model, norbornane-1-carboxylic acid. Also, the effects are nearly additive.

Discussion

The acetolysis rates vary in the range of $10^{3.1}$ in the norbornyl and norbornenyl systems (1–5). Presence of the double bond and/or the benzene ring does not result in any rate enhancement, but rate retardation. Products from 5-OTf and 4-OTf do not involve any unsaturated bridge migration. In the acetolyses of the 2 and 3 systems, the literature[4,5] shows the absence of such a migration. Therefore, the rates and products do not give any indication of π participation by the unsaturation. This seems reasonable, because the rigid bicyclic

Scheme III

5-OTf → **5-OAc 55%** + **13 45%**

6-OTf → **14 100%**

4-OTf → **4-OAc 80%** + **20%**

2 → **20%** + **57%** + **4%** + **18%**

3 → **31%** + **53%** + **2%** + **14%**

Table III. Acidity Constants of Bridgehead Carboxylic Acids

1-carboxylic acid	registry no.	pK_a in 50% EtOH–H$_2$O (v/v)
norbornane		6.37[a]
norbornene		5.98[a]
benzonorbornene		5.88[a]
benzonorbornadiene	5890-15-3	5.45[c], 5.46[b]
dibenzonorbornadiene	60070-69-1	5.50[c]
dibenzobicyclo[2.2.2]octadiene	20202-05-5	5.61[c]
benzoic acid		5.55[c], 5.50[a]

[a] Cited from ref 5. Data at 25 °C. [b] Cited from ref 6. Data at 24.6 °C. [c] Present work. Determined at 23 °C.
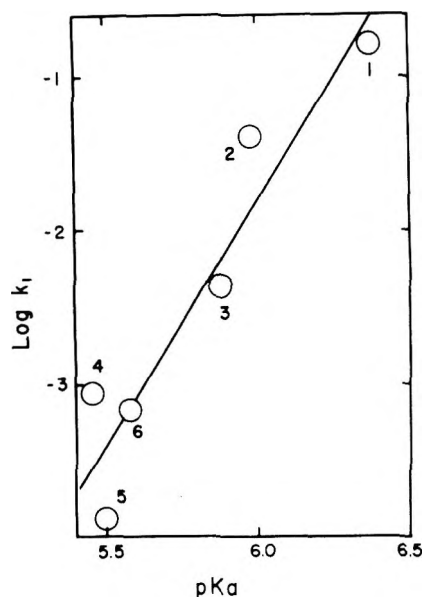
Figure 1. Correlation of log k_1 for carbinyl triflates against pK_a for bridgehead carboxylic acids: k_1 at 100 °C in acetolysis, pK_a at 23–25 °C in 50% ethanol–water, and correlation coefficient = 0.9417.

structure of the 2–5 systems prevents the achievement of the necessary perpendicular spira geometry in a phenonium ionlike transition state. Whereas in the acetolyses of the monoenes (2 and 3) the ethano bridge migration affords the [3.2.1] derivatives as the most important products, the rearrangements observed in the acetolyses of the dienes (4 and 5) were only due to the methano bridge.

Correlation between logarithms of the rate constants (Table I) and the pK_a of the corresponding bridgehead acids (Table III) was calculated by regression analysis. The correlation coefficient was 0.9417 [degree of freedom, $f = n - 2$ ($n = 6$)]. The regression line, as shown in Figure 1, had a slope of 3.1622 and an intercept of −20.7834. The fair linearity obtained suggests that the inductive factor is a significant effect.[14]

Of note are the effects of reaction temperatures and the added sodium acetate on the product composition from 5-OTf (Table II). Increasing temperature favors formation of the product by internal return, 13, and increasing amounts of sodium acetate favor the acetate of retained configuration, 5-OAc. The latter result indicates that some of 5-OAc is formed via an S$_N$2 reaction. The reactions under the kinetic conditions are dissected into the internal return path, k_{int}, and the formation of 5-OAc, k_s. Arrehenius plots of k_{int} (5.58 × 10^{-5} s^{-1} at 100 °C and 7.09 × 10^{-4} s^{-1} at 125 °C) give 29.3 kcal

mol^{-1} for $\Delta H^{\ddagger}$ and −0.044 eu for $\Delta S^{\ddagger}$. The same plots of k_s (6.93 × 10^{-5} s^{-1} at 100 °C and 4.81 × 10^{-4} s^{-1} at 125 °C) give 22.1 kcal mol^{-1} for $\Delta H^{\ddagger}$ and −18.7 eu for $\Delta S^{\ddagger}$.

Experimental Section

Melting points were taken by capillary and are corrected. Infrared spectra were determined with a 215 Hitachi grating infrared spectrophotometer and ^{1}H NMR spectra with a Varian T-60A.

Cycloaddition of Benzyne to Ethyl Cyclopentadienyl-1-carboxylate. The dimer of cyclopentadiene-1-carboxylic acid was prepared by treatment of cyclopentadienyl anion (obtained from the diene and sodium dispersion in toluene) with carbon dioxide according to the literature.[15] The dimer was converted into the ethyl ester by being warmed in ethanol containing a catalytic amount of sulfuric acid. The dimer ester was thermally decomposed into the monomer ester and immediately used for cycloaddition.

To a stirred methylene dichloride suspension of 421 mmol of the ester and 337 mmol of lead tetraacetate was dropwise added a solution of 281 mmol of 1-aminobenzotriazole in methylene dichloride at −60 °C. An exothermic reaction was observed during the addition. After stirring for 2–3 h, the precipitate was filtered and the filtrate was washed with water, dried, and evaporated. The residue was distilled under reduced pressure giving ethyl benzonorbornadienyl-1-carboxylate (7) in 88% yield (based on the triazol): bp 92 °C (3 mm); IR (film) 1735 cm^{-1} (C=O); NMR (CCl$_4$) δ 1.3 (t, 3 H, CH$_3$), 2.5 (s, 2 H, methylene bridge), 3.82 (s, 1 H, bridgehead), 4.3 (q, 2 H, COOCH$_2$CH$_3$, 6.6–7.4 (m, 6 H, vinyl and aromatic).

Diels–Alder Cycloaddition of 1,3-Butadiene to Benzonorbornadiene-1-carboxylic Acid (8). The ester 7 was hydrolyzed by 5% aqueous sodium hydroxide to 8, which had the physical constants as reported.[6] In an ampule a mixture of 505 mg of 8 and a trace of

hydroquinone was added to a chilled solution of 20 molar equiv of butadiene in 7 mL of benzene. The ampule was sealed and heated at 150 °C for 3 days. The butadiene polymer was eliminated by distillation under reduced pressure and the residue was added to *n*-hexane. Thus, 378 mg (58.1%) of the adduct 9 was crystallized, mp 179–181 °C (from CCl₄). Treatment of the mother liquor with silica gel chromatography gave a second crop, 111 mg (17.1%): NMR (CCl₄) δ 1.7–2.8 (m, 8 H, cyclohexene ring and methylene bridge), 3.0 (s, 1 H, bridgehead), 5.8–6.1 (m, 2 H= VINYL(= 6/9–7/7 (m, 4 H, aromatic), 11.9 (s, 1 H, COOH); IR (CCl₄) 1710 cm⁻¹ (C=O). Anal. Calcd for C₁₆H₁₆O₂: C, 79.97; H, 6.71. Found: C, 80.15; H, 6.69.

Methyl Dibenzonorbornadienyl-1-carboxylate (12). The adduct 9 was esterified by being warmed in methanol in the presence of catalytic amounts of sulfuric acid. A stirred mixture of 396 mg (1.56 mmol) of the ester 10, 578 mg (3.12 mmol) of *N*-bromosuccinimide, and a trace of azobis(isobutyronitrile) in 40 mL of carbon tetrachloride was refluxed under nitrogen for 2.5 h and then filtered. The filtrate was concentrated under reduced pressure and the residue was extracted to get the dibromide 11 in 95.4% yield. A solution of 11 in *o*-dichlorobenzene was added dropwise to a boiling solution of *o*-dichlorobenzene containing a molar equivalent of sodium carbonate. After being refluxed for an additional hour, the mixture was concentrated under reduced pressure. The residue was dissolved into ether and the ether solution was washed with water, dried, and evaporated affording 168 mg of 12 (43% yield): mp 123–125 °C (from methanol); NMR (CCl₄) δ 2.7 (d, 2 H, methylene bridge), 3.9 (s, 3 H, COOCH₃), 4.2 (s, 1 H, bridgehead), 6.8–7.5 (m, 8 H, aromatic); IR (CCl₄) 1741 cm⁻¹ (C=O). Anal. Calcd for C₁₇H₁₄O₂: C, 81.58; H, 5.64. Found: C. 81.79; H, 5.62.

The **carboxylic acid**, mp 197–200 °C, was obtained by alkaline hydrolysis.

Dibenzonorbornadienyl-1-carbinol (5-OH). Reduction of 12 with lithium aluminum hydride gave 5-OH, mp 167–168 °C. Anal. Calcd for C₁₆H₁₄O: C, 86.45; H, 6.35. Found: C, 86.56; H, 6.45.

The **triflate** was prepared by treatment of a solution of 5-OH in pyridine and ether with trifluoromethanesulfonic acid anhydride under ice cooling: mp 102–103 °C (from *n*-hexane); NMR (CDCl₃) δ 2.60 (d, 2 H, methylene bridge), 4.35 (1 H, bridgehead), 5.45 (s, 2 H, CH₂OSO₂), 6.9–7.5 (8 H, aromatic). Anal. Calcd for C₁₇H₁₃O₃SF₃: C, 57.62; H, 3.70; S, 9.05. Found: C, 57.80; H, 3.93; S, 9.40.

Dibenzobicyclo[2.2.2]octadienyl-1-carbinol (6-OH). Treatment of dibenzobicyclo[2.2.2]octadiene-1-carboxylic acid (obtained by Diels–Alder addition of ethylene to anthracene-9-carboxylic acid)[16] with lithium aluminum hydride in tetrahydrofuran followed by the usual workup afforded 6-OH: mp 137.5–138 °C (from methylene dichloride and *n*-hexane); NMR (CDCl₃) δ 1.2–1.9 (m, 4 H, ethylene bridge), 2.9 (s, 1 H, OH), 4.22 (broad s, 1 H, bridgehead), 4.4 (s, 2 H, CH₂OH), 7.0–7.5 (m, 8 H, aromatic). Anal. Calcd for C₁₇H₁₆O: C, 86.40; H, 6.83. Found: C, 86.41; H, 6.71.

The **triflate**: mp 105–106 °C; NMR (CDCl₃) δ 1.6 (broad s, 4 H, ethylene bridge), 4.2 (broad s, 1 H, bridgehead), 5.6 (s, 2 H, CH₂OSO₂), 7.0–7.4 (m, 8 H, aromatic). Anal. Calcd for C₁₈H₁₅O₃SF₃: C, 58.69; H, 4.10; S, 8.70. Found: C, 58.76; H, 4.27; S, 8.93.

Kinetic Studies. Standard procedures were followed for the acetolyses. Standardized 0.022 M sodium acetate in redistilled glacial acetic acid containing 1% acetic anhydride was the solvent, with a triflate concentration of 0.02 M. Aliquots were sealed in ampules and heated at the reaction temperature. The excess sodium acetate was back-titrated in the ampule with standard 0.004 M perchloric acid in acetic acid using bromophenol blue indicator. The first-order plots of triflates were linear. The rates and activation parameters were calculated using a FACOM computer.

Studies of Acetolysis Products. A 0.02 M solution of the triflate (5-OTf) in 30 mL of acetic acid containing a molar equivalent of sodium acetate and 1% acetic anhydride was sealed into an ampule and heated for about 10 half-lives at 125 °C. The reaction mixture was evaporated under reduced pressure and the residue was extracted with ether. The ether solution was washed with aqueous sodium carbonate and water, dried, and evaporated. The oil obtained was analyzed by VPC and the two products were isolated by preparative thin-layer chromatography using benzene solvent. The major and less polar

product was identified as **dibenzobicyclo[2.2.2]octadien-1-yl triflate (13)**: mp 93–94 °C; NMR (CDCl₃) δ 1.65–2.7 (m, 4 H, ethylene bridge), 4.25 (t, 1 H, bridgehead), 7.0–7.7 (m, 8 H, aromatic). Anal. Calcd for C₁₇H₁₃O₃SF₃: C, 57.62; H, 3.70; S, 9.05. Found: C, 57.74; H, 3.66; S, 9.26. The minor more polar product was identified as 5-OAc: mp 99–100 °C; NMR (CDCl₃) δ 2.1 (s, 3 H, CH₃CO), 2.59 (d, 2 H, methylene bridge), 4.3 (s, 1 H, bridgehead), 5.1 (s, 2 H, CH₂OCO), 6.8–7.4 (m, 8 H, aromatic); IR (CDCl₃) 1740 cm⁻¹ (OCOCH₃). The product composition and effects of reaction temperature and added sodium acetate on it were investigated as described in Table II.

The reaction of 4-OTf was similarly carried out at 100 °C. The previously reported 4-OAc[6] was obtained in 80% yield and the internally returned benzobicyclo[2.2.2]octadien-1-yl triflate in 20% yield as an oil. For this triflate, NMR (CDCl₃) δ 1.5–2.5 (m, 4 H, ethano bridge), 3.9 (m, 1 H, bridgehead), 7.1–7.5 (m, 4 H, aromatic). When the bridgehead proton is irradiated, the C₂ vinyl proton appears at δ 6.8 as the A part of the AB quartet and the C₃ vinyl proton at 6.5 as the B part.

Dibenzobicyclo[3.2.1]nonadien-1-yl Acetate (14). The acetolysis of 6-OTf at 110 °C afforded 14 in a nearly quantitative yield: mp 122.5–123 °C (from *n*-hexane–methylene dichloride). NMR (CDCl₃) δ 1.1–2.2 (m, 6 H, bridge protons), 2.31 (s, 3 H, OCCH₃), 4.05 (t, 1 H, bridgehead), 7.2 (8 H, aromatic); IR (CHCl₃) 1740 cm⁻¹ (OCOCH₃). Anal. Calcd for C₁₉H₁₈O₂: C, 81.98; H, 6.52. Found: C, 82.08; H, 6.52.

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Application of Electron Spin Resonance Spectroscopy to Studies of Valence Isomerization. 6. Bicyclo[4.2.0]octa-3,7-diene-2,5-semidiones[1]

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It is demonstrated that bicyclo[4.2.0]octa-3,7-diene-2,5-semidione is a more stable valence isomer than the monocyclic 2,5,7-cyclooctatriene-1,4-semidione. Oxidative decarbonylations in basic solution to yield p-benzosemiquinones are reported for the 2,5,7-cyclooctatriene-1,4-dione and 3,6-cycloheptadiene-1,2,5-trione systems. Rearrangement of bicyclo[4.2.0]oct-7-ene-2,5-semidiones to the p-semiquinones of benzocyclobutane is catalyzed by oxygen, and it is postulated that the reaction proceeds via a chain process involving the p-quinone of benzocyclobutene.

We have previously demonstrated by ESR spectroscopy that bicyclo[4.1.0]hept-3-ene-2,5-semidione is the preferred valence isomer rather than cyclohepta-1,3,5-triene-2,5-semidione.[2] The structural assignment is easily made by a comparison of the hfsc for 1 with R = H and R = CH₃. For the monocyclic structure 2, the values of $a_{R=H}{}^H$ and $a_{R=CH_3}{}^H$

R = H, a^H = 3.01 gauss
R = CH₃, $a_{CH_3}{}^H$ = 0.25 gauss
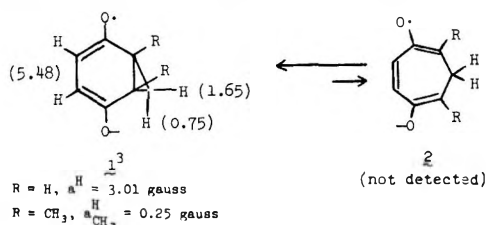
should be nearly the same, since when hydrogen or methyl is attached to an sp² carbon with spin density, $Q_{CH}{}^H = -23$ G and $Q_{CCH_3}{}^H = +28$ G.[3] When methyl is substituted for hydrogen at the 1,6 position in 1, we observe $a_{CH_3}{}^H = 0.25$ G, which is a significant decrease from $a^H = 3.01$ G for the parent system. Thus, the bicyclic structure is demanded for the semidione. The equilibrium between 1 and 2 greatly favors 1, presumably because the semidione reflects the stability of the parent dione. The bicyclic enedione which is a precursor to 1 is a stable structure, whereas a covalent structure cannot be drawn for the monocyclic dione.

We have also reported bicyclo[4.2.0]octa-3,7-diene-2,5-semidiones (4) prepared by the oxidation in basic solution of bicyclo[4.2.0]oct-7-ene-2,5-dione (3) or by reduction of substituted bicyclo[4.2.0]octa-3,7-diene-2,5-diones.[2,5] The bicyclic

3a, R = H
3b, R = CH₃

4a, R = H, a^H = 0.46
4b, R = CH₃, a^H = 0.14 gauss

not detected
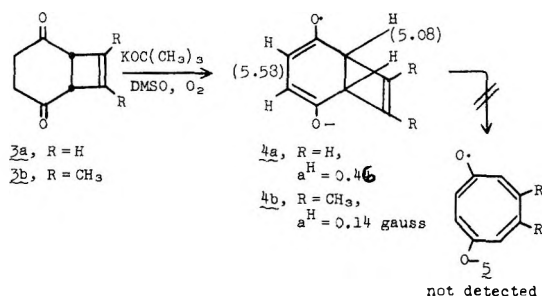
structure seems secure on the basis of the similarity of hfs between 1 and 4, as well as the appreciable difference between $a_H{}^H$ and $a_{CH_3}{}^H$ for the 7,8 substituents. Examples of 4 with methyl at the bridgehead positions have not been synthesized. However, we have examined bridgehead substitution for the benzo derivatives, 7. Table I presents the observed hfsc for several substitution patterns in 7. All of the data are consistent with the structure assigned to 7 and are consistent with the observed hfsc for 4.

The assignment of hfsc to $H_{4,7}$ (small) and $H_{5,6}$ (large) was by analogy to semidiones 9.[6] Semidione 7c with a bridgehead

8
not detected
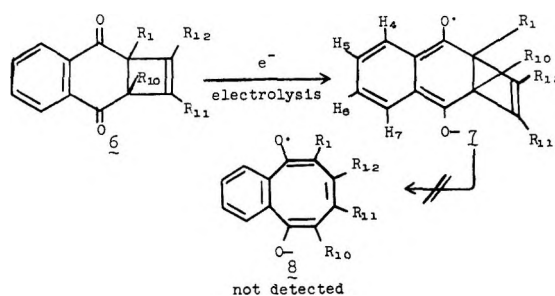
methyl was observed only as a transient species, while semidione 7d could not be observed at all. Instead, 2,3-dimethyl-

9
X = O, S, NH, CH₂, CHCH₃
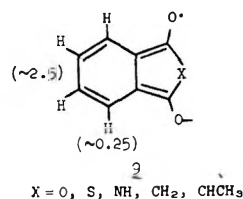
1,4-naphthosemiquinone (10) was formed, presumably via a cycloreversion process of the semidione or possibly of the

10
a^H = 0.35(2), 0.71(2), 2.48(6) gauss
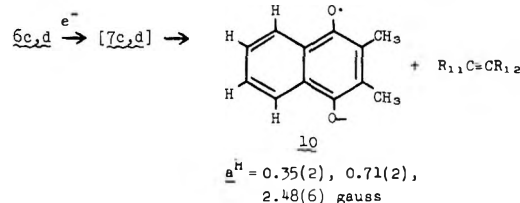
analogous dianion. Reduction of diones 6e and 6f gave the semiquinone resulting from the loss of methanol and hydrogenation of the cyclobutene ring. The formation of this product is considered below.

In order to ascertain if 4 is indeed the preferred valence isomer relative to 5 and if a rapid isomerization of 5 to 4 occurs, we have studied the formation of semidiones from the unsubstituted bicyclic bicyclo[4.2.0]octa-3,7-diene-2,5-dione (11) via reduction, from 2,4-cyclooctadiene-1,6-dione (12) via oxidation, and from 2,5,7-cyclooctatriene-1,4-dione (13) via

11   12   13
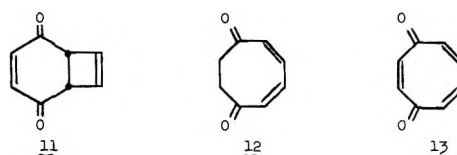
reduction. Reduction of 11 by basic DMSO[7] or electrolytically in DMSO yielded 4a with no indication of 5, but only when the system had been scrupulously deoxygenated (Figure 1a). In the presence of traces of oxygen, 4a was isomerized to the

Table I. Observed Hfsc (G) for 7 (DMSO, 25 °C)

		substituents				a^H				
registry no.	precursor	R_1	R_{10}	R_{11}	R_{12}	$H_{4,7}$	$H_{5,6}$	$H_{1,10}$	registry no.	$H_{11,12}$
21399-85-9	6a	H	H	Ph	Ph	<0.3	2.33	6.02	54388-86-2	
21399-82-6	6b	H	H	CH_3	CH_3	0.2	2.48	5.43	54338-85-1	0.20^a
21399-93-9	6c	CH_3	CH_3	Ph	H		2.20^b		66609-88-9	
21441-73-6	6d	CH_3	CH_3	CH_3	CH_3	only 10^c obsd				
66562-75-2	6e	CH_3O	H	Ph	Ph	only $15a^c$ obsd				
66562-76-3	6f	CH_3O	H	Ph	H	only $16f^c$ obsd				

^{a} $a_{CH_3}^H$. ^{b} Transient. ^{c} Registry no.: **10**, 66562-77-4; **15a**, 66673-24-3; **16f**, 66562-78-5.

p-benzosemiquinone **14a** in a catalytic process (Figure 1b). A similar isomerization catalyzed by oxygen was observed for
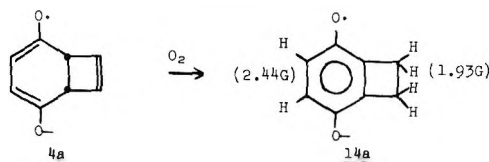
the benzo derivatives **6a,b** to give **15a,b** upon electrolytic reduction in the presence of traces of oxygen. Moreover, **6e** and

15a, $R_{11} = R_{12} = Ph$
15b, $R_{11} = R_{12} = CH_3$
15f, $R_{11} = Ph$, $R_{12} = H$
15g, $R_{11} = R_{12} = H$
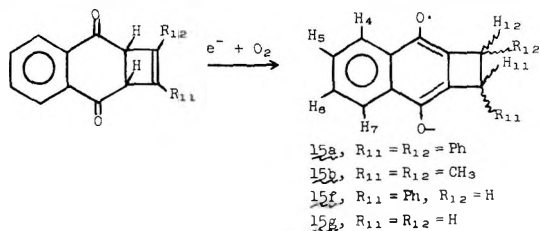
6f with a methoxy substituent at the bridgehead yielded **15a** and **15f**, respectively, as the only detectable radical anions upon electrolytic reduction or treatment with potassium *tert*-butoxide in DMSO solution. The hfsc of **15** are listed in Table II and compare favorably with the constants reported for **15g**.[8]

The conversion of **6e** and **6f** to the corresponding semiquinones **15** was somewhat surprising, because we had previously observed that a similar conversion does not occur for **16** which can be electrolytically reduced, or reduced by basic DMSO to **17** with no indication of the formation of **18**.[2] In

16a, R = H
16b, R = CH_3
17a, R = H
17b, R = CH_3
17c, R = H, bridgehead deuterium
18
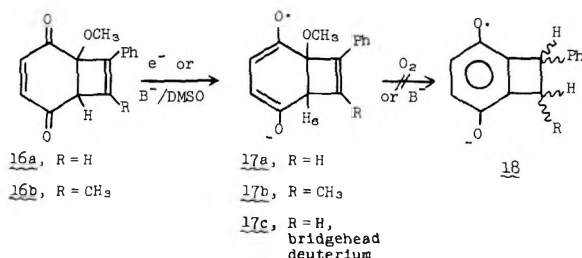
basic DMSO-d_6, **17a** undergoes hydrogen–deuterium exchange at the bridgehead position to form **17c**, but gives no indication of the elimination of methanol. The hfsc for **17a–c** are given in Table III.

The formation of **15** from **6**, or **14a** from **11**, suggests an elimination mechanism (**6e,f**) or oxidative dehydrogenation (**6a, 6b, 11**) to yield a benzocyclobutene derivative, as shown in Scheme I.

In the event that the intermediate cyclobutadiene derivative abstracts two hydrogen atoms from the starting dihydroquinones (**6a,b** and **11**), the isomerization (parts b and c of Scheme I) will be catalyzed by traces of oxygen. Such a reaction might be expected to transfer the bridgehead hydrogen atoms in a stereoselective cis manner to C-7,8. We have previously reported that **14b** and **14c** prepared from the appro-
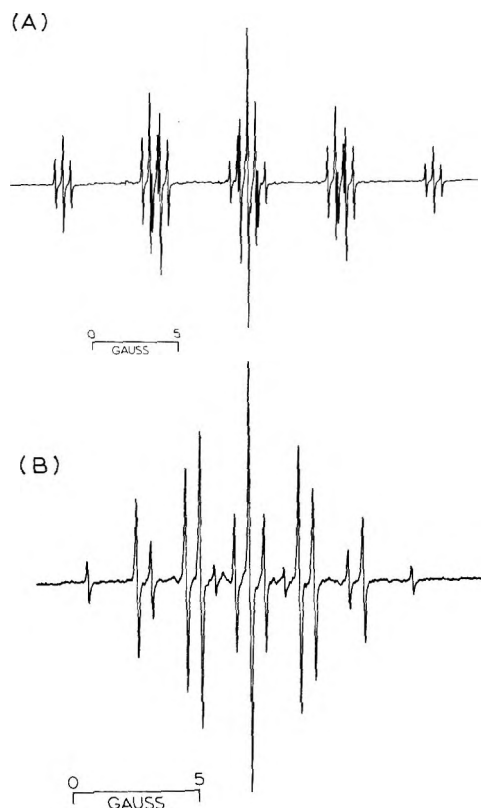
Figure 1. ESR spectra of (A) bicyclo[4.2.0]octa-3,7-diene-2,5-semidione (**4a**) in DMSO and (B) bicyclo[4.2.0]octa-3,6(1)-diene-2,5-semiquinone (**14a**) prepared by oxidation of a solution yielding spectrum (A).

Table II. Observed Hfsc (G) for 15 (DMSO, 25 °C)

substituents			a^H		
precursor	R_{11}	R_{12}	$H_{4,7}$	$H_{5,6}$	$H_{11,12}$	other
$15g^a$	H	H	0.44	0.75	2.94	
15a	Ph	Ph	0.33	0.63	2.70	
15b	CH_3	CH_3	0.26	0.52	2.25	0.13 (6 H)
15f	Ph	H	0.36	0.72	2.99	
					2.78	
					2.65	

^{a} Reference 8.

Table III. Observed Hfsc (G) for 17 (DMSO, 25 °C)

	pre-cur-sor	R	a^H		
registry no.			$H_{4,5}$	H_6	R
54338-68-0	17a	H	5.58, 5.05	4.68	0.23 (1 H)
54338-69-1	17b	CH_3	5.65, 5.10	4.70	0.49 (3 H)
66562-79-6	17c	H^a	5.62, 5.12	$a^D =$ 0.70	0.21 (1 H)

^{a} Bridgehead deuterium.

Scheme I
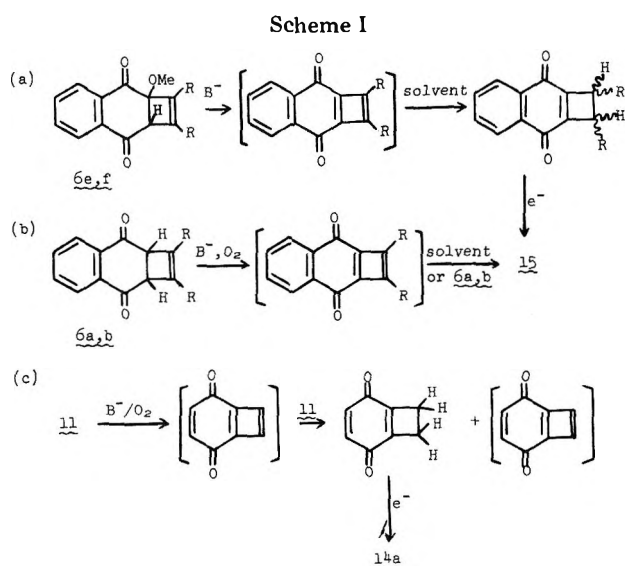
priate precursors have different ESR spectra and are not interconverted in basic solution.[2] The prediction of stereo-

$14b$, $a^H = 2.51$ (2H), 1.77 (2H) gauss

$14c$, $a^H = 2.51$ (2H), 1.71 (2H) gauss
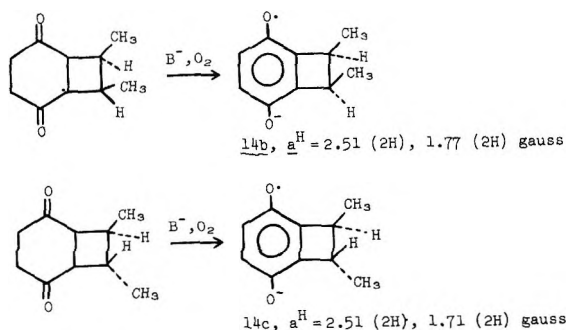
chemical control in the isomerization product was confirmed by the observation that **3b**, when treated with excess oxygen in DMSO solution, yielded only a single *p*-benzocyclobutane semiquinone and that this semidione possessed the stereochemistry of **14b** and not **14c**.[c] In a similar fashion, when **3a** was treated with oxygen in basic DMSO-d_6 solution the tetradeuterio derivative of **4a** was first formed, but excess oxygen led to the formation of the tetradeuterio derivative of **14a**, presumably with the cis stereochemistry.
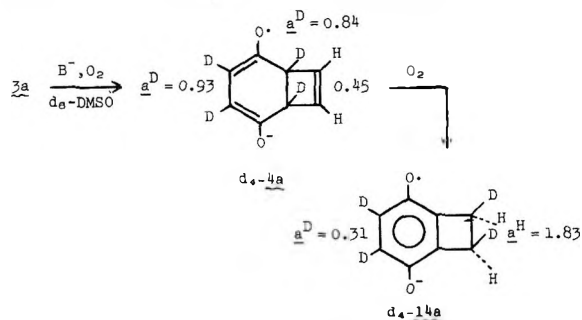
Treatment of bicyclo[4.2.0]oct-7-ene-2,5-diones (**3**) with deficient quantities of oxygen in basic solution gives **4** with little interference from **14**. The dianion of the enedione apparently is a good trap for oxygen, which decreases the probability of the further oxidation to the postulated cyclobutadiene intermediate unless excess oxygen is employed.

Photolysis of the mixture of **11** and **4a** in DMSO/potassium *tert*-butoxide was investigated as a possible route to **5**. Irradiation with UV through silica produced a new semidione possessing hfs by eight hydrogen atoms. The multiplicities suggest a symmetric structure which we postulate to be **19**. The hfs of H-2,3 are quite close to that observed in other 1,4-semidiones, including **4**, **20**,[9] and **21**.[9] The hfs of the
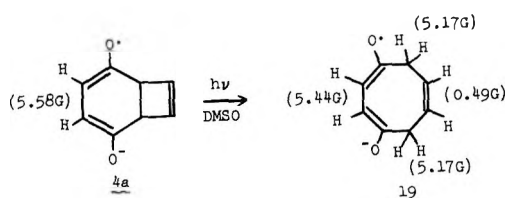
methylene groups in **19** are considerably greater than in **20** or **21**, perhaps because of conformational effects (two rapidly
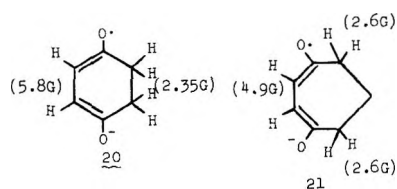
time-averaged conformations for **19**, a single rigid conformation for **20** or **21**). To exclude the alternative structure **22**, we investigated the reduction of the dienenedione **12**. Since electrolytic reduction of **12**, or treatment of **12** with deoxygenated DMSO containing potassium *tert*-butoxide, failed to produce a radical ion, we believe that **22** cannot be the structure of the above-mentioned photoreduction. Treatment
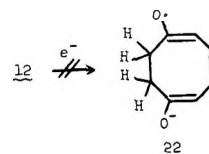
of **12** with base and oxygen in DMSO did produce semidiones, but only bicyclic semidiones. One of the semidiones was **4a** and the other semidione had nearly identical hfsc to **4a** but with one bridgehead hydrogen missing. The hfsc were nearly the same as **17a**, suggesting structure **23** for the new semidione.
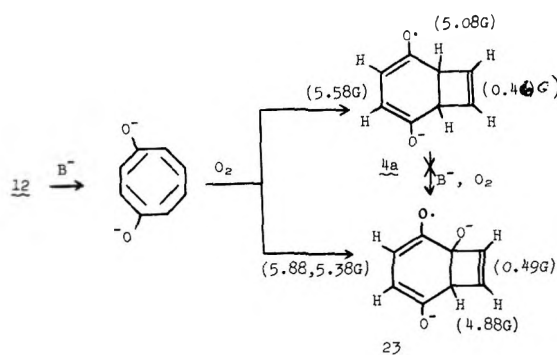
The formation of **4a** may occur via valance isomerization of the monocyclic dianion to the bicyclic dianion, followed by loss of an electron, or alternately by the loss of an electron from the monocyclic dianion followed by monocyclic–bicyclic valence isomerization (Scheme II). However, the results are strongly suggestive that **5** is thermodynamically less stable than **4a**. The semidione **23** is not observed upon oxidation of **3**, **4a**, or **11**. The formation of **23** can be easily rationalized if the monocyclic radical anion (Scheme II) is oxygenated prior to the monocyclic–bicyclic valence isomerization. Further oxygenation of the reaction mixture destroys **4a** and **23** and yields an ESR spectrum of *p*-benzosemiquinone whose formation will be discussed later.

2,5,7-Cyclooctatriene-1,4-dione[10] (**13**) decomposed rapidly in DMSO or DMF solutions. In acetonitrile the trienedione appeared stable, but no resolved ESR signals could be observed upon electrolytic reduction (mercury pool) or in tetrahydrofuran (platinum, −40 °C) or upon treatment with potassium *tert*-butoxide in DMSO. Dc polarography of the trienedione in acetonitrile with *tert*-butylammonium perchlorate (0.1 M) gave a single two-electron reduction with $E_{1/2}$

Scheme II

Table IV. McLachlan Spin Density Calculations for 24[a]

spin density	$n = 1.8, k = 1.4$	$h = 2.0, k = 1.4$
C_3, C_7	0.0464	0.0407
C_4, C_6	0.0797	0.0826

[a] $\alpha_O = \alpha + h\beta$; $\beta_{CO} = k\beta$, $\lambda = 1.2$.

Scheme IV

$\underline{a}^H = 2.05$ (2H), 1.00 (2H)G

$\underline{a}^H = 2.4$G (4H)G

Scheme V

$\underline{a}^H = 5.25, 1.55, 0.55$G
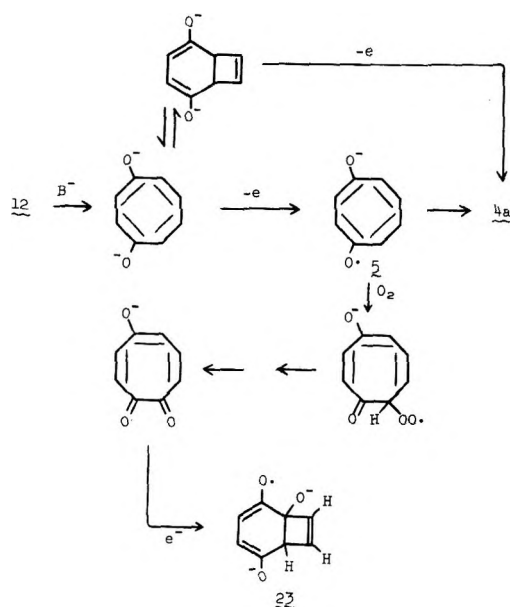
= −1.00 V (vs. SCE). From this we conclude that the radical anion is more easily reduced than the starting dione and this, connected with the instability of the parent dione, makes the detection of any radical ion (monocyclic or bicyclic) difficult when the trienedione is used as a processor. Nevertheless, the bicyclic radical ion **4a** is quite stable when prepared from a bicyclic precursor, and the absence of **4a** upon electrolytic reduction of the trienedione places some limit on the rate of the monocyclic → bicyclic valence isomerization of the as yet undetected **5** (Scheme III).

It was thus expected that treatment of **13** with basic DMSO should result in reduction to the dianion, which upon oxygenation should lead to **4a** and/or **23**. However, the only paramagnetic product we have been able to detect in this oxygenation is *p*-benzosemiquinone. *p*-Benzosemiquinone is also formed in the oxygenation of **12** and in the oxygenation of 5-hydroxy-α-tropolone in basic DMSO. Both of the ring contractions are apparently of the benzylic acid type, which has been previously observed in semidione systems.[11] The formation of *p*-benzosemiquinone from either 5-hydroxy-α-tropolone, **12**, or **13** upon oxygenation in basic DMSO solution undoubtedly follows the general outline of Scheme IV. *p*-Troposemiquinone (**24**)[12] can be detected in the oxidation of 5-hydroxy-α-tropolone with deficient oxygen in DMSO-containing potassium *tert*-butoxide. If the oxidation of 5-hydroxy-α-tropolone is conducted in the presence of hydroxide ions in DMSO, the observed semiquinone is the one derived from 1,2,4-trihydroxybenzene.[13] Apparently, under these conditions *p*-tropoquinone is hydroxylated or oxygenated to a tetraoxygenated species which then yields the trioxysemiquinone by the benzylic acid rearrangement se-

quence (Scheme V). The semiquinone of 1,2,4-trihydroxybenzene cannot be formed by the hydroxylation or oxygenation of *p*-benzosemiquinone under the reaction conditions.
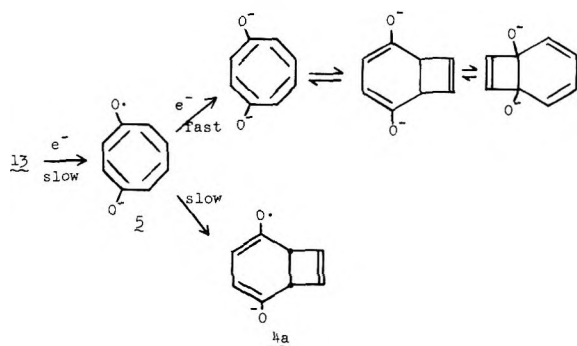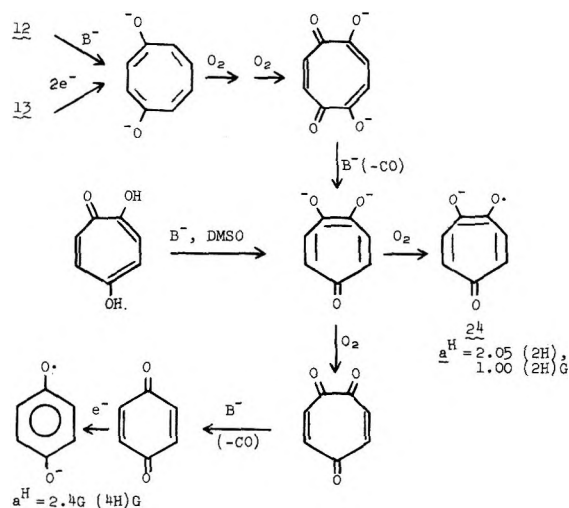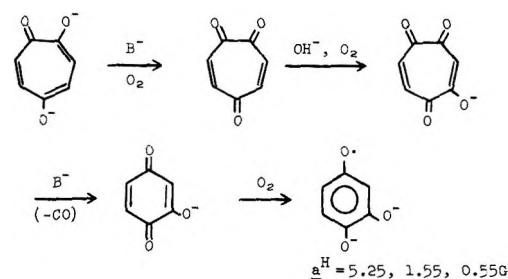
The hfsc of the 5-keto-α-tropolone semidione **24** were assigned by McLachlan calculations (Table IV).

The addition of the 5-keto group in **24** has an appreciable effect on the spin distribution of the α-tropylsemidione (**25**).[14] For **25**, $\rho_{c-3} > \rho_{c-4}$, whereas for **24** $\rho_{c-4} > \rho_{c-3}$.

Scheme III

Experimental Section

The in situ electrolytic reductions were carried out in a flat cell with a mercury pool cathode and a platinum wire anode. Approximately 1–2 mg of an unsaturated diketone was dissolved in 1 mL of dry solvent containing 0.1 M tetra-*n*-butylammonium perchlorate as the electrolyte. This solution was placed inside the electrolytic cell and degassed with a stream of prepurified nitrogen for 15 min prior to the beginning of the electrolysis.

Oxidations in basic solutions were performed by allowing air to enter the H-cell containing the DMSO solution of the dione by separating the ground glass joints of the H-cell and flat cell for brief periods (5–10 s). The solution was then shaken for 1–3 min and its ESR spectrum was then monitored.

Bicyclo[4.2.0]oct-7-ene-2,5-dione. 7,8-Dichlorobicyclo[4.2.0]octane-2,5-dione monoethylene ketal[2] (12.34 g, 0.0492 mol) was stirred with 19.3 g (0.295 mol) of zinc dust and 6.71 g (0.0492 mol) of zinc chloride in refluxing 95% ethanol for 6 h. Filtration, hydrolysis, ether extraction, and evaporation yielded a material which was chromatographed on a silica gel column with ethyl acetate (15%)–chloroform (85%) to give 5.82 g (0.0323 mol) of the monoethylene ketal of bicyclo[4.2.0]oct-7-ene-2,5-dione, bp 104 °C (0.6 Torr), in 66% yield: IR (CHCl₃) 1709, 1452, 1412, 1369, 1322, 1118 cm⁻¹; NMR (CDCl₃) δ 1.43–2.70 (m with d at 2.48, 4 H), 3.05–3.30 (m, 1 H), 3.43–3.56 (m, 1 H), 4.03 (s, 4 H), 6.10 (m, 1 H), 6.32 (m, 1 H); MS *m/e* 180 (M⁺, 56), 99 (100), 66 (63).

Anal. Calcd for C₁₀H₁₂O₃: C, 66.73; H, 6.71. Found C, 66.49; H, 6.67.

Hydrolysis of the monoethylene ketal of bicyclo[4.2.0]oct-7-ene-2,5-dione was difficult. A solution of 0.50 g (2.78 mmol) in 5 mL of dioxane containing 3 mL of 3% sulfuric acid was stirred under nitrogen for 24 h at 25 °C. The solution was neutralized with aqueous sodium bicarbonate, saturated with sodium chloride, and continuously extracted with ether for 48 h to give, after drying and evaporation of the ether, 0.35 g of product contaminated with the starting ketal. Chromatography on silica gel [ethyl acetate (20%)–benzene (80%)] gave 0.090 g (0.66 mmol, 4%) of the dione and 0.21 g of recovered ketal. The dione was a light-yellow oil with appreciable water solubility: IR (film) 1712, 1310, 1270, 1178, 819, 762, 685 cm⁻¹; NMR (CDCl₃) δ 2.46–3.33 (m, 4 H), 3.82 (s, 2 H), 6.36 (s, 2 H); MS *m/e* 136 (M⁺, 36), 108 (42), 93 (27), 79 (100), 63 (39).

High-resolution mass spectrum: Calcd for C₈H₈O₂, 136.05242. Found 136.05236.

The dione was also prepared by reduction of bicyclo[4.2.0]octa-3,7-diene-2,5-dione with a 50-mol excess of zinc dust in 10% acetic acid under nitrogen at 90 °C for 1.5 h. After cooling, filtration, and evaporation of the solvent, a crude product was obtained which after chromatography gave a 72% yield of desired bicyclic enedione.

Bicyclo[4.2.0]octa-3,7-diene-2,5-dione. The dienedione was prepared by the general route of Oda and Kitahari,[17] starting from *trans*-7,8-dibromobicyclo[4.2.0]octa-2,4-diene.[18] Irradiation of the dibromide (14.47 g, 0.0548 mol) of 1 L of acetone for 6 h in Pyrex with a Sylvania DVY 650 W tungsten–halogen projector lamp using hematoporphyrin as a singlet oxygen sensitizer gave 14.79 g (0.05 mol, 91%) of the *trans*-3,4-dibromo-9,10-dioxytricyclo[4.2.2.0²·⁵]deca-7-ene: mp 104–106 °C; NMR (CDCl₃) δ 3.57 (m, 2 H), 4.18 (m, 1 H), 4.74 (m, 3 H), 6.73 (ddd, *J* = 8, 6, 2 Hz), and 7.12 (ddd, *J* = 8, 6, 2 Hz). Reduction by LAH in THF gave the enediol in 89% yield, mp 129.5–131.0 °C, which was converted to the diacetate with acetic anhydride–pyridine in benzene solution in 94% yield. The diacetate was treated with a fourfold excess of zinc dust and a small crystal of iodine in DMSO at 90 °C to give the crystalline diene diacetate in 90% yield. Reduction of the dienediacetate with LAH in THF gave ~100% of the dienediol which was oxidized to the desired dienedione. A solution of 0.754 g (5.46 mmol) in 100 mL of CHCl₃ of the dienediol was treated with 15 g of activated MnO₂[19] for 30 h. Filtration and washing of the filter cake with ethyl acetate followed by evaporation of the solvent gave 0.493 g (3.68 mmol, 67%) of the dione which crystallized as yellow plates: mp 44–46 °C; IR (CHCl₃) 1679, 1604, 1560, and 962 cm⁻¹; NMR (CDCl₃) δ 3.95 (s, 2 H), 6.37 (s, 2 H), and 6.67 (s, 2 H).

Anal. Calcd for C₈H₆O₂: C, 71.63; H, 4.52. Found: C, 71.57; H, 4.60.

2,4-Cyclooctadiene-1,6-dione. The monocyclic dione was prepared by the flash pyrolysis of bicyclo[4.2.0]oct-7-ene-2,5-dione according to the procedure of Oda and Kitahari.[9] Passage of 201 mg (1.48 mmol) of the enedione over silica chips at 500 °C (0.03 Torr) gave 177 mg (1.30 mmol, 88%) of a yellow liquid which was microdistilled at 75 °C (0.1 Torr): NMR (CDCl₃) δ 2.84 (2, 4 H), 6.09 (dt, 2 H, *J* = 12.5, 2.5 Hz), and 6.52 (dt, 2 H, *J* = 12.5, 2.5 Hz); MS (16 eV) *m/e* 136 (M⁺, 30), 108 (100), 94 (94), 80 (28), and 66 (52).

2,5,7-Cyclooctatriene-1,4-dione. The preparation followed the procedure of Oda and Kitahari.[10] The crude pyrolysate of 305 mg (2.24

mmol) of bicyclo[4.2.0]oct-7-ene-2,5-dione was dissolved in 6 mL of CF₃CO₂H (33%)–CH₂Cl₂ (67%) and brominated with 2.20 mmol of NBS for 1 h at 25 °C. The solution was cooled in an ice bath and 4 mL of triethylamine added. Vacuum distillation of the solvent gave a residue which was chromatographed on silica gel [ethyl acetate (5%)–chloroform (95%)] to give 120 mg (0.90 mmol) of crude trienedione. Preparative GLC (0.25 in. × 6 ft DC-550, 150 °C) gave the pure trienedione as a light-yellow solid: IR (CHCl₃) 1665, 1616, 1489, 1409, 1128 cm⁻¹; NMR δ 6.03 (dt, 2 H, *J* = 14, 2 Hz), 6.43 (dt, 2 H, *J* = 14, 2 Hz), and 6.66 (s, 2 H); MS *m/e* 134 (M⁺, 22), 106 (18), 78 (100), 52 (64).

High-resolution mass spectrum: Calcd for C₈H₆O₂; 134.03678. Found 134.03711.

5-Hydroxytropolone. Following the procedure of Oda and Kitahari,[20] tropone was photooxidized with singlet oxygen using hematoporphyrin in acetone as the sensitizer to yield 56% of the endoperoxide. The endoperoxide (2.76 g, 0.02 mol) in 50 mL of 95% ethanol was stirred at 0 °C and 2.22 g (0.022 mol) of triethylamine in 100 mL of 95% ethanol was added over a period of 2 h.[21] The product was evaporated under vacuum, and the residue was washed with ethanol and sublimed to yield 5-hydroxytropolone: mp 246–247 °C [lit.[22] 245 (dec)]; NMR (DMSO-*d₆*) δ 6.95 (m, 4 H), 9.3 (m, 2 H).

1,6,7,8-Tetramethyl-3,4-benzobicyclo[4.2.0]octa-3,7-diene-2,5-dione (6d). 2,3-Dimethylnaphthoquinone (0.01 mol) and 2-butyne (0.04 mol) in 250 mL of benzene were irradiated in Vycor with a 275-W sunlamp for 70 h under nitrogen. The solvent was evaporated, and the resulting red oil was dissolved in ether and shaken with a 10% solution of sodium dithionite in 1 N NaOH to remove unreacted quinone. Evaporation of the solvent and recrystallization from CCl₄ gave 5.5% of **6d**: mp 135–136.5 °C (lit.[23] 139–140 °C); ¹H NMR (CDCl₃) δ 1.47 (s, 6 H), 1.51 (s, 6 H), and 7.16–8.19 (m, 4 H).

1,6-Dimethyl-8-phenyl-3,4-benzobicyclo[4.2.0]octa-3,7-diene-2,5-dione (6c). 2,3-Dimethylnaphthoquinone (0.013 mol) and phenylacetylene (0.019 mol) in 250 mL of benzene were irradiated in Vycor for 10 h under nitrogen. The unreacted quinone was removed with NaOH–sodium dithionite to give 36% of 6c after recrystallization from ethanol: mp 140.0–140.7 °C (lit.[23] 140–141 °C); ¹H NMR (CDCl₃) δ 1.64 (s, 3 H), 1.78 (s, 3 H) and 6.53 (s, 1 H), 7.23–7.59 (m, 5 H), and 7.65–8.30 (m, 4 H).

Other Reagents. The synthesis of the 7,8-dimethyl-3,4-benzobicyclo[4.2.0]octa-3,7-diene-2,5-dione (6b) has been previously described.[2] Compounds 6a, 6c, 6f, 16a, and 16b were kindly supplied by Professor S. D. Pappas.[24]

References and Notes

(1) Aliphatic Semidiones. 35. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

(2) G. A. Russell, J. R. Dodd, T. Ku, C. Tanger, and C. S. C. Chung, *J. Am. Chem. Soc.*, 96, 7249 (1974).

(3) a^H values given for 1 are for R = H.

(4) G. A. Russell in "Techniques of Chemistry", Vol. IV, Part I, A. Weissberger, Ed., Wiley, New York, N.Y., 1972, pp 444–452.

(5) a^H values given in the structure are for R = H.

(6) S. E. Nelson, *J. Am. Chem. Soc.*, 89, 5256 (1967).

(7) Potassium *tert*-butoxide in DMSO is an effective reducing agent for α,β-unsaturated ketones [G. A. Russell and R. L. Blankespoor, *Tetrahedron Lett.*, 4573 (1971)]. The reduction apparently involves the addition of CH₃SOCH₂⁻ to the unsaturated ketone to form an enolate anion which is the effective one-electron transfer agent [G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, 86, 1807 (1964)].

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Generality of the Photochemical Bicycle Rearrangement. Exploratory and Mechanistic Organic Photochemistry[1,2]

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The generality of the slither, or bicycle, rearrangement has been examined in three new systems: 2-methylene-4,6-diphenyl bicyclo[3.1.0]hex-3-ene (**5**), 3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene (**6**), and 3,4-benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene (**7**). In each case endo and exo stereoisomers were studied. The photochemistry of these systems consisted of slither rearrangements in which carbon-6, with its two sp[5] three-ring orbitals, bicycles around the five-ring and also out onto the exocyclic methylene group. The stereospecific slithering process is termed "bicycling", since C-6 moves stereospecifically around the five-ring with the sp[5] orbitals acting as "wheels". With the wheels staying on the five-ring and exocyclic bonds, the endo group remains endo and the exo group at C-6 remains exo. Counterclockwise bicycling is shown to be preferred to clockwise bicycling (with the molecule drawn following the convention in the text). Evidence is presented in the case of diphenyl bicyclic olefin for a minor pathway permitted for the endo but not exo stereoisomer. This involves counterclockwise bicycling just past the exo-methylene group followed by backup onto this exo moiety to give the stereoisomer of the major spiro product. In the benzo examples, bicycling over the π system of the benzo moieties is shown to be inhibited. SCF–CI calculations were carried out for the reacting species along the excited state surface leading toward product. This surface curves downward until a cyclopropyl diradical structure is reached, at which point an approach to the ground-state surface is encountered. Correlation diagram treatments were derived as well. Finally, a concept of dissection of electronic excitation into components around the molecule was introduced. This involved a ΔP matrix giving the change in bond orders of the excited state vs. the ground state. The treatment allows one to determine which molecular motions lead to a mutual approach of excited and ground states and predicts reaction pathways.

Introduction

Previously we have described the photochemical rearrangement of 6,6-dimethyl- and 5,6-diphenyl-substituted 2-methylenebicyclo[3.1.0]hex-3-enes (**1** and **2**, respectively) to give spiro[2.4]hepta-4,6-diene products (**3** and **4**).[3] The reaction was shown to proceed via the excited singlet and to be stereospecific in the one case with stereochemistry (note eq 1).

$$(1a)$$

$$(1b)$$
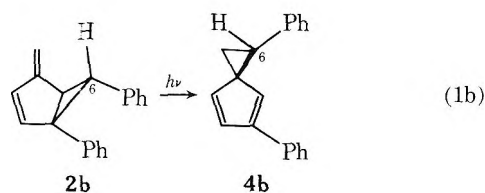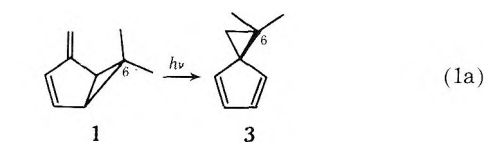
The reaction is one in which carbon-6 slithers, or bicycles, along the surface of a fulvene π system, retaining stereochemistry in such a way that the endo group at C-6 remains endo and the exo group remains exo. The reaction stereochemistry can be envisaged as involving two sp[5] hybrid orbitals bonding C-6 to the five-ring, these orbitals constituting "bicycle wheels". As the forward wheel rolls along the five-ring, the inside (endo) handlebar remains inside the five-ring and the exo one remains outside.

Because of the intriguing nature of this new reaction, we wished to explore its generality, its limitations, and structural effects governing the reaction course. Also, our single photon counting technique for determining excited singlet rate constants[4] provided a way to ascertain the reaction facility as a function of structure.

The systems selected for study were 2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene (**5**), 3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene (**6**), and 3,4-benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene (**7**). These promised to provide information on the generality of the reaction as a function of structure and also indicate if the reaction still occurred with benzo substitution. Additionally, the compounds were selected so that fluorescence emission could be used to monitor excited-state decay.

Synthesis of Reactants and Potential Photoproducts. The synthesis of the exo and endo isomers of diphenyl diene **5** (i.e., **5a** and **5b**) are shown in Scheme I; synthesis of the exo and endo isomers of benzo phenyl bicyclic olefins **6a** and **6b** and the corresponding anisyl analogues **18a** and **18b** are shown in Scheme II.

One novel feature of our synthetic efforts is the intramolecular cyclization of the α,β:γ,δ-unsaturated diazoketones (e.g., **10a,b**). Another is the three-ring formation by reaction of dimethylsulfoxonium methylide with methyleneindene π bonds to form **20a** and **22a** (note Scheme III).

With the photochemical reactants in hand, it proved stra-

Scheme I. Synthesis of Photochemical Reactants 5a and 5b

Scheme II. Synthesis of Photochemical Reactants 6a, 6b, 7a, and 7b

An = *p*-anisyl (i.e., *p*-methoxyphenyl)
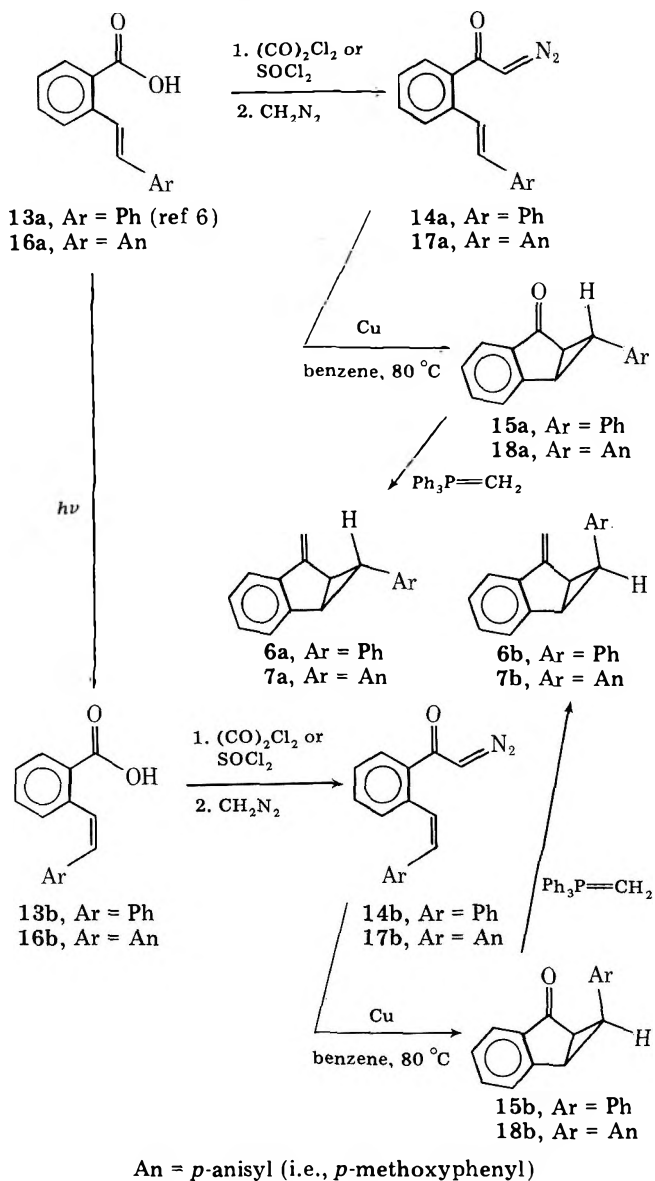
Scheme III. Synthesis of Potential Photoproducts

An = *p*-anisyl

tegic to obtain some of the more likely photoproducts. In this we were guided by the reaction course previously described.[3] These efforts are outlined in Scheme III.

The photochemical products derived from the stereoisomeric diphenyl dienes **5a** and **5b** seemed likely to be known compounds already investigated in our previous study of the 5,6-diphenyl bicyclic dienes **2a** and **2b**.

Results

Exploratory Photochemistry. Irradiation of *exo*-diphenyl diene **5a** afforded the known[3] *anti*-1,5-diphenylspiro[2.4]-hepta-4,6-diene (**4a**) as the major product along with 2,5-diphenyltoluene as a very minor product. Note eq 2a in Scheme IV. Thus the reaction is analogous to that observed in our earlier investigations.[3] Irradiation of the stereoisomeric *endo*-diphenyl diene **5b** led to a more complex product assortment (eq 2b, Scheme IV). Despite the high conversion and the expectation that product stereoisomers might interconvert, there was a slight excess of the syn isomer of the 1,5-diphenyl spiro diene **4b**. Thus, there were early indications of stereospecificity in the rearrangement, as expected from

Scheme IV. Quantum Yields and Kinetic Product Distributions[a-d]

5a $\xrightarrow{h\nu}$ **4a** + **26** (2a)

$\Phi = 0.0950$ $\Phi = 0.0087$
91.6%   8.4%
7.69×10^9 7.04×10^8

k_r 8.42×10^9 s^{-1}

5b $\xrightarrow{h\nu}$ **4b** + **4a**

$\Phi = 0.0661$ $\Phi = 0.0185$
67.9%   19.0%
4.61×10^9 1.29×10^9

$k_r = 6.81 \times 10^9$ s^{-1}

+ **26** + **27** + **28** (2b)

$\Phi = 0.0053$ $\Phi = 0.0041$ $\Phi = 0.0034$
5.4%   4.2%   3.5%
3.69×10^8 2.86×10^8 2.36×10^8

6a $\xrightarrow{h\nu}$ **20a** + **29** (3a)

$\Phi = 0.0630$ $\Phi = 0.0548$
53.5%   46.5%
2.45×10^{10} 2.13×10^{10}

$k_r = 4.59 \times 10^{10}$ s^{-1}

6b $\xrightarrow{h\nu}$ **20b** + **29** (3b)

$\Phi = 0.0094$ $\Phi = 0.0796$
10.6%   89.4%
1.83×10^9 1.55×10^{10}

$k_r = 1.73 \times 10^{10}$ s^{-1}

7a $\xrightarrow{h\nu}$ **22a** + **30** (4a)

$\Phi = 0.0588$ $\Phi = 0.0732$
44.5%   55.5%
1.69×10^{10} 2.11×10^{10}

$k_r = 3.79 \times 10^{10}$ s^{-1}

7b $\xrightarrow{h\nu}$ **30** (4b)

$\Phi = 0.0940$
100%
1.79×10^{10}

$k_r = 1.79 \times 10^{10}$ s^{-1}

An = *p*-methoxyphenyl

[a] Quantum yields and kinetic product distributions are given below each compound. Extrapolated values for diphenyl diene **5b**. [b] Rates associated with the total reaction are given for each starting material and individual rates of reaction to each product are given under product mixture compositions and are in s^{-1}. [c] In preparative irradiations 1-methyl-2-phenylnaphthalene was also isolated from **6a** and **6b** (eq 3a and 3b). [d] Quantum yield expected error limits are ±5%; rate limits are 20%.

our previous studies. As noted in eq 2b of Scheme IV, in addition to the two spiro products (i.e., **4a** and **4b**) there were formed minor amounts of 2,5-diphenyltoluene (**26**), 3,4-diphenyltoluene (**27**) and 2,4-diphenyltoluene (**28**).

Photolysis of *exo*-benzo phenyl bicyclic olefin **6a** afforded as the major product the *anti*-spiroindene **20a** (see Scheme IV, eq 3a and Scheme III) and two further products. One of these was the 1-methyl-2-phenylnaphthalene (**24**) anticipated and synthesized (vide supra). The other, product **29**, proved to be isomeric with starting material. This labile compound was found to be readily converted to the methylphenyl naphthalene **24** either by heating in refluxing benzene or on treatment with acid. The NMR spectrum revealed the presence of an exocyclic methylene group and also a styryl vinyl group. Both of these were adjacent to a single, benzylic methine. The spectral data, coupled with the rearrangement to methylphenylnaphthalene **24**, indicated 1-methylene-2-phenyl-1,2-dihydronaphthalene as the structure of the compound **29**.

Photolysis of the corresponding *endo*-benzo phenyl bicyclic olefin **6b** proved qualitatively similar. Note eq 3b of Scheme IV. However, here the syn isomer **20b** of spiroindene was formed. Also, now the major product was the methylenedihydronaphthalene **29**.

Irradiation of the corresponding benzo anisyl bicyclic olefins **7a** and **7b** proved remarkably parallel to that of the phenyl relatives (note eq 4a and 4b of Scheme IV), except that no spiro product could be found in the case of the photolysis of the *endo*-anisyl isomer **7b**.

Kinetic Product Distributions, Quantum Yields, and Multiplicity Determinations. It was of interest to determine the kinetic distribution of products. Also quantum efficiencies were desired. Finally, we wished to determine if the bicycle, or slither, reaction was a singlet process in these cases, as in the examples we studied earlier.[3]

Quantum yields were determined using the organic chemist's microbench[7] described earlier. Runs were made to varying conversions below 10% until limiting values were obtained. Analysis was by high-pressure liquid chromatography. Where very minor products were obtained, their distribution was taken from NMR analysis of higher conversion runs. In the case of *endo*-diphenyl diene **5b** it was especially necessary to check the kinetic distribution and quantum yields by extrapolation to zero conversion. The quantum yield proved only a mild function of time at the low conversions (note Experimental Section and Figure 1). However, the partitioning between stereoisomers and the stereospecificity proved more dependent on the extrapolation, as seen in Figure 1.

Quantum yields are summarized in Scheme IV and included in Table I. Details are to be found in the Experimental Section.

The quantum yields allow one to obtain the kinetic distribution of products percentage-wise, and this information, too, is included in Scheme IV.

Finally, in order to determine reaction multiplicity, sensitized irradiations were carried out. Both *m*-methoxyacetophenone and benzophenone sensitizers were used; the latter was used in the quantum yield determinations. It was observed that the endo compounds (i.e., **5b**, **6b**, and **7b**) stereoisomerized to give the corresponding exo isomers **5a**, **6a**, and

Table I. Direct and Sensitized Quantum Yields

| compd | registry no. | conditions | quantum yields[a] | | | spiro/ nonspiro ratio |
			spiro product(s)	nonspiro product(s)	reactant isomer- ization	
5a	66374-26-3	direct	0.0950	0.0087	<0.0003	10.92
		sensitized	<0.0003	<0.0003	<0.0003	
5b	66511-75-9	direct	0.0847	0.0129	<0.0003	6.56
		sensitized	0.0003	0.0003	0.159	
6a	66374-27-4	direct	0.0630	0.0548	<0.001	1.15
		sensitized	<0.001	<0.001	<0.001	
6b	66511-76-0	direct	0.0094	0.0796	<0.001	0.118
		sensitized	<0.001	<0.001	0.117	
7a	66374-28-5	direct	0.0588	0.0732	<0.001	0.803
		sensitized	<0.001	<0.001	<0.001	
7b	66511-77-1	direct	<0.001	0.0940	<0.001	<0.01
		sensitized	<0.001	<0.001	0.126	

[a] Quantum yields are extrapolated to zero conversions. Except for endo diene **5b** the dependence on extent conversion proved minor. Error limits ±5%.
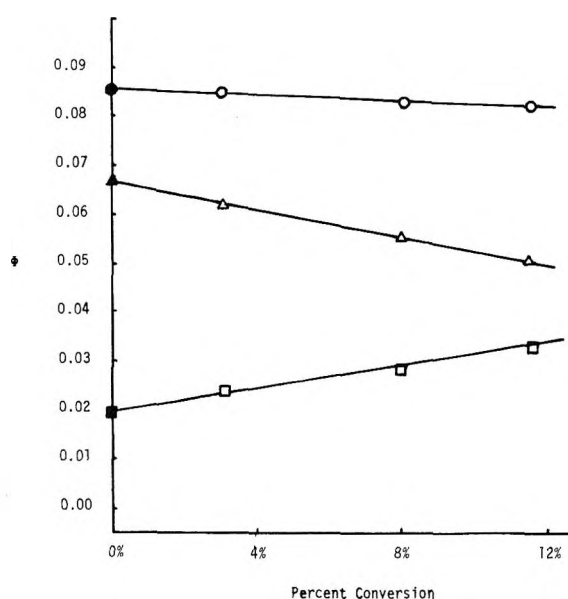
Figure 1. Plot of quantum yields of 1,5-diphenylspiro[2.4]hepta-4,6-diene (**4a,b**) from *endo*-2-methylene-4,6-diphenylbicyclo[3.1.0]-hex-3-ene (**5b**) vs. percent conversion: O, total formation of **4a** and **4b**; △, formation of **4b**; □, formation of **4a**. Darkened symbols on the ordinant indicate the extrapolated values.

7a. However, no bicycle rearrangement products could be found. The exo stereoisomers proved to be unreactive in the sensitization experiments. The sensitization results are included in Table I. Where no reaction was observed, upper limits are set.

It can be seen that the bicycle rearrangement occurs in direct irradiations and not from the triplets when independently generated. This means that the rearrangements are singlet processes.

Determination of Excited Singlet Rearrangement and Decay Rates. It was of considerable interest to determine the excited singlet rearrangement rate in order to ascertain if this was a function of structure. The method we have described earlier[4] has proven especially useful.[8,9] This involves single photon counting using an on-line minicomputer as a multichannel analyzer and also for effective deconvolution by an iterative convolution technique.

In our hands,[10] simulated deconvolution can give singlet decay rates (i.e., k_{dt}'s) and lifetimes (i.e., τ's) with an uncertainty of ±16 ps. Thus, rates as rapid as 2×10^{10} s^{-1} (i.e., a lifetime of 50 ps) may be measured with a 32% error. The k_{dt}'s obtained are used along with quantum yields (i.e., the ϕ_r's) to

give the desired excited singlet rate constants (the k_r's) as given in the equation

$$k_r = \phi_r k_{dt} \qquad (5)$$

Unfortunately, often the decay constants are faster than 2×10^{10} s^{-1} and one would like to obtain the still faster rate constants without an excessive increase in relative error. For this our method of magic multipliers[4] is of utility. This depends on the often observed increase in excited-state lifetime and fluorescence quantum yield at lower temperatures. With an increased lifetime and decreased rate of decay, an excited state decay too rapid to measure at room temperature quite often becomes accessible at 77 K. The ratio of intensities of emission at 77 K and room temperature (e.g., 293 K) is readily measurable. This ratio is our magic multiplier and is given by the equation

$$M = \phi_f^{77}/\phi_f^{rt} = k_{dt}^{rt}/k_{dt}^{77} \qquad (6a)$$

Transposition as in the equation

$$k_{dt}^{rt} = M k_{dt}^{77} \qquad (6b)$$

allows us to obtain the desired, rapid room temperature rate of decay.

The excited-state rates of decay, lifetimes, magic multipliers, and reaction rates are collected in Table II. Also, the room temperature reaction rate constants are included in Scheme IV.

Interpretative Discussion

Occurrence and Generality of the Bicycle Rearrangement. The reaction presently under study is a special case of the walk rearrangement, for which both thermal[11] and photochemical[12] examples are known. Two stereochemical courses are possible for these reactions in the case of bicyclo[n.1.0] systems. In one, the endo group becomes exo and vice versa. This is termed a "pivot mechanism". In the other the endo group remains endo and the exo group stays exo. Previously we have termed this a "slither reaction",[3,11c,12] but a "bicycle mechanism" is more descriptive (vide infra). Thus there are two variants of the rearrangement.

The photochemical rearrangement presently described involves the three-ring carbon of a 2-methylenebicyclo[3.1.0]hex-3-ene walking around the five-ring and also out onto the exocyclic π bond. Only a few examples of this reaction are known. In addition to the three examples of our previous study[3] described above, only two other examples have been observed.[13]

Hence, the present study provides needed evidence that the

Table II. Summary of Singlet Rates and Lifetimes[a]

compd	M	temp, K	τ, ps	$^1k_{dt}$, s^{-1}	^1k_r, s^{-1}
5a	42	293	12.4	8.09×10^{10}	8.42×10^9
		77	516	1.94×10^9	
5b	36	293	14.4	6.97×10^{10}	6.81×10^9
		77	524	1.91×10^9	
6a	100	293	2.57	3.89×10^{11}	4.59×10^{10}
		77	256	3.90×10^9	
6b	91	293	5.13	1.95×10^{11}	1.73×10^{10}
		77	468	1.91×10^9	
7a	120	293	3.47	2.88×10^{11}	3.79×10^{10}
		77	415	2.41×10^9	
7b	114	293	5.27	1.90×10^{11}	1.79×10^{10}
		77	601	1.66×10^9	

[a] Error limits ±20% for rates.

reaction is, indeed, general. It is seen that benzo derivatives (i.e., **6** and **7**) of the basic 2-methylenebicyclo[3.1.0]hex-3-ene system also give the rearrangement. This is relevant, since the same general system, minus the endocyclic double bond, does not give the rearrangement, but rather other photochemistry[14] as shown in eq 7.
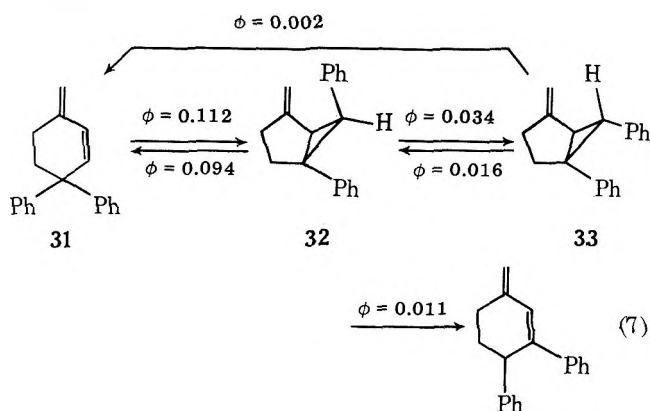
The Overall Reaction Mechanism. The first point of interest is the formation of toluenes (note eq 2a and 2b), as well as methylnaphthalenes and their 1-methylenedihydronaphthalene precursors (note eq 3a, 3b, 4a, and 4b). In our previous work we noted[3] that these can be construed as reaction mechanism "markers", telling where the reacting molecule has been mechanistically. This point can be seen by inspection of Scheme V, which gives a mechanism in terms of traditional organic resonance structures. Here the main bicycle steps are depicted with heavy arrows. The toluene derivatives can be seen to derive from biradical species along this main reaction pathway. In each case a Grob fragmentation of a 1,4-biradical is involved. The toluenes thus can be seen to provide support for the biradical species postulated, and these products trace the topology of the migration of the PhCH moiety as it traverses the molecule.

It is of some interest to note that a number of the species in Scheme V were shown to be involved in our previous study[3] beginning with the excited state of 2-methylene-5,6-diphenylbicyclo[3.1.0]hex-3-ene (**2**). The pathways utilized in that study[3] are marked in Scheme V.

The reaction mechanism in the cases of the benzo analogues is similar and discussion is deferred for pinpointing differences.

Reaction Stereospecificity. The first point to be noted is that the reaction is stereospecific as in our previous work[3] and in agreement with that of Hamer and Stubbs.[13a] Thus, the *endo*-aryl group assumes a product configuration in which the aryl group is oriented in the same direction as in the reactant.[15]

This excludes a mechanism involving complete three-ring

Scheme V. Mechanism for Rearrangement of *endo*-Diphenyl Diene 5b
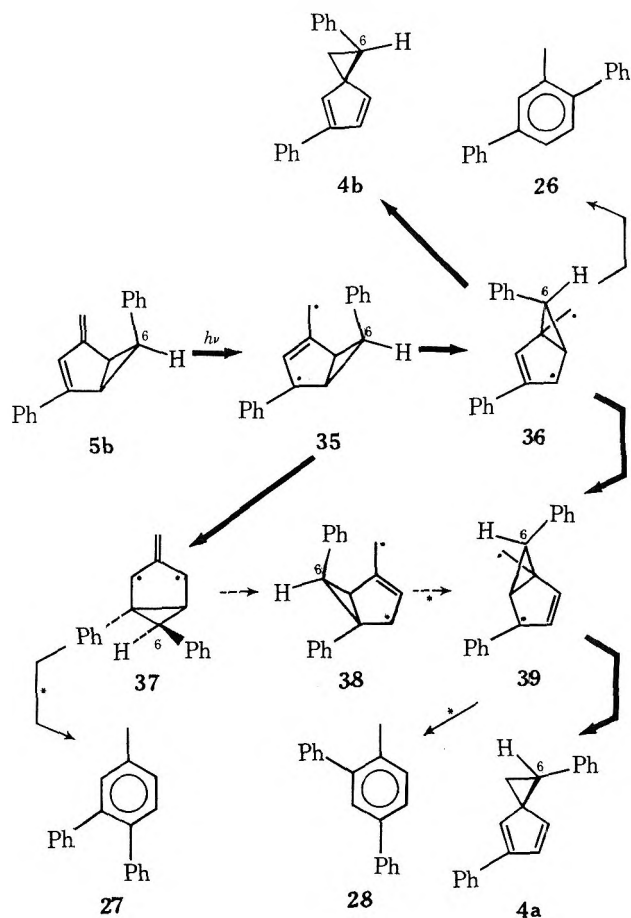
(**——**) Main bicycle pathways. (**——**) 1,4-Biradical Grob side routes. (- -) Potential but unlikely pathways in present study. (*) Pathways shown in ref 3 to be utilized in the photochemistry of 2-methylene-5,6-diphenylbicyclo[3.1.0]-hex-3-ene.

fission to give phenylcarbene plus 3-phenylfulvene (or benzofulvene), followed by readdition of the carbene to the exocyclic methylene double bond. Although, it is seen that all products derive from these two fragments, nevertheless the reaction stereospecificity rules out such a mechanism. A carbene plus fulvene pair would not remember the stereochemistry of reactant, and the same product configuration would result from either of two stereoisomeric reactants.

Scheme V presents an overall reaction mechanism. In this we have depicted the experimentally observed reaction stereochemistry without rationalization. Thus, the transforma-

Scheme VI. Two Stereochemical Mechanisms for Carbenoid Migration

PIVOT PROCESS:

PIVOT HALF MIGRATED SPECIES

40   41   42

BICYCLE PROCESS:

BICYCLE HALF MIGRATED SPECIES

40   43   44a

44a EQUIVALENT TO:

44b

Scheme VII. Topology of Bicycling (i.e., Slithering) on the Fulvene Systems

45   46

47   48
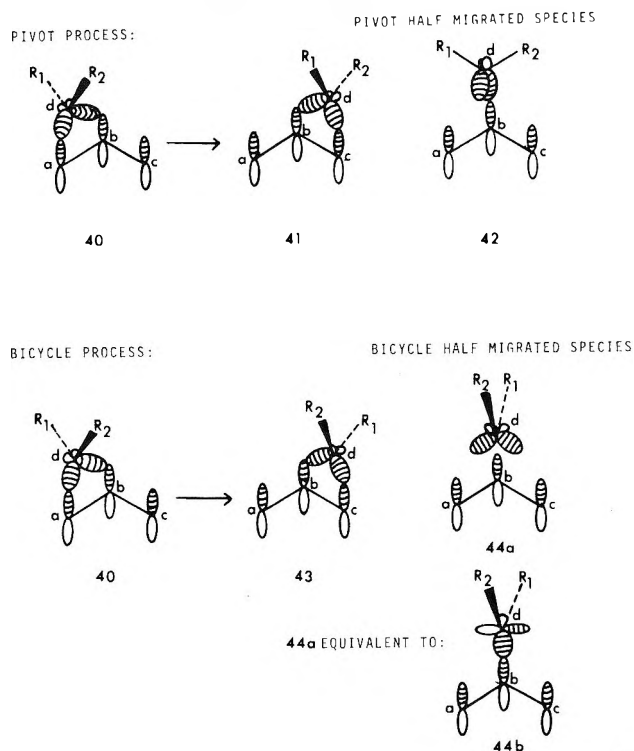
tion of excited state 35 to 36 has been shown as proceeding with the endo-phenyl remaining endo. This is tantamount to inversion of configuration[16] at the benzylic carbon (i.e., C-6 of the bicyclic system). Similarly, the conversion of bicyclic biradical 36 to bicyclic biradical 39 and the conversion of bicyclic excited state 35 to bicyclic biradical 37 are shown with the same inversion stereochemistry. Also the same is true of the final formation of the spiro three-rings of the products 4a and 4b.

A parallel reaction course is envisaged for the exo-diphenyl diene rearrangement except that the phenyl group at C-6 remains exo. For the benzo derivatives, again, the same reaction stereochemistry accounts for the observed products.

However, we have not justified the preference for this reaction stereochemistry. Years ago[12b] we noted a preference for such stereochemistry in the case of the santonin to lumisantonin conversion and more recently[11d] we have further analyzed the possible stereochemistry in such rearrangements. We termed the two alternatives pivot and slither mechanisms. Thus, in such rearrangements the migrating carbon has two stereochemical options as it moves from a set of two carbons (e.g., a and b) to the next set (i.e., b and c). The two mechanisms are depicted in Scheme VI. In each the a,b,d three-ring of species 40 is lost and converted into the b,c,d three-ring as in species 41 or 43.

As a result of pivoting about bond b–d, the pivot process can be seen to reverse the endo and exo relationships of groups R_1 and R_2. Conversely, the slither, or bicycle, process can be seen to keep the endo group R_2 endo and to maintain the exo group R_1 as exo.

It is instructive to inspect the species at half reaction. In the pivot species 42 there is a σ bond due to b–d overlap while the hybrid orbital at center d overlaps with the orbitals at a and c.

For the bicycle mechanism, there are two quantum mechanically equivalent representations for the half reaction species; these are 44a and 44b. The first, 44a, is clearly related to starting and final species (i.e., 40 and 43) except with intermediate positioning. Carbon d has two sp⁵ hybrid orbitals. The second, 44b, superficially appears different in that it
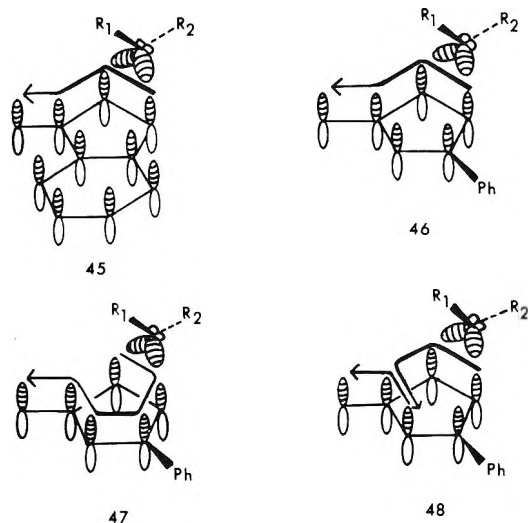
consists of a p orbital at center d and also has an sp² hybrid orbital. It can be seen to appear to maintain σ bond b–d while undergoing inversion of configuration at center d by virtue of using both lobes of its p orbital.

We have noted before[11d] that two such representations are truly equivalent.[17,18] An easy way to follow the stereochemistry of the bicycle mechanism is to consider the two sp⁵ orbitals as front and rear wheels of a bicycle which then rolls along the pathway of a π system. The two groups R_1 and R_2 are positioned as handlebars of a bicycle, and thus in bicycling around a ring the endo handlebar, or group, remains endo and the exo one stays exo.

Inspection of the six examples presently described, including three sets of endo and exo stereoisomers, reveals that the bicycle (or slither) mechanism very simply accommodates the experimental stereochemistry of endo reactant giving syn product and exo reactant giving anti product.[15] In the cases of the benzo phenyl and anisyl bicyclic olefins 6 and 7 the bicycling carbon does so in a counterclockwise[19] direction. The same is true for the exo-diphenyl diene 5a. In the case of the endo-diphenyl diene 5b the major kinetic product 4b again arises from counterclockwise bicycling. The bicycling (or slither) topology is depicted in Scheme VII.

The alternative to the bicycle mechanism consists of a series of pivot processes. It can be seen that two pivot steps of the kind depicted in Scheme VI leave an endo group (e.g., R_2) endo and an exo group (e.g., R_1) exo; this is the same outcome the bicycle mechanism affords. Thus any reaction consisting of an even number of pivot steps is stereochemically equivalent overall to a reaction resulting from the bicycle alternative.

However, a clue to the solution of this problem was found in our earlier observation that the endo isomer 2a[3b] led to enhanced Grob fragmentation of the diradical intermediate species with formation of toluene byproducts. Thus, it seemed likely that diradical species derived from the endo isomer were more likely to undergo such internal bond fission (i.e., Grob fragmentation[20]) where there was steric relief of strain deriving from endo-phenyl–five-ring interaction. Fragmentation of the cyclopropyl diradicals in the bicyclo[3.1.0]hexane framework results in flattening of the peripheral six-ring to give a 1-methylene-2,4-cyclohexadiene system.

The present study tested (1) the generality of the endo tendency to Grob fragment and (2) the effect of a strategically placed fused benzo group to enhance the endo-phenyl steric interaction.

Thus, after one step to give a diradical species 58b, a difference between the bicycle and pivot processes does exist.

Table III. Quantum Efficiencies for Bicyclic Dienes 1 and 2[3]

compd	registry no.	conditions	quantum yields		reactant isomerization
			spiro product(s)	nonspiro product(s)	
1	29443-86-5	direct	0.041	0.038	
		sensitized	0.0001	0.0001	
cis-2b	33823-63-1	direct	0.082	0.0007	
		sensitized			0.001
trans-2a	29444-92-6	direct	0.039	0.0053	
		sensitized			0.28

58b (endo) → **29**
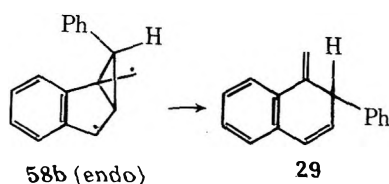
From endo reactant the bicycle process affords endo diradical, while the pivot process leads to exo diradical. The exo reactants would afford exo diradicals as **36a** and **58a** in a bicycle process but endo diradicals in a pivot mechanism. To the extent that steric factors are indeed involved, the bicycle mechanism would lead to an excess of Grob fragmentation starting with endo reactants, while the pivot mechanism would lead to an excess of fragmentation from the exo reactants.

Experimentally the same preference for the endo reactant to give toluene byproducts was indeed encountered with the total toluene product yield being greater from endo reactant, hence, signifying that this is a general trend. More dramatically, in the case of the benzo analogues, the Grob fragmentation became the predominant reaction course for the endo reactants. This predominance may arise because of greater localization of the two odd electrons as a result of fusion of the benzo ring in place of a double bond.

One point of interest is the formation of the minor reaction products in the photolysis of endo-diphenyl diene **5b**. In the case of the minor spiro diene **4a**, there are two possibilities. Note Schemes V and VII. The first possibility is that this product arises from clockwise bicycling around the five-ring (**35–37–38–39–4a** in Scheme V). It would make sense that only the endo isomer might undergo such a process, since in the exo isomer, two (bulky) phenyl groups would have to pass one another in such a mechanism. The exo isomer rearranges with no competing minor stereochemical course. The difficulty with this mechanism of clockwise bicycling is that it passes through species **38** (note Scheme V) which, in the absence of ad hoc specifications, should be the excited state of *trans*-2-methylene-5,6-diphenylbicyclo[3.1.0]hex-3-ene (**2a**). The singlet energy (115 kcal/mol) of this species is higher than that of reactant **5b** (94 kcal/mol) which has an added phenyl group at the end of a butadiene moiety. Thus any mechanism passing through this excited state (i.e., **38**) is energetically unreasonable. If **38** were ground state at this point in the mechanism, it would not proceed further, and no *trans*-2-methylene-5,6-diphenylbicyclo[3.1.0]hex-3-ene (**2a**) was observed in our studies. The second and more reasonable possibility is a counterclockwise overshoot plus backup mechanism (**35–36–39–42** in Scheme V or **48** in Scheme VII).

Another point of interest is the complete reaction stereospecificity for the benzo aryl bicyclic olefins **6** and **7** contrasted with the incomplete stereospecificity of the diphenyl bicyclic diene **5**. Reference to the structures and mechanisms in Scheme V written for the diphenyl bicyclic diene **5** reveals that utilization of either the clockwise bicycle mechanism or the counterclockwise overshoot plus backup leads to disruption of benzo aromaticity.[21] Note, for example, structures such as

(8)

clockwise mechanism **49** **50** counterclockwise overshoot path **51**
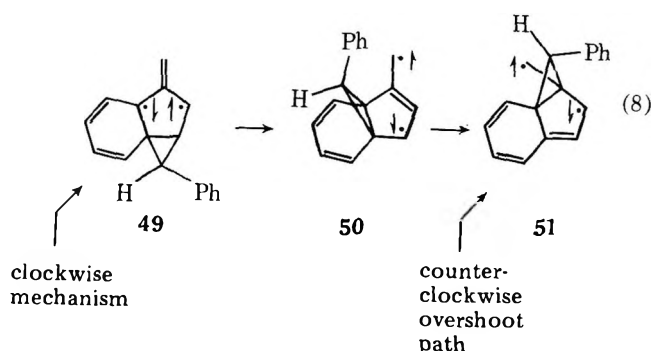
49, 50, and **51.** This leaves counterclockwise bicycling without overshoot as the preferred reaction pathway in this case.

Significance of Quantum Efficiencies and Excited Singlet Rates. To begin our discussion, we note that there is a strikingly small spread of reaction efficiencies of the various methylenebicyclic[3.1.0] systems studied (note Scheme IV and Table I, if one includes the total product distribution. Reference to our previous studies[3] (note Table III) reveals that the 2-methylene-6,6-dimethylbicyclo[3.1.0]hex-3-ene (**1**) and the 2-methylene-5,6-diphenylbicyclo[3.1.0]hex-3-enes (**2a** and **2b**) react with similar order of magnitude efficiencies. Thus all quantum yields of disappearance range from 0.04 to 0.13.

Along similar lines, we note (see Table II and Scheme IV) a remarkably small spread in the excited-state rate constants.

This suggests relatively little stabilization by the aryl groups present, whether on the migrating carbenoid carbon or substituted on the remainder of the system. Discussion of this point is deferred for consideration of the reaction electronics.

Additionally, a major conclusion which derives from our observations is that an intriguing alternative mechanism considered by Hamer and Stubbs[13a] can be ruled out. Applied to the benzo cases presently studied the mechanism predicts loss of aromaticity of the benzo ring; this is shown in eq 9.

6b

Analogy

Known (ref 13g)

(9)

20b
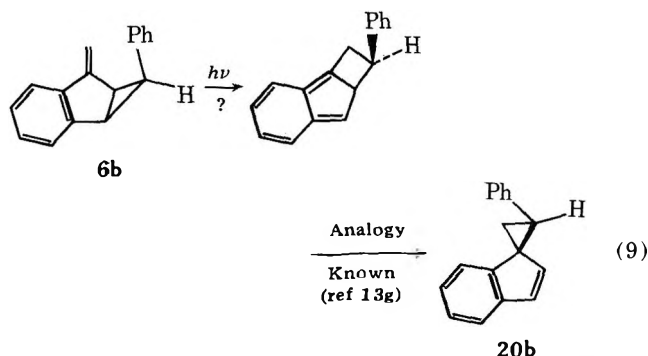
Thus, one would expect a major inhibition of the reaction efficiency and rate for the benzo analogues, and this is not observed.

Scheme VIII. Mechanism of Stereoisomerization of Triplet Bicyclic Diene
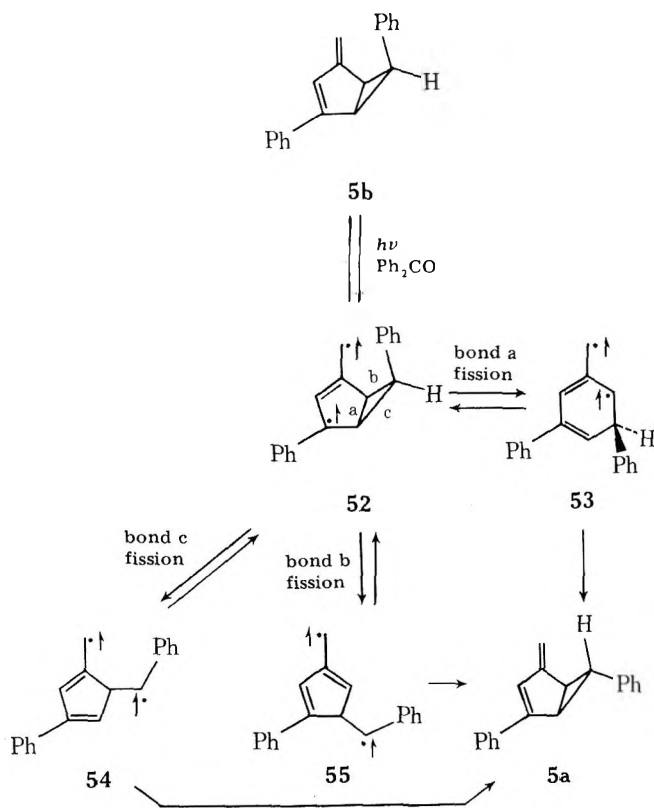
Reaction Multiplicity. Since the slither, or bicycle, rearrangement proceeds on direct irradiation but not on sensitized photolysis, this rearrangement can be seen to be a singlet process. Conversely, endo–exo isomerization of the bicyclic and benzo bicyclic olefins occurs only on sensitization, where the triplet is generated independently. This signifies that the stereoisomerization process is preferred by the triplet, but unfavorable from the singlet.

For the triplet stereoisomerization three possible bonds may be involved—a, b, or c. This is illustrated in Scheme VIII for the case of diphenyl bicyclic diene **5**; the cases of benzo bicyclic olefins **6** and **7** are parallel. In each case, after three-ring fission opening, free rotation and reclosure affords the observed stereoisomer. While there is no experimental evidence in this case, in the example of *cis*- and *trans*-5,6-diphenylbicyclo[3.1.0]hexan-2-one triplets[22] it is an out of plane bond (here b or c) which is opened in preference as a consequence of better overlap with the π system.

The preference of the triplet for this bond fission and stereoisomerization and its reluctance to undergo the bicycle reaction is discussed subsequently in connection with our MO treatment of the reactions. However, we note for the time being that there is a tendency for hydrocarbon triplets to undergo such bond fission as has been observed in the stereoisomerization of *cis*- and *trans*-4,5-diphenylbicyclo[3.1.0]-hex-2-enes,[23] since triplets can minimize energy more readily than excited singlets by such bond fission[23,24] to afford diradicals.[25] Conversely, concerted processes such as the bicycle or slither rearrangement tend to prefer the S₁ state as noted earlier.[23,24]

Theoretical

The Concept of Electronic Excitation Distribution; The ΔP Matrix and Its Variants. An index which we have found exceptionally intriguing and useful is ΔP_{rt} representing the change in bond order between atoms r and t on electronic excitation.[26a] Such an element can be derived as a difference in ground- and excited-state bond orders obtained from so-

phisticated (e.g.) SCF–CI calculations or, in a simpler SCF or Hückel approximation, just as a difference in bond orders of two MO's such as k and l, where k is the MO losing the electron and l is the MO receiving it on electronic excitation. The ΔP matrix is a convenient way of storing these elements; the element in row r and column t gives the change in bond order between atomic or hybrid orbitals r and t on excitation.

Thus, certain of the elements will be negative, indicating that on excitation the molecule has become more antibonding at these sites. Other elements will be positive, indicating that the sets of orbitals corresponding to the indices r and t have become more bonding in the excited state relative to the ground state. Still other elements will be zero or nearly zero, indicating that excitation has not perturbed the wave function at these molecular sites.

Hence it is possible to point to portions of the molecule where electronic excitation has had little or no effect and to note other portions of the molecule where the excitation energy is heavily concentrated, as evidenced by large changes in bond orders. Similarly, one can use the diagonal elements of the ΔP matrix which represent changes in electron densities at atoms resulting from electronic excitation.

As an example, one might envisage a molecule containing a 1-phenylbutadiene moiety and a separated phenyl chromophore. Inspection of the ΔP matrix shows that the elements corresponding to overlap of orbitals of the isolated benzene ring are zero, while those of the phenylbutadiene moiety are nonzero. This fits intuitive expectation that only the lower energy phenylbutadiene moiety will be excited in (e.g.) S₁. If saturated portions of the molecule were included, as in an extended Hückel or CNDO calculation, these portions would be found to be minimally affected by excitation.

Bond orders are related to energy contributions, but to obtain these where different hybridizations are encountered it is convenient to multiply each bond order term by $[H_{rt} + F_{rt}]$. (H_{rt} and F_{rt} are the matrix elements between orbitals r and t using one-electron and SCF energy operators.[26b]) This corrects for changes in S character and overlap. The resulting terms will have the reverse sign of the ΔP_{rt} matrix elements and are termed $\Delta E'_{rt}$, where $\Delta E'_{rt} = \Delta P_{rt}[H_{rt} + F_{rt}]$. The $\Delta E'_{rt}$ terms can be construed to be local contributions to the total electronic excitation energy. Contributions due to nuclear–nuclear repulsion are neglected for convenience, and for simplicity a ground-state $[H_{rt} + F_{rt}]$ is used, since we use the matrix for only semiquantitative purposes.

Thus, the use of the ΔP and ΔE' matrices involves inspection of these to note where there are large positive or negative elements and where there are zero or nearly zero elements. Small elements tell us that these local bonds are not appreciably excited independent of which type matrix we use. This leads us to the concept of local degeneracies, that is, sites of the molecule where the ground and excited states (or, more naively, highest bonding and lowest antibonding MO's) have equal energy and bond order contributions. However, it is important to note that while a negative ΔP_{rt} matrix element signifies a local increase in antibonding, the corresponding $\Delta E'_{rt}$ matrix element will be positive and signifies an increase in local electronic bond energy (i.e., for the bonding between orbitals r and t). Similarly, where a positive ΔP_{rt} occurs and thus indicates an increase in bonding between orbitals r and t on excitation, a negative $\Delta E'_{rt}$ element will result and will indicate an energy lowering (i.e., stabilization) resulting from overlap r–t.

The preceding thus describes an approach to defining the effect of electronic excitation on bonding at different sites around the molecule and also the partition of the excitation energy. Applications of the method to the systems at hand are presented below.

Migration and Redistribution of Electronic Excitation

during Reaction. Once one has developed a method for discussion of the distribution of electronic excitation in photochemical reactants, the inviting possibility suggests itself that one can follow the redistribution of this excitation as the excited-state molecule traverses the reaction coordinate. While in most photochemical reactants one generally can identify classical chromophores where excitation is likely to be concentrated, this is not invariably the case in a reacting species where bonds are in the process of being formed and broken. Additionally, there is the question whether groups which are viewed merely as substituents, such as phenyl and other aryl moieties, remain ground state in character as the reaction progresses. This should vary from case to case, and the method at hand allows one to follow the ΔP and $\Delta E'$ matrices along the reaction coordinate. Finally, one might inquire whether there is a relationship between the distribution of the local energy contributions (i.e., the $\Delta E'_{rt}$ matrix elements, or alternatively the ΔP_{r_z} matrix elements) and the reaction course.

The approach of following migration of electronic excitation during reaction is applied to the photochemistry of the present study. This application is postponed in order to allow complete presentation of the theoretical concepts.

Local Degeneracies, Squelching the ΔP's, Probing for the Ground-State Surface by Molecular Distortion, and Conversion of Electronic into Vibrational Energy. With the concept of the two matrices indicating which portions of a molecule are endowed with electronic excitation and to what extent, the question arises whether we can find molecular changes (e.g., bond stretching, twisting, etc.) which are capable of converting electronically excited sites of the molecule into unexcited sites. This is equivalent to effecting local degeneracies. Dissipation of local excitation and enforcing a local degeneracy can be effected by squelching the ΔP_{rt} or $\Delta E'_{rt}$ matrix element corresponding to that portion of the molecule.

If a ΔP_{rt} element is negative (i.e., the corresponding $\Delta E'_{rt}$ element is positive), this local excitation can be reduced by diminishing the overlap corresponding to the excited bond. We might consider stretching the bond, or alternatively, twisting it. If the ΔP_{rt} element is positive (and $\Delta E'_{rt}$ is negative), then we need to compress the bond and increase the overlap.[27]

By such molecular distortions we are, in effect, converting electronic excitation into vibrational energy. In some cases this corresponds to converting π system electronic excitation into σ bond vibrational energy.

Thus we have a mechanism for dissipating electronic energy into vibrational energy by local distortions.[28] The very rapid rate of vibrational energy equilibration postulated by the RRKM theory[29] suggests that one or two such distortions can dissipate energy subsequently to all available modes of vibration of the molecule. Thus a local leak of electronic excitation should be enough.

Distortion along one geometric coordinate leads to diminished electronic excitation and thus an approach of ground and electronically excited-state potential energy surfaces. The near degeneracy, however, is at a geometry corresponding to an upper vibrational state of the molecular ground state. For a photochemical reaction involving a very extended reaction coordinate, corresponding to a complex series of molecular reorganizations, our ΔP_{rt} will predict only a short distance along this coordinate and successive species must be treated in the same way.

Applications to the Present Case. As a beginning, to determine what electronic effects were controlling the bicycle reaction, we carried out SCF–CI calculations. At the SCF level it was possible to inspect the MO eigenfunctions for qualitative understanding; and, with configuration interaction one
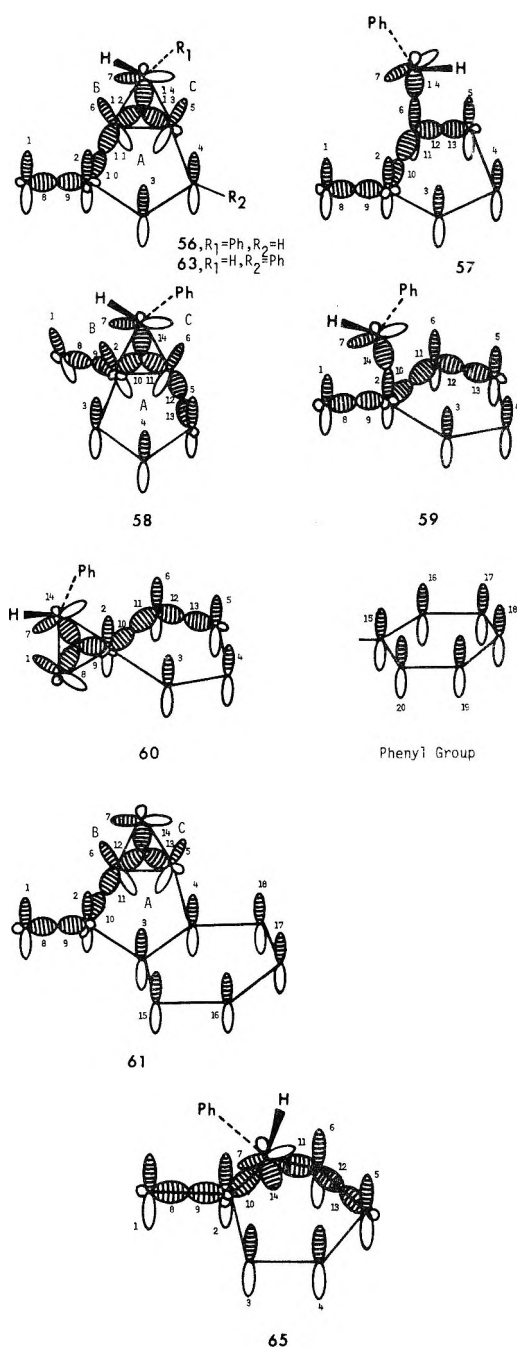
Figure 2. Basis sets for SCF–CI calculations.

could be more certain which excitations were involved. Overall bond orders and energies were derived from the total calculations, which included both singly and doubly excited configurations. For details note the section on Calculations. For the basis sets utilized note Figure 2. Our calculations were done on starting bicyclic diene **56** with one phenyl group at carbon-6 as a most appropriate model. Calculations were also carried out on the corresponding spiro product **60**, on the cyclopropyldicarbinyl diradical intermediate **58** (i.e., exo isomer of **36** without the C-4 phenyl group), and on the two 1,3-diradicals **57** and **59** (note also Figure 3). Also calculations were carried out on the benzo analogue, however, without the C-6 phenyl group (i.e., on **61**); the biradical **62**, derived from one bicycle step, was studied. Finally, the bicyclic diene **63**, having a phenyl group on the diene system, and the derived 1,4-biradical **64** (one bicycle step) were investigated. The basis set numbering for systems **56–60** are depicted explicitly in Figure 2. Similar numbering was used for **61–64** with the benzo basis orbitals indicated in Figure 2.

Table IV. Distribution of Electronic Excitation in Bicyclic Olefins 56, 61, and 63

phenyl bicyclic diene 56[a]			benzo bicyclic olefin 61[b]			phenyl bicyclic diene 63[c]		
bond r,t	ΔP_{rt}	$\Delta E'_{rt}$	bond r,t	ΔP_{rt}	$\Delta E'_{rt}$	bond r,t	ΔP_{rt}	$\Delta E'_{rt}$
1,2	-0.2620	2.3052	1,2	-0.1754	1.5487	1,2	-0.2401	2.1096
2,3	0.1624	-1.0808	2,3	0.1150	-0.7603	2,3	0.1950	-1.3076
2,6	0.0856	-0.0399	2,6	0.0310	-0.1041	2,6	0.0297	-0.0998
3,4	-0.2382	2.0939	3,4	-0.1103	0.7794	3,4	-0.3307	2.8506
4,5	0.1186	-0.4153	4,5	0.0840	-0.2848	4,5	0.0500	-0.1721
2,12	0.0313	-0.0790	2,12	0.0086	-0.0217	2,12	0.0108	-0.0271
4,13	0.0454	-0.1164	4,13	0.0182	-0.0498	4,13	0.0165	-0.0419
7,15	0.1281	-0.7178	3,15	-0.1184	0.8400	4,15	0.1893	-1.0881
15,16	-0.0969	0.6932	15,16	-0.1720	1.2520	15,16	-0.1234	0.8788
16,17	0.0390	-0.2839	16,17	-0.0500	0.3617	16,17	0.0355	-0.2588
17,18	-0.0462	0.3344	17,18	-0.0840	0.6090	17,18	-0.0595	0.4303
18,19	-0.0581	0.4213	4,18	-0.1850	1.3385	18,19	-0.0670	0.4857
19,20	0.0414	-0.3008				19,20	0.0406	-0.2952
15,20	-0.0869	0.6227	5,6	-0.0254	0.1694	15,20	-0.1203	0.8582
			5,12	-0.0047	0.0211			
5,6	-0.0234	0.1543	6,13	0.0024	-0.0108	5,6	-0.0195	0.1300
5,12	-0.0041	0.0183	12,13	0.0001	-0.0019	5,12	-0.0010	0.0045
6,13	0.0020	-0.0090				6,13	0.006	-0.0027
12,13	0.0003	-0.0057	6,7	-0.0186	0.1236	12,13	-0.0011	0.0210
			6,14	-0.0046	0.0205			
6,7	-0.0880	0.5834	7,12	-0.0122	0.0544	6,7	-0.0253	0.1680
6,14	0.0003	-0.0013	12,14	0.0018	-0.0344	6,14	-0.0028	0.0125
7,12	-0.0355	0.1577				7,12	-0.0089	0.0397
12,14	0.0024	-0.0457	5,7	-0.0433	0.2874	12,14	0.0013	-0.0248
			5,14	-0.0139	0.0620			
5,7	-0.0930	0.6044	7,13	-0.0100	0.0456	5,7	-0.0278	0.1842
5,14	-0.0095	0.0416	13,14	-0.0026	0.0497	5,14	-0.0063	0.0281
7,13	-0.0357	0.1589				7,13	-0.0091	0.0406
13,14	-0.0014	0.0267				13,14	-0.0002	0.0038

[a] Registry no.: 66374-29-6. [b] Registry no.: 65680-45-7. [c] Registry no.: 66374-30-9.

Excitation Localization in the Reactant Excited States. The first application of the ideas expressed above was determination of the distribution of electronic excitation in the reactant bicyclic diene. In view of the size of the system of interest (i.e., diphenyl bicyclic diene 5), two slightly truncated models were used. These were monophenyl-substituted bicyclic dienes 56 and 63. Selected ΔP_{rt} matrix elements for these two excited singlets are given in Table IV.

It is seen that appreciable ΔP_{rt} matrix elements are found mainly for butadiene and phenylbutadiene portions of the molecule. This corresponds to one's intuitive feeling that low-energy chromophores are selectively excited. Thus, for example, the C-6 phenyl group is only slightly perturbed on electronic excitation.

A lesser but real amount of excitation is found in the three-ring bond orbital system and also the overlapped pair 4–5. This can be seen independent of whether we look at ΔP_{rt} or $\Delta E'_{rt}$ matrix elements.

The case of the benzo bicyclic olefin 61 (note Table IV again) has appreciable elements corresponding mainly to the styryl moiety.

Diffusion of Electronic Excitation during Reaction. Utilization of ΔP_{rt} and $\Delta E'_{rt}$ Values in Following Flow and Reaction Course. Turning now to the excited-state rearrangements, we note that as the reaction proceeds, electronic excitation energy no longer is concentrated in the original diene moiety or in any single portion of the molecule. Thus, in species 57, 58, and 59 electronic excitation has diffused throughout the system. This can be seen in Table V where the appreciable ΔP_{rt} elements are spread throughout the molecular system. The same general conclusion is reached using the $\Delta E'_{rt}$ elements except that here some larger concentrations of excitation energy are found. Interestingly, the C-6 phenyl group is seen to be only slightly excited from inspection of the $\Delta E'_{rt}$ elements. Another point of interest concerns the bond

order and energy elements corresponding to 5–7 vs. 2–7 overlap in species 57. ΔP_{57} is quite negative in contrast to ΔP_{27}, which is slightly positive. A negative ΔP_{rt} suggests that the bonding should be weakened, while a positive ΔP_{rt} indicates that strengthening the bond should help the reaction. This is precisely what happens as the molecule proceeds bicycling along the reaction coordinate at this point. The corresponding argument, based on the $\Delta E'$ matrix, shows that $\Delta E'_{57}$ is very positive, while $\Delta E'_{27}$ is slightly negative. Thus it is the "high energy bond" which is selectively broken in proceeding onward to product.

These results fit the generalization that overlaps corresponding to negative ΔP_{rt} elements or positive $\Delta E'_{rt}$ elements need to be diminished to obtain photochemical reaction, while overlaps corresponding to positive ΔP_{rt} elements or negative $\Delta E'_{rt}$ elements need to be increased for reaction. If such overlap changes lead toward a photochemical reaction product, then successful photochemistry is expected. If the overlap changes do not lead toward a product, or lead away from a possible product, then the reaction is forbidden.

Interestingly, ΔP_{57} diminishes in absolute value by the time species 58 is reached. Another point of interest is that inspection of the $\Delta E'$ matrix shows that the original butadiene excitation is still present, although considerably diminished. Also, the ΔP_{rt} and $\Delta E'_{rt}$ elements tend to diminish as the 1,4-cyclopropyldicarbinyl diradical 58 is approached.

Still another point is seen in the matrices corresponding to the initial excited state 56. For each of the three cyclopropane bonds, a, b, and c, four overlaps are involved. Due to different overlaps and S character it would not be permissible to sum bond order contributions; however, summing the $\Delta E'_{rt}$ elements is reasonable. Reference to Table IV reveals that the sum of energy contributions (i.e., the $\Delta E'_{rt}$'s) for the in-plane bond a is lowest of all, and we do not expect this bond to be stretched or broken. In fact, no 3,5-diphenyltoluene product

Table V. Redistribution of Electronic Excitation along the Reaction Coordinate

bond r,t	56		bond r,t	57[a]		bond r,t	58[b]		bond r,t	59[c]	bond r,t	60[d]
	ΔP_{rt}	$\Delta E'_{rt}$		ΔP_{rt}	$\Delta E'_{rt}$		ΔP_{rt}	$\Delta E'_{rt}$		ΔP_{rt}		ΔP_{rt}
1,2	−0.2620	2.3052	1,2	−0.0976	0.8173	1,2	−0.116	0.8271	1,2	0.0101	2,3	0.0615
2,3	0.1624	−1.0808	2,3	0.0681	−0.4666	2,3	0.0209	−0.0733	1,7	−0.3671	2,6	0.0658
2,6	0.0856	−0.0399	2,6	0.0086	−0.0535	3,4	−0.0063	0.0502	1,14	0.0002	3,4	−0.3169
3,4	−0.2382	2.0939	2,7	0.0114	−0.0531	3,10	−0.0076	0.0212	2,3	−0.0257	4,5	0.2147
4,5	0.1186	−0.4153	2,14	0.0213	−0.0691	4,5	0.0083	−0.0654	2,6	0.0196	5,6	−0.3190
2,12	0.0313	−0.0790	3,4	−0.1393	1.1678	5,6	−0.0866	0.3737	3,4	−0.0121		
4,13	0.0454	−0.1164	4,5	0.1125	−0.8119	5,11	0.0157	−0.0408	4,5	−0.1430		
			5,6	−0.0119	0.0799				5,6	−0.0670	1,2	−0.0702
5,6	−0.0234	0.1543	5,7	−0.2735	1.6038	2,6	0.0506	−0.3067	6,7	0.0047	1,9	0.0113
5,12	−0.0041	0.0183	5,14	0.0469	−0.1460	2,11	0.0167	−0.0692	6,14	0.0163	2,8	−0.0116
6,13	0.0020	−0.0090	6,7	0.0151	0.0000	6,10	0.0021	−0.0095	7,8	−0.0042	8,9	0.0015
12,13	0.0003	−0.0057	6,14	−0.0011	0.0157	10,11	0.0012	−0.0229	7,9	−0.0511		
			7,10	−0.0138	0.0550				7,10	0.0407	1,7	−0.1340
6,7	−0.0880	0.5834	7,11	0.0360	−0.1179	2,7	−0.0324	0.1899	7,11	0.0094	1,14	0.0378
6,14	0.0003	−0.0013	7,12	−0.0714	0.2803	2,14	0.0188	0.0780			7,8	0.0244
7,12	−0.0355	0.1577	7,13	−0.0041	0.0163	7,10	0.0019	0.0083			8,14	−0.0069
12,14	0.0024	−0.0459				10,14	−0.0009	0.0172				
5,7	−0.0930	0.6044				6,7	−0.0245	0.1593			2,7	−0.0594
5,14	−0.0095	0.0416				6,14	0.0343	−0.1440			2,14	−0.0166
7,13	−0.0357	0.1589				7,11	0.0189	−0.0794			7,9	0.0084
13,14	−0.0014	0.0267				11,14	−0.0122	0.2345			9,14	−0.0026

[a] Registry no.: 66374-31-0. [b] Registry no.: 66374-32-1. [c] Registry no.: 66374-33-2. [d] Registry no.: 13189-30-5.

was encountered. The second bond, bond b (the one closer to the *exo*-methylene moiety), is seen in Table IV to have less excitation energy than the more remote bond c. The consequent expectation of selective fission of bond c is realized in our bicycle mechanism (vide supra). One expects the rear wheel of the bicycle to have more excitation energy than the forward wheel for forward motion.

It is noted that in species 58 the reverse is true, and that bond c has less excitation energy than bond b. While in the excited state of a reactant, relative bond excitation energies and excitation bond orders should lead the excited state forward; for such an intermediate species as 58 the significance of a tendency to move forward vs. backwards on the hypersurface is less meaningful, since few reactions have unit efficiency and reversibility at intermediate stages of the reaction is possible. On the other hand, other information suggests that at this point along the reaction coordinate we are no longer dealing with the excited state and hence the excitation properties are not meaningful.

Finally, we note that in the excited singlet of spiro product 60 excitation is heavily concentrated in the traditional chromophore, this being the diene moiety.

SCF MO Correlation Diagrams for the Bicycle Reaction and State Reaction Energetics. MO correlation diagrams were derived from the SCF portion of the calculations. Correlations were checked, not only for the species described above, but also by interpolation between these. The correlations of interest for the bicycle rearrangement of 2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene, as a suitable but reasonably sized model, are depicted in Figure 3a. The qualitative nature of these correlations was found to be the same for the benzo analogue lacking the C-6 phenyl group. Hence it is reasonable to take the correlations as characteristic of the basic rearrangement.

It was of interest to compare the rearrangement in a dihydro system lacking the endocyclic π bond of the reactant. This is shown in Figure 3b. This corresponds to conversion of one vinylcyclopropane to an isomeric vinylcyclopropane by way of an intermediate cyclopropyldicarbinyl diradical. Thus the first step is the reverse of the last stage of a di-π-methane rearrangement and the last step is the same as the corresponding part of the di-π-methane rearrangement mechanism.[30] Ex-
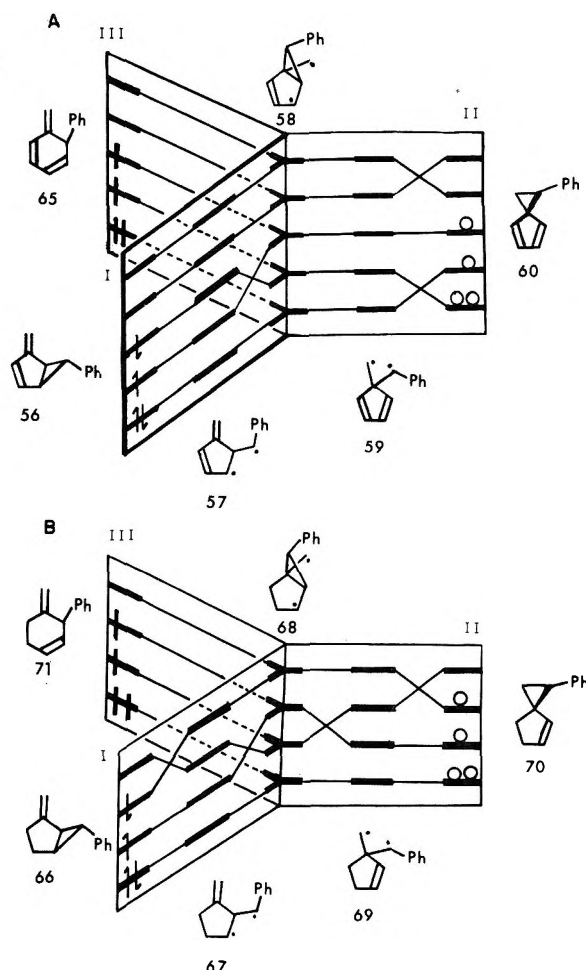
Figure 3. (a) SCF MO correlation diagram for the bicycle rearrangement. (b) SCF MO correlation diagram for the potential bicycle rearrangement of 2-methylene-6-phenylbicyclo[3.1.0]hexane.

perimentally, it is known from our earlier efforts[14] that such simple vinylcyclopropanes give different photochemistry (for example, note the vinylcyclopropane in eq 7). Since the alternative photochemistry is of efficiency comparable to the
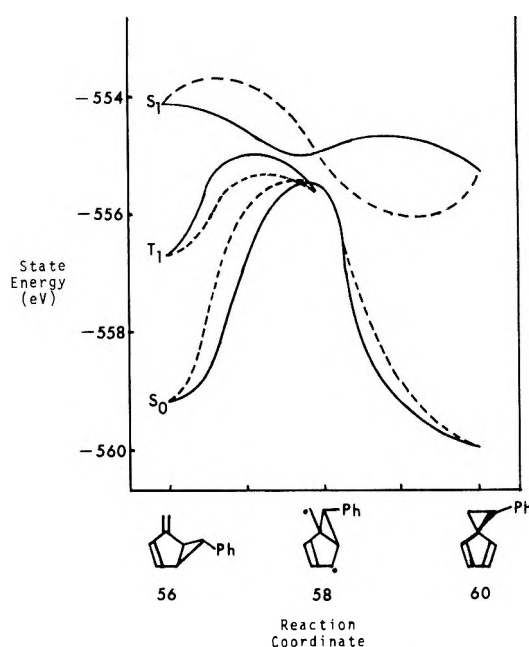
Figure 4. Rearrangement energetics for S_0 and S_1: pivot mechanism (- - -), slither or bicycle (—). Triplet surface available only between species **56** and **58**.

bicycle process, the absence of bicycling cannot be attributed to its being overshadowed by more efficient processes; and bicycling must be inherently unfavorable.

Inspection of Figure 3a, starting with bicyclic diene reactant **56**, reveals a photochemically allowed process in which loss of excitation occurs just prior to reaching the cyclopropyldicarbinyl diradical **58**. It is also seen that conversion of the ground-state configuration of **58** to triene **65** and spiroheptadiene **60** is ground-state allowed, while any reversion to bicyclic diene is ground-state forbidden.

Also of interest is consideration of the excited state of the bicycle product. We see that the excited state of spiroheptadiene **60** has only a forbidden pathway back to bicyclic diene **56** and triene **65**. This fits the experiment in which only cis-trans isomerization was observed from the spiroheptadiene products.

Now we turn to the matter of the role of the second double bond in the bicycle reaction of the 2-methylenebicyclo[3.1.0] systems, especially in view of the known[14] lack of bicycling experimentally. Inspection of the correlation diagram for the dihydro system in Figure 3b shows that two of the three bridges (i.e., I and II) do differ from those of the bicyclic diene correlation diagram as shown in Figure 3a. The conversion of vinylcyclopropane **66** to either of the potential products, vinylcyclopropane **70** or di-π-methane type diene **71**, is excited-state forbidden. In each case an upper excited state is generated along the reaction coordinate. This is related to the lack of general reversibility of the di-π-methane rearrangement.[30] Conversely, starting with the di-π-methane system **71** an excited state can proceed in allowed fashion to the vinylcyclopropane products **66** and **70**.

Finally we consider the overall state energetics along the reaction coordinate using our SCF–CI calculations. The results are depicted in Figure 4 and include both bicycle and pivot processes. Interestingly, the pivot process reveals an early barrier before the cyclopropyldicarbinyl diradical stage is reached. Conversely, the bicycle process is exothermic in S_1 and finally reaches a point along the reaction coordinate where a near degeneracy with S_0 is obtained. This agrees with our $\Delta E'$ and ΔP matrix treatment.

A final interesting aspect deals with the T_1 potential energy surface derived from our SCF–CI calculations. The results are

included in Figure 4. This shows that the bicycle reaction of the triplet is appreciably endothermic in its early stages, while opening of bond C with pivoting is much less so. Also, the surface for opening with pivoting intersects the S_0 pivot surface, thus providing a facile route for the observed stereoisomerization.

Conclusion

The bicycle, or slither, rearrangement has thus far[31] proven relatively specific to the systems studied. Nevertheless, the reaction has proven itself unusually general in these systems and promises considerable synthetic utility. With regard to the theoretical treatment of the reaction, we note that the concept of localization and delocalization of electronic excitation, along with the ΔP and $\Delta E'$ matrix treatment, needs to be tested further, but is proving of considerable generality in our experience.

Experimental Section[32]

Methyl (*E,E*)-3,5-Diphenyl-2,4-pentadienoate. The corresponding ethyl ester has been described,[33] without experimental detail, as being prepared by a procedure analogous to that detailed as follows. To a solution of 5.00 g (27.5 mmol) of trimethyl phosphonoacetate in 100 mL of 1,2-dimethoxyethane was added 18.3 mL of 1.5 M *n*-butyllithium (27.5 mmol) dropwise. After stirring 15 min, 5.73 g (27.5 mmol) of *trans*-chalcone in 75 mL of 1,2-dimethoxyethane was added dropwise. The mixture was then refluxed under nitrogen for 20 h, cooled, poured into water, and ether extracted. The extracts were dried and concentrated in vacuo to yield 6.81 g of yellow oil which was chromatographed on a 3 × 130 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 2% ether in hexane. Elution in 250-mL fractions gave: fractions 1–12, nil; fractions 13–16, 4.01 g (55%) of methyl (*E,E*)-3,5-diphenyl-2,4-pentadienoate as a colorless oil.

The spectral data were: IR (thin film) 3 24, 3.25, 3.30, 3.38, 5.86, 6.20, 6.30, 6.37, 6.71, 6.90, 6.98, 7.32, 7.66, 7.76, 7.95, 8.28, 8.40, 8.59, 9.33, 9.90, 10.26, 10.99, 11.63, 12.95, 13.26, 14.28, 14.50 μm; NMR (CDCl$_3$) τ 1.46 (d, 1 H, J = 16 Hz, γ-vinyl), 2.46–2.88 (m, 10 H, arom), 3.01 (d, 1 H, J = 16 Hz, δ-vinyl), 4.21 (s, 1 H, vinyl), 6.26 (s, 3 H, –OCH$_3$).

Anal. Calcd for C$_{18}$H$_{16}$O$_2$: C, 81.79; H, 6.10. Found: C, 81.72; H, 6.33.

(*E,E*)-3,5-Diphenyl-2,4-pentadienoic Acid. A mixture of 3.50 g (13.2 mmol) of methyl (*E,E*)-3,5-diphenyl-2,4-pentadienoate and 10.00 g (178 mmol) of potassium hydroxide in 125 mL of methanol was refluxed for 4 h, cooled, and poured into water. The solution was acidified to methyl orange with 10% hydrochloric acid and ether extracted. The extracts were water washed, dried, and concentrated in vacuo to yield 3.34 g (101%) of crystalline crude acid, mp 126–138 °C. Recrystallization from ethanol gave 3.16 g (96%) of colorless crystals of (*E,E*)-3,5-diphenyl-2,4-pentadienoic acid, mp 140–142 °C (lit.[33] mp 142–144 °C).

The spectral data were: IR (KBr) 3.27, 3.42, 3.62, 3.72, 3.85, 5.99, 6.20, 6.33, 6.39, 6.71, 6.90, 7.09, 7.75, 7.93, 8.20, 9.70, 10.19, 10.25, 10.87, 11.56, 12.99, 13.30, 14.28, 14.60 μm; NMR (acetone-d_6) τ 1.2 (s, 1 H, –CO$_2$H), 1.39 (d, 1 H, J = 17 Hz, γ-vinyl), 2.30–2.80 (m, 10 H, arom), 3.27 (d, 1 H, J = 17 Hz, δ-vinyl), 4.05 (s, 1 H, vinyl).

Anal. Calcd for C$_{17}$H$_{14}$O$_2$: C, 81.58; H, 5.64. Found: C, 81.61; H, 5.69.

(*E,E*)-1-Diazo-4,6-diphenyl-3,5-hexadien-2-one. Using the general procedure for the *E,Z* isomer,[32b] the acid chloride was prepared from 2.16 g (8.63 mmol) of (*E,E*)-3,5-diphenyl-2,4-pentadienoic acid and 1.43 g (12.0 mmol) of thionyl chloride in 30 mL of anhydrous benzene. Treatment of the acid chloride in 10 mL of anhydrous benzene with diazomethane prepared from 4.68 g (13.1 mmol) of EXR-101 and 25 mL of 33% potassium hydroxide led to 1.72 g (72%) of (*E,E*)-1-diazo-4,6-diphenyl-3,5-hexadien-2-one as a yellow oil isolated after chromatography.

The spectral data were: IR (thin film) 3.24, 3.25, 3.30, 3.44, 4.76, 5.51, 6.21, 6.37, 6.76, 6.90, 7.33, 7.46, 8.62, 8.76, 9.43, 9.71, 10.38, 13.33, 14.88 μm; NMR (CDCl$_3$) τ 1.28 (d, 1 H, J = 16 Hz, γ-vinyl), 2.40–2.80 (m, 10 H, arom), 3.32 (d, 1 H, J = 16 Hz, δ-vinyl), 4.12 (s, 1 H, vinyl), 4.60 (s, 1 H, –CN$_2$H); mass spectrum (calcd for C$_{18}$H$_{14}$N$_2$O – N$_2$, 246.104491) m/e 246.10354.

***exo*-4,6-Diphenylbicyclo[3.1.0]hex-3-en-2-one.** As in the general cyclization procedure[32b] described for the endo isomer, from 1.00 g of copper bronze, 100 mL of anhydrous benzene, and 1.60 g (5.83

mmol) of (E,E)-1-diazo-4,6-diphenyl-3,5-hexadien-2-one in 25 mL of benzene, there was obtained after chromatography and recrystallization from 95% ethanol 912 mg (63.6%) of colorless crystals, mp 136–137 °C.

The spectral data were: IR (KBr) 3.27, 3.30, 3.42, 5.93, 6.25, 6.32, 6.40, 6.70, 6.91, 7.41, 7.86, 8.47, 9.79, 10.10, 11.34, 11.47, 13.02, 13.16, 14.49 μm; NMR (CDCl₃) τ 2.30–3.00 (m, 10 H, arom), 4.00 (s, 1 H, vinyl), 6.98 (t, 1 H, J = 4 Hz, benzyl cyclopropyl), 7.30–7.48 (m, 2 H, cyclopropyl); mass spectrum (calcd for C₁₈H₁₄O, 246.104491) m/e 246.10305.

Anal. Calcd for C₁₈H₁₄O: C, 87.77; H, 5.73. Found: C, 87.80; H, 5.70.

exo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. To a stirred suspension of 2 33 g (6.52 mmol) of methyltriphenylphosphonium bromide in 75 mL of anhydrous ether under nitrogen was added 4.50 mL of 1.45 M n-butyllithium (6.52 mmol) in hexane. After stirring 15 min, 574 mg (2.33 mmol) of exo-4,6-diphenylbicyclo[3.1.0]hex-3-en-2-one in 30 mL of anhydrous ether was added dropwise. The mixture was stirred 2 h, poured into water, and ether extracted. The extracts were dried and concentrated in vacuo to yield 591 mg of residue which was chromatographed on a 2 × 40 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 5% ether in hexane. Elution in 100-mL fractions gave: fraction 1–2, nil; fractions 3–5, 551 mg (96%) of crystalline exo-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene, mp 96–98 °C. Recrystallization from 95% ethanol gave 506 mg (88%) of colorless crystals, mp 97–98 °C.

The spectral data were: IR (CHCl₃) 3.25, 3.27, 3.30, 3.33, 6.17, 6.25, 6.71, 6.92, 6.97, 7.46, 8.26, 8.50, 8.93, 9.34, 9.72, 11.43, 11.76, 14.53, 15.15 μm; NMR (CDCl₃) τ 2.36–2.56 (m, 2 H, o-vinyl arom), 2.60–3.00 (m, 8 H, arom), 3.73 (s, 1 H, vinyl), 4.91 (s, 2 H, exocyclic methylene), 7.20 (d of d, 1 H, J = 3, 6 Hz, cyclopropyl), 7.41 (d of d, 1 H, J = 3, 6 Hz, cyclopropyl), 8.90 (t, 1 H, J = 3 Hz, benzyl cyclopropyl); UV (95% EtOH) 231 nm (ε 23 500), 237 (ε 28 000), 303 (ε 22 000); mass spectrum (calcd for C₁₉H₁₆, 244.12520) m/e 244.12479.

Anal. Calcd for C₁₉H₁₆: C, 93.40; H, 6.60. Found: C, 93.38; H, 6.69.

Methyl (Z)-3,5-Diphenylpent-2-en-4-ynoate. This ester was prepared by the method of Wiley and Staples[5] from benzoylphenylacetylene[34] and methyl bromoacetate.

Methyl (E,Z)-3,5-Diphenyl-2,4-pentadienoate. A solution of 1.89 g (7.20 mmol) of methyl (Z)-3,5-diphenylpent-2-en-4-ynoate in 75 mL of methanol was stirred over 609 mg of 5% palladium on barium sulfate poisoned with 0.25 mL of synthetic quinoline under 1 atm of hydrogen. When 190 cm³ [7.62 mmol at 19 °C (730 Torr)] of hydrogen was consumed the mixture was filtered, poured into 5% hydrochloric acid, and extracted with ether. The ether extracts were washed with water, dried, and concentrated in vacuo to yield 1.86 g (98%) of methyl (E,Z)-3,5-diphenyl-2,4-pentadienoate as a colorless oil.

The spectral data were: IR (CHCl₃) 3.27, 3.31, 3.39, 5.85, 6.25, 6.30, 6.37, 6.71, 6.92, 6.99, 7.46, 7.84, 8.40, 8.64, 9.96, 11.52, 12.99, 14.43 μm; NMR (CDCl₃) τ 2.46–3.04 (m, 11 H, arom and vinyl), 3.15 (d, 1 H, J = 12 Hz, α-styryl), 3.76 (s, 1 H, vinyl), 6.28 (s, 3 H, CO₂CH₃); mass spectrum (calcd for C₁₈H₁₆O₂, 264.11503) m/e 264.11456.

Anal. Calcd for C₁₈H₁₆O₂: C, 81.79; H, 6.10. Found: C, 81.51; H, 5.94.

(E,Z)-3,5-Diphenyl-2,4-pentadienoic Acid. A mixture of 4.12 g (15.6 mmol) of methyl (E,Z)-3,5-diphenyl-2,4-pentadienoate and 5.00 g (89.0 mmol) of potassium hydroxide in 100 mL of methanol was refluxed for 2 h, cooled, and poured into water. The solution was acidified to methyl orange with 10% hydrochloric acid and ether extracted. The ether extracts were water washed, dried, and concentrated in vacuo to yield 3.83 g of crude crystalline acid, mp 131–140 °C. Recrystallization from methanol gave 3.56 g (91%) of (E,Z)-3,5-diphenyl-2,4-pentadienoic acid as colorless crystals, mp 145–147 °C.

The spectral data were: IR (CHCl₃) 3.27, 3.32, 3.76, 3.88, 5.97, 6.25, 6.31, 6.37, 6.71, 6.92, 7.07, 7.52, 7.81, 8.16, 8.35, 8.93, 9.30, 9.74, 10.00, 10.36, 10.93, 11.49, 11.90 μm; NMR (acetone-d₆) τ 2.32–3.04 (m, 11 H, arom and vinyl), 3.16 (d, 1 H, J = 12 Hz, α-styryl), 3.68 (s, 1 H, vinyl); mass spectrum (calcd for C₁₇H₁₄O₂, 250.09943) m/e 250.09873.

Anal. Calcd for C₁₇H₁₄O₂: C, 81.58; H, 5.64. Found: C, 81.70; H, 5.68.

(E,Z)-1-Diazo-4,6-diphenyl-3,5-hexadien-2-one. A mixture of 2.77 g (11.1 mmol) of (E,Z)-3,5-diphenylpentadienoic acid and 2.48 g (20.9 mmol) of thionyl chloride in 50 mL of anhydrous benzene was refluxed under nitrogen for 1.5 h, cooled, and concentrated in vacuo. The residue was dissolved in 10 mL of anhydrous benzene and added dropwise to excess distilled ethereal diazomethane prepared from 5.62 g (15.7 mmol) of EXR-101 (70% N,N'-dimethyl-N,N'-dinitroso-

terephthalamide in mineral oil) and 30 mL of 33% potassium hydroxide. After 1 h, the excess diazomethane was removed under a stream of nitrogen and the solution was concentrated in vacuo to yield 3.04 g of residue which was chromatographed on a 2.5 × 30 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in 10% ether in hexane and eluted with 20% ether in hexane. Rapid chromatography was possible and necessary. Elution in 250-mL fractions gave: fractions 1–4, nil; fractions 5–6, 655 mg of (E,E)-1-diazo-4,6-diphenyl-3,5-hexadien-2-one as determined by NMR; fraction 7, 206 mg of a ~1:1 mixture of (E,E)- and (E,Z)-1-diazo-4,6-diphenyl-3,5-hexadien-2-one as determined by NMR; fractions 8–10, 577 mg (19%) of (E,Z)-1-diazo-4,6-diphenyl-3,5-hexadien-2-one as a yellow oil which was pure as determined by NMR.

The spectral data were: IR (thin film) 3.27, 3.31, 4.81, 5.87, 6.10, 6.21, 6.41, 6.72, 6.92, 7.27, 8.76, 9.17, 9.30, 9.69, 13.05, 13.26, 13.50, 14.51 μm; NMR (CDCl₃) τ 2.40–3.05 (m, 11 H, arom and vinyl), 3.24 (d, 1 H, J = 12 Hz, vinyl), 4.16 (s, 1 H, vinyl), 4.42 (s, 1 H, –CHN₂); mass spectrum (calcd for C₁₈H₁₄N₂O − N₂, 246.10446) m/e 246.10245.

endo-4,6-Diphenylbicyclo[3.1.0]hex-3-en-2-one. To a stirred suspension of 500 mg of copper–bronze (LUCO, No. 16, 99.5% copper, Leo Uhlfelder Co., Mt. Vernon, N.Y.) in 25 mL of anhydrous benzene heated in a 60 °C bath was added dropwise 520 mg (1.90 mmol) of (E,Z)-1-diazo-4,6-diphenyl-3,5-hexadien-2-one in 10 mL of benzene. The mixture was refluxed under nitrogen for 1 h, cooled, filtered through Celite, and concentrated in vacuo to yield 535 mg of residue which was chromatographed on a 2.5 × 45 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 5% ether in hexane. Elution in 250-mL fractions gave: fractions 1–3, nil; fraction 4, 42 mg of unidentified oil; fraction 5, 102 mg of exo-4,6-diphenylbicyclo[3.1.0]hex-3-en-2-one as determined by NMR; fractions 6–7, 151 mg of endo-4,6-diphenylbicyclo[3.1.0]hex-3-en-2-one as a semisolid. Recrystallization from 95% ethanol gave 122 mg (26%) of pure product as colorless crystals, mp 151–153 °C.

The spectral data were: IR (KBr) 3.27, 3.30, 3.43, 5.92, 6.25, 6.32, 6.70, 6.88, 7.79, 8.43, 9.22, 9.79, 10.12, 11.50, 11.90, 13.26, 14.39 μm; NMR (CDCl₃) τ 2.44–3.05 (m, 10 H, arom), 3.82 (s, 1 H, vinyl), 6.84–7.18 (m, 2 H, cyclopropyl), 7.44 (dd, 1 H, J = 5, 8 Hz, benzyl cyclopropyl); mass spectrum (calcd for C₁₈H₁₄O, 246.10446) m/e 246.10366.

Anal. Calcd for C₁₈H₁₄O: C, 87.77; H, 5.73; Found: C, 87.91; H, 5.77.

endo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene.[32b] From 670 mg (1.88 mmol) of methyltriphenylphosphonium bromide in 40 mL of anhydrous ether under nitrogen, 1.30 mL of 1.45 M n-butyllithium (1.88 mmol), and 220 mg (0.893 mmol) of endo-4,6-diphenylbicyclo[3.1.0]hex-3-en-2-one in 15 mL of anhydrous ether chromatography gave 167 mg of crude endo-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene as a brown solid, mp 131–142 °C. Recrystallization from 95% ethanol gave 131 mg (60%) of pure product as colorless crystals, mp 153 °C.

The spectral data were: IR (CHCl₃) 3.25, 3.30, 3.32, 6.17, 6.25, 6.72, 6.91, 8.36, 9.32, 9.75, 11.46, 14.44, 15.15 μm; NMR (CDCl₃) τ 2.65–3.10 (m, 10 H, arom), 3.96 (s, 1 H, vinyl), 7.05 (d of d, 1 H, J = 6, 7.5 Hz, cyclopropyl), 7.25 (broad d of d, 1 H, J = 6, 8.5 Hz, cyclopropyl), 7.49 (d of d, 1 H, J = 7.5, 8.5 Hz, cyclopropyl); UV (95% EtOH) 224 nm (ε 21 400), 235 (ε 22 700), 298 (ε 19 500); mass spectrum (calcd for C₁₉H₁₆, 244.12520) m/e 244.12479.

Anal. Calcd for C₁₉H₁₆: C, 93.40; H, 6.60. Found: C, 93.46; H, 6.76.

(E)-2-Stilbenecarboxylic Acid. This compound was prepared according to the method of Booth and Turner[6] from 3-(phenylmethyl)-1(3H)-isobenzofuranone.[35]

(E)-3,4-Benzo-1-diazo-6-phenyl-3,5-hexadien-2-one. By the general procedure for diazo ketones described above,[32b] reaction of (E)-2-stilbenecarboxylic acid with 1.77 g (14.9 mmol) of thionyl chloride in 25 mL of anhydrous benzene, followed by treatment with distilled diazomethane from 9.36 g (26.2 mmol) of EXR-101 and 50 mL of 33% potassium hydroxide, afforded 2.47 g (83%) of (E)-3,4-benzo-1-diazo-6-phenyl-3,5-hexadien-2-one as a deep yellow oil which was pure by NMR analysis and used directly in the next preparation.

The spectral data were: IR (thin film) 3.22, 3.27, 4.78, 5.65, 6.25, 6.71, 6.78, 6.91, 7.43, 8.16, 8.26, 8.77, 9.90, 10.43, 11.43, 13.18, 13.53, 14.49, 14.92 μm; NMR (CDCl₃) τ 2.30–2.90 (m, 10 H, arom and vinyl), 3.04 (d, 1 H, J = 16 Hz, vinyl), 4.54 (s, 1 H, CHN₂); mass spectrum (cold inlet) (calcd for C₁₆H₁₂N₂O, 248.09496) m/e 248.09496.

exo-3,4-Benzo-6-phenylbicyclo[3.1.0]hex-3-en-2-one. Using the usual cyclization procedure,[32b] 2.00 g of copper–bronze in 60 mL of anhydrous benzene and 2.31 g (9.30 mmol) of (E)-3,4-benzo-1-diazo-6-phenyl-3,5-hexadien-2-one in 10 mL of benzene were reacted to afford, after chromatography and recrystallization from 95% eth-

anol, 1.37 g (67%) of *exo*-3,4-benzo-6-phenylbicyclo[3.1.0]hex-3-en-2-one as colorless crystals, mp 124–125 °C (lit.[36] mp 127–127.5 °C).

The spectral data were: IR (KBr) 3.27, 3.30, 3.42, 5.90, 6.25, 6.70, 6.82, 7.81, 8.05, 8.35, 8.77, 9.12, 9.98, 11.88, 11.98, 12.82, 13.16, 13.33, 14.39 μm; NMR (CDCl₃) τ 2.20–3.00 (m, 9 H, arom), 6.80 (d of d, 1 H, J = 3, 5 Hz, cyclopropyl), 7.22 (d of d, 1 H, J = 3, 5 Hz, α-carbonyl cyclopropyl), 7.44 (t, 1 H, J = 3 Hz, benzyl cyclopropyl); mass spectrum (calcd for $C_{16}H_{12}O$, 220.08865) m/e 220.08881.

Anal. Calcd for $C_{16}H_{12}O$: C, 87.24; H, 5.49. Found: C, 87.06; H, 5.53.

exo-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene. Using the general procedure above,[32b] 2.75 g (7.70 mmol) of methyltriphenylphosphonium bromide in 160 mL of anhydrous ether under nitrogen, 5.13 mL of 1.50 M *n*-butyllithium (7.70 mmol), and 849 mg (3.85 mmol) of *exo*-3,4-benzo-6-phenylbicyclo[3.1.0]hex-3-en-2-one in 25 mL anhydrous ether gave, after chromatography, 665 mg (79%) of desired olefin, mp 130–133 °C. Recrystallization from 95% ethanol gave 612 mg (73%) of *exo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene as colorless crystals, mp 135 °C.

The spectral data were: IR (KBr) 3.27, 3.32, 3.42, 6.25, 6.71, 6.90, 7.22, 8.33, 8.70, 9.35, 9.72, 11.07, 12.12, 13.25 μm; NMR (CDCl₃) τ 2.20–3.05 (m, 9 H, arom), 4.48 (s, 1 H, exocyclic methylene), 4.76 (s, 1 H, exocyclic methylene), 7.10 (d of d, 1 H, J = 3, 6 Hz, cyclopropyl), 7.20–7.40 (m, 1 H, cyclopropyl), 8.16 (t, 1 H, J = 3 Hz, cyclopropyl); UV (*t*-BuOH) 210 nm (ε 24 600), 239 (ε 27 100), 290 (ε 2870), 300 (ε 2220); mass spectrum (calcd for $C_{17}H_{14}$, 218.10955) m/e 218.10855.

Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.46; H, 6.50.

(Z)-2-Stilbenecarboxylic Acid. A solution of 4.00 g (17.6 mmol) of (E)-2-stilbenecarboxylic acid in 500 mL of benzene was purged with purified nitrogen[37] for 1 h and then irradiated with continuing purging for 8.0 h through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp. The photolysate was concentrated in vacuo to yield 3.95 g of colorless solid, mp 144–146 °C. Recrystallization from benzene afforded 3.57 g (89%) of (Z)-2-stilbenecarboxylic acid, mp 147 °C (lit.[38] mp 145–146.5 °C).

The spectral data were: IR (CHCl₃) 3.27, 3.33, 3.47, 3.77, 3.94, 5.92, 6.27, 6.41, 6.71, 6.94, 7.12, 7.69, 7.88, 8.20, 8.33, 9.30, 10.87 μm; NMR (acetone-d₆) τ 1.96–2.10 (m, 1 H, –CO₂H), 2.64 (m, 10 H, arom and vinyl), 3.42 (d, 1 H, J = 12 Hz, vinyl).

(Z)-3,4-Benzo-1-diazo-6-phenyl-3,5-hexadien-2-one. With the general procedure above for diazo ketones,[32b] from 1.02 g (4.56 mmol) of (Z)-2-stilbenecarboxylic acid, 856 mg (7.25 mmol) of thionyl chloride in 25 mL of anhydrous benzene, distilled diazomethane from 3.88 g (10.9 mmol) of EXR-101, and 20 mL of 33% potassium hydroxide there was obtained 1.05 g (93%) of (Z)-3,4-benzo-1-diazo-6-phenyl-3,5-hexadien-2-one as a deep yellow oil which was pure by NMR analysis.

The spectral data were: IR (thin film) 3.22, 3.26, 3.29, 3.38, 4.76, 5.81, 6.17, 6.63, 6.67, 6.90, 7.38, 7.75, 8.20, 8.73, 9.82, 11.36, 12.73, 13.05, 14.28 μm; NMR (CDCl₃) τ 2.30–3.02 (m, 9 H, arom), 3.12 (d, 1 H, J = 12 Hz, vinyl), 3.36 (d, 1 H, J = 12 Hz, vinyl), 4.34 (s, 1 H, –CHN₂); mass spectrum (calcd for $C_{16}H_{12}N_2O$ – N₂, 220.08881) m/e 220.08909.

endo-3,4-Benzo-6-phenylbicyclo[3.1.0]hex-3-en-2-one.[32b] From 1.00 g of copper–bronze in 25 mL of anhydrous benzene and 941 mg (3.79 mmol) of (Z)-3,4-benzo-1-diazo-6-phenyl-3,5-hexadien-2-one in 10 mL of benzene there was obtained from chromatography 374 mg (45%) of *endo*-3,4-benzo-6-phenylbicyclo[3.1.0]hex-3-en-2-one as a colorless oil.

The spectral data were: IR (KBr) 3.30, 3.33, 5.87, 6.23, 6.69, 6.80, 6.92, 7.63, 7.76, 7.91, 8.30, 8.47, 9.05, 9.35, 10.81, 10.99, 11.36, 12.12, 12.90, 13.16, 14.29 μm; NMR (CDCl₃) τ 2.34–3.02 (m, 9 H, arom), 6.52–6.88 (M, 2 H, cyclopropyl), 7.16 (d of d, 1 H, J = 5, 9 Hz, cyclopropyl); mass spectrum (calcd for $C_{16}H_{12}O$, 220.08881) m/e 220.08911.

Anal. Calcd for $C_{16}H_{12}O$: C, 87.24; H, 5.49. Found: C, 87.29; H, 5.49.

endo-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene.[32b] From 4.61 g (12.96 mmol) of methyltriphenylphosphonium bromide in 75 mL of anhydrous ether, 8.61 mL (12.9 mmol) of 1.5 M *n*-butyllithium in hexane, and 949 mg (4.31 mmol) of *endo*-3,4-benzo-6-phenylbicyclo[3.1.0]hex-3-en-2-one in 25 mL of anhydrous ether chromatography gave 864 mg (92%) of *endo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene as colorless crystals, mp 142–144 °C. Recrystallization from 95% ethanol gave 812 mg (86%) of product as colorless crystals, mp 144–145 °C.

The spectral data were: IR (CHCl₃) 3.27, 3.33, 3.42, 6.12, 6.25, 6.70, 6.81, 6.94, 8.33, 8.93, 9.35, 9.76, 10.81, 11.43, 12.82, 14.49, 15.15 μm; NMR (CDCl₃) τ 2.42–3.18 (m, 9 H, arom), 4.52 (s, 1 H, exocyclic

methylene), 4.71 (s, 1 H, exocyclic methylene), 6.94 (d of d, 1 H, J = 6, 8 Hz, cyclopropyl), 7.14 (broad d of d, 1 H, J = 6, 8.5 Hz, cyclopropyl), 7.44 (d of d, 1 H, J = 8, 8.5 Hz, benzyl cyclopropyl); UV (cyclohexane) 238 nm (ε 24 200), 252 (ε 20 100), 286 (ε 5080), 301 (ε 3890); mass spectrum (calcd for $C_{17}H_{14}$, 218.10955) m/e 218.10963.

Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.38; H, 6.60.

3-(4-Methoxyphenylmethylene)-1(3H)-isobenzofuranone. A mixture of 33.2 g (200 mmol) of 4-methoxyphenylacetic acid, 25.0 g (150 mmol) of phthalic anhydride, and 0.65 g (8.0 mmol) of sodium acetate was heated quickly to 230 °C and the temperature was raised over 3 h to 250 °C. The mixture was cooled and crystallized from 10% benzene–ethanol to yield 21.6 g (57%) of 3-(4-methoxyphenylmethylene)-1(3H)-isobenzofuranone as yellow crystals, mp 146–148 °C (lit.[39] mp 147–148 °C).

The spectral data were: IR (CHCl₃) 3.33, 3.38, 3.41, 3.45, 3.55, 5.67, 6.02, 6.27, 6.37, 6.64, 6.80, 6.85, 6.94, 7.41, 7.52, 7.69, 7.75, 7.87, 8.00, 8.26, 8.55, 8.66, 9.26, 9.71, 10.20, 11.49, 11.63, 12.20 μm; NMR (CDCl₃) τ 2.08–2.64 (m, 6 H, arom), 3.12 (d, 2 H, J = 8 Hz, anisyl), 3.60 (s, 1 H, vinyl), 6.19 (s, 3 H, –OCH₃); mass spectrum (calcd for $C_{16}H_{12}O_3$, 252.07864) m/e 252.07924.

3-(4-Methoxyphenylmethyl)-1(3H)-isobenzofuranone. To a refluxing solution of 18.3 g (72.0 mmol) of 3-(4-methoxyphenylmethylene)-1(3H)-isobenzofuranone in 100 mL of 12% potassium hydroxide in water with 2.0 mL of ethanol was added 5.00 g (76.5 mg-atoms) of zinc dust. Refluxing was continued until the mixture was no longer red and the mixture was cooled, filtered, acidified with 10% hydrochloric acid (Congo Red), and extracted with ether. The ethereal extracts were dried and concentrated in vacuo to yield 16.5 g (90%) of nearly colorless crystals, mp 81–85 °C, which were recrystallized from 95% ethanol to yield 15.6 g (85%) of 3-(4-methoxyphenylmethyl)-1(3H)-isobenzofuranone as colorless crystals, mp 86–87 °C (lit.[39] mp 87–88 °C).

The spectral data were: IR (KBr) 3.26, 3.30, 3.33, 3.41, 3.52, 5.73, 6.22, 6.32, 6.62, 6.83, 6.94, 7.43, 7.63, 7.69, 7.78, 7.87, 8.06, 8.26, 8.37, 8.44, 8.51, 9.05, 9.39, 9.52, 9.62, 9.90, 10.20, 10.99, 12.24, 12.99, 13.33, 14.39 μm; NMR (CDCl₃) τ 2.14–3.02 (m, 6 H, arom), 3.18 (d, 2 H, J = 8 Hz, anisyl, 4.34 (t, 1 H, J = 6 Hz, methine), 6.21 (s, 3 H, –OCH₃), 6.82 (t, 2 H, J = 6 Hz, –CH₂Ar); mass spectrum (calcd for $C_{16}H_{14}O_3$, 254.09429) m/e 254.09422.

(E)-4′-Methoxy-2-stilbenecarboxylic Acid. A solution of 15.5 g (60.9 mmol) of 3-(4-methoxyphenylmethyl)-1(3H)-isobenzofuranone and 4.80 g (85.5 mmol) of potassium hydroxide in 70 mL of 50% aqueous ethanol was evaporated to dryness at 100 °C. The salt was heated at 100 °C for 1.5 h at 25 Torr and then heated at 200 °C for 4 h at 25 Torr. The cooled residue was taken up in water and the resulting solution was acidified with 10% hydrochloric acid (Congo Red) and extracted with ether. The ethereal extracts were dried and concentrated in vacuo to yield 14.2 g (92%) of crude product, mp 167–176 °C. Recrystallization from methanol gave 13.6 g (88%) of (E)-4′-methoxy-2-stilbenecarboxylic acid as colorless crystals, mp 179–180 °C (lit.[39] mp 179–180 °C).

The spectral data were: IR (KBr) 2.92, 3.38, 3.79, 5.58, 6.15, 6.25, 6.41, 6.62, 6.78, 6.85, 7.06, 7.12, 7.69, 7.75, 7.84, 7.94, 8.04, 8.39, 8.52, 8.76, 9.02, 9.28, 9.73, 10.34, 11.05, 11.63, 11.81, 12.15, 12.27, 12.50, 13.34, 13.98, 14.50, 15.00 μm; NMR (acetone-d₆) τ 1.90–3.16 (m, 11 H, arom, vinyl and –CO₂H), 6.18 (s, 3 H, –OCH₃); mass spectrum (calcd for $C_{16}H_{14}O_3$, 254.09378) m/e 254.09429.

(E)-3,4-Benzo-1-diazo-6-(4-methoxyphenyl)3,5-hexadien-2-one. Using the general diazo ketone procedure,[32b] from 4.34 g (17.1 mmol) of (E)-4′-methoxy-2-stilbenecarboxylic acid, 4.34 g (34.2 mmol) of oxalyl chloride, distilled diazomethane prepared from 9.36 g (26.2 mmol) of EXR-101, and 50 mL of 33% potassium hydroxide there was obtained 4.24 g (89%) of (E)-3,4-benzo-1-diazo-6-(4-methoxyphenyl)-3,5-hexadien-2-one as a deep yellow oil which was pure by NMR analysis.

The spectral data were: IR (thin film) 3.22, 3.26, 3.33, 3.38, 3.41, 3.52, 6.25, 6.63, 6.78, 6.85, 6.94, 7.04, 7.43, 7.73, 8.02, 8.53, 8.77, 9.01, 9.72, 9.95, 10.42, 11.05, 11.47, 12.20, 13.14, 13.42, 13.70, 14.38, 15.00 μm; NMR (CDCl₃) τ 2.24–3.22 (m, 10 H, arom and vinyl), 4.45 (s, 1 H, –CHN₂), 6.23 (s, 3 H, –OCH₃); mass spectrum (cold inlet) (calcd for $C_{17}H_{14}N_2O_2$, 278.10552) m/e 278.10559.

exo-3,4-Benzo-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-en-2-one.[32b] From 2.04 g of copper–bronze in 50 mL of anhydrous benzene and 4.03 g (14.5 mmol) of (E)-3,4-benzo-1-diazo-6-(4-methoxyphenyl)-3,5-hexadien-2-one in 25 mL of benzene chromatography and recrystallization from 95% ethanol gave 1.77 g (49%) of *exo*-3,4-benzo-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-en-2-one as colorless crystals, mp 112–113 °C.

The spectral data were: IR (KBr) 3.27, 3.31, 3.42, 3.51, 5.91, 6.24, 6.62, 6.82, 7.26, 7.65, 7.80, 7.93, 8.06, 8.48, 8.80, 9.11, 9.39, 9.78, 9.98,

11.91, 12.24, 12.97, 13.88, 14.50 μm; NMR (CDCl₃) τ 2.24–3.36 (m, 8 H, arom), 6.30 (s, 3 H, –OCH₃), 6.94 (d of d, 1 H, J = 3, 5 Hz, cyclopropyl), 7.33 (d of d, 1 H, J = 3, 5 Hz, cyclopropyl), 7.55 (t, 1 H, J = 3 Hz, cyclopropyl); mass spectrum (calcd for C₁₇H₁₄O₂, 250.09938) *m/e* 250.09916.

Anal. Calcd for C₁₇H₁₄O₂: C, 81.58; H, 5.64. Found: C, 81.77; H, 5.69.

exo-3,4-Benzo-6-(4-methoxyphenyl)-2-methylenebicyclo-[3.1.0]hex-3-ene.[32b] From 4.41 g (12.4 mmol) of methyltriphenylphosphonium bromide in 100 mL of anhydrous ether, 8.30 mL of 1.50 M *n*-butyllithium solution (12.4 mmol), and 1.66 g (6.65 mmol) of *exo*-3,4-benzo-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-en-2-one in 75 mL of anhydrous ether chromatography gave 1.43 g of *exo*-3,4-benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene as a colorless oil which crystallized on standing, mp 90–92 °C. Recrystallization from 95% ethanol yielded 1.12 g (68%) of product as colorless crystals, mp 93–95 °C.

The spectral data were: IR (CHCl₃) 3.33, 3.42, 6.25, 6.62, 6.85, 7.07, 8.16, 8.33, 8.51, 9.71, 10.81, 11.43 μm; NMR (CDCl₃) τ 2.44–3.24 (m, 8 H, arom), 4.48 (s, 1 H, exocyclic methylene), 4.77 (s, 1 H, exocyclic methylene), 6.21 (s, 3 H, –OCH₃), 7.16 (d of d, 1 H, J = 3, 5 Hz, cyclopropyl), 7.31 (broad d of d, 1 H, J = 3, 5 Hz, cyclopropyl), 8.20 (t, 1 H, J = 3 Hz, cyclopropyl); UV (cyclohexane) 243 nm (ε 26 600), 248 (ε 25 900), 267 (ε 15 400), 295 (ε 5520); mass spectrum (calcd for C₁₈H₁₆O, 248.12011) *m/e* 248.12060.

Anal. Calcd for C₁₈H₁₆O: C, 87.06; H, 6.50. Found: C, 87.16; H, 6.66.

(Z)-4′-Methoxy-2-stilbencarboxylic Acid. A mixture of 2.00 g (7.87 mmol) of (*E*)-4′-methoxy-2-stilbenecarboxylic acid in 500 mL benzene was purged with purified nitrogen[37] for 30 min and then irradiated with continued purging for 4.0 h through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp. The photolysate was concentrated in vacuo to yield 2.06 g (103%) of nearly colorless solid residue, mp 156–160 °C. Recrystallization from 20% ethanol in benzene gave 1.77 g of (*Z*)-4′-methoxy-2-stilbencarboxylic acid as colorless crystals, mp 161–162 °C.

The spectral data were: IR (KBr) 2.92, 3.38, 3.79, 5.58, 6.15, 6.25, 6.41, 6.62, 6.78, 6.85, 7.06, 7.12, 7.69, 7.75, 7.84, 7.94, 8.04, 8.39, 8.52, 8.76, 9.02, 9.28, 9.73, 10.34, 11.05, 11.63, 11.81, 12.15, 12.27, 12.50, 13.34, 13.98, 14.50, 15.00 μm; NMR (acetone-*d₆*) τ 1.92–3.40 (m, 10 H, –CO₂H, arom and vinyl), 3.50 (d, 1 H, J = 12 Hz, vinyl), 6.28 (s, 3 H, –OCH₃); mass spectrum (calcd for C₁₆H₁₄O₃, 254.09429) *m/e* 254.09378.

Anal. Calcd for C₁₆H₁₄O₃: C, 75.57; H, 5.55. Found: C, 75.45; H, 5.49.

(Z)-3,4-Benzo-1-diazo-6-(4-methoxyphenyl)-3,5-hexadien-2-one. A mixture of 1.45 g (5.70 mmol) of (*Z*)-4′-methoxy-2-stilbenecarboxylic acid and 1.32 g (10.4 mmol) of oxalyl chloride was left for 2 h. Excess oxalyl chloride was removed in vacuo and 10 mL of anhydrous benzene was added. The solution was concentrated in vacuo and the residue was redissolved in 10 mL of anhydrous benzene and added dropwise to excess distilled ethereal diazomethane prepared from 2.81 g (7.9 mmol) of EXR-101 (70% *N,N′*-dimethyl-*N,N′*-dinitrosoterephthalamide in mineral oil) and 15 mL of 33% potassium hydroxide. After stirring 1.5 h at room temperature, the excess diazomethane was removed in vacuo to yield 1.50 g (95%) of (*Z*)-3,4-benzo-1-diazo-6-(4-methoxyphenyl)-3,5-hexadien-2-one as a deep yellow oil which was pure by NMR analysis. This was used in the subsequent step without further purification.

The spectral data were: IR (thin film) 3.25, 3.32, 3.39, 3.52, 4.76, 5.97, 6.21, 6.58, 6.83, 7.35, 7.81, 7.94, 8.47, 8.89, 9.26, 9.33, 9.63, 10.87, 11.90, 13.51, 14.39 μm; NMR (CDCl₃) τ 2.32–3.60 (m, 10 H, arom and vinyl), 4.32 (s, 1 H, –CHN₂), 6.34 (s, 3 H, –OCH₃); mass spectrum (calcd for C₁₇H₁₄N₂O₂ – N₂, 250.09938) *m/e* 250.09960.

endo-3,4-Benzo-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-en-2-one.[32b] From 1.15 g of copper–bronze in 20 mL of benzene and 1.42 g (5.10 mmol) of (*Z*)-3,4-benzo-1-diazo-6-(4-methoxyphenyl)-3,5-hexadien-2-one in 10 mL of benzene 369 mg (29%) of pure product as a colorless oil was obtained by chromatography.

The spectral data were: IR 3.27, 3.30, 3.42, 3.53, 5.88, 6.25, 6.66, 6.82, 7.63, 7.80, 7.91, 8.00, 8.47, 8.97, 9.31, 11.75, 12.74, 12.91, 14.40 μm; NMR (CDCl₃) τ 2.20–3.28 (m, 6 H, arom), 3.48 (d, 2 H, J = 8 Hz, *o*-anisyl), 4.48 (s, 3 H, –OCH₃), 6.64–7.00 (m, 2 H, cyclopropyl), 7.24 (d of d, 1 H, J = 5, 9 Hz, cyclopropyl); mass spectrum (calcd for C₁₇H₁₄O₂, 250.09938) *m/e* 250.09904.

Anal. Calcd for C₁₇H₁₄O₂: C, 81.58; H, 5.64. Found: C, 81.68; H, 5.39.

endo-3,4-Benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene.[32b] From 445 mg (1.25 mmol) of methyltriphenylphosphonium bromide in 25 mL of anhydrous ether, 0.835 mL (1.25 mmol) of 1.50 M *n*-butyllithium in hexane, and 148 mg (0.591

mmol) of *endo*-3,4-benzo-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-en-2-one in 25 mL of anhydrous ether chromatography afforded 106 mg (72%) of *endo*-3,4-benzo-6-(methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene as a crystalline solid, mp 121–124 °C. Recrystallization from 95% ethanol gave 97 mg (66%) of product as colorless crystals, mp 127 °C.

The spectral data were: IR (CHCl₃) 3.28, 3.33, 3.42, 3.51, 6.25, 6.82, 7.08, 7.57, 7.91, 8.33, 8.45, 9.71, 10.13, 11.55, 12.50 μm; NMR (CDCl₃) τ 2.52–3.30 (m, 8 H, arom), 4.55 (s, 1 H, exocyclic methylene), 4.68 (s, 1 H, exocyclic methylene), 6.26 (s, 3 H, –OCH₃), 6.94 (d of d, 1 H, J = 6, 7.5 Hz, cyclopropyl), 7.12 (broad d of d, 1 H, J = 6, 9 Hz, cyclopropyl), 7.50 (t, 1 H, J = 9 Hz, cyclopropyl); UV (95% EtOH) 242 nm (ε 24 800), 254 (ε 21 000), 280 (ε 7160), 305 (ε 3770); mass spectrum (calcd for C₁₈H₁₆O, 248.12011) *m/e* 248.12060.

Anal. Calcd for C₁₈H₁₆O: C, 87.06; H, 6.50. Found: C, 87.00; H, 6.36.

3-Phenyl-5-(phenylmethylene)-2-cyclopenten-1-one. The compound was prepared by the method of Borsche and Menz[40] from 3-phenyl-2-cyclopentenone.

2-Phenyl-5-(phenylmethylene)-1,3-cyclopentadiene. To a suspension of 500 mg (2.03 mmol) of 3-phenyl-5-(phenylmethylene)-2-cyclopenten-1-one in 25 mL of anhydrous tetrahydrofuran was added 1.45 mL of 1.40 M diisobutylaluminum hydride in hexane dropwise. The mixture was stirred for 30 min, poured into water, and extracted with ether. The ether extracts were washed with water, dried, and evaporated to yield 461 mg of semisolid residue which was chromatographed on a 3 × 50 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 5% ether in hexane. Elution in 125-mL fractions gave: fractions 1–2, nil; fractions 3–4, 276 mg (59%) of 2-phenyl-5-(phenylmethylene)-1,3-cyclopentadiene as a dark red-orange oil which crystallized on standing, mp 61–68 °C. Recrystallization from 95% ethanol gave 236 mg (50%) of 2-phenyl-5-(phenylmethylene)-1,3-cyclopentadiene as red-orange crystals, mp 72–73 °C.

The spectral data were: IR (CHCl₃) 3.27, 3.33, 6.18, 6.27, 6.63, 6.91, 7.30, 7.72, 8.16, 8.33, 9.73, 10.75, 11.43, 12.20, 14.60, 15.15 μm; NMR (CDCl₃) τ 2.22–3.12 (m, 13 H, arom and vinyl), 3.54 (d of d, 1 H, J = 2, 6 Hz, vinyl).

Anal. Calcd for C₁₈H₁₄: C, 93.87; H, 6.13. Found: C, 93.95; H, 6.11.

1,5-Diphenylspiro[2.4]hepta-4,6-diene. To 100 mg (4.17 mmol) of solid mineral oil free sodium hydride and 1.10 g (5.00 mmol) of solid trimethylsulfoxonium iodide[41] was added cautiously under nitrogen 6.0 mL of anhydrous dimethyl sulfoxide dropwise. After hydrogen evolution had ceased, the mixture was stirred 10 min and then 118 mg (0.512 mmol) of 2-phenyl-5-(phenylmethylene)-1,3-cyclopentadiene in 10 mL of anhydrous Me₂SO was added dropwise. After stirring 15 min, the mixture was poured into water and extracted with ether. The ether extracts were washed with water and saturated sodium chloride, dried, and concentrated in vacuo to yield 121 mg of residue which was chromatographed in a 1 × 30 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 3% ether in hexane. Elution in 50-mL fractions gave: fractions 1–2, nil; fractions 3–4, 9.72 mg of 1:1 mixture of *syn*- and *anti*-1,5-diphenylspiro[2.4]-hepta-4,6-diene as a colorless oil. The spectral data were identical with those reported previously.[3a]

1-(Phenylmethylene)-1*H*-indene. This compound was prepared by the method of Kresze, Henkel, and Goetz[42] from indene and benzaldehyde.

anti-2-Phenylspiro[cyclopropane-1,1′-[1*H*]indene]. To a dry mixture of 100 mg (4.17 mmol) of mineral oil free sodium hydride and 1.10 g (5.00 mmol) of trimethylsulfoxonium iodide was added under nitrogen 6.0 mL of anhydrous dimethyl sulfoxide.[41] After hydrogen evolution had ceased, 100 mg (0.480 mmol) of 1-(phenylmethylene)-1*H*-indene in 5 mL of anhydrous dimethyl sulfoxide was added dropwise. The mixture was stirred for 30 min, poured into water, and extracted with ether. The ether extracts were washed with water and saturated sodium chloride solution, dried, and concentrated in vacuo to yield 97.0 mg of residue, which was chromatographed on a 1 × 30 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 5% ether in hexane. Elution in 50-mL fractions gave: fractions 1–2, nil; fraction 3, 88 mg (84%) of *anti*-2-phenylspiro[cyclopropane-1,1′-[1*H*]indene] as a crystalline solid, mp 77–79 °C. Recrystallization from 95% ethanol gave 72 mg (69%) of product, mp 79–80 °C.

The spectral data were: IR (KBr) 3.27, 3.32, 3.42, 6.27, 6.71, 6.90, 7.27, 7.30, 7.87, 8.13, 8.33, 8.70, 9.35, 9.71, 9.80, 10.20, 11.11, 11.49, 12.35, 12.82, 13.25, 13.79, 14.39 μm; NMR (CDCl₃) τ 2.50–3.10 (m, 9 H, arom), 3.25 (d, 1 H, J = 6 Hz, vinyl), 4.04 (d, 1 H, J = 6 Hz, vinyl), 6.82 (t, 1 H, J = 8 Hz, cyclopropyl), 7.44 (d of d, 1 H, J = 5, 8 Hz, cyclopropyl), 8.06 (d of d, 1 H, J = 5, 8 Hz, cyclopropyl); UV (*t*-BuOH)

210 nm (ϵ 24 600), 239 (ϵ 27 100), 290 (ϵ 2870), 300 (ϵ 2220); mass spectrum (calcd for $C_{17}H_{14}$, 218.10955) *m/e* 218.10909.

Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.40; H, 6.51.

syn-2-Phenylspiro[cyclopropane-1,1'-[1H]indene]. A solution of 245 mg (1.12 mmol) of *anti*-2-phenylspiro[cyclopropane-1,1'-[1H]indene] in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 30 min and then irradiated with continued purging for 3.5 h through quartz with a Hanovia 450-W medium-pressure mercury lamp. The photolysate was concentrated in vacuo at 40 °C to yield 249 mg of a yellow oily residue which was chromatographed in portions (30.0 mg) by high-pressure liquid chromatography on a 50 × 0.96 cm silica microsphere[43] column (particle size 10–30 μm). The mixture was eluted with 0.05% acetone in hexane and recycled three times with the final cycle giving: fraction 1, 131 mg of *anti*-2-phenylspiro[cyclopropane-1,1'-[1H]indene]; fraction 2, 41 mg of a mixture of *syn*- and *anti*-2-phenylspiro[cyclopropane-1,1'-[1H]indene]; fraction 3, 35 mg of syn-2-phenylspiro[cyclopropane-1,1'-[1H]indene] as a colorless oil; fraction 4, 29 mg of a mixture of product and unidentified material.

The spectral data for the syn isomer were: IR (thin film) 3.27, 3.32, 3.40, 6.27, 7.73, 8.21, 8.70, 9.15, 9.35, 9.70, 9.86, 10.20, 11.11, 11.49, 12.82 μm; NMR (CDCl$_3$) τ 2.56–3.02 (m, 9 H, arom), 3.12 (d, 1 H, J = 5 Hz, vinyl), 3.72 (d, 1 H, J = 5 Hz, vinyl), 6.64 (t, 1 H, J = 8 Hz, cyclopropyl), 7.78–8.02 (m, 2 H, cyclopropyl); UV (95% EtOH) 235 nm (ϵ 26 600), 284 (ϵ 2470), 296 (ϵ 2050); mass spectrum (calcd for $C_{17}H_{14}$, 218.10955) *m/e* 218.10909.

Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.81; H, 6.33.

1-(4-Methoxyphenylmethylene)-1H-indene. This compound was prepared by the method of Kresze, Henkel, and Goetz[42] from indene and 4-methoxybenzaldehyde.

anti-2-(4-Methoxyphenyl)spiro[cyclopropane-1,1'-[1H]indene].[32b] From 100 mg (4.17 mmol) of mineral oil free sodium hydride, 1.10 g (5.00 mmol) of trimethylsulfoxonium iodide,[41] 6.0 mL of anhydrous dimethyl sulfoxide, 166 mg (0.697 mmol) of 1-(4-methoxyphenylmethylene)-1H-indene in 5 mL of anhydrous dimethyl sulfoxide, and product chromatography there was obtained 146 mg of *anti*-2-(4-methoxyphenyl)spiro[cyclopropane-1,1'-[1H]indene] as a nearly colorless solid, mp 104–112 °C. Recrystallization from 95% ethanol gave 118 mg (68%) of product as colorless crystals, mp 120–121 °C.

The spectral data were: IR (KBr) 3.27, 3.33, 3.42, 6.25, 6.62, 6.69, 6.87, 6.93, 7.25, 7.75, 7.84, 8.00, 8.26, 8.47, 9.11, 9.71, 10.13, 11.98, 12.42, 13.09, 13.25, 14.30 μm; NMR (CDCl$_3$) τ 2.60–3.40 (m, 8 H, arom), 3.25 (d, 1 H, J = 6 Hz, vinyl), 4.07 (d, 1 H, J = 6 Hz, vinyl), 6.18 (s, 3 H, –OCH$_3$), 6.84 (t, 1 H, J = 8 Hz, cyclopropyl), 7.76 (d of d, 1 H, J = 5, 8 Hz, cyclopropyl), 8.04 (d of d, 1 H, J = 5, 8 Hz, cyclopropyl); UV (95% EtOH) 218 nm (ϵ 22 800), 246 (ϵ 24 400), 290 (ϵ 4400), 301 (ϵ 3170); mass spectrum (calcd for $C_{18}H_{16}O$, 248.12011) *m/e* 248.11914.

Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.03; H, 6.70.

3,4-Dihydro-1-methyl-2(1H)-naphthalenone. This material was prepared by the method of Stille and Wu[44] from 3,4-dihydro-1-methylnaphthalene[45] and *m*-chloroperbenzoic acid.

1-Methyl-2-phenylnaphthalene.[32c] To phenylmagnesium bromide prepared from 270 mg (11.1 mg-atoms) of magnesium turnings and 1.73 g (11.0 mmol) of bromobenzene in anhydrous ether was added 1.76 g (11.0 mmol) of 3,4-dihydro-1-methyl-2(1H)-naphthalenone in 5 mL of anhydrous ether. The mixture was stirred for 1 h, 25 mL of 2.4 M hydrochloric acid was added, and the ethereal phase was separated. Standard workup yielded 2.60 g of yellow oil. The product mixture was dissolved in 50 mL of benzene and 2.72 g (12 mmol) of dichlorodicyanobenzoquinone and 65.0 mg (0.377 mmol) of *p*-toluenesulfonic acid were added. The mixture was refluxed for 3 h with a Dean–Stark trap, cooled, and filtered. The filtrate was diluted with ether, washed with 1 N sodium hydroxide, water, and saturated sodium chloride, dried, and concentrated in vacuo to yield 2.39 g of oil, which was chromatographed on a 2.5 × 40 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 5% ether in hexane. Elution in 100-mL fractions gave in fractions 3–5 1.687 g of 1-methyl-2-phenylnaphthalene as a colorless oil which crystallized on standing, mp 78–80 °C. Recrystallization from methanol gave 1.30 g (54%) of colorless crystals, mp 83–84 °C (lit.[46] mp 80–82 °C).

The spectral data were: IR (KBr) 3.27, 3.31, 3.42, 6.28, 6.70, 6.81, 7.25, 8.01, 8.47, 9.34, 9.74, 9.99, 10.13, 11.59, 12.20, 13.12, 13.42, 14.18 μm; NMR (CDCl$_3$) τ 1.94–3.04 (m, 11 H, arom), 7.47 (s, 3 H, methyl); mass spectrum (calcd for $C_{17}H_{14}$, 218.10955) *m/e* 218.10889.

Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.40; H, 6.66.

1-Methyl-2-(4-methoxyphenyl)naphthalene. To 468 mg (18.2 mg-atoms) of magnesium turnings covered with anhydrous ether was added 0.1 mL of dibromoethane. When reaction was initiated, 3.45 g (18.4 mmol) of 4-bromoanisole in 50 mL of ether was added dropwise. The mixture was stirred for 1 h and 2.95 g (18.4 mmol) of 3,4-dihydro-1-methyl-2(1H)-naphthalenone in 10 mL of anhydrous ether was added dropwise. The mixture was stirred for 1 h and 50 mL of 2.4 M hydrochloric acid was added. The ethereal phase was separated, washed with water and saturated sodium chloride, dried, and concentrated in vacuo to yield 4.04 g of yellow oil which was dissolved in 75 mL of benzene. To the benzene solution was added 3.75 g (16.5 mmol) of dichlorodicyanobenzoquinone and 93.4 mg (0.542 mmol) of *p*-toluenesulfonic acid and the mixture was refluxed for 4 h with a Dean-Stark trap. The mixture was cooled and filtered and the filtrate was diluted with ether, washed with 1 N sodium hydroxide, water, and saturated sodium chloride, dried, and concentrated in vacuo to yield 3.33 g of oil which was chromatographed on a 2.5 × 60 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 5% ether in hexane. Elution in 100-mL fractions gave: fractions 1–8 nil; fractions 9–11, 3.38 g of 1-methyl-2-(4-methoxyphenyl)naphthalene as a crystalline solid, mp 101–114 °C. Recrystallization from 95% ethanol gave 2.94 g (64%) of product as colorless crystals, mp 117–118 °C.

The spectral data were: IR (KBr) 3.28, 3.30, 3.33, 3.38, 3.42, 3.52, 6.23, 6.62, 6.65, 6.84, 6.90, 6.94, 7.25, 7.75, 8.00, 8.06, 8.47, 9.01, 9.66, 10.10, 11.93, 12.15, 12.27, 12.82, 13.25, 14.39 μm; NMR (CDCl$_3$) τ 1.87–3.21 (m, 8 H, arom), 6.24 (s, 3 H, –OCH$_3$), 7.43 (s, 3 H, methyl); mass spectrum (calcd for $C_{18}H_{16}O$, 248.12011) *m/e* 248.11931.

Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 86.85; H, 6.47.

Photolysis Equipment for Preparative Irradiations and Quantum Yield Determinations. All direct and sensitized preparative irradiations were performed using a Hanovia 450-W medium-pressure mercury lamp and immersion apparatus or the black box apparatus[7] as specified for each run. All direct and sensitized quantum yield determinations were performed using the microoptical bench[7] employing a Bausch and Lomb Model 33-86-79 monochromator having a 5.4-mm entrance slit and a 3.0-mm exit slit (22-nm half width theoretical band-pass) and an Osram HBO 200-W high-pressure mercury lamp. Light output was monitored using a digital electronic actinometer[47] which employed two 1P28 photomultipliers, a multiplexed voltage to frequency converter, and dual digital counters. This instrument was calibrated prior to each run and each wavelength with ferrioxalate actinometry.[48] The light absorbed in the reaction cell was ascertained by the splitting ratio method described previously.[7]

For photolyses employing the black box, the band-pass was controlled by one of the following filter solution combinations as specified for each run: filter A, cell 1, 2.0 M nickel sulfate hexahydrate in 5% sulfuric acid; cell 2, 0.8 M cobalt sulfate heptahydrate in 5% sulfuric acid; cell 3, 4.50 × 10^{-2} M stannous chloride in 10% hydrochloric acid; transmission, 0% below 285 nm, 45% at 315 nm, 0% above 340 nm; filter B, cell 1, 0.2 M nickel sulfate hexahydrate in 10% sulfuric acid; cell 2, 1.0 M cobalt sulfate heptahydrate in 10% sulfuric acid; 0.2 M stannous chloride dihydrate in 10% hydrochloric acid; transmission, 0% below 315 nm, 28% at 345 nm, 0% above 380 nm.

Exploratory Direct Photolysis of exo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. Product Isolation. A solution of 500 mg (2.05 mmol) of exo-2-methylene-4,6-diphenylbicyclo[3.1.0]-hex-3-ene in 750 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 10 h through filter A on the black box apparatus. The photolysate was concentrated in vacuo to yield 503 mg of colorless oil. The light absorbed was 5.51 mEinsteins. The residue was chromatographed in 50-mg portions on a 2.54 × 183 cm column of octadecyl-coated sponge-surfaced glass beads.[49] The column was eluted with 55% acetonitrile–water (v/v) at a flow rate of 10 mL/min and the collected eluate was concentrated in vacuo, diluted with water, and extracted with ether. The ether extracts from each fraction were dried and concentrated individually in vacuo to give: fraction 1, 349 mg of starting material; fraction 2, 119 mg of 1,5-diphenylspiro[2.4]hepta-4,6-diene[3a] as a colorless oil shown by NMR analysis to be ~96% anti isomer; fraction 3, 12 mg of 2,5-diphenyltoluene. The starting material was unchanged (IR, NMR, UV, mp) and the spiroheptadiene photoproduct had spectral data (IR, NMR, UV) identical with that reported previously[3a] as did the 2,5-diphenyltoluene[3a] (IR, NMR, UV, mp).

Exploratory Direct Photolysis of endo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. Product Isolation. A solution

of 500 mg (2.04 mmol) of *endo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene in 750 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 20 h through filter A on the black box apparatus. The photolysate was concentrated in vacuo to yield 515 mg of light yellow oil. The light absorbed was 12.77 mEinsteins. The residue was chromatographed on a 2.54 × 183 cm column of octadecyl-coated sponge-surfaced glass beads.[49] The column was eluted with 50% acetonitrile–water (v/v) at a flow rate of 18 mL/min and the collected eluate was concentrated in vacuo, diluted with water, and extracted with ether. The ether extracts from individual fractions were dried and concentrated in vacuo to give: fraction 1, 220 mg of starting material; fraction 2, 165 mg of 1,5-diphenylspiro[2.4]hepta-4,6-diene as a colorless oil which was shown by NMR analysis to be ~55% syn isomer; fraction 3, 75 mg of a ~8:1 mixture of spiro photoproduct and diphenyltoluenes as determined by NMR analysis; fraction 4, 24 mg of a ~10:1 mixture of diphenyltoluenes to spiro photoproduct. Fractions 3 and 4 were combined and rechromatographed in 25-mg portions on two serial 1.27 × 183 cm columns of octadecyl-coated sponge-surfaced glass beads.[49] The column was eluted with 50% acetonitrile–water (v/v) at a flow rate of 4 mL/min. The eluate corresponding to individual fractions was treated as above to give: fraction 1, 67 mg of 1,5-diphenylspiro[2.4]hepta-4,5-diene having essentially the same composition as a fraction 2 above; fraction 2, 14 mg of 2,5-diphenyltoluene; fraction 3, 8 mg of 3,4-diphenyltoluene; fraction 4, 6 mg of a mixture of 3,4- and 2,4-diphenyltoluenes; fraction 5, 6 mg of 2,4-diphenyltoluene. Starting material was unchanged (IR, NMR, UV, mp) and spiro photoproduct spectral data (IR, NMR) were identical with that reported previously[3a] and authentic material and the diphenyltoluenes were identical (IR, NMR) with authentic materials.[3a]

Low Conversion Direct Photolysis of endo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. A solution of 450 mg (1.84 mmol) of *endo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene in 750 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 1.0 h through filter A on the black box apparatus. The light absorbed was 0.607 mEinstein. The photolysate was concentrated in vacuo to yield 446 mg of colorless semisolid. Recrystallization of the mixture from ethanol gave 321 mg of crystalline starting material, mp 152–153 °C. The mother liquor was concentrated under nitrogen and chromatographed on a 2.54 × 183 cm column of octadecyl-coated sponge-surfaced glass beads.[49] The column was eluted with 60% acetonitrile–water (v/v) at a flow rate of 15 mL/min and the collected eluate was concentrated in vacuo, diluted with water, and ether extracted. The ether extracts from individual fractions were dried and concentrated in vacuo to yield: fraction 1, 108 mg of starting material; fraction 2, 14 mg (2.8%) of 1,5-diphenylspiro[2.4]hepta-4,6-diene as a colorless oil which was shown by NMR analysis to be 73% syn isomer, $\Phi = 0.0849$. The spiro product was identical in other respects with authentic material (IR, UV).[3a] Diphenyltoluene photoproducts were too small in amount to recover.

Intermediate Conversion Direct Photolysis of endo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. A solution of 424 mg (1.74 mmol) of *endo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene in 750 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 3.0 h through filter A on the black box apparatus. The light absorbed was 2.17 mEinsteins. The photolysate was concentrated in vacuo to yield 455 mg of nearly colorless oil which was chromatographed in portions on a 2.54 × 183 cm column of octadecyl-coated sponge-surfaced glass beads.[49] The column was eluted with 55% acetonitrile–water (v/v) at a flow rate of ~15 mL/min and the collected eluate was concentrated in vacuo, diluted with water, and ether extracted. The ether extracts were concentrated in vacuo to yield: fraction 1, 354 mg of starting material; fraction 2, 44.7 mg (10.6%), $\Phi = 0.084$, of 1,5-diphenyl-spiro[2.4]hepta-4,6-diene as a colorless oil which was shown by NMR analysis to be ~63% syn isomer. Diphenyltoluene photoproducts were not isolated.

Exploratory Sensitized Photolysis of exo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. A solution of 200 mg (0.818 mmol) of *exo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene and 5.11 g (28.0 mmol) of benzophenone in 750 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 10 h through filter B on the black box apparatus. The photolysate was concentrated in vacuo to yield 7.23 g of white crystalline residue. The light absorbed was 13.2 mEinsteins. The residue was chromatographed on a 3 × 100 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 0.5% ether in hexane. Elution in 250-mL fractions gave: 1–10,

nil; 11–12, 203 mg of crystalline starting material unchanged by GC and NMR analysis, mp 96–99 °C. A control mixture containing 0.5% endo isomer was examined under identical conditions and this conversion would have been measurable. Therefore, conversion was <0.5%, $\Phi = <3.0 \times 10^{-4}$.

Sensitized Photolysis of endo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. Quantum Yield. Product Isolation. A solution of 176 mg (0.720 mmol) of *endo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene and 5.02 g (27.5 mmol) of benzophenone in 750 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 45 min through filter B on the black box apparatus. The photolysate was concentrated in vacuo to 5.20 g of white crystalline solid. The light absorbed was 1.06 mEinsteins. The residue was chromatographed on a 3 × 100 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 0.2% ether in hexane. Elution in 250-mL fractions gave: 1–15, nil; 16–17, 41 mg (0.168 mmol) of *exo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene which was identical with authentic material (NMR, GC), 23% conversion, $\Phi = 0.159$; 18–19, 138 mg of starting endo isomer unchanged.

Exploratory Direct Photolysis of exo-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene. Product Isolation. A solution of 233 mg (1.07 mmol) of *exo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 67 min through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp. The photolysate was concentrated in vacuo at 40 °C to yield 255 mg of a colorless oil. Crystallization of the residue from *tert*-butyl alcohol gave 56.0 mg of starting material and the mother liquor was chromatographed in portions by high-pressure liquid chromatography on a 50 × 0.96 cm silica microsphere column (particle size 10–30 μm).[43] Elution with 0.03% acetone in hexane gave: fraction 1, 53.4 mg of starting material; fraction 2, 9.3 mg of mixture of starting material and 1-methylene-2-phenyl-1,2-dihydronaphthalene; fraction 3, 46.3 mg of an oil consisting of 1-methylene-2-phenyl-1,2-dihydronaphthalene containing ~8% tautomeric 1-methyl-2-phenylnaphthalene as ascertained by NMR; fraction 4, nil; fraction 5, 61.8 mg of *anti*-2-phenylspiro[cyclopropane-1,1′-[1H]indene]. The *anti*-2-phenylspiro[cyclopropane-1,1′-[1H]indene] was identical (IR, NMR, UV) with independently prepared material.

The spectral data for 1-methylene-2-phenyl-1,2-dihydronaphthalene (incessantly contaminated with 1-methyl-2-phenylnaphthalene) were: IR (thin film) 3.27, 3.30, 3.52, 6.04, 6.25, 6.71, 6.92, 9.73, 10.73, 11.46, 14.40 μm; 270-MHz NMR (acetone-d_6) τ 2.40–3.00 (m, 9 H, arom), 3.36 (d, 1 H, $J = 9.6$ Hz, vinyl), 3.84 (d of d, 1 H, $J = 9.6$, 5.0 Hz, vinyl), 4.46 (d of d, 1 H, $J = 1.8$, 0.92 Hz, exocyclic methylene), 4.88 (d of d, 1 H, $J = 1.5$, 0.92 Hz, exocyclic methylene), 5.56 (d of d of d, 1 H, $J = 5.0$, 1.8, 1.5 Hz, methine); UV (95% EtOH) 284 nm (ϵ 15 400); mass spectrum (calcd for $C_{17}H_{14}$, 218.10955) *m/e* 218.10940.

Exploratory Direct Photolysis of endo-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene. Product Isolation. A solution of 209 mg (0.958 mmol) of *endo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 1.5 h through a 2-mm Pyrex filter with Hanovia 450-W medium-pressure mercury lamp. The photolysate was concentrated in vacuo at 40 °C to yield 217 mg of a colorless oil. The residue was chromatographed in 50-mg portions by high-pressure liquid chromatography on a 50 × 0.96 cm silica microsphere column (particle size 10–30 μm).[43] Elution with 0.05% acetone in hexane gave: fraction 1, 102 mg of an oil consisting of 1-methylene-2-phenyl-1,2-dihydronaphthalene containing ~10% tautomeric 1-methyl-2-phenylnaphthalene by NMR analysis; fraction 2, 76.4 mg of starting material; fraction 3, 9.0 mg of starting material containing a trace of spiro photoproduct; fraction 4, 12.1 mg of *syn*-2-phenylspiro[cyclopropane-1,1′-[1H[indene]as a colorless oil containing <5% anti isomer by NMR analysis. The methylenedihydronaphthalene photoproduct was identical (IR, NMR, UV) with material obtained from photolysis of the exo isomer. The *syn*-2-phenylspiro[cyclopropane-1,1′-[1H]-indene] was identical (IR, NMR, UV) with independently prepared material.

Tautomerization of 1-Methylene-2-phenyl-1,2-dihydronaphthalene. A solution of 71.0 mg (0.325 mmol) of 1-methylene-2-phenyl-1,2-dihydronaphthalene containing ~12% 1-methyl-2-phenylnaphthalene by NMR and 2.5 mg of *p*-toluenesulfonic acid monohydrate (1.31 × 10⁻² mmol) in 10 mL of benzene was refluxed for 30 min. The mixture was cooled, poured into water, and ether extracted. The ether extracts were washed with saturated sodium

bicarbonate and water, dried, and concentrated in vacuo to yield 66.2 mg (93%) of crystalline residue, mp 77–80 °C which was entirely 1-methyl-2-phenylnaphthalene by NMR analysis. Recrystallization from methanol gave 46.0 mg of 1-methyl-2-phenylnaphthalene as a colorless crystals, mp 83–84 °C, which were identical (IR, NMR, mp) with independently prepared material.

In an alternate experiment, 56.6 mg (0.259 mmol) of 1-methylene-2-phenyl-1,2-dihydronaphthalene (containing ~15% 1-methyl-2-phenylnaphthalene by NMR) in 10 mL of anhydrous benzene was refluxed for 1.5 h. The mixture was cooled and concentrated in vacuo to yield 55.8 mg of a solid residue, mp 77–79 °C, which was entirely 1-methyl-2-phenylnaphthalene by comparison with independently prepared material (IR, NMR).

Exploratory Sensitized Photolysis of *exo*-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene. A solution of 226 mg (1.04 mmol) of exo-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene and 3.01 g (20.1 mmol) of 3-methoxyacetophenone in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 2.5 h with a Hanovia 450-W medium-pressure mercury lamp through a 2-mm Pyrex filter and 5 mm of 0.05 M sodium vanadate in 0.05 M sodium hydroxide solution (0% T < 330 nm) which was circulated as lamp coolant. The photolysate was concentrated in vacuo at 40 °C to yield 3.34 g of a semisolid which was chromatographed on a 2.5 × 110 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 3% ether in hexane. Elution in 125-mL fractions gave: fractions 1–7, nil; fraction 8, 221 mg of exo-3,4-benzo-2-methylene-6-phenyl-bicyclo[3.1.0]hex-3-ene unchanged.

Exploratory Sensitized Photolysis of *endo*-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene. A solution of 240 mg (1.10 mmol) of endo-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene and 3.06 g (20.4 mmol) of 3-methoxyacetophenone in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 0.75 h with a Hanovia 450-W medium-pressure mercury lamp through a 2-mm Pyrex filter and 5 mm of 0.05 M sodium vanadate in 0.05 M sodium hydroxide solution (0% T < 330 nm) which was circulated as lamp coolant. The photolysate was concentrated in vacuo at 40 °C to yield 3.41 g of a semisolid which was chromatographed on a 3 × 120 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 0.5% ether in hexane. After elution with 1.95 L of eluate, 75-mL fractions were collected giving: fractions 1–3, 95.0 mg of exo-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene having spectral properties (NMR, IR) identical with authentic material, mp 95–98 °C; fractions 4–5, 31.0 mg of a ~2:1 mixture of endo and exo isomers as determined by NMR analysis; fractions 6–10, 105 mg of unchanged (NMR, mp) starting endo isomer.

Exploratory Direct Photolysis of *exo*-3,4-Benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene. Product Isolation. A solution of 211 mg (0.850 mmol) of exo-3,4-benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated for 1 h with continued purging through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp. The photolysate was concentrated in vacuo at 40 °C to yield 226 mg of a nearly colorless oil which was chromatographed on a 20 × 20 × 0.2 cm preparative alumina (E. Merck, GF-254, Type 60/E) plate eluted twice with 10% ether in hexane. The isolated bands were: band 1 (R_f 0.82), 157 mg of a mixture of starting material and 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene as determined by NMR analysis; band 2 (R_f 0.65), 57.0 mg of anti-2-(4-methoxyphenyl)spiro[cyclopropane-1,1'-[1*H*]indene] which was identical (IR, NMR, mass spectrum, mp) to independently prepared material. The residue from band 1 was rechromatographed on a 20 × 20 × 0.2 cm preparative alumina (E. Merck, GF-254, Type 60/E) plate eluted four times with 2% ether in hexane. The isolated bands were: band 1 (R_f 0.79), 48.0 mg of unreacted starting material; band 2 (R_f 0.71), 31.0 mg of a ~3:2 mixture of unreacted starting material and 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene; band 3, 62.0 mg of an oil consisting of 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene containing ~15% tautomeric 1-methyl-2-(4-methoxyphenyl)naphthalene as ascertained by NMR; band 5, 9.1 mg of a mixture of the methylenedihydronaphthalene photoproduct, tautomeric naphthalene, and spiro photoproduct. The anti-2-(4-methoxyphenyl)spiro[cyclopropane-1,1'-[1*H*]indene] was identical (IR, NMR, UV) with independently prepared material.

The spectral data for 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene (incessantly contaminated with 1-methyl-2-(4-methoxyphenyl)naphthalene) were: IR (thin film) 3.28, 3.30, 3.33, 3.38, 3.42, 3.52, 6.23, 6.60, 6.62, 6.86, 6.90, 6.94, 7.25, 7.75, 8.00, 8.06,

8.50, 9.20, 9.66, 10.10, 11.93, 12.15, 12.27, 12.82, 13.25, 14.39 μm; NMR (CDCl$_3$) τ 2.48–3.36 (m, 8 H, arom), 3.55 (d, 1 H, J = 9 Hz, vinyl), 3.97 (dd, 1 H, J = 6, 9 Hz, vinyl), 4.58 (s, 1 H, methylene), 5.04 (s, 1 H, methylene), 5.74 (broad s, 1 H, methine); mass spectrum (calcd for C$_{18}$H$_{16}$O, 248.12011) m/e 248.11931.

Exploratory Direct Photolysis of *endo*-3,4-Benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene. Product Isolation. A solution of 197 mg (0.793 mmol) of endo-3,4-benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 1 h through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp. The photolysate was concentrated in vacuo at 40 °C to yield 213 mg of a pale yellow oil which was chromatographed on a 20 × 20 × 0.2 cm preparative alumina (E. Merck, GF-254, Type 60/E) plate eluted three times with 5% ether in hexane. The isolated bands were: band 1 (R_f 0.85), 82.0 mg of an oil consisting of 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene containing ~23% of tautomeric 1-methyl-2-(4-methoxyphenyl)naphthalene as determined by NMR; band 2 (R_f 0.70), 22.6 mg of an oily mixture of starting material, methylenedihydronaphthalene photoproduct, and tautomeric naphthalene; band 3 (R_f 0.62), 80.0 mg of unreacted starting material. The 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene was identical (IR, NMR) with the product obtained by photolysis of the exo isomer.

Tautomerization of 1-Methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene. A solution of 80.4 mg (0.324 mmol) of 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene [containing <5% 1-methyl-2-(4-methoxyphenyl)naphthalene by NMR analysis] in 25 mL of benzene was refluxed for 2.0 h. The mixture was cooled and concentrated in vacuo to yield 81.2 mg (101%) of crystalline residue, mp 113–117 °C, which was identical (NMR) with independently prepared 1-methyl-2-(4-methoxyphenyl)naphthalene. Recrystallization from 95% ethanol gave 63.0 mg (78%) of pure 1-methyl-2-(4-methoxyphenyl)naphthalene, mp 117–118 °C, which was further related (IR, mp) to independently prepared material.

Exploratory Sensitized Photolysis of *exo*-3,4-Benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene. A solution of 290 mg (1.17 mmol) of exo-3,4-benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene and 3.00 g (20.0 mmol) of 3-methoxyacetophenone in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 3 h with a Hanovia 450-W medium-pressure mercury lamp through a 2-mm Pyrex filter and 5 mm of 0.05 M sodium vanadate in 0.05 M sodium hydroxide solution (0% T < 330 nm) which was circulated as lamp coolant. The photolysate was concentrated in vacuo at 40 °C to yield 3.36 g of solid residue which was chromatographed on a 2.5 × 100 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 5% ether in hexane. Elution in 250-mL fractions gave: fractions 1–9, nil; fractions 10–11, 282 mg of exo-3,4-benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene unchanged.

Exploratory Sensitized Photolysis of *endo*-3,4-Benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene. A solution of 315 mg (1.27 mmol) of endo-3,4-benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene and 3.02 g (20.1 mmol) of 3-methoxyacetophenone in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[37] for 1 h and then irradiated with continued purging for 30 min with Hanovia 450-W medium-pressure mercury lamp through a 2-mm Pyrex filter and 5 mm of 0.05 M sodium vanadate in 0.05 M sodium hydroxide solution (0% T < 330 nm) which was circulated as lamp coolant. The photolysate was concentrated in vacuo at 40 °C to yield 3.36 g of solid residue which was chromatographed on a 2.5 × 110 cm silica gel column (Grace, grade 62, 60–200 mesh) slurry packed in hexane and eluted with 2.5% ether in hexane. After elution with 2.25 L of eluate 125-mL fractions were collected to yield: fractions 1–2, 81.0 mg of exo-3,4-benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene which was identical with authentic material (IR, NMR, mp); fraction 3, 56.6 mg of a ~3:2 mixture of endo and exo isomers of starting material as determined by NMR; fractions 4–6, 171.2 mg of starting endo isomer unchanged.

Summary of Quantum Yield Results for exo-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. All quantum yield runs were performed on the microoptical bench using 305 ± 22 nm as the irradiation wavelength. The solvent was anhydrous *tert*-butyl alcohol (40 mL) and solutions were purged with purified nitrogen for 1 h prior to and during photolysis. Analysis was by high-pressure liquid chromatography using three serial 1.6 mm × 60 cm columns of octadecyl-coated sponge-surfaced glass beads[49] and eluting at a rate of 0.4 mL/min with 50% aqueous acetonitrile. A 254-nm UV detector was

employed and 4,4'-dimethoxybiphenyl was employed as internal standard.

The data are reported as follows: starting *exo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene (mmol); light absorbed (mEinsteins); 1,5-diphenylspiro[2.4]hepta-4,6-diene photoproduct (mmol), quantum yield; diphenyltoluene photoproduct mixture (mmol), quantum yield, % conversion.

Run 1: bicyclic starting material (9.09×10^{-2} mmol); 3.50×10^{-2} mEinstein; spiro photoproduct (3.36×10^{-3} mmol), $\Phi = 9.60 \times 10^{-2}$; diphenyltoluene ($3.08 \times 10^{-4}$ mmol), $\Phi = 8.80 \times 10^{-3}$; 4.04%.

Run 2: bicyclic starting material (8.44×10^{-2} mmol); 4.92×10^{-2} mEinstein; spiro photoproduct (4.63×10^{-3} mmol), $\Phi = 9.41 \times 10^{-2}$; diphenyltoluene ($4.24 \times 10^{-4}$ mmol), $\Phi = 8.60 \times 10^{-3}$; 5.99%.

Run 3: bicyclic starting material (6.32×10^{-2} mmol); 4.78×10^{-2} mEinstein; spiro photoproduct (4.54×10^{-3} mmol), $\Phi = 9.50 \times 10^{-2}$; diphenyltoluene ($4.26 \times 10^{-4}$ mmol), $\Phi = 8.90 \times 10^{-3}$; 7.86%.

Summary of Quantum Yield Results for *endo*-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene. Quantum yield runs were performed on the microoptical bench using 305 ± 22 nm as the irradiation wavelength and anhydrous *tert*-butyl alcohol (40 mL). The sensitized quantum yield of isomerization is reported under the exploratory photolysis of the starting material (vide supra). Analysis for run 3 was by high-pressure liquid chromatography using three serial 1.6 mm × 60 cm columns of octadecyl-coated sponge-surfaced glass beads[49] and eluting at a rate of 0.4 mL/min with 45% aqueous acetonitrile. A 254-nm UV detector was employed and 4,4'-dimethoxybiphenyl was employed as internal standard. Analysis for runs 1 and 2 was by vapor-phase chromatography using a 0.64 × 150 cm column packed with 5% QF-1 on 100–120 Varaport 30 at 160 °C using 9-methylanthracene as internal standard.

The data are reported as follows: starting *endo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene (mmol); light absorbed (mEinsteins); 1,5-diphenylspiro[2.4]hepta-4,6-diene photoproduct (mmol), quantum yield; diphenyltoluene photoproducts (mmol), quantum yield; % conversion.

Run 1: bicyclic starting material (1.04×10^{-1} mmol); 2.78×10^{-2} mEinstein; spiro photoproducts (2.36×10^{-3} mmol); $\Phi = 8.49 \times 10^{-2}$; diphenyltoluenes ($3.59 \times 10^{-4}$ mmol); $\Phi = 1.29 \times 10^{-2}$; 2.61%.

Run 2: bicyclic starting material (6.65×10^{-2} mmol); 2.94×10^{-2} mEinstein; spiro photoproducts (2.50×10^{-3} mmol); $\Phi = 8.50 \times 10^{-2}$; diphenyltoluenes ($3.73 \times 10^{-4}$ mmol); $\Phi = 1.27 \times 10^{-2}$; 4.32%.

Run 3: bicyclic starting material (7.74×10^{-2} mmol); 4.96×10^{-2} mEinstein; spiro photoproducts (4.19×10^{-3} mmol); $\Phi = 8.45 \times 10^{-2}$; diphenyltoluenes ($6.59 \times 10^{-4}$ mmol); $\Phi = 1.33 \times 10^{-2}$; 6.26%.

Summary of Quantum Yield Results for *exo*-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene. All quantum yield runs were performed on a microoptical bench using 305 ± 22 nm as the irradiation wavelength and anhydrous *tert*-butyl alcohol (40 mL). Analysis was by high-pressure liquid chromatography using a 50 × 0.96 cm silica microsphere[43] column (particle size 10–30 μm) and eluting with 0.03% acetone in hexane. A 254-nm UV detector was employed and biphenyl was employed as internal standard.

The data are reported as follows: starting *exo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene (mmol); light absorbed (mEinsteins); *anti*-2-phenylspiro[cyclopropane-1,1'-[1*H*]indene] photoproduct (mmol), quantum yield; 1-methylene-2-phenyl-1,2-dihydronaphthalene photoproduct (mmol), quantum yield; % conversion.

Run 1: bicyclic starting material (9.90×10^{-2} mmol); 2.14×10^{-2} mEinsteins; spiro photoproduct (1.34×10^{-3} mmol); $\Phi = 6.26 \times 10^{-2}$; methylenedihydronaphthalene photoproduct (1.16×10^{-3} mmol); $\Phi = 5.42 \times 10^{-2}$; 2.52%.

Run 2. bicyclic starting material (1.04×10^{-1} mmol); 4.23×10^{-2} mEinstein; spiro photoproduct (2.64×10^{-3} mmol); $\Phi = 6.24 \times 10^{-2}$; methylenedihydronaphthalene photoproduct (2.28×10^{-3} mmol); $\Phi = 5.39 \times 10^{-2}$; 4.73%.

Run 3: bicyclic starting material (1.28×10^{-1} mmol); 7.68×10^{-2} mEinsteins; spiro photoproduct (4.73×10^{-3} mmol); $\Phi = 6.16 \times 10^{-2}$; methylenedihydronaphthalene photoproduct (4.12×10^{-3} mmol); $\Phi = 5.36 \times 10^{-2}$; 6.91%.

Summary of Quantum Yield Results for *endo*-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene. All quantum yield runs were performed on the microoptical bench. Runs 1–3 used 305 ± 22 nm as the irradiation wavelength. Run 4 used 345 ± 22 nm as the irradiation wavelength and benzophenone as the added sensitizer. In all runs, the solvent was *tert*-butyl alcohol and solutions were purged with purified nitrogen for 1 h prior to and during photolysis. Analysis was by high-pressure liquid chromatography using a 50 × 0.96 cm silica microsphere[43] column (particle size 10–30 μm) and eluting with 0.03% acetone in hexane. A 254-nm UV dectector was

employed and biphenyl was employed as internal standard.

The data are reported as follows: starting *endo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene (mmol); added benzophenone, if any (mmol); light absorbed (mEinsteins); *syn*-2-phenylspiro[cyclopropane-1,1'-[1*H*]indene] photoproduct (mmol), quantum yield; 1-methylene-2-phenyl-1,2-dihydronaphthalene photoproduct (mmol), quantum yield; or, isomeric *exo*-3,4-benzo-2-methylene-6-phenyl-bicyclo[3.1.0]hex-3-ene (mmol), quantum yield; % conversion.

Run 1: bicyclic starting material (1.20×10^{-1} mmol); 2.78×10^{-2} mEinstein; spiro photoproduct (2.60×10^{-4} mmol); $\Phi = 9.40 \times 10^{-3}$; methylenedihydronaphthalene photoproduct (2.20×10^{-3} mmol); $\Phi = 7.91 \times 10^{-2}$; 2.05%.

Run 2: bicyclic starting material (1.08×10^{-1} mmol); 4.77×10^{-2} mEinstein; spiro photoproduct (4.25×10^{-4} mmol); $\Phi = 8.90 \times 10^{-3}$; methylenedihydronaphthalene photoproduct (3.78×10^{-3} mmol); $\Phi = 7.92 \times 10^{-2}$; 3.89%.

Run 3: bicyclic starting material (1.42×10^{-1} mmol); 6.70×10^{-2} mEinstein; spiro photoproduct (6.23×10^{-4} mmol); $\Phi = 9.30 \times 10^{-3}$; methylenedihydronaphthalene photoproduct (5.28×10^{-3} mmol); $\Phi = 7.88 \times 10^{-2}$; 4.16%.

Run 4: bicyclic starting material (1.74×10^{-1} mmol); benzophenone sensitizer (2.93 mmol); 4.68×10^{-2} mEinsteins; exo bicyclic diene (5.48×10^{-3} mmol); $\Phi = 0.117$; 3.15%.

Summary of Quantum Yield Results for *exo*-3,4-Benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene. All quantum yield runs were performed on the microoptical bench using 305 ± 22 nm as the irradiation wavelength and anhydrous *tert*-butyl alcohol (40 mL). Analysis was by high-pressure liquid chromatography using a 50 × 0.96 cm silica microsphere[43] column (particle size 10–30 μm) and eluting with 0.03% acetone and 0.5% ether in hexane. A 254-nm UV detector was employed and benzophenone was employed as internal standard.

The data are reported as follows: starting *exo*-3,4-benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene (mmol); light absorbed (mEinsteins); *anti*-2-(4-methoxyphenyl)spiro[cyclopropane-1,1'-[1*H*]indene] photoproduct (mmol), quantum yield; 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene photoproduct (mmol), quantum yield; % conversion.

Run 1: bicyclic starting material (5.20×10^{-2} mmol); 2.01×10^{-2} mEinstein; spiro photoproduct (1.17×10^{-3} mmol); $\Phi = 5.82 \times 10^{-2}$; methylenedihydronaphthalene photoproduct (1.45×10^{-3} mmol); $\Phi = 7.21 \times 10^{-2}$; 5.04%.

Run 2: bicyclic starting material (8.25×10^{-2} mmol); 2.16×10^{-2} mEinstein; spiro photoproduct (1.26×10^{-3} mmol); $\Phi = 5.83 \times 10^{-2}$; methylenedihydronaphthalene photoproduct (1.57×10^{-3} mmol); $\Phi = 7.27 \times 10^{-2}$; 3.43%.

Run 3: bicyclic starting material (1.17×10^{-1} mmol); 2.12×10^{-2} mEinstein; spiro photoproduct (1.25×10^{-3} mmol); $\Phi = 5.90 \times 10^{-2}$; methylenedihydronaphthalene photoproduct (1.56×10^{-3} mmol); $\Phi = 7.35 \times 10^{-2}$; 2.40%.

Summary of Quantum Yield Results for *endo*-3,4-Benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene. All quantum yield runs were performed on the microoptical bench. Runs 1–3 used 305 ± 22 nm as the irradiation wavelength. Run 4 used 345 ± 22 nm as the irradiation wavelength and benzophenone as the added sensitizer. In all runs, the solvent was *tert*-butyl alcohol. Analysis was by high-pressure liquid chromatography using a 50 × 0.96 cm silica microsphere[43] column (particle size 10–30 μm) and eluting with 0.03% acetone and 0.5% ether in hexane. A 254-nm UV detector was employed and benzophenone was employed as internal standard for runs 1–3. For run 4 the internal standard employed was deoxybenzoin.

The data are reported as follows: starting *endo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene (mmol); added benzophenone, if any (mmol); light absorbed (mEinsteins); 1-methylene-2-(4-methoxyphenyl)-1,2-dihydronaphthalene photoproduct (mmol); quantum yield; or, isomeric *exo*-3,4-benzo-2-methylene-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-3-ene (mmol); quantum yield; % conversion.

Run 1: bicyclic starting material (1.13×10^{-1} mmol); 3.58×10^{-2} mEinstein; methylenedihydronaphthalene photoproduct (3.33×10^{-3} mmol); $\Phi = 9.30 \times 10^{-2}$; 2.95%.

Run 2: bicyclic starting material (9.10×10^{-2} mmol); 3.37×10^{-2} mEinstein; methylenedihydronaphthalene photoproduct (3.10×10^{-3} mmol); $\Phi = 9.20 \times 10^{-2}$; 3.41%.

Run 3: bicyclic starting material (7.22×10^{-2} mmol); 3.71×10^{-2} mEinstein; methylenedihydronaphthalene photoproduct (3.48×10^{-3} mmol); $\Phi = 9.38 \times 10^{-2}$; 4.83%.

Run 4: bicyclic starting material (9.52×10^{-2} mmol); 4.56×10^{-2} mEinstein; exo bicyclic diene (5.78×10^{-3} mmol); $\Phi = 1.26 \times 10^{-1}$;

6.15%.

Emission Studies. Magic Multipliers.[4] Emission spectra were measured using an Aminco–Kiers spectrofluorimeter equipped with a Hanovia 901C-1 150-W xenon arc lamp. For each compound, the fluorescence spectrum was measured at both 77 and 295 K with solutions having optical densities in the range of 0.8 to 1.8 in 4:1 methylcyclohexane–isopentane under otherwise identical conditions. Magic multipliers were obtained by dividing the integrated emission intensities at 77 K by the integrated emission intensities at 295 K. The average value obtained for each compound was as follows: (1) *exo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene, M = 41.7 (three runs); (2) *endo*-2-methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene, M = 36.5 (four runs); (3) *exo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene, M = 99.6 (five runs); (4) *endo*-3,4-benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene, M = 91.2 (four runs); (5) *exo*-3,4-benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]-hex-3-ene, M = 120 (four runs); (6) *endo*-3,4-benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene, M = 114 (four runs).

Single Photon Counting. The apparatus and procedure have been described previously.[4,8a] The experiments were run such that data was collected until a minimum of 2000 counts was collected in the highest channel. Data was collected at <3% of the lamp frequency to assure that few double photons were collected. Excitation wavelength ranged from 260 to 275 nm and emission was monitored in the range from 320 to 335 nm with an RCA 8850 photomultiplier. Optical densities were adjusted from 0.8 to 2.0 at the excitation wavelength. The "A value" was used as the measure of the relative fit of the computer calculated decay curve to the experimentally collected curve. The decay rate for each compound was determined to be independent of excitation wavelength, emission wavelength, and sample OD with A value <5%. All runs were performed at 77 K. The data are reported as follows: compound, average lifetime, average decay rate, number of runs, A value.

(1) *exo*-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene, 516 ps, 1.94×10^9 s^{-1}, six runs, 0.046.

(2) *endo*-2-Methylene-4,6-diphenylbicyclo[3.1.0]hex-3-ene, 524 ps, 1.91×10^9 s^{-1}, six runs, 0.049.

(3) *exo*-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene, 256 ps, 3.90×10^9 s^{-1}, six runs, 0.046.

(4) *endo*-3,4-Benzo-2-methylene-6-phenylbicyclo[3.1.0]hex-3-ene, 468 ps, 2.14×10^9 s^{-1}, six runs, 0.048.

(5) *exo*-3,4-Benzo-6-(4-methoxyphenyl)-2-methylenebicyclo-[3.1.0]hex-3-ene, 415 ps, 2.41×10^9 s^{-1}, six runs, 0.045.

(6) *endo*-3,4-Benzo-6-(4-methoxyphenyl)-2-methylenebicyclo[3.1.0]hex-3-ene, 601 ps, 1.66×10^9 s^{-1}, six runs, 0.045.

Calculations. The Pople semiempirical SCF method[17,50] (complete neglect of differential overlap) was used for closed-shell SCF calculations. A configuration interaction treatment was applied to the SCF molecular orbitals including both single and double excitations. For single excitations, the highest six occupied and lowest six unoccupied MO's were used to give 36 configurations; double excitations were selected by a first-order perturbation approach[51,52] from the 325 possible configurations obtained by promoting from the highest five occupied to the lowest five vacant MO's. Configurations were represented as a linear combination of Slater determinants such that each configuration was an eigenfunction of the spin operator S^2 as described by Murrell and McEwen.[53] Standard methods for the reduction of many electron integrals then gave general formulas used to determine matrix elements between configurations.[17,50,53] Matrix elements between doubly excited configurations were then derived.

Standard geometries for bicyclo[3.1.0]hexenyl systems were assumed and found to compare favorably with those reported for the theoretical STO-3G equilibrium geometry for the bicyclo[3.1.0]hexenyl cation.[54] The geometries for the spiro[2.4]hepta-4,6-diene systems were based on the reported MINDO/2 calculation for the ground-state optimized geometry of spiro[2.4]hepta-4,6-diene.[55] Geometries for intermediate species were assumed.

Two electron repulsion integrals were calculated by the Pariser–Parr approach.[56] Resonance integrals were calculated by the Mulliken approximation as employed by Hoffmann,[57] but with K scaled according to the CNDO/S convention of Boyd and Whitehead.[58,59] Nearest neighbor and selected 1,3 resonance integrals were used. Valence state ionization potentials were those described by Hinze and Jaffe.[60]

Calculations were performed with Fortran IV programs[51] on a PDP-11/T55 computer having 32K words of memory. Direct disk access allowed storage and use of the large matrices encountered in configuration interaction calculations.

Registry No.—4a, 29583-83-3; 4b, 29444-93-7; 8, 66374-34-3; 9a, 66374-35-4; 9a acid chloride, 66374-36-5; 9b, 66374-37-6; 9b methyl ester, 66374-38-7; 10a, 66374-39-8; 10b, 66374-40-1; 11a, 66374-08-1; 11b, 66511-71-5; 12, 66374-09-2; 13a, 5079-90-3; 13b, 66374-10-5; 14a, 17563-11-0; 14b, 66374-11-6; 15a, 66511-72-6; 15b, 66511-73-7; 16a, 66374-12-7; 16b, 66374-13-8; 17a, 66374-14-9; 17b, 66374-15-0; 18a, 66374-16-1; 18b, 66511-74-8; 19a, 5394-86-5; 20a, 66374-17-2; 20b, 66374-18-3; 21a, 66428-41-3; 22a, 66374-19-4; 23, 4024-14-0; 24, 6057-87-0; 25, 66374-20-7; 26, 33776-38-4; 27, 16776-12-8; 28, 10468-84-5; 29, 66374-21-8; 30, 66374-22-9; trimethyl phosphonacetate, 5927-18-4; *trans*-chalcone, 614-47-1; 4-methoxyphenylacetic acid, 104-01-8; 3-(4-methoxyphenylmethylene)-1(3*H*)-isobenzofuranone, 4767-61-7; 3-(4-methoxyphenylmethyl)-1(3*H*)-isobenzofuranone, 66374-23-0; 3-phenyl-5-(phenylmethylene)-2-cyclopenten-1-one, 66374-24-1; 2-phenyl-5-(phenylmethylene)-1,3-cyclopentadiene, 66374-25-2.

References and Notes

(1) (a) This is Paper 115 of our photochemical series; (b) for a preliminary report of this work see H. E. Zimmerman and T. P. Cutler, *J. Chem. Soc., Chem. Commun.*, 232 (1978).

(2) For Paper 114 see H. E. Zimmerman, M. G. Steinmetz, and C. L. Kreil, *J. Am. Chem. Soc.*, **100**, 4146 (1978).

(3) (a) H. E. Zimmerman, D. F. Juers, J. M. McCall, and B. Schroder, *J. Am. Chem. Soc.*, **93**, 3662 (1971); (b) H. E. Zimmerman, D. F. Juers, J. M. McCall, and B. Schröder, *ibid.*, **92**, 3474 (1970).

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(9) (a) Note also pioneering work by W. Ware.[9b,c] The method in ref 9b used a sum of exponentials with fixed exponents and variable preexponential terms adjusted to fit experiment. The more recent work in ref 9c uses adjustable exponents which then correspond to actual rate constants. Except for the mode of reiteration, the latter method parallels our own technique.[4] (b) W. R. Ware, L. J. Doemeny, and T. L. Nemzek, *J. Phys. Chem.*, **77**, 2038 (1973); (c) M. H. Hui and W. R. Ware, *J. Am. Chem. Soc.*, **98**, 4718 (1976).

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(12) (a) One early example is the type A dienone rearrangement;[12b] however, the actual rearrangement step is really a ground-state process and is described in ref 11c–e as "photochemistry without light": (b) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **83**, 4484 (1961); **84**, 4527 (1962); (c) H. E. Zimmerman and W. Eberbach, *ibid.*, **95**, 3970 (1973); (d) also see ref 3.

(13) (a) N. K. Hamer and M. Stubbs, *Chem. Commun.*, 1013 (1970); (b) T. Tabata and H. Hart, *Tetrahedron Lett.*, 4929 (1969). (c) Also, two examples of toluene formation have been reported which might arise either from a parallel reaction or from a different mechanism involving hydrogen migration:[13d,e] (d) M. Rey, U. A Huber, and A. S. Dreiding, *Tetrahedron Lett.*, 3583 (1968); (e) H. Hüther and H. A. Brune, *Z. Naturforsch. B*, **23**, 1616 (1968). (f) An interesting alternative mechanism has been presented in ref 13a involving a bicyclo[3.2.0]hepta-1,3-diene intermediate which has been shown[13g] to lead to the spiro product. This alternative mechanism accounts for some but not all of the experimental observations: (g) N. K. Hamer and M. Stubbs, *Tetrahedron Lett.*, 3531 (1972).

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(15) The syn and anti designations are a bit arbitrary and depend on substitution in the system under study. In our previous systems[3] the endo isomer gave anti product and exo reactant gave syn product.

(16) The formation of endo isomer from endo precursor actually is inversion of configuration at this one carbon (i.e., C-6), since breaking of one three-ring bond is on the opposite side of C-6 from bonding to this carbon. This nomenclature is a bit confusing, but valid and necessary.

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(19) This directionality depends on our arbitrary convention of viewing the molecule from the side having the three-ring projecting above the molecular plane and also on our choice of the enantiomer for discussion.

(20) For a discussion and for references note H. E. Zimmerman, J. Boettcher, N. E. Buehler, G. E. Keck, and M. G. Steinmetz, *J. Am. Chem. Soc.*, **98**, 7680 (1976).

(21) (a) It has been noted by us earlier[21b,c] that often disruption of aromaticity is a factor leading to excited-state activation barriers or to avoidance of pathways involving aromatic rings. In the present instance, avoidance of the benzo π system suggests that this is no longer appreciably excited in the diradical species along the reaction coordinate: (b) H. E. Zimmerman and W. R. Elser, *J. Am. Chem. Soc.*, **91**, 887 (1969); (c) H. E. Zimmerman and D. R. Amick, *J. Am. Chem. Soc.*, **95**, 3977 (1973).

(22) H. E. Zimmerman, K. G. Hancock, and G. C. Licke, *J. Am. Chem. Soc.*, **90**, 4892 (1968).

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(24) (a) J. Michl, *Mol. Photochem.*, **4**, 243, 257, 287 (1972); (b) J. Michl, "Chemical Reactivity and Reaction Paths", G. Klopman, Ed., Wiley, New York, N.Y., 1974, p 301.

(25) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972), have discussed diradicals at length.

(26) (a) H. E. Zimmerman, W. T. Gruenbaum, R. T. Klun, M. G. Steinmetz, and T. R. Welter, *J. Chem. Soc., Chem. Commun.*, 228 (1978); (b) H. E. Zimmerman, "Quantum Mechanics for Organic Chemists", Academic Press, New York, N.Y., 1975, note Chapter V.

(27) Obviously, we cannot convert the excited-state wave function into the ground-state one (or the LUMO into the HOMO in the simpler approximation), since the two must remain orthogonal. The two final wave functions will still differ.

(28) Our treatment is reminiscent of that of the more traditional theory of radiationless transitions, which is difficult to utilize practically. For example, note the discussion by B. R. Henry and W. Siebrant in "Organic Molecular Photophysics", J. B. Birks, Ed., Wiley, London, 1973.

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(31) (a) In our laboratories in unpublished efforts[31b] we have uncovered some extensions of the reaction; (b) H. E. Zimmerman and D. Armesto, unpublished results.

(32) (a) All melting points were determined on a calibrated hot stage apparatus. Mass spectra were obtained using an AEI MS-902 mass spectrometer at 70 eV. Proton nuclear magnetic resonance spectra were obtained using a JEOL MH-100 or Bruker WH-270 spectrometer. High-pressure liquid chromatography was performed using an LDC 254-nm UV detector which was calibrated for the relative responses of the detected compound and standard. Column chromatography employed Vycor columns such that, with packings containing Sylvania type 2282 phosphor, elution could be monitored with a hand-held UV lamp. (b) For preparations similar to one another, one example is given in detail. For full details in the related cases see ref 32c; (c) T. P. Cutler, Ph.D. Thesis, University of Wisconsin, Madison, 1977.

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Thioxanthenylidene: A Nucleophilic Carbene[1]

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Photolysis of 9-diazothioxanthene (8) in tetrahydrofuran solution has been used to generate thioxanthenylidene (7). In the presence of cyclohexene, the primary product was the dimer thioxanthenylene. In the presence of dimethyl fumarate and dimethyl maleate, the major products were the carbene adducts 12 and 13, respectively. The data clearly show that carbene 7 exhibits nucleophilic character. Attempts were made to generate thioxanthenylidene 10,10-dioxide, but its precursor, 9-diazothioxanthene 10,10-dioxide, gave only dimer and products from 1,3-cycloaddition reactions.

The electrophilic nature of a carbene can be attenuated by overlap of its vacant p orbital with electron-donating substituents or by incorporation of the vacant p orbital into an aromatic π system. The carbene can behave as a nucleophile if extensive stabilization of the vacant p orbital is achieved.[3]

Diphenylcyclopropylidene (1)[4] and cycloheptatrienylidene (2)[5,6] are prime examples of carbenes that exhibit nucleophilic reactions toward electron-deficient alkenes (e.g., fumaronitrile

and dimethyl fumarate). In these systems, the vacant p orbital has been stabilized by incorporation into a carbocyclic aromatic π system.

Heteroatom interactions with carbenic centers are also known. Pertinent to our work are the sulfur-containing car-

benes 3,[7] 4,[8,9] 5,[10] and 6.[11] Significant interaction between the sulfur atom and the carbenic center has been demonstrated in each of these systems. Reactions with alkenes have been reported for 3 and 4, but nucleophilic character has been observed only for 3 in addition reactions with electron-deficient acetylenes and in a reversible Michael reaction with dimethyl fumarate.
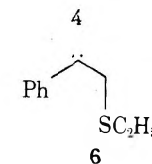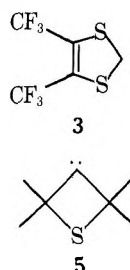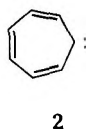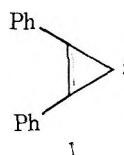
In a study of potentially nucleophilic carbenes, we have examined the generation and chemistry of thioxanthenylidene (7). The carbenic center in 7 could be highly stabilized by in-

7   A
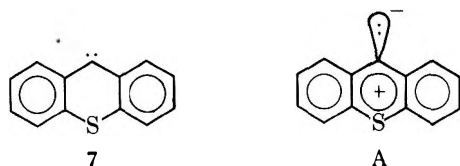
corporation into the heterocyclic aromatic π system (A), which is isoelectronic and anthracene.[12] Stable thioxanthenyl cations are well known.[13]

Recently, Durr et al.[14] have reported some preliminary work on 7. The results of our studies on 7 and a comparison with the results of Durr et al. are the main subject of this paper.

Results and Discussion

9-Diazothioxanthene (8)[15] was used as the precursor to 7. Initially we attempted to prepare 8 by nitrosation of 9-acetylaminothioxanthene, but a rapid decomposition reaction prevented this from being useful for the preparation of 8.[16] The route described by Schonberg et al.[15] was then used for the preparation of 8.

Photolytic decomposition of 8 with a 450-W medium-pressure Hanovia lamp in Vycor tubes was used to generate 7. In degassed cyclohexene solution, 7 decomposed in 30 min as evidenced from the measurement of nitrogen evolved and loss of the green color from 8. The products from this reaction are shown in Scheme I.

Dithioxanthenylene (9) is likely formed from the reaction between the carbene 7 and unreacted 8.[17] The formation of thioxanthone must result from the presence of oxygen, even though the samples were rigorously degassed, while compound 11 is the Paterno–Buchi product from 10 and cyclohexene. A reaction in dihydropyran solution gave essentially the same results, but the reaction was not clean. No evidence for a cyclopropane product was obtained in either cyclohexane or dihydropyran solutions.

Our results on the photolysis of 8 in cyclohexene solution are very similar to the results obtained by Durr et al. for photolysis of 8 in either 2-methyl-2-butene or 2,3-dimethyl-2-butene.

Scheme I

9 (29%)   10 (11%)   11 (9.5%)
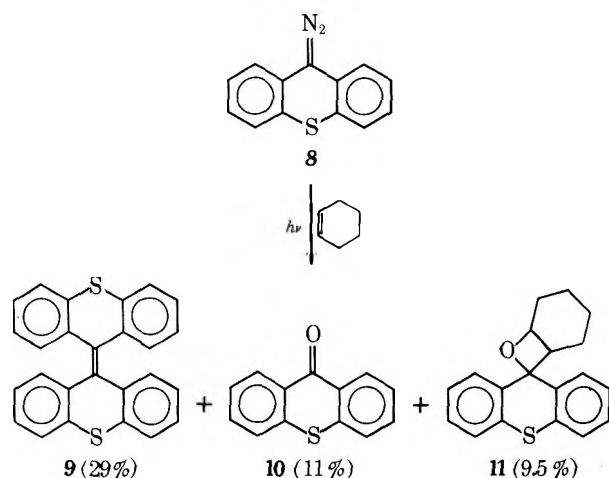
Ample precedence is available which supports dimer formation from a carbene intermediate that most likely reacts with the diazo precursor.[5,18] Thus, the formation of carbene A is inferred from these studies.

When the photolysis was carried out (Vycor filter) in a tetrahydrofuran solution containing dimethyl fumarate, the spiro adduct 12 was obtained in 32% isolated yield. The structure of 12 stands firmly on spectral and analytical data. Furthermore, the trans stereochemistry of the adduct was firmly deduced in ^{1}H NMR experiments conducted at 220 MHz. The symmetry of the trans compound leads to equivalent 1,8-peri hydrogens whose signal appeared in the NMR spectrum as a two-proton multiplet at δ 7.49, downfield from the other aromatic protons centered at δ 7.16. Moreover, on addition of Eu(fod)$_3$, the aromatic protons shifted to a clean ABCD pattern with the correct proton integration. A product with cis stereochemistry would possess nonequivalent aromatic rings and two ABCD patterns would result. Thus, the trans configuration is established. Adduct 12 showed no tendency for rearrangement (see below).

12
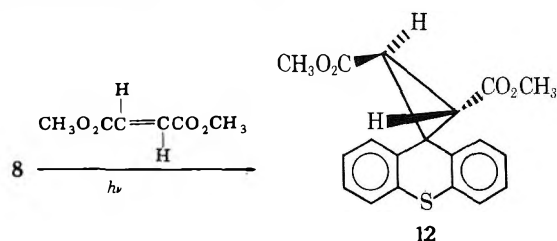
Photolysis of 8 in a tetrahydrofuran solution containing dimethyl maleate gave adduct 13 in 25% yield and thioxanthone (10) in 12% yield. No evidence was found for the presence of a spiro adduct in this reaction. The structure of 13 was
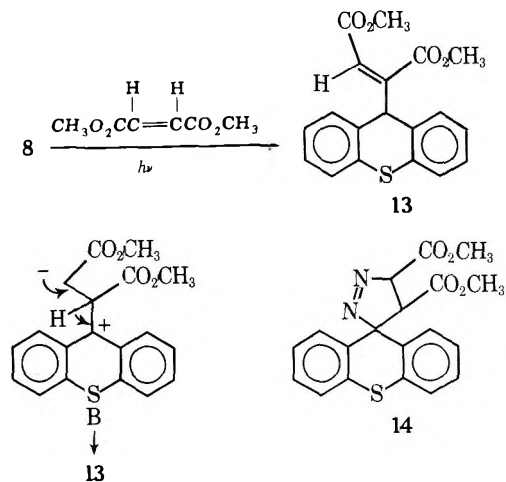
determined from spectral and analytical data. The occurrence of a singlet at δ 4.10 for the benzylic proton established the structure as nonconjugated, and the absence of allylic coupling suggests a Z configuration.[20] The nonconjugated structure is reasonable on steric grounds because a conjugated system would require an unfavorable interaction between an ester function and a peri aromatic hydrogen.[21]

The formation of 13 can be rationalized several ways. A labile spiro adduct could have formed and undergone thermal-, photochemical-, or glass-catalyzed rearrangement. Jones has observed acid-catalyzed rearrangements of spiro adducts 1 and 2 and has noted that ether solvents facilitate thermal rearrangements of spiro adducts of 2.[5] Another possibility is a Michael-type reaction between A and dimethyl maleate, and support for this process comes from Hartzler's work with dithiolium carbenes.[7] Structure B is a reasonable intermediate for both spiro rearrangement or Michael addition paths, and B could readily yield 13 as shown.[22]

Durr et al. observed that **8** reacted with *neat* dimethyl maleate in a 1,3-cycloaddition fashion to give pyrazoline **14**. Compound **14** was extremely stable to both heat and prolonged high-intensity photolysis and thus did not expel nitrogen. We have verified Durr's result and have also observed that **8** reacts in *tetrahydrofuran* solution with dimethyl maleate only under photolysis with expulsion of nitrogen.

A kinetic study showed that the rate of nitrogen evolution in the photolytic reaction of **8** with either dimethyl maleate or dimethyl fumarate in tetrahydrofuran solution was independent of the acceptor alkene concentration. A rate constant of $4.90 \pm 0.1 \times 10^{-2}$ s^{-1} for ratios of alkene to **8** ranging from 1:1 to 6:1 was obtained. These results, coupled with the observation of Durr et al. that the pyrazoline **14** is exceptionally stable to photolytic decomposition, indicate that a pyrazoline intermediate is not involved in our reaction. Moreover, the observation of dimer **9**, spiro **12**, and adduct **13** strongly suggests that carbene A is the prevailing intermediate in these reactions and that the carbene exhibits nucleophilic character.

Attempts were made to study the chemistry of thioxanthenylidene 10,10-dioxide (**15**) with the rationale that the sulfur electrons would be held in the sulfone function and therefore be unavailable for stabilization of the carbenic center. This would give an electrophilic carbene.

The photolysis of 9-diazothioxanthene 10,10-dioxide (**16**)[23] was investigated as a route to **15**. When the photolysis was conducted in cyclohexene solution, the only product observed was the dimer **17** (Scheme II). The major reaction of **16** with electron-deficient alkenes was a facile room temperature

15
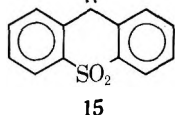
1,3-cycloaddition reaction. The pyrazoline products **18** and **19**, formed from reaction of **16** with methyl vinyl ketone (MVK) and benzyne, respectively, were characterized by spectral and analytical data. These pyrazolines were stable to photolysis but decomposed on melting. Thus, carbene formation from **15** is indicated only in the formation of dimer **17**.[17] No conclusions about its electronic character can be deduced from these results.

Experimental Section

General. All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded with a Perkin-Elmer 337 grating spectrophotometer or a Beckman Model IR-33 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained with a Varian MAT-111 spectrometer at 80 eV.
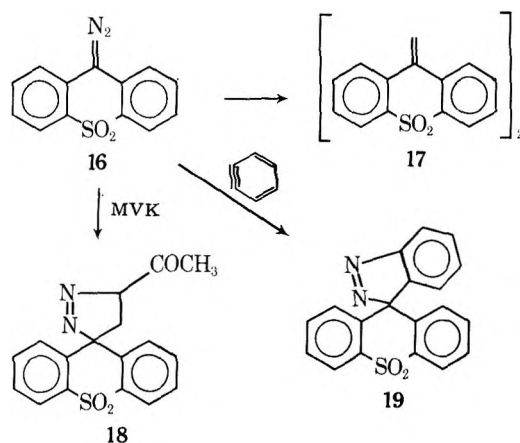
Analytical thin-layer chromatography (TLC) was accomplished on 20 × 75 mm slides coated with Malinkcrodt Silicar silica gel G at 300-μm thickness.

All photolyses were performed on degassed samples contained in closed Vycor tubes. The light source was a Hanovia 450-W medium-pressure mercury arc immersion lamp. Tetrahydrofuran was dried by distillation from lithium aluminum hydride.

Reaction mixtures were separated by column chromatography with Fisher Alumina Absorption (80–200 mesh). Chromatographic solvents were distilled before use.

Photolysis of 9-Diazothioxanthene in Cyclohexene. 9-Diazothioxanthene[15] (0.11 g, 0.5 mmol) was dissolved in 3 mL of pure cyclohexene, and the mixture was degassed in three freeze-thaw cycles. The green solution was irradiated for 50 min to give a clear yellow liquid containing a yellow precipitate.

The precipitate was identified as dithioxanthenylene (**9**): 28 mg (29%); mp 355–370 °C dec (lit.[15] decomposes above 350 °C). Anal. Calcd for C$_{26}$H$_{18}$S: C, 79.18; H, 4.57; S, 16.24. Found: C, 79.23; H, 4.46; S, 16.41.

Chromatography of the concentrated liquid (12-mL aliquots) gave two major components. The first component (fractions 9–11; benzene/hexane) was identified as 2,3-tetramethylenespiro[oxetane-4,9'-thioxanthene] (**11**) as a slightly yellow solid: 14 mg (9.5%); mp 190–191 °C; IR (KBr) 3090, 2950, 920 (s), 745 (s) cm^{-1}; NMR (CDCl$_3$) δ 0.9–2.2 (10 H, aliphatic), 6.90–7.50 (8 H, aromatic); MS *m/e* 294 (P), 278, 216 (base). Anal. Calcd for C$_{19}$H$_{18}$OS: C, 77.55; H, 6.12; S, 10.88. Found: C, 77.30; H, 6.26; S, 10.89.

The second component (fractions 13 and 14; benzene) was identified as thioxanthone (**10**): 12 mg (11%); mp 207–208 °C. The spectral properties were identical with those of an authentic sample.

Photolysis of 9-Diazothioxanthene in the Presence of Dimethyl Fumarate. A degassed solution of **8** (0.18 g, 0.8 mmol), dimethyl fumarate (0.13 g, 0.9 mmol) and tetrahydrofuran (3 mL) was subjected to photolysis for 10 min. The concentrated reaction mixture was chromatographed (CHCl$_3$) to give 86 mg (32%) of *trans*-1,2-dicarbomethoxyspiro[cyclopropane-3,9'-thioxanthene] (**12**): mp 141–143 °C (hexane); IR (KBr) 1710 (C=O), 1160 (C–O), 750 cm^{-1}; NMR (CDCl$_3$, 220 MHz) δ 3.11 (s, 2 H, cyclopropyl), 3.61 (s, 6 H, CH$_3$), 7.16 (m, 6 H, aromatic), 7.46 (m, 2 H, aromatic); MS *m/e* 340 (P), 280 (base). Anal. Calcd for C$_{19}$H$_{16}$O$_4$S: C, 67.06; H, 4.71; S, 9.41. Found: C, 67.23; H, 4.76; S, 9.14.

Photolysis of 9-Diazothioxanthene in the Presence of Dimethyl Maleate. A degassed solution of **8** (0.18 g, 0.8 mmol), dimethyl maleate (0.13 g, 0.9 mmol), and tetrahydrofuran (3 mL) was subjected to photolysis for 10 min. The concentrated solution was chromatographed (15-mL fractions) to give two compounds.

The first component (benzene) was identified as thioxanthone (22 mg, 13%) by comparison with an authentic sample (melting point, IR, and NMR).

The second component (ethyl acetate) was identified as dimethyl (9-thioxanthenyl)maleate (**13**): 40 mg (15%); mp 129–131 °C; IR (KBr) 1745 (C=O), 1560 (C=C), 1215, 1170, 1115 (C–O), 750 cm^{-1}; NMR (CDCl$_3$) δ 3.20 (s, 3 H, CH$_3$), 3.80 (s, 3 H, CH$_3$), 9.10 (s, 1 H, CH), 7.19–8.0 (m, 9 H, aromatic and alkene); MS (20 eV) *m/e* 340 (P), 212 (base). Anal. Calcd for C$_{19}$H$_{16}$O$_4$S: C, 67.06; H, 4.71; S, 9.41. Found: C, 66.93; H, 4.55; S, 9.44.

Rate of Photolytic Decomposition of 9-Diazothioxanthene in Dimethyl Fumarate and Dimethyl Maleate. A solution of **8** (123 mg, 0.55 mmol) in 3 mL of tetrahydrofuran and dimethyl fumarate or dimethyl maleate (1–6 equiv) was placed in a Vycor tube fitted with a rubber septum and a gas exit valve. The mixture was photolyzed (28 °C), and nitrogen evolution was monitored by collection over water in a buret. Plots of nitrogen concentration (corrected for water vapor) vs. time followed first-order kinetics, and thus the reaction was independent of alkene concentration. Nitrogen evolution rate was also independent of the concentration of a mixture of dimethyl maleate and dimethyl fumarate (5:1 equiv).

Photolysis of 9-Diazothioxanthene 10,10-Dioxide in Cyclohexene. A solution of **16** (0.9 g, 3.7 mmol) in 220 mL of cyclohexene was subjected to photolysis for 30 min, during which time the red color of **16** completely disappeared. A yellow precipitate of analytically pure di-9,9'-thioxanthene 10,10-dioxide (**17**) was recovered by filtration: 0.76 g (90%); mp 383–385 °C (lit.[24] mp 380 °C). Anal. Calcd for C$_{26}$H$_{16}$O$_4$S$_2$: C, 68.42; H, 3.51; S, 14.03. Found: C, 68.11; H, 3.77; S, 13.79.

Reaction of 9-Diazothioxanthene 10,10-Dioxide with Methyl Vinyl Ketone. To 0.9 g (3.7 mmol) of **16** in 50 mL of benzene was added 1 mL of methyl vinyl ketone. The red color of the diazo compound faded rapidly, and the resulting yellow solution was concentrated to a yellow solid. Recrystallization from cyclohexane/ether gave

Scheme II

0.48 g (40%) of **18** as yellow crystals: mp 149–150 °C; IR (KBr) 1710 (C=O), 1300, 1170, 830, 770, 755, 730 (aromatic) cm^{-1}; NMR (CDCl$_3$) δ 2.21 (s, 3 H, CH$_3$), 2.2–2.8 (m, 3 H, aliphatic), 7.4–8.5 (complex, 8 H, aromatic). Anal. Calcd for C$_{17}$H$_{14}$N$_2$O$_3$S: C, 62.58; H, 4.29; S, 9.82. Found: C, 62.59; H, 4.60; S, 9.94.

Reaction of 9-Diazothioxanthene 10,10-Dioxide with Benzyne. To a solution of 2.6 g (0.01 mol) of **16** and 1.35 g (0.012 mol) of iosamyl nitrite in 50 mL of methylene chloride heated at reflux was added 1.4 g (0.11 mol) of anthranilic acid in 12 mL of acetone over a period of 1.5 h. The solvent was removed to give 2.87 g of a dark residue. The residue was washed with ethanol and recrystallized from acetonitrile to give 2.85 g (86%) of **19** as orange-red crystals: mp 195–197 °C; IR (KBr) 1600 (w), 1480, 1300, 1170, 750 (aromatic) cm^{-1}; NMR (CDCl$_3$) δ 6.8, 7.75, 8.63 (complex aromatic pattern). Anal. Calcd for C$_{19}$H$_{12}$N$_2$O$_2$S: C, 68.67; H, 3.61; N, 8.43; S, 9.64. Found: C, 68.58; H, 3.55; N, 8.50; S, 9.61.

Test for Dark Reactions. Solutions of **8** in tetrahydrofuran and dimethyl fumarate or dimethyl maleate were degassed and allowed to stand in the absence of light. The solutions were monitored by NMR spectroscopy at 5-min intervals for 2 h. No evidence of any reaction was observed.

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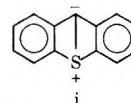
Reactions of Esters with Phosphorus Ylides. 2.[1] Mechanistic Aspects

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Esters can be directly converted into branched alkenes by reaction with an excess of a nonstabilized phosphorus ylide, (C$_6$H$_5$)$_3$P$^+$–$^-$CHR$_3$, in polar aprotic solvents or under "salt-free" conditions (Scheme I, reaction path c). On the basis of labeling experiments and the isolation of a reaction intermediate and side products, a mechanism for this conversion is proposed (Scheme II). The rate-determining step appears to be attack of the ylide carbanion on the ester carbonyl to give an alkoxybetaine **22**. This betaine rearranges to a pentacoordinate phosphorus intermediate (**23**) which, after pseudorotation, undergoes attack by a nucleophile, e.g., a second molecule of ylide to form a new phosphonium salt, triphenylphosphine oxide, and an enolate anion. After protonation of this enolate to the corresponding ketone, reaction with a third molecule of ylide provides the final product. The relation of this reaction sequence to the other known reactivities that esters can show toward phosphorus ylides is discussed.

Reaction of esters with phosphorus ylides may result in the formation of several types of products, as depicted in Scheme I. Reaction path a was first discovered by Wittig and

Schöllkopf[2] when ethyl benzoate was allowed to react with methylenetriphenylphosphorane, prepared by reacting the corresponding phosphonium bromide with phenyllithium in ether. The reaction sequence can be depicted as shown, starting with nucleophilic attack of the ylide on the ester carbonyl group to form the alkoxybetaine **1**. Loss of alkoxide ion from this betaine leads to the formation of an acylated phosphonium salt **2**. Bestmann and Arnason[3] have shown that this phosphonium salt rapidly loses a proton to a second molecule of ylide or alkoxide ion to form the acylated phosphorane **3**. Several investigators have improved this reaction by using acyl derivatives with a different leaving group (e.g., phenyl esters, phenyl thioesters[3] and imidazolides[4,5]). The phosphoranes **3** can be hydrolyzed to the corresponding ke-

Scheme I. Products from the Reaction of Esters with Phosphorus Ylides
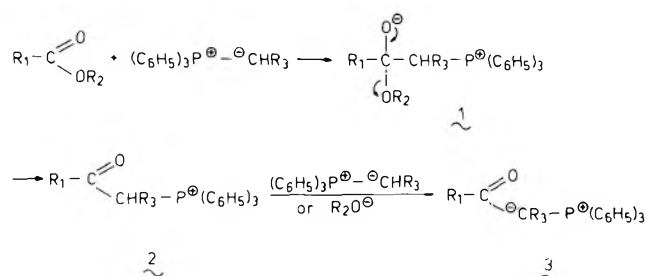
tones by refluxing with potassium hydroxide in aqueous ethanol.[3,6] Although the ylide reactivity in compounds **3** is quite low due to conjugation with the carbonyl group, aromatic aldehydes react with **3** to form the corresponding α,β-unsaturated ketones.[3,6]

When "semi-stabilized" ylides[7] such as benzylidenetriphenylphosphorane are used in conjugation with active esters (formates, oxalates, etc.), a completely different reaction (Scheme I, path b) may be observed, resulting in the formation of enol ethers **4**. The reaction is thought to proceed as a normal
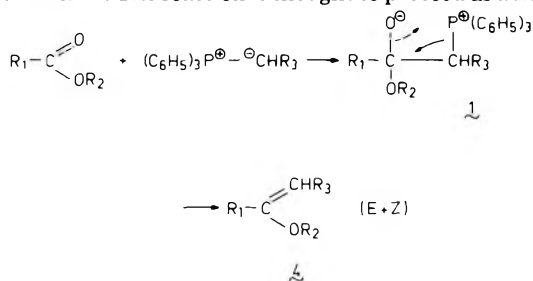
Wittig reaction on the ester carbonyl group. The reaction is usually carried out in solvents of low polarity, e.g., toluene.[8] The alkoxybetaine **1**, which is formed as before by addition of the ylide to the ester carbonyl group, now loses triphenylphosphine oxide to provide a mixture of E/Z isomers of the enol ethers **4**.[9]

Recently, when performing a Wittig reaction on a hindered γ-keto ester with an excess of methylenetriphenylphosphorane in dimethyl sulfoxide (Me$_2$SO), a third type of reaction product, the isopropenyl compound **5**, was observed.[1] This
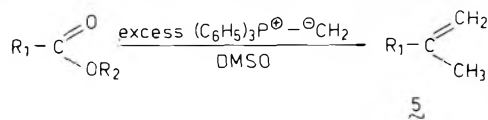
reaction was found to be generally applicable to both aromatic and aliphatic esters.[1] That indeed a different reaction path is followed in this case was shown by the observation that under the reaction conditions used phosphonium salts **2** were instantly converted into phosphoranes **3** and that these phosphoranes as well as the enol ethers **4**, prepared by independent routes, were completely stable and thus can not be intermediates (see Experimental Section). The elucidation of the mechanism which is followed in reaction path c is the subject of the present article. The scope and synthetic applications of this reaction will be published separately.[12]

Results and Discussion

Isolation of a Reaction Intermediate. When the reaction of an aromatic or aliphatic ester with excess methylenetriphenylphosphorane in Me$_2$SO is followed by GC, no intermediate products can be discovered in most cases. However, when the hindered ester ethyl o-methoxybenzoate was reacted in this way, an intermediate was observed. Upon quenching the reaction with water after 9 min at room temperature, the product contained, apart from starting material (52%) and the expected reaction product o-isopropenylanisole (**8**; 30%), 17% of a third compound which was identified as o-methoxyacetophenone (**7**). This indicated that a methyl ketone and/or its
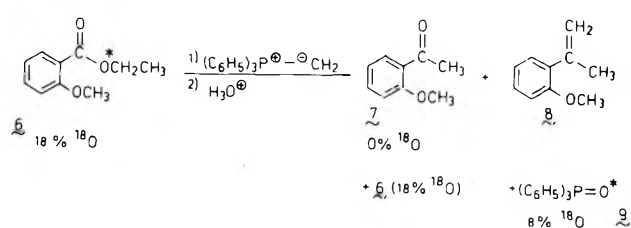
anion are intermediates in this reaction. That no signs of an intermediate methyl ketone are found in most cases is not surprising because ketones react much faster with phosphoranes than esters.[13]

Isolation of the intermediate methyl ketone provides an opportunity to determine, with the aid of labeled ester, which oxygen is the first to leave (note that in reaction path a (Scheme I) the alkoxy oxygen has left, whereas in path b this is the carbonyl oxygen). Mass spectral analysis of the reaction mixture obtained as described above from o-methoxy-2-oxabutyrophenone-2-^{18}O (**6**), containing 18% of ^{18}O, revealed that none of this isotope is retained in the methyl ketone. Surprisingly, the ^{18}O was found to end up in the triphenylphosphine oxide (**9**). This implies that the alkoxy alkyl group has become detached from its oxygen atom, a process that can only be envisaged when this oxygen has become part of an efficient nucleofugal group.

Isolation of Side Products. A clue about the fate of the ester alkyl group was found by studying the reaction of methyl nicotinate (**10**) with the smallest amount (3 equiv) of methy-

lenetriphenylphosphorane that allowed complete conversion of the ester. Two side products were found, which were identified as (*E*)- and (*Z*)-2-(3-pyridyl)-2-butene (**12**). This finding suggests that the intermediate methyl ketone (3-acetylpyridine) has also reacted with ethylidenetriphenylphosphorane. We propose that this reagent is formed in situ by alkylation of methylenetriphenylphosphorane by a process as depicted below, followed by deprotonation.
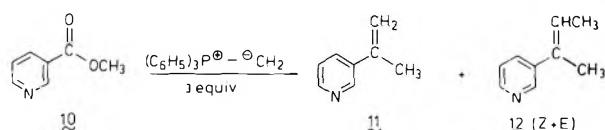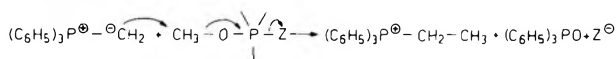
Reacting ethyl o-methoxybenzoate with 4 equiv of ethylidenetriphenylphosphorane gave, apart from the expected (*E*)- and (*Z*)-3-(o-methoxyphenyl)-2-pentene (**13**), appreciable amounts of (*E*)- and (*Z*)-1-(o-methoxyphenyl)-1-ethoxypropene (**14**). To ascertain whether these enol ethers were
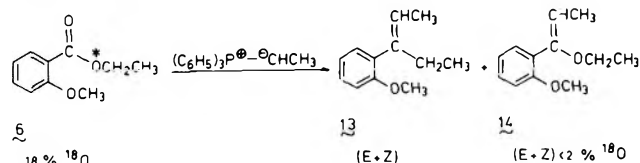
formed by a "Wittig type" reaction on the ester carbonyl (reaction path b, Scheme I), the reaction was repeated with labeled ester **6**. Mass spectral analysis showed that the enol ethers **14** are formed to an extent of at least 90% by alkylation of an intermediate enolate and not by conversion of the ester carbonyl into the ethylidene group.

Confirmation of the Presence of an Alkylating Species. The hypothesis that the ester alkoxy group is converted into an alkylating species was further substantiated by the following two experiments. (i) Addition of 1 equiv of the anion from di-*tert*-butyl α-methylmalonate (**15**) resulted in the formation of the corresponding di-*tert*-butyl α-alkyl-α-

methylmalonate (16). (ii) When isopropyl phenylacetate (17) was allowed to react with 4 equiv of "salt-free" methylene-triphenylphosphorane in benzene, a considerable amount of isopropyl α-isopropylphenylacetate (19) was formed. This sterically hindered ester is apparently stable toward attack by ylide.
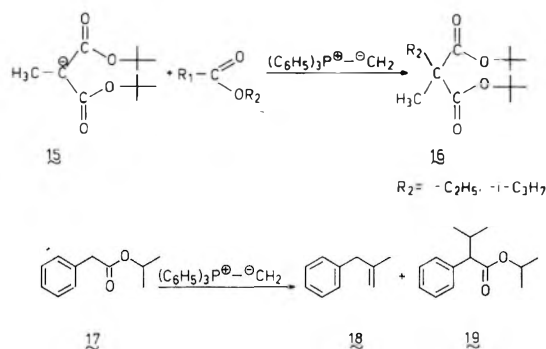
Equilibration of Enolate Ions and Phosphonium Salts. Finally, an experiment was carried out to show that enolate ions and alkyltriphenylphosphonium salts are in rapid acid–base equilibrium under the reaction conditions used. Thus, the addition of 1 equiv of ethyltriphenylphosphonium iodide to a solution of the sodium enolate of p-methoxyacetophenone (20) in Me₂SO at room temperature resulted in the formation
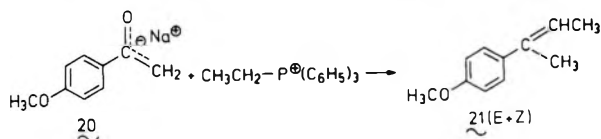
of the E and Z isomers of 2-(p-methoxyphenyl)-2-butene (21) in the same isomer ratio as in the reaction product obtained from methyl p-methoxybenzoate and ethylidenetriphenyl-phosphorane.[12] Combining the data presented thus far leads to a mechanism for the ester/ylide reaction as depicted in Scheme II. The first step in this process is thought to be attack of the ylide on the ester carbonyl to form the alkoxybetaine

Scheme II. Mechanism of the Ester/Ylide Reaction
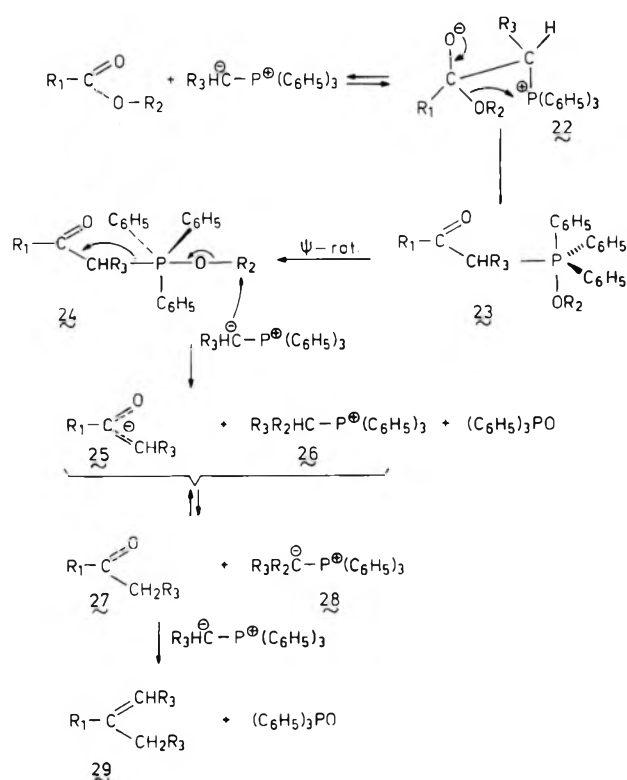
22. This betaine undergoes an intramolecular rearrangement in which the alkoxy group moves to the quaternary phosphorus atom, thus forming a pentacoordinate phosphorus intermediate 23 in which one of the apical positions is initially occupied by a phenyl group. Upon positional isomerization (pseudorotation), the energetically favored 24 is obtained, in which both polar substituents occupy apical positions.[14] The great tendency toward electron displacement in the direction of the apical axis in intermediates such as 24 is well documented.[15] Nucleophilic attack on the alkoxy group in 24 by a second molecule of ylide (or another nucleophile) therefore is likely to proceed as indicated and results in the formation of triphenylphosphine oxide, the new phosphonium salt 26, and the enolate 25. Acid–base equilibration between 25 and 26 forms the ketone 27 and the new ylide 28. Ketone 27 engages in a Wittig reaction with a third molecule of ylide to form the branched alkene 29 as the final product.

To ascertain which step in this reaction sequence is rate determining, the relative rates of a number of o-methoxy-benzoates were studied. The strong influence of the nature of the $-OR_2$ group on the reaction rate suggests that either the initial step (addition of ylide to the carbonyl group) or the nucleophilic attack on the alkoxy group in intermediate 24 is rate determining. The relative rates observed, methyl (20), ethyl (7), isopropyl (1), neopentyl (3), and *tert*-butyl (0), appear reasonable for nucleophilic addition of ylide to an ester carbonyl group.[16] Nucleophilic substitution in the intermediate 24, whether S_N2 or S_N1 in character,[17] is expected to show quite different relative rates.[16]

Comparison of the Different Reaction Paths Between Esters and Phosphorus Ylides. Comparing the mechanism of reaction paths a, b, and c makes it clear that the conformation of the initially formed alkoxybetaine is a critical factor in determining the course of the reaction. When a lithium base is used to prepare the ylide, the lithium halide formed must be expected to form a strong complex with the betaine. Schlosser[18] has proposed a twist–boat structure for such a betaine–lithium halide adduct in the Wittig reaction.

If a similar complex is formed in the case of the alkoxybetaines 1, it is quite reasonable that upon reformation of the carbonyl double bond the alkoxy group is lost, giving rise to the acylated phosphoranes 2 (Scheme I, path a). The low tendency of oxygen, complexed with lithium, to form triphenylphosphine oxide is well documented.[18]
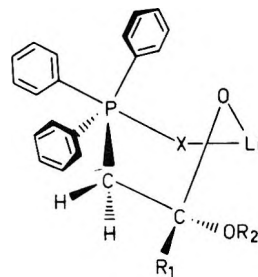
In order to obtain reaction path b the use of another cation and a "semi-stabilized" ylide[7] is necessary. Because solvents of low polarity such as toluene are used,[8] the intermediacy of an alkoxybetaine with a stereostructure as shown is also probable in these cases. The substituent that stabilized the ylide will also stabilize the incipient double bond of the enol ether. Other factors in determining the different outcome of the reaction can be higher reaction temperatures and the less strongly bonded oxygen.

When a strongly solvating aprotic solvent is used, a staggered form as depicted in structure 22 can be expected to predominate. In this situation the alkoxy group is near the quaternary phosphorus atom, a "conditio sine qua non" for the intramolecular rearrangement that is to take place in reaction path c. This strong solvation is only necessary when

alkali halide is present in the reaction mixture. Execution of the reaction under "salt-free" conditions (see Experimental Section) in a variety of solvents has proved to be an excellent way to obtain high yields of branched alkenes according to path c. This is especially beneficial in the case of aliphatic esters, where initially mixtures of products were obtained.[1]

A different improvement of the reaction is possible by adding 1 equiv of the corresponding phosphonium salt to the ylide solution. In the course of the reaction this phosphonium salt is converted into another equivalent of the same ylide so that the formation of side products by reaction with homologous ylide 28 is largely suppressed.

Finally, it is worth noting that no support for the suggestion of Vedejs and Snoble,[19] that the Wittig reaction with ketones and aldehydes occurs via a $\pi 2_s + \pi 2_a$ cycloaddition mechanism, can be derived from our experiments, which show that even esters react by nucleophilic addition of the ylides to the ester carbonyl group.

Experimental Section

Melting points were taken with a Büchi SMP-20 melting point apparatus and are uncorrected. GC analyses were run on a Hewlett-Packard 402 gas chromatograph equipped with a flame ionization detector using the columns indicated. Preparative GC was carried out using a Varian 920 gas chromatograph equipped with a thermal conductivity detector. Proton magnetic resonance spectra were recorded on a 100-Jeol PFT spectrometer. Chemical shifts are reported in parts per million on a scale relative to tetramethylsilane as an internal standard. Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constants, and interpretation). Mass spectral data were obtained with an AEI-MS 902 apparatus at an ionization potential of 70 eV.

A "dry solvent" refers to solvents distilled from calcium hydride or dried over sodium wire. The term "standard workup conditions", which is used in the following Experimental Section, refers to the following product isolation procedure: pouring the reaction mixture onto a 3-fold quantity of a mixture of crushed ice and pentane; stirring overnight; filtration of the precipitate; separation of the pentane layer and extraction of the water/Me$_2$SO layer twice with a 0.5-fold quantity of pentane; treatment of the combined pentane layers with anhydrous magnesium sulfate; filtration; solvent removal under reduced pressure; and subjection of the resulting oil to short-path distillation.

Reactivity of Phenacyltriphenylphosphonium Bromide (2; R₁ = Ph, R₃ = H) and Phenacylidenetriphenylphosphorane (3; R₁ = Ph, R₃ = H) toward Methylenetriphenylphosphorane. A dry, nitrogen-purged, 250-mL three-neck round-bottom flask fitted with an addition funnel, magnetic stirrer, and nitrogen system was charged with 2.0 g (0.05 mol) of sodium hydride[20] and 35 mL of dry Me$_2$SO to prepare a 0.05 M methylsulfinyl carbanion solution.[13a] The flask was cooled to room temperature, and a solution of 20.2 g (0.05 mol) of methyltriphenylphosphonium iodide in 70 mL of dry Me$_2$SO was added over a 30-min period. Stirring was continued for 30 min. Phenacyltriphenylphosphonium bromide[21] (11.6 g, 0.0025 mol) in 35 mL of dry Me$_2$SO was added over a 2-h period to the yellow-orange colored ylide solution. Stirring was continued for 3 h at room temperature. The resulting solution was poured into 250 mL of water and stirred for 2 h. The white precipitate was collected on a Büchner filter and dried (reduced pressure, 50 °C, calcium chloride). There was obtained 7.1 g (93%) of phenacylidenetriphenylphosphorane as a white crystalline solid: mp 176–178 °C (lit.[3,21] mp 178–180 °C); NMR (CDCl$_3$) δ 7.99–7.19 (m, 20, arom), 4.39 (d, 1, J = 24 Hz (^{1}H–^{31}P), =CH).

Reactivity of 1-Ethoxy-1-phenylethene (4; R₁ = Ph, R₂ = C₂H₅, R₃ = H) toward Methylenetriphenylphosphorane. A solution of 1-ethoxy-1-phenylethene (3.0 g, 0.02 mol), prepared as described in the literature,[22] in 10 mL of dry Me$_2$SO was added over a 30-min period at room temperature to a solution of 0.05 mol of methylenetriphenylphosphorane in 105 mL of dry Me$_2$SO, prepared as described above using 2.00 g (0.05 mol) of sodium hydride[20] and 20.2 g (0.05 mol) of methyltriphenylphosphonium iodide. Stirring was continued for 1 h at room temperature and for 1 h at 55 °C. After workup under standard conditions, there was obtained 2.8 g (93%) of starting material (4): $n^{22}$$_D$ 1.5304 (lit.[23] $n^{25.5}$$_D$ 1.5287); NMR (CDCl$_3$) δ 7.54 (m, 2, arom), 7.18 (m, 3, arom), 4.50 (d, 1, J = 2.5 Hz, =CH), 4.04 (d, 1, J = 2.5 Hz, =CH), 3.78 (q, 2, J = 7 Hz, –OCH$_2$–), 1.36 (t, 3, J = 7 Hz, –CH$_3$).

***o*-Methoxy-2-oxabutyrophenone-2-^{18}O (6).** An excess of *o*-methoxybenzoyl chloride in anhydrous diethyl ether was refluxed with absolute ethanol containing 75% ^{18}O.[24] After 1 h unlabeled absolute ethanol was added to obtain equimolarity. After workup under standard conditions, there was obtained 1.6 g (about 100%) of ethyl *o*-methoxybenzoate (6), containing 17.69 ± 0.03% of ^{18}O[25] in the ethoxy group: NMR (CDCl$_3$) δ 7.64–6.84 (m, 4, arom), 4.31 (q, 2, J = 7 Hz, –OCH$_2$–). 3.84 (s, 3, –OCH$_3$), 1.36 (t, 3, J = 7 Hz, –CH$_3$).

Isolation of a Reaction Intermediate. Reaction of *o*-Methoxy-2-oxabutyrophenone-2-^{18}O (6) with Methylenetriphenylphosphorane. To a stirred solution of 12.0 mmol of methylenetriphenylphosphorane, prepared as described above using 4.85 g (12.0 mmol) of methyltriphenylphosphonium iodide and 0.48 g (12.0 mmol) of sodium hydride,[20] in 15 mL of dry Me$_2$SO was added 0.54 g (3.0 mmol) of ester 6 in one portion (the addition funnel was rinsed with an extra 5 mL of dry Me$_2$SO) at room temperature. After workup under standard conditions, there was obtained 0.27 g of a colorless oil. The collected precipitate was dried (reduced pressure, 50 °C, calcium chloride) and consisted mainly of triphenylphosphine oxide. Preparative GC (6 m, 20% SE-30, Chromosorb W 60–80 mesh) gave three fractions which were analyzed by NMR and mass spectrometry.[25] Analytical GC (2 m, 3% SE-30, Gas Chrom Q 80–100 mesh) showed the following product distributions: 56% of *o*-isopropenylanisole (8), containing 0% of ^{18}O [$n^{22}$$_D$ 1.5330 (lit.[26] $n^{29}$$_D$ 1.5296); NMR (CDCl$_3$) δ 7.18–6.86 (m, 4, arom), 5.12 (m, 1, =CH), 5.04 (m, 1, =CH), 3.81 (s, 3, –OCH$_3$), 2.15 (s, 3, –CH$_3$)], 12% of *o*-methoxyacetophenone (7), containing 0% of ^{18}O [$n^{22}$$_D$ 1.5386 (lit.[27] $n^{20}$$_D$ 1.5393); NMR (CDCl$_3$) δ 7.66–6.95 (m, 4, arom), 3.91 (s, 3, –OCH$_3$), 2.63 (s, 3, CH$_3$)], and 32% of starting ester 6. The isolated triphenylphosphine oxide (9) contained about 8% of ^{18}O[25] (calcd,[28] 9.87%), mp 155–157 °C (lit.[29] mp 159 °C).

Isolation of Side Products. Reaction of Methyl Nicotinate (10) with Methylenetriphenylphosphorane. To a stirred solution of 0.06 mol of methylenetriphenylphosphorane, prepared as described above using 24.4 g (0.06 mol) of methyltriphenylphosphonium iodide and 2.40 g (0.06 mol) of sodium hydride,[20] in 100 mL of dry Me$_2$SO was added 2.74 g (0.02 mol) of methyl nicotinate (10) in 20 mL of dry Me$_2$SO in one portion. Stirring was continued for 1 h at room temperature and for 1 h at 55 °C. Workup under standard conditions yielded 1.83 g of a colorless oil. Preparative GC (20% SE-30) gave three fractions which were analyzed by NMR and the compositions of which were determined by analytical GC (3% SE-30): 39% of 2-(3-pyridyl)-propene (11) [$n^{23}$$_D$ 1.5418 (lit.[30] $n^{20}$$_D$ 1.5431); NMR (CDCl$_3$) δ 8.56–7.13 (m, 4, arom), 5.38 (s, 1, =CH), 5.14 (m, 1, =CH), 2.20 (s, 3, –CH$_3$)], 14% of (Z)-2-(3-pyridyl)-2-butene [(Z)-12] [NMR (CDCL$_3$) δ 8.32–7.13 (m, 4, arom), 5.59 (q, 1, J = 7 Hz, =CH), 1.98 (m, 3, –CH$_3$), 1.58 (d of m, 3, J = 7 Hz, –CH$_3$)], and 47% of (E)-2-(3-pyridyl)-2-butene [(E)-12] [NMR (CDCl$_3$) δ 8.42–7.02 (m, 4, arom), 5.80 (q, 1, J = 7 Hz, =CH), 1.97 (s, 3, –CH$_3$), 1.78 (d, J = 7 Hz, –CH$_3$)].

Reaction of *o*-Methoxy-2-oxabutyrophenone-2-^{18}O (6) with Ethylidenetriphenylphosphorane. To a stirred solution of 9.0 mmol of ethylidenetriphenylphosphorane, prepared as described above using 5.0 g (12.0 mmol) of ethyltriphenylphosphonium iodide and 0.36 g (9.0 mmol) of sodium hydride,[20] in 12 mL of dry Me$_2$SO was added 0.54 g (3.0 mmol) of ester 6 in one portion at room temperature (the addition funnel was rinsed with an extra 5 mL of dry Me$_2$SO). Stirring was continued for 2.5 h. After workup under standard conditions, there was obtained 0.73 g of a pale yellow oil. Its composition was determined by analytical GC (3% SE-30). Preparative GC (20% SE-30) gave four fractions which were analyzed by mass spectrometry and NMR: 85% of (Z)-3-(o-methoxyphenyl)-2-pentene [(Z)-13] [NMR (CDCl$_3$) δ 7.29–6.18 (m, 4, arom), 5.57 (q, 1, J = 7 Hz, =CH), 4.73 (s, 3, –OCH$_3$), 2.33 (q, 2, J = 7 Hz, –CH$_2$–), 1.43 (d, 3, J = 7 Hz, –CH$_3$), 0.93 (t, 3, J = 7 Hz, –CH$_3$)], containing 0% ^{18}O, 6% of (E)-3-(o-methoxyphenyl)-2-pentene [(E)-13] [NMR (CDCl$_3$) δ 7.28–6.76 (m, 4, arom), 5.43 (q, 1, J = 7 Hz, =CH), 3.76 (s, 3, –OCH$_3$), 2.48 (q, 2, J = 7 Hz, –CH$_2$–), 1.76 (d, 3, J = 7 Hz, –CH$_3$), 0.86 (t, 3, J = 7 Hz, –CH$_3$)], containing 0% of ^{18}O, 8% of (E)-1-(o-methoxyphenyl)-1-ethoxypropene [(E)-14] [NMR (CDCl$_3$) δ 7.46–6.80 (m, 4, arom), 5.10 (q, 1, J = 7 Hz, =CH), 3.78 (s, 3, –OCH$_3$), 3.59 (q, 2, J = 7 Hz, –OCH$_2$–), 1.79 (d, 3, J = 7 Hz, –CH$_3$), 1.28 (t, 3, J = 7 Hz, –CH$_3$)], containing 1.80 ± 0.05% of ^{18}O,[25] and 1% of (Z)-1-(o-methoxyphenyl)-1-ethoxypropene [(Z)-14] [NMR (CDCl$_3$) δ 7.46–6.80 (m, 4, arom), 4.87 (q, 1, J = 7 Hz, =CH), 3.81 (s, 3, –OCH$_3$), 2.97 (q, 2, J = 7 Hz, –OCH$_2$–), 1.44 (d, 3, J = 7 Hz, –CH$_3$), 1.20 (t, 3, J = 7 Hz, –CH$_3$)], containing 1.80 ± 0.05% of ^{18}O.[25]

Confirmation of the Presence of an Alkylating Species. Reaction in the Presence of the Anion of Di-*tert*-butyl α-Methylmalonate (15). Di-*tert*-butyl malonate[31] was alkylated in 70% yield (after vacuum distillation) using potassium *tert*-butylate in *tert*-butyl

alcohol and methyl iodide as the alkylating agent: bp 37–39 °C (0.02 mm); n^{23}_D 1.4151; NMR (CDCl$_3$) δ 3.27 (q, 1, J = 7.0 Hz, =CH), 1.47 (s, 18, *tert*-butyl CH$_3$), 1.35 (d, 3, J = 7.0 Hz, –CH$_3$).

A solution of 0.08 mol of methylenetriphenylphosphorane, prepared as described above from 32.3 g (0.08 mol) of methyltriphenylphosphonium iodide and 3.20 g (0.08 mol) of sodium hydride,[20] in 80 mL of dry Me$_2$SO was added over a 30-min period at room temperature to a stirred solution of 0.02 mol of the appropriate ester (see below) and 0.02 mol of the sodium salt of di-*tert*-butyl α-methylmalonate (15) in 20 mL of dry Me$_2$SO. Stirring was continued at room temperature for the periods of time indicated below. After workup under standard conditions, the following results were obtained.

(A) In the case of ethyl 2-naphthoate (stirring for 2 h), a yield of 6.9 g was obtained. Preparative GC (20% SE-30) gave three fractions which where identified by NMR and analytical GC (3% SE-30): 2-isopropenylnaphthalene (46%) [mp 54–55 °C (lit.[32] mp 54°C); NMR (CDCl$_3$) δ 7.76–7.32 (m, 7, arom), 5.53 (s, 1, =CH), 5.22 (m, 1, =CH), 2.32 (s, 3, –CH$_3$)], di-*tert*-butyl α-methylmalonate (16; R$_2$ = H) (34%), and di-*tert*-butyl α-methyl-α-ethylmalonate (16; R$_2$ = C$_2$H$_5$) (20%) [NMR (CDCl$_3$) δ 1.83 (q, 2, J = 7.5 Hz, –CH$_2$–), 1.45 (s, 18, CH$_3$), 1.29 (s, 3, –CH$_3$), 0.86 (t, 3, J = 7.5 Hz, CH$_3$)].

(B) In the case of isopropyl benzoate (stirring for 16 h), a yield of 4.1 g was obtained. Preparative GC (20% SE-30) gave three fractions which were identified by analytical GC (3% SE-30) and NMR: isopropenylbenzene (39%) [n^{22}_D 1.5400 (lit.[33] n^{20}_D 1.5386); NMR (CDCl$_3$) δ 7.52–7.22 (m, 5, arom), 5.35 (s, 1, =CH), 5.06 (m, 1, =CH), 2.16 (s, 3, –CH$_3$)], di-*tert*-butyl α-methylmalonate (16; R$_2$ = H) (43%), and di-*tert*-butyl α-methyl-α-isopropylmalonate (16; R$_2$ = *i*-C$_3$H$_7$) (18%) [NMR (CDCl$_3$) δ 2.40 (m, 1, J = 7.0 Hz, –CH), 1.43 (s, 18, –CH$_3$), 1.22 (s, 3, –CH$_3$), 0.91 (d, 6, J = 7.0 Hz, –CH$_3$)].

Reaction with Isopropyl α-Phenylacetate (17). To a dry, nitrogen-purged, 250-mL one-neck round-bottom flask fitted with a stopper and magnetic stirrer and charged with 11.0 g (0.04 mol) of "salt-free"[34] methylenetriphenylphosphorane in 100 mL of dry benzene was added 1.79 g (0.01 mol) of isopropyl α-phenylacetate in one portion under a nitrogen stream at room temperature. Stirring was continued for 20 h. Workup under standard condtions yielded 1.30 g (75%) of an oil. Preparative GC (20% SE-30) gave two fractions (analyzed by analytical GC (3% SE-30) and NMR): 2-benzylpropene (18; 54%) [NMR (CDCl$_3$) δ 7.34–7.10 (m, 5, arom), 4.81 (s, 1, =CH), 4.74 (s, 1, =CH), 3.34 (s, 2, –CH$_2$–), 1.71 (s, 3, –CH$_3$)] and isopropyl α-phenyl-α-isopropylacetate (19) [NMR (CDCl$_3$) δ 7.20 (m, 5, arom), 5.02 (septet, 1, J = 6 Hz, –OCH), 3.15 (d, 1, J = 10.5 Hz, –CH$_3$), 2.40 (d of septets, 1, J = 7 and 10.5 Hz, –CH(CH$_3$)$_2$), 1.24 (d, 3, J = 6 Hz, –CH$_3$), 1.16 (d, 3, J = 6 Hz, –CH$_3$), 1.08 (d, 3, J = 7 Hz, –CH$_3$), 0.72 (d, 3, J = 7 Hz, –CH$_3$)].

Equilibration of Enolates and Phosphonium Salts. Reaction of the Anion of *p*-Methoxyacetophenone (20) with Ethyltriphenylphosphonium Iodide. A dry, nitrogen-purged, 250-mL three-neck round-bottom flask fitted with a magnetic stirrer and a nitrogen system was charged with 0.80 g (0.02 mol) of sodium hydride,[20] 20 mL of dry Me$_2$SO, and 3.0 g (0.02 mol) of *p*-methoxyacetophenone. Stirring was continued at room temperature till the evolution of hydrogen had ceased. Ethyltriphenylphosphonium iodide (8.4 g, 0.02 mol) was added in one portion, and stirring was continued for 2 h at room temperature. Workup under standard conditions yielded 2.00 g (62%) of an oil. Preparative GC (20% SE-30) gave three fractions which were analyzed by analytical GC (3% SE-30) and NMR: (Z)-2-(*p*-methoxyphenyl)-2-butene [(Z)-21; 60%] [NMR (CDCl$_3$) δ 7.13 (d, 2, J = 8 Hz, arom), 6.85 (d, 2, J = 8 Hz, arom), 5.52 (q, 1, J = 7 Hz, =CH), 3.81 (s, 3, –OCH$_3$), 2.04 (s, 3, –CH$_3$), 1.64 (d, 3, J = 7 Hz, –CH$_3$)], *p*-methoxyacetophenone (10%) [mp 35–36 °C (lit.[35] mp 37–38 °C); NMR (CDCl$_3$) δ 7.90 (d, 2, J = 8 Hz, arom), 6.90 (d, 2, J = 8 Hz, arom), 3.85 (s, 3, –OCH$_3$), 2.57 (s, 3, –CH$_3$)], and (E)-2-(*p*-methoxyphenyl)-2-butene [(E)-21; 30%] [NMR (CDCl$_3$) δ 7.26 (d, 2, J = 8 Hz, arom), 6.80 (d, 2, J = 8 Hz, arom), 5.76 (q, 1, J = 7 Hz, =CH), 3.80 (s, 3, –OCH$_3$), 2.04 (s, 3, –CH$_3$), 1.81 (d, 3, J = 7 Hz, –CH$_3$)].

Determination of the Relative Rates of Some o-Methoxybenzoates in the Ester/Ylide Reaction. To a dry, nitrogen-purged, 250-mL three-neck round-bottom flask fitted with a magnetic stirrer and a nitrogen system and charged with 8.5 g (30.9 mmol) of "salt-free"[34] methylenetriphenylphosphorane in 100 mL of dry Me$_2$SO was added a mixture of 0.26 g (1.55 mmol) of methyl o-methoxybenzoate, 0.28 g (1.55 mmol) of ethyl o-methoxybenzoate, 0.30 g (1.55 mmol) of isopropyl o-methoxybenzoate, 0.32 g (1.55 mmol) of *tert*-butyl o-methoxybenzoate, 0.34 g (1.55 mmol) of neopentyl o-methoxybenzoate, and 0.20 g (1.55 mmol) of naphthalene (internal standard) in 20 mL of dry Me$_2$SO in one portion. Stirring was continued for 100 h at room temperature. The reaction was followed by GC (3% SE-30) by taking small samples from the reaction mixture and adding these

to a few drops of water and pentane. After workup of the reaction mixture under standard conditions, 1.05 g (74%) of a colorless oil was obtained consisting of o-isopropenylanisole (8; 74%), naphthalene (13%), and *tert*-butyl o-methoxybenzoate (13%). The approximate relative rates[36] were calculated to be methyl (20), ethyl (7), neopentyl (3), isopropyl (1), and *tert*-butyl esters (0).

Registry No.—2 (R$_1$ = Ph, R$_3$ = H), 6048-29-9; 3 (R$_1$ = Ph, R$_3$ = H) (uncharged form), 859-65-4; 3 (R$_1$ = Ph, R$_3$ = H) (charged form), 20913-05-7; 4 (R$_1$ = Ph, R$_2$ = Et, R$_3$ = H), 6230-62-2; 6, 66702-34-9; 7, 579-74-8; 8, 10278-02-1; 9, 791-28-6; 10, 93-60-7; 11, 15825-89-5; (E)-12, 66702-35-0; (Z)-12, 66702-36-1; (E)-13, 66702-37-2; (Z)-13, 66702-38-3; (E)-14, 66702-39-4; (Z)-14, 66702-40-7; 15 Na salt, 66702-41-8; 16 (R$_2$ = H), 34812-95-8; 16 (R$_2$ = Et), 66702-42-9; 16 (R$_2$ = *i*-Pr), 66702-43-0; 17, 4861-85-2; 18, 3290-53-7; 19, 13027-70-8; 20 ketone derivative, 100-06-1; (E)-21, 38454-63-6; (Z)-21, 38454-62-5; methylenetriphenylphosphorane, 3487-44-3; o-methoxybenzoyl chloride, 21615-34-9; ethanol-^{18}O, 36794-43-1; di-*tert*-butyl malonate, 541-16-2; 2-isopropenylnaphthalene, 3710-23-4; isopropenylbenzene, 98-83-9; ethyltriphenylphosphonium iodide, 4736-60-1; methyl o-methoxybenzoate, 606-45-1; ethyl o-methoxybenzoate, 7335-26-4; isopropyl o-methoxybenzoate, 944-95-6; *tert*-butyl o-methoxybenzoate, 16537-20-5; neopentyl o-methoxybenzoate, 66702-44-1.

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Reaction of a Mixed Anhydride with Aqueous Hydroxylamine. A Model for the Trapping by Added Nucleophiles of Anhydride Intermediates in Carboxypeptidase A Action

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As a model for experiments on the trapping by nucleophiles of acyl-enzyme intermediates formed in the action of carboxypeptidase A, the reaction of *trans-p*-chlorocinnamic propionic anhydride with aqueous hydroxylamine has been examined. Both above and below the pK_a of hydroxylamine, formation of propionohydroxamic acid was found to occur in very high yields. The other dominant product was *trans-p*-chlorocinnamic acid. The pH–rate constant profile for the attack of hydroxylamine on the mixed anhydride was sigmoidal, with an apparent pK_a value of 6.07 ± 0.11 and a limiting second-order rate constant of 2340 M^{-1} s^{-1} calculated in alkaline solution. Within the limits of our measurement, catalysis of anhydride breakdown occurred only with the unprotonated form of hydroxylamine. The results obtained suggest that if the acyl-enzyme intermediate observed in kinetic measurements on the reaction of carboxypeptidase A with *O*-(*trans-p*-chlorocinnamoyl)-L-β-phenyllactate is an anhydride species, nucleophilic trapping with hydroxylamine in the absence of interaction of the active site metal ion with the anhydride may be accomplished in reasonable yields.

The trapping of acyl-enzyme intermediates by the use of potent nucleophiles is a useful mthod which has aided in the elucidation of the structure of reaction intermediates involved in enzymic hydrolysis reactions. Trapping experiments in which hydroxylamine was employed as the nucleophile have been carried out on a variety of peptidases including chymotrypsin,[1] pepsin,[2] and bacterial carboxypeptidase.[3] In many of the trapping experiments performed, hydroxylamine was found to be incorporated into the substrate, giving rise to the formation of a hydroxamic acid derived from the substrate. The enzymes involved have generally been ones which form acyl-enzyme intermediates using serine hydroxyl groups at the active site.

Recently, in a study of the reaction of *O*-(*trans-p*-chlorocinnamoyl)-L-β-phenyllactate with carboxypeptidase A at low temperature in a mixed organic–aqueous solution, kinetic evidence was obtained for the intermediate formation of an acyl-enzyme species.[4] On the grounds that the attacking nucleophile at the enzyme active site was probably the γ-carboxylate group of Glu-270, it was proposed that the acyl-enzyme intermediate had a mixed anhydride structure. In order to test such a hypothesis, nucleophile trapping experiments have been undertaken in our laboratory on the reactions of carboxypeptidase A with ester substrates. Some evidence exists that in cases where zinc ion catalyzes the breakdown of model mixed anhydrides, it is not feasible to use hydroxylamine as a trapping nucleophile,[5] and there are a considerable number of trapping experiments which have been carried out on the native zinc-containing enzyme without any success.[6,7] Therefore, the trapping experiments which we are currently performing on the proposed mixed anhydride species formed at the active site of carboxypeptidase are being done in such a way that the trapping is carried out under conditions where the active site metal ion is coordinated to a strongly bound complexing agent. If the metal ion is prevented

from interacting with the mixed anhydride formed at the active site of carboxypeptidase, then a reasonable model for the trapping process in the case of the *trans-p*-chlorocinnamoyl-enzyme should be a study of the reaction of a mixed anhydride such as *trans-p*-chlorocinnamic propionic anhydride (I) with aqueous hydroxylamine. If trapping of the acyl-enzyme with hydroxylamine were successful, then either of the two pathways illustrated in Scheme I might be observed. According to one pathway, hydroxylamine would attack the carbonyl group derived from the active site carboxyl of the enzyme and would result in the formation of an enzyme-bound hydroxamate species. The other pathway would involve attack of the nucleophile on the substrate-derived carbonyl group. Similarly, as illustrated in Scheme II, attack at either the *trans-p*-chlorocinnamoyl group or the propionyl group of I might be observed in the reaction of aqueous hydroxylamine with this model mixed anhydride. In the present article we have described the results we have obtained both on the kinetics of reaction of hydroxylamine with I in aqueous solution and on the product distribution, and we have discussed the

Scheme I

RCOC——enzyme
‖ ‖
O O

NH₂OH ↙   ↘ NH₂OH

enzyme——C——OH   enzyme——C——NHOH
‖   ‖
O   O

−   +

RCNHOH   RCOH
‖   ‖
O   O

Scheme II

Table I. Second-Order Rate Constants for Reaction of I with Aqueous Hydroxylamine at 25 °C

pH	buffer[a]	k_2, M^{-1} s^{-1}[b]	r^2[c]
4.0	acetate	37.8	0.994
4.5	acetate	90.4	0.981
5.0	acetate	3.12×10^2	0.989
5.5	cacodylate	5.51×10^2	0.985
6.0	cacodylate	1.35×10^3	0.997
6.5	cacodylate	1.39×10^3	0.971
7.0	cacodylate	2.10×10^3	0.997
7.5	cacodylate	2.02×10^3	0.992
8.0	Tris	2.37×10^3	0.993
9.0	Tris	2.46×10^3	0.989
10.0	ammediol	2.47×10^3	0.987

[a] 9.1% (v/v) of tetrahydrofuran. Buffer concentration was 0.05 M. [b] Data were calculated from at least six points. [c] Correlation coefficients from the plots of the pseudo-first-order rate constants vs. hydroxylamine concentrations.

implications of these results for the trapping experiments being performed on reactions of carboxypeptidase A.

Results and Discussion

Kinetic Experiments on the Reaction of I with Aqueous Hydroxylamine. Kinetic experiments on the reaction of I with hydroxylamine were carried out in the presence of the nucleophile in excess. Under these conditions, the kinetics observed were pseudo-first-order in nature. Pseudo-first-order rate constants were obtained by recording the decrease in the UV absorption at 310 nm due to the disappearance of I. Plots of the rate constants measured vs. the hydroxylamine concentrations gave straight lines. From the slopes of these plots, second-order rate constants measured over a range of pH were calculated. In Table I data on the pH dependency of the second-order rate constants are illustrated. The pH–rate constant profile seen was sigmoidal and a pK value of 6.07 ± 0.11 was measured with a limiting second-order rate constant of 2340 $M^{-1} s^{-1}$ calculated in alkaline solution. The rate data obtained clearly indicated that it is the unprotonated form of hydroxylamine which is the reactive species.

Product Distribution. As discussed in the introduction two pathways are possible for the reaction of I with hydroxylamine; one pathway gives propionic acid (II) and *trans-p*-chlorocinnamohydroxamic acid (IV) while the other results in the formation of propionohydroxamic acid (III) and *trans-p*-chlorocinnamic acid (V) (Scheme II). In order to determine the degree to which each pathway is followed, the yields of the hydroxamic acids III and IV were determined. After chromatographic separation, quantitative analysis of the concentrations of the hydroxamic acids produced was carried out colorimetrically by means of the ferric ion–hydroxamate complexes,[8] as summarized in Table II. The results shown in the table indicate that formation of III predominates over that of IV over a wide pH range both above and below the pK_a of hydroxylamine. The gradually decreasing total yield of the hydroxamic acids formed as the pH was raised might be due to the increasingly competitive rate of the spontaneous hydrolysis of I under the reaction conditions.

Analysis by high-pressure liquid chromatography revealed that *trans-p*-chlorocinnamic acid (V) was obtained as a major product in the reaction of hydroxylamine with I. This result is what would be expected in view of the results just discussed for hydroxamic acid production. In Table III the relative yields of IV and V calculated from the peak areas for these compounds determined by high-pressure liquid chromatography are shown. If spontaneous hydrolyses were negligible relative to nucleophilic attack by hydroxylamine, *trans-p*-chlorocinnamic acid (V) should be produced in amounts identical to that of propionohydroxamic acid III. A slightly higher yield of V was obtained than would be expected from

the product analysis for the hydroxamic acids III and IV, and this may be due to the competing spontaneous hydrolysis of I.

The predominant formation of propionohydroxamic acid (III) and *trans-p*-chlorocinnamic acid (V) indicates clearly that hydroxylamine attacks predominantly the aliphatic carbonyl group of I. One explanation of this observation is that the carbonyl group of the *trans-p*-chlorocinnamoyl moiety in I is conjugated with a double bond; thus, the electron deficiency on the carbonyl carbon is much less than on that of the propionyl moiety. In line with our findings, the exclusive addition of isotopically labeled water to the aliphatic carbonyl group in a mixed aliphatic aromatic carboxylic acid anhydride has been reported by Bunton and Perry.[9]

In summary, the reaction of hydroxylamine with the mixed anhydride I occurred mainly at the carbonyl group of the saturated acid moiety, probably due to the greater electron deficiency of that carbonyl function. The present findings suggest that the attack of hydroxylamine on a mixed anhydride formed from the reaction of O-(*trans-p*-chlorocinnamoyl)-L-β-phenyllactate with carboxypeptidase A should result in the incorporation of the hydroxylamine in the enzyme, presumably at the Glu-270 residue. This expectation is consistent with preliminary observations in our laboratory. The tendency for hydroxylamine to attack the carbonyl group of the enzyme-bound residue is in contrast to the situation observed for hydrolysis reactions catalyzed by chymotrypsin in which hydroxylamine was found to form hydroxamic acids derived from the substrate molecules.[1] Thus, the observations described in this paper, together with preliminary data on carboxypeptidase A, show that the failure of a trapping nucleophile to attack the substrate carbonyl group does not necessarily exclude the existance of an acyl-enzyme intermediate. We are continuing to explore the incorporation of hydroxylamine in carboxypeptidases in their reactions with a number of different substrates.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on a Bruker HS-270 spectrometer at 270 MHz with a Nicolet NIC-1080 data processor system. Both kinetic experiments and product analyses were carried out with freshly prepared I in tetrahydrofuran. High-pressure liquid chromatography analysis was performed with a Perkin-Elmer series 2 liquid chromatograph.

Materials. Sodium *trans-p*-chlorocinnamate prepared from the reaction of sodium hydride with *trans-p*-chlorocinnamic acid (Aldrich) was recrystallized from aqueous ethanol. Propionyl chloride was distilled under nitrogen (bp 78–79 °C). Tetrahydrofuran was distilled from lithium aluminum hydride under nitrogen. Hydroxylamine hydrochloride (Fisher) was recrystallized from methanol. Other

Table II. Yields of Hydroxamic Acids for Reaction of I with Aqueous Hydroxylamine

pH	buffer[b]	hydroxylamine concentration, M	yields,[a] (%)		
			III	IV	total
5.0	acetate	1.82×10^{-2}	78.7 (95.5)	3.7 (4.5)	82.4
6.0	cacodylate	1.95×10^{-2}	78.3 (95.0)	4.1 (5.0)	82.4
7.0	cacodylate	1.98×10^{-2}	71.2 (94.9)	3.8 (5.1)	75.0
8.0	Tris	1.84×10^{-2}	58.5 (95.3)	2.9 (4.7)	61.4

[a] Yields were calculated on the basis of the amount of propionyl chloride used in the preparation of I, assuming quantitative conversion of the acid chloride into the mixed anhydride. Relative yields of the hydroxamic acid are shown in parentheses. The initial concentration of I was 3.9×10^{-3} M. [b] 9.1% (v/v) tetrahydrofuran was present. The buffer concentration was 0.05 M.

Table III. Relative Yields of IV and V[a]

pH[b]	relative yields, %	
	IV	V
5.0	3.6	96.4
6.0	3.5	96.5
7.0	3.7	96.3

[a] The initial concentrations of I and hydroxylamine were 3.54×10^{-4} and 1.25×10^{-2} M, respectively. [b] The buffer (0.01 M cacodylate) contained 16.7% of tetrahydrofuran.

chemicals were of C.P. grade and were used without further purification. Microanalysis was performed by Microtech Laboratories.

Preparation of Tetrahydrofuran Solution of I. A suspension of 250 mg (1.22 mmol) of sodium *trans-p*-chlorocinnamate in 5 mL of tetrahydrofuran was mixed with 40 μL (0.46 mmol) of propionyl chloride at 0 °C under nitrogen with stirring. After stirring for 1 h, the reaction mixture was centrifuged at 6000 rpm (Beckman JA-21B centrifuge with JA-20 rotor) for 15 min at 0 °C. The supernatant was collected. The precipitate was resuspended in 2 mL of cold tetrahydrofuran and centrifuged at 6000 rpm for 10 min at 0 °C. The combined supernatant was diluted in a 10-mL volumetric flask with tetrahydrofuran. A sample for NMR spectroscopy was prepared by replacing the solvent by dimethyl-d_6 sulfoxide. The NMR spectrum showed the following peaks (ppm from Me$_4$Si): 1.10 (3 H, triplet, J = 7.37 Hz), 2.63 (2 H, quartet, J = 7.37 Hz), 6.78 (1 H, doublet, J = 16.1 Hz), 7.53 (2 H doublet, J = 8.5 Hz), 7.83–7.85 (3 H, overlap of two doublets, J = 8.3 and 16.5 Hz). In a freshly prepared solution of I less than 1% *trans-p*-chlorocinnamic anhydride was found. The completion of the consumption of the propionyl chloride used in the preparation was checked by argentometric titration. One milliliter of the tetrahydrofuran solution of I prepared as described above was poured into 5 mL of deionized water. After 5 min of standing at room temperature, 5% potassium chromate was added and the resultant solution was titrated with standardized silver nitrate solution. No difference was found between the hydrolyzed sample and an appropriate blank sample.

Because on concentration I was found to isomerize readily to the symmetrical anhydride, no further attempt was made to isolate I. In tetrahydrofuran I was found to be stable at concentrations below 10^{-3} M for a couple of weeks at 4 °C.

Preparation of Hydroxamic Acid. Propionohydroxamic acid was prepared as described in the literature,[10] mp 93.5–94.5 °C (lit.[11] mp 92.5–93.0 °C). *trans-p*-Chlorocinnamohydroxamic acid was prepared by the reaction of *trans*-p-chlorocinnamoyl chloride with hydroxylamine.[7] Anal. Calcd for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.53; H, 4.15; N, 7.02.

Kinetic Experiments. Kinetic runs were carried out using a Durrum-Gibson stopped-flow spectrophotometer with a 20 mm flow cell. One volume of the tetrahydrofuran solution of I (9.2×10^{-5} M) was mixed with ten volumes of hydroxylamine solution at 25.0 °C. The reaction corresponding to the disappearance of compound I was monitored at 310 nm. The hydroxylamine solution was prepared by dissolving hydroxylamine hydrochloride in the appropriate buffer and adjusting the resultant solution to the pH desired by the addition of 1 N sodium hydroxide.

Analysis of Hydroxamic Acid Products. One milliliter of a so-

lution of I in tetrahydrofuran (4.3×10^{-2} M based on the amount of propionyl chloride used in the preparation) was mixed with 10 mL of hydroxylamine solution (the concentrations of hydroxylamine and the buffers employed are shown in Table II) at 25 °C. Hydroxylamine was purified in the same manner as described in the section where the kinetic experiments were discussed. After at least 10 min, an aliquot (1 or 2 mL) was applied to a DEAE–cellulose column equilibrated with 0.01 M Tris–HCl, pH 7.5 (void volume 8 mL). In the cases of the samples at pH 5.0 and 6.0, 0.1 mL of 1 N sodium hydroxide was added to the reaction mixture to dissolve the white precipitate which appeared. The column was connected to a Technicon Auto Analyzer (Model NC-1). Elution with 0.01 M Tris–HCl buffer at pH 7.5 was carried out for the first 15 min, followed by 0.1 M Tris–HCl at pH 7.5 at a flow rate of 1.2 mL/min. The effluent from the column was mixed with 5% FeCl$_3$·6H$_2$O in 1 N HCl at an equal flow rate. The hydroxamic acids were then detected by the use of a 1 cm flow cell equipped colorimeter (filter 570-18-28). Compound III was eluted with 0.01 M Tris–HCl at 10 min and IV appeared at 40 min after the eluent was changed to 0.1 M Tris–HCl. The yields of hydroxamic acid obtained were calculated from the peak areas. Calibration of the analytic methodology employed was performed using authentic samples.

Analysis for *trans-p*-Chlorocinnamic Acid Produced. The reaction of I with hydroxylamine in which the yield of *trans-p*-chlorocinnamic acid was determined was performed in a manner similar to that described above, except that 0.5 mL of I in tetrahydrofuran was mixed with 3.5 mL of hydroxylamine containing buffered solution. Analysis for formation of the *trans-p*-chlorocinnamic acid was carried out by high-pressure liquid chromatography using an ODC–silica gel reversed phase column and an eluent consisting of 30% acetonitrile–70% aqueous phosphate (v/v), pH 3.8. The hydroxamic acid, IV, and the carboxylic acid, V, were detected at 280 nm where the molar extinction coefficients employed were 2.7×10^4 and 2.48×10^4, respectively.

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Photochemistry of Two β,β'-Epoxy Ketones, 3-Oxatricyclo[3.2.1.0²,⁴]octan-8-one and 3-Oxatricyclo[3.3.1.0²,⁴]nonan-9-one. Intramolecular Reactions of α,β-Unsaturated Aldehydo Ketenes

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Photolysis of epoxy ketone 1 in benzene leads to aldehydo ketene 3 and β-lactone 4 as primary products. Subsequent addition of methanol furnishes the isolable products 6 and 7. Secondary photolysis of 3 yields the cycloaddition product 5. Photolysis of 1 in benzene containing 3% methanol gives 6 directly along with 10. Similar irradiation of epoxy ketone 2 leads to aldehydo ketene 15, which reacts with methanol to give the aldehydo esters 17 and 18, and which is converted thermally to enol lactone 16. These reactions provide novel information about the behavior both of 1,4 acyl alkoxy biradicals and of α,β-unsaturated aldehydo ketenes.

Relatively little information is available concerning the photochemical behavior of β,γ-epoxy cyclic ketones. Much of what is known is due to Murray and his co-workers, who suggested a sensible scheme, the key steps of which are shown in eq 1, to account for the observed photochemical rear-

rangement reactions of these compounds.[1] This scheme is closely analogous to one long used to explain photolysis products from β,γ-cyclopropyl ketones.[2] In the present report we describe the photolysis of ketones 1 and 2, two simple tri-

cyclic β,γ-epoxy ketones that, through their internal symmetry, can also be regarded as β,β'-epoxy ketones. As will be seen below, application of eq 1 to ketones with such symmetrically disposed epoxide rings leads to alkoxy acyl 1,4-biradicals, species whose behavior has not been explored in the past. In addition, since one type of product observed from these biradicals is an α,β-unsaturated aldehydo ketene, this work has also provided an opportunity to observe transformations involving intramolecular interaction of these reactive functional groups.
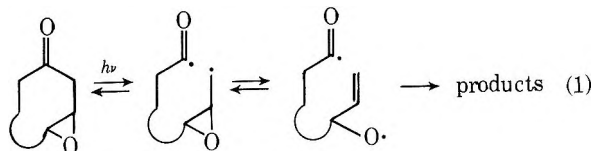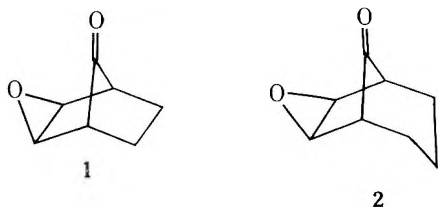
Photolysis Products. Irradiation of epoxy ketone 1[3] in dry benzene (~0.025 M; λ > 2800 Å) led to products 3–5. Neither the unstable aldehydo ketene 3 nor β-lactone 4 could be isolated, but the infrared spectra of solutions after photolysis gave typical absorption for each: 2117 cm⁻¹ for 3 and 1832 cm⁻¹ for 4. Furthermore, addition of methanol to the solutions after photolysis led to replacement of these two bands with absorption typical for an ester (1740 cm⁻¹) and a carboxylic acid (3500–2500 and 1710 cm⁻¹), which are attributed to 6 and 7, respectively. Subsequent isolation by preparative vapor phase chromatography (VPC) yielded 6, the structure of which follows unambiguously from spectral properties showing it to be an α,β-unsaturated aldehyde with a trans disubstituted double bond, an unbranched carbon chain, and a carbomethoxyl group. Reaction of the photolysate solution with ethereal diazomethane after the methanol treatment permitted conversion of carboxylic acid 7 to the conveniently
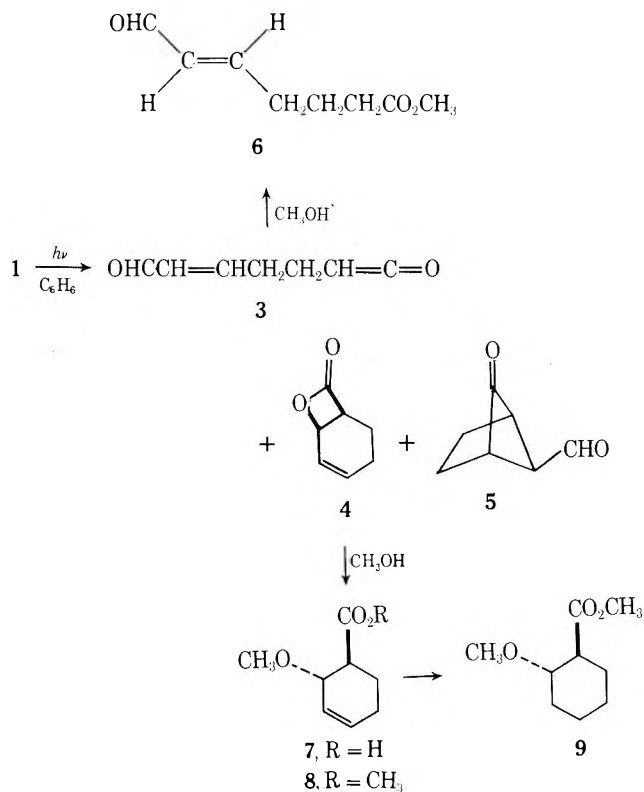
isolated (VPC) methyl ester 8. Hydrogenation of 8 over palladium on barium sulfate in methanol containing a trace of aqueous sodium hydroxide led to methyl *trans*-2-methoxy-cyclohexanecarboxylate (9), which was identical with an authentic sample and readily distinguished from the related *cis*-methoxy ester.[4] The isolation of 8 provides excellent supporting evidence for the presence of 4 in the photolysate; under the neutral conditions employed methanol is expected[5] to open a β-lactone by preferential alkyl–oxygen cleavage with inversion, and the allylic nature of this center in 4 undoubtedly facilitates this process. It is difficult to conceive of alternative structures for the photoproduct that would lead to 7 on reaction with methanol in benzene under such mild conditions.

Direct VPC isolation after photolysis of 1 without the addition of methanol furnished 5, which was identified from its spectroscopic properties as 6-oxobicyclo[2.1.1]hexane-*exo*-5-carboxaldehyde. Noteworthy spectroscopic features are strong infrared (IR) absorption at 1810[6] and 1730 cm⁻¹, a ¹³C nuclear magnetic resonance (NMR) spectrum consisting of only five signals as required by the internal symmetry of structure 5, and a ¹H NMR spectrum that permitted assignment of the indicated exo stereochemistry to the formyl group.

The signal for the aldehydic proton appears at δ 9.49 (d, J = 6.0 Hz), while the adjacent α proton [C(5)–H] also gives a doublet, δ 2.43 (J = 6.0 Hz), and thus is coupled only to the aldehydic proton. This lack of coupling with the adjacent bridgehead hydrogen atoms is typical for endo C(5) protons in bicyclo[2.1.1]hexanes; in contrast, epimeric exo protons at C(5) do show vicinal coupling to the bridgehead positions.[6,7]

Photolysis of **1** in benzene containing 3% (v/v, ~0.74 M) methanol furnished **6** directly, as well as the *cis*-hydroxy ester **10**. The structure of **10** follows from spectroscopic evidence
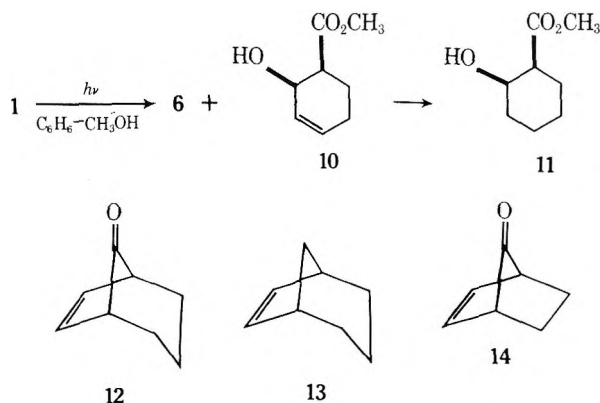
along with subsequent hydrogenation to form methyl *cis*-2-hydroxycyclohexanecarboxylate (**11**), which was identical with an authentic sample.[8]

Epoxy ketone **2**, the second substrate chosen for study, was available on oxidation of unsaturated ketone **12**[9,10] with *m*-chloroperbenzoic acid. The stereochemistry of **2** was assigned by analogy both with the rigorously proved[10] exo stereochemistry of epoxidation of the related olefin **13** as well as with the formation of **1** from norbornen-7-one (**14**).[3] Photolysis of **2** in dry benzene as described above for **1** gave the aldehydo ketene **15**. Under certain conditions discussed below, the enol lactone **16** was also obtained. The presence of **15** was signaled
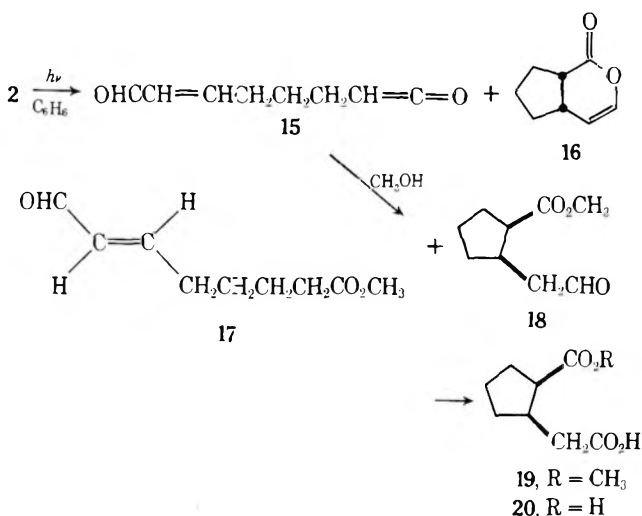
by infrared absorption at 2110 cm⁻¹ as well as through isolation of ester **17** upon treatment of the benzene solution with methanol. The structure of **17** was secured through data analogous to those noted above for aldehyde ester **6**. The major product arising from **15** on reaction with methanol was the cyclic aldehydo ester **18**, the formation of which will be discussed later. This cyclopentane was fully characterized but was surprisingly readily oxidized; in air it was rapidly converted to the related ester carboxylic acid **19**. Acid-catalyzed hydrolysis of **19** gave *cis*-2-carboxycyclopentaneacetic acid (**20**), which was identical with an authentic sample.[11] The

second product, **16**, could be obtained only by direct VPC analysis of photolysate solutions which had been irradiated a relatively short time. This limitation, along with the inherent instability of this enol lactone, made its isolation somewhat tedious. It was identified by conversion to **18** on brief exposure to dilute aqueous acid at room temperature followed by esterification with diazomethane. Spectroscopic properties of **16** agree well with those previously recorded for simple alkyl-substituted 3,4-dihydro-2-pyranones.[12] These include IR carbonyl absorption at 1765 cm⁻¹ and NMR absorption for two vinyl protons at δ 4.98 (dd, J = 6.0, 3.7 Hz) and 6.36 (dd, J = 6.0, 0.9 Hz).

Photolysis of **2** in benzene containing ~6% methanol gave directly **17** and **18**, the two products previously formed from ketene **15** on reaction with methanol.

With the exception of **10**, the compounds isolated from these photolyses are secondary transformation products of the initially formed aldehydo ketenes **3** and **15** or the β-lactone **4**. This fact, along with the observed photochemical and thermal instability of the primary products, has made the determination of yields rather inaccurate. Our best estimates for the primary products at ~80% conversion of starting epoxy ketone are **3** (~10%), **4** (15–20%), and **15** (60–70%). For the secondary products **5** and **16**, yields were quite variable since these compounds are also rather unstable under the conditions of their formation. Based on unrecovered epoxy ketone, the best observed yields were **5** (~7%) and **16** (25%). On the basis of available aldehydo ketene then, the yield of **5** was ~70% and that of **16** was ~38%. In addition to these various compounds, the photolysis of **1** also furnished at least four minor products (each <3%) that were detected by NMR and/or VPC analysis.

Discussion

The formation of **3** and **4** may be explained readily by way of α cleavage of **1** to **21** followed by rupture of the oxirane to
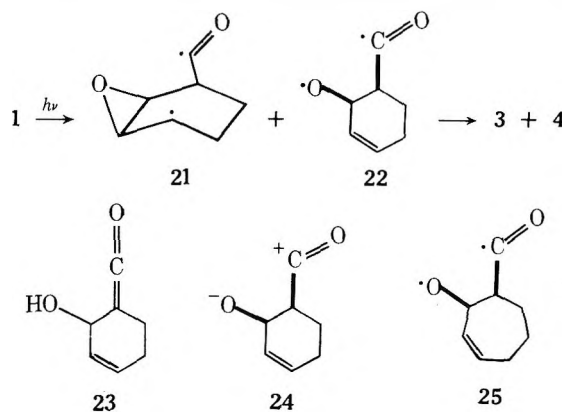
furnish **22**, steps that follow the general scheme of eq 1. Additionally, formation of **22** from **21** involves cleavage of that bond of the epoxide which is consistent with stereoelectronic control of this process and is therefore similar to the photochemical behavior of stereochemically related β,γ-cyclopropyl ketones.[13] Biradical **22** may then couple to give **4** in analogy with the formation of larger ring lactones from longer chain alkoxy acyl biradicals.[1] In agreement with the behavior of other types of 1,4-biradicals, **22** may also fragment to **3**. As initially formed, **3** presumably should have a cis disubstituted double bond, but there is ample opportunity for this to undergo subsequent photochemical isomerization before isolation as **6**. A more novel question, however, is posed by the formation of **10** on photolysis in the presence of methanol. Hydrogen migration in **22** to yield ketene **23** and subsequent stereospecific addition of methanol seemed a mechanistically unlikely path to **10**, and indeed this was ruled out by the observation that irradiation of **1** in benzene containing metha-

nol-*O-d* furnished **10** without incorporation of carbon-bound deuterium.[14] Suitable controls demonstrated that **10** does not arise from a dark reaction of **1** with methanol nor from either a photochemical or a dark reaction of **4** with methanol. These findings require that **10** result from interception by methanol of some transient species lying between **1** and **4**. Although a nonpolar radical would not be expected to react with methanol in this fashion, there are good theoretical grounds for assigning considerable polar character to biradical **22**.[15] Thus, **24** should contribute importantly to the structure of **22** or indeed may be a better representation than **22** for the species involved, and reaction of zwitterion **24** with methanol should quite specifically furnish **10**. On this interpretation then the polarization inherent in this alkoxy acyl intermediate permits a type of reaction with methanol that is not seen in alkyl acyl or dialkyl 1,4-biradicals but that here competes effectively with the coupling and fragmentation processes common to these three types of biradicals.

The same general explanation as that for the formation of **3** can account for isomerization of **2** to **15**. It is noteworthy that no substantial amount of β-lactone or hydroxy methyl ester is produced in this case. There was some spectroscopic evidence for a β-lactone from **2** [IR absorption at 1830 cm^{-1} in the crude photolysate and a small NMR signal at δ 3.4 (s) after treatment of the mixture with methanol], but no products corresponding to **4**, **7**, or **10** were isolated. The greater flexibility of the seven-membered ring of **25** may permit orientations of the 1,4-biradical that can fragment more rapidly than can **22**; in addition, this flexibility should allow the alkoxy and acyl radical centers to move much farther apart in **25** than in **22**, thus disfavoring collapse of **25** to the β-lactone.

We turn attention now to compounds **5**, **16**, and **18**, which are regarded as secondary products derived from the α,β-unsaturated aldehydo ketenes **3** and **15**. One current limitation in understanding the formation of these products is that it is impossible with the information now at hand to determine with certainty whether these cyclization products arise from the cis isomers of **3** and **15**, which presumably are the primary photoproducts, or from the trans isomers, the presence of which is indicated by isolation of **6** and **17**, or from both of these geometric isomers. Some suggestive evidence on this point is detailed below.

We consider keto aldehyde **5** to be a [2 + 2] product formed on crossed cycloaddition of the olefinic double bonds of **3**. Suitable control experiments indicated that this is a photochemical and not a thermal reaction. To our knowledge the only previously reported examples of intramolecular [2 + 2] cycloaddition of ketenes to α,β-unsaturated carbonyl compounds are the four cases reported by Becker,[16] who also showed in two instances that the sense of the cycloaddition was reversed for the ketenes relative to that observed for the analogous allenes. Thus, irradiation of ketene **26** furnished
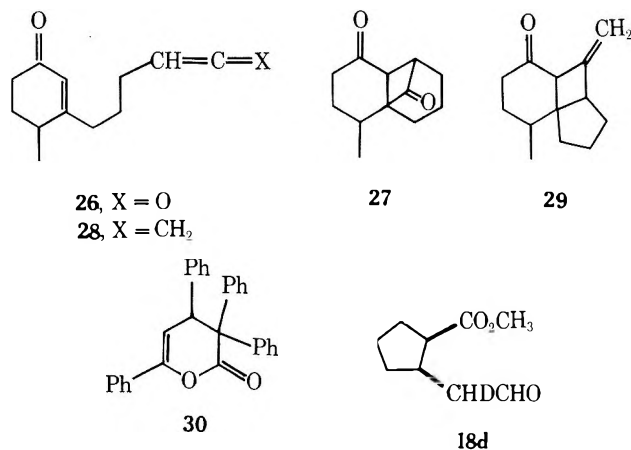
27, while allene **28** gave **29**. Since **26** and **28** are formally 1,6-heptadiene derivatives, the expected[17] sense of addition is straight (as **29**) rather than crossed (as **27**). In all four of Becker's ketenes the regiospecificity of cycloaddition was the opposite of that expected from earlier work on variously substituted dienes. It is noteworthy then that from **3** the crossed bicyclo[2.1.1]hexane **5** is the observed product; **3** is formally a 1,5-hexadiene, and such systems normally lead to crossed products.[17] That is to say, unlike the cases described by Becker, no reversal of the normal regiospecificity of addition is observed with ketene **3**.[18] If conversion of **3** to **5** is a concerted, photochemically allowed [$_\pi2_s + _\pi2_s$] reaction, it is the trans isomer of **3** that would lead to the observed exo aldehyde **5**.

Several observations indicate that enol lactone **16** is a thermal product formed only at elevated temperatures on VPC analysis of photolysis solutions containing **15**. This enol lactone appears in VPC traces after as little as 5% conversion of epoxy ketone **2**, making it unlikely that **16** is formed by secondary photolysis of the small amount of ketene **15** then present. Reaction mixtures which give VPC evidence for 20–25% of enol lactone **16** show no appropriate IR absorption at 1765 cm^{-1} for this product when examined directly before VPC. In keeping with these observations, the amount of **16** detected in VPC traces following on-column injection is considerably enhanced by raising the column temperature from 160 to 170 °C. Finally, continued irradiation of solutions containing **15** does not lead to increased formation of **16**, but rather to reduced yields of this product. This is not only consistent with the thermal formation of **16** but also suggests that **16** arises solely from cis-**15**, which is photochemically isomerized to the trans isomer on prolonged irradiation. There are few prior examples of [2 + 4] addition of the olefinic double bond of a ketene to an α,β-unsaturated carbonyl compound functioning as a diene,[19] although the reaction has been known since 1913 when Staudinger described the addition of diphenylketene to chalcone to furnish lactone **30**.[20]

The cyclic aldehydo ester **18** is clearly a nonphotochemical product from **15** since it is formed on methanol addition after irradiation, and the amount of **17** plus **18** isolated parallels the amount of ketene present as indicated by IR absorption. The amount of **18** relative to **17** decreases, however, with continued irradiation. This observation, along with the absence of the cis isomer of **17** among the isolated products, strongly suggests that cis-**15** is specifically converted to **18** on reaction with methanol and that only trans-**15** yields an open-chain aldehyde ester. A straightforward mechanism (eq 2) is available

$$15 \longrightarrow \cdots \longrightarrow 18 \quad (2)$$
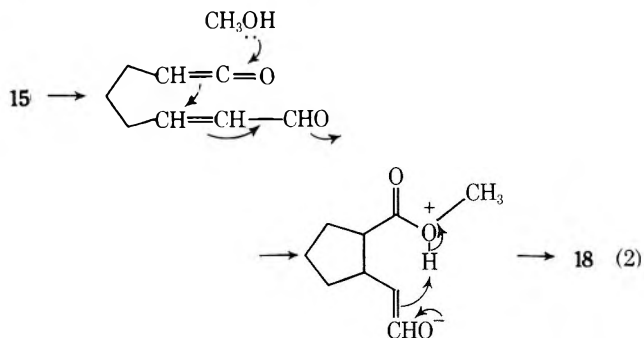
to account for this cyclization, and this pathway is consistent with our observation that use of methanol-*O-d* led to the monodeuterated aldehyde ester **18d**. It is less obvious, however, why such cyclization should lead only to the cis disubstituted cyclopentane. Reaction of simple ketenes with alcohols in inert solvent is known to be third order in alcohol, and a highly ordered cyclic intermediate has been suggested to account for this result.[21] It seems possible that formation of **18** involves a related intermediate with the ketene and enal

26, X = O
28, X = CH$_2$

27

29

30

18d

functionalities and methanol in an array that leads stereospecifically to the cis isomer observed.

These secondary reactions of the α,β-unsaturated aldehydo ketenes **3** and **15** thus provide a glimpse of the varied behavior possible when these two π systems are incorporated in a single simple molecule. It is clear that these processes require further study in less complex reaction mixtures under conditions that permit control of the geometric configuration of the conjugated double bond, and such a study is now in hand.

We note in closing that α cleavage of **1** and **2** leads to a simple secondary alkyl radical center (as in **21**) and that **1** and **2** are the first β,γ-epoxy ketones of this sort to yield recognizable products on photolysis. In previously examined β,γ-epoxy ketones it was found necessary that this be a stabilized alkyl radical (tertiary alkyl, benzyl, or cyclopropylcarbinyl) for significant formation of monomeric products.[1]

Experimental Section

General. All VPC was carried out on a Varian Aerograph Model 700 Autoprep or a Model A-90-P gas chromatograph using columns prepared from aluminum tubing and operating at a helium flow rate of 100–120 mL/min. A 5 ft × 0.25 in column packed with 25% QF-1 on 40/60 Chromosorb W was used for analytical work and isolation of compounds. A 10 ft column of the same type was used for repurification of most liquid samples for elemental analysis.

Unless otherwise specified, IR and NMR spectra were obtained for CCl₄ solutions, the former on a Perkin-Elmer Model 237 B spectrophotometer and the latter on a Varian T-60A (60 MHz) spectrometer. Varian HR-220 (220 MHz; FT mode) and Bruker HX-90 (22.63 MHz; for ¹³C) spectrometers were also used as indicated. Melting points were determined on a Thomas-Hoover apparatus and are corrected (all temperatures are given in °C). Solutions were dried over MgSO₄, Na₂SO₄, or K₂CO₃. Unless otherwise noted, solvents were removed in vacuo with a rotary evaporator. All new pure compounds for which melting points are not given were obtained as colorless oils.

Procedure for Photolysis of Ketones 1 and 2. A solution of the ketone (2–5 mg/mL) in anhydrous benzene (containing 0–6% methanol, as specified) contained in a toroidal Pyrex glass vessel (capacity ~70 mL) was flushed with dry nitrogen for 30 min and irradiated with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well. The mixture was kept in a 30 °C water bath and under nitrogen atmosphere throughout the photolysis.

exo-3-Oxatricyclo[3.2.1.0²,⁴]octan-8-one (1). Oxidation of *anti*-7-norbornenol following the procedure of Ratcliffe and Rodehorst[22] gave bicyclo[2.2.1]hept-2-en-7-one (**14**).[3] Epoxidation with *m*-chloroperbenzoic acid for 8 h at room temperature (see procedure for **2**) gave **1**:[3] IR 3039 (w), 3006 (w), 2972 (w), 2944 (w), 2911 (w), 2877 (w), 2840 (w), 1858 (m), 1788 (s), 1758 (w), 1459 (w), 1443 (w), 1366 (w), 1288 (w), 1247 (w), 1211 (w), 1138 (w), 1118 (m), 1020 (w), 980 (w), 956 (w), 872 (s), 827 (m) cm⁻¹; NMR δ 1.53–2.10 (m, 4 H), 2.20–2.50 (br s, 2 H), 3.46 (m, 2 H). A trace amount (<5%) of the Baeyer-Villiger oxidation product was observed. **1** was purified by recrystallization from hexane or by VPC (150 °C) prior to photolysis.

Photolysis of exo-3-Oxatricyclo[3.2.1.0²,⁴]octan-8-one (1). A. In 3% (v/v) Methanol/Benzene. A solution of **1** (158 mg, 1.3 mmol) in benzene (50 mL) containing 3% methanol was irradiated for 6.5 h according to the general procedure (ca. 93% conversion). VPC of the crude mixture (150 °C) showed two major products which were isolated (8 and 16% recovered yields) and identified as esters **6** and **10**, respectively. For **6** (retention time, 14–17 min): IR 3025 (w), 2988 (w), 2940 (m), 2840 (w), 2800 (w), 2713 (w), 1740 (s), 1695 (s), 1639 (w), 1433 (m), 1200 (m), 1153 (m), 1115 (m), 965 (m) cm⁻¹; NMR δ 1.50–2.10 (m, 2 H), 2.10–2.63 (m, 4 H), 3.63 (s, 3 H), 6.06 (dd, *J* = 16, 7.5 Hz, 1 H), 6.69 (dt, *J* = 16, 6.4 Hz, 1 H), 9.48 (d, *J* = 7.5 Hz, 1 H).

Anal. Calcd for C₈H₁₂O₃: C, 61.52; H, 7.75. Found: C, 61.61; H, 7.66.

For **10** (retention time, 5–6 min): IR 3600 (w), 3575–3350 (m), 3029 (w), 2950 (w), 2840 (w), 1740 and 1722 (s, merged), 1648 (w), 1433 (m), 1297 (w), 1225 and 1198 (m, merged), 1164 (m), 1092 (w), 1060 (w), 1020 (m), 983 (w), 886 (w), 857 (w), 674 (w) cm⁻¹; NMR δ 1.50–2.27 (m, 4 H), 2.27–2.70 (m, 2 H; chemical shift of one proton is variable), 3.70 (s, 3 H), 4.17–4.50 (m, 1 H), 5.53–5.83 (m, 2 H; apparent s at δ 5.60 and d at δ 5.77, *J* = 2.5 Hz, both broadened by further coupling). Double resonance experiments revealed coupling between the signals centered at δ 4.30 and 5.77.

Anal. Calcd for C₈H₁₂O₃: C, 61.52; H, 7.75. Found: C, 61.42; H, 7.69.

A sample of **10** (25 mg) in methanol (0.5 mL; containing 25 μL of

aqueous 5% NaOH) was hydrogenated (1 atm) over 5% Pd/BaSO₄. The product (**11**) isolated by VPC (128 °C) had identical IR and NMR spectra with an authentic sample of methyl *cis*-cyclohexan-2-ol-1-carboxylate prepared according to the procedure of Pascual et al.:[8] IR 3660 (w), 3650–3200 (m), 2985 (w), 2930 (m), 2857 and 2840 (w, merged), 1739 (w, sh), 1718 (s), 1440 (w, sh), 1433 (m), 1400 (w), 1350 (w), 1318 (w), 1243 (m), 1192 (m), 1171 (m), 1113 (w), 1068 (w), 1030 (w), 977 (w) cm⁻¹; NMR δ 1.00–2.13 (m, 8 H), 2.13–2.58 (m, 1 H), 2.90 (br s, 1 H; variable), 3.67 (s, 3 H), 4.02 (br s, 1 H).

At least four minor products (each <3%, based on **1**) were detected in the NMR spectrum and/or VPC analysis of the crude photolysate. One of these appeared to be **7** (methoxy signal at δ 3.3; see C below) and a second one (isolated at retention time 12–13 min) the cis isomer of **6**: IR 2944 (w), 2911 (m), 2840 (m), 2810 (w), 2710 (w), 1742 (s), 1684 (s), 1608 (w), 1432 (m), 1358 (w), 1200 (m), 1158 (m) cm⁻¹; NMR δ 1.5–2.6 (m), 3.63 (s), 6.5 (m), 10.00 (d, *J* = 7.5 Hz).

B. In 3% (v/v) Methanol-O-d/Benzene. Photolysis of **1** as in A gave **6**-*d* [deuterated α to the ester; multiplet at δ 2.10–2.63 (3 H instead of 4 H) and a splitting pattern different in the δ 1.50–2.10 region] and **10** (no deuterium incorporated; NMR signals and integrals were identical with those given above).

C. In Benzene. A solution of **1** (320 mg, 2.6 mmol) in benzene (70 mL) was irradiated for 3.5 h (80% of **1** photolyzed). Aliquots taken during the photolysis revealed the formation of a ketene aldehyde (**3**; IR bands at 2117 and 1690 cm⁻¹ in the original benzene solution) and at least three minor products (VPC). After removal of solvent, IR (CCl₄) and NMR (CDCl₃) spectra of the crude mixture revealed the major product (15–20%) to be β-lactone **4** (IR 1832 cm⁻¹; apparent dd at δ 4.85 in NMR; see D for reaction with methanol), which was not observed by IR spectroscopy in benzene or by VPC. A second product seen in the crude spectra was isolated by VPC (150 °C retention time, 8.5 min) in 6% yield and identified as 6-oxobicyclo[2.1.1]hexane-exo-5-carboxaldehyde (**5**): IR 3010 (w), 2955 (w), 2910 (w), 2879 (w), 2840 (w), 2821 (w), 2726 (w), 1810 (s), 1789 and 1767 (w, shoulders), 1729 (s), 1417 (w), 1275 (w), 1161 (w), 1118 (w), 1066 (w), 1000 (w, br), 953 (w), 897 (w) cm⁻¹; NMR (220 MHz) δ 1.89–2.09 (m, apparent 12 lines, 4 H), 2.43 (d, *J* = 6 Hz, 1 H), 3.15 (br s, 2 H), 9.49 (d, *J* = 6 Hz, 1 H); ¹³C NMR (C₆F₆) δ (Me₄Si) 23.10, 55.65, 60.36, 199.11, 201.10 (relative integral values of tertiary carbon signals at δ 55.65 and 60.36, 1:2; C–H coupled spectrum gave the following multiplicities: t, d with further fine coupling, d, s, and d, respectively). No increase in the yield of **5** was observed after 60–80% conversion of **1**.

Anal. Calcd for C₇H₈O₂: C, 67.73; H, 6.50. Found: C, 67.61; H, 6.64.

D. In Benzene, Followed by Addition of Methanol. Photolysis of **1** (285 mg) in benzene (70 mL) for 5.5 h (>90% conversion) gave a crude mixture containing **4** and **5** (ca. 8:3 in crude NMR; **4** was the major product in IR, strong band at 1832 cm⁻¹; very little **3**). The benzene solution was treated with 6% methanol (v/v) and stored overnight at 4 °C. An aliquot of this mixture was irradiated for an additional hour. VPC analysis showed no new photoproducts (only a trace of **6** and **10** due to the presence of **1** and **3**.) This aliquot was also stored at 4 °C. After removal of solvent, the spectra of the aliquot and the main reaction mixture (230 mg crude; 20–25% material loss during photolysis) both revealed the same new product, *trans*-2-methoxycyclohex-3-ene-1-carboxylic acid (**7**), formed from opening of the β-lactone: IR 3500–2500 (s), 1710 (s, br), 1644 (w), 1095 (m, br) cm⁻¹; NMR δ 1.43–2.83 (m), 3.30 (s, 3 H), 4.0 (m), 5.70 (s with fine structure, 2 H), 9.70 (br s, 1 H; variable).

The crude mixture was taken up in methanol and treated with diazomethane in ether. The major product was isolated by VPC (150 °C; retention time, 4 min; ca. 6% recovered yield based on **1**) and characterized as methyl *trans*-2-methoxycyclohex-3-ene-1-carboxylate (**8**): IR 3025 (w), 2950 (m), 2842 (w), 2810 (w), 1738 (s, br), 1428 (m), 1375 (w), 1294 (w), 1203 (w), 1189 (m), 1163 (m), 1098 (m), 1036 (w), 1017 (w), 925 (w), 906 (w), 680 (w) cm⁻¹; NMR δ 1.40–2.20 (m, 4 H), 2.20–2.67 (m, 1 H), 3.30 (s, 3 H), 3.65 (s, 3 H), 3.97 (m, 1 H), 5.68 (s with fine structure, 2 H).

Anal. Calcd for C₉H₁₄O₃: C, 63.51; H, 8.29. Found: C, 63.47; H, 8.37.

A sample of **8** (15 mg) was hydrogenated (100%) using the same conditions as for **10**. The product was identified as methyl *trans*-2-methoxycyclohexane-1-carboxylate (**9**), having IR and NMR spectra identical with an authentic sample[4] prepared from methyl *trans*-cyclohexan-2-ol-1-carboxylate[8] by treatment with diazomethane in the presence of boron trifluoride etherate: IR 2933 (s), 2856 (w), 2824 (w), 1738 (s), 1447 (w), 1428 (w), 1374 (w), 1358 (w), 1322 (w), 1258 (w), 1242 (m), 1188 (m), 1167 (m), 1121 (w), 1096 (m), 1033 (w), 989 (w), 925 (w) cm⁻¹; NMR δ 0.95–2.45 (m, 9 H), 3.23 and 3.27 (overlapping s, 3 H, and m, 1 H, respectively), 3.60 (s, 3 H).

A sample of methyl *cis*-2-methoxycyclohexane-1-carboxylate was prepared in the same manner and was shown to be different (IR, NMR) from 9.

exo-3-Oxatricyclo[3.3.1.0²,⁴]nonan-9-one (2). Bicyclo[3.2.1]-oct-6-en-8-one[9,10] (12; 1.0 g, 8.2 mmol crude) in methylene chloride (28 mL) was added to a cold (4 °C) solution of *m*-chloroperbenzoic acid (1.85 g, 9.0 mmol; 85% pure) in methylene chloride (42 mL) and stirred for 3 h at room temperature under nitrogen. The resulting mixture was washed with 5% NaOH, 10% Na_2SO_3, 5% NaOH, water, and brine and dried. Removal of solvent gave a white solid (1 g). VPC analysis (165 °C) revealed a trace of starting material and ca. 6% of the Baeyer–Villiger oxidation product in addition to the desired product. Recrystallization from hexane followed by VPC of the remaining supernatant liquid gave 2 (total 836 mg; 74% yield): mp (sealed capillary) 216.5–217.5 °C; IR 3020 (w), 2940 (m), 2855 (w), 2840 (w), 1795 (m, sh), 1770 and 1760 (s), 1445 (m), 1382 (m), 1290 (w), 1250 and 1240 (w), 1195 (m), 1165 (m), 1072 (m), 976 (m), 952 (w), 914 (m), 883 (w), 835 (s) cm⁻¹; NMR δ 1.15–2.33 (m, 6 H), 2.33–2.60 (m, 2 H), 3.47 (s, 2 H).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.37; H, 7.16.

Photolysis of 2. A. In 6% (v/v) Methanol/Benzene. A benzene solution of 2 (100 mg, 0.73 mmol) containing 6% methanol was irradiated for 2.5 h according to the general procedure. VPC analysis of the crude mixture (160 °C) revealed starting material (17%), two major (ca. 6 and 80% of the observed volatile products) products, and several minor products. The two major compounds were isolated by VPC (4 and 44% recovered yields) and characterized as 17 and 18, respectively. For 17 (retention time, 12–15 min): IR 3020 (w), 2940 (m), 2857 (w), 2810 (w), 2715 (w), 1735 (s, br), 1694 (s), 1636 (w), 1443 (w), 1433 (w), 1370 (w, br), 1290 (w), 1194 (w), 1164 (m, br), 1120 (w), 967 (w) cm⁻¹; NMR δ 1.40–2.00 (m, 4 H), 2.00–2.63 (m, 4 H), 3.62 (s, 3 H), 6.03 (dd, *J* = 7.2, 15.5 Hz, 1 H), 6.68 (dt, *J* = 6.3, 15.5 Hz, 1 H), 9.47 (d, *J* = 7.2 Hz, 1 H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.22; H, 8.52.

For 18 (retention time, 5.5 min): IR 2940 (m), 2905 (w), 2865 (w), 2840 (w), 2810 (w), 2710 (w), 1736 and 1730 (s, merged), 1430 (w), 1375 (w, br), 1189 (m), 1167 (m, br) cm⁻¹; NMR δ 1.10–2.17 (m, 6 H), 2.17–3.07 (m, 4 H), 3.59 (s, 3 H), 9.68 (t, *J* = 1.1 Hz, 1 H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.19; H, 8.24.

The ratios of 17 to 18 as well as the total yields were affected by the scale of the reaction and the length of irradiation; 18 was always the major product.

Upon exposure to air, 18 was readily oxidized to acid 19 (retention time, 10–14 min; 160 °C): IR 3500–2400 (s), 1736 and 1712 (s, merged), 1430 (w), 1295 (w), 1275 (w), 1188 (w), 1162 (m) cm⁻¹; NMR δ 1.17–2.13 (m, 6 H), 2.13–3.10 (m, 4 H), 3.60 (s, 3 H), 10.73 (br s, 1 H; variable).

Hydrolysis of 19 in concentrated HCl (110 °C, 2 h) gave *cis*-2-carboxycyclopentaneacetic acid (20), having identical IR and NMR spectra and melting point with an authentic sample:[11] mp (recrystallized from hexane/ether) 87–88 °C; mp (authentic sample, from saturated aqueous HCl) 89–91 °C (lit.[11] mp 87–89 °C); mmp 88–90 °C; IR (CHCl₃) 3500 (w), 3500–2300 (s), 1711 (s, br), 1419 (m, br), 1394 and 1375 (w, merged), 1225 (m, br), 1125 (w), 1031 (w), 915 (m, br) cm⁻¹; NMR (CDCl₃) δ 1.35–2.20 (m, 6 H), 2.20–2.73 (m, 3 H), 2.73–3.17 (m, 1 H), 10.88 (br s, 2 H).

B. In 25% (v/v) Methanol-*O*-d/Benzene. Photolysis of 2 in benzene containing 25% CH₃OD gave the two products described in A (ca. 1:10). The NMR spectrum revealed the major product to be 18d. The aldehyde signal of δ 9.68 appeared as a doublet (*J* = 1 Hz); the integral of the δ 2.17–3.07 region was equivalent to 3.2 H (80% d_1), and the multiplets revealed more fine structure.

C. In Benzene. A solution of 2 in benzene was photolyzed as above. The reaction was followed by IR (C₆H₆, original concentration) and VPC. The only new product observed by IR was ketene aldehyde 15 (2110 and 1690 cm⁻¹), which increased steadily until 80–90% of 2 was converted (ca. 1.5 h) and then decreased slowly upon continued irradiation through a uranium filter (6 h) or standing in the dark at 30 °C (12 h). When benzene was removed from an aliquot containing the maximum amount of ketene and the IR spectrum (CCl₄) of the crude product was taken, ketene was absent and the only significant band observed was at 1830 cm⁻¹ (trace of β-lactone analogous to 4). VPC analysis (column 165 °C, injector 215 °C) of aliquots during the progress of the reaction revealed a new product (retention time, 5 min) whose increase (maximum yield 20–25%, based on reacted 2) and decrease paralleled that of the ketene. When the ketene was destroyed due to long irradiation time, removal of solvent, standing in solution

overnight, or reaction with water or alcohols, none of this new product could be observed. Concentration of the original photolysate resulted in ca. 90% loss of the product, and changes in VPC conditions greatly influenced the amount observed. The product was collected and repurified by VPC (<1% yield) and identified as enol lactone 16: IR 3090 (w), 3060 (w), 2950 (m), 2868 (w), 1765 (s, br), 1662 (w), 1450 (w), 1349 (w), 1330 (w), 1227 (m), 1202 (w), 1100 (m), 1061 (m), 1036 (m), 1011 (w), 883 (w), 717 (w) cm⁻¹; NMR (220 MHz) δ 1.32–2.50 (m, 6 H), 2.73–2.88 (m, 2 H), 4.98 (dd, *J* = 3.7, 6.0 Hz, 1 H), 6.36 (dd, *J* = 0.9, 6.0 Hz, 1 H); (60 MHz) irradiation at δ 4.98 caused the δ 6.36 signal to collapse to a singlet, and irradiation at δ 6.36 gave a doublet (*J* ≃ 3.6 Hz) at δ 4.98; mass spectrum, *m/e* 138.0668 (M⁺; calcd for $C_8H_{10}O_2$, 138.0682).

A sample of 16 (ca. 3 mg) was treated with 5% aqueous HCl at room temperature for 2 h. The mixture was extracted with one portion of ether. The solution was dried and the solvent removed. IR spectroscopy of the crude product revealed no 16 but did indicate the presence of an acid aldehyde [3600–2500 (br), 2810 and 2715 (w), 1725 and 1705 (s) cm⁻¹]. Treatment of this material with diazomethane gave ester aldehyde 18, identified by its VPC retention time and characteristic IR spectrum.

D. In Benzene, Followed by Addition of Methanol. The photolysis was conducted and followed as in C. Each aliquot was immediately treated with methanol (6% by volume) in the dark. VPC revealed products 17 and 18 formed immediately. The total yield of the two paralleled the intensity of the ketene IR band prior to methanol addition and appeared to be ca. 50% at 80% conversion. The ratio of 17 to 18 varied from 1:>6 at low conversion to 1:1 at >90% conversion. Products 17 and 18 were collected by VPC (22% total recovered yield; ratio of 3:4 at 90% conversion) and shown to be identical with the products described in A (IR and NMR).

Registry No.—1, 66688-16-2; 2, 66688-17-3; 3, 66688-18-4; 4, 66688-19-5; 5, 66688-20-8; 6, 66688-21-9; *cis*-6, 66688-31-1; 7, 66688-22-0; 8, 66688-23-1; 9, 13640-66-9; 10, 66688-24-2; 11, 936-03-8; 12, 22241-76-5; 14, 694-71-3; *cis*-15, 66688-25-3; *trans*-15, 66688-26-4; 16, 66688-27-5; 17, 66688-28-6; 18, 66688-29-7; 19, 66688-30-0; 20, 18314-54-0.

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Microbial Reduction of a Series of Substituted Benzils. Optical Properties and Nuclear Magnetic Resonance Spectra of Products

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A series of para-substituted symmetric and unsymmetric benzils were reduced using *C. macerans* to yield the threo (*R,R*) diols of high optical purity and the (*S*)-benzoins with enantiomeric excesses of 20–30%. The absolute stereochemistry of the diols was established from CD measurements of the sign and magnitude of the 225-nm band and, in select cases, by chemical transformation to compounds of known configuration. The stereospecificity and/or high selectivity of these reductions are discussed. The proton NMR spectra of the isomeric erythro and threo diols were measured and assigned. Potential uses of coupling constants and chemical shifts to assign stereochemistry are discussed.

As part of a study on the stereochemical preferences of a mammalian enzyme, "hydrase", the absolute stereochemistries of several threo diols, obtained from enzymatic hydration of optically active substituted *cis*-stilbene oxides, were determined.[1] In order to examine aspects of the chemistry and spectroscopy of transformation products of these diols, we required a synthetic route capable of yielding reasonable quantities of these optically active compounds. The cis-substituted stilbene oxides had been prepared from the appropriate optically active mandelonitrile or mandelamide. This route could not be used to prepare optically active threo diols as the latter isomers were only minor products (formed in only 10–20%) in the hydride reduction of the intermediate, optically active benzoin.

One solution to this problem followed logically from our recent studies[2] on the stereospecific reductions of acetophenone and a series of substituted α-tetralone derivatives: the use of microbial reductions of substituted benzil derivatives to prepare the optically active threo diols. Prelog reported[3] that the reduction of benzil by *Curvularia falcate* yielded a mixture of erythro and threo (*S,S*) diols, in approximately equal amounts, as well as (*S*)-benzoin. In earlier studies Prelog et al. had formulated a rule,[4] shown in Figure 1, to account for the observed stereochemistry: if the ketone is placed with the larger group on the observer's left, the hydroxyl group formed is closer to the observer.

We first examined the reduction of benzil by *Cryptococcus macerans*, a microorganism that efficiently reduces acetophenone to (1*S*)-phenylethanol.[2] Microbiological reduction of benzil (**1a**) yielded (−)-(*S*)-benzoin (**2a**) and (+)-(1*R*,2*R*)-diphenylethanediol (**3a**) and only traces of the erythro isomer **4a**. The NMR spectrum of the crude extract was examined, in which the erythro and threo isomers showed easily distinguishable proton resonances for the protons on the benzylic carbons.[1] Although (*S*)-**2a** was formed in both our study and that reported by Prelog et al.,[3] there were two differences in our results. First, Prelog et al. obtained (−)-**3a**

whereas (+)-**3a** formed with *C. macerans*, and second, appreciable quantities of the erythro isomer (**4a**) were obtained in their study while only traces were observed in our reduction. In addition, formation of (*S*)-**2a** and (*R,R*)-**3a** in our reductions was particularly perplexing because it was not apparent why the configuration about the hydroxyl-bearing carbons in the two compounds differed. In order to understand how or why this occurred, we investigated the mechanism of the reduction.

In order to establish that **2a** can be reduced to **3a**, racemic **2a** was examined under standard conditions as a substrate, and it was found to be efficiently converted to (*R,R*)-**3a** in greater than 50% yield by *C. macerans*. When unreduced **2a** was reisolated, it was found to be levorotatory, i.e., to contain an excess of the *S* enantiomer. These results require (*R*)-**2a** to be reduced much more easily than the *S* enantiomer, and since the (*R,R*) diol is obtained in greater than 50% yield, a mechanism for equilibrating *R* and *S* enantiomers exists. Since under our experimental conditions **2a** formed or recovered in these reductions is optically active, the rate of equilibration (racemization) is slower than the rate of reduction. These conclusions are incorporated in Scheme I which describes the course of these reductions. No conclusion as to the stereospecificity of the conversion of **1a** to **2a** can be made on the basis of our results. However, reduction of **2a** to **3a** is remarkable in the ability of the enzyme to reduce (*R*)-**2a** while effecting very little reduction of (*S*)-**2a**. Similar differences in the reduction rates of various substituted cyclohexanone derivatives were explained by Prelog as resulting from steric interferences between substituents on the substrate with the coenzyme on the enzyme surface.[5] Our results can be rationalized if the enzyme treats the phenyl group as the large substituent and the α-hydroxybenzyl
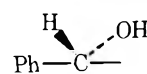
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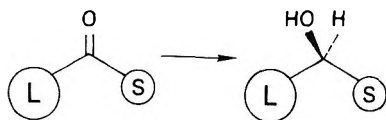
Figure 1.

It is appropriate at this point to comment on the difference between our results and those reported by Prelog et al.[3] Since the oxidoreductases that effect these reductions are a family of enzymes,[6] Prelog et al. used a purified enzyme in their studies, while we used a different microorganism and a whole cell preparation. However, these results in conjunction with an earlier study[2] on the configuration of a series of alcohols obtained by reduction of several substituted α-tetralone derivatives, indanone, and benzsuberone demonstrate that these microorganisms exhibit a consistent pattern of results which can be used to prepare products of the same configuration.

These microbial reductions potentially provide a simple procedure to prepare optically active threo diols, as the difficult separation of an equal mixture of erythro and threo isomers is not necessary. In order to demonstrate the utility of the method, and in order to further test an earlier suggestion[1] relating the sign of the CD band at 225 nm in these diols and their configuration, we have examined the effect of substituents on the aromatic ring on the course of the reduction.

The substituted benzils **1b**, **1c**, **1d**, and **1e** were studied as substrates. It is interesting to note that although two benzoins can form from each substituted benzil, only those resulting from reduction of the carbonyl adjacent to the unsubstituted ring were obtained. Their structures were assigned from a comparison of their ¹H NMR and mass spectra with the ones obtained from authentic material. The absolute stereochemistries of **2b**, **2c**, and **2d** are known,[10–12] and in each case the benzoin isolated had the *S* configuration (see Table I). The optical purities of the isolated benzoins were 20 to 30%, suggesting that either the reductions were not stereospecific or, more probably, that some racemization occurred. These results clearly parallel those observed earlier in the reduction of **1a** and indicate that the presence of a para substituent does not affect the course of the reduction. The diols isolated in these reductions were also compared to those previously reported[1] (see Table I) and the results parallel those noted for **1a**, i.e., the (*R,R*) diol forms in yields of 95% or more, with only 5% of the erythro isomer. The CD data (see Table I) are in good agreement with those previously reported for these

Scheme I

(a) X = Y = H
(b) X = CH₃, Y = H
(c) X = Cl, Y = H
(d) X = OCH₃, Y = H
(e) X = NO₂, Y = H
(f) X = Y = CH₃
(g) X = Y = OCH₃
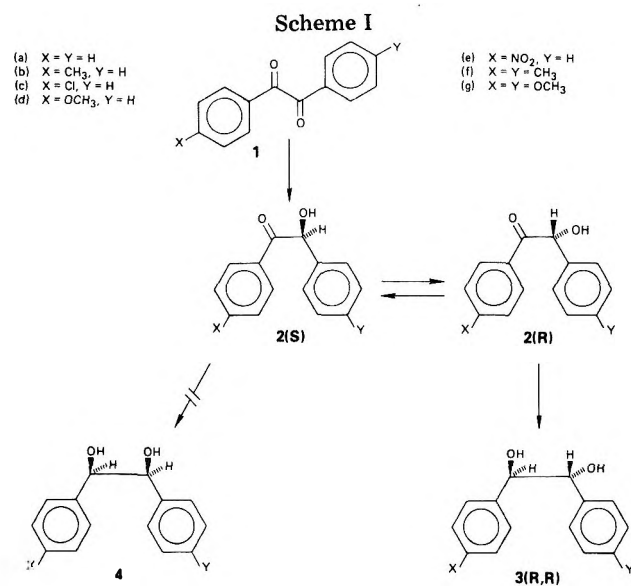
Table I. Microbiological Reductions of Benzils

Benzil	diol registry no.	diol abs. stereochemistry	diol yield %	[α]²⁵D (EtOH) obsd	[α]²⁵D (EtOH) reported[1]	CD θ(λ,nm) obsd	CD θ(λ,nm) reported[1]	benzoin yield %	benzoin abs. stereochemistry	benzoin registry no.	[α]²⁵D (EtOH) obsd	[α]²⁵D (EtOH) reported	recovered benzil, %
1a	52340-78-0	(*R,R*)	27	+91° (c 1.11)	+92°	+37000 (219)	+37680 (219)	18	(*S*)	5928-67-6	+48.5° (c 0.907, acetone)	+120.5° (c 0.413, acetone[19])	50
1f	3457-48-5	(*R,R*)	25	+107° (c 1.16)		+37600 (225)		11		1218-89-9			69
1g	1226-42-2	(*R,R*)	6	+101° (c 1.15)		+28300 (232)		2		119-52-8			90
1c	62086-76-4	(*R,R*)	41	+123° (c 1.40)	+125°	+53600 (222)	+50300 (222)	21	(*S*)	66768-22-7	+10.1° (c 1.100)	−45° [a]	31
1b	62137-63-7	(*R,R*)	38	+100° (c 1.11)	+100°	+50600 (222)	+37000 (220)	19	(*S*)	66768-23-8	+20.3° (c 3.080)	+83° [1]	47
1d	22711-21-3	(*R,R*)	24	+94° (c 1.32)		+33200 (226)		13	(*S*)	4984-91-2	+19.4° (c 0.660)	+80 (c 1.0, EtOH)[11]	60
1e	62086-77-5	(*R,R*)	2	+97° (c 1.10)	+95°	+11000 (215)	+9850 (215)			4984-91-2			95

[a] Specific rotation reported for (*R*) enantiomer.

Table II. Microbiological Reductions of Benzoins

benzoin	registry no.	diol yield, %	diol abs. stereo- chemistry	diol $[\alpha]^{25}_D$ (EtOH)	recovered benzoin yield, %	recovered benzoin $[\alpha]^{25}_D$ (EtOH)	recovered benzoin abs. stereo- chemistry
(±)-benzoin	579-44-2	59	(R,R)	+90° (c 1.11)	38	+9.10° (c 1.11)	(S)
(±)-p-chlorobenzoin	66749-61-9	55	(R,R)	+120° (c 1.35)	27	+3.30° (c 0.23)	(S)
(±)-p-methylbenzoin	66749-62-0	46	(R,R)	+97° (c 0.99)	32	+13.3° (c 1.60)	(S)
(±)-p-methoxybenzoin	4842-37-9	31	(R,R)	+96° (c 0.766)	40	+15.3° (c 1.45)	(S)

compounds. Since the introduction of a p-methoxy substituent in benzil results in a greater perturbation of benzil's absorption spectrum than does either a p-methyl or a p-chloro substituent, it was not certain that the CD curves of **3d** would show the same positive bands (θ ~40 000) at ~225 nm observed for the other (R,R) diols. The CD band observed for **3d** has the same magnitude and position as the p-methyl and p-chloro compounds. While the result may be accidental, the consistency between the CD curves of these diols and those described for **3f** and **3g** suggests that a detailed theoretical model unifying these observations could be constructed.

In our proposed description of the reduction of benzil (Scheme I), the stereospecific (or highly stereoselective) reduction of (R)-**2a** critically controlled the configuration of the diol. Therefore, in addition to examining the products from substituted benzils, we also isolated the products when racemic monosubstituted benzoins (**2b, 2c,** and **2d**) were used as substrates. The results summarized in Table II demonstrate that as with (+)-**2a**, the recovered substituted benzoin in each case is enriched in the S enantiomer. The (R,R) diol is formed along with traces of the erythro compounds, which were not isolated. The pattern and selectivity noted here are completely consistent with the description (Scheme I) for the reduction of **2a** and **1a**. The observations are thus best rationalized using Prelog's concept[4] of "product specific enzymes". This concept enables one to assign the absolute stereochemistry of the diol (+)-**3e** as (R,R). The stereochemistry thus assigned agrees with that made using the "product stereospecific enzymatic hydration" of the cis-p-nitrostilbene oxide.[1]

The ^{1}H NMR data of the substituted diphenylethanediols and diacetates are summarized in Table IV. In several cases it was possible to measure the coupling constants of the threo diols and to compare these with those of the erythro compounds, prepared by hydride reduction of the appropriate benzil. In the limited examples available, the erythro diols showed a somewhat smaller (6.0 Hz) coupling than the corresponding threo isomer (7.5–8.0 Hz). The similarities in these values, however, make any stereochemical assignment on this basis hazardous. Several investigators have prepared cyclic derivatives, i.e., dioxolanes,[7] thiono carbonates,[8] etc., in order to distinguish erythro and threo configurations.

In addition to the unsymmetrically substituted benzil derivatives mentioned above, we also examined the reduction of p,p'-dimethyl- and p,p'-dimethoxybenzil (**1f** and **1g**). The diols isolated in each case were optically active and are therefore threo. The CD curves of **3f** and **3g** each exhibited positive bands whose magnitude and position were virtually identical with those of the (R,R) diols **3a, 3b, 3c,** and **3d**. While the correlations between the sign of the 225-nm band and the absolute stereochemistry of the compounds is empirical, the conclusion from the CD data and that employing the "product specificity" argument both require **3f** and **3g** to have (R,R) configurations. As one of our purposes was to test the relation between the sign of the CD band at 225 nm and the absolute stereochemistry of the diols, we did not wish to rely on the assignment of absolute stereochemistry based solely on the stereospecificity of these enzymatic reductions, and therefore elected to determine the absolute stereochemistry of **3f** by

Table III. Solvent Effects on the Chemical Shifts of the Benzylic Hydrogens (p,p'-Dimethyldiphenyl)ethanediol[a]

	CCl₄	CDCl₃	benzene-d_6	acetone-d_6	Me₂SO-d_6
erythro	4.60	4.75	4.66	4.74	4.50
threo	4.44	4.59	4.52	4.60	4.48
differences	0.16	0.16	0.14	0.14	0.02

[a] Concentration is 0.5 mg in 5 mL of solvent.

relating it to a compound of established absolute stereochemistry. The compound chosen for comparison was dimethyl (2S,3S)-diacetoxysuccinate, synthesized from (−)-tartaric acid. A sample of **3f** was acetylated and exhaustively ozonized and the resulting acids were methylated to yield (+)-dimethyl (2S,3S)-diacetoxysuccinate which after purification was identical with the (+)-dimethyl (2S,3S)-diacetoxysuccinate prepared from (−)-tartaric acid. The absolute stereochemistry of **3f** assigned by chemical transformation supports conslusions as to the stereospecificity of these microbial reductions as well as the relation between the sign of the 225-nm CD band and these diols' absolute stereochemistry.

The three sets of symmetrically substituted erythro and threo diols allowed us to evaluate the possibility of assigning stereochemistry from the ^{1}H NMR chemical shifts of the benzylic protons. The NMR spectra were measured in several solvents in order to determine whether the polarity of the solvent affected chemical shift differences. The largest differences were observed in carbon tetrachloride and CDCl₃, and the results of these measurements are summarized in Table III. Chemical shifts of the benzylic protons of the erythro isomers were consistently at lower fields (0.2 ppm) than those of the threo isomers (see Table IV). The differences between isomers in each set arise from differences in the amounts of inter- and intramolecular hydrogen bonding and from different rotamer distributions. In polar solvents (Me₂SO) these differences are minimal; after acetylation the benzylic protons in both isomers have virtually identical chemical shifts.

Conclusion

Microbial reduction of a series of symmetric and unsymmetric para-substituted benzil and benzoin derivatives yields primarily the threo isomer in satisfactory yield and in high optical purity. The CD curves of these diols were determined and where the para substituent(s) does not severely perturb the absorption spectrum, the sign of the CD band at 225 nm correlates with the absolute stereochemistry of the diol. The ^{1}H NMR spectra of sets of erythro and threo isomers were determined; the benzylic proton of the erythro isomer in each set absorbs at lower field than that in the corresponding threo isomer.

Experimental Section

General Procedure. Melting points were determined using a hot-stage apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian HR-220-MHz instrument using

Table IV. A Comparison of the NMR Spectra of Erythro- and Threo-Substituted 1,2-Diphenylethanediols and Diacetates

erythro	registry no.	benzylic H (δ)	J_{AB}, Hz	threo	registry no.	benzylic H (δ)	J_{AB}, Hz	diff
4a	579-43-1	4.83		3a	38270-73-4	4.60		0.23
4a diacetate	6316-82-1	6.09		3a diacetate	66749-68-6	6.05		0.04
4b	51343-94-3	4.75	6.0	3b	51343-95-4	4.57	7.7	0.18
		4.77				4.59		0.18
4b diacetate	66749-63-1	6.08	6.0	3b diacetate	66769-44-6	6.03	8.3	0.05
		6.10				6.05		0.05
4c	66768-18-1	4.81		3c	66768-15-8	4.56	7.6	0.25
						4.62		0.19
4c diacetate	66749-64-2	6.04	5.8	3c diacetate	66749-55-1	6.01		0.03
		6.05						0.04
4d	66749-65-3	4.74	5.9	3d	66749-56-2	4.63	8.2	0.11
		4.76				4.66		0.10
4d diacetate	66749-66-4	6.03	6.0	3d diacetate	66749-57-3	6.01	8.3	0.02
		6.07				6.03		0.04
4f	5173-29-5	4.75		3f	66749-58-4	4.59		0.16
4f diacetate	66749-67-5	6.04		3f diacetate	66749-59-5	6.03		0.01
4g	39090-30-7	4.75		3g	42565-21-9	4.60		0.15
4g diacetate	39090-32-9	6.03	6.0	3g diacetate	66769-45-7	6.01	8.5	0.02
		6.07				6.03		0.04

FT technique; chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard, with coupling constants (J) in hertz. Optical rotations and circular dichroism spectra were recorded on a Cary 60 spectropolarimeter. Chemical ionization mass spectra were taken with a Hitachi RMS-4 instrument. Microanalyses were performed by the Microanalytical section of NIH. Preparative and analytical TLC work was performed on plates coated with Kieselgel silica gel F-254.

Compounds 1b, 1c, and 1d were prepared via intermediates 2b, 2c, and 2d by a modification of the procedure by McKenzie,[9] as illustrated by 1b.

p-Methylbenzoin (2b). A solution of mandelonitrile (6.65 g) in 100 mL of ether was added dropwise to an ether solution (100 mL) of the Grignard reagent made from p-bromotoluene (34.2 g) and Mg (4.86 g). The solution was refluxed for 1.5 h under N_2 and was then poured into ice–water (200 g) containing 10 mL of concentrated HCl. The aqueous phase was immediately extracted with ether and the aqueous solution was then treated with an additional 10 mL of concentrated HCl. The solution was stirred overnight at room temperature, at which time the p-methylbenzoin precipitated. The crystals were separated by filtration and recrystallized from 95% aqueous ethanol: 18.2 g (41%); mp 98 °C (lit.[10] mp 99 °C); ^{1}H NMR (in CDCl$_3$) δ 2.34 (3 H, s), 4.55 (1 H, broad s), 5.91 (1 H, s), 7.18 (2 H, d, J = 8.9 Hz), 7.23–7.34 (5 H, m), 7.82 (2 H, d, J = 8.9 Hz).

p-Chlorobenzoin (2c). A sample of 2c was prepared from 1-bromo-4-chlorobenzene as above in 38% yield: mp 89.5 °C (lit.[11] mp 91 °C); ^{1}H NMR (in CDCl$_3$) δ 4.50 (1 H, d, J = 6.0 Hz), 5.89 (1 H, d, J = 6.0 Hz), 7.29–7.43 (5 H, m), 7.39 (2 H, d, J = 8.5 Hz), 7.86 (2 H, d, J = 8.5 Hz).

p-Methoxybenzoin (2d). A sample of 2d was prepared from p-bromoanisol as above in 35% yield: mp 109 °C (lit.[12] mp 108–109 °C); ^{1}H NMR (in CDCl$_3$) δ 3.80 (3 H, s), 4.66 (1 H, broad s), 5.89 (1 H, s), 6.85 (2 H, d, J = 8.9 Hz), 7.26–7.32 (5 H, m), 7.90 (2 H, d, J = 8.9 Hz).

Oxidation of Benzoins to Benzils. A solution of 2b (1.6 g) in pyridine (5 mL) was added to a previously prepared solution of CuSO$_4$·5H$_2$O (4.48 g) in a mixture of pyridine (5 mL) and water (10 mL). Air was bubbled through this solution, while it was refluxed overnight. The solvent was next removed in vacuo, water (50 mL) was added, and the solution was concentrated again. The residue was extracted into ethyl acetate and the extract was washed with 5% HCl in water and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the residue purified by column chromatography over silica gel to yield 1.32 g (84% yield) of 1b, crystallized from hexane mp 30 °C (lit.[13] mp 30 °C).

The above procedure was also used to prepare 1c in 82% yield, mp 70 °C (lit.[14] mp 70 °C), and 1d in 81% yield, mp 52 °C (lit.[15] mp 52–54 °C).

A sample of 1e was prepared as described by Womack[16] in 38% yield, mp 142 °C (lit. mp 142 °C).

Preparation of erythro-p-Methyldiphenylethanediol (4b). To a slurry of LiAlH$_4$ (760 mg) in 20 mL of dry ether was added 1b (1.12 g) and the solution was stirred overnight. The reaction mixture was decomposed using 10% NaOH and worked up as usual to yield 1.1 g

of a product whose NMR spectrum indicated that it consisted of 4b and 3b in a 5:1 ratio. The product (550 mg) was warmed at 50 °C with acetic anhydride (10 mL) in pyridine (3 mL) overnight. Water (50 mL) was added and the acetic acid–pyridine–water mixture was removed in vacuo. The residue was extracted into ether, dried over Na$_2$SO$_4$, and concentrated to yield the acetates of 4b and 3b, which were separated by thick-layer chromatography on silica gel to yield the acetate of 4b (480 mg, 67% yield) and 3b (70 mg, 10% yield). The NMR spectra are summarized in Table IV.

Saponification of the diacetate of 4b in methanol (10 mL) containing water (2 mL) and KOH (200 mg) was effected by refluxing for 2 h. The solvent was removed in vacuo and the residue extracted into ethyl acetate. The organic layer was washed with water, dried over Na$_2$SO$_4$, and concentrated. The pure erythro diol, 184 mg (81% yield), was obtained by thick-layer chromatography on silica gel, mp 106 °C (recrystallized from 50% ethanol). Anal. Calcd for C$_{15}$H$_{12}$O$_2$: C, 78.95; H, 7.02. Found: C, 78.81; H, 7.15. The NMR spectra of 4b and the other erythro diols 4c, 4d, 4e, 4f, and 4g prepared by essentially the same sequence of procedures are summarized in Table IV. Physical properties and analytical data are given in Table V.

Microbial Reduction of Benzils. Benzil (1a). A 1-L Erlenmeyer flask containing 250 mL of a sterile solution of 6% glucose, 4% peptone, 4% yeast extract, and 4% malt extract was inoculated with a culture of C. macerans. The flask was shaken at 30 °C for 2 days and to the optically dense culture 100 mg of benzil (1a) was added. Shaking was continued for 7 days. The suspension was then extracted three times with 250-mL portions of ethyl acetate. The extract was dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Analysis of the crude concentrate by NMR indicated a 3:2 ratio of 3a to 2a. In addition ~5% (relative to the threo diol) of the erythro isomer was detected. The mixture was separated by thick-layer chromatography (silica gel, ethyl acetate:hexane (25:75)) to yield the threo diol 3a (27 mg), benzoin (2a) (18 mg), and unreacted benzil (1a) (50 mg). Two crystallizations from 50% EtOH provided pure threo diol 3a, mp 147 °C (lit.[1] mp 147 °C). The NMR, CD, [α]^{25}D data, and yield of this sample as well as those of the other threo diols are summarized in Tables I and II, respectively. The above benzoin 2a fraction was recrystallized from 50% EtOH to give a pure sample, mp 134 °C (lit.[9a] (S)-benzoin mp 132 °C). The NMR spectrum of this compound was identical with that of racemic material. The [α]^{25}D data of this sample and the other optically active benzoins obtained from microbial reductions are summarized in Table II.

p-Methylbenzil (1b). The microbial reduction of 1b and separation of 1b, 2b, and 3b was carried out as described for 1a. The threo diol 3b was recrystallized from 50% EtOH, mp 97 °C (lit.[1] 97 °C). The isolated benzoin 2b was recrystallized from 95% EtOH, mp 99 °C (lit.[1] mp 99 °C). the NMR and mass spectrum of this sample were identical with those of racemic material.

p-Chlorobenzil (1c). Compound 1c, synthesized as described above, was reduced by C. macerans in the same way as 1a. The crude mixture was separated by thick-layer chromatography (silica gel, ethyl acetate:hexane (25:75)) to yield 1c, 2c, and 3c. The threo diol 3c was recrystallized from 95% MeOH, mp 99 °C (lit.[1] mp 99 °C). The benzoin 2c was recrystallized from 50% EtOH, mp 92 °C (lit.[1] (R)-benzoin,

Table V. Physical Properties, Analytical Data, and Molecular Ion (Mass Spectrum)

compd	mp, °C	solvent for crystallization	anal. data		molecular ion
			calcd	obsd	
4a	134	EtOH–H$_2$O	C 78.50	78.51	
			H 6.54	6.48	
4c	131	MeOH	C 67.61	67.70	
			H 5.23	5.19	
			Cl 14.29	14.20	
4d	135	CHCl$_3$–petroleum ether	C 73.77	73.67	244
			H 6.56	6.71	
4e	123	EtOH–H$_2$O	C 64.86	64.77	
			H 5.02	5.10	
			N 5.40	5.38	
4f	128	hexane	C 79.34	79.21	
			H 7.44	7.58	
4g	164	EtOH–H$_2$O	C 70.07	70.11	274
			H 6.57	6.54	

mp 91 °C). The NMR and mass spectrum of this sample were identical with those of racemic material.

***p*-Methoxybenzil (1d).** Compound **1d**, synthesized as described above, was reduced by *C. macerans* and the crude microbial reduction mixture was separated by thick-layer chromatography (silica gel, ethyl acetate:hexane (3:7)) to yield **1d**, **2d**, and **3d**. The threo diol **3d** was purified by vacuum distillation, 120–121 °C (0.1 mmHg). Anal. Calcd for C$_{15}$H$_{16}$O$_3$: C, 73.77; H, 6.56. Found: C, 73.69; H, 6.62; MS 244 (M$^+$), 137, 107. The benzoin **2d** was recrystallized from 50% EtOH, mp 101 °C (lit.[11] (*R*)- and (*S*)-benzoin mp 102–103 °C). The NMR and mass spectrum of this sample were identical with those of racemic material.

***p*-Nitrobenzil (1e).** The crude microbial reduction mixture obtained from *C. macerans* was separated by thick-layer chromatography (silica gel, ethyl acetate:hexane (1:1)) to yield **1e** and **3e**. The threo diol **3e** was recrystallized from 50% EtOH, mp 112 °C (lit.[1] mp 112 °C).

***p,p′*-Dimethylbenzil (1f).** The crude microbial reduction mixture obtained from *C. macerans* was separated by thick-layer chromatography (silica gel, ethyl acetate:hexane (3:7)) to yield **1f** and **3f**. The threo diol **3f** was recrystallized from hexane, mp 110 °C. Anal. Calcd for C$_{16}$H$_{18}$O$_2$: C, 79.34; H, 7.44. Found: C, 79.29; H, 7.56; MS 242 (M$^+$), 121.

***p,p′*-Dimethoxybenzil (1g).** The threo diol **3g** was separated by thick-layer chromatography as described for **1a** and was recrystallized from hexane, mp 123 °C. Anal. Calcd for C$_{16}$H$_{18}$O$_4$: C, 70.07; H, 6.57. Found: C, 70.16; H, 6.48.

Microbial Reduction of Benzoins. The reduction procedure and workup were essentially the same as those of the benzil derivatives. In each reduction (racemic **2a**, **2b**, **2c**, and **2d**), the corresponding (*R,R*) threo diol was formed and the recovered benzoin contained an excess of the *S* enantiomer. The NMR, CD, [α]^{25}$_D$, and yield for these compounds are summarized in Tables II and IV, respectively.

Ozonolysis of (*R,R*)-*threo*-*p,p′*-Dimethyldiphenylethanediol Diacetate. (*R,R*)-*threo*-*p,p′*-Dimethyldiphenylethanediol diacetate was prepared by acetylation of (*R,R*)-*threo*-*p,p′*-dimethyldiphenylethanediol with acetic anhydride in pyridine in the usual manner. The resulting diacetate was purified by thick-layer chromatography on silica gel (ethyl acetate:hexane, 1:4), mp 61 °C, [α]^{25}$_D$ −28.0° (c 2.47, EtOH).

A solution of the diacetate (82 mg) in acetic acid–dichloromethane (50 mL, 1:1) was ozonized at 0 °C using a stream of ozone (2–4%) from an Ozonator, Model 03V2. When the ozonolysis was complete, after 10 h, 2 mL of 30% hydrogen peroxide was added and the reaction mixture was stirred at 50 °C for 1 h. Unreacted hydrogen peroxide was decomposed with sodium sulfite and the solvent was removed in vacuo. Excess saturated aqueous sodium bicarbonate was added to the residue and the solution was extracted with hexane. The aqueous layer was then acidified with hydrochloric acid, saturated with sodium chloride, and extracted several times with ethyl acetate. The ethyl acetate extract was washed with saturated sodium chloride, dried over sodium sulfate, and concentrated in vacuo. The NMR of this crude reaction mixture showed that 2,3-diacetoxysuccinic acid was produced in ~90% yield. A solution of this residue in ether was then esterified with freshly prepared diazomethane. The ether was then removed; distillation of the residue (97 ~ 99 °C/0.2 mmHg) yielded a colorless oil which was crystallized from hexane to give a pure sample of (+)-dimethyl (2*S*,3*S*)-diacetoxysuccinate: 44 mg; 68% yield; mp 103 °C;

[α]^{25}$_D$ +21.9° (c 1.52, CHCl$_3$). The optical purity of this sample was 92%, as shown by comparison with an authentic sample prepared from (−)-tartaric acid.

A solution of (−)-(2*S*,3*S*)-tartaric acid (75 mg) in 10 mL of methanol containing 0.3 mL of concentrated HCl was refluxed for 1 h and the solvent was removed in vacuo. The residue was treated with acetic anhydride (10 mL) and pyridine (2 mL), heated for 1 h on a steam bath, and poured into water. The mixture was extracted with benzene, and the organic phase was washed with 10% HCl and water, dried over anhydrous sodium sulfate, and concentrated. The resulting crude mixture was separated by thick-layer chromatography (silica gel, ethyl acetate:hexane, 1:9) to provide the (+)-dimethyl (2*S*,3*S*)-diacetoxysuccinate in an overall yield of 89%, 116 mg, recrystallized from hexane: mp 103 °C; [α]^{25}$_D$ +23.7° (c 1.52, CHCl$_3$); NMR (in CDCl$_3$) δ 2.18 (6 H, s), 3.80 (6 H, s), and 5.68 (2 H, s). Anal. Calcd for C$_{10}$H$_{14}$O$_8$: C, 45.80; H, 5.34. Found: C, 45.81; H, 5.29.

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Dehydrohalogenation of Some 3′,5′-Dichloro-2′,3′,5′-trideoxynucleosides[1]

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The 3′,5′-dichloro-2′,3′,5′-trideoxynucleosides prepared from the parent 2′-deoxyribonucleosides with thionyl chloride in hexamethylphosphoramide were dehydrochlorinated to their corresponding diolefinic nucleosides. Treatment of 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (1) with dilute sodium hydroxide in ethanol gave the endocyclic diolefinic nucleoside 9-[2-(5-methylfuryl)]adenine (11). In contrast, similar treatment of 1-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)thymine (3) and the corresponding uracil derivative (4) afforded the exocyclic diolefinic nucleosides 2-methylene-5(R)-(thymin-1-yl)-2,5-dihydrofuran (8) and 2-methylene-5(R)-(uracil-1-yl)-2,5-dihydrofuran (9). Dehydrochlorination of 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)hypoxanthine (2) and 1-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)cytosine (5) gave under the same conditions a mixture of the exo- and endocyclic diolefinic nucleosides. On the other hand, treatment of all 3′,5′-dichloro-2′,3′,5′-trideoxynucleosides with strong base, such as potassium *tert*-butoxide in dimethyl sulfoxide, gave exclusively the endocyclic diolefinic nucleosides.

Various synthetic approaches have been used to introduce endo- and exocyclic unsaturation into the sugar moiety of both purine and pyrimidine nucleosides.[2] For instance, Robins and co-workers[3,4] recently reported the preparation of the three possible endocylic unsaturated nucleosides derived from adenosine as well as the 2′,3′ and 3′,4′ olefinic nucleosides derived from tubercidin. The syntheses of the exocyclic 4′,5′-unsaturated nucleosides derived from adenosine and from the pyrimidine nucleosides have been described by Moffatt and colleagues.[5,6] The endocyclic diolefinic nucleosides 1-[2-(5-methylfuryl)]thymine (13) and 9-[2-(5-methylfuryl)]adenine (11) have been prepared by Horwitz et al.[7] and McCarthy and co-workers[8] from 3′,5′-di-O-mesylthymidine and 5′-S-ethyl-3′-O-tosyl-5′-thio-2′,5′-dideoxyadenosine, respectively, via base-catalyzed double-elimination reactions. On the other hand, dehydrohalogenation of 3′,5′-dideoxy-3′,-

R			
adenin-9-yl	1	6	11
hypoxanthin-9-yl	2	7	12
thymin-1-yl	3	8	13
uracil-1-yl	4	9	14
cytidin-1-yl	5	10	15

5′-diiodothymidine with silver fluoride in pyridine or of 1-(2,3,5-trideoxy-5-iodo-β-D-*glycero*-pent-2-enofuranosyl)-thymine with 1,5-diazabicyclo[4.3.0]non-4-ene in acetonitrile yielded the exocyclic diolefinic nucleoside 2-methylene-5(R)-(thymin-1-yl)-2,5-dihydrofuran (8). Our earlier observation[9] that 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (1) is readily converted to 11 in weak alkali prompted us to investigate the dehydrohalogenation of several base analogues of 1. The conversion of 1 to 11 involves the intermediacy of the exocyclic diolefinic nucleoside 2-methyl-5(R)-(adenin-9-yl)-2,5-dihydrofuran (6), which readily isomerizes to the stable endocyclic nucleoside. In contrast, treatment of the corresponding dichlorotrideoxy derivatives of thymine (3) and uracil (4) with ethanolic sodium hydroxide under identical conditions gave exclusively the exocyclic biolefinic nucleosides 8 and 9. However, when 3 or 4 are treated with a strong base such as potassium *tert*-butoxide in dimethyl sulfoxide the endocyclic dienes 1-[2-(5-methylfuryl)]thymine (13) and 1-[2-(5-methylfuryl)]uracil (14) are the only nucleoside products. Apparently the two exocyclic pyrimidine nucleosides 8 and 9 do not isomerize in weak alkali because under these conditions the thymine (pK_a = 9.8) and uracil (pK_a = 9.2) moieties carry a negative charge, thus rendering the anomeric proton less acidic. Indeed, dehydrochlorination of 1-(3,5-dichloro-2,3,5-trideoxy-β-D-

threo-pentofuranosyl)cytosine which is only partially ionized (pK_a = 12.3) in weak alkali yields a mixture of the exocyclic and endocyclic nucleosides 10 and 15. Similarily dehydrohalogenation of 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)hypoxanthine (2) (pK_a = 8.9) in dilute sodium hydroxide yields a mixture of the exocyclic and endocyclic hypoxanthine derivatives 7 and 12. It would thus appear that the anomeric proton of the hypoxanthine moiety is of intermediate acidity probably because the negative charge on the purine ring is diffuse. Attempts to isolate the exocyclic diolefinic nucleosides 7 and 10 as homogeneous preparations have been unsuccessful; during the workup both nucleosides convert to the more stable endocyclic derivatives 12 and 15. Irradiation of all the UV-quenching exocyclic biolefinic nucleosides 6–10 on paper chromatograms with UV light causes isomerization to the fluorescent endocyclic nucleosides.

While reaction of 2′-deoxycytidine with thionyl chloride in hexamethylphosphoramide yields 1-(3,4-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)cytosine (5) in good yield, similar treatment of 2′-deoxyinosine gave only dark intractable mixtures. Furthermore, deamination of 3′,5′-dichloro-2′,3′,5′-trideoxyadenosine (1) with sodium nitrite in acetic acid as described by MacNutt[10] did not yield the desired inosine derivative 2. However, smooth deamination of 1 was effected using nitrosyl chloride in dimethylformamide at 0 °C.

The ¹H NMR and ¹³C NMR spectra of all the nucleosides are consistent with the assigned structures (Tables I and II). Robins and co-workers[11] have recently shown that the 2′-pro-R proton of the pyrimidine 2′-deoxynucleosides resonates at lower field than 2′-H_S while in the case of the purine 2′-deoxynucleosides the reverse is the case. As pointed out before[12] chlorination of 2′-deoxyribonucleosides at C-3′ occurs with inversion of configuration to yield the threo isomer. Thus the chlorine atom causes shielding of 2′-H_S while 2′-H_R is no longer shielded by the hydroxyl group. As a result the 2′-protons of 5 show markedly different chemical shifts (2′-H_S at higher field) while compared to the parent deoxyribonucleoside, 2′-deoxyinosine, the order of the 2′-methylene protons of 2 is reversed (2′-H_S also at higher field). Furthermore, the anomeric proton of both 2 and 5 appears as a quartet because the coupling constants between H-1′ and the two C-2′ protons are quite distinct. The ¹³C NMR spectra of 2 and 5 also demonstrate chlorination of C-3′ and C-5′; the replacement of the hydroxyl group at both carbons by a chloro group is accompanied by a large unfield shift of both carbon resonances. The ¹H NMR spectra of the endocyclic biolefinic nucleosides show the expected proton signals for the methylfuryl moiety. While H-2′ appears as a doublet, the small long-range coupling between the methyl protons and H-3′ produces a doublet at high field corresponding to the methyl

Table I. ¹H NMR Spectral Data of Nucleosides[a]

compd	registry no.	H-1′	H-2′	H-3′	H-4′	H-5′	Other
2	66792-18-5	6.36 (q, 1) $J_{1',2'H_S} = 3.1$ $J_{1',2'H_R} = 7.5$	2.78 (o, 1) H_S 3.24 (o, 1) H_R $J_{2'H_S,2'H_R} = -14.4$ $J_{2'H_S,3'} = 1.9$ $J_{2'H_R,3'} = 5.6$	4.93 (o, 1) $J_{3',4'} = 3.8$	4.48 (sext, 1) $J_{4',5'} = 6.3$	3.94 (d, 2)	12.42 (s, 1) C_6OH 8.24 (s, 1) C_8H 8.08 (s, 1) C_2H
12	66792-19-6		6.58 (d, 1) $J_{2',3'} = 3.2$	6.30 (o, 1) $J_{3',5'} = 0.8$		2.34 (d, 3)	12.57 (s, 1) C_6OH 8.32 (s, 1) C_8H 8.09 (s, 1) C_2H
5	64710-39-0	6.00 (q, 1) $J_{1',2'H_S} = 2.2$ $J_{1',2'H_R} = 7.5$	2.42 (o, 1) H_S 3.13 (o, 1) H_R $J_{2'H_S,2'H_R} = -15.5$ $J_{2'H_S,3'} \sim 1$ $J_{2'H_R,3'} = 5.8$	4.84 (o, 1) $J_{3',4'} = 3.4$	4.50 (sext, 1) $J_{4',5'} = 6.5$	3.98 (d, 2)	9.83; 8.78 (s) NH 8.09 (d, 1) C_6H 6.22 (d, 1) C_5H $J_{5,6} = 7.9$
8	52523-38-3	7.11 (t, 1) $J_{1',2'} = 1.8$ $J_{1',3'} = 1.7$	6.77 (q, 1) $J_{2',3'} = 5.8$	6.42 (2 sextets, 1) $J_{3',5'H_Z} = 1.6$ $J_{3',5'H_E} = 0.9$		4.40 (q, 1) H_Z 4.27 (m, 1) H_E $J_{5'H_Z,5'H_E} = -3.4$	11.50 (5, 1) NH 6.97 (d, 1) C_6H 1.75 (d, 3) C_5Me $J_{6,5Me} = 1.3$
13	5983-11-9		6.36 (d, 1) $J_{2',3'} = 3.1$	6.19 (o, 1) $J_{3',5'} = 0.8$		2.27 (d, 3)	11.58 (s, 1) NH 7.57 (s, 1) C_6H 1.80 (d, 3) C_5Me $J_{6,5Me} = 1.3$
9	66792-20-9	7.11 (t, 1) $J_{1',2'} = 1.7$ $J_{1',3'} = 1.5$	6.79 (q, 1) $J_{2',3'} = 5.7$	6.42 (2 sextets, 1) $J_{3',5'H_Z} = 1.5$ $J_{3',5'H_E} = 0.9$		4.42 (q, 1) H_Z 4.27 (m, 1) H_E $J_{5'H_Z,5'H_E} = -3.3$	11.48 (s, 1) NH 7.12 (d, 1) C_6H 5.64 (q, 1) C_5H $J_{5,6} = 8.0$ $J_{5,NH} = 2.1$
14	66792-21-0		6.38 (d, 1) $J_{2',3'} = 3.2$	6.19 (o, 1) $J_{3',5'} = 0.9$		2.27 (d, 3)	11.51 (s, 1) NH 7.67 (d, 1) C_6H 5.69 (d, 1) C_6H $J_{5,6} = 8.0$
15	6679-22-1		6.18 (d, 1) $J_{2',3'} = 3.2$	6.15 (o, 1) $J_{3',5'} = 0.6$		2.26 (d, 3)	7.61 (d, 1) C_6H 7.40 (s, 2) NH_2 5.84 (d, 1) C_5H $J_{5,6} = 7.4$

[a] All spectra were determined at 80 MHz in Me_2SO-d_6; chemical shifts are in ppm downfield from external Me_4Si. Coupling constants were estimated from the peak positions determined by computer examination of the final Fourier-transformed spectrum.

Table II. ¹³C NMR Chemical Shifts of Nucleosides[a]

compd	registry no.	C-2	C-4	C-5	C-6	C-8	C-1′	C-2′	C-3′	C-4′	C-5′	C_5-Me
1	63162-55-0	152.68	149.06	118.74	155.91	138.41	82.36	41.04	59.02	81.86	43.07	
2		146.14	147.98	124.31	156.65	137.97	82.83	41.22	58.88	82.19	42.85	
12		147.09	150.17	124.23	156.71	139.15	148.37	107.86	103.42	138.57	13.22	
3	34627-68-4	150.29	163.56	109.45	135.47		83.47	40.43	59.18	81.40	41.28	12.47
8		150.49	163.60	110.62	134.99		89.22	130.68; 130.82		161.94	84.40	12.14
13		149.84	164.07	110.00	139.92		149.59	107.52	105.14	142.14	13.21	11.63
4	64032-44-6	150.44	163.19	101.67	140.11		84.06	41.50	59.02	81.88	42.56	
9		150.39	162.84	102.86	139.81		89.27	130.63; 130.72		161.77	84.60	
14		149.82	163.34	102.33	144.51		149.82	107.56	105.43	141.93	13.21	
5		143.25	159.48	93.39	146.68		86.09	40.45	58.88	83.52	41.93	
15		148.42	165.93	94.75	144.27		153.82	107.30	103.18	144.50	13.15	

[a] Chemical shifts are given relative to Me_4Si at 25.2 MHz, Me_2SO-d_6 (39.53 ppm) was used as the solvent.

group and a set of quartets at lower field corresponding to H-3′. The ¹³C NMR spectra confirm the assigned structures; all carbon resonances of the ribofuranosyl moiety have undergone drastic changes on dehydrochlorination. The resonance due to C-5′ is shifted upfield while the other four carbon resonances have undergone large downfield shifts. The NMR spectra of the exocyclic biolefinic nucleosides 8 and 9 also are in accord with the 2,5-dihydrofuran structure. The signal for C_4H is missing and the two magnetically nonequivalent ex-

ocyclic 5′-protons appear as well separated multiplets at 4.40 and 4.20 ppm. The 5′-proton cis to the ring oxygen (H_Z) was assigned to the downfield quartet because in vinyl ethers the vinylic proton cis to the oxygen is usually found 0.2–0.3 ppm downfield from the vinylic proton trans to the oxygen.[13] The ¹³C NMR spectra show that the resonances due to carbons 2′, 3′, 4′, and 5′ have undergone large downfield shifts on dehydrochlorination while the C-1′ resonance is much less affected. These spectral properties would be expected from a 2′,3′ and

4',5' unsaturated system. The IR spectra of 8 and 9 also show the C=CH$_2$ asymmetric stretching (3100, 3080 cm^{-1}) and the wagging vibration (830 cm^{-1}) for the vinyl ether.

Experimental Section

Materials. Nucleosides were purchased from Sigma Chemical Co. or P-L Biochemicals and nitrosyl chloride from Matheson Co. The dichlorotrideoxynucleosides were prepared as described before.[12]

General Procedures. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were measured on a hot stage equipped with a microscope and are not corrected. Pulse proton nuclear magnetic resonance spectra (¹H NMR) were recorded on a Varian CFT-20 spectrometer; pulse carbon-13 nuclear magnetic resonance spectra (¹³C NMR) were obtained using a Varian XL-100-15 spectrometer; chemical shifts are recorded in ppm downfield from an external standard of tetramethylsilane. Ultraviolet (UV) spectra were recorded with a Cary Model 15 spectrometer. Other absorbance measurements were made with a Zeiss PMQ II spectrophotometer. Optical rotation measurements were made in a 2 dm tube with a Schmidt–Haensch polarimeter. Descending chromatography on Whatman No. 1 paper was conducted with the following solvent systems: solvent I, 10:3:7 1-butanol–ethanol–water; II 25:18:7 sec-butyl alcohol–water–ammonium hydroxide; III 4:1:5 1-butanol–acetic acid–water. Nucleosides on paper chromatograms were detected by their absorption of ultraviolet light or by their fluorescence under ultraviolet light.

9-(3,5-Dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)-hypoxanthine (2). Nitrosyl chloride was introduced into a stirred solution of 3',5'-dichloro-2',3',5'-trideoxyadenosine (1) (2.0 g, 6.94 mmol) in dry dimethylformamide (45 mL) at 0 °C for 1.5 h. The orange colored solution was then warmed to room temperature, cooled again, added to cold water (40 mL), and neutralized with solid sodium bicarbonate. The resulting solution was applied to a column (2 × 60 cm) of Dowex 1-X2 (CO$_3$$^{2-}$) (100–200 mesh). The column was washed with water and then eluted with 2 M ammonium carbonate. The fractions containing the desired product were combined and evaporated to dryness. The residue was triturated with cold water and crystallized from aqueous ethanol to yield 1.36 g (65%) of 2: mp 121–123 °C; UV (H$_2$O, pH 7) 249 nm (ϵ 14.12 × 10^3). Anal. Calcd for C$_{10}$H$_{10}$Cl$_2$N$_4$O$_2$·0.75H$_2$O (302.63): C, 39.68; H, 3.83; Cl, 23.43; N, 18.51. Found: C, 39.38; H, 3.77; Cl, 23.39; N, 18.45.

1-(3,5-Dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)-cytosine (5). To a solution of thionyl chloride (5 mL) in hexamethylphosphoramide (25 mL) was added 2'-deoxycytidine hydrochloride (3.0 g, 11.4 mmol), and the mixture was stirred, with exclusion moisture, for 12 h at room temperature. To the reaction mixture was then added 1 M K$_2$HPO$_4$ (60 mL) and the solution was applied to a column (4 × 8 cm) of Dowex 50-X2 (H$^+$) (200–400 mesh). The column was washed with water and then eluted with 1 M ammonium hydroxide–methanol (1:1). The eluate was evaporated to dryness and the residue was crystallized from aqueous ethanol with the aid of charcoal: yield 2.14 g (62%); mp 162–164.5 °C; UV (H$_2$O, pH 7) 271 nm (ϵ 9.59 × 10^3). Anal. Calcd for C$_9$H$_{11}$Cl$_2$N$_3$O$_2$·HCl (300.57): C, 35.96; H, 4.02; Cl, 35.39; N, 13.98. Found: C, 35.98; H, 4.01; Cl, 35.36; N, 13.88.

2-Methylene-5(R)-(thymin-1-yl)-2,5-dihydrofuran (8). A solution of 3',5'-dichloro-3',5'-dideoxythymidine (3) (600 mg, 2.14 mmol) in 6 N sodium hydroxide (1.2 mL, 7.2 mmol) and ethanol (6 mL) was stirred at 70 °C for 1.5 h. Ice cold water (10 mL) was then added and the solution was adjusted to pH 9 with 10% acetic acid in ethanol and concentrated to slight turbidity under reduced pressure. The concentrated solution was kept overnight at 4 °C. The product (8) was collected by filtration, washed with cold water, and recrystallized from ethanol: yield 299 mg (68%); mp ~150 °C[14] (lit.[6] mp 163–165 °C); UV (H$_2$O, pH 7) 264 nm (ϵ 12.19 × 10^3); [α]D^{20} 168.0° (c 0.20, ethanol).

2-Methylene-5(R)-(uracil-1-yl)-2,5-dihydrofuran (9). 3',5'-Dichloro-2',3',5'-trideoxyuridine (500 mg, 1.89 mmol) was dehydrohalogenated as described for compound 8. The crude product was recrystallized from ethanol–water: yield 270 mg (74%); mp 163–165 °C; UV (H$_2$O, pH 7) 259 nm (ϵ 13.01 × 10^3); [α]D^{20} 133.9° (c 0.20, ethanol). Anal. Calcd for C$_9$H$_8$N$_2$O$_3$ (192.18): C, 56.25; H, 4.20; N, 14.58. Found: C, 56.04; H, 4.03; N, 14.30.

9-(5-Methyl-2-furyl)hypoxanthine (12). A. A solution of 3',5'-dichloro-2',3',5'-trideoxyinosine (2) (250 mg, 0.86 mmol) in 6 N sodium

hydroxide (0.67 mL, 0.40 mmol) and ethanol (3.34 mL) was stirred at 70 °C for 1.5 h. The products were separated by preparative TLC on silica gel (CHCl$_3$–methanol, 9:1). The major fluorescent product (R$_f$ 0.36) was eluted with methanol to give 67% (UV measurement) of the endocyclic biolefinic nucleoside 12, which was crystallized from ethanol: yield 86 mg (46%); mp 268–271 °C; UV (H$_2$O, pH 7) 242 nm (ϵ 23.58 × 10^3). Anal. Calcd for C$_{10}$H$_8$N$_4$O$_2$ (216.20): C, 55.55; H, 3.73; N, 25.91. Found: C, 55.34; H, 3.66; N, 25.78.

The minor UV quenching product (R$_f$ 0.27) was eluted with methanol to give 32% (UV measurement) of the exocyclic biolefinic nucleoside 7. Evaporation of the solvent gave a clear gum which contained both 7 and 12.

B. A solution of 2 (125 mg, 0.43 mmol) in dry dimethyl sulfoxide (2.5 mL) containing potassium *tert*-butoxide (148 mg, 1.32 mmol) was stirred at room temperature for 30 min. The reaction mixture was then neutralized with 3 M acetic acid and the precipitate was collected by filtration. Crystallization from ethanol gave 63.7 mg (69%) of 12 identical with the product isolated above.

1-(5-Methyl-2-furyl)thymine (13). A solution of 3',5'-dichloro-3',5'-dideoxythymidine (3) (500 mg, 1.78 mmol) in dry dimethyl sulfoxide (10 mL) containing potassium *tert*-butoxide (760 mg, 6.77 mmol) was stirred at room temperature for 2.5 h, with exclusion of moisture. The reaction mixture was then treated with ice-cold water (20 mL), neutralized with 10% acetic acid in ethanol, and evaporated to dryness under diminished pressure. The residue was triturated with cold water and crystallized from aqueous ethanol with the aid of charcoal: yield 280 mg (76%); mp 164–166 °C (lit.[7] mp 165–166.5 °C); UV (H$_2$O, pH 7) 264 (ϵ 9.28 × 10^3) and 209 nm (ϵ 13.92 × 10^3).

1-(5-Methyl-2-furyl)uracil (14). 3',5'-Dichloro-2',3',5'-trideoxyuridine (4) (250 mg, 0.94 mmol) was dehydrochlorinated as just described for 3 to yield 112 mg (62%) of 14: mp 188–189 °C; UV (H$_2$O, pH 7) 255 (ϵ 8.73 × 10^3) and 210 nm (ϵ 12.00 × 10^3). Anal. Calcd for C$_9$H$_8$N$_2$O$_3$ (192.18): C, 56.25; H, 4.20; N, 14.58. Found: C, 56.33; H, 4.21; N, 14.53.

1-(5-Methyl-2-furyl)cytosine (15). A. 3',5'-Dichloro-2',3',5'-trideoxycytidine (5) (300 mg, 1.14 mmol) was dehydrochlorinated with potassium *tert*-butoxide as described for the preparation of 13 to give 102 mg (47%) of 15: mp 260–262 °C; UV (H$_2$O, pH 7) 268 (ϵ 7.54 × 10^3) and 230 nm (ϵ 12.19 × 10^3). Anal. Calcd for C$_9$H$_9$N$_3$O$_2$ (191.19): C, 56.54; H, 4.75; N, 21.98. Found: C, 56.44; H, 4.75; N, 22.06.

B. A solution of 5 (250 mg, 0.95 mmol) in 6 N NaOH (0.48 mL) and ethanol (2.4 mL) was heated at 70 °C for 2.5 h. The reaction products were then separated by preparative TLC (silica gel; CHCl$_3$–methanol, 8:2). The major fluorescent product (R$_f$ 0.60) was eluted with ethanol to give 71% (UV measurement) of the endocyclic biolefinic nucleoside, which was crystallized from aqueous ethanol to yield 103 mg (57%) of 15 identical with the product isolated above. The minor UV quenching product (R$_f$ 0.54) was also eluted with ethanol (36%, UV measurement), but evaporation of the solvent yielded a gum which contained both 10 and 15.

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Aminoglycoside Antibiotics. 1. Regiospecific Partial Syntheses of Ribostamycin and Butirosin B

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A regiospecific partial synthesis of ribostamycin from neamine was developed. It involved the use of carbobenzyloxy groups and derived cyclic carbamate groups to protect all functional groups except for the 3'- and 5-hydroxyl groups, followed by selective protection of the 3'-hydroxyl group by tosylation or tetrahydropyranyl ether formation. Condensation with protected ribosyl chloride followed by deblocking then gave ribostamyin. A related approach was utilized for the synthesis of butirosin B. In this case the side chain, which was protected as a cyclic carbamate, could be deprotected by alkaline hydrolysis without cleavage of the side chain.

In recent years the preparation of semisynthetic aminoglycoside antibiotics has become increasingly important. Advantages shown by new compounds such as amikacin[1] and 3,4-dideoxykanamycin B[2] over their parent antibiotics, especially in their activities against resistant strains of bacteria, have stimulated research in this area. These analogues and certain others are the result of chemical modification of intact antibiotics. An alternative approach to the development of new aminoglycosides is to begin with a portion of the structure, for example the neamine or paromamine molecule, and add another sugar by glycosidic linkage. This approach has the advantage of affording new combinations of the constituent parts of aminoglycosides not accessible by modification of the intact antibiotics. Its main disadvantage lies in problems of regiospecificity and anomeric specificity in forming the glycosidic bond with the new sugar.

Our general objective in aminoglycoside synthesis is to develop regioselective methods for compounds containing the neamine unit. This unit is important because it occurs in the structures of a number of significant antibiotics including kanamycin B, neomycin, ribostamycin, and the butirosins.[3] Other investigators have addressed themselves to this problem with varying degrees of success. Substitution at O-6 of neamine was obtained in the synthesis of kanamycin B[4] and in two different syntheses of 6-O-(β-D-ribofuranosyl)neamine.[5,6] The synthesis of tobramycin from nebramine (3'-deoxyneamine)[7] and the syntheses of kanamycin C from paromamine were closely related problems.[8] Two syntheses of 6-O-(β-D-ribofuranosyl)paromamine from paromamine were reported.[9,10] The synthesis of ribostamycin from neamine provided an example of 5-O-glycosidation.[11]

The regiospecific synthesis of ribostamycin from neamine became our first specific objective. Ito and co-workers had already accomplished this goal,[11] but we felt that their method was difficult and possibly not general. They utilized intermediate 1, which had been developed by Umezawa and co-workers for the synthesis of kanamycin B[4] (4, Scheme I). Its preparation involved a difficult separation of isomeric monoketals. Furthermore, this intermediate has both 5- and 6-hydroxyl groups free. Ito reported selective glycosidation on the 5-hydroxyl group with tri-O-D-ribosyl chloride. However, Umezawa used the same intermediate for 6-O-glycosidation in the kanamycin B synthesis. A variety of other neamine derivatives with both 5- and 6-hyroxyl groups unprotected also gave preferential 6-O-glycosidation.[6,12] For this reason we decided to prepare a neamine derivative whose 5-hydroxyl group was the only unprotected function. Then there would be no doubt about the regiospecificity.

Inspection of the neamine structure revealed that every hydroxyl group, except the 5-hydroxyl group, was near enough to an amino group that a cyclic carbamate derivative could be formed by utilizing these functional groups. Thus, we visualized the tris(cyclic carbamate) 8 in which only the 5-hy-

Scheme I
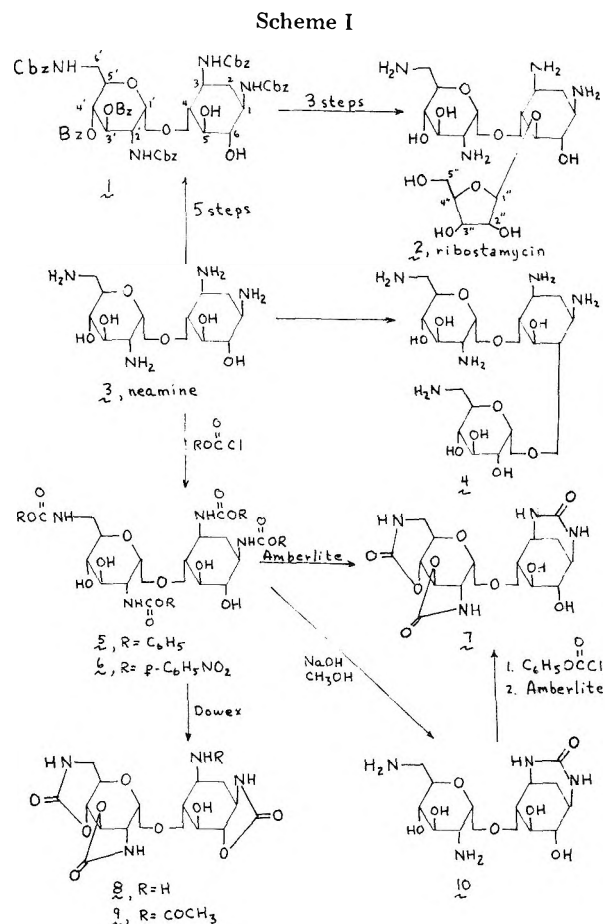
droxyl group and possibly the 3-amino group would be free. The cyclic carbamate group had been first described in carbohydrate chemistry by Miyai and Gross.[13] Umezawa prepared the bis(cyclic carbamate) of 2-deoxystreptamine.[14]

One method for cyclic carbamate synthesis is to prepare the phenylcarbamate derivative of the amino group and then treat the compound with base[14] (Scheme I). This treatment results in the displacement of phenoxide by a proximate hydroxyl group with formation of the cyclic derivative. We readily prepared the tetraphenylcarbamate and tetra-p-nitrophenylcarbamate derivatives (5 and 6) of neamine. Treatment of either derivative with the weakly basic resin Amberlite IR-45 (OH⁻ form) resulted in the nearly quantitative formation of a bis(cyclic carbamate) derivative (7) which also had a cyclic urea function. However, when the strongly basic resin Dowex 1 × 2 (OH⁻ form) was used the desired tris(cyclic carbamate) 8 was formed in 60% yield. In the course of this reaction, the 3-amino group became deprotected. It was readily reprotected as its acetyl derivative (e.g., 9).

The presence of a cyclic urea group in compound 7 was es-

tablished as follows. It lacked the infrared absorption at 5.63 μm characteristic of the N^1, O^6-five-membered cyclic carbamate group, but it had absorption at 5.71 μm characteristic of a six-membered cyclic urea. Acetylation did not occur with acetic anhydride in dry methanol, but a di-O-acetylated product was obtained with acetic anhydride in pyridine. This result shows that 7 had two free hydroxyl groups, but no free amino group. Finally, the preparation of a known[15] N^1,N^3-cyclic urea derivative (10) from tetra-N-phenoxycarbonyl-neamine and methanolic sodium hydroxide was repeated and the product was converted into 7 by preparation of the 2′,6′-di-N-phenoxycarbonyl derivative followed by treatment with Amberlite IR-45 in the OH⁻ form.

Tri-O-acetylribosyl chloride and tri-O-benzoylribosyl chloride were prepared by known procedures[16,17] and their coupling with intermediates 7 and 9 was attempted. Unfortunately, both of these intermediates were nearly insoluble in solvents such as benzene and dichloromethane which favor Koenigs–Knorr couplings with five-membered ring sugar halides. They were soluble in N,N-dimethylformamide (DMF), but the ribosyl chlorides decomposed without coupling in this solvent. A variety of promoters, including Drierite, mercuric cyanide, mercuric chloride, and silver triflate, were used, but without success.

This failure led us to look for more soluble cyclic carbamate derivatives of neamine. The bis(cyclic carbamate) 11 was readily prepared by treating tetra-N-carbobenzyloxyneamine with sodium hydride in DMF (the carbobenzyloxy derivatives do not react with Amberlite or Dowex resins). Under the conditions utilized, the third cyclic carbamate group does not form. The product (11) had both the 3′- and 5′-hydroxyl groups free, which required that we find a selective method for protecting the former hydroxyl group. Among a variety of derivatives prepared from 11 we found that the tetrahydro-pyranyl ether (THP) and the p-toluenesulfonate (Ts) formed exclusively and in high yield on the 3′-hydroxyl group. Other derivatives including p-nitrobenzoate and pivalate esters 14 and 15 were formed less selectively and they were poorly soluble in cholorform. Both the THP derivative (12) and the tosylate (13) had good solubility in chloroform, which allowed them to be used in Koenigs–Knorr condensations under optimum conditions.

Treatment of either 12 or 13 with tri-O-benzoylribosyl chloride in chloroform in the presence of mercuric cyanide and Drierite gave the glycosides 16 or 17 in approximately 50% yields (Scheme II). Hydrolysis of the benzoyl and cyclic carbamate groups with barium hydroxide, followed by catalytic hydrogenolysis, then gave the desired ribostamycin (2). It showed one spot on thin-layer chromatography and it had an R_f value identical with that of authentic ribostamycin in two solvent systems. The specific optical rotations of the two samples were nearly identical (Experimental Section) and their infrared spectra were superimposable.

Although ribostamycin is almost as potent as butirosin in antibacterial activity, butirosin is active against more strains of bacteria because its (S)-4-amino-2-hydroxybutyryl side chain inhibits inactivation by bacterial enzymes.[18] The commercial butirosin is a mixture of butirosin A and butirosin B. These two components differ in the nature of the pentose at O-5. Butirosin A has D-xylose, whereas butirosin B has D-ribose at this position.[19] Our second goal was the synthesis of butirosin analogues in which new sugars replaced the xylose or ribose unit. Again, the best way to develop intermediates and methodology for these analogues appeared to be the prior synthesis of a parent compound, butirosin B (22), since we could readily confirm the regiospecificity and anomeric purity of the product.

The hydrolysis of butirosin to 1-N-[(S)-4-amino-2-hydroxybutyryl]neamine (18) had been reported previously.[20]

Scheme II
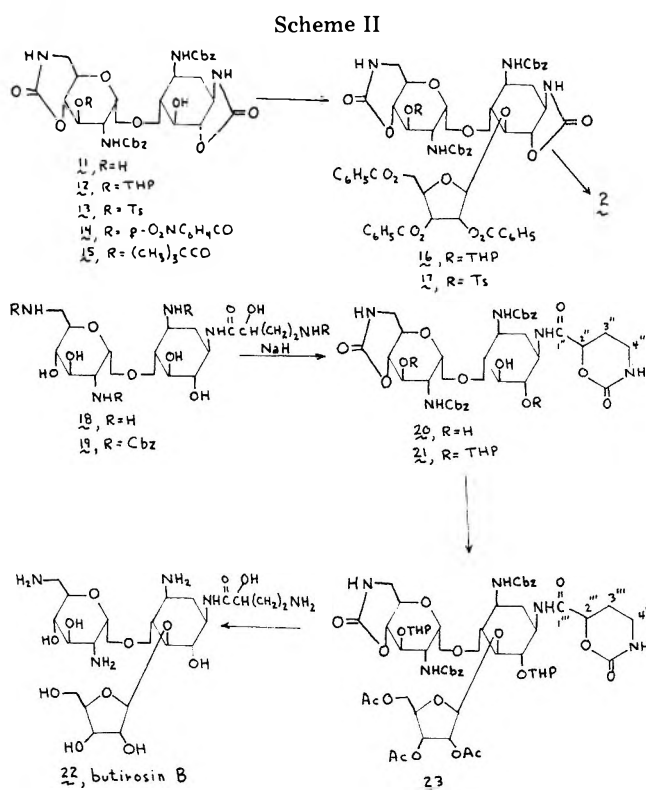
We chose the latter compound as our starting material.[21] It was converted into its tetra-N-carbobenzyloxy derivative 19 and then treated with sodium hydride in DMF to give the bis(cyclic carbamate) 20. This product has only its 3′-, 5-, and 6-hydroxyl groups free. There was some doubt as to whether we could selectively block the 3′- and 6-hydroxyl groups, but this operation was done in high yield by way of the THP derivative (21). Coupling of 21 with tri-O-acetylribosyl chloride gave the glycoside (23) in 40% yield and deblocking by alkaline hydrolysis and hydrogenolysis afforded butirosin B (22). No hydrolysis of the side chain occurred under the conditions used for cyclic carbamate hydrolysis. The structure and purity of this butirosin B were confirmed by its R_f value on TLC, which was identical with that of authentic material in two solvent systems, and the comparison of the specific optical rotations and infrared spectra of these two samples (Experimental Section).

In summary, we have developed synthetic procedures and intermediates for the regiospecific syntheses of ribostamycin and butirosin B. These procedures do not require any difficult separations of isomers and anomers. The use of these intermediates for the synthesis of novel ribostamycin and butirosin analogues is in progress.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-33 spectrophotometer as KBr pellets. Nuclear magnetic resonance spectra were recorded on a Varian EM-360 and T-60 spectrometers using Me₄Si or sodium 2,2-dimethyl-4-silapentane-5-sulfonate as the standard. Optical rotations were taken on a Carl Zeiss OLD4 automatic polarimeter under the indicated conditions. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, Purdue University and Chemalytics, Inc., Tempe, Arizona.

Tetra-N-phenoxycarbonylneamine (5). An ice-cooled solution of neamine hydrochloride (0.51 g, 1.08 mmol) and sodium bicarbonate (1.68 g, 20 mmol) in 22 mL of water was treated dropwise over 10 min with a solution of phenyl chloroformate (2.5 g, 15.5 mmol) in 36 mL of acetone. The mixture was stirred 30 min more and neutralized with 10% hydrochloric acid. The resulting precipitate was washed with ether and water and vacuum dried to give 0.62 g (72%) of 5 as a white solid: mp 266 °C dec; $[\alpha]_{546}^{22}$ +53.8° (c 1.0, DMF); IR 1720 and 1705

(NHCO I), 1525 cm^{-1} (NHCO II); NMR (Me$_2$SO-d_6) δ 6.9–7.95 (phenyl). In subsequent experiments the product was obtained in yields up to 85% by partially concentrating the reaction mixture and adding more water.

Anal. Calcd for C$_{40}$H$_{42}$N$_4$O$_{14}$: C, 59.85; H, 5.24; N, 6.98. Found: C, 59.66; H, 5.33; N, 6.92.

Tetra-N-p-nitrophenoxycarbonylneamine (6). An ice-cooled solution of neamine hydrochloride (0.365 g, 0.810 mmol) and sodium bicarbonate (0.70 g, excess) in 6 mL of water was treated over 10 min with a solution of p-nitrophenoxycarbonyl chloride (9.8 g, 3.64 mmol) in 10 mL of acetone. The precipitated product was washed with ether and water and vacuum dried to give 0.65 g (95%) of **6** as white powder; mp 210 °C dec; [α]$_{546}^{22}$ +48.95° (c 1.24, DMF); IR 1715 (NHCO I), 1515 (NHCO II), 1340 cm^{-1} (NO$_2$): NMR (Me$_2$SO-d_6) δ 7.45 (d, J = 4 Hz, aromatic) and 8.15–8.40 (d, J = 4 Hz, aromatic).

Anal. Calcd for C$_{40}$H$_{38}$N$_8$N$_8$O$_{22}$·2H$_2$O: C, 47.15; H, 4.13; N, 11.00. Found: C, 47.17; H, 4.26; N, 10.74.

2′,3′:4′,6′-N,O-Carbonyl-1,3-N,N-carbonylneamine (7). From Tetra-N-phenoxycarbonylneamine (5) or Tetra-N-p-nitrophenoxycarbonylneamine (6). A solution of **5** (0.25 g, 0.25 mmol) or an equivalent amount of **6** in 20 mL of freshly distilled N,N-dimethylformamide (DMF) was stirred with 6.0 g of DMF-washed Amberlite IR-45 (OH$^-$) at 25 °C for 18 h, filtered through a pad of diatomaceous earth, and concentrated under reduced pressure. Treatment of the residue with ether gave 1.20 g (98%) as white powder: mp >250 °C dec; [α]$_{546}^{22}$ +66.4° (c 1.0, DMF); IR 1770 (carbamate, five-membered), 1760 (ureide), 1720 (carbamate, six-membered), 1550 and 1535 cm^{-1} (NHCO II of ureide).

Anal. Calcd for C$_{15}$H$_{20}$N$_4$O$_9$·2H$_2$O: C, 41.28; H, 5.50; N, 12.84. Found: C, 41.43; H, 5.56; N, 12.84.

From 1,3-N,N-Carbonylneamine (10). An ice-cooled solution of **10** (0.55 g, 0.91 mmol) and sodium bicarbonate (0.35 g, 4.16 mmol) in 6 mL of water was treated with phenyl chloroformate (0.61 g, 3.9 mmol) in 9 mL of acetone. After 1.5 h the mixture was neutralized with hydrochloric acid and concentrated under reduced pressure. A DMF extract of the residue was concentrated and diluted with ether to give a solid. Recrystallization from DMF–ether gave 0.17 g of 1,3-N,N-carbonyl-2′,6′-di-N-phenoxycarbonylneamine as a white powder: mp 236–238 °C dec; IR 1720, 1710 (NHCO I), and 1520 cm^{-1} (NHCO II). Recrystallization of a small portion of this product from DMF–ether gave an analytical sample of mp 252–254 °C dec.

Anal. Calcd for C$_{27}$H$_{32}$N$_4$O$_{11}$: C, 55.10; H, 5.44; N, 9.52. Found: C, 54.81; H, 5.70; N, 9.23.

A solution of the above compound (0.10 g) in 10 mL of DMF was stirred with 3.0 g of DMF-washed Amberlite IR-45 resin for 15 h at 25 °C. The mixture was filtered through diatomaceous earth, concentrated under reduced pressure, and diluted with ether to give 0.049 g of **7** as a white solid identical in infrared spectrum and R_f value on TLC (acetone–DMF on silica gel) with the sample of **7** prepared as described above.

1,6:2′,3′:4′,6′-N,O-Carbonylneamine (8). A solution of tetra-N-phenoxycarbonylneamine (5; 0.90 g, 1.12 mmol) or an equivalent amount of **6** in 25 mL of freshly distilled DMF was stirred with 10.0 g of Dowex 1 × 2 resin (OH$^-$) at 25 °C for 20 h. The mixture was filtered, the resin was washed with DMF, and the combined filtrate and wash was concentrated to a small volume and treated with acetone. A resulting white precipitate gave 0.08 g (15%) of **7** after it was washed thoroughly with acetone and dried under vacuum. The resin was suspended in 10 mL of water, neutralized with 10% hydrochloric acid and washed with water and DMF. The combined washes and filtrate were treated with Amberlite IR-45 (OH$^-$) for 30 min. The mixture was filtered and the filtrate was concentrated to a small volume and diluted with acetone. A product that precipitated was recrystallized from aqueous methanol–acetone to give 0.345 g (76%) of **8**: mp >250 °C dec; [α]$_{546}^{22}$ +76.10° (c 1.10, DMF); IR 1770 (carbamate, five-membered) and 1720 cm^{-1} (carbamate, six-membered).

Anal. Calcd for C$_{15}$H$_{20}$N$_4$O$_9$·1.5H$_2$O: C, 52.15; H, 5.38; N, 13.11. Found: C, 52.25; H, 5.53; N, 13.40.

3-N-Acetyl-1,6:2′,3′:4′,6′-N,O-carbonylneamine (9). A stirred suspension of compound **8** (0.10 g, 0.25 mmol) in 5 mL of dry methanol was treated with 0.5 mL of dry methanol and 0.5 mL of acetic anhydride and the resulting mixture was stirred at 25 °C for 20 h. It was concentrated to dryness and the residue was crystallized from aqueous ethanol to give 0.082 g (74%) of **9**: mp >240 °C dec; [α]$_{546}^{22}$ +70.0° (c 0.5, DMF); IR 1765 (carbamate, five-membered), 1720 (carbamate, five-membered), 1650 (NHCO I), and 1525 cm^{-1} (NHCO II).

Anal. Calcd for C$_{17}$H$_{22}$N$_4$O$_{10}$·4H$_2$O: C, 39.69; H, 4.83; N, 10.89. Found: 39.61; H, 5.81; N, 10.92.

1,3-N,N-Carbonylneamine (10). A solution of tetra-N-phenoxycarbonylneamine (5; 0.20 g, 0.025 mmol) in 10 mL of dry methanol

was treated with sodium hydroxide (0.16 g, excess) and the resulting solution was heated under reflux for 26 h, cooled, neutralized with acetic acid, and concentrated to dryness. A DMF extract of the residue was filtered, concentrated to a small volume, and diluted with acetone, whereupon a white solid precipitated. Two recrystallizations from DMF–ether gave 0.072 g (86%) of **10**, mp 278 °C dec; IR 1720 and 1525 (NHCONH I and II), 1585 cm^{-1} (NH$_2$); NMR (Me$_2$SO-d_6) showed the NHCONH protons as a broad peak at δ 6.50–6.74.

Anal. Calcd for C$_{13}$H$_{24}$N$_4$O$_7$: C, 44.82; H, 6.89; N, 16.09. Found: C, 44.99; H, 6.62; N, 16.11.

Tetra-N-benzyloxycarbonylneamine. A mixture of neamine hydrochloride (0.5 g, 1.06 mmol) and sodium bicarbonate (1.7 g) in 70% aqueous methanol (20 mL) was cooled with stirring in an ice bath and benzyl chloroformate (2.0 g, 11.72 mmol) was added dropwise with the aid of 5 mL of methanol. The reaction mixture was stirred for 2 h at 0 °C and then evaporated to dryness under reduced pressure. The residual product was extracted three times with 25 mL of dry dioxane. The dioxane layer was concentrated to a small volume and treated with ether. The resulting white solid was washed several times with dry ether to give a pure product: 0.76 g (84%); mp 259 °C dec [lit.[6] mp 259 °C dec]; [α]$_{546}^{22}$ +51.0° (c 1.0, DMF); IR (KBr) 3580–3220 (OH and NH), 1710, 1700 and 1695 (NHCO I), and 1530 cm^{-1} (NHCO II). This method was simpler and faster than that reported in the literature.[6]

3,2′-Di-N-benzyloxycarbonyl-1,6:4′,6′-O,N-carbonylneamine (11). A solution of tetra-N-benzyloxycarbonylneamine (1.0 g, 1.10 mmol) in 15 mL of dry DMF was cooled to 0 °C in an ice bath. The reaction vessel was evacuated and filled with dry nitrogen. Sodium hydride (0.15 g, 50% in oil, 3.125 mmol) was added and the reaction mixture was stirred 30 min at this temperature and 2 h at room temperature (25 °C). After 1 h of stirring the reaction mixture solidified and more dry DMF was added. The reaction mixture was neutralized with glacial acetic acid, concentrated under reduced pressure, and treated with ice cold water. The resulting white solid was filtered and washed thoroughly with water and ether to yield **11**: 0.65 g (86%); mp 230 °C dec; TLC showed a single spot (acetone–DMF); [α]$_{546}^{22}$ +32.57° (c 0.7, DMF); IR (KBr) 3600–3200 (OH and NH), 1770 (carbamate, five-membered), 1725 (carbamate, six-membered), 1710 (NHCO I), and 1540 cm^{-1} (NHCO II); NMR (Me$_2$SO-d_6) δ 5.1 (6s, anomeric proton), 7.3 (s, aromatic protons) and 8.2 (6s, carbamate protons). A small sample was recrystallized from DMF and ether.

Anal. Calcd for C$_{30}$H$_{34}$N$_4$O$_{12}$: C, 55.05; H, 5.37; N, 8.60. Found: C, 55.20; H, 5.67; N, 8.40.

3,2′-Di-N-benzyloxycarbonyl-1,6:4′,6′-N,O-carbonyl-3′-O-(2-tetrahydropyranyl)neamine (12). A stirred solution of **11** (0.5 g, 0.78 mmol) in 5 mL of DMF was treated with 5 mL of 2,3-dihydropyran and 20 mg of p-toluenesulfonic acid. The mixture was stirred at 25 °C for 1 h, treated with 0.1 mL of triethylamine, and concentrated to dryness. A chloroform extract of the residue was washed with water, dried over MgSO$_4$, and concentrated. Addition of ether to the residue gave a white solid which showed on TLC (4:1 benzene–acetone on silica gel) one major spot and a fast-moving minor spot. The solid was purified on a short silica gel column. After elution of the impurity with benzene the product was eluted with 4:1 benzene–acetone. Recrystallization from chloroform–ether gave 0.455 g (80%) of **12**: mp 158–166 °C dec; [α]$_{546}^{22}$ +22.84° (c 1.12, CHCl$_3$); NMR δ 5.2 (anomeric proton of sugar), 6.1 (anomeric proton of tetrahydropyranyl group).

Anal. Calcd for C$_{35}$H$_{42}$N$_4$O$_{13}$: C, 57.85; H, 5.78; N, 7.17. Found: C, 5.77; H, 5.85; N, 7.40.

3,2′-Di-N-benzyloxycarbonyl-1,6:4′,6′-N,O-carbonyl-3-O-p-toluenesulfonylneamine (13). A solution of **11** (0.550 g, 0.85 mmol) and recrystallized p-toluenesulfonyl chloride (1.0 g, 5.2 mmol) in 25 mL of dry pyridine was stirred at 25 °C for 24 h. The brown solution was concentrated under reduced pressure and the residual gum was triturated several times with ether. An excess of cold water was added to precipitate a slightly colored product. The TLC in acetone showed one major product with a minor fast moving spot. The crude product was purified on a silica gel column with benzene–acetone (1:1) and recrystallization from acetone–petroleum ether (30–60 °C) to give the monotosylate **13**: 0.480 g (70%); mp 170–172 °C; [α]$_{546}^{22}$ (c 0.85, DMF); IR 1770 (carbamate, six-membered) 1710 (NHCO I), 1600 (aromatic C=C), 1520 (NHCO II), and 1175 cm^{-1} (SO$_2$); NMR (Me$_2$SO-d_6) δ 2.3 (3, s, CH$_3$), 4.9 (2, d aromatic protons), 7.3 (2, d, aromatic protons), and 7.6 (m, NH).

Anal. Calcd for C$_{37}$H$_{40}$O$_{14}$N$_4$S: C, 55.78; H, 5.02; N, 7.03; S, 6.02. Found: C, 55.81; H, 5.18; N, 6.78; S, 4.07.

3,2′-Di-N-benzyloxycarbonyl-1,6:4′,6′-N,O-carbonyl-3′-O-p-nitrobenzoylneamine (14). A stirred solution of **11** (0.43 g, 0.67 mmol) in 10 mL of dry pyridine was treated with p-nitrobenzoyl

chloride (0.30 g, 1.6 mmol). After 18 h another 0.30 g of *p*-nitrobenzoyl chloride was added and the solution was stirred at 25 °C for 20 h. It was then concentrated and the residue was washed with ether. Trituration of the gummy product with water gave a white solid which was shown by TLC (1:1 benzene–acetone on silica gel) to contain one major product and several minor ones. Column chromatography on silica gel with benzene and increasing proportions of acetone afforded compound 14. Recrystallization from *p*-dioxane–hexane gave 0.32 g (60%) of white solid: mp 211–212 °C dec; $[\alpha]^{22}_{546}$ +36.0° (c 1.0, DMF); IR 1720 and 1340 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 8.10–8.40 (4, m, protons of *p*-nitrobenzoyl group).

Anal. Calcd for $C_{37}H_{37}N_5O_{15}\cdot H_2O$: C, 54.88; H, 4.82; N, 8.65. Found: C, 54.78; H, 4.69; N, 8.45.

3,2′-Di-*N*-benzyloxycarbonyl-1,6:4′,6′-*N*,*O*-carbonyl-3′-*O*-trimethylacetylneamine (15). A solution of compound 11 (0.214 g, 0.33 mmol) in 5 mL of dry pyridine was treated with 0.4 mL (excess) of trimethylacetyl chloride. The mixture was stirred at 24 °C for 38 h and concentrated under reduced pressure, and the residue was treated with water to give a solid. TLC (3:2 acetone–benzene) on silica gel showed one major product and several minor ones. The major product was isolated by preparative TLC with the same solvent system and then it was crystallized from *p*-dioxane and petroleum ether (30–60 °C). This procedure gave 0.080 g (33%) of 15 as white crystals: mp 258 °C dec; $[\alpha]^{22}_{546}$ +40.8° (c 0.35, DMF); IR 1735 cm^{-1} (COO).

Anal. Calcd for $C_{35}H_{42}N_4O_{13}$: C, 57.85; H, 5.78; N, 7.71. Found: C, 57.64; H, 5.70; N, 7.49.

2″,3″,5″-Tri-*O*-benzoyl-3,2′-di-*N*-benzyloxy-1,6:4′,6′-*N*,*O*-carbonyl-3′-*O*-(2-tetrahydropyranyl)ribostamycin (16). A mixture of 12 (0.36 g, 0.49 mmol), vacuum dried mercuric cyanide (.032 g), Drierite (2.5 g, dried over an open flame for 2 h), and chloroform (60 mL, alcohol free) was stirred at 25 °C for 20 h. A solution of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl chloride (prepared[13] from 600 mg of the corresponding acetate) in 6 mL of dry chloroform was added and the mixture was stirred under reflux for 48 h. Another portion of the halosugar in chloroform (half of the original amount) was added and reflux was continued for 24 h. Another portion of the halosugar in chloroform (half of the original amount) was added and reflux was continued for 24 h. TLC (1:1 benzene–acetone) then showed no starting material remaining. The mixture was filtered through a pad of diatomaceous earth and this pad was washed with dry chloroform. The combined filtrate and wash was concentrated to dryness and the semisolid residue was chromatographed on a column of silica gel with benzene containing an increasing proportion of ethyl acetate (0–100%) as solvent. Concentration of the main fraction (eluted by 4:1 chloroform–methanol) gave white solid which yielded after recrystallization from ethyl acetate–petroleum ether (30–60 °C) 0.36 g (61%) of 16: mp 135–145 °C dec; $[\alpha]^{22}_{546}$ +86.77° (c 0.93, CHCl$_3$); IR 1730 cm^{-1} ($C_6H_5CO_3$); NMR (CDCl$_3$) δ 5.5 (m, anomeric proton of tribenzoylribosyl group).

Anal. Calcd for $C_{61}H_{62}N_4O_{20}$: C, 62.56; H, 5.35; N, 4.78. Found: C, 62.27; H, 5.34; N, 4.88.

2″,3″,5″-Tri-*O*-benzoyl-3,2′-di-*N*-benzyloxycarbonyl-1,6:-4′,6′-*N*,*O*-carbonyl-3′-*O*-*p*-toluenesulfonylribostamycin (17). A stirred mixture of 13 (0.75 g, 0.94 mmol), vacuum dried mercuric cyanide (0.75 g), Drierite (5.0 g, dried 2 h over an open flame), 50 mL of chloroform, and 25 mL of dioxane was treated with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl chloride (prepared[17] from 1.2 g of the corresponding acetate) in 10 mL of dry chloroform. The mixture was stirred at reflux for 80 h and filtered through a pad of diatomaceous earth. This pad was washed thoroughly with chloroform–dioxane (1:1) and the combined filtrate and wash was concentrated. A chloroform extract of the residue was chromatographed on a column of silica gel with benzene containing increasing amounts of ethyl acetate (0–100%) as solvent. The major product, eluted by 1:1 benzene–acetone, was crystallized from chloroform–hexane to give 0.74 g (63%) of 17 as white solid: mp 205–207 °C dec; IR 1730 cm^{-1} ($C_6H_5CO_2$); NMR (CDCl$_3$) δ 5.6 (m, anomeric proton of tribenzoylribosyl group).

Anal. Calcd for $C_{63}H_{60}N_4O_{21}S$: C, 60.96; H, 4.84; N, 4.52; S, 2.58. Found: C, 61.04; H, 5.01; N, 4.54; S, 2.60.

Ribostamycin (2). From Compound 16. A solution of 1.0 g of 16 in 10 mL of dioxane and 10 mL of water was warmed at 60 °C and treated with 20 mL of aqueous 1 N barium hydroxide solution. The mixture was stirred at this temperature for 16 h with additional barium hydroxide solution added occassionally to maintain strong alkalinity. The mixture was neutralized by carbon dioxide gas and then filtered through a pad of diatomaceous earth. This pad was washed with aqueous DMF and the combined filtrate and wash was concentrated under reduced pressure. Addition of water gave a brownish solid that was collected, washed with water and acetone, and dried in air. The resulting brownish solid (0.70 g) had IR absorption at 1700

and 1520 cm^{-1} (NHCO I and II), but no bands for cyclic carbamate or benzoate ester groups. It was dissolved in 20 mL of dioxane and 20 mL of water, treated with 4 mL of 1 N hydrochloric acid and 0.30 g of 10% palladium-on-charcoal, and hydrogenated at 50 psi and 25 °C for 24 h. The catalyst was removed by filtration and the filtrate was neutralized with Amberlite IR-45 resin (OH$^-$) and concentrated to a small volume. Addition of methanol and acetone to the residue gave a slightly colored product which was purified by a sequence of operations involving column chromatography on Amberlite IR-C50 (NH_4^+) with 0–0.5 N ammonium hydroxide solution as solvent, crystallization from aqueous methanol–acetone, chromatography on a column of Amberlite IR-400 (OH$^-$) with water as solvent, concentration to a small volume, and addition of methanol and acetone. This procedure gave 72 mg (19%) of ribostamycin (2) as a white solid whose IR absorption spectrum was identical with an authentic sample obtained from Mieji Laboratories. The two samples had identical R_f values on TLC in the systems chloroform–methanol–28% ammonium hydroxide–water (1:4:2:1), lower layer of the system chloroform–methanol–28% ammonium hydroxide (1:1:1), and upper layer of the preceding system. The synthetic sample had $[\alpha]^{22}_{546}$ +36.0° (c 0.52, H_2O), whereas the authentic sample had +37.8° under the same conditions.

From Compound 17. To a solution of 17 (0.70 g) in 25 mL of dry methanol was added small chips of sodium metal (0.010 g). The mixture was stirred at 25 °C for 16 h, neutralized with hydrochloric acid, and concentrated to dryness. A DMF extract of the residue was filtered through a pad of diatomaceous earth, concentrated to a small volume, and diluted with ether. The white solid that formed (0.55 g) was dissolved in 10 mL of water and 10 mL of dioxane, treated with 10 mL of 0.05 M barium hydroxide solution, and stirred at 60 °C for 3 h. Another 10 mL of the barium hydroxide solution was added and stirring at 60 °C was continued for 15 h. The mixture was neutralized with carbon dioxide gas and then filtered through a pad of diatomaceous earth. A DMF wash of this pad was combined with the filtrate and concentrated to a small volume. Addition of acetone gave a white solid (0.47 g) that showed no benzoate or cyclic carbamate carbonyl absorption in the infrared spectrum.

The white solid was dissolved in a mixture of liquid ammonia (120 mL) and ethylamine (20 mL). Sodium metal (1.0 g) was added and the dark blue solution that formed was stirred for 2 h at −30 °C. Water was added to discharge the color and the ammonia was allowed to evaporate. The residue was diluted with 10 mL of water and neutralized with Amberlite IR-C50 resin (NH_4^+), and the entire slurry was transferred to a column. It was washed with water and eluted with 2 N ammonium hydroxide until the eluate was no longer ninhydrin positive. The concentrate from this eluate was dissolved in a minimum volume of water, filtered through a pad of diatomaceous earth, and rechromatographed on the same resin with gradient elution by 0–0.3 N ammonium hydroxide. The fractions that gave spots on TLC (1:4:2:1 chlorofrom–methanol–28% ammonium hydroxide–water on silica gel) with R_f values identical with that of authentic ribostamycin were concentrated to a small volume and diluted with acetone. The white solid that precipitated (59 mg, 23%) had an infrared absorption spectrum identical with that of authentic ribostamycin and with the sample prepared from compound 16. It had a specific rotation of $[\alpha]^{22}_{546}$ +36.7° (c 0.45, H_2O) which compares with a value of $[\alpha]^{22}_{546}$ +37.8 (c 0.51, H_2O) for the authentic sample.

1-*N*-[(*S*)-4-Amino-2-hydroxybutyryl]tetra-*N*-benzyloxycarbonylneamine (19). A solution of 18[17] (1.0 g, 2.29 mmol) and 3.0 g of sodium carbonate in 50 mL of 70% aqueous methanol, cooled at 0 °C and stirred, was treated dropwise with a solution of benzyl chloroformate (5.0 g, 29.3 mmol) in 5 mL of methanol. The mixture was stirred at 0 °C for 2 h and at 25 °C for 18 h, concentrated under reduced pressure, and extracted three times with warm dioxane. This extract was concentrated under reduced pressure and the residue was treated with ether. A white solid that formed was washed thoroughly with ether to give 2.1 g (95%) of 19: mp 234–236 °C dec; $[\alpha]^{22}_{546}$ +35.5° (c 1.0, DMF); IR 1710, 1895, and 1650 (NHCO I), 1530 cm^{-1} (NHCO II); NMR (Me_2SO-d_6) δ 5.05 (2, s, CH_2), 7.4 (5, br, aromatic).

Anal. Calcd for $C_{48}H_{57}N_5O_{16}$: C, 60.06; H, 5.99; N, 7.30. Found: C, 59.95; H, 6.03; N, 7.41.

1-*N*-[(*S*)-4-Amino-2-hydroxybutyryl]-3,2′-di-*N*-benzyloxycarbonyl-4′,6′:2″,4″-*N*,*O*-carbonylneamine (20). An ice-cooled solution of 19 (1.0 g, 1.06 mmol) in 15 mL of dry DMF was treated with 50% sodium hydride in oil suspension (0.15 g, 3.1 mmol) and the mixture was stirred under nitrogen at 25 °C for 2 h. Additional dry DMF was added when the mixture became gelatinous. The mixture was worked up as described in the preparation of compound 11 to give a crude solid that was purified by reprecipitation from DMF with ether. This procedure gave 0.72 g (90%) of 20 as a white solid: mp >232

°C dec; $[\alpha]_{546}^{22}$ +27.88° (c 1.04, DMF); IR 1730 and 1720 (carbamate, six-membered), 1700 (NHCO I) and 1540 cm^{-1} (NHCO II).

Anal. Calcd for $C_{34}H_{41}N_5O_{14}$: C, 54.91; H, 5.52; N, 9.42. Found: C, 54.92; H, 5.89; N, 9.20.

1-N-[(S)-4-Amino-2-hydroxybutyryl]-3,2'-di-N-benzyloxy-carbonyl-4',6':2'',4''-N,O-carbonyl-6,3'-di(2-tetrahydropyran-yl)neamine (21). To a solution of **20** (2.0 g, 2.69 mmol) in 20 mL of dry DMF was added 10 mL (excess) of 2.3-dihydropyran and 100 mg of *p*-toluenesulfonic acid. The mixture was stirred at 24 °C for 1.5 h, neutralized with triethylamine, and concentrated under reduced pressure. Treatment of the residue with water gave a solid that was purified further by precipitation from chloroform solution with ether. The resulting white solid was chromatographed on a silica gel column. A minor impurity was eluted with benzene and then the desired product was eluted with methanol. This procedure gave 1.53 g (61%) of **21** as white solid: mp 148–152 °C dec; $[\alpha]_{546}^{22}$ −5.2° (c 1.15, CHCl$_3$).

Anal. Calcd for $C_{44}H_{57}N_5O_{16}$: C, 57.95; H, 6.30; N, 7.68. Found: C, 58.12; H, 6.51; N, 7.77.

2'',3'',5''-Tri-O-acetyl-3,2'-di-N-benzyloxycarbonyl-4',6':-2''',4'''-N,O-carbonyl-6,3'-(2-tetrahydropyranyl)butirosin B (23). A mixture of **21** (0.30 g, 0.33 mol), mercuric cyanide (0.6 g), Drierite (2.0 g), and dry methylene chloride (20 mL) was stirred at 25 °C for 2 h and treated with 2,3,5-tri-O-acetyl-1-ribosyl chloride (1.0 mmol) in 3 mL of dry methylene chloride. The resulting mixture was stirred at reflux for 48 h, diluted with methylene chloride, and filtered through a pad of diatomaceous earth. Concentration of the filtrate to a small volume and dilution with ether gave a white solid that showed one major and several minor spots on TLC (9:1 chloroform–methanol on silica gel). Purification on a silica gel column with the same solvent system gave a white solid that was recrystallized from chlororform–ether. This procedure gave 0.154 mg (40%) of **23**: mp 108–113 °C dec; $[\alpha]_{546}^{22}$ +12.0° (c 1.0, CHCl$_3$); IR 1730 and 1720 (car-bamate, six-membered), 1700 (NHCO I) and 1530 cm^{-1} (NHCO II).

Anal. Calcd for $C_{55}H_{71}N_5O_{23}$: C, 56.45; H, 6.11; N, 5.98. Found: C, 56.14; H, 5.98; N, 5.72.

Butirosin B (22). A solution of 150 mg of **23** in 10 mL of dioxane was heated at 60 °C with 10 mL of 0.1 N barium hydroxide. After 1-h intervals two additional 10-mL portions of 0.1 N barium hydroxide were added. Following a total reaction time of 7 h, the mixture was neutralized with carbon dioxide gas and filtered through a pad of diatomaceous earth. The pad was washed with DMF and the combined filtrate and wash was concentrated to a small volume and diluted with acetone. The white solid that formed showed no absorption characteristic of acetate or cyclic carbamate groups in its infrared spectrum.

A solution of the white solid in 10 mL of dioxane and 10 mL of water was treated with 0.15 g of 10% palladium-on-charcoal and 2.5 mL of acetic acid. The mixture was shaken with hydrogen at 50 psi and 25 °C for 24 h and filtered, and the filtrate was concentrated under reduced pressure. Trituration of the residue with acetone gave a white solid that showed one spot identical in R_f with authentic butirosin B[17] on TLC (1:4:2:1 chlorcform–methanol–27% ammonium hydroxide–water on silica gel). This solid was purified by successive column chromatographic separations on Amberlite IR-C-50 (NH$_4$+) with 0.1–0.5 N ammonium hydroxide, Amberlite GC-50 (NH$_4$+) with 0.1–0.5 N ammonium hydroxide, and Amberlite IR-400 (OH$^-$) with water. Concentration of the final eluate gave a white solid that was crystallized from aqueous methanol–acetone. This procedure gave

14 mg (20%) of butirosin B (**22**) with a specific rotation of $[\alpha]_{546}^{22}$ +21.8° (c 0.54, H$_2$O) which compares with $[\alpha]_{546}^{22}$ +22.8° (c 0.46, H$_2$O) for the authentic sample. The two samples were identical in their infrared absorption spectra and R_f values on TLC (1:1:1 chloroform–methanol—27% ammonium hydroxide on silica gel).

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Phenyl Migration during Preparation of Grignard Reagents

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Magnesium reacts in diethyl ether with 5-chloro-4,4-diphenyl-1-pentene, 2-chloro-1,1,1-triphenylethane, and 1-chloro-2,2,3-triphenylpropane to give Grignard reagents in which phenyl groups have undergone an appreciable amount of [1,2]sigmatropic rearrangement. In tetrahydrofuran less rearrangement was observed in the Grignard reagent. These rearrangements are believed to occur in intermediate radicals formed during preparation of the Grignard reagents.

While phenyl and other aryl groups are known to undergo migration[1] during reaction of lithium metal with certain alkyl halides to give rearranged organolithium compounds and while organolithium compounds themselves,[2] somewhat less commonly, undergo migration of aryl groups, aryl migrations during reaction of alkyl halides with magnesium to give rearranged Grignard reagents are unknown or poorly documented although rearranged hydrocarbon by-products have been reported.[3,4] Also Grignard reagents, once formed, evidently do not undergo aryl migration; thus 2,2-diphenylpropylmagnesium chloride has been prepared unrearranged from the corresponding chloride in tetrahydrofuran and did not rearrange in refluxing dioxane or in pyridine.[5]

In some preliminary experiments directed toward another goal[6] it was desired to prepare 3,3-diphenyl-5-hexenoic acid. Since 5-chloro-4,4-diphenyl-1-pentene was available, preparation of the acid by carbonation of the Grignard reagent prepared from the chloride in diethyl ether was attempted. This Grignard product, however, gave rise to a complex mixture of five carboxylic acids of which 2-benzyl-2-phenyl-4-pentenoic acid (product of 1,2 migration of phenyl) was the major component. In contrast the same Grignard preparation in tetrahydrofuran gave, as expected, nearly pure 3,3-diphenyl-5-hexenoic acid.

Since the reaction of 5-chloro-4,4-diphenyl-1-pentene is complicated likely by migration of the allyl group[6] and prototropic migration of the double bond in addition to the phenyl group, reaction of the simpler chloride 2-chloro-1,1,1-triphenylethane with magnesium[7] was studied. The results are summarized in Table I which gives the GLC-volatile products (other than triphenylethylene) from carbonation of reactions run under various conditions. It is obvious that in both diethyl ether and di-n-butyl ether the organomagnesium product is extensively rearranged with the quantity of 1,1,2-triphenylethyl Grignard reagent (product of 1,2 migration of phenyl) being comparable to that of the expected 2,2,2-triphenylethylmagnesium halide. In tetrahydrofuran, however, the quantity of rearranged organomagnesium compound is negligible. In general, the quantity of rearranged hydrocarbon 1,1,2-triphenylethane was appreciable in all of the ethereal solvents investigated; however, there are irregularities, possibly due to the adventitious presence of protonating or hydrogen atom-transfer agents.

For each run tested in Table I, within the experimental error, the total percentage of volatile rearranged products was invariable with time. *Hence the organomagnesium product itself does not rearrange at an appreciable rate.* The observed phenyl migration must, therefore, occur *during formation* of the Grignard reagent likely by way of radicals which are, in part, free enough from the surface of the magnesium to permit

rearrangement. Similar interpretations have been advanced to explain rearranged hydrocarbon by-products formed[3,4] during preparation of other Grignard reagents and to account for extensive racemization during preparation[8] of optically active Grignard reagents from optically active cyclopropyl halides. The 1,2 shift of aryl groups in free radicals is a well known reaction and occurs with special ease in the case of the 2,2,2-triphenylethyl radical.[9]

Heterogeneous reactions at metallic surfaces via radical intermediates are apt to be rather irreproducible. The total percentage of rearrangement in Table I showed considerable variability from run to run and had no consistent variation with the method of purification of the solvent or the grade of magnesium employed. The amount of rearrangement in tetrahydrofuran evidently increases with the reaction temperature and was almost negligible at 27 °C. For comparisjns at similar temperatures, the smaller amount of rearrangement in THF than in di-n-butyl ether parallels results which have been reported[10] for reaction of 6-bromo-1-hexene with magnesium where "rearrangement" corresponds to formation of the cyclopentylmethyl radical. With 2-chloro-1,1,1-triphenylethane, however, diethyl ether and di-n-butyl ether gave similar amounts of rearranged products unlike the results reported for 6-bromo-1-hexene. That the rearranged product from 2-chloro-1,1,1-triphenylethane in THF is primarily 1,1,2-triphenylethane rather than rearranged Grignard reagent as in diethyl ether may reflect the higher reactivity of THF than diethyl ether toward radicals.[8b,11]

Finally, in order to test the generality of phenyl migration in reactions of halides with magnesium, the reaction of 1-chloro-2,2,3-triphenylpropane in diethyl ether was studied. Carbonation after 4 h gave 3,3,4-triphenylbutanoic acid containing 28 mol % of 2-benzyl-2,3-diphenylpropanoic acid (product of 1,2 migration of phenyl). Upon storing a portion of this Grignard solution for 23 h at room temperature before carbonation, the proportion of rearranged acid was unchanged, a result which parallels our study upon 2-chloro-1,1,1-triphenylethane. Unlike the reactions of 1-chloro-2,2,3-triphenylpropane with lithium, potassium, and cesium in THF,[12] none of the product 2,2,4-triphenylbutanoic acid (from 1,2 migration of benzyl) was found in the reaction with magnesium.

In conclusion, 1,2 migration of phenyl (and likely other aryl groups) appears to be of rather general occurrence during reactions of β-phenylethyl halides with magnesium, especially for reactions in diethyl ether; rearrangement is likely to be observed not only in the hydrocarbon by-products but also in the Grignard reagent itself. The three chlorides studied in the present work were slow in their reactions with magnesium under all conditions tested. Also the yields of Grignard reagent were poor to moderate; the highest yield reported in Table I is only 48%, with the average yield of diethyl ether being 42%. These results contrast with yields of 96 to 99.7% which have been reported[13] for n-alkyl chlorides. It may be argued that in most of the present reactions the alkyl chloride was added

$$\text{Ph}_3\text{CCH}_2\text{Cl} \xrightarrow{\text{Mg}} \text{Ph}_3\text{CCH}_2\cdot \; + \; \text{ClMg}\cdot \longrightarrow \text{Ph}_3\text{CCH}_2\text{MgCl}$$

$$\downarrow$$

$$\text{Ph}_2\text{CCH}_2\text{Ph} \; + \; \text{ClMg}\cdot \longrightarrow \text{Ph}_2\text{C(MgCl)CH}_2\text{Ph}$$
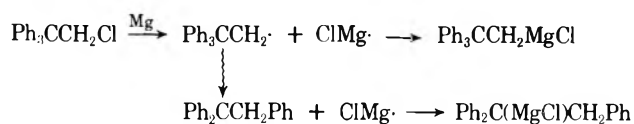
Table I. Reaction of 2-Chloro-1,1,1-triphenylethane with Magnesium

RCl, mmol	solvent	temp., °C [g]	reaction time, h	Ph$_3$CCH$_3$, mmol	Ph$_2$CHCH$_2$Ph, mmol	Ph$_3$CCH$_2$CO$_2$H, mmol	PhCH$_2$-CPh$_2$-CO$_2$H, mmol	total rear-range-ment, [h] %
6.8[a]	Et$_2$O[d]	27	5	1.38	0.15	1.75	0.48	17
6.8[a]	Et$_2$O[d]	27	7	0.24	0.08	1.77	0.58	25
		25	113	1.95	0.19	0.52	0.38	19
16.6[b]	Et$_2$O[e]	27	5	2.9	0.14	0.61	1.70	35
		25	96	0.87	0.13	2.5	2.2	41
17.0[c]	Et$_2$O[e]	27	3	3.5	0.08	2.4	1.68	23
		25	24	2.3	0.00	1.94	1.39	25
6.8[a]	THF[f]	38	23	0.37	0.07	0.026	0.001	15
		25	171	4.4	0.76	0.000	0.000	15
17.1[b]	THF[f]	45	13	5.3	0.99	0.22	0.00	15
17.3[b]	THF[e]	27	3.5	2.2	0.20	3.8	0.0	3
		25	20	2.7	0.16	1.8	0.0	3
13.2[c]	THF[e]	27	4	1.41	0.16	2.1	0.0	4[i]
17.1[a]	n-Bu$_2$O[j]	27	3	3.4	0.20	1.49	0.95	19
		25	23	2.9	0.48	1.15	0.60	21

[a] Magnesium turning for Grignard reaction from Fisher Scientific Co. [b] Doubly sublimed magnesium, freshly milled. [c] Magnesium rod from Fisher Scientific Co., freshly milled. [d] The solvent was freshly distilled from LiAlH$_4$. [e] The solvent was freshly distilled from benzophenone sodium ketyl. [f] The solvent was freshly distilled from NaAlH$_4$. [g] For the double entry the reaction was stirred for the number of hours indicated at the first temperature, a portion of the mixture was carbonated, and the remainder of the mixture was stored at room temperature for the indicated additional time before carbonation. [h] Expressed as mole percent of volatile products reported in the table. [i] Some 43% of the alkyl chloride remained unreacted. [j] The n-butyl ether was freshly distilled from molten sodium.

all at once rather than by the more orthodox procedure of adding the halide gradually; however, tests upon simple *chlorides* have shown that such differences in procedure make little or no significant difference in yields of organomagnesium chlorides.[13]

The chlorides studied here are part of a group which were designed to demonstrate the occurrence of 1,2-aryl migration in carbanions.[14] Simple molecular orbital calculations predict[15] that, other factors being equal, [1,2]sigmatropic rearrangements should occur with greater ease in free radicals than carbanions. While the lifetime or freeness of radicals being formed at a metal surface are poorly understood, the present results with magnesium were perhaps to be anticipated.

Experimental Section

All Grignard reactions were carried out, unless otherwise specified, in Morton flasks under a nitrogen atmosphere with high-speed stirring.[16] Magnesium was placed in the flask and the flask was flame dried while prepurified nitrogen was passed through the flask. Analyses by gas chromatography (GLC) were performed on instruments equipped with hydrogen-flame ionization detectors; qualitative GLC analyses are reported as "area percent" of total volatile constituents whereas "quantitative" GLC analyses were calculated with calibration factors and utilized known samples and internal standards. The 1,1,1-triphenyl-2-chloroethane,[2] 1-chloro-2,2,3-triphenylpropane,[17] 5-chloro-4,4-diphenyl-1-pentene,[6] and hydrocarbons and acids which were derived therefrom were prepared by methods which have already been given under the corresponding chloride. The reference sample of 2-benzyl-2,3-diphenylpropanoic acid was prepared essentially by the procedure of Hauser and co-workers.[18,19]

Reaction of 5-Chloro-4,4-diphenyl-1-pentene with Magnesium. A. In Diethyl Ether. To 3.4 g (0.14 g-atom) of magnesium in 85 mL of anhydrous ether was added 10 drops of methyl iodide and then the mixture was stirred with a magnetic stirrer at reflux for 30 min before addition of 14.9 g (0.058 mol) of 5-chloro-4,4-diphenyl-1-pentene in 15 mL of anhydrous ether. After 6 h at reflux temperature the reaction mixture was carbonated by addition of dry ice. The usual workup gave 3.1 g (20% yield for C$_{18}$H$_{18}$O$_2$) of acids. A GLC analysis of the acids as methyl esters on a 20 ft × ⅛ in. column packed with 15% Apiezon H on 60/80 mesh Chromosorb W at 203 °C gave products listed as area percent (relative retention time, identify): 12% (1.24, 2,2-diphenyl-4-hexenoic acid?), 57% (1.49, 2-benzyl-2-phenyl-4-pentenoic acid?), 12% (1.54, 3,3-diphenyl-5-hexenoic acid?), 7% (1.71), and 11% (1.87). The identity of the major product 2-ben-

zyl-2-phenyl-4-pentenoic acid was confirmed by NMR spectral comparisons of the methyl ester with an authentic sample;[6] the NMR spectrum of the mixture suggested that, in part, the allyl group of the reactant had been isomerized to a propenyl group in the products.

B. In Tetrahydrofuran. To 2.00 g (0.082 g-atom) of magnesium and 25 mL of THF in the usual Morton apparatus was added 1.1 g (0.008 mol) of methyl iodide. After 10 min, an additional 225 mL of THF was added and then 10.6 g (0.041 mol) of 5-chloro-4,4-diphenyl-1-pentene along with 0.6 g (0.004 mol) of methyl iodide in 10 ml of THF was added over a period of 10 min at room temperature with high-speed stirring. Since the reaction was only about half complete after 5 h of stirring at room temperature, the mixture was heated at reflux for 120 h before being cooled to 25 °C and forced onto solid carbon dioxide. The usual workup gave neutral material (chiefly 4,4-diphenyl-1-pentene by GLC analysis) and 4.8 g (43% yield) of acid which by qualitative GLC analysis as methyl esters on a 6 ft ⅛ in. column packed with Apiezon L on 80/100 mesh Varaport at 175 °C contained products, listed as previously: 93% (1.55, 3,3-diphenyl-5-hexenoic acid), 4% (1.82, unknown), and traces of two more volatile products which evidently arose from impurities in the starting chloride. Recrystallization of the acid from pentane gave a product of mp 105–106 °C which was identical in the NMR spectrum and gave no mixture melting point depression with an authentic sample[6] of 3,3-diphenyl-5-hexenoic acid (mp 106.0–106.5 °C).

Reaction of 2-Chloro-1,1,1-triphenylethane with Magnesium. These reactions were run under the general conditions and with the results summarized in Table I. For reactions with 7 mmol of 2-chloro-1,1,1-triphenylethane, 0.100 g-atom of magnesium was employed, while with 17 mmol of the chloride, 0.21 g-atom of magnesium was used. The solvent (200 mL) was freshly distilled into the reaction flask from the reagent indicated in the table. All of the reactions were initiated by addition of 2.0 mL (32 mmols) of methyl iodide. The reaction mixture was then stirred vigorously for 20 to 30 min at the reaction temperature to consume all of the methyl iodide (in a reaction, not recorded in the table, in which the methyl iodide was not all reacted with the magnesium before addition of the chloride, the rearranged Grignard reagent was found to have reacted preferentially with the methyl iodide to give 1,2,2-triphenylpropane). The 2-chloro-1,1,1-triphenylethane was then added in one portion as a solid by rotation of the goose-necked vial attached to a side arm of the Morton flask by a ⊺ 24–40 joint. The reaction mixture was stirred vigorously with the high-speed stirrer at the initial reaction temperature and for the time indicated in Table I before carbonation. In many of the runs about half of the reaction solution was transferred before carbonation through a glass transfer tube (which extended to the bottom of the reaction flask) to a glass storage vessel, all under an atmosphere of nitrogen. The transfer tube contained a Kontes high-vacuum Teflon valve which, when open, permitted transfer of

the reaction solution under a slight pressure of nitrogen. The portion of the solution in the storage vessel was kept at room temperature for the time indicated in the table before carbonation. For carbonation the reaction solutions were cooled to near 0 °C and then gaseous carbon dioxide was bubbled through the solution in the storage vessel or over the solution in the Morton flask with stirring. Carbon dioxide was passed slowly through or over the solutions overnight to ensure completion of carbonation. The reaction mixtures were then decomposed with excess dilute hydrochloric acid and extracted thoroughly with diethyl ether. The combined ethereal extracts were extracted with three 50-mL portions of 10% aqueous sodium hydroxide. The ether layer, after drying over anhydrous $MgSO_4$ and removal of ether, yielded the neutral products. The combined sodium hydroxide extracts were acidified with sulfuric acid and extracted thoroughly with diethyl ether; this ethereal extract, after drying over anhydrous $MgSO_4$ and removal of solvent, yielded the acidic products.

For quantitative analysis of the neutral products in Table I diphenylmethane was added as an internal standard; GLC analyses were done at 215 °C on a 6 ft × $1/8$ in. column packed with 10% Carbowax 20-M on 100–120 mesh Chromosorb Q. Typical retention times in minutes for the neutral products were Ph_2CH_2, 1.2; Ph_3CCH_3, 9.4; Ph_2CHCH_2Ph, 11.4; and Ph_3CCH_2Cl and $Ph_2C=CHPh$, 14.0. Unfortunately since the starting chloride decomposes to triphenylethylene under GLC conditions no analysis for triphenylethylene was possible; the combined yield of triphenylethylene and 2-chloro-1,1,1-triphenylethane for the runs of Table I varied from 4 to 16% save for the one run indicated which evidently contained much unreacted chloride.

For quantitative analysis of the acidic products in Table I diphenylacetic acid was added as an internal standard and then the acids were esterified with diazomethane. The methyl esters were subjected to GLC analysis at 200 °C on a 6 ft × $1/8$ in. column packed with 5% SE-30 on 80–100 mesh Varaport. Typical retention times in minutes for the methyl esters of the acids were Ph_2CHCO_2H, 1.6; $Ph_2C(CO_2H)CH_2Ph$, 9.2; and $Ph_3CCH_2CO_2H$, 11.2.

Reaction of 1-Chloro-2,2,3-triphenylpropane with Magnesium. Magnesium (5.0 g, 0.20 g-atom) which was freshly milled from magnesium rod (Fisher Scientific Co.) was allowed to react with 1-chloro-2,2,3-triphenylpropane (5.00 g, 16.3 mmol) in 200 mL of diethyl ether (freshly distilled from benzophenonesodium ketyl) under the same general conditions as described for 2-chloro-1,1,1-triphenylethane. About half of the solution was carbonated after 4.0 h of stirring at 27 °C and the remainder after standing at 25 °C for 23 h. The acids as methyl esters were quantitatively analyzed by GLC at 230 °C on a 6 ft × $1/8$ in. column packed with 3.5% OV-17 on 100–200 mesh Chromosorb W (AW DMCS). The 4.0-h fraction contained acids listed as mmoles (retention time in min, identity): 0.77 (12.1, $PhCH_2CPh_2CH_2CO_2H$), 0.30 (13.0, $(PhCH_2)_2CPhCO_2H$), 0.00 (14.6, $PhCH_2CH_2CPh_2CO_2H$). Likewise the 23-h fraction contained 2.5 mmol of $PhCH_2CPh_2CH_2CO_2H$, 1.00 mmol of $(PhCH_2)_2CPhCO_2H$, and no $PhCH_2CH_2CPh_2CO_2H$. In addition in both fractions there was a small amount of an unknown acid of retention time 4.8 min. The neutral products from the carbonation were analyzed by GLC on both OV-17 and Carbowax 20-M columns and were found[20] to contain primarily 1,2,2-triphenylpropane and no 1,1,3-triphenylpropane; however, separation of 1,2,2-triphenylpropane from 1,2,3-triphenylpropane proved to be difficult, such that the amount of 1,2,3-triphenylpropane, if any, can only be judged to be small.

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Dynamic Stereochemistry of Imines and Derivatives. 14. Restricted sp² –sp² Carbon–Carbon Bond Rotation in Ortho-Substituted *N*-(1-Arylethylidene)alkylamines

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A series of imines, $Ar(Me)C=NCHMe_2$, where $Ar = o\text{-}X\text{-}C_6H_4$ (X = Me, Ph, NO_2, OCH_3) or 1-naphthyl, is shown by ^{1}H NMR spectroscopy to exist in solution as an equilibrating *E/Z* isomeric mixture at ambient temperature. The observation of anisochronous *gem*-methyl signals in the *Z* isomer indicates a chiral ground-state conformation where the aryl ring is twisted out of the imino plane. Barriers to rotation around the aryl–imino bond were found by dynamic NMR studies to be $\Delta G^{\pm} = 14.4$–20.4 kcal mol^{-1}, increasing with the steric bulk of the ortho substituent. The ortho-disubstituted chiral imine $2,4,6\text{-}Me_3C_6H_2(Me)C=NCH(Ph)Me$ shows nonequivalent o-methyl groups and meta protons up to the maximum temperature investigated (~200 °C) in hydrocarbon solvents, indicating a very high barrier ($\geqslant 27$ kcal mol^{-1}) to ring rotation. However, in chlorinated hydrocarbon solvents, signal collapse is observed below 200 °C. It is suggested that a net ring rotation in the *Z* form is brought about by a mechanism involving imine–enamine tautomerism and stereomutation to the *E* isomer.

Previous papers in this series[1] have dealt with *E/Z* equilibria about the C=N bond in imines and the kinetics and mechanisms of the isomerization process. Proton chemical-shift data and a study of molecular models indicated that the *Z* isomer of imines derived from ortho-substituted aryl ketones and aldehydes adopted a nonplanar ground state having the C-aryl ring twisted out of the imino plane.[2,3] We now describe a series of ketimines derived from ortho-substituted acetophenones where the NMR data establish unambiguously that this is the case and enable the rate of rotation around the aryl–imino bond to be investigated.

1, Ar = 2-$CH_3C_6H_4$
2, Ar = 2-$C_6H_5C_6H_4$
3, Ar = 2-$NO_2C_6H_4$
4, Ar = 2-$CH_3OC_6H_4$
5, Ar = 1-naphthyl

Results and Discussion

The ^{1}H NMR spectra of the ortho-substituted *N*-(1-arylethylidene)isopropylamines 1–5 were consistent with the existence of an equilibrating *E/Z* isomer mixture in solution, as expected from the results of a previous investigation into the factors controlling imine equilibria in related compounds.[2] In the case of the crystalline compounds 2 and 3, the *Z* isomer could be isolated by recrystallization and could be observed by NMR to equilibrate slowly on dissolution. The spectra were assigned configurations on the basis that the *N*-alkyl signals (methyl and methine) are shifted to higher field in the *Z* isomer by analogy with related imines.[2,3] Furthermore, the assignments were consistent in that the more shielded CMe_2 group exhibited the signal doubling in each case (see below). The equilibrium (Table I) favored the *Z* isomer in 1, 4, and 5 but was almost exactly balanced in 2 and 3. Previous studies of *E/Z* equilibria in ketimines derived from aryl alkyl ketones have shown that the *N*-alkyl group can prefer to reside cis to the aryl group if the latter possesses ortho substituents.[2] The

E/Z ratios in 1, 3, 4, and 5 are similar to those found in their *N*-methyl analogues.[2]

An unusual feature in the spectra of compounds 1 and 2 (in CCl_4) was that the isopropyl methyl signals from the *Z* isomer were split into two doublets of equal intensity, indicating that the *gem*-methyl groups were diastereotopic. The spectra of 3 and 5 in carbon tetrachloride, on the other hand, showed the normal single doublet for each isomer. However, when the spectra were recorded in benzene-d_6 or toluene-d_8 solution, all five compounds showed doubling of the isopropyl methyl signal in the *Z* form. It is not uncommon for aromatic solvents to resolve accidentally isochronous signals by inducing a differential solvent shift.[4] In the case of imine 4, geminal anisochronism could not be detected at ambient temperature in either solvent. However, on lowering the sample temperature to −6 °C, the methyl doublet of the *Z* isomer collapsed to a broad resonance and at −12 °C resolved into two components. Therefore, in this case the equivalence of the *gem*-methyl signals at ambient temperature is not accidental, but rather it is due to an environmental averaging process that is fast on the NMR time scale above 6 °C. The isopropyl methyls of the *E* isomer in 1–5 remained isochronous down to the lowest temperature investigated (ca. −80 °C).

These results indicate that the *Z* isomer adopts a chiral conformation 6 where the aryl ring is twisted out of the imino plane. Furthermore, rotation through the coplanar states 7 and 8 to obtain the enantiomeric conformation 6′ (i.e., enan-

tiomerization) must be slow on the NMR time scale at ambient temperature (below −6 °C in the case of 4). This conclu-
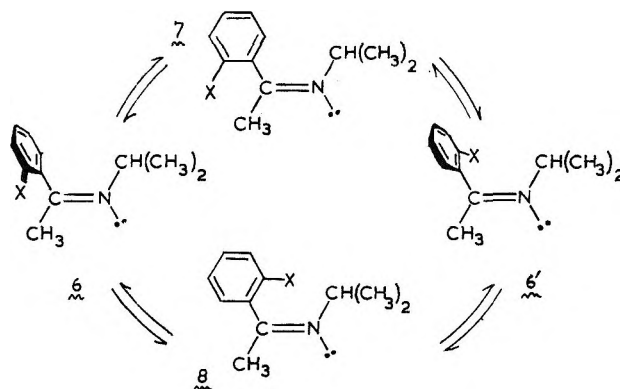
Table I. NMR Data for Diastereomeric Imines and Barriers to Rotation around the Aryl–Imino Bond in the Z Isomer

imine	% $Z^{a,b}$	$\delta_{NCH}{}^b$		$\delta_{C(CH_3)_2}{}^b$		$T_c,$	k	$\Delta G^{\ddagger}$
		Z	E	Z	E	°C	(s⁻¹)	(kcal mol⁻¹)
1	78	3.19	3.65	1.02, 1.11	1.18	74	23 ± 4^d	18.3 ± 0.2
	(77)	(3.04)	(3.72)	(0.91, 1.01)	(1.15)			
2	51	3.36	3.54	0.86, 1.03	1.14	63	23 ± 4^d	17.7 ± 0.2
	(54)	(3.20)	(3.65)	(0.72, 0.93)	(1.14)			
3	47	2.97	3.60	0.98, 1.04	1.13	56	13 ± 3^d	17.7 ± 0.2
	(48)	(2.93)	(3.86)	(0.95)	(1.13)			
4	76	3.41	3.73	1.13, 1.17	1.20	−6	9 ± 4^e	14.4 ± 0.4
	(72)	(3.08)	(3.79)	(0.95)	(1.13)			
5	84	3.23	3.80	1.06, 1.08	1.28	82	2 ± 1^e	20.4 ± 0.4
	(86)	(3.05)	(3.85)	(0.96)	(1.24)			
10	73^g	2.74, 2.80	3.32	0.87	1.07	61	74 ± 25^f	16.8 ± 0.3^g

[a] Error limits ±2. [b] Open data were obtained at 100 MHz in toluene-d_8 solution, except for 10 (see footnote g); data in parentheses refer to carbon tetrachloride solution. [c] Error limits ± 2 °C in measuring the coalescence temperature (T_c). [d] Rate constant (k) derived by computer-assisted analysis of the exchange broadened isopropyl methyl signals. [e] Estimated from $k = \pi\Delta\nu/2^{1/2}$ applied to the coalesced isopropyl methyl signals (see ref 16). [f] Estimated from $k = \pi(\Delta\nu_{AB}^2 + 6J_{AB}^2)^{1/2}/2^{1/2}$ applied to the coalesced NCH$_2$ AB system (see ref 17). [g] Data for this imine were determined in deuteriochloroform solution at 220 MHz (see text).

sion supports our previous suggestions[2,3] (based on chemical-shift data and an inspection of molecular models) that ortho-substituted C-aryl imines adopt a nonplanar conformation of this type.

The anisochronous *gem*-methyl signals of the Z isomers were observed to broaden and coalesce on raising the temperature. Rate constants (k) for rotation around the aryl–imino bond in the Z isomer at the coalescence temperature (T_c) and derived free energies of activation ($\Delta G^{\ddagger}$) are given in Table I. The magnitude of this rotational barrier is very sensitive to the ortho substituent (X) and decreases along the series X = 1-naphthyl ≫ methyl > phenyl ≈ nitro ≫ methoxyl. Enantiomerization can take place via either of the coplanar states 7 or 8, which involve X/CH$_3$ (four-bond) or X/CH(CH$_3$)$_2$ (five-bond) passing interactions, respectively. An inspection of molecular models suggests that rotation through 7 is the favored pathway. Undoubtedly the barriers are primarily "steric" in origin, though conjugating ortho substituents could also exert an effect on the aryl–imino conjugation in the coplanar states 7 and 8. However, the effect of conjugation might be reduced by steric inhibition of conjugation between the ortho substituent and the ring in 7 or 8. The $\Delta G^{\ddagger}$ values for aryl rotation in compounds 1–5 decrease roughly in line with the conformational energy of the ortho substituent (based on cyclohexane axial–equatorial equilibria) with the exception that the phenyl and methyl sequence is reversed. However, the lower barrier in 2 relative to 1 parallels the situation in substituted ethanes where the C–C rotational barrier decreases on replacing methyl by phenyl.[5] The nature of the nonbonded interactions in the transition state for rotation around the sp²–sp² C–C bond in 1–5 will differ somewhat from those obtaining in sp³–sp³ ethane systems. Mesomeric effects may also contribute; thus, the methoxyl substituent in 4 could stabilize the coplanar state 7 by increasing the conjugation energy and vice versa for the nitro substituent in 3 (cf. a recent study of central bond rotation in substituted biphenyls[6]).

None of these amines showed any splitting of the isopropyl methyl doublet for the E isomer even at low temperature (down to ca. −80 °C). Rotation about the aryl–imino bond in the E isomer should be easier than in the Z form, since the X/CH(CH$_3$)$_2$ passing interaction is absent in the coplanar conformation 9.

Compound 10 which contains a prochiral neopentyl group also exhibits restricted rotation around the 1-naphthyl–imino bond in the Z isomer. Thus, at 0 °C in deuteriochloroform solution the NCH$_2$ signal of the Z isomer was broadened, but interpretation was complicated by homoallylic coupling to the
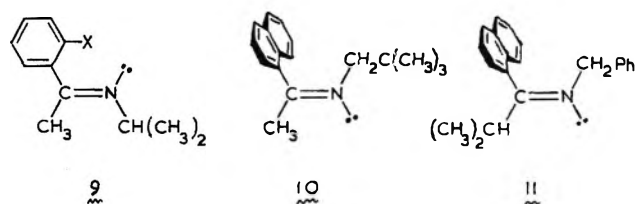
=CCH$_3$ protons (^5J = 1.5 Hz). However, the =CCD$_3$ analogue (prepared by exchange with CD$_3$OD) showed a strongly coupled AB pattern ($\Delta\nu_{AB}$ = 8.0 Hz at 100 MHz; J_{AB} = 12.9 Hz) for the NCH$_2$ signals of the Z isomer at −10 °C. The signal separation, $\Delta\nu_{AB}$, was too small to allow the dynamic coalescence point to be located, particularly since $\Delta\nu$ decreased on raising the temperature. Furthermore, $\Delta\nu_{AB}$ was even smaller (or zero) in other solvents (including toluene-d_8). Variable-temperature spectra were therefore recorded at 220 MHz in deuteriochloroform solution. The lower barrier in 10 relative to 5 (Table I) reflects the somewhat smaller steric requirements of the neopentyl group relative to isopropyl in this system. The barrier in 10 is also much lower than that reported[7] for naphthyl ring rotation in 11 ($\Delta G^{\ddagger}$ 23.6 kcal mol⁻¹), in line with the greater steric bulk of the *C*-alkyl group in the latter compound.

The stereochemical situation in these imines is somewhat similar to that obtaining in ortho-substituted benzamides (12)
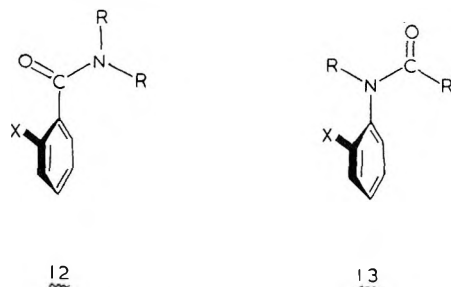
and anilides (13) which also adopt chiral nonplanar conformations and exhibit restricted rotation around the aryl–C(O) or N–aryl bonds.[8,9] The aryl rotational barrier in amide 12 (X = CH$_3$; R = CH$_2$CH$_3$)[8] appears to be ~15 kcal mol⁻¹ as compared with $\Delta G^{\ddagger}$ = 18.3 kcal mol⁻¹ in imine 1 and 20.0 kcal mol⁻¹ in anilide 13 (X = CH$_3$; R = CH$_2$Ph; R′ = CH$_3$).[9] Replacement of the o-tolyl moiety in 12 and 13 by 1-naphthyl also raises the barrier to aryl ring rotation (cf. imines 1 and 5).[8,9]

Restricted aryl ring rotation cannot normally be detected in symmetrically ortho-disubstituted compounds, with the
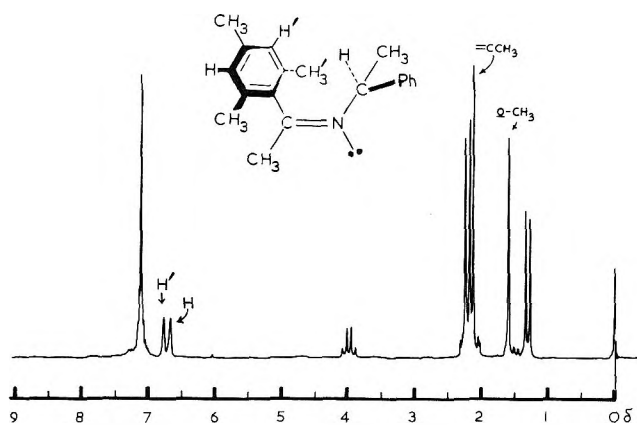
Figure 1. ^{1}H NMR spectrum of **15** at 100 MHz in carbon tetrachloride solution at 32 °C.

Figure 2. Framework model illustrating the postulated conformation of **15**.

aid of prochiral N-alkyl probes (e.g., **14**), since such compounds possess a molecular σ plane that passes through the N–R moiety in the bisected conformation depicted in **14**; hence, the paired geminal substituents in the N–R group are enantiotopic and isochronous.[4] However, if R is chiral (e.g., **15**) the o-methyl groups (and the m-hydrogen atoms) will be

14	R = CH(CH$_3$)$_2$
15	R = CH(Ph)CH$_3$
16	R = CH$_3$
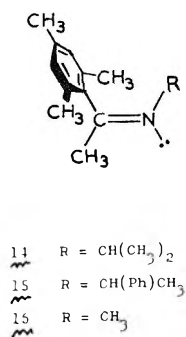
diastereotopic and potentially anisochronous, provided that rotation of the ring through the coplanar conformation is slow on the NMR time scale. The stereochemical situation is similar to that in chiral 2,6-dimethoxybenzamide investigated by Siddall and Garner.[10] Accordingly, compound **15** was prepared from 1-(2,4,6-trimethylphenyl)ethanone and (±)-1-phenylethylamine. The ^{1}H NMR spectrum in CCl$_4$ solution (Figure 1) showed one predominant isomeric form with signals at δ 1.29 (3 H, d, $^3J_{HCH}$ = 6.4 Hz, CHCH$_3$), 1.59 (3 H, s, o-CH$_3$), 2.11 (3 H, s, =CCH$_3$), 2.17 and 2.24 (each 3 H, s, o-CH$_3'$ and p-CH$_3$), 3.98 (1 H, q, $^3J_{HCCH}$ = 6.4 Hz, NCH), 6.68 (1 H, s, meta H), 6.78 (1 H, s, meta H′), and 7.11 (5 H, br s, C$_6$H$_5$). The =CCD$_3$ analogue of **15** (prepared by deuterium exchange with CD$_3$OD) showed the same chemical shifts in CCl$_4$ solution, except that the signal at δ 2.11 had disappeared, thus confirming the assignment of this signal to the =CCH$_3$ group. The highest field singlet was assigned to one of the o-methyl groups on account of the site exchange observed at high temperature in other solvents (see below). This imine will exist predominantly in the Z configuration (as depicted in **15**) by analogy with compound **1** and the closely related imine **16** (R = CH$_3$) which has been reported to exist at equilibrium as 95% Z isomer.[2] Minor signals in the spectrum of **15** at δ 1.46 (d, $^3J_{HCCH}$ = 6.5 Hz, CHCH$_3$) and 4.68 (q, $^3J_{HCCH}$ = 6.5 Hz, CHCH$_3$) are attributed to a small proportion (ca. 6%) of the E isomer.

The chemical-shift difference between the diastereotopic o-methyl groups in the predominant Z isomer is remarkably large (ca. 0.6 ppm in CCl$_4$ solution). One of these signals (δ 1.59) is at unusually high field for an aryl methyl group which typically resonates near δ 2.3. This may be rationalized in
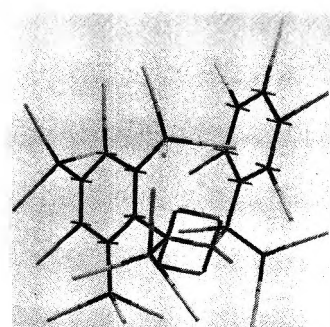
terms of a preferred ground-state conformation of the N-alkyl group which places one of the o-methyl groups in the strongly shielding region above the face of the phenyl ring in the 1-phenylethyl group as depicted in Figure 2.

Variable-temperature NMR studies on **15** in diphenyl ether indicate a very high barrier to ring rotation. Thus, the two o-methyl signals did not coalesce up to 200 °C, the highest temperature attainable. Accordingly, $\Delta G^{\ddagger}$ can be estimated to be $\geqslant 27$ kcal mol^{-1} based on a maximum observed exchange broadening of 0.7 Hz. Similarly, in decalin solution, the meta protons remained nonequivalent up to the highest temperature investigated (188 °C). However, in diphenyl ether solution at 200 °C the methyl and methine signals of the 1-phenylethyl group in the minor (E) isomer had broadened significantly. Clearly E–Z isomerization about the imino bond was occurring at an appreciable rate on the NMR time scale at 200 °C (the greater exchange broadening of the E isomer is expected as $k_{E \to Z} > k_{Z \to E}$).

Site-exchange phenomena were more evident in spectra recorded in 1,2,4-trichlorobenzene solution. The spectrum of **15** in this solvent at 50 °C was similar to that observed in carbon tetrachloride at ambient temperature, except for a virtual superimposition of the p-methyl, iminomethyl, and low-field o-methyl resonances (Figure 3a). However, at 198 °C the two o-methyl signals had coalesced to a broad resonance, and, furthermore, the NCH and NCCH$_3$ signals of the minor (E) isomer (originally at δ 4.62 and 1.36 from octamethylcyclotetrasiloxane) had coalesced with the corresponding signals of the Z isomer at δ 3.93 and 1.17 (Figure 3b). Therefore, mesityl ring rotation in the Z isomer and E–Z isomerization were both becoming fast at the same temperature (ca. 198 °C). Similar effects were observed in pentachloroethane solution, though at lower temperature (Figure 4). The nonequivalent meta-proton signals in the Z isomer and the NCH signals of the E and Z isomers both coalesced at ca. 150 °C, and, furthermore, the o-methyl signals had broadened and were approaching coalescence at 150 °C. Spectra recorded in hexachlorobutadiene solution at 150 °C showed similar effects. Accordingly, mesityl ring topomerization in the Z isomer and Z–E imine isomerization appear to be linked stereodynamic processes. Mesityl ring rotation is relatively unhindered in the minor (E) isomer; hence, Z–E imine isomerization could also bring about coalescence of the o-methyl signals in the Z isomer. Support for this suggestion is derived from the observation that the addition of a trace amount of benzoic acid to the decalin solution at 188 °C also brought about coalescence of the two meta-proton signals in the Z isomer and of the (E)- and (Z)-NCH signals. Previous work has shown that benzoic acid catalyzes E–Z isomerization;[11] hence, the observation that it also catalyzes rotation around the C–mesityl bond affords further evidence that this process is linked to the former.

Kessler[12] has previously postulated a similar linked mechanism for N-aryl rotation in the E isomer of amide **17**
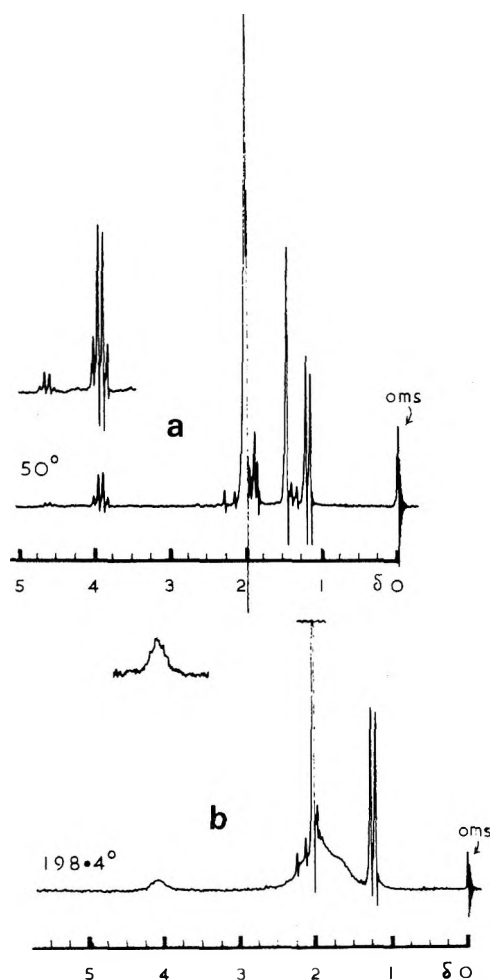
Figure 3. (a) 100-MHz NMR spectrum of **15** in 1,2,4-trichlorobenzene at 50 °C; (b) same solution at 198 °C (oms = octamethylcyclotetrasiloxane).

Figure 4. (a) 100-MHz NMR spectrum of **15** in pentachloroethane at 100 °C; (b) same solution at 150 °C (oms = octamethylcyclotetrasiloxane; ∗ denotes ^{13}C satellites of the solvent signal).

involving rotation around the amide bond and fast *N*-aryl rotation in the less hindered *Z* form.

However, the situation in **15** appears to be more complex, since the =CCH$_3$ signal also collapsed to a broad resonance in the same temperature range where the other coalescence phenomena were observed (see Figures 3 and 4). Similar behavior has previously been observed in the high-temperature NMR spectra of other imines containing a =CCH$_3$ group and is due to rapid proton exchange involving transient formation of the enamine tautomer.[13] Therefore, fast imine–enamine tautomerization can bring about both *E–Z* isomerization and a net topomerization of the diastereotopic *o*-methyl groups in the *Z* isomer (see Scheme I). The aryl bond-rotation step may take place in the *E* isomer or possibly in the enamine tautomer and is probably not rate determining. Apparently, the rate of imine–enamine tautomerization is greater in the chlorinated solvents as compared with diphenyl ether. This could be due to a solvent effect or to catalysis of the tautomerization by trace amounts of acid material generated in the

chlorinated solvents at high temperature. It has previously been noted that isomerization around the C=N bond in hydrazones is accelerated in chlorinated solvents.[14]

In conclusion, the mechanism that brings about a net rotation around the aryl–imino bond in the *Z* isomer of imine **13** appears to be facilitated by high temperature, acidity, and imine–enamine tautomerism.

Experimental Section

NMR spectra were recorded at 100 MHz on a Varian XL-100 or a Perkin-Elmer R14 spectrometer (all variable-temperature studies were performed on the XL-100). Solvents for dynamic NMR studies

Scheme I
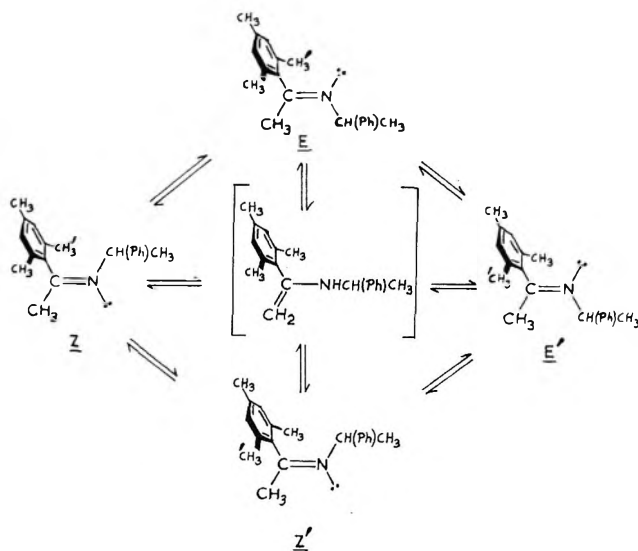
were washed with sodium carbonate solution and stored over anhydrous potassium carbonate. Probe temperature calibration and band-shape analyses were performed as described previously.[11]

2'-Phenylacetophenone (10 g, 95%) was prepared by reaction of the Grignard reagent from 2-iododiphenyl (12 g) with acetic anhydride (30 cm³) in ether at −70 °C under nitrogen, bp 80 °C (0.1 Torr) (lit.[15], 104–105 °C (1.0 Torr)). The other ketones were obtained commercially.

N-[1-(2'-Methylphenyl)ethylidene]isopropylamine (1) was obtained in 66% yield by refluxing 1-(2'-methylphenyl)ethanone (2.0 g), isopropylamine (16 cm³), and titanium(IV) chloride (1.0 cm³) in benzene for 3 h under nitrogen according to the procedure reported previously,[2] bp 58–60 °C (0.05 Torr).

Anal. Calcd for $C_{12}H_{17}N$: C, 82.2; H, 9.8; N, 8.0. Found: C, 82.2; H, 9.7; N, 7.8.

N-[1-(2'-Diphenyl)ethylidene]isopropylamine (2) was similarly prepared from 2-phenylacetophenone (3.0 g), isopropylamine (20 cm³), and titanium(IV) chloride (3.0 cm³). Recrystallization from dry ethanol gave crystals of the Z isomer (2.3 g, 64%), mp 121 °C.

Anal. Calcd for $C_{17}H_{19}N$: C, 86.0; H, 8.1; N, 5.9. Found: C, 86.3; H, 8.4; N, 5.6.

N-[1-(2'-Nitrophenyl)ethylidene]isopropylamine (3) was similarly obtained from 1-(2'-nitrophenyl)ethanone (3.0 g), isopropylamine (16 cm³), and titanium(IV) chloride (1.5 cm³). Distillation under reduced pressure followed by recrystallization from light petroleum afforded crystals of the Z isomer (2.2 g, 59%), mp 74–77 °C.

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 64.0; H, 6.8; N, 13.6. Found: C. 64.25; H, 6.9; N, 13.7.

N-[1-(2'-Methoxyphenyl)ethylidene]isopropylamine (4) was likewise obtained from 1-(2'-methoxyphenyl)ethanone (3 g) in 80% yield, bp 65 °C (0.05 Torr).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.95; N, 7.3. Found: C, 75.6; H, 8.6; N, 7.2.

N-[1-(1'-Naphthyl)ethylidene]-2,2-dimethylpropylamine (10) was similarly prepared in 45% yield from 1-(1'-naphthyl)ethanone (2 cm³), 2,2-dimethylpropylamine (10 cm³), and titanium(IV) chloride (1 cm³), bp 110 °C (0.1 Torr).

Anal. Calcd for $C_{17}H_{21}N$: C, 85.35; H, 8.8; N, 5.85. Found: C, 85.6; H, 8.8; N, 5.6.

N-[1-(2',4',6'-Trimethylphenyl)ethylidene]-1-phenylethylamine (15) was obtained in 50% yield from 1-(2',4',6'-trimethylphenyl)ethanone (2.0 g), (±)-1-phenylethylamine (16 cm³), and titanium(IV) chloride (1.0 cm³), bp 128–130 °C (0.1 Torr).

Anal. Calcd for $C_{19}H_{23}N$: C, 86.0; H, 8.7; N, 5.3. Found: C, 85.7; H, 9.0; N, 5.6.

Replacement of the =CCH₃ protons in **10** and **15** by deuterium was achieved by allowing a solution of the imine in deuteriomethanol (99.8%) to stand for a few hours. The solvent was then removed and the process repeated until NMR analysis showed that this methyl signal had essentially disappeared. Imine **5** has been reported previously.[2]

Registry No.—(E)-1, 66674-84-8; (Z)-1, 66674-85-9; (E)-2, 66674-86-0; (Z)-2, 66674-87-1; (E)-3, 66674-88-2; (Z)-3, 66674-89-3; (E)-4, 66674-90-6; (Z)-4, 66674-91-7; (E)-5, 38512-09-3; (Z)-5, 38512-03-7; (E)-10, 66674-92-8; (Z)-10, 66674-93-9; 15, 66674-94-0; 2'-phenylacetophenone, 2142-66-7; 2-iododiphenyl, 2113-51-1; 1-(2'-methylphenyl)ethanone, 577-16-2; isopropylamine, 75-31-0; 1-(2'-nitrophenyl)ethanone, 577-59-3; 1-(2'-methoxyphenyl)ethanone, 579-74-8; 1-(1'-naphthyl)ethanone, 941-98-0; 2,2-dimethylpropylamine, 5813-64-9; 1-(2',4',6'-trimethylphenyl)ethanone, 1667-01-2; (±)-1-phenylethylamine, 618-36-0.

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New Furanoid *ent*-Clerodanes from *Baccharis tricuneata*[1]

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Because of the antitumor and antiviral properties of a crude extract, the constituents of the Colombian medicinal plant *Baccharis tricuneata* (L.f.) Pers. var. *tricuneata* have been investigated. The hexane extract yielded four new *ent*-clerodanes, bacchotricuneatins A–D (**1**, **2**, **3**, and **4a**), whose structures were elucidated, primarily by ¹H and ¹³C NMR spectrometry. Proof for the structure and stereochemistry of A and B was obtained by X-ray analysis. Isolated from the ether extract were cirsimaritin, cirsiliol, and scopoletin.

Previous reports[2-4] on the pharmacological activity of some South American *Baccharis* species and their constituents made it of interest to examine the Colombian species *Baccharis tricuneata* (L.f.) Pers. var. *tricuneata*, which is widely used in folk medicine. Initial pharmacological screening revealed that an ethanol extract possessed significant antitumor and antiviral activity which corresponds to the me-

dicinal use of the plant in Colombia;[5,6] consequently, we undertook a study of its constituents. We now wish to report the isolation and structure determination of four new closely related *ent*-clerodane diterpenoids, bacchotricuneatin A–D (**1**, **2**, **3**, and **4a**). The flavonoids cirsimaritin (**6a**) and cirsiliol (**6b**) and the coumarin scopoletin (**7**) were also isolated.[7]

The hexane extract of the aerial parts of *B. tricuneata*

Table I. ¹H NMR Spectra of Bacchotricuneatins and Derivatives[a]

Compd	H-1	H-2	H-3	H-6	H-7	H-8	H-10	H-11	H-12	H-14	H-15	H-16	H-17	H-18	H-19	H-20	Misc.
1	1.25 m, 1.77 m	2.45 m, 2.27 m	6.77 dd (7, 3)	1.37 m[d], 2.17 m[d]	2.09[d], 1.91[e]	2.68 dd (14, 5.5)	1.94[e]	2.13[d], 1.94[e]	5.40 dd (11, 8)	6.43 t (1)	7.48 br	7.43 t (1)		3.94 dd (8, 2), 4.28 d (8)		0.85[b]	
2	1.21 m, 1.70 m	2.35 m, 2.22 m	6.67 dd (7, 2.5)	1.30 m, 2.07 m	1.87 m, 1.66 m	1.76[e]	1.80[e]	2.51 d[c] (8)	5.46 t (8)	6.37 br	7.46 t (1)	7.44 br	1.14[b] (6)	4.01 dd (9.5, 2), 4.65 d (9.5)			
3	1.03 m, 1.85[f]	2.47 m, 2.26 m	6.75 dd (7, 2.5)	1.38 m, 2.04 m	2.11[e], 1.85[f]	1.51 m	[g]	2.17[e]	4.95 t (7)	6.37 br	7.41 br	7.37 br	5.22 br	3.88 ddd (8, 2), 4.38 d (8)		3.6 d (9), 3.3 dd (9, 1.5)	
4a		1.53[i], 2.22[h]	5.51 m ($W_{1/2} = 9$)	1.58[i], 2.15[h]	4.03 m ($W_{1/2} = 9$)	1.67[i]				6.24 br	7.34 br	7.18 t (1)	1.04 d[b] (7)	1.36[b]	4.12 br[c]	1.02[b]	
4b			5.52 br ($W_{1/2} = 9$)		4.04 m ($W_{1/2} = 9$)					6.23 br	7.34 br	7.18 br	1.05 d[b] (7)	1.34[b]	4.5 br[b]	1.02[b]	2.07[b] (Ac)
4c			5.70 m ($W_{1/2} = 9$)		4.04 m ($W_{1/2} = 9$)	2.66 q (7)				6.26 br	7.37 br	7.22 br	0.97 d[b] (7)	1.06[b]	4.49 br[c]	0.75[b]	2.05[b] (Ac)
5			6.55 dd (5, 4)		4.04 m ($W_{1/2} = 9$)					6.24 br	7.34 br	7.31 br	1.07 d[b] (7)	1.44[b]	9.3 br	1.03[b]	

[a] Run in CDCl₃ solution with Me₄Si as internal standard. Chemical shifts are in ppm; figures in parentheses are coupling constants in hertz. Description: d, doublet; t, triplet; q, quartet; br, broadened singlet; m, multiplet. Unmarked signals are singlets. [b] Intensity of three protons. [c] Intensity of two protons. [d] In a four-proton multiplet. [e] In a three-proton multiplet. [f] In a two-proton multiplet. [g] Could not be identified. [h] In a five-proton envelope. [i] In a nine-proton envelope.

1 **2** **3**
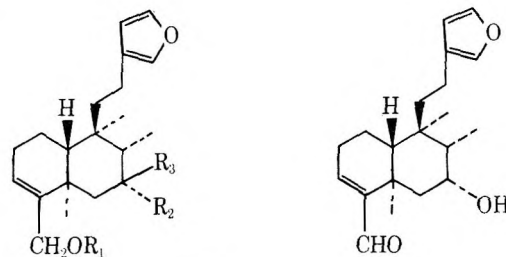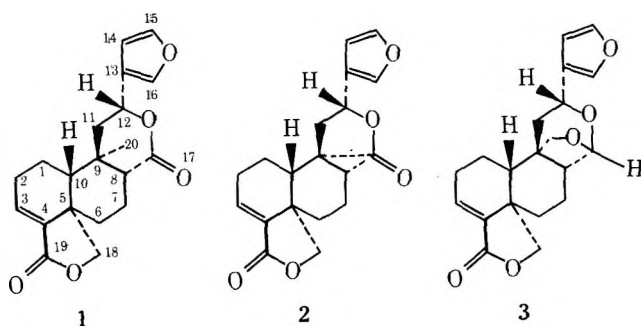
4a, R₁ = H; R₂ = OH; R₃ = H
b, R₁ = Ac; R₂ = OH; R₃ = H
c, R₁ = Ac; R₂,R₃ = =O

5
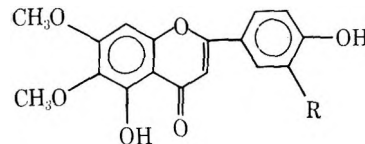
6a, R = H
b, R = OH
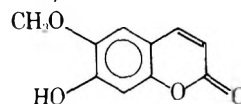
7

furnished, after extensive chromatography, three crystalline isomeric lactones $C_{20}H_{22}O_5$ (elemental analysis, high-resolution mass spectrometry), mp's 239–241, 191–192, and 188–189 °C, respectively, and one diol $C_{20}H_{30}O_3$, mp 106 °C, designated as bacchotricuneatin A, B, C, and D. All four compounds were β-monosubstituted furans as evidenced by IR absorptions at 3140, 1500, and 870 cm⁻¹, narrow multiplets in the ¹H NMR spectra at 7.4, 7.3, and 6.4 ppm, mass spectral fragments at m/e 95, 94, and 81,[8] and positive Ehrlich tests.[9] The UV spectrum of D showed only er.d absorption; in the UV spectra of A, B, and C this was masked by the absorption due to an α,β-unsaturated lactone group.[10]

The major lactone, bacchotricuneatin A, was, like B and C, an α,β-unsaturated γ-lactone (IR bands at 1750 and 1645
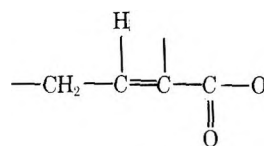
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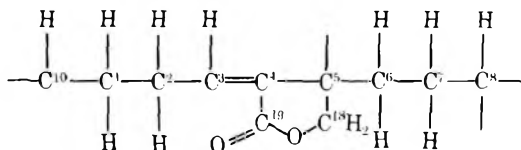
II

cm⁻¹) of the type represented by partial formula I because of the presence in the NMR spectrum of a doublet of doublets

at 6.77 ppm, characteristic of the β proton on a double bond conjugated with a carbonyl group. This proton was further coupled to a methylene group (signals at 2.45 and 2.27 ppm). The ^{13}C NMR spectra of A and B indicated the absence of additional double bonds. Incidentally, all three lactones exhibited a positive Dragendorff reaction although lacking nitrogen,[11] but surprisingly they did not give the Kedde[12] and Baljet[13] tests.

The NMR spectra of A, B, and C also contained an AB system with a chemical shift characteristic of the methylene in the grouping $-C(=O)OCH_2-$, which was attached to a tertiary carbon atom. The upfield proton of this system (H-18a) was in turn long range coupled (J = 2.5 Hz) to another proton (at 1.37 ppm in A and B and at 1.30 ppm in C). This fact, together with extensive spin decoupling experiments on compounds A, B, and C, which will not be described in detail (see Table I), permitted, for all three lactones, expansion of I to partial structure II. Partial structure II is also present in *trans*-clerodanes recently isolated form *B. conferta*,[14] *B. trimera*,[15] and *B. articulata*.[16] The obvious possibility that the compounds from *B. tricuneata* might also possess a *trans*-clerodane skeleton was verified by the additional information to be presented in the sequel.

The NMR spectrum of A also displayed a doublet of doublets (J = 11 and 8 Hz, H-12) at 5.4 ppm which could be shown to be the X part of an ABX system where A and B (H-11) resonated at 2.13 and 1.94 ppm, respectively. The chemical shift of X, which was almost identical with that of H-12 in floribundic acid (8)[17] and related clerodanes,[18,19] together with the

8   9   10
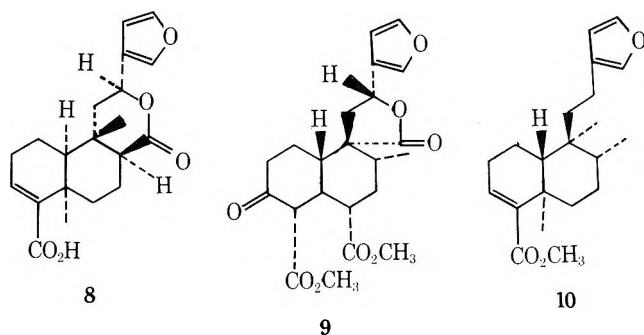
empirical formula which required two additional oxygen atoms pointed to the presence of a second lactone function probably closed to a position α to the furan ring. This was in agreement with a second carbonyl band in the IR spectrum characteristic of a δ-lactone (1725 cm^{-1}) and was supported by the ratio of the fragments IV, V, and VI in the mass spec-

m/e 95   *m/e* 95   V, *m/e* 94   VI, *m/e* 81

IV
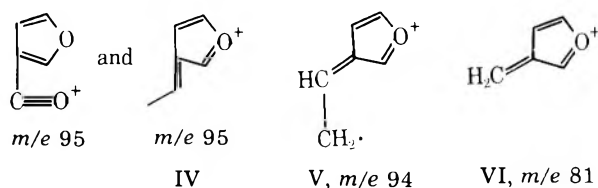
trum (98, 90, and 20%). Whereas fragment VI predominates in furan derivatives with an unsubstituted side chain, IV and V predominate in lactones similar to bacchotricuneatin.[20a,b,22]

The NMR spectrum of A also exhibited the methyl singlet of a tertiary methyl group which can only be located at C-9 of the assumed clerodane skeleton. Therefore, the missing secondary methyl ordinarily attached to C-8 was represented by the carbonyl group of the δ-lactone ring. This deduction was supported by identification of a rather deshielded doublet of doublets at 2.68 ppm as the signal of H-8; its coupling constants (J = 14 and 5.5 Hz) render obvious the equatorial attachment of the carbonyl group. Combination of all data thus

led to formula 1 (for discussion of stereochemistry see below).

The spectral properties of bacchotricuneatin B (2) closely resembled those of A. However, the two carbonyl bands of the IR spectrum had now collapsed to a single band of double intensity at 1745 cm^{-1}, and in the NMR spectrum the methyl singlet of A representing C-20 had been replaced by a doublet at 1.14 ppm, the proton responsible for the splitting being located at 1.76 ppm (H-8). The signal in the range of H-12 now appeared as a triplet [5.48 ppm (J = 8 Hz)], which was shown to be the X part of an ABX system with A and B (superposed in CDCl$_3$ at 2.41 ppm) as an eight-line multiplet exhibiting coupling constants of 8 and 14 Hz in C$_5$D$_5$N. These observations, together with biogenetic considerations, suggested that the structure of B contained a second saturated lactone ring linking an oxidized C-20 to C-12, the relationship of the furan and lactone moieties being similar to that found in corylifuran (9)[21] or teucvin.[22]

The decoupling experiments with bacchotricuneatin B also provided evidence that H-8 was adjacent to another methyl group which in turn was linked to a methylene group, one proton of which was long range coupled (*W* coupling) to H-18a. Accordingly, bacchotricuneatin A, B, and C (see below), all of which exhibited this long range coupling, seemed to possess the same trans stereochemistry as the *ent*-clerodanes from *B. trimera*[15] and *conferta*.[14] The equatorial orientation of the C-8 substituent was evident from the values cf $J_{7,8}$. In the case of 1, the chemical shift of H-20, essentially identical with that of the compounds from *B. trimera*, pointed to axial orientation of the methyl group on C-9. In the case of 2, the downfield shift of H-18b could be rationalized by assuming that the lactone carbonyl on C-9 was axial, thus bringing H-18 within its deshielding region (models). The relative stereochemistry of bacchotricuneatin A and B was therefore that shown in formulas 1 and 2, with the exception of the stereochemistry at C-12, which could not be deduced chemically or spectroscopically.

The ^{13}C NMR spectra of 1 and 2 (Table II) provided strong support for the postulated structures. Peaks with suitable shifts and off-resonance multiplicities were found for each of the carbon atoms and could be assigned by application of the usual shift parameters and comparison with data in the lit-

Table II. ^{13}C NMR Spectra of Bacchotricuneatins A, B, and D[a]

	1	2	4a
C-1	19.4 t	21.0 t	18.3 t[b]
C-2	27.6 t	28.0 t	26.4 t
C-3	135.8 d	134.3 d	121.6 d
C-4	137.9	139.4	148.5
C-5	45.0	45.4	38.2
C-6	32.8 t	33.6 t	39.6 t
C-7	20.0 t	28.0 t	73.5 d
C-8	53.7 d	43.2 d	39.2 d
C-9	36.9	50.9	37.2
C-10	47.4 d	49.5 d	46.4 d
C-11	43.4 t	42.0 t	42.3 t
C-12	69.9 d	71.8 d	17.3 t[b]
C-13	125.0	125.7	125.4
C-14	108.7 d	107.9 d	110.9 d
C-15	143.7 d	144.2 d	142.0 d
C-16	139.7 d	139.2 d	138.4 d
C-17	173.1	17.2 q	12.5 q
C-18	71.0	72.9 t	23.3 q
C-19	168.3	169.0	63.0 t
C-20	19.6 q	177.0	19.9 q

[a] Run at 67.9 MHz in CDCl$_3$ solution; shifts are in ppm. Unmarked signals are singlets. [b] Assignments may be interchanged.

Figure 1. Stereoscopic view of bacchotricuneatin A.
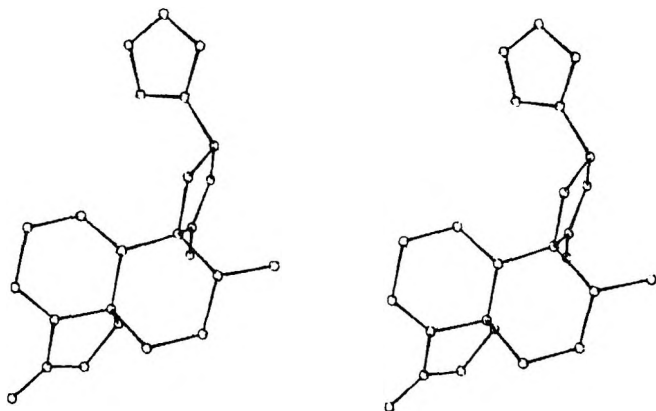
Figure 2. Stereoscopic view of bacchotricuneatin B.

Figure 3. Bond angles and bond distances in bacchotricuneatin A.

erature.[15,18,21] Final proof for the structures and evidence for the relative stereochemistry at C-12 shown in formulas 1 and 2 were obtained by X-ray analysis of A and B. Stereoscopic views of the two molecules which represent the absolute configurations (see below) are shown in Figures 1 and 2. Bond distances and angles are given in Figures 3 and 4. Tables III and IV, listing fractional coordinates for the nonhydrogen atoms, are available as supplementary material.

The third isomeric lactone, bacchotricuneatin C (3), which had IR bands at 1755 (normal intensity) and 1645 cm⁻¹, contained no hydroxyls (IR spectrum) and no methyl groups (NMR spectrum). Extensive spin decoupling experiments (see Table I) established the presence of partial structure II. Additional features, exclusive of signals associated with the β-substituted furan ring, included a second new AB system centered at 3.45 ppm ($J_{A,B}$ = 9 Hz, H-20) in the characteristic range of ether protons, one of whose components exhibited long range coupling (J = 1.5 Hz) to a proton (H-11a) in a multiplet at 2.17 ppm. Irradiation at this frequency not only sharpened the high-field component (3.3 ppm) of the new AB system but also collapsed a triplet at 4.95 ppm (J = 7 Hz, H-12) to a singlet. The coupling constants exhibited by this triplet were very similar to those of H-12 in 1, though the signal had experienced an upfield shift of 0.5 ppm. Lastly, the NMR spectrum displayed a significant one-proton singlet at 5.22 ppm. Since the four protons responsible for the new AB system, the triplet at 4.95 ppm, and the singlet at 5.22 ppm must be on a carbon linked to the two oxygen atoms of the empirical formula not included in partial structure II, the singlet was surmised to be that of an acetal hydrogen. A biogenetically plausible explanation is that both of the C-8 and C-9 methyl groups required by a presumed clerodane skeleton exist in an oxidized state, one as a primary alcohol
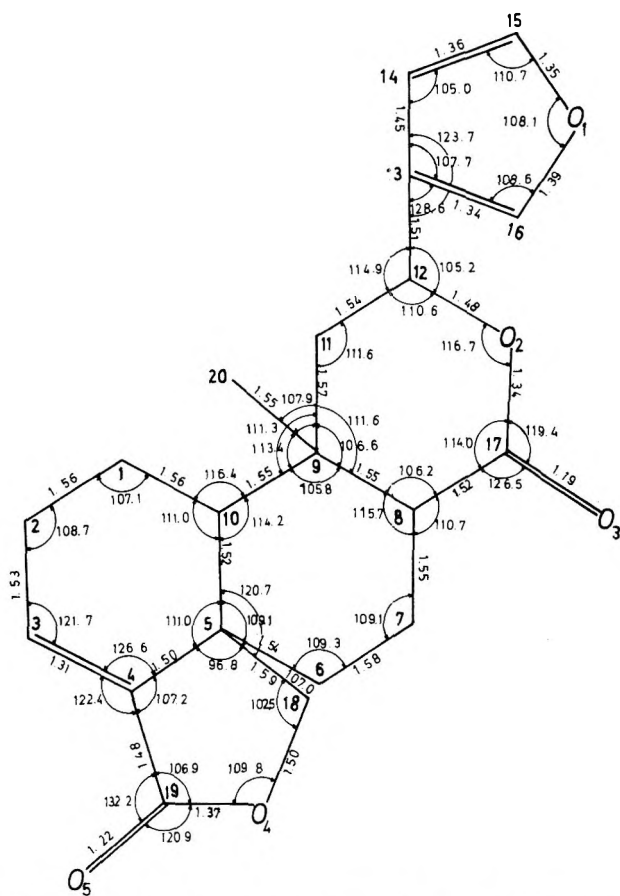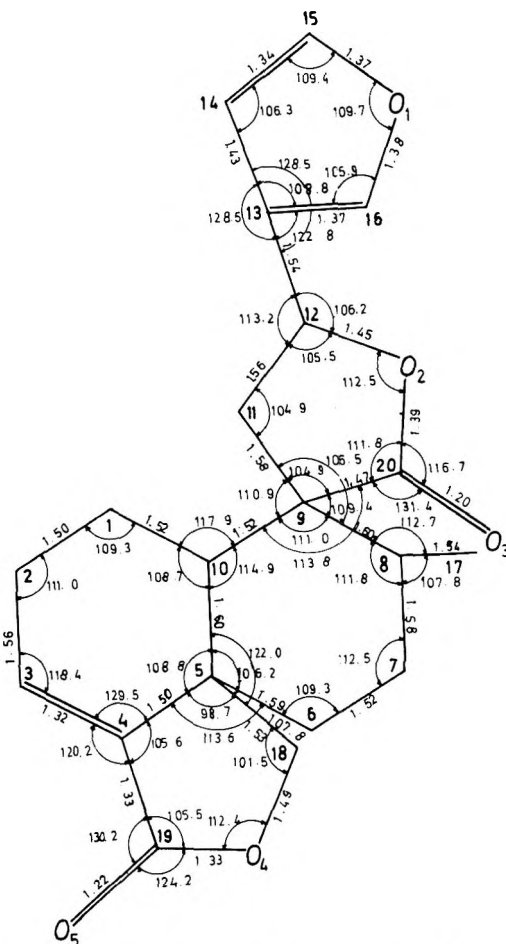
Figure 4. Bond angles and bond distances in bacchotricuneatin B.

and the other as an aldehyde which is involved in acetal formation with the primary alcohol and the customary secondary hydroxyl group on C-12. This would account not only for the empirical formula but also for the upfield shift of H-12.

Since the B proton of the AB system at 3.45 ppm was long range coupled to H-11 and since neither A nor B were coupled vicinally to other protons, the primary alcohol involved in the acetal had to be derived from C-20 and the acetal carbon from C-17. On this basis, stereoformula **3** was the only one which could be constructed with Dreiding models. This also explained one apparent anomaly in the NMR spectrum which showed H-17 as a singlet. From the model the dihedral angle between H-8 and H-17 is ca. 81°, thus leading to a vanishingly small coupling constant. Further chemical and spectroscopic studies were precluded by the small quantity of bacchotricuneatin C.

Bacchotricuneatin D, $C_{20}H_{30}O_3$ (**4a**), was a diol (IR bands at 3500 and 3400 cm^{-1}; no carbonyl absorption), the NMR spectrum of which contained, besides the usual furan peaks, an olefinic multiplet at 5.51 ppm ($W_{1/2}$ = 9 Hz; in this case, obviously not conjugated), two methyl singlets at 1.36 and 1.02 ppm, one methyl doublet at 1.04 ppm, and two signals characteristic of protons on carbons carrying a hydroxyl. A broadened two-proton singlet at 4.12 ppm which shifted downfield (to 4.51 ppm) on acetylation was allylically coupled to the olefinic proton which was in turn coupled to the protons of a methylene group at 1.53 and 2.22 ppm. The presence of a primary allylic alcohol was confirmed by MnO$_2$ oxidation to a conjugated aldehyde (**5**) [IR band at 1680 cm^{-1}; NMR, -CHO at 9.3 ppm (br), -CH$_2$CH=CCHO at 5.44 ppm (t, J = 4.5 Hz)]. Since all of the evidence again indicated the presence of a clerodane skeleton, the problem of locating the secondary hydroxyl [4.03 ppm ($W_{1/2}$ = 9 Hz)] turned out to be very easy. Irradiation at 1.67 ppm (H-8) collapsed the methyl doublet at 1.04 ppm (H-17) to a singlet and simplified the multiplet at 4.03 ppm to a doublet of doublets (J = 6 and 2.5 Hz), thus indicating axial attachment of the secondary hydroxyl group to C-7. Chemical proof was provided by Jones oxidation of **4b** to a ketone **4c** whose NMR spectrum displayed the signal of H-8 as a quartet (J = 6 Hz) shifted downfield to 2.66 ppm. In addition, the two methyl singlets exhibited significant upfield shifts, indicating the influence of the axial α-oriented C-7 hydroxyl on the two α-oriented axial methyl groups on C-5 and C-9. The ^{13}C NMR spectrum of **4a** (Table II) and the mass spectral fragmentation patterns of **4a** and its derivatives which exhibited a peak at *m/e* 81 as the predominant fragment containing the furan nucleus were in full accord with the proposed structure.

The absolute configurations of bacchotricuneatin A, B, and C are obviously the same as those of the *ent*-clerodanes from *B. trimera* because of the strong negative Cotton effects of **1**, **2**, and **3** at 240–245 nm due to the n,π* transition (*R* band) of the α,β-unsaturated lactone chromophore, the absolute configuration of the *B. trimera* compounds having been deduced in turn[15] from the similarity of the CD curves to that of (−)-methyl hardwickiate[23,24] (**10**). As for bacchotricuneatin D, axial orientation of the C-5 and C-9 methyl groups is compatible with either a *cis*-clerodane skeleton where the C-5 methyl and H-10 are α or a *trans*-clerodane skeleton (C-5 methyl α and H-10 β if the absolute stereochemistry is like that of all other *ent*-clerodanes from *Baccharis* species). However, in view of the established stereochemistry of bacchotricuneatins A–C, a trans ring junction seems much more likely. This conclusion was supported by the CD curve of **4c** which exhibited the relatively strong negative Cotton effect (Δε = −1.86) predicted for a *t*3′-decalone[25] of the depicted absolute configuration with axial methyls on the 3 and 3′ positions and an equatorial alkyl side chain on the 3 position rather than the much weaker positive or possibly weakly

negative effect (octant diagram) expected for the corresponding *c*3′eq isomer.

The ether extract of *B. tricuneata* furnished the flavones cirsiliol (6,7-dimethoxy-5,3′4′-trihydroxyflavone; **6b**)[26,27] and cirsimaritin (5,4′-dihydroxy-6,7-dimethoxyflavone; **6a**)[28,29] and the coumarin scopoletin (**7**), which were identified by comparing their spectral properties with those recorded in the literature.

Experimental Section[30]

Bacchotricuneatin A (**1**) was purified on silica gel (solvent systems: 9:1 CH$_2$Cl$_2$–EtOAc, R_f 0.48; 19:1 CHCl$_3$–EtOH, R_f 0.77) and recrystallized from CH$_2$Cl$_2$–EtOH (1:4). The slightly greenish prisms (yield 0.270 g) had mp 239–241 °C (with sublimation); [α]^{25}$_D$ −121.4° (c 0.936, CHCl$_3$); UV λ$_{max}$ 210 nm (ε 12 100; end absorption), 239 (2350); IR bands (KBr) at 3150, 1500, 870 (furan), 1750 (α,β-unsaturated γ-lactone), 1725 (δ-lactone), and 1645 (double bond) cm^{-1}; CD curve (acetonitrile) [θ]$_{282}$ 0, [θ]$_{241}$ −27 000, [θ]$_{216}$ −6600, [θ]$_{195}$ −32 000, [θ]$_{190}$ −31 300 (last reading).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 70.17; H, 6.45; mol wt, 342.1466. Found: C, 70.20; H, 5.04; mol wt (MS), 342.1468.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (composition, %) 312 (M − CH$_2$O, 100), 247 ($C_{14}H_{15}O_4$, 3), 231 ($C_{14}H_{15}O_3$, 5), 189 ($C_{12}H_{13}O_2$, 21), 149 ($C_8H_5O_3$, 18), 145 ($C_{11}H_{13}$, 41), 131 ($C_{10}H_{11}$, 27), 95 (C_6H_7O, 98), 95 ($C_5H_3O_2$, 20.8), 94 (C_6H_6O, 90), and 81 (C_5H_5O, 20).

Bacchotricuneatin B (**2**) was purified on silica gel (solvent systems: 44:1 CH$_2$Cl$_2$–EtOAc, R_f 0.22; CHCl$_3$–EtOH, R_f 0.82) and recrystallized from CH$_2$Cl$_2$–hexane (1:5). The colorless crystals (0.16 g) had mp 191–192 °C dec; [α]^{25}$_D$ −93.3° (c 0.932, CHCl$_3$); UV λ$_{max}$ 210 nm (ε 8930; end absorption), 240 (1540); IR bands (KBr) at 3160, 1490, 878 (furan), 1740 (two γ-lactones), and 1640 (double bond) cm^{-1}; CD curve (acetonitrile) [θ]$_{288}$ 0, [θ]$_{245}$ −17 600, [θ]$_{227}$ 0, [θ]$_{215}$ 10 600, [θ]$_{204}$ 0.

Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.17; H, 6.45; mol wt, 342.1466. Found: C, 70.20; H, 5.98; mol wt (MS), 342.1474.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (composition, %) 312 (M − CH$_2$O, 100), 284 ($C_{18}H_{20}O_3$, 12), 267 ($C_{18}H_{19}O_2$, 9.7), 239 ($C_{17}H_{19}O$, 9.6), 231 ($C_{14}H_{15}O_3$, 1.3), 218 ($C_{13}H_{14}O_3$, 12.5), 173 ($C_{12}H_{18}O$, 6.7), 145 ($C_{11}H_{13}$, 17), 95 (C_6H_7O, 40), 94 (C_6H_6O, 32), and 81 (C_5H_5O, 14).

Bacchotricuneatin C was purified by preparative TLC in 24:1 CHCl$_3$–EtOH (R_f 0.67) and 9:1 CH$_2$Cl$_2$–EtOAc (R_f 0.41). Recrystallization from CH$_2$Cl$_2$–EtOH (1:2) furnished colorless plates with mp 188–190 °C (yield 4 mg); UV λ$_{max}$ 210 nm (ε 14 500; end absorption), 241 (2310); IR bands (KBr) at 3140, 1505, 880 (furan), 1755 (α,β-unsaturated γ-lactone), and 1645 (double bond) cm^{-1}; CD curve (MeOH) [θ]$_{275}$ 0, [θ]$_{241}$ −26 000, [θ]$_{230}$ −14 000 (last reading).

Anal. Calcd for $C_{20}H_{22}O_5$: mol wt, 342.1466. Found: mol wt (MS), 342.1465.

Significant peaks in the low-resolution mass spectrum were at *m/e* (%) 342 (M$^+$, 1.95), 312 (M$^+$ − 30, 0.47), 261 (M$^+$ − 81, 0.73), 248 (1.6), 145 (4.7), 95 (78), 94 (43), 81 (82), and 71 (100).

The Ehrlich positive material of column 4 (1:1 CH$_2$Cl$_2$–EtOAc) was purified by preparative TLC using 19:1 CHCl$_3$–EtOH (R_f 0.38) and recrystallized from EtOAc–hexane (1:1). The yield of bacchotricuneatin D, mp 109–111 °C, was 104 mg of colorless needles: [α]^{25}$_D$ −7.41° (c 0.582, CHCl$_3$); UV λ$_{max}$, strong end absorption beginning at 217 nm; IR bands (KBr) at 3500, 3400 (OH), 3090, 1490, 870 (furan), and 1600 (double bond) cm^{-1}.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.47; H, 9.43; mol wt, 318.2195.

Found: C, 75.29; H, 9.37; mol wt (MS), 318.2187.

Other significant peaks in the high-resolution mass spectrum were at m/e (composition, %) 300 ($M^+ - H_2O$, 1.5), 288 ($M^+ - CH_2O$, 32.4), 204 ($C_{14}H_{19}O$, 19), 191 ($C_{13}H_{19}O$, 21.8), 187 ($C_{14}H_{19}$, 17.3), 145 ($C_{11}H_{13}$, 20.5), 95 (C_6H_7O, 12.9), 94 (C_6H_6O, 10.8), 93 (C_7H_9, 100), and 81 (C_5H_5O, 66).

The ether extract of *B. tricuneata*, after being stored for 10 days at $-10\ ^\circ C$, gave a precipitate (6 g) which gave a positive test for flavonoids. The crude material was chromatographed over silica gel, eluting the column in the following order: fraction 1, petroleum ether; fraction 2, benzene; fraction 3, $CHCl_3$; fraction 4, MeOH–CHCl$_3$ (1:9); fraction 5, MeOH–CHCl$_3$ (1:4); fraction 6, MeOH–CHCl$_3$ (1:1). Fractions 4–6 were combined, concentrated, and further purified by preparative TLC over silica gel, (125:72:3 benzene–acetic acid–water). There was obtained 45 mg of cirsiliol (**6b**), mp 273–275 °C, after recrystallization from MeOH (lit.[26,27] mp 278 °C): mol wt (MS), 330 (fragments at m/e 181 and 135); UV λ_{max} (MeOH) 344, 272, 255 nm; UV λ_{max} (MeOH–AlCl$_3$) 436, 339 sh, 309 sh, 275 nm; UV λ_{max} (MeOH–NaOAc) 405, 269 nm; UV λ_{max} (MeOH–NaOAc–H$_3$BO$_3$) 371, 261 nm; NMR (60 MHz, Me$_2$SO-d_6) 3.79 (C-6 OMe), 3.95 (C-7 OMe), 6.70 (H-8), 6.83 (H-3), 6.98 (br, H-5′), 7.46 (m, H-2′ and H-6′) ppm.

The yield of cirsimaritin (**6a**) was 18 mg: mp (from ethanol) 254–256 °C (lit.[28,29] mp 255–257 °C); mol wt (MS), 314 (fragments at m/e 181 and 119); UV λ_{max} (MeOH) 333, 274, 213 nm; UV λ_{max} (MeOH–AlCl$_3$) 364, 300 sh, 289 sh nm; UV λ_{max} (MeOH–AlCl$_3$–HCl) 356, 300 sh, 285 nm; UV λ_{max} (MeOH–NaOMe) 358 br, 303 sh, 274 nm; UV λ_{max} (MeOH–NaOAc) 388, 298 sh, 272 nm; NMR (60 MHz, Me$_2$SO-d_6) 3.83 (C-6 OMe), 4.03 (C-7 OMe), 6.87 (H-3), 6.98 (H-8), 7.08 (d, H-3′ and H-5′), 8.11 (d, H-2′ and H-6′) ppm.

The ether extract remaining after removal of the precipitate was evaporated, and the residue was extracted thoroughly with CHCl$_3$–H$_2$O. The CHCl$_3$ fraction, enriched in scopoletin, was chromatographed over silica gel eluting with 7:3 benzene–acetone. The fractions containing scopoletin were combined and recrystallized from CHCl$_3$: yield of 7, 57 mg; mp 205 °C (lit.[31] mp 204–205 °C); the mixed melting point with an authentic sample was undepressed; UV λ_{max} (MeOH) 229, 253, 296, 345 nm.

Anal. Calcd for C$_{10}$H$_8$O: C, 62.50; H, 4.20. Found: C, 62.48; H, 4.27.

Ehrlich Reaction. A TLC plate of bacchotricuneatin A, B, and C showed a rose red color; one of D showed a violet color when sprayed with a solution of p-dimethylaminobenzaldehyde (1 g) in MeOH–36% HCl (75:25 mL).

Selective Monoacetylation of 4a. A solution of 0.08 g of **4a** in 0.5 mL of pyridine and 0.5 mL of acetic anhydride was allowed to stand at 10 °C for 7 min and then was worked up in the usual manner. The product, 0.039 g of **4b**, was purified by preparative TLC (10:1 CHCl$_3$–EtOH), but it could not be induced to crystallize. The UV spectrum exhibited end absorption only; IR bands at 3480 (OH), 1730 (acetate), 3120, 1495, 850 (furan), and 1630 (double bond) cm^{-1}; low-resolution mass spectrum, m/e 360 (M^+, 0.04), 300 (M – HOAc, 4), 266 (4.1), 145 (16.8), 95 (24), 91 (39), 81 (33).

Oxidation of 4b. To an ice cold solution of 25 mg of **4b** in 5 mL of acetone was added 3 drops of Jones reagent with stirring. Stirring was continued for 5 min, excess oxidant was destroyed by adding 10 drops of MeOH, the solvents were removed at reduced pressure, and the residue was diluted with ice water and extracted with CHCl$_3$. The washed and dried extract was evaporated, and the residue was purified by preparative TLC (24:1 CHCl$_3$–EtOH) to yield 13 mg of gummy ketone **4c**: UV λ_{max} 278 nm (ϵ 38.5); IR bands (film) at 3130, 1500, 850 (furan), 1735 (acetate), 1710 (ketone), and 1630 (double bond) cm^{-1}; CD curve (MeOH, c 0.409) $[\theta]_{318}$ 0, $[\theta]_{291}$ −6150, $[\theta]_{253}$ 0.

Anal. Calcd for C$_{22}$H$_{30}$O$_4$: mol wt, 358.2143. Found: mol wt (MS), 358.2173.

Other significant peaks in the high-resolution mass spectrum were at m/e (composition, %) 298 ($C_{20}H_{26}O_2$, 14.1), 263 ($C_{16}H_{23}O_3$, 8.6), 203 ($C_{14}H_{18}O$, 100), 145 ($C_{11}H_{13}$, 11.6), 95 (C_6H_7O, 41.3), 94 (C_6H_6O, 5.7), and 81 (C_5H_5O, 56.4).

MnO$_2$ Oxidation of 4a. A solution of 0.02 g of **4a** in 7 mL of CHCl$_3$ was stirred with 0.08 g of freshly prepared MnO$_2$ at room temperature, the reaction being monitored by TLC. After 8 h when starting material had disappeared, the mixture was filtered and the residue thoroughly washed with CHCl$_3$. The combined filtrates and washings were evaporated. The residue was purified by preparative TLC (19:1 CHCl$_3$–EtOH) and yielded 12 mg of gummy 5: UV λ_{max} (MeOH) 217 nm (ϵ 10 800); IR bands (film) at 3135, 1500, 850 (furan), 3480 (OH), and 1680 and 1620 (α,β-unsaturated aldehyde) cm^{-1}; mass spectral peaks at m/e 316 (M^+, 18.2), 301 (M – CH$_3$, 4.1), 221 (24), 219 (100), 145 (14.6), 95 (42.7), 94 (11.5), 93 (39.8), and 81 (86.8).

Anal. Calcd for C$_{20}$H$_{28}$O$_3$: mol wt, 316.2037. Found: mol wt (MS),

316.2018.

X-Ray Analysis of Bacchotricuneatin A. The cell constants were $a = 12.454$ Å, $b = 11.043$ Å, and $c = 12.345$ Å and the space group was orthorhombic $P2_12_12_1$ with four molecules in the unit cell, as determined by systematic absences on Weissenberg and precession photographs. The density, measured by flotation in KI/H$_2$O, was 1.345 g/cm^3 and agreed with the calculated value of 1.338 g/cm^3. Single crystal data up to sin $\theta/\lambda = 0.59$ Å^{-1} were collected on an automated Siemens diffractometer with Ni-filtered Cu Kα radiation ($\lambda = 1.5418$ Å). A total of 1624 independent reflections were measured, out of which 1545 were recorded as observed [$>2\sigma(I)$]. The data collection technique used was $\theta - 2\theta$ scanning with symmetrical 2° scan ranges and a scan speed of 1°/min. Data were scaled by Wilson statistics.[32]

The structure was solved by direct methods using MULTAN.[32] Three origin and five starting reflections were selected (one for the enantiomorph) and gave 128 possible phase sets. An E map with the best of these, by means of "combined figure of merit", using 175 E gave positions for 24 of the 25 nonhydrogen atoms. A Fourier with the complete data set using the X-Ray System[33] revealed the last atom.

Refinement to convergence was carried out using a full matrix least-squares approach. A final R factor of 7.5% resulted, based on observed reflections. The function minimized was $\Sigma w \Delta^2$. Figure 1 is a stereoscopic view of the molecule; bond lengths and angles are given in Figure 3. Fractional coordination of the nonhydrogen atoms is listed in Table III of the supplementary material.

X-Ray Analysis of Bacchotricuneatin B. Crystal data were determined by preliminary precession and Weissenberg photographs and gave $a = 21.595$ Å, $b = 6.594$ Å, and $c = 12.011$ Å in the orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell. The density, measured by flotation in KI/H$_2$O, was 1.359 g/cm^3 compared with a calculated value of 1.329 g/cm^3. Intensity measurements were made in the manner described in the previous section on a crystal of size $0.6 \times 0.2 \times 0.2$ mm; 1683 reflections were measured up to $2\theta = 130°$, of which 1314 were regarded as observed. One reference reflection monitored after every 20 measurements showed no significant change in intensity. No absorption correction was applied. Data were scaled by Wilson statistics in the usual way.

The structure was solved using MULTAN. A first attempt to find an appropriate phase set for the 400 biggest E's with three origin and five starting reflections gave E maps which could not be interpreted. Reduction of the number of E's to 200, according to a proposal by Lessinger[34] by means of which the ratio of Σ_2 relations and the number of E are improved, led to the correction solution with the same origin and only three more starting reflections. An E map using these 200 phases gave the position of all 25 nonhydrogen atoms.

Three isotropic refinement cycles followed by three cycles with anisotropic temperature vibrations (3) converged at a final R of 9.2%, based on observed reflections, as described above. A stereoscopic view of the molecule is shown in Figure 2; bond distances and angles are given in Figure 4. Fractional coordinates are listed in Table IV of the supplementary material.

Registry No.—**1**, 65596-25-0; **2**, 65596-26-1; **3**, 66563-30-2; **4a**, 66563-31-3; **4b**, 66563-32-4; **4c**, 66563-33-5; **5**, 66563-34-6; **6a**, 66601-62-3; **6b**, 34334-69-5; **7**, 92-61-5.

Supplementary Material Available: Tables III and IV listing fractional coordinates of 1 and 2 (2 pages). Ordering information is given on any current masthead page.

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(1) Work at The Florida State University was supported in part by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

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Generation of Carbethoxynitrene by α Elimination and Its Reactions with Olefins under Two-Phase Conditions

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The base decomposition of ethyl p-nitrobenzenesulfonoxycarbamate (1) in organic–aqueous two-phase systems in the presence of cyclohexene and quaternary ammonium or phosphonium halides afforded 7-carbethoxy-7-azabicyclo[4.1.0]heptane (2), ethyl 3-cyclohexenylcarbamate (3), 3,3'-bicyclohexenyl, and ethyl carbamate. The reactivity of 1 and the product selectivity (addition/insertion ratio) are quite analogous to those reported for homogeneous reactions of 1 with cyclohexene, indicating the generation of a common intermediate of carbethoxynitrene by α elimination of 1. The reactions of 1 with cis- and trans-4-methyl-2-pentenes were also studied, and the results were interpreted in view of the electronic state of the nitrene.

The reactions between substances located separately in an organic phase and an aqueous phase are frequently accelerated by catalytic amounts of quaternary ammonium or phosphonium salts.[1] These systems are of particular advantage for the reactions which proceed via unstable intermediates such as carbanions,[2] ylides,[3] and carbenes[4] since most of these reactions have been considered to require aprotic solvents and strictly anhydrous conditions. Two-phase reactions by phase-transfer catalysts enable us to carry out these organic reactions using aqueous inorganic base solutions and are considered to be of great practical value.

The present study is concerned with the application of the two-phase reaction technique to the generation of carbethoxynitrene by α elimination and its reactions with olefins. Both the reactivity and selectivity of the nitrene generated in these systems will be examined in view of the effects of the aqueous phase and quaternary salts on the electronic state of the nitrene.

Results and Discussion

It has been reported by Lwowski and his co-workers that the treatment of ethyl p-nitrobenzenesulfonoxycarbamate (1) with triethylamine gives rise to carbethoxynitrene which is postulated to be of the singlet state.[5] We carried out this
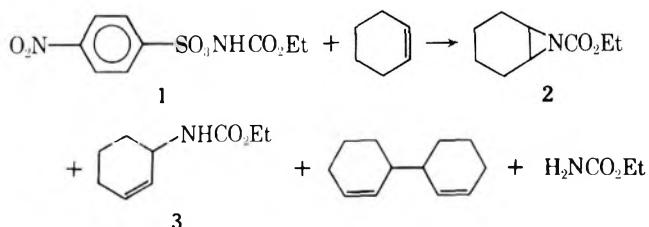
reaction in two-phase systems which consist of aqueous sodium bicarbonate solutions and dichloromethane solutions of olefins in the presence of a catalytic amount of quaternary ammonium or phosphonium halides. In the case of cyclohexene, both a presumed addition product of carbethoxynitrene to the C=C double bond, 7-carbethoxy-7-azabicyclo[4.1.0]heptane (2), and an insertion product into the C–H bond, ethyl 3-cyclohexenylcarbamate (3), were obtained together with small amounts of 3,3'-bicyclohexenyl and ethyl carbamate.

All of these compounds are common products obtained from the photodecomposition of ethyl azidoformate and from the homogeneous α elimination of 1 by triethylamine in the presence of cyclohexene.[5a,b] This indicates the formation of a common intermediate, carbethoxynitrene, also in the present two-phase system, although nitrenes have been con-
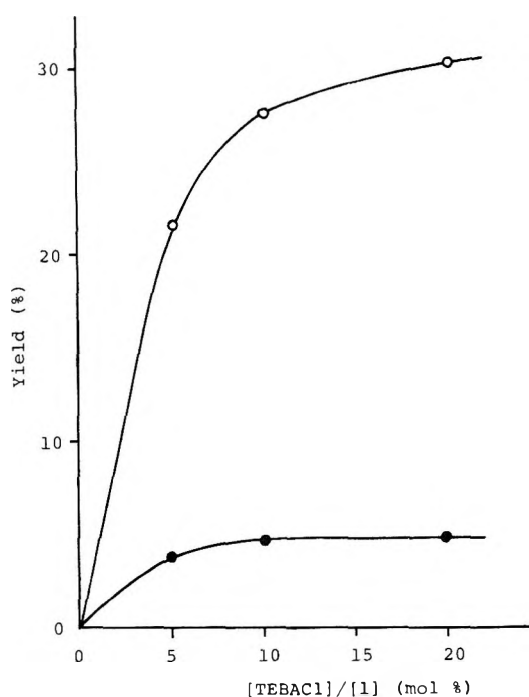
Figure 1. Yields of 7-carbethoxy-7-azabicyclo[4.1.0]heptane (2) (O) and ethyl 3-cyclohexenylcarbamate (3) (●) vs. the concentration of triethylbenzylammonium chloride (TEBACl): ethyl *p*-nitrobenzenesulfonoxycarbamate (1), 0.01 mol; cyclohexene, 0.02 mol; CH_2Cl_2, 40 mL; $NaHCO_3$, 0.03 mol; H_2O, 30 mL; room temperature for 2 h.

Table I. Reaction of Ethyl *p*-Nitrobenzenesulfonoxycarbamate (1) with Cyclohexene[a]

Catalyst	Yield, %		
	2	**3**	**2:3**
$(C_2H_5)_4NBr$	12.6	3.1	4.1
$(n\text{-}C_4H_9)_4NBr$	22.1	5.7	3.9
$(n\text{-}C_4H_9)_4PBr$	23.4	6.6	3.5
$(n\text{-}C_4H_9)_4NI$	5.9	10.3	0.57
$n\text{-}C_8H_{17}N(C_2H_5)_3Br$	19.7	4.7	4.2
$n\text{-}C_{12}H_{25}N(C_2H_5)_3Br$	19.0	4.1	4.6
$n\text{-}C_{16}H_{33}N(C_2H_5)_3Br$	22.7	4.6	4.9
$n\text{-}C_{16}H_{33}P(n\text{-}C_4H_9)_3Br$	14.6	4.6	3.2
$n\text{-}C_{16}H_{33}N(CH_3)_3Br$	22.5	4.7	4.8
$(C_6H_5CH_2)N(C_2H_5)_3Cl$	27.7	4.8	5.8
$(C_6H_5CH_2)N(C_2H_5)_3Br$	26.3	4.7	5.6
$(C_6H_5CH_2)N(C_2H_5)_3I$	6.3	5.8	1.1

[a] 1, 0.01 mol; cyclohexene, 0.02 mol; catalyst, 1.0 mmol; CH_2Cl_2, 40 mL; $NaHCO_3$, 0.03 mol; H_2O, 30 mL; room temperature for 2 h.

sidered to be sensitive to water and easily hydrolyzed under aqueous conditions.

The effect of the concentration of triethylbenzylammonium chloride (TEBACl) on the yields of 2 and 3 is shown in Figure 1. No reaction occurred without a catalyst in this system. It should be noted that the ratio of 2 to 3 is 5–6 and almost independent of the catalyst concentration. The ratio is close to that reported for the homogeneous reaction of 1 with cyclohexene,[5a,b] and this also supports the intermediacy of carbethoxynitrene.

As mentioned above, the carbethoxynitrene generated by α elimination is supposed to be a singlet nitrene. The ground state of the nitrene is triplet, and a part of the generated nitrene is expected to decay to the triplet state. On the other hand, the C–H insertion reaction at the asymmetric carbon atom of 3-methylhexane was found to proceed with complete retention of configuration, suggesting that only the singlet nitrene participates in the insertion reaction.[6] As shown in
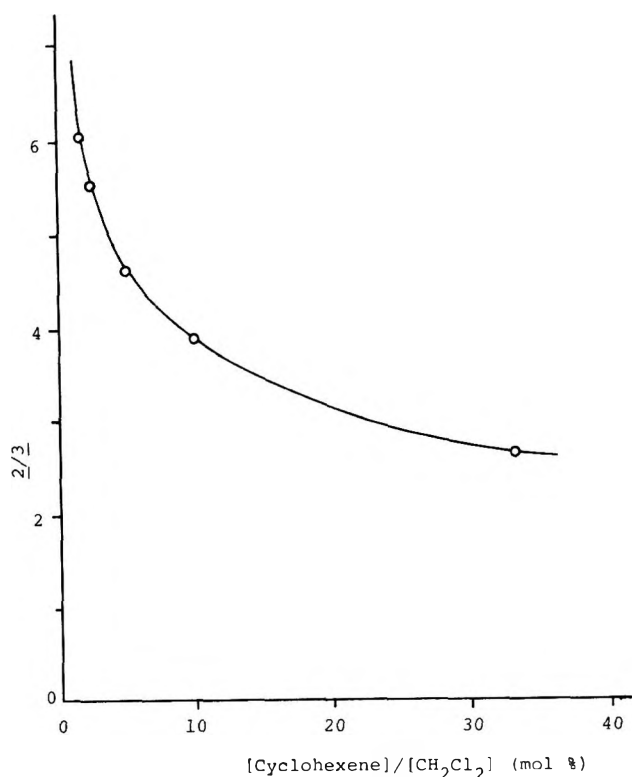
Figure 2. Effect of cyclohexene concentration on the addition/insertion product ratio: 1, 0.01 mol; TEBACl, 1.0 mmol; total volume of organic phase, 40 mL; $NaHCO_3$, 0.03 mol; H_2O, 30 mL; room temperature for 2 h.

Figure 2, a decrease in the concentration of cyclohexene in the present system leads to an increase in the ratio of the addition product to the insertion product. This can be explained as the consequence of an increasing frequency of the triplet nitrene reaction due to the lower probability of the singlet nitrene to react with cyclohexene at lower concentrations of cyclohexene.

Table I shows the variation of catalytic ability of several quaternary ammonium and phosphonium halides. There is a tendency that, among ammonium bromides used here, longer and more hydrophobic groups on nitrogen increase the catalytic ability. Therefore, it seems likely that extraction of hydroxide ion into organic phase and the subsequent formation of the anion of 1 is the major function of the catalysts. Alternatively, the anion of 1 may be formed at the interphase and then enter into the organic phase by the aid of the catalysts. Analogous results have been reported for other two-phase reactions such as the reaction of thiophenoxide ion with 1-bromooctane, where the catalytic ability depends primarily on the solubility of ammonium or phosphonium thiophenoxides in the organic phase.[7] Phosphonium salts gave a little lower ratio of 2 to 3. The best catalyst among these is TEBACl, which is one of the recommended catalysts for the generation of dichlorocarbene by α elimination of chloroform under two-phase conditions.[4]

No significant differences were observed between ammonium chlorides and bromides, but ammonium iodides gave rather unusual results as shown in Table I; the yield of the addition product decreased, while that of the insertion product increased. It might be assumed that iodide ion enters into the organic phase easier than others and consumes the triplet nitrene by unknown processes or that it interferes with the decay of the singlet nitrene to the triplet state.

The results of the reactions of 1 with *cis*- and *trans*-4-methyl-2-pentenes under two-phase conditions are summarized in Table II. From *cis*-4-methyl-2-pentene, both the

Table II. Addition of Carbethoxynitrene to *cis*- and *trans*-4-Methyl-2-pentenes under Two-Phase Conditions[a]

Catalyst	From cis olefin		From trans olefin	
	% yield of aziridine	% fraction of trans product	% yield of aziridine	% fraction of cis product
$(n\text{-}C_4H_9)_4NBr$	19.8	41.9	17.8	14.8
$(n\text{-}C_4H_9)_4NI$	6.3	15.3	5.3	11.8
$PhCH_2N(C_2H_5)_3Cl$	26.7	38.2	24.9	17.3
$PhCH_2N(C_2H_5)_3Cl$[b]	28.5	14.4	16.4	14.1
$PhCH_2N(C_2H_5)_3Br$	34.3	35.3	28.3	19.4
$PhCH_2N(C_2H_5)_3I$	11.3	10.0	4.7	6.4

[a] **1**, 0.01 mol; olefin, 0.02 mol; catalyst, 1.0 mmol; CH_2Cl_2, 40 mL; $NaHCO_3$, 0.03 mol; H_2O, 30 mL; room temperature for 2 h. [b] **1**, 0.01 mol; olefin, 0.0706 mol; catalyst, 1.0 mmol; CH_2Cl_2, 0.636 mol; $NaHCO_3$, 0.03 mol; H_2O, 30 mL; room temperature for 2 h.
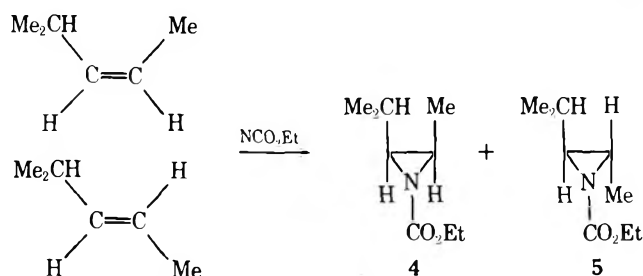
stereospecific addition product, *cis*-1-carbethoxy-2-isopropyl-3-methylaziridine (**4**), and the nonstereospecific addition product, *trans*-1-carbethoxy-2-isopropyl-3-methylaziridine (**5**), were obtained with small amounts of ethyl carbamate. In carbene reactions, the stereospecific addition is generally interpreted as indicating the reaction of a singlet carbene, while nonstereospecific addition indicates the participation of a triplet carbene.[8] The former is considered to add to olefins in one step, while the latter forms a diradical followed by spin inversion and ring closure by radical coupling. An analogous relationship between the electronic state and the stereochemistry has been postulated for carbethoxynitrene.[5c,9]

As shown in Table II, the stereospecificity of the addition of carbethoxynitrene to *cis*- and *trans*-4-methyl-2-pentenes depends on the structure of the ammonium halides. Ammonium iodides especially gave lower yields of the addition product and higher fractions of the stereospecific addition product. This indicates again that, in the case of quaternary ammonium iodide catalysts, the reaction via singlet nitrene predominates over that of triplet nitrene.

The decrease in the olefin concentration gave the anticipated result of an increase in the percent fraction of nonstereospecific addition products as seen in Table II, indicating that both the singlet and triplet nitrenes participate in the addition reaction.

Carbethoxynitrene generated in the present system also reacts with α-methylstyrene and cyclohexane to give 3-carbethoxyamino-2-phenyl-1-propene (**6**) and ethyl cyclohexylcarbamate (**7**), respectively. The yields of these products are
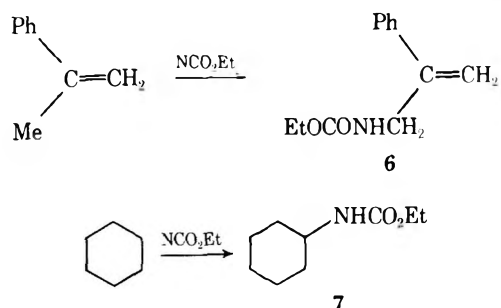
comparable to those reported for the same reactions in homogeneous systems.[5b,c]

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Hitachi 215 spectrometer, and NMR spectra were taken at 60 MHz

on a Hitachi R-20A spectrometer. Chemical shifts are reported in δ (ppm) from an internal standard of tetramethylsilane. GLC analyses were performed on a Hitachi 063 gas chromatograph. The yields of the products were determined based on calibration curves drawn using authentic samples. Elemental analyses were performed on a Perkin-Elmer 240 analyzer.

Quaternary ammonium and phosphonium halides used as phase-transfer catalysts were the products of Tokyo Kasei Kogyo Co. and were recrystallized three times from ethanol–ether or dichloromethane–ether. The purity of the salts was confirmed by melting point measurements. Olefins were distilled before use. Ethyl *p*-nitrobenzenesulfonoxycarbamate (**1**) was prepared and purified according to the method described by Lwowski,[5b] mp 117–118.5 °C (lit.[5b] mp 116.4–116.8 °C).

Anal. Calcd for $C_9H_{10}N_2O_7S$: C, 37.24; H, 3.47; N, 9.65. Found: C, 37.41; H, 3.48; N, 9.87.

Authentic samples of the reaction products of **1** with cyclohexene, *cis*- and *trans*-4-methyl-2-pentenes, α-methylstyrene, and cyclohexane were prepared by the methods described in the literature: ethyl 3-cyclohexenylcarbamate (**3**),[10] 3,3′-bicyclohexenyl,[10] *cis*- and *trans*-1-carbethoxy-2-isopropyl-3-methylaziridines (**4** and **5**),[5c] 3-carbethoxyamino-2-phenyl-1-propene (**6**),[5c] and ethyl cyclohexylcarbamate (**7**).[10] 7-Carbethoxy-7-azabicyclo[4.1.0]heptane (**2**) was isolated from the reaction products of **1** with cyclohexene and purified by distillation: bp 53–54 °C (0.5 mmHg); IR 1725 (carbonyl). 1281 and 1231 (C–O) cm^{-1}; NMR (CDCl₃) δ 1.26 (t, 3, CH₃, J = 7 Hz), 1.1–1.5 (m, 4, H-3 and H-4), ca. 1.86 (m, 4, H-2 and H-5), 2.53 (m, 2, CH), 4.04 (q, 2, OCH₂, J = 7 Hz); MS *m/e* 169.1 (M⁺).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 64.74; H, 9.11; N, 8.04.

Reactions of Ethyl *p*-Nitrobenzenesulfonoxycarbamate (1) with Cyclohexene. A solution of NaHCO₃ (0.03 mol) in H₂O (30 mL) was added to a solution of **1** (0.01 mol), cyclohexene (0.02 mol), and a phase-transfer catalyst (1.0 mmol) in dichloromethane (40 mL). The reaction mixture was stirred with a mechanical stirrer at a rate of more than 500 rpm for 2 h at room temperature. After the reaction, the mixture was diluted with 500 mL of water and extracted with dichloromethane. The organic layer was separated, washed with water, and dried over calcium chloride. The low boiling point components were distilled off under reduced pressure, and the residue was analyzed by gas chromatography using a 1 m, 10% SE-30 on 80–100 mesh Chromosorb column at 150 °C with tetralin as an internal standard. In several experiments **2** was isolated by distillation.

Reactions of Ethyl *p*-Nitrobenzenesulfonoxycarbamate (1) with *cis*- and *trans*-4-Methyl-2-pentenes. The reactions were carried out by similar methods to those described for the reaction of **1** with cyclohexene. The products were analyzed by GLC using a 2 m, 1,2,3-tris(2-cyanoethoxy)propane (TCEP) on 80–100 mesh Shimalite column at 150 °C with mesitylene as an internal standard.

Reactions of Ethyl *p*-Nitrobenzenesulfonoxycarbamate (1) with α-Methylstyrene and with Cyclohexane. The same procedure as described above was employed for these reactions, and the main products, 3-carbethoxyamino-2-phenyl-1-propene (**6**) (11%) and ethyl cyclohexylcarbamate (**7**) (13%), respectively, were identified and determined by GLC using authentic samples. A 1 m, 10% SE-30 on 80–100 mesh Chromosorb column was used at 200 and 150 °C for **6** and **7**, respectively.

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Reactions of Ketene Acetals, Ketene Thioacetals, and Ketene Aminals with Dialkyl Azodicarboxylate Esters

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Ketene acetals react with azodicarboxylate esters to give 5,6-dihydrooxadiazines. However, these compounds are not very stable and undergo thermal ring opening to give hydrazinylketene acetals. No 1,2-diazetidines could be detected in the reactions. If the starting ketene acetal bears no substitutent, the azodicarboxylate ester can react with the hydrazinylketene acetal product to give 2:1 adducts, which have been shown to be either 5-hydrazinyl-5,6-dihydrooxadiazines or dihydrazinylketene acetals. When ketene acetals with allyic hydrogens are used, such as dimethylketene dimethyl acetal, only ene reaction products are formed. When ketene thioacetals reacted with azodicarboxylate esters, the presence of 5,6-dihydrooxadiazines could not be demonstrated. Only ring-opening products, hydrazinylketene thioacetals, could be isolated. In the reactions of ketene aminals with azodicarboxylate esters a low yield of a 5,6-dihydrooxadiazine was isolated in one case; the main products were hydrolysis products of 1:1 adducts. All of the products of these reactions are very moisture sensitive, the acetal linkages undergoing facile hydrolysis to the corresponding open-chain esters.

The thermal addition of ketene acetals to anhydrides,[1] diazonium salts,[2] ketenes,[3-8] acrylate esters,[9] cyanoethylenes,[10,7] acetylenic esters,[10,11] azides,[12-14] isocyanates,[15-20] α,β-unsaturated aldehydes and ketones,[21-25] and nitroso compounds[6,7] has been reported. Ketene thioacetals undergo thermal addition to ketenes,[8] cyanoethylenes,[26] anhydrides,[26] and acetylenic esters.[27] Ketene aminals have been reported to add thermally to ketenes,[28,29] acrylate esters,[30] cyanoethylenes,[10,31-34] isocyanates,[35,36] and cyclopropenones.[37,38] Among these reports there are examples of 2 + 2, 2 + 4, and 1,3-dipolar cycloadditions, formation of substituted ketene acetals, ketene thioacetals, and ketene aminals, as well as adduct formation arising from electron transfer. All of these reactions are interrelated in that all represent the reaction of an electron-rich olefin with an unsaturated electron-poor acceptor.

The reactions of ketene acetals, ketene aminals, and ketene thioacetals with azodicarboxylate esters appear not to have been examined except for the example of Carey and Neergaard[39] indicating that an azodicarboxylate ester undergoes substitution in a ketene thioacetal. However, several related reactions have been examined, including the reaction of azodicarboxylate esters with tetramethoxyethylene,[7] tetramethoxyallene,[6] vinyl ethers,[40-49] vinyl thioethers,[41,45,46] vinyl acetates,[41,47] and enamines.[41,42,46,50]

Ketene acetals, ketene thioacetals, and ketene aminals were all found to react with dimethyl and diethyl azodicarboxylates at room temperature. The reactions were exothermic. The products of these reactions were sensitive to moisture and in some cases only hydrolysis products could be isolated.

When unsubstituted ketene acetals reacted with dimethyl and diethyl azodicarboxylates, both 1:1 and 2:1 adducts were formed. When ketene dimethyl acetal reacted with dimethyl azodicarboxylate, three products, **3a**, **4a**, and **6a**, were isolated

in a ratio of 25:3.3:1. The structure of **3a** was proven by independent synthesis by hydrogenation of the carbomethoxyhydrazone of methyl glyoxylate, followed by acylation of the product with methyl chloroformate. The elemental analysis of **4a** was also consistent with the structure **5a** and the diazetidine **7**. However, the NMR of **4a** showed two singlets for the gem methoxy groups at 3.45 and 3.57 ppm, eliminating the symmetrical structure **5a**. The IR of **4a** showed three carbonyl stretching frequencies at 1760, 1750, and 1720 cm^{-1} and a band at 1683 cm^{-1}, characteristic of the C=N stretch in 5,6-dihydrooxadiazenes,[47] eliminating structure **7**.

On standing at room temperature, **4a** is quantitatively transformed into **6a**. This transformation can be monitored by NMR. After heating for 1 h at 40 °C in deuteriochloroform, only **6a** remained. This reaction appears to involve ring opening of the 5,6-dihydrooxadiazine **4a**, presumably through a 1,4-dipolar intermediate to form **5a**, which is very moisture sensitive and hydrolyzes to **6a**. Similarly, the major product, **3a**, most likely arises by hydrolysis of **2a** obtained from ring opening of **1a**.

The reaction of ketene dimethyl acetal with diethyl azodicarboxylate gave the 1:1 adduct **3b** and the 2:1 adducts **5b** and **6b** in a ratio of 1.5:1:1 as estimated from the NMR spectrum of the reaction mixture. Only **3b** could be isolated and purified. Its structure was proven by independent synthesis as described above for **3a**. When this reaction was run in deuterated benzene in the NMR spectrometer, the first identifiable product was the 5,6-dihydrooxadiazine **4b**, as shown by the appearance of the peak at 3.82 ppm, characteristic of C-5 proton. This is followed by the appearance of the hydrazinylketene acetal **5b** as shown by the appearance of singlet at 3.12 ppm for the two methoxy groups. At the same time, the NH peak at 7.32 ppm begins to appear.

When ketene diethyl acetal was reacted with dimethyl and

Scheme I

$(RO)_2C{=}CH_2 \ + \ R'O_2CN{=}NCO_2R'$

a, R = CH$_3$; R' = CH$_3$
b, R = CH$_3$; R' = C$_2$H$_5$
c, R = C$_2$H$_5$; R' = CH$_3$
d, R = C$_2$H$_5$; R' = C$_2$H$_5$

Scheme II

$RCH{=}C(OR'')_2 \ + \ R'O_2CN{=}NCO_2R'$

a, R = Cl; R' = CH$_3$; R'' = C$_2$H$_5$
b, R = Br; R' = CH$_3$; R'' = C$_2$H$_5$
c, R = C$_6$H$_5$; R' = CH$_3$; R'' = CH$_3$
d, R = C$_6$H$_5$; R' = C$_2$H$_5$; R'' = CH$_3$

chloroform at 45 °C or when it was subjected to acid catalyzed hydrolysis, both compounds were converted into **10c**.

When diethyl azodicarboxylate and phenylketene dimethyl acetal are mixed at 10 °C in a NMR tube, the 5,6-dihydrooxadiazine **8d** is formed initially as shown by the appearance of the singlet at 5.57 ppm due to the proton at C-5. The peaks of **9d** appear later, indicating that the 5,6-dihydrooxadiazine **8d** is the precursor of the hydrazinylketene acetal **9d**. When the vinyl hydrogen of phenylketene dimethyl acetal is replaced with deuterium and reacted with diethyl azodicarboxylate, the buildup of **9d** can be observed by looking at the N–D peak in the IR spectrum at 2510 cm^{-1}. It seems likely that this reaction involves opening of the 5,6-dihydrooxadiazine to the dipolar structure **11** followed by intramolecular proton transfer to give the hydrazinylketene dimethyl acetal **9**. In principle, the dipolar intermediate **11** could also lead to a 1,2-diazetidine, but this is not observed. Examination of

diethyl azodicarboxylates the only products that could be purified were 2:1 adducts **6c** and **6d**.

When chloroketene and bromoketene diethyl acetals were reacted with dimethyl azodicarboxylate, the products were viscous oils (glasses) and attempts to purify them failed. The product from the bromo compound showed an NH stretch at 3290 cm^{-1} and two carbonyl stretching frequencies at 1770 and 1733 cm^{-1} in the IR. The NMR showed two nonequivalent methoxy groups at 3.74 and 3.80 ppm and a singlet at 6.73 ppm corresponding to CHBr. Similarly, the IR of the chloro compound exhibited an N–H at 3300 cm^{-1} and carbonyl frequencies at 1750 and 1730 cm^{-1}, and the NMR showed two nonequivalent methoxy groups at 3.60 and 3.67 ppm and a singlet at 6.43 ppm for CHCl. The spectral information is consistent with the 1:1 hydrolysis products **10a** and **10b**.

Dibromoketene diethyl acetal failed to react with dimethyl azodicarboxylate even when the reaction mixture in benzene was refluxed 67 h.

Phenylketene dimethyl acetal reacts with dimethyl azodicarboxylate to give a mixture of the 5,6-dihydrooxadiazine **8c** and the hydrazinylketene dimethyl acetal **9c** in a 2:1 ratio and with diethyl azodicarboxylate to give **8d** and **9d** in a 5:1 ratio (Scheme II). The 5,6-dihydrooxadiazines **8c** and **8d** showed the characteristic two singlets for the geminal methoxy groups at 3.27 and 3.34 ppm and at 3.28 and 3.36 ppm, respectively, corresponding to the axial and equatorial positions. When the reaction mixture containing **8c** and **9c** was heated in moist

models of the conformation **13** indicates that there is considerable steric interaction between the carboxyl groups. However, the most probable factor determining the product is that the intramolecular proton transfer **11** to **9** is fast.

When 2-phenylmethylene-1,3-dioxolane was reacted with diethyl azodicarboxylate, only the hydrazinylketene acetal **15** was isolated. However, the crude reaction mixture contained a peak at 5.50 ppm (C-5 proton) indicating the presence of the dihydrooxadiazine **14**.

14   **15**
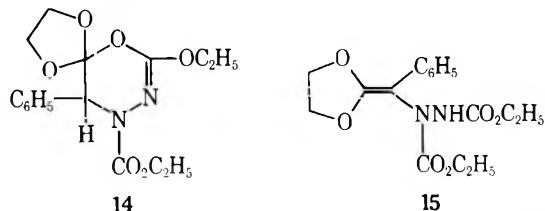
When these reactions were extended to thioacetals, only the hydrazinylketene thioacetals **16a** and **16b** could be isolated. No evidence for the formation of a 5,6-dihydrooxadiazine could be detected. Apparently they are too unstable even at room temperature.

$$RCH{=}C(SC_2H_5)_2 \ + \ CH_3O_2CN{=}NCO_2CH_3$$

a, R = H
b, R = C₆H₅   **16**
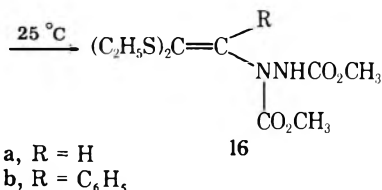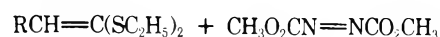
When 1,1-di(*N*-morpholinyl)ethylene was reacted with diethyl azodicarboxylate, the hydrolysis product **17a** was isolated along with some acetylmorpholine. When 1,1-di(*N*-piperidinyl)ethylene was reacted with dimethyl azodicarboxylate, the hydrolysis product **17b** was isolated along with some acetylpiperidine. In this case, a small amount of the dihydrooxadiazine **18** was also isolated. The elemental analysis of **18** was poor as it was difficult to purify, but the spectral information is consistent. The IR showed no NH, a carbonyl band at 1778 cm^{-1}, and a C=N band at 1620 cm^{-1}. The UV spectrum had maxima at 277 and 308 nm.

17a, R = O☐N; R' = C₂H₅

   b, R = ☐N; R' = CH₃   **18**
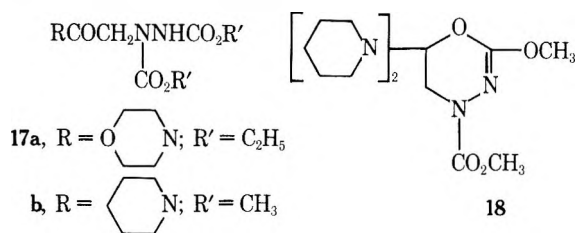
Several unsuccessful reactions were attempted. Di(4-chlorophenyl)ketene diethyl acetal failed to react with dimethyl azodicarboxylate even when the benzene solution was refluxed for 19 h. Photolysis of the mixture likewise failed to effect reaction. Phenylketene dimethyl acetal failed to react with azobenzene or azoxybenzene either thermally in refluxing benzene or photolytically. Phenylketene diethyl thioacetal likewise failed to react with azobenzene or azoxybenzene in refluxing benzene.

In each case where 2,2-disubstituted ketene acetals were reacted with azodicarboxylate esters, the reaction either failed because the substituents were electron-withdrawing groups, as in the dibromoketene diethyl acetal or di(4-chlorophenyl)-
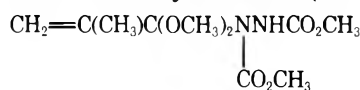
19

ketene diethyl acetal cases, or the ene reaction was observed. For example, dimethylketene dimethyl acetal reacted with dimethyl azodicarboxylate to give 2-methyl-3,3-dimethoxy-3-(*N*,*N*'-dicarbomethoxyhydrazinyl)propene-1 (**19**).

The data presented give no information as to the mechanism of 5,6-dihydrooxadiazine formation. Firl and Sommer[45] reported that *cis*-1-thioethylpropylene added to dimethyl azodicarboxylate to give 5,6-dihydrooxadiazines in a non-stereospecific manner but gave *cis*-3-methyl-4-ethylthio-1,2-dicarbomethoxy-1,2-dicarbomethoxy-1,2-diazetidine in a stereospecific manner. A dipolar intermediate was postulated in 5,6-dihydrooxadiazine formation, but not in diazetidine formation. It should be pointed out however, that the published information on the three compounds is scanty, and it is not clear how the structural and stereochemical assignments were made.

The observation that **8c** and **8d** were precursors of **9c** and **9d** raises the question as to the thermal stability of 5,6-dihydrooxadiazines in general. Accordingly, 2-methoxy-4-carbomethoxy-6-phenoxy-5,6-dihydrooxadizine, mp 103–104 °C, was prepared as described by Firl and Sommer.[43,44] When heated at 45 °C in deuterated chloroform for 3 weeks, no decomposition could be detected. Apparently, the facile ring opening of the 5,6-dihydrooxadiazines observed in this work is the result of stabilization of the dipole **11** by delocalization of the positive charge by the two alkoxy groups. This may also explain why no 1,2-diazetidines were observed in this work, i.e., if the 5,6-dihydrooxadiazine is unstable, the 1,2-diazetidine should be even less stable relative to the dipolar intermediate.

During the course of this study we noted that reactivity of the alkenes with azodicarboxylate esters followed the order ketene acetals < ketene thioacetals < ketene aminals, i.e., in order of increasing donating power of the alkene. (A similar reactivity was reported for vinyl ethers, vinyl thioethers, and enamines.[41]) This observation provides an explanation as to why 2:1 adducts were observed only in the reactions of ketene dimethyl and diethyl acetals with azodicarboxylate esters. These reactions are slow enough, and the initially formed 5,6-dihydrooxadiazine **1** unstable enough, that the corresponding hydrazinylketene acetal **2** builds up during the reaction, and since it is even a better electron donor than the starting ketene acetal, it reacts with unreacted azocompound to give 2:1 adducts, **4–6**.

Experimental Section

Diethyl azodicarboxylate was purchased from Aldrich Chemical Co. and distilled prior to use. Dimethyl azodicarboxylate was prepared by oxidation of the hydrazine by the Rabjohn procedure.[51] Ketene, chloroketene, bromoketene, and dibromoketene diethyl acetals were prepared by the McElvain and Beyerstedt procedure.[52,53] This procedure was also adopted to the preparation of phenylketene dimethyl acetal. Ketene and phenylketene diethyl thioacetals were prepared by the procedure of Rinzema, Stoffelsma, and Arens.[54] 1,1-Di(*N*-piperdinyl)ethylene and 1,1-di(*N*-morpholinyl)ethylene were obtained by the Boganz and Domasche method.[55] Di(4-chlorophenyl)-ketene diethyl acetal was prepared by the method reported by Kaluszyner, Mechoulam, and Cohen.[56,57] Dimethylketene dimethyl acetal was obtained by the McElvain and Davie[58] procedure. The McElvain and Curry method was used to prepare 2-phenylmethylene-1,3-dioxolane.[59]

In order to avoid polymerization of the acetals, all glassware was washed with dilute sodium or potassium hydroxide and water and throughly dried prior to use. The alumina used in the chromatographic separations was neutral, Brockman Activity 1, 80–100 mesh.

Reaction of Ketene Dimethyl Acetal with Dimethyl Azodicarboxylate. Ketene dimethyl acetal (1.602 g, 0.01820 mol) was dissolved in 6 mL of anhydrous benzene and dimethyl azodicarboxylate (2.655 g, 0.01820 mol) in 6 mL of anhydrous benzene was added dropwise. The temperature rose to 42 °C. After standing at room temperature for 2 days, the solvent was removed under vacuum.

A portion of the oily residue (3.934 g) was triturated with anhydrous ether to give 0.893 g of crystalline solid. A second trituration with ether gave 0.387 g (10%) of 2-methoxy-4-carbomethoxy-5-(*N,N'*-dicarbomethoxyhydrazinyl)-6,6-dimethoxy-5,6-dihydrooxadiazine (**4a**): mp 160–162 °C; IR (Nujol) 3320 (NH), 1760, 1750, 1720 (C=O), and 1683 cm⁻¹ (C=N); NMR (CDCl₃) δ 3.45 (s, 3 H), 3.57 (s, 3 H), and 3.83 (m, 13 H).

Anal. Calcd for $C_{12}H_{20}N_4O_{10}$: C, 37.89; H, 5.30; N, 14.73. Found: C, 37.73; H, 5.20; N, 14.83.

The ether solution from the first trituration was evaporated. The residue (3.041 g) was again triturated with a small volume of ether to give 0.0928 g (3%) of a second solid. Chromatography on alumina, using chloroform as the eluent, followed by recrystallization from petroleum ether–ether (1:1) gave 0.0353 g of pure methyl di(*N,N'*-dicarbomethoxyhydrazinyl)acetate (**6a**): mp 138.5–140 °C; IR (Nujol) 3400 (NH) and 1740 cm⁻¹ (C=O); NMR (CDCl₃) δ 3.79 (s, 12 H), 3.88 (s, 3 H), 6.15 (s, 1 H), and 7.28 (bs, 1 H).

Anal. Calcd for $C_{11}H_{18}N_4O_{10}$: C, 36.06; H, 4.95; N, 15.29. Found: C, 35.87; H, 5.05; N, 15.04.

Finally, evaporation of the ether soluble material left 2.948 g (73.6%) of a very viscous liquid, which was shown to be methyl *N,N'*-dicarbomethoxyhydrazinylacetate (**3a**) by comparison of its IR and NMR spectra with an authentic sample whose preparation is given below.

N-Carbomethoxyhydrazone of Methyl Glyoxylate. Dimethyl tartrate (5.34 g, 0.0300 mol) was dissolved in 50 mL of glacial acetic acid. The solution was heated at 50 °C while 13.3 g (0.0300 mol) of lead tetraacetate was introduced. Water (200 mL) was then added, followed by a solution of 6.25 g (0.0600 mol) of methyl carbazate in 25 mL of water. After standing at room temperature for 1 week, the solution was extracted with chloroform. The extract was washed twice with sodium bicarbonate (until neutral) and once with water and dried over magnesium sulfate. Evaporation of the chloroform gave 5.70 g (60.9%) of the N-carbomethoxyhydrazone of methyl glyoxylate: mp 130.5–131 °C (from chloroform–ether); IR (Nujol) 3190 (NH), 1750, 1733 (C=O), and 1691 cm⁻¹ (C=N); NMR (CDCl₃) δ 3.80 (s, 6 H) and 7.43 (bs, 1 H).

Anal. Calcd for $C_5H_8N_2O_4$: C, 37.50; H, 5.03; N, 17.49. Found: C, 37.48; H, 5.11; N, 17.44.

Methyl N'-Carbomethoxyhydrazinylacetate. The N-carbomethoxyhydrazone of methyl glyoxylate (1.304 g, 8.143 mmol) was dissolved in 35 mL of glacial acetic acid. The mixture was hydrogenated over platinum at 35 °C and 35 psi for 24 h. The mixture was diluted with 35 mL of chloroform and extracted five times with 5% hydrochloric acid. The aqueous extracts were neutralized with 10% sodium bicarbonate solution. The basic solution was extracted with chloroform. The extracts were dried over magnesium sulfate and then evaporated to give 0.920 g of oil. Chromatography on alumina, using benzene–chloroform (7:3), gave 0.539 g (58.5%) of pure methyl N'-carbomethoxyhydrazinylacetate as a viscous oil: NMR (CDCl₃) δ 3.61 (s, 3 H), 3.67 s, 3 H), 3.78 (s, 2 H), 4.46 (bs, 1 H), and 7.34 (bs, 1 H).

Anal. Calcd for $C_5H_{10}N_2O_4$: C, 37.03; H, 6.12; N, 17.27. Found: C, 37.00; H, 6.14; N, 17.10.

Methyl N,N'-Dicarbomethoxyhydrazinylacetate (3a). Methyl N'-carbomethoxyhydrazinylacetate (0.643 g, 4.08 mmol) was dissolved in 8 mL of methanol and 2 mL of water. The solution was cooled in an ice bath and 0.380 g (4.10 mmol) of methyl chloroformate and a solution of 0.211 g (1.98 mmol) of sodium carbonate in 3 mL of water were added. The temperature was kept below 15 °C. After the additions were complete, the reaction was stirred at room temperature for 30 min. It was extracted with chloroform. The extracts were dried over magnesium sulfate. Evaporation of the solvent gave 0.752 g of crude product. Chromatography on alumina using chloroform–ether (2:1) as eluent gave 0.470 g (52.3%) of methyl N,N'-dicarbomethoxyhydrazinylacetate (**3a**) as a viscous oil: IR (neat) 3280 (NH), 1748, and 1716 cm⁻¹ (C=O); NMR (CDCl₃) δ 3.72 (s, 6 H), 4.28 (s, 3 H), and 7.14 (bs, 1 H).

Anal. Calcd for $C_7H_{12}N_2O_6$: C, 38.18; H, 5.49; N, 12.72. Found: C, 38.25; H, 5.54; N, 12.69.

Reaction of Ketene Dimethyl Acetal with Diethyl Azodicarboxylate. In 6 mL of anhydrous benzene was dissolved 2.400 g (0.02726 mol) of ketene dimethyl acetal and 4.750 g (0.02726 mol) of diethyl azodicarboxylate was added dropwise. The temperature rose to 48 °C. After standing a short time at room temperature, the ben-

zene was removed under vacuum.

A portion of the residue (0.545 g) was separated by preparative TLC on silica gel (MCB, SX144-5, 60–200 mesh). Pentane–ether (1:2) was the eluent. Separation gave 0.282 g (51.8%) of methyl *N,N'*-dicarboethoxyhydrazinylacetate (**3b**). Recrystallization from ether gave pure material: mp 73–74.5 °C; IR (Nujol) 3250 (NH), 1745. and 1720 cm⁻¹ (C=O); NMR (CDCl₃) δ 1.29 (t, 6 H), 3.72 (s, 3 H), 4.25 (q, 4 H), 4.34 (s, 2 H), 7.01 (bs, 1 H). This compound was identical (IR, NMR, mixture melting point) to the authentic sample prepared below.

Anal. Calcd for $C_9H_{16}N_2O_6$: C, 43.59; H, 6.49; N, 11.28. Found: C, 43.42; H, 6.43; N, 11.20.

The NMR spectrum of the reaction mixture indicated the presence of two additional compounds. These are methyl di(*N,N'*-dicarboethoxyhydrazinyl)acetate (**6b**) (NMR (CDCl₃) δ 3.25 (s, 6 H) and 7.38 (bs, 1 H)) and 1,1-dimethoxy-2,2-di(*N,N'*-dicarboethoxyhydrazinyl)ethylene (**5b**) (NMR (CDCl₃) δ 3.78 (s, 3 H), 6.04 (s, 1 H), and 7.35 (bs, 1 H)). These assignments are consistent with those of the compounds isolated in the reaction of ketene dimethyl acetal with dimethyl azodicarboxylate. From the NMR of the reaction mixture it is estimated that the ratio of **3b**:**6b**:**5b** is 40%:28%:32%.

N-Carboethoxyhydrazone of Methyl Glyoxylate. The same procedure given above for the carbomethoxy compound gave a 35% yield of the hydrazone: mp 129–130 °C (lit.⁶⁰ mp 130 °C); NMR (CDCl₃) δ 1.3 (t, 3 H), 3.77 (s, 3 H), 4.23 (q, 2 H), and 7.41 (s, 1 H).

Methyl N'-Carboethoxyhydrazinylacetate. The same procedure was used as for the corresponding carbomethoxy compound given above except the hydrogenation time was 48 h. Workup gave a 31.7% yield: mp 53–54 °C; NMR (CDCl₃) δ 1.23 (t, 3 H), 3.66 (s, 3 H), 3.70 (s, 3 H), 4.10 (q, 2 H), and 7.31 (bs, 1 H).

Anal. Calcd for $C_6H_{12}N_2O_4$: C, 40.90; H, 6.89; N, 15.90. Found: C, 40.92; H, 6.91; N, 15.86.

Methyl N,N'-Dicarboethoxyhydrazinylacetate (3b). The reaction was run in the same way as with the corresponding carbomethoxy compound above. Evaporation of the chloroform extract gave 1.52 g (from 1.20 g, 6.83 mmol of the starting compound) of viscous oil, which solidified on standing. Recrystallization from ether gave 1.32 g (78%) of methyl N,N'-dicarboethoxyhydrazinylacetate (**3b**): mp 73–74 °C; IR (Nujol) 3250 (NH), 1745, and 1720 cm⁻¹ (C=O); NMR (CDCl₃) δ 1.29 (t, 6 H), 3.79 (s, 3 H), 4.25 (q, 4 H), 4.34 (s, 2 H), 7.01 (bs, 1 H).

Reaction of Ketene Diethyl Acetal with Dimethyl Azodicarboxylate. In 3 mL of anhydrous benzene was dissolved 1.329 g (0.01145 mol) of ketene diethyl acetal and 1.993 g (0.01145 mol) of dimethyl azodicarboxylate in 3 mL of anhydrous benzene added dropwise. The temperature rose to 48 °C. After standing at room temperature for 2 days, the solvent was removed and the residue was triturated with anhydrous ether to give 1.712 g (62.1%) of ethyl di(*N,N'*-dicarbomethoxyhydrazinyl)acetate (**6c**). Recrystallization from toluene gave pure material: mp 117–118.5 °C; IR (Nujol) 3335 (NH) and 1740 cm⁻¹ (C=O); NMR (CDCl₃) δ 1.30 (t, 3 H), 3.7 (s, 12 H), 4.25 (q, 2 H), 6.05 (s, 1 H), and 7.04 (bs, 2 H).

Anal. Calcd for $C_{12}H_{20}N_4O_{10}$: C, 37.89; H, 5.30; N, 14.73. Found: C, 37.90; H, 5.41; N, 14.73.

Reaction of Ketene Diethyl Acetal with Diethyl Azodicarboxylate. Diethyl azodicarboxylate (5.97 g, 0.0343 mol) was added dropwise to ketene diethyl acetal (3.98 mol). The temperature rose to 68 °C. On long standing, the very viscous mixture solidified. Recrystallization from petroleum ether containing a few drops of ether gave 5.43 g (73.3%) of ethyl di(*N,N'*-dicarboethoxyhydrazinyl)acetate (**6d**): IR (Nujol) 3300 (NH), 1750, and 1725 cm⁻¹ (C=O); NMR (CDCl₃) δ 1.27 (t, 6 H), 1.30 (t, 3 H), 4.15 (q, 10 H), 5.02 (s, 1 H), and 7.09 (bs, 2 H).

Anal. Calcd for $C_{16}H_{28}N_4O_{10}$: C, 44.03; H, 6.46; N, 12.83. Found: C, 43.88; H, 6.51; N, 12.81.

Reaction of Chloroketene Diethyl Acetal with Dimethyl Azodicarboxylate. Chloroketene diethyl acetal (1.870 g, 0.01253 mol) was dissolved in 10 mL of anhydrous benzene and dimethyl azodicarboxylate (1.815 g, 0.01243 mol) in 5 mL of anhydrous benzene was added dropwise. The temperature rose to 29 °C. After standing at room temperature for 3 days, the benzene was removed under vacuum. A portion of the residue (0.4206 g) was separated on a silica gel column (MCB SX1144-5, 60–200 mesh) using benzene–ether (3:1) as eluent. The main fraction, 0.209 g (49.7%), was a viscous oil (a glass) with the following spectral characteristics: IR (neat) 3300 (NH), 1750, and 1730 cm⁻¹ (C=O); NMR (CDCl₃) δ 1.18 (t, 6 H), 3.60 (s, 3 H), 3.67 (s, 2 H), 4.10 (q, 6 H), 6.43 (s, 1 H), and 6.95 (bs, 1 H). These spectral data indicate that the compound is primarily ethyl N,N'-dicarbomethoxy-2-chlorohydrazinylacetate (**10a**).

Reaction of Bromoketene Diethyl Acetal with Dimethyl Azodicarboxylate. Dimethyl azodicarboxylate (1.552 g, 0.01063 mol)

was dissolved in 6 mL of anhydrous benzene and added dropwise to a solution of bromoketene diethyl acetal (2.071 g, 0.01063 mol) in 10 mL of anhydrous benzene. The temperature rose to 30 °C. The reaction mixture was allowed to stand at room temperature for 2 days. A portion (0.450 g) of the residue, after removal of the benzene, was placed on a silica gel column (MCB SX1144-5, 60–200 mesh). Elution with benzene–ether (3:1) gave 0.1573 g (35.1%) of a viscous oil with the following spectral characteristics: IR (neat) 3300 (NH) and 1770 cm^{-1} (C=O); NMR (CDCl$_3$) δ 1.31 (t, 6 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 4.23 (q, 4 H), 6.73 (s, 1 H), and 6.85 (bs, 1 H). Since this glasslike material could not be purified, no elemental analysis was obtained. However, the spectral information is consistent with **10b**.

Reaction of Phenylketene Dimethyl Acetal with Dimethyl Azodicarboxylate. In 4 mL of dry benzene was dissolved 2.208 g (0.01512 mol) of dimethyl azodicarboxylate and 2.479 g (0.01512 mol) of phenylketene dimethyl acetal in 10 mL of dry benzene added dropwise. The temperature rose to 33 °C. After standing for 4 days, the precipitate which formed was filtered and recrystallized from toluene with a yield of 1.994 g (42.5%) of 1,1-dimethoxy-2-phenyl-2-(*N,N'*-dicarbomethoxyhydrazinyl)ethylene (**9c**): mp 138.5–140 °C; IR (Nujol) 3220 (NH), 1750, 1700 (C=O), and 1695 cm^{-1} (C=C); NMR (CDCl$_3$) δ 3.59 (s, 3 H), 3.63 (s, 3 H), 3.65 (s, 6 H), 6.95 (bs, 1 H), and 7.08–7.65 (m, 5 H).

Anal. Calcd for C$_{14}$H$_{18}$N$_2$O$_6$: C, 54.18; H, 5.84; N, 9.02. Found: C, 54.19; H, 5.85; N, 8.93.

The NMR of the original mixure before separation revealed the presence of two compounds, the isolated hydrazinylethylene **9c** (66.3%) and 2,6,6-trimethoxy-4-carbomethoxy-5-phenyl-5,6-dihydrooxadiazine (**8c**) (33.7%): NMR (CDCl$_3$) δ 3.27 (t, 3 H), 3.34 (s, 3 H), 3.7 (s, 3 H), 3.81 (s, 3 H), 5.55 (s, 1 H), and 7.08–7.25 (m, 5 H).

A portion of the oily residue remaining after separation of the hydrazinylethylene **9c**, which was enriched with the dihydrooxadiazine, was heated in wet deuteriochloroform for 30 min at 45 °C. The NMR peaks of the dihydrooxadiazine disappeared as it was transformed into methyl *N,N'*-dicarbomethoxy-2-phenylhydrazinylacetate (**10c**).

In an unsuccessful attempt to isolate the dihydrooxadiazine, a portion (0.3478 g) of the residue after separation of the bulk of the 1,1-dimethoxy-2-phenyl-2-(*N,N'*-dicarbomethoxyhydrazinyl)-ethylene (**9c**) was chromatographed on silica gel (MCB 5 × 1144-5, 60–200 mesh). Elution with chloroform–ether (3:1) gave 0.1425 g (41%) of the hydrolysis product, methyl *N,N'*-dicarbomethoxy-2-phenylhydrazinylacetate (**10c**), as a viscous oil. On trituration with ether it solidified. Recrystallization from petroleum ether containing a few drops of ether gave pure material: mp 111–112.5 °C; IR (Nujol) 3300 (NH) and 1725 cm^{-1} (C=O); NMR (CDCl$_3$) δ 3.72 (s, 3 H), 3.75 (s, 6 H), 5.95 (s, 1 H), 6.77 (bs, 1 H), and 7.23 (s, 5 H).

Anal. Calcd for C$_{13}$H$_{16}$N$_2$O$_6$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.72; H, 5.26; N, 9.29.

When 0.14 g of 1,1-dimethoxy-2-phenyl-2-(*N,N'*-dicarbomethoxyhydrazinyl)ethylene was heated in wet chloroform at 45 °C for 98 h, it was hydrolyzed quantitatively to methyl *N,N'*-dicarbomethoxy-2-phenylhydrazinylacetate (**10c**), mp 110–112.5 °C; mixture melting point gave no depression.

Reaction of Phenylketene Dimethyl Acetal with Diethyl Azodicarboxylate. In 5 mL of dry benzene was dissolved 2.475 g (0.01423 mol) of dimethyl azodicarboxylate which was added dropwise to a solution of 2.333 g (0.01423 mol) in 5 mL of dry benzene. The temperature rose to 27 °C. The reaction mixture was allowed to stand at room temperature for 6 days. The precipitated 1,1-dimethoxy-2-phenyl-2-(*N,N'*-dicarboethoxyhydrazinyl)ethylene (**9d**) was filtered to give 4.138 g (85.9%): mp 115–116 °C; IR (Nujol) 3270 (NH), 1750, 1700 (C=O), and 1690 cm^{-1} (C=C); NMR (CDCl$_3$) δ 1.21 (t, 6 H), 3.58 (s, 3 H), 3.67 (s, 3 H), 4.11 (q, 4 H), 6.83 (bs, 1 H), and 7.08–7.70 (m, 5 H).

Anal. Calcd for C$_{16}$H$_{22}$N$_2$O$_6$: C, 56.79; H, 6.55; N, 8.27. Found: C, 56.76; H, 6.62; N, 8.32.

Recrystallization of this hydrazinylethylene from moist toluene gave a quantitative yield of methyl *N,N'*-dicarboethoxy-2-phenylhydrazinylacetate (**10d**): mp 91.5–92.5 °C; IR (Nujol) 3285 (NH), 1733, and 1675 cm^{-1} (C=O); NMR (CDCl$_3$) δ 1.30 (t, 6 H), 3.77 (s, 3 H), 4.23 (q, 4 H), 6.03 (s, 1 H), 6.76 (bs, 1 H), and 7.30 (s, 5 H).

Anal. Calcd for C$_{15}$H$_{20}$N$_2$O$_6$: C, 55.54; H, 6.21; N, 8.63. Found: C, 55.53; H, 6.33; N, 8.50.

The NMR spectrum of the reaction mixture, before separation of the hydrazinylethylene, indicated the presence of two compounds, the hydrazinylethylene **9d** (83.4%) and 2-ethoxy-4-carboethoxy-5-phenyl-6,6-dimethoxy-5,6-dihydrooxadiazine (**8d**) (16.6%): partial NMR (CDCl$_3$) δ 3.28 (s, 3 H), 3.36 (s, 3 H), 4.09 (q, 4 H), 5.57 (s, 1 H).

When the above reaction was repeated, using acetonitrile as the solvent instead of benzene, a 50% yield of the hydrazinylethylene **9d** was isolated.

Reaction of 2-Phenylmethylene-1,3-dioxolane with Diethyl Azodicarboxylate. In 10 mL of dry benzene was placed 2.684 g (0.01660 mol) of 2-phenylmethylene-1,3-dioxolane and to this solution was added dropwise 2.888 g (0.01660 mol) of diethyl azodicarboxylate in 5 mL of dry benzene. After standing at room temperature for 2 days, the benzene was removed under vacuum. The oily residue was chromatographed on alumina. Elution with benzene gave 2.33 g (41.8%) of 2-[phenyl(*N,N'*-dicarboethoxyhydrazinyl)methylene]-1,3-dioxolane (**15**): mp 138–139.5 °C; IR (Nujol) 3300 (NH), 1750, 1710 (C=O), and 1665 cm^{-1} (C=O); NMR (CDCl$_3$) δ 1.23 (t, 6 H), 4.16 (q, 4 H), 4.35 (m, 4 H), 6.97–7.75 (m, 6 H).

Anal. Calcd for C$_{16}$H$_{20}$N$_2$O$_6$: C, 57.13; H, 5.99; N, 8.32. Found: C, 57.36; H, 6.02; N, 8.36.

The NMR spectrum of the crude reaction mixture showed a singlet at 4.40 ppm, suggesting the presence of a 5,6-dihydrooxadiazine, but this compound could not be isolated.

Reaction of Ketene Diethyl Thioacetal with Dimethyl Azodicarboxylate. Dimethyl azodicarboxylate (1.269 g, 8.690 mmol) was dissolved in 5 mL of anhydrous benzene and added dropwise to a solution of ketene diethyl thioacetal (1.276 g, 8.690 mmol) in 5 mL of dry benzene. The temperature rose to 37 °C. After standing at room temperature for 3 days, the solvent was evaporated. A portion (0.6221 g) of the residue was chromatographed on alumina. Elution with chloroform gave 0.3481 g (55.9%) of pure 1,1-diethylthio-2-(*N,N'*-dicarbomethoxyhydrazinyl)ethylene (**16a**) as an oil: IR (neat) 3210 (NH), 1725, 1700 (C=O), and 1650 cm^{-1} (C=C); NMR (CDCl$_3$) δ 1.18 (t, 3 H), 1.21 (t, 3 H), 2.67 (q, 2 H), 2.78 (q, 2 H), 3.71 (s, 3 H), 3.78 (s, 3 H), 7.17 (s, 1 H), 7.53 (bs, 1 H).

Anal. Calcd for C$_{10}$H$_{18}$N$_2$O$_4$S$_2$: C, 40.80; H, 6.16; S, 21.73. Found: C, 40.66; H, 5.98; S, 21.94.

Reaction of Phenylketene Diethyl Thioacetal with Dimethyl Azodicarboxylate. Dimethyl azodicarboxylate (1.317 g, 9.020 mmol) was dissolved in 5 mL of anhydrous benzene and added dropwise to a solution of phenylketene diethyl thioacetal (2.021 g, 9.202 mmol) in 10 mL of dry benzene. After standing 2 days at room temperature, the solvent was removed and a portion (0.553 g) of the residue was chromatographed on alumina. Elution with benzene–chloroform (1:1) gave 0.498 g (90.1%) of 1,1-diethylthio-2-phenyl-2-(*N,N'*-dicarbomethoxyhydrazinyl)ethylene (**16b**) as a viscous oil: IR (neat) 3290 (NH) and 1725 cm^{-1} (C=O); NMR (CDCl$_3$) δ 1.11 (t, 3 H), 1.28 (t, 3 H), 2.62 (q, 2 H), 2.87 (q, 2 H), 3.6 (s, 3 H), 3.7 (s, 3 H), 6.91 (bs, 1 H), 7.17–7.50 (m, 5 H).

Anal. Calcd for C$_{16}$H$_{22}$N$_2$O$_4$S$_2$: C, 5187; H, 5.98; N, 7.56; S, 17.30. Found: C, 51.47; H, 6.02; N, 7.47; S, 17.51.

Reaction of 1,1-Di(*N*-piperidinyl)ethylene with Dimethyl Azodicarboxylate. Dimethyl azodicarboxylate (1.746 g, 0.01145 mol) in 5 mL of anhydrous benzene was added dropwise to a solution of 1,1-di(*N*-piperidinyl)ethylene (2.415 g, 0.01195 mol) in 10 mL of dry benzene. The temperature rose to 43 °C. After standing 3 days, the benzene was removed and a portion (1.751 g) of the crude reaction mixture was chromatographed on alumina. Elution with benzene gave 0.1647 g (9.4%) of acetylpiperidine. Elution with chloroform gave 0.1080 g (6.2%) of 2-methoxy-4-carbomethoxy-6,6-di(*N*-piperidinyl)-5,6-dihydrooxadiazine (**18**): mp 161–162.5 °C (from chloroform–ether, 1:1): IR (Nujol) 1778 (C=O) and 1620 cm^{-1} (C=N); NMR (CDCl$_3$) δ 1.72 (b, 12 H), 3.46 (b, 8 H), 3.60 (s, 3 H), 3.72 (s, 3 H), and 3.75 (s, 2 H); UV (CHCl$_3$) λ 277 (E 4.92 × 10^4) 308 nm (E 5.67 × 10^4).

Anal. Calcd for C$_{16}$H$_{28}$N$_4$O$_4$: C, 56.48; H, 8.20; N, 18.98. Found: C, 55.65; H, 7.70; N. 18.98.

Further elution with chloroform gave 0.7115 g (40.6%) of *N,N'*-dicarbomethoxyhydrazinylacetylpiperidine (**17b**): mp 159–160 °C (from chloroform–ether 1:1): IR (Nujol) 3180 (NH), 1725, and 1710 cm^{-1} (C=O); NMR (CDCl$_3$) δ 1.60 (b, 6 H), 3.27–3.48 (b, 4 H), 3.70 (s, 6 H), 4.30 (s, 2 H), 7.20 (s, 1 H).

Anal. Calcd for C$_{11}$H$_{19}$N$_3$O$_5$: C, 48.43; H, 7.00; N, 15.37. Found: C, 48.13; H, 7.05; N, 15.04.

Reaction of 1,1-Di(*N*-morpholinyl)ethylene with Diethyl Azodicarboxylate. Diethyl azodicarboxylate (2.202 g, 0.01266 mol) was dissolved in 5 mL of dry benzene and this solution was added dropwise to 2.507 g (0.01266 mol) of 1,1-di(*N*-morpholinyl)ethylene in 10 mL of dry benzene. The temperature rose to 47 °C. After standing at room temperature for 3 days, the benzene was removed and a portion (1.745 g) of the residue was chromatographed on alumina. Elution with chloroform gave 1.054 g of an oil. A portion (0.6904 g) of this oil was rechromatographed. Elution with benzene–chloroform (4:1) gave 0.2144 g (31.1%) of acetylmorpholine. Elution with

benzene–chloroform (2:1) gave 0.2455 g (17.6%) of *N,N'*-dicarbo-ethoxyhydrazinylacetylmorpholine (**17a**): mp 124–125 °C; IR (Nujol) 3340 (NH), 1750, 1730, and 1662 cm^{-1} (C=O); NMR (CDCl$_3$) δ 1.30 (t, 6 H), 3.63 (b, 8 H), 4.20 (q, 4 H), 4.36 (s, 2 H), 7.21 (b, 1 H).

Anal. Calcd for C$_{12}$H$_{21}$N$_3$O$_6$: C, 47.51; H, 6.97; N, 13.85. Found: C, 47.80; H, 7.20; N, 13.71.

Reaction of Dimethylketene Dimethyl Acetal with Dimethyl Azodicarboxylate. Dimethyl azodicarboxylate (2.292 g, 0.01570 mol) was dissolved in 10 mL of anhydrous benzene and added dropwise to a solution of dimethylketene dimethyl acetal (1.821 g, 0.01570 mol) in 10 mL of dry benzene. After standing at room temperature for 1 day, the solvent was removed under vacuum. The resulting oil was triturated with carbon tetrachloride and the resulting precipitate filtered. Recrystallization from petroleum ether–ether (2:1) gave 2.8 g (68.2%) of 2-methyl-3,3-dimethoxy-3-(*N,N'*-dicarbomethoxyhydrazinyl)propene-1 (**19**): mp 101–102 °C; IR (Nujol) 3320 (NH), 1765, 1710 (C=O), and 1565 cm^{-1} (C=C); NMR (CDCl$_3$) δ 1.72 (s, 3 H), 3.13 (s, 3 H), 3.27 (s, 3 H), 3.70 (s, 6 H), 5.31 (s, 1 H), 5.40 (s, 1 H), 6.82 (bs, 1 H).

Anal. Calcd for C$_{10}$H$_{18}$N$_2$O$_6$: C, 45.79; H, 6.91; N, 10.68. Found: C, 45.99; H, 6.95; N, 10.65.

Deuterated Benzyl Cyanide. Freshly distilled benzyl cyanide (20 g, 0.1702 mol) was dissolved in 68 mL of anhydrous benzene, and a solution of sodium deuterioxide, prepared from 3.57 g (0.155 g-atom) of sodium and 68 g (3.4 mol) of heavy water, was added along with 1.95 g of Aliquat 336. The reaction mixture was stirred 40 min at room temperature and then was neutralized with ammonium chloride solution in heavy water. The benzene layer was separated and dried over anhydrous magnesium sulfate. The deuterated benzyl cyanide was distilled under reduced pressure, bp 106–107.5 °C (12 mm). The NMR (CCl$_4$) showed only the peak at 7.25 ppm for the aromatic hydrogens.

Deuterated Methyl Phenyliminoacetate Hydrochloride. Deuterated benzyl cyanide (17.8 g, 0.1495 mol) was dissolved in 5.25 g (0.1641 mol) of anhydrous methanol and the solution cooled in an ice bath. A stream of hydrogen chloride was bubbled through the mixture until 5.5 g had been absorbed. Anhydrous ether (56 mL) was added and the mixture refrigerated overnight. The product was filtered and washed with anhydrous ether until neutral and then dried in a desiccator over sodium hydroxide: yield 21.3 g (76%); IR (Nujol) 3320 (NH) and 1635 cm^{-1} (C=N); NMR (CDCl$_3$) δ 4.27 (s, 3 H) and 7.40 (s, 5 H).

Deuterated Methyl Orthophenylacetate. Deuterated phenyl-iminoacetate hydrochloride (21.3 g, 0.1511 mol) was dissolved in 25 mL of absolute methanol and the mixture allowed to stand 2 days at room temperature. Anhydrous ether (13 mL) was added and the ammonium chloride which precipitated was filtered. The solvent was evaporated from the filtrate and the residue was distilled from sodium hydride: yield 8.9 g (22.5%); bp 118–119 °C (5 mm) (lit.[61] bp 73–76 °C (0.4 mm)); NMR (CCl$_4$) δ 3.16 (s, 6 H) and 7.17 (s, 5 H).

Deuterated Phenylketene Dimethyl Acetal. Deuterated methyl orthophenylacetate (8.90 g, 0.0449 mol) was mixed with 5.40 g (0.0450 mol) of anhydrous aluminum methoxide and the mixture heated in an oil bath at 210 °C. When the evolution of alcohol ceased, the pressure was lowered and the residue fractionated through a 30 cm vacuum jacketed column: yield, 2.2 g (28.3%); bp 72–73 °C (0.9 mm); IR (neat) 1640 cm^{-1}; NMR (CDCl$_3$) δ 3.62 (s, 3 H), 3.72 (s, 3 H), and 3.26 (s, unreacted orthoester). The material obtained contained about 19% unreacted methyl orthophenylacetate.

Registry No.—**3a**, 66769-46-8; **3b**, 66750-48-9; **4a**, 66750-49-0; **5b**, 66750-50-3; **6a**, 66750-51-4; **6b**, 66750-52-5; **6c**, 66750-53-6; **6d**, 66750-54-7; **8c**, 66750-55-8; **8d**, 66750-56-9; **9c**, 66750-57-0; **9d**, 66750-58-1; **10a**, 66750-59-2; **10b**, 66750-60-5; **10c**, 66750-61-6; **10d**, 66750-33-2; **15**, 66750-34-3; **16a**, 66750-35-4; **16b**, 66750-36-5; **17a**, 66750-37-6; **17b**, 66750-38-7; **18**, 66750-39-8; **19**, 66750-40-1; ketene dimethyl acetal, 922-69-0; dimethyl azodicarboxylate, 2446-84-6; methyl glyoxylate *N*-carbomethoxyhydrazone, 66750-41-2; dimethyl tartrate, 608-68-4; methyl carbazate, 6294-89-9; methyl *N'*-carbo-methoxyhydrazinylacetate, 66750-42-3; diethyl azodicarboxylate, 1972-28-7; methyl glyoxyate *N*-carboethoxyhydrazone, 5576-74-9; diethyl tartrate, 87-91-2; methyl *N'*-carboethoxyhydrazinylacetate, 66750-43-4; ketene diethyl acetal, 2678-54-8; chloroketene diethyl acetal, 42520-09-2; bromoketene diethyl acetal, 42520-11-6; phenyl-ketene dimethyl acetal, 13049-41-7; 2-phenylmethylene-1,3-dioxo-lane, 4362-17-8; ketene diethyl thioacetal, 4992-59-0; phenylketene diethyl thioacetal, 66750-44-5; 1,1-di(*N*-piperidinyl)ethylene, 42259-31-4; *N*-acetyl piperidine, 618-42-8; 1,1-di(*N*-morpholinyl)-ethylene, 14212-87-4; *N*-acetylmorpholine, 1696-20-4; dimethylketene dimethyl acetal, 5634-54-8; benzyl-α,d_2 cyanide, 935-66-0; benzyl cyanide, 140-29-4; PhCD$_2$C(NH)OMe·HCl, 66750-45-6;

PhCD$_2$C(OH)$_2$OMe, 66750-46-7; phenylketene-2-*d*-dimethyl acetal, 66750-47-8.

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Periodate Oxidation of α-Keto γ-Lactams. Enol Oxidation and β-Lactam Formation. Mechanism of Periodate Hydroxylation Reactions

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Periodate oxidation of α-keto γ-lactams results in β-lactam formation by oxidative ring contraction and in two modes of enol oxidation. The relative rates of these oxidation paths are related to electron distribution over the three-atom portion comprising the α-keto group and the β carbon, as demonstrated by the dependence of oxidation rate and product distribution on the electronic properties of the β substituent. Depending on the β substituent, some α-keto γ-lactams are also oxidized by iodate. The two modes of enol oxidation and the factors which determine which mode predominates appear to provide a unified mechanistic interpretation for periodate hydroxylation reactions in general.

The formation of β-lactams **2** from α-keto γ-lactams **1** by oxidative ring contraction with periodate has been shown to be compatible with the presence of several substituents, X = H, CH$_3$, and Br, on the β carbon of **1**,[1] and factors which appear to influence stereochemistry have been discussed.[2]
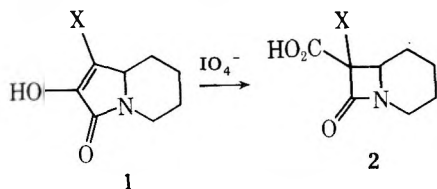
During investigations of the scope of this reaction with regard to variation of the β-substituent X, a potential precursor of a cephalosporin analogue, γ-lactam **3**, was prepared.[3] Conversion as described previously[1] gave the α-keto lactam **4**, but periodate oxidation of **4** led to no evidence for the presence of a β-lactam.[4]
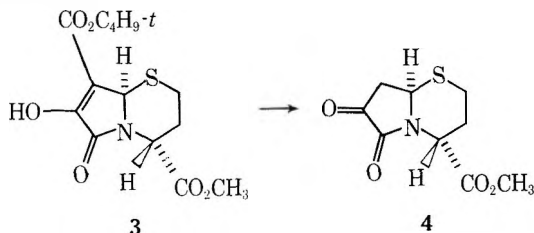
To preclude the possibility of decomposition of products under the acidic isolation conditions, we sought a method for converting acidic materials to neutral species directly in the aqueous medium in which oxidation occurs, thus allowing isolation by rapid extraction while maintaining the pH around neutrality. A procedure which appeared applicable is the esterification of carboxylic acids with triethyloxonium fluoroborate (TEOF) in neutral or slightly alkaline aqueous solution.[5]

During the development of this procedure for isolation of products from the oxidation, bromolactam **5** was oxidized and the reaction solution was treated with TEOF to yield not only the expected β-lactam esters **6**, but also a new product which we have shown to be the oxalyl derivative **7**, the product of enol oxidation of **5**. Also, oxidation of **4** followed by treatment of the reaction solution with TEOF gave only a low yield of β-lactam.[4] This result, along with the apparent preclusion of decomposition of any β-lactams produced, forced a consideration of periodate oxidation reactions which could be competitive with rearrangement. With the establishment of structure **7**, an investigation of enol oxidation of compounds of type **1** was undertaken, the results of which are the subject of this report.

The variety of periodate hydroxylation reactions is large.[6,7] These reactions are usually referred to as active methylene,

Scheme I. Proposed[8] Mechanism for Enol Oxidation by Periodate
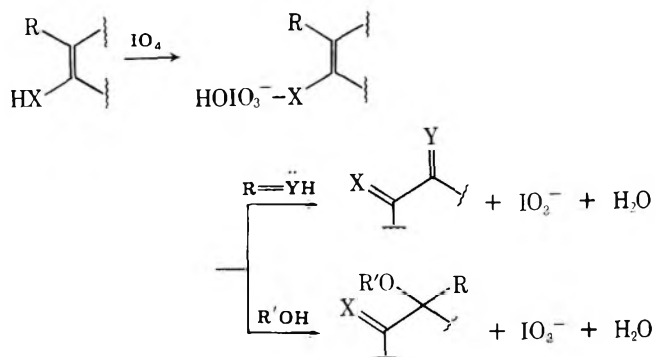
enol, and non-Malapradian oxidation, or "over-oxidation", or by reference to the entire molecular structure, e.g., oxidation of reductones, phenols, and flavonols. The analogy of the oxidation of the latter compounds to that of simple enols has been pointed out,[6] and a mechanism (Scheme I) for the oxidation of these enolic compounds has been proposed,[8] but a unified mechanistic picture encompassing periodate hydroxylation reactions in general has remained unknown.

The oxalyl products (**10** and **7**) of enol oxidation of enols **1** (X = CH$_3$ and Br) are readily accommodated by the proposed mechanism, which allows for the possibility that hydroxylic solvent is necessary for oxidation. A consequence of this possibility is that exclusion of hydroxylic solvent could leave oxidative rearrangement as the only remaining reaction. But enol **8** in chloroform solution was unreactive in the presence of tetrabutylammonium periodate, and the addition of methanol, while allowing for oxidation, led to no β-lactam formation and also gave none of the β-methoxy-α-keto γ-lactam **11**, the expected product if oxidation had taken place according to Scheme I. This result suggested the existence of an alternative mechanism for enol oxidation.

It has been noted that monocyclic α-keto γ-lactams analogous to the bicyclic lactams **1** with X = CH$_3$ and Br (**8** and **5**) display phenolic properties[9] and that the acidity of monocyclic lactams analogous to **1** with X = CO$_2$C$_2$H$_5$ (**18**) is comparable to that of carboxylic acids.[10] The similarity in properties of the bicyclic analogues **1** to those of the monocyclic compounds has been amply demonstrated.[1] Whereas the methyl and bromo analogues of **1** gave good yields of β-lactam when oxidized by periodate, the ethoxycarbonyl analogue **18** rapidly consumed more than 100 mol % of periodate with complete exclusion of the ring contraction reaction. This result suggested an inverse relationship between enol oxidation and oxidative rearrangement rates, with both rates depending on enol acidity, this in turn being influenced by the β substituent, X.

To complete a spectrum of lactams 1 with X having varying electronic properties, the methoxy analogue 15 was prepared. Oxidation of 15 proceeded rapidly, but again with complete exclusion of the rearrangement reaction. Whereas the oxalyl product 16 from the oxidation of 15 is accommodated by the proposed mechanism for enol oxidation[8] (as are the products of enol oxidation of 1 with X = CH₃ and Br), the formyl product 19, isolated after more thorough examination of the oxidation of ethoxycarbonyl analogue 18, is not. This result allows for the proposal of two mechanisms by which the enols 1 are oxidized, with the relative rates of these two enol oxidation modes and of oxidative rearrangement depending upon electron distribution over the three-atom enolic system. Having two oxidation modes available for rationalization of enol oxidation also provides for the possibility of developing a unified explanation for periodate hydroxylation reactions.

Results

Initial investigations of the scope of the oxidative ring contraction reaction were directed only to the question of whether or not oxidation would produce a β-lactam, and continuous extraction at pH 2 was a reliable method for isolation of the product β-lactam acids. Application of this procedure to isolation of products from the oxidation of bromo analogue 5 gave both cis and trans β-lactam acids, but in only 40% yield.[1] Oxidations at pHs greater or less than 6.3 reduced the yield, and oxidation at pH 5 completely eliminated the rearrangement reaction. A striking but apparently dissimilar dependence of β-lactam yield on pH during oxidation was also observed during oxidation of the unsubstituted keto lactam 21. β-Lactam yield was reduced to 50% at pH 7 and 25% at pH 8–9, although decreasing the pH to 4 reduced the yield only slightly. At pH 6.3, ethoxycarbonyl analogue 18 consumed >100 mol % of periodate and yielded no β-lactam.

Oxidation of 5 in the usual way, but followed by treatment of the reaction solution with TEOF and extraction at neutral pH, yielded three products: both isomers of β-lactam 6 and a third product, 7. The mass spectrum of 7 clearly indicated
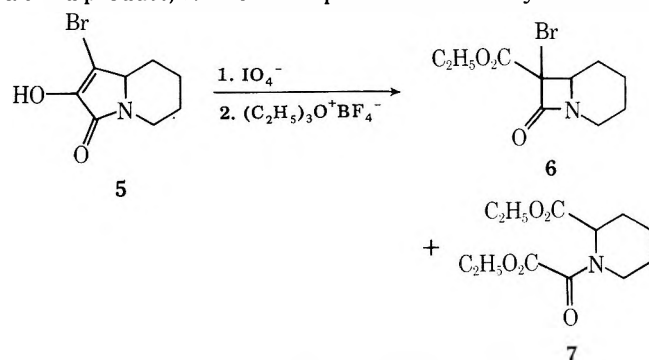
absence of bromine, the NMR spectrum showed multiple ethoxy absorptions, and absorptions consistent with the presence of ester and amide functionalities were present in the IR. These data along with the mass spectral fragmentation pattern and composition data pointed to structure 7, and it was characterized unambiguously by synthesis from ethyl pipecolate and ethyl oxalyl chloride.

Oxidation of methyl analogue 8 was then reexamined in the light of these results with 5. Methyl ketone 10 is expected if enol oxidation of 8 takes place similarly to oxidation of 5, and material with spectral and composition data consistent with structure 10 was indeed isolated. This assignment was confirmed by synthesis of 10 starting with pipecolic acid. It was necessary to block the carboxyl function as its benzyl ester before acylation with ethyl oxalyl chloride. Hydrogenolysis was followed by formation of the imidazolide, and treatment of the latter with the magnesium salt of *tert*-butyl hydrogen
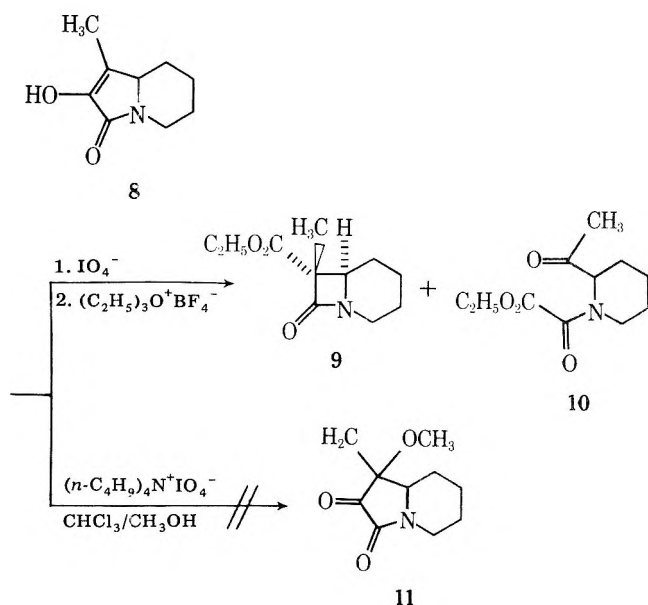
malonate gave the β-keto ester. Cleavage of the *tert*-butyl ester and decarboxylation gave the desired methyl ketone 10.
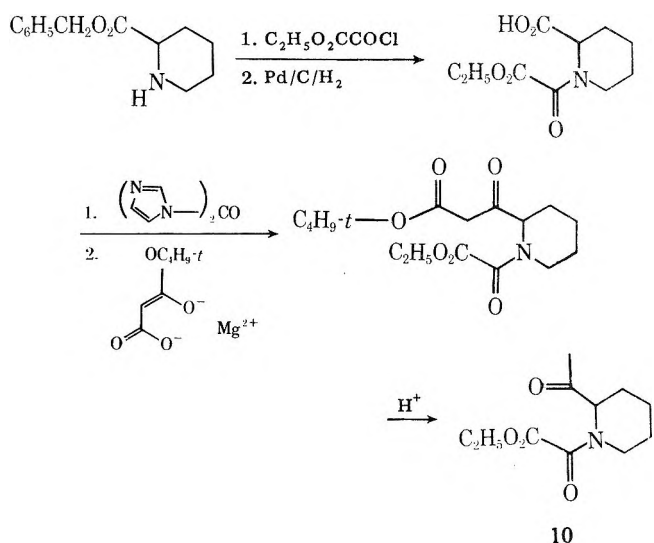
The methyl analogue 8 provided a convenient compound for an examination of the effect of conditions on mode of oxidation. The methyl group NMR absorptions for 8 and for either of the products 9 or 10 are all distinctly different, allowing determination of the oxidation mode by analysis of the crude product. Oxidation of 8 with hydrated periodic acid (H₅IO₆) in tetrahydrofuran (THF) or in aqueous acetic acid stopped after consumption of only 100 mol % of periodate, but the methyl absorptions of crude product corresponded to the presence of a methyl ketone. The phenolic character of 8 and the known reactivity of phenols with iodate suggested invoking enol oxidation by iodate followed by α-hydroxy ketone cleavage by periodate. This invocation remains at least in part equivocal, but it did call attention to the reactivity of enols 1 with iodate, which will be considered later.

The proposed mechanism for enol oxidation (Scheme I)[8] calls for participation of hydroxylic solvent in the reaction, and investigations of the oxidation of flavonols,[11] phenols[12,13] and indoles[14] support this view. On the other hand, the proposed mechanism for oxidative rearrangement[15] does not involve solvent participation. We therefore investigated the oxidation of 8 under anhydrous conditions with tetrabutylammonium periodate in chloroform,[16] determining the concentration of periodate from its UV extinction at 223 nm. (The salt was not isolated since solid tetraethylammonium per-

iodate is an explosive substance.[17]) Enol 8 was unreactive under these conditions, there being no consumption of periodate over a 2-h period. Addition of methanol allowed for oxidation,[18] but as was the case with periodic acid in THF or in aqueous acetic acid, only 100 mol % of periodate was consumed, and an IR spectrum of the solution gave absorptions consistent with a product similar to structure 10. The characteristic β-lactam carbonyl absorption was absent, and absence of the high-frequency ketone absorption expected for the β-disubstituted-α-keto γ-lactam 11 suggested that oxidation had not taken place according to Scheme I. The existence of an alternative mechanism for enol oxidation by periodate was again indicated.

Regardless of the nature of this alternative mechanism, it was necessary to know the effect on ring contraction of an electron-donating group at the β carbon of 1. We therefore sought the methoxy analogue 15, which was prepared by the imine-addition approach in a manner analogous to the preparation of methyl analogue 8.[1] Treatment of *tert*-butyl methoxyacetate with lithium cyclohexylisopropylamide, followed by condensation with diethyl oxalate gave the methoxy-substituted oxalacetate 12 in 60% yield. Condensation of 12 with Δ[1]-piperideine (13) proceeded rapidly even at 0 °C
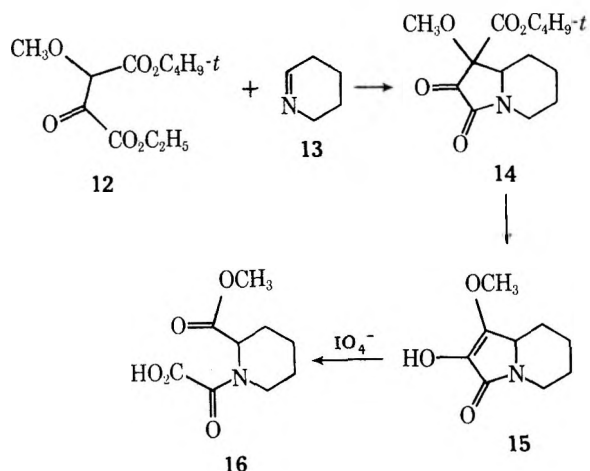
to give 14 in 30% yield. Treatment of 14 with acetic acid saturated with HBr led directly to 15, a crystalline material which was unstable to air. The spectral properties of 14 and 15 are similar to those of previously reported analogues,[1] and the NMR absorption at δ 4.2 for the methoxy group of 15 is noteworthy in that it occurs significantly downfield relative to that observed for aromatic methoxy groups.

Oxidation of 15 at pH 6.3 with 200 mol % of periodate resulted in complete consumption of periodate within a few minutes and gave glyoxylic acid 16 in 65% yield (based on 14), isolated by extraction at pH 2 of the sodium chloride saturated reaction solution. No evidence of β-lactam formation was found. Acid 16 was identical with material previously isolated
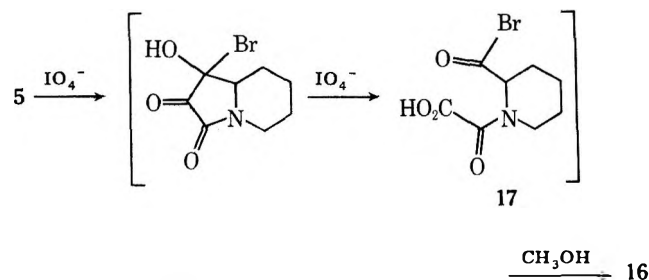
after oxidation of 5 under neutral aqueous conditions in the presence of methanol. In the latter case 16 presumably was formed via the acid bromide 17, since 5 is unreactive toward methanol, even at reflux.

A pattern in terms of both oxidation rate and product dis-

Scheme II. Application of Enol Oxidation Mechanism of Scheme I to α-Keto γ-Lactams 1, i.e., via Path a of Scheme III
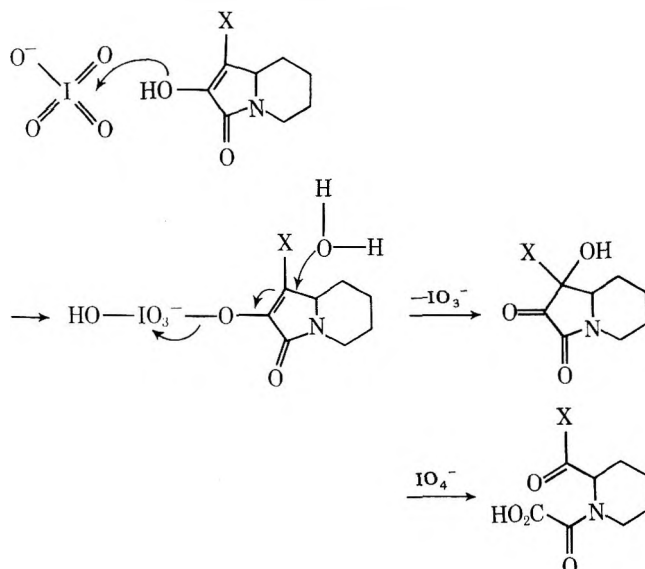
tribution was evident at this point. When oxidized by periodate in neutral aqueous solution, the methyl and bromo analogues, 8 and 5, consume 100 mol % of periodate and undergo both oxidative rearrangement and enol oxidation (Scheme II) with ~15 min required for completion of oxidation, whereas methoxy analogue 15 and ethoxycarbonyl analogue 18 consume an initial 200 mol % of periodate within a few minutes. The oxidative rearrangement reaction is excluded for both 15 and 18; 15 undergoes enol oxidation according to Scheme II, but the products of oxidation of 18 remained at this point undefined.

The oxidation of 18 was carried out by very rapid addition of a methanol solution of 18 to a vigorously stirred buffer containing 200 mol % of periodate. After recovery of 35% of starting material, a major product, 19, was isolated by chromatography. This slightly unstable oil differed in composition from 18 only by the absence of one carbon atom. The spectra of 19 resembled those of enol oxidation products 7, 10, and 16, with the notable exception that the NMR spectrum displayed a somewhat broadened singlet at δ 8.1, which remained after exposure of 19 to D₂O. On the basis of these data, this material was assigned structure 19. An alternative enol oxidation mechanism must then be operative, and the existence of this alternative mechanism is demonstrated further by the isolation of an analogous product 20 from the oxidation of methyl
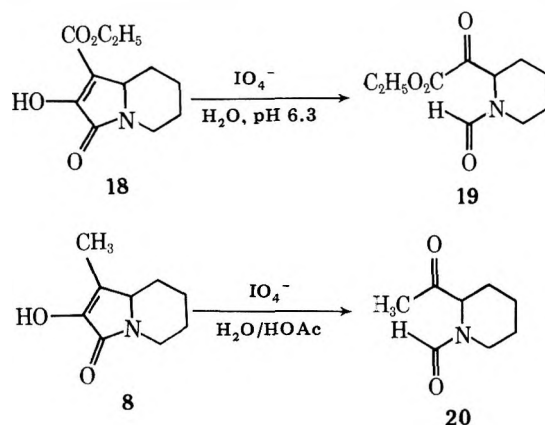
analogue 8 in aqueous acetic acid. The structural assignments for 19 and 20 are further supported by the presence of characteristic N-formyl absorptions in their ^{13}C NMR spectra, and the structure of 20 was confirmed by synthesis. Pipecolic acid was formylated by the mixed anhydride method, and the

Table I. Product Distribution from Periodate Oxidation of α-Keto γ-Lactams 1 in Water, pH 6.3

compd	registry no.	yield (%) of products from each oxidation mode			
		path a	registry no.	path b	path c
15	66551-93-7	65^a $(100)^b$	66551-94-8	0	0
5	54409-79-9	12^c $(60)^b$	66551-95-9	40	0
8	54409-78-8	45^d $(50)^b$	66551-96-0	50	0
21	35620-54-3	e		70	e
18	54409-76-6	0		0	$32^{f,g}$ $(100)^b$

[a] Isolated yield of 16, based on 14. [b] Projected yield; see text for discussion. [c] Isolated yield of 7. [d] Isolated yield of 10. [e] No attempt was made to account for remaining material. [f] Isolated yield of 19. [g] Registry no. 66551-97-1.

methyl ketone was prepared from the acid via the β-keto ester, as previously described.

Thus we find three possible oxidative modes for lactams 1. These are designated as enol oxidation path a (attack at enolic oxygen, Scheme II), ring contraction path b, and a new enol oxidation mode path c (attack at enolic carbon). These three modes are depicted in Scheme III, and the yields of products from the various lactams are summarized in Table I. Yields of β-lactam (path b) refer to isolation of the product as carboxylic acid;[1] yields in parentheses are projected yields with qualifications as discussed below.

The isolated yield of oxamic acid 16 from oxidation of methoxylactam 15 was 65%, based on 14; however, 15 decomposed in part during isolation. It is therefore likely that all of 15 which reacted with periodate was oxidized via path a, particularly in view of the absence of β-lactam formation.

From the oxidation of bromolactam 5, β-lactam esters 6 were isolated in 26% yield, and oxalyl derivative 7 was isolated in only 12% yield. However, saturation of the reaction solution with salt and extraction at pH 2 gave an additional 35% yield of a mixture of β-lactam acids and ester–acids of 7. This result and the phenolic character of 5 suggests that none of 5 was enol oxidized via path c.

Oxidation of methyllactam 8, followed by esterification, gave β-lactam 9 and methyl ketone 10 in 35 and 45% yield, respectively, for a combined yield of 80%, which corresponds with reported yields for esterification.[5] All present oxidations were carried out by adding substrate as a solution in methanol (or in THF, in the case of 5), a procedure which lowers slightly the yield of β-lactam, whereas the yields of β-lactam (path b)

Scheme III. Periodate Oxidation Modes for α-Keto γ-Lactams 1

given in Table I are from oxidation without use of cosolvent. The presumed enol oxidation yields from 5 and 8 are projected to no cosolvent reactions. In view of these yields, it appears that 8 was oxidized via its enol under these conditions only via path a, as in the case of 5.

Considering the procedure used for the production of formyl derivative 19, this compound is quite likely the initial product of oxidation of ethoxycarbonyllactam 18. Reexposure of 19 to the oxidation conditions resulted in further oxidation as would be expected since 19 is an α-ketoacyl derivative. Regardless of whether 19 is the only initial product of oxidation, the absence of β-lactam formation and the pattern revealed by oxidation of the other lactams 1 suggest that 18 was oxidized only via path c.

As noted earlier, the initially inexplicable results of the oxidation of 8 with periodic acid in THF or in aqueous acetic acid, or with tetrabutylammonium periodate in chloroform/methanol, suggested that iodate, formed on initial oxidation by periodate, might be involved in some essential way. This proposal prompted a cursory examination of the reactivity of enols 1 with iodate. Both analogues 5 and 8 were oxidized by iodate in aqueous acetic acid, whereas the more acidic analogue 18 was unreactive (analogues 15 and 21 were not tested). Since 5 gave dibromo compound 22, the oxidation very likely

proceeds via a radical mechanism.[19] The extent to which oxidation by iodate competes with oxidation by periodate under acidic or nonaqueous conditions was not determined, but it appears that these conditions allowed for a relatively rapid oxidation of 8 by the iodate initially produced.

The possibility that other glycol cleaving reagents might be capable of inducing oxidative rearrangement was investigated. Exposure of methyl analogue 8 to sodium bismuthate in acetic acid containing phosphoric acid, and to lead tetraacetate in acetic acid, resulted in oxidation, but no β-lactam formation. The same was true for oxidation of the unsubstituted analogue 21 with lead tetraacetate in acetic acid.

Discussion

The enolic portion of lactams 1 offers three atoms at which oxidation could be initiated: the enolic oxygen, the α carbon (C-8), and the β-enolic carbon (C-7). In the case of methoxy analogue 15, the methoxy group on the β carbon can be expected to induce increased electron density on the enolic oxygen, while in the case of ethoxycarbonyl analogue 18, the opposite effect of electron withdrawal would lead to increased electron density on the β carbon. For the analogues 5, 8, and 21 electron distribution over the three-atom enolic system would be intermediate between the extremes represented by 15 and 18.

A frequently proposed path for enol oxidation[6,8] begins with oxidation of the enolic oxygen by formation of a periodate ester as depicted in path a of Scheme III. Oxidative rearrangement to β-lactams **2** involves oxidation at the α carbon (C-8), as indicated in path b of Scheme III. We propose that the alternative mechanism for enol oxidation, the mechanism by which ethoxycarbonyl analogue **18** is oxidized, begins with oxidation of the β-enolic carbon (C-7) as indicated in path c of Scheme III. The relative rates of oxidation via each of the three paths a, b, and c can then be viewed as depending on electron density at each of the three atoms of the enolic portion of **1**.

A generalized form of oxidation via path a of Scheme III is given in Scheme I. For oxidation of reductone-like structures, X = Y = oxygen. For oxidation of compounds such as phenols and flavonols, X = oxygen and R does not equal a heteroatom bonded to a proton. When the reductone-like compound, catechol, was oxidized in $H_2^{18}O$, the resulting quinone was not labeled; however similar oxidation of a water-soluble guaiacol derivative (R = OCH_3; X = O) led to incorporation of label into the resulting quinone and not into the methanol released during oxidation.[8] The mechanism depicted in Scheme I gains further support in that it explains the products obtained from the oxidation of flavonols[11b] and some types of phenols[12,13] with periodic acid in methanol, and the oxidation of indoles with sodium periodate in aqueous methanol has been rationalized by invoking a variant of this mechanism in which X = N.[14] Numerous other periodate hydroxylation reactions can be viewed as proceeding via some variant of Scheme I.[6]

Application of the mechanism depicted in Scheme I to oxidation of lactams **1** is illustrated in Scheme II. Solvent attack at C-7 of the intermediate periodate ester would result in an α-hydroxy ketone which in turn would be oxidized in a classical manner to yield an oxalyl residue on the nitrogen and a carbonyl oxygen on what began as C-7 of **1**. This mechanism accounts for the exclusive product obtained from the 7-methoxy compound **15**, and the non-β-lactam products obtained from the 7-bromo and 7-methyl compounds **5** and **8** when oxidized under neutral conditions.

The proposed mechanism for oxidative rearrangement (path b of Scheme III) has been discussed[15] and involves oxidation of the α carbon (C-8) via two types of key intermediates, illustrated by structures **25** and **26** for the examples of lactams **1**. Oxidation via a hydroxycyclopropenone was invoked as a minor pathway in order to explain some scrambling of label in the product obtained from oxidation of 2-^{14}C-1-

25   **26**

21   **1**, X ≠ H   **27**
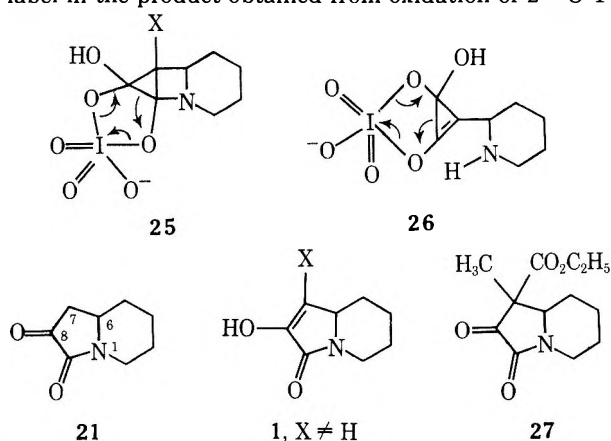
methyl-2,3-piperidinedione.[15] The proposed minor pathway cannot be operative unless both substituents on C-7 are hydrogen.

Neither oxidative rearrangement nor enol oxidation (either mode) can take place unless at least one proton is present on the β carbon (C-7). Thus lack of reactivity toward periodate observed in the case of the β-disubstituted derivative **27** not

Scheme IV. Mechanism of Enol Oxidation of α-Keto γ-Lactams 1 via Path c of Scheme III

24

29   ⇌   **28**

30
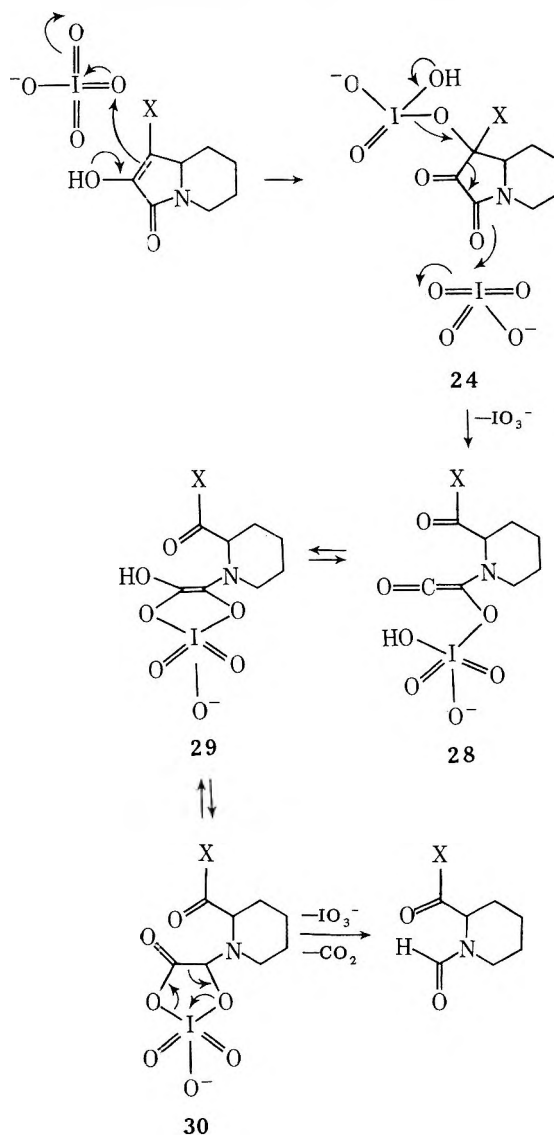
only confirms the inability of such a compound to undergo either rearrangement or hydroxylation but also indicates a resistance toward classical α-diketone-like cleavage.

Enol oxidation according to path c of Scheme III can be viewed as an example of the indicated general pattern[6] in which $R_nC^{δ-}$ is added to the already known examples of Z = N, P, or S.

$$R_nZ: + IO_4^- \rightarrow R_nZ = O + IO_3^-$$
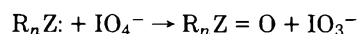
This generalization has been applied to sulfoxide formation[20] and oxidation of polycyclic aromatic hydrocarbons,[21] and the same representation has been offered as one of several rationalizations of some phenol oxidation results which appear anomalous without some alternative to oxidation via path a of Scheme III.[12]

Application of this generalization to oxidation of lactams **1** is depicted in Scheme IV. In most cases the only available path for collapse of an intermediate such as **24** would be to leave the electron pair on the C-7 oxygen, protonation of which would lead, for the case of lactams **1**, to the same α-hydroxy ketone produced according to Scheme II. But in the case of lactams **1**, the juxtaposition of the lactam carbonyl allows for an alternative mode of collapse which in turn allows for an alternative mode for a second oxidation step. Collapse of **24** as indicated in Scheme IV is aided by a concomitant oxidation to the periodate ester **28**, which in turn could form the cyclic

intermediate **29**. Tautomerization of **29** leads to **30**, which can now collapse to product by expulsion of carbon dioxide and iodate. This mechanism accounts for the products formed from the 7-ethoxycarbonyl compound **18** when oxidized under neutral aqueous conditions and from the 7-methyl compound **8** when oxidized under acidic conditions.

The products obtained from lactams **1** when oxidized under neutral aqueous conditions demonstrate the influence exerted by the β-substituent X on the relative rates of oxidation via the paths a, b, and c of Scheme III. The influence of the reaction medium on these relative rates is illustrated by isolation of products of all three paths from oxidation of methyl analogue **8**: under neutral aqueous conditions paths a and b were followed, whereas under acidic conditions the oxidation mode changed to path c.

The potential of the dual mechanism picture provided by enol oxidation paths a and c of Scheme III for development of a unified explanation for periodate hydroxylation reactions is clear from consideration of the morass of reactions referred to in the carbohydrate literature as non-Malapradian or "over-oxidation" reactions. Reactions to which these names are attached generally involve oxidation of substituted or unsubstituted malonaldehydes, malonic acids, and related derivatives. Using malonaldehydes as the example, these compounds are generally one or the other of two types, **31** or **32**. Comparison with lactams **1** reveals **32** as analogous to lactam **18** in that both contain an electron withdrawing group positioned so as to induce increased electron density on the α carbon of the enol (the middle carbon of **32**). On the other hand, the substituted malonaldehyde **31** contains an electron donating oxygen substituent in addition to the electron withdrawing aldehyde. Thus it would not be surprising if compounds such as **31** display reactivity analogous to that of enols **15**, **5**, and **8**, reacting with periodate via path a of Scheme III and showing substantial reactivity toward iodate. It would likewise be expected that compounds such as **32** would display reactivity analogous to that of **18**, reacting with periodate via path c of Scheme III and showing greatly reduced or no reactivity toward iodate. Although the initial product from com-

pounds such as **31** or **32** when oxidized by periodate in aqueous medium would be the same in any case, the reactivity patterns generally observed[22] correspond to those expected.
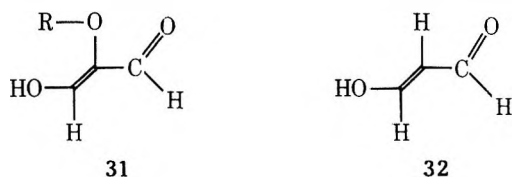
Experimental Section[23]

Oxidation of 7-Bromo-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]-non-7-ene (5). Lactam **5**[1] (1.3 g, 5.5 mmol) was added as a solution in THF (20 mL) over 10 min to a rapidly stirred buffer prepared as described previously (0.2 M, pH 6.3, 275 mL)[1] containing NaIO₄ (2.35 g, 11.0 mmol) and cooled to 6–7 °C. After completion of oxidation the solution was treated at room temperature with TEOF[24] (45 g, 230 mmol), added in portions over 40 min with pH maintained at 6–7 by addition when needed of NaHCO₃. The solution was then extracted with ethyl acetate (3 × 100 mL), and the combined extracts were washed with brine, dried (MgSO₄), and evaporated. Chromatography of the residue on silica gel (40 g) with CHCl₃ and then on kieselgel (150 g) with ether–petroleum ether (bp 30–60 °C) (3:1 v/v) gave ethyl oxalyl piperidide **7** (174 mg, 12%), the major isomer of **6** (348 mg, 23%), and the minor isomer of **6** (51 mg, 3%). NMR and IR spectra of the isomers of **6** corresponded where appropriate with the spectra of the corresponding methyl esters.[1] Ethyl oxalyl piperidide **7** was purified by bulb-to-bulb distillation at bath temperature 130 °C (0.01 mm): IR 1737, 1661 cm⁻¹; NMR δ 1.1–2.0 (11 H, m), 2.0–2.5 (1 H, m), 2.6–3.8 (2 H, m), 4.27 (4.4 H, m), 5.18 (0.6 H, m); mass spectrum *m/e* (rel intensity) 257 (M⁺, 6%), 220 (11), 184 (39), 176 (19), 156 (66), 128 (14), 91 (100).

Anal. Calcd for C₁₂H₁₉NO₅: C, 56.0; H, 7.4; N, 5.4. Found: C, 55.9; H, 7.4; N, 5.4.

Ethyl Oxalyl 2-Ethoxycarbonylpiperidide (7). Fuming sulfuric acid (20 mL, 15%) was added dropwise and with stirring to a solution of pipecolic acid (4.6 g, 36 mmol) in absolute ethanol (100 mL). The solution was refluxed for 20 h and then cooled. Aqueous sodium hydroxide (2 M, 200 mL) was added with cooling until the pH reached 6–7, followed by K₂CO₃ (41 g). The mixture was extracted with ether (3 × 150 mL) and the combined extracts were dried, evaporated, and distilled (bp 55 °C (1.4 mm) [lit.[25] bp 91–93 °C (9 mm)]) to yield 3.53 g (63%). Ethyl oxalyl chloride (273 mg, 2.0 mmol) in CH₂Cl₂ (1.0 mL) was added with stirring to the ethyl pipecolate (636 mg, 4.0 mmol) in CH₂Cl₂ (2.0 mL) at room temperature. After being stirred for 10 min, water (15 mL) and ether (15 mL) were added and the pH was adjusted to 2 with 10% HCl (1 mL), then the phases were shaken and separated. The ether layer was washed with saturated NaHCO₃ (10 mL) and then with brine (7 mL), dried (MgSO₄), and evaporated to yield 442 mg (86%) of **7**, identical with material obtained from the oxidation of bromo analogue **5** by NMR, IR, and TLC comparison.

Hydrogen Oxalyl 2-Methoxycarbonylpiperidide (16) from 5. From an oxidation of **5** in which **5** had been added as a solution in CH₃OH as described previously,[1] there was isolated by continuous extraction with CH₂Cl₂ at pH 2 a mixture of acids, part (418 mg) of which was chromatographed on kieselgel (25 g) with petroleum ether (bp 30–60 °C), ethyl acetate, acetic acid (18:27:5 v/v) to yield **16** (101 mg), which was recrystallized from CHCl₃–hexanes: mp 114–116 °C; IR 1740, 1727 (shoulder), 1660 cm⁻¹; NMR δ 1.1–2.0 (5 H, m), 2.0–2.5 (1 H, m), 2.7–3.7 (2 H, m), 3.87 and 3.90 (3 H, singlets), 4.33 (0.1 H, m), 4.57 (0.3 H, m), 5.27 (0.6 H, m), 10.9 (1 H, s); mass spectrum *m/e* (rel intensity) 215 (M⁺, 7%), 170 (59), 142 (34), 128 (88), 55 (100).

Anal. Calcd for C₉H₁₃NO₅: C, 50.2; H, 6.1; N, 6.5. Found: C, 50.2; H, 6.2; N, 6.6.

Oxidation of 7-Methyl-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]-non-7-ene (8). Ethyl Oxalyl 2-Acetylpiperidide (10). Lactam **8**[1] (200 mg, 1.2 mmol) was added as a solution in THF (4 mL) and CH₃OH (0.5 mL) over 10 min at room temperature to a rapidly stirred buffer prepared as described previously (0.2 M, pH 6.3, 60 mL)[1] containing NaIO₄ (514 mg, 2.4 mmol). After completion of oxidation (15 min) the solution was treated with TEOF (11 g, 84 mmol) as described in the oxidation of **5**. The solution was then extracted with ethyl acetate (3 × 30 mL), and the combined extracts were washed with brine (30 mL), dried (MgSO₄), and evaporated. Chromatography of the residue on silica gel (30 g) with CHCl₃ gave **10** (74 mg), an intermediate fraction (84 mg) of **10** and **9** determined by NMR inspection to contain 45 mol % of **9**, then **9** (53 mg), NMR and IR of which corresponded where appropriate with the spectra of the methyl ester.[1] Oxalyl piperidide **10** was purified by bulb-to-bulb distillation, bath temperature 120 °C (0.01 mm): IR 1742, 1727, 1661 cm⁻¹; NMR δ 1.0–1.9 (8 H, m), 1.9–2.5 (1 H, m), 2.20 and 2.24 (3 H, singlets), 3.6 (2.5 H, m), 4.4 (2 H, m), 5.1 (0.5 H, m); mass spectrum *m/e* (rel intensity) 227 (M⁺, 1%), 184 (54), 156 (71), 154 (13), 43 (100).

Anal. Calcd for C₁₁H₁₇NO₄: C, 58.1; H, 7.5; N, 6.2. Found: C, 57.9; H, 7.4; N, 6.0.

Benzyl Pipecolate. Benzyl pipecolate has been prepared previously in 8% yield by reaction of pipecolic acid with benzyl alcohol and thionyl chloride.[26] The following procedure gives the desired ester in good yield.

A mixture of toluene (50 mL), pipecolic acid (5.2 g, 40 mmol), benzyl alcohol (21 g, 195 mmol), and *p*-toluenesulfonic acid (9.6 g, 50 mmol) was heated under reflux for 60 h with removal of water. The clear orange solution was added to water (150 mL) and shaken, and the aqueous phase was subsequently washed with ether (3 × 75 mL) and then made alkaline by addition of excess saturated aqueous sodium carbonate. The solution was extracted with ether (3 × 75 mL) and the organic portions were combined and dried (MgSO₄). After filtration the ether was removed to yield benzyl pipecolate as a yellow oil (6.3 g, 72%). IR and NMR spectra of this material were identical with the reported spectra.

Ethyl Oxalyl 2-Benzyloxycarbonylpiperidide. A solution of benzyl pipecolate (6 g, 27 mmol) in dry ether (50 mL) and triethylamine (10.1 g, 100 mmol) was cooled in an ice–water bath, then a solution of ethyl oxalyl chloride (4.2 g, 30 mmol) in dry ether (20 mL) was added over 0.5 h, taking precautions for the exclusion of moisture. The resulting slurry was stirred at room temperature for a further 2 h and then added to a saturated aqueous sodium carbonate solution (50 mL); when CO₂ evolution had ceased the ether layer was separated and washed with 1 M hydrochloric acid (2 × 50 mL) and again with saturated aqueous sodium carbonate (50 mL). The organic layer was dried (MgSO₄) and after filtration the ether was removed by evaporation to yield benzyl 1-(ethyl oxalyl)pipecolate (7.33 g, 84%). Dis-

tillation (170 °C (0.15 Torr)) yielded the product as a yellow oil (6.1 g, 70%): IR 1660, 1735 cm^{-1}; NMR δ 1.10–2.00 (8 H, m), 2.05–2.60 (1.4 H, m), 3.20–3.80 (1.6 H, m), 4.35 (2.4 H, q), 5.15 (2.6 H, s), 7.40 (5 H, s).

Anal. Calcd for C$_{17}$H$_{21}$NO$_5$: C, 63.9; H, 6.6; N, 4.4. Found: C, 64.0; H, 6.6; N, 4.4.

Ethyl Oxalyl 2-Carboxypiperidide. Ethyl oxalyl 2-benzyloxy-carbonylpiperidide (3.2 g, 10 mmol) in dry ethanol (30 ml) and 10% Pd/C (0.4 g) were shaken with hydrogen for 30 min after which the suspension was filtered through celite, the ethanolic filtrate was evaporated, and the residue was dissolved in excess saturated sodium carbonate solution. This solution was washed with ether (2 × 20 mL) and then acidifed to pH 1 with 1 M hydrochloric acid and extracted with ether (3 × 50 mL). The combined ether extracts were dried (MgSO$_4$) and filtered and the ether was removed by evaporation to yield ethyl oxalyl 2-carboxypiperidide (1.49 g, 65%) as a colorless oil: IR 1625, 1735 cm^{-1}; NMR δ 1.00–2.00 (8 H, m), 2.15–2.70 (1 H, m), 3.00–3.85 (2 H, m), 4.40 (2.3 H, q), 5.15 (0.7 H, br s), 10.05 (1 H, s).

Anal. Calcd for C$_{10}$H$_{15}$NO$_5$: C, 52.4; H, 6.6; N, 6.1. Found: C, 52.3; H, 6.6; N, 6.1.

Repeating this experiment to the point of evaporation of the ethanolic filtrate gave ethyl oxalyl 2-carboxypiperidide (99% yield) whose IR and NMR spectra were identical to those obtained above and which could be used without any further purification.

Ethyl Oxalyl 2-(2-*tert*-Butoxycarbonyl)acetylpiperidide. To a stirred solution of *tert*-butyl hydrogen malonate (0.47 g, 2.93 mmol) in dry THF (10 mL) was added isopropylmagnesium bromide (5.56 mmol, as a 0.83 M solution in THF). After initial gas evolution had subsided the solution was heated under reflux until the cessation of further gas evolution (ca. 3 h).

To a stirred solution of ethyl oxalyl 2-carboxypiperidide (0.67 g, 2.93 mmol) in dry THF (10 mL) was added solid carbonyldiimidazole (0.52 g, 3.2 mmol) in portions over 5 min and the solution was stirred at room temperature for 1 h after which time all gas evolution had ceased. This solution was added over 5 min to the ice–water bath cooled solution of the magnesium salt of the dianion of *tert*-butyl hydrogen malonate prepared previously, the resulting solution was allowed to come to room temperature, and stirring was continued for a further 2 h. Ether (50 mL) was added and the resulting suspension was decomposed by the addition of 1 M hydrochloric acid (25 mL). The organic layer was separated and washed with 1 M hydrochloric acid (20 mL) and saturated aqueous sodium bicarbonate (2 × 25 mL) and dried (MgSO$_4$). After filtration the solvents were removed to yield ethyl oxalyl 2-(2-*tert*-butoxycarbonyl)acetylpiperidine (0.54 g, 58%): NMR δ 1.00–2.25 (18 H, m), 2.30–3.20 (2 H, br m), 3.52 (2 H, d), 4.40 (2.3 H, q), 5.15 (0.7 H, br s). Attempted purification of this material by bulb-to-bulb distillation (95–105 °C (0.3 mm)) led to decomposition.

Ethyl Oxalyl 2-Acetylpiperidide (10). Ethyl oxalyl 2-(2-*tert*-butoxycarbonyl)acetylpiperidide (0.52 g, 1.6 mmol) was reacted in boiling toluene (15 mL) containing *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) for 2 h. Ether (25 mL) was added to the cooled solution and this was washed with saturated aqueous sodium carbonate (2 × 25 mL) and 0.5 M hydrochloric acid and dried (MgSO$_4$).

After filtration the solvents were removed by evaporation to yield a crude product (0.24 g, 65%) which was purified by bulb to bulb distillation (95–100 °C (0.3 mm)) to yield 10 as a colorless oil (0.18 g, 49%), identical with material obtained from the oxidation of 8 by NMR, IR, and TLC comparison.

Oxidation of 8 in Aqueous Acetic Acid. Periodic acid dihydrate (137 mg, 0.6 mmol) dissolved in water (0.5 mL) was diluted with acetic acid (6 mL). Compound 8 (50 mg, 0.30 mmol) in acetic acid (1 mL) was then added over a period of 2 min. After 1.4 h ethylene glycol (28 mg, 0.45 mmol) in acetic acid (1 mL) was added, resulting, after a few seconds, in a quite cloudy solution. The solution was filtered through cotton/celite, rinsing with CHCl$_3$, then the solvents were evaporated. The residue was purified by bulb-to-bulb distillation, bath temperature 70–100 °C (0.05–0.10 mm). At the higher end of the temperature range a solid started subliming out; the distillation was stopped at this point, yielding 20 (18 mg, 32%), identical with material prepared according to the following procedure by NMR, IR, and TLC comparison.

1-Formyl-2-carboxypiperidine. Pipecolic acid (5 g, 38.8 mmol) was stirred at room temperature in formic acid (100 mL, 95–97%), and acetic anhydride (30 mL) was added over 0.5 h, causing the temperature to rise to 50–55 °C. After stirring for a further 4 h, ice–water (80 mL) was added and the aqueous acidic solvents were removed by evaporation under reduced pressure. Further drying at 60 °C (2 mm) yielded crude product (6 g, 99%) as a gum which slowly solidified over 48 h: mp 79–82 °C; NMR δ 0.85–1.95 (5 H, m), 1.95–2.45 (1 H, m),

2.50–3.20 (0.5 H, m), 3.20–3.80 (1.5 H, m), 4.00–4.50 (0.5 H m), 4.90–5.20 (0.5 H, m), 8.00 and 8.05 (1 H, s), 11.20 (1 H, br s). This material was carried on to the next stage without further purification.

1-Formyl-2-(2-*tert*-butoxycarbonyl)acetylpiperidine. To a stirred solution of *tert*-butyl hydrogen malonate (2.23 g, 13.9 mmol) in dry THF (30 mL) was added isopropylmagnesium bromide (26.5 mmol, as a 0.97 M solution in THF). After initial gas evolution had subsided the solution was heated under reflux for 3 h.

To a stirred solution of 1-formyl-2-carboxypiperidine (2.19 g, 13.9 mmol) in dry THF (30 mL) was added solid carbonyldiimidazole (2.6 g, 16 mmol) in portions and the solution was stirred at room temperature with the exclusion of moisture for 1 h. This solution was then added over 0.5 h to the previously prepared solution of the magnesium salt of the dianion of *tert*-butyl hydrogen malonate with ice–water bath cooling. The resulting milky white suspension was allowed to come to room temperature and stirred for a further 15 h. Ether (50 mL) was then added and the suspension was decomposed by the addition of 1 M hydrochloric acid (20 mL). When the mixture had formed two clear layers the organic portion was separated and washed with 1 M hydrochloric acid (2 × 40 mL) and saturated aqueous sodium carbonate (25 mL) and dried (MgSO$_4$). After filtration the solvents were evaporated to yield the desired product (0.89 g, 25%) as a colorless oil. NMR confirmed this compound as the major product with absorptions at δ 1.50 (*tert*-butyl), 3.40 (COCH$_2$CO$_2$-*t*-Bu), and 8.15 (NCHO), but absorptions at δ 3.20 and 2.22 suggested that partial cleavage of the *tert*-butyl group and subsequent decarboxylation had occurred during workup. The material was carried to the next stage with no further purification.

1-Formyl-2-acetylpiperidine (20). The preceding mixture (1.09 g) was stirred in trifluoroacetic acid (10 mL) at room temperature for 5 h after which time the acid was removed by evaporation at 40 °C under reduced pressure to yield crude 1-formyl-2-(2-carboxy)acetylperidine (0.85 g) as an orange-brown gum. Complete cleavage of the *tert*-butyl group was confirmed by NMR. This gum was vigorously stirred as a suspension in boiling toluene (10 mL) for 1 h during which time a homogeneous solution was formed. The toluene was removed by evaporation to yield a crude product (0.59 g) as a brown oil. Chromatography of this material (30 g silica, eluting with ether) yielded a mixture of compounds (0.06 g) as the first major fraction, followed by 20 (0.48 g, 72%) as a colorless oil: IR 1725, 1665 cm^{-1}; NMR δ 0.90–2.58 (6 H, m), 2.18 and 2.20 (3 H, s), 2.60–3.80 (1.8 H, m), 4.05–4.55 (0.5 H, m), 4.85–5.10 (0.7 H, br s), 8.05 and 8.10 (0.9 H, s); ^{13}C NMR δ 205.08 (keto), 162.15 and 161.61 (formyl); mass spectrum *m/e* (rel intensity) 155 (M$^+$, 2%), 112 (100); high resolution mass spectrum, calcd for C$_8$H$_{13}$NO$_2$ (M$^+$), 155.0946 found, 155.0944.

Ethyl 3-Methoxy-3-*tert*-butoxycarbonyl-2-oxopropionate (12). To absolute ether (100 mL) and isopropylcyclohexylamine (14.3 g, 0.10 mol, freshly distilled from CaH$_2$), cooled in a dry ice/acetone bath, *n*-butyllithium (35.7 mL, 2.80 M) was added dropwise over 8 min, and the solution was stirred for 30 min. Then *tert*-butyl methoxyacetate[27] (14.6 g, 0.10 mol) in absolute ether (60 mL) was added rapidly over 6 min, the cooling bath was removed after 1 h, and diethyl oxalate (14.61 g, 0.10 mol, freshly distilled from CaH$_2$) in absolute ether (15 mL) was added over 5 min. After the addition was completed, the mixture was held at room temperature for 20 min and then at 50 °C for 0.5 h. The clear solution was then cooled in an ice bath, a solution of 6 N HCl (40 mL) diluted to 80 mL with ice was added, the layers were separated, and the acidic aqueous layer was further extracted with ether (3 × 50 mL). The combined extracts were washed with brine (75 mL) and with saturated NaHCO$_3$ (50 mL), dried (MgSO$_4$), and evaporated to give 23.3 g, 18.4 g of which was distilled through a vacuum jacketed column to give 12 (12.0 g, 62%, bp 88–89 °C (0.1 mm)) which was purified further by bulb-to-bulb distillation, bath temperature 75–90 °C (0.02 mm)): IR 1764, 1733, 1656 (w) cm^{-1}; NMR (absorptions were split due to an enol content of ~10%) keto form, δ 1.38 (3 H, t), 1.47 (9 H, s), 3.57 (3 H, s), 4.38 (2 H, q), 4.88 (1 H, s), and enol form, 1.58 (9 H, s), 3.67 (3 H, s), 4.35 (2 H, q), 10.87 (1 H, s).

Anal. Calcd for C$_{11}$H$_{18}$O$_6$: C, 53.6; H, 7.4. Found: C, 53.4; H, 7.6.

7-Methoxy-7-*tert*-butyoxycarbonyl-8,9-dioxo-1-azabicy-clo[4.3.0]nonane (14). An ethanol/ether solution (50 mL) of Δ^1-piperideine (13) was prepared as described previously[1] from piperidine (3.4 g, 40 mmol) and cooled in an ice bath. With continued cooling and with rapid stirring a solution of ester 12 (4.92 g, 20 mmol) in absolute ethanol (34 mL) was added rapidly over 10 min. After completion of addition the cooling bath was removed and the solution was stirred at room temperature for 6 h. Acetic acid (1.2 g, 20 mmol) was added and then the reaction solution was evaporated. The residue was taken up in CH$_2$Cl$_2$/water (100 mL of each), the layers were separated,

and the aqueous layer was further extracted with CH$_2$Cl$_2$ (2 × 50 mL). The combined extracts were dried (MgSO$_4$) and evaporated to give a crude residue which was chromatographed on silica gel (50 g) with CHCl$_3$ to give 14: 2.33 g, 30%; mp 119.5–120.5 °C after crystallization from CHCl$_3$–hexane; IR 1773, 1745, 1718 cm^{-1}; NMR δ 1.2–2.3 (6 H, m), 1.48 (9 H, s), 2.93 (1 H, m), 3.60 (3 H, s), 3.83 (1 H, dd, *J* = 4, 10 Hz), 4.45 (1 H, br dd, *J* = 13 Hz).

Anal. Calcd for C$_{14}$H$_{21}$NO$_5$: C, 59.3; H, 7.5; N, 4.9; Found: C, 59.3; H, 7.3; N, 4.9.

7-Methoxy-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (15). To *tert*-butyl ester 14 (90 mg, 0.32 mmol) in acetic acid (0.4 mL) was added acetic acid saturated with HBr (6.0 mL). After being stirred at room temperature for 10 min, the solvent was evaporated under reduced pressure at room temperature. The residue was taken up in CHCl$_3$/CH$_3$OH, the solvent was evaporated, the residue was then dissolved in CH$_2$Cl$_2$ and dried (MgSO$_4$), and the solvent was evaporated to give crystalline residue: mp 117–122 °C dec; IR 3125 (br), 1667 (br) cm^{-1}; NMR δ 1.0–2.6 (6 H, m), 3.17 (1 H, m), 3.7–4.5 (2 H, m), 4.25 (3 H, s), 9.47 (1 H, s); mass spectrum *m/e* (rel intensity) 183 (M$^+$, 60%), 168 (37), 152 (100); high resolution mass spectrum, calcd for C$_9$H$_{13}$NO$_3$ (M$^+$), 183.0835, found, 183.0896.

Oxidation of 15. The *tert*-butyl ester 14 (283 mg, 1.0 mmol) was converted to 15 as described above, then the residue was added as a solution in CH$_3$OH (2.5 mL) to a pH 6.3 buffer (50 mL, prepared as described previously)[1] containing sodium periodate (428 mg, 2.0 mmol) over a period of 4 min. A UV spectrum of an aliquot removed 3 min later indicated that all of the periodate had been consumed. Oxidant was destroyed as described[1] with NaHSO$_3$ (832 mg, 8.0 mmol), and after adjustment of the pH to 6, the solution was extracted with CH$_2$Cl$_2$ (2 × 30 mL). The combined extracts were dried (MgSO$_4$) and evaporated to yield a residue of 23 mg. The aqueous layer was then adjusted to pH 3.0 with 3.0 M phosphoric acid, saturated with sodium chloride (pH 2.0), and extracted with three 50-mL portions of CHCl$_3$ and then continuously to yield after drying (MgSO$_4$) 140 mg (65%) of 16, identical with that described above by IR, NMR, and TLC comparison.

Oxidation of 7-Ethoxycarbonyl-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (18). Formation of 19. A solution of 18[1] (1.0 g, 4.44 mmol) in CH$_3$OH (10 mL) was added in one portion to a vigorously stirred buffer at pH 6.3 (40 mL) and at 18 °C containing NaIO$_4$ (1.71 g, 8 mmol). Reaction as evidenced by gas evolution was apparent. A starch–iodide test after 3 min showed complete consumption of periodate and the remaining oxidants were destroyed in the usual manner.[1] The solution (now at pH 2) was saturated with NaCl and extracted with chloroform (3 × 100 mL); the combined extracts were dried (MgSO$_4$) and filtered and the solvents were removed by evaporation to yield a mixture of oxidation products and starting material (1 g).

Chromatography of this material (50 g of silica/ether) yielded initial fractions which NMR suggested to be a mixture of one major and several minor components (total weight 0.6 g); the next material to be eluted was unreacted 18 (0.35 g). The mixture obtained from the previous chromatography was rechromatographed (30 g silica/CH$_2$Cl$_2$–5% ether) and the first fractions to be eluted were the major component of the mixture, 1-formyl-2-(ethyl oxalyl)piperidine (0.31 g, 32%): NMR δ 0.85–2.55 (9 H, br m with triplet centered at 1.40), 2.55–3.05 (0.5 H, br m), 3.15–3.78 (1.5 H, m), 4.02–4.60 (2 H, q), 4.70–4.90 (0.3 H, m), 5.16–5.57 (0.7 H, m), 8.05 (1 H, s); IR 1670, 1735 cm^{-1}; mass spectrum *m/e* (rel intensity) 213 (M$^+$, 2%), 185 (32), 154 (30), 126 (36), 112 (100), 83 (100), 56 (100), 55 (100); ^{13}C NMR δ 191.74 (keto), 162.61 and 161.91 (formyl). A sample for analysis was obtained by bulb-to-bulb distillation (110–120 °C (0.3 mm)).

Anal. Calcd for C$_{10}$H$_{15}$NO$_4$: C, 56.3; H, 7.1; N, 6.6. Found: C, 56.0; H, 7.1; N, 6.4.

7,7-Dibromo-8,9-dioxo-1-azabicyclo[4.3.0]nonane (22). To NaIO$_3$ (75 mg, 0.38 mmol) dissolved in water (1.0 mL) was added acetic acid (6.0 mL), then 5 (70 mg, 0.30 mmol) in acetic acid (1.2 mL) was added with stirring over 2 min. After 1.2 h, the solution was evaporated at room temperature, CH$_2$Cl$_2$ (5 mL) followed by water (5 mL) was rapidly added with vigorous stirring, the layers were separated, and the aqueous layer was extracted further with CH$_2$Cl$_2$ (10 mL). The combined extracts were dried (MgSO$_4$) and evaporated to a crystalline residue (55 mg) which was chromatographed on silica gel (0.5 g) with CHCl$_3$ to give 22 (31 mg): mp 139–142 °C dec; IR 1783, 1724 cm^{-1}; NMR δ 1.0–2.5 (6 H, m), 2.9 (1 H, m), 4.10 (1 H, dd, *J* = 4, 11 Hz), 4.35 (1 H, br dd, *J$_{\alpha,\beta}$* = 13 Hz).

Anal. Calcd for C$_8$H$_9$NBr$_2$O$_2$: C, 30.9; H, 2.9; N, 4.5; Br, 51.4. Found: C, 31.2; H, 3.0; N, 4.4; Br, 50.9.

The Action of Periodate on 7-Ethoxycarbonyl-7-methyl-8,9-dioxo-1-azabicyclo[4.3.0]nonane (27). Compound 27[1] (24 mg,

0.10 mmol) in CH$_3$OH (0.25 mL) was added to the usual buffer[1] at pH 6.3 (5 mL). No consumption of periodate was detected during the next hour. The solution was then extracted with CH$_2$Cl$_2$ (2 × 5 mL), and the combined extracts were dried (MgSO$_4$) and evaporated to yield 22 mg (91%), identical by IR comparison with starting material.

Registry No.—*cis*-6, 66551-98-2; *trans*-6, 66551-99-3; 9, 66552-00-9; 12, 66552-01-0; 13, 505-18-0; 14, 66552-02-1; 20, 66552-03-2; 22, 66552-04-3; 27, 42599-33-7; pipecolic acid, 535-75-1; ethyl pipecolate, 15862-72-3; ethyl oxalyl chloride, 4755-77-5; benzyl alcohol, 100-51-6; benzyl pipecolate, 38068-75-6; benzyl 1-(ethyl oxalyl)pipecolate, 66552-05-4; ethyl oxalyl 2-carboxypiperidide, 66552-06-5; *tert*-butyl hydrogen malonate, 40052-13-9; ethyl oxalyl 2-(2-*tert*-butyoxycarbonyl)acetylpiperidine, 66552-07-6; 1-formyl-2-carboxypiperidine, 54966-20-0; 1-formyl-2-(2-*tert*-butoxycarbonyl)acetylpiperidine, 66552-08-7; *tert*-butyl methoxyacetate, 17640-23-2; diethyl oxalate, 95-92-1.

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Chemistry of Heterocyclic Compounds. 29. Synthesis and Reactions of Multihetero Macrocycles Possessing 2,4-Pyrimidino Subunits Connected by Carbon–Oxygen and/or –Sulfur Linkages[1a]

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The 2,4-pyrimidino moiety has been incorporated into the "crown-ether" framework. 1:1 macrocycles have been characterized, whereas isomeric 2:2 and 3:3 macrocycles containing the 2,4-pyrimidino unit have been isolated and the isomeric distribution has been ascertained via NMR analysis. The 1:1 macrocycles (**11**, **12**, and **14**) undergo a facile Hilbert–Johnson reaction in the presence of methyl iodide at elevated temperature. Thermolysis of these 1:1 compounds causes a rearrangement to afford the corresponding uracil macrocycles. The CS and CSO 1:1 and 2:2 macrocycles have been prepared by similar procedures using the appropriate mercaptides.

In the course of our studies of multihetero macrocycles[2] which contain 2,6-pyridino,[3] 2,6-pyrazino,[4] 3,6-diazino,[5] and other heterocyclic subunits,[2] we have now investigated the inclusion of the 2,4-pyrimidino moiety. The general area of pyrimidines is so vast that it is beyond total review; however, Brown has made a Herculean effort to summarize the first 150 years of pyrimidine chemistry.[6,7] From a survey of pyrimidine chemistry, the inclusion of the pyrimidino moiety within a "crown-ether" framework has not been considered. The biological and medicinal interest in pyrimidines[8] affords further impetus to prepare this new type of macrocyclic system, the topic of this paper.

In view of the electron deficiency of the 2, 4, and 6 positions of the pyrimidine nucleus, halogen atoms located at these positions are susceptible to substitution by nucleophilic reagents. The general preparation of amines, ethers, and mercaptides, as well as a variety of other functions, at these positions on the pyrimidine ring is via direct displacement of chloride ion with the appropriate nucleophile.[9] Selective substitution can be also realized if the reaction conditions are controlled. For example, 2,4,6-trichloropyrimidine (**1**) reacts with sodium methoxide in methanol at 0 °C to generate **2**,[10] with 2 equiv at room temperature to give **3**,[11] and with 3 equiv at 70–100 °C to give 2,4,6-trimethoxypyrimidine (**4**).[11c,d] Thus,

1

2   **3**   **4**
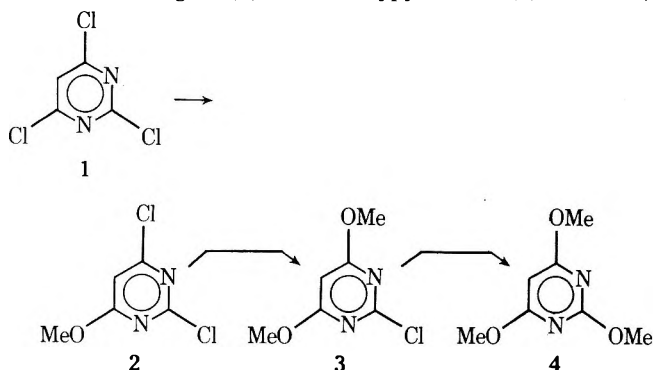
initial 4 substitution of 2,4-dichloropyrimidine (**5**) should be preferred to 2 substitution by alkoxide ion;[12] however, the picture is less simple for polysubstituted pyrimidines.[9]

A. 2,4-Pyrimidino Macrocycles with Carbon–Oxygen Bridges. (1) Diethylene Glycol. Reaction of 2,4-dichloro-

pyrimidine (**5**) with the dianion generated from anhydrous diethylene glycol and 2 equiv of sodium hydride afforded the 2:2 macrocycles **6** as the major cyclic products. When the reaction was conducted at 140 °C (in refluxing xylene), only numerous polymeric open-chain compounds were isolated but not characterized. At lower reaction temperatures (78 °C, refluxing benzene) the 3:3 macrocycle **7** was isolated along with **6**. Approximately equal amounts of the two dimers **6a** (mp 171–173 °C) and **6b** (mp 163–165 °C) were separated by careful thick-layer chromatography. Spectral data afforded little assistance in the structural assignment of these dimers[13] as well as trimer **7**; NMR chemical shift differences ($\Delta\delta$) were <0.1 ppm, and UV and IR data were nearly superimposible. The 1:1 C,O macrocycle **6** ($n = 0$) was not detected; however,

X ≠ Y = CH or N
6a,b, $n = 1$
7, $n = 2$
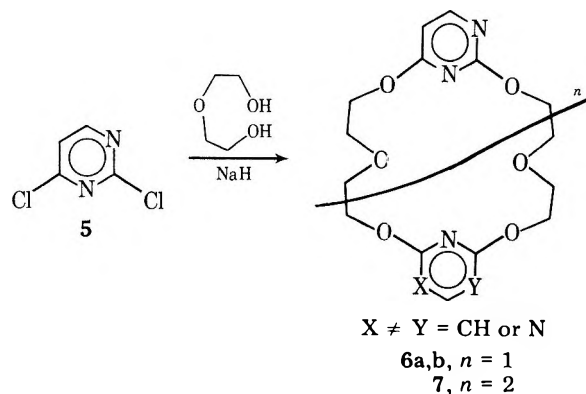
as experienced in our previous studies with this synthetic procedure,[3,5] only when the "meta" bridge possesses sulfur atoms with their diminished bond angles can the ten-membered ring be formed.

The structures of these C,O macrocycles were easily confirmed by molecular weight determination (mass spectrometry and/or osmometry) and ^{1}H NMR spectroscopy. The 5,6-pyrimidine hydrogens appear as doublets ($J = 5$ Hz) at δ 6.25–6.41 and δ 8.10–8.20, respectively, whereas the α methylenes appear as ill-defined triplets at δ 4.5–4.6.

(2) Triethylene Glycol. When 2,4-dichloropyrimidine (**5**) was treated with the disodium salt of triethylene glycol in refluxing xylene, the desired 1:1 macrocycle **8** was isolated in low yield (2%). The inseparable isomeric 2:2 macrocycles **9**

were isolated, and the isomeric ratio was easily ascertained by NMR spectroscopy to be 60:40 since both the pair of singlets for the γ methylenes and the pair of doublets for the 5 and 6 hydrogens can be accurately integrated. The major noncyclic product was the open 2:1 ether **10**, whose structure was supported by the *single* pair of doublets at δ 6.66 and 8.25 for the 5- and 6-pyrimidine hydrogens. This product further confirms the enhanced reactivity of the 4 position of **5** toward alkoxide substitution. The isomers of **10** were detected in minor amounts but were not characterized.

10

8

9 (X ≠ Y = CH or N)
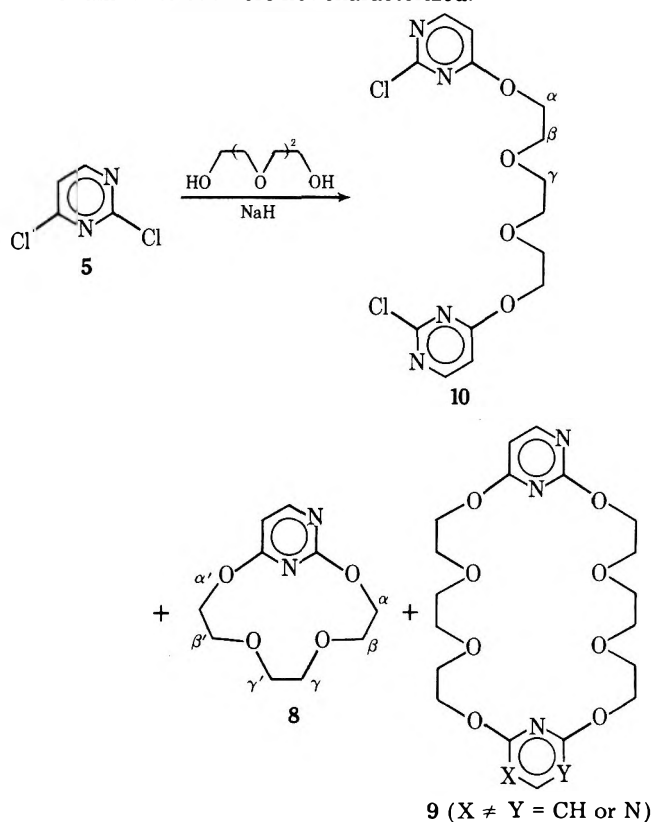
(3) Tetra-, Penta-, and Hexaethylene Glycols. The glycolates of tetra-, penta-, and hexaethylene glycols were independently reacted with **5** to afford increasing yields (8, 16, and 18%) of the 1:1 macrocycles **11**, **12**, and **14**, respectively.

11, $n = 2$
12, $n = 3$
14, $n = 4$

X ≠ Y = CH or N
13, $n = 3$
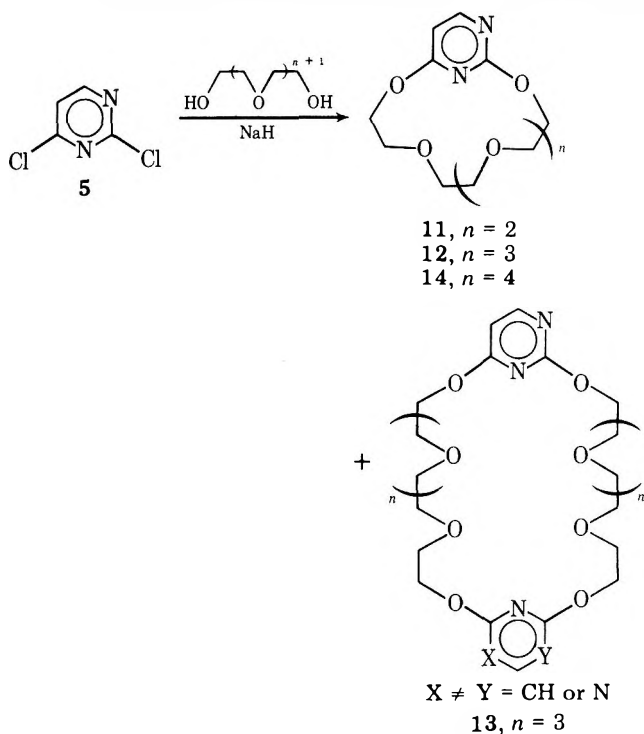
With the pentaethylene glycol, the 2:2 macrocycle **13** was also isolated in an unexpectedly high yield (8%). Fragmentation and oligomerization of these polyethylene glycols are well documented,[14] even when the reaction conditions are regulated at less than 140°C. Reduction of the reaction temperature to 80 °C generally resulted in a slight increase in the 1:1 macrocycle products and almost complete elimination of these side reactions of glycols.

In an attempt to determine the site of possible quaternization of these 1:1 macrocycles, **11**, as well as **12** and **14**, was heated with redistilled methyl iodide in a sealed tube at 100 °C for 6 hours. A single product was isolated in nearly quantitative yield and was shown by NMR spectral data and independent synthesis to be 1,3-dimethyl-2,4-dioxopyrimidine (**15**). In 1929, Johnson and Hilbert[15] first demonstrated that alkoxypyrimidines upon treatment with alkyl iodides undergo an oxygen to nitrogen rearrangement; currently, this specific rearrangement is named for the discoverers.

11, $n = 2$ **16**

15
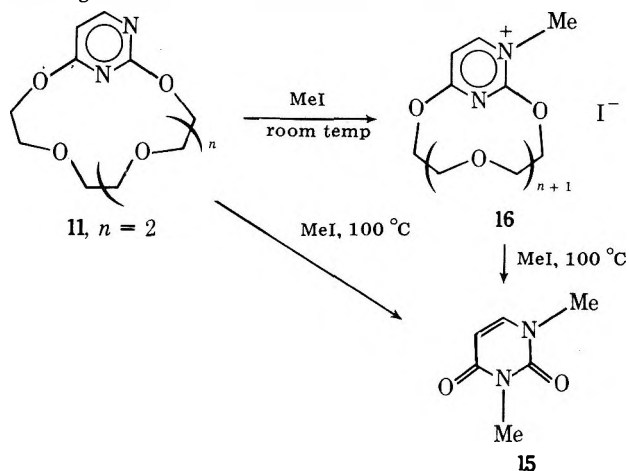
Under very mild conditions, **11** can be successfully monoquaternized with methyl iodide to give **16**, thus indicating that (1) the more readily accessible external nitrogens are initially alkylated and that (2) the Hilbert–Johnson reaction occurs via a stepwise reaction sequence of repetitious alkylation–dealkylation steps. Since the conversion of 2,4-dimethoxypyrimidine to **15** by either thermolysis at 230 °C or in the presence of methyl iodide at elevated temperatures has been demonstrated,[16] the thermolysis of **11** in a sealed tube at 250 °C for 20 h resulted in variable isolated yields of the uracil macrocycle **17**, as characterized by its NMR, IR, and physical properties. Recently, Htay and Meth-Cohn[17] have reported the synthesis of a related crown ether (**18**) which possesses a

11, R = H

17, R = H
18, R = Me
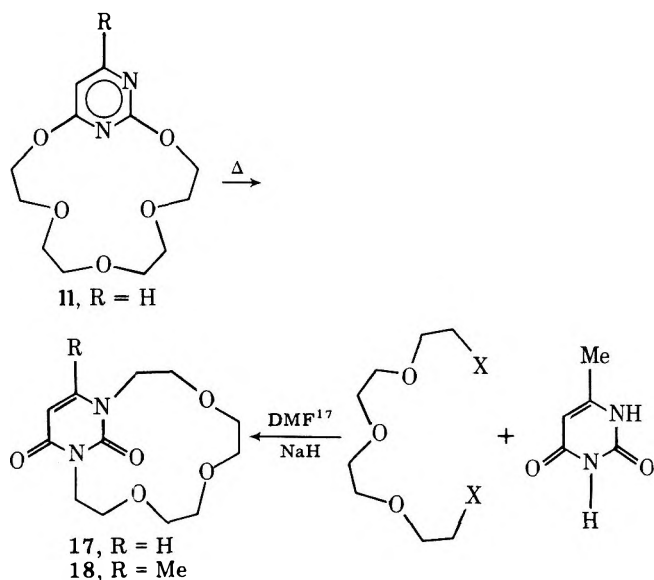
Scheme I
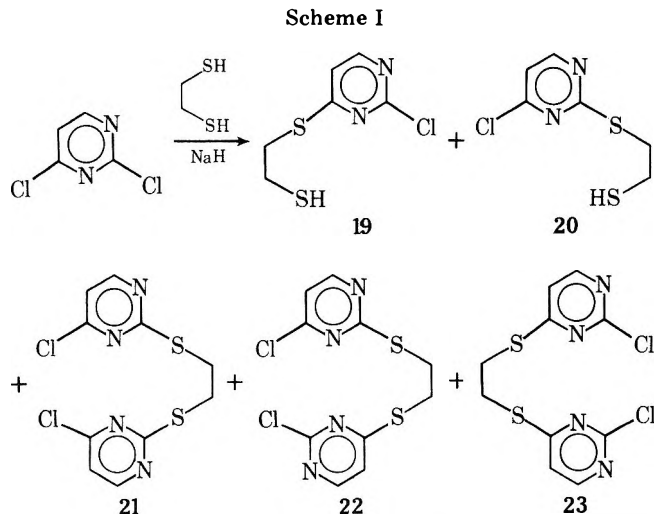
6-methyluracil moiety; their procedure reacted 6-methyluracil with α,ω-dibromoalkanes in dimethylformamide in the presence of sodium hydride, resulting in a 0.2% yield of the 1:1 macrocycle 18 (R = Me). The details of this thermal conversion (11 → 17) will be published later.[18]

B. 2,4-Pyrimidino Macrocycles with Carbon–Sulfur and Carbon–Sulfur–Oxygen Bridges. (1) Ethanedithiol. The reaction of 5 with the disodium salt of ethanedithiol gave none of the desired macrocyclic products. This lack of C,S macrocyclic products is reminiscent of the results obtained in pyridine-[19] and pyrazine-containing[4] macrocycles. The major isolated products are shown in Scheme I. The two 1:1 noncyclized thiols 19 and 20 were isolated in about equal amounts and were characterized by their NMR spectra. Generally in this carbon–sulfur series, the 2-chloro-4-thio compounds (e.g., 19) show the 5 hydrogen at ca. δ 7.0 and the 6 hydrogen at ca. δ 8.4, whereas the corresponding 4-chloro-2-thio isomer (20) possesses the two doublets at δ 7.15 and 8.25 for the 5 and 6 hydrogens, respectively.[20] Thus, from these spectral interpretations the structural assignments of the 2:1 isomers (21–23) were straightforward. As expected, 23 was obtained as the major 2:1 isomer resulting from 4,4' disubstitution, followed by 22 from 4,2' substitution, and 21 in lowest yield via 2,2' substitution.

Cyclization of 21 with diethylene glycolate under the standard conditions afforded the unusual CO–CS bridged macrocycle 24.
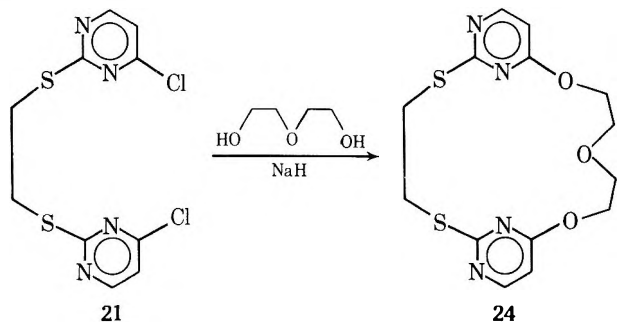
(2) Bis(2-mercaptoethyl) Sulfide. Treatment of 5 with the disodium salt of bis(2-mercaptoethyl) sulfide gave rise to the 1:1 noncyclized thiol 25 along with the desired 1:1 macrocycle 26. As experienced previously,[3,4,19] the oligomerization of bis(2-mercapto) sulfide in the presence of base was the major reaction pathway; pyrimidines containing polysulfur units were not isolated.

(3) Bis(2-mercaptoethyl) Ether. The 1:1 CSO macrocycle 27 and the corresponding 2:2 macrocycle 28 were isolated as crystalline compounds from the reaction of 5 with bis(2-mercaptoethyl) ether. The spectral data are in accord with the proposed structures. The 2,4 carbon–sulfur bonds of 27 and
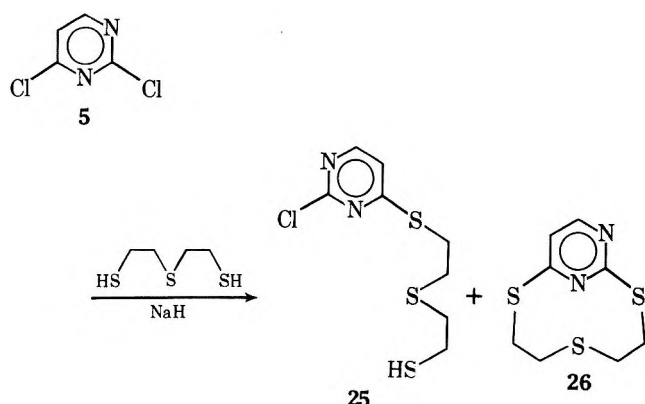
28, as well as those of 26, are confirmed by the downfield shift of the 5 hydrogen from δ 6.4 to 6.9 when compared to the corresponding 2,4 carbon–oxygen bridged macrocycles. The 6 hydrogen is generally less sensitive to the 2,4 substituents.

28 (X ≠ Y = CH or N)
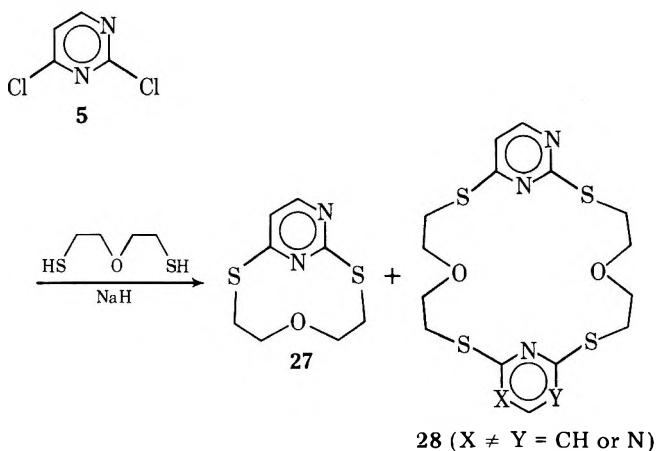
The pharmaceutical aspects of these pyrimidine-containing macrocycles are being conducted, and the results will be published elsewhere. The complexation and general chemistry is currently being investigated.[18]

Experimental Section

Although the noncyclized products could in most cases be isolated, in general, complete characterization of the materials was undertaken *only* when they were a major product of the reaction. The cited yield data were based on analytically pure components and were not maximized.

Method A. Reaction of 2,4-Dichloropyrimidine with Diethylene Glycol. General Procedure. To a suspension of oil-free sodium hydride (480 mg, 20 mmol) in anhydrous xylene (200 mL) was added diethylene glycol (1.06 g, 10 mmol) slowly with stirring under

nitrogen. After 15 minutes, a solution fo 2,4-dichloropyrimidine (1.49 g, 10 mmol) in xylene (50 mL) was added and the reaction mixture was refluxed for 30 h. After cooling, the xylene was removed in vacuo, and the residue was carefully neutralized with water. From this aqueous suspension organic components were extracted with dichloromethane and dried over anhydrous sodium sulfate, and then the solvent was removed, affording a gummy residue which was chromatographed (ThLC) eluting four times with cyclohexane–ethyl acetate (1:1) to give the following components.

Fraction A gave unreacted 2,4-dichloropyrimidine: 20 mg (1%); mp 58–60 °C; R_f 0.75.

Fraction B was recrystallized from ethanol to give colorless shining needles corresponding to the 2:2 macrocycle **6a**:[13] 105 mg (6%); mp 171–173 °C; R_f 0.07; NMR δ 3.85 (m, β,β'-CH$_2$O, 8 H), 4.52 (m, α,α'-CH$_2$O, 8 H), 6.25 (d, 5,5'-pyrim H, J = 5 Hz, 2 H), 8.1 (d, 6,6'-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2950, 1575, 1420, 1350, 1300, 1135, 1090, 980, 830 cm^{-1}; UV (ethanol) λ_{max} (ε) 218 nm (1.1 × 10^4), 260 (9.0 × 10^3).

Anal. Calcd for C$_{16}$H$_{20}$N$_4$O$_6$: C, 52.74; H, 4.59; N, 15.38; mol wt, 364. Found: C, 52.46; H, 5.48; N, 15.12; mol wt (MS), m/e 364 (M$^+$).

Fraction C gave the isomeric 2:2 macrocycle **6b** as colorless plates: 90 mg (5%); mp 163–165 °C; R_f 0.06; NMR δ 3.92 (m, β,β'-CH$_2$O, 8 H), 4.62 (m, α,α'-CH$_2$O, 8 H), 6.35 (d, 5,5'-pyrim H, J = 5 Hz, 2 H), 8.13 (d, 6,6'-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2970, 1595, 1575, 1480, 1440, 1420, 1350, 1300, 1135, 1110, 990, 825 cm^{-1}.

Anal. Calcd for C$_{16}$H$_{20}$N$_4$O$_6$: C, 52.74; H, 5.49; N, 15.38; mol wt, 364. Found: C, 52.61; H, 5.59; N, 15.17; mol wt (MS), m/e 364 (M$^+$).

Method B. Reaction of 2,4-Dichloropyrimidine with Diethylene Glycol in Benzene. To a suspension of sodium hydride (480 mg, 20 mmol) in anhydrous benzene (200 mL) were added diethylene glycol (1.06 g, 10 mmol) and 2,4-dichloropyrimidine (1.49 g, 10 mmol) sequentially, followed by refluxing for 24 h. The workup procedure mimicked the general procedure. The reaction products were chromatographed (ThLC) as above to afford the following components.

Fraction A gave unreacted 2,4-dichloropyrimidine: 10 mg (<1%); mp 58–60 °C.

Fraction B gave a small amount (7 mg) of an oil which could not be characterized.

Fraction C afforded the 2:2 macrocycle **6a**:[13] 200 mg (11%); mp 171–173 °C.

Fraction D gave the 2:2 macrocycle **6b**: 120 mg (7%); mp 163–165 °C.

Fraction E gave a thick brown oil corresponding to the 3:3 macrocycle 7: 135 mg (8%); bp 151–156 °C (0.1 mm; short path); R_f 0.02; NMR δ 3.91 (t, β-CH$_2$O, J = 5 Hz, 12 H), 4.58 (t, α-CH$_2$O, J = 5 Hz, 12 H), 6.40 (d, 5-pyrim H, J = 5 Hz, 3 H), 8.17 (d, 6-pyrim H, J = 5 Hz, 3 H); IR (neat) 2950, 2800, 1590, 1460, 1430, 1350, 1290, 1140, 1100, 1050, 990, 820 cm^{-1}.

Anal. Calcd for C$_{24}$H$_{30}$N$_6$O$_9$: C, 52.74; H, 5.49; N, 15.38; mol wt, 546. Found: 52.56; H, 5.37; N, 15.23; mol wt (MS), m/e 546 (M$^+$).

Reaction of 2,4-Dichloropyrimidine with Triethylene Glycol. The above general procedure was followed except for the substitution of triethylene glycol (1.5 g, 10 mmol). After the standard workup procedure, the residue was chromatographed (ThLC) eluting four times with cyclohexane–ethylene acetate (1:1) to afford the following major fractions.

Fraction A yielded unreacted 2,4-dichloropyrimidine: 30 mg (2%); mp 59–60 °C.

Fraction B, after recrystallization from ethanol, gave 2,2'-dichloro-4,4'-[oxytris(ethylenoxy)]dipyrimidine (10) as colorless needles: 65 mg (3%); mp 110–111 °C; R_f 0.12; NMR δ 3.65 (s, γ-CH$_2$O, 4 H), 3.87 (m, β-CH$_2$O, 4 H), 4.55 (m, α-CH$_2$O, 4 H), 6.66 (d, 5,5'-pyrim H, J = 5 Hz, 2 H), 8.25 (d, 6,6'-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2930, 1590, 1410, 1346, 1275, 1109, 1080, 940, 810, 750 cm^{-1}.

Anal. Calcd for C$_{14}$H$_{13}$N$_4$O$_4$Cl$_2$: C, 44.80; H, 4.27; N, 14.93; mol wt, 375. Found: C, 44.65; H, 4.29; N, 14.88; mol wt (MS), m/e 375 (M$^+$).

Fraction C afforded the 1:1 macrocycle 8, which was recrystallized from ethanol as shining white plates: 60 mg (2%); mp 118–121 °C; R_f 0.06; NMR δ 3.67 (s, γ,γ'-CH$_2$O, 4 H), 3.86 (m, β,β'-CH$_2$O, 4 h), 4.75 (m, α,α'-CH$_2$O, 4 H), 6.31 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.2 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2960, 1600, 1580, 1455, 1418, 1325, 1280, 1235, 1117, 1080, 1030, 920, 810 cm^{-1}; UV (ethanol) λ_{max} (ε) 230 nm (8.7 × 10^5), 270 (6.1 × 10^4).

Anal. Calcd for C$_{10}$H$_{14}$N$_2$O$_4$: C, 53.09; H, 6.19; N, 12.38; mol wt, 226. Found: C, 52.89; H, 6.26; N, 12.16; mol wt (MS), m/e 226 (M$^+$).

Fraction D, after recrystallization from ethanol, gave colorless shining plates corresponding to the isomeric 2:2 macrocycles 9: 110 mg (5%); mp 131–133 °C; R_f 0.05; NMR δ 3.66 (s, γ-CH$_2$O, 40% A isomer), 3.68 (s, γ-CH$_2$O, 60% B isomer), 3.95 (m, β-CH$_2$O, 8 H), 4.5

(m, α-CH$_2$O, 8 H), 6.35 (d, 5-pyrim H, J = 5 Hz, 40% A isomer), 6.37 (d, 5-pyrim H, J = 5 Hz, 60% B isomer), 8.15 (d, 6-pyrim H, J = 5 Hz, 60% B isomer), 8.17 (d, 6-pyrim H, J = 5 Hz, 40% A isomer); IR (KBr) 2900, 1580, 1415, 1330, 1270, 1115, 1065, 935, 810 cm^{-1}.

Anal. Calcd for C$_{20}$H$_{28}$N$_4$O$_8$: C, 53.09; H, 6.19; N, 12.38; mol wt, 452. Found: C, 52.30; H, 6.38; N, 12.14; mol wt (MS), m/e 452 (M$^+$).

Reaction of 2,4-Dichloropyrimidine with Tetraethylene Glycol. The general procedure was followed except for the substitution of tetraethylene glycol (1.94 g, 10 mmol). The various components were separated (ThLC), eluting two times with cyclohexane–ethyl acetate (1:2). The following major fractions were separated and characterized.

Fraction A afforded unreacted dichloropyrimidine: 50 mg (3%); mp 59–60 °C.

Fraction B initially afforded a thick viscous liquid, which solidified on standing. Recrystallization from 95% ethanol gave 11 as colorless needles: 200 mg (8%); mp 65–67 °C; R_f 0.05; NMR δ 3.55 (m, γ,γ',δ,δ'-CH$_2$O, 8 H), 3.92 (m, β,β'-CH$_2$O, 4 H), 4.70 (t, α- or α'-CH$_2$O, 2 H), 4.72 (t, α- or α'-CH$_2$O, 2 H), 6.35 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.20 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2890, 1570, 1456, 1442, 1403, 1345, 1325, 1260, 1130, 1032, 975, 810 cm^{-1}; UV (ethanol) λ_{max} (ε) 230 nm (9.0 × 10^4), 276 (8.0 × 10^4).

Anal. Calcd for C$_{12}$H$_{18}$N$_2$O$_5$: C, 53.33; H, 6.66; N, 10.37; mol wt, 270. Found: C, 53.16; H, 6.49; N, 10.21; mol wt (osmometry), 277 (av).

Reaction of 11 with Methyl Iodide. A mixture of 11 (314 mg, 1 mmol) and methyl iodide (600 mg) was heated in a sealed tube on a water bath for 6 h.[21] After cooling, excess methyl iodide was removed, affording a yellow residue which was crystallized from ethanol to give a pale yellow solid. Recrystallization from ethanol with decolorization afforded the crystalline 1,3-dimethyl-2,4-dioxopyrimidine (15): mp 123–124 °C (lit.[22] mp 120–121 °C); NMR (CDCl$_3$) δ 3.35 (s, N$_1$-CH$_3$, 3 H), 3.45 (s, N$_3$-CH$_3$, 3 H), 5.75 (d, 5-pyrim H, J = 8 Hz, 1 H), 7.17 (d, 6-pyrim H, J = 8 Hz, 1 H).

Thermolysis of 11. Preparation of Macrocycle 17. Macrocycle 11 (156 mg) was heated in a sealed tube at 250 °C under nitrogen for 24 h. After cooling, the shiny needles which sublimed to the end of the tube were collected. Resublimation afforded an analytical sample of the uracil macrocycle 17: 42 mg (28%); mp 128–129 °C; IR (KBr) 2910, 1680, 1660 (C=O), 1570, 1420, 985, 715 cm^{-1}.

Anal. Calcd for C$_{12}$H$_{18}$N$_2$O$_5$: C, 53.33; H, 6.66; N, 10.37. Found: C, 53.58; H, 6.58; N, 10.22.

Reaction of 2,4-Dichloropyrimidine with Pentaethylene Glycol. The general procedure was followed except for the substitution of pentaethylene glycol (2.38 g, 10 mmol). After workup, the gummy residue was chromatographed (ThLC) eluting with cyclohexane–ethyl acetate (1:3) to afford the following fractions.

Fraction A gave a small amount of starting material: 30 mg (2%); mp 58–60 °C.

Fraction B was isolated as a colorless viscous liquid, corresponding to the 1:1 macrocycle 12: 500 mg (16%); bp 178–182 °C (1.0 mm; short path); R_f 0.04; NMR δ 3.55 (bs, ε-CH$_2$O, 4 H), 3.65 (bs, γ,δ-CH$_2$O, 8 H), 3.86 (m, β,β'-CH$_2$O, 4 H), 4.65 (2 t, α,α'-CH$_2$O, 4 H), 6.41 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.20 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 2900, 1570, 1450, 1410, 1335, 1275, 1100, 1040, 980, 930, 810^{-1}; UV (ethanol) λ_{max} (ε) 242 nm (6 × 10^4), 282 (1.4 × 10^5).

Anal. Calcd for C$_{14}$H$_{22}$N$_2$O$_6$: C, 53.50; H, 7.00; N, 8.91; mol wt, 314. Found: C, 53.24; H, 7.21; N, 8.70; mol wt (MS), m/e 314 (M$^+$).

Fraction C was isolated as an oil, which was shown to be the 2:2 macrocycle 13: 260 mg (8%); bp 200–203 °C (1.0 mm; short path); R_f 0.02; NMR δ 3.64 (bs, ε-CH$_2$O, 8 H), 3.69 (bs, γ,δ-CH$_2$O, 16 H), 3.80 (m, β-CH$_2$O, 8 H), 4.68 (2 t, α-CH$_2$O, J = 5 Hz, 8 H), 6.41 (d, 5-pyrim H, J = 5 Hz, 2 H), 8.20 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 2950, 1590, 1480, 1410, 1350, 1265, 1110, 1000, 950, 910, 800, 840 cm^{-1}.

Anal. Calcd for C$_{28}$H$_{44}$N$_4$O$_{12}$: C, 53.50; H, 7.00; N, 8.91; mol wt, 628. Found: C, 53.26; H, 7.11; H, 8.73; mol wt (osmometry), 634 (av).

Reaction of 2,4-Dichloropyrimidine with Hexaethylene Glycol. The general procedure was followed except for the substitution of hexaethylene glycol (2.82 g, 10 mmol). The reaction residue was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (1:3). The following fractions were isolated and characterized.

Fraction A gave (2%) unreacted 2,4-dichloropyrimidine, mp 58–60 °C.

Fraction B afforded the 1:1 macrocycle 12 as colorless needles: 45 mg (2%); mp 65–67 °C.

Fraction C yielded a colorless liquid which corresponded to the 1:1 macrocycle 14: 620 mg (18%); bp 165–169 °C (0.5 mm; short path); R_f 0.03; NMR δ 3.71 (bs, γ-ξ-CH$_2$O, 16 H), 3.84 (m, β-CH$_2$O, 4 H), 4.59 (2 t, α-CH$_2$O, J = 5 Hz, 4 H), 6.38 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.19 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 2890, 1580, 1460, 1410, 1345,

230

1285, 1110, 1080, 985, 940, 810 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 236 nm (1.9 × 10^5), 280 (4 × 10^4).

Anal. Calcd for C$_{16}$H$_{26}$N$_2$O$_7$: C, 53.63; H, 7.26; N, 7.82; mol wt, 358. Found: C, 53.41; H, 7.16; N, 7.68; mol wt (osmometry), 364 (av).

Reaction of 2,4-Dichloropyrimidine with Ethanedithiol. The general procedure was followed except for the substitution of ethanedithiol (940 mg, 10 mmol). After workup, the residue was chromatographed (ThLC) eluting three times with cyclohexane–ethyl acetate (4:1) to afford the following fractions.

Fraction A gave 2-(2'-chloro-4'-pyrimidylthio)ethanethiol (19) as a pale tan liquid: 105 mg (5%); bp 145–150 °C (0.5 mm; short path); R_f 0.58; NMR δ 1.71 [t, –SH (slow exchange with D$_2$O), 1 H], 2.95 (m, β-CH$_2$S–, 2 H), 3.4 (m, α-CH$_2$S–, 2 H), 7.00 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.38 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 3100, 2940, 2520, 1536, 1400, 1330, 1310, 1200, 1180, 1160, 810, 740 cm^{-1}.

Anal. Calcd for C$_6$H$_7$N$_2$S$_2$Cl: C, 34.86; H, 3.38; N, 13.55; mol wt, 206.5. Found: C, 34.63; H, 3.25; N, 13.42; mol wt (osmometry), 210 (av).

Fraction B gave 2-(4'-chloro-2'-pyrimidylthio)ethanethiol (20) as a viscous liquid: 120 mg (6%); bp 156–158 °C (0.5 mm; short path); R_f 0.56; NMR δ 1.75 [t, –SH (slow exchange with D$_2$O), 1 H], 3.0 (m, β-CH$_2$S–, 2 H), 3.5 (m, α-CH$_2$S–, 2 H), 7.15 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.25 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 3100, 2940, 2540, 1530, 1500, 1400, 1320, 1270, 1180, 975, 810, 740 cm^{-1}.

Anal. Calcd for C$_6$H$_7$N$_2$S$_2$Cl: C, 34.86; H, 3.38; N, 13.55; mol wt, 206.5. Found: C, 34.79; H, 3.25; N, 13.49; mol wt (av).

Fraction C, after recrystallization from ethanol, afforded colorless flakes corresponding to 23: 160 mg (5%); mp 140–142 °C; R_f 0.54; NMR δ 3.55 (s, –S–CH$_2$CH$_2$–S–, 4 H), 7.05 (d, 5-pyrim H, J = 5 Hz, 2 H), 8.40 (d, 6-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2950, 1540, 1510, 1405, 1320, 1226, 1200, 1140, 1090, 800, 740 cm^{-1}.

Anal. Calcd for C$_{10}$H$_8$N$_4$S$_2$Cl$_2$: C, 37.61; H, 2.50; N, 17.56; mol wt, 319. Found: C, 37.41; H, 2.58; N, 17.31; mol wt (osmometry), 330 (av).

Fraction D, after recrystallization from ethanol, gave pale crystals corresponding to 22: 150 mg (5%); mp 135–136 °C; R_f 0.50; NMR δ 3.6 (m, –S–CH$_2$CH$_2$–S–, 4 H), 7.04 (d, 5-pyrim H, J = 5 Hz, 1 H), 7.18 (d, 5'-pyrim H, J = 5 Hz, 1 H), 8.2 (d, 6-pyrim H, J = 5 Hz, 1 H), 8.40 (d, 6'-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2900, 1530, 1500, 1400, 1325, 1280, 1200, 1175, 970, 810, 750 cm^{-1}.

Anal. Calcd for C$_{10}$H$_8$N$_4$S$_2$Cl$_2$: C, 37.61; H, 2.50; N, 17.56; mol wt, 319. Found: C, 37.76; H, 2.61; N, 17.28; mol wt (osmometry), 326 (av).

Fraction E, after recrystallization from ethanol, gave a colorless solid corresponding to 21: 100 mg (3%); mp 127–128 °C; R_f 0.44; NMR δ 3.57 (s, –SCH$_2$CH$_2$S–, 4 H), 7.18 (d, 5-pyrim H, J = 5 Hz, 2 H), 8.25 (d, 6-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2950, 1555, 1510, 1413, 1330, 1315, 1185, 1175, 1160, 975, 815, 750 cm^{-1}.

Anal. Calcd for C$_{10}$H$_8$N$_4$S$_2$Cl$_2$: C, 37.61; H, 2.50; N, 17.56; mol wt, 319. Found: C, 37.52; H, 2.39; N, 17.40; mol wt (MS), m/e 319 (M$^+$).

Reaction of 21 with Diethylene Glycol. Macrocycle 24. Oil-free sodium hydride (24 mg, 1 mmol) suspended in anhydrous xylene (150 mL) was stirred, and diethylene glycol (53 mg, 0.5 mmol) was slowly added followed by 21 (100 mg, 0.32 mmol). The mixture was refluxed under nitrogen for 24 h. After workup, the oily residue was chromatographed (ThLC) eluting with cyclohexane–ethyl acetate (1:1) to give, along with unreacted starting material (20 mg), macrocycle 24, which was recrystallized from ethanol as colorless needles: 62 mg (55%); mp 169–172 °C; R_f 0.13; NMR δ 3.71 (s, SCH$_2$CH$_2$S, 4 H), 3.86 (m, β-CH$_2$O, 4 H), 4.56 (m, α-CH$_2$O, 4 H), 6.30 (2 d, 5,5'-pyrim H, J = 6 Hz, 2 H), 8.10 (2 d, 6,6'-pyrim H, J = 6 Hz, 2 H); IR (KBr) 2900, 1560, 1542, 1412, 1338, 1287, 1220, 1100, 1080, 740 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 210 nm (6.3 × 10^3), 260 (6 × 10^4), 305 (1.6 × 10^4).

Anal. Calcd for C$_{14}$H$_{16}$N$_4$O$_3$S$_2$: C, 44.73; H, 4.55; N, 15.91; mol wt, 352. Found: C, 44.62; H, 4.39; N, 15.86; mol wt (MS), m/e 352 (M$^+$).

Reaction of 2,4-Dichloropyrimidine with Bis(2-mercaptoethyl) Sulfide. The general procedure was followed except for the substitution of bis(2-mercaptoethyl) sulfide (1.54 g, 10 mmol). After workup, the residue was chromatographed (ThLC), eluting two times with cyclohexane–ethyl acetate (4:1). Although most of the materials were found to be polymeric, the following two components were characterized.

Fraction A gave a thick brown liquid which solidified on standing, corresponding to 25: 85 mg (4%); mp 51–54 °C; R_f 0.61; NMR δ 1.45 [t, –SH (exchanged slowly with D$_2$O), 1 H], 3.2 (m, –SCH$_2$CH$_2$SCH$_2$CH$_2$S–, 8 H), 6.90 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.15 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (neat) 2920, 2350, 1535, 1510, 1400,

1325, 1195, 1155, 950, 810 cm^{-1}.

Anal. Calcd for C$_8$H$_{11}$N$_2$S$_3$Cl: C, 36.02; H, 4.12; N, 10.50; mol wt, 266.5. Found: C, 36.17; H, 4.31; N, 10.46; mol wt (osmometry), 242 (av).

Fraction B, after recrystallization from ethanol, gave colorless crystals corresponding to 26: 145 mg (6%); mp 173–175 °C; R_f 0.57; NMR δ 3.0 (bm, β-CH$_2$S–, 4 H), 3.5 (bm, α-CH$_2$S–, 4 H), 6.81 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.15 (d, 6-pyrim H. J = 5 Hz, 1 H); IR (KBr) 2920, 1532, 1508, 1406, 1310, 1150, 1180, 1020, 810, 753 cm^{-1}.

Anal. Calcd for C$_8$H$_{10}$N$_2$S$_3$: C, 41.73; H, 4.34; N, 12.17; mol wt, 230. Found: C, 41.69; H, 4.30; N, 12.08; mol wt (osmometry), 238 (av).

Reaction of 2,4-Dichloropyrimidine with Bis(2-mercaptoethyl) Ether. The general procedure was followed except for the substitution of bis(2-mercaptoethyl) ether (1.38 g, 10 mmol). After workup, the oily residue was chromatographed (ThLC) eluting three times with cyclohexane–ethyl acetate (4:1) to afford the following fractions.

Fraction A gave a small amount of (<20 mg) unreacted 2,4-dichloropyrimidine, mp 59–60 °C.

Fraction B afforded the 1:1 macrocycle 27 as colorless needles (from ethanol): 125 mg (6%); mp 123–125 °C; R_f 0.50; NMR δ 3.41 (m, β,β'-CH$_2$O, 4 H), 3.86 (m, α,α'-CH$_2$S, 4-H), 6.95 (d, 5-pyrim H, J = 5 Hz, 1 H), 8.19 (d, 6-pyrim H, J = 5 Hz, 1 H); IR (KBr) 2910, 2880, 1540, 1500, 1430, 1320, 1210, 1155, 1100, 980, 850, 810, 750, 700 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 210 nm (5.4 × 10^3), 255 (6.2 × 10^4), 300 (1.3 × 10^4).

Anal. Calcd for C$_8$H$_{10}$N$_2$S$_2$O: C, 44.85; H, 4.67; N, 13.08; mol wt, 214. Found: C, 44.61; H, 4.44; N, 13.11; mol wt (osmometry), 222 (av).

Fraction C was recrystallized from ethanol to give the 2:2 macrocycle 28 as light flakes: 175 mg (8%); mp 159–160 °C; R_f 0.42; NMR δ 3.41 (m, β-CH$_2$O, 8 H), 3.73 (m, α-CH$_2$S, 8 H), 6.86 (d, 5-pyrim H, J = 5 Hz, 2 H), 8.10 (d, 6-pyrim H, J = 5 Hz, 2 H); IR (KBr) 2905, 2880, 1538, 1510, 1400, 1321, 1200, 1155, 1100, 990, 820, 750 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 208 nm (9.8 × 10^3), 254 (4.1 × 10^4), 303 (1.4 × 10^4).

Anal. Calcd for C$_{16}$H$_{20}$N$_4$S$_4$O$_2$: C, 44.85; H, 4.67; N, 13.08; mol wt, 428. Found: C, 44.80; H, 4.78; N, 12.97; mol wt (osmometry), 421 (av).

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Studies on Pyrazines. 5.[1] Peracetic and Peroxysulfuric Acid N-Oxidation of Phenyl- and Chlorophenylpyrazines

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Peracetic and peroxysulfuric acid oxidations of 2-phenyl- (**2**) and 2-chloro-3-, -5-, and -6-phenylpyrazine (**4, 5,** and **6,** respectively) were carried out. On peracetic acid oxidation, **2, 4,** and **6** gave the corresponding 4-oxides and **5** gave a mixture of the 1- and 4-oxides. On the other hand, peroxysulfuric acid oxidation of **4** and **5** afforded the corresponding 1-oxides, but **2** gave a small amount of the 4-oxide and **6** was not oxidized. Structures of these N-oxides were determined by NMR spectra and dipole moment measurement. The mechanism of these oxidations is discussed.

N-oxidation of a pyrazine with usual percarboxylic acid reagents takes place on the most basic and least sterically hindered nitrogen.[2–5] The peracetic acid oxidation of a pyrazine bearing an electron-withdrawing substitutent such as halogens occurs in such a manner, e.g., 2-chloropyrazine (**3**) affords exclusively its 4-oxide.[5,6] However, a direct synthesis of 2-chloropyrazine 1-oxides, with the opposite orientation from that in the peracetic acid oxidation of chlorinated pyrazines, was recently reported by Mixan and Pew[7] by treatment of chloropyrazine with peroxysulfuric acid generated in situ from potassium persulfate and concentrated sulfuric acid. On applying these oxidation methods to 2-methyl- (**1**), 2-phenyl- (**2**), 2-chloropyrazine (**3**), and 2-chloro-3-, -5-, and -6-phenylpyrazine (**4, 5,** and **6,** respectively), we have found some interesting observations on the orientation of N-oxidations.

Results

As shown in Table I, methylpyrazine (**1**) was converted to the corresponding 1- and 4-oxides in the relative ratio of about 3:2[8] on treatment with peracetic acid by the procedure of the literature,[9,10] whereas the peroxysulfuric acid oxidation gave no N-oxide. The peracetic acid oxidation of phenylpyrazine (**2**) provided only the 4-oxide in the same manner as oxidation of 2-phenylquinoxaline with percarboxylic acids.[11,12] The peroxysulfuric acid oxidation of **2** gave a small amount (2.5%) of the 4-oxide, and the expected 1-oxide was not detected. The preparation of this 1-oxide was eventually achieved by catalytic hydrogenation of 2-chloro-3-phenylpyrazine (**4**) 4-oxide in the presence of 5% palladium on carbon and triethylamine together with other reduced products **2** and **4** as shown in Scheme I. When 10% palladium on carbon was used as the catalyst in this hydrogenation, the reaction proceeded so that it had to be controlled. Other catalysts, 5% palladium on BaSO₄ or Raney nickel, were also unappropriate for increasing the proportion of the desired product.

The peracetic acid oxidation of 2-chloro-3-phenylpyrazine (**4**) gave the 4-oxide, and the persulfate oxidation provided the 1-oxide. Thus orientation of N-oxidation of **4** is governed by an effect of the chloro substituent in the same way as that of 2-chloropyrazine (**3**), indicating no effect of the phenyl group. In contrast, oxidation of 2-chloro-5-phenylpyrazine (**5**) with peracetic acid provided equal amounts (by NMR) of the 1- and 4-oxides, and the persulfate oxidation gave only the 1-oxide. Since the 4-nitrogen atom of 2-chloro-6-phenylpyrazine (**6**) is the least sterically hindered among three chlorophenylpyrazines **4, 5,** and **6,** peracetic acid oxidation of **6** provided, as expected, the 4-oxide in excellent yield. However, the persulfate oxidation of **6** afforded no N-oxide because the 1-nitrogen is sterically hindered by two substituents. The 1-oxide of **6** was prepared in minor component (2%) by treatment of 2-chloropyrazine 1-oxide with phenylmagnesium bromide.

Scheme I

4 4-oxide   →   1 mol of H₂/5% Pd–C, triethylamine in ethyl acetate   44%

+   **4**, 2%   +   **2**, 24%   + starting material 30%

PhMgBr +
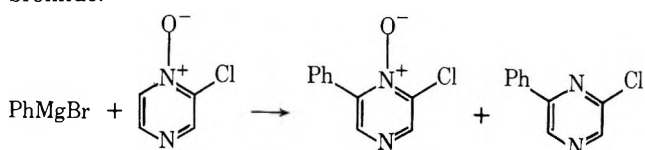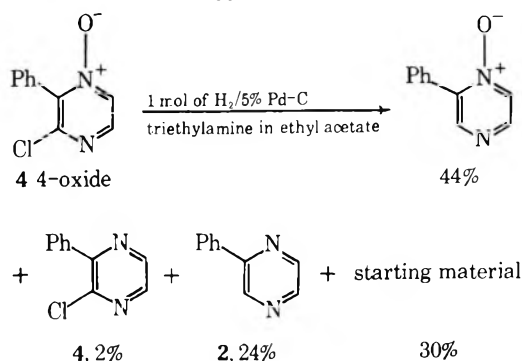
Determination of the position of the N–O group in these N-oxides was conveniently accomplished by comparison of

Table I. Preparation of Pyrazine *N*-Oxides[e]

	substituents	method[a]	products	yield, %	mp, °C (lit., °C)
1	2-methyl	A	{1-oxide}[b]	64	93–95 (90–91)[10]
			{4-oxide}		69–71 (69–70)[10]
		B		0	
2	2-phenyl	A	4-oxide	28	141–142
		B	4-oxide	2.5	
		C	1-oxide	44	132–133
3	2-chloro	A	4-oxide	61	97 (95–96)[5]
		B	1-oxide	22[d]	135–136 (133–134)[6]
4	2-chloro-3-phenyl[15]	A	4-oxide	55	151–152
		B	1-oxide	21	188–189
5	2-chloro-5-phenyl[1,16,17]	A	{1-oxide}[c]	33	146
			{4-oxide}		151
		B	1-oxide	26	
6	2-chloro-6-phenyl[1,17]	A	4-oxide	89	121–122
		B		0	
		D	1-oxide	2	128

[a] A: Acetic acid–30% hydrogen peroxide; B: sulfuric acid–potassium persulfate. C: Hydrogenation of 2-chloro-3-phenylpyrazine 4-oxide. D: Reaction of 2-chloropyrazine 1-oxide with phenylmagnesium bromide. [b] Relative ratio, 1-oxide:4-oxide 3:2. [c] Relative ratio, 1-oxide:4-oxide 1:1. [d] Lit.[7] yield 55%. We have a suspicion on this yield because our several attempts to increase the yield failed. [e] Satisfactory analytical values (±0.3% for C, H, N) were submitted with the manuscript for all oxides of 2, 4, 5, and 6.

Table II. Chemical Shift and Coupling Constant Data for Protons of the Pyrazine Ring in CDCl$_3$

compd	registry no.	chemical shift, δ			coupling constant, Hz		
		3	5	6	$J_{3,5}$	$J_{3,6}$	$J_{5,6}$
1		8.47	8.39	8.44	0	1.4	2.4
1-oxide	31396-35-7	8.49	8.36	8.27	0	0.5	4.2
4-oxide	25594-37-0	8.09	8.40	8.04	1.2	0.7	4.2
2		9.05	8.53	8.66	0	1.7	2.5
1-oxide	58861-89-5	8.59	8.33	8.17	0	0.7	4.1
4-oxide	58861-94-2	8.55	8.06	8.49	1.6	0.8	4.0
3		8.66	8.55	8.44	0	1.3	2.5
1-oxide	16025-16-4	8.69	8.41	8.30	0	0.7	4.3
4-oxide	6863-76-9	8.22	8.09	8.30	1.6	0.7	4.2
4			8.56	8.31			2.5
1-oxide	66769-58-2		8.39	8.23			4.0
4-oxide	58861-87-3		8.18	8.20			4.0
5		8.66		8.81		1.3	
1-oxide	61578-11-8	8.65		8.65		0.8	
4-oxide	61578-12-9	8.26		8.41		0	
6		8.49	8.89		0.6		
1-oxide	66769-59-3	8.56	8.46		0		
4-oxide	66769-60-6	8.08	8.45		1.2		

IR or NMR spectra of each pair of isomers. An N–O stretching frequency in the region of 1350–1260 cm^{-1} is an indication to identify the isomeric *N*-oxides of monosubstituted pyrazines 1, 2,[13] and 3 (1-oxides exhibit a deviation to lower frequencies than the corresponding 4-oxides).[6,14] However, *N*-oxides of disubstituted pyrazines 4, 5, and 6 do not show such a tendency. The NMR spectra are more informative, e.g., each pair of isomers, except for *N*-oxides of 1 and 2, conforms to the rule that the ring protons of 2-substituted pyrazine 4-oxides generally resonate at higher field than those of the corresponding 1-oxide isomers.[6,7] The coupling constants for the ring protons in pyrazine *N*-oxides were also found to be useful for the elucidation of *N*-oxide position (1-oxides: $J_{3,5}$ = 0 Hz, $J_{3,6}$ = 0.5–0.8 Hz, $J_{5,6}$ = 4.0–4.3 Hz; 4-oxides: $J_{3,5}$ = 1.2–1.6 Hz, $J_{3,6}$ = 0–0.8 Hz, $J_{5,6}$ = 4.0–4.2 Hz, respectively). A more reliable identification, however, is achieved by comparison of dipole moments of each pair of isomers. Particularly, the observed dipole moments of pyrazine 4-oxides and 2-phenylpyrazine 1-oxide are in good agreement with a vectorial sum calculated from the empirical group moments (C–Cl: 1.38 D, C–Ph: 0.84 D, and N–O: 1.62 D; see Table III). A considerable deviation (0.48–0.57 D) lower than the calculated value in 1-oxides of 3, 4, and 5 may be ascribed to the inductive replusion with the electron-withdrawing chlorine and oxygen atoms.

Discussion

With the results obtained, the mechanisms of the peracetic and peroxysulfuric acid oxidations were considered. In general, the N-oxidation reaction depends on a combination of an electronic and a steric effect.[2,3] On peracetic acid oxidations of 2, 3, and 6, which have phenyl, chloro, or both the substituents in the 2 or 2,6 positions, the yields of their 4-oxides were 28, 61, and 89%, respectively. The extent of these N-oxidations presumably depends on electronic effects since the N-oxidation reactions are not sterically inhibited at all. The yields of *N*-oxides are likewise subject to a steric effect by the pyrazine substituents. In the peracetic acid oxidation of 5, the steric hindrance by the phenyl group is evident from the low yield of the 4-oxide while the oxidation on the 1-nitrogen adjacent to the chloro substituent was suppressed. An extreme case for the steric inhibition by the phenyl group is a failure of persulfate oxidation on the 1-nitrogen of 6 whereas 2,6-dichloropyrazine forms the 1-oxide in good yield under the same conditions.[7] In the case of 4, however, the steric effect of the phenyl group could be hardly recognized on oxidation of the 4-nitrogen adjacent to this substituent because the yield of the 4-oxide was close to that of 2-chloropyrazine 4-oxide.

The generally accepted mechanism of N-oxidation involves nucleophilic attack of the lone pair of electrons on nitrogen

Table III.^{a} Dipole Moments of Substituted Pyrazines in Benzene at 25 °C

compd		dϵ/dω	dρ/dω	$T^{P_{2\infty}}$	P	μ, D	calcd value, D	$\Delta\mu^f$
2		0.717 ± 0.001	0.2162 ± 0.0003	61.2 ± 0.1	46.8	0.84 ± 0.003		
	1-oxide	1.63 ± 0.09	0.298 ± 0.001	91.5 ± 0.5	51.8	1.39 ± 0.01	1.40	0.01
	4-oxide	3.0 ± 0.2	0.299 ± 0.002	135.8 ± 1.4	51.8	2.03 ± 0.02	2.09	0.06
3		1.88 ± 0.02	0.2933 ± 0.0002	66.5 ± 0.7	27.5	1.38 ± 0.01^b		
	1-oxide	3.90 ± 0.09	0.395 ± 0.002	120.1 ± 1.2	32.5	2.07 ± 0.02	2.60	0.53
	4-oxide	2.24 ± 0.07	0.389 ± 0.002	79.7 ± 0.8	32.5	1.52 ± 0.01^d	1.51	0.01
4		1.325 ± 0.004	0.290 ± 0.001	91.0 ± 0.4	51.6	1.39 ± 0.01	1.20	−0.19
	1-oxide	2.912 ± 0.008	0.346 ± 0.006	155.8 ± 0.7	56.6	2.20 ± 0.01	2.68	0.48
	4-oxide	0.55 ± 0.02	0.3395 ± 0.0004	64.5 ± 2.3	56.6	0.62 ± 0.09	0.70	0.08
5		2.762 ± 0.007	0.279 ± 0.001	143.3 ± 0.6	51.6	2.12 ± 0.01	2.22	0.10
	1-oxide	4.431 ± 0.003	0.354 ± 0.001	214.1 ± 0.6	56.6	2.77 ± 0.01	3.34	0.57
	4-oxide	2.325 ± 0.003	0.3397 ± 0.007	133.5 ± 0.3	56.6	1.94 ± 0.004	1.99	0.05
6		2.56 ± 0.05	0.2904 ± 0.0002	135.2 ± 1.8	51.6	2.02 ± 0.03	1.94	0.08
	4-oxide	3.20 ± 0.02	0.3294 ± 0.0006	168.3 ± 1.1	56.6	2.33 ± 0.03	2.34	0.01
	pyrazine 1-oxide	3.36 ± 0.03	0.329 ± 0.001	81.2 ± 0.7	27.6	1.62 ± 0.01^{c,e}		

^{a} The dipole moment of the 1-oxide of **6** could not be measured because of insufficient amount of the sample. ^{b} Lit.[18] 1.42 D. ^{c} Lit.[18] 1.62 D. ^{d} Lit. 1.46 D: H. Lumbroso and G. Palamidessi, *Bull. Soc. Chim. Fr.*, 3150 (1965). ^{e} Lit. 1.66 D: H. Lumbroso and G. Palamidessi, *Bull. Soc. Chim. Fr.*, 3150 (1965). ^{f} $\Delta\mu = \mu_{calcd} - \mu_{found}$.

Table IV. UV Spectra of 4, 5, and 6^a

compd	nm (log ϵ)
4	237 (3.89), 249 (3.86), 287 (3.89)
5	254 (4.23), 291 (3.99), 311 (4.03)
6	252 (4.03), 290 (3.98), 310 (4.03)

^{a} In 95% C$_2$H$_5$OH.

on the outermost oxygen of the peracid.[2–4,7] The orientation of substituent pyrazines is governed by the relative basicities of the ring nitrogen.[2–5,7] The inductive effect of the substituent is assumed to be one factor in the difference in basicities of the ring nitrogens; e.g., peracetic acid oxidation of methylpyrazine **1**, having an electron-donating methyl group, leads to the formation of the 1-oxide rather than the 4-oxide in spite of the steric hindrance of the methyl group. In the same manner, the orientation of peracetic acid oxidation of chloropyrazines **3**, **4**, and **6** can be explained by the reduction of basicity of the 1-nitrogen by the electron-withdrawing inductive effect of the 2-chloro substituent. However, the 1:1 formation of the 1- and 4-oxides of **5** on peracetic acid oxidation cannot be elucidated by the inductive effect alone.

Another factor in the direction of peracetic acid oxidation is suggested to be the mesomeric interaction of the substituent with the pyrazine ring. It is particularly useful in elucidation of the effect of the phenyl group on the regiospecificity in which the nitrogen furthest removed from this substituent is exclusively oxidized. Namely, in peracetic acid oxidations of phenylchloropyrazines **5** and **6**, each phenyl group of which is conjugated with the pyrazine ring, the site of N-oxidation is controlled by the phenyl as well as by the chloro substituents. This behavior is significantly illustrated by the peracetic acid oxidation of **5**, in which the phenyl and chloro substituents lead the competitive formations of the 1- and 4-oxides, respectively. On the other hand, the excellent reactivity on the 4-nitrogen of **6** can be attributed to the combined influence of both the substituents. However, unlike the phenyl group of **5** and **6**, that of **4** is interfered in resonance conjugation with the pyrazine ring by the steric hindrance of the adjacent chloro substituent,[19,20] accordingly the influence of the phenyl group on the N-oxidation vanishes, thus the peracetic acid oxidation of **4** is governed only by the chloro substituent. This exclusive oxidation on the 4-nitrogen is seen in **4** but not in 2-me-

thoxy-3-phenylpyrazine which gives only the 4-oxide under the same conditions.[15]

The difference between persulfate and peracetic acid oxidations may be mainly acidic strength of the solvents. In concentrated sulfuric acid, the ring nitrogens of pyrazine and 2-methylpyrazine (**1**) were strongly diprotonated resulting in no formation of any N-oxide by the persulfate oxidation. Similarly, 2-phenylpyrazine (**2**) gave a low yield of the 4-oxide by treatment with peroxysulfuric acid. In contrast, the equilibrium of chloropyrazines favors protonation on the nitrogen furthest removed from the chloro substituent[7] as a result of reduction of basicity on the 1-nitrogen by the electron-withdrawing chlorine atom. In persulfate oxidation of **4** and **5**, the phenyl group has no effect on the direction and the ease of oxidation. Thus, they provided the corresponding 2-chloropyrazine 1-oxides in the same ratio as **3**.

Experimental Section

All melting points were determined in capillary tubes and are corrected. Satisfactory analytical data (±0.3% for C, H, N, Cl) were reported for all new compounds listed in Table I. Infrared spectra were recorded on a Hitachi Model EPI-G$_3$ spectrometer, the UV spectra on a Shimazu Model UV-220 spectrometer, and the NMR spectra on a JEOL Model JNM-MH-100 instrument with tetramethylsilane as an internal standard.

Dipole Moment Measurements. Dipole moments were calculated by the method of Halverstadt and Kumler[21] from measurements of the dielectric constant (ϵ) and the specific gravity (ρ) of the solvent (benzene) and four different solutions of each compound. The specific gravities were measured with a 5-mL Lipkin-Davison's pyknometer. Dielectric constants at 25 °C were derived from measurements with a Yamato FAM-3A capacitance bridge and a glass cell. The electronic polarization was obtained by summation of bond electronic polarizabilities which were taken for C$_{Ar}$–C$_{Ar}$, C$_{Ar}$–N$_{Ar}$, C–C, C–H, C–Cl, and N–O as 2.69, 2.64, 1.30, 1.68, 6.51,[22] and 5.00,[18] respectively. No allowance was made for atomic polarization. The dielectric constant and specific gravity of benzene were taken as 2.2741 and 0.8732, respectively, at 25 °C.

2-Phenylpyrazine (2). A mixture of 5-phenylpyrazinedicarboxylic acid[23] (mp 193 °C, 17.5 g, 0.072 mol), which was prepared by potassium permanganate oxidation of 2-phenylquinoxaline, and powdered copper (II) oxide (0.7 g) was heated and distilled at 200–236 °C to give 12.7 g of colorless solid. Redistillation at 80 °C (5 mm) afforded 9.5 g (85%) of **2**,[24] which was recrystallized from ethanol to provide colorless needles, mp 72–73 °C.

This pyrazine **2** was also prepared by hydrogenolysis of chlorophenylpyrazine. A solution of **3** (5.52 g, 0.029 mol) in a mixture of ethyl acetate and triethylamine (9:1 v/v, 100 mL) was hydrogenated in the presence of 10% palladium on carbon (2.0 g) under atmospheric

pressure until the uptake of hydrogen ceased (720 mL of hydrogen at 20 °C for ca. 2 h). Then the resulting mixture was filtered and evaporated under reduced pressure. The residue was washed with cold water, dried in air, and recrystallized from ethanol to give 4.10 g (91%) of 2.

General Preparation of Pyrazine N-Oxides. The peracetic acid oxidations were accomplished according to the procedure of the literature,[5,6,9,10,15] and the peroxysulfuric acid oxidation followed a procedure by Mixan and Pew.[7] The ratio of the 1- and 4-oxides of 1 in the reaction mixture was determined by GC (5% PEG succinate on Chromosorb WAW DMCS, 1 m glass column at 135 °C), and the separation was achieved by the procedure of Gumprecht and co-workers.[10] As the N-oxides of 4 and 5 were contaminated with a considerable amount of the starting pyrazines, the N-oxides were purified by column chromatography on silica gel (1 g/10 g). The first elution with benzene gave the starting pyrazine, and the second elution with benzene–chloroform or chloroform provided the N-oxide. The separation of the 1- and 4-oxides of 5 was carried out on a Merck PLC plate (silica gel 60 F_{254}) eluted with benzene.

2-Phenylpyrazine 1-Oxide. A solution of 2-chloro-3-phenylpyrazine (4) 4-oxide (1.652 g, 8.0 mmol) in 40 mL of ethyl acetate containing triethylamine (0.81 g, 8.0 mmol) was stirred with hydrogen (198 mL at 29 °C) in the presence of 5% palladium on carbon (0.5 g) under atmospheric pressure. The mixture was filtered and evaporated under reduced pressure. The residue was washed with cold water, dried in air, and dissolved in benzene, which was passed through a column of silica gel (30 g). The chromatogram was developed with benzene and successively benzene–chloroform (3:1), to afford 2, 4, and the starting N-oxide. Further elution with chloroform gave 0.605 g (44%) of 2-phenylpyrazine 1-oxide, which was recrystallized from ethanol to give colorless prisms.

2-Chloro-6-phenylpyrazine 1-Oxide (6). A solution of phenylmagnesium bromide in dry tetrahydrofuran (THF) (2.2 mol/L, 20.0 mL, 0.044 mol) was added dropwise to a stirred solution of 2-chloropyrazine 1-oxide (2.512 g, 0.019 mol) in 80 mL of THF and refluxed for 5 h. The mixture was washed with saturated aqueous ammonium chloride, dried over magnesium sulfate, and evaporated under reduced pressure. The residue (ca. 5 g) was dissolved in benzene and the solution was passed through a column of silica gel (80 g). The first elution with petroleum ether–benzene (1:1) gave biphenyl, and the second elution with benzene afforded 2.934 g of 6. Further development with chloroform gave 0.080 g (2%) of the N-oxide, which was recrystallized from ethanol to give colorless crystals.

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Novel Rearrangement of Ketazine Dianion: New Synthetic Route to Pyrrole, Tetrahydropyridazine, and Pyrazole

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The dianions of alkyl aryl ketazines, generated by treating alkyl aryl ketazines with 2 equiv of lithium diisopropylamide, rearranged selectively to pyrrole, tetrahydropyridazine, or pyrazole depending on the nature of the ketazine. The main factor governing the course of the reaction is the electron density on the carbon termini. Ketazine dianions bearing electron-releasing groups (i.e., propiophenone, butyrophenone, and tetralone azines) on their carbon termini rearrange to pyrroles, while ketazine dianions without substituents (i.e., acetophenone and acetonaphthone azines) and with electron-withdrawing substituents rearrange to tetrahydropyridazines and pyrazoles, respectively.

Coupled with the development of versatile methods for preparing systems suitable for rearrangement, various modifications of the Cope and Claisen rearrangements have been exploited in recent years[1] and the high stereoselectivity has prompted several applications of these rearrangements in the syntheses of natural products.[2] One of the current topics in this field is the hetero-Claisen rearrangement[3] (especially thio-Claisen rearrangement[4]), which generally proceeds highly

stereoselectively at relatively low temperatures. Further, interesting anion-assisted oxy-Cope and Claisen rearrangements have been reported; i.e., R. E. Ireland et al.[5] have reported that the rearrangement of the enolate anion of allyl esters proceeds easily at room temperature. The oxy-Cope rearrangement was also accelerated enormously by the metalation of the hydroxyl group.[6]

In this context, we have been interested in the possibility

Table I. Reaction of Ketazine Dianion [a]
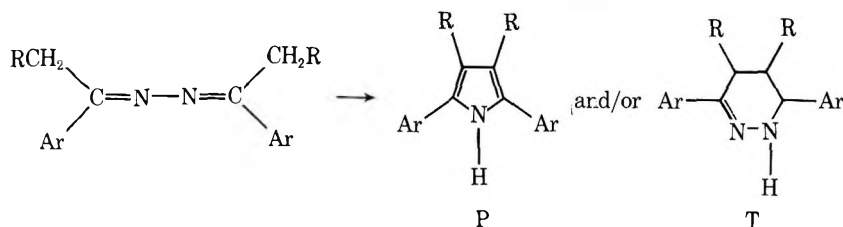
Entry	Ketazines		Registry no.	LDA, equiv	Solvent	Products [b] (isolated yield)	Registry no.
	Ar	R					
1	Ph	CH$_3$	17745-97-0	2.2	THF	P (52%)	17799-61-0
2	Ph	CH$_3$		2.2	Ether	P (25%)	
3	Ph	CH$_3$CH$_2$	17745-98-1	3.0	THF	P (34%)	66575-47-1
4	(tetralone azine)		66575-46-0	3.0	THF	P (68%)	41403-73-0
5	p-Tolyl	H	21399-33-7	3.0	THF	P (24%)	21399-23-5
6	Ph	H	729-43-1	2.2	THF	T (34%)	16080-63-0
7	Ph	H		2.2	Ether	P (30%)	838-40-4
8	β-Naphthyl	H	55043-66-8	3.0	THF	T (17%)	62441-52-5
9	p-Anisyl	H	21399-23-5	3.0	THF	P (6%), T (7%)	21399-24-6, 66575-48-2
10	p-Anisyl	H		3.0	THF [c]	P (26%)	
11	p-Anisyl	H		4.4	THF–HMPA [c]	T (13%) [d]	

[a] Unless otherwise specified, the reaction was performed at room temperature and analyzed after 24 h. [b] The symbols P and T are meant to refer to pyrrole and tetrahydropyridazine, respectively. The other products were mainly constituted of tarry materials, which remained at the starting spot on a silica gel plate (8:1 PhH/EtOAc and/or 2:1 hexane/acetone). [c] Refluxed for 4 h. [d] In addition to tetrahydropyridazine, 1-(1-p-anisyl)ethyl-3-p-anisylpyrazole (registry no., 66531-47-3) was also isolated in 17% yield.[10]

of the rearrangement of the dianion of a ketazine, which might provide a new synthetic route to a 1,4-diketone or its equivalent from a simple ketone (eq 1).
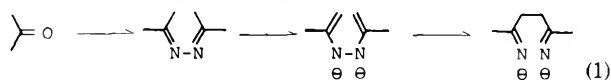
During the course of our study,[7] we have found that the dianions of alkyl aryl ketazines rearrange selectively to pyrroles, tetrahydropyridazines, or pyrazoles at temperatures ranging from room temperature to THF reflux depending on the nature of the ketazines and the reaction solvents. To our knowledge, this is the first reported example of the rearrangement in which a dianion participates. Herein we report the novel Cope-type rearrangement of ketazine dianions and some mechanistic aspects of this rearrangement.

Results and Discussion

Recently the rearrangement of monoanions of dialkyl ketazines to 1,3-disubstituted pyrazoles with one carbon homologation has been reported.[8] Compared with the relative difficulty even in monoanion generation of dialkyl ketazines, the dianions of alkyl aryl ketazines were easily generated by treatment with lithium diisopropylamide (LDA). Ketazine dianions were first generated by F. E. Henoch et al. in 1969,[9] who treated acetophenone azine with 2 equiv of n-butyllithium in ether and showed the generation of the dianion by alkylation of both methyl groups. This method was not satisfactory for the generation of dianions of ketazines other than acetophenone azine, owing to the nucleophilic attack of n-butyllithium on the C=N carbon of ketazines. The generation of dianion under the reaction conditions employed by us was confirmed by the introduction of one deuterium in each methyl group of acetophenone azine (1). Thus, 1 was treated with 2.2 equiv of lithium diisopropylamide (LDA) in THF at room temperature for 30 min and then quenched with degassed D$_2$O. The NMR spectrum of the recovered crude sample showed a decrease of area intensity of methyl groups

by two protons and a change from a singlet to a triplet (J = 2.2 Hz). After allowing this deep reddish brown dianion solution to stir for 24 h at room temperature under argon, the reaction was quenched with degassed water. By thorough examination of the crude reaction mixture by means of column chromatography, 3,6-diphenyl-1,4,5,6-tetrahydropyridazine (2) was obtained in 34% yield as the only isolable product (eq 2). On the other hand, pyrrole derivative 4 was obtained by
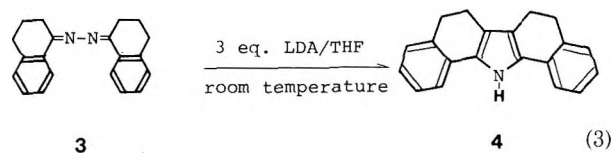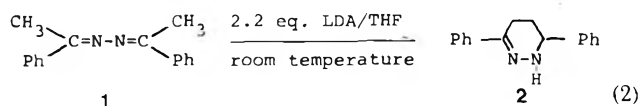
the similar treatment of α-tetralone azine (3) in 68% isolated yield (eq 3). Thus, 3 was treated with 3.0 equiv of LDA in THF at room temperature. Immediately after the addition of 3 to a THF solution of LDA, the yellow color of 3 turned to deep reddish brown and then to deep green within a few minutes. The completion of the rearrangement was observed within 1 h by TLC monitoring. In a similar fashion, seven alkyl aryl ketazines were examined and found to give pyrrole and/or tetrahydropyridazine depending on the nature of the ketazines and solvent systems. The results are summarized in Table I.

Generally, the reactions to give pyrroles proceeded faster than those to give tetrahydropyridazines. Propiophenone and butyrophenone azines (entires 1 and 3), like tetralone azine, rearranged completely to pyrroles within 1 or 2 h at room temperature, while the reactions of acetophenone and β-acetonaphthone azines (entries 6 and 8) were sluggish and even after 24 h a small amount of the starting azine remained.

Except for the case of p-methoxyacetophenone azine (entires 9 and 11[10]), the rearrangement was selective to give pyrrole or tetrahydropyridazine.

It seems worthwhile to consider some aspects of the reaction mechanism in order to understand the selectivity of this rearrangement. By analogy with the results of the x-ray analysis of hexatriene dianion[11] and taking into consideration the large coordination ability of a nitrogen atom to a metal cation, the structure of the most stable form of these dianions may be depicted as in 5 (eq 4), where lithium is coordinated by ni-

trogen to form a five-membered cyclic structure. On the bases of the selectivity and the large differences in reactivities between the two pathways to give pyrrole 9 and tetrahydropyridazine 11, two different kinds of intermediates (6 and 7) which equilibrate with 5 seem to contribute to these rearrangements.
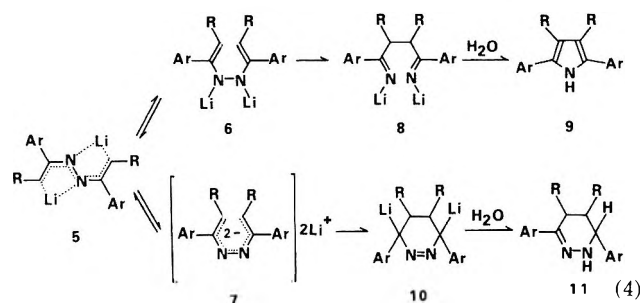
These intermediates 6 and 7 are two extremes, with the anionic charges localized on nitrogen atoms to which lithium ions are bound tightly in the former and the anionic charges delocalized over the system in the latter. In going from acetophenone azine to α-tetralone azine, the intermediate 6 might become more favorable than 7 due to the destabilization of the carbanion by introduction of an alkyl group (and to a lesser extent by the substitution of electron-releasing groups on the benzene ring; p-tolyl and p-anisyl). The intermediate 6 could be expected to rearrange to 8, which is the direct precursor of pyrrole,[12] in a [3.3] sigmatropic fashion rapidly and exothermally owing to the large difference of the heat of formation[13] of these two intermediates and the separation of the vicinal anionic charges to 1,6 positions. The mechanism leading to tetrahydropyridazine is not clear. It may involve a stepwise cyclization mechanism or an 8π-electrocyclic reaction. This reaction could be expected to be slow owing to an electrostatic repulsion between the bond-forming carbon termini bearing anionic charges.

The reaction scheme proposed above is in good accord with the solvent effect observed for the reaction of acetophenone azine. That is, although propiophenone azine gave pyrrole selectively both in ether and THF (entries 1 and 2), acetophenone azine gave tetrahydropyridazine in THF, while it rearranged to pyrrole selectively in ether (entries 6 and 7). This intriguing contrast may be explained on the basis of the difference of solvation ability between these two solvents.[14a] In going to ether with its smaller solvation ability, the intermediate 6 with less ionic character becomes more favorable than 7 and results in pyrrole formation. Analogously, the solvent dependence of product distribution may be explained in the case of p-methoxyacetophenone azine (entries 10 and 11[10]). Furthermore, the temperature dependence on the product selectivity observed in entries 9 and 10 supports this rationale. That is, while at room temperature p-methoxyacetophenone azine rearranges to a 1:1 mixture of pyrrole 9 and tetrahydropyridazine 11, at THF reflux temperature, owing to desolvation,[14] the equilibrium becomes favorable to an intermediate 6, tightly bound by cations, and gives pyrrole 9 selectively.

As one extreme, where carbanions were stabilized by phenyl substituents, benzyl phenyl ketazine (12) was treated with 2 equiv of LDA in THF at room temperature for 24 h and in this case the complete recovery of 12 was observed. Under forcing conditions, 12 took a completely different course of reaction to provide 3,4,5-triphenylpyrazole (14; eq 5). That is, dianion

$$(5)$$
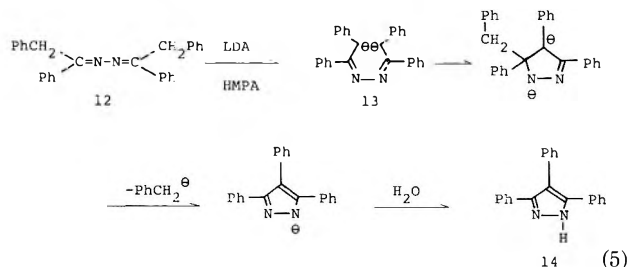
13 was heated at 65 °C for 1 h in THF–HMPA (3:1) to give 14 in 70% isolated yield (based on 12 consumed; 65% conversion).

For the formation of 14, stepwise ionic cyclization, probably initiated first by the attack of benzylic carbanion on the C=N carbon followed by elimination of benzyl anion as shown in eq 5, seems to be most probable.

In conclusion, ketazine dianions rearrange selectively to one of three kinds of products, pyrrole, tetrahydropyridazine, and pyrazole, in a strikingly different reactivity. The main factor controlling this reactivity and selectivity seems to be the electron density on the carbon termini. Ketazine dianions bearing electron-releasing groups on carbon termini rearrange to pyrroles, whereas those without substituents (i.e., acetophenone and acetonaphthone azines) or with electron-withdrawing substituents rearrange sluggishly to tetrahydropyridazines or pyrazoles, respectively.

The pyrrole synthesis reported here is a contrast to the Piloty pyrrole synthesis,[15] the acid-catalyzed pyrrole synthesis from ketazine at high temperatures (ZnCl$_2$ or HCl at 180 to 220 °C), while it shows a similarity to the Fischer indole synthesis[16] in a mechanistic point of view.[17]

Experimental Section

Melting points were uncorrected. The elemental analyses were performed at the Microanalysis Center of Kyoto University. Infrared spectra were measured with a Hitachi Model EPI-G3 grating spectrophotometer, and ^{1}H NMR spectra were recorded with either a Varian HA 100 or a Jeol JNM-PMX 60 spectrometer. Mass spectra were measured with a Hitachi Model RMU 6C spectrometer.

Ketazines. Ketazines were prepared in quantitative yields from the corresponding ketones and hydrazine hydrate in refluxing ethanol in the presence of a catalytic amount of acetic acid. They were purified by repeated recrystallization.

Solvents. THF and diethyl ether were dried over sodium–benzophenone, and diisopropylamine and hexamethylphosphoric triamide were dried over calcium hydride and distilled under argon prior to use.

3,4-Dimethyl-2,5-diphenylpyrrole. Under argon, a solution of diisopropylamine (3.3 mmol) in dry THF (10 mL) was treated with n-butyllithium (15% hexane solution; 3.3 mmol) at 0 °C, and after 10 min propiophenone azine (1.5 mmol) dissolved in THF (5 mL) was added to the solution of lithium diisopropylamide in THF at room temperature. Immediately, the yellow color of the starting ketazine turned to deep reddish brown, and gradually to deep green within a few minutes. After stirring for 24 h at room temperature, the reaction mixture was quenched with degassed water and extracted with ether. After drying over sodium sulfate and evaporation of the solvent, 3,4-dimethyl-2,5-diphenylpyrrole was isolated in 52% yield by silica gel column chromatography using benzene as an eluent: mp 138–139 °C (lit.[18] mp 136 °C); MS m/e 247 (M$^+$, 100%), 246 (48); IR (KBr) ν_{max} 3410 (s), 1603 (s), 1495 (s), 765 (s), 702 (s), 694 (s) cm^{-1}; NMR (CDCl$_3$; Me$_4$Si) δ 2.13 (6 H, s), 7.43 (10 H, aromatic protons), 7.9 (1 H, br).

3,4-Diethyl-2,5-diphenylpyrrole. n-Butyrophenone azine was reacted with 3.0 equiv of LDA in THF at room temperature for 24 h. After the usual workup and subsequent purification by column chromatography (silica gel, benzene elution), 3,4-diethyl-2,5-diphenylpyrrole was isolated in 34% yield: mp 81–85 °C; MS m/e 275

(M+, 98%), 265 (100); IR (KBr) ν_{max} 3450 (m), 1607 (m), 770 (s), 702 (s) cm^{-1}; NMR (CDCl$_3$; Me$_4$Si) δ 1.22 (6 H, t, J = 7.0 Hz), 2.68 (4 H, q, J = 7.0 Hz), 7.1–7.6 (10 H, aromatic protons), 7.93 (1 H, br). Anal. Calcd for C$_{20}$H$_{21}$N: C, 87.23; H, 7.69. Found: C, 86.93; H, 7.63.

Dibenzo[a,i]-3,4,5,6-tetrahydrocarbazole (4). α-Tetralone azine was reacted in a similar way to propiophenone azine to give 4 in 68% isolated yield after purification by silica gel column chromatography with benzene elution: mp 162–163 °C; MS m/e 271 (M+, 100%); IR (KBr) ν_{max} 3455 (m), 1613 (s), 760 (s) cm^{-1}; NMR (CDCl$_3$; Me$_4$Si) δ 2.7 (8 H, m), 7.2 (8 H, aromatic protons), 8.35 (1 H, br). Anal. Calcd for C$_{20}$H$_{17}$N: C, 88.53; H, 6.32; N, 5.16. Found: C, 88.69; H, 6.18; N, 5.13.

2,4-Di-p-tolypyrrole. p-Methylacetophenone azine was reacted and worked up in a similar way to propiophenone azine to give 2,4-di-p-tolylpyrrole in 24% isolated yield after purification by silica gel column chromatography with hexane–acetone gradient elution: mp 196.0–196.5 °C (lit.[19] mp 203–204 °C); MS m/e 247 (M+); IR (KBr) ν_{max} 3475 (s), 1510 (m), 780 (s) cm^{-1}; NMR (CDCl$_3$; Me$_4$Si) δ 2.36 (6 H, s), 6.50 (2 H, d, J = 2.4 Hz), 7.30 (8 H, AA'BB'), 8.50 (1 H, br). Anal. Calcd for C$_{18}$H$_{17}$N: C, 87.40; H, 6.93; N, 5.66. Found: C, 87.63; H, 6.95; N, 5.42.

3,6-Diphenyl-1,4,5,6-tetrahydropyridazine (2). Acetophenone azine (1.5 mmol) was treated with LDA (3.3 mmol) in THF (15 mL) for 24 h at room temperature. In this case, the first formed deep reddish brown color of the reaction mixture did not change to deep green as in the case of propiophenone azine. After the usual workup, a 34% yield of 3,6-diphenyl-1,4,5,6-tetrahydropyridazine (2) was isolated by recrystallization from benzene–hexane: mp 158.0–159.5 °C (lit.[20] mp 157–158 °C); MS m/e 236 (M+, 100%); 159 (32), 132 (57); IR (KBr) ν_{max} 3300 (m), 1596 (m), 1498 (s), 753 (s), 692 (s) cm^{-1}; NMR (CDCl$_3$; Me$_4$Si) δ 2.2 (2 H, m), 2.7 (2 H, m), 4.2 (1 H, m), 5.9 (1 H, br), 7.3–7.7 (10 H, aromatic protons).

3,6-Di-β-naphthyl-1,4,5,6-tetrahydropyridazine. β-Acetonaphthone azine was reacted in a similar way to acetophenone azine. Recrystallization of the reaction mixture from dichloromethane–benzene–hexane gave 3,6-di-β-naphthyl-1,4,5,6-tetrahydropyridazine in 17% yield: mp 231–232 °C; MS m/e 336 (M+); IR (KBr) ν_{max} 3210 (m), 1604 (m) cm^{-1}; NMR (CDCl$_3$; Me$_4$Si) δ 2.4 (2 H, m), 2.8 (2 H, m), 4.4 (1 H, m), 6.0 (1 H, br), 7.3–8.2 (14 H, aromatic protons). Anal. Calcd for C$_{24}$H$_{20}$N$_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.64; H, 5.78; N, 8.58.

Rearrangement of p-Methoxyacetophenone Azine in THF. To p-methoxyacetophenone azine (1.5 mmol) was added a solution of LDA (4.5 mmol) in THF (15 mL) at room temperature. Gradually the dark reddish brown homogeneous reaction mixture became heterogeneous, owing to the precipitation of solid. After stirring for 24 h at room temperature, the reaction mixture was quenched with degassed water and extracted with dichloromethane. The reaction mixture was subjected to column chromatography (silica gel, with benzene–ethyl acetate gradient elution) to give 6% of 2,5-di-p-anisylpyrrole and 7% of 3,6-di-p-anisyl-1,4,5,6-tetrahydropyridazine. 2,5-Di-p-anisylpyrrole: mp 228–229 °C (lit.[19] mp 232 °C); MS m/e 279 (M+, 100%); 264 (94); IR (KBr) ν_{max} 3475 (m), 2850 (w), 1505 (s), 840 (s) cm^{-1}; NMR (acetone-d$_6$) δ 3.81 (6 H, s), 6.46 (2 H, d, J = 2.0 Hz), 7.32 (8 H, AA'BB').

3,6-Di-p-anisyl-1,4,5,6-tetrahydropyridazine: mp 164–165 °C; MS m/e 296 (M+); IR (KBr) ν_{max} 3390 (m), 1615 (m), 1510 (s), 828 (s) cm^{-1}; NMR (CDCl$_3$; Me$_4$Si) δ 2.2 (2 H, m), 2.66 (2 H, m), 3.80 (6 H, s), 4.1 (1 H, m), 5.68 (1 H, br), 6.9–7.6 (8 H, aromatic protons). Anal. Calcd for C$_{18}$H$_{20}$N$_2$O$_2$: C, 72.95; H, 6.80; O, 10.80; N, 9.45. Found: C, 72.66; H, 6.84; O, 11.07; N, 9.43.

To p-methoxyacetophenone azine (1.5 mmol) was added a solution of LDA (4.5 mmol) in THF (15 mL) at room temperature. Then the reaction mixture was refluxed for 3 h. After the usual workup, a 26% yield of 2,5-di-p-anisylpyrrole was isolated by silica gel column chromatography using benzene–ethyl acetate as an eluent. In this reaction the concomitant formation of tetrahydropyridazine was not observed by TLC examination of the reaction mixture.

Rearrangement of p-Methoxyacetophenone Azine in THF–HMPA. To a solution of LDA (4.4 mmol) in THF (10 mL)–HMPA (0.7 mL) was added a THF (5 mL) solution of p-methoxyacetophenone azine (1 mmol) at room temperature. Then the reaction mixture was refluxed for 4 h. After the usual workup, 13% of 3,6-di-p-anisyl-1,4,5,6-tetrahydropyridazine and 17% of 1-(1-p-anisyl)-ethyl-3-p-anisylpyrazole were isolated by means of column chromatography and subsequent recrystallization from ethanol. 1-(1-p-Anisyl)ethyl-3-p-anisylpyrazole (oil): MS m/e 281 (M+ –.CH$_3$O, <1%), 250 (22), 135 (100); IR (neat) ν_{max} 2440 (w), 1618 (m), 840 (s) cm^{-1}; NMR (CDCl$_3$; Me$_4$Si) δ 1.87 (3 H, d, J = 10.2 Hz), 3.75 (3 H, s), 5.50 (1 H, q, J = 10.2 Hz), 6.43 (1 H, d, J = 2.2 Hz), 7.27 (1 H, d, J =

2.2 Hz), 6.8–7.8 (8 H, m). Anal. Calcd for C$_{19}$H$_{20}$N$_2$O$_2$: C, 74.00; H, 6.54. Found: C, 74.00; H, 6.70.

Rearrangement of Acetophenone Azine in Ether. To acetophenone azine (1 mmol) was added an ether solution (15 mL) of LDA (2.2 mmol) at room temperature. The heterogeneous reaction mixture was stirred for 24 h at room temperature. After the usual workup and purification by silica gel column chromatography (using benzene as an eluent), 2,5-diphenylpyrrole was obtained in 30% of the isolated yield (based on the consumed ketazine; 65% conversion): mp 142–143 °C (lit.[19] mp 143 °C); MS m/e 219 (M+); IR (KBr) ν_{max} 3460 (m), 1610 (s), 1490 (s), 755 (s), 695 (s) cm^{-1}; NMR (CCl$_4$; Me$_4$Si) δ 6.45 (2 H, d, J = 3.0 Hz), 7.0–7.7 (10 H, m), 7.85 (1 H, br s).

3,4,5-Triphenylpyrazole (14). Into a solution of LDA (9 mmol) in 20 mL of THF was added a solution of benzyl phenyl ketone azine (12) in 10 mL of THF and 10 mL of HMPA at room temperature, and then the reaction mixture was heated at 65 °C for 1 h. During the reaction, the color changed from deep blue to deep green. Degassed water was added, and the reaction mixture was extracted with benzene. Evaporation of solvent and subsequent recrystallization from acetone gave 14 as colorless crystals in 70% isolated yield (based on ketazine consumed; 65% conversion): mp 259–260 °C (lit.[21] mp 295–261 °C); IR (KBr) ν_{max} 3220 (vs), 1490 (m), 1440 (m), 1150 (m), 980 (s), 770 (s), 720 (s), 690 (s) cm^{-1}; NMR (Me$_2$SO-d$_6$) δ 7.7 (m, 15 H), 13.5 (br s, 1 H). Anal. Calcd for C$_{21}$H$_{16}$N$_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.39; H, 5.59; N, 9.51.

Deuterium Oxide Quenching of Acetophenone Azine Dianion. A 1.5-mmol amount of acetophenone azine dianion was treated with 3.3 mmol of LDA in THF at room temperature for 0.5 h. Then the reaction mixture was poured into ether–D$_2$O saturated with NaCl and degassed and cooled at 0 °C. The organic layer was separated and dryed over sodium sulfate. After subsequent evaporation of the solvent, starting acetophenone azine was recovered. The NMR spectrum of the recovered crude sample showed a decrease of area intensity of the methyl group by two protons and a triplet (J = 2.2 Hz). Rearranged product was not detected within this reaction time. The mass spectrum also supports the introduction of two deuteriums: MS m/e 239 (M + 1, 8.0%), 238 (M+, 37), 237 (M − 1, 25), 236 (M − 2, 12), 77 (100). Cf. acetophenone azine: MS m/e 237 (M + 1, 9.4%), 236 (M+, 53), 235 (M − 1, 12), 221 (100).

Registry No.—12, 30506-03-7; 14, 18076-30-7.

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3H-1,2-Benzodithiole Oxides: Studies Directed toward the Generation of o-Thiobenzoquinone Methide and Benzo[b]thiete

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o-Thiobenzoquinone methide (1) has been generated by photodesulfonylation of 3H-1,2-benzodithiole 2,2-dioxide (3) in benzene and was trapped with added N-phenylmaleimide as the [4 + 2] (or [8 + 2]) adduct (4). The 2,2-dioxide 3 was prepared in ~10% yield by either oxidation of 3H-1,2-benzodithiole (5) or oxidative cyclization of 2-mercaptomethylthiophenol (7) with m-chloroperoxybenzoic acid (MCPBA). Peroxyacetic acid oxidation of 7 also afforded 3 in low yield, along with the monoxides 3a and 6a; under somewhat more vigorous conditions 7 gave 3H-1,2-benzodithiol-3-one 1-oxide (8) in 29% yield. The 1-oxide 8 was also isolated (15% yield) along with a 65% yield of the corresponding 1,1-dioxide 9 from a direct oxidation of 3H-1,2-benzodithiol-3-one with MCPBA. Mild periodate oxidation of 5 at 24 °C cleanly afforded the monoxides 3a and 6a in a 1:1 ratio; brief treatment of this difficultly separable mixture with aqueous Na$_2$CO$_3$ led to complete disproportionation of 3a to 3 and 5 under conditions which left 6a unaffected and allowed its isolation and further oxidation with periodate (65 °C) to yield pure 3H-1,2-benzodithiole 1,1-dioxide (6). Alternatively, a 1:1 mixture of 3 and 6 could be obtained directly from 5 by vigorous periodate oxidation run at 70 °C and catalyzed by I$_2$. Irradiation of pure 6 under conditions used for the photolysis of 3, as well as in the presence of benzophenone as a sensitizer, did not yield any of the desired benzo[b]thiete (2), nor was the formation of any adduct (4) of 1 (assuming that a conversion of 2 to 1 might occur) with added N-phenylmaleimide observed.

The original objectives of the research described in this report were the generation of o-thiobenzoquinone methide (1)[2] and a determination of whether or not 1 exists in equilibrium with its valence tautomer, benzothiete (2).[3] In pursuing these goals we reasoned that photochemically or thermally induced extrusion of SO$_2$ from 3H-1,2-benzodithiole 2,2-dioxide (3) might yield 1 and/or 2 directly[4] and that 1 would be sufficiently reactive toward dienophiles to undergo [4 + 2] (or [8 + 2]) cycloaddition reactions to yield stable adducts (e.g., 4 via condensation with N-phenylmaleimide[2]), thereby demonstrating its potential use in synthesis[5] as well as providing proof of its generation in solution. The 2,2-dioxide 3 might, in turn, be readily accessible by regioselective peroxyacid oxidation of the 2-sulfur atom (i.e., the presumably more electron-rich alkyl-substituted sulfur) of 3H-1,2-benzodithiole (5), an assumption that we initially felt was warranted by the results of a model study of the m-chloroperoxybenzoic acid oxidation of benzyl and ethyl phenyl disulfides.[6] In the event that nonregioselectivity proved to be the case in the oxidation of 5,[7,8] obtention of 6 (and/or 6a) would allow us, in addition, to test a direct and previously unexplored route to the parent benzothiete system (2) via extrusion of SO$_2$ from 6.[9]
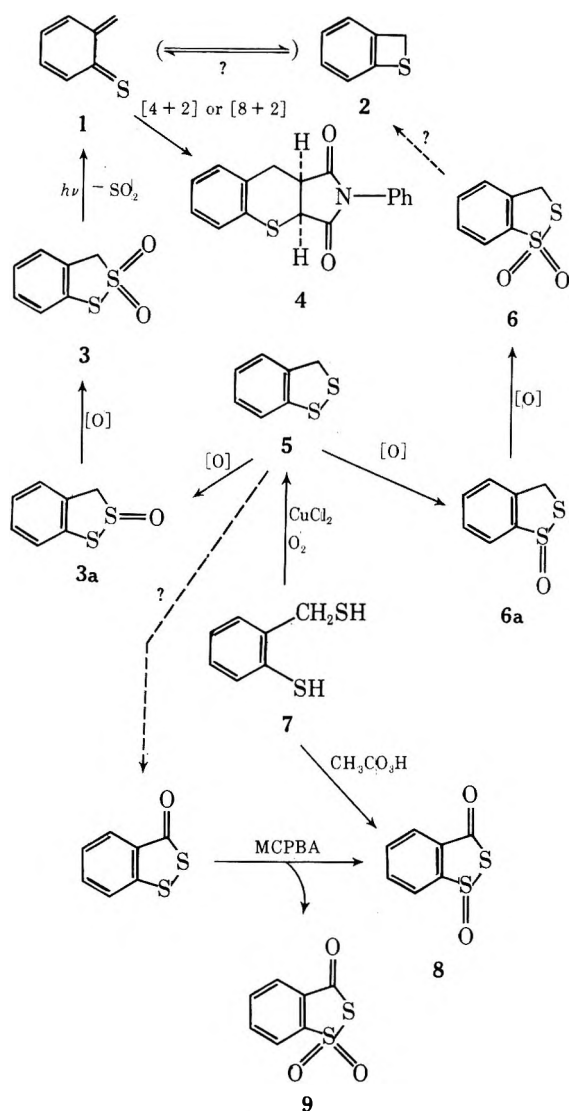
Results and Discussion

3H-1,2-Benzodithiole (5) was first prepared by slow addition of a 2% solution of 2-mercaptomethylthiophenol (7) to a 7.5% solution of ferric chloride in acetic acid–methanol at 10 °C as described by Lüttringhaus and Hägele.[10] Attempts to improve on their reported 40% yield of 5 led us to develop a modified procedure (see Experimental Section) whereby 5 was eventually obtainable in 81% yield (ca. 85% pure by ^{1}H NMR assay) by slow addition of a 1% alcoholic solution of 7 to a vigorously stirred 2% solution of cupric chloride dihydrate in either ethanol or methanol at 24 °C in the presence of air.[11] As had been observed previously,[10] 5 was found to deteriorate

rapidly in the absence of solvent, and efforts to purify crude 5 by distillation in vacuo or by column chromatography (SiO$_2$; Al$_2$O$_3$) led to intractable decomposition products. Consequently, it was necessary to use 5 directly as obtained (after extraction) from the CuCl$_2$-catalyzed oxidation of 7 or to store 5 at −10 °C as a 2–3% solution in methylene chloride or diethyl ether until needed.

Preliminary studies on the oxidation of 5 with 2 mol equiv of m-chloroperoxybenzoic acid (MCPBA) in CH$_2$Cl$_2$ at 25 °C afforded small amounts (<10% yield) of a crystalline solid which analyzed correctly for C$_7$H$_6$O$_2$S$_2$. The product exhibited strong infrared bands at 1150 and 1335 cm^{-1} (−S−SO$_2$−) and ^{1}H NMR signals at δ 4.70 (s, 2) and 7.37 (broad s, 4). The data led to a tentative assignment of either 3 or 6 as possible structures for the new compound. A distinction in favor of structure 3 for the product was allowed by the observation that the ^{13}C NMR signal due to the [13]CH$_2$ group in the new thiolsulfonate appears at 64.8 ppm downfield from Me$_4$Si, a typical value for ^{13}C in the −SSO$_2$CH$_2$Ph moiety.[12]

Closer examination of the ^{1}H NMR spectrum of the crude product mixture derived from the oxidation of 5 with MCPBA indicated that two other products (which later proved to be 3a and 6a) were also formed in low yield. However, no improvement beyond the original optimum yield (ca. 10%) of isolable 3 could be effected despite considerable efforts in varying the reaction conditions.

A literature report[13] describing the peroxyacetic acid oxidation of the mercaptans RSH, where R = cyclopentyl and cyclohexyl, to yield the corresponding thiolsulfonates RSO$_2$SR in 34 and 61% yields led us to attempt a direct peroxyacid-mediated oxidative cyclization of 2-mercaptomethylthiophenol (7) to 3 and/or 6. Indeed, upon treatment of 7 with 3 mol equiv of MCPBA in CH$_2$Cl$_2$ at 0 °C, an 11% yield of 3 was obtained. Similarly, treatment of 7 with excess commercial 40% peroxyacetic acid in CHCl$_3$ at 0–5 °C for 1 h afforded what later proved to be (by ^{1}H NMR assay) a 3:6:7 mixture of

material which consisted of a ca. 1:1 mixture of **5** and the unchanged oxidation product of **5** exhibiting the AB pattern centered at δ 4.91. The reappearance of the disulfide **5** and the loss of the periodate oxidation product of **5** having the 2 H singlet at δ 4.60 led us to believe that the latter, possibly a thiolsulfinate (**3a** or **6a**), had undergone disproportionation on the column to the disulfide **5** and either **3** or **6**. Subsequently, we also observed that when an aqueous acetonitrile solution of a similar 1:1 mixture of periodate oxidation products of **5** was shaken vigorously with an aqueous sodium carbonate solution for several minutes, and the solution was then extracted immediately with methylene chloride and assayed (¹H NMR), the final mixture was found to consist of **5**, **3**, and the (unchanged) periodate oxidation product of **5** exhibiting the AB pattern at δ 4.91 in a ratio of 1:1:2, respectively. The result clearly suggested that, at least in this experiment, a selective disproportionation of the periodate oxidation product having the 2 H singlet at δ 4.60 was indeed occurring, and the result was rationalized as being in apparent analogy with a similar disproportionation of the thiolsulfinate **10**, which has been reported by Oae and co-workers[18] to occur upon attempted alkaline hydrolysis of **10** to yield the disulfide **11** and thiosulfonate **12**. This explanation led to the conclusion
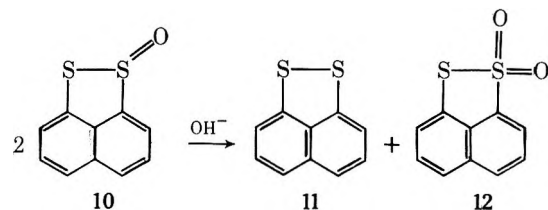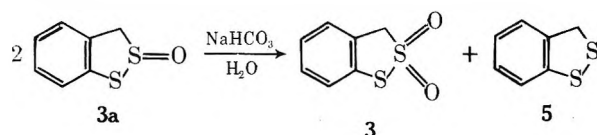
that *both* of the original periodate oxidation products derived from **5** must necessarily be thiolsulfinates (i.e., **3a** and **6a**) by virtue of the presence of magnetically nonequivalent geminal protons (AB pattern, *J* = 15 Hz, at δ 4.91) in the remaining unaffected periodate oxidation product. It remained then only to assign a precise structure, **3a** or **6a**, to each of the two thiolsulfinates since without a knowledge of the precise mechanism for the thiolsulfinate disproportionation the location of the sulfur-bound oxygen atoms in the final thiolsulfonate product (**3**) could not serve as an indicator for the location of the oxygen in the thiolsulfinate precursor of **3**.

Column chromatography (SiO₂) of the total product obtained from the disporportionation experiments described above led to isolation of 30% of pure **3** (based on the weight of the starting 1:1 mixture of **3a** and **6a** and the stoichiometry assumed for the disproportionation in the above discussion) and 48% of the pure unaffected periodate oxidation product. In agreement with its formulation as a thiolsulfinate (**3a** or **6a**), the compound analyzed correctly for $C_7H_6OS_2$ and exhibited, in addition to the AB pattern at δ 4.91 (*J* = 15 Hz) in its ¹H NMR spectrum, an infrared ν_{max} at 1080 cm⁻¹ (–S–S(O)–). The choice of **6a** as the correct structure of this thiolsulfinate was made possible by the observation that further oxidation of the pure thiolsulfinate with potassium metaperiodate in aqueous acetonitrile at higher temperatures (65–68 °C) afforded a new compound ($C_7H_6O_2S_2$), *isomeric* with the thiolsulfonate **3**, in nearly quantitative yield. In support of its structural assignment as the remaining thiolsulfonate (**6**), the product exhibited strong IR ν_{max} signals at 1315 and 1160 cm⁻¹ (–S–SO₂–) and ¹H NMR signals at δ 4.78 (s, 2) and 7.4–7.9 (m, 4).

The quantitative formation of **6** by periodate oxidation of the thiolsulfinate having an AB pattern centered at δ 4.91 suggests that (in the simplest case) the latter is **6a** and that the thiolsulfinate found earlier to readily disproportionate preferentially over **6a** while in contact with aqueous sodium carbonate is **3a**. Support for this scheme comes from the ob-

3, 3a, and **6a** in about 40% yield. However, a somewhat more vigorous peroxyacetic acid oxidation of **7** (1 h at 0 °C followed by 3 h at 24 °C) afforded not **3**, but instead a colorless crystalline substance which analyzed for $C_7H_4O_2S_2$ as the only readily isolable product. The structure of this product, which was obtained pure in 29% yield, was tentatively formulated as **8** on the basis of its infrared and ¹H NMR spectra (ν_{max} at 1705 and 1095 cm⁻¹; multiplet at δ 7.7–8.2).

The formation of **8** via oxidation of **7** was presumed to occur via hydride removal from the initially formed and reactive 3H-1,2-benzodithiole system (**5**) to yield 3H-1,2-benzodithiol-3-one,[14] followed by subsequent peroxyacid oxidation at the more electron-rich 1-sulfur. On this basis, a direct preparation of **8** was attempted. Treatment of 3H-1,2-benzodithiol-3-one[15] with 2 mol equiv of MCPBA at <−20 °C for ca. 1 h was followed by stirring for 24 h at 20 °C. Two products were obtained; the minor product, obtained pure in 15% yield, was **8**, and the major product, obtained pure in 65% yield, analyzed for $C_7H_4O_3S_2$ and was tentatively formulated as **9** on the basis of its IR (ν_{max} 1710, 1335, 1168, and 1160 cm⁻¹) and ¹H NMR (multiplet at δ 7.7–8.3) spectra.[16]

A search for alternative oxidants which might convert **5** both cleanly and efficiently to, preferably, **3** and/or **6** led to a study of periodate oxidation[17] of the disulfide **5**. In a preliminary experiment, oxidation of **5** with 1 mol equiv of sodium metaperiodate at 24 °C for ca. 1.5 h gave a 1:1 mixture of the two derivatives of **5**, one having a 2 H singlet at δ 4.60 and the other exhibiting an AB pattern (*J* = 15 Hz) centered at δ 4.91. An attempt to separate the components of the product mixture by alumina chromatography led to a 40% recovery of

servation that in a periodate oxidation of **5** also run at 70 °C a 1:1 mixture of **3** and **6** was obtained, presumably via a straightforward and approximately quantitative oxidation of **3a** to **3** and **6a** to **6** in a reaction mixture in which the maximum amounts of **3a** and **6a** that ever form as intermediates are also in a ca. 1:1 ratio (the ratio expected based on the results of the separate NaIO₄ oxidation described earlier in which 1:1 formation of **3a** and **6a** occurred upon oxidation of **5** with NaIO₄ at 24 °C). Consequently, it was concluded that of the two thiolsulfinates, **3a** and **6a**, that were formed in a 1:1 ratio in the periodate oxidation of **5**, it was **3a** which, on brief treatment with aqueous sodium carbonate, disproportionated to **5** and **3** in a 1:1 ratio (under conditions which left **6a** unaf-

fected). These conclusions of course rely on the basic assumption that further periodate oxidation of **3a** yields **3** and of **6a** yields **6**.[19]

With pure samples of both **3** and **6** in hand, it remained only to test our assumptions regarding their suitability as precursors for the generation of *o*-thiobenzoquinone methide (**1**) and benzo[*b*]thiete (**2**).

Irradiation of solutions of **3** was carried out using a mercury lamp and a quartz apparatus. An insoluble solid, presumably polymeric, was obtained from photolysis of a methanolic solution of **3**. Subsequent photolyses of **3** were performed in chloroform, benzene, and THF and in presence of maleic anhydride or *N*-phenylmaleimide. Of these solvents, only benzene finally proved to be a satisfactory one. Generated by the photodesulfonylation of **3** in benzene, *o*-thiobenzoquinone methide (**1**) could be trapped with reasonable efficiency with *N*-phenylmaleimide to afford the adduct **4** in 43% yield. The reaction of **1** with maleic anhydride also afforded a similarly constituted adduct, but in low yield (¹H NMR assay). No adduct was formed in the presence of dimethyl acetylenedicarboxylate;[5] only an insoluble solid was obtained. In chloroform and THF solutions, dark-colored products were produced and purification of the desired adduct was more difficult. In the absence of a trapping agent (e.g., *N*-phenylmaleimide), polymeric amorphous solids which were insoluble in common organic solvents were generally formed.

Irradiation of **6** in either benzene or diethyl ether solution containing added *N*-phenylmaleimide under conditions similar to those used for the photolysis of **3** led to formation of an intractable amorphous product; none of the desired benzothiete **2** or the adduct of **1** (assuming that a conversion of **2** to **1** might occur) was observed. In an attempted sensitized photolysis of **6** in benzene solution containing benzophenone and *N*-phenylmaleimide using Pyrex-filtered ultraviolet light, only an insoluble amorphous solid was obtained.

Alternative explanations (also suggested by the referees) for the formation of the adduct **4** might invoke the stepwise addition to *N*-phenylmaleimide of either the diradical **13** (with loss of SO₂ at an intermediate step) or the triplet diradical **14**. Although we have no data which can definitively rule out these possibilities, the absence (¹H NMR assay) of any trans-fused **4** in the crude product from which *cis*-**4** was isolated suggests that the product arose predominantly from a concerted [4 + 2] cycloaddition of **1** to *N*-phenylmaleimide.
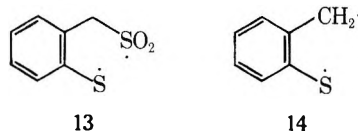
13   **14**

Experimental Section[20]

3*H*-1,2-Benzodithiole-3-thione was prepared in 73% yield by treatment of 2,2′-dithiodibenzoic acid with P₄S₁₀ in refluxing pyridine, as described by E. Klingsberg and A. M. Schreiber.[26]

3*H*-1,2-Benzodithiol-3-one was prepared in 48% yield by addition of thiolacetic acid to a solution of 2-thiolbenzoic acid in concentrated H₂SO₄, as described by McKibben and McClelland:[15] IR (CHCl₃) 1780 (w), 1670, and 895 cm⁻¹; ¹H NMR (CDCl₃) δ 7.2–7.7 (m, 3) and 7.8–8.1 (m, 1).

2-Mercaptomethylthiophenol (7). Method A. A solution of 46 g (0.25 mol) of 3*H*-1,2-benzodithiole-3-thione in 500 mL of anhydrous Et₂O–THF (1:1) was added dropwise during 1.25 h to a stirred suspension of 20 g of LiAlH₄ in 500 mL of Et₂O under N₂. The reaction mixture was stirred for 16 h at 25 °C. Unreacted LiAlH₄ was decomposed by the addition of 2-propanol (150 mL). The mixture was acidified with 450 mL of 10% H₂SO₄ solution, and the product was extracted into Et₂O. After washing with brine, the combined extracts were dried (MgSO₄) and concentrated. Distillation of the remaining 40 g of yellow liquid afforded 36 g (92%) of pure 2-mercaptomethylthiophenol as a pale yellow liquid: bp 64 °C (0.05 mm) [lit.[10] bp 125–126 °C (12 mm)]; ¹H NMR (CDCl₃) δ 1.83 (t, *J* = 7.5 Hz, 1), 3.63 (s, 1), 3.79 (d, *J* = 7.5 Hz, 2), and 7.0–7.6 (m, 4).

Method B. 3*H*-1,2-Benzodithiol-3-one (41 g) was reduced with LiAlH₄ essentially as described above for the corresponding 3-thione. The combined ethereal extracts were mixed with ice water and extracted with 1 L of 6% KOH solution. The aqueous alkali extracts were acidified with 10% H₂SO₄ and extracted with Et₂O. The combined Et₂O extracts were washed with H₂O, dried (MgSO₄), and concentrated in vacuo to yield 35 g of yellow oil. Distillation in the range of 77–90 °C (0.20–0.25 mm) afforded 24 g of a 3:1 mixture (¹H NMR assay) of 2-mercaptomethylthiophenol and 2-hydroxymethylthiophenol. The latter compound[21] (in CDCl₃) exhibited ¹H NMR signals at δ 2.1–2.8 (broad s, 1), 3.63 (s, 1), 4.67 (s, 2), and 7.0–7.6 (m, 4).

3*H*-1,2-Benzodithiole (5). A solution of 5.0 g of pure 2-mercaptomethylthiophenol in 420 mL of CH₃OH was added dropwise from a Hershberg addition funnel to a vigorously stirred solution of 10.0 g of CuCl₂·2H₂O in 500 mL of CH₃OH at 24 °C during 14 h. A slow stream of air was bubbled through the reaction mixture during the addition and while the mixture was stirred for an additional 3 h. The reaction mixture was decanted, diluted with ice water, and extracted with Et₂O. The combined extracts were washed with water. Partial removal of the Et₂O in vacuo afforded 200 mL of a dilute (ca. 2%) solution of **5**, which was dried (MgSO₄) and stored at ca. −10 °C. Complete removal of the solvent from an aliquot (15 mL) afforded 0.300 g (81%) of crude **5** (ca. 85% pure by ¹H NMR assay) as a deep yellow oil which evaporatively distilled at a bath temperature of 93–95 °C (3 mm) [lit.[10] bp 130–133 °C (12 mm)] ¹H NMR (CDCl₃) δ 4.33 (s, 2) and 6.85–7.35 (m, 4).

Reaction of 3*H*-1,2-Benzodithiole (5) with *m*-Chloroperoxybenzoic Acid (MCPBA). A solution of 0.75 g (0.0040 mol) of purified MCPBA in 25 mL of CH₂Cl₂ was added dropwise during 7 min at 24 °C to a stirred CH₂Cl₂ solution (100 mL) containing 0.61 g (0.0040 mol) of 3*H*-1,2-benzodithiole (**5**), and the reaction mixture was stirred for an additional 3 min. Another 0.75 g (0.0040 mol) of MCPBA in 25 mL of CH₂Cl₂ were added during the next 7 min, and the mixture was stirred for 12 h at 25 °C. Removal of the solvent left a pale yellow solid which was mixed with anhydrous Et₂O and filtered to remove some insoluble viscous material. The ether filtrate was washed successively with dilute NaHCO₃ solution and brine and dried (MgSO₄). Removal of the solvent in vacuo afforded 0.41 g of a mixture of products which included **3**, **3a**, and **6a** in a ratio of 5:2:3, respectively, as determined by a ¹H NMR assay. The mixture was dissolved in CH₂Cl₂, washed with dilute NaHCO₃ solution, and dried (MgSO₄). Evaporation of the CH₂Cl₂ gave 0.180 g of a white solid. Recrystallization from anhydrous Et₂O afforded two kinds of visually distinct crystals (plates and needles) which were manually separated to yield 0.088 g of bis(*m*-chlorobenzoyl) peroxide, mp 124–125 °C dec (lit.[22] mp 125.0 °C dec), and 0.069 g (10%) of 3*H*-1,2-benzodithiole 2,2-dioxide (**3**) colorless needles: mp 117–118 °C; ¹H NMR (CDCl₃) δ 4.70 (s, 2) and 7.37 (m, 4); IR (CHCl₃) 1335 and 1150 cm⁻¹; mass spectrum (70 eV), *m/e* 186 (M⁺); UV (EtOH) λmax 205 nm (ε 26 380), 237 (9300), and 274 (570); ¹³C NMR (CDCl₃) δ 64.8 (¹³CH₂) and 125.0–129.6 (¹³C₆H₄).

An analytically pure sample of **3** exhibited mp 118–119.5 °C. Anal. Calcd for C₇H₆O₂S₂: C, 45.14; H, 3.25; S, 34.43. Found: C, 45.34; H, 3.42; S, 34.23.

Reaction of 2-Mercaptomethylthiophenol with Commercial 40% Peroxyacetic Acid (CH₃CO₃H) under Controlled Conditions. Commercial 40% CH₃CO₃H[23] (0.9 mL) in 5 mL of CHCl₃ was added during 5 min to 40 mL of CHCl₃ containing 0.2 g of 2-mercap-

tomethylthiophenol at 0 °C. The reaction mixture was stirred for 1 h at 0–5 °C, washed with water, and dried (MgSO$_4$). Evaporation of the solvent in vacuo afforded 0.1 g of 3:6:7 mixture of 3 [^{1}H NMR (CDCl$_3$) δ 4.70 (s, 2) and 7.37 (m, 4)], 3a [^{1}H NMR (CDCl$_3$) δ 4.60 (s, 2) and 7.1–7.6 (m, 4)], and 6a [^{1}H NMR (CDCl$_3$) AB pattern centered at δ 4.93 (*J* = 15 Hz), 7.3–7.7 (m, 3), and 7.7–8.0 (m, 1)], respectively (^{1}H NMR assay).

Reaction of 2-Mercaptomethylthiophenol with Commercial 40% Peroxyacetic Acid: Formation of 3H-1,2-benzodithiol-3-one 1-Oxide (8). To a solution of 3.50 g of a 3:1 mixture of 2-mercapto-methylthiophenol and 2-hydroxymethylthiophenol in 50 mL of CHCl$_3$ at 0 °C was added 12 mL of commercial 40% peroxyacetic acid[23] during 10 min, and the mixture was stirred for 1 h at 0 °C and for 3 h at 24 °C. The reaction mixture was diluted with ice water and extracted with Et$_2$O. The organic extract was washed with water and dried (MgSO$_4$), and the solvent was evaporated in vacuo, yielding a brown viscous material which on precipitation from a cold chloroform–hexane solution (−25 °) gave 1.2 g of 3H-1,2-benzodithiol-3-one 1-oxide (8) as an off-white solid, mp 99–101 °C (39% yield based on starting 2-mercaptomethylthiophenol). Recrystallization of 0.20 g of the crude product from chloroform–hexane afforded 0.15 g (29%) of pure 8 as colorless needles: mp 101.5–103 °C; ^{1}H NMR (CDCl$_3$) δ 7.7–8.2 (m); IR (CHCl$_3$) 1780 (w), 1705, 1095, and 890 cm^{-1}; mass spectrum (70 eV), *m/e* 184 (M$^+$).

An analytically pure sample of 8 exhibited mp 101.5–103 °C. Anal. Calcd for C$_7$H$_4$O$_2$S$_2$: C, 45.64; H, 2.19; S, 34.81. Found: C, 45.61; H, 2.22; S, 34.92.

3H-1,2-Benzodithiol-3-one 1-Oxide (8) and 3H-1,2-Benzodi-thiol-3-one 1,1-Dioxide (9). A solution of 2.20 g of *m*-chloroperox-ybenzoic acid (85%; 0.010 mol) in 35 mL of CH$_2$Cl$_2$ was added during 0.5 h to a stirred solution of 0.84 g (0.005 mol) of 3H-1,2-benzodithiol-3-one in 35 mL of CH$_2$Cl$_2$ at −20 to −23 °C. Stirring was continued below −30 °C for 45 min and at +20 °C for an additional 24 h. The reaction mixture was fractionally crystallized several times from CCl$_4$–Et$_2$O to yield 0.65 g (65%) of 9 as colorless crystals: mp 70–72 °C;[24] ^{1}H NMR (CDCl$_3$) δ 7.7–8.3 (m); IR (CHCl$_3$) 1785 (w), 1710, 1335, 1168, 1160, and 895 cm^{-1}; mass spectrum (70 eV), *m/e* 200 (M$^+$).

An analytical sample of 9, later found to contain ca. 5% of 8 (IR), had mp 71–73 °C. Anal. Calcd for C$_7$H$_4$O$_3$S$_2$: C, 41.99; H, 2.01; S, 32.02. Found: C, 42.20; H, 2.17; S, 32.06. Pure 9 exhibited mp 98–99 °C.

The remaining isolable material (0.15 g, 15%) was 8: mp 101–103 °C; ^{1}H NMR (CDCl$_3$) δ 7.7–8.2 (m); IR (CHCl$_3$) 1780 (w), 1705, 1095, and 890 cm^{-1}.[24]

Reaction of 3H-1,2-Benzodithiole (5) with Sodium Metaperiodate at 24 °C: Formation of a 1:1 Mixture of 3a and 6a. A solution of 0.87 g of 5 (ca. 85% pure) in 50 mL of acetonitrile was added dropwise during 10 min to a stirred aqueous solution (100 mL) containing 1.80 g (0.004 mol) of NaIO$_4$ at room temperature (24 °C) and stirred for an additional 1.25 h. The reaction mixture was washed successively with water and brine and dried (MgSO$_4$). The solvent was removed in vacuo to yield 0.88 g (92%) of a 1:1 mixture of 3a and 6a (which was of ca. 85% purity by a ^{1}H NMR assay) based on the relative integrated areas beneath a 2 H singlet at δ 4.60 (due to 3a) and an AB pattern centered at δ 4.91 (i.e., consisting of 2 doublets (*J* = 15 Hz) centered at δ 4.58 and 5.25 (due to 6a)).

The mixture of thiolsulfinates was quite stable under a variety of nonbasic conditions: e.g., the mixture was (i) stored for 6 days at 24 °C in the presence of diffuse light, (ii) heated in an NMR tube (CDCl$_3$ solution) for 13 h at 50 °C followed by 25 h at 58–60 °C, (iii) refluxed with 3% aqueous acetic acid containing acetonitrile for 13 h, and (iv) distilled at reduced pressure, bp 88–96 °C (0.16 mm), without any apparent change in every case.[25]

Reaction of a 1:1 Mixture of 3H-1,2-Benzodithiole 2-Oxide (3a) and 3H-1,2-Benzodithiole 1-Oxide (6a) on Alumina. A 1:1 mixture of 500 mg of 3a and 6a was chromatographed on 10 g of neutral alumina (Woelm activity grade III) using petroleum ether (bp 63–69 °C) followed by CH$_2$Cl$_2$ as eluents to yield 100 mg of crude 5, purity ca. 75% (^{1}H NMR assay), and 90 mg of crude 6a, purity ca. 90% (^{1}H NMR assay).

Reaction of a 1:1 Mixture of 3H-1,2-Benzodithiole 2-Oxide (3a) and 3H-1,2-Benzodithiole 1-Oxide (6a) with Aqueous Sodium Carbonate: Disproportionation of 3a to Form 3 and 5. A solution of 2.5 g of a 1:1 mixture of 3a and 6a in 150 mL of acetonitrile and 65 mL of water was mixed with 1.1 g of anhydrous Na$_2$CO$_3$ in 10 mL of water in a separatory funnel and shaken vigorously for 3 min. A deep yellow color immediately developed. The reaction mixture was mixed with ice, acidified with 5% H$_2$SO$_4$ solution 3 min later, and immediately extracted with CH$_2$Cl$_2$. The combined organic extracts were washed successively with brine and water and dried (MgSO$_4$). The

solvent was removed in vacuo, yielding 1.6 g of a mixture of 3, 5, and 6a in a ratio of 1:1:2 (^{1}H NMR assay). The crude product was chromatographed on silica gel (34 g). Elution with 3% Et$_2$O in petroleum ether (bp 33–37 °C) gave 0.5 g of a viscous yellow residue containing 5, which was discarded. Subsequent elution with a 2:1 mixture of Et$_2$O–CH$_2$Cl$_2$ afforded 0.50 g of a yellow solid which on crystallization from CCl$_4$–CH$_2$Cl$_2$ and recrystallization from absolute EtOH afforded 0.20 g (30%) of pure 3: mp 116–118 °C; ^{1}H NMR (CDCl$_3$) δ 4.70 (s, 2) and 7.37 (m, 4).

Further elution with methylene chloride afforded 0.60 g (48%) of pure 6a as a bright yellow oil: bp 140 °C (0.06 mm); ^{1}H NMR (CDCl$_3$) AB pattern centered at δ 4.91 (*J* = 15 Hz), 7.3–7.7 (m, 3), and 7.7–8.0 (m, 1); IR (CH$_2$Cl$_2$) 1080 and 1055 cm^{-1}; mass spectrum (70 eV), *m/e* 170 (M$^+$). Anal. Calcd for C$_7$H$_6$OS$_2$: C, 49.38; H, 3.55; S, 37.67. Found: C, 49.18; H, 3.48; S, 37.77.

3H-1,2-Benzodithiole 1,1-Dioxide (6). A mixture containing a small crystal of iodine (10 mg), 0.30 g (0.0017 mol) of the pure 1-oxide 6a, and 0.45 g (0.0019 mol) of KIO$_4$ in 42 mL of water–acetonitrile (5:2) was heated to 65 °C during 15 min and maintained at 65–68 °C under N$_2$ for 1.25 h. The reaction mixture was cooled, diluted with water, and extracted with diethyl ether. The combined ether extracts were washed successively with a minimum amount of dilute NaHSO$_3$ solution (to remove iodine) and brine and dried (MgSO$_4$). Removal of the solvent in vacuo gave 0.30 g of crude 6 as an off-white grayish solid, mp 118–121 °C. Recrystallization from CH$_2$Cl$_2$ afforded 0.26 g (79%) of pure 6 as colorless crystals: mp 121–122.5 °C; ^{1}H NMR (CDCl$_3$) δ 4.78 (s, 2) and 7.4–7.9 (m, 4); IR (CH$_2$Cl$_2$) 1315, 1160, and 1125 cm^{-1}; mass spectrum (70 eV), *m/e* 186 (M$^+$); UV (EtOH) λ$_{max}$ 213 nm (ε 5810), 260 (570), 266 (720), and 273 (620).

An analytical sample of 6 had mp 121–122.5 °C. Anal. Calcd for C$_7$H$_6$O$_2$S$_2$: C, 45.14; H, 3.25; S, 34.43. Found: C, 45.39; H, 3.33; S, 34.64.

Reaction of 3H-1,2-Benzodithiole (5) with Potassium Metaperiodate for a Prolonged Period. A solution of 0.78 g of 5 (ca 85% pure) in 55 mL of 10:1 acetonitrile–diethyl ether was added dropwise during 25 min and at 20 °C to a stirred aqueous solution (300 mL) containing 2.20 g (ca. 0.01 mol) of KIO$_4$, and the reaction mixture was stirred for an additional 50 h under N$_2$. The reaction mixture was extracted with Et$_2$O, and the combined extracts were dried (MgSO$_4$). Evaporation of the solvent in vacuo yielded 0.63 g of crude product which included 3, 3a, and 6a in a ratio of 2:3:3, respectively (^{1}H NMR assay).

Reaction of 3H-1,2-Benzodithiole (5) with Potassium Metaperiodate at Elevated Temperature. A solution of 250 mg of 5 (ca. 85% pure) in 12 mL of acetonitrile was added dropwise at room temperature to a stirred aqueous solution (70 mL) containing 700 mg (3.0 mmol) of KIO$_4$, and the reaction mixture was stirred for an additional 0.5 h. One small crystal of iodine (10 mg) was added, and the mixture was heated under N$_2$ at 70 °C for 1 h. The reaction mixture was cooled and extracted with Et$_2$O. The combined Et$_2$O extracts were washed with a minimum amount of dilute NaHSO$_3$ solution (to remove iodine) and water and dried (MgSO$_4$). Removal of the solvent in vacuo left 100 mg of a solid residue. Recrystallization from ethanol afforded 52 mg of a ca. 1:1 mixture (mp 88–105 °C) of 3 [^{1}H NMR (CDCl$_3$) δ 4.70 (s, 2) and 7.37 (m, 4)] and 6 [^{1}H NMR (CDCl$_3$) δ 4.78 (s, 2) and 7.4–7.9 (m, 4)].

Generation and Trapping of o-Thiobenzoquinone Methide (1): Photolysis of 3H-1,2-Benzodithiole 2,2-Dioxide (3) in the Presence of N-Phenylmaleimide. A solution of 80 mg of pure 3 and 120 mg of N-phenylmaleimide in 25 mL of anhydrous benzene was irradiated in a standard photolysis apparatus for 5 h using a 450-W high-pressure Hanovia Hg lamp and a quartz lamp well. The solution was maintained near room temperature by cooling the outer jacket of the irradiation vessel in a water bath (20–30 °C). Prior to and during the irradiation, argon was slowly bubbled through the solution to aid in deoxygenating and to provide agitation. Removal of the solvent in vacuo left a solid material which was partially dissolved in a small amount of CHCl$_3$–CCl$_4$, and the suspension was filtered to remove colored impurities. The filtrate was concentrated in vacuo to give a crude solid material which was chromatographed on silica gel using a 1:1 mixture of anhydrous benzene–diethyl ether as eluent to afford a yellow solid containing unreacted N-phenylmaleimide and the adduct 4 (^{1}H NMR assay). The solid was partially dissolved in a small amount of petroleum ether (bp 63–69 °C)–diethyl ether, and the suspension was filtered to yield 80 mg (ca. 63%) of crude 4 as the remaining insoluble yellow-brown solid, mp 159–164 °C. Recrystallization from CH$_2$Cl$_2$–hexane yielded 55 mg (43%) of pure 4 as tan-colored crystals: mp 166–168 °C (lit.[2] mp 167–168 °C); mass spectrum (70 eV), *m/e* 295 (M$^+$). The ^{1}H NMR spectrum of 4 in CDCl$_3$ was identical with that already reported.[2]

References and Notes

(1) Abstracted in part from the Ph.D. Dissertation of Ajit Kumar Bhattacharya, Washington University, St. Louis, Mo., 1975.

(2) The generation of vinyl-substituted *o*-thiobenzoquinone methides (allides) had been invoked earlier by R. S. Becker and J. Kolc [*J. Phys. Chem.*, **72**, 997 (1968)] to explain the photochromic behavior of 2*H*-thiochromene and 2,2-diphenyl-2*H*-thiochromene upon irradiation in 3-methylpentane at 77 K. During the course of our work a report appeared on the generation of *o*-thiobenzoquinone methide (1) by photodecarbonylation of 1-thia-2-indanone: G. Jacqmin, J. Nasielski, G. Billy, and M. Remy, *Tetrahedron. Lett.*, 3655 (1973). The formation of 1 was established by its reaction in the presence of added *N*-phenylmaleimide as a trapping agent to give the [4 + 2] (or [8 + 2]) adduct 4.

(3) The heretofore elusive parent benzothiete system (2) has only recently been prepared for the first time: W. J. M. van Tilborg and R. Plomp, *J. Chem. Soc., Chem. Commun.*, 130 (1977). See also E. Voigt and H. Meier, *Angew. Chem., Int. Ed. Engl.*, **15**, 117 (1976). Benzothiete (2) was reported to be stable for several days at room temperature; at temperatures > 100 °C it dimerizes to 6*H*,12*H*-dibenzo[*b*,*f*][1,5]dithiocin, apparently via 1.

(4) For example, extrusion of SO₂ during irradiation of the sultone derived from *o*-hydroxytoluene-α-sulfonic acid has been reported to yield *o*-quinone methide by O. L. Chapman and C. L. McIntosh, *J. Chem. Soc., Chem. Commun.*, 383 (1971).

(5) The potential synthetic utility of the reaction of 1 and substituted analogues of 1 with acetylenes was also of interest to us as a possible route to the relatively inaccessible 1-thio-2-chromenes, which might serve as precursors of 1-thianaphthalenes; see A. G. Hortmann, R. L. Harris, and J. A. Miles, *J. Am. Chem. Soc.*, **96**, 6119 (1974).

(6) A. K. Bhattacharya and A. G. Hortmann, *J. Org. Chem.*, **43**, 2728 (1978).

(7) It should be noted that 1,2-dithioles are generally more reactive toward chemical oxidants than either cyclic disulfides with larger rings or open-chain disulfides (B. Lindberg and G. Bergson, *Ark. Kemi*, **23**, 319 (1965), and references cited therein), presumably as a consequence of significant differences in electronic interactions between the nonbonding electrons on the sulfurs in the 1,2-dithiole rings (which are constrained with regard to rotation about the S–S bond, resulting in a dihedral angle [φ] of ca. 25° between the C–S bonds) vs. similar interactions in acyclic disulfides ([φ] ∼ 90 °). Hence, it seems probable that in unsymmetrically substituted disulfides the relative reactivity of one sulfur vs. the other toward a particular reagent will also vary markedly where comparisons are being made between acyclic disulfides vs. 1,2-dithioles. Consequently, considering the present state-of-the-art in predicting the outcome of, e.g., peroxyacid oxidations of unsymmetrical acyclic disulfides (see ref 6), predictions regarding the relative reactivities of the sulfurs of unsymmetrical 1,2-dithioles in similar reactions would seem to be, at best, tenuous.

(8) Cf. R. M. Wilson, D. N. Buchanan, and J. E. Davis, *Tetrahedron. Lett.*, 3919 (1971); L. Field in "The Organic Chemistry of Sulfur", S. Oae, Ed., Plenum Press, New York, N.Y., 1977, Chapter 7.

(9) An elegant example of photochemically induced extrusion of SO₂ from a dithiole 1,1-dioxide to afford a thietane derivative appears in the efficient synthesis of the single-atom (sulfur) peri-bridged naphthalene derivative naphtho[1,8-*bc*]thiete by UV irradiation of naphtho[1,8-*cd*]-1,2-dithiole 1,1-dioxide (12): J. Meinwald and S. Knapp, *J. Am. Chem. Soc.*, **96**, 6532 (1974); see also J. Meinwald, S. Knapp, S. K. Obendorf, and R. E. Hughes, *ibid.*, **98**, 6643 (1976). A thermally induced extrusion of SO₂ from a 1,2-dithiolane 1,1-dioxide to yield a thietane in 55% yield has also been reported: A. Padwa and R. Gruber, *J. Org. Chem.*, **35**, 1781 (1970).

(10) A. Lüttringhaus and K. Hägele, *Angew. Chem.*, **67**, 304 (1955).

(11) Cf. the oxidation of a series of alkyl- and arylthiols in aqueous alkaline solution in the presence of various metal ions and oxygen: J. D. Hopton, C. J. Swan, and D. L. Trimm, *Adv. Chem. Ser.*, No. 75, 216 (1968).

(12) The ^{13}C NMR chemical shifts for –^{13}CH₂– in the following compounds were used for comparison (see ref 6): PhSSCH₂Ph, δ 43.3; PhSSO₂CH₂Ph, δ 65.9; and PhSO₂SCH₂Ph, δ 40.2. In contrast to the situation regarding such differences for ^{13}C chemical shifts, it should be noted that similar comparisons

(13) of differences in chemical shifts of protons of the type –CH₂SS(O)₂– vs. –CH₂S(O)₂S– or –CH₂SS(O)– vs. –CH₂S(O)S– are generally of little value in distinguishing between pairs of structurally related compounds bearing these structural moieties since the differences in the proton shifts are generally <∼0.3 ppm (see, e.g., the chemical shifts for the CH₂ protons in 3 vs. 6 and in 3a vs. 6a (vide infra) and for the CH₂ protons in the pairs of thiolsulfonates reported in ref 6). Such insignificant differences in proton chemical shifts are also commonplace within the same compound; e.g., in dibenzyl thiolsulfonate the two –CH₂– singlets appear at δ 4.02 and 4.19, and in the corresponding thiolsulfinate they appear at δ 4.23 and 4.27 (P. Allen, Jr., P. J. Berner, and E. R. Malinowski, *Chem. Ind. (London)*, 208 (1963).

(13) L. N. Aristarkhova and B. G. Boldyrev, *Zh. Org. Khim.*, **8**, 2071 (1972); *Chem. Abstr.*, **78**, 57832n (1973). See, however, W. G. Filby, K. Günther, and R. D. Penzhorn, *J. Org. Chem.*, **38**, 4070 (1973).

(14) Cf. the formation of 1,2-dithiolium cations via oxidation of 1,2-dithiole derivatives: H. Prinzbach and E. Futterer, *Adv. Heterocycl. Chem.*, **7**, 39 (1966). Collapse of a peroxyester formed by C–O bond formation between the peroxyacid and the 3*H*-1,2-benzodithiolium cation might reasonably lead to the intermediate 3*H*-1,2-benzodithiol-3-one.

(15) M. McKibben and E. W. McClelland, *J. Chem. Soc.*, 170 (1923). See also A. T. Fanning, Jr., G. R. Bickford, and T. D. Roberts, *J. Am. Chem. Soc.*, **94**, 8505 (1972).

(16) The observation that all of the ^{1}H NMR signals due to aromatic protons in 8 and 9 appear downfield from δ 7.6 lends further support to these structural assignments as opposed to alternate structures having no oxygen substitution at the 1-sulfur since the latter types of compounds generally show ^{1}H NMR signals upfield from δ 7.6 associated with proton(s) ortho to nonoxygenated sulfur substituents on phenyl rings; see, e.g., the ^{1}H NMR spectra of aromatic protons in 7, 5, 3, and 3a vs. 6 and 6a and the spectra of the phenyl-substituted disulfides and thiolsulfonates reported in ref 6 above.

(17) For a review, see A. J. Fatiadi, *Synthesis*, 229 (1974). For examples of periodate oxidation of disulfides to thiolsulfinates and thiolsulfonates, see J. E. McCormick and R. S. McElhinney, *J. Chem. Soc., Perkin Trans 1*, 2795 (1972); P. K. Srivastava and L. Field, *J. Org. Chem.*, **37**, 4196 (1972); and H. Yanagawa, T. Kato, H. Sagami, and Y. Kitahara, *Synthesis*, 607 (1973). See also A. Padwa and R. Gruber, cited in ref 6 above, and Oae et al., (ref 18).

(18) S. Tamagaki, H. Hirota, and S. Oae, *Bull. Chem. Soc. Jpn.*, **46**, 1247 (1973). Disproportionations of thiolsulfinates in alkaline media to give thiolsulfonates and disulfides might involve initial attack of hydroxide ion at either the sulfenyl sulfur (–S–) or the sulfinyl sulfur (–S(O)–); see J. L. Kice and T. E. Rogers, *J. Am. Chem. Soc.*, **96**, 8009 (1974).

(19) An alternative to the above explanation in which the structures of 3a and 6a are switched would require the periodate oxidation of 3a to yield 6, possibly by way of disproportionation of an intermediate α-disulfoxide (see footnote 4 in ref 6), to explain the concommitant transposition of the oxygen on S-2 in 3a to S-1 in 6. To explain, however, the apparently also exclusive formation of 3 from 6a in this context would require *exclusive formation of the stereoisomer of the above α-disulfoxide* in order to avoid the obvious problem of a common intermediate in the two reactions, a rationalization which, although conceivable, appears improbable.

(20) Melting points were determined in unsealed capillary tubes using a Unimelt apparatus (Arthur H. Thomas Co.) and are uncorrected. Boiling points are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were obtained using a Varian Associates A-60A instrument; tetramethylsilane (Me₄Si) was used as an internal standard (δ = 0.00 ppm). Infrared spectra (IR) were recorded on a Perkin-Elmer Model 457 grating spectrophotometer. Ultraviolet (UV) spectra were obtained on a Cary Model 14 Instrument. Mass spectra were run on a Varian Model M-66 spectrometer. ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Bruker 90-MHz spectrometer operating in the pulsed Fourier transform mode; ^{13}C NMR chemical shifts are reported in δ (ppm downfield from Me₄Si) based on δ$_{Me_4Si}$ = δ$_{CDCl_3}$ − 77.0 = 0.00 ppm. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(21) G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *J. Org. Chem.*, **30**, 4074 (1965).

(22) G. Tsuchihashi, S. Miyajima, T. Otsu, and O. Simamura, *Tetrahedron*, **21**, 1039 (1965).

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(24) In later preparations of larger quantities of pure 8 and 9 for photochemical studies, B. H. Lee of this laboratory has found that treatment of 3*H*-1,2-benzodithiol-3-one with 3 mol equiv of MCPBA under similar conditions (−30 °C for 30 min and then 25 °C for 35 h) afforded 9 essentially uncontaminated with 8. Alternatively, oxidation using an equimolar amount of MCPBA (−30 °C for 20 min and then 25 °C for 1.5 h) afforded essentially pure 8 in 78% yield.

(25) The above results are surprising in view of the fact that acyclic thiolsulfinates, in general, are unstable compounds which readily undergo thermally induced disproportionation to yield the corresponding disulfides and thiolsulfonates. For example, methyl methanethiolsulfinate (MeSS(O)Me), upon standing for a few days at room temperature, gives a mixture of dimethyl disulfide and methyl methanethiolsulfonate; see E. Block and J. O'Connor, *J. Am. Chem. Soc.*, **96**, 3921 (1974).

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Seven-Membered Heterocycles. 9. Synthesis and Properties of Some 5-Alkyl and 5-Aryl Derivatives of 1-Benzothiepin

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7a-Chlorocyclopropa[b][1]benzothiopyran-7-one (2) and 7a-bromocyclopropa[b][1]benzothiopyran-7-one (3) each reacted with Grignard reagents to give the corresponding cyclopropyl alcohols 4–10 (Table I). The alcohols 5, 7, and 8 were oxidized to the corresponding sulfones 11, 12, and 13, respectively, and 7a-chloro-7-hydroxy-7-phenylcyclopropa[b][1][benzothiopyran was oxidized to the corresponding sulfoxide 14. The reaction of 4 with HCl gave the ring-opened product 2,4-dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (15) in high yield, and the reaction of 4 with HBr produced 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (20) in excellent yield. The reaction of 15 with potassium *tert*-butoxide produced only low yields of the desired 4-chloro-5-phenyl-1-benzothiepin (16), and reactions of 15 and 20 utilizing a variety of reagents and conditions attempting to form 16 were tried. Interestingly, the alcohol 4 rearranged when heated in the presence of a trace of *p*-toluenesulfonic acid to produce 2-chloro-1-phenylnaphthalene (17), presumably via extrusion of sulfur from 16. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) promoted the dehydrobromination reaction at room temperature, which conveniently provided the corresponding 1-benzothiepins 1, 16, 24, 26, 27, and 28 (Table III) and the sulfones 22 and 25. The phenyl- and benzyl-substituted 1-benzothiepins 16, 24, and 26 were crystalline compounds. The thermal decomposition of the 1-benzothiepins was studied by NMR spectroscopy, and the effect of substituents on the stability of the ring is discussed.

Several methods have become available for the synthesis of 1-benzothiepins. One approach involves the derivatization of enolized ketones,[3–6] while another involves ring opening of annulated benzo[b]thiophenes.[7,8] Both of these methods have produced highly substituted and relatively stable 1-benzothiepins. The enolization approach has also been recently utilized to obtain 1-benzothiepin 1-oxides,[9] which are thermally less stable than the corresponding 1-benzothiepins, and 1-benzothiepinium ions,[10] which are thermally more stable than the corresponding 1-benzothiepins. We have reported[11] the use of a halogenation–dehydrohalogenation sequence for the synthesis of the parent 1-benzothiepin and chlorinated derivatives. Another synthesis[12,13] of 1-benzothiepin and other derivatives has been reported utilizing a rhodium complex promoted isomerization. As yet, however, the properties of 1-benzothiepins have not been fully investigated. In particular, the effect of structure on the the thermal stability of these compounds remains unresolved.
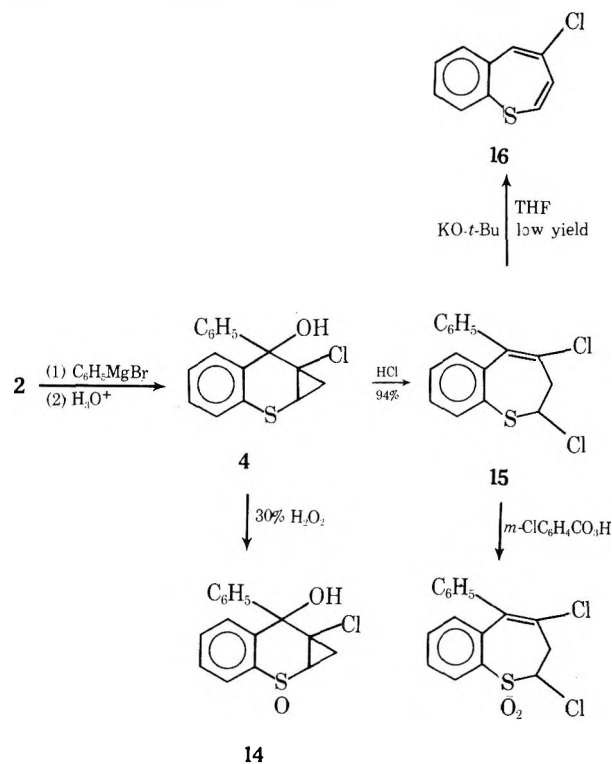
We previously reported[11] the preparation of 4-chloro-1-benzothiepin (1), achieved via the key intermediate 7a-chlorocyclopropa[b][1]benzothiopyran-7-one (2). The ketone 2

2 → **1**

(1) NaBH₄
(2) HCl
(3) KO-t-Bu/t-BuOH
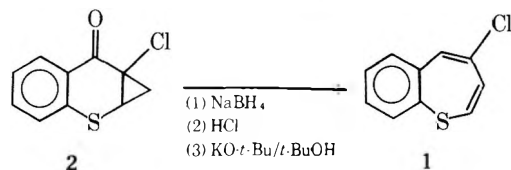
underwent reduction with sodium borohydride to give the corresponding alcohol which was ring opened with HCl to provide the precursor to 1. We also observed that 2 underwent a Grignard reaction which provided the prospect of synthesizing various 5-alkyl or 5-aryl derivatives of 1-benzothiepin, and in this paper we report the successful isolation of such compounds.

Ketone 2 and 7a-bromocyclopropa[b][1]benzothiopyran-7-one (3)[14] were each reacted with various Grignard reagents and upon hydrolysis gave the corresponding alcohols listed in Table I. The alcohols 4–9 were characterized by IR and NMR spectral data and elemental analyses. Compounds 5, 7,[15] and 8 were oxidized with *m*-chloroperbenzoic acid to the corresponding sulfones 11, 12,[15] and 13, respectively, and 4 was oxidized with 30% hydrogen peroxide to the corresponding sulfoxide 14 (Table I). The stereochemistry of the alcohols was not determined. The reaction of 4 with HCl provided the

precursor, 2,4-dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (15), in excellent yield, and 15 was characterized by IR, NMR, and mass spectral data, elemental analyses, and further as its sulfone. Treatment of 15 with potassium *tert*-butoxide at room temperature in THF produced the desired 4-chloro-5-phenyl-1-benzothiepin (16); however, low yields and difficulties in purification led to further investigations.

16

KO-t-Bu | THF low yield

2 (1) C₆H₅MgBr / (2) H₃O⁺ → **4**

4 → (HCl 94%) → **15**

4 → (30% H₂O₂) → **14**

15 → (*m*-ClC₆H₄CO₃H)

The facile ring opening of the cyclopropyl alcohol 8 by HCl prompted an attempt to obtain 16 in one step from 4 by treatment with a trace of *p*-toluenesulfonic acid in refluxing benzene. 2-Chloro-1-phenylnaphthalene (17) was isolated from the reaction, which indicates that 16 may have formed but was unable to survive the conditions. The formation of 17 could be rationalized by the loss of a proton from the intermediate homoallylic cation 18 formed after the loss of H₂O from 4.
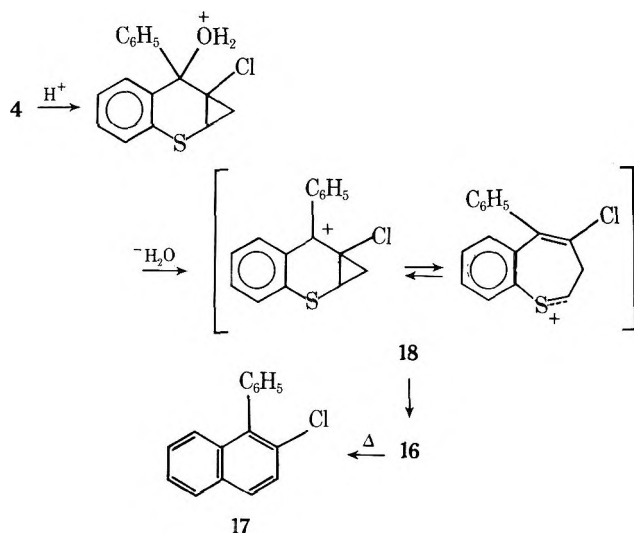
2,4-Dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (15) did not react with the following reagents at the temperatures given

Table I. Properties of the Cyclopropyl Alcohols
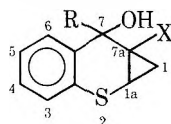
Compd	Registry no.	Substituents	Melting point, °C	Isolated yield,[a] %
4	66768-90-9	R = C_6H_5; X = Cl	132.5–134	82
5	66768-91-0	R = C_6H_5; X = Br	129–131	22
6	66768-92-1	R = $CH_2C_6H_5$; X = Cl	87–88	84
7[15]	66768-93-2	R = CH_3; X = Cl	Oil	90
8	66768-94-3	R = CH_2CH_3; X = Cl	Oil	90
9	66768-95-4	R = CH_2CH_2-CH_2CH_3; X = Cl	Oil	100
10	66768-96-5	R = CH_3; X = Br	Oil	95
11	66768-97-6	Sulfone of 5	186–188	16
12[15]	66768-98-7	Sulfone of 7	106–107	50
13	66768-99-8	Sulfone of 8	151–153	20
14	66769-00-4	Sulfoxide of 4	201–204 (dec)	53

[a] Yields for sulfones and sulfoxide were not optimized.

Table II. Properties of the 1-Benzothiepins and 1-Benzothiepin 1,1-Dioxides

| Compd	Registry no.	Substituents	Physical appearance	Melting point, °C	Isolated yield, %
1	44887-88-1	4-Chloro	Yellow oil		35[a]
16	66769-01-5	4-Chloro-5-phenyl	Crystalline	87–88	76
24	66769-02-6	4-Chloro-5-benzyl	Crystalline	80–81	82
26	66769-03-7	4-Bromo-5-phenyl	Crystalline	81–82	24
27	66768-76-1	4-Chloro-5-methyl	Colorless oil		43[a]
28	66768-77-2	4-Bromo-5-methyl	Colorless oil		29[b]
22	66768-78-3	Sulfone of 16	Crystalline	170–172	74 (33)[c]
25	66768-79-4	Sulfone of 24	Crystalline	181–182	82 (66)[c]

[a] Overall yield from ketone 2. [b] Overall yield from ketone 3. [c] Yield from oxidation of the corresponding 1-benzothiepin.

phenyl-1-benzothiepin (16) as a white crystalline solid, mp 87–88 °C. The structural assignment of 16 was based on IR and NMR spectral data, elemental analyses, an extrusion reaction, and oxidation to the corresponding sulfone 22. 4-Chloro-5-phenyl-1-benzothiepin 1,1-dioxide (22) was also prepared in good yield by DBN treatment of 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin 1,1-dioxide (23). The sulfone 22 was characterized by IR and NMR spectral data and elemental analyses.

and for at least 1 h of reaction time: *tert*-butoxide (−78, −20, and 0 °C); 1,8-bis(dimethylamino)naphthalene (30 °C); 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (23 and 66 °C); and lithium chloride in DMF (23, 50, 75, and 100 °C). Interestingly, compound 15 underwent substitution at C-2 in water–acetone solution to give 4-chloro-2-hydroxy-5-phenyl-2,3-dihydro-1-benzothiepin (19). The structural assignment of 19 was based on IR, which had strong absorption at 3580 cm^{-1}, NMR, which had a doublet of doublets at δ 5.93 and a singlet at δ 5.67, and elemental analyses. Sodium ethoxide also promoted substitution according to NMR analyses of reaction product mixtures.

These results led to the introduction of bromine at C-2 in place of chlorine simply by treating the cyclopropyl alcohol 8 with HBr. 2-Bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (20) gave results similar to those for 15 when reacted with potassium *tert*-butoxide or potassium 2,6-di-*tert*-butylphenoxide at room temperature. However, reaction of 20 with DBN in THF at room temperature provided, after chromatography on alumina, an 82% yield of 4-chloro-5-

Utilizing DBN in the final step thus permitted the synthesis of several 5-aryl- and 5-alkyl-1-benzothiepin derivatives, which are listed in Table II. 4-Chloro-5-benzyl-1-benzo-

Table III. Thermal Decomposition of 1-Benzothiepins
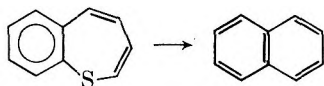
Compd	Substituents	Approximate half-life,[a] h	
		Room temp	30 °C
29	None	17[11]	
1	4-Chloro	22[11]	12[c]
30	2-Chloro	42[11]	
16	4-Chloro-5-phenyl	27[c]	17[c]
24	4-Chloro-5-phenyl	46[c]	22[c]
26	4-Bromo-5-phenyl	47[b]	
27	4-Chloro-5-methyl		25[c]
28	4-Bromo-5-methyl		29[c]

[a] First order. [b] CDCl₃ as solvent (present work). [c] CCl₄ as solvent (present work).

thiepin (24) and its corresponding sulfone 25 were prepared similarly to and characterized the same as 16 and 22, respectively. 4-Bromo-5-phenyl-1-benzothiepin (26) was prepared in a manner similar to that for 16 and 24 by ring opening of 5 followed by DBN treatment of 21. The 1-benzothiepin 26 was characterized by IR and NMR spectral data, elemental analyses, and an extrusion reaction. The preparation of the methyl-substituted 1-benzothiepins and 4-chloro-1-benzothiepin (1) was accomplished by reacting the crude product from HBr ring opening of the cyclopropyl alcohols with an excess of DBN. Thus, 4-chloro-5-methyl-1-benzothiepin (27) (43% overall yield from ketone 2), 4-bromo-5-methyl-1-benzothiepin (28) (29% overall yield from ketone 3), and 4-chloro-1-benzothiepin (1) (35% overall yield from ketone 2) were isolated as oils and characterized by IR and NMR spectral properties and a thermal extrusion reaction.

The NMR spectral data for the 1-benzothiepins 16, 24, 26, 27, and 28 were consistent with the data for other known 1-benzothiepins. The protons at C-2 and C-3 appear in the olefinic reagion (δ 5.9–6.5) as a doublet of doublets, and the coupling constants are 8–10 Hz. In the case of 24, the benzylic protons appear as a singlet at δ 4.20, and for 27 and 28 the methyl protons appear as a singlet at δ 2.43 and 2.33, respectively. The NMR spectra for all of the corresponding naphthalene compounds do not contain absorption in the olefinic region, and benzyl and methyl protons are shifted downfield by 11–22 Hz.

The extrusion reactions were thus conveniently followed by NMR spectroscopy. We previously reported half-lives at room temperature in CCl₄ for 1-benzothiepin (29), 2-chloro-1-benzothiepin (30), and 4-chloro-1-benzothiepin (1). Reactions of 1-benzothiepins 16, 24, and 26 were thus monitored by NMR spectroscopy at room temperature in CCl₄ (26 in CDCl₃). In order to eliminate any temperature variation, the 1-benzothiepins 1, 16, 24, 27, and 28 were monitored by NMR spectroscopy at 30° in CCl₄, and the results are given in Table III. From this table it is apparent that a slight increase in the stability of the thiepin ring by phenyl, benzyl, methyl, chloro, and bromo substituents is suggested. Furthermore, greater stabilization is achieved by groups with greater electron-donating ability. This trend supports the recent observations reported by Murata and Tatsuoka.[13] An explanation for these observations awaits further study. Hopefully, more work on the mechanism of sulfur extrusion, which is believed to procede via a thianorcaradiene intermediate,[3,8] would offer a reasonable solution.

After the extrusion reactions of 16, 24, 27, and 28 were complete, the corresponding naphthalenes were isolated and characterized by IR and NMR spectra. Elemental analyses

were consistent with the molecular formulas of the new naphthalene compounds, 2-chloro-1-phenylnaphthalene (17) and 1-benzyl-2-chloronaphthalene (31). Sulfur was also isolated from the decomposition reactions of 16 and 24.

Experimental Section

General. All melting points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. IR spectra were determined on a Beckman IR-8 spectrophotometer, NMR spectra were recorded on a Varian Model T-60 or EM-360 spectrometer, and the mass spectra were obtained on a Nuclide Corp. 12-90G high-resolution mass spectrometer. Reagents were used as received unless otherwise stated.

7a-Chloro-7-hydroxy-7-phenylcyclopropa[b][1]benzothiopyran (4). A solution of 7a-chlorocyclopropa[b][1]benzothiopyran-7-one[14] (2.7 g, 0.013 mol) in anhydrous ether (30 mL) was added dropwise over a period of 25 min to a solution containing phenylmagnesium bromide (prepared from 7.5 g of bromobenzene and 0.95 g of magnesium turnings in 40 mL of ether). The mixture was heated at reflux for 1 h. The yellow solution was allowed to cool to room temperature and was then hydrolyzed by careful addition of first 10% NH₄Cl and then 10% H₂SO₄. The mixture was finally extracted with 50 mL of ether, and the ether portion was washed with water (2 × 50 mL) and then dried (MgSO₄). Removal of the solvent gave a yellow solid which was recrystallized from hexane–benzene to give 3.07 g (82%) of pale yellow crystals of 4: mp 132.5–134 °C; IR (CHCl₃) 3580 cm⁻¹ (OH); NMR (CDCl₃) δ 1.53 (overlapping dd, 2, $J_{C_{1a}-C_{1x}}$ = 9 Hz, $J_{C_{1a}-C_{1y}}$ = 7 Hz, C₁ H's), 3.00 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 9 Hz, $J_{C_{1a}-C_{1y}}$ = 7 Hz, C₁ₐ H), 3.20 (s, 1, OH), 7.00–7.50 (m, 7, C₄ H, C₅ H and phenyl H's), 7.64–8.16 (m, 2, C₃ H and C₆ H); mass spectrum (70 eV), m/e (relative intensity) 288 (58), 253 (51), 105 (100), 77 (65).

Anal. Calcd for C₁₆H₁₃ClOS: C, 66.54; H, 4.53; Cl, 12.28. Found: C, 66.44; H, 4.44; Cl, 12.00.

7a-Bromo-7-hydroxy-7-phenylcyclopropa[b][1]benzothiopyran (5). Using the same procedure described for the preparation of 4, 7a-bromocyclopropa[b][1]benzothiopyran-7-one[14] (0.85 g, 3.9 mmol) provided, after recrystallization from cyclohexane, 280 mg (22%) of 5: mp 129–131 °C; IR (CHCl₃) 3565 cm⁻¹ (OH); NMR (CDCl₃) δ 1.6 (dd, 2, J = 8 Hz, C₁ H's), 3.1 (m, 2, OH, C₁ₐ H's), 7.2–7.9 (m, 9, aromatic H's).

Anal. Calcd for C₁₆H₁₃OSBr: C, 57.84; H, 3.64; S, 9.65; Br, 24.05. Found: C, 57.63; H, 3.80; S, 9.58; Br, 23.89.

7a-Chloro-7-hydroxy-7-benzylcyclopropa[b][1]benzothiopyran (6). Using the same procedure described for the preparation of 4, 7a-chlorocyclopropa[b][1]benzothiopyran-7-one[14] (3.7 g, 18 mmol) in ether (20 mL) was added to a solution containing benzylmagnesium chloride (prepared from 3.70 g of benzyl chloride and 0.69 g of magnesium turnings in 40 mL of ether). After reaction and workup, 2.4 g (84%) of colorless crystals of 6 was isolated: mp 84–86 °C; IR (CHCl₃) 3590 (OH) cm⁻¹; NMR (CDCl₃) δ 1.0–1.4 (m, 2, C₁ H's), 2.45–2.90 (m, 3, C₆H₅CH₂ and C₁ₐ H), 3.43 (s, 1, OH), 6.5–7.3 (m, 9, aromatic H's). Recrystallization from hexane–CHCl₃ provided an analytical sample, mp 87–88 °C.

Anal. Calcd for C₁₇H₁₅ClOS: C, 67.43; H, 4.99; S, 10.59. Found: C, 67.45; H, 5.04; S, 10.45.

7a-Chloro-7-hydroxy-7-methylcyclopropa[b][1]benzothiopyran (7). Using the same procedure described for the preparation of 4, 7a-chlorocyclopropa[b][1]benzothiopyran-7-one[14] (1.30 g, 6.2 mmol) in ether (25 mL) was added to a solution of methylmagnesium chloride in THF (25 mL, 80 mmol) (Fisher Scientific Co.). After workup, the solvent was removed under vacuum to give 1.25 g (90%) of 7 as a yellow oil: IR (CHCl₃) 3450 cm⁻¹ (OH); NMR (CDCl₃) δ 1.22 (dd, 2, $J_{C_{1x}-C_{1a}}$ = 8 Hz, $J_{C_{1y}-C_{1a}}$ = 7 Hz, C₁ H's), 1.60 (s, 3, CH₃), 2.41–2.70 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 8 Hz, $J_{C_{1a}-C_{1y}}$ = 7 Hz, C₁ₐ H), 3.1 (s, 1, OH), 6.95–7.25 (m, 3, aromatic H's), 7.7–7.88 (m, 1, C₉ H); mass spectrum (70 eV), m/e (relative intensity) 226 (48), 191 (38), 175 (100), 147 (83). Elemental analyses were performed on the corresponding sulfone 12.[15]

7a-Chloro-7-hydroxy-7-ethylcyclopropa[b][1]benzothiopyran (8). Using the same procedure described for the preparation of 4, 7a-chlorocyclopropa[b][1]benzothiopyran-7-one[14] (5.00 g, 24 mmol) in ether (40 mL) was added to a solution containing ethylmagnesium iodide (prepared from 11.1 g of ethyl iodide and 1.74 g of magnesium turnings in 60 mL of ether). After workup, the solvent was removed under vacuum to give 5.15 g (90%) of 8 as a yellow oil: IR (neat) 3490 cm⁻¹ (OH); NMR (CDCl₃) δ 0.67 (t, 3, J = 8 Hz, CH₃), 1.33 (dd, 2, J = 6 Hz, C₁ H's), 2.20 (s, 1, OH), 2.21 (q, 2, J = 8 Hz, CH₂), 2.65 (dd, 1, J = 6 Hz, C₁ₐ H), 7.1–7.9 (m, 4, aromatic H's).

Anal. Calcd for $C_{12}H_{13}ClOS$: C, 59.86; H, 5.44. Found: C, 59.79; H, 5.53.

7a-Chloro-7-hydroxy-7-*n*-butylcyclopropa[*b*][1]benzothiopyran (9). Using the same procedure described for the preparation of **4**, 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one[14] (1.6 g, 7.6 mmol) in ether (15 mL) was added to a solution containing *n*-butylmagnesium bromide (prepared from 3.18 g of *n*-butyl bromide and 0.56 g of magnesium turnings in 35 mL of ether). Workup gave 2.05 g (100%) of **9** as a yellow oil: IR (neat) 3420 cm⁻¹ (OH); NMR (CDCl₃) δ 0.7–1.4 (m, 11, *n*-butyl and C₁ H's), 2.59 (dd, 1, J = 8 Hz, C₁ₐ H), 4.93 (s, 1, OH), 7.0–7.8 (m, 4, aromatic H's).

Anal. Calcd for $C_{14}H_{17}ClOS$: C, 62.56; H, 6.37. Found: C, 62.78; H, 6.20.

7a-Chloro-7-hydroxy-7-ethylcyclopropa[*b*][1]benzopyran 2,2-Dioxide (13). After a solution of 7a-chloro-7-ethyl-7-hydroxycyclopropa[*b*][1]benzothiopyran (1.10 g, 4.6 mmol) in CHCl₃ (20 mL) was added in one portion to a stirred solution of *m*-chloroperbenzoic acid (2.42 g, 14 mmol) in CHCl₃ (25 mL) maintained at 0 to −5 °C, the reaction mixture was allowed to warm to room temperature and was kept overnight at ambient temperature. *m*-Chlorobenzoic acid was removed by filtration and washed with CHCl₃ (2 × 10 mL). The combined CHCl₃ portions were washed with 10% Na₂CO₃ (2 × 20 mL) and water (2 × 20 mL) and dried (MgSO₄). The solvent was removed, and two recrystallizations of the colorless oil from 95% ethanol gave 0.25 g (20%) of **13**: mp 151–153 °C; IR (CHCl₃) 3460 (OH), 1290 and 1130 (–SO₂–) cm⁻¹.

Anal. Calcd for $C_{12}H_{13}ClO_3S$: C, 52.84; H, 4.80. Found: C, 53.00; H, 4.92.

7a-Chloro-7-hydroxy-7-methylcyclopropa[*b*][1]benzothiopyran 2,2-Dioxide (12). A solution of 7a-chloro-7-hydroxy-7-methylcyclopropa[*b*][1]benzothiopyran (1.07 g, 4.7 mmol) in CHCl₃ (30 mL) was added in one portion to a solution of *m*-chloroperbenzoic acid (2.47 g, 14.2 mmol) in CHCl₃ (20 mL) at −20 °C, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was processed as described in the preparation of **13** and gave, after recrystallization from CHCl₃–hexane, 0.60 g (50%) of **12**: mp 106–107 °C; IR (CHCl₃) 3500 (OH), 1320 and 1140 (SO₂) cm⁻¹; NMR (CDCl₃) δ 1.33–1.70 (m, 2, C₁ H's), 1.85 (s, 3, CH₃), 3.26–3.62 (dd, 1, C₁ H), 4.88 (s, 1, OH), 7.33–8.08 (m, 4, aromatic H's).

Anal. Calcd for $C_{11}H_{11}ClO_3S$: C, 51.07; H, 4.29; Cl, 13.78; S, 12.39. Found: C, 51.29; H, 4.28; Cl, 14.01; S, 12.51.

7a-Bromo-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran 2,2-Dioxide (11). A solution of 7a-bromo-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (0.76 g, 2.3 mmol) in CHCl₃ (3 mL) was added dropwise to a solution of *m*-chloroperbenzoic acid (0.77 g, 4.5 mmol) in CHCl₃ (12 mL) at −10 to −15 °C, and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was processed as described in the preparation of **13** and gave, after recrystallization from 95% ethanol, 0.13 g (16%) of **11**: mp 186–188 °C; IR (KBr) 3460 (OH), 1295 and 1140 (SO₂) cm⁻¹; NMR (acetone-*d₆*) δ 1.9 (m, 2, C₁ H's), 1.95 (s, 1, OH), 3.95 (dd, 1, C₁ₐ H), 7.2–7.8 (m, 9, aromatic H's).

Anal. Calcd for $C_{16}H_{13}BrO_3S$: C, 52.61; H, 3.58; S, 8.78. Found: C, 52.75; H, 3.50; S, 8.56.

7a-Chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran 2-Oxide (14). A solution of 7a-chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (500 mg, 1.73 mmol) in acetone (10 mL) and 30% hydrogen peroxide (3.5 mL) was refluxed for 3 h, after which time 30% hydrogen peroxide (3.5 mL) was again added and the solution was heated at reflux for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (25 mL). The ether portion was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was removed, crystallization of the residue from 95% ethanol gave 280 mg (53%) of **14**: mp 201–204 °C dec; IR (CHCl₃) 3570 (OH) and 1020 (SO) cm⁻¹.

Anal. Calcd for $C_{16}H_{13}ClO_2S$: C, 63.05; H, 4.30; S, 10.52. Found: C, 63.35, 63.52; H, 4.45, 4.42; S, 10.57, 10.39.

2,4-Dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (15). Hydrogen chloride was bubbled into a solution of 7a-chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (6.60 g, 0.023 mmol) in CHCl₃ (30 mL) for 15 min at room temperature. The excess HCl was then removed from the solution under a stream of nitrogen, and the CHCl₃ solution was dried (MgSO₄). Removal of the solvent gave 6.60 g (94%) of **15**, mp 119–121 °C. Several recrystallizations from hexane–benzene gave an analytical sample: mp 123–124 °C; IR (CHCl₃) 3050 (w), 1600 (m), 1490 (m), 1460 (m), 1430 (m), 1160 (m), 1075 (m), 1050 (m), 950 (m), 680 (s) cm⁻¹; NMR (CDCl₃) δ 3.05 (m, 2, C₃ H's), 6.02 (dd, 1, $J_{C_2-C_{3a}}$ = 6 Hz, $J_{C_2-C_{3b}}$ = 11 Hz, –SCHClCH$_a$H$_b$–), 6.89–7.86 (m, 9, aromatic H's); mass spectrum (70

eV), *m/e* (relative intensity) 306 (6), 271 (18), 244 (100), 235 (67).

Anal. Calcd for $C_{16}H_{12}Cl_2S$: C, 62.55; H, 3.94; Cl, 23.08. Found: C, 62.58; H, 3.85; Cl, 22.92.

2-Bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (20). HBr gas (generated by the addition of water to PBr₃) was bubbled into a solution of 7a-chloro-7-phenyl-7-hydroxycyclopropa[*b*][1]benzothiopyran (4.30 g, 14.9 mmol) in CHCl₃ (50 mL) for 30 min at room temperature. The excess HBr was then removed from the solution under a stream of nitrogen, and the CHCl₃ solution was dried (MgSO₄). The solvent was removed under vacuum and gave 4.82 g (92%) of **20**, mp 118–122 °C. Several recrystallizations from hexane–benzene gave an analytical sample: mp 121–122 °C; IR (CHCl₃) 3070 (w), 3010 (w), 1600 (w), 1495 (m), 1465 (m), 1435 (m), 1150 (m), 1085 (m), 955 (m), 695 (s) cm⁻¹; NMR (CDCl₃) δ 3.11 (m, 2, C₃ H's), 6.09 (dd, 1, $J_{C_2-C_{3a}}$ = 6 Hz, $J_{C_2-C_{3b}}$ = 11 Hz, C₂ H). 6.89–7.95 (m, 9, aromatic H's); mass spectrum (70 eV), *m/e* (relative intensity) 350 (8), 315 (23), 271 (76), 244 (100), 235 (88).

Anal. Calcd for $C_{16}H_{12}BrClS$: C, 54.64; H, 3.44; S, 9.12. Found: C, 54.82; H, 3.55; S, 8.95.

2,4-Dibromo-5-phenyl-2,3-dihydro-1-benzothiepin (21). Using the same procedure described for the preparation of **15**, 7a-bromo-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (0.41 g, 1.2 mmol) provided, after recrystallization from hexane, 0.47 g (95%) of **21**: mp 108–110 °C; IR (CHCl₃) 1150 (m), 690 (s), 650 (m), 600 (m) cm⁻¹; NMR (CDCl₃) δ 3.30 (m, 2, C₃ H's), 6.15 (dd, 1, $J_{C_2-C_{3x}}$ = 6 Hz, $J_{C_2-C_{3y}}$ = 12 Hz, C₂ H's), 7.25 (m, 9, aromatic H's).

Anal. Calcd for $C_{16}H_{12}Br_2S$: C, 48.49; H, 3.05; S, 8.09; Br, 40.34. Found: C, 48.60; H, 3.02; S, 8.14; Br, 39.90.

2-Bromo-4-chloro-5-benzyl-2,3-dihydro-1-benzothiepin (32). Using the same procedure described for the preparation of **20**, 7-benzyl-7a-chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran (2.85 g, 9.4 mmol) provided, after recrystallization from hexane–CHCl₃, 3.03 g (88%) of **32**: mp 102–103 °C; IR (CHCl₃) 3070 (m), 2940 (w), 1625 (m), 1600 (m), 1495 (s), 1465 (s), 1430 (s), 1145 (s), 955 (s), 685 (s) cm⁻¹; NMR (CDCl₃) δ 3.13 (m, 2, C₃ H's), 3.99 (d, 2, C₆H₅CH₂), 6.11 (dd, 1, $J_{C_2-C_{3a}}$ = 6 Hz, $J_{C_2-C_{3b}}$ = 11 Hz, C₂ H), 7.0–8.0 (m, 9, aromatic H's).

Anal. Calcd for $C_{17}H_{14}BrClS$: C, 55.83; H, 3.86; S, 8.77. Found: C, 55.64; H, 3.78; S, 8.59.

4-Chloro-2-hydroxy-5-phenyl-2,3-dihydro-1-benzothiepin (19). A solution of 2,4-dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (0.30 g, 0.98 mmol), acetone (10 mL), and water (4 mL) was allowed to stand overnight at room temperature. An additional 1 mL of water was added, and white solid precipitate formed which was filtered and allowed to dry. The yield of crystalline **19** was 0.24 g (84%): mp 159–161 °C; IR (CHCl₃) 3580 cm⁻¹ (OH); NMR (acetone-*d₆*) δ 2.80 (m, 2, C₃ H's), 5.67 (s, 1, OH), 5.93 (dd, 1, $J_{C_2-C_{3x}}$ = 5 Hz, $J_{C_2-C_{3y}}$ = 10 Hz, C₂ H), 6.83–7.72 (m, 9, aromatic H's). Several recrystallizations from hexane–benzene gave an analytical sample, mp 160–161 °C.

Anal. Calcd for $C_{16}H_{13}ClOS$: C, 66.54; H, 4.54; S, 11.10. Found: C, 66.67, 66.52; H, 4.44, 4.48; S, 10.90, 10.83.

Reaction of 7a-Chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (4) with Trace Amounts of *p*-Toluenesulfonic Acid in Refluxing Benzene. In a 100-mL round-bottom flask fitted with a Dean-Stark trap and reflux condenser a solution of 7a-chloro-7-phenyl-7-hydroxycyclopropa[*b*][1]benzothiopyran (0.80 g, 2.8 mmol) and *p*-toluenesulfonic acid (20 g, 0.10 mmol) in 50 mL of benzene was stirred magnetically and refluxed for 1 h. The yellow solution was allowed to cool and then was washed with 10% Na₂CO₃ (2 × 45 mL) and water (45 mL) and dried over MgSO₄. Removal of the solvent under vacuum left an orange oil which had IR and NMR spectra which were identical with those of 2-chloro-1-phenylnaphthalene. Repeated vacuum sublimation provided white crystals of 2-chloro-1-phenylnaphthalene, mp 49–51 °C.

2-Bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin 1,1-Dioxide (23). After a solution of 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (2.00 g, 5.7 mmol) in CHCl₃ (7 mL) was added dropwise over a 15-min period to a stirred solution of *m*-chloroperbenzoic acid (2.45 g, 14 mmol) in CHCl₃ (20 mL) maintained at 0 to −5 °C, the reaction mixture was allowed to warm to room temperature and was kept overnight at ambient temperature. *m*-Chlorobenzoic acid was removed by filtration and washed with CHCl₃ (2 × 7 mL). The combined CHCl₃ portions were washed with 10% Na₂CO₃ (2 × 40 mL) and water (2 × 40 mL) and dried (MgSO₄). The solvent was removed, and recrystallization of the solid residue from 95% ethanol and benzene gave 0.85 g (39%) of **23**: mp 208–211 °C dec; IR (CHCl₃) 1330, 1140, 1115 cm⁻¹ (–SO₂–); NMR (CDCl₃) δ 3.27 (m, 2, C₃ H's), 5.47 (dd, 1, C₄ H), 6.98–8.28 (m, 9, aromatic H's). Several recrystallizations from 95% ethanol gave an analytical sample, mp 209–211 °C dec.

Anal. Calcd for $C_{16}H_{12}BrClO_2S$: C, 50.09; H, 3.15; S, 8.36. Found: C, 50.22; H, 3.20; S, 8.19.

2-Bromo-4-chloro-5-benzyl-2,3-dihydro-1-benzothiepin 1,1-Dioxide (33). Following the procedure described for the preparation of 23, 5-benzyl-2-bromo-4-chloro-2,3-dihydro-1-benzothiepin (1.00 g, 2.7 mmol) gave, after recrystallization from 95% ethanol and benzene, 0.68 g (67%) of 33: mp 181–183 °C; IR (CHCl₃) 1325 and 1115 cm⁻¹ (SO₂); NMR (CDCl₃) δ 3.21 (m, 2, C₃ H's), 4.11 (s, 2, C₆H₅CH₂), 5.49 (dd, 2, $J_{C_2-C_{3x}}$ = 6 Hz, $J_{C_2-C_{3y}}$ = 10 Hz, C₂ H's), 7.2–7.8 (m, 8, aromatic H's except C₉ H), 8.20 (m, 1, C₉ H). Recrystallization from 95% ethanol and benzene gave an analytical sample, mp 182–183 °C.

Anal. Calcd for $C_{17}H_{14}BrClO_2S$: C, 51.34; H, 3.55; S, 8.06. Found: C, 51.25; H, 3.64; S, 7.95.

4-Chloro-5-phenyl-1-benzothiepin (16). A solution of 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (1.02 g, 2.84 mmol) in THF (3 mL) was added in one portion to a solution of 1,5-diazabicyclo[4.3.0]-5-nonene (DBN) (0.52 g, 4.2 mmol) in THF (3 mL) at room temperature. After the reaction mixture was stirred for 2 h, the red solution containing some precipitate was poured into 10% HCl solution (20 mL) and the aqueous solution was extracted with CHCl₃ (2 × 15 mL). The extract was washed with water, dried (MgSO₄), and concentrated in vacuo (below room temperature). The yellow oil which solidified on cooling was chromatographed on aluminum oxide (Merck 71707, 25 g) with hexane as the eluent, and the first 50-mL fraction gave 0.58 g (76%) of 16 as a white crystalline solid: mp 86–88 °C; IR (CHCl₃) 3070 (m), 3020 (m), 1590 (m), 1490 (m), 1470 (s), 1445 (m), 1080 (s), 1045 (s), 845 (s), 695 (s) cm⁻¹; NMR (CCl₄) δ 6.20 (d, 1, $J_{C_3-C_2}$ = 9 Hz, C₂ H), 6.44 (d, 1, $J_{C_2-C_3}$ = 9 Hz, C₃ H), 6.8–7.6 (m, 9, aromatic H's). Recrystallization from pentane–CHCl₃ gave an analytical sample, mp 87–88 °C (sent out packed in dry ice).

Anal. Calcd for $C_{16}H_{11}ClS$: C, 70.97; H, 4.09; S, 11.83. Found: C, 70.81; H, 4.21; S, 11.70.

4-Chloro-5-benzyl-1-benzothiepin (24). Using the same procedure described for the preparation of 16, 5-benzyl-2-bromo-4-chloro-2,3-dihydro-1-benzothiepin (1.00 g, 2.7 mmol) in THF (5 mL) was reacted with DBN (0.51 g, 4.1 mmol) in THF (5 mL) at room temperature. Chromatography provided 0.63 g (82%) of 24 as a light yellow crystalline solid: mp 80–81 °C; IR (CCl₄) 3075 (m), 3040 (m), 2960 (w), 1495 (m), 720 (m), 690 (s) cm⁻¹; NMR (CCl₄) δ 4.20 (s, 2, C₅H₅CH₂), 6.20 [d, 2 (total weight of C₃ H and C₂ H), $J_{C_3-C_2}$ = 10 Hz, C₂ H], 6.40 [d, 2 (total weight of C₂ H and C₃ H), $J_{C_2-C_3}$ = 10 Hz, C₃ H], 7.0–7.4 (m, 9, aromatic H's). Recrystallization from hexane provided an analytical sample, mp 80–81 °C.

Anal. Calcd for $C_{17}H_{13}ClS$: C, 71.69; H, 4.60. Found: C, 71.81; H, 4.60.

4-Bromo-5-phenyl-1-benzothiepin (26). Using the same procedure described for the preparation of 16, 2,4-dibromo-5-phenyl-1-benzothiepin (150 mg, 0.38 mmol) in THF (6 mL) was reacted with DBN (0.99 g, 0.80 mmol) in THF (5 mL) at room temperature. Chromatography followed by recrystallization from pentane provided 30 mg (24%) of 26: mp 81–82 °C; IR (CDCl₃) 3060 (w), 1035 (m), 840 (m) cm⁻¹; NMR (CDCl₃) δ 6.50 (dd, 2, C₂ H and C₃ H), 7.4 (m, 9, aromatic H's).

Anal. Calcd for $C_{16}H_{11}BrS$: C, 60.96; H, 3.52; S, 10.17. Found: C, 60.86; H, 3.45; S, 9.92.

4-Chloro-5-methyl-1-benzothiepin (27). 7a-Chlorocyclopropa[b][1]benzothiopyran-7-one (3.00 g, 14.2 mmol) was reacted with excess methylmagnesium chloride and provided the alcohol 7 as previously described. Reaction of 7 with HBr, following the procedure described for the preparation of 20, gave 2.90 g of crude 2-bromo-4-chloro-5-methyl-1-benzothiepin. The olefin (1.00 g, 3.4 mmol) was converted to 27 with a threefold excess of DBN following the procedure described for the preparation of 16. The crude product was passed through two columns of alumina (15 g each) eluting with hexane to provide 0.44 g (43% overall yield from ketone 2) of 27 as a colorless oil: IR (neat) 3070 (w), 2970 (w), 1475 (m), 985 (s), 840 (s), 760 (s), 725 (s) cm⁻¹; NMR (CCl₄) δ 2.43 (s, 3, CH₃), 6.07 [d, 2 (total weight of C₃ H and C₂ H), $J_{C_3-C_2}$ = 9 Hz, C₂ H], 6.25 [d, 2 (total weight of C₂ H and C₃ H), $J_{C_2-C_3}$ = 9 Hz, C₃ H], 7.1–7.4 (m, 4, aromatic H's). Further characterization was provided by examination of the products from thermal decomposition.

4-Bromo-5-methyl-1-benzothiepin (28). Using the same procedure described for the synthesis of 27, 7a-bromocyclopropa[b][1]benzothiopyran-7-one (3.00 g, 11.8 mmol) was converted to 28 (29% overall yield from ketone 3), isolated as a pale yellow oil: IR (neat) 3070 (w), 2990 (w), 760 (s) cm⁻¹; NMR (CCl₄) δ 2.33 (s, 3, CH₃), 5.90 [d, 2 (total weight of C₃ H and C₂ H), $J_{C_3-C_2}$ = 8.5 Hz, C₂ H], 6.29 [d, 2 (total weight of C₂ H and C₃ H), $J_{C_2-C_3}$ = 8.5 Hz, C₃ H], 7.0–7.6 (m, 4, aromatic H's). Further characterization was provided by examination of the products from thermal decomposition.

4-Chloro-5-phenyl-1-benzothiepin 1,1-Dioxide (22). Method A. To a stirred solution of 1,5-diazabicyclo[4.3.0]-5-nonene (0.23 g, 1.85 mmol) in THF (5 mL) was added at room temperature, in one portion, 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin 1,1-dioxide (0.48 g, 1.25 mmol) in THF (11 mL). After the reaction mixture was stirred for 2 h at room temperature, the yellow mixture was poured into 10% HCl solution (25 mL). The aqueous solution was extracted with CHCl₃ (2 × 15 mL), washed with H₂O, and dried (MgSO₄). The CHCl₃ was removed under pressure and left 0.31 g (82%) of 22: mp 178–180 °C; IR (KBr) 1300 and 1160 cm⁻¹ (–SO₂–); NMR (CDCl₃) δ 6.77 [d, 2 (total weight of C₃ H and C₂ H), $J_{C_2-C_3}$ = 14 Hz, C₂ H], 6.94 [d, 2 (total weight of C₂ H and C₃ H), $J_{C_3-C_2}$ = 14 Hz, C₃ H], 7.1–7.8 (m, 8, aromatic H's except for C₉ H), 8.10 (m, 1, C₉ H). Two recrystallizations from hexane–CHCl₃ provided an analytical sample, mp 181–182 °C.

Anal. Calcd for $C_{16}H_{11}ClO_2S$: C, 63.47; H, 3.66; S, 10.59. Found: C, 63.33; H, 3.72; S, 10.59.

Method B. To a solution of m-chloroperbenzoic acid (222 mg, 1.3 mmol) in CHCl₃ (3 mL) maintained at −15 to −20 °C was added dropwise over a 10-min period 4-chloro-5-phenyl-1-benzothiepin (174 mg, 0.64 mmol) in CHCl₃ (3 mL). The reaction mixture was stirred overnight at 0 °C. After the reaction mixture was filtered, the precipitate was washed with CHCl₃ (2 × 3 mL) and the washings were combined with the filtrate and washed with 10% Na₂CO₃ solution and water and dried (MgSO₄). Removal of the solvent left 127 mg (66%) of a colorless oil which solidified upon cooling and addition of hexane. Recrystallization from CHCl₃–hexane gave 22, mp 180–181 °C. A mixture melting point with an authentic sample was not depressed, and the IR spectrum was identical with that of an authentic sample.

4-Chloro-5-benzyl-1-benzothiepin 1,1-Dioxide (25). Method A. Following the same procedure described for the preparation of 22, 5-benzyl-2-bromo-4-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (0.51 g, 1.3 mmol) gave, after recrystallization from hexane–benzene, 0.30 g (74%) of 25: mp 160–162 °C; IR (CHCl₃) 1325 and 1145 cm⁻¹ (SO₂). Two more recrystallizations from hexane–benzene provided an analytical sample, mp 170–172 °C.

Anal. Calcd for $C_{17}H_{13}ClO_2S$: C, 64.45; H, 4.14. Found: C, 64.51; H, 4.20.

Method B. Following the same procedure described for the preparation of 22 (except the reaction was left at room temperature overnight), 5-benzyl-4-chloro-1-benzothiepin (232 mg, 0.8 mmol) gave, after chromatography on aluminum oxide (Merck 71707, 20 g) eluting with a 1:1 mixture of hexane–CHCl₃, 1-benzyl-2-chloronaphthalene (100 mg, 49%) and 25 (84 mg, 33%), each identified by comparison of its IR spectrum with that of an authentic sample.

Thermal Decomposition of 1-Benzothiepins. Approximately 1 M solutions of 1, 12, 19, 22, and 23 in CCl₄ and 21 in CDCl₃ were prepared, and the decomposition to sulfur and the corresponding naphthalenes was monitored by NMR spectroscopy (see Table III).

After the decomposition of 4-chloro-5-phenyl-1-benzothiepin (16) (46 mg, 0.17 mmol) was complete, the solvent was evaporated and the resulting solid was washed with pentane (20 mL). The solid (1 mg, 19%) was identified as sulfur by a mixed melting point with an authentic sample, mp 120–121 °C. Removal of the solvent under vacuum left 30 mg (75%) of 2-chloro-1-phenylnaphthalene (17) as a colorless oil: IR (CCl₄) 3070 (m), 1130 (s), 855 (m, two adjacent H's) cm⁻¹; NMR (CCl₄) δ 7.2–7.9 (m, aromatic H's). Recrystallization from methanol provided an analytical sample, mp 50–51 °C.

Anal. Calcd for $C_{16}H_{11}Cl$: C, 80.50; H, 5.64. Found: C, 80.37; H, 4.66.

A similar workup for the decomposition of 5-benzyl-4-chloro-1-benzothiepin (224 mg, 0.8 mmol) gave 4 mg (16%) of sulfur and 140 mg (69%) of 1-benzyl-2-chloronaphthalene (31): mp 59–61 °C; IR (CHCl₃) 3070 (m), 3010 (m), 1130 (s), 945 (s), 825 (m, two adjacent H's), 800 (s), 700 (m), 690 (m) cm⁻¹; NMR (CCl₄) δ 4.56 (s, 2, C₆H₅CH₂), 7.1–8.1 (m, 11, aromatic H's).

Anal. Calcd for $C_{17}H_{13}Cl$: C, 80.79; H, 5.18. Found: C, 80.61; H, 5.37.

A similar workup for the decomposition of 4-chloro-5-methyl-1-benzothiepin gave 2-chloro-1-methylnaphthalene:[16] IR (neat) 830 (m, two adjacent H's), 800 (s), 760 (m), 735 (m) cm⁻¹; NMR (CCl₄) δ 2.65 (s, 3, CH₃), 7.2–7.9 (m, 6, aromatic H's).

A similar workup for the decomposition of 4-bromo-5-methyl-1-benzothiepin gave 2-bromo-1-methylnaphthalene:[17] IR (neat) 815 (m, two adjacent H's), 800 (s), 760 (m), 735 (m) cm⁻¹; NMR (CCl₄) δ 2.61 (s, 3, CH₃), 7.2–8.0 (m, 6, aromatic H's).

Registry No.—2, 40322-30-3; **3**, 40322-58-5; **15**, 66768-80-7; **17**,

66768-81-8; **19**, 66768-82-9; **20**, 66768-83-0; **21**, 66768-84-1; **23**, 66768-85-2; **31**, 66768-86-3; **32**, 66768-87-4; **33**, 66768-88-5; 2-bromo-4-chloro-5-methyl-1-benzothiepin, 66768-89-6; 2-chloro-1-methylnaphthalene, 20601-21-2; 2-bromo-1-methylnaphthalene, 20601-22-3.

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Direction of Cyclization in the Fischer Indole Synthesis. Mechanistic Considerations

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The effects of acid catalysts and temperature in the uncatalyzed reaction on the direction of cyclization of unsymmetrical ketone phenylhydrazones in the Fischer indole synthesis have been examined. Higher acidity, as previously reported, and higher temperature in the thermal process cause cyclization toward the less substituted position. The observations are considered in terms of a refined version of the first two stages of the mechanism of the reaction.

A perplexing aspect of the Fischer indole synthesis[2] has been the cyclization of phenylhydrazones of unsymmetrical ketones to form two possible indoles. The early generalizations of Plancher,[3] suggesting that the course of the reaction depends only on the structure of the ketone moiety of the


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2 and/or **3** + NH$_3$
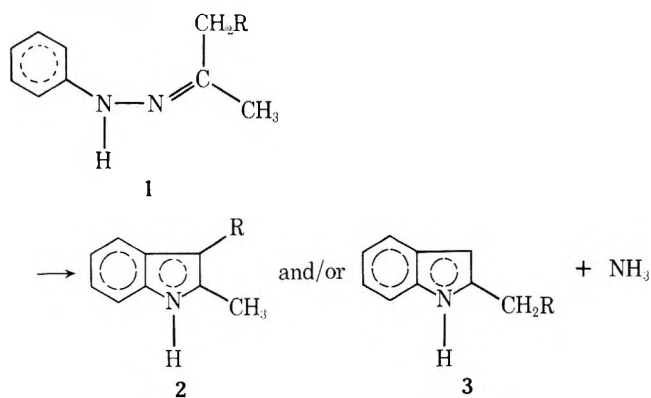
phenylhydrazone, have not been sustained by more recent investigations[4-7] in which the ratio of the products has been found to vary with the nature of the acid used as the catalyst, its concentration, or its absence in a thermal cyclization.

While Lyle and Skarlos[5] suggested that the direction of cyclization was an effect of the size of the acid, Illy and Funderburk[6] and Palmer and McIntyre[7] independently provided convincing evidence that the course of the reaction was governed by the acidity of the reaction medium. The trend evident in the results of these more recent studies[5-7] is that weaker acids or lower acid concentrations promote cyclization toward the more branched carbon atom (**1** → **2**) and stronger acids or higher acid concentrations enhance the extent of cyclization at the less branched position (**1** → **3**).

Most of these observations have been made on a variety of phenylhydrazone structures with several acid catalysts under nonuniform conditions. Since the direction of enolization is necessarily central to the mechanism[2] of the Fischer indole synthesis, a systematic examination of this phenomenon should provide further information regarding the character of the mechanistic steps. For this purpose, 2-alkylcyclohexanone phenylhydrazones were selected for cyclization under varying conditions of acidity and temperature. This substrate provides two reaction pathways of similar energy requirements since both products are known to form in good yield under moderate reaction conditions.[4a,c,8]

4

5 + **6**
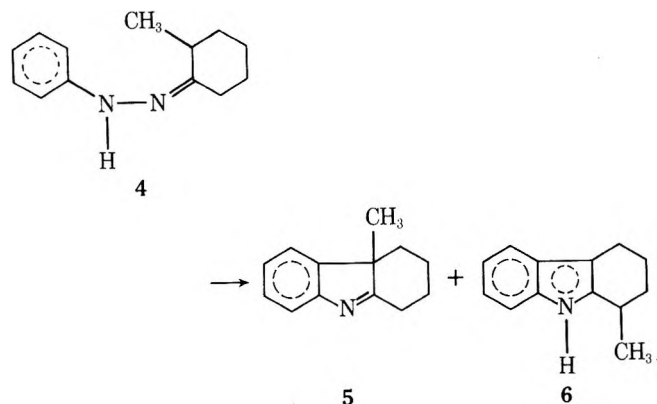
In Table I are listed the product ratios observed in the cyclization of 2-methylcyclohexanone phenylhydrazone (**4**) with various acids at 80 °C. The trend is similar to that found previously.[4a,8a] The results also parallel those of Illy and Funderburk[6] for the phenylhydrazone of methyl isopropyl ketone.

The product ratios observed with various concentrations of sulfuric acid in ethanol as the catalyst at 80 °C are given in Table II. As with the results reported by Illy and Funderburk[6] and Palmer and McIntyre[7] for acyclic ketone phenylhydraz-

Table I. Effect of Acid Catalyst on the Product Ratio at 80 °C

Acid	$-H_o{}^a$	Ratio[b]
Acetic	ca. −2.5	40
$H_2SO_4{}^c$	0.43	1.8
$BF_3{}^d$	7–10	0.9
$ZnCl_2{}^d$		0.3
PPA[e]	ca. 7	0.2

[a] C. H. Rochester, "Acidity Functions", Academic Press, New York, N.Y., 1970, Chapter 2. [b] Indolenine/indole. [c] 10% in ethanol. [d] Ethanol solvent. [e] Polyphosphoric acid.

Table II. Effect of Acid Concentration on the Product Ratio at 80 °C

% $H_2SO_4{}^a$	$-H_o{}^b$	Ratio[c]
10	0.43	1.8
20	1.10	0.8
40	2.54	0.4
60	4.51	0.5
80	7.52	0.7

[a] Ethanol solvent. [b] See footnote a in Table I. [c] Indolenine/indole.

Table III. Temperature Effect on the PPA-Catalyzed Reaction

Temp, °C	Ratio[a]
80	0.2
125	0.4
160	1.0[b]

[a] Indolenine/indole. [b] Minor decomposition observed (GC).

Table IV. Temperature Effect on the Uncatalyzed (Thermal) Reaction

Temp, °C	Ratio[a]
155	2.0[b]
200	0.5
245	0.2

[a] Indolenine/indole. [b] Some unreacted phenylhydrazone remained (GC).

Table V. Solvent Effect on the 10% H_2SO_4 Catalyzed Reaction at 80 °C

Solvent alcohol	Ratio[a]
Methyl[b]	1.4
Ethyl	1.8
2-Propyl	2.2
tert-Butyl	3.1

[a] Indolenine/indole. [b] At 65 °C.

Table VI. Product Ratios from the Cyclization of 2-Alkylcyclohexanone Phenylhydrazones with Various Acids at 80 °C

Acid catalyst	Product ratios[a]			
	2-Methyl	2-Ethyl	2-Isopropyl	2-tert-Butyl
Acetic	40	12	6.5	0[d]
$H_2SO_4{}^b$	1.8	4.1	0.8	0
$BF_3{}^c$	0.9	2.7	0.1	0
$ZnCl_2{}^c$	0.3	3.0	0.5	0
PPA	0.2	4.4	0.6	0

[a] Indolenine/indole. [b] 10% in ethanol. [c] Ethanol solvent. [d] Only indole formed.

ones, these ratios show a trend toward the formation of more of the indole product **6** at higher acidities. Values for the Hammet acidity function, H_o, in Tables I and II are probably not valid for the present solvent and temperature, but they do indicate a gross correlation of product ratio with acidity. The reason for the formation of a maximum amount of the indole at a concentration of about 40% H_2SO_4 with some increase in the amount of indolenine at higher acid concentrations is not immediately obvious.

To examine the temperature effect in the cyclization of **4**, the PPA-catalyzed reaction was selected since the temperature could be increased without changing other reaction conditions. The product ratios are listed in Table III. In line with the previous observation that the formation of the indole **6** is favored by higher acidity, the decrease in the proportion of indole formed at higher temperatures suggests that a protonated intermediate leading to the indole dissociates at higher temperatures, permitting somewhat more of the indolenine **5** to form.

This increased formation of indolenine at higher temperatures in the acid-catalyzed reaction is in contrast to the trend in the uncatalyzed (thermal) cyclization (Table IV) in which higher temperatures increase the amount of indole produced. These opposite temperature effects are not inconsistent in a reaction involving two competing pathways, each favored by different factors.

A further examination of the effect of the extent of protonation was made by determining the product ratios from reactions catalyzed by 10% H_2SO_4 in a series of alcohols as solvent (Table V). Increased bulk of the R group in $ROH_2{}^+$ reduces the effectiveness of the acid in protonating the reaction intermediate involved in the formation of the indole, resulting in a larger indolenine/indole ratio.

A measure of the steric control of the reaction was determined by examining the product ratio in the indolization of the phenylhydrazones of 2-ethyl-, 2-isopropyl-, and 2-tert-butylcyclohexanones with several acid catalysts (Table VI). The trends are generally parallel to those observed in the case of the 2-methyl compound except that $ZnCl_2$ and PPA produce somewhat more indolenine from the 2-ethyl and 2-isopropyl structures and that the 2-tert-butyl compound forms only indole. While the general picture evident from the data in Table VI is that increased bulk at the tertiary carbon atom favors the formation of indole by cyclization at the secondary position, there does not seem to be much indication that the size of the acid provides a significant directive influence on the course of the reaction.

The observations summarized in Tables I–IV can be interpreted in terms of the accepted mechanism[9] for the Fischer indole synthesis as outlined in Scheme I.

One consideration fundamental to a reaction in which two products are formed competitively is the relative stability of the two products and the possibility of their interconversion. Intuitively, the indole structure **16**, because of its greater aromaticity, might be expected to be at a lower energy level than the indolenine **15**. Support for this assumption is found in the well-established rearrangements of 3,3-disubstituted indolenines to 2,3-disubstituted indoles.[10] However, the suggested[1a] stability of the trisubstituted indolenine **15** toward rearrangement was confirmed under the experimental conditions of the present investigation.[11b]

The rate-determining step of the Fischer indole synthesis has not been identified. The kinetics of the reaction have received only cursory examination[8a,12] to indicate that the reaction is first order in phenylhydrazone when carried out in acetic acid solution and first order each in phenylhydrazone

Scheme I
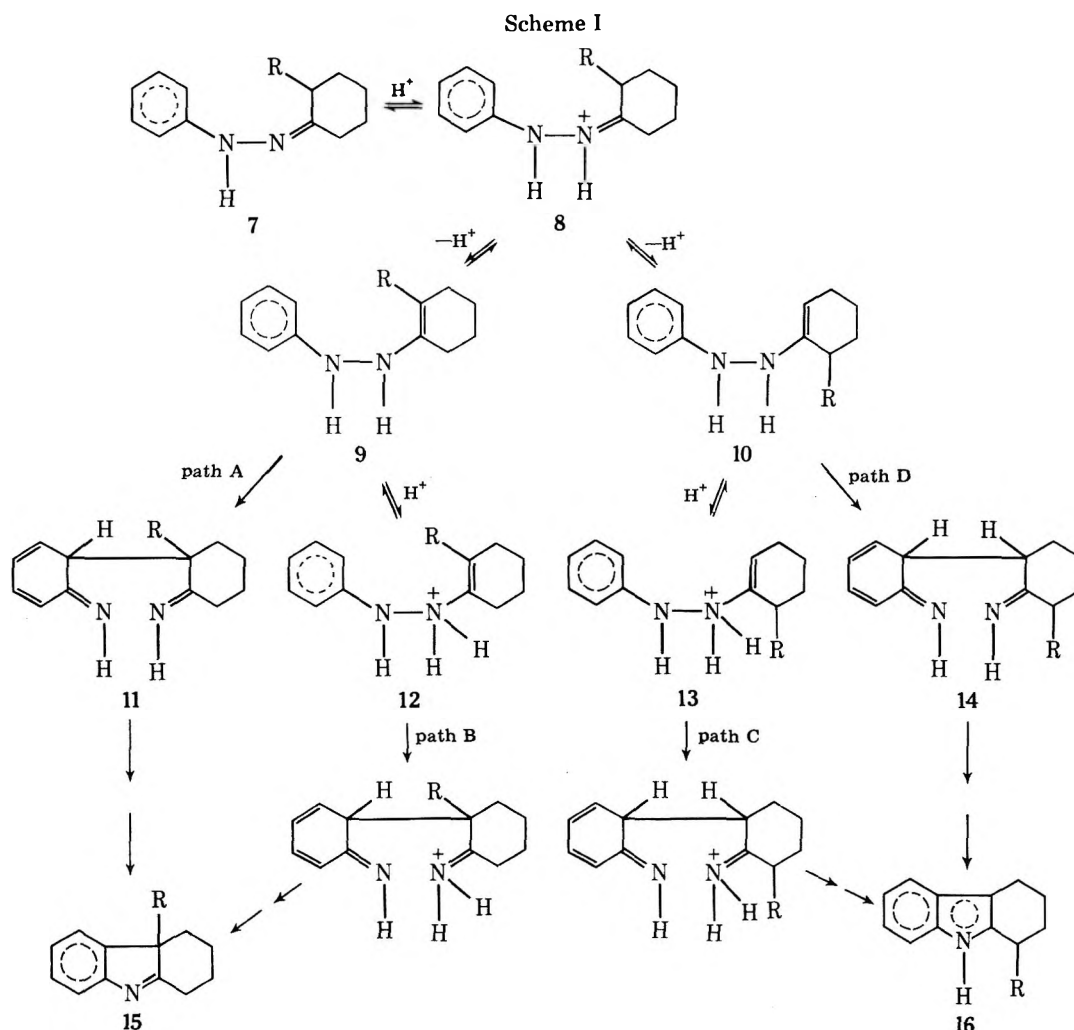
and acid when the cyclization occurs in sulfuric acid solution. However, the effect of substituent groups on the rate of the reaction[12] and the analogy[13] to the Claisen rearrangement are compatible with a rate determining [3,3] sigmatropic rearrangement of the enehydrazine to the diimine (steps A, B, C, or D in Scheme I).

The two possible pathways which the reaction of an unsymmetrical phenylhydrazone may follow are determined by the two enehydrazines, **9** and **10**, the formation of which would be facilitated by protonation of the phenylhydrazone, although acid catalysis is not essential. Equilibrium concentrations of N-unsubstituted enehydrazones are too low to be detected by physical methods,[2] but the relative tendency of **9** and **10** to form should be in favor of the more highly substituted double-bond isomer **9**.[14] Support for this idea is found in the significant amount of cyclization at the more substituted carbon atom, even at relatively high acidities, in the case of the phenylhydrazones of methyl ketones.[6,7] Among other examples,[2] the cyclization of **17** shows a preference for
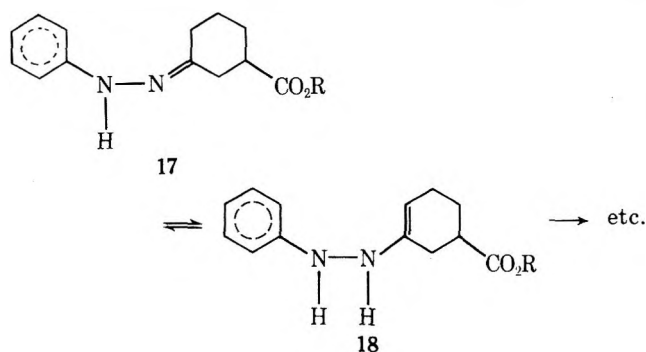
enehydrazone **18**, estimated to be about 0.6 kcal/mol more stable than the alternate possibility, although the same degree of substitution at the α-carbon atoms is involved in each case.[15]

In the uncatalyzed reaction at low temperatures, the greater stability of the more substituted π bond (**9**) prevails, forming more of the indolenine and suggesting that the energy requirements are less along this pathway (kinetic control). At higher temperatures, sufficient energy is available to permit formation of more of the less substituted enehydrazine **10**, shifting the product ratio from 2:1 indolenine **15** to 5:1 indole **16** (thermodynamic control). Steric hindrance to the cyclization through the more stable enehydrazine **9** intervenes as the size of the alkyl group is increased (Table VI).

At low acidities, e.g., with acetic acid, the large proportion of indolenine formed suggests that the acid is serving only to catalyze enehydrazine formation.

The role of the acid catalyst at higher acidities in the shifting of the product ratio toward larger proportions of indole was considered by earlier investigators to be the consequence of further protonation of reaction intermediates. Illy and Funderburk[6] did not specify the site of this protonation. Palmer and McIntyre[7] pictured the reaction course to be controlled by acid-catalyzed formation of the enehydrazines.

Schiess and Grieder[16] prepared a series of N,N'-dimethyl enehydrazines, including **19**, and studied their conversion to the corresponding indoles, both thermally and under acid catalysis. The acid-catalyzed reaction was found to be many times faster than the thermal process, suggesting the intervention of an N-protonated form such as **12** or **13** in a *charge induced pericyclic reaction*.[13a]
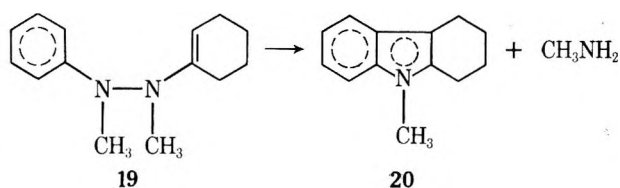
Therefore, the energy barrier for the rearrangement of **12** or **13** is apparently less than that for the corresponding rearrangement of the unprotonated enehydrazines **9** or **10**, and under conditions of higher acidity pathways B or C should be followed to a greater extent than A or D. If routes B or C are both relatively fast, the fact that C is preferred to B could be a reflection of the greater stability of the indole product compared to the indolenine (thermodynamic control).

An alternative explanation of the acidity effect exists as the consequence of the fact that substitution on the β-carbon atom of enamines lowers basicity.[17] Thus, at higher acidity enehydrazine **10** should be more readily protonated than the isomeric structure **9**, favoring the formation of **13** and reaction path C leading to indole.[18]

Therefore, the effects of acidity and temperature on the direction of cyclization in the Fischer synthesis appear to be accommodated in terms of a partitioning of the reaction between the two pathways shown in Scheme I. Confirmation of these suggestions lies in a study of the activation parameters of the reaction.

Experimental Section

Melting points were observed on a Fisher-Johns apparatus using a calibrated thermometer. Boiling points are uncorrected. Gas chromatographic (GC) analysis was performed on a Varian Aerograph Model 2700 (thermal conductivity detector) using a 5 ft, 3% SE 30 on 100–200 mesh Varaport 30 column. Pure samples of the indolenine **5**, mp 71 °C (lit.[4a] mp 72 °C), and the indole **6**, mp 68 °C (lit[4a] mp 68 °C), were prepared for the determination of retention times.

2-Alkylcyclohexanols. The 2-alkylphenol (10 g) in 80 mL of 95% aqueous ethanol was hydrogenated over 1.0 g of 5% Ru/C at 125 °C and 1500 psi for 7 h.[19] The catalyst was removed by filtration, water was added, and the cyclohexanol was extracted with ether. The dried (Na$_2$SO$_4$) ether solution was evaporated and the product distilled under vacuum. The yields were essentially quantitative: **2-ethylcyclohexanol**, bp 50 °C (1 mm) [lit.[20] bp 75 °C (12 mm)]; **2-isopropylcyclohexanol**, bp 56 °C (1 mm) [lit.[21] bp 114 °C (28 mm)]; **2-tert-butylcyclohexanol**, bp 65 °C (1 mm) [lit.[22] by 99–103 °C (23 mm) (cis isomer)], mp 54 °C [lit.[22] mp 56.8–57.7 °C (cis isomer)].

2-Alkylcyclohexanones.[23] The 2-alkylcyclohexanol, dissolved in a small amount of acetone (distilled over KMnO$_4$), was titrated with Jones reagent to a slight excess of the equivalence point (1.0 mL of Jones reagent per 0.5 g of the cyclohexanol). During the addition period, the mixture was stirred and the temperature was maintained between 20 and 25 °C by a water bath. The reaction mixture was stirred overnight, water was added, and the 2-alkylcyclohexanone was removed by extraction several times with ether. The dried (Na$_2$SO$_4$) ether solution was evaporated, and the cyclohexanone was purified by vacuum distillation. **2-Ethylcyclohexanone:** 75% yield; bp 54 °C (4 mm) [lit.[24] bp 42 °C (2 mm)]. **2-Isopropylcyclohexanone:** 80% yield; bp 58 °C (1 mm) [lit.[21] bp 72 °C (9 mm)]. **2-tert-Butylcyclohexanone:** 85% yield; bp 62 °C (4 mm) [lit.[22] bp 62.5 °C (4 mm)].

2-Alkylcyclohexanone Phenylhydrazones. Equimolar amounts of the ketone and phenylhydrazine were heated with stirring in a water bath at 90–95 °C for 3 h, and the resulting phenylhydrazone was purified by vacuum distillation; the yields were 85–95%: **2-methylcyclohexanone phenylhydrazone**, bp 140 °C (1 mm); **2-ethylcyclohexanone phenylhydrazone**, bp 147 °C (1 mm); **2-tert-butylcyclohexanone phenylhydrazone**, bp 160 °C (1 mm).

Cyclization of the Phenylhydrazones. A. Acetic Acid. A solution of 1.0 g of the phenylhydrazone in 10 mL of glacial acetic acid was heated in a water bath at 80 °C for 0.5 h. The reaction mixture was diluted with water and made alkaline, and the products were extracted with benzene. The dried (Na$_2$SO$_4$) benzene solution was analyzed by GC.

B. Sulfuric Acid. The phenylhydrazone (1.0 g) was dissolved in 10 mL of a solution of sulfuric acid in ethanol (10, 20, 40, 60, or 80% H$_2$SO$_4$ by weight), and the solution was heated to 80 °C for 0.5 h.

Water was added, the solution was made alkaline, and the products were extracted with benzene and analyzed as above. Similar runs were made with 10% H$_2$SO$_4$ in methyl, isopropyl and tert-butyl alcohols.

C. Zinc Chloride. The phenylhydrazone (12 g) was dissolved in 50 mL of absolute ethanol containing 70 g of anhydrous zinc chloride. The solution was protected from atmospheric moisture and refluxed for 5 h. Water was added and the mixture was made sufficiently alkaline to dissolve the Zn(OH)$_2$. The products were extracted with benzene and analyzed as above.

D. Boron Trifluoride. A solution of boron trifluoride in ethanol was prepared by distilling the ether from a 2:1 volume mixture of ethanol and boron trifluoride etherate. A solution of 10 g of the phenylhydrazone in 60 mL of the ethanolic BF$_3$ solution was refluxed until no more salt precipitation was evident (approximately 1 h). After dilution with water, the mixture was made basic and extracted with benzene and the products were analyzed as above.

E. Polyphosphoric Acid. PPA was heated to 80 °C in a water bath, and the phenylhydrazone (1.0 g/15 g of PPA) was added in small amounts so that the temperature did not rise. Heating was continued for 1 h. Ice was added, the mixture was made alkaline, and the products were extracted with benzene and analyzed as above. Other PPA runs were made at 125 and 160 °C with the 2-methyl compound.

F. Thermal Cyclization. Solutions of 5 g of 2-methylcyclohexanone phenylhydrazone in 30 mL of diethylene glycol were heated at 155, 200, or 245 °C (reflux). The reaction mixture was poured into water and extracted with benzene. These reactions were slow and required at least 10 h for reasonable completion. At 155 °C some phenylhydrazone remained unreacted.

Determination of Product Stability. Samples (1 g) of the indolenine **5** and the indole **6** were heated in the following solvents as indicated: 10 mL of 20% ethanolic H$_2$SO$_4$ at 80 °C for 1 h; 10 mL of 40% ethanolic H$_2$SO$_4$ at 80 °C for 1 h; 10 g of polyphosphoric acid at 125 °C for 3 h; 10 mL of diethylene glycol at 200 °C for 10 h. The reaction mixtures were diluted with water, the acid solutions were made basic, and the mixtures were extracted with benzene. The dried (Na$_2$SO$_4$) benzene solutions were analyzed by GC. In none of these cases was any of the isomeric substance detectable in the material following the heating.

References and Notes

(1) Taken in part from the M.S. Thesis of W.N.S., Northern Illinois University, 1973.

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(9) For summaries, see the reviews listed in ref 2. Abundant evidence exists for each of the intermediates listed in Scheme I except for the protonated species **12** and **13**.

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(14) W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967). The bromination of 2-methylcyclohexanone occurs largely at the 2 position: E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Am. Chem. Soc.*, **77**, 5415 (1955).

(15) B. Lacourne, G. Milcent, and A. Oliver, *Tetrahedron*, **28**, 667 (1972).

(16) P. Schiess and A. Grieder, *Helv. Chim. Acta*, **57**, 2643 (1974). For another example of the rapid acid-catalyzed cyclization of an isolated enehydrazine, see H. Posvic, R. Dombro, H. Ito, and T. Telinski, *J. Org. Chem.*, **39**, 2575 (1974).

(17) R. L. Hinman, *Tetrahedron*, **24**, 185 (1968).
(18) The relative basicity of **9** and **10** may be complicated by some tendency of **10** to protonate at the β-carbon atom.[16] Since the C_α-protonated structure cannot undergo the sigmatropic rearrangement,[16] clearly the formation of the N-protonated structure **13** must occur to an extent sufficient to permit the rearrangement to take place at a reasonable rate.
(19) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, N.Y., 1967, p 344.

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Notes

Fischer Indole Synthesis from
cis- and *trans-*9-Methyl-3-decalone

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In the Fischer indole synthesis with the phenylhydrazone of an unsymmetrical ketone the direction of cyclization is governed in part by the relative stability of the two possible enehydrazines.[2] This regioselectivity has been well established[3] in the 3-keto steroid system in which 5α-cholestanone yields the linear indole **1** and the 5β isomer forms the angular product **2**. The same directions of enolization are observed in

1   **2**
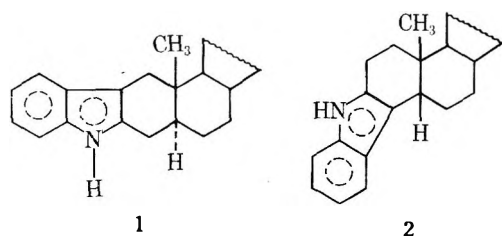
the bromination of the respective 3-ketones[4] in which relief of strain is maximized by enolization of the trans isomer parallel to the ring fusion and of the cis isomer toward the ring fusion.[5] In contrast, Stork and Dolfini[6] observed a linear product from both the cis and trans isomers of the bicyclic azadecalin system **3**. This behavior is analogous to the formation of the 2-bromo derivative from both *cis-* and *trans-*9-methyl-3-decalone (**4**).[7]

3   **4a** (cis)
            4b (trans)
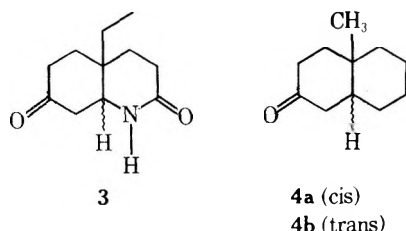
Unlike the more rigid cis steroid, the cis isomer of the bicyclic system can exist in two chair–chair conformations,[8] **5** and **6**. In the more stable of these two conformers, **6**, greater relief of strain results through enolization toward position 2 than toward position 4.

To confirm the course of cyclization in the Fischer indole synthesis with the decalin system, cyclization of the phenylhydrazones of both *cis-* and *trans-* **4** was carried out. That the product in each case was the linear indole **7** was deter-

5   **6**
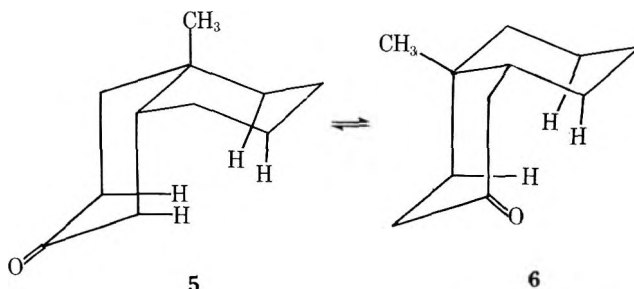
mined from the mass spectral fragmentation to the *m/e* 143 ion (**8**), a fragmentation not available to the angular structure. The mass spectra of **7a** and **7b** are quite similar, showing only

7a (cis)   **8** (*m/e* 143)
7b (trans)
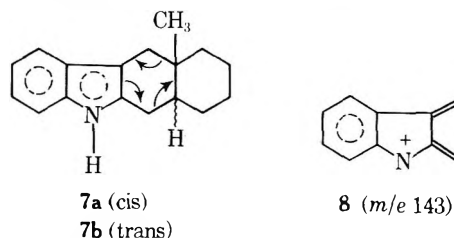
slight intensity differences. Between the parent peak (*m/e* 239) and the base peak (*m/e* 143), the greatest difference lies in the presence of the *m/e* 224 (P − 15) peak in the trans isomer **7b**, reflecting a greater tendency of this isomer to lose the angular methyl group. In the mass region below the base peak, the spectra are both very similar to the mass spectrum of 1,2,3,4-tetrahydrocarbazole because of fragmentation of the common ion **8** and are typical of the spectra of alkylindoles.[9]

Experimental Section[10]

***cis-*9-Methyl-3-decalone (4a).** 9-Methyl-Δ⁴-3-octalone was prepared by the procedure of Yanagita and Yamaka,[7] bp 93–96 °C (1.5 mm) [lit.[7] bp 102–110 °C (2.5 mm)]. Hydrogenation of the unsaturated ketone using 10% palladium on carbon at atmospheric pressure[7] afforded the cis saturated ketone **4a**: mp 46–47 °C (lit.[7] mp 47 °C); NMR δ 1.33 (CH₃).
Anal. Calcd for C₁₁H₁₈O: C, 79.52; H, 10.84. Found: C, 79.38; H, 10.67.
***trans-*9-Methyl-3-decalone (4b).** Reduction of the unsaturated ketone with Li in liquid NH₃[11] furnished the trans isomer: bp 98–101 °C (5 mm) [lit.[11] bp 95–112 °C (7 mm)]; NMR δ 1.15 (CH₃).
Anal. Calcd for C₁₁H₁₈O: C, 79.52; H, 10.84. Found: C, 79.34; H, 10.79.
Phenylhydrazones. Equimolar quantities of the above ketones and phenylhydrazine were stirred at room temperature for 24 h. The mixture was taken up in ether and dried over Na₂SO₄. The ether was removed under vacuum and the phenylhydrazone distilled under vacuum.
***cis-*9-Methyl-3-decalone Phenylhydrazone:** bp 174–178 °C (1 mm); NMR δ 1.35 (CH₃).
Anal. Calcd for C₁₇H₂₄N₂: C, 79.69; H, 9.38; N, 10.94. Found: C, 79.56; H, 9.16; N, 10.23.
***trans-*9-Methyl-3-decalone Phenylhydrazone:** bp 180–185 °C

Indolization of the Phenylhydrazones. A solution of 4.0 g of the phenylhydrazone and 26 g of anhydrous ZnCl$_2$ in absolute ethanol was refluxed for 5 h. Water was added, and the mixture was made alkaline with sufficient sodium hydroxide to dissolve the Zn(OH)$_2$ precipitate and extracted with ether. The ether extracts were washed with 1.0 N HCl, water, and 10% NaHCO$_3$ and dried over Na$_2$SO$_4$. The ether was evaporated, and the indole was purified by vacuum distillation. *cis*-6a,10a-10a-Methyl-6,6a,7,8,9,10,10a,11-octahydro-5*H*-benzo[*b*]-carbazole (**7a**): bp 180–184 °C (1 mm); mp 44–46.5 °C; yield, 44%; UV max 229 nm (log ε 4.43), 284 (3.79), 291 (3.74); NMR δ 1.05 (CH$_3$); mass spectrum, *m/e* (relative intensity) 239 (30), 238 (4), 183 (9), 182 (15), 180 (10), 170 (4), 168 (16), 167 (18), 144 (20), 143 (100), 129 (10), 127 (8), 117 (5), 116 (4), 115 (12), 77 (14), 76 (4), 65 (6), 63 (5), 51 (8), 50 (3), 39 (23).

Anal. Calcd for C$_{17}$H$_{21}$N: C, 85.35; H, 8.75; N, 5.86. Found: C, 85.43; H, 8.53; N, 5.44.

The same product was obtained by heating the phenylhydrazone in glacial acetic acid at 80 °C for 5 h (yield, 36%).

trans-6a,10a-10a-Methyl-6,6a,7,8,9,10,10a,11-octahydro-5*H*-benzo[*b*]carbazole (**7b**): bp 189–194 °C (1 mm); yield, 41%; UV max 228 nm (log ε 4.45), 284 (3.78), 291 (3.74); NMR δ 0.88 (CH$_3$); mass spectrum, *m/e* (relative intensity) 239 (69), 238 (10), 224 (7), 183 (8), 182 (13), 180 (9), 170 (7), 168 (12), 167 (12), 144 (32), 143 (100), 129 (12), 127 (6), 117 (3), 116 (3), 115 (7), 77 (7), 76 (2), 65 (3), 63 (4), 51 (4), 50 (1), 39 (3).

Anal. Calcd for C$_{17}$H$_{21}$N: C, 85.35; H, 8.79; N, 5.86. Found: C, 84.96; H, 8.38; N, 5.46.

The same product was obtained by heating the phenylhydrazone in glacial acetic acid at 80 °C for 5 h (yield, 31%).

Mass Spectrum of 1,2,3,4-Tetrahydrocarbazole:[12] MS *m/e* (relative intensity) 171 (24), 170 (12), 114 (14), 143 (100), 129 (6), 127 (7), 117 (4), 116 (5), 115 (18), 77 (10), 76 (6), 65 (5), 63 (10), 51 (10), 50 (6), 39 (12).

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Reaction of Picryl Chloride with 3,5-Dinitrotriazole: Formation of 1-Picryl-3-nitro-5-chloro-1,2,4-triazole and 1-Picryl-3-nitro-1,2,4-triazol-5-one

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The reaction of picryl chloride with 3,5-dinitrotriazole salts (K$^+$, Li$^+$) in dry acetonitrile results in a complex mixture of products which include 1-picryl-3-nitro-5-chloro-1,2,4-triazole (**2**), 1-picryl-3-nitro-1,2,4-triazol-5-one (**4**), 2,4,6-trinitrophenol (picric acid), and oxides of nitrogen. The products (**2**
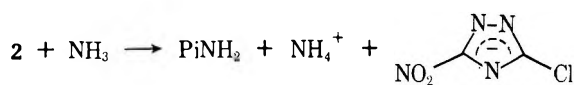
and **4**) were identified by mass spectroscopy (parent ions), IR (characteristic bands for aromatic H; NH and C=O for **4**), NMR (singlets for picryl H; broad singlet (NH) for **4**), and elemental analysis. Additional evidence for the structure of **2** was its reaction with ammonia to give 2,4,6-trinitroaniline and ammonium chloronitrotriazole. Further support for the structures of **2** and **4** is that the formation of these products can be rationalized via the expected primary reaction intermediate, 1-picryl-3,5-dinitro-1,2,4-triazole (**1**) (see Scheme I).

Positional isomers for the intermediate **1** and compounds **2** and **4** are possible and the structures assigned to these species are the most likely ones based on previous structure

Scheme I
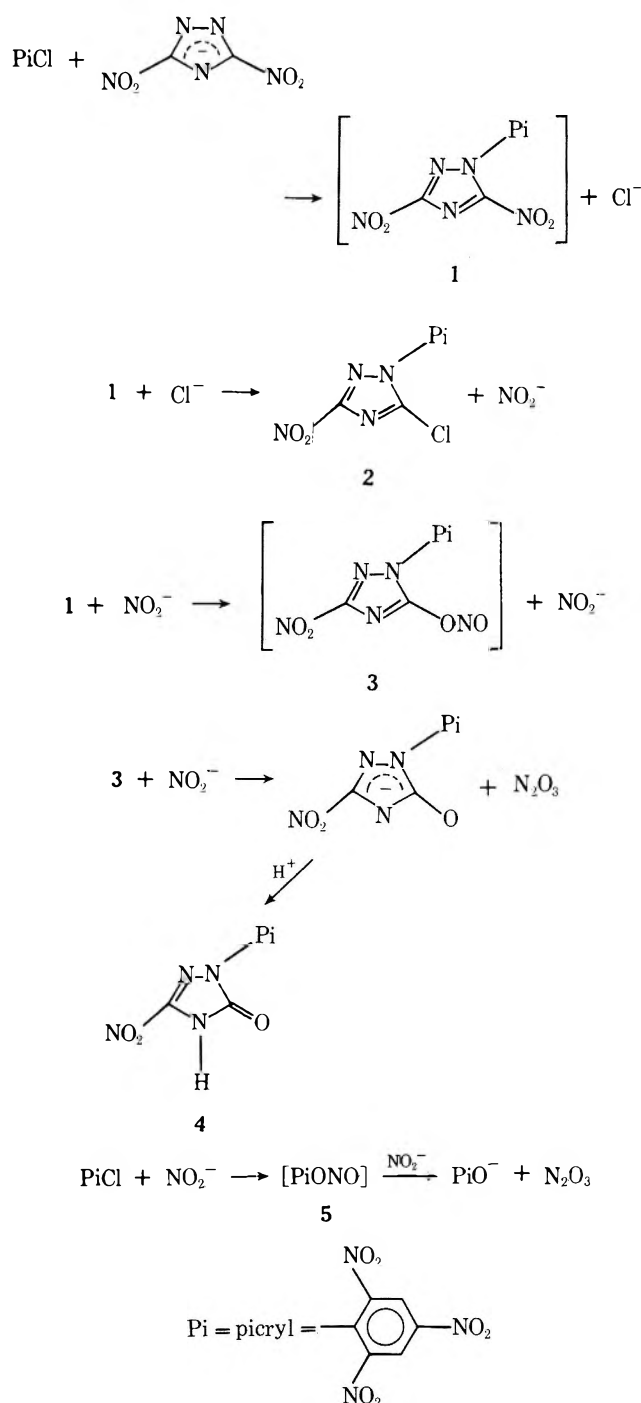
determinations for 3,5-dinitrotriazole reaction products. For example, methylation of 3,5-dinitrotriazole gives only the N_1-alkylation product, 1-methyl-3,5-dinitrotriazole (6), and no methylation at the N_4 position occurs even though a variety of methylating agents and reaction conditions were employed.[1] Similarly, reaction of 3,5-dinitrotriazole and its salts with epoxides[2] and allyl halides[3] gives the N_1-substituted products.[4] Thus the structures for 2 and 4 (and the intermediate 1) were assigned with the picryl group attached to the N_1 position of the triazole ring.

The reaction of 6 with nucleophiles results in replacement of the nitro group in the 5 position of the triazole ring. Thus, heating 6 with aliphatic amines gives the respective 5-amino derivatives[5] and, under similar conditions, 6 with triethylamine in aqueous dioxane yields 1-methyl-3-nitro-1,2,4-triazol-5-one[5] and with concentrated hydrochloric acid yields 1-methyl-3-nitro-5-chloro-1,2,4-triazole.[6] Based on this evidence the displacement of the nitro group from 1 (resulting in the formation of 2 and 4) was assumed to take place at the 5 position.

The following pathway for the reaction of picryl chloride with 3,5-dinitrotriazole salts seems plausible and accounts for the observed products. Attack of 3,5-dinitrotriazole anion on picryl chloride displaces chloride ion to give the intermediate product, 1-picryl-3,5-dinitro-1,2,4-triazole (1); chloride ion in turn displaces nitrite from 1 to give 2; nitrite ion can then attack both 1 and starting picryl chloride to give 4 and picric acid, respectively, along with oxides of nitrogen (whose evolution is observed). The complexity of the overall reaction apparently results from an unusual concurrence of species being generated in the reaction: Although the nitro groups in the starting 3,5-dinitrotriazole anion are not labile, attachment of the picryl group to the triazole ring (1) sufficiently activates a nitro group to allow displacement by Cl⁻ generated from picryl chloride during the formation of 1; the species (NO$_2^-$) displaced from 1 by chloride ion can attack the starting picryl chloride to produce the nitrite ester (5), a process which generates additional chloride ion; attack of nitrite ion on the initial product (1) to give 3 produces no net loss in nitrite ion but further reaction of nitrite with 3 (as well as with 5) to form N_2O_3 gas irreversibly removes nitrite ion from the system (thereby driving any reversible reactions involving nitrite ions toward completion).

The reactions of 1 and picryl chloride with nitrite ion are analogous to the reactions of 1,2,4-trinitrobenzene and 2,4-dinitrohalobenzenes with nitrite to give 2,4-dinitrophenoxide and oxides of nitrogen.[7] In the reaction described here sufficient nitrite ion may not be available for complete conversion of the intermediate nitrite esters (3 and 5) to 4 and picric acid, but hydrolysis of 3 and 5 during workup would give the same products. Although it appears possible that 2 might hydrolyze to 4 during workup this was shown not to be the case. The hydrolysis of 2 in aqueous acetonitrile is quite slow and the products are picric acid and chloronitrotriazole.

The reaction of picryl chloride with 3,5-dinitrotriazole salts was monitored by TLC analysis (Silica Gel F-254 plates with toluene as developer). There appeared to be a gradual increase in 2 as the picryl chloride disappeared but at no time was there any evidence for a buildup of the intermediate (1).

The isolated yields of 2 from potassium dinitrotriazole, lithium dinitrotriazole, and a mixture containing potassium dinitrotriazole and 1 equiv of lithium chloride were 16, 20, and 28%, respectively. The increase in yield of 2 when lithium chloride is added to the reaction mixture would be expected since the increased chloride ion concentration would favor the reaction of 1 with chloride rather than nitrite ion. Presumably there was a decrease in the amount of 4 formed under these conditions but this was not established due to uncertainties in the yield of 4 (due to losses of 4 during the workup while

attempting to separate it from picric acid and 3,5-dinitrotriazole).

Experimental Section

General. Caution! The compounds described herein are explosives and should be handled with care. Potassium and lithium dinitrotriazole were prepared by treating an ether–acetone solution of 3,5-dinitro-1,2,4-triazole[8] with the respective metal carbonates until the solution was slightly basic to wet litmus paper. The insoluble material was removed and washed well with acetone, and the dinitrotriazole salt was crystallized from the filtrate by concentration and addition of ether. The lithium salt after drying in a vacuum desiccator over phosphorus pentoxide retains appreciable water of hydration and melts with loss of water at ca. 120 °C, then slowly resolidifies and remelts at 315 °C dec. The potassium salt, after the same drying conditions, retains little or no water of hydration and has mp 223–225 °C. The IR spectra of the hydrated dinitrotriazole salts (K⁺, Na⁺, Li⁺) show a large rather sharp peak near 3570–3600 cm⁻¹ as well as two additional peaks between 3500 and 3200 cm⁻¹. A peak at 1645 cm⁻¹ is also characteristic of the hydrates.

NMR spectra were determined on a Varian HA-100 spectrometer and the chemical shifts are relative to tetramethylsilane. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The melting points are uncorrected.

1-Picryl-3-nitro-5-chloro-1,2,4-triazole (2). Potassium dinitrotriazole (3.1 g, 0.157 mol) was dissolved in 25 mL of hot dry acetonitrile (dried by distillation from phosphorus pentoxide) and the solution was stirred with 3A molecular sieves for 20 h. Picryl chloride (3.1 g, 0.125 mol) was added and the mixture (protected by a phosphorus pentoxide–drierite drying tube) was stirred at gentle reflux for 46 h (Brown oxides of nitrogen were visible throughout the reaction). The cooled reaction mixture was filtered, the filtrate was poured into 200 mL of ice water, and the mixture was stirred for a short time until the precipitated oil turned to a semisolid. The aqueous solution was decanted from the semisolid which was then extracted into 50 mL of methylene chloride. The methylene chloride solution was dried over magnesium sulfate and then quickly passed through a short column of silica gel 60 (ca. 1 in. long and ⅞ in. in diameter contained in a 15-mL sintered glass funnel).

Concentration of the methylene chloride solution and addition of hexane gave 0.7 g (16%)[9] of cream-colored crystals, mp 158–160 °C. Recrystallization from methylene chloride raised the mp to 163–164 °C: NMR (CD$_3$COCD$_3$) δ 9.54 (s); mass spectrum m/e 359, 361 (M⁺, chlorine isotopes).

Anal. Calcd for C$_8$H$_2$N$_7$O$_8$Cl: C, 26.71; H, 0.56; N, 27.27; Cl, 9.86. Found: C, 26.74; H, 0.68; N, 27.17; Cl, 10.01.

1-Picryl-3-nitro-1,2,4-triazol-5-one (4). The cooled reaction mixture from a run similar to that described above but starting with 10 g of picryl chloride was poured into 600 mL of ice water and the aqueous solution was decanted from the precipitated semisolid. The aqueous solution was first extracted with 150 mL of ether, strongly acidified with 30% sulfuric acid, and extracted a second time with 150 mL of ether. Removal of the solvent from the second ether extract gave a residue which was first extracted with 30 mL of 30% sulfuric acid and then with 40 mL of water at 60 °C.[10] The insoluble material (1 g, mainly 4 with some picric acid) was removed by filtration and then crystallized from acetone–water to give 0.45 g, mp 269–273 °C dec. Recrystallization from acetone/1,2-dichloroethane raised the mp to 276–278 °C dec: NMR (CD$_3$COCD$_3$) δ 9.24 (s, 2, aromatic H), 8.31 (broad s, 1, NH); mass spectrum m/e 341 (M⁺); IR (KBr) 3335 (NH), 1760 (C=O) cm⁻¹.

Anal. Calcd for C$_8$H$_3$N$_7$O$_9$: C, 28.16; H, 0.89; N, 28.74. Found: C, 28.06; H, 0.90; N, 28.61.

Reaction of 1-Picryl-3-nitro-5-chloro-1,2,4-triazole (2) with Ammonia. A solution of 1.50 g of 1-picryl-3-nitro-5-chloro-1,2,4-triazole in 30 mL of methanol containing anhydrous ammonia gas was stirred at ambient temperature for 50 min. The precipitated crystals[11] (2,4,6-trinitroaniline) were removed by filtration and the solvent was allowed to evaporate from the filtrate. The residue was stirred with 5 mL of distilled water and the insoluble material (additional 2,4,6-trinitroaniline) was removed by filtration. The filtrate was first extracted with ether (to remove traces of trinitroaniline) before the water was allowed to evaporate to give crystals (0.62 g) of ammonium chloronitrotriazole, mp 170–174 °C dec. Crystallization from acetone–ether raised the mp to 173–175 °C dec.

Anal. Calcd for C$_2$H$_4$ClN$_5$O$_2$: C, 14.51; H, 2.44; N, 42.31; Cl, 21.42. Found: C, 14.43; H, 2.37; N, 42.58; Cl, 21.34.

Treatment of the ammonium chloronitrotriazole with dimethyl sulfate gave 1-methyl-3-nitro-5-chloro-1,2,4-triazole, mp 89–90 °C (lit.[6] mp 88–89 °C).

Acknowledgment. The author is grateful to R. N. Rogers and Mary Fowler of Los Alamos Scientific Laboratory for preliminary information regarding their procedure for the preparation of 3,5-dinitrotriazole.

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(8) L. I. Bagal, M. S. Pevzner, A. N. Frolov, and N. I. Sheludyakova, *Khim. Geterotsikl. Soedin.*, 6, 259 (1970). The English translation of this article states that 214 mL of H₂SO₄ is used in the preparation of the 3,5-dinitrotriazole. The number of milliliters of concentrated H₂SO₄ required for the reaction is only 10% of this amount. By using the smaller amount of H₂SO₄ we were able to obtain approximately the same yield of hydrated sodium dinitrotriazole as reported in the article.

(9) Lithium dinitrotriazole gave a 20% yield of product, mp 161–163 °C. Potassium dinitrotriazole with 1 equiv of lithium chloride gave a 28% yield of product, mp 162–164 °C.

(10) The 30% sulfuric acid extract removes mainly 3,5-dinitrotriazole after which the warm water extract removes mainly picric acid. Addition of concentrated hydrochloric acid to the warm water extract gave 0.5 g of picric acid.

(11) The crystals were shown to be 2,4,6-trinitroaniline by comparison (mp, UV, TLC) with an authentic sample.

Synthesis of Indole-2-carboxylic Esters

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Recently, we reported that N-methyl-3-hydroxyindolines can be prepared in excellent yield by photocyclization–rearrangement of 2-(N-methylanilino)acetoacetates.[1] In acetic acid, the 3-hydroxyindolines undergo rapid dehydration to give N-methylindoles; alternatively, irradiation of the 2-(N-methylanilino)acetoacetate in acetic acid solution produces indoles directly. Experiments designed to probe the mechanism of 3-hydroxyindoline formation indicate that cyclization is completely stereoselective and occurs from the enol tautomer of the 2-anilinoacetoacetate.

The 2-(N-methylanilino)acetoacetate required for indole preparation is conveniently prepared by reaction of the appropriate N-methylaniline with 2-chloro- or 2-bromoacetoacetate. However, reaction of aniline with ethyl 2-chloroacetoacetate (1) results in enamine formation to give 2 instead of the desired substitution product. Herein, we describe a useful, high yield preparation of N-unsubstituted-2-anilinoacetoacetates as well as their photoconversion to N-unsubstituted indoles.
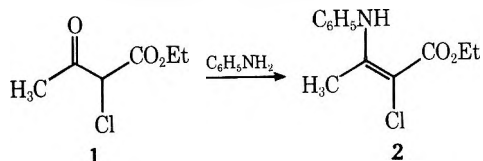
In 1960, Beyer and Badicke reported that the semicarbazone of ethyl 2-chloroacetoacetate 3a undergoes base-catalyzed 1,4-elimination of hydrogen chloride to give azoene 4a and that 4a reacts in Michael fashion at C(2) with aniline to give the semicarbazone of ethyl 2-anilinoacetoacetate 5 in 65% yield.[2] We find the N-carbomethoxyhydrozone 3b to be a superior intermediate;[3] azoene 4b is produced by treatment of 3b with mild base, and 4b reacts with a variety of aniline derivatives to give addition products 6 in excellent yield (Table I).

Regeneration of the ketone carbonyl group in 6 is best accomplished by reaction with aqueous titanium trichloride,[4] from which the 2-anilinoacetoacetates 7 can be obtained

3a, X = CONH₂
b, X = CO₂CH₃

4

5, X = CONH₂; Ar = C₆H₅
6, X = CO₂CH₃

7
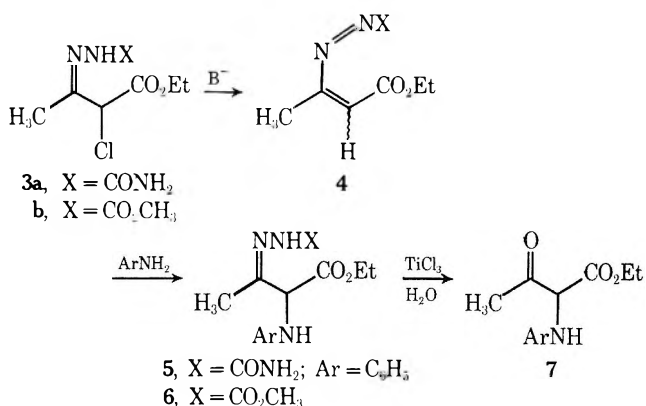
without the need for further purification. Pyrex-filtered irradiation of 7 in degassed benzene–methanol–acetic acid solution gives indoles 8 in excellent yield (Table I). We note that, except for example 7e, alkoxy, halogen, and carbomethoxy

$$7 \xrightarrow{h\nu} \textbf{8}$$

8
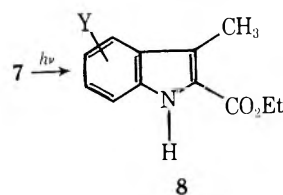
substituents on the benzene ring are compatible with photocyclization. On the other hand, the p-nitro derivative 7i failed to give an indole on extended irradiation. With meta-substituted anilines, cyclization results in both 6- and 4-substituted indoles; however, with m-bromo-2-anilinoacetate 7j, cyclization occurs mainly away from the bromine atom to give a 6-bromoindole as the major reaction product by a factor of 10:1. A halogen atom can serve as a blocking group as illustrated with example 7n, in which cyclization gives only the 4-methoxy-7-chloroindole. Eventual removal of halogen by hydrogenolysis or lithium aluminum hydride reduction would give the 4-methoxyindole with complete overall regioselectivity.

The methodology presented here represents the first report of N-unsubstituted indole preparation by photochemical means. We consider photocyclization of 2-anilinoacetoacetates to be a useful alternative to the traditional Bischler indole synthesis. Carbon–carbon bond formation occurs in the absence of strong acids, and, in contrast to the Bischler synthesis, electron deficient aniline derivatives give indoles in high yield. It should be noted that indole-2-carboxylic esters may be hydrolyzed and decarboxylated on treatment with copper chromite in quinoline.[5]

1   **2**

Table I. Preparation of *N*-Carbomethoxyhydrozones 6 and Their Conversion to 2-Carboethoxy-3-methylindoles 8

	Ar	registry no.	6 (% yield)	registry no.	mp, °C	8 (% yield)[a]	registry no.	mp, °C[b]
a	C_6H_5	62-53-3	92	66552-27-0	155–156	96	26304-51-8	134–135 (lit. 133.5–134)[h]
b	2-$CH_3OC_6H_4$	90-04-0	98	66552-28-1	162–163	94	66552-39-4	116–117
c	3-$CH_3OC_6H_4$	536-90-3	95	66552-29-2	115–116	93		c
d	4-$CH_3OC_6H_4$	104-94-9	95	66552-30-5	118–119	89	16381-42-3	151–152 (lit. 150)[i]
e	2-$CH_3O_2CC_6H_4$	134-20-3	95	66552-31-6	165–166	0[d]		
f	3-$CH_3O_2CC_6H_4$	4518-10-9	97	66552-32-7	127–128	84		e
g	4-$CH_3O_2CC_6H_4$	619-45-4	90	66552-33-8	116–117	90	66552-40-7	164–165
h	2-Cl-5-$CH_3OC_6H_3$	2401-24-3	79	66552-34-9	135–137	95	66552-41-8	120–121
i	4-$NO_2C_6H_4$	100-01-6	43	66552-35-0	191–192	0		
j	3-BrC_6H_4	591-19-5	67	66552-36-1	143–144	50		f
k	3-$PhCH_2OC_6H_4$	1484-26-0	88	66552-37-2	111–113	95		g
l	C_6H_5[j]	103-32-2	87	66552-38-3	119–120	93	66552-42-9	61–62

[a] Yield based on starting hydrazone 6. [b] Recrystallized from 95% ethanol. [c] A mixture of 6-methoxy (mp 123–124 °C, lit. 122 °C, T. Wieland and D. Grimm, *Chem. Ber.*, 98, 1727 (1965)) and 4-methoxy (mp 152–153 °C) isomers (1:1) were produced which were separated by thick layer chromatography (silica gel, methylene chloride solvent). [d] Irradiation of 7e gave a complex mixture of uncharacterized products. [e] A mixture of 6-carbomethoxy (mp 154–155 °C) and 4-carbomethoxy (mp 131–132 °C) isomers (56:44) were produced which were separated by thick layer chromatography (silica gel, methylene chloride solvent). [f] A mixture of 6-bromo and 4-bromo isomers (10:1) which were not separated. [g] A mixture of 6-benzyloxy and 4-benzyloxy isomers (1:1) which were not separated. [h] T. Lesiak, *Prsemysl. Chem.*, 41, 140 (1962). [i] M. Julia and J. Lallemand, *Bull. Soc. Chim. Fr.*, 2046 (1973). [j] In this case, *N*-benzylaniline was employed; thus, secondary amines will add to C(2) of azoene 4.

Experimental Section

General. ^{1}H NMR spectra were obtained on a Varian A-60A or EM-390 NMR spectrometer (tetramethylsilane internal standard, deuteriochloroform solvent). Infrared spectra were recorded on a Perkin-Elmer Model 137B infrared spectrometer, and melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus and are uncorrected. Photochemical reactions were performed in sealed test tubes degassed by four cycles of a freeze–pump–thaw routine. The light source for irradiation was a 450-W Ace-Hanovia medium pressure, mercury vapor lamp. Mass spectra were obtained on a Finnigan 3300 gas chromatograph–mass spectrometer.

Ethyl 2-Chloro-3-anilino-2-butenoate (2). A stirred solution of ethyl 2-chloroacetoacetate[6] (1) (4.74 g, 29 mmol), pyridine (2.4 mL), and aniline (4 mL, 44 mmol) in ethanol (7 mL) was refluxed for 12 h. After rotoevaporation of solvent, the residue was dissolved in chloroform (50 mL) and washed successively with 1 N hydrochloric acid (3 × 15 mL) and water (3 × 20 mL) and dried over anhydrous magnesium sulfate. Rotoevaporation of solvent and distillation gave 2 [4.11 g, 64%, bp 106–108 °C (0.03 mm)]: ^{1}H NMR δ 1.33 (3 H, triplet, J = 7.5 Hz), 2.20 (3 H, singlet), 4.26 (2 H, quartet, J = 7.5 Hz), 6.93–7.55 (5 H, multiplet), 11.75 (1 H, broad singlet); IR (neat) 6.08, 6.26, 6.32, 8.00 μm; electron impact mass spectrum *m/e* 241 (16%), 239 (45%), 203 (20%), 160 (22%), 158 (43%), 132 (100%).

Ethyl 2-Chloroacetoacetate Carbomethoxyhydrazone (3b). To a stirred solution of 1 (16.21 g, 0.10 mol) in anhydrous ether (100 mL) was added methylhydrazine carboxylate[7] (8.90 g, 0.10 mol). After the suspension was stirred at room temperature for 24 h, the solid was filtered and washed with petroleum ether (75 mL) to give **3b** (21.40 g, 92%, mp 103–103.5 °C): ^{1}H NMR δ 1.29 (3 H, triplet, J = 7.0 Hz), 1.96 (3 H, singlet), 3.83 (3 H, singlet), 4.25 (2 H, quartet, J = 7.0 Hz), 5.13 (1 H, singlet), 7.93 (1 H, broad singlet); IR (Nujol) 3.13, 5.71, 5.78 μm.

Ethyl 3-Carbomethoxyazocrotonate (4b). To a suspension of hydrazone 3b (21.40 g, 90 mmol) in ether (200 mL) was added a 1 N sodium bicarbonate solution (150 mL). After stirring at room temperature for 45 min, the red ether solution was separated and dried over anhydrous magnesium sulfate. Rotoevaporation of solvent gave 4 as a bright red liquid [16.89 g, 93%, bp 68–70 °C (0.05 mm)]:[8] ^{1}H NMR δ 1.35 (3 H, triplet, J = 7.0 Hz), 2.25 (3 H, singlet), 4.05 (3 H, singlet), 4.31 (2 H, quartet, J = 7.0 Hz), 6.97 (1 H, quartet, J = 1.0 Hz); IR (neat) 5.66, 5.79, 6.06 μm.

Ethyl 2-Anilinoacetoacetate Carbomethoxyhydrazone (6a). General Procedure. To a stirred solution of 4 (408 mg, 2.04 mmol) in tetrahydrofuran (THF) or anhydrous ether (1 mL) was added a solution of aniline (190 mg, 2.04 mmol) in THF or ether (2.5 mL). After solidification and standing at room temperature for 7 h, *n*-pentane (3.5 mL) was added and the solid filtered and dried to give

6a (547 mg, 92%, mp 155–156 °C): ^{1}H NMR δ 1.25 (3 H, triplet, J = 7.0 Hz), 1.76 (3 H, singlet), 3.86 (3 H, singlet), 4.25 (2 H, quartet, J = 7.0 Hz), 4.86 (2 H, sharp singlet and broad singlet superimposed), 6.76 (3 H, multiplet), 7.20 (2 H, multiplet), 7.78 (1 H, singlet); IR (Nujol) 2.95, 3.13, 5.74, 5.81 μm.

Using the appropriately substituted aniline ($ArNH_2$), hydrazones 6b–l were prepared on the same scale (~2 mmol) by the same procedure with the following exceptions noted.

6d. The ether solution of 4 was cooled to 0 °C during the addition of the *p*-anisidine solution.

6e. The THF solution of 4 and methyl anthranilate was heated at 70 °C for 15 h and then cooled to 0 °C before the addition of pentane (8 mL).

6f. The THF solution of 4 and methyl *m*-aminobenzoate was heated at 70 °C for 1 h, the solvent removed by a stream of nitrogen gas, and the residue triturated with *n*-pentane.

6g. The THF solution of 4 and methyl *p*-aminobenzoate was heated at 70 °C for 5 h, the solvent rotoevaporated, and the residue triturated with ether.

6i. The THF solution of 4 and *p*-nitroaniline was heated at 70 °C for 24 h.

6l. The ether solution of 4 and *N*-benzylaniline was stirred at room temperature for 24 h.

Ethyl 2-Anilinoacetoacetate (7a). General Procedure. To a stirred solution of hydrazone 6a (150 mg, 0.51 mmol) in acetone (2 mL) was added a 20% aqueous solution of titanium trichloride (0.6 mL, 0.78 mmol). After stirring at room temperature for 1.5 h, ether (30 mL) and water (10 mL) were added. The organic layer was separated, washed with water (3 × 10 mL), and dried over anhydrous magnesium sulfate. Rotoevaporation of solvent gave 7a: ^{1}H NMR δ [keto ester tautomer, 62%] 1.23 (1.86 H, triplet, J = 7.0 Hz), 2.28 (1.86 H, singlet), 4.25 (1.24 H, quartet, J = 7.0 Hz), 5.08 (0.62 H, singlet), [enol ester tautomer, 38%], 1.13 (1.14 H, triplet, J = 7.0 Hz), 2.03 (1.14 H, singlet), 4.20 (0.76 H, J = 7.0 Hz), 12.36 (0.38 H, singlet), ~5.03 (1 H, broad singlet), 6.47–6.90 (3 H, multiplet), 7.04–7.34 (2 H, multiplet); IR (neat) 2.94, 5.71, 5.79, 6.06, 6.21 μm.

2-Anilinoacetoacetates (7b–l) were prepared on the same scale (~0.5 mmol) by the same procedure and were used without further purification in the subsequent photoreaction. It is interesting to note that 7i was prepared without reduction of the NO_2 group by $TiCl_3$.[9]

Irradiation of Ethyl 2-Anilinoacetoacetate (7a). A solution of 7a (as obtained from the reduction–hydrolysis of hydrazone 6a) in benzene–methanol–acetic acid (15:15:1, 3.5 mL) in a sealed, degassed test tube[10] was irradiated through Pyrex for 20 h. Rotoevaporation of solvent and trituration with pentane gave ethyl 3-methylindole-2-carboxylate 8a (100 mg, 96% from hydrazone 6a, mp (EtOH) 134–135 °C): ^{1}H NMR δ 1.43 (3 H, triplet, J = 7.0 Hz), 2.61 (3 H, singlet), 4.41 (2 H, quartet, J = 7.0 Hz), 7.16–7.76 (4 H, multiplet); IR (Nujol) 3.03, 5.97 μm.[11]

References and Notes

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(2) H. Beyer and G. Badicke, *Chem. Ber.*, **93**, 826 (1960). For other recent work with azoenes, see C. E. Sacks and P. L. Fuchs, *J. Am. Chem. Soc.*, **97**, 7372 (1975).

(3) The methyl ester analogue of **4** has been prepared by S. Sommer, *Tetrahedron Lett.*, 117 (1977).

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(5) B. Heath-Brown and P. G. Philpott, *J. Chem. Soc.*, 7185 (1965).

(6) W. R. Boehme, *Org. Synth.*, **33**, 43 (1953).

(7) Aldrich Chemical Co., Inc.

(8) Only a small portion of azoene **4** was distilled successfully; an attempted large-scale distillation resulted in violent and rapid decomposition. The crude product is of excellent purity but polymerizies to a clear red solid after about a month even when stored at low temperatures.

(9) J. E. McMurray and J. Melton, *J. Org. Chem.*, **38**, 4367 (1973).

(10) A. G. Schultz and M. B. DeTar, *J. Am. Chem. Soc.*, **98**, 3564 (1976); see Experimental Section.

(11) Compounds **3b**, **6a**, **7a**, **8b**, **8h**, and **8l** gave satisfactory C, H elemental analyses (Spang Microanalytical Laboratory, Eagle Harbor, Mich.).

Mixed Carboxylic–Sulfinic Anhydrides? Concerning the Synthesis of 1,2-Oxathiolan-5-one 2-Oxide

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In 1969 Chiang, Luloff, and Schippes[1] reported the synthesis of 1,2-oxathiolan-5-one 2-oxide (**1**) by the chlorination of 3,3′-dithiodipropionic acid in methylene chloride. The reported analytical data for C, H, and S, as well as the molecular weight (Rast), were in good agreement with structure **1**, and the infrared and NMR spectra could also be assigned to **1**. To our knowledge this is the only reported example of a stable mixed carboxylic–sulfinic anhydride, though a mixed anhydride of this type was postulated as an intermediate in the reaction of sodium *p*-toluenesulfinate with acyl chlorides.[2]
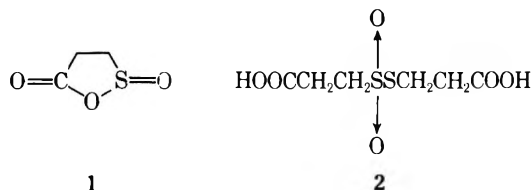
In our hands, the chlorination of 3,3′-dithiodipropionic acid as directed[1] did not give **1**. The only precipitate found in the reaction was unreacted 3,3′-dithiodipropionic acid which is quite insoluble in methylene chloride. We suggest that the product obtained by Chiang et al.[1] was not the carboxylic–sulfinic anhydride **1** but the thiosulfonate, *S*-(2-carboxyethyl)-3-thiosulfopropionic acid (**2**), which was formed by exposing the reaction mixture to moist air. That **2** should be

found is not surprising as the chlorination of disulfides in the presence of carboxylic acids followed by the addition of water leads to thiosulfonates.[3] Indeed the addition of 2 mol of chlorine per mol of 3,3′-dithiodipropionic acid produced no precipitate until the mixture came into contact with moist air. The product that precipitates was shown to be **2** by comparison of its melting point, mixture melting point, and infrared and NMR spectra with an authentic sample prepared by the peracetic acid oxidation of 3,3′-dithiodipropionic acid.[4]

The following evidence suggesting that the compound prepared by Chiang et al.[1] is **2** and not **1** is put forth. First, the reported melting point of **2** (146–147 °C)[4] is virtually the same as that reported for **1** (148–150 °C). Second, the infrared spectrum of **2** has all the major absorptions (±10 cm^{-1}) reported for **1** though of course the assignments are different. Note particularly that assignment of the 1700-cm^{-1} absorption to a carboxylic acid carbonyl is more reasonable than assigning it to a cyclic anhydride.[5] Third, the NMR spectrum of **2** is similar to that reported[1] for **1**; however, we propose that the reported split doublet at δ 3.0 is really two overlapping triplets which we observed at δ 2.73 and 2.76 and that the multiplets at δ 3.4 and 3.9 are the triplets we observed at δ 3.29 and 3.79. Fourth, attempts to determine a Rast molecular weight of **2** gave widely varying results due to decomposition. Fifth, **2** was soluble in hot water and insoluble in cold water as reported for **1**. The report[1] that **1** dissolves in aqueous basic solution and is recovered unchanged upon neutralization can be rationalized since the action of hydroxide ion on thiosulfonates produces disulfides and sulfinic acids.[6] In this case, the 3,3′-dithiodipropionic acid which precipitates on neutralization could easily be mistaken for starting material since it is similar in appearance and melting point (157–159 °C).[7] Sixth, when **2** is heated with *o*-chloroaniline, 3,3′-sulfonyldipropio-*o*-chloroanilide is produced as reported[1] for **1**. Although we cannot explain the fact that the reported percentage hydrogen for **1** is 0.59% too low for **2**, we are satisfied that the compound described by Chiang et al.[1] is the thiosulfonate **2** and the existence of a stable mixed carboxylic–sulfinic anhydride has yet to be demonstrated.

Experimental Section[8]

Preparation of *S*-(2-Carboxyethyl)-3-thiosulfopropionic Acid (2). (a) To a stirred slurry of 0.2 mol of 3,3′-dithiodipropionic acid (Aldrich) in 100 mL of dichloromethane in a 500-mL, three-necked flask equipped with a thermometer, chlorine addition tube, and condenser with a calcium chloride drying tube was added 0.4 mol of chlorine gas over a period of 90 min. The temperature was kept at −30 ± 10 °C during the addition. The flask was allowed to warm to room temperature after addition had been completed. The reaction mixture was filtered to remove unreacted 3,3′-dithiodipropionic acid and the yellow filtrate, upon standing for 2 h, yielded compound **2** upon filtration. Compound **2** was recrystallized several times from water yielding 8.95 g: mp 149–150 °C dec; ^{1}H NMR (Me$_2$SO-d$_6$, 100 MHz) δ 3.79 (t, *J* = 6 Hz, 2 H), 3.29 (t, *J* = 6 Hz, 2 H), 2.76 (t, *J* = 6 Hz, 2 H), 2.73 (t, *J* = 6 Hz, 2 H); IR (KBr) 3200–2400 (broad, OH), 1690 (acid C=O), 1310 and 1110 (SO$_2$), and 1240 and 1160 (C–O stretch).

(b) Compound **2** was also prepared by the peracetic acid oxidation of 3,3′-dithiodipropionic acid in a manner similar to Dickinson,[4] mp 149–150 °C dec [lit.[4] mp 146–147 °C dec].

Preparation of 3,3′-Sulfonyldipropio-2-chloroanilide. Prepared according to the directions of Chiang et al.[1] from compound **2** and 2-chloroaniline, mp 233–235 °C [lit.[1] mp 234–235 °C].

References and Notes

(1) Y. H. Chiang, J. S. Luloff, and E. Schippes, *J. Org. Chem.*, **34**, 2397 (1969).

(2) M. Kobayashi, *Bull. Chem. Soc. Jpn.*, **39**, 967 (1966).

(3) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **24**, 973 (1959), and (b) L. Field and P. M. Giles, *ibid.*, **36**, 309 (1971).

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(5) For example, the carbonyl absorptions in succinic anhydride are reported at 1786 and 1850 and we found the carbonyl absorption of
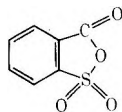
to be at 1820 while the carbonyl absorption of 3,3'-dithiodipropionic acid is reported at 1690. Reported spectra are found in "Aldrich Library of Infrared Spectra", 2nd ed, 1974.

(6) W. E. Savige and M. A. Maclaren in "The Chemistry of Organic Sulfur Compounds", Vol 2, N. Karasch and C. Y. Meyers, Ed., Pargammon Press, Oxford, 1966, p 374, Chapter 15.

(7) "Aldrich Catalog/Handbook of Organic and Biochemicals", No. 18, Aldrich Chemical Co., Milwaukee, Wis., 1977, p 343.

(8) Melting points are uncorrected and no attempt was made to maximize yields. Infrared spectra were obtained using a Perkin-Elmer 727B spectrophotometer and nuclear magnetic resonance spectra were obtained using a Varian XL-100 spectrometer.

Reaction of Phenylglyoxal with Aniline under Acidic Conditions

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The reaction of phenylglyoxal with aniline in an acid medium has been investigated previously by two different groups.[1,2] Yates reported the isolation of only one product which he thought was phenylglyoxal anil (**1**). Proctor and co-workers made a more detailed investigation of this reaction in which they proposed structure **2** for Yates' product and isolated two new compounds: the major product (32%), which was not assigned a structure, and a minor product (10.5%). The minor product was reported to be the trans isomer of **1**.

PhCOCH=NPh
1

PhCOCHNHPh
|
PhCOCH₂NPh
2
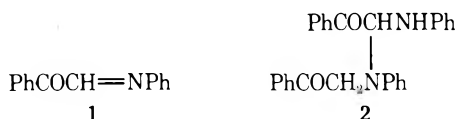
In this work, Proctor also described the synthesis of the two stereoisomers of **1** by a different reaction. Treatment of *N*-(*p*-toluenesulfonyl)phenacylaniline with base resulted in the formation of *cis*-**1** and this, in turn, was isomerized to the trans isomer by reaction with a palladium catalyst.

It was of interest to us to repeat some of the above work to confirm the reported structures and to identify Proctor's major product of undetermined structure. We have reinvestigated the reaction of phenylglyoxal with aniline and have isolated compounds **3**, **4**, and **5** in pure form. Despite several attempts, we have failed to recover **1** from the reaction mixture or to detect its presence; however, *cis*- and *trans*-**1** were prepared from *N*-(*p*-toluenesulfonyl)phenacylaniline and these structures were confirmed by reduction to **6**.

Compound **3** (0.3% yield)[3] is the product originally found by Yates. In support of its structure, it can be synthesized by the alkaline oxidation of phenacylaniline; presumably via initial oxidation to **1** followed by an aldol type condensation of phenacylaniline with **1**. Compound **3** also undergoes a retro-aldol reaction with concentrated HCl to give phenacylaniline back again.

PhCOCHNHPh
|
PhCOCHNHPh
3

PhCOCH(NHPh)₂
4

5

PhCHOHCH₂NHPh
6
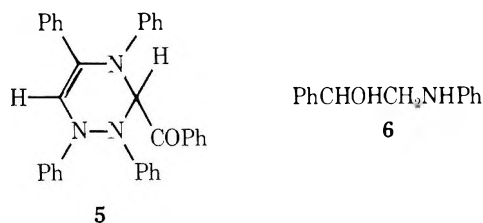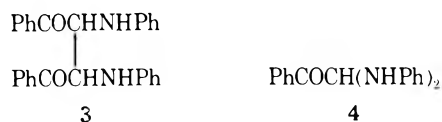
The IR and NMR spectra of **3** provide conclusive evidence for its structure and show, furthermore, that it exists as the intramolecularly hydrogen bonded configuration **7**.

7
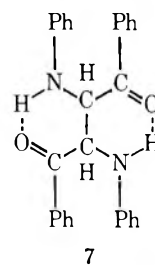
The ¹H NMR spectrum in anhydrous dimethyl-d_6 sulfoxide shows broad peaks at δ 5.65, 5.74 (2 H), and 6.11. The combined areas of the peaks at δ 5.65 and 6.11 correspond to 2 H but their area ratio is 1.8 to 1. Addition of D₂O to the sample showed that the δ 5.65 and 6.11 peaks were due to NH.

The signal at δ 5.65 is very nearly the same as the corresponding NH absorption of phenacylaniline (δ 5.70) in the same solvent. Therefore, the δ 5.65 peak is due undoubtedly to hydrogen bonding of **3** to solvent while the δ 6.11 peak represents the intramolecular hydrogen bonds in **7**.

The IR spectrum can be explained similarly. Compound **3** has absorption at 1665 cm⁻¹ in the solid state. It is insoluble in most solvents but partially soluble in a few such as pyridine. An IR spectrum taken in pyridine has a shoulder at approximately 1695 cm⁻¹ on one of the pyridine absorption bands. This is an indication that some of the intramolecular hydrogen bonding in **7** is broken and the normal carbonyl frequency is observed.
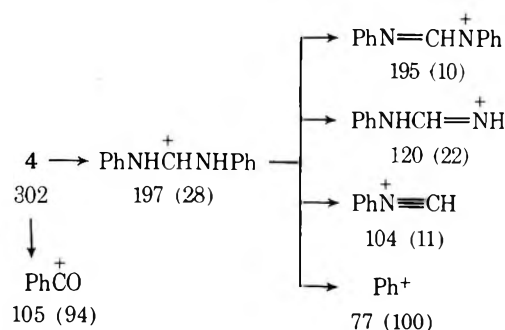
The mechanism by which **3** is formed from phenylglyoxal and aniline is purely a matter of speculation due to its low yield. No analogy appears to exist for what amounts to a reductive coupling of **1** under acidic conditions. A low yield of **3** was obtained when *cis*-**1** was treated with acid but little can be inferred from this experiment.

Compound **4** (9% yield) proved to be a very unstable material as its structure would indicate. On standing or heating, it liberated aniline to give a mixture of products containing predominantly **5**. A good analysis could not be obtained for this substance due to its instability and difficulty in drying but its structure could be deduced from the following information.

The IR and NMR spectra indicate the presence of two NH groups, an aromatic ketone, and a one-proton singlet (>CH). The UV spectrum was similar to that of phenacylaniline but did have an increased intensity of absorption. The mass spectrum of **4** was unusual but particularly informative.

High resolution mass measurements show an apparent molecular ion at *m/e* 197 with an elemental composition of C₁₃H₁₃N₂. This cannot be a true molecular ion because of the inconsistency of the even number of nitrogens with an odd number molecular weight. If one infers the presence of a benzoyl group from the IR then a likely molecular formula would be C₂₀H₁₈N₂O. Thus there would have to exist in the

Scheme I

$$4 \longrightarrow PhNHCH\overset{+}{N}HPh$$

302   197 (28)

$$\longrightarrow PhN{=}\overset{+}{CH}NPh \quad 195\ (10)$$

$$\longrightarrow PhNHCH{=}\overset{+}{N}H \quad 120\ (22)$$

$$\longrightarrow PhN{\equiv}\overset{+}{CH} \quad 104\ (11)$$

$$\longrightarrow Ph^+ \quad 77\ (100)$$

$$\downarrow$$

$$Ph\overset{+}{C}O$$

105 (94)

Scheme II

$$5 \longrightarrow$$

493 (0)

388 (57)

$$\downarrow$$

$$Ph\overset{+}{C}O$$

105 (21)

$$\longrightarrow PhN{=}\overset{+}{CH}NPh \quad 195\ (12)$$

$$\longrightarrow PhN{=}\overset{+}{N}Ph \quad 182\ (100)$$

$$\longrightarrow Ph\overset{+}{C}{\equiv}NPh \quad 180\ (10)$$

$$\longrightarrow PhN{\equiv}\overset{+}{CH} \quad 104\ (24)$$

$$\longrightarrow Ph^+ \quad 77\ (57)$$

compound a structural feature which allows facile elimination of the benzoyl group to give a stable positive ion fragment. Structure 4 would give a positive ion that would be stabilized by dispersal of the charge onto the two adjacent nitrogens. It should be noted that 3 is reported to yield a molecular ion.

The observed fragmentation pattern of 4 (see Scheme I) provides excellent support for its structure, particularly the appearance of fragments at m/e 105 and 120.

Compound 4 is formed undoubtedly by the addition of aniline to phenylglyoxal anil. Such reactions of primary amines with imines are well known, although the adduct is usually not sufficiently stable to isolate.[4]

The compound described by Proctor as being the major product of the reaction was shown to be a mixture (see the Experimental Section) containing 5. Compound 5 was isolated in 13% yield. We propose that it is formed by an unusual Michael condensation of 4 with 1 to give a ketone which eventually undergoes ring closure to yield the final product. This type of condensation shows the strong tendency of 1 to behave as an α,β-unsaturated ketone as well as an α-diketone.
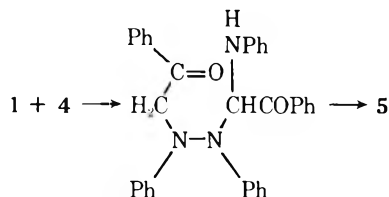
Compound 5 has IR and NMR spectra consistent with its structure. The aromatic ketone and enamine structure are indicated by absorption at 1695 and 1660 cm^{-1}. The ^{1}H NMR spectrum exhibits two one-proton singlets in the appropriate region.

Analysis of 5 gave a molecular formula of $C_{34}H_{27}N_3O$, but again a true molecular ion could not be observed in the mass spectrum. High resolution measurements show an apparent molecular ion at m/e 388 with an elemental composition of $C_{27}H_{22}N_3$. For the reasons cited previously, it is evident that the molecule readily loses a benzoyl group to yield the stable m/e 388 positive ion.

The fragmentation pattern observed for 5 is explained well by its structure (see Scheme II). The appearance of the ion at m/e 182 (shown by high resolution measurements to be $C_{12}H_{10}N_2$) is an excellent indication of the presence of the hydrazobenzene portion within the compound.

When 5 was treated with hydrogen over a palladium catalyst until 1 mol was absorbed, there was formed a mixture of products which could not be characterized. Presumably, hydrogenation yields a benzylamine which undergoes further hydrogenolysis.

It is clear that the reaction of phenylglyoxal with aniline in an acid medium is a very complicated one. Most of the products obtained in either the pure state or as oils and mixtures undergo changes in their properties on standing and appear to be quite unstable. Only 3 and 5, both of unexpected structure, can be considered to be stable products from the reaction.
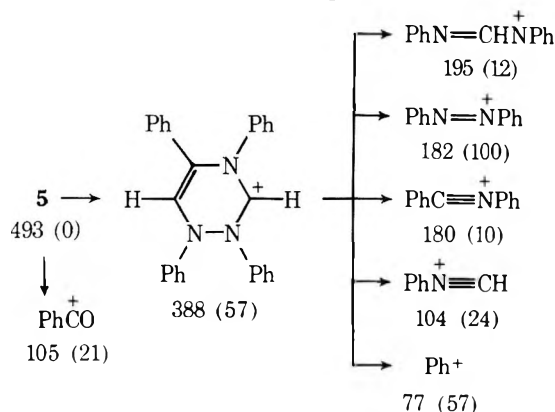
Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on Perkin-Elmer Model 137 and Model 21 spectrophotometers. Ultraviolet spectra were run on a Hitachi Perkin-Elmer Model 139 UV–visible spectrophotometer, and the NMR spectra were obtained on a Varian Associates Model A-60 instrument. Mass spectral data were obtained at an ionizing voltage of 70 eV on a Varian MAT CH-7 mass spectrometer. Carbon and hydrogen analyses were performed by Galbraith Analytical Laboratories, Knoxville, Tenn.

Phenacylaniline. To a solution of 13.84 g (69.5 mmol) of phenacyl bromide[5] in 70 mL of 95% ethanol was added 13.70 mL (150 mmol) of aniline and the solution was allowed to stand at room temperature overnight. The solid which separated was filtered and recrystallized from 95% ethanol to give 9.96 g of yellow needles: mp 96–98 °C (lit.[2] mp 98 °C); UV λ_{max} (EtOH) 246 (ϵ 15 800), 286 nm (ϵ 2020); NMR (CDCl$_3$) δ 4.08 (s, 1 H), 4.60 (s, 2 H), 6.6–8.1 (m, 10 H); NMR (Me$_2$SO-d_6) δ 4.65 (d, J = 6.5 Hz, 2 H), 5.70 (t, J = 6.5 Hz, 1 H), 6.6–8.1 (m, 10 H). The broad singlet at δ 4.08 in CDCl$_3$ and the peak at δ 5.70 in Me$_2$SO-d_6 disappear when D$_2$O is added, and the one at δ 4.64 collapses to a sharp singlet.

Reduction of Phenacylaniline. A mixture of 498 mg (2.36 mmol) of phenacylaniline and 91 mg (2.41 mmol) of NaBH$_4$ in 7.0 mL of 95% ethanol was heated on a steam bath for 5 min. After cooling to room temperature, the mixture was poured onto 10 g of crushed ice whereupon a yellow oil was deposited. The oil was extracted into ether which was then dried over anhydrous MgSO$_4$ and evaporated to dryness under reduced pressure. All efforts to induce the resulting oil to crystallize failed so the hydrochloride was prepared.[6]

Dry hydrogen chloride was passed over the surface of a solution containing 475 mg of the oil dissolved in 10 mL of dry ether at 0 °C until no more solid was formed. The mixture was then filtered to give a white solid which was recrystallized from ethanol–ether. In this way was obtained 331 mg (56% from phenacylaniline) of 2-anilino-1-phenylethanol hydrochloride: mp 142.5–144 °C; IR (Nujol) 3320, 2600 (broad), 1590, 1060 cm^{-1}.

Anal. Calcd for C$_{14}$H$_{16}$NOCl: Cl, 14.20. Found: Cl, 14.42 (gravimetric).

Oxidation of Phenacylaniline. A mixture of 1.18 g (5.59 mmol) of phenacylaniline, 17 mL of 95% ethanol, and 0.05 mL of piperidine was heated under reflux on the steam bath for 4 h. After standing overnight open to the air, the solid which separated was filtered and recrystallized from ethyl acetate to give 0.35 g (30%) of 3: mp 184–185 °C (lit.[2] mp 187 °C); NMR (Me$_2$SO-d_6) δ 5.65 (broad, 0.7 H), 5.74 (broad, 2 H), 6.11 (broad, 1.3 H), 6.5–8.0 (m, 20 H). Addition of D$_2$O caused the disappearance of the signals at δ 5.65 and 6.11 and that at δ 5.74 narrowed to a singlet.

When the reaction was run under a nitrogen atmosphere no 3 was formed and phenacylaniline was recovered in 70% yield.

Hydrolysis of 3. A mixture containing 100 mg (0.24 mmol) of 3 and 5 mL of concentrated HCl was heated at 100 °C for 5 min and then filtered quickly. An equal volume of water was added to the filtrate which was then made alkaline with dilute NaOH. The solid which separated was filtered to give 14 mg of a product melting at 90–95 °C whose IR spectrum proved to be identical with that of phenacylaniline.

The residue from the initial heating weighed 30 mg and the IR spectrum showed that it was essentially recovered 3. Therefore, the

yield of phenacylaniline in the above reaction is 40% based on un-recovered **3**.

Preparation and Reduction of *cis*- and *trans*-1. The cis and trans anils were prepared as described previously and observed to have the reported spectral characteristics.[2] Each of the anils was reduced with NaBH$_4$ in the manner indicated for reduction of phenacylaniline. The hydrochlorides (34% from *cis*-1 and 46% from *trans*-1) were compared to each other and to the hydrochloride of **6**. All three compounds proved to be the same by virtue of melting point, mixture melting point, and identity of IR spectra.

The cis anil was reacted with aniline in the manner described by Yates for reaction of phenylglyoxal with aniline.[1] A 4.5% yield of impure **3** was obtained; mp 169–173 °C.

Reaction of Phenylglyoxal with Aniline. Phenylglyoxal hydrate[7] was reacted with freshly distilled aniline using the procedure described by Proctor.[2] In a typical run, 7.70 g (50.6 mmol) of phenylglyoxal hydrate, 4.17 g (50.6 mmol) of aniline, and 10 mL of acetic acid in 50 mL of 95% ethanol were heated on a steam bath for 30 min to give 10.80 g of an orange oil. TLC showed that a minimum of seven compounds were present in the oil which was chromatographed on 100 g of Florisil.[8] Elution with 2:1 hexane–benzene gave, after crystallization from acetone, 34 mg (0.3%) of impure **3**, mp 165–168 °C. The IR spectrum of this material was identical to that of pure **3** obtained in other ways and it also did not depress the melting point of pure **3**.

The majority of the product was eluted with benzene in several fractions. Crystallization of the early benzene fractions yielded 2.54 g of yellow crystals, mp 68–76 °C. Recrystallization of the material from heptane failed to change the melting point significantly. The substance had the spectral properties described by Proctor for his major product but its mass spectrum was very complex. All of the ions observed for **5** were also observed for this material; in addition, ions were seen at *m/e* (rel intensity) 518 (23), 354 (5), 313 (11), 222 (5), 122 (5), and 120 (6). The compound of mass 518 is unstable. After standing for 1 month, no ion above *m/e* 389 was observed. Instead, an intense peak at *m/e* 93 was detected, probably due to aniline released in the decomposition.

When the mother liquors from the crystallization of the above product were allowed to evaporate slowly, rounded domes of yellow crystals were formed. Crystallization of these from 95% ethanol yielded 1.07 g (13%) of **5**: mp 173–175 °C. The anlytical sample melted at 175.5–176.5 °C: IR (Nujol) 1695, 1660, 1590, 1205 cm^{-1}; UV λ_{max} (EtOH) 243 (ϵ 34 400), 285 nm (ϵ 12 900); NMR (CDCl$_3$) δ 5.85 (s, 1 H), 6.47 (s, 1 H), 6.6–8.0 (m, 25 H); MS *m/e* (rel intensity)388 (57), 195 (12), 182 (100), 180 (10), 105 (21), 104 (24), 77 (57), 51 (8). High resolution mass measurements gave *m/e* 388.1824 (C$_{27}$H$_{22}$N$_3$ requires 388.1815) and *m/e* 182.0869 (C$_{12}$H$_{10}$N$_2$ requires *m/e* 182.0844).

Anal. Calcd for C$_{34}$H$_{27}$N$_3$O: C, 82.72; H, 5.52; N, 8.51. Found: C, 83.06; H, 5.61; N, 8.39.

Compound **5** underwent reaction when boiled in ethanol containing 10% concentrated HCl and also absorbed H$_2$ at atmospheric pressure in the presence of a Pd on charcoal catalyst. Apparent mixtures of products were formed.

The final homogeneous fraction was eluted from the column with 1:1 CHCl$_3$–MeOH. Low-temperature (−80 °C) crystallization from ethanol gave 0.68 g (9%) of **4**, mp 125–128 °C. The melting point is not indicative of the purity of the compound since an odor of aniline begins to emanate from the solid well below the melting temperature. TLC of the sample on silica gel gave one well defined spot while older, decomposed samples gave at least four spots. The substance had: IR (Nujol) 3410, 1695, 1590, 1215 cm^{-1}; UV λ_{max} (EtOH) 246 (ϵ 24 100), 286 nm (ϵ 3650); NMR (CDCl$_3$) δ 4.56 (broad, 2 H), 6.39 (s, 1 H), 6.6–8.1 (m, 15 H). Addition of D$_2$O caused the signal at δ 4.56 to disappear. MS *m/e* (rel intensity) 197 (28), 195 (10), 122 (24), 120 (22), 105 (94), 104 (11), 77 (100), 51 (24). High resolution measurements gave *m/e* 197.1076 (C$_{13}$H$_{13}$N$_2$ requires 197.1080). Compound **4** could not be dried adequately without decomposition so the mass spectrum had a water peak at *m/e* 18.

The other fractions obtained from the chromatography were solids or oils which could not be characterized.

Registry No.—*cis*-**1**, 66749-85-7; *trans*-**1**, 66749-86-8; **3**, 66749-87-9; **4**, 66749-88-0; **5**, 66749-89-1; **6**, 31121-09-2; **6**·HCl, 3099-27-2; phenacylaniline, 5883-81-8; phenacyl bromide, 70-11-1; aniline, 62-53-3; phenylglyoxal, 1074-12-0.

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(3) The yield of this material varies depending on the procedure used to prepare it. Yates' procedure gives about 3% yield and simply heating phenylglyoxal hydrate and aniline together in ethanol in the absence of an acid catalyst for several hours also gives about a 3% yield.

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(7) H. A. Riley and A. R. Gray, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 509.

(8) The adsorbent was 60–200 mesh supplied by Matheson, Coleman and Bell.

Palladium-Catalyzed Reaction of 3-Bromopyridine with Allylic Alcohols: A Convenient Synthesis of 3-Alkylpyridines

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Compared with a wide variety of convenient methods for 2- and 4-alkylpyridines, the synthesis of 3-alkylpyridines is less common and rather laborious.[1] 3-Alkylpyridines have usually been prepared either by the alkylation of 3-pyridyllithium[2] or 3-picolyllithium[3] or by elaboration of nicotinic acid.[4] Therefore, and because of their particular pertinence to the alkaloids[5] and use in synthesis[6] (e.g., as a precursor of 1,5-diketones), a convenient preparative method for 3-alkylpyridines would be desirable.

In this context, we have examined the palladium-catalyzed alkylation of pyridine at the 3 position, as an extension to the phenylation reaction of allylic alcohols, recently reported by Heck et al.[8] and Chalk et al.[9]

3-Bromopyridine has reacted smoothly and selectively at the 3 position of allylic alcohols to give 3-(3′-pyridyl) ketones or aldehydes in the presence of 1 mol % of Pd(OAc)$_2$ (based on 3-bromopyridine, eq 1). In some cases, depending on the
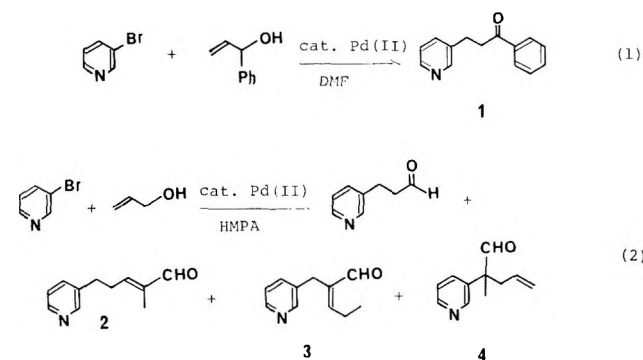
structure of the allylic alcohols and the reaction conditions, the positional isomer [2-(3′-pyridyl) ketone or aldehyde, **5**] and unsaturated alcohol **6** were also obtained as minor prod-

ucts. In Table I are summarized the reaction conditions and product distribution obtained with five kinds of allylic alcohols. Alcohols examined were allyl alcohol, α-, β-methallyl

### Table I. Reactions of 3-Bromopyridine with Allylic Alcohols

| entry | alcohol | registry no. | reaction conditions[a] | | | | | product distribution[b] | | |
			solvent	additive	temp °C	time h	conv %	3-(3'-pyridyl)[c]	2-(3'-pyridyl)[c]	others
1	CH₂=CHCH₂-OH	107-18-6	HMPA	PPh₃	95	9	100	45 (17)		17 (5)[d] 8 (2)[e] 18 (5)[f] 12[g]
2	CH₂=C(CH₃)-CH₂OH	513-42-8	HMPA	PPh₃	100	48	100	96 [100/0] (50)		4[h] (2)
3	CH₂=C(CH₃)-CH₂OH		DMF	PPh₃	100	50	100	97 [100/0]		3[h]
4	CH₂=CHCH-(CH₃)OH	598-32-3	HMPA	PPh₃	120	5	100	92 [90/10] (44)	8 (4)	
5	CH₂=CHCH-(CH₃)OH		HMPA	NaI	120	10	77	85 [99/1]	15	
6	CH₂=CHCH-(CH₃)OH		HMPA	none	120	6	96	82 [99/1]	18	
7	CH₂=CHCH-(CH₃)OH		DMF	PPh₃	120	7	97	90 [82/18]	2	9[g]
8	CH₂=CHCH-(CH₃)OH		DMF	none	120	9	97	93 [100/0] (87)	7 (7)	
9	CH₃CH=CH-CH(CH₃)OH	1568-50-2	HMPA	PPh₃	120	24	100	84 [98/2] (62)	16 [95/5] (13)	
10	CH₃CH=CH-CH(CH₃)OH		HMPA	none	120	24	100	61 [98/2]	39 [99/1]	
11	CH₃CH=CH-CH(CH₃)OH		DMF	PPh₃	120	10	93	87 [83/17]	4 [63/37]	9[g]
12	CH₃CH=CH-CH(CH₃)OH		DMF	none	120	24	99	77 [99/1] (71)	21 [100/0] (18)	2[g]
13	CH₂=CHCH-(Ph)OH	4393-06-0	HMPA	PPh₃	120	6	100	93 [93/7] (80)		7[g]
14	CH₂=CHCH-(Ph)OH		HMPA	none	120	24	100	93 [100/0]		7[g]
15	CH₂=CHCH-(Ph)OH		DMF	PPh₃	120	5	100	91 [76/24]		9[g]
16	CH₂=CHCH-(Ph)OH		DMF	none	120	24	99	93 [100/0] (91)		7[g]

[a] The usual reaction scale is as follows: 3-bromopyridine (4.0 mmol), allylic alcohol (6.0 mmol), Pd(OAc)₂ (0.04 mmol), NaHCO₃ (4.8 mmol) in 3 mL of a solvent. As an additive, PPh₃ (0.12 mmol) or NaI (0.14 mmol) was added in the cases indicated. Bath temperatures were controlled within ±0.5 °C. Conversion is based on 3-bromopyridine consumed. [b] Calcd from the area intensities on VPC (SiDC 550, He). The values in the parentheses refer to the isolated yields. The values in the brackets refer to the ratio of carbonyl to alcohol. [c] 3-(3'-Pyridyl) and 2-(3'-pyridyl) refer to the products 3-(3'-pyridyl)carbonyl and alcohol, and 2-(3'-pyridyl)carbonyl and alcohol, respectively. [d] 2-Propylidene-3-(3'-pyridyl)propanal; registry no. 66702-64-5. [e] 5-(3'-Pyridyl)-2-methylpent-2-enal; registry no. 66702-65-6. [f] 2-Methyl-2-(3'-pyridyl)pent-4-enal; registry no. 66702-66-7. [g] Unknowns consist of more than one peak of less than 5%.

alcohols, methylpropenylcarbinol, and phenylvinylcarbinol. In these reactions, 3,3'-bipyridyl formation reaction did not occur to a detectable extent. The reactivity and regioselectivity depend on the structure of allylic alcohols. The methyl substituent on the olefinic carbon of allyl alcohol markably suppressed the reaction rate as observed in the reactions with β-methallyl alcohol and methylpropenylcarbinol. The size of the alkyl and aryl groups at the 1 position of the allyl alcohol did not affect their reactivity. While there was no significant solvent effect on the reactivity between dimethylformamide (DMF) and hexamethylphosphoric triamide (HMPA), the former is the best choice of solvents as judged by selectivity for the 3 position. For example, the C-3/C-2 ratio changed from 82:18 (in HMPA, entry 6) to 93:7 (in DMF, entry 8). DMF was also a satisfactory solvent for practical reasons since the products could be isolated without an aqueous workup by distillation of the filtered reaction mixture. With aqueous workup, the isolated yields fall to half owing to the high water solubility of products (especially with a short alkyl chain; entries 1, 2, 4, and 13).

Triphenylphosphine raised the reactivity and the 3-pyridylation selectivity, but in the presence of this cocatalyst, an appreciable amount of 6 was produced. The latter effect is amplified in DMF. The unsaturated alcohol formation is characteristic of this pyridylation, not observed to such a large extent for the arylation[9] or thienylation[7] of allylic alcohols under similar conditions. In the pyridylation reaction, pyridine as well as triphenylphosphine seems to act to displace the olefinic group from the metal (path b, Scheme I), before the complete addition–elimination sequences of hydridopalladium complex to give carbonyl compound (path a). Thus

Scheme I
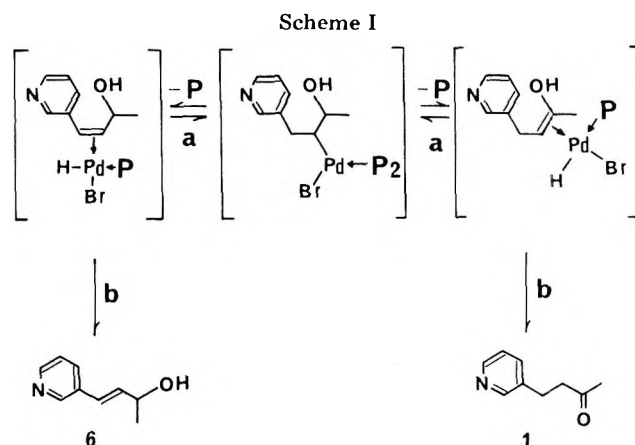
formed free metal hydride cannot isomerize the olefin and decomposes rapidly in the presence of base.

A particularly interesting feature of the reaction with allyl alcohol, not observed with other allylic alcohols, is the formation of aldol condensation products 2 and 3 (eq 2, entry 1), a process that has been postulated to explain the low isolated yield of 3-phenylpropionaldehyde.[9] Apparently these products arise from 3-(3'-pyridyl)propionaldehyde and propionaldehyde, formed in situ by olefin migration. Furthermore the isolation of 2-methyl-2-(3'-pyridyl)pent-4-enal (4) suggests that under the present reaction conditions the π-allylpalladium complex, probably formed by the oxidative addition of Pd(0) to allyl alcohol, reacted with the enolate of 2-(3'-pyridyl)propionaldehyde.[10]

In conclusion, the present palladium-catalyzed reaction is a good method to prepare the 3-alkylpyridines, with the following advantages. (a) The manipulation is very easy (not rigorously sensitive to moisture) and applicable to a large scale reaction. (b) By the combination with an appropriate allylic alcohol, we can modify the alkyl substituent with a carbonyl group at the 3' position, permitting further transformations.

Experimental Section

General Procedure for the Reactions of 3-Bromopyridine and Allylic Alcohols. The general procedure was exemplified by the reaction of 3-bromopyridine and α-methallyl alcohol (entry 4, Table I). Into an argon purged mixture of Pd(OAc)$_2$ (9 mg, 0.04 mmol), PPh$_3$ (31.5 mg, 0.12 mmol), and NaHCO$_3$ (404 mg, 4.8 mmol) were added 3-bromopyridine (632 mg, 4 mmol), α-methallyl alcohol (432 mg, 6 mmol), and 3 mL of HMPA by means of a syringe. The slurry mixture was stirred and heated at 120 °C for 5 h. The reaction was monitored by means of VPC (SiDC 550, He) by sampling 2 μL from the reaction mixture at an appropriate interval. The reaction mixture was poured into 20 mL of water and extracted with ether (30 + 20 + 20 mL). The combined ether extracts were washed with 10 mL of saturated NaCl and dried over MgSO$_4$. Evaporation of a solvent and the subsequent distillation (Kugelrohr 150 °C (15–5 mmHg)) gave a colorless oil (48% isolated yield), which consisted of 83% of 2-(3'-pyridyl)ethyl methyl ketone, 9% of 1-(3'-pyridyl)-1-buten-3-ol, and 8% of 1-(3'-pyridyl)-ethyl methyl ketone.

For the reaction in DMF (entry 8), the workup was undertaken as follows. The reaction mixture diluted with 20 mL of ether was filtered through a Florisil column (mesh 100–200, 1 cm length). Distillation of filtrate gave 545 mg of colorless oil (94% isolated yield, Kugelrohr 150 °C (13–10 mmHg)), consisting of 93% of methyl 2-(3'-pyridyl)-ethyl ketone and 7% of methyl 1-(3'-pyridyl)ethyl ketone.

Registry No.—1, 39976-56-2; 5 (R = H; R = Me), 66702-67-8; 5 (R = R' = Me), 66702-68-9; 6 (R = H; R' = Me), 66702-69-0; 6 (R = R' = Me), 66702-70-3; 6 (R = H; R' = Ph), 66702-71-4; 3-(3-pyridyl)-propanal, 1802-16-0; 2-methyl-3-(3-pyridyl)propanal, 66417-76-3; (E)-2-methyl-3-(3-pyridyl)propenal, 66702-72-5; 4-(3-pyridyl)-2-butanone, 55161-19-8; 4-(3-pyridyl)-3-penten-2-ol, 66702-73-6; 3-(3-pyridyl)-3-penten-2-ol, 66702-74-7.

Supplementary Material Available: ^{1}H NMR, IR, and mass spectra of 3- and 2-(3'-pyridyl)aldehydes and ketones and related compounds (5 pages). Ordering information is given on any current masthead page.

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Magnetic Equivalence and Nonequivalence of Methylene Groups Adjacent to an Asymmetric Center in a Series of γ-Phenyl-γ-butyrolactones[1]

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In recent studies, several γ-benzyl-γ-phenyl-γ-butyrolactones were prepared as intermediates in the synthesis of benzyltetralins and benzyltetralols.[2,3] The NMR spectrum of α,α-dimethyl-γ-phenyl-γ-butyrolactone (1) attracted our
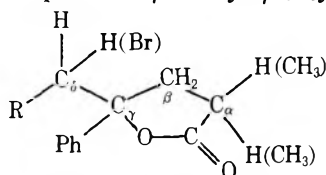

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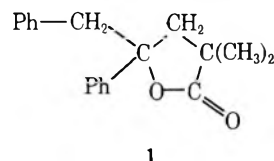
interest because it showed a clear AB pattern (centered at ca. δ 3.1) for one of the methylene groups and a sharp singlet (at δ 2.38) for the other. The ring methylene hydrogens would certainly be expected to be nonequivalent, and the benzyl methylene hydrogens might also be expected to be nonequivalent since they are adjacent to an asymmetric center. This spectrum was compared with those of the diastereomers of α-methyl-γ-benzyl-γ-phenyl-γ-butyrolactone[4,5] (Z-2 and E-2); see Table I. The spectra of Z-2 and E-2 indicate that both the ring methylene and benzyl methylene hydrogens are nonequivalent in these lactones. This aroused our curiosity as to which pair of methylene hydrogens in lactone 1 were the NMR equivalent ones.

To determine this, we first prepared the dideuterio analogue of 1 in which the deuterium atoms were placed unequivocally in the benzyl position. As may be seen in Table I, this lactone (1d) had an NMR spectrum identical with that of lactone 1 except that the singlet at δ 2.38 was missing. This proved that this singlet comes from the benzyl methylene hydrogens of lactone 1 and not from the β hydrogens of the lactone ring. Hence the β hydrogens of lactone 1 are nonequivalent, as expected, but the benzyl methylene hydrogens are NMR equivalent.

The same test was applied to lactone Z-2. Its α,α-dideuteriobenzyl derivative was also synthesized. As may be seen in Table I, this lactone (Z-2d) had an NMR spectrum virtually identical with that of lactone Z-2 except that the AB signal at δ$_A$ 3.20, δ$_B$ 3.09 was missing, confirming the analysis of the spectrum of lactone Z-2 as presented in Table I. Comparing the assigned NMR signals of lactone 1 with those of Z-2 and E-2 (Table I) reveals the surprising fact that the chemical shifts of the benzyl and methylene hydrogens are virtually reversed in these compounds!

An attempt was made to sort out the ABC signal from the α- and β-hydrogens remaining in lactone Z-2d. It consisted of two separated multiplets at δ 1.74–2.22 and δ 2.62–3.03,

Table I. NMR Spectra of γ-Phenyl-γ-butyrolactones[a]

registry no.	lactone	δ	β	α	CH₃
60484-03-9	R = Ph, δ H₂, α-(CH₃)₂ (1)	s, 2.38	AB, δA = 3.20, δB = 3.00, J ≈ 13 Hz		s, 0.85 s, 0.95
66687-62-5	R = Ph, δ D₂, α-(CH₃)₂ (1d)		AB, δA = 3.19, δB = 3.00, J ≈ 13 Hz		s, 0.85 s, 0.95
38436-24-7	R = Ph, δ H₂, α H, α-CH₃ (Z-2)[b]	AB, δA = 3.20, δB = 3.09, J = 14 Hz	ABC, 1.74–3.03, J(gem) = 11 Hz, J(vic) ≈ 8 Hz		d, 1.05 J = 6.5 Hz
66687-63-6	R = Ph, δ D₂, α-CH₃ (Z-2d)[b]		ABC, 1.74–3.03		d, 1.06 J = 6 Hz
38436-23-6	R = Ph, δ H₂, α H, α-CH₃ (E-2)[b]	AB, δA = 3.28, δB = 3.10, J = 14 Hz	ABC, 2.00–2.90		d, 1.06 J = 6 Hz
66719-16-2	R = Ph, δ H, Br, α-(CH₃)₂ (3)	s, 5.17	AB, δA = 2.86, δB = 2.54, J ≈ 13 Hz		s, 0.87 s, 1.14
66687-64-7	R = Ph, δ H₂, α-H₂ (4)	AB, δA = 3.21, δB = 3.05, J ≈ 15 Hz	AA′BB′, 1.85–2.65		
66687-65-8	R = CH₃, δ H₂, α-(CH₃)₂ (5)	q, 1.75–2.10, J ≈ 7 Hz	AB, δA = 2.43, δB = 2.27, J ≈ 12 Hz		s, 0.88 s, 1.24
66687-66-9	R = n-Pr, δ H₂, α-(CH₃)₂ (6)	m, ~1.68–2.20	AB, δA = 2.46, δB = 2.26, J ≈ 13 Hz		s, 0.87 s, 1.26
894-15-5	R = Ph, α-(CH₃)₂ (7)		s, 2.82		s, 1.06
66687-67-0	R = p-CH₃C₆H₄, α-(CH₃)₂ (8)		s, 2.82		s, 1.05

[a] Spectra of lactones Z-2, Z-2d, E-2, 3, and 4 were determined in CDCl₃ solution. Others were determined in CCl₄ solution. [b] Spectra of lactones Z-2, Z-2d, and E-2 were recorded on a HA-100 spectrometer. Others were recorded on a 60 MHz spectrometer.

indicating that one of the three protons is chemically shifted away from the other two. A deuterium exchange of the α proton was attempted with the aim of ascertaining its contribution to the NMR spectrum. Although complete exchange with the α proton was not effected by two treatments with LiOD in D₂O and 1,2-dimethoxyethane, the following changes in the NMR spectrum were observed: (1) after the first treatment, the doublet of the α-methyl group became smaller and a small singlet peak appeared in the middle of the doublet; and (2) after the second treatment the doublet became a broad singlet and the relative area of the resonance in the region δ 1.74–2.22 became smaller and about equal to the area in the region δ 2.62–3.03. These observations imply that considerable deuterium exchange of the α-proton occurred and that this α proton is one of the two which produce the signal at δ 1.74–2.22. Thus, the α-proton and one of the two β-methylene protons must produce the signal at δ 2.62–3.03.

Bromination of lactone 1 with N-bromosuccinimide gave the bromo lactone 3. Obviously, one the basis of the NMR spectrum of 3, the bromine replaced one of the benzyl hydrogens, as expected. The remaining benzyl hydrogen signal was shifted far downfield to δ 5.17 and the AB signal of the ring methylene hydrogens was shifted slightly upfield.

For comparison of a γ-phenyl-γ-butyrolactone with no substituents in the α position, γ-benzyl-γ-phenyl-γ-butyrolactone (4) was synthesized and its NMR spectrum was recorded. The benzyl methylene hydrogens were nonequivalent, giving an AB signal in the same region as those of lactones Z-2 and E-2. The α- and β-methylene hydrogens gave a typical AA′BB′ signal.

Two γ-phenyl-γ-butyrolactones with a γ-alkyl substituent were synthesized, in one case ethyl (5) and in the other n-butyl (6). Both showed the AB signal characteristic of the nonequivalent β-methylene ring hydrogens. The δ-methylene hydrogens of the γ-ethyl lactone (5) gave a quartet of broad peaks indicating an uncertain degree of nonequivalence, and

those of the γ-butyl lactone (6) gave an unresolved multiplet.

Of the final two lactones which were synthesized, one has two phenyl groups in the γ position (7) and the other has one phenyl and one p-tolyl group (8). Lactone 7 was expected to show equivalent β-methylene hydrogens, and it did, with a singlet at δ 2.82. Lactone 8 was of some interest because it also showed equivalence of the β-methylene hydrogens with a singlet at the same place. Although in the strictest sense they are not equivalent owing to the difference between the phenyl and the p-tolyl groups in the γ position, apparently the site of difference, the para position of the p-tolyl group, is too far away to affect the resonance of the β-methylene hydrogens.

We are grateful to Dr. Ben Shoulders of this Department for help in interpreting the NMR spectra described.

Experimental Section

General Procedures. Melting points were determined with a Laboratory Devices Mel-Temp capillary apparatus and are uncorrected. Infrared spectra of all new compounds were recorded on a Beckmann Model IR-5A spectrometer and were compatible with the expected structures. Nuclear magnetic resonance spectra were recorded at 60 MHz on a Varian A-60 or a Perkin-Elmer R12A spectrometer and at 100 MHz on a Varian HA-100 spectrometer. The solvents used are specified in Table I. All chemical shifts are reported as δ values in ppm downfield from Me₄Si as the zero standard. Microanalyses of new compounds were performed by Galbraith Laboratories, Knoxville, Tenn. and were in satisfactory agreement (±0.4% for C and H) with described structures.[6]

Synthesis of the γ-Phenyl-γ-butyrolactones. The new lactones were synthesized by a procedure analogous to that described previously for the Z and E isomers of α-methyl-γ-benzyl-γ-phenyl-γ-butyrolactone (Z-2 and E-2).[4] The appropriate Grignard reagents were added to the methyl esters of β-benzoylpropionic acid, α-methyl-β-benzoylpropionic acid, and α,α-dimethyl-β-benzoylpropionic acid. In the case of the dideuterio lactones (1d and Z-2d), the α,α-dideuteriobenzyl chloride required for the Grignard reagent was prepared by reduction of benzoyl chloride with lithium aluminum deuteride.

The physical constants of the lactones were as follows: 1, mp 97–99 °C; 1d, mp 97–100 °C; Z-2d, mp 134–135 °C; 3, mp 149–151 °C; 4, mp 78–80 °C; 5, bp 145–148 °C (0.3 mm); 6, mp 69–72 °C; 7, mp 110–112 °C; 8, bp 180–185 °C (0.6 mm).

The NMR spectra of the lactones are presented in Table I.

Bromination of α,α-Dimethyl-γ-benzyl-γ-phenyl-γ-butyro-lactone. To 2.80 g (0.01 mol) of the title lactone in 50 mL of CCl₄ was added 1.78 g (0.01 mol) of N-bromosuccinimide and 50 mg of benzoyl peroxide. The mixture was stirred and irradiated with a sunlamp for 3 h and then cooled. Succinimide was removed by filtration and the filtrate was washed with hot water, dried, and concentrated, yielding a white crystalline solid. Recrystallization from ether–chloroform (1:1 v/v) gave α,α-dimethyl-γ-(α-bromobenzyl)-γ-phenyl-γ-butyrolactone (3): 2.99 g (75%); mp 149–151 °C.

Anal. Calcd for $C_{19}H_{19}O_2Br$: C, 63.50; H, 5.29. Found: C, 63.56; H, 5.30.

Deuterium Exchange with (Z)-α-Methyl-γ-(α′,α′-dideuter-iobenzyl)-γ-phenyl-γ-butyrolactone. (Z-2d). A small piece of lithium wire was dissolved in 5 g of D_2O. In a 10-mL flask was placed 0.5 g of the title lactone dissolved in a few milliliters of 1,2-dime-thoxyethane. The lithium deuteroxide solution was added and then more 1,2-dimethoxyethane was added dropwise until the mixture became homogeneous. The solution was heated at 80 °C for 1 h and stirred at room temperature overnight. The solvent was evaporated and then D_2O was added, producing a cloudy solution from which white crystals soon separated. The crystals were washed with D_2O and recrystallized from methanol; 0.4 g of product was recovered, mp 134–135 °C. The NMR spectrum of the recovered lactone indicated partial exchange of hydrogen in the α position. The deuterium exchange procedure was repeated, giving the deuterated lactone whose NMR spectrum is described in the body of the paper.

Registry No.—Methyl β-benzoylpropionate, 25333-24-8; methyl α-methyl-β-benzoylpropionate, 36057-38-2; methyl α,α-dimethyl-β-benzoylpropionate, 15118-66-8.

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(6) The only exception to this statement is that the microanalysis for C, H of lactone 1 was inadvertently overlooked. However, reliable evidence of this structure has been provided by a published X-ray crystal structure determination.⁵

New Mild Conditions for the Synthesis of α,β-Unsaturated γ-Lactones. β-(2-Phthalimidoethyl)-Δ^{α,β}-butenolide

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In connection with a synthetic approach to D ring lactone erythrina alkaloids,² particularly cocculolidine (1),³ we needed an efficient route to β-(2-phthalimidoethyl)-Δ^{α,β}-butenolide (2a).

Despite the variety of methods that have been devised for the synthesis of the frequently encountered Δ^{α,β}-butenolide system⁴ and the relatively simple structure of this particular example, such a route proved to be surprisingly difficult to develop. We did meet with some initial success in that the reaction between ethyl bromoacetate and 1-acetoxy-4-phthalimido-2-butanone (3a) under classic Reformatsky conditions gave⁵ acetoxy lactone 4, which we find eliminates HOAc on heating in N,N-diethylaniline to give 2a cleanly and
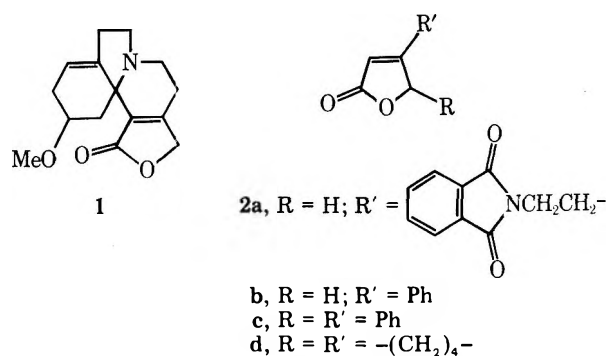
in high yield. The Reformatsky reaction with α-acetoxy ketones has recently been stated⁴ to be the method of choice for the preparation of Δ^{α,β}-butenolides. Unfortunately, in spite of considerable effort, the best yields that could be obtained in that step were low (20–21%) and even then somewhat variable with respect to product isolation, so that a better overall route to 2a was needed.

More recent variations⁶,⁷ in the Reformatsky procedure as well as other established methods⁸⁻¹¹ of introducing appropriate two carbon units as applied to 1-substituted 4-phthalimido-2-butanones (3), with the exception of BF₃-catalyzed addition of ethoxyacetylene¹² to α-chloro ketone 3b,⁵ were useless. The latter reaction gave in about 50% yield a product which appeared, as judged by the NMR spectrum, to be the expected α,β-unsaturated esters 5, but without se-

2a, R = H; R′ =
b, R = H; R′ = Ph
c, R = R′ = Ph
d, R = R′ = –(CH₂)₄–

3a, Z = OAc
b, Z = Cl
c, Z = N₃
d, Z = OCOCH₂Br
e, Z = Br
f, Z = OCOCH₂P⁺Ph₃ Br⁻
g, Z = OCOCH=PPh₃

4

5
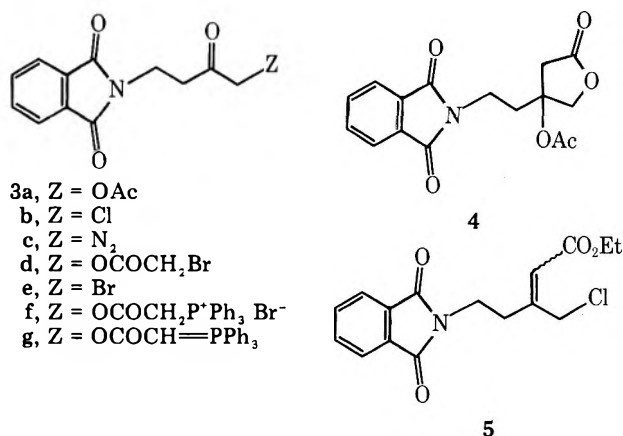
lectivity with respect to the required Z isomer and in any case as a very dark oil which resisted attempts at purification and complete characterization.

We then turned to an intramolecular approach to carbon–carbon bond formation, specifically via the Wittig reaction (eq 1).


$$\text{(1)}$$
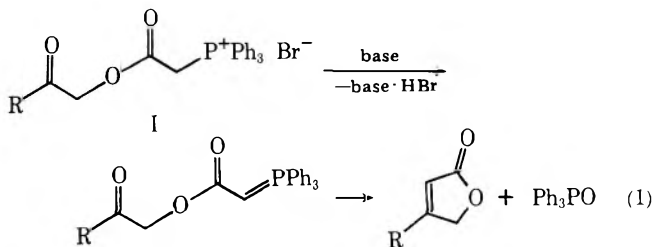
Compounds of type I have been cyclized to Δ^{α,β}-butenolides once before. In the two reported¹³ examples (eq 1, R = steroidal), similar moderate yields were obtained using the rather diverse systems NaH/Me₂SO (100 °C for 4 h; 51%) and K₂CO₃/t-BuOH (reflux 8 h; 67%); apparently, the exact nature of the base is not critical, and thus it seemed that one more compatible with our system could be effective. It was further hoped that less drastic conditions (purification was by chromatography) would suffice.

The details of the preparation of type I salts have not been previously published. On heating with bromoacetic acid in C_6H_6, diazo ketone **3c**[5] was converted to bromoacetoxy ketone **3d**; a cleaner alternative was to treat **3c** with aqueous HBr to give bromo ketone **3e** and react this with $Et_3N/BrCH_2CO_2H$ to give **3d**. The latter two reactions proceeded readily at room temperature in Me_2CO, and isolation of **3e** was unnecessary. Treating **3d** with Ph_3P (3 equiv) in C_6H_6 at 25 °C gave the requisite phosphonium salt **3f**; both conversions of **3c** → **3f** were essentially quantitative, as is the preparation[5] from β-alanine of **3c** itself.

When a suspension of **3f** in excess Et_3N was stirred at room temperature overnight, there was obtained in high yield a white solid consisting of $Et_3N \cdot HBr$ and a new air-unstable material. The identity of this compound as phosphorane **3g** was clear from the IR spectrum, which in the 1650–600 cm^{-1} region is very similar to that of ethoxycarbonylmethylene-triphenylphosphorane[14] ($Ph_3P=CHCO_2Et$) and marked by an intense band at 1625 cm^{-1} (P=C). That this highly reactive intermediate could be intercepted at all is attributable to its very low solubility in the Et_3N, because mere dissolution in a good solvent, e.g., $CHCl_3$, resulted in its virtually instantaneous and quantitative conversion to **2a** and Ph_3PO.

Both steps could be easily and cleanly carried out in one operation by simply treating the phosphonium salt with a slight excess of Et_3N under homogeneous conditions. Thus, a CH_2Cl_2 solution of **3f** containing 1.2 equiv of the amine allowed to stand at room temperature gave a quantitative yield of the desired product mixture, from which **2a** was obtained by recrystallization in 71% yield. Continuous monitoring of the reaction at ca. 40 °C by IR spectroscopy (see Experimental Section) revealed it to be complete within 30 min at this temperature.
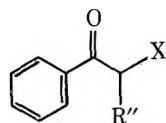
a, R″ = H; b, R″ = Ph
6, X = Br
7, X = OCOCH₂Br
8, X = OCOCH₂P⁺Ph₃ Br⁻
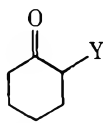
9a, Y = OCOCH₂Br
b, Y = OCOCH₂P⁺Ph₃ Br⁻
c, Y = OCOCH₂P(O)(OEt)₂

As this procedure constitutes an especially efficient and mild overall route to a $\Delta^{\alpha,\beta}$-butenolide, its generality was briefly explored; the conversion of **3e** to **3d** had extended the range of potential starting materials from α-diazo ketones to the more generally available α-bromo ketones, and the latter were utilized. The 2-bromoacetophenones **6a** and **6b** reacted smoothly via the respective intermediates **7a,b**[15] and **8a,b**[15] to give the corresponding butenolides **2b**[16] and **2c**,[17] isolated as was **2a**. The cyclizations, which again gave spectrally clean mixtures of lactone, Ph_3PO, and $Et_3N \cdot HBr$, were monitored as before and found also to proceed rapidly (Table I).

As applied to the preparation of bicyclic lactone **2d**,[18] the same sequence failed in the first step, with little if any bromoacetoxy ketone **9a** resulting from the treatment of 2-bromocyclohexanone[19] with the $Et_3N/BrCH_2CO_2H$ reagent. The preparation of phosphonium salt **9b** was not further explored, but instead a mild intramolecular[13] route to **2d** through the Horner–Emmons[11] reagent **9c** was examined. Reaction of 2-bromocyclohexanone with potassium diethylphosphonoacetate[20] [$(EtO)_2P(O)CH_2CO_2^-K^+$] at room temperature gave **9c**[15] directly in 91% yield, the use of the preformed phosphonate thus avoiding both bromo ester **9a** and the usual high temperature Arbuzov conditions used for the preparation of phosphonates.[13,21] The cyclization to **2d** could be accomplished, but comparably mild conditions were ineffective and the crude product obtained (NaH, refluxing C_6H_6, ca. 50%

Table I. Cyclization of Phosphonium Salts[a]

salt	registry no.	salt concn, M	product[b]	registry no.	reaction time, h[c]
3f	66792-64-1	0.071	**2a**	66792-67-4	0.5
8a	66792-65-2	0.10	**2b**	1575-47-9	0.5
8b	66792-66-3	0.10	**2c**	6620-27-5	0.1

[a] All reactions carried out in $CHCl_3$ at ~40 °C using 1.2 mol of Et_3N/mol of salt. [b] As equimolar mixture with Ph_3PO and $Et_3N \cdot HBr$. [c] As indicated by IR analysis (see Experimental Section).

yield) was admixed with unidentified materials; this route to **2d** is, however, potentially advantageous for its brevity.

Type I phosphonium salts are thus seen to cyclize to give $\Delta^{\alpha,\beta}$-butenolides with a facility not previously appreciated. This factor and the ease with which the salts may be prepared combine to produce a route to these lactones which gives excellent overall yields while completely avoiding elevated temperatures. Comparable phosphonates may also be obtained under equally mild conditions, although their cyclization has not been effected as easily.

Experimental Section

Melting points are uncorrected. IR spectra were obtained with a Beckman 4230 spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R-24 (60 Mz) instrument or a Jeol PS-100 (100 Mz, FT mode) using $CDCl_3$ as solvent and Me_4Si as an internal standard. Combustion analyses were performed on a Perkin-Elmer 240 automatic elemental analyzer.

1-Bromoacetoxy-4-phthalimido-2-butanone (3d). A. Directly from 3c. A solution of 1.5 g (0.0064 mol) of diazo ketone **3c**[5] and 1.1 g (0.0079 mol) of bromoacetic acid in 40 mL of dry benzene was heated at 65–80 °C for 2.5 h, cooled, washed with H_2O and 1 N $NaHCO_3$, dried ($MgSO_4$), and evaporated to give 2.2 g (96%) of **3d** as a yellow solid, mp 106–111 °C. An analytical sample had mp 114.5–115 °C (C_6H_6–cyclohexane); NMR δ 2.9 (t, 2 H, J = 7 Hz), 3.9 (s, 3 H), 4.0 (t, 2 H, J = 7 Hz), 4.8 (s, 2 H), 7.8 (m, 4 H); IR (Nujol) 1760, 1715 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}BrNO_5$: C, 47.48; H, 3.42; N, 3.95. Found: C, 47.48; H, 3.31; N, 3.89.

B. Via 1-Bromo-4-phthalimido-2-butanone (3e). To a solution of 10.54 g (0.0434 mol) of **3c** in 160 mL of Me_2CO was added 48% HBr dropwise until gas was no longer evolved (0.25 h). The solution was stirred another 0.25 h and evaporated to give 12.44 g (97% crude yield) of **3e** as an off-white free-flowing solid. One recrystallization from EtOH gave 10.53 g (82%) as pure white needles, mp 113–114 °C. An analytical sample had mp 118.5–119.5 °C; NMR δ 3.1 (t, 2 H, J = 7 Hz), 4.0 (s, 2 H), 4.1 (t, 2 H, J = 7 Hz), 7.8 (m, 4 H); IR (Nujol) 1720 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 49.01; H, 3.39; N, 4.56.

To a solution of 1.14 g (0.00385 mol) of **3e** and 0.535 g (0.00385 mol) of bromoacetic acid in 25 mL of Me_2CO was added 0.540 mL (0.00388 mol) of Et_3N. After 5 h a quantitative yield of $Et_3N \cdot HBr$ was filtered off. The residue from evaporation of the filtrate was dissolved in $CHCl_3$, and this solution was washed (1 N $NaHCO_3$ and saturated NaCl), dried ($MgSO_4$), and evaporated to give **3d** as a white solid, 1.32 g (97%).

Carbo(4-phthalimido-2-oxo)butoxymethylenetriphenylphosphonium Bromide (3f). To a solution of 5.96 g (0.0168 mol) of **3d** in benzene was added 13.41 g (0.0511 mol) of Ph_3P. After 20 h the mixture was filtered to give 10.4 g (100%) of **3f** as a bright yellow solid, mp 144–146 °C dec. An analytical sample had mp 148–148.5 °C (EtOH) and was colorless; NMR δ 2.8 (t, 2 H, J = 7 Hz), 3.9 (t, 2 H, J = 7 Hz), 4.7 (s, 2 H), 5.7 (d, J = 14 Hz), 7.8 (m, 19 H); IR (Nujol) 1720, 1740 cm^{-1}.

Anal. Calcd for $C_{32}H_{27}BrNO_5P$: C, 62.35; H, 4.41; N, 2.27. Found: C, 62.09; H, 4.82; N, 2.19.

β-(2-Phthalimidoethyl)-$\Delta^{\alpha,\beta}$-butenolide (2a). A. From β-Acetoxy-β-(2-phthalimidoethyl)-γ-butyrolactone (4). A solution of 2.59 g (0.00817 mol) of **4**[5] in 25 mL of N,N-diethylaniline was refluxed for 0.5 h under N_2, and the solution was poured into 100 mL of 6 N HCl with rapid stirring. The resulting suspension was cooled

and filtered, giving **2a** as an off-white solid (2.01 g, 96%), mp 180–183 °C, after drying in vacuo. An analytical sample had mp 182.5–184 °C (EtOH); NMR δ 2.8 (t, 2 H, J = 7 Hz), 3.9 (t, 2 H, J = 7 Hz), 4.8 (d, 2 H, J = 2 Hz), 5.9 (t, 1 H, J = 2 Hz), 7.8 (m, 4 H); IR (Nujol) 1760 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.45. Found: C, 65.35; H, 4.21; N, 5.47.

B. From Phosphonium Salt 3f. To a solution of 1.10 g (0.00179 mol) of **3f** in 25 mL of CH_2Cl_2 was added 0.30 mL (1.2 equiv) of freshly distilled Et_3N. After 20 h the solution was evaporated and dried in vacuo to give 1.32 g (100%) of a tan solid whose IR and NMR spectra were the sum of those of **2a**, Ph_3PO, and $Et_3N \cdot HBr$. The hydrobromide was removed by treatment with H_2O, and the residue was recrystallized once from EtOH to give the product as a white solid (0.327 g, 71%), mp 176–179 °C.

Lactones 2b and 2c. The preparations of **2b** and **2c** from bromo ketones **6a** and **6b**, respectively, were analogous to that for the conversion of **3e** to **2a**, and the yields were essentially quantitative. For **2b**: mp 91–92.5 °C (lit.[16] mp 94 °C); NMR δ 5.2 (d, 2 H, J = 2 Hz), 6.3 (t, 1 H, J = 2 Hz), 7.5 (m, 5 H); IR (Nujol) 1745 cm^{-1}. For **2c**: mp 151–152.5 °C (lit.[17] mp 152–153 °C); NMR δ 6.3 (d, 1 H, J = 2 Hz), 6.6 (d, 1 H, J = 2 Hz), 7.4 (m, 10 H); IR (Nujol) 1740 cm^{-1}.

Isolation of Phosphorane 3g. A suspension of 1.00 g (0.00162 mol) of **3f** in 25 mL of Et_3N was stirred for 17 h. Evaporation of the excess amine in vacuo, stirring with H_2O, and filtration left 0.819 g (94%) of **3g** as a white solid that turned brown on standing in air. On moderately fast heating it partially melted at 97.5–99 °C, resolidified, and slowly decomposed above 120 °C; IR (Nujol) 1725, 1625 cm^{-1}.

IR Analysis of Phosphonium Salt Cyclizations. To a solution of the salt in $CHCl_3$ was added 1.2 equiv of Et_3N. The sample was immediately placed in the spectrophotometer, and the increase in adsorption of the solution at 1175 cm^{-1} (P=O) was continuously recorded via time drive to give a smooth curve; the reaction was taken to be over when the curve leveled off. The equilibrium temperature attained in the IR beam was found to be ca. 41 °C (thermocouple), but since the samples were initially at room temperature the reactions are probably somewhat faster than shown in Table I.

2-Diethylphosphonoacetoxycyclohexanone (9c). A solution of 2.38 g (0.0134 mol) of 2-bromocyclohexanone[19] and 4.12 g (0.0176 mol) of potassium diethylphosphonoacetate[20] in 50 mL of CH_2Cl_2 was allowed to stand for 4 days. Precipitated KBr was filtered off, the filtrate was evaporated, and the residue was partitioned between H_2O and $CHCl_3$. The organic layer was dried ($MgSO_4$), evaporated, and dried in vacuo to give **9c** as a pale yellow spectrally clean liquid: 3.56 g (91%); NMR δ 1.2–2.7 (m, 8 H), 1.35 (t, 6 H, J = 7 Hz), 3.09 (fine split d, 2 H, J = 1 and 21 Hz), 4.20 (fine split quintet, 4 H, J = 1 and 7 Hz), 5.19 (dd, 1 H, J = 6 and 11 Hz); IR (neat) 1750, 1730, 1265, 1025 cm^{-1}.

Registry No.—**3c**, 7504-49-6; **3d**, 66792-68-5; **3e**, 51132-00-4; **3g**, 66792-69-6; **4**, 65465-68-1; **6a**, 70-11-1; **6b**, 1484-50-0; **7a**, 53392-50-0; **7b**, 66792-70-9; **9c**, 66792-71-0; **9** (Y = Br), 822-85-5; bromoacetic acid, 79-08-3; potassium diethylphosphonoacetate, 34170-84-8.

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Formation of 2,3-Dihydro-2,2-diphenylbenzo[b]furan-3-one by Reaction of gem-Dichloroaziridine with Phenol: Multiplicity of Reactions of gem-Dichloroaziridines under Acidic Conditions

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We have observed the formation of 4,4-diphenyl-1,2,3,4-tetrahydroisoquinolin-3-one (**5b**) and 1,1-diphenyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (**5c**) by treatment of 1-

a, $n = 0$; b, $n = 1$; c, $n = 2$
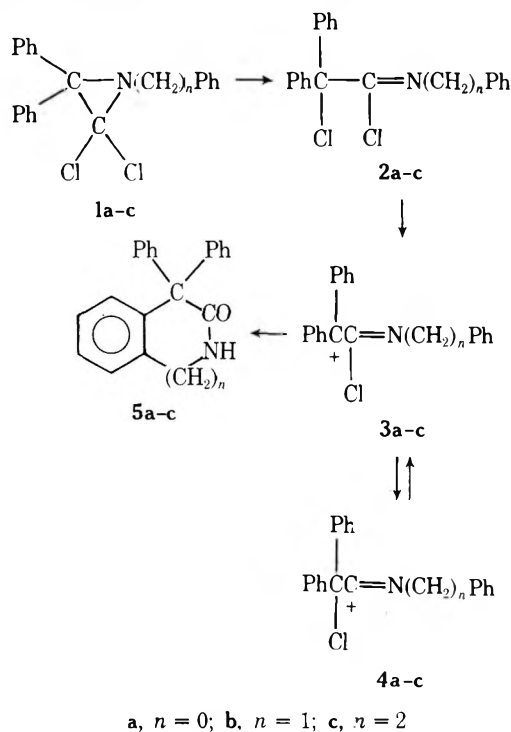
benzyl-2,2-dichloro-3,3-diphenylaziridine (**1b**) and 2,2-dichloro-3,3-diphenyl-1-(2-phenylethyl)aziridine (**1c**), respectively, with sulfuric acid in acetic acid.[1] It was assumed that the reactions proceed through cleavage of the C(3)–N bond and subsequent or simultaneous migration of a chlorine atom to the C(3) position to form N-benzyl- or N-(2-phenylethyl)-α-chloro-α,α-diphenylacetimidoyl chloride (**2b** or **2c**). The subsequent intramolecular Friedel–Crafts reaction and hydrolysis give the cyclic compounds **5b** or **5c**. In the case of N-phenyl compound **1a**, the intermediate (**2a**) was isolated by thermal isomerization. It was converted to 3,3-diphenyloxindole (**5a**) in good yield by treatment with sulfuric acid–acetic acid.[1,2]

Since the hydrolysis, methanolysis, and aminolysis of 2,2-dichloro-1,3-diphenylaziridine were reported to give compounds **6**,[3] **7**,[4] and **8**,[5] both of the two chlorine-carrying
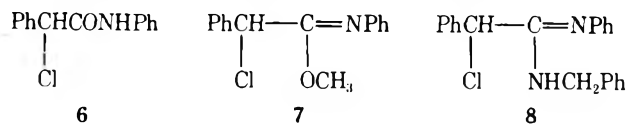

carbon atoms in **2** are considered to be sensitive to nucleophilic attack. Therefore, we expected the formation of heterocyclic compounds by intermolecular reactions of **1** with nucleophilic aryl compounds. We wish now to report the formation of 2,3-dihydro-2,2-diphenylbenzo[b]furan-3-one (**12**) by the reaction of **1c** with phenol.

When **1c** was reacted with phenol in benzene in the presence

of stannic chloride at room temperature, 2,3-dihydro-2,2-diphenyl-3-(2-phenylethyl)iminobenzo[*b*]furan (**11**) was obtained in 39% yield. By the treatment of an ethanolic solution of **11** with hydrochloric acid solution at reflux temperature, 2,3-dihydro-2,2-diphenylbenzo[*b*]furan-3-one (**12**) was obtained in 55% yield.

A similar reaction of **1b** with phenol in the presence of stannic chloride in benzene afforded the noncyclic compound α-(*p*-hydroxyphenyl)-α,α-diphenylacetonitrile (**14**) in 43% yield. Considering the results of intramolecular cyclization of the *gem*-dichloroaziridines (**1a–c**) under acidic conditions and solvolyses of 1,3-diphenyl-2,2-dichloroaziridine as described above, the following reaction mechanism was tentatively proposed.
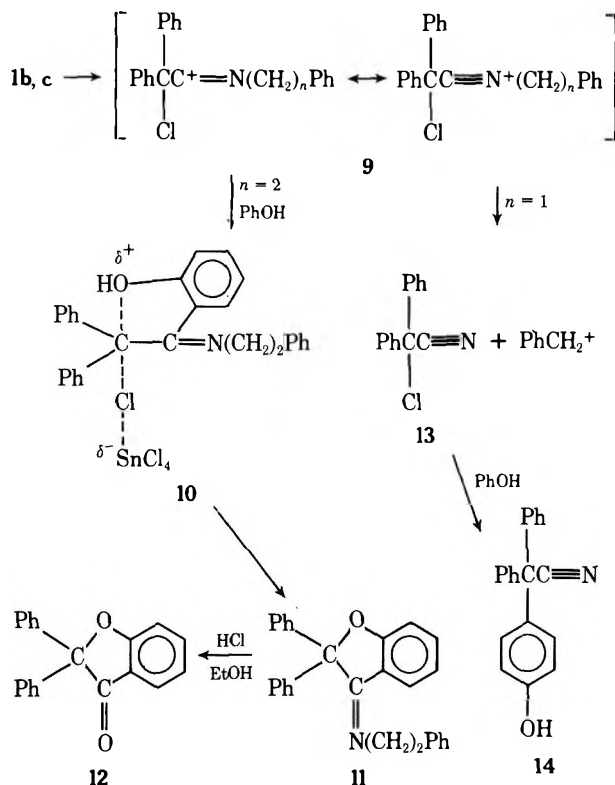
Divergent processes and different kinds of products from **1b** and **1c** may be attributed to the difference in nature of the group on the nitrogen atom. Stable carbonium ion forming groups such as a benzyl group would favor the von Braun type of degradation to give the nitrile **13**, which reacts subsequently with phenol to give **14**. The intermediate imidoylcarbonium ion **9** from **1c**, having a 2-phenylethyl group on the nitrogen, would attack phenol at the ortho position to form **11**. It is interesting to note that the alkylation of phenol with **1b** occurs at the para position while that with **1c** occurs at the ortho position. This seems to add an example to the known experimental criteria that secondary carbonium ions predominantly attack the ortho position of phenol while tertiary carbonium ions attack the para position.[8] Alternatively, the ortho substitution by **9** may be favored by the formation of cyclic intermediate **10** in the presence of SnCl₄. The reaction of **1c** with phenol is expected to serve as a general method for the synthesis of 2,3-dihydro-2,2-diphenylbenzo[*b*]furan-3-ones.

Experimental Section

Infrared spectra were obtained in KBr disks on a Jasco IRA-2 spectrometer, and NMR spectra were taken on a Hitachi R-20A spectrometer. Mass spectra were recorded on a Hitachi RMU-7M spectrometer. Combustion analyses were performed on a Perkin-Elmer 240 analyzer.

Reaction of 2,2-Dichloro-3,3-diphenyl-1-(2-phenylethyl)-aziridine (1c) with Phenol. To a solution of 3.68 g (0.01 mol) of **1c**

in 30 mL of benzene was added slowly a solution of 5.21 g (0.02 mol) of stannic chloride and 1.88 g (0.02 mol) of phenol in 30 mL of benzene. The mixture was stirred at room temperature for 36 h and then poured into water. The organic layer was separated, washed with aqueous sodium hydrogen carbonate and then with water, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a silica gel column using benzene as an eluent to give pure 2,3-dihydro-2,2-diphenyl-3-(2-phenylethyl)iminobenzo[*b*]furan (**11**) in 39% yield: mp 109–110 °C; IR 1650 cm⁻¹ (C=N); NMR (CDCl₃) δ (ppm) 3.10 (t, 2, CH₂Ph), 4.17 (t, 2, CH₂N=C), 7.30 (m, 19, Ph); MS 389 (M⁺), 298, 284, 270, 165, 105.

Anal. Calcd for C₂₈H₂₃NO: C, 86.34; H, 5.95; N, 3.60. Found: C, 86.09; H, 5.94; N, 3.52.

Hydrolysis of 2,3-Dihydro-2,2-diphenyl-3-(2-phenylethyl)-iminobenzo[*b*]furan (11). A solution of 0.2 g (0.51 mmol) of **11** in 11 mL of ethanol was treated with 1 mL of 12 M hydrochloric acid under reflux for 2 h. The acidic solution was neutralized with an ethanolic sodium hydroxide solution, and the sodium chloride that precipitated was removed. After evaporation of the solvent, the residue was chromatographed on a silica gel plate using carbon tetrachloride as an eluent. Isolation of the product band and extraction with acetone followed by evaporation of the solvent gave pure 2,3-dihydro-2,2-diphenylbenzo[*b*]furan-3-one (**12**): mp 91–92 °C (lit.⁶ mp 90 °C); IR 1710 cm⁻¹ (C=O); NMR (CDCl₃) δ (ppm) 7.3 (m, Ph); MS 286 (M⁺), 258, 257, 181, 165, 109, 77, 76.

Anal. Calcd for C₂₀H₁₄O₂: C, 83.90; H, 4.93. Found: C, 83.14; H, 4.97.

Reaction of 1-Benzyl-2,2-dichloro-3,3-diphenylaziridine (1b) with Phenol. To a solution of 3.54 g (0.01 mol) of **1b** in 30 mL of benzene was added slowly a solution of 5.21 g (0.02 mol) of stannic chloride and 1.18 g (0.02 mol) of phenol in 30 mL of benzene. The mixture was stirred for 36 h at room temperature and worked up by a similar method to that described for the reaction of **1c**. The yield of α-(*p*-hydroxyphenyl)-α,α-diphenylacetonitrile (**14**) was 43%: mp 194.5–195 °C (lit.⁷ mp 191–192 °C); IR 3400 (OH), 2225 (C≡N) cm⁻¹; NMR (CDCl₃) δ (ppm) 6.5–7.2 (m, Ph); MS 285 (M⁺), 208, 190, 181, 165, 153, 152.

Anal. Calcd for C₂₀N₁₅NO: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.51; H, 5.33; N, 4.96.

Registry No.—**1b**, 31528-96-8; **1c**, 61123-19-1; **11**, 66749-69-7; **12**, 66479-70-0; **14**, 13343-54-9; phenol, 108-95-2.

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A Facile Synthesis of 2-(Trifluoromethyl)histamine and 2-(Trifluoromethyl)-L-histidine

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Our observations of the potent and selective biological activities of 2-fluoro-L-histidine[2] and 2-fluorohistamine[3] stimulated efforts to prepare and test additional analogues of metabolically significant imidazoles, particularly those with other electronegative groups at C-2. The more obvious synthetic approaches begin with a preformed 2-substituted imidazole, followed by elaboration of the histidine or histamine side chain.[4] There are, however, significant advantages to the

use of L-histidine or histamine as starting materials: (1) ready availability; (2) shorter synthetic sequences; and (3) direct entry into the L-amino acid series. These advantages were realized in the syntheses of 2-amino-L-histidine and 2-aminohistamine[5] and in their subsequent conversions to the 2-fluoro[6] and 2-chloro[7] analogues. The trifluoromethyl group, because of its strong electronegativity, was of particular interest to us; however, the only documented synthesis of 2-trifluoromethylimidazoles involves condensation of α-diketones with trifluoroacetaldehyde and ammonia,[8] a method limited in both scope and yield, and not entirely suitable for our purposes.

A few 2-alkylimidazoles have been obtained by condensation of cis-1,2-dibenzamido-1-alkenes (2), the products resulting from Bamberger cleavage of imidazoles, with appropriate carboxylic anhydrides at high temperature (140–180 °C).[9] Substituents introduced at C-2 by this method include methyl, ethyl, phenyl, and benzyl. We considered the possibility that an analogous ring closure (3) might be achieved with trifluoroacetic anhydride and anticipated the need for sealed tubes to achieve the high reaction temperatures. To our surprise and gratification, the condensation occurred readily in solvent trifluoroacetic anhydride at reflux (40 °C) and provided good yields (70%) of α-N-benzoyl-2-trifluoromethyl-histamine (3c) and α-N-benzoyl-2-trifluoromethyl-L-histidine methyl ester (3e). Attempted removal of the benzoyl blocking groups by alkaline hydrolysis resulted in concomitant breakdown of the trifluoromethyl group,[10] but acid hydrolysis was successful and led to 2-trifluoromethylhistamine (3d) and
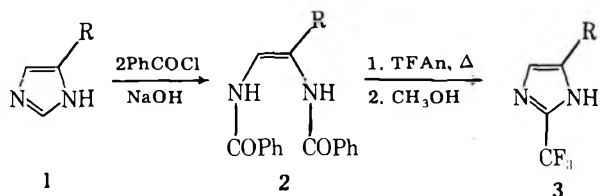
a, R = H
b, R = CH₃
c, R = CH₂CH₂NHCOPh
d, R = CH₂CH₂NH₂
e, R = CH₂CH(NHCOPh)COOCH₃
f, R = CH₂CH(NH₂)COOH

2-trifluoromethyl-L-histidine (3f). In their classical synthesis of histidine via 2e and 2-mercaptohistidine, Ashley and Harington[11] had demonstrated the absence of racemization at any step in the sequence. In the reaction of 2e with trifluoroacetic anhydride, azlactone formation (the only remaining source of racemization) cannot occur because the carboxyl group is protected as its ester. Consequently, we tentatively assume the optical rotations observed for 3e and 3f to represent those of the essentially unracemized L-amino acid.

Encouraged by these results, we then applied the cyclization method to the simpler dibenzamidoalkenes 2a and 2b. The expected products, 3a and 3b, were obtained, but in considerably lower yield than 3c or 3e. In the case of 2a, the major fraction consisted of a complex mixture of materials much more polar than 3a; with 2b, however, the principal products consisted of two (or more) relatively nonpolar, crystalline compounds with molecular weights above 550. The structures of these products have not yet been elucidated. We assume that the more favorable results with 2c and 2e are related to the steric bulk of their side chains in promoting cyclization and/or maintaining the cis geometry of the olefin in the acidic medium.

The conversion of 2 to 3 probably involves the pathway shown in Scheme I. This scheme suggests 2-phenylimidazoles as alternative products of cyclization; although such products have not been detected in the present work, they do occur as minor products in the reaction of 2 with trichloroacetic anhydride.[12] Cyclization of 2c has not been detected up to 110 °C in the absence of acid anhydride, and a triacylated species

Scheme I
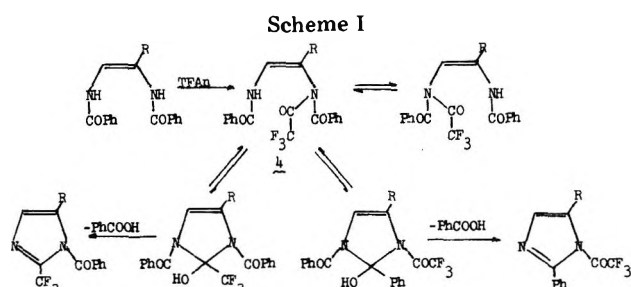
is presumed to be a requisite intermediate. The facility of the reaction with trifluoroacetic anhydride may be due, therefore, to its high reactivity as an acylating agent,[13] and/or the high electrophilic reactivity of the trifluoroacetyl carbonyl group in 4.

In view of the biological activity found for 2-fluorourocanic acid,[14] the trifluoromethyl analogue also became a goal of synthesis. It was already known that imidazoles with electronegative substituents at C-4 (or C-5) fail to undergo the Bamberger cleavage reaction.[15] Consistent with this property, urocanic acid (or its esters) did not undergo cleavage with benzoyl chloride, thus precluding synthesis by direct introduction of the trifluoromethyl group. In an alternative approach, we considered use of 4-hydroxymethylimidazole, but this compound also failed to undergo Bamberger cleavage.

The NMR spectra of ring protons in the trifluoromethylimidazoles are displaced downfield to an extent qualitatively consistent with the effect of a strong electronegative substituent. As expected, the substituent also reduces the values of pK_1 and pK_2 for the imidazole ring, to the extent predicted by Hammett correlations.[16]

Experimental Section[17]

2-Trifluoromethylimidazole (3a). A solution of 2.8 g (0.01 mol) of 2a[18] in 80 mL of trifluoroacetic anhydride was stirred and refluxed for 2 h, during which time the solution developed a reddish yellow color and a colorless precipitate separated. Another portion of 2.8 g of 2a was then added and refluxing was continued for 5 h. The solvent was removed by distillation and 100 mL of methanol was added to the residue. The solution was refluxed for 1 h and stored overnight at room temperature. A colorless precipitate was filtered off (1.2 g) which proved to be starting material (2a). The solvent was evaporated and the tarry residue (9.7 g) was applied to a column of silica gel 60 (250 mL). Elution with ether–petroleum ether (1:1) gave 0.55 g of Pauly-positive material. This fraction was sublimed (1 mm, 50–70 °C bath) to give 0.13 g (4.8%) of 3a as a colorless powder. Recrystallization from chloroform afforded needles: mp 145–146 °C; NMR (acetone-d_6) δ 7.29 (2, s, H-4,5).

Anal. Calcd for C₄H₃F₃N₂ (136.1): C, 35.31; H, 2.22; F, 41.88; N, 20.59. Found: C, 35.39; H, 2.21; F, 41.93; N, 20.66.

Further elution of the column with ethyl acetate gave ca. 5 g of a complex mixture of Pauly-negative materials, none of which have yet been identified. Numerous variations in procedure failed to improve the yield of 3a.

4(or 5)-Methyl-2-trifluoromethylimidazole (3b). A solution of 1.4 g (5 mmol) of 2b[19] in 80 mL of trifluoroacetic anhydride was stirred and refluxed. The starting material dissolved within a few minutes and a new, colorless product began to separate. Three additional portions (1.4 g each) of 2b were added at 1-h intervals and, after a total of 6 h of reflux, the solvent was distilled. The reddish yellow residue was dissolved in 100 mL of methanol and the solution was refluxed for 1 h. The solution was stored overnight at room temperature and a colorless, Pauly-negative precipitate (2.0 g) was separated. This material crystallized from ethyl acetate as needles (mp 220–222 °C, m/e 569). The methanol filtrate was evaporated and the yellow residue (11.2 g) was applied to a column of silica gel 60 (150 mL). Elution with ether–petroleum ether (1:1) first gave 2.2 g of a Pauly-negative material which crystallized from ethyl acetate (mp 121–122 °C, m/e 578). Continued elution gave 1.9 g of benzoic acid and, finally, 0.50 g of Pauly-positive material. The latter fraction was sublimed (1 mmHg, 50–70 °C bath) to give 0.113 g (3.8%) of 3b as a colorless powder. Recrystallization from water gave plates: mp 103–105 °C; NMR (acetone-d_6) δ 2.26 (3, s, CH₃), 6.96 (1, s, H-4 or 5).

Anal. Calcd for C₅H₅F₃N₂ (150.1): C, 40.01; H, 3.36; N, 18.66; F,

37.97. Found: C, 39.77; H, 3.43; N, 18.93; F, 37.78.

α-N-Benzoyl-2-trifluoromethylhistamine (3c). A solution of 4.13 g (0.01 mol) of **2c** (mp 198–199 °C)[20] in 80 mL of trifluoroacetic anhydride was stirred and refluxed for 1 h. A second portion of **2c** (4.13 g) was added and refluxing was continued for 5 h. The solvent was distilled and a solution of the residue in 100 mL of methanol was refluxed for 1 h. The solution was stored overnight at room temperature and a colorless, Pauly-negative precipitate (1.46 g) was separated. This material crystallized from ethanol (mp 261 °C dec, *m/e* 492). Evaporation of the methanol filtrate gave a tarry residue which was chromatographed on 200 mL of silica gel 60. Elution with ether gave 3.9 g (68.8%) of **3c** as pale yellow crystals. Recrystallization from benzene–tetrahydrofuran gave colorless plates: mp 179–180 °C; NMR (CDCl$_3$) δ 2.95 (2, t, *J* = 7 Hz, β-CH$_2$), 3.67 (2, t, *J* = 7 Hz, α-CH$_2$), 7.07 (1, s, H-4 or 5), 7.4–8.0 (5, m, C$_6$H$_5$).

Anal. Calcd for C$_{13}$H$_{12}$N$_3$F$_3$O (283.3): C, 55.13; H, 4.27; N, 14.83; F, 20.12. Found: C, 55.23; H, 4.42; N, 14.50; F, 19.98.

2-Trifluoromethylhistamine Dihydrochloride (3d). A solution of 2.13 g (7.5 mmol) of **3c** in 200 mL of 3 N hydrochloric acid and 15 mL of ethanol was heated on steam for 24 h. The reaction mixture was evaporated to dryness under reduced pressure. The residual material was freed of benzoic acid by trituration, twice with ether and twice with 2-propanol, giving 1.56 g (82.5%) of **3d·2HCl**. Recrystallization from ethanol gave colorless needles: mp 210–212 °C; NMR (D$_2$O) δ 3.14, 3.26 (4, q, A$_2$B$_2$, *J* = 6.0 Hz, α and β CH$_2$'s), 7.52 (1, s, H-4 or 5).

Anal. Calcd for C$_6$H$_8$N$_3$F$_3$·2HCl (252.1): C, 28.59; H, 4.00; N, 16.67; F, 22.61. Found: C, 28.36; H, 4.35; N, 16.42; F, 22.88.

α-N-Benzoyl-2-trifluoromethyl-L-histidine Methyl Ester (3e). A suspension of 4.71 g (0.01 mol) of **2e**[21] in 80 mL of trifluoroacetic anhydride was stirred and refluxed for 2 h (solution was complete after 0.5 h). An additional 4.71 g of **2e** was added and refluxing was continued for 5 h. The solvent was removed by distillation and a solution of the residual material in 100 mL of methanol was refluxed for 0.5 h. The solvent was evaporated and the residual material was chromatographed on 200 mL of silica gel 60. Elution of the column with ether gave benzoic acid, followed by **3e**. The Pauly-positive fractions were pooled and concentrated to give 4.8 g (70.3%) of light yellow crystals. Recrystallization from benzene gave **3e** as colorless plates: mp 157–159 °C; NMR (CDCl$_3$) δ 3.25 (2, d, *J* = 5.8 Hz, β-CH$_2$), 3.70 (3, s, OCH$_3$), 5.05 (1, t, *J* = 5.8 Hz, α-CH), 6.95 (1, s, H-4 or 5), 7.4–8.0 (5, m, C$_6$H$_5$); [α]^{20}D −37.7° (c 0.5, CH$_3$OH).

Anal. Calcd for C$_{15}$H$_{14}$F$_3$N$_3$O$_3$ (341.3): C, 52.79; H, 4.14; N, 12.31; F, 16.70. Found: C, 52.53; H, 4.17; N, 12.04; F, 16.29.

2-Trifluoromethyl-L-histidine Dihydrochloride (3f). A solution of 2.05 g (6 mmol) of **3e** in 200 mL of 3 N hydrochloric acid and 20 mL of ethanol was heated on steam for 24 h. The reaction mixture was concentrated to 100 mL and was extracted with three 50-mL portions of ether to remove benzoic acid. The aqueous layer was evaporated to dryness to give **3f·2HCl** as a colorless powder, mp 237–238 °C. This material was triturated twice with ether and was dried overnight in vacuo at 50 °C. Crystallization of the salt or of the neutral amino acid could not be effected: NMR (D$_2$O) δ 3.32 (2, d, *J* = 7.0 Hz, β-CH$_2$), 4.32 (1, t, *J* = 7.0 Hz, α-CH), 7.44 (1, s, H-4 or 5); [α]^{20}D −3.80° (c 0.6, H$_2$O, pH 1.9), −14.06° (c 5, H$_2$O, pH 7.2).

Anal. Calcd for C$_7$H$_8$O$_2$N$_3$F$_3$·2HCl (296.1): C, 28.40; H, 3.40; N, 14.19; F, 19.25. Found: C, 28.22; H, 3.32; N, 13.79; F, 19.08.

p*K* Determinations. p*K* values were obtained by titration in aqueous solution at 25 °C, calculations being based on 7–10 readings. For **3a**: pK_1 = 2.06 ± 0.03; pK_2 = 10.00 ± 0.05. For **3b**: pK_1 = 2.54 ± 0.02; pK_2 = 10.34 ± 0.06.

Registry No.—**2a**, 35511-28-3; **2b**, 66675-19-2; **2c**, 66675-20-5; **2e**, 66675-21-6; **3a**, 66675-22-7; **3b**, 66675-23-8; **3c**, 66675-24-9; **3d·2HCl**, 66675-25-0; **3e**, 66675-26-1; **3f·2HCl**, 66675-27-2.

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Acid-Catalyzed Rearrangements of the Dihydroxyacetone Side Chain in Steroids during Ketal Exchange

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Discussion

The synthesis of steroid derivatives often makes it necessary to protect the hydroxy groups that are present. One method of accomplishing this goal is by converting the substrate into a ketal or an ortho ester. Gardi et al.[2] reported that the reaction of hydrocortisone and prednisolone with 2,2-diethoxypropane gave not only the expected 17α,21-acetonides (1 and 2, respectively) but also the 17α,21-acetonide 11β-(1'-ethoxy-1'-methyl)ethyl ethers (3 and 4, respectively). Similarly, the reaction of hydrocortisone with triethyl orthoacetate gave 17α,21-(1'-ethoxy)ethylidenedioxy 11β-(1',1'-diethoxy)ethyl ether (5) in addition to the expected 17α,21α-(1'-ethoxy)-ethylidenedioxy derivative (6).

The Italian workers[2,3] relied on relatively mild conditions which involved a brief distillation of benzene suspensions of the steroid in the presence of a ketal, acetal, or ortho ester and a trace of an acid catalyst. However, in our hands this procedure generally did not lead to the previously reported protected steroid by-products. Instead, ketal exchange yielded 10 and 11 which are formally the result of a Mattox[4] rearrangement although in one reaction the Mattox rearrangement product itself underwent exchange at the 11β position to yield 17. Only if the 21 position of the dihydroxyacetone side chain was acylated was an 11β-ether obtained without rearrangement, and this required a much longer reaction time.[2] The Mattox rearrangement of a dihyroxyacetone side chain is commonly encountered whenever steroids come in contact with acidic media; however, this is its first observation during acetonide formation.[5]

The reaction of hydrocortisone with 2,2-dimethoxypropane consistently gave four products: a trace of 11β-hydroxy-3-methoxy-3,5-pregnadien-20-one 17α,21-acetonide (9),[6] 40–50% of hydrocortisone 17α,21-acetonide (1),[2] 12–15% of 10, and 2–3% of 11. 10 and 11 had almost identical mass spectra and infrared spectra but their NMR spectra and TLC behavior were decidedly different. The mass spectra of 10 and 11 showed an M$^+$ at (*m/e*) 416 instead of at (*m/e*) 489 for the
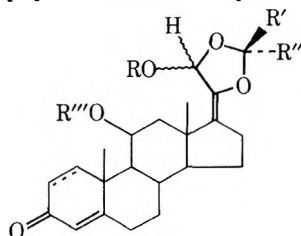
Scheme I
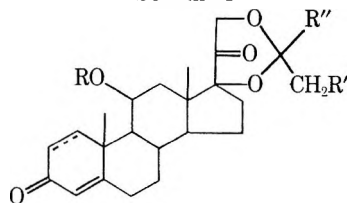
1, R, R' = H; R'' = CH₃
2, R, R' = H; R'' = CH₃; Δ¹

3, R = (CH₃)₂COC₂H₅; R' = H; R'' = CH₃

4, R = (CH₃)₂COC₂H₅; R' = H; R'' = CH₃; Δ¹

5, R = CH₃C(OC₂H₅)₂; R' = H; R'' = OC₂H₅
6, R, R' = H; R'' = OC₂H₅
7, R, R', R'' = H

8, R = CH₃CHOC₂H₅; R', R'' = H

9

13, R = H
14, R = OH

18, R = CH₃CHOC₂H₅; R' = H
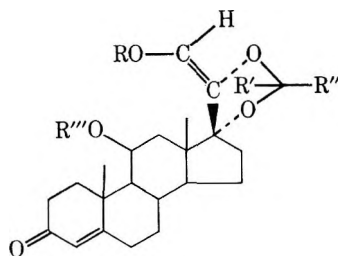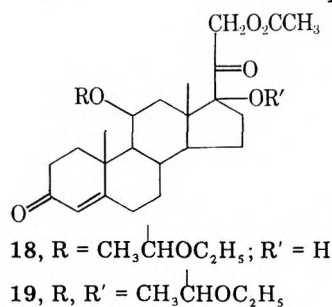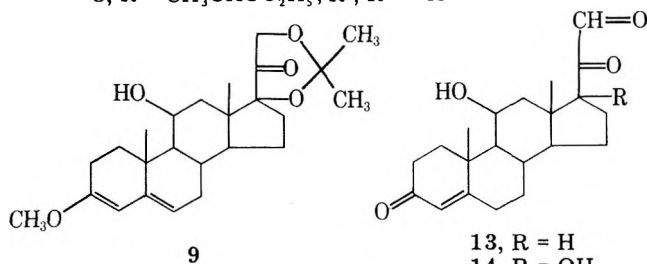
19, R, R' = CH₃CHOC₂H₅

11, R, R', R'' = CH₃; R''' = H

17, R = C₂H₅; R' = H; R'' = CH₃; R''' = CH₃CHOC₂H₅

10, R, R', R'' = CH₃; R''' = H
12, R = C₂H₅; R', R'' = CH₃; R''' = H
15, R = C₂H₅; R', R'' = CH₃; R''' = H; Δ¹

16, R = C₂H₅; R' = CH₃; R'' = H; R''' = CH₃CHOC₂H₅

expected bisacetonide;[2] the infrared spectra exhibited an O–H absorption. The integration of the region from δ 3.0–0.8 in the NMR spectra of 10 and 11 did not show the expected two sets of (CH₃)₂C(O–)₂ absorptions;[2] only one set of absorptions was observed. They also showed that the 21-CH₂OH group had been degraded. Instead of a two-proton absorption, an ab-

sorption which integrated for only one proton was found downfield in the region from δ 5.6–5.3. The NMR spectra of 10 and 11 also contained absorptions due to CH₃O.

Hydrolysis of 10 and 11 confirmed that they were not the by-products previously isolated.[2] Instead of hydrocortisone, aldehydes were isolated under conditions from which hydrocortisone was obtained from the acetonide 1.[7] Aldehyde 13 which was obtained by hydrolysis of 10 was identified by comparison with a sample of aldehyde obtained by an independent synthesis.[8] The spectral properties of aldehyde 14 from the hydrolysis of 11[9] corresponded in all important points to the properties of 13.

Since reaction of 13 with 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid did not afford 10, it is not likely that 13 is formed first and then undergoes reaction with 2,2-dimethoxypropane although hydrocortisone under the same conditions but in the absence of the 2,2-dimethoxypropane does produce trace amounts of 13. Also, since further reaction of 1 with 2,2-dimethoxypropane did not produce 9, 10, or 11, acetonide 1 is apparently not involved in the formation of 10 or 11.

Reaction of hydrocortisone with 2,2-diethoxypropane in the presence of p-toluenesulfonic acid gave the same qualitative results as its reaction with 2,2-dimethoxypropane,[10] the structure of 12 being assigned by spectroscopic comparison with 10 and by elemental analysis. Reaction of prednisolone with 2,2-diethoxypropane also failed to give the previously reported bisacetonide,[2] giving instead 15 which is analogous to the products isolated from the reaction of ketals with hydrocortisone.

Only in two cases was it possible to obtain 11β-ethers. Reaction between hydrocortisone and 1,1-diethoxyethane gave a complex mixture which could only partially be separated. Compound 7, as well as the rearranged 11β-ether 16, was isolated and fully characterized. Evidence for the presence of 8 and 17 in the remaining mixture was based on the mass spectra M⁺ (m/e) 460 for 8 and 488 for 17. Reaction between 1,1-diethoxyethane and hydrocortisone 21-acetate gave not only the 11β- (18) but also the bis[11β,17α-(1'-ethoxy)ethoxy] derivative (19). It required 2 h to effect complete dissolution of the steroid reactant and resulted in rather poor yields of the desired products.[11]

Reinvestigation of the reaction of hydrocortisone with trialkyl orthoacids gave only the previously reported diastereomers resulting from exchange and no by-products or rearrangement products.

In conclusion, it has been shown that the by-products obtained during ketal exchange with steroids were not bisketals but instead were the result of a Mattox rearrangement of an intermediate in the ketal exchange.

Experimental Section

Reaction of 2,2-Dimethoxypropane with Hydrocortisone. All exchange reactions, unless otherwise stated, were run in the following manner. A modification of the procedure of Gardi et al.[2] was used. Hydrocortisone (12.0 g, 0.033 mol) was suspended in 1500 mL of boiling benzene and 100 mL of benzene was distilled. Then 16 mL of dimethoxypropane was added to the benzene suspension and 6 mL

of a hot solution of 0.4% *p*-toluenesulfonic acid in benzene was added immediately afterwards. Benzene was distilled at a rapid rate from the suspension and after 15 min a clear solution was obtained; the distillation was continued for 10 min more. Pyridine (0.5 mL) was added to quench the reaction which then was cooled to room temperature. The benzene was evaporated in vacuo and the resulting residue was chromatographed on SilicAR CC-7 (600 g) using ether–heptane 1:9 to 2:8 to ether–acetone–heptane 2:1:7 as the eluents in the above order to give four fractions.

The first fraction (<50 mg) was obtained as a white solid; an analytically pure sample was not obtained. The NMR spectrum of the crude material suggested its identity as 11β-hydroxy-3-methoxy-3,5-pregnadien-20-one 17α,21-acetonide (9): TLC (silica gel, ether) R_f 0.57; NMR (CDCl$_3$) δ 5.10 (broad s, 2, CH=C), 4.65–4.35 (s, 1, CHO), 4.17 (AB quartet, J = 18 Hz, $\Delta_{\nu AB}$ = 12.5 Hz, 2, O=CCH$_2$O), 3.60 (s, 3, CH$_3$O), 1.47 and 1.43 (two s, 6, -O(CH$_3$)$_2$CO-), 1.21 (s, 3, CH$_3$C), 0.91 (s, 3, CH$_3$C), and 3.0–0.8 (m, 17, CH$_2$ and CH, and 1, OH).

The second fraction deposited 0.26 g (mp 173–177 °C) of 11β-hydroxy-3-methoxy-4,17(20)-pregnadien-3-one 20,21-acetonide (10) as fine white needles when the ether was allowed to evaporate at room temperature: TLC (silica gel, ether) R_f 0.44; IR (KBr) 3440 (s, OH), 1710 and 1605 (w), and 1645 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 5.66 (s, 1, O=CCH=C), 5.33 (s, 1, OCHO), 4.5–4.3 (m, 1, CHOH), 3.4 (s, 3, OCH$_3$), 1.53, 1.50, and 1.47 (three s, 9, CH$_3$C and O(CH$_3$)$_2$CO), and 1.17 (s, 3, CH$_3$C); [α]^{26}D +150° (c 0.59, CH$_3$OH); mass spectrum (*m/e*) 416 (M$^+$); UV (CH$_3$OH) λ_{max} 242 nm (ε 15 900).

Anal. Calcd for C$_{25}$H$_{36}$O$_5$: C, 72.08; H, 8.71. Found: C, 71.93; H, 8.79.

The mother liquor from the second fraction was concentrated and the resulting residue was crystallized from ether–hexane to give 1.88 g (mp 164–168 °C) of 10 as white crystals. This second crop of crystals had the same infrared, UV, and mass spectrum as the first as well as the same TLC and elemental analysis, but the optical rotation ([α]^{26}D + 123° (c 0.55, CH$_3$OH)) and NMR spectra were different with the methoxy signal at δ 3.4 and the methyl signal at δ 1.17 being split.[12]

The third fraction gave 323 mg (mp 144–146 °C) of 11β-hydroxy-21-methoxy-4,20-pregnadien-3-one 17α,20-acetonide (11) as a fibrous white solid from heptane: TLC (silica gel, ether) R_f 0.36; IR (KBr) 3400 (s, OH), 1710 and 1605 (w), and 1645 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 5.63 (s, 1, O=CCH=C), 5.5–5.35 (m, 1, C=CHO), 4.5–4.3 (m, 1, CHOH), 3.37 (s, 3, OCH$_3$), 1.50, 1.43, and 1.40 (three s, 9, CH$_3$C and O(CH$_3$)$_2$CO), and 1.13 (s, 3, CH$_3$C); UV (CH$_3$OH) λ_{max} 242 nm (ε 16 600); [α]^{26}D +163° (c 0.45, CH$_3$OH); mass spectrum (*m/e*) 416 (M$^+$).

Anal. Calcd for C$_{25}$H$_{36}$O$_5$: C, 72.08; H, 8.71. Found: C, 72.19, H, 8.87.

The fourth fraction deposited 3.71 g (mp 184–185 °C) (lit.[2] mp 194–195 °C) of 11β-hydroxy-4-pregnene-3,20-dione 17α,21-acetonide (1) as fine white needles: TLC (silica gel, ether) R_f 0.28; IR (KBr) 3460 (s, OH), 1700 and 1600 (m), and 1645 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 5.67 (s, 1, O=CCH=C), 4.5–4.3 (m, 1, CHOH), 4.3–4.15 (m, 2, OCH$_2$C=O), 1.47 (s, 9, O(CH$_3$)$_2$CO and CH$_3$C), and 0.93 (s, 3, CH$_3$C): UV (CH$_3$OH) λ_{max} 242 nm (ε 16 300); [α]^{27}D +147° (c 0.62, CH$_3$OH), (lit.[2] [α]D +142° (dioxane)); mass spectrum (*m/e*) 402 (M$^+$).

Anal. Calcd for C$_{24}$H$_{34}$O$_5$: C, 71.61; H, 8.51. Found: C, 71.46; H, 8.41.

The mother liquor from the fourth fraction was concentrated to give 0.79 g (mp 181–182 °C), 0.75 g (mp 177–179 °C) and 0.57 g (mp 176–178 °C) of the 17α,21-acetonide as successive crops of crystals which were identical in all other ways with the first crop of crystals.

The following reactions were run in a similar manner:

Reaction of 2,2-Diethoxypropane with Hydrocortisone. This reaction gave 242 mg (mp 156–159 °C, 7% yield from ether–hexane, 20:20) of 11β-hydroxy-21-ethoxy-4,17(20)pregnadien-3-one 20,21-acetonide (12) as the first fraction: IR (KBr) 3470 (s, OH), 1710 and 1605 (w), and 1650 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 5.70 (s, 1, CH=C), 5.40 (s, 1, OCHO), 4.5–4.3 (m, 1, CHOH), 3.95–3.4 (m, 2, CH$_2$O), 2.7–0.7 (m, 33, CH$_3$, CH$_2$, and CH); [α]^{29}D + 101 ° (c 1, CH$_3$OH); mass spectrum (*m/e*) 430 (M$^+$); TLC (silica gel, ether) R_f 0.48.

Anal. Calcd for C$_{26}$H$_{38}$O$_5$: C, 72.51; H, 8.89. Found: C, 72.25; H, 9.03.

The second fraction (1.04 g, mp 171–173 °C 30% yield) gave 1 which was identical with 1 obtained above.

Reaction of 1,1-Diethoxyethane with Hydrocortisone. This reaction gave 1.54 g (mp 45–55 °C) of 11β-(1′-ethoxy)ethoxy-21-ethoxy-20,21-ethylidenedioxy-4,17(20)-pregnadien-3-one (16) as the first fraction: 12% yield; TLC (silica gel, ether) R_f 0.64; IR (KBr) 1660 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 5.70 (s, 1, O=CCH=C), 5.65–5.35

(m, 2, CH$_3$CH(O-)$_2$ and C=CCH(O-)$_2$), 4.87 (q, 1, J = 5 Hz, CH$_3$CH(O-)$_2$), 4.45–4.10 (m, 1, CHO), 3.9–3.3 (m, 4, CH$_2$O); [α]^{25}D +106° (c 0.49, dioxane); mass spectrum (*m/e*) 488 (M$^+$).

Anal. Calcd for C$_{29}$H$_{44}$O$_6$: C, 71.28; H, 9.08. Found: C, 71.01; H, 9.34.

A number of other fractions were obtained at this point which were mixtures. Structures for the components of the mixtures suggested by mass spectra and NMR spectra are presented in the discussion.

The final fraction (1.30 g, mp 191–195 °C, from ether–cyclohexane) was identified as 11β-hydroxy-17α,21-ethylidenedioxy-4-pregnene-3,20-dione (7): 13% yield; TLC (silica gel, ether) R_f 0.33; IR (KBr) 3440 (s, OH) and 1695 and 1655 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 5.70 (s, 1, O=CCH=C), 5.0 (q, 1, J = 5 Hz, CH$_3$CH(O-)$_2$), 4.65–4.35 (m, 1, CHO), 4.32 (s, 2, O=CCH$_2$O), 1.47 (s, 3, CH$_3$C), 1.00 (s, 3, CH$_3$C), 1.41 (d, J = 5 Hz, 3, CH$_3$CH(O-)$_2$), and 2.8–0.8 (m, 17, CH$_2$, CH, 1, OH); [α]^{27}D +148° (c 0.5, dioxane); mass spectrum (*m/e*) 388 (M$^+$).

Anal. Calcd for C$_{23}$H$_{32}$O$_5$: C, 71.10; H, 8.30. Found: C, 71.49; H, 8.47.

Reaction of 1,1-Diethoxyethane with Hydrocortisone 21-Acetate. This reaction gave 0.86 g (an oil) of 11β,17α-bis[(1′-ethoxy)ethoxy]-21-acetyloxy-4-pregnene-3,20-dione (19) as the first fraction: 7% yield; TLC (silica gel, ether) R_f 0.43; IR (KBr) 1740, 1720, and 1660 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 5.70 (s, 1, O=CCH=C), 5.07 (AB quartet, J = 16 Hz. $\Delta_{\nu AB}$ = 12 Hz, 2, O=CCH$_2$O), 4.95–4.5 (m, 2, CH$_3$CH(O-)$_2$), 4.5–4.2 (m, 1, CHO), 3.6–3.05 (m, 4, CH$_3$CH$_2$O-), 2.17 (s, 3, CH$_3$C=O), 1.45 (s, 3, CH$_3$C), 0.81 (s, 3, CH$_3$C), and 2.7–0.7 (m, 29, CH, CH$_2$, and CH$_3$); [α]^{25}D +127° (c 0.5, dioxane); mass spectrum (*m/e*) 548 (M$^+$).

The second fraction (3.83 g, mp 127–129 °C from petroleum ether bp 30–37 °C) was identified as 11β-(1′-ethoxy)ethoxy-17α-hydroxy-21-acetyloxy-4-pregnene-3,20-dione (18): 32% yield; TLC (silica gel, ether) R_f 0.25; IR (KBr) 3500 (s, OH) and 1730, 1715, and 1645 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 5.7 (s, 1, O=CCH=C), 4.97 (s, 2, O=C-CH$_2$O), 4.70 (q, J = 5 Hz, 1, CH$_3$CH(O-)$_2$), 4.5–4.35 (m, 1, CHO), 3.55 (q, J = 7 Hz, CH$_3$CH$_2$O), 2.18 (s, 3, CH$_3$C=O), 1.45 (s, 3, CH$_3$C), 0.87 (s, 3, CH$_3$C), and 2.8–0.8 (m, 23, CH, CH$_2$, CH$_3$, 1, OH); [α]$^{24.5}$D +188° (c 0.53, dioxane); mass spectrum (*m/e*) 476 (M$^+$).

Anal. Calcd for C$_{27}$H$_{40}$O$_7$: C, 68.04; H, 8.46. Found: C, 68.03; H, 8.41.

Reaction of 2,2-Diethoxypropane with Prednisolone. This reaction gave 0.38 g (mp 167–170 °C) of 11β-hydroxy-21-ethoxy-1,4,17(20)-pregnatrien-3-one 20,21-acetonide (15) as white crystals from the first fraction. The filtrate was further concentrated to give 0.21 g (mp 147–151 °C, total yield of 17%) more of 15. The samples were identical by TLC (silica gel, ether): IR (KBr) 3380–3360 (m, OH), 1710 (w), 1600 and 1580 (m), and 1640 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 6.7 (AX quartet, 2, J_{AX} = 10 Hz, $\Delta_{\nu AX}$ = 63 Hz, O=CCH=CH=CH), 5.97 (sharp m, 1, O=CCH=C), 5.33 (sharp m, 1, =CCH (O-)$_2$), 4.5–4.3 (m, 1, CHOH), 3.85–3.35 (m, 2, CH$_3$CH$_2$O), 3.0–0.7 (m, 29, CH$_3$, CH$_2$, CH, OH); [α]^{25}D + 93.5° (c 0.5, C$_2$H$_5$OH); mass spectrum (*m/e*) 428 (M$^+$).

Anal. Calcd for C$_{26}$H$_{36}$O$_5$: C, 72.86; H, 8.42. Found: C, 72.41; H, 8.10.

The second fraction (R_f 0.38) was concentrated in vacuo to give 1.47 g (mp 202–210 °C, 44% yield) of prednisolone 17α,21-acetonide (2) as a white solid: IR (KBr) 3360 (m, OH), 1705 (m, C=O), 1645 (s, C=O), and 1600 cm^{-1} (m, C=C); NMR (CDCl$_3$) δ 6.7 (AX quartet, 2, J_{AX} = 10 Hz, $\Delta_{\nu AX}$ = 63 Hz, O=CCH=CH); 5.97 (sharp m, 1, O=CCH=C), 4.6–4.35 (m, 1, CHOH), 4.2–4.05 (m, 2, O=CCH$_2$OC), 3.0–0.7 (m, 25, CH$_3$, CH$_2$, CH, 1, OH); [α]^{25}D +110° (c 1, dioxane) (lit.[2] [α]D +104° (dioxane)); mass spectrum (*m/e*) 400 (M$^+$).

Anal. Calcd for C$_{24}$H$_{32}$O$_5$: C, 71.97; H, 8.05. Found: C, 71.85; H, 7.83.

The Hydrolysis of 11β-Hydroxy-21-methoxy-4,17(20)-pregnadien-3-one 20,21-Acetonide (10). The procedure of Robinson et al.[7] was used. The 20,21-acetonide (10) (200 mg) was suspended in 1.5 mL of glacial acetic acid and 0.5 mL of water and heated at 95 °C for 1 min. The solution that resulted was evaporated to dryness and the residue was extracted with 100 mL of ether. The ether solution exhibited only one spot upon analysis by TLC (silica gel, ether). It was dried over Na$_2$SO$_4$ and concentrated to 20 mL then diluted with 80 mL of heptane to give 143 mg (mp 178–190 °C) of 11β-hydroxy-3,20-dioxo-4-pregnen-21-al (13) as a tan solid whose spectral properties (NMR, IR, UV) and TLC were identical with those of the aldehyde prepared by a known route.[8]

The Hydrolysis of 11β-Hydroxy-21-methoxy-4,20(21)-pregnadien-3-one 17α,20-Acetonide (11). The same procedure as above was used except that the residue obtained upon concentration of the reaction mixture was crystallized from CH$_2$Cl$_2$–heptane (2:20 mL) to give 55 mg (from 95 mg of 11, mp 110.5–115 °C foaming) of

$11\beta,17\alpha$-dihydroxy-3,20-dioxo-4-pregnen-21-al (**14**) with 0.5 M CH_2Cl_2 as a solvate: TLC (silica gel, ether) R_f 0.23; IR (KBr) 3500 (w), 3400 (m, OH) and 1655 and 1635 cm^{-1} (s, C=O); NMR (CDCl$_3$) δ 9.77 (s, 1, CH=O), 6.1–5.7 (m, 1, OH), 5.73 (s, 1, O=CCH=C), 5.31 (s, 1, CH$_2$Cl$_2$), 4.6–4.35 (m, 1, CHO), 1.5 (s, 3, CH$_3$C), 1.37 (s, 3, CH$_3$C), and 2.8–0.85 (m, 17, CH, CH$_2$, and 1, OH); UV (CH$_3$OH) λ_{max} 242 nm (ϵ 17 000) and 278.5 nm (ϵ 13 300); $[\alpha]^{25}$D +117.7° (c 0.95, dioxane); mass spectrum (m/e) 359 (M$^+$ − 1).

Anal. Calcd for $C_{21}H_{28}O_5 \cdot 0.5CH_2Cl_2$: C, 64.08; H, 7.25. Found: C, 64.30; H, 7.15.

The NMR and mass spectra of the crude product were identical with those of the pure aldehyde as its solvate except for the presence of the singlet at δ 5.31 in the NMR spectrum due to CH$_2$Cl$_2$.

Registry No.—**1**, 34332-34-8; **2**, 13542-30-8; **7**, 66777-47-7; **8**, 66777-48-8; **9**, 55388-47-1; **10** isomer 1, 66777-49-9; **10** isomer 2, 66777-50-2; **11**, 66777-51-3; **12**, 66777-52-4; **13**, 20287-97-2; **14**, 14760-49-7; **15**, 66777-53-5; **16**, 66777-54-6; **17**, 66777-55-7; **18**, 66777-56-8; **19**, 66777-57-9; hydrocortisone, 50-23-7; 2,2-dimethoxypropane, 77-76-9; 2,2-diethoxypropane, 126-84-1; 1,1-diethoxyethane, 105-57-7; hydrocortisone 21-acetate, 50-03-3; prednisolone, 50-24-8.

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(11) The fact that the acetonide **1** does not undergo further exchange at the 11β position while hydrocortisone 21-acetate and 11β-hydroxy-21-ethoxy-20,21-ethylidenedioxy-4,17(20)-pregnadien-3-one do suggests that the substituents on the dihydroxyacetone side chain affect the reactivity of the 11β-hydroxy: R. Gardi, R. Vitali, G. Falconi, and A. Ercoli, *J. Med. Chem.*, **15**, 556 (1972).
(12) These results are consistent with **10** being a mixture of two geometrical isomers.

Acid-Catalyzed Addition of Secondary Phosphines to Vinyl Ethers

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Although certain olefins with electron-withdrawing substituents (e.g., acrylonitrile[1] or alkyl acrylates[2]) add P–H bonds without catalysts, phosphine addition to double bonds normally requires radical initiation,[3,4] or an acidic or basic catalyst.[4] Because of the relatively high basicity of substituted phosphines, the acid-catalyzed reactions require nearly stoichiometric amounts of acid and do not proceed to tertiary phosphines.[5] We have found, however, that vinyl ethers add secondary phosphines in the presence of catalytic amounts of acid to yield the tertiary phosphine (Markownikoff product) in good yields.

Results and Discussion

Heating a mixture of di-*tert*-butylphosphine and methyl vinyl ether without added catalyst to above 130 °C yields after several hours di-*tert*-butyl(1-methoxyethyl)phosphine, a product unexpected from base- or radical-catalyzed reactions.[4] In fact, adding catalytic amounts (<5 mol %) of acid to the mixtures greatly reduces the reaction time. Similarly, diethylphosphine reacts with methyl vinyl ether and acid to yield diethyl(1-methoxyethyl)phosphine (eq 1).

$$(C_2H_5)_2PH + CH_2CHOCH_3 \xrightarrow[\text{AIBN}]{\text{H}^+} (C_2H_5)_2PCH(CH_3)OCH_3 \quad (1)$$

$$\searrow (C_2H_5)_2PCH_2CH_2OCH_3 \quad (2)$$
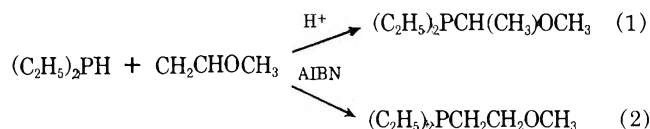
Using the same reagents (diethylphosphine and methyl vinyl ether) and a radical initiator, the reaction is regioselective for the *opposite* addition product, diethyl(2-methoxyethyl)phosphine (eq 2). However, attempts to perform this reaction with di-*tert*-butylphosphine gave no addition, except for slow formation of the Markownikoff product. (The expected product, di-*tert*-butyl(2-methoxyethyl)phosphine, was prepared by another method for characterization. It is a stable compound under workup and distillation conditions, with a VPC retention time different from that of the 1-methoxyethyl isomer, and would have been detected by VPC and NMR had it been present.) Although reasons for the failure of $[(CH_3)_3C]_2PH$ to add to the olefin by a radical process are not clear, steric hindrance may contribute to the unreactivity of the $[(CH_3)_3C]_2P\cdot$ radical ($[(CH_3)_3C]_2CH\cdot$ is a persistent radical[6]).

The ability of vinyl ethers to react by an acid-catalyzed process in the presence of strongly basic secondary and tertiary alkyl phosphines[7] contrasts with the behavior reported for other olefins;[5] this reaction appears to be more closely related to the acid-catalyzed addition of phosphines to aldehydes,[8,9] which proceeds through the tertiary phosphine to a quaternary phosphonium salt, [(RCHOH)$_4$P]X. The character of the oxygen-stabilized carbonium ion intermediate in our proposed mechanism (eq 3) reflects this similarity.

$$BH^+ + CH_2=CHOR \rightleftharpoons B$$

$$+ CH_3CH^+OR \xrightarrow{R'_2PH} R'_2PC(CH_3)HOR + BH^+ \quad (3)$$

$$B = R'_2PH, R'_2PC(CH_3)HOR$$
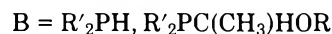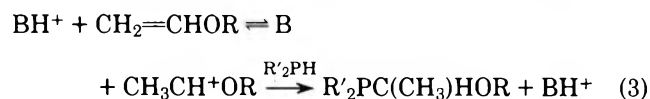
Experimental Section

Di-*tert*-butylphosphine[10,11] and diethylphosphine[12] were prepared by literature methods. These compounds and the products are air sensitive and were handled under an atmosphere of prepurified N$_2$. ^{1}H NMR spectra were recorded on a Varian EM-360A instrument. Vapor-phase chromatographic analyses were performed on a Hewlett-Packard 5840 instrument using 20 in. × ^{1}/$_8$ in. UCW-982 on Chromosorb W columns. Carbon–hydrogen analyses were performed in the Union Carbide Analytical Section by Mr. J. T. Hildebrand; satisfactory analyses were obtained on methiodide and PtCl$_2$ derivatives of all of the products. Methiodide derivatives were prepared by adding an acetone solution of methyl iodide to an acetone solution of the phosphine; the product crystallizes after several hours. Platinum(II) derivatives of the formula PtCl$_2$(phosphine)$_2$ were prepared by stirring the phosphine with Na$_2$PtCl$_4$ or PtCl$_2$(NCC$_6$H$_5$)$_2$ in methanol and crystallizing the product from CH$_2$Cl$_2$–methanol.

Reactions of Di-*tert*-butylphosphine with Methyl Vinyl Ether, with and without Acid. Two NMR tubes, one containing about 0.02 g of CF$_3$CO$_2$H (0.18 mmol), were charged with 0.3 g of di-*tert*-butylphosphine (2.1 mmol) and about 0.4 mL of methyl vinyl ether (9 mmoles) was condensed into each. The contents were frozen and the tubes were flame-sealed under vacuum. NMR spectra were recorded both before and after heating at 130 °C for 30 min. The tube without added acid showed no discernible reaction; the tube with acid exhibited about 70% conversion to di-*tert*-butyl(1-methoxyeth-

yl)phosphine. The tubes were opened, and VPC analyses confirmed these results.

Reactions of Di-*tert*-butylphosphine with Methyl Vinyl Ether, with and without AIBN. Two NMR tubes, one containing 0.05 g of AIBN (0.3 mmol), were charged with 0.3 g of di-*tert*-butylphosphine (2.1 mmol) and about 0.4 mL of methyl vinyl ether (9 mmol) was condensed into each. The contents were freeze–thaw-degassed and the tubes were sealed under vacuum. Both were heated at 80 °C for 5 h; no reaction was observed by NMR. The temperature was then raised to 140 °C, and after 4 h at this level a reaction was beginning in the tube without AIBN. After 18 h more, this reaction had gone to completion, yielding di-*tert*-butyl(1-methoxyethyl)-phosphine. The reaction in the other tube was also yielding the same product, but was less than 50% complete. A reaction at 140 °C with di-*tert*-butyl peroxide in place of AIBN gave similar results.

Di-*tert*-butyl(1-methoxyethyl)phosphine. An excess of methyl vinyl ether (4 mL, 90 mmol) was condensed into a heavy-walled glass tube containing a mixture of 4.0 g of di-*tert*-butylphosphine (27 m moles) and 0.1 mL of trifluoroacetic acid (0.6 mmol). The contents were frozen and the tube was flame-sealed under vacuum, then heated to 130 °C for 1.5 h. The contents were distilled (bp 54–56 °C (0.4 mm)) to give 3.38 g (60%) of the product: ^{1}H NMR (neat) δ 1.15 (d, $^3J_{PH}$ = 10.5 Hz, 9 H, C(CH$_3$)$_3$), 1.22 (d, $^3J_{PH}$ = 10.5 Hz, 9 H, C(CH$_3$)$_3$, diastereotopic *tert*-butyl groups), 1.45 (d of d, $^3J_{HH}$ = 7 Hz, $^3J_{PH}$ = 15 Hz, 3 H, CH$_3$), 3.20 (s, 3 H, OCH$_3$), 3.72 (q of d, $^3J_{HH}$ = 7 Hz, $^2J_{PH}$ = 3 Hz, 1 H, CH).

Diethyl(1-methoxyethyl)phosphine. Excess methyl vinyl ether (4 mL, 90 mmol) was condensed onto a mixture of 2.0 g of diethylphosphine (22 mmol) and 0.05 mL of CF$_3$CO$_2$H (0.3 mmol) in a heavy-walled glass tube. The tube was then sealed, heated at 130 °C for 3 h, cooled, and opened. Vacuum distillation (bp 90–93 °C (40 mm)) gave 2.3 g (70%) of the product: ^{1}H NMR (CDCl$_3$) δ 0.7–1.7 (m, 13 H, CH$_2$CH$_3$ and CH$_3$), 3.38 (s, 3 H, OCH$_3$), 3.55 (m, 1 H, CH).

Di-*tert*-butyl(2-methoxyethyl)phosphine. A solution of [(CH$_3$)$_3$C]$_2$PLi[13] in 120 mL of THF (distilled from LiAlH$_4$) was prepared from 7.85 g of di-*tert*-butylphosphine (53.8 mmol) and 37 mL of 1.8 M phenyllithium solution (66 mmol). To this was added 6.5 g (69 mmol) of 2-chloroethyl methyl ether[14] (prepared from 2-methoxyethanol, thionyl chloride, and pyridine) in 50 mL of THF. The mixture was stirred for 1 h, and then 5 mL of methanol was added. Solvents were removed by distillation at atmospheric pressure, leaving a thick mixture. About 30 mL of ethyl ether was added; the suspension was filtered, washed with 100 mL of H$_2$O, and dried over MgSO$_4$. Vacuum distillation (bp 65–70 °C (0.15 mm)) gave 6.55 g (60%) of the product: ^{1}H NMR (CDCl$_3$) δ 1.22 (d, $^3J_{PH}$ = 11 Hz, 18 H, (CH$_3$)$_3$C), 1.70 (m, 2 H, PCH$_2$), 3.30 (s, 3 H, OCH$_3$), 3.50 (m, 2 H, OCH$_2$).

Diethyl(2-methoxyethyl)phosphine. Excess methyl vinyl ether (1.5 mL, 34 mmol) was condensed into a mixture of 0.95 g of diethylphosphine (11 mmol) and 0.10 g of AIBN (0.6 mmol) in a heavy-walled glass tube. The tube was sealed and heated at 80 °C for 2 h. Vacuum distillation (bp 96–99 °C (40 mm)) of the contents gave 0.98 g (64%) of the product: ^{1}H NMR (CDCl$_3$) δ 0.7–1.5 (m, 10 H, CH$_2$CH$_3$), 1.6 (m, 2 H, PCH$_2$), 3.35 (s, 3 H, OCH$_3$), 3.50 (overlapping triplets, $^3J_{HH}$ and $^3J_{PH}$ = 8 Hz, 2 H, OCH$_2$).

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Stereochemistry of the Photoinduced Addition of Methanol to Pummerer's Ketone, a 2-Cyclohexenone

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By using methanol-*d*, we recently showed that the photoinduced addition of methanol to 2-cycloheptenone, 2-cyclooctenone, and related compounds involves two steps: (a) photoisomerization to the *trans*-cycloalkenone, and (b) regio- and stereospecific syn addition of methanol to the ground state trans ketone.[1,2]
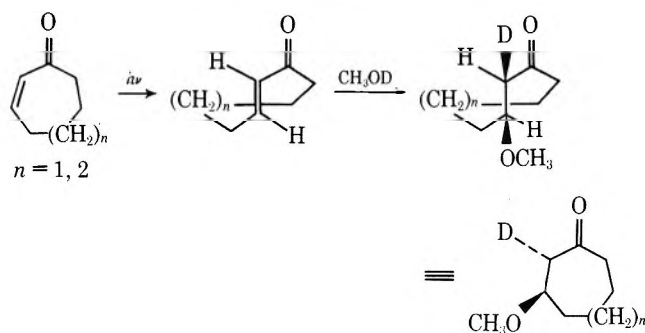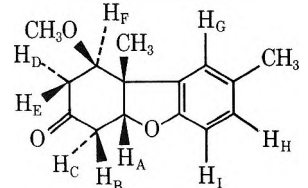

It was desirable to extend these studies to a 2-cyclohexenone, where photoisomerization to a trans ketone presumably would be more difficult.[3] Unfortunately, irradiation of 2-cyclohexenone itself in methanol gives only a 0.7% yield of 3-methoxycyclohexanone,[4] too low for convenient stereochemical study. Several derivatives of 2-cyclohexenone also give only disappointingly small yields of alcohol or water addition products.[5] The only exception we know of is Pummerer's ketone (1),[6] which is reported to give the crystalline methanol adduct 2 in 79% yield.[7] Accordingly, we studied and
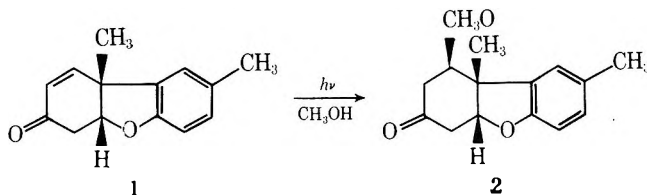
report here the stereochemistry of this reaction with CH$_3$OD, and also the isotope effect for the addition.

Results

Although we confirm the overall stereochemical assignment[7] of the methoxyl and angular methyl in 2 as being cis, we find some discrepancies in the previous[7] proton NMR assigments. Since the correct assignments, particularly those for H$_D$ and H$_E$, were essential for establishing the stereochemistry of CH$_3$OD addition, we examined the 180 MHz proton spectrum of 2 in detail. The results, with the previous and new assignments, are given in Table I. The previous assignments of H$_D$ and H$_E$ should be reversed, as should those

<div align="center">

Table I. The ¹H NMR Assignments of 2

</div>

	assignment, δ^a			coupling constants, Hz	
proton	previous	present[c]	(CDCl₃)	previous[7]	present[c]
H_A	4.47 (t)	4.69 (t)	AB	3.5	3.5
H_B	2.87 (q)	2.59 (dd)	AC	3.5	3.5
H_C	2.59 (q)	2.93 (dd)	BC	17.0	16.7
H_D	1.96 (q)	2.67 (dd)	DE	17.5	17.2
H_E	2.60 (q)	1.99 (dd)	DF	3.5	3.5
H_F	3.51 (q)	3.49 (dd)	EF	12.0	12.1
H_G	6.5–7.2	7.10 (bs)	HI		7.5
H_H	6.5–7.2	6.96 (bd)			
H_I	6.5–7.2	6.64 (d)			
OCH₃	3.37 (s)	3.41 (s)			
CH₃(arom)	2.3 (s)	2.33 (s)			
CH₃(ang)	(s)[b]	1.58 (s)			

a Peak multiplicities are represented by s (singlet), d (doublet), t (triplet), and q (quartet). *b* Not specified, but between δ 1.22 and 1.60. *c* Determined on a Bruker WH 180 spectrometer.

of H_B and H_C. All other assignments are correct. H_D and H_E were identified by their coupling constants with H_F (cis, *J* = 3.5 Hz, and trans, *J* = 12.1 Hz, respectively). Evidence regarding the assignments of H_B and H_C comes from the Eu(fod)₃-shifted spectrum of **2d** (vide infra.)[8]

Irradiation of **1** in CH₃OD gave a single methanol adduct, assigned structure **2d**. The NMR spectrum of **2d** was modified

2d
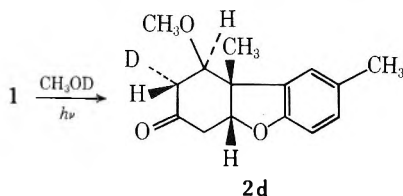
from that of **2** only in the following ways. The peak at δ 2.67 (H_D) was absent, and H_E appeared as a broad doublet at δ 1.95, *J* = 12.5 Hz, coupled with H_F, which was a doublet at δ 3.47. Irradiation at H_A, H_E, and H_F verified the various coupling constants. A Eu(fod)₃ shift study showed that coordination occurs mainly with the carbonyl oxygen. The Δ values (extrapolated shift for 1:1 mol ratio of shift reagent/substrate) for H_B and H_E were nearly equal (6.8 and 6.5, respectively). The larger Δ value for H_C (7.7) than for H_B is consistent with H_C being in a pseudo-equatorial position, closer to the carbonyl oxygen.

These results show that the photoinduced addition of methanol to Pummerer's ketone occurs in a stereospecific trans manner. Since the ring juncture between the aliphatic five- and six-membered rings is cis, it is not surprising that methanol attacks from the exo (or β) face, so that the methoxyl and methyl groups end up cis to one another. It was quite surprising, however, that protonation occurred from the underneath (or α) face of the molecule. One possible explanation is that irradiation of **1** results in an excited state or intermediate in which the carbon–carbon double bond is twisted more than 90°. In this event, only syn addition to that "trans" double bond would be possible, since one face of the double bond would be blocked by the ring. The double bond can only twist in the sense shown, since a twist in the opposite direction would move the double bond into the face of the aryl and dihydrofuran rings. Consequently, the angular methyl and methoxyl must be cis to one another, with the deuterium trans
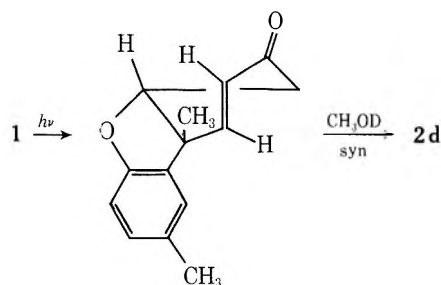
to the methoxyl. A short-lived intermediate has recently been detected in the flash photolysis of 2-cyclohexenone, and the authors suggest that it may be a "trans" isomer.[3b]

By irradiating **1** in a mixture of CH₃OH/CH₃OD and measuring the ratio of **2/2d** formed (by mass spectrometry) we find an isotope effect of 4.3 ± 0.5 in favor of protio addition. This effect is comparable to that observed for the addition of methanol to *trans*-cycloheptenone (4.3) and *trans*-2-cyclooctenone (5.7)[2] although we expected a much smaller effect for **1**, reasoning that the "trans" intermediate should be more strained, hence less selective than for larger rings.

Experimental Section

References and Notes

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(9) The mass spectrum shows, in addition to M^+ (246; for **2d**, 247) and $M^+ -$ methanol (214; for **2d**, 215 and 214), two sets of interesting fragmentation peaks. A retro-Diels–Alder[10] of the enol can give

m/e 146   m/e 100 (101)
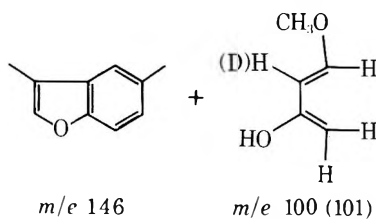
accounting for the same base peak in **2** and **2d**. The peaks at m/e 160 and 159 in both compounds may arise from α-carbonyl and benzylic cleavage to give

m/e 160   m/e 159
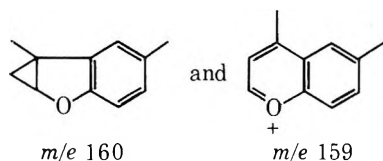
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Determination of pK Values for the Bisulfite Adducts of Cytidine 5'-Monophosphate by Carbon-13 Nuclear Magnetic Resonance

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Addition of bisulfite to carbon 6 of biologically important pyrimidines is a well-studied reaction,[1-3] having been investigated for nucleosides,[4] nucleotides,[5] and nucleic acids.[6] From a bioorganic standpoint the most intriguing event is the bisulfite-catalyzed deamination of cytidine to form uridine, the biological implications of which have been previously demonstrated.[7,8] Shapiro et al.[9] have advanced a mechanistic rationale (Scheme I) which includes both the protonated and nonprotonated cytidine–bisulfite adducts. In this mechanism the assumption was made that there is only one adduct formed. The present communication characterizes the two diastereomeric bisulfite adducts of cytidine 5'-monophosphate (CMP, **4**) (Scheme II) and reports the pK values for the N-3 proton dissociation of these two adducts.

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Scheme I
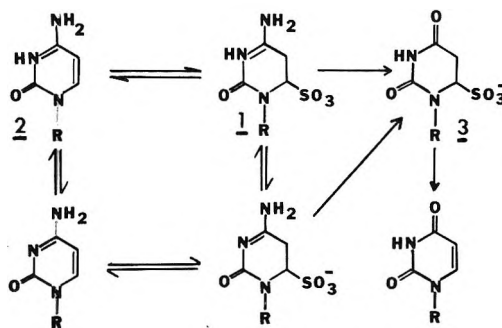
^{13}C NMR spectroscopy of an aqueous solution of CMP (**4**) yields a nine-line spectrum (Table I). Upon addition of bisulfite, a spectrum is obtained which is a composite of the original spectrum and those of two new compounds (Table I). Significantly, the signals corresponding to the sp^2 carbons of CMP (C-6, 142.7 ppm, and C-5, 97.3 ppm) are diminished. The CMP–bisulfite adducts (**5A** and **5B**) each display a set of signals of unequal intensity which includes carbon 2, carbon 4, and the sugar carbons. Based on their relative intensities, the signals can be grouped into two sets (CMP/HSO$_3^-$ A and CMP/HSO$_3^-$ B) and assigned to the appropriate carbons of the adducts[10] (Table I). In addition, two new sets of signals corresponding to the sp^3 carbons at positions 5 and 6 of the adducts are observed at 28.8 and 28.5 ppm (C-5) and 68.1 and 66.1 ppm (C-6). These are readily assigned by analogy with the known spectra for the bisulfite adducts of uracil and uridine.[4,11] When the sample is allowed to stand for longer periods (24 h), two more nine-line spectra are observed. The new carbon signals are assigned (Table I) as the diastereomeric bisulfite adducts of uridine monophosphate (**6A** and **6B**, Scheme II). This assignment is made on the basis of data previously reported from our laboratories in which uridine[4] and uracil[11] were substrates of similar bisulfite addition.

Shapiro et al.[9] reported a pK value of 5.3 for the N-3 proton dissociation in the cytidine–bisulfite adduct. This value was determined by ^{1}H NMR spectroscopy with deuterium oxide as the solvent. Thus, corrections were made to account for the effect of the deuterated solvent on the observed pH values. In light of the evidence for the existence of two diastereomeric bisulfite adducts of CMP, and because one of the parameters in the kinetically derived mechanism is the pK of these species, we were prompted to determine the pK values for each adduct.

The system under study using ^{13}C NMR spectroscopy initially consists of an aqueous solution containing only CMP (**4**) and its bisulfite adducts (**5A** and **5B**). However, after 24 h it was found to contain five discrete chemical species (Scheme II): CMP, its two diastereomeric bisulfite adducts (**5A** and **5B**), and two diastereomeric bisulfite adducts of uridine 5'-monophosphate (UMP) (**6A** and **6B**). These five species have a total of 18 possible pK values. Theoretically it is possible,
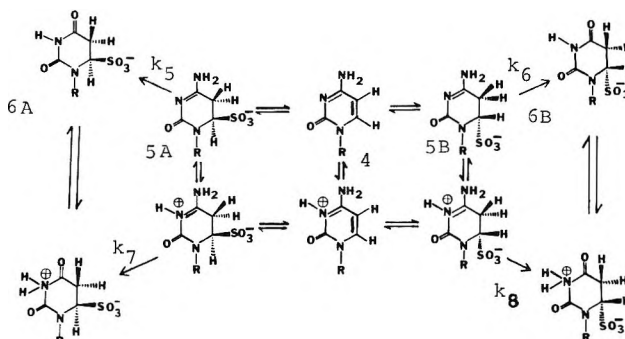
Scheme II

Table I. Chemical Shift Assignments (ppm)[a]

Compd	Registry no.	C-2	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'
CMP	63-37-6	157.1	165.9	97.5	142.6	90.3	70.5	75.3	84.4[b]	64.6[b]
CMP/HSO$_3^-$ A	66687-68-1	156.8	170.1	29.0	70.30	94.27	71.05	75.3	83.16[b]	64.71[b]
CMP/HSO$_3^-$ B	66687-69-2	155.8	169.8	29.0	65.88	91.97	69.83	72.57	83.16[b]	64.00[b]
UMP/HSO$_3^-$ A	66748-91-2	153.70	172.93	33.28	66.77	92.45	71.17	74.89	83.08[b]	64.82[b]
UMP/HSO$_3^-$ B	66748-92-3	154.58	172.93	33.66	65.88	94.69	70.78	72.45	83.48[b]	65.57[b]

[a] Assignments for CMP, the two diastereomeric bisulfite adducts of CMP, and the two diasteromeric bisulfite adducts of UMP which result from deamination; pH 5.3. [b] Denotes signals which are split into doublets by the ^{31}P nucleus.
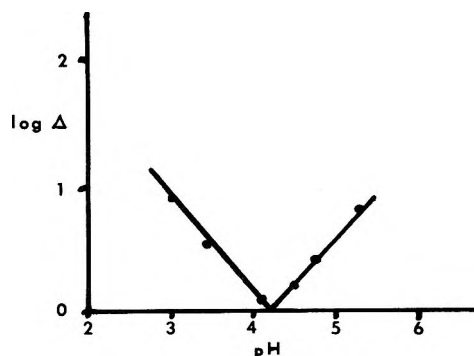
Figure 1. A plot of log Δ vs. pH for cytidine 5'-monophosphate, where Δ is $(\delta_{max} - \delta)/(\delta - \delta_{min})$. The intercept (log $\Delta = 0$) is that point where the pH value is equal to the pK value. In this instance the pK value of CMP is found to be 4.2.

Table II. pK Values for the Components Found in a Reaction Mixture of CMP and Bisulfite

	pK (obsd)	pK^a
Uridine[b]	9.20	9.2
CMP	0.6–1.0	0.8[a]
	4.20	4.2
	6.08	5.97
CMP/HSO$_3^-$ A	5.20	
CMP/HSO$_3^-$ B	4.82	

[a] See ref 14. [b] Registry no.: uridine, 58-96-8.

using ^{13}C NMR spectroscopy, to determine each and every pK value for the components of this complex mixture. This is accomplished by plotting the ^{13}C chemical shifts for each species as a function of pH. As an initial test of this approach and in order to simplify the results observed for the reaction mixture, the pH dependence of the uridine and CMP ^{13}C NMR spectra was measured. Large shifts are observed for C-2 and C-4 and to a lesser extent for C-6 upon removal of the proton from N-3. Not as obvious are two smaller changes in the chemical shift for C-5' (and to a lesser extent C-4') of CMP corresponding to the successive removal of protons from the phosphate moiety. Accurate numerical values for the four pK_a's can be obtained from the Henderson–Hasselbach equation as described by Dorman and Roberts[12]

$$\text{pH} = \text{p}K + \log \left| \frac{(\delta_{max} - \delta)}{(\delta - \delta_{min})} \right| \tag{1}$$

where δ is the observed chemical shift in ppm for a particular carbon atom and δ_{max} and δ_{min} are the maximum and minimum observed chemical shifts, respectively.

An example of these plots is illustrated in Figure 1 for C-4 of CMP. Agreement between the values measured here and those previously reported in the literature is excellent as
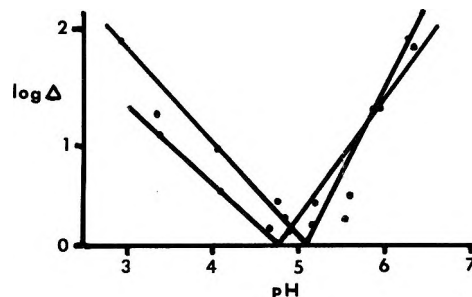

Figure 2. A plot of log Δ vs. pH for diastereomeric bisulfite adducts of CMP$_x$, where Δ is $(\delta_{max} - \delta)/(\delta - \delta_{min})$. The graphs intercept the x axis at 4.82 and 5.2, indicating that these are the pK values of the adducts.

shown in Table II. This is particularly interesting in light of the potential deviations expected from operating with relatively concentrated solutions at high ionic strength.[13]

With the data for CMP available, the more complex reaction mixture is readily interpreted. Samples containing equimolar amounts of CMP and bisulfite were prepared, their pH and ionic strength were adjusted, and after standing for exactly 24 h their ^{13}C spectra were obtained. The pK's of the phosphate groups are not expected to change appreciably, and they are not involved in the proposed deamination mechanism. Therefore, attention was focused on the pH region corresponding to the deprotonation of N-3 in the adducts. Unfortunately, desulfonation of the uridylate adducts (6A and 6B) to form UMP occurs at pH below the pK of the deprotonation of N-3 in the UMP adducts. The CMP adducts are more stable, and the corresponding signals (C-2, C-4, and C-5) display the expected pH dependence. The final results are listed in Table II and plotted in Figure 2. Henderson–Hasselbach plots, as in Figure 1, yield values for the pK_a's of each individual adduct.

It is most significant that the pK values for the diastereomeric bisulfite adducts of CMP are different. This would imply that if the deamination step for CMP follows that of cytidine (Scheme I), being pH dependent, it may proceed at significantly different rates for the individual diastereomers. For example, at pH 4.5 the diastereomer with a pK value of 4.82 will be 48% dissociated while the other diastereomer (pK value 5.20) will only be 20% dissociated. Thus, if in Scheme II the rate constants for the deamination of the nonprotonated diastereomers (k_5 and k_6) are much smaller than those for the protonated species (k_7 and k_8), then the rates will be reflected by the concentration of the protonated species. Therefore, the rate of deamination of the diastereomer with the lower pK value will be faster than for the diastereomer with the larger pK value. In light of the data presented here, it appears that the mechanism for the bisulfite-catalyzed deamination of CMP is far more complicated than the one previously advanced.[9]

Experimental Section

Sample Preparation. Uridine was purchased from Aldrich Chemical Co. (Milwaukee, Wis.), and cytidine 5'-monophosphate was purchased from Sigma Chemical Co. (St. Louis, Mo.). These compounds were used without further purification. Typically, samples were prepared as aqueous solutions containing either 100 mg per mL or 200 mg per mL of the nucleoside or nucleotide, with or without equimolar sodium bisulfite. Concentrated HCl or sodium hydroxide (8 M) was used to obtain specific pH values. Sufficient solid potassium chloride was added to maintain the final ionic strength at a fixed value of 1.0; pH measurements were carried out at 30 °C with an IL Delta Matic pH meter (Perkin-Elmer).

NMR Measurements. All carbon-13 spectra were measured on samples in 8 mm sample tubes. A capillary tube containing 20% of 1,4-dioxane and 80% of deuterium oxide was used as a lock signal and an external reference. The observed chemical shifts were converted to the Me_4Si scale using $\delta(C - dioxane) = 67.40$ ppm. Spectra were recorded on a Varian CFT-20 (16K) spectrometer equipped with a single side-band crystal filter for signal to noise ratio improvement and a Sykes diskette unit for storage. All ^{13}C NMR spectra were measured corresponding to a 4000 Hz (200 ppm) spectral width in 4096 data points.

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A Carbon-13 Nuclear Magnetic Resonance Study of Dibenzoylcystine Gels

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Gels are semirigid colloidal systems rich in liquid. Protoplasm ranks as the most widespread example of this peculiar state of matter. Two not entirely distinct theories have been advanced to explain gelation. The first, championed by Bradford[1] in the 1920's, maintains that the sol-to-gel transformation is a type of crystallization (the gel consisting of two phases composed of microcrystalline forms surrounded by water[2]). Alternatively, a gel may be formed by noncrystalline aggregates which cross-link in solution so as to entrain the dispersing medium in the capillary spaces between them.[3,4]

Dibenzoylcystine (I) is conspicuous among those organic substances that gel (e.g., agar, gelatin, poly(2-hydroxyethyl methacrylate), etc.) because of its simple structure.[5,6] Dibenzoylcystine is unique for another reason; a stiff hydrogel is produced by only 3×10^{-3} M disperse phase! In contrast to gelatin which associates in solution,[7,8] dibenzoylcystine seems to be a "fibrillary crystalline gel".[9] We describe herein an examination of dibenzoylcystine gels by ^{13}C NMR spin–lattice relaxation times (T_1).

Table I. Carbon-13 Spin–Lattice Relaxation Times in Seconds (T_1) of Dibenzoylcystine Gels at 37 °C

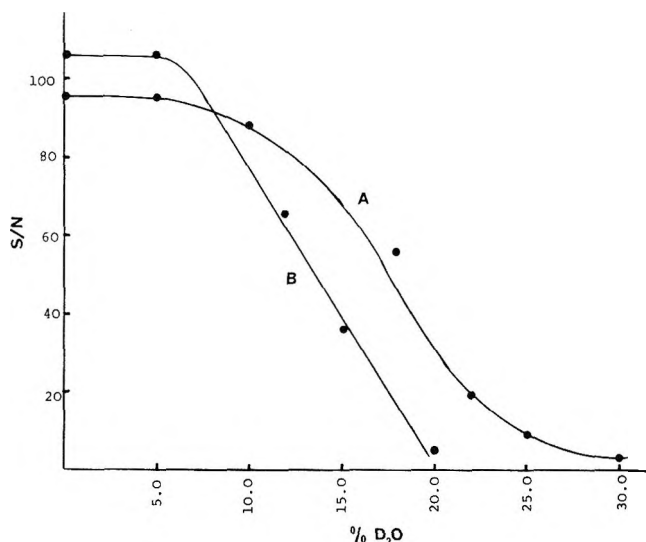| conditions	physical state	T_1 ortho	T_1 para
0.62 M in Me_2SO	liquid	0.35	0.16
0.30 M in Me_2SO	liquid	0.49	0.16
0.30 M in 10% D_2O–Me_2SO	soft gel	0.41	0.14
0.30 M in 20% D_2O–Me_2SO	thick gel	0.41	0.15
0.30 M in 20% D_2O–Me_2SO (sonicated)	thick gel	0.42	0.16

Figure 1. ^{13}C NMR signal-to-noise values for 0.32 M (curve A) and 0.63 M (curve B) dibenzoylcystine in Me_2SO with varying concentrations of D_2O at 37 °C using a constant number of transients (10 000 for A and 1000 for B).

$$C_6H_5CONHCHCH_2SSCH_2CHNHCOC_6H_5$$
$$\underset{HOOC}{|} \qquad \underset{COOH}{|}$$
$$I$$
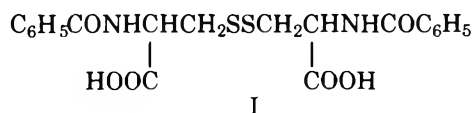
T_1 studies provide information on molecular motion without the need for an external probe.[10,11] If a gel-forming compound associates in solution akin to surfactants, then T_1 values should decrease only modestly (two- to five-fold) relative to the monomeric state.[12] If a clear gel behaves as a two-phase system, then the ^{13}C NMR line widths and T_1's should be affected dramatically.[13] It is the purpose of this note to differentiate these alternatives with gels of a simple organic substance.

Since dibenzoylcystine in water does not form clear gels at the relatively high concentrations required for T_1 measurements, we used a dimethyl sulfoxide–water solvent system. A 0.30 M solution of I in pure Me_2SO is a fluid liquid; adding 10% water (v/v) produces a transparent semisolid gel. Further quantities of water (20%) give a thick white material. Thus, the gel consistency can be varied continuously by regulating the water content. The following T_1 values in seconds were found for 0.62 M I in pure Me_2SO at 37 °C: carbonyls (2.2 and 2.3); methine (0.15); C_1, C_2, C_3, and C_4 of aromatic ring (2.3, 0.35, 0.35, and 0.16, respectively).[14] These are quite ordinary values for an organic molecule the size of I.[15] In Table I we tabulate T_1 values for two aromatic carbons of I in Me_2SO-d_6 with and without D_2O. It is seen that gelation, in contrast to micellization,[12] need not alter the T_1's. Dibenzoylcystine apparently exists in two *non-exchanging* states: (a) a monomeric species which possesses normal T_1 values and line widths and (b) an aggregate whose ^{13}C resonances are broadened to the point of unobservability by ^{13}C–^1H dipolar

interactions associated with long correlation times. If this conclusion is correct, then one would expect the signal-to-noise ratio (S/N) of the ^{13}C NMR spectra to decrease as added D_2O diminishes the monomer concentration. This is found to be the case (Figure 1). The point at which the S/N begins its precipitous decline depends on the concentration of I. Furthermore, soft gels form at D_2O levels where there is no decrease in S/N. Thus, *both* theories for gelation, mentioned above, may have merit. The soft gels, induced by low water concentrations, behave as if they are one phase as far as we can determine by ^{13}C NMR. Solid dibenzoylcystine with broad resonances predominates in the stiffer more opaque gels. Presumably, the increased viscosity and opacity of the gels at higher water concentrations is related to the appearance of a solid phase. In any event, soluble monomer entrapped within the microcrystalline network neither exchanges with the fibrillar species (on the NMR time scale) nor experiences difficulty moving about. Since the gelatinizing properties of I are destroyed by replacing the –S–S– linkage with –CH_2–CH_2– or –CH=CH–,[9] the C–S–S–C dihedral angle[16] of 90° probably plays a key role in the formation of the molecular fibers.

Experimental Section

Spin–lattice relaxation time measurements on decoupled ^{13}C resonances were carried out with a Varian CFT-20 spectrometer using the inversion–recovery method.[17] A typical experiment included a pulse width of 24 μs (calibrated), pulse delay $\geq 4T_1$, 10 points per run, and 1000–2000 accumulations per point. The T_1 values (accurate to ±15%) are sufficiently small that degassing of the samples was not necessary. Signal-to-noise ratios were estimated from the height of the ortho-carbon peak divided by the height of the noise. Dibenzoylcystine was prepared by benzoylation of L-cystine, mp 190–192 °C (lit.[5] 190–192 °C). A small amount of benzoic acid impurity was removed by filtration from hot water.

Registry No.—Dibenzoylcystine, 25129-20-8.

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Preparation of Highly Enriched Diazomethane-d_2

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Several reports of preparations of deuterated[2,3a] or tritiated diazomethane[4] have appeared in the literature, but none of
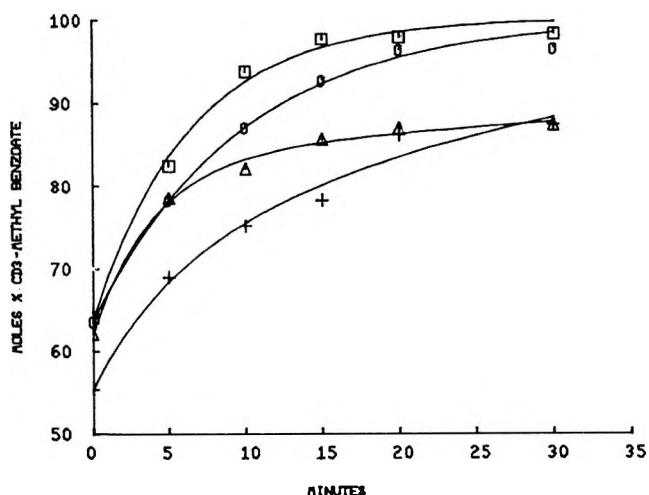

Figure 1. Time course experiments to measure the rate of deuterium incorporation in diazomethane. Key: +, system 1; $\triangle$, system 2; O, system 3; $\square$, system 4. Curves were drawn using a computer program assuming a first-order two-compartment model (systems 1 and 2) and a first-order one-compartment model (systems 3 and 4).

the available methods are suitable for routine preparation of highly enriched (>98%) material. The need for single isotopically labeled species as internal standards for quantitative mass spectral assays has led us to examine techniques for producing deuterated diazomethane (CD_2N_2) of 99% isotopic purity. We wish to report a convenient phase transfer catalyzed method using a diethyl ether solution of CH_2N_2 with NaOD and D_2O.

Diazomethane may be labeled by generation from labeled precursors,[5] nonlabeled precursors in the presence of labeled solvents and base,[3a] or by subsequent exchange with D_2O.[6] McManus et al.[5] used generation from labeled hydrazine and chloroform to obtain 92% labeled CD_2N_2 with yields of 10–20%. They had attempted direct NaOD/D_2O exchange for two 30-min periods as previously reported by others[6] but experienced the loss of 95% of the original diazomethane. Probably the most widely used method is that of Campbell[3a] who reacted nondeuterated nitrosamide precursors with deuterated solvent and base to effect a 50–60% yield of CD_2N_2 with from 83 to 97% deuterium depending upon the ratio of reagents to precursor. Fales et al. used this method in a convenient micro apparatus[7b] and reported 71% deuteration (50% CD_3) of methyl benzoate in 60% yield. Facile exchange of diazomethane protons requires that the glass apparatus, solvents, etc., be proton free or back exchanges will result in lowered isotopic yields for any of the above procedures.

Trying to improve upon the method of Campbell, we felt that diazomethane could be enriched by multiple exchanges with D_2O. We investigated the use of several solvent mixtures and phase transfer catalysts[8] to promote rapid exchange with minimum decomposition: system 1, diethyl ether (3 mL)/5% NaOD in D_2O (2 mL); system 2, diethyl ether:THF (1:1, 3 mL)/5% NaOD in D_2O (2 mL); system 3, diethyl ether (3 mL)/5% hexadecyltributylphosphonium bromide (HDTPB)–NaOD in D_2O (2 mL); system 4, diethyl ether (3 mL)/5% cetyltrimethylammonium bromide (CTAB)–NaOD in D_2O (2 mL).

Figure 1 summarizes several time course experiments. Equilibration was reached in 20–30 min with each of the four solvent systems tested with the phase transfer catalysts promoting higher incorporation of deuterium more rapidly. The low solubility of NaOD and D_2O in diethyl ether limits contact of diazomethane with exchange media in the absence of phase transfer catalysts. The curves describing systems 1 and 2 plateau before reaching the theoretical enrichment if all the D_2O were accessible for exchange and are best fit with a
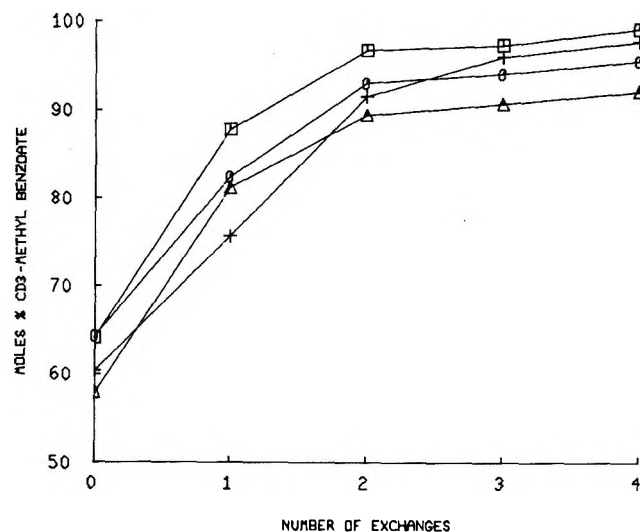
Figure 2. Multiple exchange experiments. Experimental points are connected. Key: +, system 1; △, system 2; ○, system 3; □, system 4.

function reflecting separate rates for exchange and solubility.

Multiple exchanges were effected by mixing fresh aqueous solutions in systems 1–4 in a microgenerator, separating the phases after 15 min, and either reacting the diazomethane with benzoic acid-*O-d* or mixing with additional aqueous phase. An exchange time of 15 min was chosen as a compromise between enrichment and yield of diazomethane. Highest enrichments were observed in systems 1 (97.7 mol % D_3) and 4 (99.1 mol % D_3) as shown in Figure 2. The lower isotopic enrichment observed with system 3 was probably due to the hygroscopic nature of the catalyst and the difficulty of preparing a D_2O solution with 99% deuterium.

Yields were somewhat variable, but using the precautions of keeping all solutions and flasks cold and basic, 25–35% of theoretical yield was obtained after five exchanges. For unexchanged diazomethane, 50–60% yield was obtained. Use of phase transfer catalysts did not significantly alter yields. We have used the methods described to exchange diazomethane generated on a larger scale (50–100 mmol) with similar enrichments and yields.

Experimental Section

Low resolution electron ionization mass spectra were recorded with a Finnigan 3200 quadrupole GC–MS. Samples were introduced via the gas chromatograph using a 10% Apolar 10c on 100/200 mesh gas Chromosorb Q (2 m × 2 mm) column at a temperature of 145 °C. Data were obtained by selected ion recording from m/e 134–144 ($M^{+.}$). Precise isotopic enrichments were calculated by comparing labeled vs. unlabeled methyl benzoate using LABDET, a program in the NIH-EPA Chemical Information System.[9] Prior to all series of experiments, glassware was washed with D_2O and heated to 200 °C for 12 h. Anhydrous solvents were partitioned with D_2O prior to use.

Phase Transfer Catalysts. Cetyltrimethylammonium bromide (CTAB) was purchased from Aldrich. Hexadecyltributylphosphonium bromide[8] (HDTPB) was prepared by heating 1-bromohexadecane (10 g, 0.06 mol) and tri-*n*-butylphosphine (12.2 g, 0.06 mol) at 60–70% for 3 days. The resulting solid was filtered and recrystallized from hexane. The product was freeze dried giving the salt in 63% yield: mp 53–54 °C (lit.[8] mp 54 °C). A solution of 5% NaOD (Aldrich, 99 + atoms % D) and 5% quaternary ammonium or phosphonium salt in D_2O was used in all exchanges.

Benzoic Acid-*O-d*. Monodeuterated benzoic acid was prepared by exchanging benzoic acid five times with excess methanol-*O-d* (Merck, 99.7 atoms % D). Generally, for each series of experiments the final stock solution of benzoic acid-*O-d* in methanol-*O-d* (150 mg/10 mL) was equally divided between five screw capped tubes (Kimax) and the solvent was removed with dry nitrogen. The residue was redissolved in diethyl ether (1 mL).

Diazomethane-*d2*. Partially deuterated diazomethane was prepared in a diazomethane microgenerator by the action of 40% NaOD on *N*-methyl-*N*-nitrosoguanidine (13 mg) as described by Fales and Jaouni.[7a] The product was trapped in ice-cooled diethyl ether (3 mL) over a 30-min period.

(a) Time Course Study. Following generation of diazomethane the apparatus was opened and 2 mL of the ice-cooled aqueous catalytic solution was transferred into the trap. After resealing the microgenerator the two phases were mixed by intermittent shaking over 30 min. At various time intervals (0, 5, 10, 15, 20, and 30 min) aliquots of the diazomethane–diethyl solution were transferred to ice-cooled benzoic acid-*O-d* solutions and capped. After a further 10 min at room temperature excess diethyl ether was removed with dry nitrogen and the residue was dried under vacuum.

(b) Multiexchange Study. Same procedure as for (a). Each exchange was allowed to proceed for 15 min with intermittent shaking. After this time the aqueous phase was withdrawn by pipet and replaced with fresh catalytic solution. Following the final exchange, the ethereal diazomethane solution was transferred to the reaction tube as outlined.

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Approaches to the Mitomycins: A Novel Pyrrole Photooxidation Product

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The photooxidation of pyrroles has been studied thoroughly in the past decade and a half.[2] The oxidation has been of some use in the introduction of the angular oxygen function in mitomycin-like molecules.[3] The accepted mechanism of the reaction has featured the photosynthesis of singlet oxygen which then attacked pyrrole. The transient endoperoxide 2, which is initially formed, then fragments to yield a variety of products. One important proposed pathway involves cleavage of the O–O bond of 2 to yield 5-hydroxypyrrolines 3, while a second postulated route requires bimolecular nucleophilic opening of the endoperoxide to yield 4a or a unimolecular opening to yield peroxy isopyrrole 4b which is trapped by nucleophiles.[4] In either event, products such as 5 and 6 are obtained. In addition it has been suggested that either endoperoxide 2 or hydroperoxide 4b can rearrange to a dioxetane 7 which can then fragment to ring-cleaved products. In this note, we wish to describe a product of pyrrole photooxidation that has hitherto been unobserved and which might require reconsideration of currently accepted mechanisms.
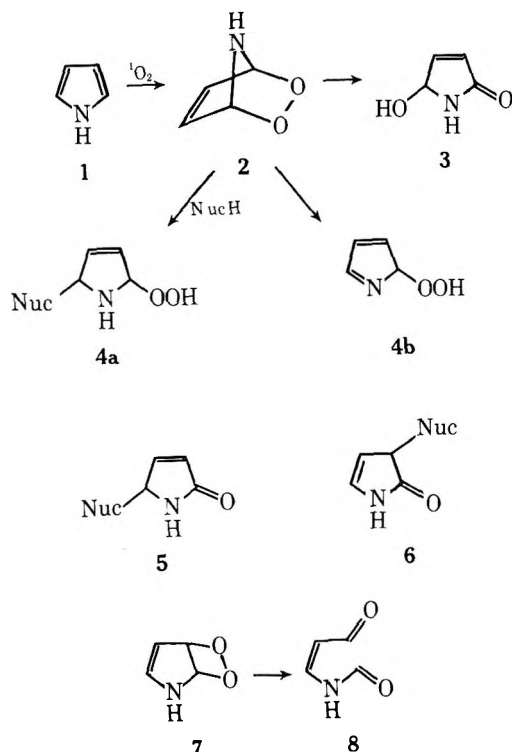
When pyrrole alcohol **9** is photooxygenated in methanol using Rose Bengal as a sensitizer, there can be isolated in 74% yield the oxygen insertion product **10**. Ether **10** is very reactive and can be further oxidized to lactam **11**. Insertion product

9, R = OCH₃
12, R = H

10, R = OCH₃
13, R = H

11, R = OCH₃
14, R = H
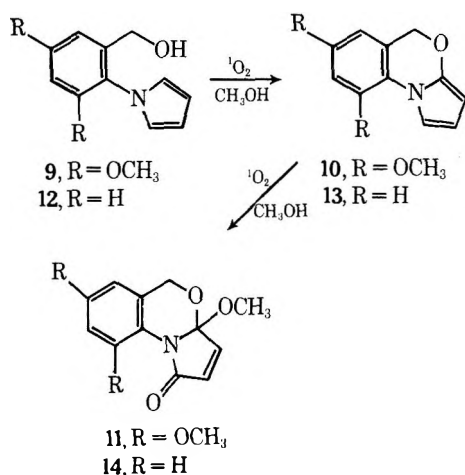
10 is unambiguously characterized by its NMR spectrum, which, inter alia, exhibits three pyrrole protons, its mass spectrum, m/e 231, and its IR spectrum with no carbonyl band. Lactam **11** with its C=O at 1704 cm⁻¹ in the IR and its extra OCH₃ δ 3.30, and its benzylic AB quartet δ 4.62 and 5.08 (J = 15 Hz), in the NMR was easily identified as well. When the oxidation was attempted with pyrrole **12**, only lactam **14** could be isolated. Although there was some TLC evidence for **13** having a transitory existence, its isolation was not achieved. In order to be certain that ether **10** was indeed a photooxidation product, we performed three control experiments, namely treatment of **9** with dye and oxygen in the dark, irradiation of **9** with dye under anaerobic conditions, and irradiation of **9** with oxygen but in the absence of a sensitizer. All these experiments failed to yield insertion product.

In order to rule out some exceptional behavior of the particular aromatic system, we studied the oxidation of **15** where the alcohol is blocked with a dimethyl-*tert*-butylsilyl group. Photooxidation yielded the normal lactam **16** demonstrating

that in the absence of a free alcohol function, the dimethoxyphenylpyrrole system is not unusual in its reaction with a singlet oxygen. Furthermore, hydrolysis of the silyl ether to afford free alcohol **17** revealed no unusual interaction; thus we discount any mechanism for the oxidation of **9** which requires a normal product such as **17** which would be subsequently transformed to **10**.

15

16, R = Si-t-BuMe₂
17, R = H
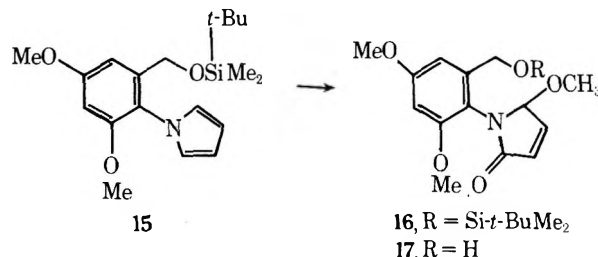
There are several plausible mechanisms that can rationalize the oxygen oxidative insertion of the alcoholic oxygen into the pyrrole. They all predict H₂O₂ as a reduction product to account for the two hydrogens released in the insertion reaction. Thus, the initial reactant solution was subjected to the Ti(SO₄)₂ assay[5] which afforded the yellow color indicative of H₂O₂, whereas control solutions gave negative results.

Our observations do not permit the postulation of a mechanism of pyrrole oxidation different from that in the literature, but they do suggest the presence of some novel participation by alcohols in the photooxidation process. Extrapolation of our observation could explain the isolation of small amounts of maleimides in many photooxidations of pyrroles. An intermolecular version of our reaction would yield alkoxy- or hydroxypyrroles which upon oxidation with a second equivalent of ¹O₂ would be converted to maleimide.

Experimental Section

1-(2,4-Dimethoxy-6-hydroxymethylphenyl)pyrrole (9). A solution of 1-(2,4-dimethoxy-6-methoxycarbonylphenyl)pyrrole (6 g, 0.023 mol) in 50 mL of ether was added to lithium aluminum hydride (1 g, 0.26 mol) in 100 mL of anhydrous ether at such a rate that a gentle reflux was maintained. The solution was refluxed for 45 min longer under N₂. After workup, evaporation of the solvent afforded 5.11 g (95%) of off-white crystalline pyrrole alcohol **9**: mp 125–127 °C; NMR (CDCl₃) δ 1.93 (1 H, br s), 3.75 (3 H, s), 3.89 (3 H, s), 4.38 (2 H, s), 6.35 (2 H, t, J = 2.1 Hz), 6.54 (1 H, d, J = 2.6 Hz), 6.69 (2 H, t, J = 2.1 Hz), 6.75 (1 H, d, J = 2.6 Hz).

Anal. Calcd for C₁₃H₁₅NO₃: C, 66.9; H, 6.5; N, 6.0. Found: C, 66.85 H, 6.51; N, 5.96.

1-(2-Hydroxymethylphenyl)pyrrole (12). To a suspension of lithium aluminum hydride (0.5 g, 0.013 mol) in 40 mL of anhydrous ether was added 1-(2-carboxyphenyl)pyrrole (2.01 g, 0.01 mol) in 20 mL of ether slowly with stirring. The solution was refluxed under N₂ for 1 h. After workup evaporation of the solvent yielded almost pure alcohol **12** as an oil (1.71 g, 99%) which solidified and was recrystallized from hexane, to afford 1.49 g (85%) of pyrrole alcohol **12** as white needles: mp 42–43 °C; NMR (CDCl₃) δ 2.36 (1 H, br s), 4.54 (2 H, s), 6.36 (2 H, t, J = 2.2 Hz), 6.90 (2 H, t, J = 2.2 Hz), 7.3–7.6 (4 H, m).

7,9-Dimethoxy-5H-pyrrolo[1,2-a][3,1]benzoxazine (10). A solution of 1-(2-hydroxymethyl-4,6-dimethoxyphenyl)pyrrole (9) (233 mg, 1 mmol) and Rose Bengal (15 mg) in 150 mL of methanol was irradiated with four General Electric cool white fluorescent lamps (15 W per lamp) for 2 h while a slow stream of O₂ was swept through the solution. Removal of the solvent afforded a dark pink residue which was subjected to preparative TLC on silica gel using CHCl₃ to yield 170 mg (74%) of the oxygen-inserted product **10** (Rf 0.81) which was very unstable and turned red on exposure to light and air: NMR (CDCl₃) δ 3.75 (3 H, s), 3.85 (3 H, s), 4.95 (2 H, s), 5.45 (1 H, dd, J = 3.5, 2.0 Hz), 6.01 (1 H, t, J = 3.5 Hz), 6.30 (1 H, d, J = 2.5 Hz), 6.52 (1 H, d, J = 2.5 Hz), 7.25 (1 H, dd, J = 3.5, 2.0 Hz); mass spectrum m/e (rel intensity) 231 [M⁺] (100), 216 [M − 15] (10), 202 [M − 29] (10), 188 [M − 43] (13.8).

3a,7,9-Trimethoxy-5H-pyrrolo[1,2-a][3,1]benzoxazin-1(3aH)-one (11). A solution of pyrrole alcohol **9** (233 mg, 1 mmol) and Rose Bengal (25 mg) in 150 mL of methanol was irradiated under the conditions described for the formation of oxazine **10**. Irradiation

of the reaction mixture was continued even after the disappearance of the starting material. Evaporation of the solvent after 5 h of irradiation of the reaction mixture afforded a dark pink residue which upon preparative TLC in CHCl₃ gave 24 mg (10%) of oxazine **10** from the fastest band and 129 mg (46%) of alkoxy lactam **11** from a slower moving band (R_f 0.17): NMR (CDCl₃) δ 3.30 (3 H, s), 3.83 (3 H, s), 3.94 (3 H, s), 4.62 and 5.08 (2 H, AB quartet, J_{AB} = 15 Hz), 6.31 (1 H, d, J = 6.0 Hz), 6.58 (1 H, d, J = 2.5 Hz), 6.72 (1 H, d, J = 2.5 Hz), 7.02 (1 H, d, J = 6.0 Hz): IR (CHCl₃) 1704 cm⁻¹; mass spectrum *m/e* (rel intensity) 277 (5), 262 (100).

3a-Methoxy-5H-pyrrolo[1,2-*a*][3,1]benzoxazin-1(3a*H*)-one (14). A solution of alcohol **12** (173 mg, 1 mmol) in 100 mL of methanol with added Rose Bengal (10 mg) was irradiated under the conditions described for the formation of **10**. After the consumption of the starting material which took 6 h, no oxazine **13** could be isolated by preparative TLC in CHCl₃, but an alkoxy lactam **14** was obtained from a slow moving band (R_f 0.12) as a yellow solid: (56 mg, 20%) NMR (CDCl₃) δ 3.34 (3 H, s), 4.92 and 5.37 (2 H, AB quartet, J_{AB} = 15 Hz), 6.44 (1 H, d, J = 6.0 Hz), 7.17 (1 H, d, J = 6.0 Hz), 7–7.3 (3 H, m), 8.12 (1 H, dd, J = 8.0, 2.5 Hz).

1-[α-(*tert*-Butyldimethylsiloxy)-4,6-dimethoxy-o-tolyl]pyrrole (15). To a solution of pyrrole alcohol **9** (466 mg, 2 mmol) in 2 mL of DMF were added dimethyl-*tert*-butylsilyl chloride (450 mg, 3 mmol) and imidazole (204 mg, 3 mmol) at 0 °C under nitrogen. The solution was stirred at this temperature for 10 min and at room temperature for 1 h. Workup involved diluting the reaction mixture with ether. The ethereal layer was washed with H₂O and dried over Na₂SO₄ and the solvent was removed in vacuo. Silica gel chromatography of the crude reaction mixture on three 20 × 20 cm preparative TLC plates (CHCl₃) yielded 556 mg (80%) of silyl ether **15** as a colorless gum. An analytical sample was prepared by sublimation of **15** at 100 °C (0.03 Torr): NMR (CDCl₃) δ 0.05 (6 H, s), 0.90 (9 H, s), 3.72 (3 H, s), 3.85 (3 H, s), 4.42 (2 H, s), 6.31 (2 H, t, J = 2.1 Hz), 6.48 (1 H, d, J = 2.5 Hz), 6.62 (2 H, t, J = 2.1 Hz), 6.83 (1 H, d, J = 2.5 Hz).

Anal. Calcd for C₁₉H₂₉NO₃Si: C, 65.70; H, 8.35; N, 4.02. Found: C, 65.80; H, 8.33; N, 4.08.

1-[α-(*tert*-Butyldimethylsiloxy)-4,6-dimethoxy-o-tolyl]-5-methoxy-3-pyrrolin-2-one (16). A 250-mL Pyrex graduated cylinder inside of which was placed a filter (soft glass) was charged with alcohol **15** (150 mg, 0.43 mmol), Rose Bengal (15 mg), and 150 mL of methanol. The solution, with a slow stream of oxygen passed through, was irradiated with a Sylvania tungsten Halogen quartz lamp No. Q/Cl (80 V) which was in a water-cooled immersion apparatus. The reaction was carried out at 0 °C in an ice bath and was monitored by TLC (3% MeOH/CHCl₃). After 40 min the reaction was complete. The solvent was removed on a rotary evaporator below 45 °C, and the dark residue was roughly separated by column chromatography on silica gel (8 in. × 1 in.) eluting successively with CHCl₃ and 3% MeOH/CHCl₃. The combined fractions were purified by preparative thin-layer chromatography to give one major product (R_f 0.46 in 3% MeOH/CHCl₃) (68 mg, 45%): IR (CHCl₃) 1710 cm⁻¹ (C=O); NMR (CDCl₃) δ 0.6 (6 H, s), 0.98 (9 H, s), 3.28 (3 H, s), 3.76 (3 H, s), 3.83 (3 H, s), 4.78 (2 H, s), 5.65 (1 H, m), 6.25 (1 H, dd, J = 6.0, 1.0 Hz), 6.43 (1 H, d, J = 2.5 Hz), 6.88 (1 H, d, J = 2.5 Hz), 7.03 (1 H, dd, J = 6.0, 1.5 Hz).

Desilylation of 16. A solution of silyl lactam **16** (40 mg, 0.11 mmol) in 5.5 mL of an acetic acid–H₂O–THF mixture (3:1:1.5) was stirred overnight at 50 °C. The reaction mixture was diluted with EtOAc and washed with 5% NaHCO₃, water, and brine and then dried with Na₂SO₄. Removal of solvent afforded 30 mg of crude alcohol **17**: NMR (CDCl₃) δ 3.32 (3 H, s), 3.80 (3 H, s), 3.88 (3 H, s), 4.52 (2 H, s), 5.72 (1 H, m), 6.38 (1 H, dd, J = 6.0, 1.0 Hz), 6.52 (1 H, d, J = 2.5 Hz), 6.72 (1 H, d, J = 2.5 Hz), 7.2 (1 H, dd, J = 6.0, 1.0 Hz); IR (CHCl₃) 1710 cm⁻¹.

Registry No.—**9**, 66769-50-4; **10**, 66769-51-5; **11**, 66769-52-6; **12**, 61034-86-4; **14**, 66769-53-7; **15**, 66769-54-8; **16**, 66787-42-6; **17**, 66769-55-9; 1-(2,4-dimethoxy-6-methoxycarbonylphenyl)pyrrole, 66769-56-0; 1-(2-carboxyphenyl)pyrrole, 10333-68-3; dimethyl-*tert*-butylsilyl chloride, 18162-48-6.

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Preparation of Carboxylic Acids from Protected Aldehydes

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The acetal is the most common protecting group for aldehydes and 1,3-dioxolanes are the most commonly encountered type of acetal, usually prepared by reaction of the aldehyde with ethylene glycol with azeotropic removal of water (eq 1).[1] Regeneration of the carbonyl is normally carried out with aqueous acid.[2]

$$RCHO + HO\diagup\diagup OH \xrightarrow{-H_2O} R \diagup \hspace{-0.3em} \underset{O}{\overset{O}{\diamond}} \quad (1)$$
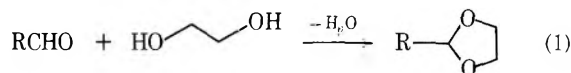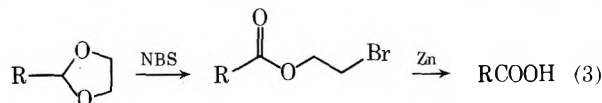
We have been concerned with the general problem of converting dioxolanes into carboxylic acids without employing acid to first remove the protecting group (eq 2). The nonacidic

$$R \diagup \hspace{-0.3em} \underset{O}{\overset{O}{\diamond}} \xrightarrow{H^+} RCHO \xrightarrow{[O]} RCOOH \quad (2)$$
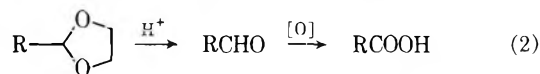
alternative to eq 2 would allow the introduction of acid groups into a molecule containing various acid-sensitive functionalities.[3]

Our solution to this problem is outlined in eq 3. Prugh and McCarthy in 1966[4] showed that cyclic acetals are converted
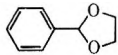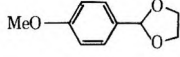
$$R \diagup \hspace{-0.3em} \underset{O}{\overset{O}{\diamond}} \xrightarrow{NBS} R \overset{O}{\diagup\hspace{-0.2em}} O \diagdown\diagup Br \xrightarrow{Zn} RCOOH \quad (3)$$
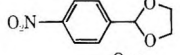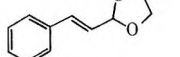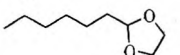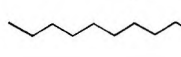
into bromo esters when treated with *N*-bromosuccinimide (NBS).[5,6] Indeed, a variety of dioxolanes give good yields of the corresponding 2-bromoethyl esters when refluxed with NBS in CCl₄ (see Table I). For example, 2-phenyl-1,3-dioxolane gives a 98% yield of 2-bromoethyl benzoate (88% after distillation).

The transformation of eq 3 is completed by a zinc-induced 1,2 elimination which yields the acid upon workup (see Table I). Despite the precedent for this second step,[7,8] a variety of reaction conditions failed to give any acid from 2-bromoethyl benzoate. Zinc in refluxing THF gave no reaction. Even zinc which had been activated with copper sulfate was ineffective and ultraactive zinc from the potassium metal[9a] or sodium naphthalenide[9b] reduction of zinc chloride also failed to promote elimination. Zinc in refluxing methanol or ethanol gives 42–46% benzoic acid plus 47–52% of transesterification product. Ester interchange can be avoided by using zinc in refluxing aqueous THF to give a 44% yield of benzoic acid and a 41% recovery of starting material. Addition of catalytic sodium iodide improves the yield of benzoic acid from this reaction to 86% with only 13% of starting material recovered.

Because of the general catalytic effect of zinc halides,[10,11] we tried a mixture of zinc and zinc chloride. Indeed, this combination of reagents in refluxing THF for 24 h converts

Table I. Conversion of Dioxolanes into Carboxylic Acids

acetal	registry no.	% yield of 2-bromoethyl ester (a)	registry no.	% acid[b,c]	registry no.
	936-51-6	98 (88)	939-54-8	99[d]	65-85-0
	2403-50-1	68 (59)	19263-28-6	96[d]	100-09-4
	2403-53-4	60 (51)	23574-40-5	58[e]	62-23-7
	5660-60-6	91 (75)	39257-72-2	91[e]	621-82-9
	1708-34-5	87 (70)	5454-31-9	91[e]	111-14-8
	4353-06-4	67 (55)	52001-54-4	76[e]	334-48-5

[a] % yield of purified material. [b] Pure by NMR and mp. [c] Based on recovered starting material. [d] Using zinc (5 equiv) and catalytic sodium iodide (2–5 mol %) in refluxing 50% aqueous THF. [e] Using zinc (5 equiv) and zinc chloride (1 equiv) in refluxing dimethyl sulfoxide (Me₂SO).

2-bromoethyl benzoate into benzoic acid (61%) with a 30% recovery of starting material. Cleavage of other 2-bromoethyl esters may require Me$_2$SO as a solvent in order to maintain synthetically useful yields.

Two recent literature methods for the conversion of 2-haloethyl esters to acids offer excellent alternatives for the second step of eq 3. Ho[12] has shown that thiocarbonate ion gives 75–86% yields of acids and Ugi[13] used cobalt(I)–phthalocyanine to cleave bromoethyl and chloroethyl esters to acids.[14]

Experimental Section

^{1}H NMR spectra were obtained on a Varian T-60 nuclear magnetic resonance spectrometer. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected.

The typical experimental procedure for benzaldehyde follows.

2-Bromoethyl Benzoate. 2-Phenyl-1,3-dioxolane (17.8 g, 0.12 mol; prepared from benzaldehyde and 1.2 equiv of ethylene glycol at reflux in benzene containing catalytic p-TsOH with water removal (Dean-Stark trap) for 6 h) was dissolved in 150 mL of CCl$_4$. NBS (21.4 g, 0.12 mol) was added along with a catalytic amount of benzoyl peroxide and the mixture was refluxed overnight. The succinimide was filtered off and the filtrate was washed with aqueous Na$_2$S$_2$O$_3$ and then water. The CCl$_4$ solution was dried (MgSO$_4$) and concentrated to give 26.8 g (98%) of an orange liquid which was distilled to yield 24.1 g (88%) of a colorless liquid: bp 90–92 °C (0.5 mm); NMR (CCl$_4$) δ 3.7 (t, J = 6 Hz, 2 H), 4.7 (t, J = 6 Hz, 2 H), 7.6 (m, 3 H), 8.2 (m, 2 H).

Benzoic Acid. The ester above (1.00 g, 4.36 mmol) was dissolved in 20 mL each of THF and water. Zinc powder[15] (1.43 g, 21.8 g-atom) and sodium iodide (20 mg) were added. The mixture was refluxed for 24 h, cooled, and filtered. Acidification of the filtrate and extraction with ether gave a solution which was further extracted with aqueous NaHCO$_3$. The remaining ether was dried and concentrated to give 0.13 g (13%) of starting material (as determined by NMR). The bicarbonate layer was acidified and extracted with ether to yield 0.46 g (86%) of white solid (benzoic acid), mp 119–121 °C. Thus, the yield of benzoic acid is 99% based on recovered starting material.

Registry No.—Benzaldehyde, 100-52-7; p-anisaldehyde, 123-11-5; p-nitrobenzaldehyde, 555-16-8; cinnamaldehyde, 104-55-2; heptanal, 111-71-7; decanal, 112-31-2; ethylene glycol, 107-21-1.

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(3-Methyl-3-methoxy-1-butynyl)copper, a Useful Reagent for the Generation of Mixed Cuprates

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The use of mixed cuprate (Gilman) reagents derived from terminal alkynes, RC≡CCuR$_T$, for the selective transfer of alkyl or alkenyl groups (R$_T$) was introduced several years ago[1] for the purpose of conserving valuable R$_T$ groups in synthetic processes such as cross coupling or enone conjugate addition. These cuprates are generally formed by reaction of a cuprous

Table I.

3, R =	Registry no.	Substrate	Registry no.	Products[a]	Registry no.	Yield, %
n-Bu	66777-74-0	[cyclohexyl–I]	626-62-0	[cyclohexyl–n-Bu]	1678-93-9	40[b]
n-Bu		[cyclohexenone]	930-68-7	[n-Bu-cyclohexanone]	39178-69-3	100[b]
n-Bu		[PhCH₂CH₂CH₂Br]	4392-24-9	[Ph–CH=CH–CH₂–n-Bu]	829-99-2	62[b]
				[Ph–CH(n-Bu)–CH=CH₂]	40395-23-1	32[b]
i-C₃H₅	66777-75-1	[cyclohexenone]		[isopropenyl cyclohexanone]	6611-97-8	95[b]
t-Bu	66777-76-2	[cyclohexenone]		[t-Bu cyclohexanone]	936-99-2	95[b]
[OTHP structure]	66777-77-3	[dimethoxybenzyl iodide]	66769-61-7	[dimethoxybenzyl OTHP product]	66769-62-8	92[c]

[a] Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for each product. [b] Yield by VPC analysis. [c] Isolated yield.

acetylide (RC≡CCu) with an organolithium compound (R$_T$Li). Although such mixed Gilman reagents have proved to be of considerable value in synthesis, there have been certain practical problems connected with their use. Simple *n*-alkynylcopper compounds such as 1-pentynylcopper are only sparingly soluble in the ususal solvents (tetrahydrofuran (THF) or ether) for cuprate reactions, which can cause mixed cuprate formation to be slow or variable in rate. The use of the more soluble cuprous *tert*-butylacetylide[1b] is not very satisfactory because of the high cost of *tert*-butylacetylene (ca. $1/g).

We have recently described the use of a mixed cuprate system derived from the soluble cuprous acetylide 1 in the preparation of a key intermediate for maytansine synthesis.[2] This readily available and inexpensive reagent is an effective and practical alternative to cuprous *tert*-butylacetylide. We describe here the details for the preparation of the precursor acetylene 2 as well as the general applicability of 1 to the formation of highly reactive cuprates 3.
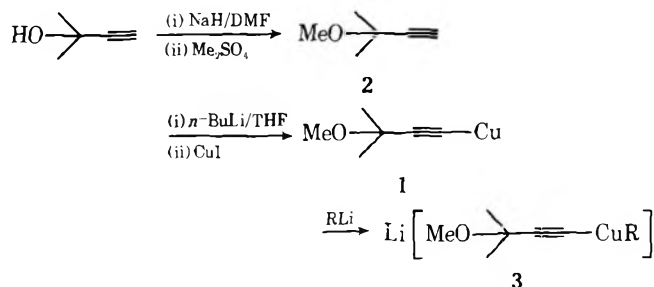
The requisite acetylene, 3-methyl-3-methoxy-1-butyne (2), is easily prepared in 84% yield by treatment of commercially available 2-methyl-3-butyn-2-ol[3] with 1.5 equiv of sodium hydride followed by the addition of 1.5 equiv of dimethyl sulfate, without prior purification of the reagents or solvent; bp of 2, 77–80 °C (lit.[4] bp 80 °C).

The addition of a THF solution of the lithio derivative of 2 to a suspension of CuI in THF at 0 °C produces a red-orange solution of 1. Upon concentration under reduced pressure, 1

is obtained as a red oil which solidifies upon trituration with hexane. 1 is very soluble in THF, moderately soluble in ether (ca. 0.1 M at 0 °C), and insoluble in hexane. Mixed cuprates 3 were prepared by the addition of 1 to the desired lithio reagent at −78 °C. The results of several representative reactions as shown in Table I indicate the general utility of 1 as a precursor for mixed Gilman reagents.[5]

Experimental Section

3-Methoxy-3-methyl-1-butyne (2). A slurry of sodium hydride (7.2 g, 150 mmol; 50% in mineral oil) in 150 mL of DMF was cooled to 0 °C, and 8.4 g (100 mmol) of 2-methyl-3-butyn-2-ol[3] dissolved in 100 mL of DMF was added dropwise over 30 min. The reaction mixture was stirred for an additional 30 min, and dimethyl sulfate (19 g, 14.3 mL, 150 mmol) was slowly added over a 20-min period. After stirring for an additional 5 min at 0 °C, the flask was allowed to warm to room temperature and stirring was continued for 45 min. Excess sodium hydride was then destroyed by the dropwise addition of glacial acetic acid to the cooled (0 °C) reaction mixture. Direct distillation through a 30 cm Vigreux column afforded 8.2 g (84%) of pure material: bp 77–80 °C (lit.[4] bp 80 °C); IR (liquid film) 3290, 1080 cm^{-1}; NMR (CDCl₃) δ 3.35 (s, 3 H), 2.38 (s, 1 H), 1.46 (s, 6 H).

Representative Cuprate Reaction Employing Cuprous Acetylide 1. A 1 M solution of 3-methoxy-3-methyl-1-butyne (2) in THF was treated at 0 °C with 1 equiv of *n*-butyllithium. The clear, colorless solution was stirred for 5–10 min and transferred into a slurry of cuprous iodide in THF (1 mmol/mL), precooled to 0 °C. The resulting red-orange solution of 1 was then stirred at this temperature for 30 min and subsequently transferred either by syringe or canula to a −78 °C solution of the desired lithio reagent (0.5–1 M). Under the above conditions, a virtually instantaneous reaction occurred, yielding a pale yellow to colorless solution of the mixed cuprate 3. The use of the more concentrated conditions led to the appearance of a white precipitate during cuprate formation (presumably lithium iodide) which readily dissolved at around −30 °C to give homogeneous solutions of 3. A typical reaction then involved adding the substrate neat or as a solution in THF at −78 °C followed by warming to −20 °C and stirring for several hours. Standard extractive workup employing pH 8 aqueous ammonia in saturated ammonium chloride gave products which were either virtually pure (by GLC and NMR) or, in a few cases, contaminated by small quantities of the conjugated diyne, resulting from oxidative coupling of the acetylenic ligand.

The formation of the mixed Gilman reagents 3 can also be accomplished satisfactorily by the addition of the organolithium reagent to a solution of the cuprous acetylide 1.

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Electrochemical Reduction of 1-Benzyl-3-carbamoylpyridinium Chloride, a Nicotinamide Adenine Dinucleotide Model Compound

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The electrochemical reduction of pyridine nucleotides, e.g., nicotinamide adenine dinucleotide (NAD$^+$), and related model compounds has been the subject of active investigation, extensively reviewed.[2-4] It has been consistently found that one- or two-electron reduction products are formed, i.e., respectively tetrahydrobipyridine derivatives and dihydropyridines.

Only in a few cases has the detailed structure of the tetrahydrobipyridines been determined,[5] while generally the structure has been postulated exclusively on the grounds of UV spectroscopic evidence. It appears that further research on the structure of these dimeric compounds is highly desirable, also in view of their possible biological role; for example, a dimer from the NAD$^+$ has been reported[6] to be involved in the plant phenol oxidase activity.

In this paper we report the results obtained in the electrochemical one-electron reduction of 1-benzyl-3-carbamoylpyridinium chloride (1), a model compound strictly related to the natural coenzyme. The previously reported[7,8] polarographic behavior of 1-benzyl-3-carbamoylpyridinium ion has been confirmed by our experiments. It is essentially characterized by two reduction waves, the first one (wave A) pH independent and the second (wave B) appearing only at alkaline pH values. The first step implies the reversible transfer of one electron to the pyridinium cation to give a radical which irreversibly dimerizes, as shown by fast-scan cyclic voltammetry tests.[9]

Electrolyses of 1 have been performed at different potential values within the wave A plateau, in about 0.1 M solution buffered in the pH range 8 to 10. Under these conditions, a precipitate is invariably formed and adsorption effects, already noted by other workers,[9] were pronounced enough to block the electrode surface and reduce to zero value the current within a short time after the beginning of the electrolysis. This difficulty has been overcome using a 1:1 (v/v) mixture of benzene and aqueous solution under vigorous stirring. In such a way, the precipitate is washed away from the electrode

and transferred into the interphase aqueous solution–benzene, ensuring successful completion of the electrolysis. Under these conditions, a faradaic n value of 1 ± 0.1 has been measured.

From the crude reduction product the dimers 2 and 3 have been isolated and purified following the procedure described in the Experimental Section. The UV spectra of both 2 and 3 are closely similar and will be discussed in detail below.

However, a feature must be immediately emphasized,
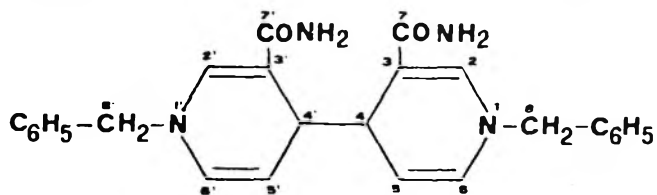
2 and 3

namely the absence of any 1,2-dihydropyridine long-wavelength (above 400 nm) absorption, which excludes structures involving dimerization at position 2, and thus restricts the possible structure of these products to 4,4'-, 6,6'- or 4,6'-linked dimers.

In the ^{1}H NMR spectra of both 2 and 3 (Table I) only 13 protons are detectable, namely 5 aromatic, 3 vinyl, 2 methylene, 1 methine, and 2 amide protons, showing the symmetry of the structure and disproving the occurrence of mixed dimers. The following additional ^{1}H NMR data are relevant to the assignment of the structure: (i) the chemical shifts of the methine protons in both 2 and 3 are clearly indicative of 1,4- rather than 1,6-dihydropyridine moieties, by comparison with ^{1}H NMR spectra of the dihydropyridine monomers 4 and 5;[10] (ii) the value of the coupling constant ($J \approx 8$ Hz) between the two hydrogens on the unsubstituted double bond indicates that its position is α with respect to the ring nitrogen atom, as it is known that this value is greater (about 10 Hz)[5a,10-12] for double bonds in position β with respect to the nitrogen atom. Therefore, these data provide reasonable evidence for a symmetric dimeric 4,4'-linked structure for both 2 and 3.

Table I. ^{1}H NMR Data for Dimers 2 and 3

2			3	
δ, ppm	J, Hz	Protons	δ, ppm	J, Hz
7.5–7.1		aromatic	7.5–7.1	
7.24 (d)	1.2	H$_2$ + H$_{2'}$	7.13 (d)	1.4
6.97		amide	6.33	
6.02 (dd)	1.2	H$_6$ + H$_{6'}$	5.89 (dd)	1.4
	7.9			7.8
4.36 (dd)	4.7	H$_5$ + H$_{5'}$	4.47 (dd)	4.6
	7.9			7.8
4.35		benzyl	4.30	
3.24 (d)	4.7	H$_4$ + H$_{4'}$	3.35 (d)	4.6

Table II. ^{13}C NMR Data for Compounds 2, 3, 4, and 5

2 δ, ppm	carbon atoms	3 δ, pm	4 δ, ppm	carbon atoms	5 δ, ppm
169.3	C$_7$ + C$_{7'}$	170.3	169.0	C$_7$	167.5
138.1	C$_2$ + C$_{2'}$	138.5	137.8	C$_2$	144.9
130.2	C$_6$ + C$_{6'}$	129.7	129.5	C$_6$	47.0
102.2	C$_5$ + C$_{5'}$	102.2	101.8	C$_5$	109.1
101.6	C$_3$ + C$_{3'}$	102.0	100.3	C$_3$	99.2
56.2	C$_8$ + C$_{8'}$	56.3	55.9	C$_8$	58.5
38.9	C$_4$ + C$_{4'}$	39.2	22.3	C$_4$	122.5
	benzene rings				
138.2	C$_1$	138.0			
128.3	C$_3$ + C$_5$	128.2			
127.1	C$_2$ + C$_6$	127.2			
127.1	C$_4$	127.0			

Clear-cut evidence has been attained from a detailed analysis of ^{13}C NMR spectra of compounds **2, 3, 4,** and **5** (Table II); comparison of the spectra shows that **2** and **3** are very similar to **4** and different from **5**. In particular the chemical shift values of the methine carbon atom of the dimers

4   **5**
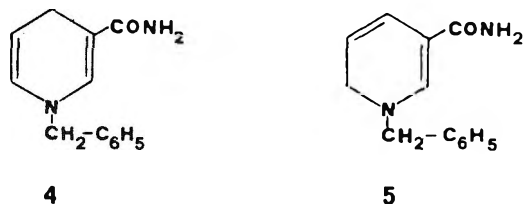
(δ ~39) must be compared with the chemical shift values of the C-4 in the 1,4-dihydropyridine monomer **4** (δ 22.3) and of the C-6 in the 1,6-dihydropyridine monomer **5** (δ 47.0).

Since it is well known that the introduction of a carbon as a substituent implies a low-field shift of the carbon on which the substitution takes place, and in analogous cases a shift has been found of about 16 ppm,[13] the value observed for the methine carbon in both **2** and **3** fits the value expected for 4,4'-linked dimers. As a whole, ^{1}H and ^{13}C NMR spectra unambiguously demonstrate a 1,1'-dibenzyl-3,3'-dicarbamoyl-1,1',4,4'-tetrahydro-4,4'-bipyridine structure for both **2** and **3,** which are therefore a diasteroisomeric pair with respect to the C_4–$C_{4'}$ stereochemistry.

Both compounds **2** and **3** show two UV absorption bands at ca. 270 and 350 nm, respectively; at first sight, such spectral feature is surprising for 1,4-dihydropyridine dimeric structures as **2** and **3,** since it has been claimed[14-16] that the presence of two maxima in the 250–370-nm region is rather typical of 1,6-dihydropyridine dimeric structures. For instance, Wallenfels et al.[14] on treating 1-benzyl-3-carbamoylpyridinium cation with various reducing agents (Cr^{2+}, Mg powder, etc.) have isolated only one dimer, identified as 1,1'-dibenzyl-3,3'-dicarbamoyl-1,1',6,6'-tetrahydro-6,6'-bipyridine on the grounds of the presence in the UV spectrum of two absorption maxima at 275 and 355 nm and of the ^{1}H NMR spectrum as well. We have performed the reduction of **1** with Mg powder, following the procedure reported.[14]

In our hands, the reaction has given two dimers, identical in all respects to **2** and **3.** In particular, NMR evidence has shown that the compound identified by Wallenfels as a 6,6'-linked dimer is identical to **2,** and therefore must be regarded as a 4,4'-linked dimer.[17]

From the above considerations, it is clear that 4,4'-linked dimers as well can display UV spectra characterized by two absorption bands in the 250–370-nm region. While, undoubtedly, the intriguing question concerning the spectra-structure correlations for this class of compounds deserves careful reinvestigation, the present data clearly show, contrary to the current literature statements, that the presence of two absorption bands in the 250–370-nm region cannot be used as a diagnostic tool for structures implying dimerization at the 6 position.

Experimental Section

Compound **1** was prepared according to ref 19. The melting points were taken upon a Kofler apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 177 grating spectrophotometer as Nujol mulls and UV spectra on a Perkin-Elmer 402 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in CD_3SOCD_3 on a Varian XL-100-15 spectrometer; the chemical shifts are reported as δ units relative to Me$_4$Si (δ is 0 ppm) as internal standard. The same apparatus described in a previous paper[20] was used for the electrochemical measurements. Britton–Robinson and NH_3–NH_4Cl buffers were used; the solutions were deoxygenated with 99.99% pure nitrogen or argon, and the temperature was kept at 25.0 ± 0.1 °C. Macroscale electrolysis used a mercury pool electrode (area 63.6 cm^2) in a water-jacketed three-compartment cell; agar salt bridges

were inserted on the counter and reference sides of the medium-porosity glass frits separating the compartments. The reference compartment contained a saturated calomel electrode and the counter compartment contained a platinum-gauze cylinder immersed in saturated KCl solution. Buffer solutions were preelectrolyzed at the same potential of the electrolysis. Nitrogen or argon, equilibrated by bubbling through buffer solution, was continuously passed through the cell during the electrolysis.

Electrochemical Reduction of 1-Benzyl-3-carbamoylpyridinium Chloride (1). In a typical run, 6.0 g of **1** was dissolved in 300 mL of 0.1 M NH_3–0.1 M NH_4Cl aqueous solution, an equal volume of benzene was added, and the resulting system was electrolyzed at −1.30 V under vigorous magnetic stirring. Usually the electrolysis took about 10 h to reach completion, as inferred from the complete disappearance of the reduction wave (A) of compound **1** and from the constant value of the current, equal to that obtained at the same potential with a solution containing only the supporting electrolyte. During the electrolysis, the deviation of the voltmeter was ±1 mV with respect to the imposed potential.

After the electrolysis, the benzene–water suspension of the solid reaction product was filtered and small amounts of the mercury pool were removed to give a crude reaction mixture (5.0 g), which was suspended in 2-propanol (40 mL) and stirred at room temperature for 5 min; the solid recovered by filtration, further extracted with boiling 2-propanol (40 mL), recovered by filtration, aand dried under vacuum was essentially pure **2** (2.3 g). An analytical sample of **2** was obtained upon crystallization from MeOH: **2;** mp 180–181 °C dec; UV$_{max}$ (MeOH) 268 (ϵ 6250), 348 nm (ϵ 7250); IR $\bar{\nu}$ 3370, 3170, 1660, 1630, 1595, 1585 cm^{-1}; NMR see Tables I and II. Anal. Calcd for $C_{26}H_{26}N_4O_2$: C, 73.21; H, 6.14; N, 13.14. Found: C, 72.86; H, 5.83; N, 13.23.

The combined mother liquors were evaporated to dryness under reduced pressure and the oily brown residue was treated with cold MeOH (20 mL); the solid formed was recovered by filtration, washed with cold MeOH, and crystallized twice from 2-propanol to give pure **3** (0.6 g): mp 188–189 °C dec; UV$_{max}$ (MeOH) 276 (ϵ 6000), 354 nm (ϵ 8100); IR $\bar{\nu}$ 3470, 3350, 3180, 1680, 1670, 1640, 1600, 1580, 1565, 1555 cm^{-1}; NMR see Tables I and II. Anal. Calcd for $C_{26}H_{26}N_4O_2$: C, 73.21; H, 6.14; N, 13.14. Found: C, 72.98; H, 6.09; N, 12.91.

Chemical Reduction of 1. Mg powder (8.0 g) was added portionwise to a stirred solution of **1** (8.0 g) in H_2O (160 mL) containing NH_4Cl (14.0 g) and 33% aqueous NH_3 (5 mL), kept at 40–45 °C, during 2.5 h. After this time, the reaction mixture was stirred at room temperature for 4 h and the solid was collected by suction and treated with H_2O and CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and evaporated; the residue was worked up as above, to give **2** and **3.**

Registry No.—**1,** 5096-13-9; **2–3** isomer 1, 66788-25-8; **2–3** isomer 2, 66788-26-9; **4,** 952-92-1; **5,** 2288-38-2.

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(17) ^{1}H NMR data reported by Wallenfels:[10] δ 7.33, 6.10, 4.38 (vinyl protons), 3.23 (methine proton), 7.08 (NH$_2$). It should be pointed out that Kano et al.[18]

by photochemical reduction of 1-benzyl-3-carbamoylpyridinium cation have obtained a dimer, to which they assigned a 6,6'-linked structure by comparison with the product reported by Wallenfels.[14] Consequently, the Kano's photoproduct as well as Kano's is identical to 2 and therefore must be regarded as a 4,4'-linked dimer.

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Facile Preparation of Optically Active c-2,t-3-Dimethyl-r-1-methoxycyclopropane

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The thermal chemistry of cyclopropane and its derivatives has attained considerable theoretical importance.[3] Elegant experimental studies[4] have complemented and supported the earlier conceptual insights. Mechanistic attention is now shifting to an understanding of substituent and activation effects on reaction stereochemistry as well as the correspondence of observed kinetic parameters with the thermochemical estimates.

For the detailed investigation of the rearrangement chemistry of 2,3-dimethyl-r-1-methoxycyclopropane[5,6] and an eventual determination of the dynamic stereochemistry of the stereomutation process, we required each enantiomer of the chiral isomer (7). In this note we present a convenient as well as reliable synthesis of optically active c-2,t-3-dimethyl-r-1-methoxycyclopropane (7).

Results and Discussion

Our approach to the preparation of optically active cyclopropane 7 was patterned after the generalized DePuy synthesis[7] of cyclopropanols as illustrated in Scheme I.

The cupric trifluoromethanesulfonate catalyzed cyclo-

propanation of *trans*-2-butene (1) was accomplished in 33% isolated yield.[9,10] Basic saponification of the ethyl c-2,t-3-dimethyl-r-1-cyclopropanecarboxylate (2) was found to be unreliable, but transesterification with formic acid[11] afforded c-2,t-3-dimethylcyclopropane-r-1-carboxylic acid (3) in 82% yield. The resolution of 3 was achieved through fractional recrystallization of the diastereomeric quinine salts.[12] Optically active carboxylic acid 3 was then transformed into optically active c-2,t-3-dimethyl-r-1-methoxycyclopropane (7) through a sequence beginning with a methyllithium treatment and subsequent hydrolysis. Baeyer–Villiger oxidation of the resulting methyl ketone with trifluoroperacetic acid, treatment with methyllithium to produce the cyclopropanol 6, and immediate methylation with diazomethane catalyzed by boron trifluoride etherate or aluminum trichloride[13] completed the synthesis. An alternate direct conversion of the acetate 5 into the ether 7 employing methyllithium treatment and subsequent reaction with dimethoxycarbonium tetrafluoroborate[14] was less effective.

The overall yield of 7 was 2.7% based on ethyl diazoacetate. The optically active cyclopropyl ether 7, with $[\alpha]^{22}_{237} +13.4°$, was found to be chromatographically and spectroscopically identical with an authentic sample obtained from the Schöllkopf reaction between *trans*-2-butene, dichloromethyl methyl ether, and methyllithium.[15]

Experimental Section

^{1}H NMR spectra were obtained on a Varian T-60 instrument. Infrared spectra were recorded on a Beckman IR-20 spectrophotometer. Mass spectra were secured on a Finnigan 1015D quadrupole mass spectrometer with a variable leak inlet, an ion source temperature of 55 °C, and an ionization potential of 70 eV. Analytical and preparative gas chromatographic separations were achieved on Varian Model A90-P and 1400 instruments. Optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter.

Cupric Trifluoromethanesulfonate.[16] In a 750-mL conical flask was placed 12.5 g (101 mmol) of cupric carbonate in 280 mL of acetonitrile. To the stirred suspension, 25.0 g (167 mmol) of trifluoromethanesulfonic acid was cautiously added over 10 min. The reaction mixture was stirred an additional 30 min, filtered into a 1-L round-bottom flask, and concentrated under reduced pressure to give a blue solid which was dried by heating in the same vessel with a Fisher burner at 0.1 Torr to give 28.9 g (96%) of cupric trifluoromethanesulfonate.

(±)-Ethyl c-2,t-3-Dimethyl-r-1-cyclopropanecarboxylate (2).[9,10] *trans*-2-Butene (1.2 L) was condensed in a 5-L round-bottom flask fitted with an addition funnel, a dry ice–acetone cooled condenser,[17] a nitrogen inlet, and a paddle stirrer. Anhydrous ethyl ether (1 L) and finely ground cupric trifluoromethanesulfonate (20.0 g, 55 mmol) were added to the flask before ethyl diazoacetate[8] (82.0 g, 720 mmol) in ethyl ether was added dropwise over 1.5 h. The solution was allowed to reflux as it was stirred for 4.5 h. It was then stirred without the reflux condenser for 2 h as the alkene was boiled off. A solution of 50% ammonium hydroxide was added to the dark residue until two distinct phases were formed. Ammonium hydroxide washes were continued until clear. After washing with water (3 × 75 mL), the ethereal solution was dried (MgSO₄), filtered, and concentrated by distillation [bp 34–37 °C (9 Torr)] to give 34.0 g (33%) of 2, which was identified from its ^{1}H NMR [(60 MHz, CDCl₃) δ 4.18 (ester methylene, q, $J = 7$ Hz, 2 H) and 1.60–0.93 (methyl and cyclopropyl, m, 12 H)], IR [(neat film) $\bar{\nu}_{CH}$ 3010–2885, $\bar{\nu}_{C=O}$ 1755, and $\bar{\nu}_{C-O}$ 1240 cm⁻¹], and electron impact mass spectra [(70 eV) m/e 142 (M⁺), 127 (M⁺ – CH₃), 97 (M⁺ – C₂H₅O), and 69 (M⁺ – C₂H₅CO₂)].

(±)-c-2,t-3-Dimethyl-r-1-cyclopropanecarboxylic Acid (3). A 500-mL three-neck round-bottom flask was fitted with an addition funnel and a nitrogen inlet, as well as with a distillation head and condenser. The flask was charged with 63.0 g (440 mmol) of (±)-ethyl c-2,t-3-dimethyl-r-1-cyclopropanecarboxylate (2), formic acid (5.1 g, 110 mmol), and 2 drops of concentrated sulfuric acid. Ethyl formate was distilled from the mixture at 54 °C while additional formic acid (25.3 g, 550 mmol) was added at a rate equal to the distillation throughput rate. The distillation was continued until only formic acid was being collected. Vacuum distillation [bp 52–54 °C (0.2 Torr)] afforded 41.3 g (82%) of (±)-c-2,t-3-dimethyl-r-1-cyclopropanecarboxylic acid (3), whose structure was confirmed from its ^{1}H NMR [(60

Scheme I
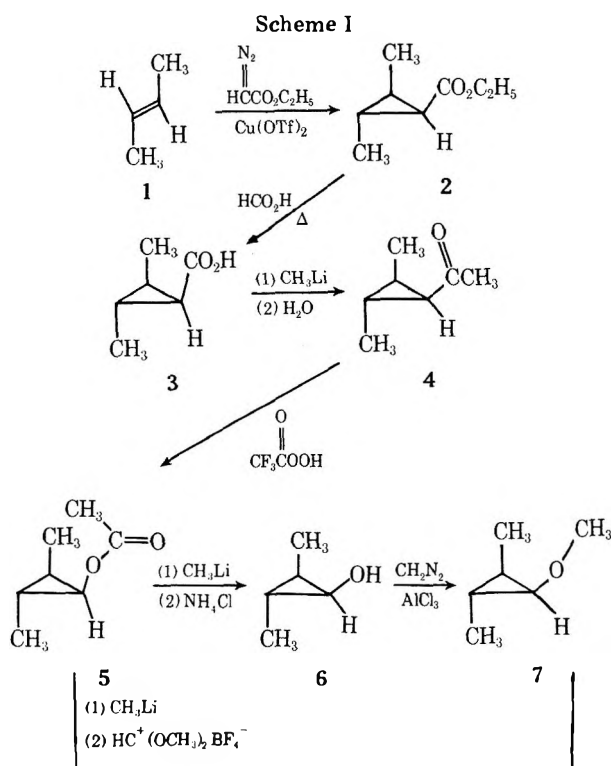
MHz, CDCl$_3$) δ 12.04 (carboxyl, s, 1 H) and 1.41–0.62 (methyl and cyclopropyl, m, 9 H)] and IR spectra [(neat film) $\bar{\nu}_{OH}$ 3520–3160, $\bar{\nu}_{C-H}$ 2880, $\bar{\nu}_{C=O}$ 1695, and $\bar{\nu}_{C-O}$ 1240 cm^{-1}], as well as from the electron impact mass spectrum (70 eV) of the corresponding methyl ester (from a diazomethane treatment) [*m/e* 128 (M$^+$), 113 (M$^+$ – CH$_3$), 97 (M$^+$ – CH$_3$O), and 69 (M$^+$ – CH$_3$CO$_2$)].

(−)-*c*-2,*t*-3-Dimethyl-*r*-1-cyclopropanecarboxylic Acid [(−)-3]. Diastereomeric salts were prepared from (±)-*c*-2,*t*-3-dimethyl-*r*-1-cyclopropanecarboxylic acid (3; 32.0 g, 280 mmol) and quinine monohydrate (50.0 g, 150 mmol) in 400 mL of absolute ethanol in a 3-L round-bottom flask. The mixture was heated at reflux for 1 h before 1.6 L of water was added. After 24 h, the crystals were collected (60.5 g; mp 124–126 °C) and redissolved in 2:1 water/ethanol. After an additional 60 h, the crystals were collected (36.0 g; mp 134–136 °C), redissolved in 1:1 water/ethanol, and allowed to stand for an additional 48 h. The collected crystals (34.4 g; mp 137–138 °C) were heated with aqueous methanol at 70 °C. After removing the methanol by distillation, the aqueous solution was made acid with dilute hydrochloric acid. The product was extracted into ether (5 × 50 mL), washed with water (3 × 30 mL), dried (MgSO$_4$), filtered, and distilled [bp 74–76 °C (6–8 Torr)] to give 5.5 g (17%) of (−)-*c*-2,*t*-3-dimethyl-*r*-1-cyclopropanecarboxylic acid (3), [α]$^{22}_{589}$ −23.72° (*c* 0.0137, C$_2$H$_5$OH).^{12,19}

(−)-*c*-2,*t*-3-Dimethyl-*r*-1-cyclopropane Methyl Ketone [(−)-4]. To a 2-L three-neck round-bottom flask fitted with a magnetic stirring bar, addition funnel, and reflux condenser was added (−)-*c*-2,*t*-3-dimethyl-*r*-1-cyclopropanecarboxylic acid [(−)-3; 6.1 g, 54 mmol] and 250 mL of anhydrous ether. Methyllithium (370 mmol) in ethyl ether was rapidly added, and the reaction mixture was subsequently heated at reflux for 1 h. The reaction was quenched with saturated ammonium chloride solution and extracted into ether. After washing with water (3 × 50 mL), drying (MgSO$_4$), and filtering, the optically active product^{20} (4.68 g, 82%) was isolated by distillation: bp 44–48 °C (32 torr); [α]$^{22}_{589}$ −27.17° (*c* 0.0138, C$_2$H$_5$OH). The structure of the product was confirmed from its ^{1}H NMR [(60 MHz, CDCl$_3$) δ 2.08 (methyl, s, 3 H), 1.57 (methine, m, 1 H), and 1.28–0.90 (methyl and cyclopropyl, m, 8 H)], IR [(neat film) $\bar{\nu}_{C-H}$ 3010–2880 and $\bar{\nu}_{C=O}$ 1685 cm^{-1}], and electron impact mass spectra [(70 eV) *m/e* 112 (M$^+$), 97 (M$^+$ – CH$_3$), and 69 (M$^+$ – CH$_3$CO)].

(−)-*c*-2,*t*-3-Dimethyl-*r*-1-cyclopropyl Acetate [(−)-5]. In a 250-mL three-neck round-bottom flask fitted with a magnetic stirring bar, addition funnel, and reflux condenser was placed (−)-*c*-2,*t*-3-dimethyl-*r*-1-cyclopropyl methyl ketone (4.7 g, 42 mmol), sodium hydrogen phosphate (28.3 g, 200 mmol), and methylene chloride (50 mL). Freshly prepared trifluoroperacetic acid [from freshly distilled trifluoroacetic anhydride (20.8 g, 104 mmol) and 90% hydrogen peroxide (4 mL)] was added to the mixture at a rate which produced a steady reflux. The reaction mixture was stirred and heated at reflux for 8 h. After washing with saturated ammonium chloride (3 × 15 mL) and water (3 × 15 mL), the product was extracted into ether (5 × 25 mL), dried (MgSO$_4$), filtered, and distilled [bp 46–48 °C (30 torr)] to yield 3.6 g (67%) of the optically active acetate, [α]$^{22}_{589}$ −44.88° (*c* 0.0088, C$_2$H$_5$OH). The product structure was confirmed from its ^{1}H NMR [(60 MHz, CDCl$_3$) δ 3.65 (methine, m, 1 H), 1.98 (acetate methyl, s, 3 H), 1.2–0.9 (ring methyls, m, 6 H), and 0.9–0.4 (cyclopropyl, m, 2 H)], IR [(neat film) $\bar{\nu}_{C-H}$ 3020–2890, $\bar{\nu}_{C=O}$ 1755, and $\bar{\nu}_{C-O}$ 1240 cm^{-1}], and electron impact mass spectra [(70 eV) *m/e* 128 (M$^+$), 113 (M$^+$ – CH$_3$), and 69 (M$^+$ – CH$_3$CO$_2$)].

(+)-*c*-2,*t*-3-Dimethyl-*r*-1-methoxycyclopropane (7). To a 250-mL three-neck round-bottom flask fitted with a magnetic stirring bar and an addition funnel containing (−)-c-2,*t*-3-dimethyl-*r*-1-cyclopropyl acetate (5; 3.0 g, 24 mmol) in 100 mL of anhydrous ether was added freshly prepared methyllithium (52 mmol) in ether. After stirring the reaction mixture for 1 h at room temperature, saturated boric acid solution was added (30 mL) and the organic phase was dried (MgSO$_4$), filtered, and analyzed by infrared spectroscopy; $\bar{\nu}_{C=O}$ at 1755 cm^{-1} had disappeared and a $\bar{\nu}_{O-H}$ at 3650–3150 cm^{-1} had appeared, indicating the presence of the cyclopropanol 6. Aluminum chloride (50 mg) was added to the ethereal solution before diazomethane^{18} was bubbled through in a stream of nitrogen. The reaction was followed by infrared spectroscopy, where the disappearance of $\bar{\nu}_{O-H}$ after 10 h signaled the end of the reaction. (+)-*c*-2,*t*-3-Dimethyl-*r*-1-methoxycyclopropane was isolated in 18% yield by preparative gas chromatography utilizing a 4.6 m × 3.2 mm, 10% SE-30 on Chromosorb W stainless steel column operated at 75 °C, [α]$^{22}_{237}$ +13.4° (*c* 0.095, C$_2$H$_5$OH). The optically active product was found to be identical both chromatographically and spectroscopically with authentic racemic material.^{15}

(±)-*c*-2,*t*-3-Dimethyl-*r*-1-methoxycyclopropane (7). An authentic sample of the cyclopropyl ether was prepared by the method of Schöllkopf.^{15}

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(20) An identical procedure from (+)-3 gave (+)-4,^{19} [α]$^{22}_{589}$ +5.38°.

# A Novel and Convenient Synthesis of Dibenz[a,c]anthracene

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Dibenz[*a,c*]anthracene (1) is a relatively rare and expensive polycyclic hydrocarbon available synthetically only through complex multistep procedures.^{1} Consequently, relatively little is known concerning its chemistry or that of its derivatives, few of which are known.^{1} However, 1 has been found to be a weak tumor initiator,^{2} stimulating interest in its chemical and biological properties and the nature of its potentially activated metabolite(s).

We now wish to report an unexpectedly simple and conve-

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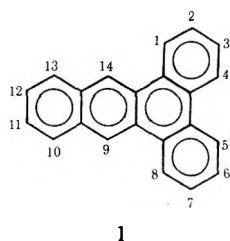
nient synthesis of 1. The method involves direct reductive cyclization of 2-(9'-phenanthroyl)benzoic acid (2) to 1 with hydroiodic acid in refluxing acetic acid. The keto acid 2 is readily available through reaction of phthalic anhydride with the Grignard reagent of 9-bromophenanthrene.[3]


2   3
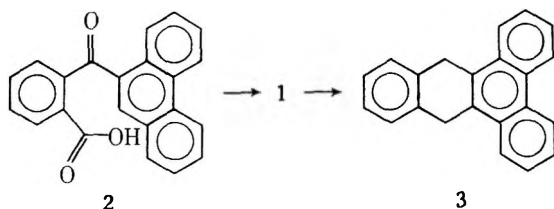
Initial experiments with 2 were carried out with red phosphorus and HI with the expectation that the product would be the reduced acid 4. The conditions employed were patterned after those described for reduction of other aryl keto acids, utilizing a large excess of P and a reaction period of 10 days.[4] The major product (75%), obtained as fine white needles, mp 205.5–206.5 °C, showed no carbonyl absorption in the infrared region, while the integrated proton NMR spectrum exhibited a benzylic peak as a sharp singlet at δ 4.50 and aromatic protons consistent with the 9,14-dihydrodibenz[a,c]anthracene structure 3. In confirmation of this assignment, treatment of 3 with o-chloranil in refluxing benzene gave 1 essentially quantitatively. Compound 1 was also obtained as a minor product (15%) of reductive cyclization of 2, affording a 90% net overall yield of 1. When reaction time was decreased to 1 day, 1 was obtained as essentially the sole product (90%). When the proportion of red phosphorus was decreased or this element eliminated entirely, 1 was also obtained as the sole product in excellent yield. It appears, therefore, that 1 is the primary product of reduction of 2 by HI, and 3 is formed through relatively slower further reduction of 1.

4   5

6
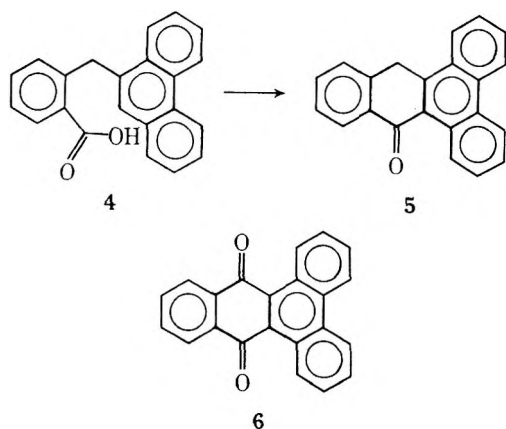
Formation of 1 from 2 is explicable through either (A) reduction to 4 followed by HI catalyzed cyclization to the ketone 5 and reduction of the latter to 1 or (B) initial cyclization of 2 to the quinone 6 followed by reduction of the latter to 1. Reduction of quinones by P and HI to dihydro and further hydrogenated derivatives is a known reaction, although vigorous conditions (200 °C, long reaction periods) are generally employed.[1,4,5] To test the latter possibility, the quinone 6 was

synthesized by cyclization of 2 with sulfuric acid and treated with HI under the optimum conditions employed for reduction of 2. Dibenz[a,c]anthracene was obtained in good yield, supporting the feasibility of path B. Attempted synthesis of the reduced acid 4 by Clemmensen or Wolff–Kishner reduction afforded only recovered 2 and 4-(9-phenanthryl)-phthalazinone (7), respectively. Although Bergmann and Berlin[6] report Clemmensen reduction of 2 to 4, they provide only minimal detail and this reaction could not be repeated. Incidentally, cyclization of 2 to the quinone did not take place under the strongly acid conditions of this reaction nor in liquid HF, suggesting that path B is less likely than path A. That reduction of 2 by HI most likely precedes cyclization is further supported by reactions carried out for shorter reaction periods (7–10 h) which furnished mixtures of products shown to contain as much as 60% of 4 by NMR spectroscopy (characteristic benzylic peak at δ 4.9). It appears likely, therefore, that while both paths A and B are feasible, that A predominates because of the greater facility of reduction than cyclization of 2.

7
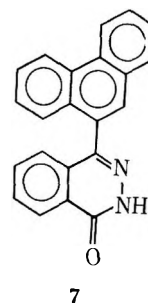
The unexpected ease of cyclization of 4 and/or 2 in comparison with analogous keto acids is ascribed to the relatively high olefinic character of the phenanthrene 9,10 bond in these compounds. Analogous reaction with P and HI of o-(1-naphthoyl)benzoic acid, which lacks such a bond, furnished only the product of carbonyl reduction, o-(1-naphthylmethyl)benzoic acid.

These experiments suggest that HI may be a generally useful reagent for selective reduction of quinones directly to the corresponding aromatic hydrocarbons and for selective reduction of the carbonyl groups of keto acids, an important step in the synthesis of polycyclic arenes.[1] Research is in progress to examine these possibilities.

Conversion of dibenz[a,c]anthracene to 10,11-dihydrodibenz[a,c]anthracene, a key intermediate in the synthesis of the diolepoxide derivative 8, a potential biologically active metabolite[8] of 1, has been described recently;[7] synthesis of 8 will be reported separately.

8
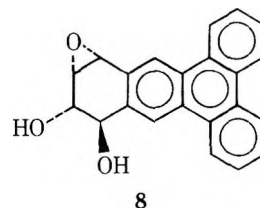
Experimental Section

9,14-Dihydrodibenz[a,c]anthracene (3). A heterogeneous solution of 2[3] (5.2 g, 16 mmol), red phosphorus (4.5 g, 144 mmol), and 50% HI (30 mL) in glacial acetic acid (240 mL) was refluxed for 3 days and then cooled and poured into water. The precipitate was filtered, washed consecutively with water and ethanol, then dried under vacuum. The product was crystallized from benzene to provide 3 (3.0 g) as silky needles: mp 205.5–206.5 °C; NMR (CDCl$_3$) δ 4.50 (s, 4, benzylic), 7.15–7.48 (m, 4, H$_{10-13}$), 7.48–7.80 (m, 4, H$_{2,3,6,7}$), 7.98–8.40 (m, 2, H$_{1,8}$), and 8.57–8.90 (m, 2, H$_{4,5}$). The second crop contained a mixture of 1 and 3 (1.0 g) in the ratio of 1:2. Overall yields of 3 and 1 are 75 and 15%, respectively.

A similar reaction employing a reaction period of 10 days as reported earlier for reduction of other keto acids to acids[4] afforded essentially the same yield of 3 (74%).

Dibenz[a,c]anthracene (1). (1) Dehydrogenation of 3. Reaction of 3 (4.73 g, 17 mmol) with o-chloranil (4.6 g, 19 mmol) was carried out in refluxing freshly distilled benzene (100 mL) for 20 h. The reaction mixture was cooled and chromatographed on a short column of neutral alumina eluted with benzene. The product was recrystallized from benzene to afford 1 as fine white needles (4.65 g, 98%): mp 205–206 °C (lit.[8] mp 200–201.5 °C); NMR (CDCl$_3$) δ 7.38–7.78 (m, 6, H$_{2,3,6,7,11,12}$), 7.86–8.20 (m, 2, H$_{10,13}$), 8.33–8.87 (m, 4, H$_{1,4,5,8}$), and 9.05 (s, 2, H$_{9,14}$).

(2) Reduction of 2 with P/HI. Reaction of 2 (1.3 g, 4 mmol) with red phosphorus (0.37 g, 12 mmol) and 50% HI (10 mL) was carried out in refluxing glacial acetic acid (80 mL) for 24 h and worked up according to the procedure employed for 3. There was obtained essentially pure 1 (1.03 g, 93%) identical by NMR and TLC with an authentic sample.

(3) Reduction of 2 with HI. Repetition of the previous reaction with omission of P gave 1 (1.03 g, 94%). The latter was dissolved in the minimum volume of benzene and purified by passage through a short column of Florisil and recrystallized from ethanol to furnish pure 1 (932 mg, 86%) as pale yellow silky needles, mp 205–206 °C.

Dibenz[a,c]anthracene-9,14-dione (6). To a solution of 2 (474 mg, 1.5 mmol) and boric acid (494 mg, 8 mmol) in water (0.4 mL) was added concentrated sulfuric acid (1.5 mL). The resulting solution was heated at 80 °C for 7 h, cooled to room temperature, and sufficient 20% H$_2$SO$_4$ added to make the concentration of H$_2$SO$_4$ 50%. Water (100 mL) was added and the precipitate filtered, washed with water, boiled with 2% caustic soda (10 mL), filtered, and washed with water again. There was obtained 6 (363 mg, 78%) as a yellow solid: mp 181–182 °C (lit.[9] mp 181–183 °C); NMR (CDCl$_3$) δ 7.62–7.93 (m, 6, H$_{2,3,6,7,11,12}$), 8.0–8.3 (m, 2, H$_{10,13}$), 8.52–8.82 (m, 2, H$_{4,5}$), and 9.2–9.5 (m, 2, H$_{1,8}$); IR (KBr) 1670 cm^{-1} (C=O).

In a separate experiment 2 failed to cyclize to 6 in liquid HF at room temperature for 18 h.

Reduction of Dibenz[a,c]anthracene-9,14-dione (6). (1) Reduction of 6 with HI. A solution of 6 (185 mg) in 1.5 mL of 50% HI and 10 mL of acetic acid was heated at reflux for 24 h. Workup following the same general procedure employed in other reactions gave pure 1 (148 mg, 89%), mp 206–207 °C.

(2) Reduction of 6 with P/HI. Reaction of 6 (285 mg) with P and HI under the conditions employed for reductive cyclization of 2 afforded a product (125 mg) shown by NMR and TLC analysis to consist of 1 and 3 in the ratio 2:1.

Wolff–Kishner Reaction of 2. The keto acid 2 (2.0 g, 6.1 mmol) was initially converted to its methyl ester in methanol (20 mL) saturated with HCl and maintained at reflux for 1.5 h. Conventional workup afforded methyl 2-(9′-phenanthroyl)benzoate: 1.72 g (83%); mp 58–60 °C; NMR (CDCl$_3$) δ 3.35 (s, 3, CH$_3$) and 7.48–7.80, and 8.49–9.10 (m, 12, aromatic).

A solution of the methyl ester of 2 (1.53 g, 4.5 mmol) in n-butyl alcohol (20 mL) was added to a solution of hydrazine hydrate (5.7 mL) in the same solvent (20 mL) and the resulting solution was heated at reflux for 18 h. Reaction was quenched with ice water and neutralized with HCl. Conventional workup gave 7 as a white crystalline solid (1.25 g, 86%): mp 260–262 °C; NMR (Me$_2$SO-d_6) δ 7.16 (dd, 1, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 3 Hz, H$_5$), 7.4–8.1 (m, 8, aromatic), 7.95 (s, 1, H$_{10'}$), 8.33 (dd, 1, $J_{7,8}$ = 7 Hz, $J_{6,8}$ = 3 Hz, H$_8$), 8.95 (m, 2, H$_{4',5'}$), and 11.35 (s, 1, NH); the NH peak underwent exchange with D$_2$O.

Anal. Calcd for C$_{22}$H$_{14}$N$_2$O: C, 81.97; H, 4.38; N, 8.69. Found: C, 81.95; H, 4.41; N, 8.68.

Acetylation of 7 (250 mg, 0.77 mmol) with pyridine (3 mL) and acetic anhydride (30 mL) at room temperature overnight furnished the N-acetate of 7 (262 mg, 89%) as a white solid: mp 224–226 °C; NMR (CDCl$_3$) δ 2.78 (s, 3, OAc), 7.19 (dd, 1, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 3 Hz, H$_5$), 7.4–8.0 (m, 8, aromatic), 7.87 (s, 1, H$_{10'}$), 8.42–9.05 (m, 3, H$_{8,4',5'}$); IR (CHCl$_3$) 1690 (C=O) and 1770 cm^{-1} (CH$_3$C=O).

Attempted conversion of 7 to 4 by heating a solution of the former and KOH in refluxing diethylene glycol for 3 days according to the general procedure described by Fieser and Fieser[9] furnished only recovered 7.

Registry No.—1, 215-58-7; 2, 66859-11-8; 2 methyl ester, 66859-12-9; 3, 35281-25-5; 6, 3228-74-8; 7, 66859-13-0; 7 N-acetate, 66859-14-1.

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Synthesis of Aryloxiranes

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Polynuclear aromatic hydrocarbons are metabolically converted into derivatives of oxiranes which are implicated as the ultimate carcinogens in chemical carcinogenesis.[1] The in vitro and in vivo conversions of the ubiquitous benzo[a]pyrene (1) to the derivatives of isomeric 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrenes, commonly known as BP diolepoxides (BPDE, such as 2), have been
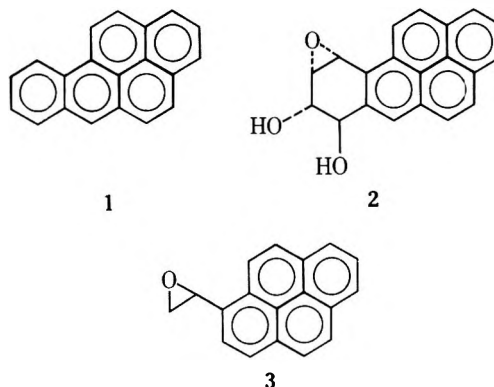
shown to be an important event in the mechanism of chemical carcinogenesis in benzo[a]pyrene.[2] Isomeric BPDEs are chemically reactive compounds via their oxiranyl function to cellular macromolecules[3] and are highly biologically active in a variety of testing systems including Ames' bacteria and cell cultures.[1,4] Simple aryloxiranes which contain both the aromatic π system as well as the reactive oxiranyl group of these activated carcinogens are a group of interesting compounds. A few of these compounds have been found to possess both carcinogenic and mutagenic activities.[5] Since BPDEs and related compounds are usually prepared by multistep synthesis and the metabolically activated forms of many other polynuclear aromatic hydrocarbons are not yet established, in order to carry out a structure–activity relationship study in chemical mutagenesis and carcinogenesis, aryloxiranes may serve well as model substances for metabolically activated forms of polynuclear aromatic hydrocarbons. This note deals with the synthesis of a group of aryloxiranes by three different methods.

We first attempted and failed to synthesize 9-anthryloxirane by the epoxidation of 9-vinylanthracene with m-chlo-

Table I

compd	registry no.	method	yield,[a] %	physical constant [lit. value]
1-pyrenyloxirane	61695-74-7	A	69	mp 66–68 °C (ethanol) [oil][b]
		B	82	mp 67–68 °C (ethanol)
9-anthryloxirane	61695-73-6	A	94	mp 68–69 °C (ethanol) [mp 76.5–78.0 °C (CCl₄)][b]
		B	65	mp 68–69°
1-naphthyloxirane	62222-40-6	A	82	bp 80–82 °C (0.075 mm) [bp 90–96 °C (0.10–0.13 mm)][c]
2-naphthyloxirane	20861-99-8	A	94	mp 57–58 °C (methanol) [mp 55.5–56.5 °C, 58–59 °C][b,d]
7-benzanthryloxirane	61695-72-5	A	81	mp 116–118 °C (ethanol) [mp 116–118 °C][b]
6-chrysenyloxirane	66842-41-9	B	85	mp 155–156 °C (acetone–petroleum ether)
10-methyl-9-anthryloxirane	66842-42-0	B	90	mp 100–101 °C (ethanol)
9-phenanthryloxirane	33424-05-4	B	90	mp 65–67 °C (ethanol)
9,10-bis(oxiranylanthracene)	66842-43-1	B	92	mp 200–201 °C (acetone)
9,10-dimethyl-2-anthryloxirane	66842-44-2	C	82[e]	mp 134–135 °C (aqueous ethanol)

[a] All yields given are for isolated products. All compounds exhibit the typical ABX pattern for oxirane in their NMR spectra, proper UV and IR spectra, and correct elemental analysis. [b] R. G. Harvey, J. Pataki, R. N. Wilke, J. W. Flesher, and S. Soedigdo, *Cancer Lett.*, **1**, 339 (1976). [c] S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6060 (1958). [d] R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1000 (1968). [e] The yield is for the conversion of α-bromo-9,10-dimethyl-2-acetylanthracene to the oxirane.

roperbenzoic acid (reaction 1). At elevated temperatures, anthraquinone was isolated as the major product, and no oxirane was detected in the reaction mixture. Since the vinyl derivatives of many polynuclear aromatic hydrocarbons were unknown or not readily available at that time,[5] this approach was abandoned. In a preliminary communication, Harvey and his co-workers reported the synthesis of a few aryloxiranes by the reaction of aromatic aldehydes and Corey's dimethylsulfonium methylide reagent[6] generated from the sulfonium iodide and n-butyllithium.[5] The products were isolated by chromatography and no yields were reported. Independently, we also applied this method for the synthesis but used sodium hydride as the base; the products were formed in high purity and were isolated in good yields directly by recrystallization (method A, reaction 2). Subsequently, we found that these oxiranes may be prepared conveniently in comparable yields by the application of phase transfer catalysis technique to the Corey's reaction without the use of the moisture and air sensitive reagents (method B).[7] In the synthesis of 9,10-dimethyl-2-anthryloxirane, the starting material of the Corey reaction, 9,10-dimethylanthracene-2-carboxaldehyde, is not known and our attempt to prepare this compound via the Vilsmeier reaction was not successful.[8] Therefore, an alternative synthesis from 2-acetyl-9,10-dimethylanthracene via the α-bromo derivative was developed (method C, reaction 3). The results are tabulated in Table I.
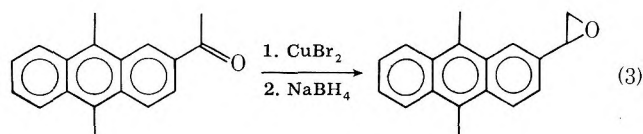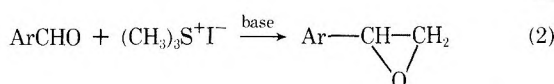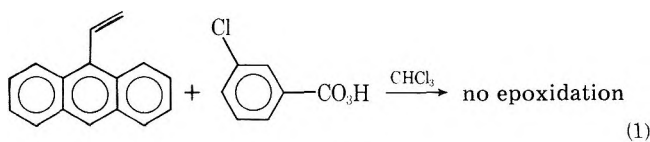
Preliminary investigation on the mutagenicity of these aryloxiranes by Miller, Miller, and Drinkwater with the Ames' systems, Salmonella typhimurium TA-98 and TA-100, indicated that these oxiranes are highly active mutagens.[9] Particularly, 1-pyrenyloxirane (3) exhibits mutagenicity at a level comparable to 7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (2), the common isomer of BPDE.

Therefore, these aryloxiranes not only exhibit interesting biological properties but also may serve as model compounds for the activated forms of polynuclear hydrocarbons.

Experimental Section

All ultraviolet spectra were obtained with a Cary-14 spectrophotometer, infrared spectra with a Perkin-Elmer 737 spectrophotometer, and NMR spectra with a Bruker HX-270 (270 MHz) spectrometer with tetramethylsilane (Me₄Si) as the internal standard. Melting points were determined on a Fisher–Jones melting point apparatus and were uncorrected.

The following compounds were purchased from the Aldrich Chemical Co. and purified by recrystallization from the solvent indicated: trimethylsulfonium iodide (ethanol, mp 215 °C), anthracene-9-carboxaldehyde (ethanol, mp 103 °C), 2-naphthaldehyde (methanol, mp 60 °C), and 9,10-dimethylanthracene (ethanol, mp 182 °C). The following compounds were purchased from the respective suppliers and used without further purification: sodium hydride (50% oil dispersion, Ventron), sodium borohydride (Ventron), cupric bromide (Mallinckrodt), acetyl chloride (Baker and Adamson), tetrabutylammonium iodide (Aldrich), phenanthrene-9-carboxaldehyde (Aldrich), and 10-methylanthracene-9-carboxaldehyde (Aldrich). 1-Naphthaldehyde (Aldrich) was purified by chromatography over neutral alumina. Dimethyl sulfoxide was purified by vacuum distillation over calcium hydride, bp 35–36 °C (0.15 mm). Benzene and tetrahydrofuran were purified by distillation over lithium aluminum hydride.

Pyrene-1-carboxaldehyde was prepared by the method of Tanikawa and co-workers, mp 125–127 °C((ethanol);[10] benzanthracene-7-carboxaldehyde was prepared by the method of Fieser and Hartwell, mp 146–148 °C (ethanol);[8] chrysene-6-carboxaldehyde was prepared by the method of Buu-Hoi and co-workers, mp 166–168 °C (benzene);[11] anthracene-9,10-dicarboxaldehyde was prepared from 9,10-bis(chloromethylanthracene) by the method of Klanderman, mp 241–244 °C dec (dichloromethane);[12,13] 9,10-dimethyl-2-acetylanthracene was prepared by the method of Van Hove, mp 164–165 °C (ethanol).[14]

Method A. 1-Pyrenyloxirane. All operations before the addition of water were carried out under an atmosphere of dry nitrogen. Sodium hydride in 50% oil dispersion (1.055 g, 22 mmol) was placed in a 250-mL round-bottomed flask with a magnetic stirrer and was washed with 40 mL of petroleum ether (bp 30–60 °C). The mixture was stirred, the hydride was allowed to settle, the solvent was decanted, and the hydride was dried under reduced pressure. A 1:1 (v/v) mixture of prepurified Me₂SO and tetrahydrofuran (20 mL) was added to the hydride, and the whole system was cooled in a salt–ice bath (bath temperature, −5 °C). With magnetic stirring, a solution of 4.59 g (22.5 mmol) of recrystallized trimethylsulfonium iodide in 15 mL of purified Me₂SO was added dropwise to the mixture. Some gas evolution was noted. A solution of 3.83 g (16.6 mmol) of pyrene-1-carboxaldehyde in 10 mL of purified tetrahydrofuran was added dropwise next. Stirring was continued with cooling for 10 more min after the addition and then for another 60 min after the bath was removed.

The reaction mixture was then decomposed with 180 mL of water, extracted with 150 mL of ethyl ether, washed with water, and dried

over magnesium sulfate. Removal of the solvent under reduced pressure gave a yellow oily residue which solidified upon trituation with methanol. Crystallization of the residue from methanol afforded 2.83 g (69% yield) of pale yellow crystals, 1-pyrenyloxirane: mp 66–68 °C; IR (KBr) 3050 (m), 1220 (m), 1180 (m), 1030 (m), 880 (s), 840 (s), 820 (s), 735 (s), and 715 cm^{-1} (s); UV$_{max}$ (methanol) 342 (48 900), 325 (31 300), 312 (12 600), 275 (52 800), 264 (26 400), 254 (11 400), 241 (80 700), and 232 nm (43 600); NMR δ_{Me_4Si} (CDCl$_3$) 2.88 (dd, 1 H, J = 6 and 3 Hz), 3.37 (dd, 1 H, J = 6 and 4 Hz), 4.70 (broad t, 1 H, J = 3 and 4 Hz), 7.88–8.13 (m, 8 H), and 8.27 (d, 1 H, J = 9 Hz).

Anal. Calcd for C$_{18}$H$_{12}$O: C, 88.50; H, 4.95. Found: H, 4.84.

Method B. 1-Pyrenyloxirane. In a 500-mL round-bottomed flask were placed 5.915 g (25.7 mmol) of pyrene-1-carboxaldehyde and 0.676 g (1.83 mmol) of tetrabutylammonium iodide in 100 mL of dichloromethane. A layer (100 mL) of 50% (w/w) aqueous sodium hydroxide was introduced underneath this solution. Trimethylsulfonium iodide (6.067 g, 29.7 mmol) was then added and the whole mixture was warmed up to 60 °C with vigorous stirring under nitrogen atmosphere for 72 h until the originally undissolved sulfonium salt entered the solution.

The reaction mixture was next poured into 200 mL of an ice–water mixture, and the organic phase was separated, washed with water, and dried over magnesium sulfate. Dichloromethane was removed under reduced pressure to give an oily yellow residue. Crystallization of the oily residue from ethanol gave 5.15 g (82% yield) of pale yellow prisms of 1-pyrenyloxirane, mp 67–68 °C.

α-Bromo-2-acetyl-9,10-dimethylanthracene. Finely ground cupric bromide (1.165 g, 5.22 mmol) and 8 mL of ethyl acatate were placed in a 50-mL round-bottomed flask fitted with a reflux condenser and a magnetic stirrer. The solution was brought to reflux in an oil bath. 2-Acetyl-9,10-dimethylanthracene (0.619 g, 2.50 mmol) was dissolved in 8 mL of hot chloroform and introduced into the flask. The resulting reaction mixture was refluxed for 5 h with vigorous stirring to ensure complete exposure of the cupric bromide to the reaction medium. The completion of the reaction could be judged from the color change of the solution from green to amber, disappearance of all black solid, and cessation of hydrogen bromide evolution. After removal of cuprous bromide by filtration, the solution was treated with Norite A. Concentration of the filtrate under reduced pressure gave a greenish brown solid. Recrystallization from benzene afforded 0.521 g (64% yield) of a yellow compound, α-bromo-2-acetyl-9,10-dimethylanthracene: mp 176–178 °C dec; IR (KBr) 1665 (s), 1615 (m), 1290 (m), 1260 (s), 1020 (m), and 750 cm^{-1} (s); UV$_{max}$ (methanol) 426 (3800), 375 (3690), 355 (3400), 338 (2480), 270 (36 700), and 245 nm (29 600); NMR δ_{Me_4Si} (CDCl$_3$) 3.09 (s, 3 H), 3.18 (s, 3 H), 4.61 (s, 2 H), 7.60 (m, 2 H), 7.98 (d, 1 H, J = 9 Hz), 8.36 (m, 3 H), and 9.07 (s, 1 H).

Anal. Calcd for C$_{18}$H$_{15}$OBr: C, 66.07; H, 4.62; Br, 24.42. Found: C, 66.11; H, 4.70; Br, 24.36.

Method C. 9,10-Dimethyl-2-anthryloxirane. A solution of 0.186 g (0.569 mmol) of α-bromo-2-acetyl-9,10-dimethylanthracene in 10 mL of ethanol was placed in a 25-mL round-bottomed flask with a magnetic stirrer and heated on an oil bath. Into the hot alcoholic solution was added dropwise a solution of 0.0245 g (0.648 mmol) of sodium borohydride in 1 mL of water. The resulting solution was allowed to reflux for 3–5 min and then filtered while still hot. When the volume of the solution was reduced by a gentle stream of nitrogen, light yellow crystals began to appear. The light yellow platelets were collected by filtration to give 0.116 g (82% yield) of 9,10-dimethyl-2-anthryloxirane: mp 134–135 °C; IR (KBr) 1380 (s), 1390 (s), 1250 (m), 870 (s), 815 (s), 800 (s), and 750 cm^{-1} (s); UV$_{max}$ (methanol) 397 (7500), 376 (8200), 357 (5210), and 262 (191 000); NMR δ_{Me_4Si} (CDCl$_3$) 2.98 (dd, 1 H, J = 6 and 3 Hz), 3.08 (s, 3 H), 3.10 (s, 3 H), 3.26 (t, 1 H, J = 6 and 4 Hz), 4.11 (t, 1 H, J = 3 and 4 Hz), 7.32 (d, 1 H, J = 8 HZ(= 7/5[(dd, 2 H, J = 8 and 4 Hz), and 8.28–8.32 ppm (broad d, 4 H).

Anal. Calcd for C$_{18}$H$_{16}$O: C, 87.06; H, 6.49. Found: C, 86.63; H. 6.51.

Registry No.—Pyrene-1-carboxaldehyde, 3029-19-4; anthracene-9-carboxaldehyde, 642-31-9; 1-naphthaldehyde, 66-77-3; 2-naphthaldehyde, 66-99-9; benz[a]anthracene-7-carboxaldehyde, 7505-62-6; chrysene-6-carboxaldehyde, 22138-85-8; 10-methyanthracene-9-carboxaldehyde, 7072-00-6; phenanthrene-9-carboxaldehyde, 4707-71-5; anthracene-9,10-dicarboxaldehyde, 7044-91-9; α-bromo-9,10-dimethyl-2-acetylanthracene, 66842-45-3; trimethylsulfonium iodide, 2181-42-2; tetrabutylammonium iodide, 311-28-4; 2-acetyl-9,10-dimethylanthracene, 15254-37-2; 9,10-dimethylanthracene, 781-43-1.

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A Unique Ring Contraction of 1,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-ones to 1-Methyl-2-(methylamino)-4(1*H*)-quinazolinones via an Intermediate Dimroth Rearrangement[1]
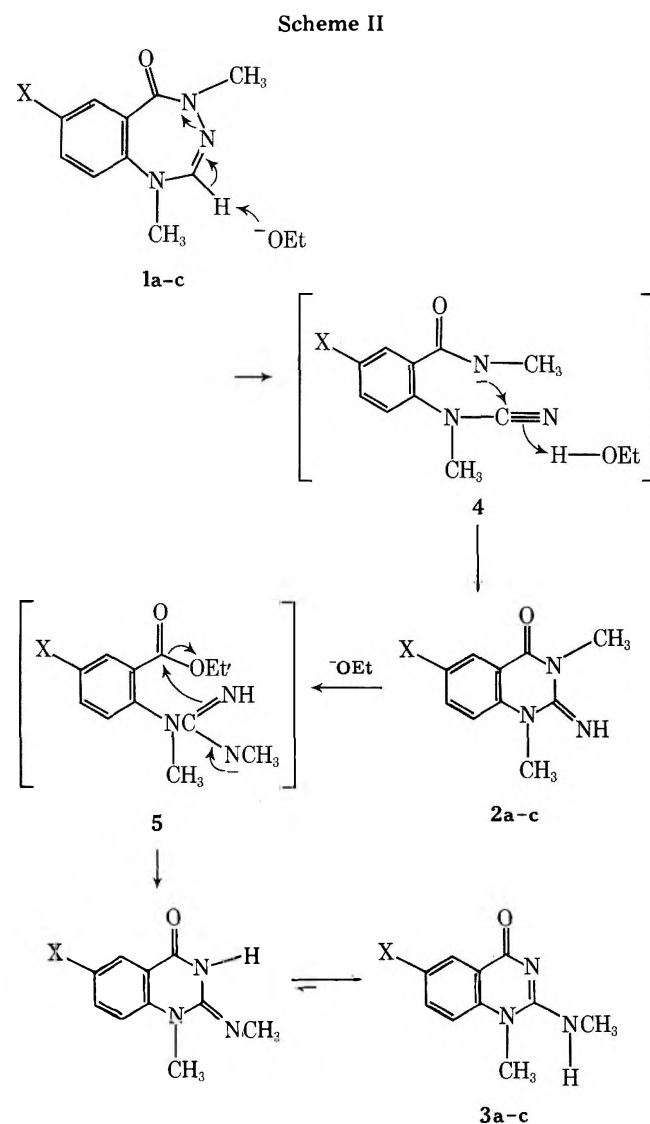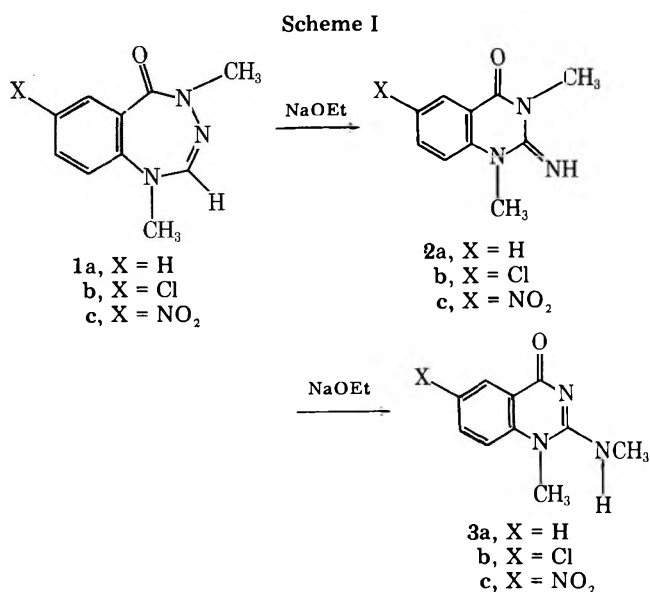
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We have previously reported the synthesis of substituted 3,4-dihydro- and 1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones[2] from o-aminobenzoyl hydrazides[3] and the discovery of a new alkoxide-induced ring contraction of the former compounds to 3-(methylamino)-4(3*H*)-quinazolinones.[4] We now wish to report a unique, base-catalyzed, ring contraction of the 1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones in which the rearrangement takes place through a Dimroth-like intermediate (Scheme I).

The reaction is believed to proceed via abstraction of the C$_2$ proton by the ethoxide to yield the highly stable 2-cyanamidobenzamide anion (4). This anion then cyclizes by intramolecular attack of the amide nitrogen on the cyano carbon to give the 1,3-dimethyl-2-imino-4(3*H*)-quinazolinones (2) (Scheme II). These quinazolinones can be isolated from

Scheme I

1a, X = H
b, X = Cl
c, X = NO$_2$

2a, X = H
b, X = Cl
c, X = NO$_2$

3a, X = H
b, X = Cl
c, X = NO$_2$

Scheme II

1a–c

4

5

2a–c

3a–c

the reaction mixture or allowed to react further with the alkoxide. Attack of the alkoxide ion on the carbonyl carbon of **2** effects a Dimroth rearrangement,[5] presumably to yield a nonisolable 2-guanidinobenzoate (**5**) which spontaneously ring closes to the 1-methyl-2-(methylamino)-4(1*H*)-quinazolinones (**3**).

Compound **3a** has previously been reported by Doleschall and Lempert[6] in a multistep synthesis with 7% overall yield

and had physical properties in agreement with that of the rearrangement product isolated herein.

The 2-imino- (**2a–c**) and 2-(methylamino)quinazolinones (**3a–c**) were easily distinguished on the basis of the *N*-methyl doublet in the ¹H NMR spectra of the methylamino compounds. The intermediate imino form was stable to acid and, indeed, **2b** and **2c** were each refluxed for 3 h in 1:1 glacial acetic acid/concentrated hydrochloric acid with recovery of the unchanged HCl salts of **2b** and **2c**. However, the imino form is base labile and will slowly rearrange, even in the solid state, if not completely free of base.

Compounds **1a, 2a,** and **3a** could readily be separated by TLC on silica gel plates (absolute ethanol, R_f 0.80, 0.39, and 0.54, respectively). However, it was found much easier to precipitate the imino form (**2a**) from the reaction medium as the hydrobromide salt, since **1a**·HBr and **3a**·HBr remained in solution. This was confirmed by the addition of aqueous HBr to pure solutions of **1a** and **3a**.

Solubility properties of **2b** and **3b** and of **2c** and **3c** were different enough to allow separation of the two isomers without the addition of HBr.

Experimental Section

Melting points, uncorrected, were determined on a Thomas-Hoover apparatus using open capillaries. Infrared spectra were recorded on a Perkin-Elmer Model 283 spectrometer using KBr disks. ¹H NMR were obtained on a Hitachi Perkin-Elmer R20A nuclear resonance spectrometer. Combustion analyses were provided by Dr. George I. Robertson, Florham Park, N.J.

1,3-Dimethyl-2-imino-4(1*H*,3*H*)-quinazolinone (2a). To a slurry of 7.00 g (0.037 mol) of **1a** in 50 mL of absolute ethanol was added a freshly prepared solution of 0.85 g (0.037 mol) of sodium in 30 mL of absolute ethanol. The solid completely dissolved upon heating to reflux. The solution was refluxed for 45 min and then cooled to room temperature for 20 min. A 35% aqueous solution of HBr was added dropwise, with stirring, to precipitate a white solid. The solid was collected on a filter and washed with ethanol. Recrystallization from 75% ethanol yielded 6.50 g (65%) of analytically pure **2a**·HBr: mp 294–295 °C; IR (KBr) 3320, 3220, 3060, 1712, 1655, 1619, 1578 cm⁻¹; NMR (Me₂SO-d_6) δ 3.50 (s, N₁-CH₃), 3.73 (s, N₃-CH₃), 7.35–8.20 (m, 4 H, ArH), 9.15 (s, br, C=N⁺H₂). Anal. Calcd for C₁₀H₁₂BrN₃O: C, 44.46; H, 4.48; N, 15.56. Found: C, 44.41; H, 4.52; N, 15.31.

Neutralization of the hydrobromide salt was accomplished by the addition of a 50% NaOH solution to an aqueous solution of the salt followed by extraction into chloroform. Removal of the dried (Na₂SO₄) chloroform in vacuo gave nearly quantitative amounts of **2a**. Recrystallization from water gave an analytically pure sample of **2a**: mp 131–132 °C; IR (KBr) 3355 (=NH), 1681 (C=O), 1605 (C=N) cm⁻¹; NMR (Me₂SO-d_6) δ 3.31 (s, N₃-CH₃), 3.43 (s,N₁-CH₃), 6.63 (s, br, =NH), 6.89–7.91 (m, 4 H, ArH). Anal. Calcd for C₁₀H₁₁N₃O: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.47; H, 5.76; N, 21.93.

1-Methyl-2-(methylamino)-4(1*H*)-quinazolinone (3a). 1a (7.00 g, 0.037 mol) was treated as described above except that the reflux was continued for 15 h. Upon cooling, the reaction mixture yielded 2.85 g of an off-white solid. The solid was recrystallized from ethanol, yielding 2.30 g (32.8%) of **3a**: mp 323–324 °C (lit.[6] mp 324–326 °C); IR (KBr) 3220 (NH), 2960 (CH), 1625 (C=O) cm⁻¹; NMR (Me₂SO-d_6) δ 2.88 (d, *J* = 5 Hz, NHCH₃), 3.47 (s, NCH₃), 6.97–7.82 (m, 5 H, ArH, NH). Anal. Calcd for C₁₀H₁₁N₃O: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.61; H, 5.94; N, 21.91.

Similar treatment of **2a** with ethanolic ethoxide rearranged it to **3a**.

6-Chloro-1,3-dimethyl-2-imino-4(1*H*,3*H*)-quinazolinone (2b) and 6-Chloro-1-methyl-2-(methylamino)-4(1*H*)-quinazolinone (3b). To a slurry of 11.18 g (0.005 mol) of **1b** in 25 mL of absolute ethanol was added 25 mL of an anhydrous ethanolic solution of 0.115 g (0.005 mol) of sodium. The mixture was heated to reflux for 22 h, during which a solid formed. The mixture was cooled, and the solid was collected on a filter. The solid was washed twice in hot ethanol and filtered each time from the hot solution. The washings were set aside to cool. The solid that did not dissolve in the ethanol was recrystallized twice from glacial acetic acid. Pure **3b** (2.68 g, 24%) was obtained: mp 362–363 °C; IR (KBr) 3240 (NH), 1630 (C=O) cm⁻¹; NMR (TFA) δ 3.37 (d, *J* = 5 Hz, NHCH₃), 3.85 (s, NCH₃), 7.45–8.30 (m, ArH, NH). Anal. Calcd for C₁₀H₁₀ClN₃O: C, 53.70; H, 4.51; N, 18.79. Found: C, 53.50; H, 4.73; N, 18.50.

The washings that were saved from above were chilled in an ice bath, causing colorless needles to crystallize. The needles were recrystallized three times from ethanol to yield 3.88 g (34.8%) of **2b**: mp 157–157.5 °C; IR (KBr) 3340 (=NH), 1680 (C=O), 1605 (C=N), cm⁻¹; NMR (Me₂SO-d₆) δ 3.32 (s, N₁-CH₃), 3.42 (s, N₃-CH₃), 6.78 (s, NH), 7.05–7.80 (m, 3 H, ArH). Anal. Calcd for C₁₀H₁₀ClN₃O: C, 53.70; H, 4.51; N, 18.79. Found: C, 53.45; H, 4.68; N, 18.49.

6-Nitro-1,3-dimethyl-2-imino-4(1*H*,3*H*)-quinazolinone (2c). To a slurry of 3.27 g (0.014 mol) of **1c** in 25 mL of ethanol was added a freshly prepared solution of 0.07 g (0.003 mol) of sodium in 25 mL of absolute ethanol. The slurry was heated to reflux, causing the solid to dissolve and the solution to turn a deep red color. The reflux was continued for 24 h and the solution was then cooled to room temperature. An olive-green solid crystallized from the cooled solution and was collected. Recrystallization from dioxane yielded 1.37 g (41.9%) of **2c** as golden-yellow crystals: mp 251–252 °C; IR (KBr) 3330 (=NH), 1680 (C=O), 1607 (C=N) cm⁻¹; NMR (TFA) δ 3.83 (s, N₁-CH₃), 4.00 (s, N₃-CH₃), 7.70–8.30 (m, 5 H, ArH, =N⁺H₂). Anal. Calcd for C₁₀H₁₀N₄O₃: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.18; H, 4.35; N, 23.70.

6-Nitro-1-methyl-2-(methylamino)-4(1*H*)-quinazolinone (3c). To 1.00 g (0.0043 mol) of **2c** was added 50 mL of absolute ethanol containing 0.10 g (0.0043 mol) of sodium. The solution was refluxed for 24 h and then allowed to stand overnight at room temperature. A solid crystallized in the reaction vessel and was filtered off. Anal-

ysis showed this solid to be starting material; 0.22 g (22%) was recovered. The reaction solution was then concentrated in vacuo to an oil which was induced to crystallize by scratching in a dioxane/ether solution. The crystals were collected and recrystallized from 50% ethanol to yield 0.30 g (30%) of **3c** as yellow crystals: mp >370 °C dec; IR (KBr) 3235 (NH), 1638 (C=O), 1603 (C=N) cm⁻¹; NMR (TFA) δ 3.45 (d, J = 4 Hz, NHCH₃), 3.95 (s, NCH₃), 7.85 (d, J = 10 Hz, H₈), 8.20 (br, NH₂⁺), 8.84 (d, J = 10 Hz of d, J = 3 Hz, H₇), 9.23 (d, J = 3 Hz, H₅). Anal. Calcd for C₁₀H₁₀N₄O₃: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.01; H, 4.52; N, 23.73.

Registry No.—1a, 59169-91-4; **1b**, 59169-92-5; **1c**, 59169-93-6; **2a**, 66809-70-9; **2a** HBr, 66809-71-0; **2b**, 66809-72-1; **2c**, 66809-73-2; **3a**, 5544-06-9; **3b**, 66809-74-3; **3c**, 66809-75-4.

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(2) R. W. Leiby and N. D. Heindel, *J. Org. Chem.*, **41**, 2736 (1976).
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Communications

Deuterium Nuclear Magnetic Resonance. Evaluation of the Positional Distribution of Low Levels of Deuterium in the Presence of Eu(fod)₃

Summary: ²H NMR spectroscopy, in conjunction with the shift reagent Eu(fod)₃, has been used to detect and quantify the positional incorporation of low levels of ²H in catalytically deuterated saturated carboxylic acid esters.

Sir: While ¹H NMR can be used effectively to determine the extent of ²H incorporation in organic molecules, it has severe limitations. First, ¹H NMR requires that the molecule under study contain high concentrations of ²H, since this technique can evaluate ²H only by difference. Secondly, when ²H is largely dispersed throughout a molecule even in relatively high total concentration, analysis becomes very difficult because of insignificant changes observed in the area of each of the dispersed ¹H resonances. As an alternate method, mass spectrometry can furnish information concerning the total level of isotopic incorporation; however, in most instances it cannot define the positional distribution of ²H owing to ²H–¹H scrambling during the fragmentation process.

Although two orders of magnitude less sensitive in response to a magnetic field than ¹H, the ²H nucleus is more amenable to Fourier transform methods.[1] Under complete proton decoupling conditions, ²H resonances are normally observed as single resonances (no ²H–²H spin coupling is observed), having chemical shifts closely corresponding to their ¹H counterparts.[2] Also, because of their relatively short longitudinal relaxation time, T_1, multiple transients may be rapidly accumulated with short repetition times.[1] For example, a 100-mg sample of molecular weight of 200–300, containing 5% ²H, which in magnetic response is equivalent to 0.05% ¹H, can yield an excellent quantitative spectrum within 0.5 h from 300 transients (repetition time only 5 s and a pulse angle of 60°).

²H NMR in the presence[2,3] and absence[4,5] of lanthanide shift reagents can be used to examine positional substitution patterns in both static and rapidly exchanging ¹H, ²H systems. Such a technique seemed amenable to our studies concerning the catalytic incorporation of ²H into the saturated alkyl chains of carboxylic acids, since no other approach could quantify and evaluate the positional distribution of the low levels of widely dispersed ²H. Typically, not more than a total of 29%, and in some cases as little as 2%, ²H was incorporated into our representative samples. All ²H spectra were obtained by use of a ³¹P 10-mm probe of a JEOL FX-60Q NMR spectrometer,[6] which normally operates at 24 MHz with a ²H lock channel of 9.2 MHz. By reversing the offset/rf power modules and exchanging the lock and observation lines, we could lock
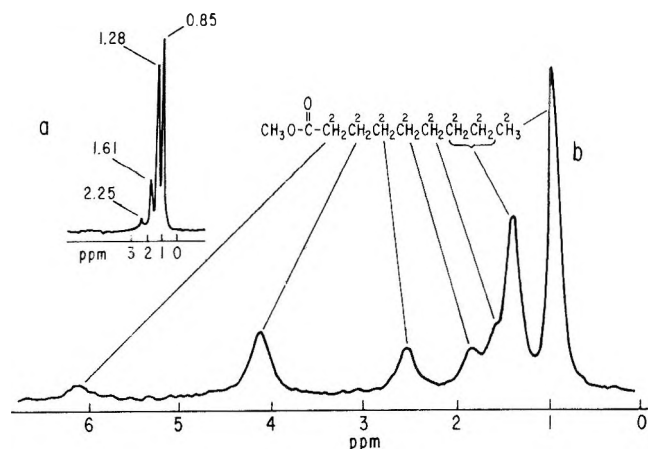

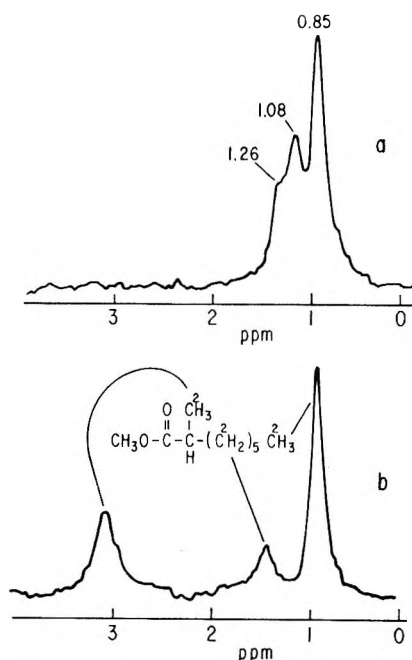**Figure 1.** ²H spectrum of: (a) methyl nonanoate, 255 transients, 4.4-s repetition rate, displayed spectral width = 500 Hz, 4K data points; (b) methyl nonanoate in the presence of Eu(fod)₃ shift reagent, molar ratio of Eu(fod)₃/substrate = 0.7, 200 transients, 4.4-s repetition rate, displayed spectral width = 62.5 Hz. Total ²H content ≈ 29%.

Table I. Observed ¹H and ²H Shifts (ppm) and ²H Positional Distribution and Content[a]

$$\underset{\underset{R\quad R'}{}}{CH_3O\overset{\overset{\textstyle O}{\|}}{C}CH-CH(CH_2)_x R''}$$

	sample size, g	CH₃	2-CH₃	3-CH₃	(CH₂)ₓ	2-CH₂	3-CH₂	2-CH	3-CH	total % ²H content
					¹H shifts (δ)[b]					
methyl nonanoate R = R' = H; R'' = CH₃; x = 5		0.86			1.25	2.30	1.6[c]			
methyl 2-methyloctanoate R = R'' = CH₃; R' = H; x = 4		0.90	1.16		1.30			2.42		
methyl 3-methylpentanoate R = R'' = H; R' = CH₃; x = 1		0.86		0.90	1.28	2.10			1.90	
dimethyl 1,7-heptanedioate R = R' = H; R'' = CO₂CH₃; x = 5					1.30	2.30	1.50			
					²H Shifts (δ)[d]					
methyl nonanoate	0.085	0.85 (0.35)			1.28 (0.10)[e] (0.39)[f]	2.25 (0.03)	1.61 (0.13)			29
methyl 2-methyloctanoate	0.128	0.85 (0.61)	1.08 (0.24)		1.26 (0.15)			nf		8.7
methyl 3-methylpentanoate	0.103	0.90 (0.68)		0.90 (0.32)	nf	nf			nf	12.6
dimethyl 1,7-heptanedioate	0.096				1.30[g] (0.39)	2.25[h] (0.15)	1.50[i] (0.46)			8.1

[a] Content given as total percent deuterium incorporation determined by mass spectrometry. Numbers in parentheses represent the fractional distribution of ²H found from the Eu(fod)₃ spectrum. All proton shift assignments were in agreement with those reported in the Aldrich Catalog of proton NMR spectra. [b] Shifts were recorded in CCl₄ relative to internal Me₄Si. [c] Not clearly resolved at 60 MHz. [d] Shifts were recorded in CCl₄ and reported relative to 2% internal CDCl₃ referenced as 7.25 ppm. nf = no deuterium found at these positions. [e] Represents the 4-CH₂ position. [f] Represents 5- through 8-CH₂ positions. [g] Represents only the 5-CH₂ position. [h] Represents 2- and 8-CH₂ positions. [i] Represents 3-, 4-, 6-, and 7-CH₂ positions.

Figure 2. ²H spectrum of: (a) methyl 2-methyloctanoate, 200 transients, 4.4-s repetition rate, displayed spectral width = 125 Hz, 8K data points; (b) methyl 2-methyloctanoate in the presence of Eu(fod)₃ shift reagent, molar ratio of Eu(fod)₃/substrate = 0.25, 208 transients, 4.4-s repetition rate, displayed spectral width = 125 Hz. Total ²H content = 8.7%.

Table I lists the ¹H and the corresponding ²H shifts observed for the methyl esters derived from catalytically deuterated carboxylic acids. Total percent ²H incorporation into the esters was determined by mass spectrometry and the positional distribution by ²H NMR. Figure 1a shows the ²H spectrum of methyl nonanoate with 29% ²H incorporation in the alkyl chain. In this spectrum the 2- and 3-methylene and terminal methyl ²H resonances were clearly defined, whereas the remaining ²H in the chain are seen as a single resonance. Although this spectrum was obtained at only 9.2 MHz, it illustrates the separation which is achievable from single line resonances in the absence of couplings. Note that the 3-position ²H is readily distinguished, whereas the corresponding ¹H spectrum yields only a broad shoulder. A predominance of incorporation is apparent in the terminal methyl group, while the 2 position appears to have a low concentration. In the presence of shift reagent [Eu(fod)₃] (Figure 1b), the distribution of ²H throughout the chain is easily ascertained (Table I). While such a separation was obtained for a ¹H spectrum of this ester in the presence of a shift reagent,[8] it was not posssible to quantify the low levels of ¹H depleted in each resonance peak. Figure 2a shows the ²H spectrum of methyl 2-methyloctanoate, Figure 2b the corresponding spectrum in the presence of Eu(fod)₃ shift reagent. The latter spectrum clearly demonstrates the presence of ²H in positions 3 to 7 and the terminal and 2-position methyl groups of this carboxylic ester. No resonance corresponding to the 2-methine ²H was observed. A predominance of incorporation is seen in the terminal methyl group resonances, which separate from the 2-methyl group under the influence of shift reagent (Figure 2b). Figures 3a and 3b illustrate the exclusive substitution of ²H in the 3-methyl and terminal methyl groups of methyl 3-methylpentanoate and the dramatic resolution obtainable with the shift reagent. Dimethyl 1,7-heptanedioate exhibits

onto the ³¹P resonance of H₃PO₄ in a 1.8-mm capillary tube secured in the center of the 10-mm tube with a drilled out vortex plug and observe ²H at 9.2 MHz.[7]
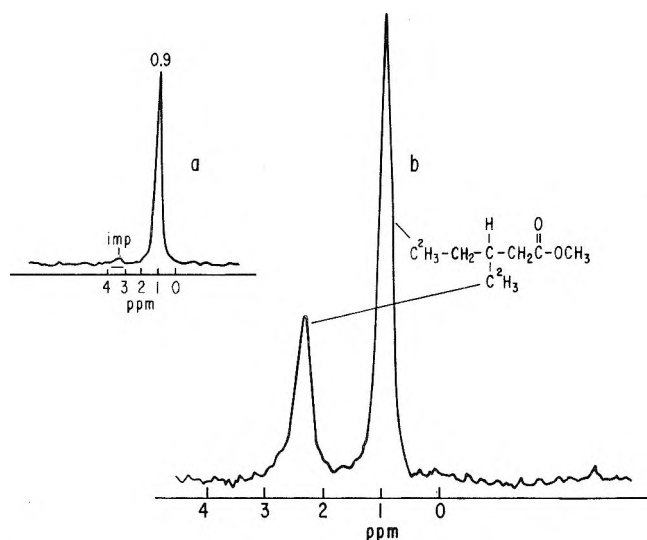
Figure 3. ^{2}H spectrum of: (a) methyl 3-methylpentanoate, 428 transients, 4.4-s repetition rate, displayed spectral width = 500 Hz, 8K data points; (b) methyl 3-methylpentanoate in the presence of Eu(fod)$_3$ shift reagent, molar ratio of Eu(fod)$_3$/substrate = 0.25, 400 transients, 4.4-s repetition rate, displayed spectral width = 125 Hz. Total ^{2}H content = 12.6%.

a somewhat broadened spectrum in the presence of Eu(fod)$_3$ because of the increased molecular weight and longer T_1 values of the double coordination site complex. However, the ^{2}H distribution for three distinct regions along the chain was still evident (Table I).

A full report concerning the catalytic procedures used for the ^{2}H exchange reactions into various compounds and their analyses by mass spectrometry and ^{2}H NMR spectroscopy will be the subject of future publications.

References and Notes

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(10) Federal Research, Science and Education Administration, U.S. Department of Agriculture.

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Cuprates Derived from
endo-(*n* + 3)-**Bromobicyclo[***n***.1.0]alkanes and Related Compounds and Their Reaction with β-Iodo Enones. Facile Homo-[1,5]-sigmatropic Hydrogen Migrations Involving** *endo-*(*n* + 3)-(3-Keto-1-cycloalkenyl)bicyclo[*n*.1.0]alkanes

Summary: The tricyclic compounds **6, 7, 13, 15, 21,** and **26,** efficiently obtained by reaction of the appropriate β-iodo enone (**4** or **5**) with cuprate reagents derived from *endo-*(*n* + 3)-bromobicyclo[*n*.1.0]alkanes and related compounds, un-

dergo facile and, in the case of compounds **21** and **26**, completely site-selective homo-[1,5]-sigmatropic hydrogen migrations to afford, respectively, products **28–33**, inclusive.

Sir: Recent reports[1–4] have indicated that various lithium cyclopropylcuprates may have considerable potential as reagents in organic synthesis. Our initial work in this area was concerned with the reactions of lithium phenylthio(cyclopropyl)cuprate and lithium phenylthio(2-vinylcyclopropyl)cuprate with β-iodo enones to produce intermediates which could be employed in cyclopentane-[2a] and cycloheptanetype[2b] annelation processes. More recently, we have been engaged in studies concerning the preparation and reactivity of more highly substituted cyclopropylcuprate reagents. We report herein some preliminary results regarding (a) the preparation of cuprate reagents derived from *endo-*(*n* + 3)-bromobicyclo[*n*.1.0]alkanes and related compounds, (b) the reaction of these reagents with β-iodo enones, and (c) the thermal sigmatropic rearrangement of the resultant intermediates to produce 2-cycloalken-1-ones which are uniquely functionalized on the β carbon of the α,β-unsaturated ketone system. Apart from the intrinsic interest in this work from a methodological point of view, we feel that the final rearrangement products possess considerable potential as intermediates in projected natural product syntheses.
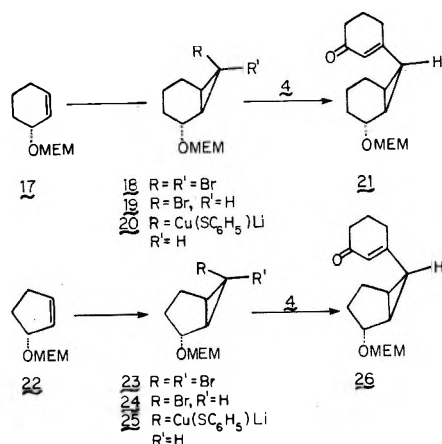
Reduction of 7,7-dibromonorcarane (**1**) with Zn–HOAc[5] afforded a mixture of monobromo derivatives in which the endo isomer **2**[6,7] predominated (ratio of endo/exo ≈ 10:1). Treatment of **2** with 2 equiv of *t*-BuLi (ether, −78 °C), dilution of the resultant solution with THF, addition of 1 equiv of C$_6$H$_5$SCu,[8] and warming the mixture to −20 °C gave a solution of the cuprate reagent **3**. When the latter was allowed to react (−20 °C, 2 h; 0 °C, 2 h) with each of the β-iodo enones **4**[9] and **5**,[2a] the corresponding endo enones **6** and **7** were obtained in excellent yields (93 and 83%, respectively, Scheme I).

Treatment of 6,6-dibromobicyclo[3.1.0]hexane (**8**)[10] with *n*-Bu$_3$SnH[11] afforded a 1:1 mixture of the corresponding monobromo derivatives **9** and **10**[12] (Scheme I). Conversion of this material into a mixture of the corresponding cuprate reagents **11** and **12**, followed by reaction of the latter with 3-iodo-2-cyclohexen-1-one (**4**),[9] gave a mixture of compounds **13** (46%) and **14** (48%), which could be separated readily by column chromatography on silica gel. In similar fashion, reaction of the mixture of **11** and **12** with the β-iodo enone **5**[2a] produced the epimeric derivatives **15** and **16** (isolated yields 35 and 41%, respectively).
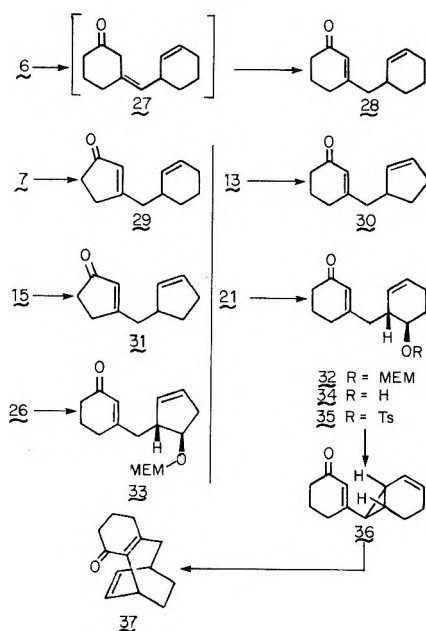
Conversion of the MEM ethers[13] of 2-cyclohexen-1-ol (**17**) and 2-cyclopenten-1-ol (**22**) into the corresponding dibro-

Scheme I

Scheme II

17 18 R = R' = Br   21
19 R = Br, R' = H
20 R = Cu(SC$_6$H$_5$)Li
   R' = H

22 23 R = R' = Br   26
24 R = Br, R' = H
25 R = Cu(SC$_6$H$_5$)Li
   R' = H

Scheme III

32 R = MEM
34 R = H
35 R = Ts
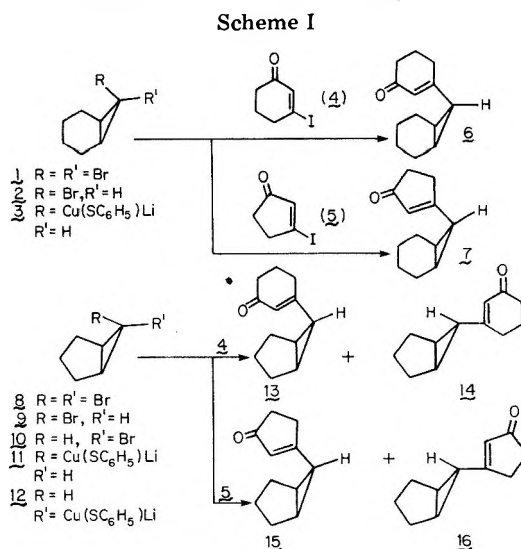
mocyclopropanes **18** and **23** was accomplished (83, 84%, respectively) by standard methodology (CHBr$_3$, NaOH–H$_2$O–EtOH, C$_6$H$_5$CH$_2$N$^+$Et$_3$Cl$^-$; Scheme II).[14,15] Reduction (**18**: Zn, HOAc; **23**: *n*-Bu$_3$SnH) of these dibromo compounds, followed by chromatographic purification of the crude products, afforded the pure *endo*-bromides **19** and **24**. The latter substances were transformed into the corresponding cuprate reagents **20** and **25** which, upon reaction with the iodo enone **4**, gave the unsymmetrical tricyclic derivatives **21** and **26** (97 and 62%, respectively).

Although the *endo*-enones **6, 7, 13, 15, 21,** and **26** were sufficiently stable to withstand purification by distillation under reduced pressure (e.g. **21** was distilled at 150–160 °C, 0.1 mm), each of these compounds rearranged smoothly and cleanly when heated (neat) at temperatures >200 °C (Scheme III). For example, when **6** was heated at 210–215 °C for 10 min, the substituted cyclohexenone **28** was obtained in 95% yield. Clearly, under these conditions, the product **27** initially formed by homo-[1,5]-sigmatropic hydrogen migration[16] isomerized to the more stable conjugated isomer **28**. In similar fashion, enones **7, 13,** and **15** could be smoothly transformed into the corresponding rearrangement products **29** (98%), **30** (87%), and **31** (90%), respectively.

Thermolysis of the unsymmetrical *endo*-enones **21** and **26** represent especially interesting examples of the present methodology. In each case, the rearrangement process was very clean (**32,** 89%; **33,** 78%), and a careful analysis of each of

the crude reaction products (after brief treatment with NaOMe–MeOH[17]) failed to produce evidence for the formation of any other product. At present, the reasons underlying the highly site-selective nature of these homo-[1,5]-sigmatropic hydrogen shifts remains obscure. However, it is clear that these high selectivities could be very useful from a synthetic point of view.

Removal of the MEM group (ZnBr$_2$, CH$_2$Cl$_2$)[13] from **32**, followed by tosylation of the resultant alcohol **34**, gave the tosylate **35**. Brief treatment of the latter with 1.2 equiv of *t*-BuOK in *t*-BuOH (15 min, room temperature) gave (68% from **34**) the *exo*-enone **36**.[18,19] When a solution of **36** in *o*-dichlorobenzene (bp 179 °C) was refluxed for 40 h, the tricyclic enone **37** (resulting from Cope rearrangement[20]) was formed in 94% yield.

Work in this area is continuing.

References and Notes

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(12) Attempted reduction of **8** with Zn–HOAc gave very poor yields of **9** and **10**.
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(14) M. Makosza and M. Fedorynski, *Synth. Commun.,* **3,** 305 (1973).
(15) For steric reasons dibromocyclopropanation of **17** and **22** would be expected to occur from the side of the molecule opposite the O–MEM group. Independent evidence for the stereochemistry of **18** was obtained as follows. Removal of the MEM group, followed by oxidation of the resultant alcohol A, gave the corresponding ketone. Reduction of the latter afforded an alcohol which was clearly epimeric with A.
(16) For a recent review regarding this type of reaction, see S. W. Spangler, *Chem. Rev.,* **76,** 187 (1976).
(17) In these cases, the initial thermolysis products contained small amounts of the unconjugated ketones (analogous to **27**), which were isomerized to the conjugated isomers by the base treatment.
(18) Compound **36** could also be obtained by reaction of 3-iodo-2-cyclohexen-1-one with the cuprate reagent derived from *exo*-7-bromo-2-norcarene.
(19) The facility with which the transformation of **35** into **36** occurred also provided excellent evidence to support the stereochemical assignment made for compound **17** (see ref 15) and for the subsequent intermediates derived from **17**.
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(21) On sabbatical leave from Moorhead State University, Moorhead, Minnesota.

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One-Step Catalytic Synthesis of
2,2,3-Trimethylbutane from Methanol

Summary: Catalytic reaction of methanol in the presence of zinc iodide produces butane and higher hydrocarbons with a high degree of branching and an unexpectedly high triptane (2,2,3-trimethylbutane) content.

Sir: It has been reported[1] that polyphosphoric acid at 200 °C promotes condensation of methanol to C_4^+ hydrocarbons. The hydrocarbon product was not unusual, being about what one would expect from condensation in highly acid medium with carbonium ion intermediates. Subsequently, aromatic-rich gasoline production from methanol was reported using a zeolite catalyst.[2] We have carried out preliminary experiments with bulk zinc iodide at 200 °C as catalyst and found that it promotes conversion of methanol directly to gasoline-range hydrocarbons. The product is quite different from that reported for polyphosphoric acid or zeolite catalysis in that it is unusually rich in highly branched compounds, particularly 2,2,3-trimethylbutane (triptane). Thus, when 39.4 g of methanol and 200 g of zinc iodide were heated together for 2 h at 200 °C under 200 psi of N_2, 7.2 g of gasoline-range hydrocarbon could readily be distilled from the reaction vessel. Careful analysis of the gasoline-range product showed it to be 49.7% triptane. The formation of this high a yield of triptane in a thermal reaction is unique to our knowledge. Only traces of hydrocarbons lighter than butane were found. The triptane was unequivocally identified by a combination of capillary gas chromatography, infrared, GC/mass spectrographic, and NMR analyses. Table I shows the composition of this gasoline as identified by capillary GC analysis. Conversion of methanol was >99%. Only traces of C_1 to C_3 hydrocarbons were found. Isobutane was the only C_4 hydrocarbon produced in <2% yield. Most of the heavier hydrocarbons were in the useful gas–oil boiling point range (230–370 °C ~56% basis carbon fed; higher boiling ~2–3% basis carbon). There was little solid residue. Carbon material balance was 98%.

Triptane is one of the most desirable known gasoline component hydrocarbons, based on its unusually high motor and research octane numbers, and its desirable boiling point. The formation, in high selectivity, of such an unusual hydrocarbon as triptane, together with the unusual nature (high branching–high octane) of the rest of the mixture produced, indicates that the reaction of methanol in the presence of zinc iodide is proceeding via unusual intermediates and/or reactions. It is highly unlikely that the products obtained could have been formed by typical carbonium ion or even free-radical reaction pathways, since the product pattern is different from acid-catalyzed isomerization and alkylation. Most likely, a novel intermediate is formed by dehydration of methanol, which condenses to form the observed products. As a working hypothesis, we postulate that the intermediate may be a carbene (CH_2) complexed with the salt, similar to the Simmons–Smith reagent.[3] Such a complexed methylene would be expected to be much more selective in its reactions than free methylene, and plausible reaction pathways have been postulated that explain the high selectivity to triptane observed in the methanol–zinc iodide reaction.

We shall publish supporting evidence for carbenoid and organozinc intermediates and a detailed mechanism consistent with the high triptane yield and lack of C_1, C_2, and C_3 products. The reaction has been established as catalytic in zinc iodide by recovering zinc salt and reuse. Zinc bromide also catalyzes methanol to triptane conversion at 220–245 °C, but at the high temperatures required for zinc chloride catalysis most of the unusual selectivity to triptane is lost. Subsequent publications shall give additional details of this intriguing chemistry.

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Table I. Gasoline-Range Products from Methanol

| hydrocarbon product	% wt
2-methylbutane	1.8
other C_5	0.1
2.3-dimethylbutane	3.8
2-methylpentane	1.7
3-methylpentane	1.3
n-hexane	0.0
other C_6	0.1
2,2,3-trimethylbutane	49.7
2,2-dimethylpentane	0.1
2,3-dimethylpentane	2.4
2-methylhexane	0.8
3-methylhexane	0.6
n-heptane	0.1
other C_7	2.1
2,2,4-trimethylpentane	1.0
2,3,4-trimethylpentane	1.8
2,3,3-trimethylpentane	1.7
other C_8	5.0
2,2,5-trimethylhexane	1.2
2,3,5-trimethylhexane	0.9
other C_9	5.6
C_{10}–C_{13}	18.2
Total C_5–C_{13}	100.0

Stereochemical Course of the Fragmentation of Allylsulfinic Acids

Summary: Diastereomers of 5-(*p*-tolylsulfonamido)-(*Z*)-3-hexene-2-sulfinic acid fragment in D_2O to different diastereomers of 4-deuterio-5-(*p*-tolylsulfonamido)-(*E*)-2-hexene.

Sir: The fragmentation of homoconjugated sulfinic acids is known to proceed with apparently exclusive allylic rearrangement (eq 1).[1] Recently attention has been drawn to the synthetic potential of the retro reaction as a means of isomerizing and functionalizing alkenes.[2] We report evidence of a stereochemical nature which tends to support a cyclic mechanism for this transformation.


$$\text{(1)}$$
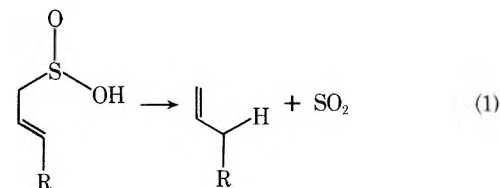
The sulfinamides **1** and **2** have been prepared by cycloaddition of *N*-sulfinyl-*p*-toluenesulfonamide to (*E,E*)- and (*E,Z*)-2,4-hexadiene, respectively.[3] Upon treatment with aqueous sodium hydroxide (scission of S–N bond), followed by acidification of the sulfinate salt with hydrochloric acid,[1] both **1** and **2** yielded 5-(*p*-tolylsulfonamido)-(*E*)-2-hexene (**3a**) as the only isolable product (eq 2).[4]

1   2

$$3a, R = R' = H$$
$$b, R = D; R' = H$$
$$c, R = H; R' = D$$
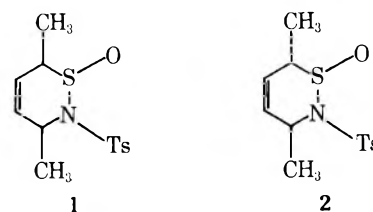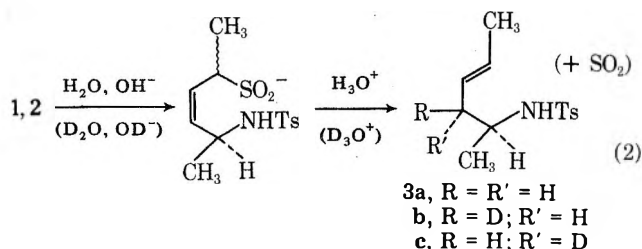
When the hydrolysis sequence with 1 and 2 was repeated in deuterated medium, the isolated sulfonamides (3) contained approximately one atom of carbon-bound deuterium in the 4 position of the hydrocarbon chain, as estimated by NMR absorption intensity. Close inspection of the IR spectra of the hydrolysis products reveals subtle differences in 3 obtained from 1 and 2 in H_2O and D_2O. The product **3a**, whether obtained from 1 or 2, has an absorption at 9.6 μm. This adsorption is greatly diminished in the deuterium-containing products, **3b** and **3c**. However, the product from 1 has a new adsorption a 10.6 μm, and that from 2 has a correspondingly unique (although not so well resolved) absorption at 11.25 μm.[5] It is suggested that the diastereomers **3b** and **3c** are formed stereospecifically from 1 and 2, respectively. Although the IR analysis is semiquantitative, **3c** (as obtained from 2) seems to be free of **3b** (<10%), and **3b** (as obtained from 1) has at most 15% cross-contamination with **3c**. The conclusion of a stereoisomeric relationship is reaffirmed by easily recognized differences in the splittings of the pertinent NMR absorption multiplets ($\delta \sim 3.4$).[6] The assignments of **3b** and **3c** follow from mechanistic considerations, although the possibility of the reverse relative configuration may not be excluded on the evidence presented.

Formation of diastereomeric products (**3b,c**) implies diastereomeric transition states. Configurational control is succinctly rationalized by a cyclic retro-ene mechanism (eq 3).
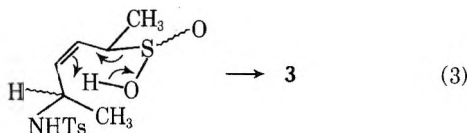
Strong preference for a chair conformation transition state explains both predominant (*E*)-alkene formation in 3 as well as diastereomeric induction at the 4 position. As a minimum conclusion, it appears that asymmetry at the 2 position ($-CHMeSO_2H$) is transmitted to the 4 position more efficiently than is asymmetry at the adjacent 5 position ($-CHMeNHTs$). A contrary result (including some (*Z*)-alkene from at least one isomer) might have been expected were deuterium delivered from solvent in an extended conformation of the fragmenting sulfinic acid, although a nonconcerted mechanism involving irreversible C-protonation followed by fragmentation would be consistent with a small amount of product crossover, which the experimental evidence does not exclude.

References and Notes

(1) O. Wichterle and J. Rocek, *Chem. Listy*, **47**, 1768 (1953); *Collect. Czech. Chem. Commun.*, **19**, 282 (1954); G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *Angew. Chem., Int. Ed. Engl.*, **1**, 89 (1962); W. Wucherpfennig, *Tetrahedron Lett.*, 3235 (1967); *Justus Liebigs Ann. Chem.*, **746**, 16 (1971).
(2) M. M. Rogić and D. Masilamani, *J. Am. Chem. Soc.*, **99**, 5219 (1977); T. Hori, S. P. Singer, and K. B. Sharpless, *J. Org. Chem.*, **43**, 1456 (1978), and earlier work by these authors.
(3) W. L. Mock and R. M. Nugent, *J. Am. Chem. Soc.*, **97**, 6521 (1975).
(4) Isolated as a chromatographically purified oil in 81% yield, with superimposable spectra for **3a** from 1 and 2. (*E*)-Alkene is indicated by IR absorption at 10.3 μm. The sharp and well-resolved methyl doublets in the NMR spectrum show no indication of a minor isomer [(*Z*)-alkene, <5%]. Material recovered from deuteriolysis was subjected to ND → NH exchange before spectral analysis.
(5) Such differences in vibrational frequencies have been used previously for distinguishing diastereomers: C. R. Childs and K. Bloch, *J. Org. Chem.*, **26**, 1630 (1961).
(6) For copies of NMR spectra see Ph. D. Thesis of R. M. Nugent, *Diss. Abstr. Int. B*, **33**, 4735 (1973).
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Chlorotrimethylsilane and Allyltrimethylsilane

Aldrich is pleased to offer two new silylated compounds which are useful for a variety of synthetic applications.[1]
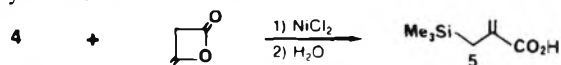
Chloromethyltrimethylsilane Me_3Si⌃Cl (1)

Deprotonation of **chloromethyltrimethylsilane (1)** with *sec*-**butyllithium** yields the α-chloro-α-trimethylsilyl carbanion (2).[2] This species has been used by Magnus for carbonyl group homologations to form aldehydes and methyl ketones.[2] The intermediate α,β-epoxysilanes (3) are also important intermediates for stereospecific olefin syntheses.[2,3]
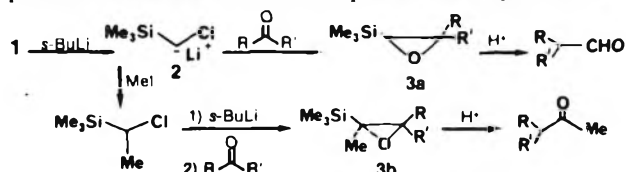
Chloromethyltrimethylsilane (1) reacts with magnesium to form the Grignard reagent 4,[4] which has been used for a variety of transformations[4] including the Peterson olefination:[5,6]

Reagent 4 also reacts with ketene dimer to give the novel carboxylic acid 5.[7]

Anions such as 2 react with trialkylboranes to give 1-silyl-1-boryl compounds 6.[8]
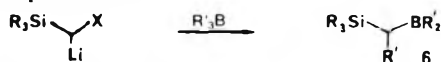
Chloromethyltrimethylsilane (1) undergoes α-elimination when treated with the H⁺arpoon base LiTMP; the resulting carbene can be trapped *in situ* by olefins to give silylcyclopropanes (7) in moderate yields.[9]
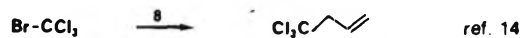

Allyltrimethylsilane

The anion derived from **allyltrimethylsilane (8)** has recently been used as a β-acylcarbanion equivalent.[10] Thus, treatment of **8** with *sec*-butyllithium followed by the addition of an aldehyde or ketone provides, after epoxidation and oxidation, good yields of lactones.[10] The anion derived from **8** also reacts with a variety of other functional groups.[11]
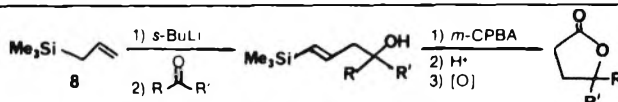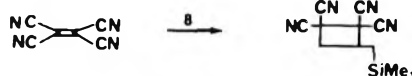

Allyltrimethylsilane (8) reacts with carbonyl compounds in the presence of Lewis acids to give β,γ-unsaturated alcohols,[12] and with acid chlorides to form β,γ-unsaturated ketones:[13]
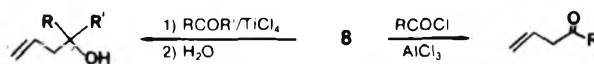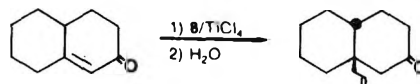

Other synthetic applications of **allyltrimethylsilane (8)** follow.

Recently, **8** has been used for the *in situ* generation of **iodotrimethylsilane (TMSI)**.[17]

TMSI is available from Aldrich, too!

References:
(1) For a review of the use of silicon reagents in organic synthesis, see E. W. Colvin, *Chem. Soc. Rev.*, **7**, 15 (1978); (2) P.D. Magnus, *et al.*, *J. Am. Chem. Soc.*, **99**, 4536 (1977); F. Cooke and P.D. Magnus, *Chem. Commun.*, 513 (1977); P. Magnus and G. Roy, *ibid.*, 297 (1978); (3) P.F. Hudrlik, *et al.*, *J. Org. Chem.*, **40**, 2263 (1975); P.F. Hudrlik, *et al.*, *J. Am. Chem. Soc.*, **99**, 1993 (1977); (4) C.R. Hauser and C.R. Hance, *ibid.*, **74**, 5091 (1952); (5) D.J. Peterson, *J. Org. Chem.*, **33**, 780 (1968); (6) R.K. Boeckman and S.M. Silver, *Tetrahedron Lett.*, 3497 (1973); (7) K. Itoh, M. Fukui, and Y. Kurachi, *Chem. Commun.*, 500 (1977); (8) G.L. Larson, *et al.*, Abstracts, 175th National Meeting of the American Chemical Society, Anaheim, CA, March 1978, ORGN 44; (9) R.A. Olofson, D.H. Hoskin, and K.D. Lotts, *Tetrahedron Lett.*, 1677 (1978); (10) D. Ayalon-Chass, E. Ehlinger, and P. Magnus, *Chem. Commun.*, 772 (1977); (11) R.J.P. Corriu, J. Masse, and D. Samate, *J. Organometal. Chem.*, **93**, 71 (1975); (12) A. Hosomi and H. Sakurai, *Tetrahedron Lett.*, 1295 (1976); (13) R. Calas, *et al.*, *J. Organometal Chem.*, **85**, 149 (1975); (14) H. Sakurai, A. Hosomi, and M. Kumada, *J. Org. Chem.*, **34**, 1764 (1969); (15) G.D. Hartman and T.G. Traylor, *Tetrahedron Lett.*, 939 (1975); (16) A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.*, **99**, 1673 (1977); (17) M.E. Jung, University of California, Los Angeles, personal communication