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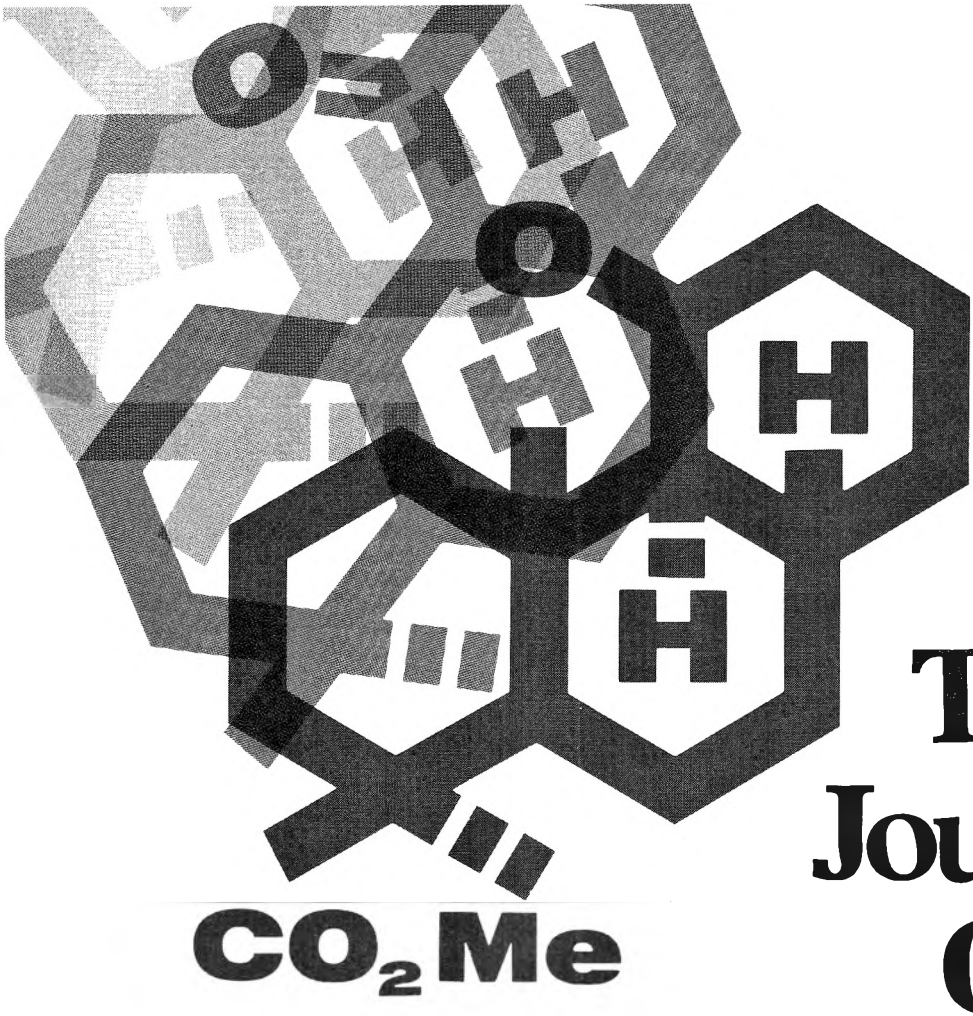

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AUTHOR INDEX

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JUNE 27, 1975

A Novel Reaction of Xenon Trioxide: Organic π Bond Epoxidation. II. Concerning the Mechanism

Scott A. Shackelford* and George U. Yuen[1]

Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received December 20, 1974

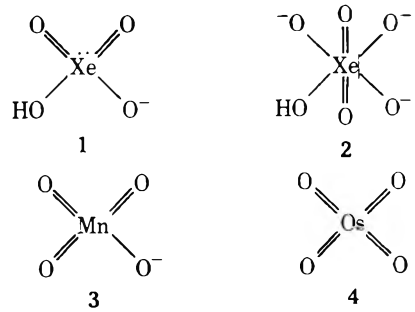
The partially stereoselective epoxidation of alkenes by alkaline xenon trioxide solution was investigated by the employment of reaction quenching techniques, relative reaction rates, and competitive norbornene/cyclohexene product formation ratios. Exclusive peroxide-like attack by the alkaline xenon trioxide reagent toward alkenes was confirmed; no potentially competitive cis-1,2-hydroxylation pathway was detected. Relative rate and product formation ratios, coupled with previously reported stereochemical data, suggest that this epoxidation proceeds via a cyclic, partially bridged three-membered complex that undergoes competitive σ-bond rotation to produce stereoselective epoxide products. The initially formed epoxide product was found to resist direct oxidative attack by the alkaline xenon trioxide reagent. Such resistance to oxidative attack is not found in certain other oxygen containing hydrocarbons, namely, primary and secondary alcohols, aldehydes, and carboxylic acids.

Previously, we reported the epoxidation of alkenes by alkaline xenon trioxide solution.[2] This theoretically intriguing epoxidation proceeded either in a homogeneous aqueous *tert*-butyl alcohol solvent or heterogeneous water emulsion and demonstrated a slight degree of stereoselectivity with pure cis and trans alkenes. Unlike many inorganic oxides that effect cis-1,2-hydroxylation across an olefinic π bond (e.g., OsO_4, MnO_4^-), only epoxide products, or products resulting from in situ hydrolysis of the initially formed epoxides, were isolated from these alkaline xenon trioxide reactions. Hence, this powerful oxidizing reagent chemically reacts like a peroxide in its attack toward organic π bonds. Similar chemical behavior was noted when sodium perxenate and norbornene reacted in an alkaline water emulsion.[2]

This paper describes the employment of reaction-quenching techniques, relative reaction rate measurements, and the well-documented norbornene/cyclohexene reaction rate ratio technique[3-6] to study the reaction mechanism for the epoxidation of alkene hydrocarbons by alkaline xenon trioxide. Additionally, some important experimental procedures are described herein, which were not reported in a previous preliminary communication[2] and are pertinent to the discussion and conclusions drawn in this paper.

Results and Discussion

Reaction Quenching Study. Product isolation from our previous alkaline xenon trioxide oxidations of alkenes produced no derivatives resulting from a cis-1,2-hydroxylation pathway.[2] However, in alkaline xenon trioxide solution, vicinal diol compounds are oxidatively cleaved to generate aldehyde moieties which subsequently are oxidized stepwise, to the corresponding carboxylic acid, and onto carbon dioxide.[7-13] Conceivably, then, a potential competing cis-1,2-hydroxylation reaction pathway could escape detection during product analysis through further in situ oxidation of the initially formed cis vicinal diol derivative. This possibility, coupled with the formal structural similarities of the alkaline xenon trioxide species (1 and 2) to other inorganic oxides that effect cis-1,2-hydroxylation of alkenes (3 and 4), prompted us to investigate the exclusiveness of the observed epoxidation reaction pathway.



Under similar reaction conditions employed in the alkaline xenon trioxide epoxidations, the rate of *cis*-1,2-cyclohexanediol oxidation in alkaline xenon trioxide solution was followed by monitoring xenon trioxide consumption through arsenic(III) oxide iodometric titration of aliquoted reaction samples. A sample of *trans*-1,2-cyclohexanediol was also run in parallel with the cis isomer; the initial rates determined for each compound are listed in Table I.

Two experiments between cyclohexene and alkaline xenon trioxide were then conducted under similar reaction conditions employed for the *cis*- and *trans*-1,2-cyclohexanediol oxidation rate study. In the first, after the alkaline xenon trioxide was added dropwise over 33 min, the reaction proceeded for 35 min before the reaction was quenched; the previous oxidation rate data obtained indicated that the total 68-min reaction time corresponded to

Table I
Aqueous Oxidation Rate of Cyclohexanediols with Alkaline XeO_3 at 0° (pH 8)

Species oxidized	Mol/l. min	% reaction monitored
cis-1,2-Cyclohexanediol[a]	8.5×10^{-6}	88.1
trans-1,2-Cyclohexanediol[a]	4.3×10^{-6}	46.3
cis-1,2-Cyclohexanediol[b]	8.3×10^{-6}	79.2

[a] Parallel kinetic run. [b] Later individual kinetic run.

Table II
Aqueous *tert*-Butyl Alcohol Oxidation Rate of Vicinal vs. Nonvicinal Diols by Alkaline Trioxide at 7.5° (pH 9)

Species oxidized	Initial rate, mol/l. hr	% reaction monitored
trans-1,2-Cyclohexanediol	5.0×10^{-5}	83.5
Norbornanediol[16]	1.4×10^{-5}	58.4
Blank alkaline XeO_3	4.7×10^{-6}	27.0

the *cis*-1,2-cyclohexanediol oxidation as proceeding less than 39% toward completion. If cis-1,2-hydroxylation were a significant competitive reaction pathway to epoxidation, some *cis*-1,2-cyclohexanediol would have remained unoxidized after quenching the reaction.

This first experiment was quenched by adding excess potassium iodide and acidifying the solution to instantly reduce the remaining alkaline xenon trioxide species.[14] Acid hydrolysis ensued and work-up produced a white solid identified as pure *trans*-1,2-cyclohexanediol derived from the hydrolysis of the initially formed cyclohexene oxide. No *cis*-1,2-cyclohexanediol was detected.

The second experiment was run similarly and was quenched by adding excess potassium iodide to reduce any perxenate species. Direct removal of the organic species via chloroform extraction followed. Analysis of the organic extract revealed cyclohexene oxide, but no *cis*-1,2-cyclohexanediol nor any trans isomer.

Because no *cis*-1,2-cyclohexanediol was produced in the two quenched reactions between cyclohexene and alkaline xenon trioxide, cis-1,2-hydroxylation may be ruled out as a potentially significant competitive reaction pathway to the epoxidation reaction mode. In conjunction with this quenching study, it was noted that *cis*-1,2-cyclohexanediol is oxidized significantly more rapidly than its trans isomer (Table I). Subsequent reaction rate studies showed that alkaline xenon trioxide also oxidized nonvicinal diols (Table II);[15] thus, alkaline xenon trioxide does not exhibit the oxidative selectivity toward vicinal diol compounds demonstrated by periodic acid.

Reaction Rate Studies. Xenon trioxide in alkaline solution transforms to the xenate ion ($HXeO_4^-$), which disproportionates to form perxenate ions, oxygen, and elemental xenon (eq 1);[17] once the pH-dependent perxenate ion

$$2HOXeO_3^- + 2OH^- \longrightarrow XeO_6^{4-} + Xe + O_2 + 2H_2O \quad (1)$$

forms, it decomposes to the xenon(VI) species and oxygen.[17] Equation 2 represents the perxenate ion decomposition which at pH 11.5 proceeds about 1% per hour and at pH 8 proceeds about 1% per minute. Once a xenon trioxide

Table III
Initial Reaction Rates for Consumption of Xenon Trioxide with Norbornene and Cyclohexene Epoxides at 7.5° (pH 10)

Reactant	Initial rate, mol/l. hr	% reaction monitored
exo-2,3-Norbornene oxide	9.4×10^{-6}	59.0
1,2-Cyclohexene oxide	1.3×10^{-5}	98.0
Blank (alkaline XeO_3)	9.4×10^{-6}	54.0

solution is brought to an alkaline pH, the xenon oxide species are gradually depleted from solution through the reaction pathways described by eq 1 and 2. For this reason

$$2XeO_6^{4-} + 4H_2O \longrightarrow 2HXeO_4^- + O_2 + 6OH^- \quad (2)$$

all reaction rate data sets presented are comprised of one reaction blank containing only the alkaline xenon trioxide reagent. The inherent rate of xenon trioxide depletion was determined in each data set to verify whether or not reaction between the alkaline xenon trioxide reagent and the organic reactant was proceeding. Each reaction rate data set was obtained under similar but not identical reaction conditions. Stock solutions were prepared and the pH was adjusted separately for each kinetic experiment. Therefore, reaction rate comparisons are valid only within each data set; comparison of reaction rates between two different data sets likely will conjure misconceptions.

Certain oxygen-containing organic compounds are readily oxidized by the reagent.[7-13] The oxidative stability of the epoxide product, generated in the alkaline xenon trioxide oxidation of alkenes, was determined utilizing comparative reaction rates. Most epoxides slowly undergo alkaline hydrolysis via a trans opening to produce the corresponding vicinal diol. As discussed, vicinal diols are directly oxidized by xenon trioxide eventually to carbon dioxide. However, unlike most epoxides, *exo*-2,3-norbornene oxide does not hydrolyze in moderately alkaline solution and forms nortricyclanol only in very strong base.[16] Since it does not hydrolyze to the reaction rate complicating oxidizable diol, *exo*-2,3-norbornene oxide was used to test the stability of epoxides toward direct oxidative attack by the alkaline xenon trioxide reagent. A set of reaction rate data was determined with three parallel reactions in a 65% aqueous *tert*-butyl alcohol reaction solution at pH 10. One reaction solution contained *exo*-2,3-norbornene oxide, the second 1,2-cyclohexene oxide in identical concentration, and the third reaction was a blank. All three solutions were thermally equilibrated (7.5°) in a constant-temperature bath before a 2:1 excess of xenon trioxide was introduced into each alkene oxide reaction solution and into the blank solvent solution in equal initial concentrations. The initial reaction rates obtained (Table III) show no appreciable rate difference between the norbornene oxide solution and the alkaline xenon trioxide disproportionation in the blank solution. Thus, *exo*-2,3-norbornene oxide is stable toward direct oxidative attack by alkaline xenon trioxide, even in a 2:1 excess of this reagent, and depletion of the initially formed epoxide products in the alkene epoxidation reaction does not occur through direct oxidative attack by the alkaline xenon trioxide reagent. This suggests that the significantly more rapid consumption of xenon trioxide with the cyclohexene oxide solution must result from the secondary alkaline xenon trioxide diol oxidation initiated from alkaline hydrolysis of the initial cyclohexene oxide to *trans*-1,2-cyclohexanediol. However, the possibility that *exo*-2,3-norbornene oxide's inertness toward direct oxidation by the alkaline xenon trioxide is unique cannot be totally dismissed.

Table IV
Initial Reaction Rates of Concentrated vs. Dilute Cyclohexene with Alkaline XeO_3 at 7.5° (pH 10)

Reactant	Initial rate, mol/l. hr	% reaction monitored
Concentrated cyclohexene	9.1×10^{-5}	91.9
Dilute cyclohexene	3.8×10^{-5}	88.5
Blank (alkaline XeO_3)	2.9×10^{-5}	69.7

A second reaction rate data set was obtained to determine the importance of alkene participation in the epoxidation reaction. Three parallel reactions were employed; one reaction contained "concentrated" cyclohexene (2.97 mmol), a second reaction contained "dilute" cyclohexene (0.297 mmol), and the third reaction was a blank devoid of cyclohexene. The reactions were conducted in a 57% aqueous *tert*-butyl alcohol solution adjusted to pH 10. The initial reaction rates obtained (Table IV) indicate a significant sevenfold rate enhancement for the "concentrated" cyclohexene reactant after substraction of the blank. Such rate enhancement verifies alkene participation in the epoxidation reaction's rate-determining step,[18] and suggests interaction between the alkene's unsaturated bond and the alkaline xenon trioxide species or an oxidizing species generated therefrom.

Relative Norbornene/Cyclohexene Product Formation Ratios. Relative product formation or reaction rate ratios between norbornene and cyclohexene have proved to be valuable chemical tools to decipher the size and nature of suspected cyclic, bimolecular transition states in alkene addition reaction.[3-6] Generally, three-membered transition states provide a ratio on the order of 10 while five-membered ones afford ratios ranging between 10^2 and 10^3. Product formation ratios can be obtained from product yields of a reaction containing equimolar amounts of two competing alkenes and the reagent under evaluation;[6] direct competitive reaction rates obtained with this tested reagent and each alkene in separate reactions offers a second evaluative method.[3-5] The apparent bimolecular interaction between the alkene and the alkaline xenon trioxide or perhaps an epoxidizing species generated therefrom, plus the slight degree of stereoselectiveness exhibited in this epoxidation reaction[2] with pure cis and trans acyclic alkenes, allows consideration of two potential bimolecular, cyclic transition states—a three-membered or five-membered species.

Competitive norbornene/cyclohexene product formation ratios with alkaline xenon trioxide were obtained from competitive reactions conducted in both homogeneous aqueous *tert*-butyl alcohol solvent and heterogeneous water emulsion. Excess but equimolar amounts of norbornene and cyclohexene were stirred in the same reaction solution ($8 < pH < 9$) until all xenon trioxide was consumed. The resulting volatile epoxides were acid hydrolyzed in situ to their respective diols prior to work-up to minimize product loss.[19] After work-up the norbornanediol and cyclohexanediol product mixture was analyzed by gas–liquid chromatography;[16,20] triangulated peak area measurements of each diol product afforded competitive product formation ratios (Table V) that clearly reveal a three-membered transition state species.

Because previous norbornene/cyclohexene reaction rate ratios were accomplished in much less polar solvents than those necessarily employed for the xenon trioxide reagent, duplicate reactions were conducted in our highly polar solvents substituting *m*-chloroperbenzoic acid for the alkaline xenon trioxide.

Table V
Norbornene/Cyclohexene Relative Rate Ratio vs. Cyclic Transition State Size

Reagent	Ref	Cyclic transition state size	Norbornene/cyclohexene rel rate ratio
Perlauric acid	3	3	1.2
Mo(VI) HMPA	6	3	1.94
m-Chloroperbenzoic acid	6	3	2.39
Basic xenon trioxide[a]	This work	?	2.4
Basic xenon trioxide[b]	This work	?	2.7
Cr(VI) oxidation	4	3	5.5
Ag^+ complex formation	21	3	17
OsO_4 in pyridine	22	5	72.3
OsO_4 in ether	6	5	320
Diphenylnitrilimide addition	24	5	283
Benzonitrile oxide addition	24	5	1800
Phenyl azide addition	3, 23, 24	5	6500
Picryl azide addition	3, 23	5	8000

[a] Homogeneous, aqueous *tert*-butyl alcohol solvent. [b] Heterogeneous water solvent.

Table VI
Norbornene/Cyclohexene Product Formation Ratios from Alkaline XeO_3 and *m*-Chloroperbenzoic Acid Epoxidation

Reagent	Product formation ratio
Alkaline XeO_3[a]	2.4
m-Chloroperbenzoic acid[a]	1.8
Alkaline XeO_3[b]	2.7
m-Chloroperbenzoic acid[b]	1.6

[a] Homogeneous aqueous *tert*-butyl alcohol solvent. [b] Heterogeneous water emulsion.

Table VI lists these results and good agreement between the *m*-chloroperbenzoic acid standard and the xenon trioxide epoxidant in both polar solvent systems was obtained. Additionally, the *m*-chloroperbenzoic acid ratios are in line with those formerly reported in the less polar solvents (Table V).

A relative norbornene/cyclohexene reaction rate ratio was secured directly from a parallel reaction rate experiment where equimolar amounts of norbornene and cyclohexene were each treated separately with alkaline xenon trioxide in 65% aqueous *tert*-butyl alcohol (pH 10) at 7.5°. A blank of the alkaline xenon trioxide was also run, and the reaction rate data was secured and treated as previously described. The initial reaction rates (Table VII) provide a norbornene/cyclohexene reaction rate ratio equal to 7.5 after subtraction of the blank xenon trioxide; once again, this value fits well within the range attributed to bimolecular, three-membered transition states (Table V).

Table VII
Initial Reaction Rates of Norbornene and Cyclohexene with Alkaline XeO_3 at 7.5° (pH 10)

Reactant	Initial rate, mol/l. hr	% reaction monitored
Norbornene	2.9×10^{-5}	66.2
Cyclohexene	1.6×10^{-5}	61.6
Blank (alk XeO_3)	1.4×10^{-5}	41.4

Conclusions

Chemical reaction between alkene hydrocarbons and alkaline xenon trioxide solution initiates a peroxide-type attack upon the alkene π electrons to produce epoxide derivatives. Epoxidation is the only significant reaction mode detected with alkenes. While some of the initially formed epoxide product is lost during the reaction, through alkaline hydrolysis to diol compounds and subsequent alkaline XeO_3 oxidation of these diols to carbon dioxide, the epoxide product itself is apparently stable toward direct oxidative attack by the alkaline xenon trioxide reagent, and no epoxide is probably lost via direct secondary oxidations.

Previous epoxidations of pure *cis*- and *trans*-stilbene plus *cis*- and *trans*-2-octene in alkaline XeO_3 solution demonstrated a slight degree of stereoselectivity in the isomeric epoxide products.[2] Therefore, some structural rigidity must exist in this reaction's rate-determining step to account for such results. The alkene does interact with the epoxidizing species during the course of reaction as reflected in the concentrated/dilute cyclohexene reaction rates. The competitive norbornene/cyclohexene ratios verify the epoxidation as proceeding via a cyclic three-membered species involving alkene π bond and the oxidant.

The experimental results obtained to date for the alkaline XeO_3 epoxidation of alkenes are consistent with the formation of a weakly bridged, cyclic three-membered complex in the epoxidation's rate-determining step. This intermediate complex forms from an interaction between the alkene and either the alkaline xenon trioxide species or an oxidizing species generated therefrom. This weakly bridged, three-membered cyclic complex, once formed, undergoes significant competitive σ bond rotation about the carbon–carbon single bond to form the nonstereospecific cis/trans epoxide mixture. In the highly polar solvents, as required by the alkaline xenon trioxide reagent, charge localization would be favored over charge dispersal in the partially bridged intermediate species. Charge localization would tend to weaken the cyclic bridging in the intermediate complex and allow significant, competitive σ bond rotation that would result in the low degree of stereoselectivity observed[2] in the epoxidation of acyclic cis/trans alkenes.

Experimental Section

General Procedures. All common reagents and extraction solvents employed were Mallinckrodt AR, Matheson Coleman and Bell AR, or Baker Analyzed. The water used in all reactions and in the dilution of xenon trioxide solution was taken directly from a deionized water line in the laboratory; the *tert*-butyl alcohol solvent was Mallinckrodt AR that had been triply distilled. All glassware and Teflon-coated stirring bars were soaked in a clean, steam-heated, deionized water bath containing a small amount of Alconox soap. The equipment was then thoroughly rinsed with deionized water followed by one rinse with distilled Mallinckrodt AR acetone that was stored over 4A molecular seieves. The cyclohexene (Mallinckrodt AR Grade) was distilled once and the norbornene (MCB Practical) was twice distilled unless stated otherwise. *cis*-Stilbene was synthesized by previously described methods;[25] GLC analysis showed it to be 99.3% isomerically pure.

Glassware joints were treated with vacuum grease or were wrapped with Teflon tape to avoid trapping any xenon trioxide solution in the joints. (*Dry xenon trioxide is explosive and detonates very easily!*)[26] Reactions were stoppered because most alkenes employed were rather volatile. Both the homogeneous and heterogeneous xenon trioxide–alkene reactions were stirred with Teflon coated bars, and unless stated otherwise, all pH adjustments were made with 1% sodium hydroxide or 2 *N* sulfuric acid. The pH measurements were taken with wide-range pH hydrion paper, and organic extracts were dried over anhydrous magnesium sulfate or sodium sulfate.

Table VIII
Gas Chromatography Columns Employed in Experiments with the Compounds Listed

9 ft × 0.25 in. 20% Carbowax 20M on 70/80 Mesh Anakrom ABS
cis- and *trans*-1,2-cyclohexanediol, cyclohexene oxide, *cis*- and *trans*-1,2-cyclopentanediol, cyclopentene oxide, *exo*-2,3-norbornene oxide, bicyclo[2.2.2]oct-2-ene oxide
1.45 m × 0.25 in. 5% SE-30 on 70/80 Mesh Anakrom ABS
syn- and *anti*-2,7-norbornanediol and *syn*- and *anti*-2,5-norbornanediol mixture (single peak), *trans*-1,2-cyclohexanediol
6 ft × 0.05 in. 5% QF-1 on 100/120 Mesh Varaport 30
cis-Stilbene, *cis*-stilbene oxide, *trans*-stilbene, *trans*-stilbene oxide

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Mass spectra were determined on an Atlas CH-4B mass spectrometer; nuclear magnetic resonance spectra were recorded on a Varian A-60 instrument, and all infrared plots were secured on a Beckman IR-33 in potassium bromide pellets or as a thin film between sodium chloride or silver chloride disks. Gas–liquid partition chromatograms were obtained on an Aerograph Dual Column Model A-350-B chromatograph; Table VIII records the columns employed to identify, separate, and isolate the compounds listed. Isomeric percent analyses obtained by GLC were determined by triangulation. In several cases where interfering peaks made direct measurement of peak width at one-half the peak's height impossible, a standard peak of equal size obtained from a pure sample was used to gain this necessary measurement. All reported product yields were calculated as quantitative theoretical yields assuming a 3:1 alkene to XeO_3 reaction stoichiometry and are not corrected for work-up losses.

In all reaction rate studies, where iodometric titration analysis was employed, starch indicator was added near the end point to sharpen detection. The xenon trioxide was purchased from PCR in 100-ml quantities as 0.1 *N* solution.

***trans*-1,2-Cyclohexanediol from Cyclohexene and Xenon Trioxide.** A 100-ml water solution containing 0.12335 g (1.508 mmol) of cyclohexene was rapidly stirred and cooled while submerged in an ice–salt bath. One milliliter of 0.28 *M* (0.28 mmol) XeO_3 was diluted with 60 ml of H_2O and brought to pH 9–10 by the dropwise addition of 10% NaOH. Over 1.25 hr the XeO_3 solution was added to the stirred cyclohexene emulsion. The reaction mixture was maintained at ice bath temperature for an additional 3.5 hr, then was allowed to gradually equilibrate to room temperature over the next 44 hr. The solution was brought to pH 3 by dropwise addition of 6 *N* H_2SO_4 and left at room temperature for 141.5 hr. The aqueous reaction solution was concentrated to 50 ml over a Bunsen burner, and the concentrate was extracted 12 times with ~50 ml of $CHCl_3$. The combined $CHCl_3$ extracts were concentrated to 50 ml and dried. In vacuo solvent removal gave 0.0152 g (15.6%) of crude white solid: ir (KBr) 3400 (OH), 2950 and 2880 (CH), 1040, 930, and 670 cm^{-1} (characteristic trans isomer fingerprint absorptions); micro-NMR ($DCCl_3$) δ 4.48 (2 H, m, methine), 3.38 (2 H, s, hydroxy), 2.25–1.00 (8 H, m, cyclohexyl); GLC on the Carbowax 20M column (210°) D_r' 11.25 cm only (commercial *trans*-1,2-cyclohexanediol D_r' 11.25 cm and *cis*-1,2-cyclohexanediol D_r' 10.10 cm).

***exo*-2,3-Norbornene Oxide from Norbornene and Xenon Trioxide.** A 15-ml H_2O solution containing 0.1570 g (1.67 mmol) of once-distilled norbornene was stirred and cooled in an ice–salt bath for 1.5 hr. Ten milliliters of 0.1 *N* (0.167 mmol) XeO_3 was adjusted to pH 9 and added dropwise over 15 min to the stirred norbornene solution. The reaction solution and ice bath were placed into a cold room (3°) for 3 hr. Then the reaction vessel was re-

moved from the cold room and packed into a fresh ice bath, which was allowed to melt and equilibrate to room temperature. After 22.25 hr reaction time, the solution was yellow and at a neutral pH. The pH was adjusted to 8; the same pH adjustment was necessary after an additional 8 hr. All XeO_3 was consumed after a total of 54.5 hr; the solution was saturated with NaCl and extracted four times with diethyl ether. The combined extracts were concentrated to 50 ml, then dried, filtered, and concentrated further by rotary evaporation to 0.1 ml for GLC analysis; GLC on the Carbowax 20M column (163°) D_r' 5.74 cm only (*exo*-2,3-norbornene oxide D_r' 5.74 cm); mass spectrum M^+ 110 from a sample collected off the Carbowax column at 187° that gave a fragmentation pattern identical with known *exo*-2,3-norbornene oxide that was also collected off the same column (187°); ir (neat) 3010–2880 (CH), 845 cm^{-1} (oxide); the reaction sample was subjected to a second GLC analysis on the Xe-60 column (150°) D_r' no peaks at 5.02–5.20 or at 4.10–4.20 cm (known *exo-cis*-2,3-norbornane diol D_r' 4.12 cm and known *syn*- and *anti*-2,5- and -2,7-norbornanediol mixture (single peak) D_r' 5.06 cm).

***syn*- and *anti*-2,5- and -2,7-Norbornanediol Mixture from Norbornene and Xenon Trioxide.** A 15-ml H_2O solution containing 0.1560 g (1.66 mmol) of norbornene was cooled with stirring for 1.5 hr in an ice–salt bath. Ten milliliters of 0.1 *N* (0.167 mmol) XeO_3 was adjusted to pH 9 and added dropwise over 6 min to the stirred norbornene solution. The ice bath was allowed to equilibrate to room temperature environment; after 12 hr the solution pH was neutral and was adjusted to pH 8. After 23.5 hr of reaction, the pH was again adjusted to 8; the same adjustment was made 6.25 hr later. After a total reaction time of 38 hr, all xenon trioxide was spent; the yellow solution was adjusted to pH 3 and left for 108 hr at room temperature. Then the aqueous solution was concentrated to 20 ml, adjusted to pH 11, and extracted six times with ~50 ml of diethyl ether. The aqueous layer was saturated with NaCl and six additional ethereal extractions were accomplished. The combined extracts were concentrated to 30 ml, dried, and filtered. In vacuo solvent removal left a crude brownish oil weighing 0.0254 g. The oil was redissolved in 0.2 ml of ether. It was then analyzed and purified by preparative GLC to yield 0.0080 g (12.5%) of white solid: ir (KBr) 3390 (OH), 2970 and 2890 cm^{-1} (CH); mass spectrum M^+ 128; GLC on the Xe-60 column (152°) D_r' 5.06 cm only [*syn*- and *anti*-2,5- and -2,7-norbornanediol mixture (single peak) D_r' 5.02 cm and *exo-cis*-2,3-norbornanediol D_r' 4.06 cm].

Stilbene Oxide from *cis*-Stilbene and Xenon Trioxide (Heterogeneous Reaction at 3°). A solution containing 2 ml of H_2O and 0.06055 g (0.336 mmol) of 99.3% *cis*-stilbene was cooled with stirring in a cold room (3°) for 35 min. Ten milliliters of 0.1 *N* (0.167 mmol) XeO_3 at pH 9 was added over a 5-min period to the stilbene–H_2O solution. For the next 280 hr, the reaction proceeded until all xenon trioxide was depleted; at 24-, 51-, 72-, and 122-hr reaction intervals, the solution was adjusted from near neutral pH to pH 8. The reaction solution was extracted once with diethyl ether; the aqueous layer was then saturated with NaCl. Three more ethereal extracts were taken; the combined ether extracts were dried, filtered, and concentrated to about 0.2 ml. Preparative GLC on the QF-1 column (139°) allowed the identification and isolation of four compounds: unreacted *cis*-stilbene, *cis*-stilbene oxide, *trans*-stilbene, and *trans*-stilbene oxide was the elution order on the QF-1 column. The GLC results showed that 1.4% of the initial *cis*-stilbene was converted to the cis oxide; GLC results of a blank indicated only 2.8% isomerization of the *cis*-stilbene to the trans isomer under the reaction conditions described. Peak 1: ir (neat) 3100, 3080, and 3040 (CH), 1600, 1575, 1495, and 1450 cm^{-1} (phenyl); mass spectrum M^+ 180. Peak 2: mass spectrum M^+ 196, characteristic stilbene oxide peaks *m/e* 167 and 105. Peak 3: ir (KBr) 3100, 3080, and 3040 (CH), 1600, 1580, 1495, and 1450 cm^{-1} (phenyl); mass spectrum M^+ 180. Peak 4: mass spectrum, M^+ 196, characteristic stilbene oxide peaks *m/e* 167 and 105.

Stilbene Oxide from *cis*-Stilbene and Xenon Trioxide (Homogeneous Reaction at 25°). Ten milliliters of 0.1 *N* (0.167 mmol) XeO_3 was cooled in a cold room (3°) for 1.25 hr. A solution containing 20 ml of *tert*-butyl alcohol and 0.06047 g (0.336 mmol) of 99.3% *cis*-stilbene was taken into the cold room. After the xenon trioxide solution was adjusted to pH 9, it was added over 3 min to the stirred *cis*-stilbene solution. When the solution showed $7 < pH < 8$, it was adjusted to pH 8. The reaction proceeded for 0.25 hr in the cold room and was then removed to a room temperature environment. During the reaction, adjustments to pH 8 were made at 3.0-, 8,0-, 31.5-, 36.5-, and 46.5-hr intervals. After 57.75 hr, all XeO_3 was consumed and a yellowish solution remained. The reaction solution was saturated with NaCl and extracted three times with diethyl ether. The combined extracts were concentrated to 75 ml, dried, and filtered. The solution was concentrated to about 0.2 ml. Analysis by GLC on the QF-1 column (139°) identified and isolated four compounds that eluted from the column in the order *cis*-stilbene, *cis*-stilbene oxide, *trans*-stilbene, and *trans*-stilbene oxide; GLC results of a blank indicated only 6.4% isomerization of the *cis*-stilbene to the trans isomer under the reaction condition described. Peak 1: ir (neat) 3100, 3070, and 3040 (CH), 1600, 1575, 1495, and 1450 cm^{-1} (phenyl). Peak 2: mass spectrum M^+ 196, characteristic stilbene oxide peak *m/e* 167. Peak 3: ir (KBr) 3100, 3070, and 3040 (CH), 1600, 1575, 1495, and 1450 cm^{-1} Peak 4: mass spectrum M^+ 196, characteristic stilbene oxide peaks *m/e* 167 and 105.

***exo*-2,3-Norbornene Oxide from Norbornene and Sodium Perxenate.** A solution containing 5 ml of water and 0.15700 g (1.67 mmol) of norbornene was cooled for 20 min in an ice–salt bath; it was then placed into a cold room (3°) and stirred for another 45 min. Next, 0.05250 g (0.167 mmol) of Na_4XeO_6 was added to the stirred solution and a very high solution pH (ca. 12) resulted. After 5 hr the yellow reaction solution was removed from the cold room, placed into an ice bath, and equilibrated to room temperature. After a total reaction time of 33.25 hr, all Xe species were spent. The solution was saturated with NaCl and was extracted three times with diethyl ether. The combined extracts were dried, filtered, and concentrated to about 0.3 ml. The concentrate was analyzed by GLC, and the products were isolated: GLC on the Carbowax 20M column (174°) D_r' 3.48 and 6.80 cm (*exo*-2,3-norbornene oxide D_r' 3.48); mass spectrum M^+ 110, the smaller peak at D_r' 6.80 cm remained unidentified but gave a mass spectrum, parent peak *m/e* 124, and a fragmentation pattern similar to, but different from, that of *exo*-2,3-norbornene oxide.

***cis*- and *trans*-1,2-Cyclohexanediol Oxidation Rates with Xenon Trioxide.** Two 20-ml H_2O solutions, one containing 0.0334 mmol of *cis*-1,2-cyclohexanediol and the other containing an identical concentration of *trans*-1,2-cyclohexanediol, were submerged into a constant-temperature ice bath (0°). The solutions were allowed to temperature equilibrate. Next, 5% NaOH was added to 6 ml of 0.1 *N* XeO_3 solution until a pH 9 was reached. Into each homogeneous diol solution was pipetted 2 ml (0.0334 mmol) of the alkaline XeO_3; an oxidation reaction at pH 8 resulted. At appropriate intervals, 2-ml aliquots were pipetted from the reaction solutions and were each transferred into an erlenmeyer flask that contained 1.5 g of KI. Two milliliters of 2 *N* H_2SO_4 were added to liberate iodine. Thirty seconds later, 1.5 g of $NaHCO_3$ was added to the flask which was then swirled and allowed to stand for 5 min. Iodometric titration with 0.002 *N* arsenic(III) oxide with starch indicator determined the concentration of unreacted XeO_3. A titer to determine initial XeO_3 concentration at time zero was obtained by placing 1 ml of the freshly prepared alkaline XeO_3 into 10 ml of water. A 1-ml aliquot was pipetted, treated, and titrated as described above. The individual *cis*-1,2-cyclohexanediol rate study was set up and analyzed in an identical manner.

Direct *cis*-1,2-Cyclohexanediol Formation Check in Alkaline XeO_3 Epoxidation of Alkenes. A 100-ml H_2O emulsion containing 0.1187 g (1.45 mmol) of cyclohexene was cooled via stirring while submerged in an ice–salt bath. Ten milliliters of 0.1 *N* (0.167 mmol) XeO_3 was diluted with 50 ml of H_2O and adjusted to pH 9 with 1% NaOH. The alkaline XeO_3 was added dropwise to the stirred cyclohexene emulsion over 33 min. Reaction proceeded for an additional 35 min before quenching by the introduction of 70 mg of KI. After dropwise addition of 2 *N* H_2SO_4 followed until pH 3 was reached,[14] the acidified reaction solution was left for 97.5 hr at room temperature. The solution was then made alkaline (pH 9) and was extracted 12 times with ~50-ml $CHCl_3$ portions. The combined $CHCl_3$ extracts were concentrated to 50 ml, dried, and filtered. The remaining solvent was removed in vacuo to yield 8.8 mg (15.1%) of crude off-white solid; GLC on a 9 ft × 0.25 in. 20% Carbowax 20M column (211°) produced only one peak with a retention time identical with that of commercial *trans*-1,2-cyclohexanediol, mass spectrum M^+ 116. Another sample of cyclohexene (0.1218 g, 1.49 mmol) was added to a stirred 100-ml H_2O solution, and the solution was cooled for 2.25 hr in an ice–salt bath in a cold room. Ten milliliters of 0.1 *N* (0.167 mmol) XeO_3 were pipetted into 50 ml of H_2O; the solution was adjusted to pH 9. The alkaline XeO_3 was added dropwise to the stirred cyclohexene over 32 min and the reaction was then continued for an additional 36 min. KI (0.100 g) was introduced into the reaction; immediately 5 ml of $NaHCO_3$ buffered 0.2 *N* arsenic(III) trioxide was added. Nine $CHCl_3$ extractions followed; the combined extracts were dried, fil-

tered, and concentrated via rotary evaporation to 0.3 ml; GLC on the Carbowax 20M column (160 and 220°) showed cyclohexene oxide in low concentration; no *cis*- or *trans*-1,2-cyclohexanediol was detected.

General. Relative Reaction Rate Data Sets. The various sets of comparative reaction rates were monitored at specific time intervals by direct iodometric titration of the unconsumed alkaline xenon trioxide present in the reaction aliquots. The concentration of unconsumed xenon trioxide was plotted against time, and initial reaction rates were obtained. All reaction rate data sets were conducted in alkaline aqueous *tert*-butyl alcohol solution with three parallel reactions being run in each data set; one reaction was always the blank alkaline xenon trioxide reagent previously described in the Results and Discussion.

Competitive *exo*-2,3-Norbornene Oxide vs. 1,2-Cyclohexene Oxide Reaction Rate Determination. A stock solution containing 77 ml of *tert*-butyl alcohol and 143 ml of H_2O was prepared and adjusted to pH 10 with 10% NaOH. Into a 100-ml volumetric flask was weighed 0.00918 g (0.0835 mmol) of norbornene oxide; the volumetric flask was then filled to its mark with the stock solution. Twenty milliliters (0.0167 mmol) of norbornene oxide solution was pipetted into a 35-ml round-bottom flask which was then stoppered, placed into a constant-temperature bath in a cold room, and stirred. Into another 100-ml volumetric flask was placed 0.00812 g (0.0830 mmol) of cyclohexene oxide which was diluted with the stock solution to the mark. Twenty milliliters (0.0166 mmol) of cyclohexene oxide solution was pipetted into a second 35-ml, single-necked, round-bottom flask which was stoppered, placed into the constant-temperature bath in the cold room, and stirred. Ten milliliters of the stock solution was pipetted into a 10-ml pear-shaped flask; it was stoppered and placed into the same constant-temperature bath. All three solutions were temperature equilibrated; the two epoxide solutions were stirred. Into each 35-ml flask was pipetted 2 ml of 0.1 *N* (0.0334 mmol) XeO_3, and into the 10-ml flask was pipetted 1 ml (0.0167 mmol) of XeO_3; the 10-ml flask was stirred with a glass rod to effect a homogeneous solution. Aliquot removal and analysis were accomplished as previously described.

Concentrated vs. Dilute Cyclohexene Reaction Rate Determination. A stock solvent solution for all three kinetic reactions was prepared by mixing 29 ml of *tert*-butyl alcohol with 39 ml of H_2O and was adjusted to pH 10. Into two 35-ml, single-neck, round-bottom flasks was pipetted 20 ml of the stock solution, and into a 10-ml, single-neck, pear-shaped flask was pipetted 10 ml of the stock solution. The three flasks were placed into a constant-temperature bath (7.5°) and equilibrated. To one 35-ml flask were added 30 μl (0.297 mmol) of cyclohexene, and to the other 3 μl (0.0297 mmol) of cyclohexene; in both cases the cyclohexene was injected directly into the stirred solutions with a syringe. Into each cyclohexene solution were pipetted 2 ml of 0.1 *N* (0.0334 mmol) XeO_3 and into the 10-ml pear-shaped titer flask was placed 1 ml of 0.1 *N* (0.0167 mmol) XeO_3. The titer solution was initially stirred with a glass stirring rod to effect a homogeneous solution. At appropriate intervals, 2-ml aliquots were pipetted from the cyclohexene solutions, and 1-ml aliquots were pipetted from the titer solution. A 1-ml aliquot was taken immediately upon mixing the titer solution and represented the initial molar concentration of xenon trioxide in all three reactions. The 2-ml cyclohexene solution aliquots were placed onto 1.5 g of KI in a 125-ml erlenmeyer flask; the aliquot was acidified with 2 ml of 2 *N* H_2SO_4 acid and was then swirled. Thirty seconds after the acid addition, the aliquot solution was buffered with 1 g of $NaHCO_3$ and the inner walls of the flask were washed with a water bottle. The solution was swirled and left to stand at room temperature for 5 min. It was then titrated with $NaHCO_3$-buffered 0.002 *N* arsenic(III) oxide.

Norbornene–Cyclohexene Competitive Reaction with Xenon Trioxide (Heterogeneous). Into the same reaction vessel was weighed 0.07828 g (8.33 mmol) of norbornene and 0.06789 g (8.29 mmol) of cyclohexene; the cyclohexene dissolved the norbornene. The stoppered reaction flask was placed into a cold room and packed into an ice bath; then 5 ml of H_2O was added to the reaction flask. Ten milliliters of 0.1 *N* (0.167 mmol) XeO_3 was adjusted to pH 9 and added to the stirred mixed olefin emulsion over a 2-min period. The ice bath was removed, and the reaction was stirred for 145 hr in the cold room; adjustments to maintain a solution pH of 8 were made at 11, 48, 59, 74, and 116 hr into the reaction. After 145 hr the XeO_3 was depleted, and the reaction solution was acidified to pH 3 and left for 144 hr at room temperature. The pH was then adjusted to 8, and the solution was saturated with NaCl. Six $CHCl_3$ extractions were accomplished; the combined extracts were dried, filtered, and concentrated to about 0.2 ml. Analysis for the percentage of each diol product was made by GLC, and each diol was isolated from the XE-60 column (148°): D_r' 1.10, 1.62, 1.90, 2.40, and 4.46 cm [*trans*-1,2-cyclohexanediol D_r' 1.90 cm and norbornanediols mixture (single peak) D_r' 4.46 cm]. Peak 3: mass spectrum M^+ 116; ir (KBr) 3400 (OH), 2950 and 2880 (CH), 1040, 930, and 670 cm^{-1} (characteristic *trans*-1,2-cyclohexanediol fingerprint absorptions). Peak 5: mass spectrum M^+ 129 with the remaining fragmentation pattern identical with those of known norbornanediols;[16] ir (KBr) 3400 (OH), 2970 and 2890 cm^{-1} (CH).

Norbornene–Cyclohexene Competitive Reaction with *m*-Chloroperbenzoic Acid (Heterogeneous). The reaction was conducted as previous described except that 0.06800 g (0.334 mmol) of 85% *m*-chloroperbenzoic acid (MCPBA) was substituted for the XeO_3 without any initial pH adjustments. After an identical work-up, the amount of each diol product was determined by GLC and isolated from the XE-60 column (144°): D_r' 2.16 and 5.62 cm [*trans*-1,2-cyclohexanediol D_r' 2.12 cm and norbornanediol mixture (single peak) D_r' 5.62 cm]. Peak 1: ir (KBr) 3400 (OH), 2940 and 2870 (CH), 1040, 830, and 670 cm^{-1} (characteristic *trans*-1,2-cyclohexanediol fingerprint absorptions). Peak 2: ir (KBr) 3400 (OH), 2970 and 2880 cm^{-1} (CH).

Norbornene–Cyclohexene Competitive Reaction with Xenon Trioxide (Homogeneous). Ten milliliters of 0.1 *N* (0.167 mmol) XeO_3 was cooled in a cold room for 1.25 hr. A solution containing 0.05780 g (0.616 mmol) of norbornene, 0.05172 g (0.631 mmol) of cyclohexene, and 15 ml of *tert*-butyl alcohol, was prepared and placed in the cold room. The xenon trioxide solution was adjusted to pH 9 and was added to the stirred *tert*-butyl alcohol solution over 2.5 min. After 15 min, the entire solution was adjusted to pH 8 and left to stir in the cold room. Adjustments to pH 8 were made at 21.75, 48.0, 67.75, 72.75, 88.25, and 96.25 hr after reaction was initiated. After a total of 111 hr, XeO_3 was absent; the solution was brought to pH 3 and left at room temperature for 145 hr. The solution was adjusted to pH 9, saturated with NaCl, and then extracted six times with $CHCl_3$. The combined $CHCl_3$ extracts were dried, filtered, and concentrated to about 0.2 ml. Analysis by GLC followed to identify, isolate, and determine the percentage of each diol product formed: GLC on the XE-60 column (144°) D_r' 1.52, 1.98, 2.28, 2.72, 3.16, and 5.92 cm (norbornanediols mixture D_r' 5.60 cm and *trans*-1,2-cyclohexanediol D_r' 2.50 cm). Peak 6: mass spectrum M^+ 128; ir (KBr) 3400 (OH), 2970 and 2890 cm^{-1} (CH). Peak 4: mass spectrum M^+ 116 detected among other characteristic *trans*-1,2-cyclohexanediol fragmentations.

Norbornene–Cyclohexene Competitive Reaction with *m*-Chloroperbenzoic Acid (Homogeneous). The reaction was conducted as previously described except that 0.03400 g (0.167 mmol) of 85% MCPBA was substituted for the XeO_3 without any initial pH adjustments. After an identical work-up, the diol percentage was determined by GLC analysis, which was also used to preparatively isolate and purify the reaction products: GLC on the XE-60 column (145°) D_r' 0.80, 1.36, 1.80, 2.38, 2.58, 3.02, and 6.42 cm (norbornanediols mixture D_r' 5.20 cm and *trans*-1,2-cycohexanediol D_r' 2.88 cm). Peak 5: mass spectrum M^+ 116. Peak 7: mass spectrum M^+ 128.

Competitive Norbornene vs. Cyclohexene Reaction Rate Determination. A stock solution was prepared by mixing 28 ml of *tert*-butyl alcohol and 52 ml of H_2O; the resultant mixture was adjusted to pH 10 with 10% NaOH. Into one 35-ml, single-neck, round-bottom flask was pipetted 20 ml of the stock solution; the flask was stoppered, and the solution was stirred in a constant-temperature bath (7.5°) for 1 hr. Next, 3.4 μl (0.0336 mmol) of cyclohexene were injected into the solution with a microsyringe. Into a 100-ml volumetric flask was weighed 0.00948 g (0.1008 mmol) of norbornene and 30 ml of stock solution was added. Ten milliliters of the norbornene solution and 10 ml of the original stock solution were pipetted into a second 35-ml, single-neck, round-bottom flask to give 0.0336 mmol of norbornene in the reaction solution. The norbornene solution was stoppered and placed into the constant-temperature bath. Into a 10-ml pear-shaped flask was pipetted 10 ml of the stock solution for the initial XeO_3 concentration and XeO_3 disproportionation rate determinations. This flask was stoppered and placed into the constant-temperature bath. After temperature equilibration, 2 ml of 0.1 *N* (0.0334 mmol) XeO_3 was pipetted into each 35-ml flask; into the 10-ml flask was pipetted 1 ml of 0.1 *N* (0.0167 mmol) XeO_3. Aliquot removal and analysis were accomplished as previously described.

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Registry No.—*trans*-1,2-Cyclohexanediol, 1460-57-7; cyclohexene, 110-83-8; xenon trioxide, 13776-58-4; *exo*-2,3-norbornene oxide, 3146-39-2; norbornene, 498-66-8; *syn*-2,5-norbornanediol, 21462-09-9; *anti*-2,5-norbornanediol, 21462-10-2; *syn*-2,7-norbornanediol, 17366-25-5; *anti*-2,7-norbornanediol, 17289-99-5; *cis*-stilbene, 645-49-8; *cis*-stilbene oxide, 1689-71-0; *trans*-stilbene oxide, 1439-07-2; sodium perxenate, 26304-24-5; *cis*-1,2-cyclohexanediol, 1792-81-0; *m*-chloroperbenzoic acid, 937-14-4.

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Mechanisms of the Borate Ester Induced Decomposition of Alkyl Hydroperoxides

Philip F. Wolf,* James E. McKeon, and David W. Cannell

Research and Development Laboratories, Union Carbide Corporation, Tarrytown, New York, 10591

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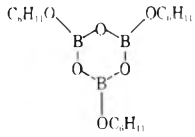
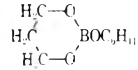
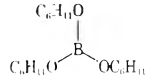
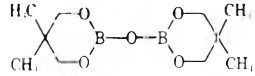
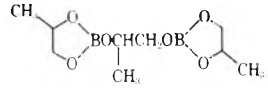
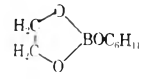
A comparison has been made of the relative rates of tetralin hydroperoxide (THPO) decomposition in *cis*-2-octene, induced by seven different alkyl borate esters. This has demonstrated that the relative acidity of the boron atom, as a result of either the presence of B–O–B bonds or the hybridization of the boron caused by the O–B–O dihedral angle, determines the rate and efficiency of epoxide formation. It is also shown that the highly acidic borate esters, phenyl metaborate, phenyl orthoborate, and triacetyl borate, which decompose THPO approximately 600 times as fast as the most reactive alkyl borate ester, fail to epoxidize olefins but lead to an acid-catalyzed rearrangement of the hydroperoxide producing *o*-(4-hydroxyphenyl)butyraldehyde. The unsaturated borate ester, 2-*n*-butoxy-4,5-diphenyl-1,3,2-dioxaborole (**5**), prepared from *n*-butyl orthoborate and benzoin, reacts rapidly with THPO to give, on hydrolysis, a 4:1 mixture of benzil and benzoic anhydride. Autoxidation of **5** in chlorobenzene produced a 1.2:1 mixture of benzil and benzoic acid. The borate induced decomposition of *tert*-butyl hydroperoxide (*t*-BuOOH) in cyclooctane or *n*-decane is shown to enhance the formation of cyclooctanol and *n*-decanols. This selectivity is interpreted to occur through an induced SH2 (bimolecular homolytic substitution) reaction of solvent alkyl radical on *t*-BuOOH coordinated to borate ester.

We have previously described the generation of a species capable of liberating electrophilic oxygen through the reaction of an alkyl hydroperoxide and a metaborate ester. This intermediate complex has been shown to readily epoxidize olefins or hydroxylate highly nucleophilic aromatic rings and concomitantly produce an alcohol from the hydroperoxide. We have also shown that the presence of a suitable acceptor is critical to efficient consumption of the available nucleophilic oxygen.[1]

Our previous work had shown that the alkyl hydroperoxide–alkyl metaborate system epoxidized olefins in a manner quite similar to that observed with peracetic acid[2] and the hydroperoxide–transition metal system.[3] Thus, more highly substituted olefins are epoxidized more rapidly, stereospecifically, and with no kinetic preference for cis or trans isomers. Unlike peracetic acid, which is relatively stable in hydrocarbons at temperatures at which it readily epoxidizes olefins, the hudroperoxide–metaborate mixture (in hydrocarbon solvent) decomposes at the same rate at which it epoxidizes 1-octene. A unique example of this is the cyclohexyl metaborate induced decomposition at 120° of cumene hydroperoxide in 2-octene and *n*-octane, respectively. In the olefinic solvent, the reaction products are 2-epoxyoctane and 2,2-dimethylbenzyl alcohol. In *n*-octane the reaction gives only acetone and phenol, the products of the well-known acid-catalyzed rearrangement of cumene hydroperoxide.[4] We had previously proposed several related types of metaborate ester–hydroperoxide intermediates to account for the observed reactions.

Recently, Sheldon and VanDoorn[5] have reported studies which expanded the scope of the borate–hydroperoxide system as an epoxidizing agent. These workers have demonstrated that both metaborate esters and the intrinsically less acidic orthoborate esters are capable of acting as catalysts for olefin epoxidation by *tert*-butyl hydroperoxide if sufficiently strong electron-withdrawing groups are at-

Table I
Epoxidation of *cis*-2-Octene by Tetralin Hydroperoxide at 80° Induced by Various Borate Esters

Registry no.	Borate ester[a]	Relative reactivity[b]	Yield of epoxide[c]
		220	100
1172-69-6	Cyclohexyl metaborate (CHMB)		
		1[d]	~20
55089-02-6	2-Cyclohexyloxy-1,3,2-dioxaborinane		
		1[d]	Nil
2467-16-5	Cyclohexyl orthoborate (CHOB)		
		10	83
55089-03-7	2,2′-Oxybis-5,5-dimethyl-1,3,2-dioxaborinane		
		4	50
1216-17-7	Tris(1-methylethylene glycol)biborate		
		4	55
55089-04-8	2-Cyclohexyloxy-1,3,2-dioxaborolane		

[a] The equivalents of borate ester present (measured in gram-atoms of boron) in the reaction solutions is identical with the moles of tetralin hydroperoxide present. [b] Measured as first-order decomposition rate constant for tetralin hydroperoxide. [c] Measured as *cis*-2,3-epoxyoctane. [d] Same absolute decomposition rate constant as for tetralin hydroperoxide with no additive.

tached to boron. It was also noted that bulky substituents about the boron atom extended catalytic lifetimes, apparently owing to steric inhibition of alcoholysis and concurrent catalyst deactivation by the reaction coproduct, *tert*-butyl alcohol. We have now examined additional details relating to borate ester–hydroperoxide intermediates. This paper reports those and related findings.

Results and Discussion

We had previously observed that the decomposition of tetralin hydroperoxide (THPO) at 80° induced by an equimolar quantity of cyclohexyl metaborate (CHMB) (the 1:1 *M* dehydro adduct of cyclohexanol and boric acid) in the presence of *cis*-2-octene is accelerated some 220-fold over that for the noncatalyzed decomposition of THPO in *cis*-2-octene, producing an almost quantitative yield of *cis*-2,3-epoxyoctane and α-tetralol in the former case. In addition, we had observed that cyclohexyl orthoborate (3:1 *M* dehydro adduct of cyclohexanol and boric acid) neither accelerated the decomposition of THPO nor led to epoxide formation.

Studies on the hydrolysis of trialkyl-substituted borate esters has shown that the cyclic metaborate esters with bulky substituents are substantially more reactive than the analogous acyclic orthoborates.[6] This has been taken as evidence for steric inhibition of the transient quaternization of boron by coordination with an unshared pair of electrons on the water oxygen in the borate ester. If an analogous interaction is the sole factor in facilitating the epoxidation of olefins by hydroperoxides, then one might anticipate that methyl orthoborate would be an effective catalyst for the epoxidation reaction. Such is not the case; methyl orthoborate exhibits no catalytic activity in the decomposition of THPO in olefinic solvents.

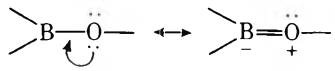
In an effort to determine what structure–reactivity feature is significant in producing an effective catalyst we have synthesized a number of known borate esters and examined their efficacy, at equimolar concentration with the hydroperoxide, in inducing the epoxidation of *cis*-2-octene by THPO. Table I presents the data from that study.

2-Cyclohexyloxy-1,3,2-dioxaborinane is structurally similar to the cyclohexyl metaborate ring system but contains only one boron atom. From a steric point of view the acid–base interaction of the borate ester with a hydroperoxide could occur as readily with 2-cyclohexyloxy-1,3,2-dioxaborinane as with cyclohexyl metaborate. As can be seen, the compound is only modestly active in the epoxidation reaction. The presence of tris(1-methylethylene glycol)biborate accelerates the decomposition of THPO fourfold and leads to a 50% yield of epoxide while 2,2′-oxybis-5,5-dimethyl-1,3,2-dioxaborinane produces a tenfold rate enhancement in THPO decomposition and gives 83% yield of the epoxide.

We had previously considered the possibility that the high reactivity of metaborates was not only due to their ability to coordinate with hydroperoxides but that one of the two remaining free boron atoms in the ring could weakly coordinate with the olefin and thereby facilitate epoxidation. The data presented in Table I are, to a degree, consistent with that idea. The catalytic activity of the various borate esters increases, along with epoxide productivity, as the proximity of two boron atoms in a given molecule increases.

The above data are better explained based on a variation in the reactivity due to the acid hardness of the various borate esters relative to the hydroperoxides as hard bases, where the acidities of the borate ester will vary as a function of the substituents about, and the hybridization of, a given boron atom. This conclusion is consistent with that reported earlier by Sheldon and VanDoorn.[5]

In cyclohexyl metaborate each boron atom of the six-membered ring can draw electron density from a single cyclohexyloxy group through a $p\pi$–$p\pi$ interaction.



This resonance form is stabilized inductively by the cyclohexane ring. On the other hand, the three adjacent B–O bonds in the cyclic system will inductively destabilize the already electron-deficient borons in the presence of the electronegative oxygens. Using CHMB as a benchmark, cyclohexyl orthoborate and 2-cyclohexyloxy-1,3,2-dioxaborinane would have substantially less acidic boron owing to the electron donation from each of three alkoxy linkages. The relative acidity of 2,2′-oxybis-5,5-dimethyl-1,3,2-dioxaborinane, compared to the two above compounds, should be higher owing to the presence of the B–O–B bond.

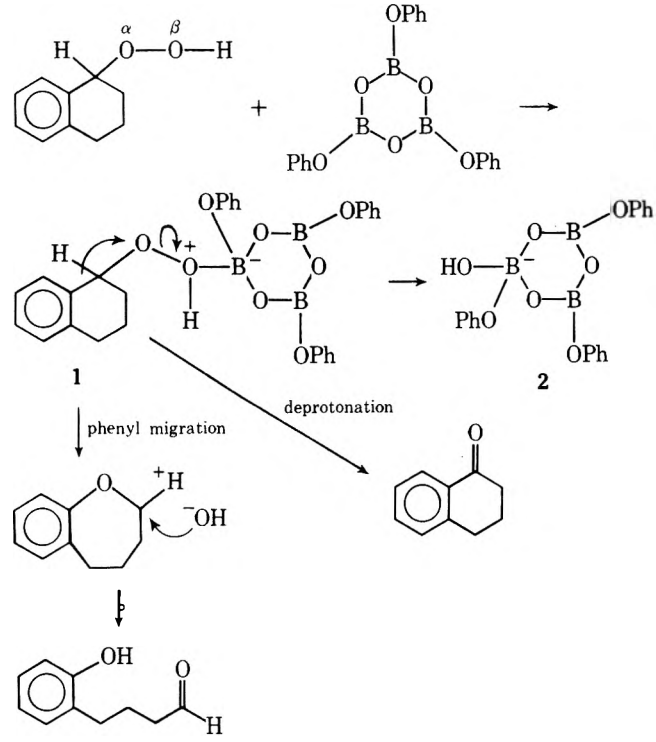
Tris(1-methylethylene glycol)biborate, in which the borons are insulated from each other by a 1,2-dioxoethylene bridge, still accelerates the decomposition of THPO. The enhanced acidity of this biborate is due to the change in hybridization of the boron in a five-membered ring.[7] The O–B–O bond angles about the boron are compressed from the normal trigonal (sp^2) 120° toward the tetrahedral (sp^3) required for quaternization, thereby facilitating coordination with a base. The simpler five-membered ring borate 2-cyclohexyloxy-1,3,2-dioxaborolane produces a rate enhancement and epoxide formation identical with that observed with the five-membered ring biborate.

The effect of even more highly acidic borate esters on the decomposition of THPO can be seen from the following series of experiments. A re-examination of the decomposition of 0.4 *M* THPO in chlorobenzene induced by equimolar CHMB at 120° showed that on completion of the reaction a product distribution of 81 mol % α-tetralol, 8 mol % α-tetralone, and 11 mol % 1,2-dihydronaphthalene was obtained. In a separate experiment it was shown that α-tetralol dehydrates under the reaction conditions to 1,2-dihydronaphthalene at a rate sufficient to produce the amount found after the experiment described above was completed. Hence, the initial α-tetralol selectivity from the THPO–CHMB reaction in chlorobenzene is 92%.

Replacing the CHMB with an equivalent amount of phenyl metaborate (PMB) alters the course of this reaction dramatically. Admixture of THPO and PMB in chlorobenzene at room temperature results in a vigorous exothermic reaction (to ~40°) in which over 90% of the active oxygen titer is consumed in 10 min. The final product mixture contains no tetralol, but instead the aldol condensation product of 4-(o-hydroxyphenyl)butyraldehyde and a small quantity of α-tetralone. If mesitylene is used as solvent the same result is obtained, giving a 95% yield of the aldol dimer and a 5% yield of α-tetralone. This result is the antithesis of what is observed with CHMB and THPO in mesitylene. This latter reaction is immeasurably slow at room temperature, but at 90° rapidly yields mesitol (2,4,6-trimethylphenol) by hydroxylation of the solvent and concurrently produces α-tetralol on reduction of the THPO.[1]

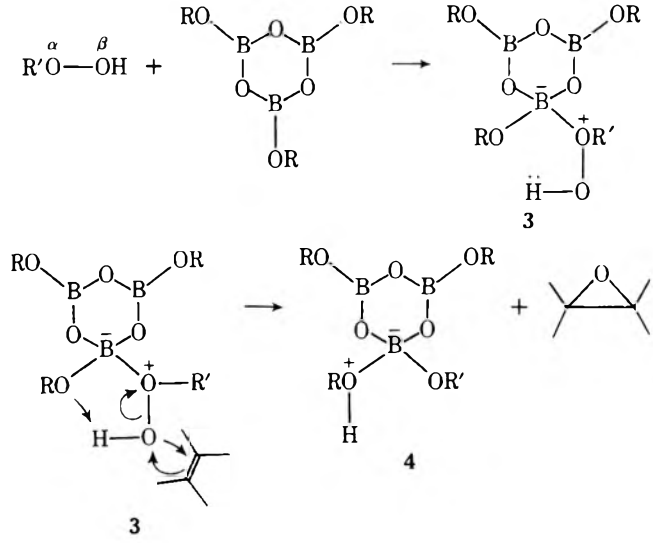
Although the formation of 4-(*o*-hydroxyphenyl)butyraldehyde from THPO in the presence of PMB or triphenyl orthoborate (POB) could be verified by 2,4-DNP[8] formation or titration of its aldol dimer with hydroxylamine hydrochloride,[9] actual isolation of the aldehyde was unsuccessful in the presence of the phenol generated by borate hydrolysis. Successful isolation of 4-(*o*-hydroxyphenyl)-butyraldehyde (see Experimental Section) was achieved from reaction mixtures in which the highly acidic triacetyl borate was used.

Scheme I



The enhanced acidity of PMB compared to CHMB is a result of the phenyl rings acting as electron sinks to generate a high level of electron deficiency at the boron atoms. This is just the opposite effect created by the presence of an aliphatic alkoxy substituent on boron. The observed reaction can be rationalized as shown in Scheme I.

We had previously[1] indicated our preference in the reaction of THPO–CHMB in mesitylene hydroxylation or olefin epoxidation for an intermediate borate–hydroperoxide complex which involved a boron–oxygen interaction at the α oxygen atom of the hydroperoxide as shown below.



In the two mechanisms pictured above, the acidity of the borate ester determines which peroxidic oxygen will develop positive charge and ultimately lead to a O–O bond scission. If, as one would expect, there is a dynamic equilibrium in which the borate ester is forming a reversible complex with either the α or β oxygens of the hydroperoxide, then we must determine the difference in the transient B–O bond formed between a hydroperoxide and PMB (complex 1) from that formed with CHMB (complex 3)

which causes it to proceed to products from those particular complexes.

The collapse of complex **1** to give 4-(o-hydroxyphenyl)butyraldehyde or α-tetralone is estimated to be at least 600 times faster than that of complex **3** to produce, for example, epoxide and α-tetralol. The formation of products from complex **1** is unimolecular while that of **3** is clearly bimolecular, requiring an intimate association of the acceptor (i.e., olefin) and the complex.[10] Since in both cases the same bond is breaking, the difference must be in the ability of the two borate esters to stabilize the resulting leaving group. In the transition state where complex **1** leads to O–O bond rupture the leaving group is the anion, phenyl metaborate hydroxide (**2**) having a formal negative charge on the tetrahedral boron atom. The electron-withdrawing phenoxy groups can stabilize this species while the electron-donating cyclohexyloxy group would be destabilizing.

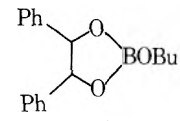
Complex **3**, which also leads to O–O fission, produces a strikingly different and undoubtedly lower energy leaving group. Formation of this species is the result of an intramolecular proton transfer to give **4**, which has an alcohol coordinated to a metaborate ester and will be in equilibrium with the free alcohol and metaborate and thereby require minimal stabilization by the borate ester. This proton transfer step is clearly required for heterolysis of the O–O bond. Cumyl methyl peroxide is unreactive in the presence of CHMB under conditions where cumene hydroperoxide readily epoxidizes olefins.

Hence, there is a spectrum of simple borate esters of varying acidity which include those which are too weak (i.e., acyclic orthoborates and six-membered ring orthoborates) to effectively interact with a hydroperoxide and facilitate a heterolysis of the O–O bond competitive with thermally induced homolysis. This is followed by borate esters of moderate acidity, i.e, five-membered ring orthoborates, biborates, and most effective, alkyl metaborates, which cleave the hydroperoxide O–O bond, generating, in the presence of a suitable acceptor, what may formally be considered a hydroxonium ion, $[HO^+]$.[11] Beyond this are the highly acidic phenyl borate esters and triacetyl borate, which can heterolyze the hydroperoxide so that the electron-deficient center ends up on the oxygen attached to a carbon atom, $[RO^+]$.

This reactivity pattern is obviously dependent on the facility with which the organic moiety of the hydroperoxide can absorb the positive charge. Sheldon and VanDoorn[5] have observed epoxidation of 2-octene by *tert*-butyl hydroperoxide in the presence of PMB in a yield of 26–59%.

This type of selectivity is also consistent with the observations of Sheldon[12] in his study on the metal-catalyzed epoxidation of olefins. The selectivity of Mo(VI), Ti(IV), and V(V) complexes in catalyzing epoxide formation from hydroperoxides is related to their being hard acids. As has been pointed out, in the case of molybdenum catalysis,[12] independent of which oxidation state the metal is initially in, the active species in solution is a Mo(VI) complex. The hardness can be correlated with the ability of an alkyl hydroperoxide, acting as a Lewis base, to coordinate with the metal. Efficient epoxidation in this case requires that the transition metal–hydroperoxide complex not have a favorable internal redox potential for electron transfer. This latter process would lead to radical formation and is the reason why metals such as Cr(VI) are ineffective catalysts. With borate esters no redox processes are possible.

In the course of these studies we had the opportunity to examine the reactivity of the unsaturated borate ester 2-*n*-butoxy-4,5-diphenyl-1,3,2-dioxaborole (**5**). This compound, described by Bolban et al.,[13] is readily synthesized by heating an equimolar mixture of benzoin and tributyl borate at 100° and 2 mmHg pressure and distilling off butanol as **5**, an orange, viscous liquid, is formed. Compound **5** is unstable in water or air. Based on our previous discussion the Lewis acid acidity of **5** should be greater than that of a simple five-membered ring borate but probably less than that of PMB. The purity of **5** as synthesized above is no greater than 80%, as attested to by the ratio of the aromatic and aliphatic proton in the NMR spectrum of this residue product (see Experimental Section). The titer for boron is also high by approximately 20% based on that required for **5**.

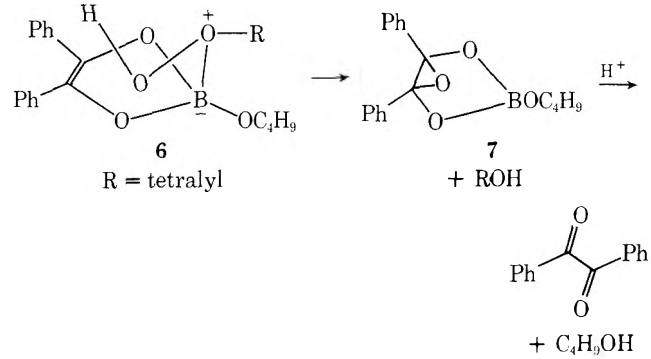


5

The reactivity of dioxaborole **5** with THPO was indeed dramatic. In cyclohexane the presence of an equimolar amount of **5** caused THPO to completely disappear in the time required to bring the solution to reflux (81°). At 25°, in cyclohexane or in *cis*-2-octene, 75% of the active oxygen titer disappeared within 1 min of mixing the reactants. In the latter solvent only a trace of *cis*-2-epoxyoctane was observed by VPC analysis. Hydrolysis of a number of reaction mixtures, separation and drying of the organic phase, and removal of the volatile components from the reaction products always gave the same results.

The residue, a yellow oil mixed with some solid in 70% yield, was a mixture readily analyzed by infrared and identified through comparison with the spectra of authentic materials. The characteristic infrared bands of benzil (approximately 80% of the total oxidation product) and α-tetralol were readily identified as the major products of the reaction, and only a trace of unreacted benzoin could be identified. However, an additional and unexpected minor product (approximately 20% of the total oxidation product), benzoic anhydride, was shown to be present by its characteristic carbonyl doublet in the infrared at 1785 and 1725 cm^{-1}. The starting dioxaborole (**5**) produced only benzoin when hydrolyzed in aqueous ethanol. Separation and individual characterization of the products of the THPO–dioxaborole reaction prior to hydrolysis proved impractical and was abandoned.

The presence of benzil as the major oxidation product from the reaction of dioxaborole **5** and THPO is explicable by the scheme presented below. In addition the formation



6 R = tetralyl

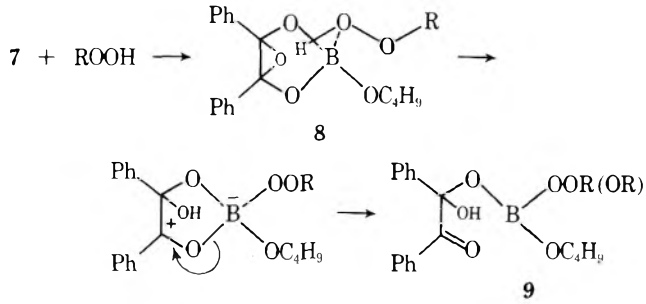
7 + ROH

+ C_4H_9OH

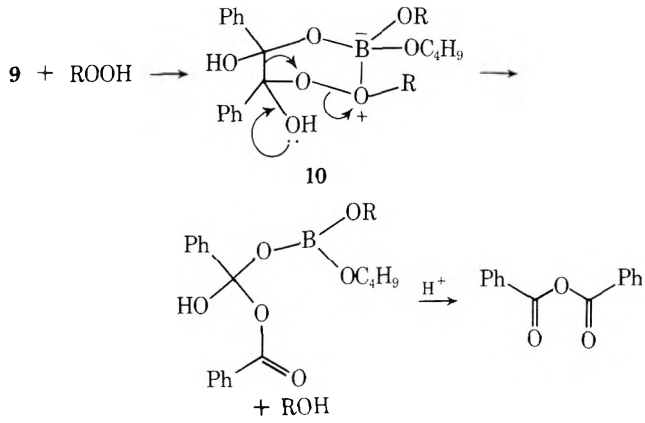
of benzil is consistent with the thesis that the electron-deficient oxygen (incipient or fully formed) requires a nucleophilic site (i.e., an olefinic linkage in close proximity to the developing oxidizing species). The intermediate **6** is structurally analogous to that postulated in the vanadium-catalyzed epoxidation of allylic alcohols.[14]

The oxidation to benzoic anhydride can be rationalized in the following way. Complex **8** formed from a second mole

of tetralin hydroperoxide reacting with **7** will provide a source of protons to open the oxirane ring. The resultant 1,3-dipolar species can then open the dioxaborole ring to a borated α-ketal ketone (**9**). The carbonyl in this species could, in turn, convert to a hydroxy peroxide (**10**), which would be uniquely arranged to facilitate a Baeyer–Villiger rearrangement through a six-membered ring coordination of the peroxide α oxygen and the pendant borate group.



A sequence could be pictured in which the major reaction product, benzil, reacts further with THPO to form a hydroxy hydroperoxide. This intermediate could then decompose, directly or by assistance from the borate ester. This alternative does not seem valid. The decomposition of 0.1 *M* THPO in cyclohexane in the presence of equimolar benzil at 24° is approximately 5×10^3 times slower than observed for THPO in the presence of dioxaborole **5**. In the course of this decomposition ~60% of benzil is consumed and benzoic acid is identified as the major product. When 1 equiv of the weakly acidic borate ester, 2-butoxy-1,3,2-dioxaborinone, is added to a cyclohexane solution 0.1 *M* each in THPO and benzil, the hydroperoxide decomposition is slightly accelerated and only 10% of the benzil initially present is consumed. Finally, when CHMB is the borate ester added the THPO decomposition is further accelerated and only a trace of benzil is consumed.



The ability of a hydroperoxide–borate complex, such as **8**, to function as an acid of sufficient strength to open an epoxide ring has been demonstrated in the epoxidation of 2-methyl-1-heptene with THPO and CHMB at 60°. In addition to 1,2-epoxy-2-methylheptane a small amount (~5 mol%) of 2-methylheptaldehyde is formed. After the tetralin hydroperoxide is consumed the resultant mixture is stable. Under reaction conditions a mixture of 1,2-epoxy-2-methylheptane is stable in the presence of either CHMB or THPO alone. However, a solution of 1,2-epoxy-2-methylheptane in cyclohexane at 60° in the presence of an equimolar mixture of both THPO and CHMB rapidly converts the epoxide to the isomeric aldehyde and concomitantly depresses the rate of THPO decomposition 150-fold. This phenomenon is dependent on the presence of groups in the epoxide capable of stabilizing a positive charge as the oxirane ring opens prior to hydride transfer and aldehyde formation, i.e., 1,2-epoxyoctane is stable under the above reaction conditions.

In the terse published description on the preparation of 2-*n*-butoxy-4,5-diphenyl-1,3,2-dioxaborole (**5**) the only physical property mentioned was the compounds sensitivity to air.[13] This is readily observable since the orange solutions of **5** produce dark "Schlieren" lines on exposure to the air.

The autoxidation of the dioxaborole **5** by pure oxygen, in the absence of initiators, at 80° in chlorobenzene is very rapid. The uptake of oxygen by **5** begins, with no observable induction period, at a rate of approximately 7.2×10^{-3} mol oxygen/mol min and maintains that rate throughout the course of the oxidation. Approximately 0.85 molar equiv of oxygen is absorbed based on the estimated purity of the dioxaborole. By comparison there is no observable consumption of oxygen by tetralin under identical conditions for a 2-hr period. At 120°, after an approximately 400-sec induction period, tetralin is oxidized at a maximum rate of 3×10^{-5} mol oxygen/mol min.

The products in the crude reaction mixture, accounting for a quantitative material balance based on the estimated real initial concentration of **5** were characterized by ir, NMR, and product isolation with individual characterization. The products identified were benzil, benzoic acid, and, again, benzoic anhydride. Benzil and benzoic acid were the major isolated products in a ratio of 1.2:1.0. Benzoic anhydride was identified spectroscopically as a trace reaction product.

In the presence of 4 mol % *p*-hydroquinone an autoxidation of dioxaborole **6** run identically with the one above absorbed oxygen at the same rate and gave the same products, benzil, benzoic acid, and benzoic anhydride, in identical product ratios. By comparison, tetralin in the presence of 4 mol % *p*-hydroquinone fails to consume any oxygen within a 5100-sec period at 120°.

The mechanism of borane autoxidation has been studied in detail by Davies.[15] It was originally believed, on the basis of inhibitor studies, that the reaction of O_2 and a trialkylborane (R_3B) proceeded through a polar intermediate, $R_3\bar{B}$–O–O^+, followed by alkyl migration to give isolable peroxyboranes, R_2BOOR. From more recent work using galvinoxyl as an inhibitor and optically active 1-phenylethylboronic acid and epimeric norborn-2-yl boranes in various autoxidation experiments, evidence has been presented which is consistent with a free-radical chain reaction in which the boron atom acts as an extremely active scavenger for peroxy radicals.

The question of the intermediacy of radicals or charged species in the reaction of **5** with oxygen is, as yet, unanswered. If a boron–oxygen intermediate complex is formed then some polar contribution to this species is possible. Davies and Ingold[16] have examined the reactions of various peroxy radicals with several organoboranes. A progressively decreasing rate of reaction of alkyl peroxy radicals with the boranes was noted as the number of B–O bonds in the molecules increased. This decreasing rate of substitution on boron by peroxy radical was ascribed to a decrease in boron atom acidity due to a pπ–pπ interaction with the lone pairs on oxygen and hence the resonance contribution of $\bar{B}{=}O^+$. This observation, coupled with the lack of a ready source of alkyl radicals, suggests that an alternate mechanism is operative with borates. Equivalent intermediates for product formation can be rationalized through oxygen addition to either boron or the double bond. It would appear that benzil is formed in a process involving 2 mol of **5** and 1 mol of oxygen. This comes from the stoichiometry of the reaction

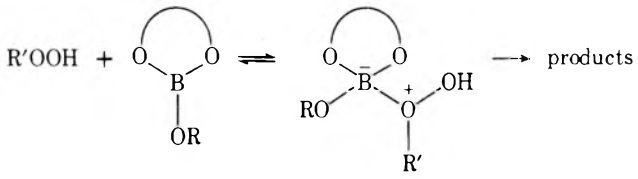
Table II
First-Order Decomposition of 0.350 *M tert*-butyl Hydroperoxide in Hydrocarbon Solvents at 120°

Rxn no.	Solvent[a]	Borate (*M*/1)	k_1, hr^{-1} [b]	Products: Alcohol, *M*/1	Products: Ketone, *M*/1	Total available oxygen as ol + one, %	Ol/one
1	C		0.027	0.077	0.029	30.3	2.7
2	C	CHMB (0.38)[c]	0.032	0.247	0.035	80.6	7.1
3	C	CHOB[d] (0.35)	0.031	0.167	0.036	58.0	4.6
4	C	*n*-BuOB[e] (0.35)	0.031	0.159	0.040	56.9	4.0
5	D		0.004	0.050	0.062	32.0	0.8
6	D	CHMB (0.38)[c]	0.029	0.110	0.015	34.7	7.3

[a] C, cyclooctane; D, *n*-decane. [b] First-order kinetics were observed for at least 3 half-lives for all reactions. [c] Concentrations of CHMB (cyclohexyl metaborate) were based on molecular weight of monomer, $C_6H_{11}OBO$. [d] CHOB = cyclohexyl orthoborate. [e] *n*-BuOB = *n*-butyl orthoborate (registry no., 688-74-4).

as well as the fact that hydrogen peroxide, which is stable under these reaction conditions, is not found in the aqueous fraction after hydrolysis of the crude product.

One of the most striking features of the CHMB-catalyzed decomposition of alkyl hydroperoxides is that the loss of active oxygen is accelerated even if a nucleophile, such as an olefin or mesitylene, is not present to scavenge the incipient hydroxonium ion. Thus the decomposition of 0.08 *M* THPO in the presence of 0.08 *M* CHMB in cyclohexane at 80° is 63 times faster than for the uncatalyzed decomposition of THPO in cyclohexane.



It is unlikely that a highly energetic species such as [OH^+] would form in cyclohexane. No hydride abstraction by THPO–CHMB in cumene to give α-methylstyrene or products thereof was observed. This is in spite of the fact that hydroxylation of the aromatic ring in cumene to give isopropyl phenols is only a minor reaction. Neither is oxygen evolution observed in the above reaction media.

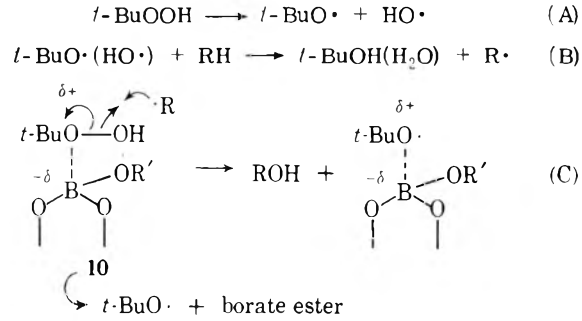
For a probe of the borate induced decomposition of alkyl hydroperoxides in aliphatic hydrocarbon solvents we chose to use a hydroperoxide which was relatively unreactive and would have limited prerogatives in product formation: *tert*-butyl hydroperoxide (*t*-BuOOH). Cyclooctane and *n*-decane, each with eight methylene groups, were chosen as hydrocarbon solvents.

On a per-hydrogen basis cyclooctane has been shown to be about twice as susceptible to hydrogen abstraction by moderately reactive radicals[17] than are typical acyclic secondary hydrogens or cyclohexane ring hydrogens. No data comparing solvent hydrogen selectivities of *tert*-butoxy or *tert*-butylperoxy radicals for cyclooctane vs. other hydrocarbons are presently available.

The decomposition of 0.35 *M* *t*-BuOOH at 120° in cyclooctane, as shown in Table II, is more than six times as fast as that in *n*-decane as measured by first-order rate constants (k_1) (0.027 hr^{-1} vs. 0.004 hr^{-1}). In cyclooctane 30.3% of the consumed *t*-BuOOH is accounted for as cyclooctanol (COL) and cyclooctanone (CON) present in a 2.7:1 ratio. In *n*-decane 32% of the consumed *t*-BuOOH is accounted for as *n*-decanols and *n*-decanones in a 0.8:1 ratio.

When *t*-BuOOH is decomposed at 120° in cyclooctane in the presence of 1 equivalent of CHMB a modest increase in the first-order rate constant of 0.032 hr^{-1} is observed. More significantly, 80.6% of the consumed *t*-BuOOH is converted to COL and CON in a 7.1:1 ratio. Replacing CHMB with cyclohexyl orthoborate or *n*-butyl orthoborate, two borates which would not induce the heterolysis of a hydroperoxide O–O bond, resulted in approximately the same modest rate enhancement. A product accountability of nearly 60% based on *t*-BuOOH was obtained with COL to CON ratios of 4.6:1 and 4.0:1, respectively. Finally, the presence of equimolar CHMB and *t*-BuOOH in *n*-decane accelerates the first-order rate of decomposition of *t*-BuOOH sevenfold to k_1 = 0.029 hr^{-1} and the 34.7% accountability of active oxygen gives a decanol to decanone ratio of 7.3:1. No evidence of oxygen evolution was observed in any of these reactions and *tert*-butyl alcohol was the only observed product from *t*-BuOOH.[18]

These data are consistent with the following chain reaction sequence, which can be considered a borate induced



SH2 (bimolecular homolytic substitution[19]) reaction. The SH2 reaction has been well documented in homolytic peracid decompositions.[20,21] Since the complex of a hydroperoxide coordinated to a borate ester has electron distribution similar to peracids and similar nonradical reaction characteristics,[1] the occurrence of SH2 reactions can be considered another extension of the previously observed analogies. A possible termination step for this reaction in cyclooctane, which has good active oxygen accountability, might be either cyclooctyl radical coupling to bicyclooctyl or *tert*-butoxy–cyclooctyl radical coupling to the ether. Neither of these products has been identified in reaction residues.

In cyclooctane solvent the amount of CON produced by *t*-BuOOH decomposition increases about the same small amount over that observed in the uncatalyzed reaction as do the reaction rates when borate esters are added. Thus, essentially *all* the new product formed as a result of *t*-BuOOH coordination with borate ester is cyclooctanol. In the presence of borate esters there are two parallel reactions taking place: the normal decomposition of *t*-BuOOH which leads to cyclooctyl radicals which are only 30% efficient in giving COL and CON on reacting with *t*-BuOOH and the borate induced SH2 decomposition of *t*-BuOOH via intermediate **10** which scavenges cyclooctyl radicals with an extremely high efficiency to give *only* cyclooctanol.

In *n*-decane the situation is quite different. The CHMB accelerated decomposition of *t*-BuOOH not only increases the amount of *n*-decanols produced but substantially decreases the amount of decanones formed. In this case, secondary decyl radicals (see Experimental Section) are generated more rapidly in the presence of CHMB. Thus, the lower energy borate induced decomposition pathway diverts radicals from the noncatalytic reaction routes to follow the more favorable SH2 reaction. This results in the formation of alcohol at the expense of ketone, as seen in the last entry in Table II.

That portion of alcohol and ketone formed in both solvents by more classical routes has been suggested to involve[22] coupling of alkyl radicals and *tert*-butylperoxy radicals, followed by homolysis of the *tert*-butyl alkyl peroxide and disproportionation of, or hydrogen abstraction by, the resulting alkoxy radicals.

$$R\cdot + t\text{-BuOO}\cdot \longrightarrow t\text{-BuOOR}$$

$$t\text{-BuOOR} \longrightarrow t\text{-BuO}\cdot + \cdot OR$$

$$2RO\cdot \longrightarrow ROH + R{=}O$$

$$RO\cdot + RH \longrightarrow ROH + R\cdot$$

Conclusions

The results of the above observations coupled with those previously reported[1,3] indicate that a broad spectrum of hydroperoxide–borate–substrate interactions are possible. The course of a given reaction is generally determined by one of the three reacting compounds. The major variations of this system are presented below.

1. With an alkyl metaborate or alkyl orthoborate of appropriate acidity all hydroperoxides coordinate with boron to produce a species similar to a peracid which can either epoxidize olefins or hydroxylate highly nucleophilic aromatics.

2. With phenyl borates or other highly acidic borates *t*-BuOOH will epoxidize olefins[3] but aralkyl hydroperoxides will preferentially undergo a Baeyer–Villiger-type rearrangement.

3. In the absence of a suitable acceptor (i.e., in an aliphatic hydrocarbon) *t*-BuOOH will undergo an SH2 reaction induced through coordination with boron, while the tertiary aralkyl hydroperoxide, cumene hydroperoxide, will rearrange to acetone and phenol.[1]

Experimental Section

Chlorobenzene, 1,2-dichloroethane, cyclooctane, cyclohexane, *n*-decane, and mesitylene were obtained from Aldrich Chemical Co. and purified by standard procedures. Benzoin and *n*-butyl borate obtained from the same source were used as received. *cis*-2-Octene (99.9%) obtained from Chemical Samples Co. was used as received. The *tert*-butyl hydroperoxide obtained from Lucidol initially at 90% active oxygen titer afforded on reduced pressure distillation material which gave a greater than 99% titer for active oxygen.

Tetralin hydroperoxide, a colorless, crystalline solid, mp 55–56°, was prepared according to the procedure described by Knight and Swern,[23] and gave a 99% titer for active oxygen. Tetralol, bp 128–129° (10 mm), was prepared by the lithium aluminum hydride reduction of a tetralone–tetralol mixture (approximately 50:50) obtained from Union Carbide Corp. Tetralone was obtained from Eastman Chemical Co. Mesitol was synthesized as previously described.[1]

Borate Syntheses. Cyclohexyl metaborate, a colorless solid, mp 163–166°, was prepared according to the procedure of O'Connor and Nace.[24] Cyclohexyl orthoborate, a colorless, waxy solid,[24] mp 65–67°, bp 90° (2 mm), was prepared by the method of O'Brien.[25]

The several borates prepared from diols were all synthesized in the same fashion. A mixture of boric acid or boric anhydride and diol in a molar proportion calculated to produce the desired derivative was added to benzene. The mixture was heated to reflux and the stoichiometric amount of water was collected in a Dean-Stark trap. The resulting product was either distilled or allowed to crystallize from the benzene solution. All products gave the appropriate titers for boron using the mannitol method.[26] The colorless liquids, 2-cyclohexyloxy-1,3,2-dioxaborinane, bp 132–133° (10 mm) [reported bp 87–91° (0.8 mm)],[27] 2-cyclohexyloxy-1,3,2-dioxaborolane, bp 116° (10 mm) [reported bp 119–120° (10 mm)],[28] and 2,2′-oxybis-5,5-dimethyl-1,3,2-dioxaborinane, bp 120–125° (0.05 mm) [reported bp 134–140° (0.5 mm)],[29] were stored, after distillation, in a drybox and transferred into reaction mixtures under anhydrous conditions. Tris(1-methylethylene glycol)biborate was obtained as a viscous oil.[30]

Phenyl metaborate and phenyl orthoborate were synthesized from phenol and boric acid (1:1 and 3:1 mole ratios, respectively) by azeotropic removal of water from refluxing toluene. Upon distillation of the toluene a crystalline residue product was obtained which was used without further purification. Triacetyl borate synthesis has recently been described by Ritscher.[31]

Reaction Kinetics and Epoxide Analysis. Hydroperoxide consumption was followed iodometrically by the method of Wibaut.[32] Analyses for 2,3-epoxyoctanes were performed by VPC on a 6 ft × 0.25 in. Carbowax 20M on Chromosorb T column programmed at 6°/min from 80 to 150° with a He gas flow rate of 50 ml/min. The retention time for *trans*-2,3-epoxyoctane is 4.76 min and for *cis*-2,3-epoxyoctane is 5.28 min.

Isolation and Characterization of 4-(o-Hydroxyphenyl)-butyraldehyde.[33] Triacetyl borate (9.4 g, 0.05 mol) in 100 ml of 1,2-dichlorethane was added to a room temperature solution of 8.2 g (0.05 mol) of THPO in 50 ml of dichloroethane in a 500-ml three-necked round-bottom flask fitted with mechanical stirrer, thermometer, and reflux condenser. Within 1 min after mixing the reaction temperature rose to ~60° and the active oxygen titer dropped to zero. The resulting solution was washed with water, dilute bicarbonate, and saturated salt and dried over magnesium sulfate.

Removal of the solvent gave 8 g of material which was passed down a chromatography column containing 100 g of silica gel. After extensive elution with benzene several fractions were collected. On evaporation of solvent these gave a yellow oil exhibiting carbonyl, hydroxyl, aliphatic, and aromatic C–H stretching vibrations in the infrared.

Isolation of this compound by preparative VPC on Carbowax 20M on Chromosorb W gave an oil which was identified by the ir and NMR spectra to be 4-(o-hydroxyphenyl)butyraldehyde: ir (KBr) 3420, 2930, 1720, 1240, and 750 cm^{-1}; NMR ($CDCl_3$) δ 1.97 (m, 2 H), 2.53 (t, J = 6 Hz, 2 H), 2.68 (m, 2 H), 6.99 (m, 4 H), 9.78 (t, J = 1.2 Hz, 1 H). No phenolic proton was identified in this sample, possibly owing to the presence of volatile liquid-phase components from the VPC column which blocked out the δ 4–5 region of the NMR.

Synthesis of 2-*n*-Butoxy-4,5-diphenyl-1,3,2-dioxaborole (5). A predried, 250-ml flat-bottomed three-necked flask equipped with magnetic stirrer, thermometer, and serum cap was charged with 5.31 g (0.025 mol) of benzoin (oven dried, 100°) and 13.50 ml (0.050 mol) of *n*-butyl borate. This reaction system was attached to a short-path (gooseneck) distillation system connected to a vacuum pump. The system was purged with dry nitrogen by means of a syringe needle through the serum cap. The stirred reaction vessel was immersed into an oil bath whose temperature was gradually raised from 75 to 100° during the course of the reaction. The pressure was maintained at 2–5 mmHg. Upon heating, the initially colorless heterogeneous reaction mixture turned light orange, and then suddenly a vigorous ebullation took place. At this time, the reaction became homogeneous and *n*-butyl alcohol was distilled through the short path system into a receiver. After the reaction was over the excess *n*-butyl borate was removed by distillation at 100° (0.05 mmHg). The resulting thick orange liquid was used without further purification: ir (neat) 2960, 1852, 1473, 1390, 1260, 1065, 1027, 763, and 687 cm^{-1}; NMR ($CDCl_3$) 0.95 (t, J = 6 Hz, 3 H), 1.54 (m, 4 H), 4.12 (t, J = 6 Hz, 2 H), 7.48 ppm (m, <10 H). The ratio of the aromatic to butyl protons in several spectra was always less than the theoretical 10:9. This ratio did, however, vary, and the low proton count in the aromatic region was apparently due to excess *n*-butyl borate present in the product. Consistent with this is the observation that hydrolyzed samples of dioxaborole **5** give high boron titers.

On hydrogenation at 1 atm, a 1-g sample of **5** in 25 ml of ethyl acetate containing 0.049 g of PtO_2 absorbed 1.09 molar equiv of hydrogen. Filtration gave a colorless solution, which on evaporation of the solvent left an oily residue. One recrystallization from

ethanol–water gave the solid *meso*-1,2-diphenyl-1,2-ethanediol, mp 135–137° (reported[34] mp 136–137°).

Reaction of 5 with Tetralin Hydroperoxide. To 0.735 g (0.0025 mol) of dioxaborole (1) in a 125-ml erlenmeyer flask, 0.410 g (0.0025 mol) of tetralin hydroperoxide in 25 ml of cyclohexane was added. Within 30 min at room temperature in the drybox, the solution had turned from bright orange to yellow and the hydroperoxide titer was only 7% of the original value. The solution was allowed to stand overnight after which time the titer for hydroperoxide was zero. The cyclohexane solution was washed three times with 25-ml portions of water and once with a saturated salt solution and dried over sodium sulfate. Removal of the solvent left 0.54 g of a yellow oil mixed with some crystals. The infrared spectrum (neat) of this residue exhibited the characteristic bands of benzil (1675 and 873 cm^{-1}) and tetralol (3330, 774, and 739 cm^{-1}) as the major products. Analysis by VPC on a 6 ft × 0.25 in. Carbowax 20M on Chromosorb T column programmed at 6° from 80 to 220° with an upper limit hold and a He gas flow of 50 ml/min showed the major products of the reaction to be an approximately 1:1 mixture of tetralol (retention time 22.35 min) and benzil (37.95 min) with a trace of tetralone (20.75 min) present. A second product of benzoin oxidation present in ~20% yield was shown to be benzoic anhydride by the characteristic carbonyl doublet at 1785 and 1725 cm^{-1}. A trace amount of benzoic acid was also shown to be present by ir and VPC analyses.

Autoxidation of Dioxaborole 5. A 25-ml chlorobenzene solution in a 100-ml two-necked flat-bottom flask containing approximately 0.025 mol of the dioxaborole was brought to 80° under 1 atm of oxygen. Upon commencement of stirring oxygen uptake began. Within 80 min the oxidation ceased and 0.85 mol of oxygen per mole of dioxaborole was absorbed. A similar reaction containing 0.11 g of *p*-hydroquinone required 70 min to reach completion having absorbent 0.67 mol of oxygen per mole of dioxaborole. After most of the chlorobenzene was distilled off, the residue (4.69 g) was dissolved in 30 ml of ether washed three times with 25 ml of water and once with 25 ml of saturated salt solution, and dried over sodium sulfate. Evaporation of the ether left a solid residue. The infrared spectrum of these residues had the characteristic bands of benzil, benzoic acid, and a small amount of benzoic anhydride. The NMR of these residues exhibited only aromatic protons, δ 7.30–8.43, and a single acid proton, δ 12.27. The ratio of benzoic acid to benzil was established as 1.0:1.2. Pure samples of benzil (mp 95–96°) and benzoic acid (mp 120–122°) could be isolated from these and other autoxidations of dioxaborole **5.**

Decomposition of *t*-BuOOH in Saturated Hydrocarbon Solvents. A typical reaction was run by charging a 20-ml spherical reactor equipped with a pressure stopcock with 10 ml of hydrocarbon solvent and the appropriate amount of borate ester (when used). This solution was purged with dry nitrogen for 10 min and the stopcock was then closed. A serum cap was placed over the stopcock extension and a nitrogen head was maintained in this region above the stopcock by inserting a syringe needle attached to the dry nitrogen line with ~5 lb positive pressure. The reactor was placed in the constant-temperature bath at 120° and heated for 5 min. The addition of 0.8 ml of *t*-BuOOH followed directly. This was considered as time zero. The progress of the reaction was followed iodometrically and was run for 10 half-lives prior to product analysis.

Product analyses of the reaction in cyclooctane were performed by vapor phase chromatography on a 5% Carbowax 20M on Chromosorb T column, 0.25 in. × 11.5 ft. The separation was performed using a temperature program of 80–170° at 10°/min. followed by a hold at 170°, with a He gas flow of 50 ml/min. Under these conditions the retention times (minutes) follow: cyclooctanone (18.5), cyclooctanol (23.2), cyclohexanol (13.5), cyclohexanone (12.2) and the internal standard, chlorobenzene (10.5).

Analysis for the products in decane was performed on a 12 ft × 0.25 in., 5% DEGS on Chromosorb G column. All the other parameters were as reported for the cyclooctane reaction analyses. Under these conditions the observed retention times (minutes) follow: 4- and 5-decanone (15.0), 3-decanone (15.8), 2-decanone (16.6), 4- and 5-decanol (18.0), 3-decanol (18.5), and 2-decanol (19.3). No 1-decanol or *n*-decanal was observed in either reaction. Quantitatively, the 2, 4, and 5 isomers of both alcoholic and ketonic products appeared in equal amounts while the 3 isomers appeared in an amount which was 50–75% that of the other isomers. The retention times (minutes) follow: cyclohexanone (12.3), cyclohexanol (13.6), and for the internal standard, 1,2,4-trichlorobenzene (21.6). In neither the cyclooctane nor the decane system was it possible to separate the small quantities of olefinic products of solvent dehydrogenation possibly present.

In order to reproducibly analyze by VPC it was necessary to free any potential products from boron in those solutions containing borate esters. Initial attempts to add a large excess of methanol and thereby convert all the available borated material to trimethyl borate failed, apparently owing to deposition of boron on the VPC column. This ultimately led to low analyses for alcohols based on established internal standard factors. Satisfactory reproducibility of analyses was obtained by adding an equal volume of aqueous mannitol solution just prior to injection to those reaction solutions containing borate esters. All factors were redetermined under the identical two-phase conditions and no loss of any of the organic products of interest from the hydrocarbon phase to the aqueous mannitol phase was observed.

Acknowledgment. We would like to express our gratitude to Drs. N. A. Clinton and J. S. Ritscher for their many helpful comments.

Registry No.—**5,** 55089-01-5; 4-(o-hydroxyphenyl)butyraldehyde, 55089-05-9; triacetyl borate, 4877-24-5; tetralin hydroperoxide, 771-29-9; benzoin, 119-53-9.

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Reaction of Diacetyl Peroxide with Phenyl Alkyl Ketones. A Re-examination

Henry C. McBay

Department of Chemistry, Morehouse College and the Atlanta University Center Science Research Institute,[1a] Atlanta, Georgia 30314

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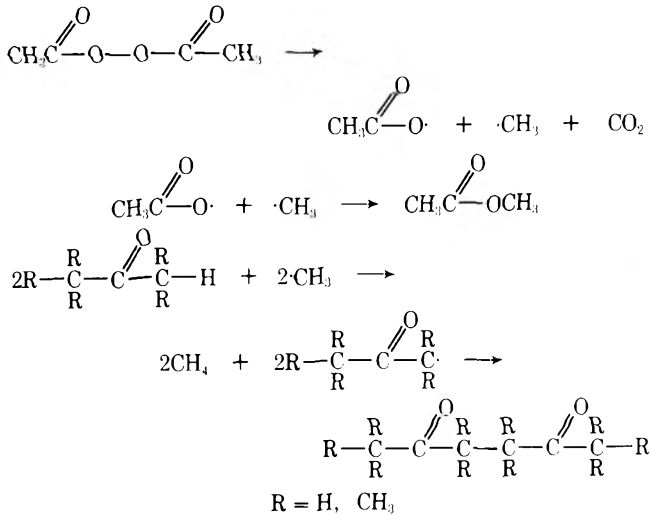
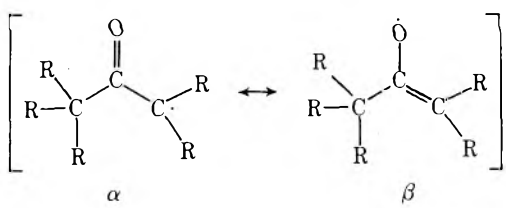
The re-examination of an old reaction is reported. Based on new evidence regarding the structure of the phenacyl free radical a more detailed interpretation of the mechanism of the reaction is presented. The failure of phenacyl radicals to dimerize is explained by the delocalized, nonclassical nature of its structure. The suggested structure consistent with both physical and chemical evidence is that of the 1-keto spiro[2.5]octadienyl radical. The low methane to peroxide ratios obtained are accounted for by methyl substitution to form methyl acetophenones. The collective data are explainable in terms of the postulate that the methyl free radical is solvated by acetophenone into a spin-correlated π-complex which is the principal doublet species in these reactions.

The progress which has been made during the past 25 years in the chemistry of organic free radicals is dramatically exemplified by ref 1 and 2. An earlier study[1b] of the reactions of diacetyl peroxide with ketones showed that the methyl free radical generated by the thermolysis of the peroxide formed 1,4-diketones from aliphatic ketones through dehydrodimerization. While the existence of 2-alkanonyl

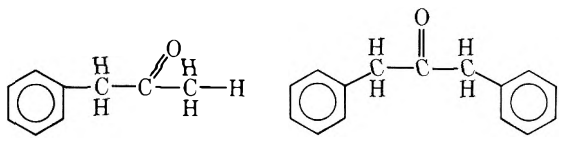


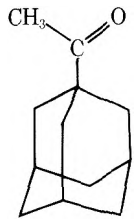
radicals was confidently postulated as intermediates in these dimerization reactions, the evidence (product isolation) was purely chemical and thus indirect. The structures of these intermediate 2-alkanonyl radicals which are involved in these successful dimerizations have recently been determined by electron spin resonance spectroscopy. They have been reported[2c] to have the following structure, with



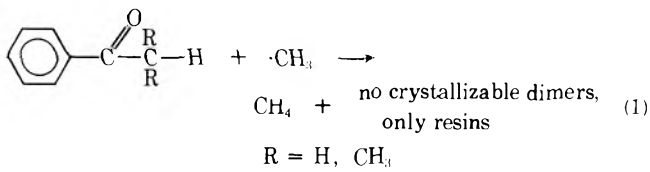
α β

85% contribution from canonical α and 15% from canonical β. Among aliphatic ketones which have subsequently been dimerized[3] by this technique are the following.





In striking contrast to this free-radical dimerization of aliphatic ketones, the phenyl ketones *with the phenyl group attached directly to the carbonyl group* give no crystallizable dimers, only resinous polymeric material, under identical conditions.[1b]



(1)

Results and Discussion

There are several aspects of this latter reaction (eq 1) which appeared worthy of further investigation.

(I) The marked decrease in methane to peroxide ratios observed with phenyl ketones as contrasted with results obtained with completely aliphatic ketones.

(II) The failure of phenyl ketones with benzoyl functions in their structure to form dimeric 1,4-diketones in the manner similar to that of purely aliphatic ketones.

(III) The occurrence of wine-colored resinous polymeric material as the principal product of the reactions of these phenyl ketones and the absence of such resins among the products of the purely aliphatic ketones.

(IV) The persistence in the polymer of the (C=O) breathing frequency at 5.94[4] μ while the doublet at 6.24 and 6.32 μ attending the C_6H_6 $\leftrightarrow$ (C=O) breathing has nearly vanished. (This evidence is specifically consistent with the interpretation that the intermediate phenacyl free radicals rearrange to 1-keto spiro[2.5]octadienyl radicals before they are trapped by acetophenone and thus incorporated into the polymer.) The interpretation here proposed is that the C_6H_6 $\leftrightarrow$ (C=O) doublet has completely vanished in the spectrum of the polymer leaving exposed the much less intense aromatic >C=C< stretching frequency. The fact that ESR studies[5] indicate complete rearrangement of the radical tends to support this interpretation.

(V) The occurrence in the ir spectra of these polymers of broad and intense ether bands at 8.05 μ, actually 7.65–8.40 μ, is here interpreted as ketal linkages. (These cannot be

methyl ketals. Zeisel methoxy determinations[6] on the gunks show essentially no methoxy groups in the structure.)

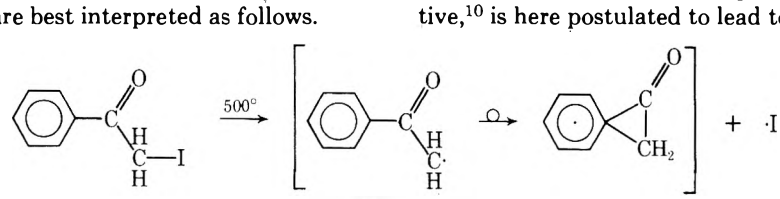
Evidence supporting this assignment in the infrared spectra of these resins is the fact that these polymers have been partially degraded by acid-catalyzed hydrolysis to regenerate the free derivatizable keto groups, thus restoring the intensity of the composite carbonyl band in the infrared absorption spectrum.

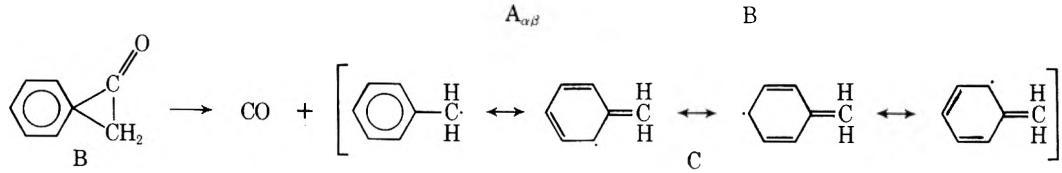
We have demonstrated that those methyl free radicals which have failed to appear as methane gas were actually substituted into the aromatic ring of the phenyl ketone substrate. Methyl acetophenones have been isolated from the reaction mixture when acetyl peroxide is decomposed in acetophenone. It has been demonstrated that methyl benzophenone appears among the products of the reaction of diacetyl peroxide with benzophenone. The mixture of methyl acetophenones has been resolved by gas chromatography into the ortho, meta, and para methyl components with a ratio of approximately 26:14:60, respectively.

Preliminary ESR studies[5] suggest that the phenacyl free radical which was the expected intermediate in these reactions is a delocalized species under the conditions of the reaction. The spin density at the specific α carbon at which dimerization might be expected to occur is greatly reduced by delocalization, and failure to couple at this position is no longer difficult to understand. It has been demonstrated that there are two discrete isomeric free radicals with the molecular formula $C_6H_5COCH_2$. The radical with high spin density at the α carbon atom is thus far known only at 4 K in an argon matrix.

When generated by the ultraviolet photolysis of phenacyl iodide at 4 K in an argon matrix a partially delocalized phenacyl free radical has been detected. The ESR spectrum of this radical indicates that the spin density, ρ_C, on the oxygen is 0.13 while on the methylenic carbon this density, ρ_C, is 0.87. Similar ESR measurements on the analogous pentadeuteriophenacyl radical provide evidence that this particular phenacyl free radical at 4 K has no spin density delocalized into the benzene ring.

When phenacyl iodide is pyrolized at 500° and deposited immediately on a sapphire rod in a matrix of neon at 4 K one obtains the ESR spectrum known for the benzyl radical. When the pyrolysis products of phenacyl iodide under similar conditions are fed directly into the mass spectrometer the results obtained are best interpreted as follows.

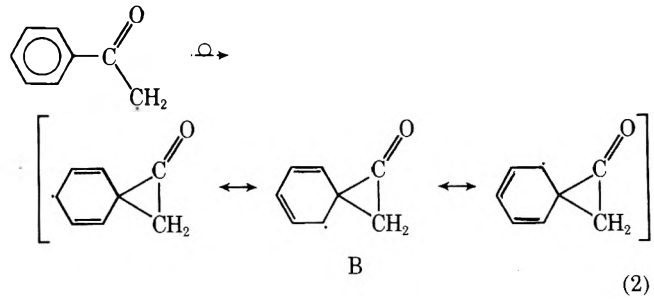




The combined results of mass spectrometry and ESR spectrometry clearly support the conclusion that CO is eliminated at 500°. It seems necessary to postulate the occurrence of the rearrangement *before* the loss of CO since neither the mass spectrometry nor the ESR spectrometry shows evidence of a free $\cdot CH_2$ fragment.

The rearrangement of free radicals is a well-known phenomenon.[7] The 1,2 shift of a phenyl group in a doublet species such as is here described was first demonstrated by Urry and Kharasch.[8]

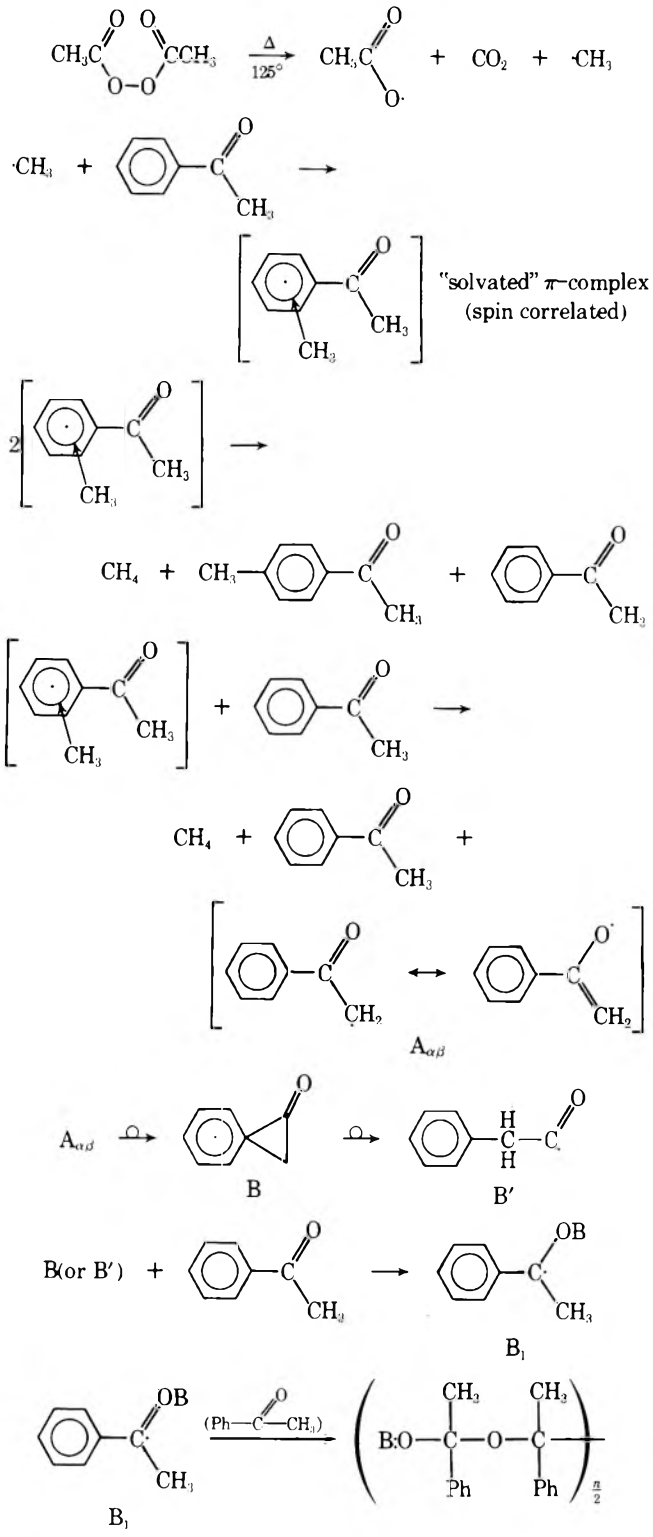
Results more recently reported[9] indicate that in specific instances the process of radical rearrangement might be reversible with a critically temperature-dependent free-energy change. The temperature at which the two isomeric structures are at equilibrium, $(\Delta G = 0)_{T=T_i}$, is designated by those authors as the inversion temperature. The inversion temperature at which this presumed rearrangement (eq 2) occurs is not now known nor is the minimum temperature known at which the decarbonylation occurs. The absence of bibenzyl among the products of the attempted dimerization together with the persistence of aliphatic carbonyl bands in the infrared spectra of these resins indicate that decarbonylation does not occur at 125°, the temperature of these reactions. The temperature at which the proposed inversion of phenacyl occurs as well as the ESR spectrum of this delocalized and inverted radical are under investigation in these laboratories.



(2)

The fact that the quantities of the products, methyl acetophenones, obtained from methyl insertion are extremely small in contrast with the quantities of resins may well be explained in terms of the postulate that the methyl free radical is solvated by acetophenone into a spin-correlated π complex. The concentration of this complex is always extremely low at any time during the reaction because of the fact that the diacetyl peroxide dissolved in acetophenone is added one drop at the time beneath the surface of acetophenone preheated to 125°. In this manner each small portion of diacetyl peroxide is presumably decomposed before the next portion is added. Certainly much care is taken to avoid the build-up of appreciable quantities of diacetyl peroxide during the reaction. (See Experimental Section part of ref 1.) The probability, therefore, of a collision between two particles of π complex, which collision, if effective,[10] is here postulated to lead to methyl insertion, is very small. On the other hand, the probability that such a solvated methyl radical might collide with a solvent molecule, acetophenone, to generate the phenacyl free radical, B, is much greater. This species denoted by B, the 1-keto spiro[2.5]octadienyl radical, would because of resonance stabilization be expected to have a longer half-life than that of the indicated isomer, A, and in presence of a fairly good scavenger, or "trapping agent", might initiate a chain condensation reaction leading to polymeric resinous material. The initiator, B, or B′, is thus incorporated into the

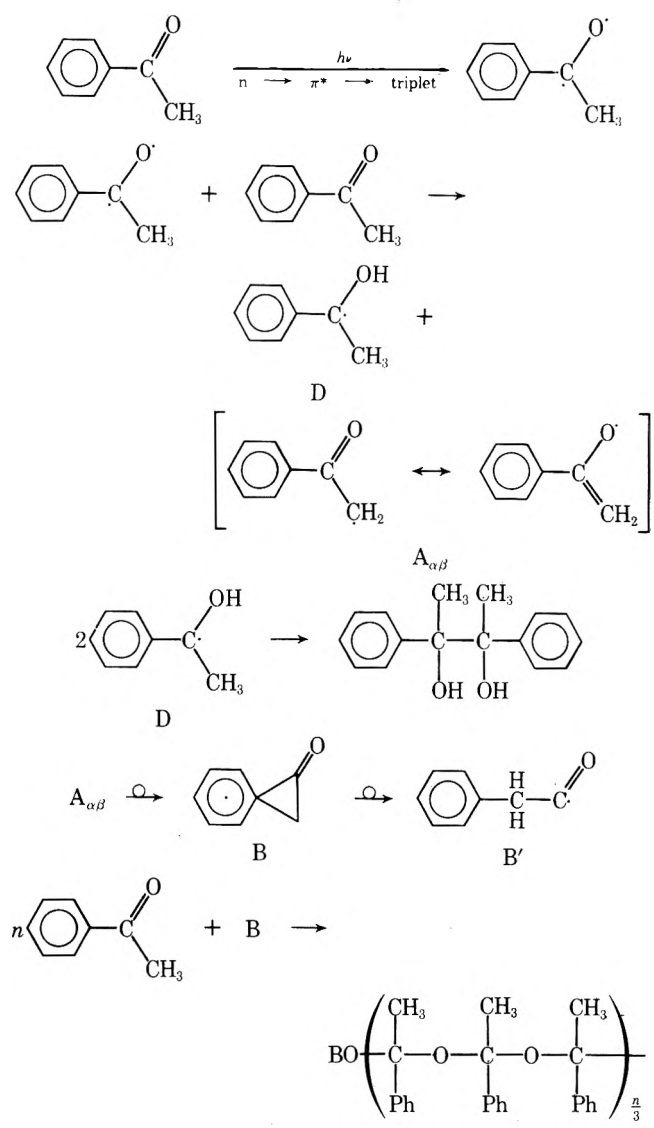
Scheme I



polymer, and the greatly diminished, but still present, carbonyl band in the infrared absorption spectrum of the polymer is thereby explained. These polymers have average molecular weights of ca. 648, indicating an average of 5.33 monomer units per molecule of polymer. The yields of polymer are in every case good, indicating that the initiator is quite effective but these radical chains are indeed not very long.

These results suggest also that as the polymer builds itself through successive attacks on carbonyl by residual radicals of nth order, the ability to attack carbonyl decreases. When n = 5 or 6 the condensation process no longer competes successfully with chain termination probably via disproportionation.

Scheme II



The reaction scheme shown in Scheme I for the overall reaction of diacetyl peroxide with acetophenone is consistent with these collective facts.

Note that although B_1 is a benzyl-type free radical its dimerization is sterically retarded. In the absence of the less hindered carbonyl function in acetophenone providing an alternate reaction path this radical would be expected to dimerize.

As a further test for the validity of this composite interpretation an attempt was made to generate the phenacyl free radical in solution of acetophenone by yet another method. The triplet state of acetophenone would be expected to act as an hydrogen abstractor in the presence of hydrogen atoms on a carbon adjacent to the carbonyl function. The cogency of the argument here presented provides the following distinctly predictable interpretation of the results which would be expected when acetophenone is subjected to ultraviolet irradiation either neat or in solution of a relatively inert solvent. The reaction scheme shown in Scheme II outlines that interpretation.

When a dilute solution (0.5 N) of acetophenone in n-heptane was irradiated with the unfiltered mercury arc of a high-pressure ultraviolet lamp, the results obtained were precisely those predicted and outlined here. Both meso and

racemic forms of the glycol, 2,3-diphenyl-*n*-butanediol-1,2, were isolated. The resinous polymer which was obtained exhibited properties identical with those attending the resin obtained from the reaction of diacetyl peroxide with acetophenone described earlier.

It is apparent from Scheme II that there might be competition between B and D for addition to the carbonyl group of the acetophenone to initiate the chain polymerization reaction. One must conclude from the results that B adds much faster to the carbonyl than does D. This is not surprising since benzyl-type free radicals are well known to dimerize with great facility.

When a series of alkyl phenyl ketones are irradiated in 2-propanol,[11] a solvent with an easily abstractable tertiary hydrogen, the meso and racemic forms of the corresponding glycols are obtained *without* the accompaniment of the polymeric resins derived from the ketones. These results are consistent with the interpretations here presented.

Experimental Section

The preparation of the peroxide, its thermolysis in solutions of the alkyl phenyl ketones, and the recommended precautions attending these techniques are all described in the eariler reports.[1b]

Isolation and Identification of the Methyl Insertion Products. After the acetyl peroxide (32.9 g, 0.28 mol) dissolved in acetophenone (386.8 g) was completely decomposed in acetophenone (103.5 g, 0.86 mol),[1] the unreacted monomeric material was stripped from the polymer by distillation at reduced pressure through a 20-plate column. The collected distillates from three such reactions were combined, and this mixture was carefully distilled through a 100-plate Podbilniak column. The last fraction, bp 60.0° (0.5 mm) (10.0 g), was submitted[12] for ir analysis. This spectrum was superimposable upon the infrared spectrum of an authentic synthetic mixture of 5% *p*-methylacetophenone and 95% acetophenone. This mixture was resolved[13] by GLC technique. It was shown to be 5% methylated material and 95% acetophenone. The results showed 60:26:14% para:ortho:meta-substituted acetophenones, respectively. The column used was a 4-m, 0.6-cm diameter, glass column packed with 20% Ucon LB-550-X resin on 60/80 mesh Chromosorb operating at 215°.

Ultraviolet Irradiation of Acetophenone.[14] The photolysis vessel was a 3-l, three-necked, cylindrically shaped, flat-bottomed flask. The outer necks were 24/40 outer joints for thermometer and condenser. The middle neck was a 60/50 joint for the quartz water-jacketed immersion well which accommodates the Hanovia high-pressure mercury vapor lamp, 500 W, type 679A. Acetophenone (2.5 l., 0.5 *M*) (150.2 g) in *n*-heptane was irradiated for 24 hr by the full mercury arc with nitrogen purging and magnetic stirring. The solution acquired a red-brown color and some material was deposited on the surface of the quartz well. No gases were generated. The *n*-heptane was removed by distillation at atmospheric pressure, and the unreacted acetophenone [40.1 g, bp 40° (30 mm), n^{20}D 1.5330] was removed at reduced pressure. The remaining fractions collected are tabulated below.

Fraction	Bp, °C (0.5 mm)	Weight, g
1	54–104	2.1
2	104–135	28.8
3	135–145	15.9
4	145–146	24.2
5	146–130	11.8

The resinous residue weighed 24.7 g. It had a reddish-brown color and it was soluble with decreasing order in ligroin, ether, acetone, and ethanol. To remove all monomeric materials this residue was subjected to continuous extraction for 30 hr with absolute methanol. It was shown to have properties identical with those of the polymer obtained from the reaction of diacetyl peroxide with acetophenone.

Fractions 2, 3, and 4 deposited crystals and fraction 5 completely crystallized. All of these fractions were pale yellow in color. The crystals from all fractions were collected on a sintered disk by suction filtering. Recrystallization from 60% aqueous methanol gave needle-like crystals which melted sharply at 116°.

Upon cooling to −80° the mother liquor from this recrystallization gave 2.1 g of material which melted after purification by elution chromatography at 44–45°. Five grams of the yellow oil obtained from the suction filtering was subjected to similar elution chromatography on a column (30 cm long and 2.5 cm i.d.) packed with activated alumina using 25-ml portions of methanol, methanol–2-propanol (1:1), 2-propanol, 2-propanol–benzene (1:1), and benzene. The solvents from each fraction of eluate were evaporated on a steam bath and fraction 2 yielded 2.3 g of crystals. Upon recrystallization from methanol–water these crystals melted at 44–45°. The high-melting (116°) and low-melting (44–45°) crystals gave molecular weights and C and H analyses consistent with 2,3-dihydroxy-2,3-diphenyl-*n*-butane, which exists in two isomeric forms. Neither of these materials depressed the respective melting points of authentic samples of the meso form (mp 117–118°)[15] and the racemic form (mp 45°)[15] of this material.

Registry No.—Diacetyl peroxide, 110-22-5; acetophenone, 98-86-2.

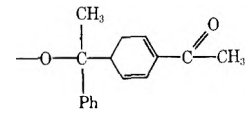
References and Notes

(1) (a) Publication No. 65 from the AUCSRI. (b) M. S. Kharasch, H. C. McBay, and W. H. Urry, *J. Am. Chem. Soc.*, **70**, 1269 (1948); C. G. Moore, *J. Chem. Soc.*, 236 (1951).

(2) (a) D. M. Camioni and D. W. Pratt, *J. Am. Chem. Soc.*, **94**, 9258 (1972); (b) D. M. Camaioni, H. F. Walter, and D. W. Pratt, *ibid.*, **95**, 4057 (1973); (c) D. M. Camaioni, H. F. Walter, J. E. Jordan, and D. W. Pratt, *ibid.*, **95**, 7978 (1973); (d) H. Zelder and R. L. Livingston, *J. Chem. Phys.*, **45**, 1946 (1966).

(3) H. C. McBay, unpublished results.

(4) A plausible interpretation for the persistence in the polymer of this absorption band at 5.94 μ suggested by one of the referees is chain termination by addition to the ring to give such (nonaromatic) end groups as below.



(5) P. H. Kasai, D. McCleod, and H. C. McBay, *J. Am. Chem. Soc.*, **96**, 6864 (1974).

(6) (a) S. J. M. Zeisel, *Monatsh. Chem.* **6**, 989 (1885); **7**, 406 (1886); *Int. Congr. Appl. Chem.*, **2**, 63 (1898); (b) J. T. Hewitt and T. S. Moore, *J. Chem. Soc.*, **81**, 318 (1902); (c) J. T. Hewitt and W. J. Jones, *ibid.*, **115**, 193 (1919).

(7) For a general discussion of this phenomenon see R. K. Freidlina, *Adv. Free-Radical Chem.*, **1**, 211–278 (1965). See also J. W. Wilt, "Free Radicals", Vol. I, J. K. Kochi, Ed., Wiley-Interscience, New York, N.Y., 1973, Chapter 8.

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(9) (a) J. K. Kochi, P. J. Krusic, and D. R. Eaton, *J. Am. Chem. Soc.*, **91**, 1877 (1969); (b) *ibid.*, **91**, 1879 (1969); (c) L. K. Montgomery and J. W. Matt, *ibid.*, **89**, 3050 (1967); (d) T. A. Halgren, M. E. H. Howden, M. E. Medof, and J. D. Roberts, *ibid.*, **89**, 3051 (1967).

(10) It is suggested here that a collision between two solvated complexes leading to methyl insertion might require the occurrence of a concerted process at the moment of impact. This process would involve the removal of a hydrogen atom from the acetophenone moiety of the complex in concert with the replacement of that hydrogen by the methyl radical of the other complex. A necessary condition attending this process is a critically specific geometric orientation of these two complexes at the moment of impact. Little need be said of the necessary geometrics attending a collision between a π complex and an uncomplexed solvent molecule generating the phenacyl radical. See L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964. See also G. A. Russell, *Tetrahedron*, **8**, 101 (1960). Shelton presents convincing evidence for and a discussion of the mechanism here implied for the formation of a π complex and the subsequent rearrangement to a σ complex in homolytic aromatic substitution enhanced by the presence of electron-withdrawing groups: J. R. Shelton and A. L. Lipman, Jr., *J. Org. Chem.*, **38**, 2386 (1974).

(11) C. C. Arrington, M.S. Thesis, Atlanta University, Atlanta, Ga., 1964.

(12) These spectra were made by the Truesdale Laboratories, Los Angeles, Calif., using KBr disks with the polymer dispersed. A Perkin-Elmer Model 21 spectrometer was used.

(13) These separations were performed by Dr. Robert C. Petterson, Health Research Center, New Orleans, La.

(14) This experiment was performed by Frank C. Greene.

(15) These materials were generously provided by C. C. Arrington, who prepared them by action of methyl Grignard with benzil. See J. M. Johlin, *J. Am. Chem. Soc.*, **39**, 291 (1917), Chu and Chu, *J. Chin. Chem. Soc. (Peking)*, **9**, 190 (1942).

Dichlorotris(triphenylphosphine)ruthenium-Catalyzed Hydrogen Transfer from Alcohols to Saturated and α,β-Unsaturated Ketones[1]

Yoel Sasson and Jochanan Blum*

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

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Dichlorotris(triphenylphosphine)ruthenium has been shown to be an efficient catalyst for the selective transfer hydrogenation of α,β-unsaturated ketones by primary and secondary carbinols. Kinetic studies were carried out using 1-phenylethanol as hydrogen donor and benzylideneacetophenone as acceptor. The catalysis is inferred to proceed in the following order: (a) dissociation of $RuCl_2(PPh_3)_3$, (b) coordination of the acceptor to the metal, (c) coordination of the alcohol and the formation of a metal alkoxide, (d) hydrogen transfer from the alkoxyl ligand to the coordinated ketone, and (e) release of product. These data are compatible with the expression rate = $kK_1K_2[S^1][S^2][C]_0/(1 + K_1[S^1] + K_1K_2S^1][S^2] + K_3[S^2])$ where $[S^1]$, $[S^2]$, and $[C]_0$ are acceptor, donor, and catalyst concentration, respectively. Step d was considered rate determining on bases of kinetic isotope effect measurements. $RuCl_2(PPh_3)_3$ has been shown to catalyze also hydrogen transfer from secondary carbinols to saturated ketones provided that the ketones involved in the reaction have significantly different oxidation potentials. Kinetic studies of the reaction of dibenzyl ketone and 1-phenylethanol indicate similarity of the three intial steps to those of the former catalysis, but the following step is assumed to involve hydrogen transfer from the alkoxyl ligand to the metal. The hydride attacks then the coordinated ketone with the higher oxidation potential.

The transfer hydrogenation of olefins by carbinols and soluble transition metal catalysts has received considerable attention in recent years.[2] However, only few of the examples reported have synthetic value, and little is known about the mechanism of this process.

Among the more active catalysts studied in our laboratory is dichlorotris(triphenylphosphine)ruthenium, $RuCl_2(PPh_3)_3$ (1). It was found to promote hydrogen transfer, not only from alcohols[2k,m,3-7] but also from hydrocarbons,[3] aldehydes,[8] acids,[8,9] amides,[10] and other hydrogen donors,[9] and proved to be particularly effective in the reactions formulated in eq 1 and 2.

$$R^1R^2CHOH + R^3CH{=}CHCOR^4 \longrightarrow R^1R^2CO + R^3CH_2CH_2COR^4 \quad (1)$$

$$R^1R^2CHOH + R^3R^4CO \rightleftharpoons R^1R^2CO + R^3R^4CHOH \quad (2)$$

In this paper we describe a detailed investigation of this catalyst system, including kinetic measurements and mechanistic studies on the Ru(II)-catalyzed transfer hydrogenation of α,β-unsaturated ketones and the equilibration of *saturated* ketones and secondary carbinols.

Results

Outline of Catalysis. As described in the Experimental Section, the transfer hydrogenation of benzylideneacetophenone to 3-phenylpropiophenone is accomplished simply by heating the unsaturated ketone with benzyl alcohol and the ruthenium catalyst (molar ratio $1:1:2 \times 10^{-3}$) for 2 hr at 180°. The scope and potential synthetic application of this catalysis for the selective reduction of enones is demonstrated by the examples listed in Tables I and II and by experiments described in ref 2k, 3–5, and 7. Both primary and secondary carbinols may serve as hydrogen donors in the catalysis. The former ones, however, have the advantage of being highly selective and transfer hydrogen exclusively to the unsaturated C=C bonds. Secondary alcohols may, under suitable conditions, affect the carbonyl group as well, and therefore should be applied as reducing agents for saturated ketones (eq 2).[2m,6]

Tertiary carbinols do not donate hydrogen to unsaturated substances, but readily form ethers in the presence of 1.[11]

Ether formation from primary and secondary carbinols is exceedingly slow, except for some cases in which the generation of stable carbocations is facilitated by strong electron-donating groups [e.g., 1-(4-methoxyphenyl)ethanol]. In experiments with such carbinols large excess of the donor is required.

Although simple olefins can be used as hydrogen acceptors in the catalytic process, they have the disadvantage of being reduced very slowly by 1. On the other hand, substrates with activated double bonds react usually at high rates and give good yields. Particularly good results are obtained with α,β-unsaturated ketones (Table II). Olefinic and acetylenic bonds in $ArCH{=}CHBr$, $ArCH{=}CHNO_2$, $ArCH{=}CHSO_2CH_3$, $ArCOCH{=}CHCOAr$, $Ar(CH{=}CH)_2Ar$, and $ArC{\equiv}CCOR$ are hardly affected. These compounds form stable chelates with the ruthenium catalyst.

For kinetic measurements we chose the reduction of benzylideneacetophenone by 1-phenylethanol (eq 3). The reaction proceeds smoothly in an *irreversible* fashion (unaffected by addition of the products to the reaction mixture) and may give over 95% 3-phenylpropiophenone and acetophenone. Subsequent reduction of the saturated ketones according to eq 2 is negligible under our experimental conditions. A typical reaction curve for the transfer hydrogenation of a solution of 0.1 *M* benzylideneacetophenone by 1 *M* 1-phenylethanol and 10^{-3} *M* $RuCl_2(PPh_3)_3$ in diphenyl ether at 180° is given in Figure 1. The rate is shown to be virtually constant over the first 60% of the reaction, but the contribution of first and higher order terms becomes significant at advanced states.

$$C_6H_5CH(OH)CH_3 + C_6H_5CH{=}CHCOC_6H_5 \xrightarrow{\text{cat.}} C_6H_5COCH_3 + C_6H_5CH_2CH_2COC_6H_5 \quad (3)$$

Dependence on Donor, Acceptor, and Catalyst Concentration. Plots of the initial rate against the concentration of the hydrogen donor and of the unsaturated ketone are shown in Figures 2 and 3.

Both functions are nonlinear and the dependence of the initial rate on the concentration decreases gradually. While in the acceptor the rate becomes independent of the concentration above 0.2 *M*, in the alcohol it reaches its maximum value only in the pure substrate. Plots of the reciprocal functions, i.e., rate^{-1} vs. concentration^{-1}, yield linear dependence with positive intercept in both cases (vide infra Figures 7 and 8). These results suggest that coordination and activation of the carbinol and of the unsaturated ketone take place prior to the rate-determining step.

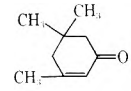
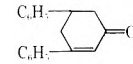
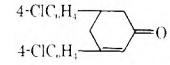
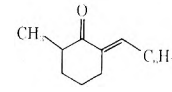
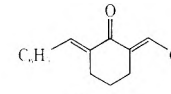
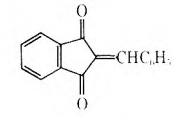
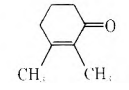
The dependence on catalyst concentration is linear

Table I
$RuCl_2(PPh_3)_3$-Catalyzed Transfer Hydrogenation of Benzylideneacetophenone by Various Carbinols at 180° [a]

Expt	Carbinol	Reaction time, min	Yield of $C_6H_5(CH_2)_2$-COC_6H_5, %
1	$C_6H_5CH_2OH$	40	90
2	4-$CH_3C_6H_4CH_2OH$	40	93
3	3-$CH_3OC_6H_4CH_2OH$	40	83
4	4-$CH_3OC_6H_4CH_2OH$	15	91
5	4-$ClC_6H_4CH_2OH$	60	82
6	3-$FC_6H_4CH_2OH$	180	60
7	4-$FC_6H_4CH_2OH$	60	78
8	$C_6H_5OCH_2OH$	40	50
9	$CH_3(CH_2)_6CH_2OH$	120	68
10	4-$HOCH_2C_6H_4CH_2OH$ [b]	15	79
11	$HOCH_2CH_2OH$	60	45
12	$HOCH_2(CH_2)_4CH_2OH$ [b]	40	48
13	$HOCH_2CH_2OCH_2CH_2$-OH	20	80
14	$CH_3(CH_2)_2CH(OH)CH$-$(C_2H_5)CH_2OH$ [b]	40	23
15	$C_6H_5CH(OH)CH_3$	60	80
16	4-$CH_3C_6H_4CH(OH)$-CH_3	40	96
17	4-$ClC_6H_4CH(OH)CH_3$	60	26
18	4-$FC_6H_4CH(OH)CH_3$	60	36
19	β-$C_{10}H_7CH(OH)CH_3$ [b]	20	41
20	$CH_3(CH_2)_7CH(OH)CH_3$	120	38
21	$(CH_3)_2CHCH(OH)CH$-$(CH_3)_2$	120	25
22	c-$C_3H_5CH(OH)$-c-C_3H_5 [c]	120	30
23	$CH_3CH(OH)CH(CH_3)$-$CH(OH)(CH_2)_2CH_3$ [b]	40	63
24	c-$C_6H_{11}OH$ [b,c]	120	34
25	3,4-Dimethylcyclo-hexanol [b]	120	36
26	*trans*-1,4-Dihydroxy-cyclohexane [b]	120	63

[a] Except in expt 10, 12, 14, 19, and 23-26, the reaction mixture consisted of a solution of 0.4 *M* benzylideneacetophenone and 10^{-3} *M* catalyst in the carbinol. [b] A solution of 0.2 *M* benzylideneacetophenone, 2 *M* carbinol, and 10^{-3} *M* catalyst in freshly purified diphenyl ether was used. [c] In a sealed tube.

Table II
$RuCl_2(PPh_3)_3$-Catalyzed Transfer Hydrogenation of Various α,β-Unsaturated Ketones by Benzyl Alcohol under Comparable Conditions [a]

Expt	Unsaturated ketone	Yield, %
1	$C_6H_5CH{=}CHCOCH_3$	95
2	$C_6H_5CH{=}CHCO(CH_3)_3$	42
3	4-$CH_3OC_6H_4CH{=}CHCOCH_3$	96
4	$C_6H_5CH{=}CHCOC_6H_5$	92
5	4-$CH_3C_6H_4CH{=}CHCOC_6H_5$	94
6	4-$CH_3OC_6H_4CH{=}CHCOC_6H_5$	93
7	4-$ClC_6H_4CH{=}CHCOC_6H_5$	90
8	4-$FC_6H_4CH{=}CHCOC_6H_5$	92
9	3,4-$(CH_3O)_2C_6H_3CH{=}CHCOC_6H_5$	89
10	4-$CH_3OC_6H_4CH{=}CHCOC_6H_4$-4-$CH_3$	89
11	4-$CH_3C_6H_4COCH{=}CHC_6H_5$	88
12	4-$CH_3OC_6H_4COCH{=}CHC_6H_5$	96
13	4-$ClC_6H_4COCH{=}CHC_6H_5$	91
14	4-$FC_6H_4COCH{=}CHC_6H_5$	94
15	$C_6H_5C(CH_3){=}CHCOC_6H_5$	45
16	$C_6H_5CH{=}C(CH_3)COC_6H_5$	44
17	$C_6H_5(CH{=}CH)_2COCH_3$	*b*, *c*
18	$(C_6H_5CH{=}CH)_2CO$	*b*, *d*
19		54
20		52 [e]
21		52 [e]
22		36 [e]
23		*b*, *f*
24		45
25		0

[a] A solution of 0.4 *M* ketone and 10^{-3} *M* catalyst in benzyl alcohol was heated for 60 min at 180°, then immediately cooled to room temperature. [b] Kinetic measurements indicate that no direct conversion of dienone to the saturated ketone takes place. The monounsaturated ketone can be reduced completely to the saturated carbonyl compound upon further heating at 180°. [c] 55% $C_6H_5(CH_2)_4COCH_3$ and 40% $C_6H_5CH{=}CH(CH_2)_2COCH_3$. [d] 50% $(C_6H_5CH_2CH_2)_2CO$ and 26% $C_6H_5CH_2CH_2COCH{=}CHC_6H_5$. [e] As a mixture of cis and trans isomers. [f] 38% 2,6-dibenzylcyclohexanone and 56% 2-benzyl-6-benzylidenecyclohexanone.

below 6×10^{-4} *M* and suggests pseudo-first-order behavior. At higher concentration ($>10^{-3}$ *M*) the rate approaches a constant value, probably due to solubility limits and to the dimerization and/or polymerization[12-14] of the dissociated ruthenium catalyst (see also ref 15).

Structure–Activity Correlation. The data given in Tables I and III indicate that benzyl alcohols are more reactive than straight-chain aliphatic ones. As carbinols that are substituted by electron-releasing groups increase the activity and vice versa, it can be assumed that abstraction of a hydrogen atom, α to the hydroxyl group, as hydride is involved in the rate-determining step. This assumption is further supported by evaluation of the kinetic isotope effect measurements using deuterated 1-phenylethanol (Table IV).

Upon introduction of Cl, F, OCH_3, or CH_3 groups in the 4 and/or 4′ position in benzylideneacetophenone we found that electronic factors have no significant effect on the reaction rate and yield. The results resembled those of the unsubstituted parent compound. A decrease in rate has, however, been noted when sterically hindered hydrogen acceptors were reduced (Table V). This, once again, suggests that the coordination of the acceptor to the metal atom takes place prior to the rate-determining step. Since shielding of either the C=C double bond or the carbonyl group causes rate reduction, one may conclude also that coordination of α,β-unsaturated ketones involves *both* these functions. The reduced affinity of an α-substituted chalcone toward the ruthenium catalyst, as compared with that of the parent compound, can be derived from plots of the corresponding rate vs. ketone concentration. While, e.g., in the unsubstituted acceptor the highest rate is reached already above 0.2 *M* (Figure 3), in α-methylbenzyl-

Table III
Initial Rates of Transfer Hydrogenation of Benzylideneacetophenone by Various Carbinols[a]

Expt	Carbinol	Initial rate, mmol/min
1	Octan-1-ol	2.11
2	Decan-1-ol	1.24
3	3,4-Dimethylcyclohexanol	1.17
4	Ethylene glycol	2.95
5	Diisopropylcarbinol	0.83
6	Benzyl alcohol	8.96
7	3-Methoxybenzyl alcohol	5.00
8	4-Methoxybenzyl alcohol	30.00
9	3-Flucrobenzyl alcohol	1.38
10	4-Flucrobenzyl alcohol	4.89
11	1-Phenylethanol	5.35
12	1-(4-Tolyl)ethanol	9.67
13	1-(4-Chlorophenyl)ethanol	1.74
14	1-(4-Fluorophenyl)ethanol	2.19

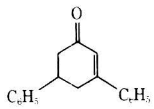
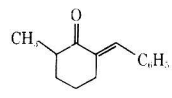
[a] Reaction system was 0.4 *M* ketone and 10^{-3} *M* catalyst in the carbinol at 180°.

Table IV
Kinetic Isotope Effect Measurements[a]

Carbinol	k_H/k_D[b]
$C_6H_5CD(OD)CH_3$	2.59
$C_6H_5CD(OH)CH_3$	2.57
$C_6H_5CH(OD)CH_3$	1.17

[a] Reaction system was 0.4 *M* benzylideneacetophenone and 10^{-3} *M* $RuCl_2(PPh_3)_3$ in deuterated 1-phenylethanol at 170°. [b] The *k* values are calculated from the reduced rate equation rate = $k[C]_0$ as described later.

Table V
Initial Rates of Transfer Hydrogenation of Some α,β-Unsaturated Ketones by Benzyl Alcohol[a]

Expt	Hydrogen accepter	Initial rate, mmol/min
1	$CH_2{=}CHCOC_2H_5$[b]	44.0
2	$C_6H_5CH{=}CHCOCH_3$	21.0
3	$C_6H_5CH{=}CHCOC_6H_5$	9.0
4	$C_6H_5CH{=}CHCOC(CH_3)_3$	3.1
5	$C_6H_5C(CH_3){=}CHCOC_6H_5$	3.2
6	$C_6H_5CH{=}C(CH_3)COC_6H_5$	3.1
7		3.5
8		2.6

[a] Reaction system was 0.4 *M* ketone and 10^{-3} *M* catalyst in benzyl alcohol at 180°. [b] In a sealed ampoule.

ideneacetophenone, $C_6H_5CH{=}C(CH_3)COC_6H_5$, this is achieved only above 1.6 *M*.

A remarkable phenomenon has been observed in the transfer hydrogenation of mixtures of sterically hindered and unhindered unsaturated ketones. While, e.g., benzylideneacetophenone and α-methylbenzylidenacetophenone react separately with 1-phenylethanol in comparable velocities (ratio of initial rates was found to be 2.8:1), a *mixture* of these ketones yields no 3-phenylbutyrophenone until practically all the benzylideneacetophenone has been consumed. This can be rationalized by the "blocking" of all

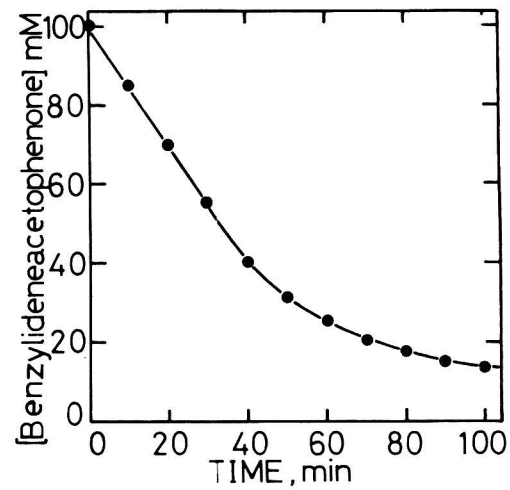


Figure 1. Plot of conversion vs. reaction time: 0.1 *M* benzylideneacetophenone, 1 *M* 1-phenylethanol, and 10^{-3} *M* $RuCl_2(PPh_3)_3$ in diphenyl ether at 180°.

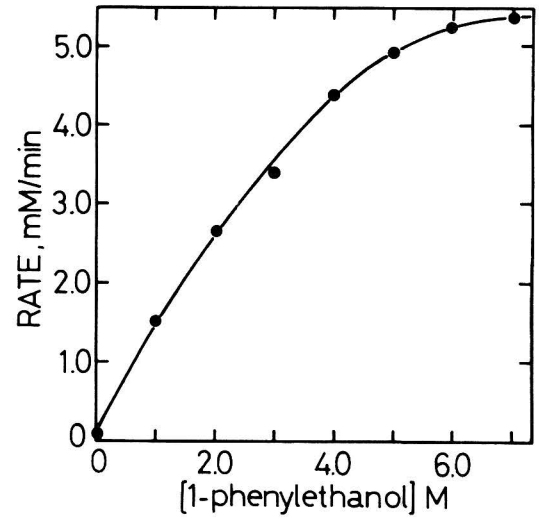


Figure 2. Dependence of initial rate on the concentration of 1-phenylethanol in diphenyl ether at 180°, with 0.4 *M* (initial concentration) benzylideneacetophenone and 10^{-3} *M* $RuCl_2(PPh_3)_3$.

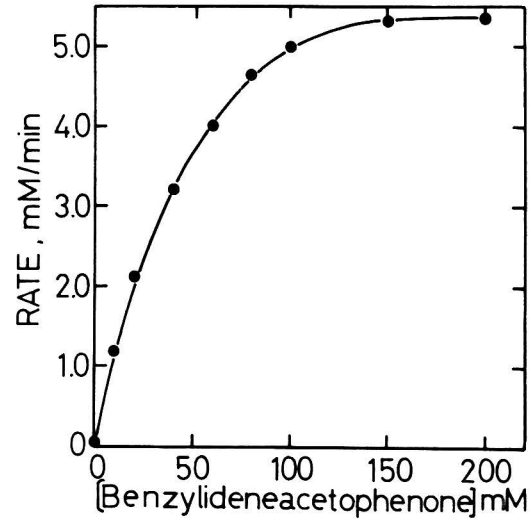


Figure 3. Dependence of initial rate on the concentration of benzylideneacetophenone at 180°. Catalyst concentration 10^{-3} *M* in 1-phenylethanol.

available active sites in the catalyst by the ketone of the higher affinity to the metal catalyst, preventing, thus, the activation of the bulky α-methyl derivative. (Cf. similar

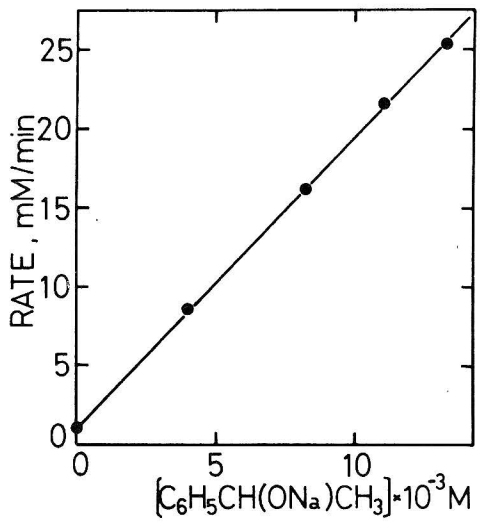


Figure 4. Influence of $C_6H_5CH(ONa)CH_3$ on the initial rate of transfer hydrogenation of benzylideneacetophenone (initial concentration 0.4 M in 1-phenylethanol) at 120°. Catalyst concentration 10^{-3} *M*.

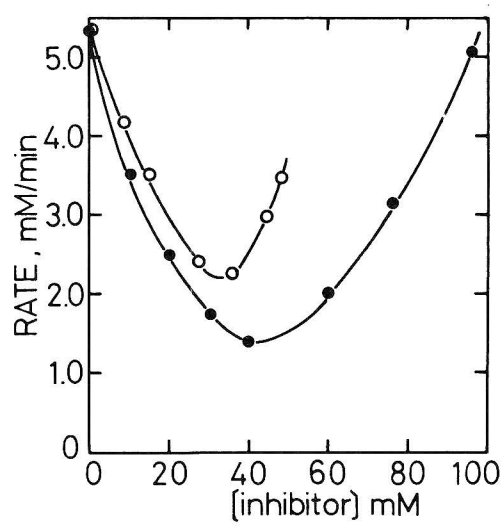


Figure 5. Effect of addition of triphenylphosphine (●) and tribenzylamine (○). Reaction system: 0.4 *M* ketone and 10^{-3} *M* $RuCl_2(PPh_3)_3$ in 1-phenylethanol at 180°.

competitive behavior in some other transition metal catalyzed reactions.[15])

The influence of the electronic structure of the catalyst upon reactivity was studied by utilizing ruthenium complexes of general formula $RuCl_2[(4\text{-}X\text{-}C_6H_4)_3P]_3$ in reaction 3. The initial rates for various substituents X are listed in Table VI. Since the formation of a metal hydride intermediate should be favored by electron-attracting groups, it is obvious that such a hydride cannot be a key step in the overall reaction.

Table VI
Reactivities of Various Catalysts of Formula $RuCl_2[(4\text{-}X\text{-}C_6H_4)_3P]_3$[a]

Registry no.	Substituent X	Initial rate, mmol/min
39042-64-3	Cl	2.05
39152-69-7	F	2.53
15529-49-4	H	2.78
36733-05-8	CH_3	4.50
39114-24-4	OCH_3	5.40

[a] Reaction system was 0.4 *M* benzylideneacetophenone and 10^{-3} *M* ruthenium catalyst in 1-phenylethanol at 170°.

Inhibitors and Cocatalysts. Reaction 3 is strongly accelerated by bases and decelerated by acids. A typical example of such an acceleration is shown in Figure 4. Although the sodium enolate, $C_6H_5CH(CH_3)O^-Na^+$, acts in this case primarily as a cocatalyst, it should be recalled that bases by themselves are capable of catalyzing hydrogen transfer from carbinols to unsaturated acceptors in the *absence* of transition-metal complexes, albeit by a different mechanism.[16] Kinetic measurements, now carried out, for the reaction of benzylideneacetophenone and 1-phenylethanol in the presence of various strong bases, free from transition-metal compounds, indicate that the reaction rate falls usually much behind that of the $RuCl_2(PPh_3)_3$-catalyzed reaction.[17]

Tertiary alcohols, which by themselves are inactive as hydrogen donors, serve as inhibitors in reaction 3. The addition of a 2 *M* solution of 2-phenylpropon-2-ol, e.g., to the reaction mixture of benzylideneacetophenone (0.4 *M*) and 1 (10^{-3} *M*) in 1-phenylethanol causes the initial rate to decrease by 45%. It seems, thus, that the tertiary carbinol competes with 1-phenylethanol for the active sites at the central ruthenium atom.

Some olefins, e.g., allylbenzene, which proved to be transfer hydrogenated much slower than chalcone, interfere with the reduction of the latter. A 1 *M* solution of allylbenzene is sufficient to bring reaction 3 to a standstill.

The effect of addition of triphenylphosphine on the reaction rate is shown in Figure 5. Below 40 m*M* any addition of PPh_3 inactivates the ruthenium catalyst, probably by preventing $RuCl_2(PPh_3)_3$ from dissociation into free phosphine and the active species $RuCl_2(PPh_3)_2$ (**2**).[12,18] At higher concentration of triphenylphosphine the rate starts to increase again, possibly owing to an independent base-catalyzed reaction exerted by the addendum itself.

That considerable dissociation of $RuCl_2(PPh_3)_3$ indeed takes place under the temperature conditions of the catalysis has been proven by heating the starting catalyst in boiling oxygen-free decalin. After 20 min 80% of PPh_3 could be isolated. In addition this experiment yielded 70% of $[RuCl_2(PPh_3)_2]_x$ which catalyzes reaction 3 at similar rate recorded for the tris(triphenylphosphine) complex. In the presence of oxygen $RuCl_2(O_2)(PPh_3)_2$[19] separated. This complex does not catalyze reaction 3 at all. Another *inactive* ruthenium compound, $RuCl_2(CO)_2(PPh_3)_2$, is formed when $RuCl_2(PPh_3)_3$ is heated *in the absence* of a hydrogen acceptor above 150° in a primary alcohol solvent (e.g., benzyl alcohol).

The effect of several tertiary amines seems to be similar to that of PPh_3, although the mechanisms involved may be much more complicated. Tribenzylamine, e.g., causes the initial rate to drop from 5.35 mmol/min (zero amine concentration) to ~2.20 mmol/min on addition of 0.3 m*M*. At higher amine concentration a sharp increase in rate is noted and extensive ligand exchange occurs.

Some alkyl and aryl chlorides (e.g., chloroform, carbon tetrachloride, chlorobenzene, α-chloronaphthalene) act as powerful inhibitors. These compounds slowly coordinate with the catalyst[25] to give ruthenium complexes which are inactive in the transfer hydrogenation reaction.

Deuterium Labeling Studies. Mass spectral analyses of the 3-phenylpropiophenone obtained by transfer hydrogenation of benzylideneacetophenone using deuterated 1-phenylethanol are given in Table VII. Since $RuCl_2(PPh_3)_3$ has been shown to catalyze also internal H–D exchange in carbinols,[11,21] these figures do not give quantitative information on the chalcone transfer deuteration. They indi-

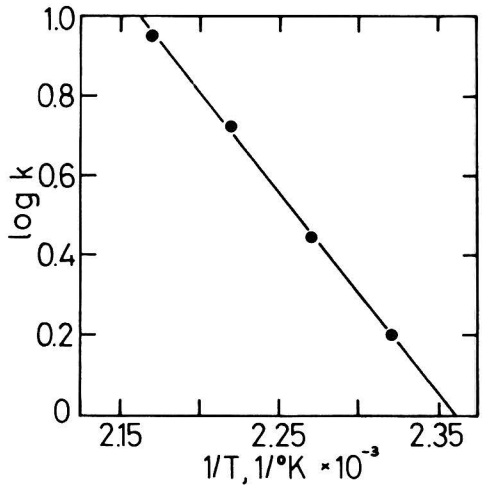


Figure 6. Arrhenius plot of transfer hydrogenation of benzylideneacetophenone by 1-phenylethanol at 160–190°.

cate, however, clearly enough, that the α hydrogen atom in the alcohol is transferred preferentially to the β carbon in the chalcone molecule and the hydroxylic proton attacks mainly at the α carbon. As the peak *m/e* 91 represents the fragment $[C_6H_5CH_2]^+$, a low ratio of intensities 91:92 indicates deuteration at the β carbon. A low ratio *m/e* 105:106 provides rough information on α-carbon labeling. (Both fragments $[C_6H_5CH_2CH_2]^+$ and $[C_6H_5CO]^+$ have similar masses.)

The last two experiments in Table VII show that the aromatic solvent exchanges part of its hydrogen atoms with the protons of the carbinol and are, in turn, transferred to the ketone.

The overall stereochemistry of the transfer hydrogenation was found to be exclusively cis addition, just as in some typical transition metal catalyzed hydrogenation reactions (see, e.g., ref 22 and 23). When, e.g., a solution of 10^{-2} *M* benzylidenepinacolone in benzyl alcohol-d_3, $C_6H_5CD_2OD$, was heated at 170° in the presence of 2.5×10^{-5} *M* $RuCl_2(PPh_3)_3$, essentially pure *threo*-4,4-dimethyl-1-phenylpentan-3-one-d_2, $C_6H_5CHDCHDCOC(CH_3)_3$, was obtained. The threo configuration (and thus cis addition) could easily be established by virtue of the low coupling constant, J = 3.9 Hz. The corresponding value for the erythro isomer is expected to be 10–14 Hz.[24]

Dependence on Temperature. Initial rates (reaction 3) were measured at four temperatures ranging from 160 to 190° for several benzylideneacetophenone concentrations between 0.01 and 0.4 *M*. From the Arrhenius plot of log *k* (see below) against $1/T \times 10^{-3}$ (Figure 6) a value for the activation energy, E_a, of 25.4 kcal mol^{-1} is obtained; $\Delta H^{\ddagger}$ = 24.3 kcal mol^{-1} and $\Delta S^{\ddagger} = -7.55$ ev.

Side Reactions. In order to carry out the above catalysis, free from undesired side reactions, primary alcohols, rather than secondary ones, should be utilized as hydrogen donors. The use of positively substituted primary carbinols is undesired as well, since ether formation takes place in the presence of $RuCl_2(PPh_3)_3$.[11,25]

Although dichlorotris(trisphenylphosphine)ruthenium catalyzes double-bond migration in several unsaturated systems,[10,26] it seldom promotes the isomerization of α,β-unsaturated ketones. Carvone is the only example we came across that is isomerized faster than being transfer hydrogenated.[7] Carvacrol is formed instead of dihydrocarvone.

The most undesired side reaction in process 1 is, obviously, reaction 2. Fortunately, the saturated ketone formed in reaction 1 is transferred to an alcohol only when a large *excess* of a *secondary* carbinol with high reduction potential (such as α-tetralol[27]) is used as hydrogen donor. Aldehydes and primary alcohols (that are aldehyde precursors) inhibit reaction 2 most efficiently. The side reaction can thus be completely eliminated by addition of a few drops of benzaldehyde, and the unsaturated ketone can be transfer hydrogenated exclusively at the C=C double bond. Reaction 2 may, however, have synthetic value of its own (Table VIII shows a few examples) and should deserve some attention.

Table VII
Transfer Hydrogenation of Benzylideneacetophenone by Deuterated 1-Phenylethanol[a]

Carbinol	Isotopic composition of product, % d_0	d_1	d_2	Intensities ratio of masses 91/92	105/106
$C_6H_5CD(OD)CH_3$	29	45	26	1.1	1.3
$C_6H_5CD(OH)CH_3$	46	45	9	1.1	2.7
$C_6H_5CH(OD)CH_3$	67	30	3	3.1	1.6
$C_6H_5CD(OD)CH_3$, C_6H_6[b]	46	38	16	1.4	3.4
$C_6H_5CH(OH)CH_3$, C_6D_6[b]	83	15	2	6.0	5.0

[a] Reaction system was 0.4 *M* benzylideneacetophenone and 10^{-3} *M* $RuCl_2(PPh_3)_3$ in the carbinol at 170°. [b] A 1:1 mixture of carbinol and benzene was used instead of pure carbinol.

Table VIII
Examples of $RuCl_2(PPh_3)_3$-Catalyzed Transfer Hydrogenation of Saturated Ketones by 1-Phenylethanol[a]

Starting ketone	Hydroxylic product	Yield, %
Cycloheptanone	Cycloheptanol	64
$(C_6H_5)_2CO$	$(C_6H_5)_2CHOH$	53
$C_6H_5COCH_2C_6H_5$	$C_6H_5CH(OH)CH_2C_6H_5$	60
$(C_6H_5CH_2)_2CO$	$(C_6H_5CH_2)_2CHOH$	57
4-$ClC_6H_4COCH_3$	4-$ClC_6H_4CH(OH)CH_3$	51

[a] Reaction system: 0.5 *M* ketone and 10^{-3} *M* catalyst in 1-phenylethanol at 180° for 1 hr.

The kinetic behavior of reaction 2 resembles in some, though not in all, respects that of reaction 3. The equilibration of dibenzyl ketone and 1-phenylethanol (eq 4) was chosen for the kinetic studies.

$$C_6H_5CH_2COCH_2C_6H_5 + C_6H_5CH(OH)CH_3 \rightleftharpoons C_6H_5CH_2CH(OH)CH_2C_6H_5 + C_6H_5COCH_3 \quad (4)$$

The difference between the redox potentials of the reagents and products in this system is remarkably large[26] and the reaction is, therefore, practically irreversible.

Starting with 0.5 *M* dibenzyl ketone and 10^{-3} *M* catalyst at 180°, the reaction curve is similar to that shown in Figure 1 for reaction 3. The rate is apparently constant in the first 60% of the reaction as long as terms of higher order are still small.

A plot of the initial rate vs. 1-phenylethanol concentration indicates a steady, but nonlinear, increase in rate up to 4.8 mmol/min in the pure alcohol. The dependence on dibenzyl ketone concentration is similar, but the rate reaches its highest and constant value already above 0.3 *M*. Plots of the reciprocal functions (i.e., rate^{-1} vs. concentration^{-1}) have linear dependence as shown in Figures 7 and 8.

Rate dependence on catalyst concentration was found to be exactly the same as observed for reaction 3.

When dibenzyl ketone is substituted by 0.5 *M* solutions of cycloheptanone, benzyl phenyl ketone, benzophenone, 4-methoxy-, or 4-chloroacetophenone the initial rates are

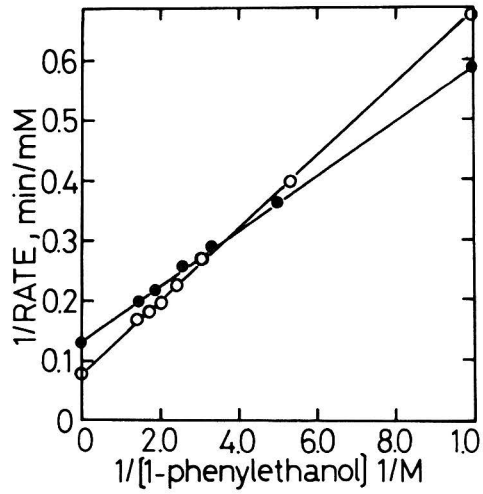


Figure 7. Plot of 1/initial rate of dibenzyl ketone (●) and benzylideneacetophenone (○) consumption against 1/1-phenylethanol concentration. (In the former system 0.5 *M* ketone and 10^{-3} *M* catalyst in 1,3-diisopropylbenzene were allowed to react at 180°; the unsaturated ketone was allowed to react in diphenyl ether under conditions of Figure 2.)

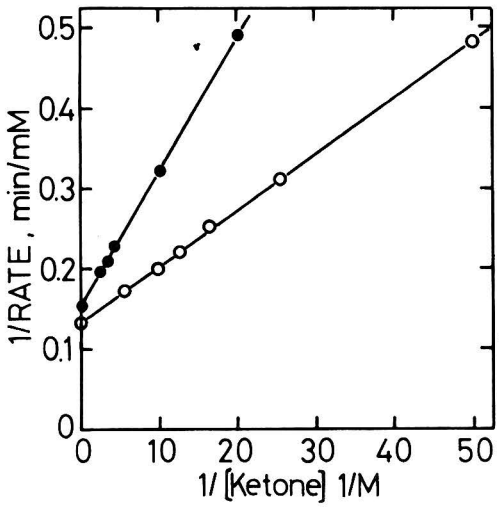


Figure 8. Plot of 1/initial rate against 1/dibenzyl ketone concentration (●) (reaction 4) and against 1/benzylideneacetophenone concentration (○) (reaction 3); catalyst concentration 10^{-3} *M* in 1-phenylethanol at 180°.

all of the same order (5.2, 5.1, 4.4, 5.0, and 4.3 mmol/min, respectively), practically independent of the nature of the ketone. Though the magnitude of the oxidation potentials should not effect the kinetics, ketones with very low oxidation potentials (e.g., α-tetralone and 2,3-dimethylcyclohexanone[27]) do not react to any measurable extent.

Electronic and steric factors in the starting carbinol exhibit a larger effect on the reaction rate. Dibenzyl ketone (0.5 *M*) is reduced at 180° by excess diisopropylcarbinol, 3,4-dimethylcyclohexanol, 1-(4-chlorophenyl)-, 1-phenyl-, and 1-(4-tolyl)ethanol at 0.8, 1.4, 3.6, 4.8, and 5.5 mmol/min (initial rates), respectively.

The k_H/k_D values for the reduction of dibenzyl ketone, under our standard conditions, using $C_6H_5CD(OD)CH_3$, $C_6H_5CD(OH)CH_3$, and $C_6H_5CH(OD)CH_3$, are 1.68, 1.52, and 1.04, respectively. These results suggest that α-hydrogen abstraction (as a metal hydride) may be involved in the rate-determining step. This assumption is further supported by the fact that electronic factors in the ruthenium catalyst provoke an influence on the reaction rate opposite to that found in the transfer hydrogenation of benzylideneacetophenone. (Compare Table VI and Table IX.)

Table IX
Effect of Electronic Changes in the Catalyst $RuCl_2[(4\text{-}X\text{-}C_6H_4)_3P]_3$ on the Rate of Reaction 4[a]

Substituent X	Initial rate, mol/min
CH_3O	3.56
CH_3	3.96
H	4.80
F	5.42
Cl	6.44

[a] Reaction system was 0.5 *M* dibenzyl ketone and 10^{-3} *M* catalyst in 1-phenylethanol at 180°.

Qualitative information on deuterium transfer from deuteriophenylethanols to dibenzyl ketone can be drawn from mass spectral analysis of the mixtures of deuterated 1,3-diphenylpropan-2-ol formed. The parent peak either loses H_2O to give $[C_6H_5CH{=}CHCH_2C_6H_5]\cdot^+$ (*m/e* 194) which, in turn, is converted into $[C_6H_5CH{=}CH]^+$ (*m/e* 103) by loss of a benzyl radical, or cleaves to $[C_6H_5CH_2CHOH]^+$ (*m/e* 121), which, by a concerted mechanism, gives $C_7H_8^+$ of mass 92. In addition moderate cleavage of both the parent peak and P − H_2O to $[C_6H_5CH_2]^+$ (*m/e* 91) and $(C_6H_5)^+$ (*m/e* 77) occurs.

Therefore, the intensity ratio of fragments *m/e* 195 to *m/e* 194 $[M^+ - H_2O]$ and of *m/e* 104 to *m/e* 103 reflect on the deuteration at the benzylic carbon, while the degree of labeling at the OH group can be estimated by the ratio of *m/e* 93 to *m/e* 92 intensities. On the ground of the 195/194 and 104/103 values given in Table X, it can be concluded that the benzylic hydrogen atom in 1-phenylethanol is transferred mainly to the α carbon in the acceptor. Likewise the transfer of the hydroxylic proton of the donor to the oxygen atom in the acceptor can be suggested by virtue of the 93/92 values that are larger when OD-containing 1-phenylethanol was used than by application of the undeuterated carbinol or $C_6H_5CD(OH)CH_3$. The ratios 123/121 and 122/121 refer to the species with both hydroxylic and benzylic hydrogen atoms and reflect only on the number of deuterium atoms transferred.

Table X
Mass Spectral Analysis of Labeled 1,3-Diphenylpropan-2-ols Obtained from Dibenzyl Ketone and Deuterated 1-Phenylethanol[a]

	Intensity ratio of masses				
Hydrogen donor	93/92	104/103	122/121	123/121	194/195
$C_6H_5CH(OH)CH_3$	0.15	0.23	0.22	0.03	0.19
$C_6H_5CH(OD)CH_3$	0.30	0.40	0.39	0.08	0.37
$C_6H_5CD(OH)CH_3$	0.15	1.32	1.55	0.29	0.97
$C_6H_5CD(OD)CH_3$	0.30	1.58	1.65	0.70	1.03

[a] The 1,3-diphenylpropan-2-ols were analyzed after 30 min by GC–MS on 10% Carbowax 20M on Chromosorb W. The reaction system was 0.5 *M* dibenzyl ketone and 10^{-3} *M* $RuCl_2(PPh_3)_3$ in phenylethanol at 180°.

In contrast to the effect of tribenzylamine on reaction 3, this base, and other ones, inhibits reaction 4, even at very low concentration. Triphenylphosphine, on the other hand, has the same effect on both catalyses.

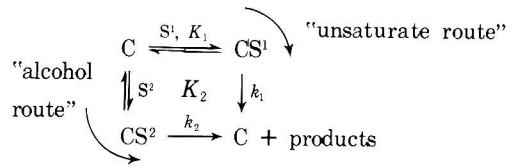
Discussion

It is obvious that both donor and acceptor are activated by the ruthenium catalyst. There rises, however, the question whether the alcohol precedes the unsaturated ketone

in coordination to the central metal atom or vice versa.

Following the mechanisms suggested for some other catalytic reactions [e.g., the homogeneous Rh(I)-catalyzed hydrogenation of olefins[15]] one might propose the formal Scheme I for the transfer hydrogenation reaction 1.

Scheme I



C, catalyst; S^1, hydrogen acceptor; S^2 hydrogen donor

The possible pathways to be considered are, thus, (a) the "unsaturate route" in which fast equilibration of the catalyst and the acceptor is followed by a slow reaction with the carbinol and (b) the "alcohol route" which requires the reversible coordination of the alcohol to the metal prior to a slow interaction of the complex, CS^2, with the acceptor. A "random mechanism" in which both routes operate simultaneously is, of course, possible as well.

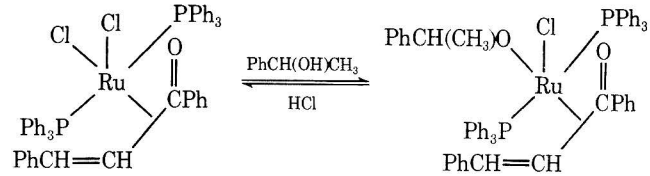
The kinetic measurements show that the catalysis follows neither a simple "alcohol route" (in which $K_2 = k_2 = 0$, and the rate law $-d[S^1]/dt = -d[S^2]/dt = k_1K_1[S^1][S^2][C]_0/(1 + K_1[S^1])$; $[C]_0$ = initial catalyst concentration), nor an isolated "unsaturate route" in which $K_1 = k_1 = 0$. The "random mechanism" for which the rate expression is $-d[S^2]/dt = (k_1K_1 + k_2)[S^1][S^2][C]_0/(1 + K_1[S^1] + K_2[S^2])$ must also be excluded on the basis of the observation that the rate dependence on the donor $[S^2]$ (in excess acceptor) is nonlinear. Further indication that the catalysis is not likely to follow the "alcohol route" or a "random mechanism" can be found in the competition experiment in which no reduction of the α-methylbenzylideneacetophenone has occurred before all the sterically unhindered chalone was consumed (cf. ref 27). In fact, the kinetic measurements can be interpreted by assuming the "unsaturate route", for which $k_2 = 0$ but $K_2 > 0$, to be the main pathway in reaction 3. The independent interaction of the catalyst with the donor, that leads to a positive value for K_2, has been demonstrated by the ability of $RuCl_2(PPh_3)_3$ to catalyze racemization,[11] H–D exchange,[11,21] ether formation,[11] and isomerization[20] in suitable carbinols even in the presence of α,β-unsaturated ketones. The dissimilarity between this suggestion and the mechanisms assigned to some other homogeneous transfer hydrogenation reactions is remarkable [cf., e.g., the recently reported reaction of cycloheptene and 2-propanol in the presence of $HRh(PPh_3)_4$[2p]].

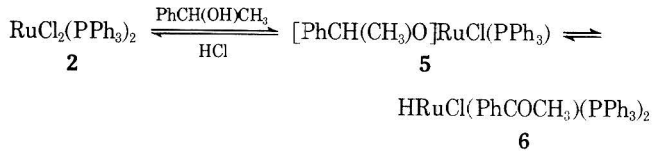
We propose, thus, reaction 1 to proceed in the following order.

A. Activation of the Catalyst. Although recent studies indicate that no more than 5% of $RuCl_2(PPh_3)_3$ (**1**) is dissociated into PPh_3 and $RuCl_2(PPh_3)_2$ (**2**) at low temperatures, we proved that above 150° dissociation is nearly complete. Under these conditions, the recombination of PPh_3 and **2** to the trisphosphine complex can be considered rather small by virtue of the relatively large amount of free phosphine needed to create a significant effect on the reaction rate. The 14-electron complex **2** forms chlorine-bridged dimers and polymers in highly concentrated solutions,[13,28] but on high dilution the monomeric species predominates (as proved by molecular weight determination) and hence the linear dependence of rate on the catalyst at least below 6×10^4 *M*.

B. Coordination and Activation of the Acceptor. As no stable ruthenium complex of α,β-unsaturated ketone could be isolated, we presume that the acceptor coordinates to the metal in the same manner as to some Pd and Pt compounds (cf., e.g., Pt complexes of mesityl oxide[29,30]). Whether the >C=C–C=O group is linked to the metal via the C=C π electrons,[31] the carbonyl bond,[19,32] or via both unsaturated functions[33] is yet uncertain. However, one can say with confidence that the adducts are unstable and decompose easily to the starting materials. The equilibrium constant K_1 is expected to be only slightly influenced by electronic variations but more severely by steric effects in the unsaturated ketone (see also ref 23).

C. Coordination of the Hydrogen Donor. The interaction of metal complexes with primary and secondary carbinols results, usually, in metal hydride formation.[34] The steps in these reactions are assumed to be conversion into a metal alkoxide complex[11,35] (rarely isolable[36]) and β-hydrogen transfer from the alkoxide ligand to the metal atom.[11,34c] Accordingly, we suggest that complex **3** formed in step B reacts with the donor to give an alkoxide **4** and a proton. This step is inhibited by acids and promoted by bases.





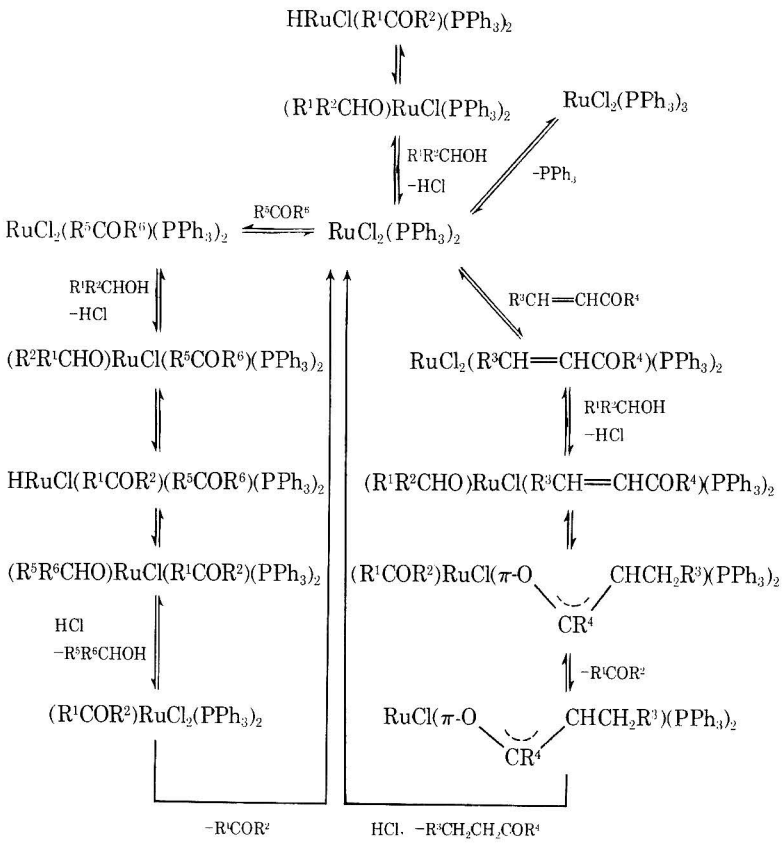
In an independent course the donor might coordinate directly to the active catalyst **2** to give alkoxide **5** which, in turn, rearranges to the pentacoordinated hydride **6**. It seems that this complex is unable to react with the acceptor to form an unfavorable heptacoordinated adduct. Therefore, **5** and **6** are not regarded as reaction intermediates in catalysis 1, but are assumed to play a part in the racemization,[11] H–D exchange,[11] ether formation,[11] and isomerization[20] of alcohols reported previously.

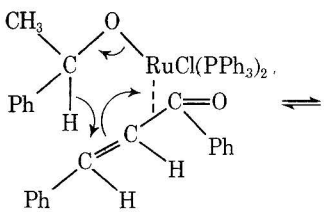
D. Hydrogen Transfer. Transformation of the alkoxide **4** to a (heptacoordinated) hydrido complex, in a similar manner as in step **5** → **6**, would be expected to be facilitated by electron-attracting substituents on the ruthenium catalyst. In fact, the experiments with $RuCl_2[(4\text{-}X\text{-}C_6H_4)_3P]_3$ proved that this is not the case and *electron-releasing* groups X increase the rate and vice versa. To rationalize our observations we assume that the β-hydrogen atom in the alkoxide moiety is transferred directly to the β carbon (as proved by deuterium labeling) in a concerted reaction. Preferential attack at the β position, due to electronic and steric effects, is the feature of many other catalytic hydrogen transfer reactions (e.g., hydrogenation of olefins by cobalt complexes[37,38]).

The kinetic isotope effect indicates that this step is rate determining in the overall reaction.

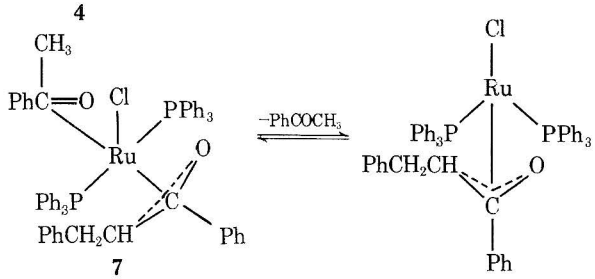
The hydride transfer yields presumably a π-oxopropenyl complex **7**.[39,40] The strong trans effect of the π-oxopropenyl ligand facilitates release of the phenethoxyl residue as acetophenone (or as the corresponding aldehyde or ketone when other carbinols are used as hydrogen donor).

Scheme II





4



7 8

E. Release of the Product. The high electron density on the π-oxopropenyl ligand increases the sensitivity to electrophilic attack of a proton, which might occur (not necessarily in acidic media[41]) either at the oxygen atom to yield an enol or at the α carbon to give immediately the saturated ketone. Since the overall reaction proved to be stereospecific, the second possibility is the one to be preferred.

The complete cycle of the $RuCl_2(PPh_3)_3$-catalyzed transfer hydrogenation of α,β-unsaturated ketones is summarized in the right wing of Scheme II.

Since under our experimental conditions $RuCl_2(PPh_3)_3$ can be assumed to dissociate almost completely, in a practically irreversible fashion, to the active catalyst **2** (that stays mostly in the monomeric form), we can apply the kinetic Scheme III for reaction 1.

Since all the reversible steps are known to play a part in some homogeneous hydrogenation and isomerization reactions at much lower temperatures, we assume fast equilibration for these steps at 180°. The rate law for the offered scheme would then be

Scheme III

$$C + S^1 \overset{K_1}{\rightleftharpoons} CS^1$$

$$CS^1 + S^2 \overset{K_2}{\rightleftharpoons} CS^1S^2$$

$$CS^1S^2 \overset{k}{\longrightarrow} C + \text{products}$$

$$C + S^2 \overset{K_3}{\rightleftharpoons} CS^2$$

C, S^1, and S^2 have the same assignments as in Scheme I

$$\text{rate} = -\frac{d[S^1]}{dt} = \frac{kK_1K_2[S^1][S^2][C]_0}{1 + K_1[S^1] + K_1K_2[S^1][S^2] + K_3[S^2]}$$

When large excess of S^1 is present (i.e., above "saturation" concentration of 0.2 *M* at which the rate becomes invariable), the rate law becomes

$$\text{rate} = \frac{kK_2[S^2][C]_0}{1 + K_2[S^2]}$$

and when S^2 is in excess (i.e., >7 *M*) the rate can be expressed as

$$\text{rate} = \frac{kK_1K_2[S^1][C]_0}{K_3 + K_1K_2[S^1]}$$

These two simplified equations represent the observed rate dependence on the acceptor and donor, respectively, as shown in Figures 2 and 3, and which are both linear in reciprocal form (Figures 7 and 8).

When excess of both acceptor and donor are used ("total saturation") the rate expression reduces to rate = $k[C]_0$

and then the magnitude of k can be obtained directly from the initial rate of the reaction.

Finally we discuss briefly the mechanism of reaction 4, in which dibenzyl ketone is reduced to 1,3-diphenylpropan-2-ol.

For the same kinetic reasons mentioned previously for reaction 1, we propose that the acceptor is the first one to be added, reversibly, to the active catalyst **2**. Support in this assumption (on a "ketone route") can be found in the work of Stephenson and Wilkinson,[42] who prepared stable Ru(II)- and Ru(III)–acetone complexes, some by using ruthenium–carbinol adducts as starting materials. The complex $(PhCH_2COCH_2Ph)RuCl_2(PPh_3)_2$ (**9**), so formed, is assumed to react with 1-phenylpropanol to give the alkoxide $[PhCH(CH_3)O]RuCl(PhCH_2COCH_2Ph)(PPh_3)_2$ (**10**) and HCl. Unlike in **4**, an α-hydrogen atom of the alkoxyl moiety might be transferred to the metal, in the rate-determining step, to give a hexacoordinated hydride, $HRuCl(PhCOCH_3)(PhCH_2COCH_2Ph)$ (**11**). This is supported by the experiments with various catalysts $RuCl_2[(4\text{-}X\text{-}C_6H_4)_3P]_3$ (Table IX), in which electron-releasing groups X proved to decrease the reaction rate and vice versa. The hydride is now expected to attack the coordinated ketone with the higher oxidation potential to give $[PhCH_2CH(CH_2Ph)O]RuCl(PhCOCH_3)(PPh_3)_2$ (**12**), which in turn can react like **8** with a proton to form 1,3-diphenylpropan-2-ol and $RuCl_2(PhCOCH_3)(PPh_3)_2$. Elimination of acetophenone from the latter results in reforming of the active catalyst **2**.

The complete cycle of reaction 2 is summarized in the left wing of Scheme II.

Experimental Section

The catalyst $RuCl_2(PPh_3)_3$ was prepared according to Stephenson and Wilkinson.[42] The substituted triarylphosphine derivatives of this complex, $RuCl_2[(4\text{-}CH_3C_6H_4)_3P]_3$, $RuCl_2[(4\text{-}CH_3OC_6H_4)_3P]_3$, $RuCl_2[(4\text{-}ClC_6H_4)_3P]_3$, and $RuCl_2[(4\text{-}FC_6H_4)_3P]_3$ were prepared as reported previously.[43]

Dichlorobis(triphenylphosphine)ruthenium polymer, $[RuCl_2(PPh_3)_2]_x$, was obtained in 70% yield by refluxing a solution of 500 mg of $RuCl_2(PPh_3)_3$ in 20 ml of peroxide-free decalin for 30 min under argon. The black solid that separated (mp 225° dec) was not identical with the brown complex reported by Poddar and Agarwala[13a] but proved to have similar catalytic activity.

Anal. Calcd for $(C_{36}H_{30}Cl_2P_2Ru)_x$: C, 62.0; H, 4.3; Cl, 10.2. Found: C, 62.3; H, 4.3; Cl, 10.3.

Dichlorocarbonylbis(triphenylphosphine)ruthenium, $RuCl_2(CO)_2(PPh_3)_2$. A solution of 100 mg of $RuCl_2(PPh_3)_3$ in 10 ml of benzyl alcohol was refluxed under argon. Upon cooling 60 mg (76%) of light yellow crystals separated: mp 160° (from benzene–hexane); $\nu_{C=O}$ (Nujul) 2000, 2070 cm^{-1}. (The NMR and ir spectra and the application of $C_6H_5CD_2OD$ proved the absence of metal-bound hydride).

Anal. Calcd for $C_{38}H_{30}Cl_2O_2P_2Ru$: C, 60.6; H, 4.0; Cl, 9.4. Found: C, 60.3; H, 4.4; Cl, 9.8.

Most carbinols and ketones were obtained from commercial sources (of highest grades available) and were freshly distilled in vacuo and degassed or recrystallyzed before use. The commercial solvents (hydrocarbons, aryl chlorides, and ethers) were purified by chromatography on alumina and distilled in vacuo. The noncommercial carbinols were prepared by the standard procedure from the corresponding esters, aldehydes, or ketones with $LiAlH_4$ ($LiAlD_4$ for deuterated compounds). Noncommercial ketones were obtained by aldol condensation of the appropriate ketones and aldehydes in basic media[44] except for 2,3-dimethyl-,[45] 3,5-diphenyl-,[46] and 3,5-di(4-chlorophenyl)cyclohex-2-enone,[47] which were prepared by other methods reported in the literature.

The products were identified by comparison of their spectral properties with those of authentic samples.

An Example of Transfer Hydrogenation of an α,β-Unsaturated Ketone. A mixture of 2.08 g (10^{-2} mol) of benzylideneacetophenone, 1.08 g (10^{-2} mol) of benzyl alcohol, and 19 mg (2×10^{-5} mol) of $RuCl_2(PPh_3)_3$ was refluxed under nitrogen for 2 hr. The catalyst was removed by flush distillation of the reaction mixture at 0.5 mm. Analysis by GC–MS (Varian 111) using both a 15% SE-30 on Chromosorb W and a 10% Carbowax 20M on Chromosorb W column indicated that 94% of the starting ketone was reduced to 3-phenylpropiophenone. The crystaline ketone of mp 72° separated on addition of ethanol to the reaction mixture.

Large-scale transfer hydrogenation of unsaturated ketones was carried out in ethylene glycol as described previously.[4]

An Example of Transfer Hydrogenation of a Saturated Ketone. A solution of 1.05 g (5×10^{-3} mol) of dibenzyl ketone and 10 mg (10^{-5} mol) of $RuCl_2(PPh_3)_3$ in 10 ml of 1-phenylethanol was heated at 180° under nitrogen for 4 hr. The mixture was flash distilled and analyzed by GC–MS on 10% Carbowax 20M on Chromosorb W. The yield of 1,3-diphenylpropan-2-ol was 93%.

The kinetic measurements were carried out in 20-ml reaction tubes equipped with gas inlets and outlets, immersed in an oil bath thermostat (accuracy ±0.2°). Samples were withdrawn and immediately frozen each 3–5 min during the first 20 min of the reaction and in intervals of 10–15 min thenceforth. GLC analysis (Packard gas chromatograph, Model 7400) was on a 1.8-m long column packed with either 3% SE-30 or 3% Carbowax 20M on Chromosorb W at 160–240° in accord with the sample injected. The initial rate was calculated in each case from the average of at least five experiments.

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Registry No.—$[RuCl_2(PPh_3)_2]_x$, 34076-51-2; $RuCl_2(CO)_2(PPh_3)_2$, 14564-35-3; benzylideneacetophenone, 94-41-7; benzyl alcohol, 100-51-6; 1-phenylethanol, 98-85-1; dibenzyl ketone, 102-04-5.

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Photochemical Reduction in the *N*-Acylketimine System

Albert Padwa* and William P. Koehn

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

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Irradiation of a series of *N*-(α-alkylbenzylidene)benzamides in hydrogen-donating solvents results in reduction of the carbon–nitrogen double bond. The photoreduction involves an electronically excited state and does not occur by the chemical sensitization path encountered with simple *N*-alkylimines. Sensitization and emission studies show that the reaction is derived from an n–π^* triplet state. The failure of the imine nitrogen to initiate Norrish type II reactions suggests that the intermolecular hydrogen abstraction by the excited *N*-acylketimine occurs on the oxygen atom of the carbonyl group rather than on the nitrogen atom of the imine chromophore. Stern–Volmer quenching plots show that the rates of hydrogen abstraction of the *N*-acylketimines are low compared with those of aryl ketones. The low quantum efficiency of the photoreduction is attributed to both a low bimolecular hydrogen abstraction rate ($k_r = 1 \times 10^3$ l. mol^{-1} sec^{-1}) and a fast rate of triplet decay.

Aryl imines are known to undergo reduction and reductive dimerization on irradiation in 2-propanol.[1-5] Although the reaction bears analogy to aryl ketone photoreduction, the available data indicate that the reaction is quite different mechanistically in that it appears not to involve the excited state of the imine as an intermediate in the reduction.[1] The reaction has been shown to proceed via an α-amino radical formed by hydrogen atom transfer to the imine from a ketyl radical.[1] The ketyl radical is derived from carbonyl compounds present in starting material as an impurity, an added sensitizer, or as a photogenerated species (see Scheme I).

Scheme I

$$Ph_2C{=}O \xrightarrow{h\nu} Ph_2C{=}O^{*1} \longrightarrow Ph_2C{=}O^{*3}$$

$$Ph_2C{=}O^{*3} + (CH_3)_2CHOH \longrightarrow (Ph)_2\dot{C}OH + (CH_3)_2\dot{C}OH$$

$$(Ph)_2\dot{C}OH + (Ph)_2C{=}NR \longrightarrow Ph_2C{=}O + (Ph)_2\dot{C}NHR$$

$$(CH_3)_2\dot{C}OH + (Ph)_2C{=}NR \longrightarrow (CH_3)_2C{=}O + (Ph)_2\dot{C}NHR$$

$$2(Ph)_2\dot{C}NHR \longrightarrow (Ph)_2C{=}NR + (Ph)_2CHNHR$$

A number of related reports have appeared in the literature showing that reactions apparently involving sensitization by benzophenone in hydrogen-donating solvents proceed, in fact, via formation of ketyl radicals.[6-10] The term "chemical sensitization" was suggested to distinguish between such cases and sensitization involving excitation-energy transfer.[2]

Recently, Okada, Nozaki, Toshima, and coworkers reported that the photoreduction of *N*-(α-phenylbenzylidene)benzamide (1) in 2-propanol proceeds via an electronically excited triplet state (i.e., intramolecular chemical sensitization), in contrast with other diarylketimine photoreductions.[11-14] Similar results were reported by Fraser-Reid and coworkers with related compounds.[15]

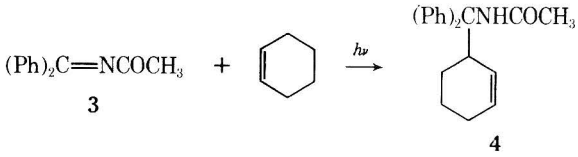
$$(Ph)_2C{=}NCOPh \xrightarrow{h\nu} [(Ph)_2C{=}NCOPh]^*$$

$$[(Ph)_2C{=}NCOPh]^* + (CH_3)_2CHOH \longrightarrow (Ph)_2C{=}N\dot{C}(OH)Ph + (CH_3)_2\dot{C}OH$$

$$2[(Ph)_2C{=}N\dot{C}(OH)Ph \longleftrightarrow (Ph)_2\dot{C}N{=}C(OH)Ph] \longrightarrow Ph_2C{=}NCOPh + Ph_2CHNHCOPh$$

1 2

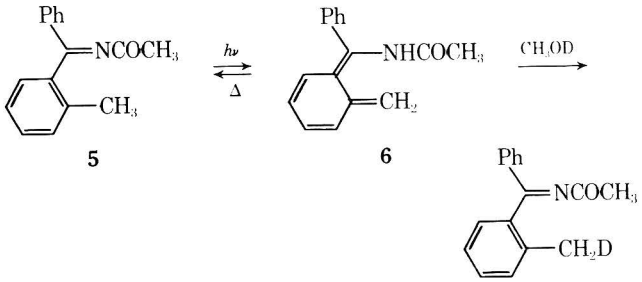
The Japanese workers also reported that the excited triplet state of *N*-acyldiphenylmethylenimine (3) can abstract the allylic hydrogens of cyclic and acyclic olefins and produce photochemical addition products (i.e., 4). The photoreduction and addition reactions were completely



3 4

quenched by piperylene and were markedly retarded by diphenyl sulfide, a good radical scavenger. The yield of photoadduct **4** was enhanced when benzophenone or acetophenone was used as a triplet sensitizer. The mechanism proposed to account for these observations involved excitation of the ketimine followed by intersystem crossing and hydrogen atom abstraction from the solvent by the triplet state.[11-13]

Further support for the involvement of the triplet state in these systems was obtained by studying the photochemistry of several *o*-alkyl aromatic imines (**5**).[14] Irradiation of **5** was reported[14] to result in an isomerization to an enamide derivative (**6**) by a path similar to that observed with the related *o*-alkylbenzophenone system.[16,17]

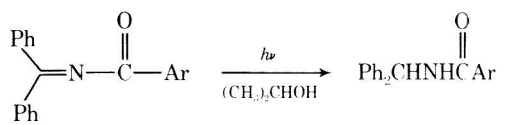


5 6

On the basis of these observations it would appear as though the mechanism for the reduction of *N*-acylimines is quite different from that followed by *N*-alkylimines. This difference is undoubtedly related to the presence of the carbonyl group in the *N*-acylimine system. These *N*-acylimines are formally aza analogs of α,β-unsaturated ketones. A comparison of the photoreduction of these compounds with the extensively studied α,β-unsaturated ketone system[18] could be of practical and theoretical interest. This comparison and our interest in the chemical consequences of electronic excitation of the C–N double bond prompted us to examine the photoreduction of a number of substituted *N*-acylimines. In this paper we wish to describe results which show that the photoreduction of the *N*-acylimine system can proceed by "chemical sensitization" and by hydrogen abstraction from the triplet state. The specific route followed appears to be a function of the substituent groups present about the 2-azaenone chromophore.

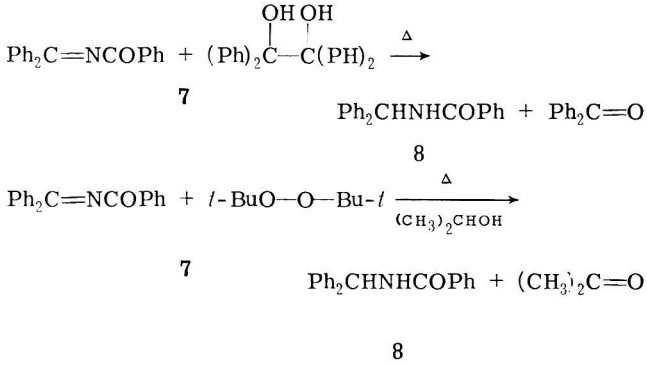
Results and Discussion

Photoreduction in the *N*-Aroyldiphenylketimine System. Irradiation of *N*-diphenylmethylenebenzamide (**7**) in 2-propanol using an internal water-cooled mercury arc lamp equipped with a Pyrex filter for 24 hr afforded *N*-benzhydrylbenzamide (**8**) and acetone in quantitative yield. Similarly, *N*-diphenylmethylene-*p*-anisamide (**9**) in 2-propanol was photoreduced to *N*-benzhydryl-*p*-methoxybenzamide (**10**). In agreement with the Japanese



7, Ar = Ph **8**, Ar = Ph
9, Ar = *p*-$OCH_3C_6H_4$ **10**, Ar = *p*-$OCH_3C_6H_4$

workers,[11] we were unable to detect any dimeric material in the reaction mixture. The quantum yield for the photoreduction of **7** in 2-propanol is extremely low (Φ ca. 10^{-6}) but increases substantially when benzophenone or acetophenone is used as a sensitizer ($\Phi \sim 2 \times 10^{-3}$). The quantum yield is also enhanced when a small amount of water is added to the reaction mixture. High-energy sensitizers such as triphenylene, that do not undergo photoreduction in alcohol, are ineffective as sensitizers. These results suggest that the triplet state of the imine is not the active hydrogen-abstracting species. That the phosphorescence of benzophenone is not appreciably quenched (EPA at 77 K) by the imine is also inconsistent with energy transfer. When an experiment was run using benzophenone ketyl radicals, generated from the thermal decomposition of benzpinacol,[19] reduction of **7** to **8** (also **9** to **10**) occurred. Similarly, thermal decomposition of di-*tert*-butyl peroxide



7 **8**

in 2-propanol in the presence of **7** afforded **8** in high yield. These observations when taken together suggest that the photoreduction of **7** in 2-propanol does not involve the excited triplet state of the imine but is brought about by one or more of the intermediates of the ketone photoreduction. The ability of piperylene and diphenyl disulfide to retard the formation of **8** (or **10**) is perfectly consistent with the "chemical sensitization" scheme outlined above (see Scheme I).

Some comment is in order concerning the low quantum efficiency of the ketone-sensitized photoreductions in 2-propanol. We have previously suggested that the lack of reactivity of the singlet excited state of the imine can be attributed to rotation about the π bond in the excited state thereby allowing for dissipation of electronic energy.[1] We have recently reported that photoisomerization about the C–N double bond can also be induced by triplet excitation.[20] This would suggest that if triplet energy transfer from benzophenone to **7** (or **9**) occurred, it would be followed by a facile photoisomerization and thereby minimize the bimolecular hydrogen abstraction from the triplet state of the imine. Alternatively, if hydrogen atom transfer from the ketyl radical to the imine were inefficient, a low quantum yield for photoreduction would result.

Photoreduction in the *N*-(α-Alkylbenzylidene)benzamide System. The above results clearly indicate that the electronically excited triplet state of *N*-diphenylmethylenebenzamide (**7**) is not involved in the photoreduction in 2-propanol. Instead, photoreduction in this solvent system occurs by "chemical sensitization". This situation does not hold, however, when cyclohexene is used as the solvent. Toshima and coworkers have presented convincing evidence demonstrating the involvement of the electronically excited triplet state of *N*-acyldiphenylmethylenimine in the photochemical addition to cyclic and acyclic olefins.[12] Also, Koch and coworkers have recently shown that the reactions of the related cyclic keto imino ether system proceed through an electronically excited state.[21] In order to probe the excited-state behavior of the *N*-aroylimine system, we have studied the photochemistry of several *N*-(alk-

ylbenzylidene)benzamides which contain a long alkyl side chain. Our expectation was that if hydrogen abstraction occurred on the nitrogen atom of the electronically excited *N*-aroylimine chromophore, then a Norrish type II reaction would occur if the side chain possessed α hydrogens. While Norrish type II photoreactions have been extensively studied for aliphatic,[22] aromatic,[22] and α,β-unsaturated ketones,[23] little is known about the Norrish type II behavior of structurally related imines. Nevertheless, there are several examples reported in the literature where γ-hydrogen transfer to excited imines occurs.[21,24,25]

Our preliminary experiments indicated that a simple straight-chain alkyl group was unsuitable, since attempts to prepare *N*-(α,*n*-butylbenzylidene)benzamide (**11**) resulted in its rearrangement to the more thermodynamically stable *N*-(1-phenylpentenyl)benzamide (**12**).[26] This difficulty could be overcome by working with systems which were disubstituted in the α position so as to preclude a 1,3-hydrogen shift. An appropriate model system which was selected for study was *N*-(*α-tert*-pentylbenzylidene)-benzamide (**13**). This *N*-acylimine could be readily prepared by treating phenylmagnesium bromide with 2,2-dimethylbutyronitrile followed by the subsequent addition of benzoyl chloride. The structure of **13** is based on analytical, infrared, ultraviolet, NMR, and mass spectral data (see Experimental Section). Irradiation of **13** in 2-propanol using an internal water-cooled mercury arc equipped with a Vycor filter for 24 hr afforded *N*-(*α-tert*-pentylbenzyl)-benzamide (**14**), mp 123–124°, as the only identifiable photoproduct. The identity of benzamide **14** was established by comparison with an authentic sample prepared from the sodium borohydride reduction of **13**. This product was also formed when the irradiation of **13** was carried out using 95% ethanol or cyclohexane as the solvent. Extended irradiation of **13** in benzene, however, resulted in the complete recovery of starting material.

The failure of **13** to form a type II product on irradiation in benzene prompted us to examine the photochemistry of *N*-[*α*-(2,2-dimethylbutyl)benzylidene]benzamide (**15**). In this case, a type II reaction would involve hydrogen transfer from a more reactive secondary position. Wagner and coworkers have previously reported a 15-fold increase in the rate of abstraction of a secondary over a primary hydrogen in the Norrish type II reaction of aromatic ketones.[27] We found, however, that when the irradiation of **15** was carried out in 2-propanol or cyclohexane, the only product formed was the corresponding reduced amine **16**.

Table I
Quantum Yields for the Photoreduction of *N*-(α-Alkylbenzylidene)benzamides[a]

Compd	Solvent	Sensitizer[b]	$\Phi^c \times 10^2$
13	2-Propanol		0.081
13	2-Propanol (95%)		0.068
13	2-Propanol	α,α-Dimethylbutryophenone	0.075
13	2-Propanol	Acetophenone	0.13
13	Cyclohexane		0.23
13	Cyclohexane	*m*-Methoxyacetophenone	0.021
15	2-Propanol		0.053
15	Cyclohexane		0.21
17	2-Propanol		0.062
17	Cyclohexane		0.40
17	Cyclohexane	*m*-Methoxyacetophenone	0.08

[a] Average of three or more determinations. [b] >95% of light being absorbed by the sensitizer. [c] Quantum yield for product formation.

We have also studied the photochemistry of *N*-(*α-tert*-pentylbenzylidene)-*p*-anisamide (**17**). The effect of placing an electron-donating group on the benzene nucleus of an aryl ketone has been independently studied by Yang[28] and Wagner.[27,29] Electron-releasing substituents were found to increase the lifetime of the triplet state and also decrease the rate constant for type II photoelimination. Wagner suggested that the inefficient hydrogen abstraction which occurs with these *p*-methoxy substituted aryl ketones actually occurs from low equilibrium populations of an upper n–π^* triplet state.[29] On the basis of his observations, we anticipated that a similar situation would exist in the *N*-acylimine system. Irradiation of **17** in cyclohexane or 2-propanol gave *N*-(*α-tert*-pentylbenzyl)-*p*-anisamide (**18**) as the only identifiable photoproduct (see Experimental Section).

Surprisingly, both the quantum yield (see Table I) and the rate constant for the photoreduction of **17** are of the same order of magnitude as those obtained with *N*-benzoylimines **13** and **15**. This result will be discussed in some detail at a later point.

We had previously observed that the quantum efficiency of the *N*-alkylimine photoreduction was markedly enhanced when 2-propanol was diluted with water.[1] This behavior was attributed to the partial hydrolysis of the imine in the aqueous solvent followed by chemical sensitization by the small amount of the carbonyl compound formed. If chemical sensitization were to play an important role in the *N*-benzoylimine system, we would expect that the addition of a small amount of water or the deliberate addition of α,α-dimethylbutyrophenone would cause an increase in the quantum efficiency of the photoreduction of **13**. As can be seen from Table I, the photoreduction of **13** was actually

less efficient in 95% 2-propanol. The fact that the reaction was not enhanced by the addition of water or 2,2-dimethylbutyrophenone provides strong evidence that these photoreductions are not proceeding via a "chemical sensitization" route.

Quantum yields for the triplet-sensitized photoreductions were also determined. Some of the data listed in Table I reflect the quantum efficiency of the photoreduction as a function of the sensitizer used. When acetophenone was employed, the quantum yield for the photoreduction of **13** was enhanced by ca. 60%. The possibility exists that both acetophenone and α,α-dimethylbutyrophenone promote the photoreduction via the chemical sensitization route. In order to avoid this complication, *m*-methyoxyacetophenone was used as a triplet sensitizer. This ketone has a quantum yield of only 0.006 for hydrogen abstraction,[28] a high intersystem crossing efficiency ($\Phi_{ISC} = 0.96$),[27] and a high triplet energy (E_T = 74 kcal/mol).[28] From the results outlined in Table I it can be seen that *m*-methoxyacetophenone was capable of promoting the photoreduction of both **13** and **17**. The quantum efficiencies of the sensitized reactions, however, were significantly reduced. Chapman and coworkers had previously reported that the quantum yield for sensitized photoreactions using *m*-methoxyacetophenone depends on the concentration of the sensitizer.[30] His results showed that high concentrations of sensitizer markedly diminished the quantum efficiency of the photoreaction. This observation was attributed to self-quenching of the sensitizer via excimer formation. Since it was necessary to use high concentrations of *m*-methoxyacetophenone (0.1–0.3 *M*) to assure complete absorption of the incident light (>95%), it would appear as though self-quenching of the sensitizer also occurs with the *N*-acylimine system. This would account for the diminished quantum yields in the sensitized experiments using *m*-methoxyacetophenone. At any rate, the data clearly implicate the involvement of a triplet state in the photoreduction of *N*-acylimines **13, 15,** and **17.**

Further support for an electronically excited triplet state in these photoreductions was obtained from quenching and emission studies. *cis*-Piperylene and naphthalene were employed as photochemical quenchers. Over the concentration range, 0.0001–0.001 *M cis*-piperylene, the quantum efficiencies for the photoreduction of **13, 15,** and **17** were significantly diminished. The lowest lying triplet states of *N*-benzoylimines **13** and **15** were demonstrated to be n–π^* as evidenced from their phosphorescence emission spectra in a methanol–ethanol glass (4:1) at 77 K. We note that the 0–0 bands of **13** and **15** correspond to a triplet energy of 68 kcal and the vibrational spacing between the 0–0 and 0–1 band corresponds to 1550 cm^{-1}. The 77 K lifetimes of both imines were determined to be 6 msec, also consonant with an n–π^* assignment. Surprisingly, the triplet excitation energy of *p*-anisamide **17** was found to have a value of 68 kcal, although in this case the vibrational spacing between the 0–0 and 0–1 band was 1100 cm^{-1} and the triplet lifetime was 17 msec. The longer lifetime and smaller vibrational spacing found with **17** would tend to indicate that this imine has some π–π^* character mixed in with the n–π^* state.[31,32] Wagner had previously noted that the intermediate lifetimes and other phosphorescence properties of a number of para-substituted acetophenones can be attributed to strong mixing of n–π^* and π–π^* triplets.[29] He pointed out that mixed triplet states may be close enough energetically to equilibrate before emitting and that, although the major phosphorescence component arises from both states, it occurs principally from the faster emitting n–π^* state. This situation may also obtain for *p*-anisamide **17.**

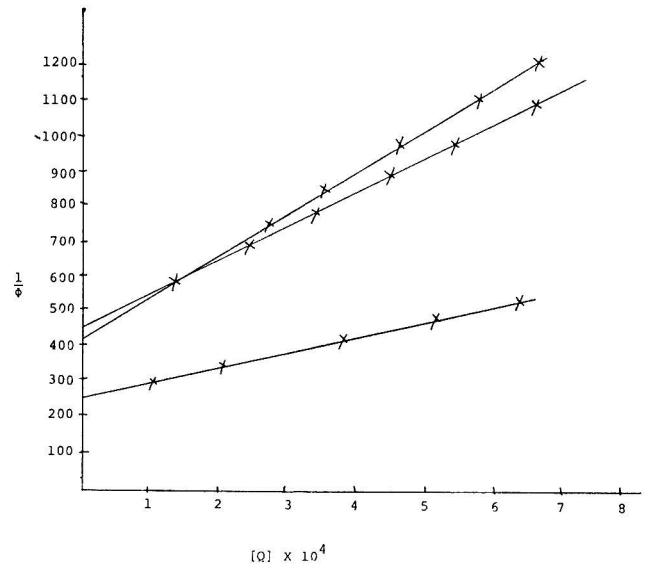


Figure 1. Stern–Volmer plot for the photoreduction of *N*-acylimines **13, 15,** and **17** in cyclohexane.

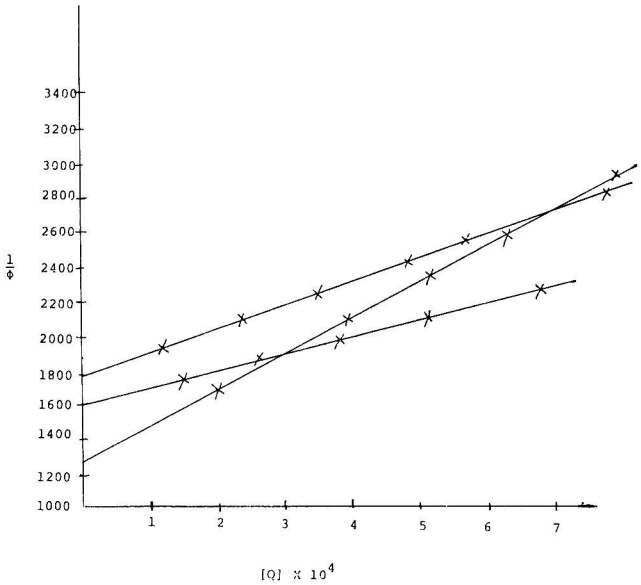


Figure 2. Stern–Volmer plot for the photoreduction of *N*-acylimines **13, 15,** and **17** in 2-propanol.

The quantum yields for the photoreduction of *N*-acylimines **13, 15,** and **17** are considerably smaller than the values obtained for typical aryl ketones.[33] One possibility to account for the low efficiency of the *N*-acylimine system may be related to some molecular feature of the molecule which retards formation of the diradical and allows direct radiationless decay to compete with chemical reaction of the triplet. In order to determine the rates of hydrogen abstraction and radiationless decay we have studied the variation of the quantum yield for photoreduction vs. quencher concentration. Figures 1 and 2 represent plots of the reciprocal of the quantum yield for product formation against piperylene concentration in both cyclohexane and 2-propanol. The Stern–Volmer formulation for quenching a bimolecular hydrogen abstraction of an excited triplet state (rate constant k_r) results in the following expression

$$\frac{1}{\Phi} = \frac{1}{\phi_{ISC}}\left[1 + \frac{k_d}{k_r[RH]} + \frac{k_q[Q]}{k_r[RH]}\right]$$

where ϕ_{ISC} is the intersystem crossing efficiency. The slope of the plot gives $(1/\phi_{ISC})(k_q/k_r[RH])$ and the intercept

Table II
Stern–Volmer Kinetic Data for the Photoreduction of *N*-Acylimines 13, 15, and 17[a]

Compd	Solvent	Φ_{ISC}	Intercept	Slope × 10^6	$k_r \times 10^3$	$k_d \times 10^6$
13	Cyclohexane[b]	0.21	440	1.17	4.64	4.06
13	2-Propanol	0.23	1260	2.16	0.76	2.62
15	Cyclohexane	0.31	460	0.88	4.23	5.67
15	2-Propanol	0.32	1890	1.27	0.88	6.67
17	Cyclohexane	0.31	250	0.37	9.97	7.40
17	2-Propanol	0.33	1600	0.95	1.16	7.49

[a] 2537-Å light. [b] k_q (cyclohexane) = 1.1×10^{10} l. mol^{-1} sec^{-1}. S. L. Murov, "Handbook of Photochemistry", Marcel Dekker, New York, N.Y., 1973, p 55.

gives $(1/\phi_{ISC})(1 + k_d/k_r[RH])$. The fact that *cis*-piperylene is isomerized to *trans*-piperylene in the presence of excited *N*-acylimine clearly indicates that **13, 15,** and **17** do in fact intersystem cross. The intersystem crossing efficiency (ϕ_{ISC}) of each of the three *N*-acylimines was independently determined according to the procedure of Lamola and Hammond[34] and is summarized in Table II. Quenching of the triplet state of the *N*-acylimines will be diffusion controlled since the triplet excitation level of all three imines is 68 kcal/mol. From the observed slopes of the Stern–Volmer plots and using $k_q = 5 \times 10^9$ l. mol^{-1} sec^{-1},[35] the values of k_r can be determined (see Table II). Knowing k_r, ϕ_{ISC}, and the intercept we can determine k_d (unimolecular rate of triplet decay to ground state).

The bimolecular rate constant for hydrogen abstraction in 2-propanol by the *N*-acylimine triplet is approximately 1×10^3 l. mol^{-1} sec^{-1}. This bimolecular rate of hydrogen abstraction is quite low compared to the $k_h^{bi} = 4 \times 10^5$ l. mol^{-1} sec^{-1} reported[36] for acetophenone triplet in 2-propanol and the $k_h^{bi} = 6 \times 10^5$ l. mol^{-1} sec^{-1} found[36] for benzophenone triplet in the same solvent. We can see that the rate of hydrogen abstraction is of the order of 100-fold smaller for these *N*-acylimines than for the aromatic ketones. It should be noted, however, that the bimolecular rate constant and quantum efficiency of the photoreduction are comparable to the values reported for α,β-unsaturated ketones (i.e., $\Phi \sim 0.003$ and $k_h^{bi} = 3 \times 10^3$ l. mol^{-1} sec^{-1}).[37,38] Another interesting facet is the rapid rate constant of unimolecular decay of the *N*-acylimine triplet, $k_d \sim (2.6\text{–}7.5) \times 10^6$ sec^{-1}. This is faster than the comparable decay rate constants of acetophenone and benzophenone, which are of the order of 10^5 sec^{-1}.[36,39,40]

Considerable information has now been accumulated about the photochemical reduction of *N*-(α-alkylbenzylidene)benzamides. The more readily derived facts about the photoreduction are the following. (a) The photoreduction of the *N*-acylimine system proceeds from an electronically excited state and does not occur by the chemical sensitization path encountered with simple *N*-alkylimines.[1-4] (b) The quantum efficiencies and rates of hydrogen abstraction are low compared to arylketone photoreductions but are on the same order of magnitude as α,β-unsaturated ketone photoreductions. (c) Sensitization and emission studies show that the photoreduction is derived from an $n\text{–}\pi^*$ triplet state. (d) The absence of Norrish type II products indicates that hydrogen abstraction by the excited *N*-acylimine occurs on the oxygen atom of the carbonyl group rather than on the nitrogen atom of the imine chromophore. (e) The inefficiency of the photoreduction can be attributed to an inherently small bimolecular hydrogen abstraction rate as well as a rapid triplet degradation path. Syn–anti isomerization about the C–N double bond provides an attractive rationale to account for the ease of triplet decay as well as the low intersystem crossing of the excited singlet state.

Two additional points merit some comment. One has to do with the fact that the photoreduction of *N*-diphenylmethylenebenzamide (**7**) in 2-propanol proceeds via the chemical sensitization path. It would appear as though the hydrolytic or photooxidative generation of benzophenone in this solvent system is relatively fast. The lack of reactivity of the excited state of **7** in 2-propanol suggests that the triplet state undergoes an extremely efficient nonradiative decay to ground state, thereby precluding hydrogen abstraction and allowing the benzophenone-induced "chemical sensitization" path to predominate. Another point worth noting is that the rate of hydrogen abstraction of *N*-(α-*tert*-pentylbenzylidene)-*p*-anisamide (**17**) is comparable to the rate observed with the related *N*-benzoylimine system (i.e., **13** or **15**). This observation indicates that any effect the *p*-methoxy group may have in stabilizing the $\pi\text{–}\pi^*$ character of the excited triplet state of the ketimine is small when compared to the effect it has on arylketone excited states. The reason for this is not at all clear and further work needs to be done before an adequate explanation can be offered.

Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a Jeol MH-100 spectrometer.

Attempted Synthesis of *N*-(α-*n*-Butylbenzylidene)benzamide. To a Grignard solution of *n*-butylmagnesium bromide (prepared from 3.6 g of magnesium turnings and 20.5 g of *n*-butyl bromide in 300 ml of ether) was added 15.4 g of benzonitrile in 30 ml of ether. The mixture was heated at reflux for 15 min, cooled to room temperature, and then quenched with 21 g of benzoyl chloride in 30 ml of ether. The resulting mixture was heated at reflux for 15 min and then decomposed with 30 ml of a saturated ammonium chloride solution. The ether layer was separated, washed with 30 ml of water, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure left a solid which was identified as *N*-(1-phenylpentenyl)benzamide (**12**) on the basis of its physical data: ir (KBr) 2.90, 6.01, 6.41, 6.95, 7.15, 7.60, 7.80, 8.51, 8.95, 9.42, 9.80, 10.81, 12.45, and 14.20 μ; NMR (CCl_4) δ 7.1–7.8 (m, 11 H), 5.95 (t, 1 H), 2.15 (m, 2 H), 1.42 (m, 2 H), and 0.90 (t, 3 H).

Preparation of *N*-Diphenylmethylene-*p*-anisamide. A solution containing 39.2 g of bromobenzene in 350 ml of ether was added to a three-neck flask which contained 6.6 g of magnesium turnings in 25 ml of ether. After heating at reflux for 2 hr, a solution containing 23.7 g of benzonitrile in 30 ml of anhydrous ether was added to the above mixture. The mixture was heated at reflux for 30 min, after which time it was quenched with 36 g of *p*-anisoyl chloride in 30 ml of ether. The solution was heated to reflux for an additional 30 min and was then decomposed with 250 ml of a saturated ammonium chloride solution. The ethereal solution was separated and dried over magnesium sulfate. Evaporation of the solvent left an oil which was recrystallized from aqueous methanol to give 22 g of *N*-diphenylmethylene-*p*-anisamide (**9**) as a white solid: mp 157–159°; ir (KBr) 6.01, 7.10, 8.65, 9.25, 9.75, 9.95, 10.40, 10.51,

10.85, 11.70, 12.21, 12.70, 13.15, and 14.35 μ; NMR ($CDCl_3$) δ 7.8 (d, 2 H, J = 8.5 Hz), 6.8 (d, 2 H, J = 8.5 Hz), 7.40 (m, 5 H), 3.72 (s, 3 H); uv (95% ethanol) 275 nm (ε 22,000); MS m/e 285, 180, 135, 105, and 78 (base).

Preparation of N-(α-tert-Pentylbenzylidene)benzamide (13). A solution containing 5.31 g of bromobenzene in 40 ml of ether was added to a three-neck flask which contained 0.825 g of magnesium turnings in 5 ml of ether. After heating at reflux for 1 hr, a solution containing 3.0 g of 2,2-dimethylbutyronitrile[41] in 20 ml of benzene was added to the solution. The mixture was heated at reflux for 5 hr and stirred at room temperature for an additional 12 hr, after which time it was quenched with 3.66 ml of benzoyl chloride in 30 ml of ether. After heating the mixture at reflux for 4 hr, it was cooled and quenched with 30 ml of a saturated ammonium chloride solution. The aqueous layer was extracted with 50 ml of ether and the combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a yellow oil. Recrystallization of the oil from ether–pentane gave 2.7 g of N-(α-tert-pentylbenzylidene)benzamide (**13**) as a white solid: mp 51–52°; ir (KBr) 3.40, 6.01, 6.22, 9.75, 9.95, 10.20, 10.65, 13.15, 13.80, 14.25, and 14.50 μ; uv (cyclohexane) 237 nm (ε 12,800), 270 (1280), 300 (360), and 320 (225); NMR ($CDCl_3$) δ 7.4 (m, 10 H), 1.72 (2 H, q, J = 8.0 Hz), 1.27 (6 H, s), 1.07 (3 H, t, J = 8.0 Hz); m/e 279 (M^+), 251, 236, 167, 160, 105 (base), 91, and 77.

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.77; H, 7.66; N, 4.94.

Preparation of N-[α-(1,1-Dimethylbutyl)benzylidene]-benzamide (15). A solution containing 2.75 g of bromobenzene in 40 ml of anhydrous ether was added to a three-neck flask which contained 0.425 g of magnesium turnings in 5 ml of ether. After heating at reflux for 2 hr, a solution containing 1.75 g of 2,2-dimethylvaleronitrile[42] in 20 ml of benzene was added to the solution. The above mixture was heated at reflux for 5 hr and stirred at room temperature for an additional 12 hr, and then quenched with 1.8 ml of benzoyl chloride in 15 ml of ether. After heating the mixture at reflux for 4 hr, it was cooled and quenched with 30 ml of a saturated ammonium chloride solution. The aqueous layer was extracted with ether and the combined ethereal extracts were dried over magnesium sulfate and concentrated under reduced pressure to give 3.54 g of an orange oil. This crude oil was subjected to thick layer chromatography using a 20% ether–pentane mixture as the eluent. The major component (R_f 0.43) (60%) was a clear oil whose structure was assigned as N-[α-(1,1-dimethylbutyl)benzylidene]-benzamide (**15**) on the basis of its spectral data: ir (neat) 3.25, 5.95, 6.05, 6.22, 9.45, 10.15, 10.45, 10.60, 10.90, 11.91, 12.22, 13.05, 13.80, and 14.40 μ; NMR ($CDCl_3$) δ 6.9–7.8 (m, 10 H), 1.58 (m, 4 H), 1.24 (s, 6 H), and 0.92 (m, 3 H); uv (cyclohexane) 237 nm (ε 14,400), 285, (1130), 295 (500), 305 (415), 320 (280); MS m/e 293 (M^+), 251, 236, 182, 146, 105 (base), 91, and 77.

Preparation of N-(α-tert-Pentylbenzylidene)-p-anisamide (17). A solution containing 7.1 g of bromobenzene in 40 ml of ether was added to a three-neck flask which contained 1.1 g of magnesium turnings in 10 ml of ether. After heating at reflux for 1 hr, a solution containing 4.0 g of 2,2-dimethylbutyronitrile[41] in 40 ml of benzene was added to the solution. The above mixture was heated at reflux for 4 hr and stirred for an additional 12 hr at room temperature and then quenched with 3.72 g of p-anisoyl chloride in 30 ml of ether. After heating the mixture for 4 hr, it was cooled and quenched with 30 ml of a saturated ammonium chloride solution. The aqueous layer was extracted with ether and the combined ethereal extracts were dried over magnesium sulfate and concentrated under reduced pressure to give 7.4 g of an orange oil. The crude oil was purified by thick layer chromatography using a 50% ether–pentane mixture as the eluent. The major component of the mixture (R_f 0.3) (60%) was a clear oil whose structure was assigned as N-(α-tert-pentylbenzylidene)-p-anisamide (**17**) on the basis of its spectral data: ir (neat) 3.30, 5.95, 6.01, 7.90, 8.51, 9.02, 9.31, 9.70, 9.93, 10.15, 11.02, 11.71, 12.01, 12.60, 12.95, 13.52, and 14.25 μ; NMR ($CDCl_3$) δ 7.45–6.90 (9 H, m), 3.68 (3 H, s), 1.24 (6 H, s), 1.68 (2 H, q J = 7.6 Hz), 1.02 (3 H, t, J = 7.6 Hz); uv (cyclohexane) 215 nm (ε 28,400) and 262 (19,000); MS m/e 176, 105 (base), 91, and 77.

Irradiation of N-(α-tert-Pentylbenzylidene)benzamide. A solution containing 347 mg of N-(α-tert-pentylbenzylidene)benzamide (**13**) in 150 ml of cyclohexane was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a Vycor filter for 10 hr. Removal of the solvent left a yellow oil which was purified by thick layer chromatography. The major band isolated from the thick layer plate using a 50% ether–pentane mixture as the eluent (R_f 0.5) was a white solid, mp 123–124°, whose structure was assigned as N-(α-tert-pentylbenzyl)benzamide (**14**) on the basis of the following data: ir (KBr) 2.90, 3.40, 6.11, 6.35, 9.2, 9.35, 9.70, 10.81, 11.35, 12.50, 12.96, 13.70, 14.23, and 14.70 μ; NMR ($CDCl_3$) δ 7.65–7.20 (m, 10 H), 5.00 (d, 1 H, J = 9.2 Hz), 1.36 (2 H, d, J = 7.6 Hz), 6.65 (1 H, d, J = 9.2 Hz), 0.96 (6 H, s), 0.90 (3 H, t, J = 7.6 Hz); MS m/e 281 (M^+), 211, 105 (base), 91, and 77.

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.12; H, 8.17; N, 4.77.

An authentic sample of N-(α-tert-pentylbenzyl)benzamide (**14**) was independently prepared by the sodium borohydride reduction of N-(α-tert-pentylbenzylidene)benzamide (**13**). To a solution containing 300 mg of **13** in 25 ml of 95% ethanol was added 124 mg of sodium borohydride. The mixture was stirred for 12 hr at room temperature and the solvent was removed under reduced pressure. The residual oil was taken up in ether and washed with a 10% hydrochloric acid solution followed by water. The ethereal layer was dried over magnesium sulfate and the ether was removed under reduced pressure to give 254 mg of a white solid, mp 123–124°, whose physical properties were identical in every detail with those of the sample of N-(α-tert-pentylbenzyl)benzamide isolated from the photolysis of **13**.

Irradiation of N-[α-(1,1-Dimethylbutyl)benzylidene]benzamide. A solution containing 200 mg of N-[α-(1,1-dimethylbutyl)benzylidene]benzamide (**15**) in 150 ml of 2-propanol was irradiated under an argon atmosphere using a 450-W Hanovia lamp equipped with a Vycor filter for 12 hr. Removal of the solvent left a pale yellow oil which was purified by thick layer chromatography. The major component (60%) (R_f 0.47) was a white solid, mp 147–148°, whose structure was assigned as N-[α-(1,1-dimethylbutyl)]benzamide (**16**) on the basis of the following data: ir (KBr) 2.90, 6.07, 6.72, 7.20, 7.40, 8.75, 9.65, 10.81, 11.30, 12.45, 13.51, 14.15, and 14.55 μ; NMR ($CDCl_3$) δ 7.75–7.30 (10 H, m), 6.78 (1 H, d, J = 9.2 Hz), 5.08 (1 H, d, J = 9.2 Hz), 1.31 (4 H, m), 0.94 (6 H, s), and 0.88 (3 H, t, J = 2 Hz); MS m/e 295 (M^+), 211, 105 (base), 91, and 77.

Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.72. Found: C, 81.29; H, 8.60; N, 4.72.

An authentic sample of N-(α-(1,1-dimethylbutyl)benzyl)benzamide was independently prepared by the sodium borohydride reduction of **15**. To a solution containing 390 mg of **15** in 25 ml of 95% ethanol was added 165 mg of sodium borohydride. The mixture was stirred for 12 hr at room temperature and the solvent was removed under reduced pressure. The residual oil was taken up in ether and washed with a 10% hydrochloric acid solution followed by water. The ethereal solution was dried over magnesium sulfate and the ether was removed under reduced pressure to give 200 mg of a white solid, mp 147–148°, whose physical properties were identical in every detail with those of the sample of N-[α-(1,1-dimethylbutyl)benzyl]benzamide isolated from the irradiation of **15**.

Irradiation of N-(α-tert-Pentylbenzylidene)-p-anisamide (17). A solution containing 150 mg of N-(α-tert-pentylbenzylidene)-p-anisamide in 200 ml of cyclohexane was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a Vycor filter for 12 hr. Removal of the solvent left a pale yellow oil which was purified by thick layer chromatography. The major photoproduct was a white, crystalline solid, mp 118–120°, whose structure was assigned as N-(α-tert-pentylbenzyl)-p-anisamide (**18**) on the basis of the following data: ir (KBr) 3.01, 3.36, 6.10, 7.35, 7.70, 8.51, 9.02, 9.46, 9.72, 11.85, 13.11, 13.90, and 14.30 μ; NMR ($CDCl_3$) δ 7.68 (2 H, d, J = 8.0 Hz), 6.82 (2 H, d, J = 8.0 Hz), 7.24 (5 H, s), 6.64 (1 H, d, J = 9.2 Hz), 5.04 (1, H, d, J = 9.2 Hz), 3.76 (3 H, s), 1.36 (2 H, q, J = 7.6 Hz), 0.94 (6 H, s), and 0.86 (3 H, t, J = 7.6 Hz); uv (95% ethanol) 252 nm (ε 14,500); MS m/e 309, 281, 266, 224, 196, 135 (base), and 107.

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 76.85; H, 8.07; N, 4.15.

An authentic sample of N-(α-tert-pentylbenzyl)-p-anisamide was prepared by the sodium hydride reduction of N-(α-tert-pentylbenzylidene)-p-anisamide using the procedure outlined above for the reduction of N-(α-tert-pentylbenzylidene)benzamide (**15**). The white solid obtained from the borohydride reduction of **17**, mp 118–120°, was identical in every detail with the sample of **18** isolated from the irradiation of N-(α-tert-pentylbenzylidene)benzamide (**17**).

Quantum Yield Determinations. Solutions were prepared in various solvents as described in the Results and Discussion, and 3.0 ml of each was placed in separate culture tubes (13 × 100 mm). Each sample was degassed to 0.005 mm and sealed in vacuo. In a given run all tubes were irradiated in parallel for the same length of time in a merry-go-round apparatus which assured that each sample absorbed the same intensity of light. Cyclopentanone solu-

tions were used as the chemical actinometer for which a quantum yield of 0.38 was used[43] giving a reproducible light intensity of 2.10×10^{16} quanta sec^{-1}. Analyses were performed on a Hewlett-Packard Model 5750 gas chromatograph using a 10% FS-1265 Diasaport S column at 210–235.[6] The mole ratio:area ratio response of the instrument was calibrated for each aroylimine and internal standard used, so that yields of product could be measured accurately. The conversions were run to 10% or less. The mass balance in these runs were generally better than 95%.

Emission Studies. The emission spectra were made on an Aminco-Bowman spectrophotofluorometer equipped with a phosphoroscope and transmission attachments. The spectrophotofluorometer was equipped with a 1P21 photomultiplier and a high-pressure xenon lamp, as supplied by the manufacturer. The emission spectra were measured in a methanol–ethanol (4:1) or methylcyclohexane glass. The solvent was checked for emission each time a spectra was recorded. No interference due to solvent was found at any time. All compounds having short radiative lifetimes were measured by photographing the decay curve on an oscillograph. The chopper speed was adjusted manually to obtain the decay curve. The logarithmic intensities of the decay curve were plotted vs. time and the slope of the line at a logarithmic value of 2.303 gave the mean lifetime (τ_0).

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Registry No.—**9**, 36728-20-8; **12**, 55030-00-7; **13**, 55030-01-8; **14**, 55030-02-9; **15**, 55030-03-0; **16**, 55030-04-1; **17**, 55030-05-2; **18**, 55030-06-3; *n*-butyl bromide, 109-65-9; benzonitrile, 100-47-0; benzoyl chloride, 98-88-4; bromobenzene, 108-86-1; 2,2-dimethylbutyronitrile, 20654-46-0; 2,2-dimethylvaleronitrile, 20654-47-1; *p*-anisoyl chloride, 100-07-2.

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A Convenient Synthesis of Protiated and Specifically Deuterated Secondary Azoalkanes

P. L. Grizzle,[1a] D. W. Miller,[1b] and S. E. Scheppele*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

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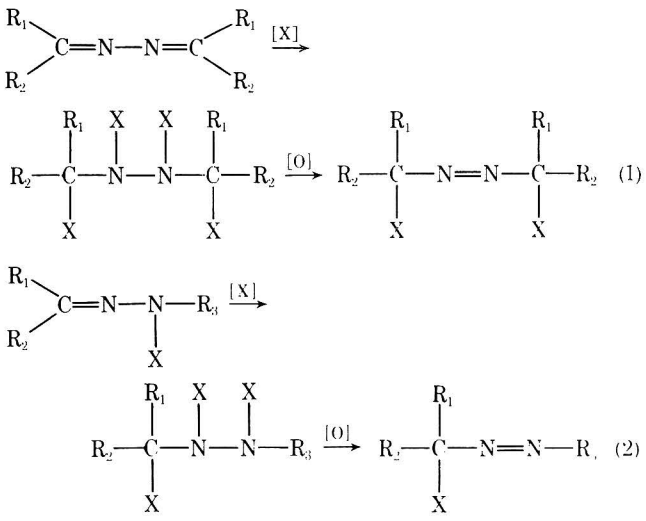
A convenient synthesis of secondary azo compounds is reported. The method involves addition of chlorine to the azine or hydrazone in CH_2Cl_2 followed by reduction of the dichloro- or chloroazoalkane with $LiAlH_4$ or $LiAlD_4$ in ether. The preparation of a variety of symmetrical secondary azoalkanes demonstrates the applicability of the technique. The procedure is applicable to the synthesis of (*sec*-alkylazo)alkanes and presumably of (*sec*-alkylazo)-2,4,6-trichlorobenzenes. The isotope purity of the azoalkane is fixed by that of the azine or hydrazone precursor and of the $LiAlD_4$.

Secondary deuterium isotope effects[2] in and the rates[3] of thermolysis of secondary azoalkanes have been extensively utilized in investigations of the mechanism of azo compound pyrolysis and of the effect of substituents on the energetics of free-radical formation. We report a convenient synthesis of secondary azoalkanes and their specifically deuterated congeners possessing essentially the maximum number of atoms of deuterium.

The classical method (Scheme I) for the synthesis of symmetrical (eq 1) or unsymmetrical (eq 2) secondary azoalkanes involves catalytic reduction of the corresponding azine or hydrazone to the hydrazine followed by oxidation;

Scheme I



X = H or D

usual oxidizing reagents are yellow mercuric oxide,[2a,f,g,3c,i,4] hydrogen peroxide,[3b,c,5] and cupric chloride.[3i]

However, a number of complications have been observed with Scheme I. Rather vigorous conditions have been required for the reduction of some azines to the hydrazines,[3b,c,4] e.g., ring-substituted acetophenone azines.[3b,4] Reduction of *tert*-butyl phenyl ketazine (**1**) in ethanol with Pd at room temperature gave only hydrazone; reduction of the hydrazone in glacial acetic acid yielded both the hydrazine and 2,2-dimethyl-1-phenylpropylamine. All attempts to reduce 2,2-dimethylpropiophenone methylhydrazone (**2**) and phenylhydrazone (**3**) failed. Similarly, low-pressure hydrogenation of benzophenone phenylhydrazone was unsuccessful.[3d] Difficulties have also been encountered with the oxidation step in reaction rate and product yield.[6]

Scheme I imposes limitations on the synthesis of specifically deuterated azo compounds. Generally some fraction of the sample is not specifically labeled because some exchange of aliphatic protium (deuterium) normally accompanies reduction with $D_2(H_2)$;[2a,c,d,g,i] exchange of aromatic protium (deuterium) in the reduction is usually negligible.[2a,c,d,g,i,j,7] Furthermore, in catalytic deuteration the number of atoms of D introduced is variable and less than the maximum.[2a,c,g,h,j] This result presumably reflects catalytic exchange between the deuterium gas and hydroxylic protium; water present in the solvent or absorbed on the walls of the hydrogenation vessel and exchangeable protium in the solvent constitute sources of the latter.

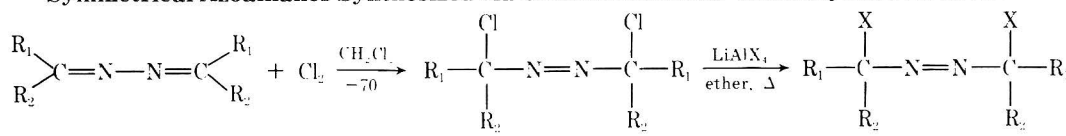
Lithium aluminum hydride and deuteride are ideal reagents to obviate problems in the reduction step of Scheme I. Although some success has been realized in the reduction of hydrazones (eq 2) with these reagents,[2b,3d] the $LiAlH_4$ reduction of azines to hydrazines (eq 1) has been remarkably unsuccessful[3c,8] except in the case of simple aliphatic azines.[9]

Consequently, a chlorine addition–metal hydride reduction method was developed. The general reaction scheme and the azoalkanes so prepared are given in Table I. The addition–reduction method bypasses the oxidation step in Scheme I and incorporates (a) the desirable properties of $LiAlH_4$ ($LiAlD_4$), (b) the propensity of ketazines to undergo 1,4 addition of Cl_2 to form 1,1′-dichloroazoalkanes,[10] and (c) the facileness with which the latter undergo nucleophilic substitution.[10b,c,11] Azine and excess Cl_2 were combined in CH_2Cl_2, usually at −70°. After removal of the CH_2Cl_2 the 1,1′-dichloroazoalkane, depending upon its stability, was either purified before reaction with the metal hydride or immediately treated with the hydride in refluxing diethyl ether. The general utility of this approach is demonstrated by the variety of azines which were converted to the corresponding azoalkanes; see Table I.

The structures of 1,1′-dichloro-1,1′-diphenylazobutane and 1,1′-dichloro-1,1′,3,3,3′,3′-hexaphenylazopropane were confirmed by NMR and MS; their reduction to **9** and **10** also provides confirmation of structure.

As reported[10d] **1** smoothly added Cl_2 (3 hr) to give 1,1′-dichloro-2,2,2′,2′-tetramethyl-1,1′-diphenylazopropane (**13**). In contrast to the reaction of **1** with H_2/Pd (see eq 1), reaction of **13** with $LiAlH_4$ ($LiAlD_4$) for 4 hr gave **11** (**12**). 4-Bromoacetophenone azine (**14**) and 3,3-diphenylpropiophenone azine (**15**) were smoothly and rapidly converted to **5** and **10** analogously. It is noteworthy that **5** could not be

Table I
Symmetrical Azoalkanes Synthesized via Chlorine Addition–Metal Hydride Reduction



X = H or D

Compd	X	R_1	R_2	Mp or bp, °C (mm)[a]	Atoms of D	Yield[b]
3[c]	H	CH_3	C_6H_5	72–73		52
4	D	CH_3	C_6H_5	72–73	1.960 ± 0.002[d]	64
5[e]	H	CH_3	*p*-Br-C_6H_4	107.5–108		41
6[f]	H	CH_3	*p*-CH_3-C_6H_4	78–79		48
7[g]	H	CH_3	2-$C_{10}H_7$	144–144.5		58
8[h]	H	CH_3	C_2H_5	48–49 (25)		63
9[i]	H	C_3H_7	C_6H_5	60–61		42
10[j]	H	$(C_6H_5)_2CHCH_2$	C_6H_5	146.5–147.5		60
11[k]	H	*i*-C_4H_9	C_6H_5	155.5–156.5		61
12	D	*i*-C_4H_9	C_6H_5	156–156.5	1.998 ± 0.003[d]	63

[a] Melting points and boiling points are not corrected. [b] Yield based on azine. [c] W. A. Schulze and H. L. Lochte, *J. Am. Chem. Soc.*, **48**, 1030 (1926). [d] Determined by duplicate combustion analysis; uncertainty is average deviation. [e] Anal. Calcd for $C_{16}H_{16}N_2Br_2$: C, 48.51; H, 4.07; N, 7.07; Br, 40.34. Found: C, 48.61; H, 4.11; N, 7.13; Br, 40.32. [f] Reference 3b. [g] Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.22; H, 6.74; N, 8.06. [h] Reference 3h. [i] Reference 2j. [j] Anal. Calcd for $C_{42}H_{38}N_2$: C, 88.38; H, 6.71; N, 4.91. Found: C, 87.94; H, 6.60; N, 5.38. [k] Anal. Calcd for $C_{22}H_{30}N_2$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.81; H, 9.07; N, 9.06.

prepared via eq 1 because attempts to reduce **14** were unsuccessful. Furthermore, in the synthesis of **10** via eq 1, low-pressure hydrogenation (Pd to azine ratio in grams was 3:1) required from 15 to 48 hr depending upon the solvent, and oxidation of the hydrazine with yellow mercuric oxide required 24 hr. Pure **7** was easily obtained via chlorine addition–metal hydride reduction but not via eq 1. The low-pressure catalytic hydrogenation of methyl 2-naphthyl ketazine continued after uptake of 2 mol of H_2 per mole of azine; one or more of the double bonds in the 2-naphthyl moiety evidently underwent reduction. The applicability of the chlorine addition–metal hydride reduction method to the preparation of aliphatic secondary azoalkanes was demonstrated by the conversion of 2-butanone azine to **8.**

If substitution of Cl_2 competed appreciably with its addition, the chlorine addition–metal hydride reduction method would not be a satisfactory route to deuterated azo compounds because $LiAlD_4$ cleavage of carbon–chlorine bonds other than the C-1–Cl and C-1′–Cl bonds would result in substitution of deuterium for protium. Similarily, in the conversion of deuterated azines to the corresponding azo compounds, use of $LiAlH_4$ would result in substitution of protium for deuterium. The hydrogenolysis of bonds linking chlorine to an aromatic ring with metal hydride would not be expected.[12]

The following evidence reveals that such substitution is negligible. The chemical shifts observed in and the proton ratios obtained upon integration of the NMR spectra of the chloroazoalkanes were consistent with the presence of chlorine only at C-1 and C-1′. Mass spectra were obtained for the chloroazoalkane precursors to **3** (**4**), **6, 7, 9,** and **10.** These spectra were characterized by ions formally derived from formation and subsequent fragmentation of the substituted alkyl radicals from C–N bond homolysis. Neither the ion intensities nor the high-resolution data showed any evidence for the presence of chlorine at positions other than C-1 and C-1′. Finally, **4** and **12** containing 1.960 and 1.998 atoms of D, respectively, were obtained upon $LiAlD_4$ reduction of 1,1′-dichloro-1,1′-diphenylazoethane (**16**) and **13.** The same $LiAlD_4$ was used in preparation of **12** and benzyl alcohol-α,α-d_2.[13] It is thus noteworthy that the atom % D of the former as determined by combustion, 99.9 ± 0.3, is in good agreement with the value for the latter as determined by low-voltage mass spectrometry,[13] 99.3 ± 0.3. Different $LiAlD_4$ was used in synthesis of **4.** Since **4** and **12** do not contain in excess of two atoms of D, either the formation of or the reduction of chlorine-substituted 1,1′-dichloroazoalkanes must be negligible. These conclusions concerning the extent to which substitution of chlorine accompanies its addition to azines are supported by the results of Malament and McBride.[10d]

Pyrolysis of recrystallized **11** in ethylbenzene yielded only 81.6% of the theoretical quantity of nitrogen gas.[14] This result was attributed to the presence of a trace amount of **16** in the sample. Although the thermal decomposition of 1,1′-dichloroazoalkanes proceeds predominantly by C–N bond homolysis,[10,15] there may be some C–Cl bond cleavage, which under our conditions would lead to formation of traces of HCl. The HCl would catalyze the isomerization of **11** to hydrazone; the uv spectrum of the residue from pyrolysis displayed absorption characteristic of the hydrazone. The 99.1% yield of nitrogen obtained upon heating a mixture of pyridine[16] and **11** (6:1 mole ratio) in ethylbenzene supports this explanation.

Since 1,1′-dichloroazoalkanes undergo hydrolysis,[10b–d,17] the crude azoalkanes were solvolyzed homogeneously in ether–acetone–water containing equimolar amounts of $AgNO_3$; in all cases formation of traces of AgCl was observed. The azoalkane was then purified by column chromatography over silica gel followed by recrystallization. The chromatography step, which is not unique to the chloride addition–metal hydride reduction method, and which may have been unnecessary, was introduced to facilitate removal of colloidal silver and silver salts. After purification, a 99.2 and 99.7% yield of nitrogen was obtained upon pyrolysis of **11** and **12,** respectively, in ethylbenzene. Similar results were obtained for decomposition of **3** and **4** prepared by both chlorine addition–metal hydride reduction and eq 1.[14]

(*sec*-Alkylazo)benzenes cannot be prepared by chlorine addition–metal hydride reduction because substitution of chlorine for aromatic hydrogen is known to accompany its addition to phenylhydrazones.[18] However, (2,2-dimethyl-1-phenylpropyl)azomethane (**17,** $R_1 = C_6H_5$; $R_2 = (CH_3)_3C$; $R_3 = CH_3$) and (2,2-dimethyl-1-phenylpropyl-1-*d*)azomethane (**18**) were prepared from **2** via chlorine addition–metal hydride reduction. Deuterium analysis of **18** yielded 1.072 atoms of D, indicating that 0.092 atoms of H (1.072 − 1.960/2) had been replaced by chlorine in the addition step. This extent of deuterium–protium exchange is in almost all cases less than that observed in the catalytic deuteration of azines or hydrogenation of deuterated azines. Thus it appears that chlorine addition–metal hydride reduction is applicable to the synthesis of (*sec*-alkylazo)alkanes and (*sec*-alkylazo)-2,4,6-trichlorobenzenes, since Moon[18] has demonstrated that 2,4,6-trichlorophenylhydrazones react with Cl_2 to form [(1-chloroalkyl)azo]-2,4,6-trichlorobenzenes.

Experimental Section

General. NMR spectra were recorded on a Varian XL-100 spectrometer. Chemical shifts are reported with respect to tetramethylsilane. Mass spectra were obtained using a CEC 21-110B spectrometer at 70 eV. Elemental and deuterium analyses were performed by Galbraith Laboratories, Inc., and Mr. Josef Nemeth, Urbana, Ill., respectively.

Butyrophenone (Aldrich), 4-bromoacetophenone (Aldrich), 4-methylacetophenone (Aldrich), methyl 2-naphthyl ketone (Eastman), acetophenone (Baker), and 2-butanone (Mallinckrodt) were commercial samples and used without further purification. 3,3-Diphenylpropiophenone was prepared by the procedure of Vörlander and Friedberg.[19]

Preparation of 2,2-Dimethylpropiophenone. In a 1-l. four-necked flask equipped with an additional funnel, mechanical stirrer, reflux condenser, and a section of Gooch tubing for solid introduction were placed 60 ml of dry ether and 36 ml of an ethereal solution of phenylmagnesium bromide (Arapaho, 0.1082 mol). The flask was cooled to 0° and anhydrous cadmium chloride (10.35 g, 0.0565 mol) was slowly added via the Gooch tubing to the stirred solution. The mixture was allowed to warm to room temperature and refluxed for 20 min. The major portion of the ether was removed by distillation and 120 ml of dry benzene was added. Distillation was continued until the distillate was ether free, as analyzed by gas chromatography. The flask and its contents were then cooled to 10°, 2,2-dimethylpropanoyl chloride (10.0 g, 0.0833 mol, Aldrich) in 30 ml of dry benzene was slowly added, and the resulting mixture was stirred for 4 hr. The reaction mixture was hydrolyzed at 5–7° by addition of 140 ml of 20% sulfuric acid. The organic phase was separated, washed twice with a saturated solution of sodium bicarbonate and repeatedly with water, and dried over anhydrous magnesium sulfate. The solution was filtered and the benzene distilled. Distillation at 91–93° (6.5 mm) [lit.[20] bp 103–104° (13 mm)] afforded 11 g (82%) of product.

Preparation of Ketazines. All ketazines were prepared by the method of Cohen et al.[3b] Acetophenone azine,[21] 4-bromoacetophenone azine,[22] 4-methylacetophenone azine,[23] methyl 2-naphthyl ketazine,[24] 2-butanone azine,[3h] 2,2-dimethylpropiophenone azine,[10d] and butyrophenone azine[2j] have been previously described.

Preparation of 3,3-Diphenylpropiophenone Azine. 3,3-Diphenylpropiophenone (30 g, 0.105 mol) and 95% hydrazine (1.71 g, 0.0525 mol) were refluxed for 6 hr in absolute ethanol (50 ml) containing 10 drops of glacial acetic acid. The reaction mixture was cooled to room temperature and filtered. The crude azine was re-

crystallized twice from a 9:1 mixture of absolute ethanol and benzene: 26.8 g (90%); mp 137.5–138°; mass spectrum, M^+ *m/e* 568.288 (calcd for $C_{42}H_{36}N_2$, 568.288); NMR ($CDCl_3$) δ 3.33 (d, 4 H), 4.34 (t, 2 H), 6.92–7.38 (m, 30 H).

Preparation of 2,2-Dimethylpropiophenone Methylhydrazone. 2,2-Dimethylpropiophenone (10 g, 0.0617 mol) and methylhydrazine (3.5 g, 0.0761 mol) were refluxed for 5 days in absolute ethanol (30 ml) containing 5 drops of glacial acetic acid. The crude product, obtained upon removal of the ethanol at reduced pressure, was taken up in ether, washed with a saturated solution of sodium bicarbonate and with water, dried over anhydrous magnesium sulfate, and filtered. Removal of the ether at reduced pressure and recrystallization of the crude product from hexanes yielded 7.0 g (60%) of product: mp 54.5–55°; mass spectrum, M^+ *m/e* 190.147 (calcd for $C_{12}H_{18}N_2$, 190.147); NMR ($CDCl_3$) δ 1.14 (s, 9 H), 2.76 (s, 3 H), 4.25 (broad, 1 H), 7.05 and 7.36 (m, total 5 H).

General Procedure for the Addition of Chlorine to Ketazine. The method was essentially the one described by Moon.[18] A 5% solution of the ketazine in methylene chloride was cooled to −70° in a Dry Ice–acetone bath. Liquid chlorine (2 mol/mol ketazine) at −70° was rapidly added in the dark to the stirred solution. The mixture was stirred at −70° for 2 hr and then at −40° for an additional 1 hr. The excess chlorine and the methylene chloride were removed at reduced pressure. The crude chloroazo compounds were purified when possible by recrystallization from acetone, hexanes, or a binary acetone–hexanes solvent.

The preparation of 1,1′-dichloro-1,1′-diphenylazoethane,[10a] 1,1′-dichloro-1,1′-bis(4-bromophenyl)azoethane,[10b] 1,1′-dichloro-1,1′-bis(4-methylphenyl)azoethane,[10b] 1,1′-dichloro-1,1′-di(2-naphthyl)azoethane,[10d] 1,1′-dichloro-2,2′-azobutane,[10c] and 1,1′-dichloro-2,2,2′,2′-tetramethyl-1,1′-diphenylazopropane[10d] have been reported previously. The following new 1,1′-dichloroazoalkanes were prepared.

1,1′-Dichloro-1,1′-diphenylazobutane. Butyrophenone azine was quantitatively converted to this azo compound by the above procedure. The crude product was recrystallized from hexanes: mp 85.5–86.0° dec; NMR ($CDCl_3$) δ 0.81 (t, 6 H), 1.29 (m, 4 H), 2.47 (m, 4 H), 7.37 and 7.65 (m, total 10 H).

1,1′-Dichloro-1,1′,3,3,3′,3′-hexaphenylazopropane. Addition of liquid chlorine to 3,3-diphenylpropiophenone azine by the general procedure afforded a quantitative yield. Recrystallization from hexanes yielded material melting with decomposition at 227–228°; NMR ($CDCl_3$) δ 3.26 (m, 4 H), 4.07 (t, 2 H), 6.80–7.36 (m, 30 H).

(2,2-Dimethyl-1-chloro-1-phenylpropyl)azomethane. Addition of liquid chlorine to 2,2-dimethylpropiophenone methylhydrazone by the general procedure yielded an unstable, yellow, viscous oil. The NMR spectrum of the product in $CDCl_3$ changed rapidly with time. Short exposure to the atmosphere resulted in the rapid evolution of gas. Owing to instability of this product no quantitative data were obtained.

General Procedure for the $LiAlH_4$ Reduction of the 1,1′-Dichloroazoalkanes. Each of the 1,1′-dichloroazoalkanes was reduced with excess lithium aluminum hydride to the corresponding secondary azoalkanes (Table I). The reflux time varied with the compound; completion of the reaction was taken as the disappearance of the green color in the reaction mixture. The preparation of 2,2′-azobutane illustrates the general procedure.

In a 500-ml three-necked flask equipped with an addition funnel, condenser, and mechanical stirrer were placed 2.5 g (0.066 mol) of lithium aluminum hydride and 50 ml of dry ether. The stirred solution was cooled to 0° and 11 g (0.052 mol) of 1,1′-dichloro-2,2′-azobutane in 200 ml of dry ether was added in ca. 15 min. The mixture was allowed to warm to room temperature and then refluxed for 19 hr. The aqueous and organic phases obtained upon hydrolysis of the ice-cooled mixture by the slow addition of a saturated solution of sodium potassium tartrate (100 ml) with vigorous stirring were separated. The former phase was removed and extracted three times with ether, and the ether extracts were combined with the latter phase. The ethereal solution was washed twice with water, dried over anhydrous magnesium sulfate, filtered, and freed of ether under reduced pressure. Distillation of the crude yellow oil yielded 4.8 g (63%) of **8**, bp 48.5–49.0° (25 mm) [lit.[3h] bp 49–52° (27 mm)].

1,1′-Bis(4-bromophenyl)azoethane (5). Using a reflux time of 19 hr, **5** was prepared by the general procedure. A 41% yield was obtained after recrystallization from methanol: mp 107.5–108°; NMR ($CDCl_3$) δ 1.46 (d, 6 H), 4.52 (q, 2 H), 7.22 (d, 4 H), 7.44 (d, 4 H).

1,1′-Di(2-naphthyl)azoethane (7). Using a reflux time of 20 hr, **7** was prepared by the general procedure. A 58% yield was obtained after recrystallization from a 3:1 mixture of methanol and acetone: mp 144–144.5°; NMR ($CDCl_3$) δ 1.60 (d, 6 H), 4.83 (q, 2 H), 7.48 (m, 6 H), 7.80 (m, 8 H).

1,1′,3,3,3′,3′-Hexaphenylazopropane (10). Using a reflux time of 18 hr, **10** was prepared by the general procedure. A 60% yield was obtained after recrystallization from methanol: mp 146.5–147.5° dec; NMR ($CDCl_3$) δ 2.78 (m, 4 H), 3.53 (m, 2 H), 4.42 (m, 2 H), 6.82–7.50 (m, 30 H).

1,1′-Diphenyl-2,2,2′,2′-tetramethylazopropane (11). Using a reflux time of 4 hr, **11** was prepared by the general procedure. A 61% yield was obtained after recrystallization from methanol: mp 155.5–156.5°; NMR ($CDCl_3$) δ 1.00 (s, 18 H), 4.17 (s, 2 H), 7.11 (s, 10 H).

1,1′-Diphenyl-2,2,2′,2′-tetramethylazopropane-*1,1′-d*$_2$ (12). Using lithium aluminum deuteride instead of lithium aluminum hydride in the general procedure, **12** was prepared with a reflux time of 4 hr. A 63% yield was obtained upon recrystallization from methanol: mp 156–156.5°; NMR ($CDCl_3$) δ 1.00 (s, 18 H), 7.11 (s, 10 H).

(2,2′-Dimethyl-1-phenylpropyl)azomethane (17). Using the procedure for the reduction of 1,1′-dichloroazoalkanes, **17** was prepared with a reflux time of 15 hr. Crude **17** was purified by column chromatography (column dimensions, 4.7 × 60 cm) using Baker AR grade silica gel as the substrate and a 2:1 mixture of benzene and hexanes as the eluting solvent followed by distillation: yield 56%; bp 52–54° (0.7 mm); NMR ($CDCl_3$) δ 0.94 (s, 9 H), 3.70 (s, 3 H), 4.10 (s, 1 H), 7.29 (m, 5 H).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.75. Found: C, 75.76; H, 9.56; N, 14.38.

(2,2-Dimethyl-1-phenylpropyl-*1-d*)azomethane (18). Using lithium aluminum deuteride, **18** was prepared and purified by the procedure described for **17**: yield 60%; bp 50–51° (0.6 mm): NMR ($CDCl_3$) δ 0.94 (s, 9 H), 3.70 (s, 3 H), 7.29 (m, 5 H).

Purification Procedure for Secondary Azo Compounds. Azo compounds and silver nitrate (mole ratio 1:1) were added to a ternary solution of ether, acetone, and water. The resulting solution was stirred in the dark for 24 hr. The ether and acetone were removed under reduced pressure and the azo compound was taken up in ether. The ether solution was washed twice with a saturated solution of sodium carbonate and then with water, dried over anhydrous magnesium sulfate, filtered, and freed of ether at reduced pressure. The crude product was purified by column chromatography (column dimensions, 4.7 × 60 cm) using silica gel as the substrate and either benzene, hexanes, or a binary mixture of benzene–hexanes as an eluting solvent, followed by distillation or recrystallization.

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Registry No.—**1,** 55043-54-4; **2,** 55043-55-5; **3,** 5661-68-7; **4,** 55043-56-6; **5,** 55043-57-7; **6,** 32234-13-2; **7,** 55043-58-8; **8,** 3742-58-3; **9,** 35115-95-8; **10,** 55043-59-9; **11,** 55043-60-2; **12,** 55043-61-3; **13,** 55043-62-4; **14,** 21399-36-0; **15,** 55043-63-5; **16,** 19727-23-2; **17,** 55043-64-6; **18,** 55043-65-7; acetophenone azine, 729-43-1; 4-methylacetophenone azine, 21399-33-7; methyl 2-naphthyl ketazine, 55043-66-8; 2-butanone azine, 5921-54-0; butyrophenone azine, 17745-98-1; 2,2-dimethylpropiophenone azine, 55043-67-9; 3,3-diphenylpropiophenone, 606-86-0; 2,2-dimethylpropiophenone, 938-16-9; phenyl bromide, 108-86-1; hydrazine, 302-01-2; methylhydrazine, 60-34-4; 1,1′-dichloro-1,1′-diphenylazobutane, 55043-68-0; 1,1′-dichloro-1,1′,3,3,3′,3′-hexaphenylazopropane, 55043-69-1; (2,2-dimethyl-1-chloro-1-phenylpropyl)azomethane, 55043-70-4; 1,1′-dichloro-2,2′-azobutane, 52406-48-1.

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Intramolecular 1,3-Dipolar Cycloadditions of Aryl Azides Bearing Alkenyl, Alkynyl, and Nitrile Groups

Raffaello Fusco,* Luisa Garanti, and Gaetano Zecchi

Istituto di Chimica Industriale dell'Università, Centro del C.N.R. per la Sintesi e Stereochimica di Speciali Sistemi Organici, 20133 Milano, Italy

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Azido compounds **1** containing dipolarophile groups, such as C=C, C≡C, and C≡N bonds, were synthesized from the corresponding anilines and thermally decomposed in aromatic hydrocarbon solvents. Bridgehead nitrogen aziridines **3** were obtained from **1a–c**, probably through an intramolecular cycloaddition leading to unstable Δ^2-1,2,3-triazolines. From **1d–g**, the corresponding 1,3-cycloaddition products, namely the fused-ring triazoles **7** and tetrazoles **8**, were isolated in good yields.

1,3-Dipoles bearing an additional function able to behave as a dipolarophile appear to be very interesting substrates. In fact, the intramolecular cycloaddition of a properly functionalized 1,3-dipole represents a general scheme for the synthesis of fused ring heterocycles. Nevertheless, in spite of the copious literature on 1,3-dipolar cycloadditions, intramolecular examples have as yet received little attention.

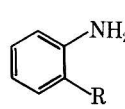
With azides, intramolecular cycloadditions have been occasionally reported,[1,2] but systematic data are available only for a series of azidoalkenes.[3] Also, a mechanism involving an intramolecular 1,3-dipolar cycloaddition to the carbonyl function is possibly operating in the formation of 3-arylanthranils from 2-azidobenzophenones, as proposed on the basis of a kinetic investigation.[4].

The present paper describes the results which we obtained from a series of structurally related aryl azides bearing different dipolarophile groups.

Results and Discussion

Azido compounds **1** were synthesized from the corresponding anilines **2** by diazotization and treatment of the intermediate diazonium salts with sodium azide.

1a, R = $OCH_2CH{=}CH_2$
b, R = $OCH_2C(Me){=}CH_2$
c, R = $OCH_2CH{=}CHPh$
d, R = $OCH_2C{\equiv}CH$



2e, R = $OCH_2C{\equiv}CPh$
f, R = OCH_2CN
g, R = CH_2CH_2CN

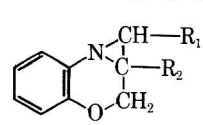
Reaction yields as well as physical and spectral data are collected in Table I.

All the compounds studied were decomposed by refluxing in aromatic hydrocarbon solvents. Temperatures were chosen on the basis of the different substrate reactivities. Each run was continued until all the starting material was consumed as indicated by thin layer chromatographic analyses of the reaction mixture.

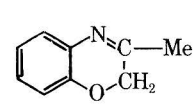
Experimental conditions and reaction products, which are summarized in Table II, will now be considered and discussed for the different kinds of substrates.

Aryl Azides Bearing an Alkenyl Substituent. The decomposition of azides **1a**, **1b**, and **1c** was performed in boiling benzene, the reaction time being respectively 6, 11, and 16 hr. In the case of **1a**, the crude product was a mixture of two components, which were isolated by column chromatography and identified as 1,1a-dihydro-2*H*-azirino[2,1-*c*][1,4]benzoxazine (**3a**) and 3-methyl-2*H*-1,4-benzoxazine (**4**).[5] However, the reactions of **1b** and **1c** gave essentially only the aziridines **3b** and **3c**, respectively.

Structures **3a–c** were assigned on the basis of elemental analyses, NMR spectra, and chemical behavior. The chemical shifts found for the protons of the aziridine ring in these



3a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Me$
c, $R_1 = Ph$; $R_2 = H$



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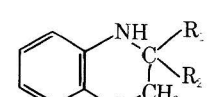


5a, $R_1 = H$; $R_2 = Me$
b, $R_1 = R_2 = Me$
c, $R_1 = H$; $R_2 = CH_2Ph$

Table I
Preparation of Azido Compounds 1[a]

Compd	Yield, %	Mp, °C	NMR spectrum ($CDCl_3$), τ (J, Hz)
1a	80	Oil[b]	2.8–3.4 (4 H, m, aromatics), 3.6–4.2 (1 H, m, CH═), 4.3–4.9 (2 H, m, CH_2═), 5.48 (2 H, m, CH_2O)
1b	88	Oil[b]	2.8–3.3 (4 H, m, aromatics), 4.8–5.1 (2 H, m, CH_2═), 5.54 (2 H, s, CH_2O), 8.15 (3 H, s, CH_3)
1c	63	49	2.5–3.2 (9 H, m, aromatics), 3.29 (1 H, d, $J = 16$, CH═), 3.61 (1 H, dt, $J = 5$ and 16, CH═), 5.28 (2 H, d, $J = 5$, CH_2O)
1d	29	Oil[c]	2.7–3.1 (4 H, m, aromatics), 5.30 (2 H, d, $J = 2.5$, CH_2O), 7.44 (1 H, t, $J = 2.5$, CH≡)
1e	68	Oil[b]	2.5–3.1 (9 H, m, aromatics), 5.12 (2 H, s, CH_2O)
1f	63	67	2.9 (4 H, m, aromatics), 5.19 (2 H, s, CH_2O)
1g	76	Oil[b]	2.5–3.0 (4 H, m, aromatics), 6.9–7.6 (4 H, m, CH_2CH_2)

[a] All compounds listed gave, in the ir spectrum, a strong band in the region 2120–2130 cm^{-1}. [b] Purity better than 95% (NMR). [c] The NMR analysis showed, together with **1d**, 15% of triazole **7a** (see later in the text).

compounds (Table III) agree with those reported for several aziridines.[6] Also, the absence of a geminal coupling in the case of **3a** and **3b** is not unprecedented for bridgehead nitrogen aziridines.[7] For compound **3c**, the vicinal coupling constant observed for the aziridine protons (3.5 Hz) compares well to trans coupling given in the literature.[6]

Catalytic hydrogenation of **3a–c** afforded the corresponding benzomorpholines **5a–c**. Compound **5a**[5] was also obtained from **4** by reduction with $LiAlH_4$.

It is noteworthy that aziridines **3a–c** are thermally stable (distillation in vacuo was possible without change), while they are readily transformed in the presence of acidic species, which cause extensive resinification, particularly in the case of **3a**.

The following points help to explain the above reactions. The known behavior of several Δ^2-1,2,3-triazolines, which thermally decompose to give aziridines[8–11] and imine derivatives,[10] suggests that the formation of **3a–c** and **4** could in-

Table II
Decomposition of Azido Compounds 1[a]

Compd	Solvent	Time, hr	Product(s) (yield, %)	Isolation procedure[b]
1a	Benzene	6	**3a** (58) + **4** (28)	A [diethyl ether–triethylamine (9:1)]
1b	Benzene	11	**3b** (69)	A [diethyl ether–triethylamine (9:1)]
1c	Benzene	16	**3c** (70)	B (*n*-pentane)
1d	Benzene	0.5	**7a** (75)	A (diethyl ether)
1e	Toluene	3	**7b** (78)	B (benzene)
1f	Xylene	4	**8a** (45)	A [benzene–ethanol (9:1)]
1g	Xylene	17	**8b** (25)	A [benzene–ethanol (9:1)]

[a] By refluxing 0.1 *M* solutions. [b] A = silica gel chromatography (eluent in parentheses), B = crystallization (solvent in parentheses).

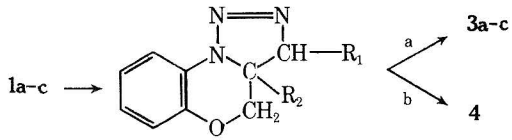
Table III
Physical, Spectral, and Analytical Data of Fused Ring Heterocycles 3, 7, and 8

Compd	Mp, °C (bp, °C)	Recrystn solvent	NMR spectrum ($CDCl_3$), τ (J, Hz)	Empirical formula	Anal., % Calcd C, H, N Found C, H, N
3a	(78–80, 0.001 mm)		2.6–3.3 (4 H, m, aromatics), 5.55–6.10 (2 H, m, CH_2O), 7.05–7.35 (1 H, m, CH), 7.60, 7.94 (each 1 H, two d, $J = 5$ and 4, CH_2N)	C_9H_9NO	73.45, 6.16, 9.52 73.68, 6.08, 9.23
3b	(83–85, 0.1 mm)		2.6–3.3 (4 H, m, aromatics), 5.83, 6.08 (each 1 H, AB type, $J = 11$, CH_2O) 7.76 (2 H, s, CH_2N),[a] 8.65 (3 H, s, CH_3)	$C_{10}H_{11}NO$	74.51, 6.88, 8.69 74.12, 6.50, 8.89
3c	74	*n*-Pentane	2.5–3.2 (9 H, m, aromatics), 5.6–5.8 (2 H, m, CH_2O), 6.75 (1 H, d, $J = 3.5$, CH), 7.0–7.2 (1 H, m, CH)	$C_{15}H_{13}NO$	80.69, 5.87, 6.27 80.55, 5.77, 6.30
7a	52	*n*-Pentane	1.8–2.0, 2.6–2.9 (1 H and 3 H, m, aromatics), 2.40 (1 H, s, CH), 4.62 (2 H, s, CH_2O)	$C_9H_7N_3O$	62.42, 4.07, 24.27 61.92, 3.70, 24.27
7b	195	Benzene	1.8–2.0, 2.2–2.9 (1 H and 8 H, m, aromatics), 4.43 (2 H, s, CH_2O)	$C_{15}H_{11}N_3O$	72.27, 4.45, 16.86 72.24. 4.43, 16.94
8a	152	Diethyl ether	1.9–2.2, 2.5–3.0 (1 H and 3 H, m, aromatics), 4.37 (2 H, s, CH_2O)	$C_8H_6N_4O$	55.17, 3.47, 32.17 55.40, 3.56, 32.07
8b	113	Diethyl ether	1.9–2.2, 2.4–2.7 (1 H and 3 H, m, aromatics), 6.5–6.9 (4 H, m, CH_2CH_2)	$C_9H_8N_4$	62.77, 4.68, 32.54 62.89, 4.90, 32.07

[a] Splitting of this signal was observed in benzene-d_6 at 100 MHz, where two singlets appeared each counting for one proton (τ 8.05, 8.14).

volve, as the first stage, an intramolecular cycloaddition leading to the unstable triazolines **6** (see Scheme I). The in-

Scheme I

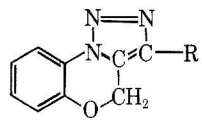


6

tervention of such an intermediate was deduced in the case of **1b** by carrying out the decomposition at room temperature in hexadeuteriobenzene and monitoring the reaction progress by NMR analyses; in addition to the signals of the starting azide and the final product, the spectrum showed a set of signals, which disappeared when the reaction went to completion. These signals are reasonably attributed to the triazoline **6**, R_1 = H; R_2 = Me [τ 6.43 (2 H, s, CH_2O), 6.79, 7.35 (each 1 H, AB type, J = 10.5 Hz, CH_2N), 9.20 (3 H, s, CH_3)].

The subsequent decomposition of the intermediate triazolines involves nitrogen extrusion according to one or both of the pathways shown in Scheme I. The lack of the products formed through pathway b when starting from azide **1b** is well accounted for by the lower migratory aptitude of the methyl group with respect to the hydrogen atom.[12] Instead, in the case of **1c**, the stabilizing effect of the phenyl group on the adjacent electron-deficient carbon atom may be invoked to justify the observed behavior.

Aryl Azides Bearing an Alkynyl Substituent. While the transformation of azide **1e** was complete after 3 hr refluxing in toluene, under the same conditions compound **1d** entirely disappeared after ca. 15 min. In fact the slow reaction of the latter azide even at room temperature made it impossible to purify. However, in spite of their different reactivities, both azides **1d** and **1e** gave the triazole derivative of formula **7** as the only decomposition product (see Table III for physical, analytical, and NMR data).



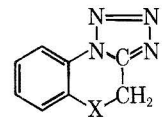
7a, R = H
b, R = Ph

Although the isolation of **7a,b** from **1d,e** is not surprising, it is noteworthy as the first example of intramolecular cycloaddition of the azido group to the acetylenic function. The greater reactivity of **1d** in comparison to **1e** is somewhat unexpected considering that the conjugated alkynes are usually better dipolarophiles than the unconjugated.[13] On the other hand, the bulky phenyl substituent may hinder the approach of the reactant groups; in this regard, phenyl azide cycloadds to methyl propiolate 50 times faster than to ethyl phenylpropiolate.[14]

Aryl Azides Bearing a Nitrile Function. Azidonitriles **1f,g** were found to be more stable compounds than the related azides **1a–e**. In fact, as shown in Table II, a higher temperature was required for their decomposition.

Starting from both **1f** and **1g**, the reaction led, apart from some untractable tar, to the tetrazole derivative **8** in satisfactory yields. Physical, analytical, and spectral data are given in Table III.

The ring closure leading to **8a,b** can reasonably be interpreted in terms of an intramolecular 1,3-dipolar cycloaddition. Actually, in intermolecular reactions, only nitrile groups activated by electron-withdrawing substituents



8a, X = O
b, X = CH_2

have been shown to behave as dipolarophiles toward azides.[15] Unactivated 4-azidobutyronitrile and 5-azidovaleronitrile gave 1,5-polymethylenetetrazoles only in the presence of an acidic catalyst.[15,16]

Clearly, in the case of **1f,g**, the mutual ortho disposition of the two interreacting groups provides a favorable stereochemical constraint to the intramolecular approach. Some activating effect by the oxygen atom could be responsible for the greater reactivity of **1f** with respect to **1g**.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 377 spectrophotometer. NMR spectra were taken on a Varian A-60A instrument with Me_4Si as internal standard.

Anilines **2a**,[17] **2d**,[18] **2e**,[19] and **2f**[20] were prepared as reported.

Aniline 2b. A solution of $SnCl_2$ (17.9 g) in concentrated HCl (98 ml) was slowly added to a solution of 2-methyl-3-(2-nitrophenoxy)propene[21] (15.0 g) in acetic acid (90 ml) at 15°. Zinc powder (50.3 g) was then added portionwise under stirring and cooling. After 45 min at room temperature, the mixture was filtered and the solvent was partly removed under reduced pressure. The residue was treated with chloroform and water, then the aqueous layer was separated, made alkaline by ammonia, and extracted with chloroform. The organic solution was dried over $MgSO_4$ and evaporated and the oily residue was distilled in vacuo to give aniline **2b** in 44% yield: bp 105–110° (0.5 mm); ir (film) 3500, 3430 cm^{-1} (NH_2); NMR ($CDCl_3$) τ 3.0–3.6 (4 H, m, aromatics), 4.8–5.2 (2 H, m, CH_2=), 5.58 (2 H, s, CH_2O), 6.31 (2 H, broad s, NH_2), 8.17 (3 H, s, CH_3).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 74.02; H, 7.98; N, 8.45.

3-(2-Nitrophenoxy)-1-phenylpropene. A mixture of 2-nitrophenol (20.8 g), potassium carbonate (20.7 g), cinnamyl bromide (30.5 g), and dry acetone (200 ml) was refluxed for 6 hr. The solvent was partly removed, ether and water were then added, and the organic layer was dried on $MgSO_4$ and evaporated. The residue was taken up with a small amount of benzene and filtered to afford 3-(2-nitrophenoxy)-1-phenylpropene in 73% yield: mp 72–73° (*n*-hexane–benzene); NMR (CCl_4) τ 2.2–3.5 (10 H, m, aromatics and CH=), 3.77 (1 H, dt, J = 15 and 5 Hz, CH=), 5.30 (2 H, d, J = 5 Hz, CH_2O).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 71.00; H, 5.04; N, 5.49.

Aniline 2c. A solution of $SnCl_2$ (10.0 g) in concentrated HCl (75 ml) was slowly added to a solution of 3-(2-nitrophenoxy)-1-phenylpropene (13.5 g) in acetic acid (370 ml) at 15°. Zinc powder (37 g) was added portionwise under stirring and cooling. After 1 hr at room temperature, the mixture was filtered and the solution was adjusted to pH 5 by ammonia; then the solvent was removed in vacuo. The residue was made alkaline by ammonia and extracted several times with chloroform. The organic solution was washed with 10% NaOH, dried over $MgSO_4$, and evaporated. The residue was taken up with diisopropyl ether. Addition of *n*-hexane caused separation of aniline **2c** in 20% yield: mp 75–76°; ir (Nujol) 3550, 3430 (NH_2), 1630 cm^{-1} (C=C); NMR (CCl_4) τ 2.5–3.0 (4 H, m, C_6H_4), 3.1–3.8 (6 H, m, C_6H_5 and CH=CH), 5.38 (2 H, d, J = 5 Hz, CH_2O), 6.40 (2 H, broad s, NH_2).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.15; H, 6.50; N, 6.38.

Aniline 2g. A mixture of 2-nitrocinnamonitrile[22] (11.0 g), 10% Pd/C (1.0 g), and ethanol (150 ml) was stirred under hydrogen atmosphere while cooling at 15°. When the absorption became slow (4.5 l.), the mixture was filtered and fresh catalyst was added (1.0 g). The hydrogen absorption continued until an overall amount of 6.2 l. was taken up. The catalyst was filtered off, the filtrate was concentrated, and the residue gave aniline **2g** in 69% yield: bp 128–132° (0.1 mm); ir (film) 3220 (NH_2), 2180 cm^{-1} (C=N); NMR ($CDCl_3$) τ 2.8–3.5 (4 H, m, aromatics), 6.45 (2 H, broad s, NH_2), 7.0–7.7 (4 H, m, CH_2CH_2).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.20; H, 6.99; N, 19.01.

Preparation of Azides 1. General Procedure. A solution of sodium nitrite (0.052 mol) in water (10 ml) was added dropwise to a solution of aniline **2** (0.050 mol) in 4 *N* HCl (60 ml) under vigorous stirring and ice cooling. The mixture was then neutralized by $NaHCO_3$ and a solution of sodium azide (0.050 mol) in water (35 ml) was slowly added at ca. 5°. After 30 min, the mixture was extracted with ether and the organic solution was dried over $MgSO_4$. The solvent was removed under reduced pressure and afforded practically pure azide **1**, with the exception of **1c** and **1d**, which were purified by silica gel chromatography using as eluent respectively benzene and a solution of diethyl ether–*n*-hexane (4:1). See Table I.

Decomposition of Azides 1. General Procedure. A 0.1 *M* solution of azide **1** was refluxed until all the starting material was consumed (see Table II for solvents and reaction times). The solvent was then evaporated under reduced pressure and the residue was worked up according to the procedure indicated in Table II. Physical, spectral, and analytical data of compounds **3, 7,** and **8** are collected in Table III. Compound **4**[5] gave the following NMR spectrum ($CDCl_3$): τ 2.6–3.3 (4 H, m, aromatics), 5.53 (2 H, s, CH_2), 7.90 (3 H, s, CH_3).

Catalytic Hydrogenation of Aziridine 3a. A solution of **3a** in ethanol (40 ml) was stirred under hydrogen atmosphere in the presence of Pd/C. When the theoretical amount of hydrogen was absorbed, the catalyst was filtered off and the solvent was evaporated. Distillation in vacuo of the oily residue furnished compound **5a** in 65% yield: bp 80–83° (0.4 mm) [lit.[5] bp 150–152° (24 mm)]; NMR, see ref 23.

Catalytic Hydrogenation of Aziridine 3b. Compound **5b** was obtained from **3b** according to the above procedure in 72% yield: bp 85–88° (0.4 mm); NMR ($CDCl_3$) τ 3.1–3.6 (4 H, m, aromatics), 6.20 (2 H, s, CH_2), 6.70 (1 H, broad s, NH), 8.81 (6 H, s, two CH_3).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.65; H, 7.95; N, 8.37.

Catalytic Hydrogenation of Aziridine 3c. The above procedure, when starting from **3c** (0.2 g), led to **5c** in 67% yield: mp 63° (*n*-pentane); NMR ($CDCl_3$) τ 2.5–3.6 (9 H, m, aromatics), 5.6–6.5 (4 H, m, OCH_2CH and NH), 7.1–7.4 (2 H, m, CH_2).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.60; H, 6.58; N, 6.05.

Reduction of 4. A solution of ketimine **4** (0.155 g) in anhydrous THF (10 ml) was added under stirring to a suspension of $LiAlH_4$ (0.4 g) in THF (50 ml). After 5 hr refluxing, the excess of $LiAlH_4$ was decomposed by ethyl acetate, water was added, and the mixture was extracted several times with ether. The organic solution was dried over Na_2SO_4 and evaporated. The residue was distilled in vacuo to afford **5a** in 65% yield.

Registry No.—**1a,** 55000-07-2; **1b,** 55000-08-3; **1c,** 55000-09-4; **1d,** 55000-10-7; **1e,** 55000-11-8; **1f,** 55000-12-9; **1g,** 55000-13-0; **2a,** 27096-64-6; **2b,** 55000-14-1; **2c,** 55000-15-2; **2d,** 52536-39-7; **2e,** 52536-40-0; **2f,** 31507-29-6; **2g,** 55000-16-3; **3a,** 55000-17-4; **3b,** 55000-18-5; **3c,** 55000-19-6; **4,** 55000-20-9; **5a,** 32329-20-7; **5b,** 55000-21-0; **5c,** 55000-22-1; **6** (R_1 = H; R_2 = Me), 55012-68-5; **7a,** 235-23-4; **7b,** 55000-23-2; **8a,** 55000-24-3; **8b,** 35213-60-6; 2-methyl-3-(2-nitrophenoxy)propene, 13414-54-5; 2-nitrophenol, 88-75-5; cinnamyl bromide, 4392-24-9; 3-(2-nitrophenoxy)-1-phenylpropene, 55000-25-4; 2-nitrocinnamonitrile, 55000-26-5.

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Synthesis of 3,4-Dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones

Norton P. Peet* and Shyam Sunder

Pharmaceutical Chemistry, Research and Development, Dow Chemical Company, Midland, Michigan 48640

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Two new routes to the title compounds have been developed. 3,4-Dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (**3**) was prepared by treating 2-carboalkoxyphenyl isocyanate (**1**) with methylhydrazine and cyclizing the semicarbazide ester (**2**) with base. The 4-methyl isomer of **3** (**7a**) was prepared by treating 2-isocyanatobenzoyl chloride (**6a**) with methylhydrazine. Two reports which disclose syntheses of extensive numbers of 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones are shown to be in error. These routes lead, instead, to 3-amino-2,4(1*H*,3*H*)-quinazolinediones.

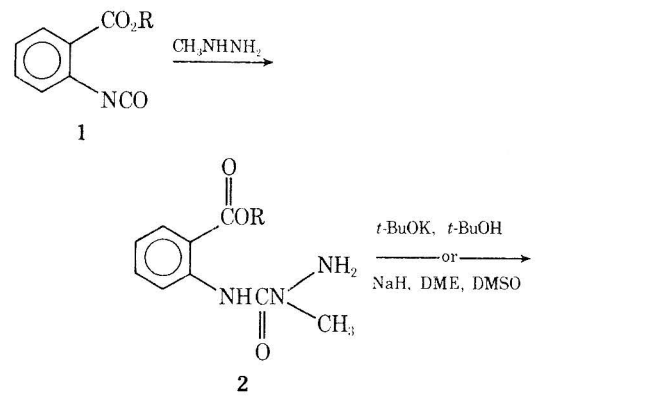
In the past several years much research effort has been expended on the preparation of benzodiazepines for evaluation as potential psychotherapeutic agents. All six classes are known, and their chemistry and pharmacology have been studied extensively.[1]

Pharmaceutical interest in the benzotriazepines has evolved from the benzodiazepines. Of the six possible classes[2] of benzotriazepines, only three have been studied to date. No representatives of the benzo-1,2,3-, 1,2,4-, or 2,3,4-triazepine classes are known. Benzo-1,3,4-triazepines[3] and benzo-1,2,5-triazepines[4] are well documented in the literature. Benzo-1,3,5-triazepines[5] are documented in a few instances.

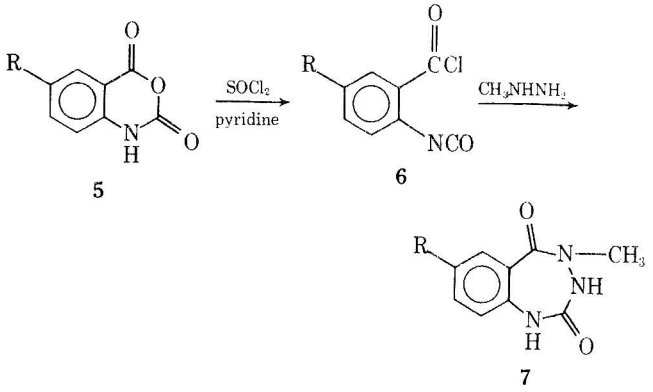
This report deals specifically with 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones. We have developed new, unequivocal entries into this class of compound which allow us to critically examine the few reported entries, and the compounds which have been made by these routes and assigned as 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones.

Treatment of 2-carboalkoxyphenyl isocyanates **1a** and

Scheme I



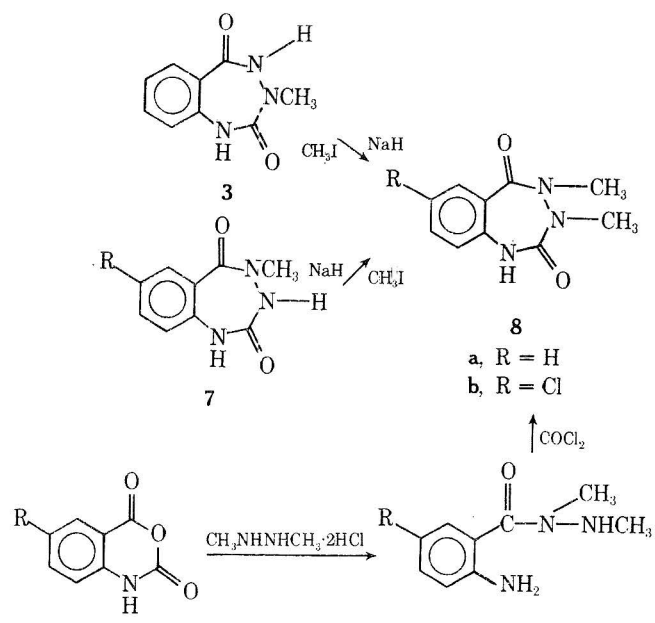
Scheme II



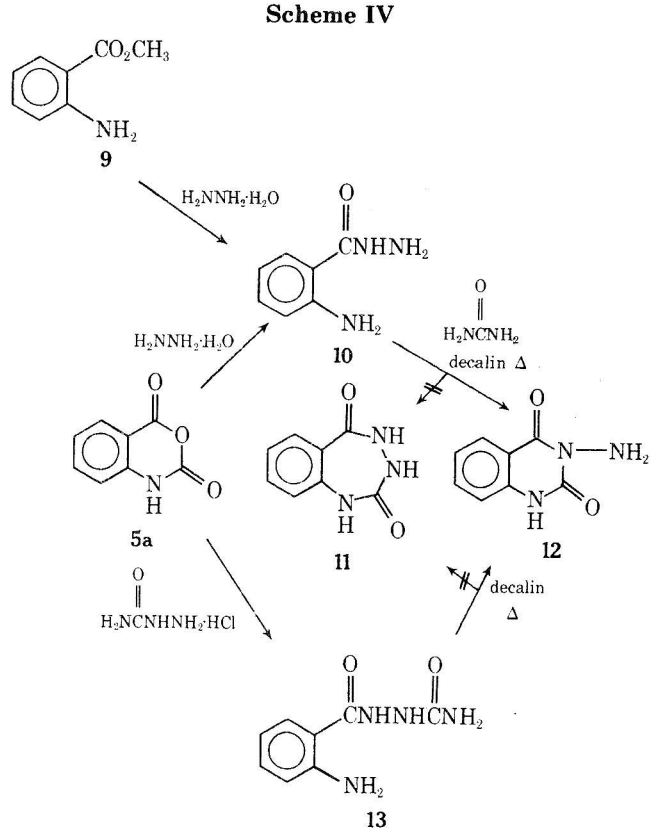
more susceptible to nucleophilic attack, respectively, than the isocyanato group, we have controlled the site for initial attack by the methyl-bearing nitrogen of methylhydrazine and effected selective syntheses for the isomeric benzotriazepinediones **3** and **7a**.

Alkylation of either **3** or **7a** with methyl iodide, using sodium hydride as the base in DMF, yielded the same dimethylbenzotriazepinedione **8a**. The results of these experiments served to relate **3** and **7a** to each other and to the known literature compound **8a**, which was prepared from isatoic anhydride and *sym*-dimethylhydrazine by Hromatka et al.[9] as shown in Scheme III. Compound **7b** was also converted to the known compound **8b** in similar fashion. Hromatka et al. report two other authentic benzo-

Scheme III



Scheme IV



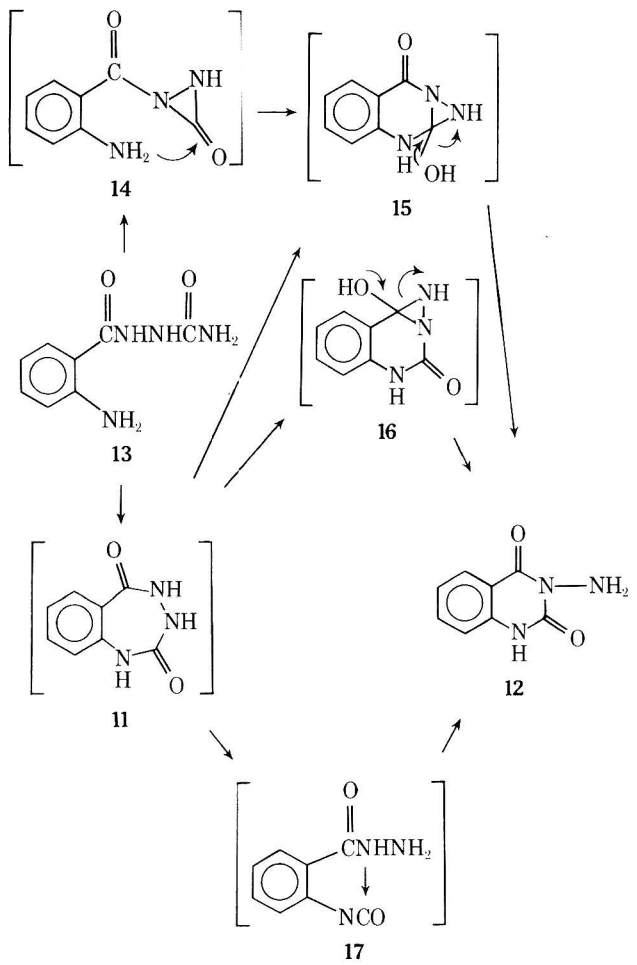
1b with methylhydrazine gave the semicarbazides **2a**[6] and **2b**. Cyclization of **2a** with potassium *tert*-butoxide in *tert*-butyl alcohol or **2b** with sodium hydride in dimethoxyethane (DME) and dimethyl sulfoxide (DMSO) gave a mixture of benzotriazepinedione **3** and a compound to which we assign structure **4**, as shown in Scheme I. Compounds **3** and **4** were separated by subjecting the mixture to Soxhlet extraction with dioxane. The electron impact mass spectrum of **4** contained no parent peak. The fragmentation pattern resembled that of **3**.

Treatment of isatoic anhydride (**5a**) with thionyl chloride and a catalytic amount of pyridine gave 2-isocyanatobenzoyl chloride (**6a**), as reported.[8] Reaction of **6a** with methylhydrazine yielded benzotriazepinedione **7a**, isomeric with **3**. A solid polymeric material was also formed in the reaction, but it is worthy of note that **7a** was the *only isolable monomeric material*. Likewise, 2-isocyanato-5-chlorobenzoyl chloride (**6b**) was prepared and treated with methylhydrazine to yield **7b** as the sole monomeric product. (See Scheme II.) Thus, by varying the electrophilic reactivity of the *o*-carboxy-derived group on the phenyl isocyanate from carboalkoxy to carbonyl chloride, groups which are less and

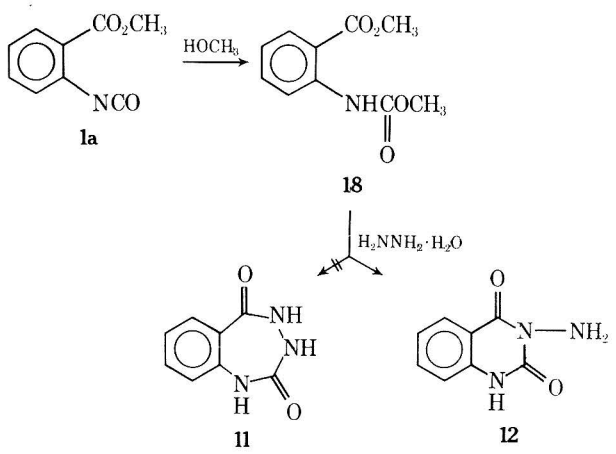
triazepinediones in addition to compounds **8a** and **8b.** These compounds represent the only authentic group of 3,4-dihydro-1*H*-1,3,4-benzotriazepinediones in the literature (vide infra). It is interesting to note that compounds **3** and **7** are selectively alkylated in the 4 and 3 positions, respectively, with no apparent competitive alkylation at position 1, since *N*-phenylamides are N-alkylated under these conditions.[10] This selectivity is apparently another demonstration of the α effect.[11]

Langis and Charest[12] report two methods for the preparation of 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione (**11**) and derivatives of **11.** Their methods for **11** involve the cyclization of 1-(2-aminobenzoyl)semicarbazide in decalin at reflux and treatment of 2-aminobenzoylhydrazine (**10**) with urea in decalin at reflux. In a reexamination of their work, we treated **10** with urea in decalin at reflux and found that the product of this reaction was 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**12**) and not **11** (Scheme IV). The product of this reaction was identical in all respects with a sample of **12** whose synthesis is reported in the literature.[13] We feel that 19 of the 21 additional compounds reported as benzotriazepinediones by Langis and Charest, which were prepared (with one exception) by treating 2-aminobenzoylhydrazines (most of which contained substituents on the terminal hydrazide nitrogen) with urea in decalin at reflux, are probably 3-amino-2,4(1*H*,3*H*)-quinazolinediones.[14]

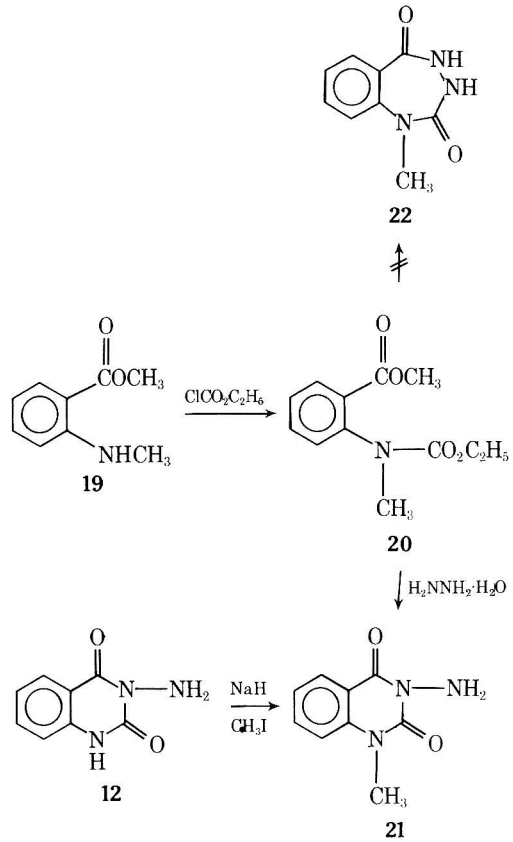
Thermal cyclization of 1-(2-aminobenzoyl)semicarbazide (**13**) in decalin also yielded 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**12**) in good yield (Scheme IV). This transformation is less obvious than the conversion of **10** to **12.** It is possible that **11** is an intermediate in this cyclization, generating **12** through the secondary intermediates **15, 16,** or **17.** Alternatively, **12** could arise from intermediate **14.**



Scheme V



Scheme VI



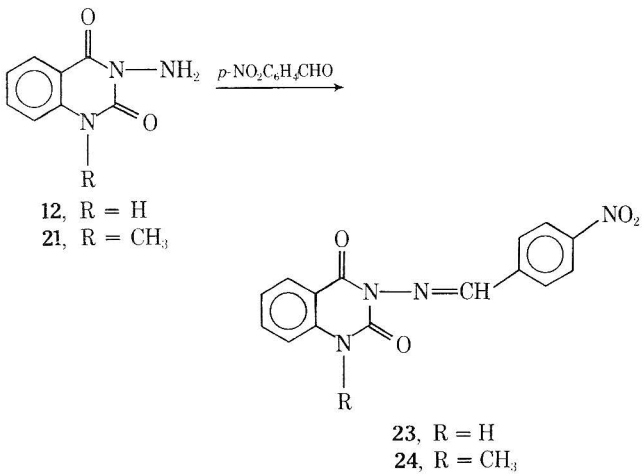
A recent U.S. Patent by Bailey[15a] discloses a preparative method for 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones. The general method of preparation involves the condensation of alkyl *N*-carboxyanthranilates with hydrazines. In a reexamination of this reaction, we treated methyl *N*-carbomethoxyanthranilate (**18**) with hydrazine hydrate and isolated only the quinazolinedione **12,** in good yield (Scheme V).

We next prepared intermediate **20,** which is also reported by Bailey, and treated it with hydrazine hydrate. The product isolated was 1-methyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione (**21**) and not **22,** as reported by Bailey. Confirmation of structure was achieved by methylating **12** to yield **21.** See Scheme VI.

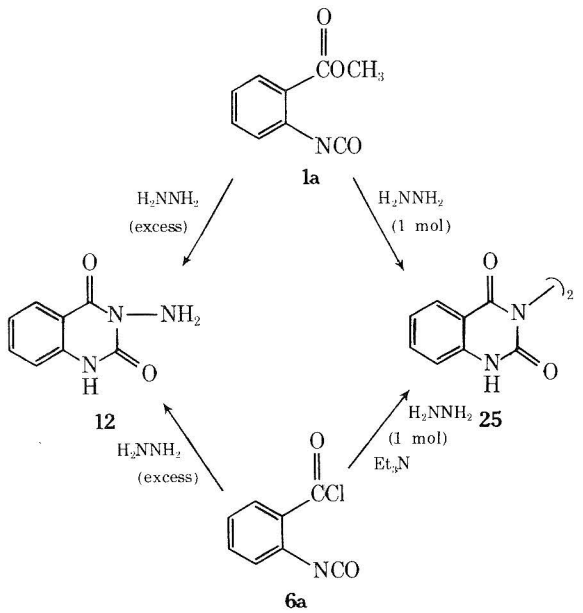
We feel that the above results cast serious doubt on the structures of at least 70 of the 77 compounds disclosed as benzotriazepinediones by Bailey.[15b] It appears that the six-membered quinazolinedione ring system is thermodynamically favored over the seven-membered benzotriaze-

pinedione ring system, and that even in well-intentioned experiments designed to produce the latter system, quinazolinediones result where possible.

Additional confirmation for the presence of primary amino functionalities in **12** and **21** was established chemically. Both **12** and **21** were condensed with *p*-nitrobenzaldehyde to yield the respective Schiff bases **23** and **24**.



Other available possible precursors to **12** (or **11**) were **1a** or **6a**. The addition of **1a** or **6a** to excess hydrazine afforded almost quantitative yields of **12**. However, when the order of addition was reversed and equimolar amounts of hydrazine were used, good yields of bis compound **25** resulted.



Experimental Section

Preparation of Methyl 2-{[(1-Methylhydrazino)carbonyl]amino}benzoate (2a). A 422-g (2.38 mol) quantity of 2-carbomethoxyphenyl isocyanate (**1a**)[16] in 500 ml of CH_2Cl_2 was added to a solution of 110 g (2.38 mol) of methylhydrazine (Aldrich) in 500 ml of CH_2Cl_2 over a 60-min period with ice-bath cooling. The solution (whose ir spectrum showed no N=C=O stretch) was concentrated and the resulting solid was recrystallized in crops from CH_2Cl_2–hexane to yield 406 g (77%) of **2a** as clear prisms: mp 123.5–125.5°; ir (Nujol) 3350, 3260, and 3210 (NH), 1700 (ester C=O), 1670 cm^{-1} (semicarbazide C=O); NMR ($CDCl_3$) δ 11.64 (s, 1, NH), 8.82–8.58 (m, 1, aromatic), 8.00–7.85 (m, 1, aromatic), 7.64–7.30 (m, 1, aromatic), 7.07–6.75 (m, 1, aromatic), 3.97 (s, 2, NH_2), 3.83 (s, 3, OCH_3), 3.19 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.80; H, 5.87; N, 18.61.

A 4.46-g (20.0 mmol) quantity of **2a** and 3.02 g (20.0 mmol) of *p*-nitrobenzaldehyde (Aldrich) in 150 ml of ethanol were heated at reflux for 3 hr. The precipitate was removed by filtration to yield 5.93 g (83%) of the Schiff base: mp 232–242° (EtOH); ir (Nujol) 3200, 1680, 1580 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.73. Found: C, 57.10; H, 4.59; N, 15.83.

Preparation of 3,4-Dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (3). A. *tert*-Butoxide Method. A solution of 53.4 g (0.239 mol) of **2a** and 26.8 g (0.239 mol) of potassium *tert*-butoxide (Aldrich) in 1100 ml of *tert*-butyl alcohol was heated at reflux under a nitrogen atmosphere for 18 hr. The solution was evaporated to one-third volume, diluted with water (1 l.), and acidified with concentrated HCl. The resulting precipitate was collected and washed with ether to yield 28.4 g of a mixture containing **3** and **4**, mp 229–231°. The mixture was subjected to Soxhlet extraction with dioxane to remove, as prisms from the cooled dioxane extract, 16.1 g (35%) of **3**: mp 242–245°; ir (Nujol) 3240 and 3110 (NH), 1710 (C=O), 1670 cm^{-1} (C=O); NMR (DMSO) δ 10.10 (s, 1, NH), 9.54 (s, 1, NH), 7.85–6.97 (m, 4, aromatic), 2.93 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 191 (molecular ion).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.70; H, 4.81; N, 21.70.

The material remaining in the thimble, after additional lixiviation with hot dioxane (4 × 100 ml), yielded 7.83 g (17%) of **4**: mp 237–239°; ir (Nujol) 3350 and 3230 (NH), 1675 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 217 (1), 191 (33), 163 (83), 162 (97), 146 (93), 30 (100). A field ionization mass spectrum displayed a parent peak at *m/e* 382.

Anal. Calcd for $C_{18}H_{18}N_6O_4$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.40; H, 5.05; N, 22.25.

A 100-MHz NMR spectrum of **4** was obtained in DMSO-d_6 and in DMSO-d_6 with added trifluoroacetic acid (TFA). The added TFA served to sharpen the spectrum and to shift any signals due to H_2O or exchangeable protons downfield. The DMSO-d_6–TFA spectrum indicated the presence of two or more conformers in solution, showing NH resonances at δ 11.78, 11.72, 11.17, 10.14, and 8.86, aromatic multiplets at 8.14–7.89 (4), 7.80–7.34 (6), and 7.34–7.00 (6), and methyl signals at 3.34 (broad, 3), 3.23 (sharp, 3), 2.79 (sharp, 3), and 2.71 (broad, 3). The integral intensities of the NH signals could not be accurately determined, but it was clear that the integral ratio of total aromatic protons to total NCH_3 protons was 4:3, respectively.

B. Sodium Hydride Method. A 31.9-g (0.167 mol) quantity of **2b** (mp 152–154°, prepared in similar fashion to **2a** in 84% yield) and 10.2 g (0.423 mol) of NaH (Alfa) in 600 ml of dimethoxyethane and 30 ml of DMSO were heated at reflux for 15 hr. (The reaction was monitored by withdrawing aliquots and diluting them with water. When starting ester still remained, its presence was evident at this point by its appearance as a precipitate.) The reaction mixture was cooled, diluted with 3 l. of ice-cold water, and acidified with concentrated HCl to yield a tan precipitate which was collected and dried to yield 22.4 g. Lixiviation with several portions of hot dioxane left 4.31 g (14%) of **4**. Crystallization of **3** from the hot dioxane extract yielded 6.97 g (22%).

Preparation of 2-Isocyanatobenzoyl Chlorides 6a and 6b. 2-Isocyanatobenzoyl chloride (**6a**) was prepared as reported[8] in 82% yield, bp 85° (0.3 mm) [lit.[8] bp 105° (6 mm)].

A 496-g (2.51 mol) quantity of 5-chloroisatoic anhydride (Aldrich), 2 kg of $SOCl_2$, and 3 ml of pyridine were heated at reflux. After 8 days (solution had not resulted), an additional 1 kg of $SOCl_2$ and 2 ml of pyridine were added. After 2 weeks, 2 l. of dioxane was added. After 3 weeks at reflux, solution had resulted, and the reaction solution was cooled and concentrated to yield a slurry. Filtration removed 176 g of yellow solid.[17] The filtrate (475 g) was distilled to yield 153 g (31%) of **6b**: mp 53–57°; bp 115–117° (1.3 mm); ir (Nujol) 3100 (CH), 2280 (NCO), 1740 cm^{-1} (C=O).

Preparation of 3,4-Dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (7a). To a stirred solution of 20.5 g (0.113 mol) of **6a** in 1 l. of CH_2Cl_2 at 0° was added a solution of 5.21 g (0.113 mol) of methylhydrazine and 114 g (0.113 mol) of triethylamine in 200 ml of CH_2Cl_2 over a 30-min period. The reaction solution was cloudy during the addition, clear at the end, and after ca. 15 min a precipitate began forming. After 20 hr, the precipitate was collected, washed with H_2O, and dried to yield 3.04 g of solid. The filtrate was washed with H_2O and concentrated to 150 ml. An additional 0.08 g of solid was precipitated and collected as above: total yield of **7a** 3.12 g (14.4%);[18] mp 266–267°; ir (Nujol) 3270 and 3190 (NH), 1725 (C=O), 1630 cm^{-1} (C=O); NMR (DMSO) δ 9.44 (s, 1, NH), 8.84 (s, 1, NH), 7.90–6.93 (m, 4, aromatic), 3.30 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 191 (molecular ion).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.70; H, 4.73; N, 22.17.

Preparation of 3,4-Dihydro-4-methyl-7-chloro-1*H*-1,3,4-benzotriazepine-2,5-dione (7b). To a stirred solution of 131 g (0.607 mol) of **6b** in 1200 ml of CH_2Cl_2 at 0° was added a solution of 28.0 g (0.607 mol) of methylhydrazine and 61.4 g (0.607 mol) of triethylamine in 400 ml of CH_2Cl_2 over a 30-min period. The reaction appearance was identical with that of **7a.** After 1 hr the precipitate was collected and dried to yield 19.8 g (14%), mp 280–284°, of **7b:** mp 293–295° (dioxane–hexane); ir (Nujol) 3250 and 3150 (NH), 1725 (C=O), 1630 cm^{-1} (C=O); NMR (DMSO) δ 9.73 (s, 1, NH), 9.03 (s, 1, NH), 7.88–7.02 (m, 3, aromatic), 3.27 (s, 3, CH_3).

Anal. Calcd for $C_9H_8ClN_3O_2$: C, 47.90; H, 3.57; N, 18.62. Found: C, 48.10; H, 3.64; N, 18.99.

Preparation of 3,4-Dihydro-3,4-dimethyl-1*H*-1,3,4-benzotriazepine-2,5-dione (8a). A. From 3. To a stirred mixture of 0.900 g (37.5 mmol) of NaH in 20 ml of DMF under nitrogen was added 5.73 g (30.0 mmol) of **3.** To the resulting yellow solution was slowly added 10 ml of CH_3I with ice-bath cooling. The reaction was exothermic and a white precipitate resulted. After 2 hr of stirring at room temperature, the reaction mixture was partitioned between H_2O and CH_2Cl_2 and the organic extracts were dried (Na_2SO_4) and concentrated to leave an oil which was triturated with ether to yield 3.80 g (62%) of **8a:** mp 185–188° (lit.[9] mp 189–190°); ir (Nujol) 3260 (NH), 1705 (C=O), 1625 cm^{-1} (C=O); NMR (DMSO) δ 9.78 (s, 1, NH), 8.05–7.05 (m, 4, aromatic), 3.23 (s, 3, CH_3), 2.94 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.50; H, 5.48; N, 20.52.

B. From 7a. To a stirred mixture of 1.20 g (50.0 mmol) of NaH in 25 ml of DMF under nitrogen was added 8.70 g (45.5 mmol) of **7a.** To the resulting yellow solution was slowly added 15 ml of CH_3I with ice-bath cooling. The reaction was exothermic and a white precipitate resulted. After 3 hr of stirring at room temperature the reaction mixture was partitioned between H_2O and CH_2Cl_2 and the organic extracts were dried (Na_2SO_4) and concentrated to yield 8.60 g of white solid after trituration with hexane, mp 175–185°. Crystallization from CH_2Cl_2–hexane yielded 5.40 g (58%) of **8a,** mp 186–189°; ir of this sample was identical with that made from **3,** and a mixture melting point of the two samples was undepressed.

Preparation of 3,4-Dihydro-3,4-dimethyl-7-chloro-1*H*-1,3,4-benzotriazepine-2,5-dione (8b). To a stirred mixture of 0.96 g (40.0 mmol) of NaH in 25 ml of DMF under nitrogen was added 9.02 g (40.0 mmol) of **7b.** After 5 min of stirring a 10-ml volume of CH_3I was added slowly with ice-bath cooling. The mixture was partitioned between H_2O and CH_2Cl_2 and the organic extracts were dried (Na_2SO_4) and concentrated to leave 12.9 g of sticky solid. Recrystallization (CH_2Cl_2–ethanol) afforded 5.34 g (55%) of **8b:** mp 218–220° (lit.[9] mp 222°); ir (Nujol) 3250 and 3175 (NH), 1705 (C=O), 1635 cm^{-1} (C=O); NMR (DMSO) δ 9.53 (s, 1, NH), 7.77–6.95 (m, 3, aromatic), 3.22 (s, 3, CH_3), 2.97 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{10}ClN_3O_2$: C, 50.11; H, 4.20; N, 17.53. Found: C, 50.40; H, 4.23; N, 17.63.

Preparation of 3-Amino-2,4(1*H*,3*H*)-quinazolinedione (12). A. From Methyl 2-[(Methoxycarbonyl)amino]benzoate (18). To 35.4 g (0.200 mol) of **1a** was added 10 ml of methanol with ice-bath cooling. After the exothermic addition the ir (neat) showed no remaining isocyanate. The excess methanol was evaporated to leave 40.69 (97%) of **18** as a light oil (lit.[19] mp 59–61°): ir (neat) 3300 (NH), 1715 (carbamate C=O), 1690 cm^{-1} (ester C=O).

To 40.6 g (0.194 mol) of **18** in 250 ml of absolute ethanol was added 85 ml of hydrazine hydrate (Eastman). After 15 min of stirring a voluminous precipitate was present.[20] After 16 hr at reflux, the reaction mixture was cooled and the precipitate was collected and dried to afford 30.7 g (89%) of **12:** mp 287.5–290° (lit.[14] mp 291.5–293°); ir (Nujol) 3340 (NH), 1725 (C=O), 1645 cm^{-1} (C=O); NMR (DMSO) δ 10.50–8.33 (broad signal, NH), 8.12–7.05 (m, 4, aromatic), 5.52 (s, 2, NH_2).

An 8.85-g (50.0 mmol) quantity of **12,** 7.88 g (52.1 mmol) of *p*-nitrobenzaldehyde (Aldrich), and 450 ml of absolute ethanol were heated at reflux for 36 hr. The mixture was cooled and the precipitate was removed by filtration and washed with ethanol to leave 14.4 g (93%) of Schiff base **23:** mp 318–319°; ir (Nujol) 3190 (NH), 1720 (C=O), 1665 cm^{-1} (C=O); NMR (DMSO) δ 8.75 (s, 1, aldimine), 8.35–6.90 (m, 8, aromatic).

Anal. Calcd for $C_{15}H_{10}N_4O_4$: C, 58.06; H, 3.25; N, 18.06. Found: C, 58.23; H, 3.30; N, 18.02.

B. From 2-Aminobenzoylhydrazine (10). 2-Aminobenzoylhydrazine, mp 118–122° (lit.[21] mp 120–121°), was prepared in 86% yield according to the method of Barlin.[21,22] A 30.2-g (0.200 mol) quantity of **10,** 12.0 g (0.200 mol) of urea, and 300 ml of decalin were heated at reflux until evolution of ammonia ceased (4 hr). The reaction mixture was cooled and the precipitate was collected, washed with ether, and recrystallized (DMSO–H_2O) to yield 28.69 g (82%) of **12** (mp 281–284°).

C. From 1-(2-Aminobenzoyl)semicarbazide (13). A sample of **13,** mp 194–196°, was prepared using the method described by Langis and Charest[12] for 1-(2-amino-5-chlorobenzoyl)semicarbazide. A 10.0-g (0.0515 mol) quantity of **13** and 75 ml of decalin were heated at reflux for 3 hr. The mixture was cooled and the precipitate was collected, washed with ether, and recrystallized (DMSO–H_2O) to yield 6.10 g (67%) of **12** (mp 286–290°).

Preparation of 1-Methyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione (21). A. From Methyl 2-[(Methyl)amino]benzoate (19). 2-[(Methyl)amino]benzoic acid was converted to ester **19,** bp 75° (0.15 mm) [lit.[23] bp 130–131° (15 mm)], using a standard procedure.[24] Carbamate ester **20,** bp 120–125° (0.50 mm) [lit.[15] bp 95–104° (0.12–0.20 mm)], was prepared from **19** and ethyl chloroformate in 66% yield. A solution of 5.50 g (23.2 mmol) of **20** and 13.0 ml of hydrazine hydrate in 40 ml of ethanol was heated at reflux for 2 hr. The mixture was cooled and the precipitate was collected, washed with ethanol, and dried to yield 2.23 g (50%) of **21:** mp 240–241°; ir (Nujol) 3310 and 3240 (NH), 1710 (C=O), 1640 cm^{-1} (C=O); NMR (TFA) δ 8.70–7.60 (m, 4, aromatic), 3.92 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 191 (molecular ion).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.30; H, 4.69; N, 22.15.

A 1.00-g (5.23 mmol) quantity of **21,** 0.790 g (5.23 mmol) of *p*-nitrobenzaldehyde, and 50 ml of absolute ethanol were heated at reflux for 8 hr. The mixture was cooled and the precipitate was removed by filtration and washed with ethanol to leave 1.30 g (77%) of Schiff base **24:** mp 246–247°; ir (Nujol) 1700 (C=O), 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.45; H, 3.44; N, 17.33.

B. From 12. To a stirring mixture of 2.27 g (94.5 mmol) of NaH in 40 ml of DMF under nitrogen was added 16.8 g (94.5 mmol) of **12.** After 5 min, a 20-ml volume of CH_3I was added slowly and with cooling, to produce a white precipitate in the exothermic reaction medium. After 4 hr of stirring the reaction mixture was diluted with water and the resulting precipitate was collected and dried to yield 10.7 g (59%) of **21** (mp 228–235°). Recrystallization of a portion from ethanol gave white plates, mp 238–241°, whose ir was identical with that of the material prepared in part A.

Preparation of 3,3′(2*H*,2′*H*)-biquinazoline-2,2′,4,4′-(1*H*,1′*H*)-tetrone (25). A. From 6a. To 18.2 g (0.100 mol) of **6a** in 100 ml of CH_2Cl_2 at 0° was added a solution of 3.22 g (0.100 mol) of 95% hydrazine (Eastman) and 10.1 g (0.100 mol) of triethylamine in 50 ml of CH_2Cl_2 over a 30-min period. The mixture was stirred for 1 hr and the precipitate was collected, washed with water, and dried to afford 21.1 g (66%) of **25:** mp >340° (DMSO–H_2O); ir (Nujol) 3280 (NH), 1625, 1605, 1580 cm^{-1}; NMR (DMSO) δ 8.45–7.25 (m, aromatic); mass spectrum (70 eV) *m/e* 322 (molecular ion).

Anal. Calcd for $C_{16}H_{10}N_4O_4$: C, 59.63; H, 3.13; N, 17.39. Found: C, 59.88; H, 3.05; N, 17.50.

B. From 1a. To 17.7 g (0.100 mol) of **1a** in 75 ml of CH_2Cl_2 at 0° was added 3.22 g (0.100 mol) of 95% hydrazine in 20 ml of CH_2Cl_2 over a 20-min period. After 1 hr the precipitate was collected to afford 13.6 g (42%) of **25** (mp >340°) whose ir was identical with that made in part A.

Additional Preparations of 12. A. From 6a. To an ice-cold solution of 16.0 g (0.500 mol) of hydrazine in 100 ml of CH_2Cl_2 was added 9.08 g (50.0 mmol) of **6a** in 50 ml of CH_2Cl_2 over a 35-min period. After 1 hr the precipitate was removed by filtration, washed with H_2O, and dried to yield 8.02 g (90%) of **12,** mp 280–284°.

B. From 1a. To an ice-cold solution of 32.0 g (1.00 mol) of hydrazine in 200 ml of CH_2Cl_2 was added 17.7 g (0.100 mol) of **1a** in 100 ml of CH_2Cl_2 over a 60-min period. After 1 hr the precipitate was removed by filtration and washed with CH_2Cl_2 to yield 15.6 g (88%) of **12,** mp 283–287°.

Acknowledgment. We thank W. H. Braun and G. McGowan (Toxicology Department) for spectral data and Dr. D. L. Trepanier for helpful suggestions. We also wish to thank Drs. J. P. Heeschen and J. C. Tou (Analytical Labo-

ratories) for the 100-MHz NMR and field ionization mass spectral studies, respectively.

Registry No.—**1a,** 1793-07-3; **2a,** 55043-76-0; **2a** Schiff base, 55043-77-1; **2b,** 55043-78-2; **3,** 55043-79-3; **4,** 55043-80-6; **5b,** 4743-17-3; **6a,** 5100-23-2; **6b,** 18928-48-8; **7a,** 55043-81-7; **7b,** 55043-82-8; **8a,** 23829-79-0; **8b,** 23829-80-3; **10,** 1904-58-1; **12,** 30386-01-7; **13,** 55043-83-9; **18,** 7143-42-2; **19,** 85-91-6; **20,** 33923-02-3; **21,** 55043-84-0; **23,** 55043-85-1; **24,** 55043-86-2; **25,** 55043-87-3; methylhydrazine, 60-34-4; *p*-nitrobenzaldehyde, 555-16-8; potassium *tert*-butoxide, 3999-70-0; methanol, 67-56-1; urea, 57-13-6; ethyl chloroformate, 541-41-3.

References and Notes

(1) (a) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68,** 747 (1968); (b) L. H. Sternbach in "The Benzodiazepines", Raven Press, New York, N.Y., 1973, pp 1–27.

(2) Class here refers to position of the nitrogen atoms in the triazepine ring and not to positions of unsaturation. The six classes, thus, refer to nitrogen atoms in the following positions: 1,3,4; 1,2,5; 1,3,5; 1,2,4; 1,2,3; and 2,3,4.

(3) For example, see H. Kohl, P. D. Desai, A. N. Dohadwalla, and N. J. de Souza, *J. Pharm. Sci.*, **63,** 838 (1974).

(4) (a) For example, see S. Rossi, British Patent 1,219,847; *Chem. Abstr.*, **74,** 141901j (1971); S. Rossi, German Patent 2,064,207; *Chem. Abstr.*, **75,** 76854a (1971). (b) We have developed a new entry into this class of compound in our laboratories which will be the subject of a later report.

(5) For example, see G. Doleschall, G. Hornyak, B. Agai, G. Simig, J. Fetter, and K. Lempert, *Tetrahedron Lett.*, 5069 (1973), and references cited therein.

(6) The structure of **2a** follows from spectral and chemical evidence. The NCH_3 and NH_2 signals in the NMR spectrum of **2a** appear as singlets at δ 3.19 and 3.97, respectively. Compound **2a** formed a Schiff base with *p*-nitrobenzaldehyde (see Experimental Section). Based on the known relative nucleophilicities of the nitrogen atoms in methylhydrazine, **2a** is the expected isomer from the reaction of **1a** with methylhydrazine. Other authors[7] have reported reactions of methylhydrazine with phenyl isocyanates to yield products analogous to **2,** but offer no evidence to distinguish their products from the other possible isomers.

(7) (a) M. Wilcox, *J. Med. Chem.*, **11,** 171 (1968); (b) French Patent 1,521,959; *Chem. Abstr.*, **71,** 3166k (1969).

(8) Y. Iwakura, K. Uno, and S. Kang, *J. Org. Chem.*, **31,** 142 (1966).

(9) O. Hromatka, F. Krenmüller, and M. Knollmüller, *Monatsh. Chem.*, **100,** 934 (1969).

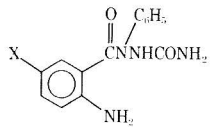
(10) (a) E. Thielepape, *Chem. Ber.*, **68,** 751 (1935); (b) W. S. Fones, *J. Org. Chem.*, **14,** 1099 (1949); (c) see also the preparation of **21** from **12** in the Experimental Section.

(11) A. K. Butler in "Organic Reaction Mechanisms", B. Capon and C. W. Rees, Ed., Wiley, New York, N.Y., 1972, p 189.

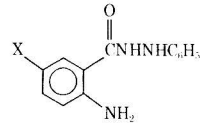
(12) A. L. Langis and M. P. Charest, *Chim. Ther.*, 349 (1967).

(13) R. L. Jacobs, *J. Heterocycl. Chem.*, **7,** 1337 (1970). We thank Dr. Jacobs, of Sherwin-Williams Chemicals, for an authentic sample of this compound. Compound **12** was also identical with a commercial sample of 3-amino-2,4(1*H*,3*H*)-quinazolinedione obtained from Carbolabs Inc., New Haven, Conn.

(14) Two of the benzotriazepinediones reported by Langis and Charest were prepared from the *N*-(2-aminobenzoyl)semicarbazides i and ii by thermal cyclization in decalin. Since the reported melting points for the products thus obtained from i and ii do not closely jibe, respectively, with those of compounds obtained from their treatment of iii and iv with urea in decalin (compounds which we suspect are quinazolinediones), the products derived from i and ii may be authentic benzotriazepinediones.



i, X = H
ii, X = Cl



iii, X = H
iv, X = Cl

(15) (a) D. M. Bailey, U.S. Patent 3,607,866 (1971); *Chem. Abstr.*, **75,** 140910v (1971); (b) Dr. Bailey has examined a preprint of this manuscript and concurs with these findings.

(16) N. P. Peet and S. Sunder, *J. Org. Chem.*, **39,** 1931 (1974).

(17) The structure of this material has been identified and will be disclosed in a future report.

(18) The reactant concentration in this preparation was 0.094 *M*. When run at a reactant concentration of 0.25 *M*, the yield of **7a** was 10.7%.

(19) E. Kühle and R. Wegler, *Justus Liebigs Ann. Chem.*, **616,** 183 (1958).

(20) An aliquot of the reaction mixture withdrawn at this point showed the precipitate to be **12.**

(21) G. B. Barlin, *J. Appl. Chem.*, **12,** 148 (1962).

(22) We have also prepared **10** by heating isotoic anhydride and hydrazine hydrate neat or in DMF at 50°.

(23) J. R. A. Pollack and R. Stevens, Ed., "Dictionary of Organic Compounds", Vol. 4, Oxford University Press, London, 1965, p 2119.

(24) A. I. Vogel, "Practical Organic Chemistry", Longmans, Green and Co., New York, N.Y., 1956, p 1000.

Synthesis of Fused Phenothiazines. 2,3-Dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione and 6*H*,16*H*-[1,5]Diazocino[3,2,1-*kl*:7,6,5-*k'l'*]diphenothiazine-6,16-dione

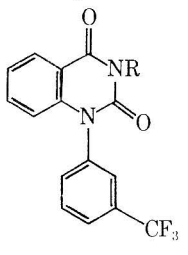
Joseph Weinstock,* Dimitri E. Gaitanopoulos, and Blaine M. Sutton

Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

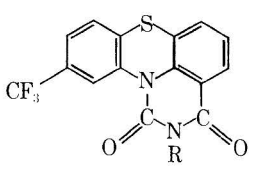
Received February 25, 1975

10-Trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-3-one-1-thione (**6**) was prepared starting from 8-trifluoromethylphenothiazine-1-carboxylic acid (**3**) by thermal cyclization of the acid isothiocyanate. This was converted to tee 1,3-dione by acid hydrolysis of the 1-methyl mercaptan derivative. Alkylation and oxidation to sulfoxide and sulfone derivatives are described. Pyrolysis of the anhydride of **3** gave 3,13-bis(trifluoromethyl)-6*H*,16*H*-[1,5]diazocino[3,2,1-*kl*:7,6,5-*k'l'*]diphenothiazine-6,16-dione.

Quinazoline-2,4-diones (**1**), derived from flufenamic acid, were recently described as anti-inflammatory agents.[1]



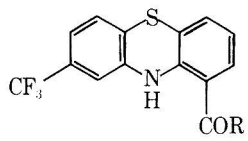
1



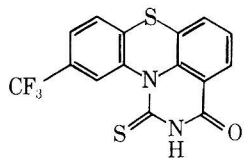
2

Since we previously observed anti-inflammatory properties with 8-trifluoromethylphenothiazine-1-carboxylic acid (**3**),[2] an analog of flufenamic acid, we undertook preparation of some pyrimidinediones (**2**) derived from **3.**

Typical syntheses of quinazolinediones such as **1** involve fusing the *N*-arylanthranilic acid, ester, or amide with urea, thiourea, or ethyl carbamate at 200°.[3] However, these reaction conditions using **3** returned unreacted starting material. Also treatment of the ethyl ester of **3** with sodium cyanate in trifluoroacetic acid, another quinazoline-1,3-dione synthesis,[4] also failed. A possible cause for these failures was a low reactivity of the diaryl nitrogen owing to it



3, R = OH
4, R = Cl
5, R = NCS



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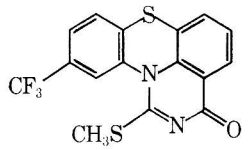

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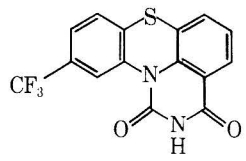

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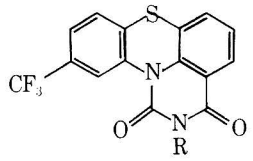
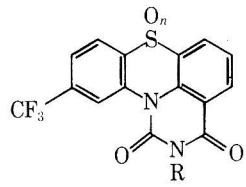


9, R = CH_2CH_3
10, R = CH_2CH_2OH
11, R = $CH_2CHOHCH_2OH$
12, R = $CH_2CHOAcCH_2OAc$



13, $n = 1$
14, $n = 2$

being part of the phenothiazine ring system. It appeared that building the new ring in a stepwise fashion using reactive intermediates might overcome this problem.

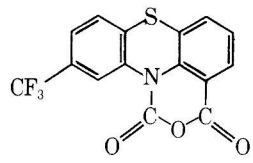
Reaction of **3** with phosphorus trichloride and dimethylformamide in chloroform gave the acid chloride **4** in 86% yield. Treatment of **4** with potassium thiocyanate in acetone gave **5** in 97% yield, which on heating to 220° in diphenyl ether cyclized to form **6** in 91% yield. Since attempts to hydrolyze **6** with chloroacetic acid failed, **6** was alkylated with iodomethane and potassium hydroxide in acetone to give **7** in 93% yield. Hydrolysis of this with HCl in aqueous ethanol gave the target compound **8** in 98% yield.

In order to obtain compounds likely to have the desired biological activity, **8** was alkylated using alkyl halides and sodium hydride in DMF to obtain **9** and **10.** Alkylation of **8** with 2,3-diacetoxy-1-chloropropane and subsequent hydrolysis with methanolic hydrochloric acid led to **11.** Oxidation of **8** and its N-alkylated derivatives with *m*-chloroperbenzoic acid gave the sulfoxides **13** shown in Table I. Oxidation with excess hydrogen peroxide in glacial acetic acid gave the sulfones **14** also shown in Table I.

Table I
2-Alkyl-10-trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione Sulfoxides (13) and Sulfones (14)[a]

Compd[a]	R	n	Yield, %	Mp, °C	S[c]
13a	H	1	76	302–304	M
14a	H	2	85	290–293	M
13b	CH_2CH_3	1	75	184–186	M
14b	CH_2CH_3	2	89	208–210	M
13c	CH_2CH_2OH	1	77	205–206	E
14c	CH_2CH_2OH	2	58	189–192	B
13d	$CH_2CHOHCH_2OH$	1	36	224–225	CM
14d	$CH_2CHOHCH_2OH$	2	90[b]	223–226	BM

[a] The compounds were characterized by ir (Nujol): sulfoxides ~9.5 μ and sulfones ~8.5 μ. [b] Crude yield. [c] Solvents of crystallization: B, 1-chlorobutane; C, chloroform; E, ethanol; M, methanol; CM, chloroform–methanol; BM, 1-chlorobutane–methanol. [d] Satisfactory analytical data (±0.3% for C, H, N) were reported for compounds **13a–d** and **14a–c**; the data for **14d** agreed with the formula $C_{18}H_{13}F_3N_2C_6S\cdot\frac{3}{4}H_2O$. Ed.



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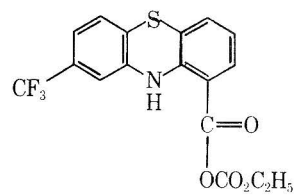

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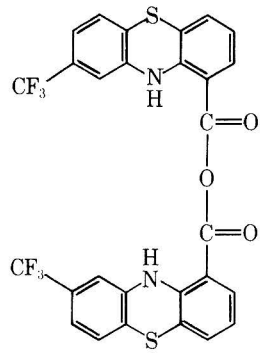

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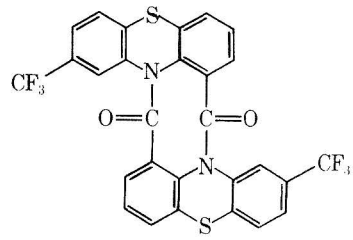
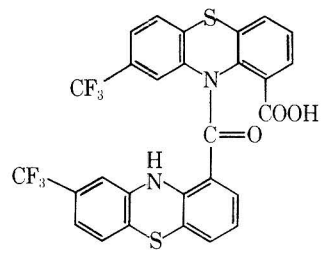


18



19

In an attempt to form the isatoic anhydride **15,** which is an oxygen analog of **2,** the triethylamine salt of the carboxylic acid **3** was treated with ethyl chloroformate.[5] This gave the mixed anhydride **16** in 81% yield. In an attempt to force the formation of **15, 16** was heated at 260° for 20 min. However, the cyclic dilactam **18** was formed in about 30% yield. The structure of **18** was established by elemental analysis, absence of NH bonds in the ir, and correct M^+ ion in the mass spectrum. When the mixed anhydride was allowed to reflux with excess ethyl chloroformate, a red product was formed which was identified as the symmetrical anhydride **17.** Heating this in diphenyl ether gave **18** in 54% yield. In addition, **17** was seen in the reaction mixture during the pyrolysis of **16** to **18,** suggesting that it was an intermediate. An O to N acyl group migration in **17** could form **19,** which in turn could lose water to give **18.** Thus the conversion of **17** to **18** is facile because only intramolecular reactions are involved.

Experimental Section

Melting points (uncorrected) were determined using a Thomas-Hoover capillary melting point apparatus. NMR spectra were obtained in a Varian T-60 instrument, and ir on a Perkin-Elmer 735 infrared spectrophotometer. Mass spectra were determined using a Hitachi Perkin-Elmer RMN-6E spectrometer. For thin layer chromatography the following solvent systems were used: chloroform for **4** and **5;** 75% chloroform–cyclohexane for **16, 17,** and **18;** and 95% chloroform–methanol for all the other compounds.

8-Trifluoromethylphenothiazine-1-carboxylic Acid Chloride (4). 8-Trifluoromethylphenothiazine-1-carboxylic acid (62.2 g, 0.20 mol) was added to a stirred mixture of chloroform (300 ml) and phosphorus trichloride (300 ml). The resulting brown suspension was cooled in an ice bath while dimethylformamide (50 ml) was added slowly until a reddish brown solution formed. After the mixture was stirred for 4 hr at room temperature, the chloroform and excess phosphorus trichloride were evaporated under reduced pressure. The resulting reddish-brown solid residue was dissolved in boiling *n*-hexane (1.5 l.). The hot clear reddish solution was decanted from a viscous, insoluble material, and on cooling, large red

needles formed. The solid was collected by filtration and washed with hexane to give 57.0 g (86%) of the desired product: mp 124–126°; ir (Nujol) 3.00 (NH), 5.86 μ (C=O).

8-Trifluoromethylphenothiazine-1-carboxylic Acid Isothiocyanate (5). A solution of 56.5 g (0.172 mol) of 8-trifluoromethylphenothiazine-1-carboxylic acid chloride in 450 ml of acetone was added over a 15-min period to a stirred solution of 25.0 g (0.257 mol) of potassium thiocyanate in 200 ml of acetone. The resulting reddish-brown suspension was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure to approximately 300 ml and then diluted with 700 ml of water. The product was collected by filtration and washed thoroughly with water to give 58.7 g (97%) of light brown crystals: mp 145–150°; ir (Nujol) 5.10 (N=C=S), 5.86 μ (C=O); NMR ($CDCl_3$) δ 6.55–7.39 (m, 5 H, 3,4,6,7,9-H), 7.60 (d, 1 H, 2-H), 10.6 (s, 1 H, NH).

10-Trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazin-3-one-1-thione (6). A slurry of 53.7 g (0.168 mol) of **5** in 30 ml of diphenyl ether was heated in an oil bath at 210° for 1 hr. The reaction mixture first became a homogenous liquid and then turned into a solid mass. The cooled reaction mixture was refluxed for several minutes in 100 ml of toluene and cooled to room temperature, and the insoluble material was collected by filtration and washed with several small portions of toluene to give 48.7 g (91%) of a yellowish product, mp 296–299°. The material was sufficiently pure for use in the next step. A small sample was recrystallized from ethanol for analysis: mp 297–299°; ir (Nujol) 3.12 and 3.22 (NH), 5.85 μ (C=O); NMR ($CDCl_3$–DMSO-d_6) δ 7.20–8.15 (m, 5 H, 4,5,6,8,9-H), 8.49 (s, 1 H, 11-H), 13.00 (s, 1 H, NH).

1-Methylmercapto-10-trifluoromethyl-3*H*-pyrimido[5,6,1-*kl*]phenothiazin-3-one (7). A 53.6-g (0.152 mol) sample of **6** was added to a stirred solution of 8.95 g (0.160 mol) of potassium hydroxide in 1680 ml of acetone and 720 ml of water. After all the solid had dissolved and a clear yellow solution formed, 22.8 g (10 ml, 0.160 mol) of methyl iodide was added all at once. A slight rise in temperature was noticed, and 2 min later the product began to precipitate. The reaction mixture was stirred at room temperature for 18 hr, diluted with 1 l. of water, and then chilled in an ice bath for several hours. The resulting light yellow solid was collected by filtration and washed with water to give 51.5 g (93%) of product, mp 225–228°. The material was used in the next step without any further purification. A small sample was crystallized from ethanol for analysis: mp 229–231°; ir (Nujol) 5.91 μ (C=O); NMR ($CDCl_3$ δ 2.75 (s, 3 H, CH_3S), 7.44 (m, 4 H), 8.00 (m, 2 H).

10-Trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione (8). A stirred suspension of 53.6 g (0.146 mol) of **7** in 240 ml of concentrated hydrochloric acid and 800 ml of ethanol was heated under reflux for 4 hr. After the reaction mixture was concentrated to approximately one-half its original volume by boiling off the excess solvents, and then chilled, the product was collected by filtration and washed thoroughly with water to give 47.7 g (98%) of pale yellow needles, mp 278–280°. A sample was crystallized from ethanol: mp 278–280°; ir (Nujol) 3.12 and 3.3 (NH), 5.80 and 5.89 μ (C=O); NMR ($CDCl_3$–DMSO-d_6) δ 7.60–8.00 (m, 5 H), 8.10 (s, 1 H, 11-H), 11.80 (s, 1 H, NH).

Alkylation of the Pyrimidophenothiazine-1,3-dione (8). Preparation of 2-Ethyl-10-trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione (9). A 4.2-g (0.100 mol) sample of 57% sodium hydride in mineral oil was added to a stirred solution of 28.0 g (0.0834 mol) of **8** in 220 ml of dry dimethylformamide. The mixture was stirred for 1 hr at room temperature, then 16.8 g (8.6 ml, 0.108 mol) of ethyl iodide was added. The resulting greenish-yellow turbid mixture was stirred for 4.5 hr at room temperature and then filtered to give a clear yellow solution. The filtrate was evaporated to dryness under reduced pressure, and the pasty residue was triturated with petroleum ether to remove the mineral oil. The crude solid product was precipitated from a methanol–water mixture to give 28.8 g of a yellow powder. The material was crystallized from ethanol to give 23.2 g (73%), mp 148–150°. A further crystallization of a small sample raised the melting point to 150–152°: ir (Nujol) 5.82 and 5.95 μ (C=O); NMR ($CDCl_3$) δ 1.40 (t, 3 H, CH_3) 4.21 (q, 2 H, CH_2), 7.10–7.70 (m, 6 H) 7.85–8.2 (m, 2 H).

A twofold excess of sodium hydride and a fourfold excess of 2-bromoethanol were used to prepare **10.** The crude material was purified by column chromatography (silica gel, chloroform, and then 90% chloroform–methanol). The product crystallized from methanol in 47% yield: mp 90–93°; ir (Nujol) 2.95 (broad OH), 5.82 and 6.00 μ (C=O); NMR ($CDCl_3$) δ 2.75 (s, broad, 1 H, OH), 3.92 and 4.40 (2 t, 4 H, CH_2CH_2), 7.00–7.80 (m, 5 H), 7.90 (s, 1 H, 11-H).

3-Chloro-1,2-diacetoxypropane,[6] bp 80–83° (0.1 mm) (0.112 mol), and sodium hydride (0.0801 mol) were used to prepare **12.** The reaction mixture was heated at 100–110° for 40 hr in the presence of a catalytic amount of potassium iodide. The product was isolated as an oil and was used in the next step without purification. A small amount was purified by column chromatography (silica gel, chloroform) for spectral studies: ir (neat) 5.70 (C=O, acetyl), 5.80 and 5.95 μ (C=O, dione); NMR ($CDCl_3$) δ 2.08 and 2.12 (2 s, 6 H, 2 CH_3), 3.6–4.8 (m, 5 H, CH_2CHCH_2), 7.40 (m, 4 H), 8.00 (m, 2 H).

2-(2,3-Dihydroxypropyl)-10-trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione (11). A mixture of 48.1 g (0.0975 mol) of the crude **12** in 200 ml of methanol and 25 ml of concentrated hydrochloric acid was heated under reflux for 0.5 hr, then allowed to stand overnight at room temperature. The white solid that precipitated was isolated by filtration and washed with water to give 12.9 g of crude **11.** Additional material was obtained from the mother liquor. Overall crude yield was 24.6 g (62%). The first crop was recrystallized twice from chloroform to give 10.13 g of product: mp 159–162°; ir 2.96–3.06 (broad OH), 5.82 and 5.95 μ (C=O); NMR ($CDCl_3$–DMSO-d_6) δ 3.60 and 3.66 (2 s, 2 H, 2 OH), 3.8–4.68 (m, 5 H, CH_2CHCH_2), 7.00–7.60 (m, 4 H), 7.70–8.10 (m, 2 H).

Oxidation of the Pyrimidophenothiazine-1,3-diones. Preparation of the Sulfoxides. A 10% excess of *m*-chloroperbenzoic acid was added in small portions to a stirred, cold (0–5°) solution or suspension of the substrate (1 g/10 ml) in absolute methanol. The resulting mixture was stirred for 0.5–1 hr in the cold and then for an additional 1–4 hr at room temperature. The product precipitated from the reaction mixture, and after chilling was collected by filtration and washed with ice-cold methanol.

Preparation of the Sulfones. A solution of the substrate in glacial acetic acid (1 g/20 ml) and 3 equiv of 30% hydrogen perioxide was heated at 75–85° for 3–6 hr, cooled, and diluted with water to precipitate the product. The product was collected by filtration and washed with water.

Carbonic Acid Monoanhydride with 8-Trifluoromethylphenothiazine-1-carboxylic Acid Ethyl Ester (16). Triethylamine (3.04 ml, 0.022 mol) was added dropwise to a cold (0–5°), stirred suspension of 8-trifluoromethylphenothiazine-1-carboxylic acid (6.22 g, 0.020 mol) in 40 ml of ethyl chloroformate. The resulting orange suspension was stirred at room temperature for 15 hr, then diluted with dry benzene (100 ml), and the insoluble triethylamine hydrochloride was removed by filtration. After the filtrate was evaporated under reduced pressure, the solid, orange residue was suspended in light petroleum ether (50 ml) and filtered to give 6.22 g (81%) of the mixed anhydride: mp 91–94°; ir (Nujol) 3.02 (NH), 5.55 and 5.85 μ (C=O); NMR ($CDCl_3$) δ 1.40 (t, 3 H, CH_3), 4.40 (q, 2 H, CH_2), 6.60–7.29 (m, 5 H), 7.50 and 7.60 (2 d, 1 H, 2-H), 9.81 (s, 1 H, NH).

8-Trifluoromethylphenothiazine-1-carboxylic Acid Anhydride (17). A solution of 3.0 g (0.00785 mol) of **16** in 10 ml of ethyl chloroformate was heated under reflux for 18 hr. The dark red solution was chilled in an ice bath, and the resulting orange precipitate was collected by filtration and washed with a small portion of ethyl chloroformate and then with light petroleum ether to give 0.87 g (50%) of product, mp 207–208°. The mother liquor was evaporated under reduced pressure, and the oily residue was found to be unreacted starting material. A small sample of **17** was crystallized from chloroform for analysis: mp 207–209°; ir (Nujol) 3.2 (NH), 5.71 and 6.90 μ (C=O); NMR ($CDCl_3$) δ 6.60–7.20 (m, 10 H, 3,4,5,6,7,9- and 3′,4′,5′,6′,7′,9′-H), 7.55 and 7.69 (2 d, 2 H, 2- and 2′-H), 9.80 (s, 2 H, 2 NH).

3,13-Bis(trifluoromethyl)-6*H*,16*H*-[1,5]diazocine[3,2,1-*kl*:7,6,5-*k′l′*]diphenothiazine-6,16-dione (18). A mixture of 1.50 g (0.00239 mol) of **17** and 2 ml of diphenyl ether was heated in an oil bath at 260–265° for 45 min, producing a dark, olive-green solution which solidified when cooled to room temperature. Light petroleum ether (30 ml) was added to the cooled reaction mixture, and the insoluble material was collected by filtration and washed with a small portion of petroleum ether to give 1.22 g of yellow powder. This was dissolved in 50 ml of chloroform, and the resulting solution was extracted with 5% sodium bicarbonate to remove some acid **3.** The chloroform layer was dried with anhydrous sodium sulfate and the resulting dark amber solution was decolorized with Norit. The resulting yellow solution was concentrated to approximately 15 ml and diluted with 50 ml of petroleum ether. After the mixture was chilled in an ice bath for several hours, the light yellow, crystalline product was collected by filtration and washed with petroleum ether to give 0.75 g (54%) of **18:** mp 295–297°; ir

6.90 μ (C=O); NMR (TFA) δ 7.20–7.80 (m, 10 H, 1,2,7,8,9,11,12,17,18,19-H), 8.10 (s, 2 H, 4,14-H); mass spectrum *m/e* 586 (M^+).

Compound **18** was also prepared by pyrolyzing **17** at 260°; the yields, however, were lower.

Acknowledgments. We are indebted to our Analytical and Physical Chemistry Section personnel for analytical and physical data: Miss Edith Reich for elemental analysis and Dr. Edward White and Mr. Gerald Roberts for mass spectra.

Registry No.—**3,** 7220-56-6; **4,** 24539-01-3; **5,** 55223-38-6; **6,** 55223-39-7; **7,** 55223-40-0; **8,** 55223-41-1; **9,** 55223-42-2; **10,** 55223-43-3; **11,** 55223-44-4; **12,** 55223-45-5; **13a,** 55223-46-6; **13b,** 55223-47-7; **13c,** 55223-48-8; **13d,** 55223-49-9; **14a,** 55223-50-2; **14b,** 55223-51-3; **14c,** 55223-52-4; **14d,** 55223-53-5; **16,** 55637-96-2; **17,** 55223-54-6; **18,** 55223-55-7; 3-chloro-1,2-diacetoxypropane, 869-50-1.

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New Syntheses of Thiadiazinones, Thiazolidinedione Hydrazones, and Hydroxythiazoles from Phenyl(trichloromethyl)carbinols[1]

Wilkins Reeve* and Eugene R. Barron

Chemistry Department, University of Maryland, College Park, Maryland 20742

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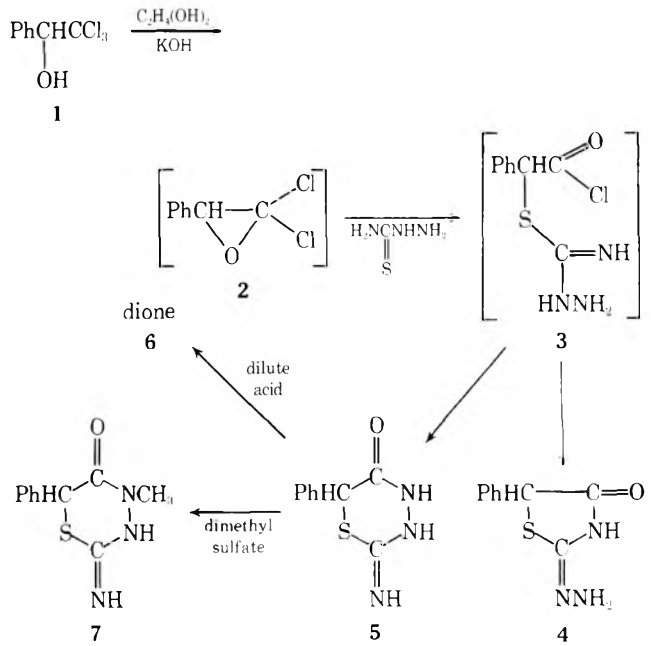
Phenyl(trichloromethyl)carbinol reacts with thiosemicarbazide under basic reaction conditions to form dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one (**5,** 18% yield) and 5-phenyl-2,4-thiazolidinedione 2-hydrazone (**4,** 10% yield), with acetone or benzaldehyde thiosemicarbazones to form derivatives of **4** (65% yield), and with thioacetamide to form 4-hydroxy-2-methyl-5-phenylthiazole (**11,** 18% yield). In the first step of the synthesis of these compounds, phenyl(trichloromethyl)carbinol is postulated to be converted into a dichloro epoxide **2,** and this is attacked by the thioenolate anion of the nucleophile to form an amino acid chloride which then undergoes ring closure to form the heterocyclic ring. The chemistry of the various compounds is discussed.

We have reported two reactions of phenyl(trichloromethyl)carbinol (**1**) with nucleophiles resulting in the formation of heterocyclic rings.[2,3] The thiourea case[2] provides an excellent example of a nucleophile with two reactive sites reacting initially at the α carbon of the carbinol followed by a subsequent ring closure to form the heterocyclic ring. The purpose of this research was to extend the thiourea work to other nucleophiles likewise having two reactive sites. The mechanisms by which methoxide reacts with phenyl(trichloromethyl)carbinol to form α-methoxyphenylacetic acid have been elucidated,[4] and by analogy, the nucleophiles studied here are believed to react by the mechanism given below in Scheme I.

Thiosemicarbazide. The first nucleophile examined was thiosemicarbazide. The initial step in the reaction of this with phenyl(trichloromethyl)carbinol dissolved in ethylene glycol containing potassium hydroxide involves the attack of the thioenolate anion at the α carbon of the intermediate epoxide (**2**) formed in situ from the carbinol (**1**). The postulated intermediate **3** has three –NH– groups available for reaction with the acid chloride and two (**4** and **5**) of the three possible compounds were formed. Compound **5,** dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one, was easily isolated (as the monohydrate) in 18% yield because of its insolubility in the reaction mixture in the pH range of 9.4–5. The structure of this new compound was proven as follows. Hydrolysis with dilute acid gives ammonia and dione **6;** elemental analysis of **6** shows that it must contain the hydrazine moiety so that the ring closure must occur by the acid chloride (**3**) reacting with the hydrazine function. Compound **6** is neutral as would be expected for a diamide; this rules out the 3-amino-2-imino-5-phenyl-4-thiazolidinone structure and establishes the presence of the thiadiazinone ring. This was further collaborated by

Scheme I

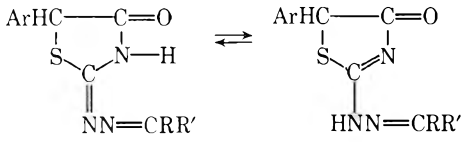


methylation of **5** with dimethyl sulfate and alkali; only a monomethyl derivative (**7**) could be isolated whereas the aminothiazolidinone should form a dimethyl derivative. As expected, **7** could be hydrolyzed to a neutral dione with 2 *N* hydrochloric acid. The position of the methyl group in **7** was established by desulfurization with Raney nickel to *N*-methylphenylacetamide. Upon refluxing **7** with 20% hydrochloric acid for 3 hr the diazine ring opened and reclosed to form 5-phenyl-2,4-thiazolidinedione in 85% yield

together with methylhydrazine, isolated as the sulfate. This rearrangment of 1,3,4-thiadiazines to five-membered rings in strongly acid solution is frequently observed.[5] Under the same hydrolysis conditions, hydrazine was obtained from **5.**

After 5 was filtered off, compound **4** remained in solution and was too soluble to be isolated directly. On adding acetone, the known 5-phenyl-2,4-thiazolidinedione-2-isopropylidenehydrazone slowly precipitated (10% yield) over a period of 1 week. After removal of **4,** acidification of the reaction mixture gave a crude acid fraction which was converted to a mixture of methyl esters. Sixteen components were shown to be present by GLC. Of these the major peak (63% of the ester mixture, 8% yield) was methyl phenylacetate, identified by comparison of the ir and NMR spectra of a collected sample with those of an authentic sample.

Thiosemicarbazones. The thiosemicarbazones of acetone and benzaldehyde were found to react with phenyl(trichloromethyl)carbinol under the same reaction conditions to give the known thiazolidinones **8a** and **8b.** The six-membered ring thiadiazinones cannot be formed from the semicarbazones, and the thiazolidinones are therefore obtained in higher yields.



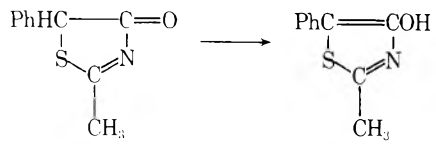
8 **9**

a. Ar = Ph; R = CH_3; R′ = CH_3; 63% yield
b. Ar = Ph; R = Ph; R′ = H; 69% yield
c. Ar = *p*-ClPh; R = CH_3; R′ = CH_3; 79% yield
d. Ar = *p*-CH_3OPh; R = CH_3; R′ = CH_3; 31% yield

The mechanism of formation of these compounds is the same as that shown for compound **4** (Scheme I). Tautomeric structures such as **9** can be written for the **8** series of compounds but NMR spectral evidence supports formula **8.** All of the series **8** compounds have very similar chemical shifts for the carbon-5 proton (δ 5.5), and for the NH proton (δ 12). This latter value is reasonable for structure **8** since the corresponding imino proton of 5-phenyl-2,4-thiazolidinedione has a δ 12.2 value. The alternate structure **9** would be expected to have the NH resonance occur around δ 10.3, the value for the NH proton of benzaldehyde phenylhydrazone.

The reactions of *p*-chlorophenyl(trichloromethyl)carbinol and *p*-methoxyphenyl(trichloromethyl)carbinol with acetone thiosemicarbazone were also studied to see if the yields of products obtained followed the same trends previously observed in the reactions of these carbinols with cyanamide[3] or methoxide;[6] this was found to be the case. The effect of the negative groups was to raise the yield whereas the presence of the *p*-methoxy substituent caused the yield to be halved.

Thioamides. A third class of nucleophiles with the S=CNH– function are the thioamides. Thioacetamide was allowed to react with phenyl(trichloromethyl)carbinol under the same conditions as before, and 4-hydroxy-2-methyl-5-phenylthiazole (**11**) was isolated in 18% yield.



10 **11**

The formation of the hydroxythiazole involves the attack of the thioenolate anion on the epoxide **2** in a manner strictly analogous to that given in Scheme I, followed by ring closure to **10** and enolization to **11.** The structure of this new compound was established from its chemical reactions and its spectral data. Hydrolysis with strong base gave α-mercaptophenylacetic acid, isolated as dithiobis(phenylacetic acid). A molecular weight determined by the Rast method demonstrated **11** to be monomeric. The material forms an acetate derivative with acetic anhydride. That the hydroxythiazole and its acetate exist entirely in the enol form follows from their ir and NMR spectra. The hydroxythiazole exhibits a broad absorption band at 2700–2000 cm^{-1}, suggestive of a hydrogen-bonded hydroxyl group, and there is no carbonyl absorption in the expected 1650–1800-cm^{-1} range. Its NMR spectrum shows a broad singlet at δ 11.2 characteristic of an enol. Structure **10** would have a characteristic carbon-5 proton resonance at δ 5.7 and this is missing from both the hydroxythiazole and its acetate ester. The above spectral data conclusively show the product to be in the enol form **11** rather than the keto form **10.** This is quite interesting, since 4-hydroxythiazoles, like hydroxythiophenes, usually exist mostly in the keto form and are labile substances which decompose in a few days even at room temperature.[7] In contrast, a sample of **11** has not undergone any decomposition, as judged by its ir spectra, after standing for 7 years at room temperature protected from light. Jensen's 4-hydroxythiazoles had a phenyl group substituted at the 2 position[7] and it would appear that the presence of the phenyl group in our compound at the 5 position, in conjugation with the double bond, stabilizes the enolic form.

Unlike Jensen's 4-hydroxy-2-phenylthiazoles,[7] compound **11** remains in the monomeric form on refluxing a solution of it dissolved in either water, benzene, or alcohol. It was soluble in dilute base and reprecipitated unchanged on acidification. However, exposure to sunlight for several months changed approximately half of the sample to a dark tan, insoluble, polymeric material, which, however, slowly dissolved in sodium hydroxide solution and then yielded **11** on acidification. The polymeric material analyzed for $C_{10}H_9NOS$, like **11,** but had a strong carbonyl absorption at 1695 cm^{-1} and no absorption around 2500 cm^{-1}. It is obviously some polymeric form of **10,** but its exact structure is unknown.

After removal of the hydroxythiazole, a large crude acid fraction was isolated which accounted for all of the remaining phenyl(trichloromethyl)carbinol. Esterification with methanol, followed by GLC analysis of the ester mixture, showed it to be a mixture of ten compounds of which the major one (58%) was methyl phenylacetate.

Thiocyanate. Another nucleophile with both sulfur and nitrogen bonded to a carbon is thiocyanate anion. Unfortunately, a complex mixture of products resulted from the reaction of this nucleophile with phenyl(trichloromethyl)carbinol, and only dithiobis(phenylacetic acid) and thiobis(phenylacetic acid) could be isolated in 17 and 3% yields, respectively. Again there was a large crude acid fraction. This was converted into a mixture of methyl esters with diazomethane and shown to consist of 16 components by GLC. The major compound (36%) was methyl phenylacetate.

Comments on Nucleophiles. Thiourea and the three classes of nucleophiles studied here all have the –NHC=S moiety in common and all react satisfactorily with phenyl(trichloromethyl)carbinols. The sulfur anions of these compounds are highly reactive in the SN2 epoxide ring opening reaction; they are so much more reactive than the anion from the solvent, ethylene glycol, that the solvent does not compete. The high reactivity of the amino group toward

the acid chloride causes the heterocyclic ring to form. The initial attack on the epoxide ring by the sulfur anion is the most important of the various steps involved. Evidence for this comes from our unsuccessful attempts to substitute urea for thiourea. Despite repeated attempts under varying conditions, none of the substituted oxazolidinone could be obtained. Guanidine was another nucleophile which failed to react with phenyl(trichloromethyl)carbinol under the usual conditions, presumably because all of the guanidine was in the form of the unreactive guanidinium ion.

Experimental Section

All melting points and boiling points are corrected. The ir spectra were recorded on a Perkin-Elmer Model 337. The NMR spectra were recorded on a Varian Model A-60 with tetramethylsilane as the internal standard. When dimethyl sulfoxide was used a solvent, the solvent peak at δ 2.62 was used as the reference. Analyses are by Dr. Franz J. Kasler.

Dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one (5). To a solution of 68 g (0.3 mol) of phenyl(trichloromethyl)carbinol[8] and 45.5 g (0.5 mol) of thiosemicarbazide in 500 ml of ethylene glycol was added dropwise, over a 75-min period, a solution of 110 g (1.7 mol) of potassium hydroxide pellets in 350 ml of ethylene glycol. The temperature was maintained at 46–47° during the addition and kept at this temperature for an additional 2 hr. As the reaction proceeded the color of the reaction mixture became deep brown. The insoluble potassium chloride was filtered off and washed with methanol. The mother liquor was diluted with an equal volume of ice and water, and extracted twice with a large volume of ether. The chilled aqueous solution was acidified to pH 9.4 with hydrochloric acid; a heavy precipitate formed immediately. The mixture was chilled overnight and filtered, and the crude product (11.7 g, 18% of theory) was washed thoroughly with water. When inserted in the melting point bath at 177° the material decomposed at 187–188°. The infrared spectrum of this crude material was identical with that of a pure sample. The product was purified by dissolving in 250 ml of 95% ethanol, decolorizing, filtering, and diluting with 100 ml of water. There was obtained 10.6 g of dihydro-2-imino-6-phenyl-2*H*-1,3,4-thiadiazin-5-(6*H*)-one monohydrate. An analytical sample was prepared by recrystallizing the material two additional times from water–ethanol: mp 188.5–189.5° dec; ir (KBr) 3425, 3310, 3180, 3030, 2915, 1625, 1580, 1470, 1400, 1340, and 730 cm^{-1}; NMR (DMSO) δ 10.42 [s, 1, –C(=NH)NHNH–], 7.38 (s, 5, Ph), 6.15 [s, 2, –C(=NH)NHNH–], 4.83 (s, 1, >CH–), 3.72 (s, 2, H_2O).

Anal. Calcd for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92; N, 18.65; S, 14.23. Found: C, 48.07; H, 5.16; N, 18.40; S, 14.18.

The anhydrous material was prepared by heating the monohydrate in a vacuum oven at 70° for 4 hr. A 1.0527-g sample of the monohydrate lost 0.0826 g of water or 7.85% of its weight (theory, 8.00%): mp 189–190°; ir (KBr) 3440, 3280, 3150, 2910, 1640, 1590, 1470, 1375, 1325, 1250, 1030, 865, 740, 695, and 530 cm^{-1}; NMR (DMSO) δ 10.57 [s, 1, –C=NH)NHNH–], 7.43 (s, 5. Ph), 6.21 [s, 2, –C(=NH)NHNH–], 4.92 (s, 1, >CH–).

Anal. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38. Found: C, 52.04; H, 4.60.

Dihydro-6-phenyl-2*H*-1,3,4-thiadiazine-2,5(6*H*)-dione (6). The above material (5 monohydrate) was hydrolyzed to **6** by refluxing 4 g with 78 ml of 28% sulfuric acid for 40 min. Water (75 ml) was added and the mixture was chilled in an ice bath. White crystals and some gum-like material separated from the solution. The gum was discarded and the crystalline material filtered and washed with cyclohexane, giving 1.8 g of material (51% of theory). Crystallization from 60 ml of 95% ethanol gave 0.85 g of the almost pure **6**, mp 130–132°. After two additional recrystallizations the melting point was 135°; ir (KBr) 3350, 3270, 3200, 1760, 1690, 1600, 1490, 1460, 1390, 1175, 920 855, 775, 740, 705, 640, and 535 cm^{-1}; NMR (DMSO) δ 7.6 (s, 5, Ph), 5.86 (s, 1, >CH), 5.3 (broad s, 2, –NH–).

Anal. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; S, 15.40. Found: C, 52.06; H, 4.10; N, 13.41; S, 15.60.

The dione **6** can also be prepared by substituting 2 *N* hydrochloric acid for the 20% sulfuric acid; however, if 20% hydrochloric acid is used, 5-phenyl-2,4-thiazolidinedione is formed.

Dihydro-2-imino-4-methyl-6-phenyl-2*H*-1,3,4-thiadiazin-5(6*H*)-one (7). Compound **5** (4.85 g, 0.0215 mol of the monohydrate) was suspended in 100 ml of 2 *N* sodium hydroxide and 18 ml of dimethyl sulfate was added over a period of 1 hr while the flask was maintained at room temperature. The reaction mixture was stirred for an additional 1 hr and chilled in an ice bath, and the precipitate (3.5 g, 74% of theory) was filtered and washed, first with water and then with cyclohexane. The melting point was 167.5–169.5°; this was raised to 171° by recrystallization first from a water–alcohol mixture and then from 95% alcohol. Ir (KBr) 3400, 3320, 3185, 2930, 1620, 1550, 1450, 1390, 1340, 1230, 1090, 980, 835, 775, 745, 725, 690, and 530 cm^{-1}; NMR (DMSO) δ 7.53, (s, 5, Ph), 6.50 (s, 2, =NH and –NH–), 5.06 (s, 1, >CH–), 3.03 (s, $-CH_3$).

Anal. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99; S, 14.49. Found: C, 54.34; H, 5.14; N, 19.10; S, 14.49.

The methyl group of **7** was proven to be in the 4 position by refluxing 1.3 g of **7** dissolved in 80 ml of ethanol with 30 g of Raney nickel overnight, and isolating 0.75 g (99% of theory) of *N*-methylphenylacetamide from the reaction mixture. After two recrystallizations from cyclohexane the material melted at 58–59° (lit.[9] mp 58°) and its ir and NMR spectra agreed with those in the literature.[10]

Dihydro-4-methyl-6-phenyl-2*H*-1,3,4-thiadiazine-2,5(6*H*)-dione. This preparation was carried out by the same procedure for hydrolyzing **5** to **6**, but with 2 *N* hydrochloric acid. The crude product (0.25 g, 16% of theory) was recrystallized from ethanol three times and then melted at 146°: ir (KBr) 3240, 1760, 1690, 1500, 1450, 1360, 1170, 1130, 1085, 870, 730, and 695 cm^{-1}; NMR (F_3CCOOH) δ 11.0 (s, protons of solvent and –NH–), 7.29 (s, 5, Ph), 5.47 (s, 1, >CH–), 3.05 (s, 3, $-CH_3$).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.54, N, 12.60; S, 14.43. Found: C, 53.88; H, 4.60; N, 12.69; S, 14.22.

Hydrolysis of Compounds 5 and 7 to 5-Phenyl-2,4-thiazolidinedione. This was accomplished by refluxing 1.5 g of **5** or **7** with 25 ml of 20% hydrochloric acid for 3 hr and allowing the reaction mixture to slowly cool to room temperature. On chilling, 1 g (85% of theory) of 5-phenyl-2,4-thiazolidinedione was obtained and recrystallized from aqueous ethanol: mp 126–128.5° (lit.[2] mp 129°); ir identical with that in ref 2; NMR (DMSO) δ 12.2 (s, 1, –NH–), 7.45 (s, 5, Ph), 5.7 (s, 1, >CH–).

Evaporation to dryness of the mother liquors from the hydrolysis reaction mixture followed by addition of aqueous sulfuric acid and methanol gave hydrazine sulfate and methyl hydrazine sulfate precipitates, which were identified by their melting points and ir spectra.

5-Phenyl-2,4-thiazolidinedione 2-Isopropylidenehydrazone. Acetone Derivative of 4. This was obtained by allowing **4**, formed along with **5** (see preparation of **5** above), to react with acetone; it was also prepared directly from phenyl(trichloromethyl)carbinol and acetone thiosemicarbazone.

A. Accompanying Preparation of 5. After **5** was filtered off in the preparation given above, the mother liquor was extracted twice with ether and this operation was repeated after the solution was made neutral and also strongly acid. The aqueous layer was then neutralized and filtered, and acetone was added. A precipitate gradually formed; after 10 days 7 g (9% of theory) of the 5-phenyl-2,4-thiazolidinedione 2-isopropylidenehydrazone was obtained, mp 195–200°. Several recrystallizations from 95% ethanol raised the melting point to 201–202° (lit.[11] mp 198–199°). The ir and NMR spectra were identical with those of a pure sample prepared as described immediately below.

B. From Acetone Thiosemicarbazone (8a). To a solution of 31.5 g (0.24 mol) of acetone thiosemicarbazone and 45.1 g (0.2 mol) of phenyl(trichloromethyl)carbinol in 250 ml of ethylene glycol was added a solution of 70 g (1.07 mol) of potassium hydroxide pellets in 200 ml of ethylene glycol over a period of 50 min while the temperature was maintained at 47–50°. The flask was kept at 45° for an additional 2 hr and then allowed to slowly cool to room temperature. The insoluble potassium chloride (26 g) was filtered off, and the solution was diluted with an equal volume of ice and water and extracted with 600 ml of ether. The aqueous solution was chilled to 0°, the pH was adjusted to 7, and the mixture was chilled overnight. There was obtained 31 g (63% of theory) of material, mp 201°. Recrystallization from aqueous ethanol gave 27 g of pure 5-phenyl-2,4-thiazolidinedione-2-isopropylidenehydrazone: mp 201–202° (lit.[11] mp 198–199°); ir (KBr) 3145, 3070–3000, 2930, 2815, 1720, 1640, 1620, 1500, 1460, 1430, 1350, 1260, 1240, 1170, 1075, 870, 800, 760, 725, 690, 675, 570, and 545 cm^{-1}; NMR (DMSO) δ 11.9 (broad s, 1, –NH–), 7.53 (s, 5, Ph), 5.48 (s, 1, >CH–), 2.07 and 2.04 [two s, 6, $=C(CH_3)_2$].

5-Phenyl-2,4-thiazolidinedione 2-benzylidenehydrazone (8b) was prepared in 69% yield from benzaldehyde thiosemicarba-

zone by the same procedure as for **8a**: mp 256–268° (lit.[11,12] mp 257°, 260–261°); NMR (DMSO) δ 12.2 (broad s, 1, –NH–), 8.44 (s, 1, PhCH=N–), ten protons of two phenyl rings gave signals at 7.8–7.7 (m), 7.50 (s), and 7.42 (s), 5.52 (s, 1, PhCHS–).

Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.07; H, 4.44; N, 14.23; S, 10.86. Found: C, 65.08, H, 4.65; N, 14.50; S, 11.08.

5-(*p*-Chlorophenyl)-2,4-thiazolidinedione 2-isopropylidenehydrazone (8c) was prepared in 79% yield from *p*-chlorophenyl(trichloromethyl)carbinol[13] as above mp 227°; NMR (DMSO) δ 12.0 (broad s, 1, –NH–), 7.51 (s, 4, Ph), 5.47 (s, 1, >CH–), 3.73 and 3.71 (s, 6, $-CH_3$).

Anal. Calcd for $C_{12}H_{12}N_3OSCl$: C, 51.15; H, 4.29; N, 14.91; Cl, 12.58. Found: C, 51.42; H, 4.56; N, 14.74; Cl, 12.80.

5-(*p*-Methoxyphenyl)-2,4-thiazolidinedione 2-isopropylidenehydrazone (8d) was prepared in 31% yield from *p*-methoxyphenyl(trichloromethyl)carbinol[13] as above. The material did not melt sharply; after repeated crystallization from aqueous ethanol, it melted at 169–175° when inserted in the melting point bath at 165° and the temperature raised at 2°/min: NMR (DMSO) δ 11.8 (broad s, 1, –NH–), 7.4–6.9 (quartet, 4, Ph), 5.35 (s, 1, >CH–), 3.82 (s, 3, $-OCH_3$), 2.07 and 2.03 (s, 6, $-CH_3$).

Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15; S, 11.56. Found: C, 56.45; H, 5.54; N, 15.05; S, 11.28.

4-Hydroxy-2-methyl-5-phenylthiazole (11). To a solution of 45 g (0.2 mol) of phenyl(trichloromethyl)carbinol and 30 g (0.38 mol) of thioacetamide in 250 ml of ethylene glycol was added 70 g (1.06 mol) of potassium hydroxide pellets in 200 ml of ethylene glycol over an 80-min period at 50°. The mixture was maintained at 50° for an additional 2.5 hr and stirred overnight while cooling to room temperature. The potassium chloride was filtered off, the filtrate and methanol washings were diluted with an equal volume of ice water and extracted with ether to remove neutral material, and the pH of the aqueous solution was adjusted to 9 with hydrochloric acid. The product which precipitated (7.1 g, mp 206–209°, 18% yield) was recrystallized twice from benzene and then weighed 3.3 g and melted at 210–212.5° (same melting point procedure as for **8d**): ir (halocarbon and Nujol oil mulls) 3100–2900, 2700–2000, 1580, 1450, 1425, 1230, 1190, 1030, 995, 865, 755, and 685 cm^{-1}; NMR (DMSO) δ 11.2 (broad s, 1, –OH), 7.8–7.1 (m, 5, Ph); NMR (F_3CCOOH) δ 7.50 (s, 5, Ph), 2.86 (s, 3, $-CH_3$).

Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32; S, 16.77; mol wt, 191. Found: C, 62.92; H, 4.64; N, 7.35; S, 16.80; mol wt (Rast), 182 and 211.

Compound **11** was hydrolyzed by refluxing 0.9 g with 16 ml of aqueous 25% potassium hydroxide for 18 hr. The solution was acidified to pH 7.5 and filtered. An intense purple color developed on adding 3 drops of 5% ferric chloride to the aqueous solution. Air was blown through the solution at room temperature for 3 hr until the purple color was discharged. Dithiobis(phenylacetic acid), mp 208–211°, was isolated which was identical in all respects with an authentic sample.

4-Acetoxy-2-methyl-5-phenylthiazole was prepared by refluxing 1 g of **11** with 10 ml of acetic anhydride for 1 hr. The excess reagents were removed by distillation at 10 mm, and the acetoxythiazole (1 g, 82% of theory) was then distilled, bp 184–190° (10 mm), mp 72–77°. The distillate solidified, and crystallization from ethanol–water raised the melting point to 82°: ir (halocarbon and Nujol oil mulls) 1770, 1540, 1490, 1445, 1375, 1320, 1305, 1275, 1250, 1190, 1040, 1030, 1000, 870, 765, 690, 585, 565, and 550 cm^{-1}; NMR (CCl_4) δ 7.3 (m, 5, Ph), 4.25 (s, 3, ring $-CH_3$), 3.87 (s, 3, acetate $-CH_3$).

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.76; H, 4.75; N, 6.03; S, 13.74. Found: C, 61.95; H, 5.00; N, 6.12; S, 13.45.

Registry No.—**1**, 2000-43-3; **4**, 55073-89-7; **5**, 55073-90-0; **6**, 55073-91-1; **7**, 55073-92-2; **8a**, 55073-93-3; **8b**, 55073-94-4; **8c**, 55073-95-5; **8d**, 55073-96-6; **11**, 55073-97-7; thiosemicarbazide, 79-19-6; dihydro-4-methyl-6-phenyl-2*H*-1,3,4-thiadiazine-2,5(6*H*)-dione, 55073-98-8; 5-phenyl-2,4-thiazolidinedione, 4695-17-4; acetone thiosemicarbazone, 1752-30-3; benzaldehyde thiosemicarbazone, 1627-73-2; *p*-chlorophenyl(trichloromethyl)carbinol, 5333-82-4; *p*-methoxyphenyl(trichloromethyl)carbinol, 14337-31-6; 4-acetoxy-2-methyl-5-phenylthiazole, 55073-99-9.

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Synthesis of *p*-Methylthiobenzyl Chloride. A Case of Isomer Control in an Electrophilic Substitution[1]

Seemon H. Pines,* Robert F. Czaja, and N. Lee Abramson

Merck Sharp & Dohme Research Laboratories, A Division of Merck & Co., Inc., Rahway, New Jersey 07065

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Reaction of thioanisole and methylal with ~2 mol of aluminum chloride under mild Friedel–Crafts conditions yields 74% *p*-methylthiobenzyl chloride (**1**) accompanied by only ~0.5% of its ortho isomer. Both the yield and isomer ratio change dramatically when 1 mol of aluminum chloride is used. The effect of weaker Lewis acids is reported, and the combined results are rationalized in terms of a mechanism where a thioanisole–Lewis acid complex is proposed as a key to the unique results.

We have devised a superior, direct synthesis of *p*-methylthiobenzyl chloride (**1**) via a new chloromethylation of thioanisole. Besides its immediate practical value,[2] the reaction study provides new information on the behavior of thioanisole in Friedel–Crafts chemistry.[3] For this reason, some of our developmental observations and conclusions are included in this paper.

The title compound is reported to be formed in 23% yield from the chloromethylation of thioanisole with chloromethyl methyl ether[4] in acetic acid.[5] Our scrutiny of that reaction by vapor phase chromatography shows about a 4.5:1 ratio of **1** and its isomer, *o*-methylthiobenzyl chloride (**2**), which are not practicably separable. Attempted monochloromethylation with aqueous formaldehyde and hydrochloric acid gave an even poorer isomer ratio, 7:4.[6] Apparently, the most satisfactory authenticated preparation of **1** is a multistep procedure involving lithium aluminum hydride reduction of *p*-methylthiobenzoic acid, followed by

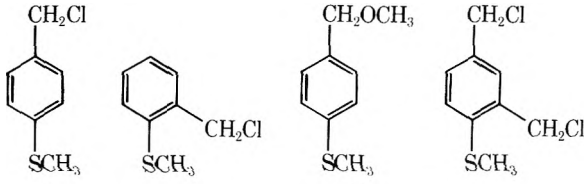
Table I
Chloromethylation of Thioanisole with Methylal and Lewis Acids

	Yield, %			
	2.2 mol[a]		1.1 mol[a]	
Lewis acid	Para	Ortho	Para	Ortho
$AlCl_3$	74	0.5	27[b]	24[b]
$AlCl_3$, moderated[c]	55	8		
$TiCl_4$	60	5	24	16
$SnCl_4$	47	4.5	19	19
$FeCl_3$	15	0.8	2	15

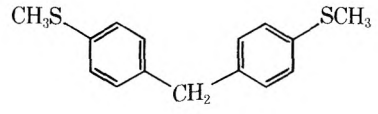
[a] Moles of Lewis acid per mole of thioanisole. [b] Actually 1.3 mol of $AlCl_3$ in this case. [c] 1 mol of methanol per mole of $AlCl_3$ added before methylal and thioanisole.

thionyl chloride treatment of the resultant purified *p*-methylthiobenzyl alcohol.[7]

By contrast, we find that reaction of thioanisole with methylal and aluminum chloride in 1,2-dichloroethane (EDC) gives 74% of **1** accompanied by only ca. 0.5% of the ortho isomer, **2**. Some 10–12% of thioanisole remains unreacted. Other constituents of the product include 3–5% of methyl *p*-methylthiobenzyl ether (**3**), a trace of its ortho isomer, 1–2% of 2,4-bis(chloromethyl)thioanisole (**4**), and up to 0.5% of bis(4-methylthiophenyl)methane (**5**).



1 **2** **3** **4**



5

Methanol-attenuated $AlCl_3$ and some of the weaker common Lewis acids are less effective reactant–catalysts, as can be seen from Table I. Both the product yield and specificity diminish with their use. The optimum mole ratio of Lewis acid is slightly above 2:1, relative to thioanisole. Reaction still occurs with lower catalyst levels, but the outcome is drastically altered. For instance, the almost exclusive para orientation with 2 mol of $AlCl_3$ drops to near 50:50 ortho to para substitution when only 1 mol of $AlCl_3$ is used. The stannic chloride case changes similarly. The ferric chloride reactions give about 15% yield whether 2 or 1 mol of $FeCl_3$ is used; in the former case, para substitution dominates; in the latter case, ortho substitution is found.

It is worthy of note that in the low (overall) yield reactions, the remaining thioanisole is generally not found unreacted, nor is it present as a simple monosubstituted product. Rather, the lack of simple GC-volatile products suggests that higher condensation products result with the less favorable reaction conditions.

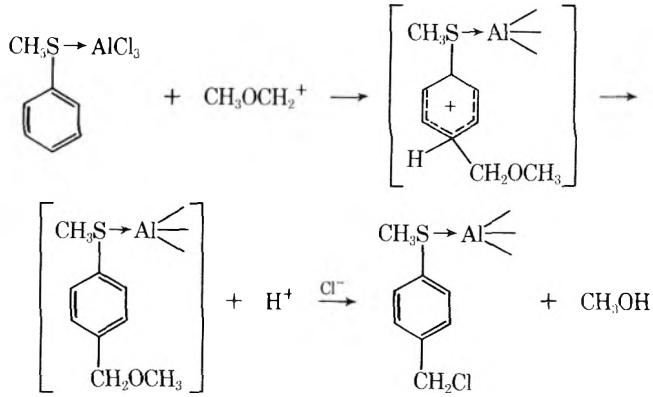
Further inferences concerning the reaction pathway can be drawn from other experiments. The best results are obtained when the thioanisole is added gradually at or below 5–10° to the EDC solution of methylal and $AlCl_3$. If, on the other hand, $AlCl_3$ is slowly added to the other reactants, the yield of **1** drops below 40%, the para:ortho ratio to 30.

The product complex which crystallizes from the reaction mixture has been examined by a number of analytical probes. Since GC and ^1H NMR analyses show that it still contains small amounts of thioanisole and traces of the methoxy methyl analog **3**, and since the solid is extremely susceptible to hydrolysis in atmospheric moisture, we cannot propose a firm structure. From the elemental analysis, we tentatively consider the product complex to be represented by the structure p-$CH_3SC_6H_4CH_2Cl$·$(AlCl_2OCH_3)_2$. Zeisel determination shows 10.4% methoxyl (cf. 14.4% for 2 OCH_3's). Raman spectroscopy is quite enlightening.[8a] Bands at 629 and 653 cm^{-1} can be assigned to the in-plane ring bending and CH_3–S stretch modes, respectively. The comparable bands for the uncomplexed **1** are found at 634 and 673 cm^{-1}. The decrease is indicative of bond weakening, and is consonant with the formulation of the material as a Lewis acid–Lewis base pair. Similar shifts are observed in comparing the spectra of thioanisole and the thioanisole–$AlCl_3$ complex. Changes in the ring breathing mode at 1090 cm^{-1} show the same phenomenon. The low-energy region (<200 cm^{-1}) is suggestive of a polymeric lattice; X-ray diffraction methods support crystallinity.[8b]

Table II shows the gas chromatographic analyses of aliquots which were taken to determine the optimum reaction time. The experiment differed slightly in that the thioanisole was added rapidly below 5°, and the reaction was then brought to 20° at which point slurry samples were quenched and injected into the chromatograph. The results are tabulated in *area* percent, normalized to 100. While this disregards other lesser by-products, it provides the desired information.

Critical examination of the data of Table II might suggest that either the ortho isomer rearranges to para (to account for the high initial para:ortho ratio), or that the ortho isomer is formed by some other reaction mechanism (see below). A spiking experiment showed that when ortho isomer, **2**, was added initially to a reaction, it was recovered virtually unchanged in the product. While rearrangements under Lewis acid catalysis are well known, they have not been noted for chloromethyl groups.

All of these results and others are consistent (in the preferred case) with an electrophilic substitution in which the substrate is not thioanisole per se, but a thioanisole–aluminum chloride complex[9] as suggested in the scheme below.[10]



The initial methoxymethylation and cleavage by chloride have precedent in other chloromethylations using chloromethyl ethers.[12] During the course of this reaction, the Friedel–Crafts activity of the Lewis acid becomes markedly diminished, not only by formation of methanol, but more importantly by the nature of the product complex. If it did not, we might expect that the once-formed **1** would alkylate the remaining thioanisole in accord with the results of a benzylation study by Olah and coworkers.[13] In fact, when we applied these same reaction conditions to some other aromatic compounds which do not carry a methylthio substituent, much of the substrate was converted to higher

Table II
$AlCl_3$ (2.2)–Methylal (1.1) Chloromethylation of Thioanisole (1) at 20°[a]

Time, min	Thioanisole	Isomers[b] Para	Ortho
0	94.8	4.4	0.8
10	91.9	7.1	1.0
20	87.2	11.8	1.0
30	79.3	19.5	1.2
70	62.6	35.8	1.6
90	55.0	43.3	1.7
180	32.1	65.9	2.0
300	23.5	74.6	1.9
1320	16.3	82.6	1.1

[a] Parenthetic numbers are mole ratios. All values are GC, area percent normalized to 100. [b] Includes methoxymethyl analogs.

molecular weight products; the initially formed substituted benzyl chloride (i.e., benzyl cation) was too reactive to survive in its environment.

This is not the first example of variable orientation in a chloromethylation. Several reports of dependence upon reaction conditions can be found in the review of Olah and Tolgyesi.[12] The available latitude in isomer control (cf. with ferric chloride) in addition to the ability to achieve greater than 100:1 isomer ratios makes this reaction unique.[14]

Norman and Radda[15] have applied and extended the Hammond postulate[16] to the overall problem of the ortho:para ratio in aromatic substitution. They point out convincingly that with highly reactive electrophiles operating on −I, +R aromatics, the −I effect operates most powerfully on the ortho position, thus increasing the *relative* para position reactivity. Since Lewis acid complexation would be expected to enhance −I character of the methylthio group,[17] we can expect that those Lewis acids forming the strongest complexes would lead to chloromethylation products with the highest para:ortho ratio. This appears to be the case (Table I).

A simple explanation for the case of low Lewis acid mole ratios is harder to construct. If we accept a concept of dynamic exchange[17]

$$C_6H_5SCH_3 + C_6H_5S^*CH_3{\cdot}AlCl_3 \rightleftharpoons C_6H_5S^*CH_3 + C_6H_5SCH_3{\cdot}AlCl_3$$

and equate excess Lewis base with a resultant weaker complex, then at lower mole ratios, competition for the Lewis acid by both thioanisole and methylal would diminish the enhancement of the −I effect noted above. Furthermore, a consequence of this competition would be to allow secondary reactions to occur with uncomplexed thioanisole, lowering overall yields. These arguments are in accord with our observations and also satisfy the results of the experiment in which aluminum chloride is added slowly, where the mole ratio is low during part of the reaction. Likewise, they are consonant with the known condensation of thioanisole with chloromethyl methyl ether in the presence of boron trifluoride etherate (mole ratio 10:1:1) where an 83% yield of bis(4-methylthiophenyl)methane (**5**) is obtained.[18]

Other explanations might be offered to rationalize the different results in terms, e.g., of the timing of the transition state on the reaction coordinate. In any event, the reason for the difference is suggested to be complexation with sulfur.

Experimental Section[19,20]

***p*-Methylthiobenzyl Chloride. Preferred Procedure.** *Caution! This product is a severe skin irritant. Appropriate protection against contact is advised.* To a stirred slurry of 61.4 g (0.46 mol) of anhydrous $AlCl_3$ in 200 ml of 1,2-dichloroethane was added dropwise over 30–35 min 18.2 g (0.24 mol) of methylal while keeping the temperature at 5–10°. Thioanisole (24.8 g, 0.2 mol) was then added similarly over ca. 1 hr. The reaction was brought to and held at 25° with stirring for 6–10 hr. Crystallization commenced during the warm-up to room temperature. The reaction was then quenched by the dropwise addition of 225 ml of water below 25° internal temperature with vigorous agitation.[21] The organic layer was separated, combined with an extract of the aqueous phase, and washed rapidly with 50 ml of water. Evaporation in vacuo gave a concentrate which contained[22] 25.5 g (74%) of *p*-methylthiobenzyl chloride. Present also were 3.1 g (12.6%) of unreacted thioanisole, and the following by-products in the percent indicated: o-methylthiobenzyl chloride (0.4%), methyl *p*-methylthiobenzyl ether (4.8%), 2,4-bis(chloromethyl)thioanisole (2.2%), and bis(*p*-methylthiophenyl)methane (0.1%).

Chloromethylation–Inverse Addition. A solution of 16.8 g (0.22 mol) of methylal and 24.8 g (0.2 mol) of thioanisole in 150 ml of EDC was stirred at ca. 10° while a slurry of 58.6 g (0.44 mol) of $AlCl_3$ in 75 ml of EDC was added over a 90-min period. At the end of the addition, the temperature was brought to 24–26°, and held there for 6 hr. After the usual quench and work-up, gas chromatography showed the presence of 13.1 g (37.8%) of **1**, 0.42 g (1.2%) of ortho isomer **2**, and 6.35 g (25.7%) of unreacted thioanisole. The remainder of the substrate was presumably lost to higher molecular weight (less volatile) products.

Isolation of Product Complex. A portion of a reaction was filtered cold immediately after the thioanisole addition, and the filtrate was allowed to crystallize for 4 hr in the usual way. It was filtered and washed with sieve-dried EDC (drybox) and pumped dry for 120 hr.

A portion (350 mg) was suspended in 1 ml of CCl_4, cooled in an ice bath, and quenched by the addition of ice, then concentrated HCl. The CCl_4 layer and an extract of the aqueous layer were dried over $MgSO_4$ and examined by GC and ^1H NMR. The GC showed, area percent relative to **1**: 0.074 thioanisole, 0.018 **2**, 0.002 **3**. The NMR signals were as expected for **1**, but with 6–7% excess aromatic and S–CH_3 signal. Raman (partial) spectrum: 629 (in-plane ring bend), 653 (C–S stretch), 1080–1099 (Ar–S stretch), 1595 cm^{-1} (C=C).

Anal. Found: C, 28.56; H, 3.87; Cl, 39.4; S, 8.37; Al, 12.72; OCH_3, 10.4. These values satisfy the following relationship: $C_{10}H_{16.2}Cl_{4.7}O_{1.9}S_{1.1}Al_2$.

Preparation and Characterization of Pure Substances. Pure samples of all derivatives of thioanisole mentioned were synthesized and purified according to standard methods. Their physical constants (melting point or boiling point and refractive index) agree well with literature values. NMR spectra were unambiguous. One compound is new, methyl *o*-methylthiobenzyl ether, made by reaction of **2** with sodium methoxide in methanol: bp 82–83° (0.35 mm); $n^{23}D$ 1.5680; NMR ($CDCl_3$) δ 2.4 (s, 3, CH_3S), 3.4 (s, 3, CH_3O), 4.5 (s, 2, CH_2), 7.2 (m, 4, aromatic).

Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19; S, 19.06. Found: C, 64.54; H, 7.30; S, 18.93.

Registry No.—**1**, 874-87-3; **2**, 26190-68-1; **3**, 16155-09-2; methylal, 109-87-5; thioanisole, 100-68-5; methyl o-methylthiobenzyl ether, 55102-98-2.

References and Notes

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(2) As part of a multistep synthesis to be published in due course.
(3) A recent report: S. Clementi and P. Linda, *Tetrahedron*, **26**, 2869 (1970). References to prior studies are included therein.
(4) The standards advisory committee on carcinogens of the Occupational Safety and Health Administration have defined this compound as a carcinogen. It may be used only in rigidly defined laboratory facilities. See Federal Register, Vol. 38, No. 173, p 24375, Sept 7, 1973.
(5) N. P. Buu-Hoi and N. Hoán, *J. Org. Chem.*, **17**, 350 (1952).
(6) (a) Unpublished work from these laboratories modeled after the procedure of A. Müller, M. Mészáros, M. Lempert-Sreter, and I. Szára, *J. Org. Chem.*, **16**, 1003 (1951). Bischloromethylation has been achieved in this medium by J. H. Wood, M. A. Perry, and C. C. Tung, *J. Am. Chem. Soc.*, **72**, 2989 (1950). (b) We have repeated the uncatalyzed reaction of ethyl phenyl sulfide with paraformaldehyde and HCl, which is reported[6c] to give 86% of *p*-ethylthiobenzyl chloride. The distilled product shows the same refractive index as reported,[6c] but analysis by GC and NMR clearly shows it to be a ~6:4 ratio of the ortho and para isomers. (c) A. F. Prokof'eva, N. N. Mel'nikov, and I. L. Vladimirova, *Zh. Obshch. Khim.*, **38**, 2355 (1968). We thank Dr. R. Dewey for calling our attention to this paper.
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(8) (a) We are deeply indebted to Dr. Alan J. Rein of these laboratories for the Raman experiments and the interpretation of their significance. (b) We thank Dr. J. McCauley for this information.

(9) Complexes of thioanisole with (a) $AlCl_3$ and (b) $SnCl_4$ have recently been reported; see (a) G. H. Smith and F. J. Hamilton, *J. Phys. Chem.*, **72**, 3567 (1967); (b) I. P. Goldshtein, E. N. Kharlamova, and E. N. Guryanova, *Zh. Obshch. Khim.*, **38**, 1925 (1968).

(10) (a) A referee has suggested that if the aluminum chloride–methylal complex is very bulky, steric hindrance may account for the predominant product. We had discounted this possibility since the Sn, Ti, and Fe complexes should be bulkier than the one with aluminum, and should thus give even higher selectivity. Olah[11] has recently relegated steric factors to eighth in a list of eight influences on reactivity and selectivity in Friedel–Crafts chemistry. (b) The same referee has, in questioning the proposed mechanism, pointed out that a good case can be made that the thioanisole–aluminum chloride complex might be meta directing, and that it certainly should be deactivating. His first point probably rests on the well-known predominant meta direction of sulfoxides and sulfonium ions. We agree with the latter point concerning deactivation, and cite it as further evidence for complexation. The reaction is certainly slower (Table II) than would be expected for an aromatic substrate which has been reported to react 2.5 times as fast as mesitylene in electrophilic reaction.[3]

(11) G. A. Olah in "Friedel-Crafts Chemistry", Wiley, New York, N.Y., 1973, p 393.

(12) G. A. Olah and W. S. Tolgyesi in "Friedel-Crafts and Related Reactions", Vol. 2, G. A. Olah, Ed., Wiley, New York, N.Y., 1964, Part 2, Chapter XXI. See also "Aromatic Haloalkylations", Ph.D. Dissertation of D. A. Beal, Case Western Reserve University, 1973.

(13) G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

(14) After our work was completed, we happened upon a reference to the influence of, inter alia, the amount of aluminum chloride used in the chloromethylation of 2-acetyl- and 2-formylthiophene with chloromethyl methyl ether or bis(chloromethyl) ether. Variable orientation was obtained in that case also. The authors ascribed the effect to the influence of complexation with the carbonyl moiety. See L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, *J. Org. Chem. USSR*, **7**, 1809 (1971).

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(17) Further evidence for a complex comes from the NMR spectrum of 1:1 aluminum chloride–thioanisole solutions. The aromatic protons are shifted selectively downfield, relative to thioanisole alone. The methyl proton singlet is also shifted downfield. The NMR spectrum of a 2:1 mole ratio of thioanisole and aluminum chloride shows chemical shifts intermediate between thioanisole and 1:1 thioanisole–aluminum chloride.

(18) V. A. Topchil and S. V. Zavgorodnii, *Zh. Org. Khim.*, **5**, 130 (1969).

(19) Commercially available reagents and solvents were used as purchased. NMR spectra were obtained on $CDCl_3$ solutions of the compounds with a Varian A-60A or Jeolco C-60HL spectrometer. The Raman spectra were obtained with a Carey Model 82 spectrometer excited with a Spectra-Physics Model 165-03 argon ion laser.

(20) We have been unable to detect the presence of either chloromethyl methyl ether or bis(chloromethyl) ether during reaction or work-up. Nevertheless, in view of the carcinogenicity of these two compounds,[4] considerable care should be exercised in experiments of this type.

(21) Some experiments were quenched *into* a large amount of water, and up to 3–5% hydrolysis of the product to the corresponding carbinol occurred. Rapid quench onto ca. 250 g of ice and water gave satisfactory results.

(22) GC analyses were run on a 6 ft × 0.125 in. S. S. column packed with 10% SP-2401 on 100/120 mesh Supelcoport, programmed from 110 to 170° at 4°/min. Thermal conductivity detection was used. The identity of the individual components was secured not only by mixed chromatograms with the pure substances, but also by GC–mass spectral methods. Quantitation of the thioanisole and **1** was by the internal standard method (tetradecane). The minor components are reported on an area percent rather than weight percent basis. We thank Mr. W. E. Tait for assay support.

Isonucleosides. I. Preparation of Methyl 2-Deoxy-2-(purin-9-yl)arabinofuranosides and Methyl 3-Deoxy-3-(purin-9-yl)xylofuranosides

John A. Montgomery,* Sarah D. Clayton, and H. Jeanette Thomas

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

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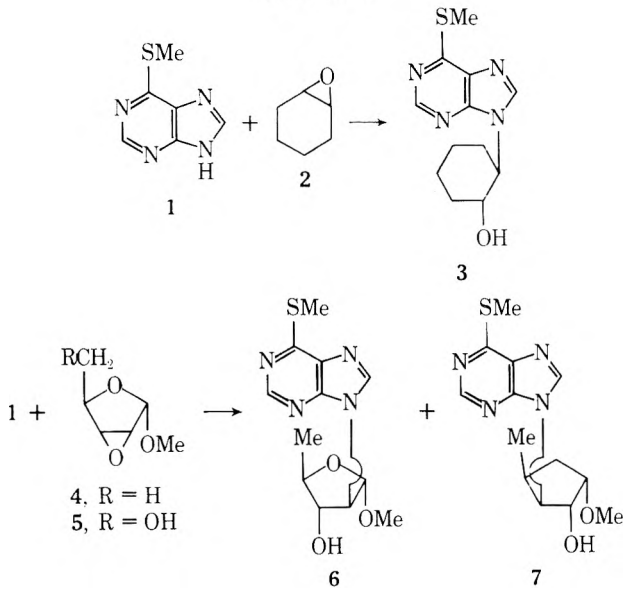
Since the reaction of 6-(methylthio)purine with methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside in the presence of base gave two products, the desired methyl 2,5-dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**6**) and methyl 3,5-dideoxy-3-[6-(methylthio)-9-purinyl]-α-D-xylofuranoside (**7**), resulting from attack by the purine anion on both C-2 and C-3 of the sugar, an alternative route to **6** and related structures was developed. The best procedure appeared to consist of reaction of 5-amino-4,6-dichloropyrimidine with **4** or **5** followed by ring closure of the resultant diaminopyrimidines to the corresponding purines. Replacement of the chloro group of **22** then gave the desired isonucleosides **23** and **24**.

In naturally occurring nucleosides and nucleotides, the purine ring is attached to C-1 of ribose or 2-deoxyribose, this linkage being part of an aminal structure, which is quite susceptive to both hydrolytic and enzymatic cleavage. The reasons for our interest in analogs of the naturally occuring nucleosides have been adequately discussed.[1] Available data indicate that if N-9 of the purine ring is attached to C-2 rather than C-1 of a pentofuranose, with the hydroxyl group at C-3 trans to the purine ring and the hydroxymethyl group at C-4 cis (see **23**), the resulting sugar derivative, which we have named isonucleoside, is likely to be a substrate for the anabolic enzyme adenosine kinase.[2] If the nucleotide is formed intracellularly by this enzyme, it may be capable of interfering with vital cellular metabolism (e.g., the biosynthesis or function of nucleic acids), and this type of structure would be of great potential interest.

Since one approach to the synthesis of such compounds is the reaction of a purine anion with the appropriate sugar epoxide, the reaction of 6-(methylthio)purine (**1**) with cyclohexene oxide (**2**) in the presence of pyridine was investigated and found to proceed satisfactorily (although the yield was low, no attempt was made to optimize it). That attack occurred as expected at N-9 of **1** to give the desired 9-(*trans*-2-hydroxycyclohexyl)-6-(methylthio)purine (**3**) (Scheme I) was demonstrated by comparing the uv spectrum of **3** with that of 7- and 9-benzyl-6-benzylthiopurine.[3] Since it is well known that epoxides open by rearward nucleophilic attack to give trans products, that aspect of the structural assignment was not open to question.

The success of the reaction of **1** with **2** caused us to study the reaction of **1** with methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside[4] (**4**), since it had been reported that attack by ammonia on **4** occurred exclusively at C-2 to give the arabino sugar derivate (**9**).[5,6] Attack by the anion of 6-(methylthio)purine on **4** was expected to give the desired arabino sugar **6** with the purine attached at C-2 and the hydroxyl at C-3 trans. The reaction of **1** with **4** proved sluggish, and more drastic conditions had to be employed than in the case with **2**. Less than half of **1** reacted and two sugar-containing products were formed (TLC). Although we original-

Scheme I

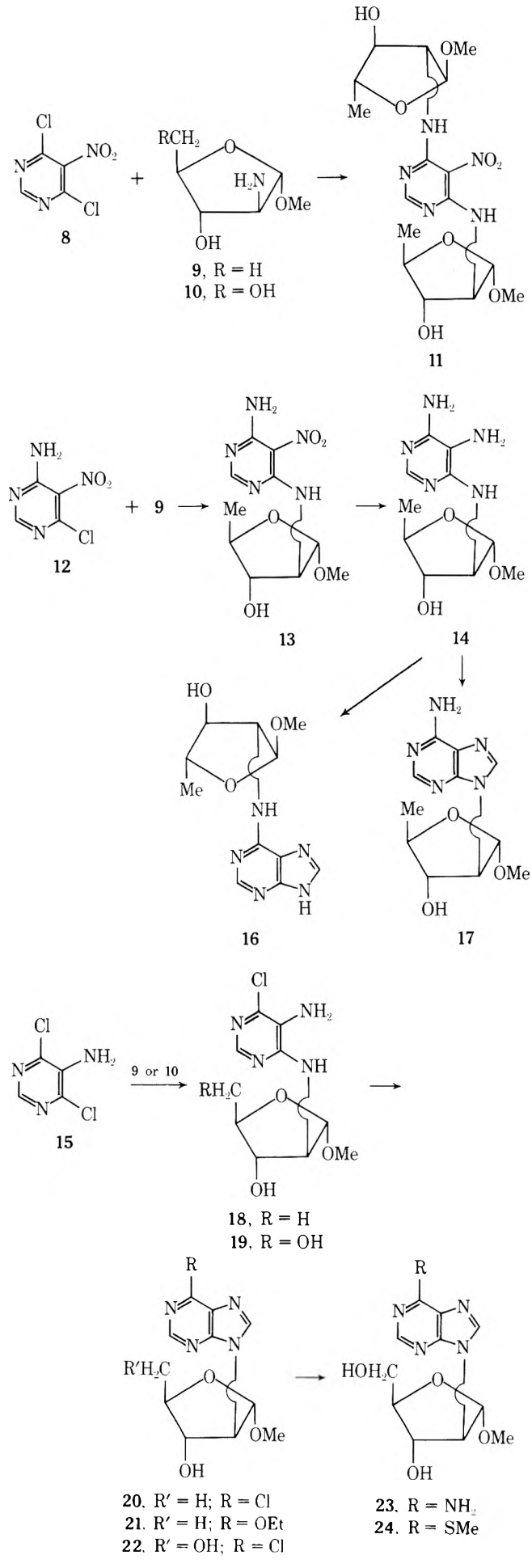


ly attributed the formation of two products to the conditions necessarily employed, further work established that, in fact, the reaction of **4** with ammonia gives almost equal amounts of **9** and **25** resulting from attack at both C-2 and C-3.[7] The identities of the two products obtained from the reaction of **1** with **4** were established by their ^{1}H NMR spectra (see Experimental Section) as methyl 2,5-dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**6**) and methyl 3,5-dideoxy-3-[6-(methylthio)-9-purinyl]-α-D-xylofuranoside (**7**); the ratio of isolated products was about three **6** to one **7**. Later, because of the difficulties encountered with alternative routes, we also investigated the reaction of **1** with **5**,[7] but this reaction proved even more difficult—after 20 hr much decomposition had occurred and a complex mixture of at least six components (TLC) resulted. Reaction of **1** with the 5-*O*-benzyl derivative[8] of **5** was not significantly better, so an alternative approach was finally adopted.

The alternative approach was based on a synthesis of 9-substituted purines developed in our laboratories some time ago.[9,10] At least three variations of this synthesis are possible and, because of the low yield obtained in the reaction of 5-amino-4,6-dichloropyrimidine (**15**) with **9**, they were all investigated. The low yield in the conversion of **15** to **18** resulted from side reactions encountered using conditions necessary to cause the relatively unreactive **15** to react with **9**. Among these side reactions were sugar decomposition, anomerization (^{1}H NMR), and displacement of the methoxy group of **9** (or **18**) by the solvent, 1-butanol (MS).

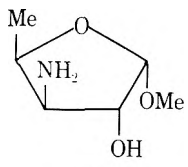
The much more reactive 5-nitro-4,6-dichloropyrimidine was next allowed to react with **9** using conditions that in other cases prevent disubstitution.[11,12] In this case, little or no monosubstituted pyrimidine formed, and only the bis compound, bis[methyl 2,5-dideoxy-2,2′-[(5-nitro-4,6-pyrimidinediyl)diimino]-α-D-arabinofuranoside] (**11**), could be isolated (Scheme II). This problem could be avoided by the use of 4-amino-6-chloro-5-nitropyrimidine (**12**), which is quite reactive despite the presence of the amino group. Methyl 2-(6-amino-5-nitro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**13**), obtained in high yield from **12**, was readily reduced with Raney nickel and hydrogen to the 5-aminopyrimidine **14**. Ring closure of **14** with formamide at 100° gave a mixture of the desired compound, methyl 2-(6-amino-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (**17**), and the isomeric methyl 2,5-dideoxy-

Scheme II

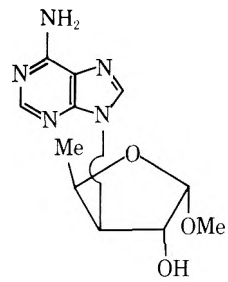


2-(6-purinylamino)-α-D-arabinofuranoside (**16**).[13] At 150° only **17** was detected (indicating that rearrangement of **16** to **17** may be possible), but the harsher conditions of this reaction caused much decomposition and only a low yield of **17** could be obtained. The much milder ring closure of **14** with diethoxymethyl acetate give, not unexpectedly, only methyl 2,5-dideoxy-2-(6-purinylamino)-α-D-arabinofuranoside (**16**).[14]

Because the separation of **9** and **25** is difficult and wasteful, the mixture was carried through the reaction sequence described above (**12** → **13** → **14** → **17**) for pure **9** in the hope that the separation of **17** from **26** would be easier than that of **9** from **25**. Although the former separation is probably somewhat better, this overall approach does not appear to be a significant improvement.



25



26

Thus, none of the obvious variations of the alternative pathway were entirely satisfactory, but the route via **18** was finally chosen because of its greater versatility. Ring closure of **18** with triethyl orthoformate and concentrated HCl was preferable to closure with diethoxymethyl acetate, in keeping with published results,[15] but still only a 54% yield was obtained. When an attempt was made to raise the yield by the addition of more acid and a longer reaction period, only methyl 2,5-dideoxy-2-(6-ethoxy-9-purinyl)-α-D-arabinofuranoside (**21**), resulting from displacement of the chloro group of **20**, was isolated.

We now turned our attention to the potentially more interesting sugar **10** (whose derivatives may be enzymatically phosphorylated), and converted it to methyl 2-(5-amino-6-chloro-4-pyrimidinylamino)-2-deoxy-α-D-arabinofuranoside (**19**) by reaction with 5-amino-4,6-dichloropyrimidine (**15**). Ring closure with triethyl orthoformate and concentrated HCl gave methyl 2-(6-chloro-9-purinyl)-2-deoxy-α-D-arabinofuranoside (**22**), which was converted by standard nucleophilic displacement reactions to the adenosine analog methyl 2-(6-amino-9-purinyl)-2-deoxy-α-D-arabinofuranoside (**23**) and the 6-(methylthio)purine ribonucleoside analog methyl 2-deoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**24**).

None of these isonucleosides so far evaluated for cytotoxicity or activity against leukemia L1210 have been found to be active.

Experimental Section

All evaporations were carried out in vacuo with a rotary evaporator. Analytical samples were normally dried in vacuo over P_2O_5 at 100° for 2–4 hr. Brinkman 8-in., 2-mm silica gel plates were used for preparative chromatographic separations and Analtech precoated (250 μ) silica gel G(F) plates for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated $(NH_4)_2SO_4$. Melting points were determined with a Mel-Temp apparatus and are not corrected. The uv absorption spectra were determined in 0.1 *N* HCl, pH 7 buffer, and 0.1 *N* NaOH with a Cary Model 17 spectrophotometer; the uv maxima are reported in nanometers ($\epsilon \times 10^{-3}$). The ^1H NMR spectra were obtained with a Varian XL-100-15 spectrometer in the solvents indicated with tetramethylsilane as an internal reference. Chemical shifts (δ in parts per million) quoted in the case of multiplets are measured from the approximate center. Mass spectral data were taken from low-resolution spectra determined with a Hitachi Perkin-Elmer RMU-7 double-focusing instrument (70 eV) (M = molecular ion).

9-(*trans*-2-Hydroxycyclohexyl)-6-(methylthio)purine (3). A solution of 6-(methylthio)purine (**1**, 166 mg, 1 mmol) and cyclohexene oxide (**2**, 117 mg, 1.2 mmol) in ethanol (15 ml) containing pyridine (1 ml) was allowed to reflux for 26 hr with two additions of cyclohexene oxide (0.2 ml). Evaporation of the solution gave a dark residue that crystallized on the addition of absolute ethanol. This material (140 mg), shown by TLC to contain two purines, was chromatographed on a silica gel plate using 19 $CHCl_3$:1 MeOH as the developer. Elution of the heavier band gave 82 mg of homogeneous material that was recrystallized from ethanol: yield 50 mg (19%); mp 202–204°; uv (pH 1) 295 nm (17.7); uv (pH 7 and 13) 286 nm (19.1), 293 (19.1).

Anal. Calcd for $C_{12}H_{16}N_4OS$: C, 54.52; H, 6.10; N, 21.19. Found: C, 54.38; H, 5.86; N, 21.08.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-tosyl-β-D-arabinofuranoside. A mixture of 1,2-*O*-isopropylidene-3,5-*O*-ditosyl-β-D-arabinofuranoside[16] (254.7 g, 0.51 mol) and lithium aluminum hydride (80 g) in tetrahydrofuran (2 l.) was refluxed overnight (TLC for complete reaction) before it was treated successively with H_2O (80 ml), 15% NaOH (80 ml), and H_2O (240 ml). The gelatinous solid was removed by filtration and washed with ether. The combined filtrates (ether and tetrahydrofuran) were evaporated to dryness; a solution of the residue in $CHCl_3$ was washed with 1 *N* NaOH and then water and dried over $MgSO_4$ before evaporation to dryness, yield of chromatographically pure product 137.9 g (82%), MS 313 $[(M - CH_3)^+]$. This material, identical with that prepared by the tosylation of 5-deoxy-1,2-*O*-isopropylidene-α-D-arabinofuranoside,[17] was used in the next step[6] without further purification.

Methyl 2,5-Dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (6) and Its Xylo Isomer (7). A mixture of 6-(methylthio)purine (**1**, 332 mg, 2.00 mmol), methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside[6] (**4**, 260 mg, 2.00 mmol), and K_2CO_3 (276 mg, 2.00 mmol) in dry DMA (15 ml) was refluxed with stirring for 3 hr before it was filtered, and the filtrate was evaporated to dryness. The residue, when chromatographed on silica gel plates using 99 $CHCl_3$:1 MeOH as developer, gave two principal bands. About 180 mg (54%) of 6-(methylthio)purine was recovered from the slower traveling band. The second band proved to be a mixture of two purine-containing sugars (uv, char), which was resolved into two bands by chromatography on another plate using 6 BuOH:1 H_2O as the developer. Elution of the faster traveling band gave 102 mg (19%) of methyl 2,5-dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**6**): mp 133–134°; uv (pH 1) 223 nm (11.8), 294 (17.2); uv (pH 7 and 13) 222 nm (12.2), 288 (19.1); ^1H NMR (DMSO-d_6) δ 1.35 (d, 3 H_5'), 2.7 (s, SMe), 3.3 (s, OMe), 4.0 (m, H_4'), 4.3 (m, H_3'), 4.8 (m, H_2'), 5.24 (d, $J_{1'2'}$ = 4 Hz, H_1'), 5.75 (broad d, OH), 8.62 and 8.76 (2 s, purine H).

Anal. Calcd for $C_{12}H_{16}N_4O_3S \cdot 0.2C_4H_9OH$: C, 49.41; H, 5.83; N, 18.00. Found: C, 49.31; H, 5.45; N, 18.04.

The identity of this purinyl sugar was confirmed by an NOE experiment. Irradiation of the methyl group at C_4 of the sugar gave a 15–20% enhancement of the signal from the proton at C_3 whereas irradiation 200 Hz upfield from the methyl group signal caused no change, indicating that the proton at C_3 must be on the same side of the ring as the methyl group and, therefore, that the purine must be attached at C_2.

Elution of the slower traveling band gave 42 mg (7%) of the second purinyl sugar, which could not be induced to crystallize. It was identified as methyl 3,5-dideoxy-3-[6-(methylthio)-9-purinyl]-α-D-xylofuranoside (**7**): ^1H NMR (DMSO-d_6) δ 0.75 (d, 3 H_5'), 2.7 (s, SMe), 3.4 (s, OMe), 4.6 (m, H_4'), 5.0 (m, H_3', H_2', H_1'), 5.55 (broad, OH), 8.62 and 8.75 (2 s, purine H).

The extremely high-field chemical shift of the signal due to the three protons at C_5 is a result of the anisotropic effect of the purine ring. There is essentially no effect on this signal when the purine is attached at C_2 (see above) rather than C_3 in keeping with the observed effects of the purine ring on the methyl signal of a *cis*-acetoxy group at C_2 and C_3 of acetylated purine nucleosides.[18]

Bis[methyl 2,5-dideoxy-2,2'-[(5-nitro-4,6-pyrimidinediyl)diimino]-α-D-arabinofuranoside] (11). A $CHCl_3$ (8 ml) solution of methyl 2-amino-2,5-dideoxy-α-D-arabinofuranoside[7] (**9**, 149 mg, 1 mmol) was added slowly to a vigorously stirred mixture of 4,6-dichloro-5-nitropyrimidine (**8**, 194 mg, 1 mmol) and $NaHCO_3$ (84 mg, 1 mmol) in $CHCl_3$ (15 ml). Vigorous stirring was continued overnight and then the $CHCl_3$ solution was washed with water and dried over $MgSO_4$ before evaporation to dryness. Trituration with

ether removed 4,6-dichloro-5-nitropyrimidine, leaving the product, a light yellow solid: mp 202–204°; ^{1}H NMR ($CDCl_3$) δ 1.36 and 1.12 (2 s, 2-C-Me), 3.44 (s, 2-OMe), 3.65 (m, 2 H_3'), 4.17 (m, 2 H_4'), 4.4 (m, 2 H_2' and 2 O_3' H), 4.97 (d, $J_{1'2'}$ = 2 Hz, 2 H_1'), 8.15 (s, H_2), 9.45 (hroad, 2 NH).

Anal. Calcd for $C_{16}H_{25}N_5O_8$: C, 46.26; H, 6.07; N, 16.86. Found: C, 46.00; H, 5.92; N, 16.85.

When the reaction was carried out in the presence of acetic acid, a lower conversion to the bis compound resulted.

Methyl 2-(6-Amino-5-nitro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (13). A mixture of methyl 2-amino-2,5-dideoxy-α-D-arabinofuranoside[7] (**9**, 1.2 g, 8.24 mmol), 4-amino-6-chloro-5-nitropyrimidine (**12**, 2.88 g, 16.5 mmol), and triethylamine (1.67 g, 16.48 mmol) in 1-butanol was refluxed for 1.3 hr. More pyrimidine (1.44 g, 8.24 mmol) and triethylamine (0.84 g, 8.24 mmol) were added and the mixture was refluxed for 1 hr. After filtration, the solution was evaporated to dryness. Treatment of the residue with MeOH caused it to gel: yield 1.91 g (78%); mp 153–155°; uv (pH 1) 242, 296 sh, 339 nm (23.4, 4.22, 6.94); uv (pH 7 and 13) 342 nm (10.1).

Anal. Calcd for $C_{10}H_{15}N_5O_5 \cdot 0.2C_4H_9OH$: C, 43.23; H, 5.71; N, 23.34. Found: C, 43.37; H, 5.72; N, 23.52.

Methyl 2-(5,6-Diamino-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (14). Methyl 2-(6-amino-5-nitro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**13**, 428 mg) in EtOH (150 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel catalyst (75 mg wet) for 20 hr. The catalyst was removed by filtration before the solution was evaporated to dryness. The residual chromatographically homogeneous syrup (264 mg, 69%) was used in the next step without further purification: uv (pH 1) 225, 292 nm (15.8, 8.95); uv (pH 7 and 13) 222, 279 nm (22.7, 8.34).

Methyl 2,5-Dideoxy-2-(6-purinylamino)-α-D-arabinofuranoside (16). A solution of methyl 2-(5,6-diamino-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**14**, 200 mg) in diethoxymethyl acetate (10 ml) was allowed to stand at room temperature for 3 days before it was evaporated to dryness. A solution of the yellow syrupy residue in MeOH (22 ml) containing NaOMe (108 mg) was refluxed for 0.5 hr, neutralized with HOAc, and evaporated to dryness. The orange syrupy residue was chromatographed on silica gel plates using 17 $CHCl_3$:1 MeOH as the developer. Elution with MeOH gave 172 mg (65%) of a solid that was recrystallized from EtOH: mp 212–214°; uv (pH 1) 279 nm (19.8); uv (pH 7) 267 nm (18.5); uv (pH 13) 274 nm (17.5); ^{1}H NMR (DMSO-d_6) δ 1.28 (d, 3 H_5'), 3.26 (s, OMe), 3.8 (m, H_3' and H_4'), 4.6 (m, H_2'), 4.84 (d, $J_{1'2'}$ = 3.5 Hz, H_1'), 7.9 (broad d, NH), 8.13 and 8.2 (2 s, purine H).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.59; H, 5.50; N, 26.18.

Methyl 2-(6-Amino-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (17). A solution of methyl 2-(5,6-diamino-6-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**14**, 216 mg) in formamide (10 ml) was heated at 150° for 3 hr before it was evaporated to dryness. The residue was chromatographed on a silica gel plate using 17 $CHCl_3$:1 MeOH once and then 9 $CHCl_3$:1 MeOH twice as developers, yield 52 mg (23%). This material was recrystallized from EtOH: mp 211–212°; uv (pH 1) 258 nm (15.2); uv (pH 7 and 13) 261 nm (15.3); ^{1}H NMR (DMSO-d_6) δ 1.32 (d, 3 H_5'), 3.27 (s, OMe), 3.95 (m, H_4'), 4.2 (m, H_3'), 4.7 (m, H_2'), 5.19 (d, $J_{1'2'}$ = 4 Hz, H_1'), 5.68 (d, O_3' H), 7.2 (s, NH_2), 8.15 and 8.24 (2 s, purine H).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.91; H, 5.65; N, 26.45.

Methyl 2-(6-Amino-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (17) and Methyl 3-(6-Amino-9-purinyl)-2,5-dideoxy-α-D-xylofuranoside (26). Reaction of a mixture[7] of methyl 2-amino-2,5-dideoxy-α-D-arabinofuranoside (**9**) and methyl 3-amino-3,5-dideoxy-α-D-xylofuranoside (**25**, 0.982 g, 6.68 mmol) with **12** (2.33 g, 13.4 mmol) as described above for pure **9** gave 1.62 g (85%) of the pyrimidinylamino sugars (**13** and its xylo isomer). Hydrogenation of half of this material with Raney nickel catalyst as described above for **13** gave 646 mg (38%) of a mixture of **14** and its xylo isomer. A solution of this mixture in formamide (30 ml) was heated at 150° for 2 hr before it was evaporated to dryness. The residue was resolved by repeated chromatography on silica gel plates using first 9 $CHCl_3$:1 MeOH and then 43 BuOH:7 H_2O as developers. The isomers were both eluted with and recrystallized from MeOH. The faster traveling material (81 mg) was essentially identical with **17** obtained as described above. The slower traveling material (**26**, 15 mg) melted at 208–210°: uv (pH 1) 258 nm (14.2); uv (pH 7 and 13) 260 nm (15.6); ^{1}H NMR (DMSO-d_6) δ 0.73 (d, 3 H_5'), 3.4 (s, OMe), 4.5 (m, H_4'), 4.95 (m, H_1', H_2', and H_3'), 5.4 (m, O_2'H), 7.2 (broad s, NH), 8.14 and 8.25 (2 s, purine H). The unusually high-field signal (0.73 ppm) due to the three protons at C_5 is a result of the anisotropic effect of the purine ring attached at C_3 of **26** (see above, ^{1}H NMR spectrum of **7**).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 50.02; H, 5.49; N, 26.68.

Methyl 2-(5-Amino-6-chloro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (18). A solution of methyl 2-amino-2,5-dideoxy-α-D-arabinofuranoside[7] (**9**, 2.64 g, 18 mmol), 5-amino-4,6-dichloropyrimidine (**15**, 5.91 g, 36 mmol), and triethylamine (5.04 ml, 36 mmol) in 1-butanol (300 ml) was refluxed for 18 hr before it was evaporated to dryness. The residue was purified by chromatography on a silica gel column using a gradient elution with $CHCl_3$ → 97 $CHCl_3$:3 MeOH. In this manner the 5-amino-4,6-dichloropyrimidine was separated from the product, yield 1.38 g (27%). This material, which was chromatographically homogeneous, was used in the next step without further purification: uv (pH 1) 305 nm (12.8); uv (pH 7 and 13) 261, 292 nm (8.20, 9.35).

Methyl 2-(5-Amino-6-chloro-4-pyrimidinylamino)-2-deoxy-α-D-arabinofuranoside (19). A solution of methyl 2-amino-2-deoxy-α-D-arabinofuranoside[7] (**10**, 0.864 g, 5.3 mmol), 5-amino-4,6-dichloropyrimidine (**15**, 1.74 g, 10.6 mmol), and triethylamine (1.48 ml, 10.6 mmol) in 1-butanol (120 ml) was refluxed for 18 hr before it was evaporated to dryness. The residue was chromatographed on silica gel plates (9 $CHCl_3$:1 MeOH). The major band was eluted with MeOH: yield 1.18 g (46%); mp indefinite; uv (pH 1) 304 nm (11.8); uv (pH 7 and 13) 261, 291 nm (7.60, 8.65). This chromatographically homogeneous material was used in the next step without further purification. Unchanged **10** was also recovered from the silica gel plates.

Methyl 2-(6-Chloro-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (20). The addition of concentrated HCl (0.13 ml) to a suspension of methyl 2-(5-amino-6-chloro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**18**, 338 mg) in ethyl orthoformate (4 ml) caused solution. After standing at room temperature for 18 hr, the solution deposited a white solid, which was removed by filtration, washed with ethyl orthoformate, and dried: yield 187 mg (54%); mp 195°; uv (pH 1 and 7) 265 nm (9.21); uv (pH 13) 263 nm (8.22).

Anal. Calcd for $C_{11}H_{13}ClN_4O_3$: C, 46.41; H, 4.60; N, 19.62. Found: C, 46.27; H, 4.43; N, 19.63.

Methyl 2-(6-Ethoxy-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (21). A solution of methyl 2-(5-amino-6-chloro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**18**, 338 mg) in triethyl orthoformate containing 0.26 ml of concentrated HCl was allowed to stand for 3 days at room temperature before it was neutralized with aqueous Na_2CO_3. Evaporation of the solution gave a residue which was purified by chromatography on silica gel plates using 97 $CHCl_3$:3 MeOH as the developer. Elution with MeOH gave a white solid which was recrystallized from MeOH: yield 192 mg (56%); mp 195–197°; uv (pH 1, 7, and 13) 252 nm (11.1).

Anal. Calcd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04. Found: C, 53.00; H, 5.97; N, 19.14.

Methyl 2-(6-Amino-9-purinyl)-2-deoxy-α-D-arabinofuranoside (23). The addition of concentrated HCl (0.11 ml) to a suspension of methyl 2-(5-amino-6-chloro-4-pyrimidinylamino)-2-deoxy-α-D-arabinofuranoside (**19**, 291 mg) in triethyl orthoformate (33 ml) caused immediate solution. After standing for 18 hr at room temperature, the solution was evaporated to dryness (no heat). A solution of the residue (**22**) in ethanolic ammonia (10 ml, saturated at 0°) was heated at 80° for 18 hr before it was evaporated to dryness. The residue was chromatographed on silica gel plates (9 $CHCl_3$:1 MeOH). After elution the product was converted to its picrate salt in MeOH. The picrate was converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}) in MeOH, yield 105 mg. Recrystallization of this material from EtOH gave 40 mg (14%) of pure product: mp 175–177°; uv (pH 1) 258 nm (14.4); uv (pH 7 and 13) 260 nm (14.8); ^{1}H NMR (DMSO-d_6) δ 3.28 (s, OMe), 3.66 (m, 2 H_5'), 3.9 (m, H_4'), 4.46 (m, H_3'), 4.75 (m, H_2'), 4.94 (m, O_5'H), 5.18 (d, $J_{1'2'}$ = 4 Hz, H_1'), 5.7 (d, O_3'H), 7.24 (broad s, NH_2), 8.16 and 8.23 (2 s, purine H).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 47.25; H, 5.27; N, 24.88.

Methyl 2-[6-(Methylthio)-9-purinyl]-2-deoxy-α-D-arabinofuranoside (24). Conversion of **19** (1.18 g) to **22** was effected as described above. A solution of the residue (**22**) from this procedure in 8.2 ml of 1 *N* NaSMe in MeOH was refluxed for 0.5 hr before it was filtered, neutralized with HOAc, and evaporated to dryness. The residue was chromatographed on silica gel plates (9 $CHCl_3$:1

MeOH). The major band was eluted and the material was rechromatographed using 9 $CHCl_3$:1 MeOH and again using ethyl acetate. The major band was eluted with MeOH and the solution was evaporated to a white glass that could not be induced to crystallize from EtOH: yield 255 mg (20%); uv (pH 1) 287 sh, 294 nm (14.0, 16.4); uv (pH 7 and 13) 287, 293 nm (18.0, 17.8); ^{1}H NMR (DMSO-d_6) δ 2.68 (s, SMe), 3.3 (s, OMe), 3.7 (m, 2 H_5'), 3.9 (m, H_4'), 4.5 (m, H_3'), 4.9 (H_2'), ca. 5 (broad, OH), 5.24 (d, $J_{1'2'}$ = 4 Hz, H_1'), 5.85 (broad, OH), 8.58 and 8.75 (2 s, purine H).

Anal. Calcd for $C_{12}H_{16}N_4O_4S \cdot 0.25C_2H_5OH$: C, 46.36; H, 5.45; N, 17.30. Found: C, 46.32; H, 5.31; N, 17.08.

Acknowledgments. This investigation was supported by Contract NO1-CM-43762 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare. The authors wish to thank Dr. W. C. Coburn, Jr., and the members of the Molecular Spectroscopy Section of Southern Research Institute for the analytical and spectral data reported and Mrs. Martha Thorpe for her help in the interpretation of the NMR spectra.

Registry No.—**1**, 50-66-8; **2**, 286-20-4; **3**, 55073-67-1; **4**, 55073-68-2; **6**, 55073-69-3; **7**, 55073-70-6; **8**, 4316-93-2; **9**, 52630-74-7; **10**, 52706-45-3; **11**, 55073-71-7; **12**, 4316-94-3; **13**, 55073-72-8; **14**, 55073-73-9; **15**, 5413-85-4; **16**, 55073-74-0; **17**, 55073-75-1; **18**, 55073-76-2; **19**, 55073-77-3; **20**, 55073-78-4; **21**, 55073-79-5; **22**, 55073-80-8; **23**, 55073-81-9; **24**, 55073-82-0; **25**, 52630-73-6; **26**, 55073-83-1; 5-deoxy-1,2-*O*-isopropylidene-3-*O*-tosyl-β-D-arabinofuranoside, 55073-84-2; 1,2-*O*-isopropylidene-3,5-*O*-ditosyl-β-D-arabinofuranoside, 55073-85-3.

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Naturally Occurring Lactones and Lactams. VIII.[1] Lactonization of Unsaturated β-Keto Esters. Total Synthesis of Carlic Acid, Carlosic Acid, and Viridicatic Acid

Axel Svendsen and Per M. Boll*

Department of Chemistry, Odense University, DK-5000 Odense, Denmark

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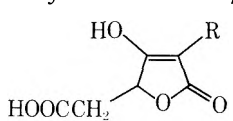
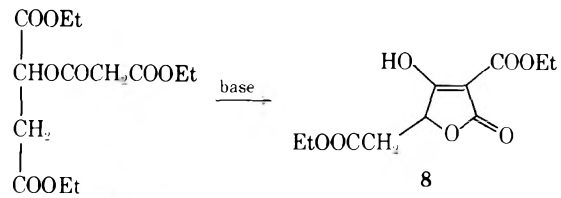
Treatment of diethyl *trans*-2-ethoxycarbonyl-3-oxo-4-hexenedioate (**11**) with concentrated sulfuric acid and subsequent hydrolysis gave the tetronic acid synthon **4**. In contrast diethyl cinnamoyl malonate (**19**) and diethyl crotonoyl malonate (**20**) were lactonized to δ-lactones. Extension of the synthetic principle to α-fumaroyl-β-keto esters provided a total synthesis of the naturally occurring tetronic acids carlosic acid (**2**) and viridicatic acid (**3**). Synthesis of carlic acid (**1**) along this route has been unsuccessful so far, whereas acylation of 5-methoxycarbonylmethyltetronic acid (**15**) with 4-chlorobutanoyl chloride and subsequent hydrolysis afforded the desired natural product.

As part of our attempts to develop general methods for the synthesis of the mold tetronic acids carlic acid (**1**, cf. **1a**), carlosic acid (**2**), and viridicatic acid (**3**), we have considered using the parent acid **4** as a synthon, since it has been demonstrated that Friedel–Crafts acylation of the tetronic acid nucleus may lead to natural products.[2-4]



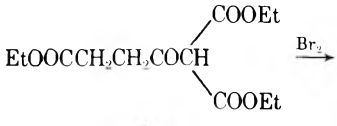
1. R = $COCH_2CH_2CH_2OH$
2. R = $COCH_2CH_2CH_3$
3. R = $COCH_2CH_2CH_2CH_2CH_3$
4. R = H
5. R = $COCH_3$
6. R = Br

The synthon **4** has already been obtained in a minor quantity from a hydrogenation product of dimethyl ketipinate (dimethyl 3,4-dioxomuconate, **13**)[5] and from cyclization of the acetoacetyl derivative of dimethyl malate with potassium *tert*-butoxide in *tert*-butyl alcohol acting as condensing agent.[4] We therefore turned our interest to the ethoxycarbonylacetyl derivative of diethyl malate (**7**), since this compound on cyclization might give **8** from which the 3-ethoxycarbonyl group could easily be removed.



7 8

It proved, however, to be very difficult to find an appropriate reagent for the Dieckmann cyclization of **7**. Earlier reactions of this type have been carried out successfully with metallic sodium[6] and especially with diisopropylmagnesium bromide in ether[7] as bases. These reagents, as well as sodium hydride in various solvents, e.g., ether, benzene, toluene, or hexamethylphosphoric triamide, induced no cyclization.



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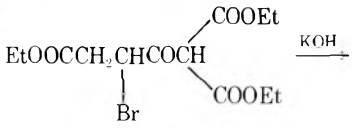
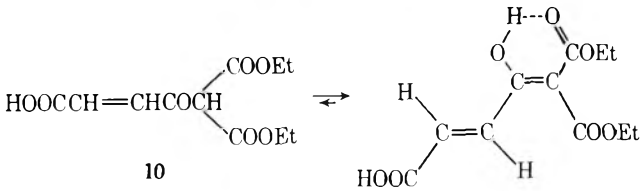
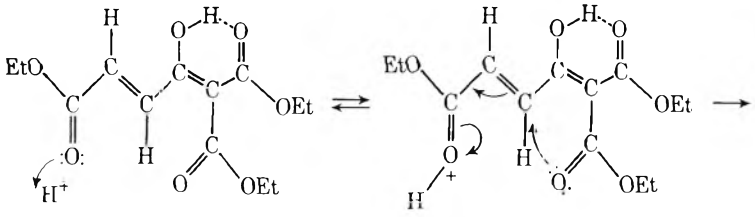
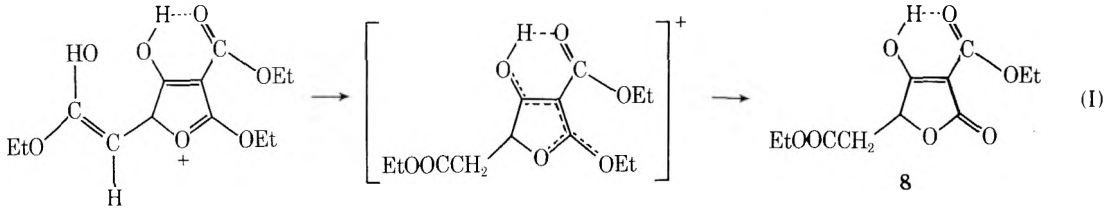




10 10a



11



(I)

8

behaved analogously. To gather information about the cource and time of reaction for the cyclization a number of NMR spectra were recorded directly on the reaction mixture, the very distinct signals of the ethylenic protons of **11** serving as an excellent means of inspecting the progress of the reaction. Immediately after dissolution these signals started fading away concomitant with the appearance of new signals at higher field. Furthermore, the originally equivalent ester methylene protons were divided into two groups of clearly different shift values. This was also the case—though to a minor extent—for the ester methyl groups. These observations lend support to the following ionic mechanism (mechanism I).[13]

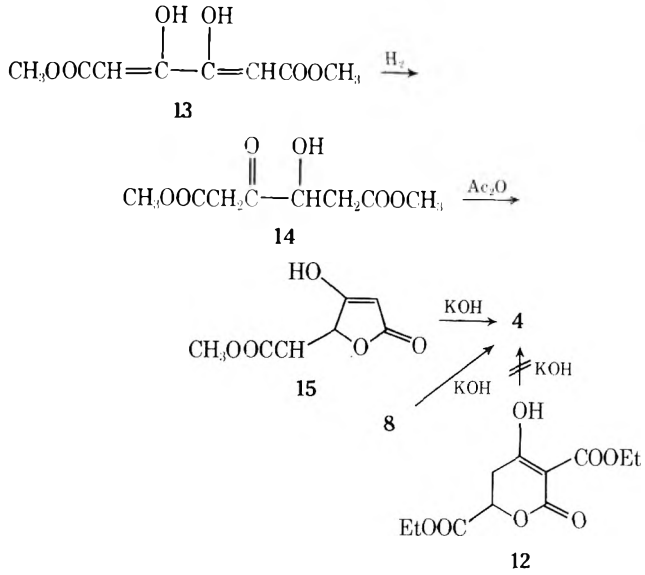
Acid-catalyzed Michael addition of one of the malonic ester groups of **11** to the ethylenic bond which has been made nucleophilic by the presence of the terminal ester group leads to the intermediate cyclic oxonium ion stabilized by extensive delocalization of the positive charge. The oxonium ethyl group is thereby rendered clearly different from the remaining two ester ethyl groups and should appear at a different shift value. In the hydrolysis step, expulsion of ethanol finally stabilizes the molecule. The time necessary for the complete disappearance of the ethylenic proton signals and thus for complete cyclization in a repeated number of runs amounted to 40 min, but already after 15 min only one-third of the original peak integration value was left. This indicates a half-life for the reaction in the range of 8–10 min.

In the light of the aforementioned cyclization of dimethyl acetoacetylmalate it was surprising to notice that even potassium *tert*-butoxide in *tert*-butyl alcohol did not give detectable amounts of **8**, the only isolable product being fumaric acid.

Considering our recent report on the synthesis of tetronic acids by cyclization of brominated β-keto esters an alternative route to **8** might be bromination of diethyl 2-ethoxycarbonyl-3-oxoadipate (**9**) and subsequent cyclization with 2.5 *N* potassium hydroxide. However, this procedure failed to give **8**, since elimination coincident with partial saponification was the predominant reaction, giving the unsaturated diester **10** as a crystalline solid in good yield. From the NMR data this compound exists predominantly in the enol form **10a**. This mode of reaction was not unexpected but equivalent to that of diethyl 3-oxoadipate.[8]

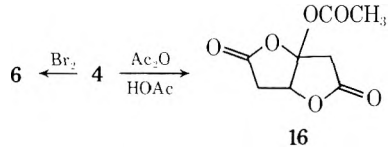
On searching through the existing literature on lactones we found that some unsaturated acids and esters have been lactonized under various conditions.[9-11] It was natural, therefore, to investigate the utility of **10** in this respect. Thus, when dissolved in concentrated sulfuric acid and left standing at 0° for 24 hr **10** after hydrolysis was transformed into a new solid product, the NMR spectrum of which revealed the absence of the characteristic ethylenic protons of the starting material. Furthermore, TLC and uv properties were in accordance with those of a tetronic acid or a similar system. On the basis of these findings and analytical data the structure **17** was assigned to this new compound. As a synthetic simplification the following investigations were carried out with the ethyl ester of **10**. This compound **11** was easily prepared by condensation of *trans*-β-ethoxycarbonylacrylyl chloride and diethyl malonate,[12] and on treatment with concentrated sulfuric acid

It was not possible a priori to predict whether **11** would cyclize according to this mechanism or according to mechanism II proposed for compounds **19** and **20** below. If the course of mechanism II was taken, simple polarization considerations of the ethylenic bond would not allow for a reliable prediction of which of two possible carbonium ions would be the one most readily formed, since the difference in directing power of a keto group vs. an ester group is too small. This problem was even more pronounced because enolization of the keto group might totally change the picture. Further, the order of stability of the two oxonium ions, another fact which may influence the pathway, is difficult to anticipate. The only possible means of ruling out any inoperative mechanism was an analysis of the structure of the product. In this respect the NMR data are of little value since the possible products **8** and **12**, as the only crucial difference, would exhibit two similar ABX systems which could not be told apart directly, and uv spectral data of similar systems[14] are too few to make any clear distinction. Finally, an unambiguous structure assignment was made by chemical means. Following the reported procedure,[5] dimethyl ketipinate (**13**) was catalytically hydrogenated to yield after the absorption of 1 mol of hydrogen the



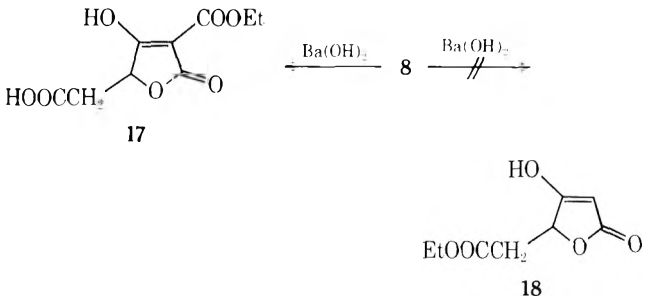
acyloin **14**, which when refluxed in acetic anhydride afforded the methyl ester **15** of the synthon **4**. Saponification of **15** by means of concentrated hydrochloric acid afforded **4**. This compound was identical in all respects with the saponification product of **8**.

In this way it was established that the cyclization product of **11** was the desired tetronic acid **8** and not the δ-lactone **12**. As further pieces of evidence treatment of our hydrolysis product **4** with acetic acid–acetic anhydride afforded the dilactone **16** identical with that reported starting from dimethyl ketipinate,[5] and bromination of **4** gave **6**,



which is the common degradation product of the three naturally occurring tetronic acids **1**, **2**, and **3**.

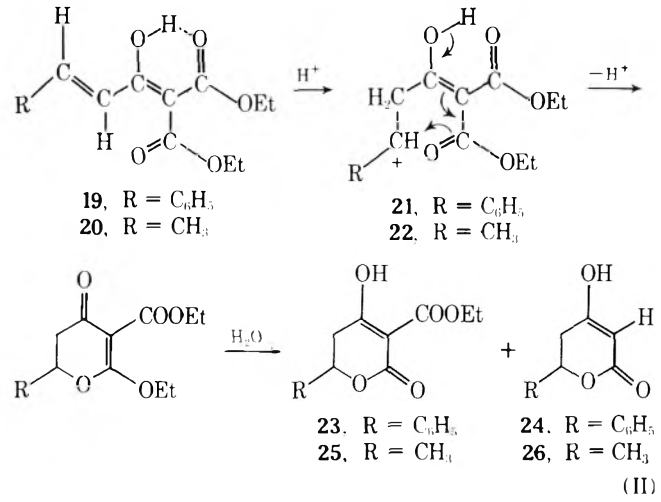
One procedure for the transformation of 3-ethoxycarbonyltetronic acids to 3-unsubstituted species is conversion to barium salt and subsequent acidification and decarboxylation.[15,16] Applying this method to **8** we obtained the saponification product **17** instead of the monoester **18**. Treat-



ment of **8** with 1 *N* potassium hydroxide or refluxing in water gave the free acid **4**. Proper conditions for the selective decarboxylation to **18** were not found.

The generality of the lactonization procedure was studied with the cinnamoyl malonate **19** and the crotonoyl malonate **20** as substrates. For these compounds mechanism I depicted above for **11** obviously is invalid. Alternatively, the following reaction sequence consistent with the isolated products is suggested (mechanism II).

Maintaining the idea of a carbonium ion mechanism operating, this time with initial protonation of the ethylenic bond, it would be predicted for both that the lactones **23** and **25**, respectively, were the most likely products. In the



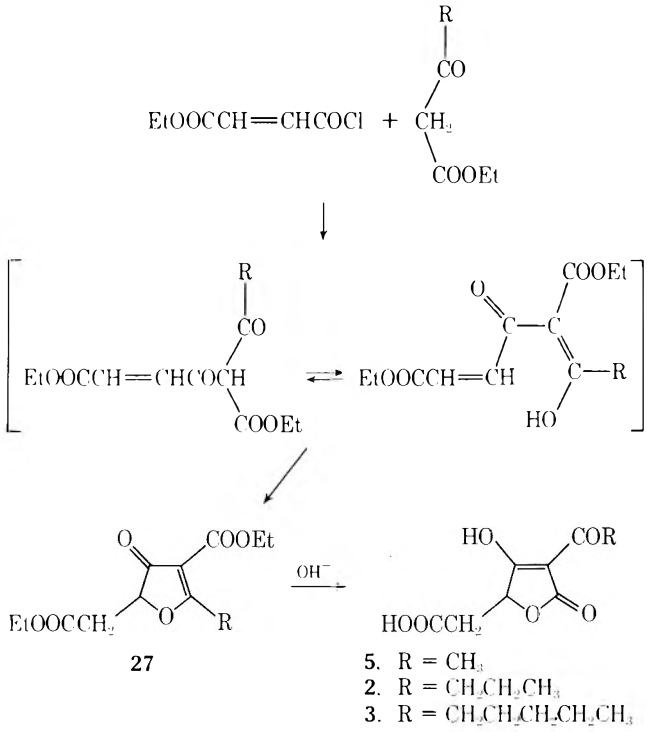
(II)

case of **19** the carbonium ion **21** should be greatly favored, since this is a benzylic cation to which resonance delocalization imparts a unique stability. The isolation of **23** in high yield confirmed this assumption. From NMR studies on the reaction mixture by inspection of the ethylenic proton signals a half-life of the reaction in the range of 20–25 min was roughly estimated. When dissolved in water and refluxed until the calculated amount of carbon dioxide had been evolved, **23** gave the lactone **24**.[17] In the case of **20** the resonance effect of the carbonyl group is unidirectional, but the carbonium ion **22**, being a normal secondary cation, has no special possibility of stabilization. This fact is reflected in the NMR investigations of the reaction from which the cyclization appeared to be more sluggish with a half-life of 80–90 min and from the low yield of product. In fact only the decarboxylated lactone **26** was isolated in a minor quantity.

The convenient lactonization of **11** led us to examine the possibility of a natural product total synthesis applying an extension of this principle. Thus for the synthesis of a 3-acylated tetronic acid diethyl malonate should be replaced by the appropriate β-keto ester and this condensed with *trans*-β-carbethoxyacrylyl chloride and cyclized with concentrated sulfuric acid.

Starting with ethyl acetoacetate as the simplest model substance condensation was attempted with sodium hydride in various solvents. The acetoacetate anion was created as a suspension in the solvent and a equivalent amount of acid chloride was added to the suspension. The strongly colored products had very complex NMR spectra which showed no ethylenic protons. This was believed, initially, to be due to a double attack to the acetoacetate anion on the acid chloride. After several experiments with various bases, ethylmagnesium bromide in methylene chloride was found to be the reagent of choice.[18] The bromomagnesioacetoacetate was readily soluble in methylene chloride and it was possible, therefore, to add this complex slowly to the acid chloride, thus preventing a double attack. Surprisingly, the clean reaction all the same gave a product without ethylenic protons. A closer examination revealed that the initially formed condensation product readily enolized via the acetoacetate keto group and the enol group added to the double bond forming the 3-oxo-4,5-dihydrofuran **27** (R = CH_3). A related reaction leading to 3-oxo-4,5-dihydrofurans has been encountered in the condensation of β-keto esters with α-halo acid chlorides.[19] Finally action of dilute sodium hydroxide rearranged **27** to the desired tetronic acid **5**.

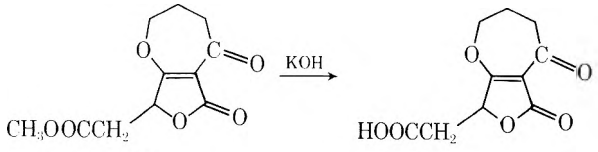
Substituting ethyl acetoacetate with ethyl 3-oxohexanoate and ethyl 3-oxodecanoate, the same sequence of reactions gave carlosic acid (**2**) and viridicatic acid (**3**), respec-



27

5. R = CH_3
2. R = $CH_2CH_2CH_3$
3. R = $CH_2CH_2CH_2CH_2CH_3$

tively.[1,20] Recently we have prepared ethyl 6-chloro-3-oxohexanoate, the requisite β-keto ester for the construction of the carlic acid side chain.[21] Condensation of this ester with *trans*-β-ethoxycarbonylacrylyl chloride and treatment of the condensation product with dilute base produced a compound $C_{10}H_{10}O_6$ of mp 187–190° [lit.[22] mp of (−)-carlic acid 176°]. Uv data were in accordance with those of **2** and **3** but NMR data disagreed with those expected for carlic acid. Finally, since the synthesis of carlic acid along this route seemed to have failed, the utility of the synthon **4** with respect to acylation was investigated. Recently the acylation of tetronic acids unsubstituted in the 3 position has been reported to proceed well in nitrobenzene with $TiCl_4$ as Friedel–Crafts catalyst.[4] As **4** contains two acidic groups capable of reacting with an acid chloride, 2 equiv of 4-chlorobutanoyl chloride was mixed with a solution of **4** in nitrobenzene. $TiCl_4$ catalyst was added and the reaction mixture was kept at 60° for 14 hr. On work-up no carlic acid was isolated. In contrast the methyl ester **15** was readily acylated when treated with an equivalent amount of 4-chlorobutanoyl chloride in nitrobenzene at 60° for 3 hr. Carlic acid methyl ester (**28**) was obtained in 68% yield. Hydrolysis to free carlic acid proceeded well with 3 *N* potassium hydroxide, yielding the desired natural product **1a**.



28 1a

Experimental Section

Microanalyses were performed at the Microanalytic Department of the University of Copenhagen. Melting points were determined on a Büchi apparatus. Nuclear magnetic resonance (NMR) spectra were recorded on a Jeol C-60 HL spectrometer with Me_4Si as internal standard. The chemical shifts are expressed in δ values (parts per million) downfield from Me_4Si. Coupling constants are expressed in hertz. Ultraviolet (uv) spectra were recorded on a Beckman Acta III spectrophotometer with absolute ethanol as solvent. The progression of the reactions was monitored conveniently by thin layer chromatography (TLC) with ether or a mixture of benzene–ethanol–acetic acid (9:2:1 v/v) as eluent.

Ethyl Chlorocarbonylacetate. Ethyl hydrogen malonate (180 g, 1.36 mol) was cooled at 0° and thionyl chloride (50 ml) was added dropwise in 30 min. The mixture was allowed to warm at room temperature and left at this temperature for 24 hr. Distillation gave a forerun of excess thionyl chloride and then pure title compound was collected, bp 74° (11 mm), yield 167 g (81%).[23]

Diethyl Ethoxycarbonylacetylmalate (7). Diethyl malate (95 g, 0.5 mol) was dissolved in dry ether (200 ml) at 0°. Ethyl chlorocarbonylacetate (75 g, 0.5 mol) was added rapidly without any noticeable reaction. To this mixture pyridine (45 g, slight excess) was added dropwise with precipitation of the hydrochloride. After complete addition and stirring for a further 2 hr 4 *N* hydrochloric acid (200 ml) was added to remove excess pyridine and the organic phase was separated and dried (Na_2SO_4). The ether was distilled off in vacuo, leaving 150 g of slightly colored oil. Two distillations gave 89 g (59%) of colorless product: bp 138–140° (0.05 mm); $n^{25}D$ 1.4374; NMR ($CDCl_3$) δ 1.29 (6 H, t, J = 7 Hz), 2.92 (2 H, d, J = 6 Hz, $COCH_2CH$), 3.43 (2 H, s, $COCH_2CO$), 4.21 (2 H, q, J = 7 Hz), 4.24 (2 H, q, J = 7 Hz), 4.27 (2 H, q, J = 7 Hz), 5.55 (1 H, t, J = 6 Hz, CH_2CHO). Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.30; H, 6.76. Found: C, 51.31; H, 6.63.

Attempted Cyclization of Diethyl Ethoxycarbonylacetylmalate (7). Potassium *tert*-butoxide (12.0 g, 0.11 mol) was suspended under nitrogen in *tert*-butyl alcohol (45 ml) distilled from calcium hydride. The triester **7** (30.4 g, 0.1 mol) was added dropwise with evolution of heat. When the addition was complete the mixture was refluxed for 40 min and left overnight at ambient temperature. After chilling at 0° 4 *N* hydrochloric acid (30 ml) and water (200 ml) were added. The aqueous solution was extracted with ether (2 × 100 ml) and the combined ether extracts were dried (Na_2SO_4). The ether was removed in vacuo and further volatile material distilled off at 110° (15 mm). From the remaining oil (27.5 g) a solid separated. Redissolution of the oil in ether (100 ml) and filtration gave 2.7 g of white solid material of mp 220° identified as fumaric acid.

***trans*-1-Ethyl Hydrogen 2-Ethoxycarbonyl-3-oxo-4-hexenedioate (10a).** The triester **9** (144 g, 0.5 mol) was dissolved in chloroform (400 ml) and chilled at 0°. A solution of bromine (80 g, 0.5 mol) in chloroform (400 ml) was added dropwise over a period of 3 hr. After standing at ambient temperature for 12 hr the solvent was removed in vacuo, leaving 188 g of yellow oil, $n^{24}D$ 1.4750. With vigorous stirring 18.8 g of this oil was added dropwise to 3 *N* potassium hydroxide (100 ml) at 0°. After 4 hr the reaction mixture was acidified with 4 *N* hydrochloric acid (60 ml) and extracted with ether (3 × 50 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated in vacuo to give 12.3 g of solid product. Recrystallization from chloroform–light petroleum (boiling range 50–70°) afforded 8.9 g (69%) of **10**: mp 102–104° (lit.[12] mp 107°); NMR ($CDCl_3$) δ 1.34 (6 H, t, J = 7 Hz), 4.31 (4 H, q, J = 7 Hz), 6.76 (1 H, d, J = 15.5 Hz), 7.56 (1 H, d, J = 15.5 Hz), 11.53 (2 H, br, s).

3-Ethoxycarbonyl-5-carboxymethyltetronic Acid (17). Solid **10** (5.2 g, 0.02 mol) was added in portions to magnetically stirred concentrated sulfuric acid (20 ml) at 0°. When all solid material had been completely dissolved the reaction mixture was left at 0° for 26 hr, after which time it was poured onto ice (60 g). The aqueous phase was exhaustively extracted with ether and the ether and some water from the extraction process were removed in vacuo to leave 4.5 g of slightly colored solid of mp 130–134°. A sample for analysis recrystallized from benzene–ethyl acetate had mp 137–139° when heated quickly. When heated slowly the compound started melting at 137° but the liquefaction was not complete until at 180°. This may be due to transesterification: NMR (DMSO-d_6) δ 1.27 (3 H, t, J = 7.5 Hz), 2.21–3.15 (2 H, m, eight lines), 4.19 (2 H, q, J = 7.5 Hz), 4.91–5.16 (1 H, m, four lines), 12.08 (2 H, s); uv λ_{max} 223 nm (log ε 4.04) and 246 (4.12).

Anal. Calcd for $C_9H_{10}O_7$: C, 46.96; H, 4.38. Found: C, 46.75; H, 4.46.

3-Ethoxycarbonyl-5-ethoxycarbonylmethyltetronic Acid (8). *trans*-Diethyl 2-ethoxycarbonyl-3-oxo-4-hexenedioate (**11**, 28.6 g, 0.1 mol) was added dropwise with stirring to concentrated sulfuric acid (100 ml) at 0°. After standing at this temperature for 24 hr the mixture was poured on ice (600 g) and exhaustively extracted with ether. Drying (Na_2SO_4) and evaporation of the solvent gave 25.4 g of a viscous yellow oil. The oil was redissolved in ether (25 ml) and chilled at −15°. Filtration of the precipitated crystals produced 13.2 g of snow-white material. Repeating this procedure a total of 17.4 g (67%) was obtained: mp 77–79°; uv λ_{max} 220 nm (log ε 4.09) and 244 (4.18); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 1.37 (3 H, t, J = 7 Hz), 2.45–3.19 (2 H, m), 4.15 (2 H, q, J = 7 Hz), 4.36 (2 H, q, J = 7 Hz), 5.20 (1 H, dd, J = 4.5 and 7.0 Hz).

Anal. Calcd for $C_{11}H_{14}O_7$: C, 51.16; H, 5.47. Found: C, 51.35; H, 5.51.

3-Ethoxycarbonyl-5-carboxymethyltetronic Acid (17). The parent diethyl ester **8** (2.60 g, 0.01 mol) was dissolved in a solution of barium hydroxide (3.5 g) in water (100 ml) and left at room temperature for 18 hr. The white precipitate was filtered, dissolved in 4 *N* hydrochloric acid (30 ml), and heated briefly at 70°. After chilling at 0° the aqueous solution was extracted with ethyl acetate (3 × 15 ml). The pooled organic extracts were dried (Na_2SO_4) and evaporated in vacuo to leave a solid mass. The mass was broken up, washed with ether, and filtered to give 0.74 g of white solid, mp 130°. Recrystallization from ethyl acetate raised the melting point to 137–139° when heated quickly. Further data were identical with those given above.

5-Carboxymethyltetronic Acid (4). A solution of the diester **8** (13.0 g, 0.05 mol) in a mixture of water (250 ml) and potassium hydroxide (16.3 g of 86% pellets) was left at room temperature for 5 days, after which time 4 *N* hydrochloric acid was added to pH <1. The aqueous solution was exhaustively extracted with ether and the ether was stripped off, leaving 5.0 g of white solid, mp 185°. One recrystallization from ethyl acetate raised the melting point to 187–191° (lit.[5] mp 187–191°). In an alternative procedure, which is more rapid but gives lower yield, **8** (7.8 g, 0.03 mol) was dissolved in water (60 ml) and heated to boiling. A vigorous evolution of gas started and within 30 min the theoretical amount of carbon dioxide (720 ml) had been collected. Exhaustive ether extraction and evaporation of the ether in vacuo gave a crude product which was recrystallized from benzene–acetic acid, yield 1.35 g (28%) of white material: mp 187–191°; NMR (DMSO-d_6) δ 2.17–3.11 (2 H, m), 4.96 (1 H, s) 4.95–5.21 (1 H, m), 10.30 (2 H, s); uv λ_{max} 222 nm (log ϵ 4.06).

3-Bromo-5-carboxymethyltetronic Acid (6). The parent acid **4** (1.3 g, 8.2 mol) was suspended in acetic acid (20 ml) and heated at 35–40°. A solution of bromine (0.8 g) in acetic acid (5 ml) was added dropwise, producing a clear solution which was stirred for a further 2 hr. The solvent was distilled off in vacuo, leaving a slightly colored solid, mp 172–175° dec. Recrystallization from acetic acid raised the melting point to 195–197° (lit.[24] mp 198–199°), NMR (DMSO-d_6) δ 2.25–3.15 (2 H, m), 5.05–5.28 (1 H, m, four lines).

2,5-Dioxo-7-acetoxyfuro[3,2-*b*]furan (16). A solution of 5-carboxymethyltetronic acid (**4**, 950 mg) in a mixture of acetic acid (9 ml) and acetic anhydride (1.5 ml) was refluxed for 30 min. The solvent was distilled off at 50° (11 mm) and the residue was dissolved in ethyl acetate (50 ml) and extracted with saturated aqueous sodium hydrogen carbonate, then water. Drying (Na_2SO_4) of the organic phase and evaporation of the solvent in vacuo left an oil (500 mg) which rapidly crystallized. The solid material was filtered and recrystallized from toluene: mp 108–109° (lit.[5] mp 109.5–111°); NMR ($CDCl_3$) δ 2.55–3.60 (4 H, m), 2.13 (3 H, s), 5.09–5.25 (1 H, m, four lines). This was in accordance with previous data.[5]

3-Ethoxycarbonyl-6-phenyltetrahydropyran-2,4-dione (23). Diethyl cinnamoylmalonate (14.5 g, 0.05 mol) was dissolved in concentrated sulfuric acid (50 ml) and left at 0° for 24 hr. Work-up performed as for **8** gave an oil (13.1 g) which rapidly solidified. Washing with cold ether, filtration, and recrystallization from ethyl acetate afforded 10.1 g (77%) of the title compound: mp 97–99°; NMR ($CDCl_3$) δ 1.39 (3 H, t, J = 7.5 Hz), 2.60–3.33 (2 H, m), 4.38 (2 H, q, J = 7.5 Hz), 5.20–5.50 (1 H, m, four lines), 7.31 (5 H, s), 11.31 (1 H, s); uv λ_{max} 251 nm (log ϵ 4.06).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.30; H, 5.49.

6-Phenyltetrahydropyran-2,4-dione (24). 23 (1.3 g, 0.005 mol) was dissolved in water (30 ml) and refluxed until the gas evolution ceased (30 min). Upon cooling the precipitated solid was filtered and recrystallized from benzene to yield 450 mg of the title compound: mp 126–130° (lit.[17] mp 120–127°); NMR (DMSO-d_6) 2.25–3.15 (2 H, m), 5.05 (1 H, s), 5.25–5.55 (1 H, m, four lines), 7.35 (5 H, s), 11.40 (1 H, s); uv λ_{max} 242 nm (log ϵ 4.01).

6-Methyltetrahydropyran-2,4-dione (26). Diethyl crotonoylmalonate (11.9 g, 0.05 mol) was dissolved in concentrated sulfuric acid and left for 72 hr at 0°. Work-up as above gave 8.1 g of yellow oil. The oil was dissolved in light petroleum (boiling range 50–70°) and placed at 0° for 6 days. The precipitated crystals were filtered and washed with cold ether to give 1.1 g of product. Recrystallization from benzene–ethyl acetate gave analytically pure **26:** mp 121–122°; NMR (DMSO-d_6) δ 1.29 (3 H, d, J = 6 Hz), 2.35 (2 H, d, J = 8 Hz), 4.09–4.68 (1 H, m), 4.91 (1 H, s), 11.21 (1 H, s, br); uv λ_{max} 239 nm (log ϵ 4.07).

2-Methyl-3-ethoxycarbonyl-4-oxo-5-ethoxycarbonylmethyl-4,5-dihydrofuran (27, R = CH_3). To ethyl acetoacetate (26.0 g, 0.2 mol) in methylene chloride (100 ml) was added ethylmagnesium bromide in the same solvent at 0° until the evolution of ethane ceased. The clear solution was transferred to a dropping funnel and added dropwise to a solution of *trans*-3-ethoxycarbonylacrylyl chloride (32.5 g, 0.2 mol) in methylene chloride (50 ml) at 0°. After complete addition and standing at ambient temperature for 12 hr the reaction mixture was poured into ice-cold 2 *N* hydrochloric acid (300 ml) and shaken thoroughly. The organic layer was separated, washed with brine (200 ml), and dried ($NaSO_4$). Evaporation of the solvent in vacuo left 51.5 g of oily product. The oil (3 × 2.0 g) was chromatographed on three silica gel plates with ether as eluent. The bands with R_f 0.63 on reextraction with ether gave 2.90 g of slightly colored **27:** NMR (CCl_4) δ 1.25 (3 H, t, J = 7 Hz), 1.31 (3 H, t, J = 7 Hz), 2.28–3.13 (2 H, m), 2.55 (3 H, s), 4.11 (2 H, q, J = 7 Hz), 4.18 (2 H, q, J = 7 Hz), 4.59–4.86 (1 H, m, four lines).

3-Acetyl-5-carboxymethyltetronic Acid (5). Crude **27** (25.0 g) was dissolved in tetrahydrofuran (50 ml) and 2.5 *N* potassium hydroxide (100 ml) was added at 0°. The mixture was stirred at ambient temperature for 12 hr and then extracted with ether (3 × 50 ml). The aqueous phase was acidified with 4 *N* hydrochloric acid to pH <1 and exhaustively extracted with ether to give 21.5 g of an oil which partly solidified. Filtration and washing with ether afforded 13.7 g of **5,** mp 160–165°. Recrystallization from acetic acid yielded 11.3 g of analytically pure product: mp 178–180° (lit.[20] mp 176–177°); NMR (DMSO-d_6) δ 2.30–3.10 (2 H, m), 2.44 (3 H, s), 4.72–4.91 (1 H, m, four lines), 10.14 (2 H, s, br); uv λ_{max} 228 nm (log ϵ 3.78) and 267 (4.09).

(±)-Carlosic Acid (2). Ethyl 3-oxohexanoate (7.9 g, 0.05 mol) in methylene chloride (50 ml) was condensed with *trans*-3-ethoxycarbonylacrylyl chloride (8.2 g, 0.05 mol) in methylene chloride (50 ml) exactly as described above for ethyl acetoacetate to give 13.2 g of crude oil: NMR (CCl_4) δ 1.03 (3 H, t, br), 1.14 (3 H, t, J = 7 Hz), 1.32 (3 H, t, J = 7 Hz), 1.40–1.95 (2 H, m), 2.27–3.18 (4 H, m), 4.11 (2 H, q, J = 7 Hz), 4.19 (2 H, q, J = 7 Hz), 4.60–4.85 (1 H, m, four lines). The oil (2.8 g) was dissolved in tetrahydrofuran (10 ml) and a mixture of water (50 ml) and sodium hydroxide (2 g) was added. After stirring for 12 hr work-up as above afforded 2.2 g of a brown solid. Recrystallization from ethyl acetate gave 1.8 g of analytically pure title compound: mp 160–163° [lit.[22] mp of (−) form 181°]; NMR [$CDCl_3$–DMSO-d_6 (4:1)] 0.98 (3 H, t, br), 1.36–2.01 (2 H, m), 2.43–3.16 (4 H, m), 4.80–5.03 (1 H, m, four lines), 10.68 (2 H, s); uv λ_{max} 228 nm (log ϵ 3.78) and 268 (4.11).[26]

Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30. Found: C, 52.55; H, 5.51.

(±)-Viridicatic Acid (3). Ethyl 3-oxodecanoate (9.3 g, 0.05 mol) and *trans*-3-ethoxycarbonylacrylyl chloride (8.2 g, 0.1 mol) condensed as above gave 15.0 g of crude oil. The oil (3.0 g) was treated as described for **2** with a mixture of water (50 ml) and sodium hydroxide (2.0 g) to yield 800 mg of product. Recrystallization twice from ethyl acetate gave 500 mg of pure **3:** mp 158–160° [lit.[25] mp of (−) form 174.5°]; NMR (DMSO-d_6) δ 0.88 (3 H, deformed t), 1.08–1.95 (6 H, m), 2.50–3.10 (4 H, m), 4.80–5.03 (1 H, m, four lines), 11.15 (2 H, s); uv λ_{max} 232 nm (log ϵ 3.92) and 267 (4.13).[26]

Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.10; H, 6.20.

Attempted Synthesis of (±)-Carlic Acid (1a). Ethyl 6-chloro-3-oxohexanoate (9.63 g, 0.05 mol) and *trans*-3-ethoxycarbonylacrylyl chloride (8.2 g, 0.05 mol) condensed as above gave 16.1 g of crude oil. Further treated as above, this oil (3.6 g) gave a solid (850 mg) which upon recrystallization from ethyl acetate had mp 187–190° [lit.[22] mp of (−)-carlic acid 176°]; NMR [$CDCl_3$–DMSO-d_6 (4:1)] 1.12–1.50 (4 H, m), 2.43–3.14 (3 H, m), 4.82–5.09 (1 H, m, four lines), 11.89 (2 H, s, br) (this is not in accordance with the expected spectrum); uv λ_{max} 228 nm (log ϵ 3.74) and 275 (4.12).

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 52.90; H, 4.36.

(±)-Carlic Acid Methyl Ester (28). 5-Methoxycarbonylmethyltetronic acid (**15,** 0.86 g, 5 mmol) was dissolved in nitrobenzene (25 ml) and 4-chlorobutanoyl chloride (0.73 g, 5 mmol) was added. To this mixture titanium tetrachloride (1.5 ml) was cautiously added with vigorous stirring to produce, finally, a clear solution. The reaction mixture was immersed in an oil bath at 60° for 3 hr and then left at ambient temperature for 50 hr. The reaction mixture was poured all at once into a mixture of concentrated hydrochloric acid (50 ml) and crushed ice (100 g) and extracted with chloroform (3 × 30 ml) and ether (30 ml). The combined organic extracts in turn were extracted with saturated aqueous sodium hydrogen carbonate (2 × 50 ml) and the aqueous phase was separated

and extracted with ether (30 ml) to remove traces of nitrobenzene. The sodium hydrogen carbonate extract was acidified to pH <1 by dropwise addition of concentrated hydrochloric acid and reextracted with chloroform (4 × 15 ml). The pooled chloroform extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to leave 1.20 g of viscous brown oil, which after standing for 2 days at 5° crystallized. Attempted recrystallization from benzene at this stage failed and the crude product was chromatographed on a 1-in. column packed with 60 g of silica gel with chloroform–acetic acid (19:1) as eluent. This procedure afforded a product which when recrystallized from benzene gave 0.7 g (68%) of pure **28**: mp 119–121°; NMR ($CDCl_3$) δ 2.00–2.59 (2 H, m, five lines). 2.63–3.26 (2 H, m), 3.45 (2 H, t, J = 8 Hz), 3.70 (3 H, s), 4.82 (2 H, t, J = 7 Hz), 4.70–4.96 (1 H, m); uv λ_{max} 221 nm (log ϵ 3.65) and 274 (4.25).

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.95; H, 5.13.

(±)-Carlic Acid (1a). Carlic acid methyl ester (0.70 g) was dissolved in 3 *N* potassium hydroxide (10 ml) and left at room temperature for 72 hr. The solution was acidified with concentrated hydrochloric acid to pH <1 and evaporated to dryness in vacuo. The remaining solid mass was extracted with boiling chloroform (8 × 10 ml) and the chloroform was removed, leaving 0.54 g of crystalline material, mp 176–180°. One recrystallization from ethyl acetate–ethanol gave 0.50 g (76%) of pure carlic acid: mp 177–180° [lit.[22] mp of (−)-carlic acid 176°]; NMR (DMSO-d_6) δ 1.90–2.48 (2 H, m, five lines), 2.50–3.15 (2 H, m), 3.36 (2 H, t, J = 8 Hz), 4.70 (2 H, t, J = 7.5 Hz), 4.55–5.00 (1 H, m); uv λ_{max} 226 nm (log ϵ 3.73) and 273 (4.23).[26]

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 52.90; H, 4.57.

Registry No.—**1**, 55088-89-6; **1a**, 55088-90-9; **2**, 54423-52-8; **3**, 54397-56-7; **4**, 54397-59-0; **5**, 55088-91-0; **6**, 55088-92-1; **7**, 55088-93-2; **8**, 54397-58-9; **9**, 40421-01-0; **10**, 55088-94-3; **10a**, 55088-95-4; **11**, 55088-96-5; **15**, 54423-53-9; **16**, 55088-97-6; **17**, 54397-60-3; **19**, 55088-98-7; **20**, 55088-99-8; **23**, 55089-00-4; **24**, 41479-98-5; **26**, 33177-29-6; **27** (R = CH_3), 53252-38-3; **28**, 54397-61-4; ethyl chlorocarbonylacetate, 36239-09-5; ethyl hydrogen malonate, 1071-46-1; thionyl chloride, 7719-09-7; diethyl malate, 7554-12-3; fumaric acid, 110-17-8; bromine, 7726-95-6; ethyl acetoacetate, 141-97-9; *trans*-3-ethoxycarbonylacrylyl chloride, 26367-48-6; ethyl 3-oxohexanoate, 3249-68-1; 3-oxodecanoate, 13195-66-9; ethyl 6-chloro-3-oxohexanoate, 54362-87-7.

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Synthetic Study of (±)-Canadensolide and Related Dilactones. Double Lactonization of Unsaturated Dicarboxylic Acids via Acyl Hypoiodite Intermediates

Michiharu Kato, Masanori Kageyama, Reiko Tanaka, Kozo Kuwahara, and Akira Yoshikoshi*

Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan

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Stereospecific oxidation of **12a** and **12b**, followed by methylenation, yielded **1b** and **1a**, respectively. The latter product was identified as (±)-canadensolide and has resulted in a revision of the stereochemistry previously proposed for this natural dilactone. Furthermore, a new stereospecific double lactonization reaction of olefinic dicarboxylic acids has been found. Besides a demonstration with some model compounds, it has been used to lactonize **54** and **57** giving **1b** and **1a**, respectively.

Canadensolide (**1a**) is a mold metabolite produced by *Penicillium canadense* and has an antigerminative activity against fungi, e.g., *Botrytis alii*. It was isolated from the culture filtrate, along with other closely related compounds, and their structures were assigned by McCorkindale et al.[1] A structural feature of canadensolide is its di-γ-lactone system, and the analogous di-γ-lactone structure has been found in other acetogenins, dihydrocanadensolide[1] (**2**), avenaciolide[2] (**3a**), 4-isoavenaciolide[3] (**3b**), and ethisolide[3] (**3c**), and in the sesquiterpenoids picrotoxinine[4] (**4a**) and picrotine[4] (**4b**).

We were interested in the synthesis of canadensolide and related di-γ-lactone systems.[5] Our synthetic design envisaged a double lactonization of unsaturated tricarboxylic acids, such as **5** or **6**, which would lead to the dilactonic carboxylic acid (**7**). The extra carboxyl group in **7** might then be utilized for the introduction of an exocyclic methylene group.

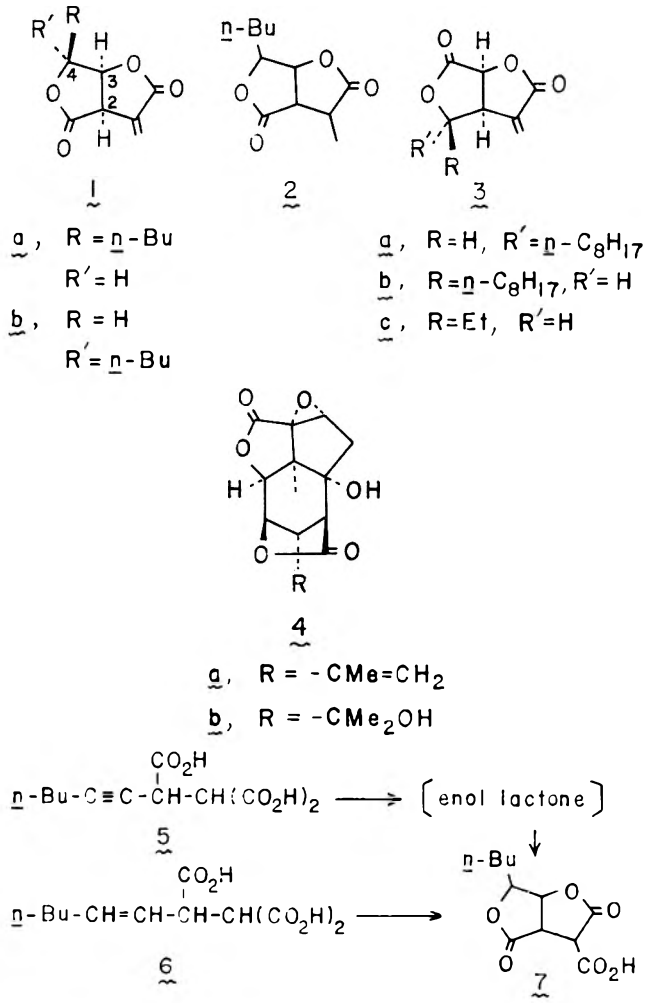
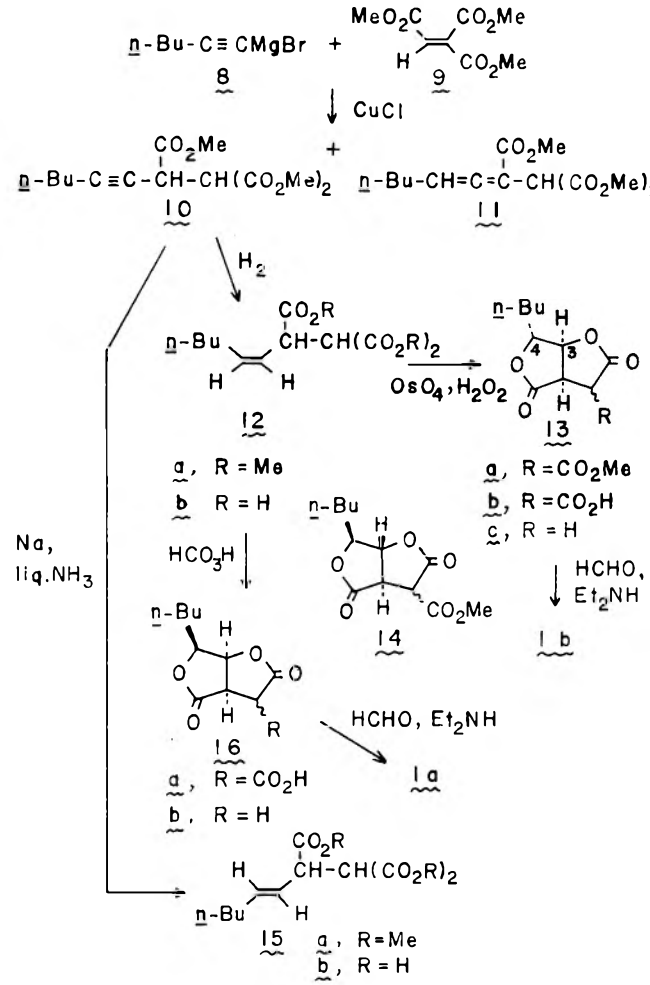


Chart I



Stereochemistry of Canadensolide. The original stereochemistry of canadensolide (**1b**) was assigned on the basis of NMR evidence.[1] Alignments of protons at C(2), C(3), and C(4) have been given on their NMR coupling constants, i.e., $J_{2,3}$ = 6.5 and $J_{3,4}$ = 4.5 Hz, respectively. However, it is recognized that the Karplus relation between coupling constants and dihedral angles largely depends upon the electronegativity of substituents, bond angles, and bond lengths.[6] Thus to confirm the stereochemistry of canadensolide assigned by McCorkindale et al.,[1] we attempted the synthesis according to formula **1b** via stereochemically well-documented reactions.[7]

1-Hexynylmagnesium bromide (**8**) was allowed to react with trimethoxycarbonylethylene[8] (**9**) in the presence of cuprous chloride and gave an adduct (**10**) (73% yield) accompanied by a minor amount of the allene derivative[9] (**11**) in a ratio of 20:1 (GLC) (Chart I). Hydrogenation of **10** over Lindlar catalyst yielded the cis olefinic ester (**12a**) in 74% yield, which when submitted to oxidation with Milas' reagent afforded a crystalline dilactone (22% yield). The structure (**13a**) depicted for this dilactone was supported by its spectra. The lack of stereoselectivity presumed for this oxidation led us to anticipate the formation of two diastereomeric cis oxidation intermediates, one of which should give **13a** upon lactonization. The other diastereomer should give largely strained trans dilactone (**14**), provided that its double lactonization were possible under reaction conditions used. Nevertheless, we did not encounter the latter lactone or its progenitors and, in fact, the facile formation of a single dilactone, obtained under such mild reaction conditions, suggested the product to be an unstrained cis-fused compound (**13a**). When lactone **13a** was hydrolyzed by heating with dilute hydrochloric acid at 55°, the corresponding carboxylic acid (**13b**) was obtained; on the other hand, heating with the same mineral acid at 100–110° resulted in the formation of the decarboxylation product (**13c**). The latter compound was also obtained from the cis olefinic acid (**12b**), itself prepared by alkaline hydrolysis of **12a**, upon treatment with Milas' reagent followed by acetic anhydride (29% yield). The dilactone **13c** has been prepared by Mukaiyama et al.[10] using an alternative route, and our compound was identified by comparison with their compound. To introduce an exo methylene group, the carboxylic acid **13b** was treated, according to Parker and Johnson,[5b] with formalin and diethylamine in acetic acid and then with sodium acetate. The unsaturated lactone **1b** was obtained in 64% yield. The NMR spectrum of **1b** was similar to that of canadensolide, but they were distinctly different. A prominent difference was that the coupling constant between protons at C(3) and C(4) for this compound is 1.5 Hz, whereas 4.5 Hz has been reported for the corresponding proton coupling of natural product. These results raised doubts about the orientation assigned to the *n*-butyl group in canadensolide and therefore we turned to a synthesis of its epimer (**1a**) by analogous routes.

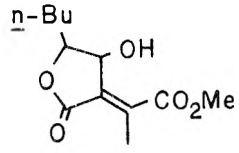
The acetylenic ester **10** yielded the trans olefinic ester **15a** on treatment with sodium in liquid ammonia (69% yield). A similar cis oxidation of **15a** with Milas' reagent then afforded a mixture from which we failed to separate the desired dilactonic ester. Trans oxidation of the cis olefinic ester **12a** with performic acid also gave an inseparable mixture. However, when the former product was heated with dilute sulfuric acid, crystals could be isolated, whose spectra seemed to be consistent with formula **16b.** In addi-

Table I
Double Lactonization of Norbornenedicarboxylic Acid (22)

Run	Salt of 22	Reaction conditions: Solvent	Reagent	Temp, °C (time, hr)	Yield of 23, %
1	Na[a]	DMSO	I_2	Room temp (12)	0
2	K[b]	*t*-BuOH	I_2	Room temp (15) and then 50 (2)	0
3	K[b]	DMSO + H_2O (40:1)	I_2, KI	50 (18)	27
4	Na[a]	DMSO	I_2, AgOAc	50 (15)	64
5	Ag[c]	DMSO[d]	I_2, AgOAc	60 (12)	92

[a] Neutralized with sodium bicarbonate. [b] Neutralized with potassium *tert*-butoxide. [c] Prepared from the sodium salt by an exchange reaction with silver nitrate. [d] When dimethylformamide was used as solvent, **23** was obtained in 88% yield.

tion the coupling constant between C(3) and C(4) protons in the NMR spectrum was 4.0 Hz. The performic acid oxidation product of **12a** was then heated with dilute hydrochloric acid at 55°, and the resulting thick oily hydrolysis product, probably consisting of dilactonic acid (**16a**) for the most part, was treated with formalin and diethylamine as in the previous case. The unsaturated dilactone (**1a**) obtained was completely identical with natural canadensolide by spectral comparison.[11] We thus conclude that the relative stereochemistry of canadensolide should be revised to that depicted in **1a**.[12] Consequently, the configuration of the butyl groups assigned to other mold metabolites correlated to canadensolide, i.e., dihydrocanadensolide[1] (**2**) and the monolactonic ester[1] (**17**), should also be revised.



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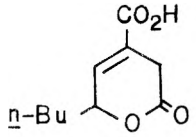
Double Lactonization. At the outset we examined the double lactonization of the acetylenic acid **5**, which was obtained in 85% yield by alkaline hydrolysis of **10** under mild conditions. The hydrolysis product was accompanied by a minor amount of δ-lactone **18**, which was probably formed



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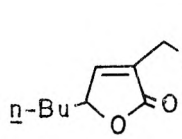

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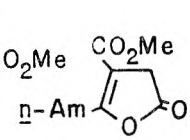

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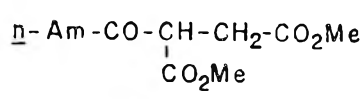

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by partial lactonization of **5** upon acidification or during silica gel chromatography of the hydrolysis product. Attempted double lactonization of **5** failed to lead to dilactones. Treatment of **5** with silver nitrate in aqueous dioxane followed by diazomethane provided the butenolide **19** in good yield, which was also obtained by heating **5** followed by esterification. The acetylenic acid lactonized in cold sulfuric acid giving an enol-γ-lactone in good yield, and the product was characterized as its ester **20**. On the other hand, treatment of **5** with dilute sulfuric acid in the presence of mercuric salt followed by esterification yielded the major hydration product **21**, along with **19** and unidentified compounds. Although it was of interest that the acetylenic acid underwent lactonization and decarboxylation at different positions depending upon reaction conditions, such attempts to form the desired dilactone seemed to be hopeless. We then decided to examine the oxidation of related olefinic acids.

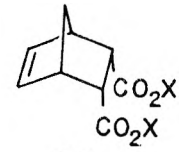
Table II
Double Lactonization of Some Olefinic Dicarboxylic Acids via Acyl Hypoiodites

Acid	Product	Yield, %
22a[13]	**23**[14]	92
24	**25**[16]	56
26	**27**[16]	60
28[17]	**29**	52
30[18]	**31**	77
32	**33**	47
34[19]	**35**[b]	32

[a] The yields were not optimized. [b] Dimethylformamide was used as solvent for convenience of work-up.

When an olefinic polycarboxylic acid undergoes halolactonization, the halogen atom of the initially formed halolactone may then serve as a leaving group for the intramolecular attack of carboxylate ion in the second lactonization that leads to the dilactone, provided that stereochemical requirements are satisfied.

Prior to the examination of the olefinic acids, such as **48**, we began with norbornenedicarboxylic acid[13] (**22a**) as a



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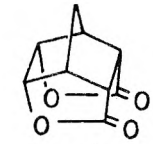
a, X = H
b, X = I



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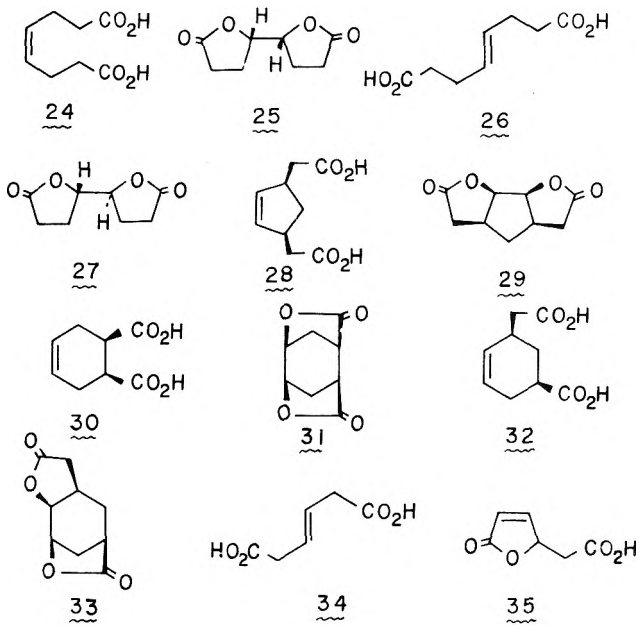
model compound. Some typical runs are summarized in Table I.

Under anhydrous conditions aprotic (run 1) or protic solvent (run 2) did not effect double lactonization, while addition of water (run 3) gave dilactone[14] **23** in low yield.[15] Addition of silver acetate to promote the ionization of iodine atom of the intermediate iodolactone improved the yield of **23** remarkably (run 4). An almost quantitative yield was obtained when the silver salt of the acid was treated with iodine and silver acetate in dimethyl sulfoxide (run 5). Under the last-mentioned reaction conditions diacyl dihypoiodite (**22b**) is likely involved as a reactive intermediate.

This double lactonization using silver salts was examined with some other olefinic dicarboxylic acids, and the results are summarized in Table II.

It was found that this reaction is general in nature and results in good yields of dilactones. An exception, however, is the silver salt of *trans*-dihydromuconic acid (**34**), which gave the butenolide **35** upon treatment with iodine and silver acetate but no lactone. Its formation can be rationalized in terms of a faster elimination of hydrogen iodide than the rate of the second lactonization, since the inter-

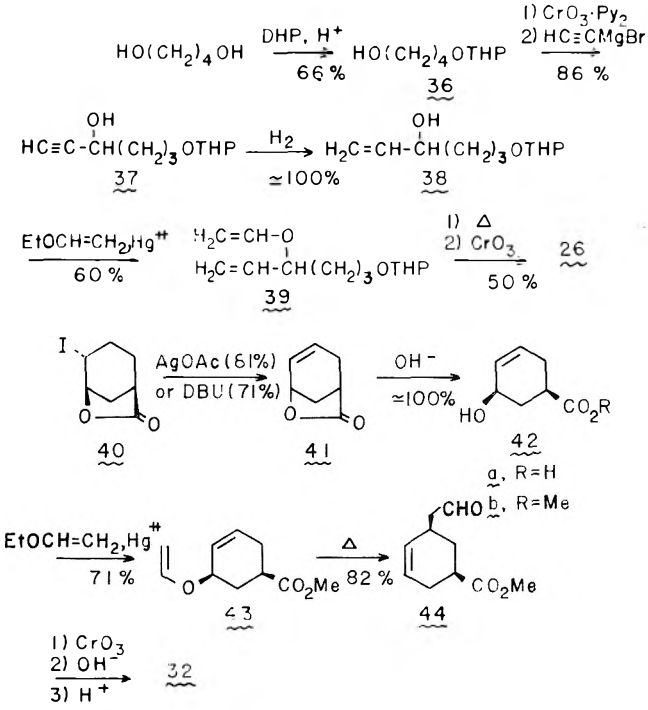
mediate is anticipated to be a β-iodobutyrolactone. Dilactone **33** involves a dilactonic structure which has been



found in some picrotoxane sesquiterpenoids, e.g., picrotoxinine[4] (**4a**) and picrotine[4] (**4b**).

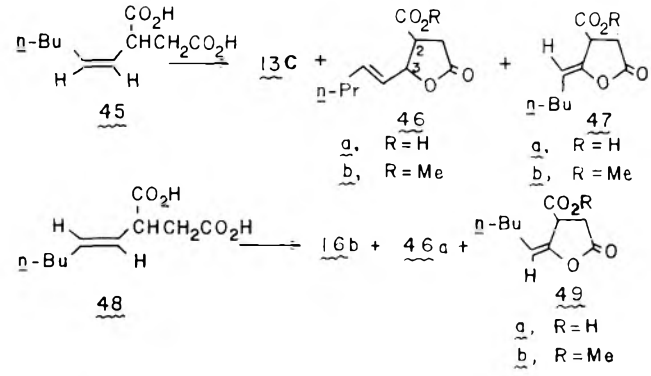
The synthesis of the new olefinic acids used is as follows. The dimethyl ester of (*Z*)-4-octenedioic acid (**24**) was prepared by hydrogenation of dimethyl 4-octynedioate[20] over Lindlar catalyst. Dicarboxylic acids **26**[22] and **32** were prepared as shown in Chart II.

Chart II



Next we utilized the above double lactonization reaction for the synthesis of canadensolide and related dilactones. Cis and trans olefinic dicarboxylic acids, **45** and **48**, were prepared by decarboxylation of the tricarboxylic acids **12b** and **15b**, respectively. The latter tricarboxylic acid was obtained by alkaline hydrolysis of the corresponding ester **15a**. Under standard conditions, silver salts of **45** and **48** yielded 4-*epi*-norcanadensolide (**13c**) and norcanadensolide (**16b**) in 30 and 41% yields, respectively (Chart III). As

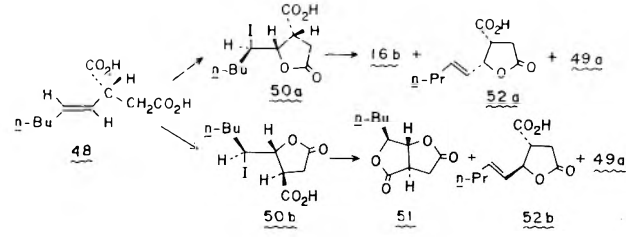
Chart III



acidic by-products, the former silver salt gave butyrolactones **46a** and **47a**, while the latter provided **46a** and butyrolactone **49a** isomeric with **47a**. These by-products were characterized as methyl esters (**46b**, **47b**, and **49b**). It is noteworthy that the same butyrolactone (**46a**) was obtained from both of the silver salts, and that isomeric butyrolactones, **47a** and **49a**, were formed in respective reactions. Stereochemical assignments for **47a** and **49a** were made on the basis of the difference in chemical shift values in the NMR spectra of their esters, **47b** and **49b**; i.e., the former ester showed an olefinic proton signal at a distinctly higher field than did the corresponding proton of the latter ester ($\Delta\delta$ 0.47 ppm).

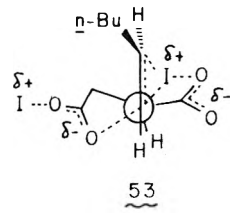
These results suggested the following mechanistic pathway for the formation of the lactones. The carboxyl group that participated in the first lactonization is the less substituted one, because we observed no formation of $\Delta^{\alpha,\beta}$-butenolide, which would be a possible product if the more substituted carboxyl formed the first lactone ring, as we saw in the case of **34**. This is simply explained in terms of the sterically hindered approach of the more substituted carboxyl group. Chart IV demonstrates the reaction of the

Chart IV



trans olefinic acid **48** (silver salt). Two diastereomeric iodolactone intermediates, **50a** and **50b**, may be formed. Assuming that the second lactonization proceeds by bimolecular substitution, the former intermediate (**50a**) would give norcanadensolide (**16b**), whereas **50b** would lead to the formation of strained dilactone **51**. Either of the intermediates should afford the same butyrolactone (**49a**) by trans elimination of hydrogen iodide with methine proton, whereas by trans elimination of hydrogen iodide with one of methylene protons they would produce butyrolactones **52a** and **52b**, respectively. A similar discussion leads us to assume the formation of 4-*epi*-norcanadensolide (**13c**), butyrolactones **52a** and **52b**, and **47a** from the cis olefinic acid **45**. The stereochemistry of the butyrolactone **46b** could not be assigned directly from the coupling constant (6 Hz) between protons at C(2) and C(3). It should be noticed, however, that only one isomer (**46a**) was obtained from both of the cis and trans olefinic acids (**45** and **48**). This fact allowed us to conclude that in the first iodolactonization step, the iodine atom of the more substituted hypoiodite group partic-

ipated in the transition state of this reaction as shown in **53**. Such a fixation of the conformation in the transition



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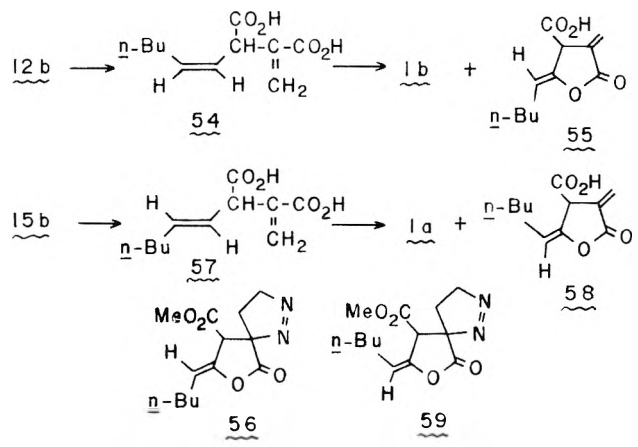
state accounts well for the formation of the same butyrolactone (**46a**) from either of the olefinic acids. If this mechanism is operative, the butyrolactone must be cis disubstituted, i.e., **52a**, although we did not verify it.

Finally the double lactonization reaction was applied to the synthesis of (±)-canadensolide and its 4 epimer (Chart V). Cis and trans olefinic tricarboxylic acids, **12b** and **15b**,

Chart V



were treated with formalin and dimethylamine, affording unsaturated dicarboxylic acids **54** and **57** in yields of 43 and 42%, respectively. When the silver salt of **54** was treated under similar conditions, (±)-4-*epi*-canadensolide (**1b**, 14% yield) and an acidic product were obtained. Similarly **57** gave (±)-canadensolide (**1a**, 21% yield) accompanied by an acidic product. Although lower yields than those of the corresponding nordilactones were obtained in the above reactions, it may be partly ascribed to an increased strain in the formation of lactone rings due to the replacement of sp^3 by sp^2 carbon atoms. The acidic by-products were treated with diazomethane, giving pyrrazolines **56** and **59**, respectively. This indicated that the acidic products in the above reactions were unsaturated butyrolactones **55** and **58**, respectively.

Experimental Section

All melting points and boiling points are uncorrected. IR spectra were taken on a Hitachi EPI-S2 or a G-2 spectrometer. NMR spectra were obtained by a Jeol Model C-60HL spectrometer using Me_4Si (δ 0) as an internal standard and $CDCl_3$ as the solvent unless otherwise indicated. Coupling constants (J) are given in hertz. Mass spectra were obtained on a Hitachi RMU-6D spectrometer. GLC analyses were performed on a Jeol Model JGC-750 instrument using the following columns: A (20% PEG, 2 m × 3 mm) and B (10% SE-30, 2 m × 3 mm).

1,1,2-Tricarbomethoxy-3-octyne (10). A solution of 1-hexyne[23] (2.83 g) in dry tetrahydrofuran (20 ml) was added to a stirred Grignard reagent solution, prepared from ethyl bromide (3.71 g) and magnesium (816 mg) in the same solvent (20 ml), at room temperature. After the mixture had been stirred overnight, anhydrous cuprous chloride (15 mg) was added. Tricarbomethoxyethylene[8] (**9**, 5.39 g) in dry tetrahydrofuran (100 ml) was then added dropwise to the above solution in an ice bath. The reaction mixture was stirred at room temperature overnight, and then water (150 ml) and 3 *N* hydrochloric acid (10 ml) were added. The product was extracted with ether, and the combined extracts were washed with water and brine and dried. Removal of the solvent gave a brownish-red oil,[24] which was chromatographed on silica gel. Elution with petroleum ether–ether (3:1) afforded **10** (5.79 g, 73%) as a colorless oil. An analytical sample was obtained by distillation (bath temperature, 120°) in vacuo (0.3 mm). The distillate gradually crystallized on standing: mp 26–27.5°; ir (KBr) 2220 and 1760–1740 cm^{-1}; NMR (CCl_4) δ 0.89 (t, 3 H, J = 6.0 Hz), 1.1–1.6 (hr m, 4 H), 2.14 (br t, 2 H, J = 6.0 Hz, $CH_2C{\equiv}$), 3.75 and 3.78 (s, 3 H each), and 4.0 (br s, 2 H, $CHCO_2Me$).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.38; H, 6.92.

Methyl 2,3-Dimethoxycarbonyl-3,4-nonadienoate (11). The ester **10** (300 mg) was added to a solution of sodium amide prepared from sodium (70 mg) and liquid ammonia (200 ml), and the mixture was stirred for 2 hr. After evaporation of liquid ammonia, water (50 ml) was added to the residue. The product was extracted with ether, and the combined extracts were washed with water and brine and dried. Removal of the solvent gave a yellow oil (300 mg), which was chromatographed on silica gel. Elution with petroleum ether–ether gave the recovered acetylenic ester **10** (150 mg) and then oily **11** (70 mg, 23%). An analytical sample was obtained by distillation (hath temperature, 120°) in vacuo (0.3 mm): ir (liquid film) 1960, 1755 (sh), and 1710 cm^{-1}; NMR δ 0.91 (t, 3 H, J = 6 Hz), 1.1–1.6 (m, 4 H), 1.97–2.35 (m, 2 H, $CH_2CH{=}C{=}C$), 3.78 (s, 9 H), 4.55 (d, 1 H, J = 1.5 Hz, $CHCO_2Me$), and 5.80 (dt, 1 H, J = 7.0 and 1.5 Hz, $CH{=}C{=}C$).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.34; H, 7.34.

Methyl 2,3-Dimethoxycarbonyl-(*Z*)-4-nonenoate (12a) and Its Parent Acid (12b). The ester **10** (470 mg) was hydrogenated over 5% palladium on barium sulfate (20 mg) in methanol (3 ml) containing synthetic quinoline (20 mg). After 1 equiv of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated in vacuo. The residual oil was chromatographed on silica gel. Petroluem ether–ether (3:1) eluted **12a** (350 mg, 74%). An analytical sample was obtained by distillation (bath temperature, 150–160°) in vacuo (0.3 mm): ir (liquid film) 1760 (sh) and 1745 cm^{-1}; NMR 0.92 (t, 3 H, J = 6 Hz), 1.1–1.6 (m, 4 H), 1.9–2.4 (m, 2 H), 3.75 and 3.72 (s, 3 H each), 4.0 [m, 2 H, $CHCO_2Me$ and $CH(CO_2Me)_2$], 5.25 (m, 1 H, J = 10.5, 10, and 1.2 Hz, Bu-CH=C**H**), and 5.72 (m, 1 H, J = 10.5, 7.2, and 1.0 Hz, Bu**CH**=C).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.93; H, 7.52.

A suspension of the ester **12a** (685 mg) in an aqueous solution (10 ml) of sodium hydroxide (396 mg) was stirred for 5 hr at room temperature and then at 60–70° for 1 hr. After cooling, ether (10 ml) was added, and the stirred mixture was carefully acidified with dilute hydrochloric acid in an ice bath until the aqueous layer turned slightly acidic. The ether layer was washed with water and brine and then dried. Removal of the solvent gave a crystalline mass (ca. 600 mg). Recrystallization from ether afforded colorless crystals: mp 146.5° dec; ir (KBr) 3400–2500 and 1704 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.48; H, 6.48.

1-Methoxycarbonyl-4-*epi*-norcanadensolide (13a). A solution of osmium tetroxide (150 mg) in *tert*-butyl alcohol (3 ml) was added dropwise to a stirred mixture of the cis olefinic ester **12a** (3.0 g) and a hydrogen peroxide–*tert*-butyl alcohol solution[25] (30 ml) in an ice bath. After the exothermic reaction had subsided, the mixture was kept in a refrigerator overnight and then at room temperature for 20 hr. The mixture was poured into water (200 ml) containing a small amount of sodium bisulfite and extracted with ether. The combined extracts were washed with water and brine and then dried. Removal of the solvent left a pale yellow oil, which was chromatographed on silica gel. Petroleum ether–ether (1:2) eluted a semisolid material. Recrystallization from ether gave **13a** (550 mg, 22%) as colorless platelets: mp 117–118°; ir (KBr) 1800 (sh), 1778, 1742, 1180, and 965 cm^{-1}; NMR δ 0.93 (t, 3 H, J = 6 Hz), 1.2–1.9 (m, 6 H), 3.8–3.9 [m, 2 H, C(1) and C(2) protons], 3.90 (s, 3 H), 4.73 [t, 1 H, J = 6.0 Hz, C(3) proton], 5.05 [br d, 1 H, J = 6.7 Hz, C(4) proton]. The NMR spectrum in DMSO-d_6 demonstrated that despite the narrow melting range, this compound was a mixture of epimers regarding the methoxycarbonyl group.

Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.42; H, 6.03.

4-*epi*-Norcanadensolide (13c). From 13a. A suspension of **13a** (350 mg) and 6 *N* hydrochloric acid (10 ml) was heated at 100–110° for 1.5 hr. After cooling, brine (5 ml) was added, and the mix-

ture was extracted three times with ether. The combined extracts were washed with brine and dried. Removal of the solvent gave a yellow syrup (350 mg), which gradually crystallized on standing. Recrystallization from ether gave needles: mp 85–86°; ir (KBr) 1780, 1200, 1180, 1050, 1010, 1000, and 990–970 cm^{-1}; NMR δ 0.93 (t, 3 H), 1.1–1.9 (m, 6 H), 2.88 (d, 1 H, J = 5.3 Hz), 2.9 (d, 1 H, J = 7.5 Hz), 3.5 (m, 1 H, J = 7.5, 6.0, and 5.3 Hz), 4.90 (d, J = 6.0 Hz), and 4.70 (t, 1 H, J = 6.0 Hz).

This compound was identified by comparison of its ir and NMR spectra with those of an authentic sample.[10]

From 12b. Osmium tetroxide (70 mg) in *tert*-butyl alcohol (1 ml) was added to a stirred mixture of **12b** (3.00 g) and a hydrogen peroxide–*tert*-butyl alcohol solution[25] (15 ml). The reaction was exothermic. The mixture was allowed to react in a refrigerator for 20 hr and then for 12 hr at room temperature with occasional swirling. Ether (20 ml) and sodium bisulfite (ca. 2 g) were added to the reaction mixture, and the mixture was stirred for 10 min in an ice bath. The mixture was filtered, and the ether layer was separated and dried. Removal of the solvent left a yellow oil (2.85 g). A mixture of the oil and acetic anhydride (20 ml) was heated at 110–120° for 3 hr, and excess acetic anhydride was distilled off to leave a dark red oil. The oily residue was dissolved in ether (50 ml), and the solution was washed with aqueous sodium bicarbonate, water, and brine, and then dried. Removal of the solvent gave a neutral oil (870 mg), which was chromatographed on silica gel. Elution with petroleum ether–ether (1:4) afforded colorless crystals (588 mg, 29%). Recrystallization from ether gave **13c** as colorless needles, mp 85–86°.

4-*epi*-Canadensolide (1b). A suspension of **13a** (190 mg) in 6 *N* hydrochloric acid (9 ml) was warmed at 55° until a clear solution was obtained. The resulting solution was diluted with water (10 ml) and extracted with ether. The extracts were washed with brine and dried. Evaporation of the solvent gave **13b** as an oil (150 mg), which yielded **13a** by treatment with diazomethane.

To a solution of **13b** (270 mg) in acetic acid (1.5 ml) was added diethylamine (250 mg) and then 30% formaline (0.7 ml) in an ice bath. After the mixture was stirred until the evolution of carbon dioxide ceased, sodium acetate (400 mg) was added, and the mixture was heated at 90–100° for 10 min. The reaction mixture was diluted with water and extracted with ether. The extracts were washed with water and brine and dried. Removal of the solvent gave a pale yellow oil (190 mg), which was then chromatographed on silica gel. Petroleum ether–ether (2:3) eluted **1b** (150 mg, 64%). Recrystallization from ether gave colorless needles: mp 47.5–48.5°; ir (KBr) 1780 and 1665 cm^{-1}; NMR δ 0.95 (t, 3 H, J = 6 Hz), 1.2–1.9 (m, 6 H), 4.09 [dt, 1 H, J = 6.8 and 2.2 Hz, C(2) proton], 4.75 [dt, 1 H, J = 1.5 and 7.0 Hz, C(4) proton], 4.98 [dd, 1 H, J = 1.5 and 6.8 Hz, C(3) proton], and 6.23 and 6.54 (d, 1 H, J = 2.2 Hz each, $=CH_2$).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.64; H, 6.30.

Methyl 2,3-Dimethoxycarbonyl-(*E*)-4-nonenoate (15a) and Its Parent Acid (15b). To a stirred solution of **10a** (6.0 g) in liquid ammonia (500 ml) were added pieces of sodium (6 g) over 10 min, and the mixture was stirred for 5 hr. Excess ammonium chloride was added cautiously. After the mixture turned pale yellow, stirring was continued at room temperature to allow the ammonia to evaporate. The pasty residue was dissolved in water and extracted with ether. The combined extracts were washed with water and brine and dried. An oily fraction (4.12 g, 69%) boiling at 130° (bath temperature) in vacuo (0.2 mm) was collected. GLC analysis (column B) showed the fraction to be greater than 95% in purity: ir (liquid film) 1740 and 970 cm^{-1}; NMR δ 0.90 (t, 3 H), 1.1–1.6 (m, 4 H), 1.9–2.3 (m, 2 H, allylic methylene), 3.72 and 3.74 (s, 3 H each, OMe), 3.6–3.9 [m, 2 H, C**H**$(CO_2Me)_2$], 5.42 (dt, 1 H, J = 15.0 and 7.0 Hz, $CH_2CH{=}C$), and 5.81 (dd, 1 H, J = 15.0 and 6.0 Hz, $CH_2CH{=}CH$).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.55; H, 7.53.

A mixture of **15a** (2.95 g) and a solution of sodium hydroxide (1.59 g) in water (15 ml) was stirred at room temperature for 10 hr and then at 70° for 3 hr. The resulting clear solution was washed with ether, and the aqueous layer was acidified with 6 *N* hydrochloric acid in an ice bath. After saturating with sodium chloride, the liberated acid was extracted with ether, and the extracts were washed with brine. Removal of the solvent left **15b** as crystals (2.50 g), which when recrystallized from ether gave an analytical sample: mp 166° dec; ir (KBr) 3500–2500, 1700, 970, and 900 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.38; H, 6.82.

(±)-Canadensolide (1a) and Dilactone 16b from Cis Olefinic Ester (12a) *via* Performic Acid Oxidation. Hydrogen peroxide (30%, 1.0 g) was added in one portion to a stirred solution of **12a** (2.0 g) in formic acid (6.0 ml) at room temperature. After stirring for 5 min at the same temperature, the mixture was stirred at 40–50° for 7 hr. The reaction mixture was poured into ice water and extracted with ether. The combined extracts were washed with water and brine and dried. Evaporation of the solvent left a pale yellow oil (1.98 g), which was chromatographed on silica gel (60 g). Ether eluted an oily fraction (1.17 g), which showed an ir absorption at 1780 cm^{-1}.

After the above lactonic fraction (170 mg) and 50% aqueous sulfuric acid (10 ml) had been heated at 120° for 2 hr with stirring, the reaction mixture was diluted with water (10 ml) and then saturated with sodium chloride. The product was extracted with ether, and the extracts were washed with cold water and then brine and dried. Work-up in a usual manner left a semisolid (ca. 50 mg), which was recrystallized from ether, giving **16b** (24 mg) as colorless needles: mp 81–82.5°; ir (KBr) 1770 cm^{-1}; NMR δ 0.93 (t, 3 H), 1.45 (m, 4 H), 1.85 (m, 2 H), 2.91 [1 H, d, J = 7 Hz, C(1) proton], 2.93 [1 H, d, J = 6 Hz, C(1) proton], 3.50 [q, 1 H, J = 6.0 Hz, C(2) proton], 4.70 [dt, 1 H, J = 4.0 and 7.0 Hz, C(4) proton], 5.09 [dd, J = 6.0 and 4.0 Hz, C(3) proton].

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.34; H, 6.60.

A heterogeneous mixture of the lactone fraction (1.0 g) and 6 *N* hydrochloric acid (55 ml) was stirred at 55° for 5 hr under nitrogen. The resulting clear solution was saturated with sodium chloride and then extracted with ether. The combined extracts were washed with brine and dried. Removal of the solvent left a pale yellow viscous oil (855 mg), whose ir spectrum (liquid film) showed broad absorptions at 3400–2500 and 1780–1720 cm^{-1}. The oil was dissolved in acetic acid (10 ml), and diethylamine (2.1 ml) was added dropwise with stirring. After stirring for 15 min, aqueous formalin (3.5 ml) was added. Stirring was continued for an additional 30 min, and then sodium acetate (3.0 g) was added. The mixture was heated at 80° for 10 min. Work-up in a usual manner afforded a semisolid (102 mg), which was purified by preparative silica gel TLC, giving **1a** (84 mg). Recrystallization from ether gave an analytical sample as colorless needles: mp 92.5–93.5°; ir (KBr) 1770 and 1666 cm^{-1}; NMR δ 0.95 (t, 3 H), 1.5 (m, 4 H), ca. 1.9 (br q, 2 H), 4.07 [dt, 1 H, J = 6.8 and 2.1 Hz, C(2) proton], 4.70 [dt, 1 H, J = 4.5 and 6.7 Hz, C(4) proton], 5.22 [dd, 1 H, J = 6.8 and 4.5 Hz, C(3) proton], and 6.18 and 6.49 [d, 1 H, J = 2.1 Hz each, C(1) protons].

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.63; H, 6.68.

The ir and NMR spectra were superimposable with those of natural canadensolide.

Hydrolysis of Acetylenic Ester 10. A suspension of **10** (5.7 g) in a solution of sodium hydroxide (4.08 g) in water (50 ml) was stirred at room temperature for 7 hr under nitrogen. The mixture was extracted with ether to remove the neutral portion, and the aqueous layer was separated. Ether was added to the aqueous layer, and the mixture was carefully acidified with 3 *N* hydrochloric acid with stirring in an ice bath. The aqueous layer was extracted with ether. The combined organic layers were washed with cold water and brine and dried. Removal of the solvent at room temperature left a semisolid (5.2 g), which was chromatographed on silica gel. Elution with petroleum ether–ether (6:4) gave **18** (610 mg). Recrystallization from ether afforded colorless needles: mp 122–123°; ir (KBr) 3400–2500, 1740, 1698, and 1670 cm^{-1}; NMR[26] δ 0.96 (t, 3 H), 1.2–1.7 (m, 4 H), 1.7–2.1 (m, 2 H), 3.38 (dd, 2 H, J = 3.0 and 1.7 Hz, CH_2CO), 5.22 (octet, 1 H, J = 6.0, 3.1, and 3.0 Hz, OCH), 7.15 (dt, 1 H, J = 3.1 and 1.7 Hz, =CH), and 11.1 (s, 1 H, CO_2H). The NMR assignments were verified by DNMR experiments.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.82; H, 7.14.

Successive elution with petroleum ether–ether (2:8) gave **5** (3.95 g, 85%). Recrystallization from ether yielded colorless crystals: mp 157°; ir (KBr) 3550–2400 and 1720 cm^{-1}; NMR δ 0.9 (t 3 H), 1.05–1.4 (m, 4 H), 2.2 (br t, 2 H), 3.55 and 3.77 [d, J = 7 Hz each, 2 H in total, C**H**$(CO_2H)CH(CO_2H)_2$], and 6.68 (s, 3 H, CO_2H).

Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.64; H, 5.90.

Treatment of **5** with ethereal diazomethane gave **10**.

Silver Salt Catalyzed Lactonization of 5. A mixture of **5** (560 mg), silver nitrate (10 mg), water (1 drop), and dioxane (6 ml) was stirred at 40–50° for 15 hr under nitrogen. The reaction mixture was poured into distilled water (20 ml) and extracted with ether

three times. The combined extracts were washed with water and then dried. Evaporation of the solvent left a pale yellow oil (560 mg), which was treated with ethereal diazomethane. An oil obtained was chromatographed on silica gel. Elution with petroleum ether–ether (2:1) afforded **19** (489 mg, 98%) as a colorless oil. An analytical sample was obtained by distillation (bath temperature 105°) in vacuo (0.8 mm): ir ($CHCl_3$) 1750–1740 and 880 cm^{-1}; NMR δ 0.95 (t, 3 H), 1.1–1.8 (m, 6 H), 3.25 (br t, 2 H, J = 1.5 Hz), 3.73 (s, 3 H), 4.93 (m, 1 H, CHO), and 7.40 (q, 1 H, J = 1.5 Hz, =CH).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.22; H, 7.77.

This butenolide was also obtained by heating **5** at 175–180° for 1 hr followed by treatment with diazomethane.

Lactonization of 5 with Sulfuric Acid. The acetylenic acid **5** (800 mg) was added to concentrated sulfuric acid (4 ml) in an ice bath, and the solution was stirred for 1 hr with cooling and then at room temperature for an additional 1 hr. The mixture was poured into ice water and extracted with ether. The combined extracts were washed with brine and dried. Concentration in vacuo left a semisolid (600 mg). The latter material was treated with a slight excess of diazomethane. After work-up, the product was purified by silica gel chromatography. Petroleum ether–ether (8:2) eluted **20** (574 mg, 82%), whose analytical sample was obtained by distillation (bath temperature 110°) in vacuo (0.4 mm) as a colorless oil: ir ($CHCl_3$) 1821, 1718, and 1660 cm^{-1}; NMR δ 0.92 (t, 3 H), 1.1–1.9 (m, 6 H), 2.83 (t, 2 H, J = 7.5 Hz, CH_2C=), 3.35 (br s, 2 H, CH_2CO), and 3.75 (s, 3 H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.11; H, 7.75.

Lactonization of 5 with Dilute Sulfuric Acid Containing Mercuric Salt. Red mercuric oxide (10 mg) was added to a stirred mixture of **5** (760 mg), 60% sulfuric acid (1 ml), and dioxane (1 ml). After stirring had been continued at room temperature for 12 hr, the reaction mixture was poured into ice water. The product was extracted with ether, and the combined extracts were washed with brine and dried. Removal of the solvent in vacuo yielded an oil, which was then treated with diazomethane in slight excess. Work-up gave a yellow oil (ca. 750 mg). GLC analysis (column B) showed a main peak and three minor peaks, one of which was identified as **19** by peak enhancement experiments. Petroleum ether–ether (2:8) eluted the main product **21** (395 mg) as a colorless oil: ir ($CHCl_3$) 1745 and 1728 cm^{-1}; NMR (benzene) δ 0.80 (t, 3 H), 0.95–1.7 (m, 6 H), 2.10 (t, 2 H, J = 6 Hz, CH_2CO), 2.85 (d, 2 H, J = 7.5 Hz, CH_2CO_2Me), 3.39 (s, 6 H), and 3.93 (t, 1 H, J = 7.5 Hz, $CO\text{-}CHCO_2Me$); MS m/e 145 (base peak), 99, and 55.

Anal. Calcd for $C_{12}H_{20}O_5$: C. 59.00; H, 8.25. Found: C, 59.36; H, 7.99.

Dilactone (23) from Norbornene-*endo*-dicarboxylic Acid (22a). Finely pulverized **22a**[13] (183 mg, 1 mmol) was dissolved in a solution of sodium hydroxide (104 mg, 2.6 mmol) in water (3 ml). A solution of silver nitrate (357 mg, 2.1 mmol) in water (5 ml) was added with stirring to the above solution, and the mixture was stirred for an additional 30 min. The silver salt was collected by filtration and washed with water and then with ether. The salt was dried in vacuo at room temperature in the dark. Iodine (507 mg, 4 mmol) was added to a stirred suspension of the pulverized silver salt in dry dimethyl sulfoxide (5 ml). After stirring for 30 min, silver acetate (527 mg, 2.1 mmol) was added, and the mixture was stirred at 60° for 12 hr. Chloroform (10 ml) was added to the cooled mixture, and inorganic materials were filtered off. The filtrate was concentrated under reduced pressure at 60° to small bulk. The residue then was dissolved in chloroform (30 ml) and washed with water. The solution was dried and evaporated to give **23** (166 mg, 92%). Trituration of the product with hot ether gave an analytical sample as colorless, fine needles: mp 265–266° (lit. mp 274–275°,[14b] 264–265° [14a]); ir (KBr) 1800 and 1780 cm^{-1} (lit. 5.53 and 5.60 μ,[14b] 1795 and 1770 cm^{-1} [14c]); NMR[26] (DMSO-d_6) δ 1.80 (t, 2 H, J = 2 Hz), 3.06 (m, 2 H), 3.39 (m, 2 H), and 4.78 (t, 2 H, J = 2 Hz).

Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.19; H, 4.71.

Dimethyl Ester of (*Z*)-4-Octenedioic Acid (24). A solution of methyl 4-octynedioate[20] (1.60 g) in methanol containing synthetic quinoline (0.2 ml) was hydrogenated over 5% palladium–barium sulfate (150 mg) at room temperature. Hydrogen uptake ceased after 1 equiv of hydrogen had been absorbed. After filtration of the catalyst, the filtrate was concentrated in vacuo. The oily residue was dissolved in ether, and the solution was washed with water and brine and dried. Evaporation of the solvent left the dimethyl ester of **24** (1.12 g) as an oil. An analytical sample was obtained by distillation (bath temperature 130°) in vacuo (8 mm): ir (liquid film) 1735 cm^{-1}; NMR δ 2.46 (m, 8 H), 3.70 (s, 6 H), and 5.45 (br m, 2 H).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.70; H, 8.06.

***meso*-4,5-Dihydroxyoctanedioic Acid Di-γ-lactone (25).** A heterogeneous mixture of the above dimethyl ester of **24** (1.27 g), sodium hydroxide (762 mg), and water (15 ml) was stirred at room temperature for 1 hr under nitrogen, and then at 60° for 4 hr. The resultant solution was washed once with ether. Ether was added to the aqueous layer, and the mixture was acidified with dilute hydrochloric acid with stirring in an ice bath. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined organic layers were washed with brine and dried. Evaporation of the solvent left a solid, which was washed with a small amount of a mixture of ether and petroleum ether (1:1) to give crude **24** (813 mg, ca. 73%) as an amorphous powder. The crude acid was used without further purification.

To a stirred suspension of the silver salt of **24** [prepared in a similar manner from **24** (1.14 g) and silver nitrate (2.48 g)] in dimethyl sulfoxide (10 ml), iodine (3.37 g) and then silver acetate (2.22 g) were added. The mixture was then stirred at 65° for 12 hr. Work-up gave **25** (620 mg, 56%) as the neutral product. Recrystallization from ethyl acetate gave colorless needles: mp 104–105° (lit.[16a] mp 106°); ir (KBr) 1785 (sh) and 1765 cm^{-1}; NMR δ 1.8–2.7 [m, 8 H, C(2) and C(3) protons] and 4.60 [m, 2 H, C(4) proton].

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.45; H, 5.87.

Monotetrahydropyranyl Ether (36) of 1,4-Butanediol. A solution of 1,4-butanediol (3.0 g), freshly distilled dihydropyran (2.8 g), and *p*-toluenesulfonic acid (20 mg) in tetrahydrofuran (100 ml) was stirred at −25° for 3 hr. The mixture was then allowed to warm to room temperature during a 1-hr period and was stirred for an additional 10 hr at the same temperature. A few drops of pyridine were added to the mixture to quench the catalyst. The mixture was diluted with ether, washed with water and brine, and dried. Evaporation of the solvent left an oil, which was chromatographed on a silica gel column. Ether–petroleum ether (1:2) eluted an oily diether of 1,4-butanediol (1.25 g, 15%): ir (liquid film) 1120, 1060, 1030, 900, 860, and 810 cm^{-1}; NMR δ 1.6 (m, 16 H), 3.2–4.1 (m, 8 H), and 4.60 (br t, 2 H).

Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 64.85; H, 10.09.

Further elution with the same solvent gave **36** (3.85 g, 66%) as a colorless oil: ir (liquid film) 3400, 1060, 1030, 900, 860, and 810 cm^{-1}; NMR δ 1.70 (m, 10 H), 3.20 (br s, 1 H, OH), 3.3–4.1 (m, 6 H, CH_2O), and 4.68 (br t, 1 H, OCHO).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.68; H, 10.48.

Ethynyl Carbinol (37). To an ice-cooled and stirred suspension of chromic anhydride–dipyridine complex[27] (29.9 g) and Celite 535 (25 g) in dry methylene chloride (150 ml) was added dropwise a solution of **36** (2.18 g) in methylene chloride (50 ml) under an argon atmosphere. After stirring for 15 min, sodium hydrogen sulfate monohydrate (30 g) was added, and the resultant mixture was stirred for an additional 15 min at room temperature. The organic layer was separated, and the solid was washed with a small amount of methylene chloride. The combined methylene chloride solutions were evaporated at 0° to leave an oil, which was dissolved in a small amount of ether. The solution was filtered through a Celite 535 column. The filtrate was evaporated in vacuo to give an aldehyde (2.06 g) as a colorless oil: ir (liquid film) 2750 and 1720 cm^{-1}; NMR δ 1.3–2.2 (m, 8 H), 2.60 (t, 2 H, $J \simeq$ 7.5 Hz with fine splittings, CH_2CHO), 3.3–4.1 (m, 4 H, CH_2O), 4.65 (br t, 1H, OCHO), and 9.80 (t, 1 H, J = 1.5 Hz, CHO).

Although the crude product showed a single spot on TLC, no analytically pure sample was obtained because of its instability.

After dry tetrahydrofuran (100 ml) had been saturated with acetylene with stirring, ethylmagnesium bromide solution, prepared from magnesium (350 mg) and ethyl bromide (1.57 g) in the same solvent, was added dropwise at room temperature. Stirring was continued for an additional 30 min while the reaction flask was cooled in an ice bath, and then a solution of the above aldehyde (2.06 g) in the same solvent (15 ml) was added dropwise. Stirring was further continued, while the solution was allowed to warm to room temperature. The resultant brown mixture was poured into a cold saturated ammonium chloride solution. The aqueous layer was extracted with ether several times, and the combined organic layers were washed with water and brine and dried. Evapora-

tion of the solvent left an oil, which was purified by passing through a short silica gel column to give **37** (2.04 g, 86% from **36**) as a pale yellow oil: ir (liquid film) 3400, 3210, 1120, 1070, 1020, 910, 900, and 865 cm^{-1}; NMR δ 1.3–2.0 (m, 10 H), 2.50 (d, 1 H, $J \simeq 1.5$ Hz, ≡CH), 3.2–4.1 (m, 5 H), 4.5 (br s, 1 H, OH), 4.68 (br t, 1 H, OCHO).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.98; H, 9.34.

Allylic Carbinol (38). The ethynyl carbinol (**37**, 2.04 g) in methanol (20 ml) containing synthetic quinoline (0.15 ml) was hydrogenated over 5% palladium–barium sulfate (200 mg). Hydrogen uptake ceased after 1 equiv of hydrogen had been absorbed. The catalyst was filtered off, and the filtrate was concentrated in vacuo to leave an oil, which was dissolved in ether (30 ml). The solution was washed with water and brine and dried. Removal of the solvent in vacuo gave **38** (2.05 g) as a colorless oil, which showed a single spot on TLC: ir (liquid film) 3400, 3050, 1640, 1110, 1070, 1030, 900, 860, and 810 cm^{-1}; NMR δ 1.4–2.0 (m, 10 H), 2.76 (br s, 1 H, OH), 3.3–4.4 (m, 5 H, CH_2O and CHO), 4.65 (br t, 1 H, OCHO), 4.5–5.0 (m, 2 H, $=CH_2$), 5.95 (dq, 1 H, J = 17.3, 10.5, and 6.0 Hz, =CH).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97: H, 10.07. Found: C, 65.98; H, 10.15.

Vinyl Ether 39. A mixture of **38** (2.00 g), freshly distilled ethyl vinyl ether (4 ml), and mercuric acetate (100 mg) was gently refluxed for 48 hr under nitrogen. After cooling to 0°, saturated sodium bicarbonate solution (4 ml) was added and the mixture was stirred for 15 min. The reaction mixture was extracted with ether three times, and the combined extracts were washed with water and brine and dried. The solvent was removed, and the residual oil was chromatographed on a short silica gel column using methylene chloride as eluent to give **39** (1.10 g, 60%) as a pale yellow oil: ir (liquid film) 3050, 1636, 1615, 1130, 1120, 1070, 1030, 985, and 900 cm^{-1}; NMR δ 1.1–2.0 (m, 10 H), 3.2–4.4 (m, 5 H, CH_2O and CHO), 4.0 (dd, 1 H, J = 7.5 and 1.3 Hz, OCH=CH_cH_t), 4.32 (dd, 1 H, J = 14.0 and 1.3 Hz, OCH=CH_cH_t), 4.60 (br t, 1 H, OCHO), 5.02–5.4 (m, 2 H, CH=CH_2), 5.85 (dq, 1 H, J = 18.0, 9.0, and 5.7 Hz, CH=CH_2), and 6.34 (q, 1 H, J = 14.0 and 7.5 Hz, OCH=CH_2).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.74; H, 9.71.

Further elution with ether gave the unreacted **38** (821 mg).

***(E)*-4-Octenedioic Acid (26).** The vinyl ether **39** (2.00 g) in a sealed tube was heated at 190° for 20 min to give an oily aldehyde quantitatively: ir (liquid film) 2720, 1720, 1130, 1120, 1070, 1030, and 970 cm^{-1}. The oil was dissolved in acetone (30 ml) and Jones reagent was added at 0° until the orange color of the reagent persisted for 5 min. After the excess reagent was destroyed by the addition of 2-propanol, the reaction mixture was diluted with brine (30 ml) and extracted with ether. The combined extracts were washed with brine and evaporated to leave an oil. The oil was dissolved in acetone (10 ml), and 10% sulfuric acid (2 ml) was added. After warming at 55° for 30 min, the solution was cooled in an ice bath and treated with a slight excess of Jones reagent. Work-up in a usual manner gave a semisolid (1.15 g), which was washed with a small amount of cold ether to give a colorless solid. Recrystallization from ether gave **26** (750 mg, 50%) as a colorless powder: mp 174.5–176° (lit.[22] mp 175–176°); ir (KBr) 3500–2300, 1700, 980, and 940 cm^{-1}; NMR[26] (DMSO-d_6) δ 1.24 (br m, 8 H), 5.41 (br m, 2 H), and 12.4 (br s, 2 H).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.60; H, 7.07.

***dl*-4,5-Dihydroxyoctanedioic Acid Di-γ-lactone (27).** To a stirred suspension of the silver salt, prepared from **26** (150 mg) in a similar manner, in dimethyl sulfoxide (3 ml) was added iodine (454 mg). After stirring had been continued for an additional 15 min, silver acetate (301 mg) was added, and the mixture was stirred at 60° for 15 hr. Work-up in a usual manner afforded colorless crystals (98 mg, 60%), whose recrystallization from ethyl acetate gave an analytical sample as colorless needles: mp 55–56° (lit.[16b] mp 55–56°); ir (KBr) 1780 cm^{-1}; NMR δ 2.1–2.9 (br m, 4 H) and 4.63 (m, 2 H).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.16; H, 5.91.

Dilactone 29. The dimethyl ester of **28**[17] (250 mg) was heated with a solution of sodium hydroxide (125 mg) in a mixture of water (3 ml) and methanol (3 drops) at 60°. The resultant homogeneous solution was washed with ether, and the aqueous layer was treated with a solution of silver nitrate (408 mg) in water (1 ml) to give a silver salt. Iodine (610 mg) was added to a stirred suspension of the dried silver salt in dimethyl sulfoxide (8 ml), and then silver acetate (400 mg) was added. The mixture was stirred at 60° for 12 hr. Work-up in a usual manner gave a semisolid, which was poured on a short silica gel column, and the product was eluted with methylene chloride to give **29** (115 mg, 52%). An analytical sample was obtained by recrystallization from ethyl acetate as colorless needles: mp 116–117°; ir (KBr) 1770 cm^{-1}; NMR δ 1.2–3.2 (br m, 8 H) and 5.02 (m, 2 H).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.34; H, 5.60.

Dilactone 31. To a stirred suspension of the silver salt of **30**[18] (170 mg), iodine (508 mg) and then silver acetate (351 mg) were added at 50–60°. The mixture was stirred for 5 hr and worked up to give crystals (129 mg, 77%), whose recrystallization from ether afforded colorless needles: mp 205–206°; ir (KBr) 1840 and 1770 cm^{-1}; NMR[26] δ 2.22 (dq, 2 H, J = 19.2, 4.8, and 2.0 Hz, exo methylene protons), 2.73 (d, 2 H, J = 19.2 with fine splittings, endo methylene protons), 2.98 (q, 2 H, J = 4.8 and 2.0 Hz, CHC=O), and 3.23 (m, 2 H, CHO).

Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.03; H, 4.91.

5-Hydroxy-3-cyclohexenecarboxylic Acid Lactone (41). A. With Silver Acetate. A suspension of **40**[21] (4.03 g) and silver acetate (3.51 g) in dry dimethyl sulfoxide (50 ml) was heated at 130–140° for 2 hr under nitrogen. The reaction mixture was diluted with chloroform (100 ml) and filtered. The filtrate was washed with water and brine and dried. After removal of the solvent, the residue was distilled (bath temperature ca. 150°) in vacuo (20 mm) to give **41** (1.61 g, 81%) as an oil: ir (liquid film) 1800 (sh), 1770, and 1735 cm^{-1} (sh); NMR δ 2.0–2.8 (m, 4 H), 2.89 (m, 1 H, CHC=O), 4.77 (br t, 1 H, J = 4.5 Hz, CHO), 5.7–6.5 (m, 2 H, =CH).

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.93; H, 6.37.

B. With 1,5-Diazabicyclo[5.4.0]undecene-5. A solution of **40** (20.16 g) and 1,5-diazabicyclo[5.4.0]undecene-5 (18.24 g) in dry benzene (300 ml) was refluxed for 6 hr under nitrogen. The solution was washed with water and dried. The oil obtained by evaporation of the solvent was distilled in vacuo to afford **41** (6.1 g, 71%).

Hydroxy Acid 42a and Its Methyl Ester 42b. A suspension of **41** (2.48 g) and a solution of sodium hydroxide (1.04 g) in water (4 ml) was stirred at room temperature for 3 hr. The solution obtained was washed with ether. Chloroform (10 ml) was added to the aqueous layer, the mixture was acidified with powdered oxalic acid with stirring, and then sodium chloride and magnesium sulfate were added until the mixture became pasty. The paste was packed in a column and eluted with chloroform. The combined chloroform eluents were concentrated. The residual solid was washed with hot ether to give **42a** (2.5 g, quantitative yield) as a colorless powder: ir (KBr) 3350, 2600, 1710, and 950 cm^{-1}; NMR δ 1.0–1.6 (m, 1 H), 1.95–2.5 (m, 5 H), 4.2 (m, 1 H, CHOH), 5.68 (br s, 2 H, =CH).

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.85; H, 7.09.

Treatment of **42a** with a slight excess of ethereal diazomethane gave oily **42b:** ir (liquid film) 3350, 1725, and 1650 cm^{-1}; NMR δ 2.0–3.0 (m, 6 H), 3.74 (s, 3 H), 4.38 (m, 1 H, CHO), and 5.85 (br s, 2 H, =CH(/

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.18; H, 8.17.

Vinyl Ether 43. A mixture of **42b** (435 mg), ethyl vinyl ether (10 ml), and mercuric acetate (150 mg) was refluxed for 3 days under nitrogen. The reaction mixture was diluted with ether (ca. 30 ml), washed with 5% sodium bicarbonate, water, and brine, and then dried. After removal of the solvent, the residue was distilled (bath temperature ca. 120°) in vacuo (25 mm) to give **43** (367 mg, 71%) as a colorless oil: ir (liquid film) 3010, 1730, 1630, and 1610 cm^{-1}; NMR δ 2.0–3.0 (m, 5 H), 3.70 (s, 3 H), 4.5 (m, 1 H, CHO), 4.08 (dd, 1 H, J = 6.8 and 1.5 Hz, OCH=CH_cH_t), 4.35 (dd, 1 H, J = 14.5 and 1.5 Hz, OCH=CH_cH_t), 5.82 (m, 2 H, CH=CH in the cyclohexene ring), and 6.40 (dd, J = 14.5 and 6.8 Hz, OCH=CH_2).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.52; H, 7.62.

Formyl Ester 44. The vinyl ether **43** (1.31 g) was heated in a sealed tube at 200° for 1 hr. Distillation (bath temperature ca. 130°) in vacuo (10 mm) gave **44** (1.08 g, 82%) as a colorless oil: ir (liquid film) 2710, 1730–1720, and 1650 cm^{-1}; NMR δ 1.0–3.0 (m, 8 H), 3.65 (s, 3 H), 5.62 (m, 2 H, =CH), and 9.25 (t, 1 H, J = 2 H, 2 Hz, CHO).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.96; H, 8.31.

Dicarboxylic Acid 32. A solution of **44** (273 mg) in acetone (10 ml) was treated with slightly excess Jones reagent at 0°. Work-up in a usual manner afforded the monomethyl ester of **32** (232 mg) as a colorless oil: ir (liquid film) 3500–2500, 1725, and 1705 cm^{-1}; NMR δ 1.0–3.0 (m, 8 H), 3.67 (s, 3 H), 5.68 (m, 2 H, =CH), and 10.6 (br s, 1 H, CO_2H).

The monomethyl ester (207 mg) was dissolved in a solution of sodium hydroxide (52 mg) in water (2 ml), and the solution was stirred overnight at room temperature under nitrogen. The reaction mixture was acidified with 6 *N* hydrochloric acid in an ice bath and then saturated with sodium chloride. The product was extracted with methylene chloride, and the combined extracts were washed with cold brine and dried. Removal of the solvent gave **32** (173 mg, 67% from **44**) as a colorless powder: ir (KBr) 3350, 1700, and 1650 cm^{-1}.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.58. Found: C, 58.94; H, 6.87.

Dilactone 33. A suspension of the silver salt (587 mg), prepared from **32** (347 mg) in a similar manner, was successively treated with iodine (813 mg) and silver acetate (551 mg). Work-up gave **33** (143 mg, 47%). Recrystallization from ethyl acetate afforded colorless needles: mp 159–160°, ir (KBr) 1775 cm^{-1}; NMR[26] δ 1.0–2.1 (5 H), 2.4–2.8 (4 H), 4.60 (dd, 1 H, *J* = 9 and 2 Hz, CHO), and 5.05 (dd, 1 H, *J* = 6.4 and 2 Hz, CHO(/

Anal. Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.07; H, 5.50.

Butenolide 35. Iodine (1.27 g) was added to a stirred suspension of the silver salt, prepared from dihydromuconic acid[19] (**34**, 350 mg), in dimethylformamide (5 ml). After stirring for 20 min, silver acetate (835 mg) was added, and the mixture was stirred at 70° for 24 hr. The reaction mixture was diluted with wet ether (10 ml), and the organic layer was separated and concentrated to leave a brown oil. An ethereal solution of the oil was treated with slightly excess diazomethane in an ice bath. The solvent was removed to leave an oil, which was poured on a short silica gel column. Ether eluted **35** (120 mg, 32%) as an oil: ir ($CHCl_3$) 1760 and 1735 cm^{-1}; NMR δ 2.80 (dd, 2 H, *J* = 7.5 and 1.5 Hz, C**H**$_2$CO$_2$Me), 3.75 (s, 3 H, OMe), 5.50 (tdd with fine splittings, 1 H, *J* = 7.5, 2.3, and 1.5 Hz, CHO), 6.23 (dd, 1 H, *J* = 6.0 and 2.3 Hz, =CHC=O), and 7.67 (dd, 1 H, *J* = 6.0 and 1.5 Hz, C**H**=CHC=O).

Anal. Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 53.98; H, 5.34.

2-[(*Z*)-1-Hexenyl]butanedioic Acid (45). A mixture of **12b** (5.3 g) and xylene (20 ml) was gently refluxed for 2 hr under nitrogen. After evolution of carbon dioxide had ceased, the solution was stirred for an additional 1 hr with heating. Removal of the solvent in vacuo gave a colorless solid, whose ir spectrum showed it to be a mixture of dicarboxylic acid (1710 cm^{-1}) and anhydride (1860 and 1790 cm^{-1}). The mixture was refluxed with water (15 ml) for 1 hr. The resulting solution was saturated with sodium chloride and extracted with ether. The combined extracts were dried. Evaporation of the solvent gave colorless crystals (3.91 g, 88%). Recrystallization from ether–petroleum ether (1:1) afforded an analytical sample as colorless leaflets: mp 112–113°; ir (KBr) 3400–2500, 1695, and 950 cm^{-1}; NMR δ 0.90 (t, 3 H), 1.1–1.6 (m, 4 H), 1.9–2.4 (m, 2 H, CH_2C=), 2.52 (dd, 1 H, *J* = 18 and 6 Hz, one of C**H**$_2$CO$_2$H), 2.99 (dd, 1 H, *J* = 18 and 9 Hz, one of C**H**$_2$CO$_2$H), 3.82 (m, 1 H), 5.37 (t, 1 H, *J* = 10.5 Hz, =C**H**CHCO$_2$H), 5.75 (dt, 1 H, *J* = 10.5 and 4.7 Hz, CH_2C**H**=), and 11.6 (br s, 2 H, CO_2H).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.23; H, 8.43.

2-[(*E*)-1-Hexenyl]butanedioic Acid (48). A suspension of **15b** (2.5 g) in xylene (25 ml) was refluxed for 4 hr. Evaporation of the solvent at 70° in vacuo gave an oil. The oil was refluxed with water (10 ml) for 1 hr. The solution was extracted with ether, and the combined extracts were dried. Removal of the solvent afforded an oil (2.00 g), which gradually crystallized on standing to give colorless crystals. The crystals were chromatographed on silica gel, and ether eluted **48** (1.50 g, 73%). Recrystallization from petroleum ether containing a small amount of ether gave colorless needles: mp 86–87°; ir (KBr) 3400–2600, 1695, 970, and 950 cm^{-1}; NMR δ 0.90 (t, 3 H), 1.1–1.6 (m, 4 H), 1.9–2.3 (m, 2 H, CH_2C=), 2.55 (dd, 1 H, *J* = 16.5 and 6 Hz, one of C**H**$_2$CO$_2$H), 2.95 (dd, 1 H, *J* = 16.5 and 8.3 Hz, one of C**H**$_2$CO$_2$H), 3.53 (br m, 1 H, C**H**CO$_2$H), 5.42 (dd, 1 H, *J* = 17 and 6 Hz, =C**H**CHCO$_2$H), 5.78 (dt, 1 H, *J* = 17 and 5.7 Hz, CH_2C**H**=), and 11.75 (s, 2 H, CO_2H).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.12; H, 7.92.

Silver Salt Double Lactonization of 45. To a stirred suspension of the silver salt (3.44 g), prepared from **45** (1.660 g), in dimethyl sulfoxide (25 ml) there was added iodine (4.24 g), and then after stirring for 30 min silver acetate (2.84 g) was added. Stirring was continued for an additional 4 hr at room temperature, and then at 60° for 12 hr. The reaction mixture was diluted with methylene chloride (70 ml) and filtered. The filtrate was concentrated in vacuo at 50–60°, and the residue was dissolved in methylene chloride (100 ml). The solution was washed with sodium bicarbonate solution (20 ml), water, and brine. Evaporation of the organic layer left a brown oil, which was chromatographed on a silica gel column using methylene chloride–ether (1:1) as eluent, giving **13c** (493 mg, 30%).

The sodium bicarbonate extracts were acidified with 6 *N* hydrochloric acid. Extraction of the mixture with ether, followed by evaporation of the extracts, gave an acidic, oily product (463 mg). Treatment of the oil with ethereal diazomethane gave a mixture of methyl esters (470 mg). The mixture was separated by preparative silica gel TLC using ether–petroleum ether (1:2) as solvent, affording two oily butyrolactones, **46b** (340 mg, 19%) and **47b** (130 mg, 7%).

46b: ir (liquid film) 1785 and 1740 cm^{-1}; NMR[26] δ 0.90 (t, 3 H), 1.38 (quintet, 2 H, *J* = 7 Hz), 2.05 (q, 2 H, *J* = 7 Hz, C**H**$_2$CH=), 2.73 [dd, 1 H, *J* = 17 and 10 Hz, $CHCO_2$ (lactone)], 2.94 [dd, 1 H, *J* = 17 and 7.6 Hz, $CHCO_2$ (lactone)], 3.1 (m, 1 H, C**H**CO$_2$Me), 3.75 (s, 3 H, OMe), 4.96 (t, 1 H, *J* = 6.0 Hz, CHO), 5.45 (dd, 1 H, *J* = 16 and 6 Hz, =CHCO), and 5.85 (dt, 1 H, *J* = 16 and 7 Hz, CH_2C**H**=).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.85; H, 7.22.

47b: ir (liquid film) 1810, 1740, and 1700 cm^{-1}; NMR[26] δ 0.90 (t, 3 H), 1.1–1.5 (m, 4 H), 2.15 (m, 2 H), 2.78 [dd, 1 H, *J* = 18 and 9.6 Hz, $CHCO_2$ (lactone)], 3.12 [dd, 1 H, *J* = 18 and 5.6 Hz, $CHCO_2$ (lactone)], 3.78 (s, 3 H, OMe), 3.9 (m, 1 H, C**H**CO$_2$Me), 4.85 (dt, 1 H, *J* = 6.8 and 1.2 Hz, CH=).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.17; H, 7.37.

Silver Salt Double Lactonization of 48. A suspension of the silver salt, prepared from **48** (500 mg), in dimethyl sulfoxide (5 ml) was treated similarly with iodine (1.27 g) and silver acetate (835 mg). Work-up of the neutral product gave **16b** (205 mg, 41%). After the treatment of the acidic product with ethereal diazomethane, preparative silica gel TLC gave two oily esters, **46a** (84 mg, 16%) and **49b** (18 mg, 3%): ir (liquid film) 1805, 1740, and 1695 cm^{-1}; NMR[26] δ 0.91 (t, 3 H), 1.2–1.5 (m, 4 H), 2.06 (m, 2 H, CH_2C=), 2.84–2.92 [m, 2 H, CH_2CO_2 (lactone)], 3.75 (s, 3 H, OMe), 3.95 (m, 1 H, C**H**CO$_2$Me), and 5.32 (dt, 1 H, *J* = 7 and 1.7 Hz, CH=).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.28; H, 7.67.

2-[(*Z*)-1-Hexenyl]-3-methylenebutanedioic Acid (54). To a stirred solution of **12b** (3.66 g) and 40% aqueous dimethylamine (1.69 g) in methanol (2.5 ml) there was added a solution of 37% aqueous formalin (2.5 g) in methanol (2.5 ml) at −20°. Carbon dioxide evolution was observed during the addition. The resulting mixture was stirred for 7 hr, while the temperature was allowed to rise gradually to room temperature. The reaction mixture was finally refluxed for 1 hr. After removal of the solvent in vacuo, the residue was dissolved in water (5 ml). Ether was added to the solution, which was then acidified with 6 *N* hydrochloric acid, with stirring in an ice bath. After the mixture had been saturated with sodium chloride, the product was extracted with ether. Removal of the solvent gave **54** (1.377 g, 43%) as a semisolid, which was recrystallized from ether–petroleum ether (1:4) to give a pure sample as colorless crystals: mp 105–106°; ir (KBr) 3500–2500, 1705, 1625, 970, 945, and 770 cm^{-1}; NMR δ 0.90 (t, 3 H), 1.1–1.5 (m, 4 H), 2.1 (m, 2 H), 4.25 (br d, 1 H, *J* = 7.5 Hz, C**H**CO$_2$H), 5.4–6.0 (m, 2 H, C**H**=C**H**), 5.85 and 6.51 (s, 1 H each, $=CH_2$), and 11.60 (s, 2 H, CO_2H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.43; H, 7.85.

2-[(*E*)-1-Hexenyl]-3-methylenebutanedioic Acid (57). A solution of 37% aqueous formalin (1.25 g) in methanol (3 ml) was added to a stirred solution of **15b** (2.78 g) and 40% aqueous dimethylamine (1.23 g) in methanol (3 ml) at −20°. The mixture was stirred for 7 hr; meanwhile the temperature was allowed to rise gradually to room temperature, and then the mixture was refluxed for 1 hr. Work-up as described above gave a colorless semisolid (ca. 1.8 g), whose recrystallization from ether–petroleum ether (1:4) afforded analytically pure **57** (1.04 g, 42%) as colorless needles: mp 84–85°; ir (KBr) 3500–2500, 1965, 1625, and 980 cm^{-1}; NMR δ 0.90

(t, 3 H), 1.1–1.5 (m, 4 H), 2.05 (m, 2 H), 4.05 (br d, 1 H, J = 7 Hz, C**H**CO_2H), 5.3–5.9 (m, 2 H, C**H**=C**H**), 5.83 and 6.47 (s, 1 H each, CH_2=), and 10.5 (s, 2 H, CO_2H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.03; H, 7.80.

Silver Salt Double Lactonization of 54. Iodine (2.28 g) was added to a stirred suspension of the silver salt, prepared from **54** (950 mg), in dimethyl sulfoxide (10 ml) at room temperature, and then silver acetate (1.50 g) was added after 10 min. The mixture was stirred at 70° for an additional 15 hr. After most of the solvent was removed, the residue was diluted with methylene chloride (10 ml) and filtered. The filtrate was successively washed with water, aqueous sodium thiosulfate, and water. The acidic product was extracted with aqueous sodium bicarbonate solution. Removal of the solvent from the organic layer left a semisolid, which was purified by preparative silica gel TLC using methylene chloride as solvent, giving **1b** (125 mg, 14%) as colorless needles.

Ether was added to the above sodium bicarbonate extracts, and the mixture was carefully acidified with 6 N hydrochloric acid with stirring in an ice bath. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were evaporated in vacuo at 0° to give an oil (470 mg), which was immediately treated with excess diazomethane. Removal of the solvent in vacuo at 0° left an oil. The oil was purified by preparative silica gel TLC using petroleum ether–ether (2:1) as solvent, giving **56** (100 mg, 8%) as an unstable oil: ir (liquid film) 1785, 1730, and 1550 cm^{-1}; NMR δ 0.90 (t, 3 H), 1.1–1.6 (m, 6 H), 1.6–2.2 (m, 3 H, C**H**$_2$CH= and C**H**CO_2Me), 3.65 (s, 3 H, OMe), and 4.65–5.05 (m, 3 H, CH_2N= and CH=).

No analytical sample was obtained owing to its instability.

Silver Salt Double Lactonization of 57. Iodine (1.22 g) was added to a stirred suspension of the silver salt, prepared from **57** (500 mg), in dimethyl sulfoxide (4 ml) at room temperature, and then silver acetate (802 mg) was added after 10 min. The mixture was stirred at 60° overnight. Work-up of the reaction mixture as described for the double lactonization of **54** gave **1a** (114 mg, 21%).

An acidic product obtained was treated with excess diazomethane and purified by preparative silica gel TLC, giving **59** (79 mg, 13%) as a colorless oil: ir (liquid film) 1785, 1725, and 1550 cm^{-1}; NMR δ 0.93 (t, 3 H), 1.1–1.6 (m, 6 H), 1.6–2.4 (m, 3 H, C**H**$_2$CH= and C**H**CO_2Me), 3.63 (s, 3 H, OMe), and 4.85–5.15 (m, 3 H, CH= and CH_2N=).

Anal. Calcd for $C_{13}H_{18}O_4N_2$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.75; H, 7.07; N, 10.36.

Registry No.—**1a,** 35093-30-2; **1b,** 35093-28-8; **5,** 54911-70-5; **10,** 54984-23-5; **11,** 35093-25-5; **12a,** 54911-71-6; **12b,** 54911-72-7; **13a** epimer 1, 36283-63-3; **13a** epimer 2, 36283-62-2; **13b,** 51016-86-5; **13c,** 35093-27-7; **15a,** 54911-73-8; **15b,** 54911-74-9; **16b,** 35093-29-9; **18,** 54911-75-0; **19,** 54911-76-1; **20,** 54911-77-2; **21,** 54911-78-3; **22a,** 3853-88-1; **23,** 5826-27-7; **24** dimethyl ester, 54432-94-9; **25,** 54933-62-9; **26,** 48059-97-8; **27,** 54933-63-0; **28** dimethyl ester, 39590-03-9; **29,** 54911-79-4; **30** silver salt, 55000-29-8; **31,** 54911-80-7; **32,** 54911-81-8; **32** monomethyl ester, 54911-82-9; **33,** 54911-83-0; **34,** 29311-53-3; **35** methyl ester, 54911-84-1; **36,** 51326-51-3; **36** diether, 15057-13-3; **36** aldehyde analog, 54911-85-2; **37,** 54911-86-3; **38,** 54985-60-3; **39,** 54911-87-4; **40,** 19914-92-2; **41,** 4720-83-6; **42a,** 54911-88-5; **42b,** 54911-89-6; **43,** 54911-90-9; **44,** 54911-91-0; **45,** 54911-92-1; **46a,** 54911-93-2; **46b,** 54911-94-3; **47b,** 54911-95-4; **48,** 54911-96-5; **49b,** 54911-97-6; **54,** 54911-98-7; **56,** 54911-99-8; **57,** 54912-00-4; 1-hexyne, 693-02-7; tricarbomethoxyethylene, 51175-48-5; performic acid, 107-32-4; silver nitrate, 7761-88-8; silver acetate, 563-63-3; dimethyl 4-octynedioate, 23542-39-4; 1,4-butanediol, 110-63-4; dihydropyran, 25512-65-6; ethyl vinyl ether, 109-92-2; 1,5-diazabicyclo[5.4.0]undecene-5, 6674-22-2.

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Birch Reduction of [2.2]Paracyclophane-2-carboxylic Acid

James L. Marshall* and Ban-Huat Song[1]

Department of Chemistry, North Texas State University, Denton, Texas 76203

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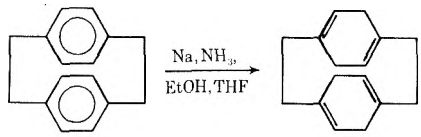
The Birch reduction of [2.2]paracyclophane-2-carboxylic acid (3) gives the tetrahydro product **4b** in which the double bonds of each deck are only partially overlapping; i.e., the Birch reduction proceeds in a manner previously observed for [2.2]paracyclophane (1) itself. This stereochemistry is demonstrated by reducing the pseudo-*gem*-deuterio derivative of **3**. The stereochemistry of the carboxylate group in **4b** is shown to be pseudo-equatorial. The system **4b** thus furnishes a unique NMR system for study in which a 1,4-dihydrobenzene ring is strongly puckered, the 1 substituent is not in the pseudo-axial orientation, and there exist two homoallylic protons to the 1 substituent.

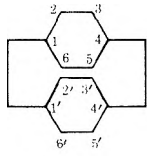
It has recently been shown[2] that the tetrahydro Birch reduction product of [2.2]paracyclophane (**1**) is *dl* (**2**) with the double bonds on each deck only partially overlapping.



1 2

This structure elucidation was accomplished by means of the proton NMR analysis of the tetraepoxide derivative of **2**. Because this analysis embodied a complex and involved argument, it seemed desirable to demonstrate that this stereochemistry[3] prevailed in another system which could be analyzed in a more straightforward fashion. Because of the ease of the Birch reduction of aromatic carboxylic acids and because of the synthetic availability of [2.2]paracyclophane-2-carboxylic acid (**3**), we chose to study the Birch reduction of **3**. An additional attractive feature of working with **3** would be the possibility of obtaining in the Birch reduction product a unique 1,4-dihydro-1-benzoic acid moiety forced into a puckered conformation and amenable to proton NMR analysis. In particular, if kinetic control would prevail, as expected, the approach of the hydrogen would occur from the top of **3** to force the carboxylate into a pseudo-equatorial orientation, contrasted with previous studies where the substituent was pseudo-axial.[4]

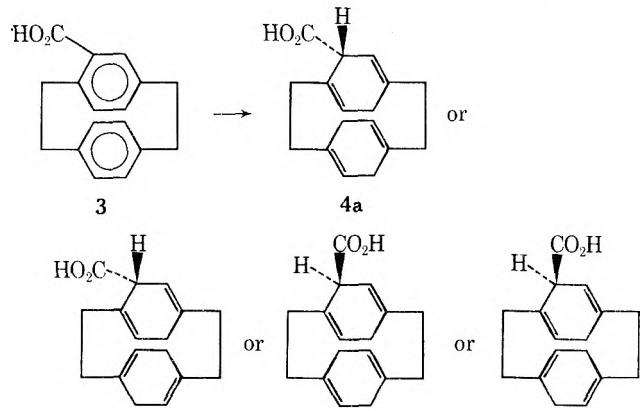
General Considerations. In this paper we shall use the numbering scheme shown by **1a**. This numbering scheme



1a

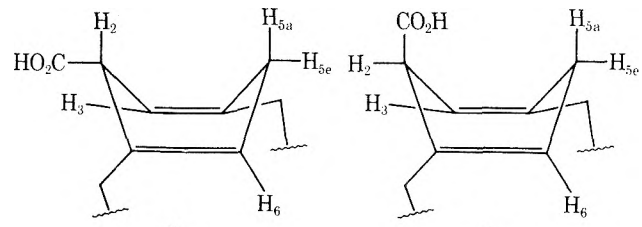
differs from that of Cram[5] in that our [2.2]paracyclophane-2-carboxylic acid would be named by his method [2.2]paracyclophane-4-carboxylic acid. This new numbering scheme was adopted so as to allow facile nomenclature involving stereochemical[3] comparison between the two decks. Assuming that the reduction of the top ring of **3** would go 1,4 to the carboxylate group, there would a priori exist four possible products (see **4a–d**). In **4a,b** the carboxylate group is pseudo-equatorial and in **4c,d** is pseudo-axial. In **4a** and **4c** the double bonds are "eclipsed" (i.e., the double bonds in the upper deck overlie those in the lower deck); in **4b** and **4d** the double bonds are "staggered" (i.e., the double bonds in the upper deck only partially overlap those of the lower deck).

In any of the structures **4a–d**, the two decks would be expected to be puckered, for two reasons. (1) There would be a great deal of steric interaction between the two decks of **4**. (This steric interaction for [2.2]paracyclophane itself has been shown to be quite severe, leading to distortion of the aromatic rings.)[6] Inspection of models of **4a–d** suggests that this steric difficulty is greatly relieved by puckering, which increases the distance between the two decks. (2) NMR analysis of the tetraepoxide derivative of **2** shows[2] that at least in this compound the decks are indeed strongly puckered.



3 4a 4b (found) 4c 4d

The puckered top deck of **4** is shown in **5a,b.** In **5a** the carboxylate group is pseudo-equatorial (corresponding to **4a,b**) and in **5b** is pseudo-axial (corresponding to **4c,d**).



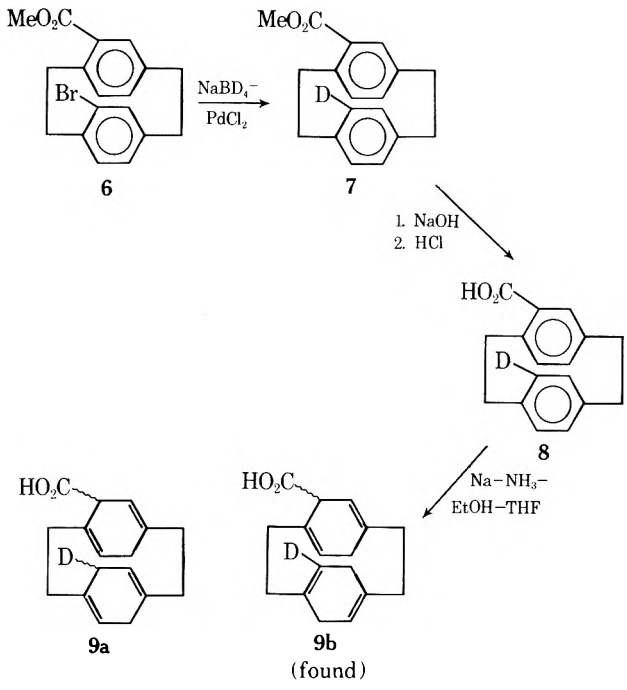
5a 5b

Birch Reduction of 3 and Subsequent Structure Elucidation. The Birch reduction of **3** gave **4** in 85% yield, mp 158–159°; the elemental analysis and mass spectrum indicated that four hydrogens had been added, and the ultraviolet spectrum of **4** showed no conjugated chromophore (the uv spectrum was quite similar to that of **2**[7]). By catalytic dehydrogenation **4** could be reconverted to **3**. The only structures so far consistent with these data were **4a–d.**

The sharp melting point of **4** and the existence of only one methine (H_2) absorption in the proton NMR spectrum (δ 3.25) indicated that one isomer predominated.

In an attempt to elucidate the structure of **4** in a manner similar to that of **2**, the synthesis of an epoxide derivative

Scheme I



of **4** was attempted.[2] However, treatment of **4** under epoxidation conditions resulted only in oxidation back to **3**.

Olefin Stereochemistry[3] Elucidation. An umambiguous assignment of the stereochemistry[3] of the olefins of **4** was afforded by the Birch reduction of the pseudo-*gem*-deuterio derivative **8**. Scheme I shows the reasoning behind this approach. The compound 2′-bromo-2-carboxymethyl-[2.2]paracyclophane (**6**), prepared according to the procedure of Cram,[8] would be treated with sodium borodeuteride–palladium chloride according to the procedure of Bosin[9] to give **7**. Saponification of **7** would give **8**. The Birch reduction of **8** would give **9**, whose deuterium would be aliphatic in **9a** (the "eclipsed" isomer) or olefinic in **9b**, (the "staggered" isomer). Proton NMR spectroscopy would easily distinguish between **9a** and **9b**.

The product **7** actually obtained upon the indicated treatment of **6** indicated clean substitution of a deuterium at the 2′ position: the mass spectral analysis of **7** showed 97% d_1 deuterium incorporation and the NMR spectral pattern of **7** lacked a one-proton absorption that the methyl ester of **3** possessed at the highest field part of the aromatic region (the shielding cone of the carboxyl group would be most effective for the 2′ proton).[10] The aromatic NMR pattern of **8** was the same as that of **7**.

The Birch reduction of **8** gave **9** in 91% yield. The comparison of the NMR spectrum of **9** with that of the nondeuterated analog **4** is shown in Figures 1a and 1b. The aliphatic regions of the NMR spectra of **4** and **9** were virtually identical, whereas the olefinic regions were different: the olefin region of **4** showed three signals at δ 5.30, 5.45, and 5.75 integrating for 1:2:1 (within 5%) while that of **9** showed the same three regions integrating for 1:1:1 (within 5%). [The olefinic proton NMR assignments that appear in Figure 1 follow from consideration of the respective coupling patterns (vide infra).] Thus, the correct choice for **9** was **9b**; isomers **4a** and **4c** were eliminated from consideration; and it was concluded that the Birch reduction product **4** had the double bonds "staggered" (either **4b** or **4d**).

Choice of the Correct Epimer 4b or 4d. The two structures remaining as candidates for **4** were the epimers **4b** or **4d**. Choice of the correct epimer was possible by an NMR study of **4**, including selective decoupling experiments,

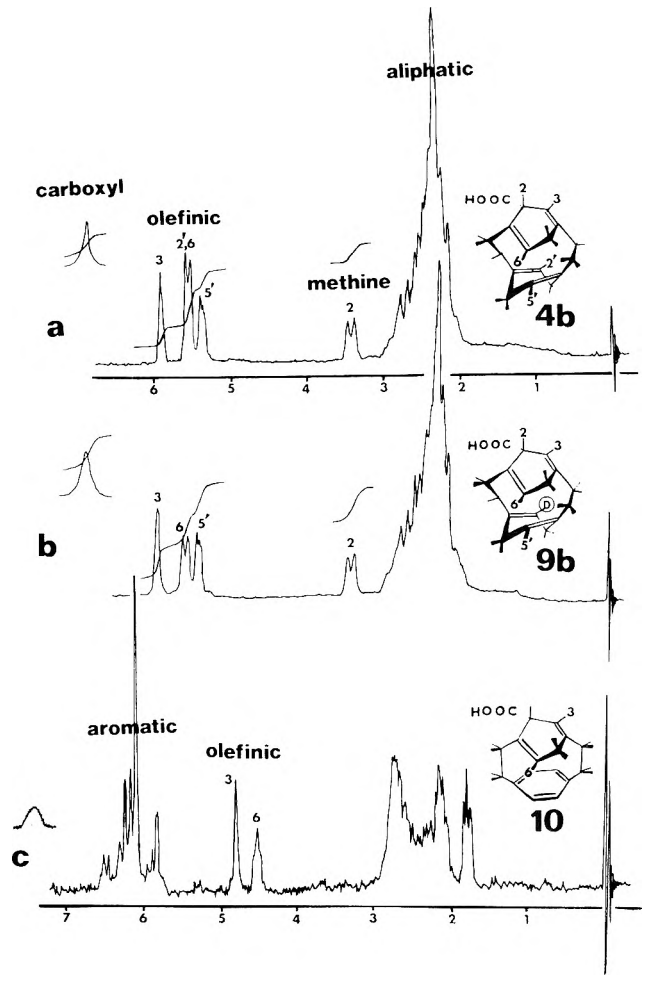
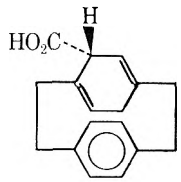


Figure 1. 100-MHz proton NMR spectra of various Birch reduction products of [2.2]paracyclophane-2-carboxylic acid: **4b** (a), **9b** (b), and **10** (c).

while using **5a** and **5b** as geometrical models for **4b** and **4d**, respectively. A ten-step argument follows that allows assignments for each of the olefinic signals appearing in Figure 1 and which allows unequivocal assignment of **4b** (**5a**) as the complete structure of **4**.

(1) The 2′ proton was obviously one of the signals at δ 5.54, since this proton signal disappeared upon deuterium substitution (Figure 1b). (2) The methine proton (H_2) appeared as a doublet with J = 8.8 Hz (see Figure 1). If the correct choice of structures was **5b**, then this large coupling observed for H_1 should arise from the vicinal coupling between H_2 and H_3 (whose dihedral angle would approach 0°). However, irradiation of each of the olefin regions did not remove this coupling of 8.8 Hz (irradiation of the olefin signal at δ 5.91 *did* sharpen the doublet). This experiment established the carboxyl group as pseudo-equatorial. (3) Supporting the conclusion of 2, irradiation of the methine proton did not remove the large coupling of any of the olefin signals (but did sharpen the appearance of the δ 5.91 signal). (4) It thus appeared that the δ 5.91 signal was H_3 and that the dihedral angle of H_3 and H_2 was far from 0° and was closer to 90° (i.e., the correct structure was **5a**). One would in fact expect H_3, vicinal to the electronegative carboxylate group, to be the furthest downfield olefin signal. (5) The other olefinic protons of **4**, however, would each be eclipsing (at least approximately) a methylene proton and therefore would have large splitting. This is what was observed (see Figures 1a and 1b). (This argument assumes that the bottom deck is puckered also.). (6) To confirm that the large splittings of these three olefinic protons

were due to coupling with the methylene protons, various frequencies in the methylene region were irradiated. Indeed, irradiation at δ 2.4 collapsed the patterns at δ 5.37 and 5.54 to broad singlets. (7) This same irradiation at δ 2.4 collapsed H_2 to a singlet. Thus, this splitting was undoubtedly due to homoallylic coupling with one of the H_5 protons.[11] (8) To differentiate between the two remaining unassigned olefin signals (H_6 and $H_{5'}$) experiment 3 was repeated with special attention devoted to the signals at δ 5.54 and 5.37. The H_6 proton should engage in allylic coupling with H_2 whereas the $H_{5'}$ proton could not. When H_2 was irradiated, there was slight sharpening in the δ 5.54 region while the δ 5.37 region was unchanged. Thus, H_6 was assigned as one of the protons at δ 5.54 and $H_{5'}$ was assigned as the δ 5.37 signal. (9) Being closer to the carboxyl group, H_6 would be expected to be downfield from $H_{5'}$. These were in fact the assignments made in 8 immediately above. (The fact that the 2′ proton is no longer the highest field olefin proton suggests that the carboxyl group is rotated to a different orientation in **4** from that in **3**.) (10) When the dihydro Birch reduction product of **3** was made (see **10**)—the synthetic intermediate during the reduction of **3**



10

to produce **4**—it was observed in the proton NMR spectrum (see Figure 1c) that the downfield olefinic signal (H_3) was relatively sharp, again consistent with an approximately orthogonal relationship with H_2.

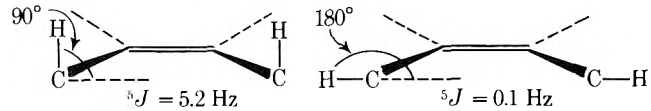
It had been originally hoped that a study of compound **10** would give more definitive stereochemical information. Unfortunately, the methine proton (H_2) had moved upfield and lay hidden under the broad aliphatic absorptions.

That the proton absorptions for H_2 and the olefinic protons H_3 and H_6 had all moved upfield suggested more severe steric compression[12] in **10** than in **4**; this is as expected, because the aromatic ring of **10** could not easily pucker.

Discussion

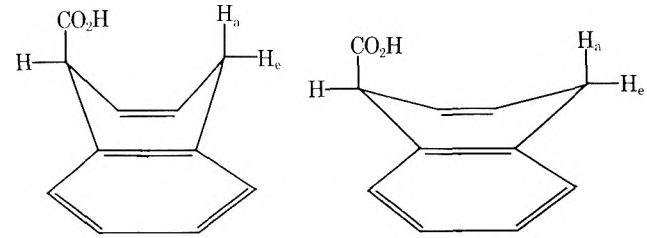
Stereochemistry[3] of Double Bonds. In the stepwise reduction of **3**, one would expect that the top ring would be reduced first, since the carboxylate group would activate this ring to Birch reduction. Indeed, by using less sodium in the Birch reduction of **3**, the 2,5-dihydro product **10** was isolated. In the mechanistic steps from **10** to **4**, the carboxylate groups should now not influence the sterochemical course of the reduction, since the carboxylate group is now no longer conjugated with the π system. Thus, further reduction of **10** should proceed just as it would without the carboxylate group, and the final product **4** should have the same olefinic stereochemistry[3] as the Birch reduction product **2** of [2.2]paracyclophane (**1**). Indeed, CNDO/2 calculations based on likely intermediates during the reduction of **1** suggested[2] that the "staggered" arrangement should result, and this "staggered" stereochemistry[3] was concluded to prevail in the Birch reduction of both **1** and **3**. The conclusions of the present work thus corroborate those of the previous paper.

Homoallylic Coupling. Barfield and Sternhell have recently shown[13] that in homoallylic coupling (^5J HC–C=C–CH) an angular dependence should be observed whereby this coupling should increase as the H–C bonds become more nearly parallel to the p orbitals of the olefin. Examples **11** and **12** demonstrate the calculated extremes in $|^5J_\pi|$ for a cis olefin.



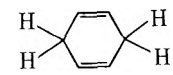
11 **12**

For a 1,4-cyclohexadiene, a double homoallylic path is possible and even larger ^5J values may be observed, but the same steric dependence should prevail. In view of this expectation, the homoallylic J values of 1,4-dihydronaphthoic acid[4] (**13**) appear anomalous: the NMR data strongly indicate a preference of the carboxylate group for a pseudoaxial conformation, but a pseudo-equatorial H_1 proton in a strongly puckered system (**13a**) should couple to an insignificant extent (<1 Hz) with the H_4 protons. Even in a "flattened boat" conformation (**13b**) the calculated ^5J



13a **13b**

values are only about 1 Hz. The ^5J values actually observed for **13** are 3.8 and 4.4 Hz. Furthermore, for simple 1,4-dihydrobenzene derivatives (**14**), which apparently are flat,[14]



14

one would again predict a ^5J somewhat less (~5 Hz)[15] than the >8 Hz actually observed. One is thus faced with the choice that (1) the theoretical treatment is qualitatively correct for 1,4-cyclohexadienes but underestimates the ^5J values; or (2) for 1,4-cyclohexadienes an entirely new treatment is necessary. There is a priori no reason to believe that possibility 2 is correct. Thus, it would be desirable to obtain homoallylic ^5J values in 1,4-cyclohexadienes whose conformation would definitely predict a small (≪1 Hz) coupling. The present study gives such an example.

As discussed above, the methine (H_2) NMR absorption of **4b** was a doublet of 8.75 Hz. Close inspection of this doublet at expanded scale and a careful LAOCOON III[16] study placed an upper limit of 1 Hz of the other couplings involving H_2. Considering the vicinal couplings involving H_2, that $^3J_{23}$ < 1 Hz indicates that the involved dihedral angle is very close to 90° and that the ring is definitely puckered with the carboxylate group pseudo-equatorial—compare this ^3J value with the analogous value in **13** (a "flattened boat"), 2.4 Hz, and in **14** (which is flat), 3.1 Hz.[14] This puckered conformation as shown in **5a** would from Barfield's treatment predict (1) $J_{2,5e}$ should be small (<1 Hz); (2) $J_{2,5a}$ (in **4b**) > ^5J (in **14**) > ^5J (in **13**). These predictions are in fact what are observed.

Therefore, the present work supports previous work[14] suggesting that 1,4-cyclohexadiene is not normally puckered and indicates that with highly puckered 1,4-cyclohexadienes significant homoallylic coupling will not occur with the pseudo-equatorial protons. The present work further supports qualitatively the theoretical homoallylic work of Barfield and Sternhell with regard to 1,4-cyclohexadienes.

Experimental Section

Melting points were determined by a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 237 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Jelco JNM-PS-100, with tetramethylsilane as an internal standard reference, utilizing field sweep internal lock mode. Elemental analyses were performed by C. F. Geiger, Ontario, Calif.

[2.2]Paracyclophane-2-carboxylic acid (3) was prepared according to the procedure of Cram.[5]

Birch Reduction of 3. Preparation of 2,5,3′,6′-Tetrahydro-[2.2]paracyclophane-(e)-2-carboxylic Acid (4b). Compound **3** (218 mg, 0.865 mmol) was dissolved in dry tetrahydrofuran in a 250-ml three-necked flask equipped with a mechanical stirrer. Liquid ammonia (75 ml) was distilled into the flask. Over a period of 1 hr, 400 mg of sodium in small pieces and 4 ml of absolute ethyl alcohol dropwise were added. After 3 hr of further stirring, the blue-brown color had disappeared. Ammonium chloride (1.5 g) was cautiously added followed by 60 ml of water. After standing overnight, the reaction mixture was mixed with 130 ml of ice–water and very carefully acidified to a pH of 4 with dilute hydrochloric acid. The tetrahydrofuran solvent was removed under vacuum, and the resulting residue was filtered, dissolved in chloroform, dried (magnesium sulfate), and concentrated to give 187 mg of white crystals (85%), mp 155–158°. Recrystallization from petroleum ether gave an analytical sample: mp 158–159°; ir (KBr) 795 cm^{-1}; NMR ($CDCl_3$) δ 2.1–2.9 (14 H, $-CH_2-$), 3.45 (d, J = 8.75 Hz, 1 H, H_2), 5.37 (m, 1 H, H_3), 5.54 (d, J = 8 Hz, 2 H, H_2 and H_6), 5.91 (m, 1 H, H_5), 10.1 (s, 1 H, CO_2H); mass spectrum m/e 256 (M^+); uv, end absorption to 240 nm. NMR is shown in Figure 1.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.30; H, 8.14.

Dehydrogenation of 4b. Compound **4b** (300 mg) was refluxed in 100 ml of dry benzene with 290 mg of 10% palladium on charcoal to give after filtering 250 mg (84%) of **3**, mp 190–195°, ir, NMR, and mass spectrum identical with those of authentic samples. Recrystallization from acetic acid gave a pure sample, mp 221–222° (lit. mp 222.5–224°), mmp 221–222°.

2′-Bromo-2-carboxymethyl[2.2]paracyclophane (6) was prepared according to the procedure of Cram[8] in 52% yield.

2′-Deuterio-2-carboxymethyl[2.2]paracyclophane (7). To a stirring mixture of 700 mg of **6**, 50 ml of methanol-*O*-*d*, and 720 mg of predried palladium chloride, held at 40°, was added 849 mg of sodium borodeuteride in portions over a period of 15 min. After a subsequent 1 hr of stirring, the stirring mixture was immersed in a constant-temperature water bath at 80° for 5 min. Immediately after, the stirring mixture was immersed in an ice–water bath and 70 ml of 0.7 *N* hydrochloric acid was added. The alcohol was removed under vacuum and the product was dissolved in chloroform. This chloroform solution was dried (magnesium sulfate) and concentrated under vacuum to give 490 mg (90%) of **7**, mp 135–138° (lit. mp of nondeuterated compound, 139–140°).[8] The mass spectrum indicated 97% deuterium incorporation. The NMR was complex but lacked a signal integrating for 1 H that existed at the highest field portion of the aromatic region in the nondeuterated compound.

2′-Deuterio[2.2]paracyclophane-2-carboxylic Acid (8). Compound **7** (400 mg) was refluxed in 100 ml of 0.25 *N* sodium hydroxide in 5:1 methanol–water for 4 hr. The mixture was cooled and dilute hydrochloric acid was added to precipitate the product **8**. The product was collected by filtration and recrystallized from acetic acid to give 361 mg (95%) of **8**, mp 220–222° (lit. mp of nondeuterated compound, 222.5–224°).[5] The NMR was virtually identical with that of **7** in the aromatic region.

2′-Deuterio-2,5,3′,6′-tetrahydro[2.2]paracyclophane-2-carboxylic Acid (9b). The procedure used to reduce **8** to give **9** was identical with that for the nondeuterated (**3** → **4**) compounds. In such a manner was obtained 320 mg (91%), mp 156–158.5°. The NMR lacked an olefinic signal that existed for **4** (see Figure 1); mass spectrum m/e 257 (M^+).

2,5-Dihydro[2.2]paracyclophane-2-carboxylic Acid (10). Compound **3** was reduced in a manner identical with that to obtain **4** except that only 9% the sodium was used as for **4** (only the reactive carboxyl aromatic ring is reduced here, and accordingly only a small amount of sodium is required). In such a manner was obtained 177 mg (86%): mp 152–153.5°; NMR ($CDCl_3$) δ 1.75–2.95 (13 H, $-CH_2-$ and H_2), 4.59 (m, 1 H, H_6), 4.85 (broad s, 1 H, H_3), 9.65 (s, 1 H, CO_2H); mass spectrum m/e 254 (M^+).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.34. Found: C, 80.31; H, 7.56.

Attempted Epoxidation of 4b. The same procedure was used as for **2**.[2] In such a manner was obtained a 80:20 mixture of **4b:3.**

Acknowledgments. The authors gratefully acknowledge the financial support of the Robert A. Welch Foundation, Grant No. B-325, and of North Texas State University Faculty Research.

Registry No.—**3,** 18931-39-0; **4b,** 54844-44-9; **6,** 24417-98-9; **7,** 54910-36-0; **8,** 54910-37-1; **9b,** 54910-38-2; **10,** 54844-45-0.

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(3) As a referee pointed out, there is a question whether "stereochemistry" or "structure" is correct here. We prefer "stereochemistry", because in principle the two possible double bond arrangements—"eclipsed" (**4a** or **4c**) and "staggered" (**4b** or **4d**)—can be introconverted by rotation of one of the decks. For an example, see G. C. Whitesides, B. A. Pawson, and A. C. Cope, *J. Am. Chem. Soc.*, **90,** 639 (1968).
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(11) The only other possibility would be a four-bonded coupling of H_2 with a bridging methylene proton. However, this is not a reasonable possibility because (1) such a large $^4J_{HH}$ value is unprecedented; (2) the geometry is wrong anyway (ref 10, p 143).
(12) There is some question whether this effect is from steric compression directly or from the shielding effect of the aromatic ring currents (ref 10, p 65). We prefer the former explanation, because the protons in question are on the *periphery* of the ring. In any case, that protons become shielded as the rings in [*m,n*]paracyclophanes approach one another is well established: D. J. Cram and L. A. Singer, *J. Am. Chem. Soc.*, **85,** 1084 (1963); D. J. Cram and R. C. Helgeson, *ibid.*, **88,** 3515 (1966).
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Preparations and Properties of Higher [2^n]Paracyclophanes, Cyclic Oligomers of *p*-Xylylene

Iwao Tabushi,* Hidenori Yamada, and Yasuhisa Kuroda

Department of Pharmaceutical Sciences, Kyushu University, Maidashi, Fukuoka, 812 Japan

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Syntheses and some properties of [2.2.···2]paracyclophanes [cyclic *n*-mer of *p*-xylylene, abbreviated as [2^n]paracyclophane or n°-PCP (n = 3, 4, 5, 6, and 8)] are described. At room temperature, NMR spectra of these compounds showed two singlets of benzene and ethylene proton resonances. At low temperature, however, broadening of signals of the ethylene protons were observed, while the shape of a benzene singlet was not remarkably changed. This broadening was due to the internal rotation (axial–equatorial exchange) of the ethylene protons. Based on temperature-dependent NMR spectra, energy barrier of this conformation change was concluded to be in the interesting order, 4°-PCP ([2.2.2.2]paracyclophane or [2^4]paracyclophane; similar abbreviations are used throughout this paper) > 5°-PCP > 6°-PCP > 3°-PCP. The activation energy of this conformation change for 4°-PCP was evaluated to be 3.8 kcal/mol.

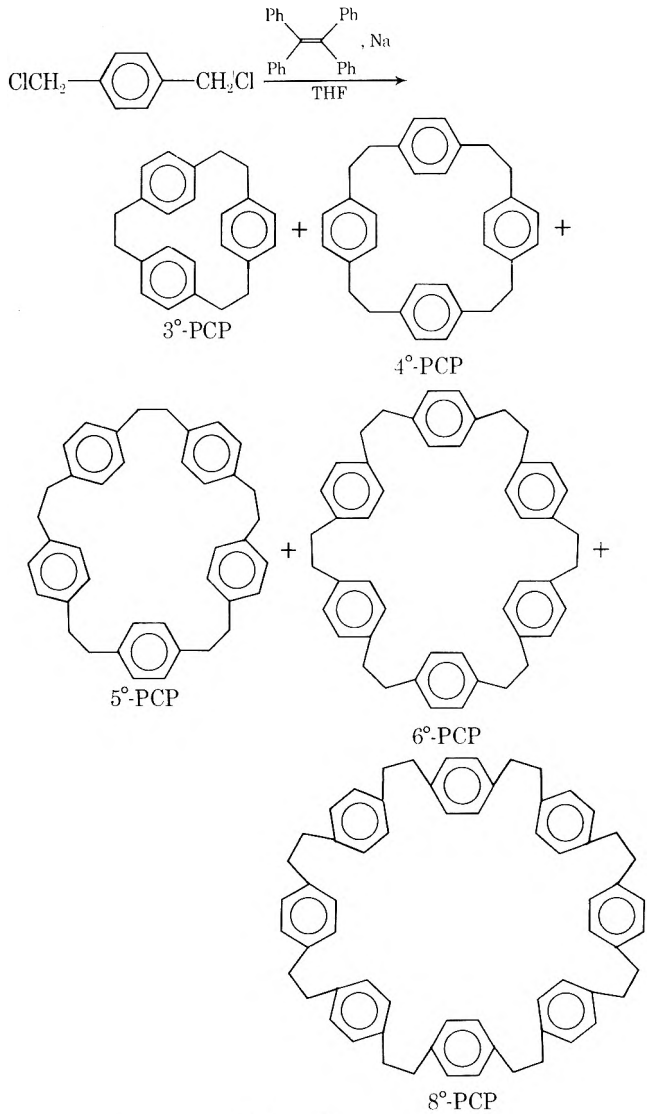
In earlier papers we have described the chemistry of [2.2.2]paracyclophane (3°-PCP) and [2.2.2.2]paracyclophane (4°-PCP) where the planarity of benzene rings was concluded on spectroscopic ground to be satisfactorily retained.[1,2] In this article, we wish to report the preparations and some properties of higher [2^n]-paracyclophanes (n°-PCPs), cyclic oligomers of *p*-xylylene, in connection with conformation problems which may be very important in their inclusion.[3]

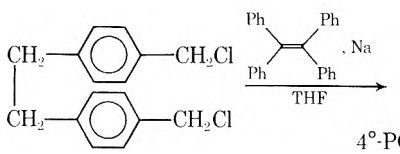
Preparations of 5°-PCP, 6°-PCP, and 8°-PCP were successful by the modified Wurtz condensation[4,5] of *p*-xylylene chloride,[6] and each paracyclophane was isolated by means of column chromatography coupled with fractional crystallization. 6°-PCP and 8°-PCP were also prepared by the modified Wurtz condensation of *p,p'*-di(chloromethyl)-1,2-diphenylethane.[7] Table I shows some physical properties of n°-PCPs. Some irregular changes in melting points of present n°-PCPs are similar to those of reported [2^n]metacyclophanes.[8]

Table I
Physical Properties of n°-PCPs

n°-PCP	Mp, °C	Recrystn solvent	Crystal form	Ref
2°-PCP[a]	285–287	Acetic acid	Needle	*b*
3°-PCP	168	*n*-Hexane	Feather	*c*
4°-PCP	185	*n*-Hexane–benzene	Prism	*d*
5°-PCP	170–172	*n*-Hexane–benzene	Prism	*e*
6°-PCP	200–202	*n*-Hexane–benzene	Plate	*e*
8°-PCP	273–275	*n*-Hexane–benzene	Scale	*e*

[a] [2.2]Paracyclophane. [b] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, 73, 5691 (1951). [c] Reference 1. [d] Reference 2. [e] This work.





4°-PCP + 6°-PCP + 8°-PCP

NMR Spectra of n°-PCPs. At room temperature, each paracyclophane showed two singlet NMR absorptions due to aromatic and aliphatic protons. The aromatic δ value showed the presence of a considerable shielding effect, the magnitude of which decreased with increase of macrocyclic ring size (Table II). These observations suggest that benzene rings predominantly (in a statistical sense) take the "face" conformation[9] where the aromatic protons are shielded by other benzene rings and the magnitude of shielding effect diminishes with increase in the transannular distance of a paracyclophane. In order to investigate the conformation problem of these paracyclophanes, the NMR spectra of 3°-PCP, 4°-PCP, 5°-PCP, and 6°-PCP were measured in $CDCl_3$–CH_2Cl_2 or CS_2 solution at low temperature. The results at −75° in $CDCl_3$–CH_2Cl_2 solution are

Table II
δ Values and Line Broadening[a] of *n*°-PCPs

Compd	δ (room temp, CCl_4, Me_4Si) CH_2	Arom	Ref	Line broadening[a] (−75°, $CDCl_3$–CH_2Cl_2) CH_2	Arom
p,*p*′-Dimethylbibenzyl	2.80	6.94	*b*		
2°-PCP	3.04	6.30	*c*		
3°-PCP	2.93	6.62	*d*	4.9/2.0	3.1/2.0
4°-PCP	2.84	6.65	*e*	*f*	2.8/1.8
5°-PCP	2.76	6.68	*g*	7.5/1.8	2.5/1.8
6°-PCP	2.84	6.75	*g*	7.5/3.3	3.0/3.3
8°-PCP	2.84	6.82	*g*		

[a] Relative half-width in hertz (half-width of protons of paracyclophanes compared with that of added CH_2Cl_2). [b] F. A. Bovey, "NMR Data Tables for Organic Compounds", Vol. 1, Wiley, New York, N.Y., 1967, p 426. [c] D. J. Wilson, V. Boekelheide, and R. W. Griffin, Jr., *J. Am. Chem. Soc.*, **82**, 6302 (1960). [d] Reference 1. [e] Reference 2. [f] Below the coalescence temperature. [g] This work.

Table III
Uv Spectra of *n*°-PCPs[a] and *p*-Xylene[b]

Compd	λ_1, mμ (log ε)	λ_2, mμ (log ε)	λ_3, mμ (log ε)	λ_4, mμ (log ε)
p-Xylene[c]	274 (2.85)	269 (2.75)	266 (2.73)	260 (2.60)
2°-PCP[d]	302 sh (2.19)		285 (2.41)	
3°-PCP	276 (2.89)	269 sh (2.88)	267 (2.95)	262 (2.83)
4°-PCP	274 (3.13)	267 sh (3.16)	265 (3.20)	260 (3.09)
5°-PCP	274 (3.24)	267.5 sh (3.22)	265.5 (3.28)	260 (3.15)
6°-PCP	273.5	267 sh	265	260
8°-PCP	274	267.5 sh	265.5	260

[a] In hexane. [b] In heptane. [c] "UV Atlas of Organic Compounds", Vol. III. [d] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951).

listed in Table II together with δ values at room temperature. Under the condition investigated and among the compounds investigated, only ethylene protons of 4°-PCP coalesced at −71° in $CDCl_3$–CH_2Cl_2 or −85° in CS_2 ($\Delta G^{\ddagger}_{-85°}$ = 9.1 kcal/mol in CS_2). During the temperature change, the signal of ethylene protons changed from singlet to AB quartet as shown in Figure 1. This indicates that the conformation change including ethylene proton (such as axial–equatorial exchange) begins to freeze at low temperature. The peak separations of ethylene protons of 4°-PCP at various temperatures are listed in Table III. The chemical shift difference ($\Delta\delta$, $\nu_A - \nu_B$) for frozen 4°-PCP was estimated to be 51 Hz by means of computation analysis so as to give the largest correlation coefficient for the linear relationship between $1/T$ and $\log 2\pi(\nu_A - \nu_B)\tau$ where $\frac{1}{2}\tau$ was the rate of exchange of nuclei (Figure 2). Thus, the activation energy (E_a) of this conformation change was estimated to be 3.8 kcal/mol and the frequency factor, k_0, to be 3.0×10^6 Hz. The ethylene protons of the other paracyclophanes did not separate until −111° in CS_2 but line broadening was observed, the magnitude of which was in the order, 5°-PCP ≃ 6°-PCP > 3°-PCP. Therefore, the observed barrier ($\Delta G^{\ddagger}$) of the conformation change of ethylene protons of these paracyclophanes is concluded to be in the interesting order 4°-PCP > 5°-PCP ≃ 6°-PCP > 3°-PCP. On the other hand, aromatic protons of each paracyclophane showed only small line broadening, which indicated

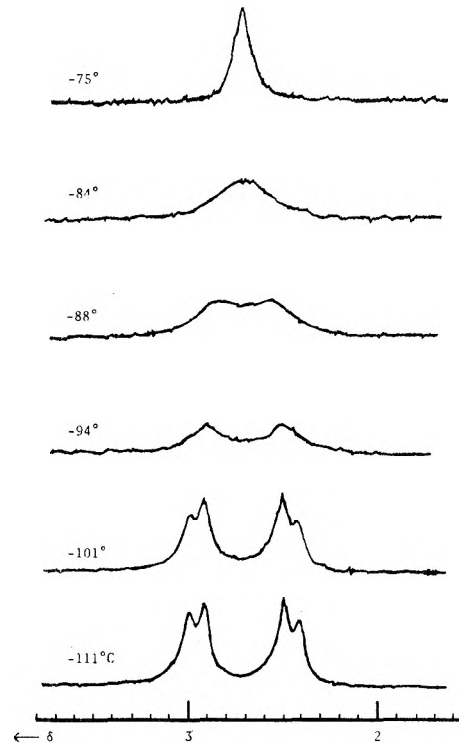


Figure 1. ^1H NMR spectra of ethylene protons in 4°-PCP at several temperatures, 100 MHz, Me_4Si, in CS_2.

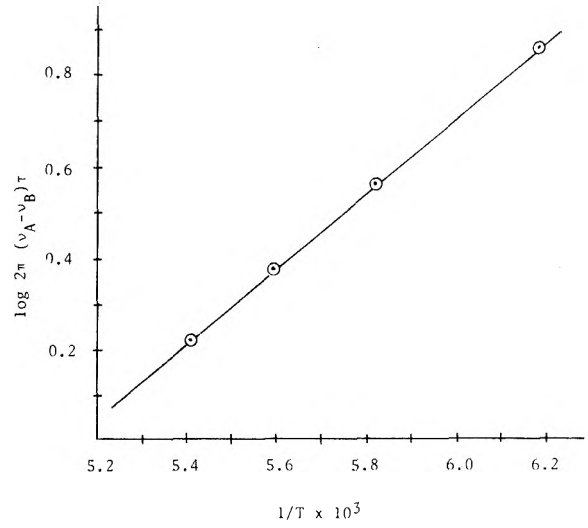


Figure 2. Temperature dependence of the rate of exchange of nuclei of ethylene protons of 4°-PCP.

that motions of benzene rings were not remarkably restricted under the condition investigated (vide infra).

The conformation change for 4°-PCP (Figure 3) is understood as the axial–equatorial change from the following considerations.

(1) Ethylene protons of 4°-PCP were frozen to two kinds of protons at low temperature (Figure 2) and the chemical shift difference ($\Delta\delta$) for the two different protons was estimated to be 0.51 ppm. This value was reasonably ascribed to the axial–equatorial difference based on the following reason. The shift difference between the axial and equatorial benzyl protons by the shielding effect from benzene rings for an "all face" [9] conformation (benzenes are perpendicular to the hypothetical molecular plane) was calculated, as an extreme, by computer with Johnson's equation[10] to be ca. 1.0 ppm, while for an "all lateral" conformation (benzenes are on the plane) as an opposite extreme (Figure

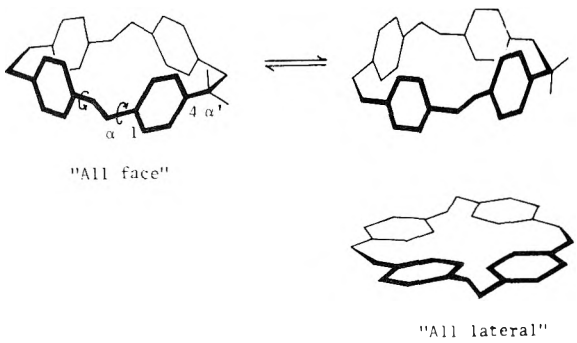


Figure 3. The axial-equatorial exchange of ethylene protons of 4°-PCP.

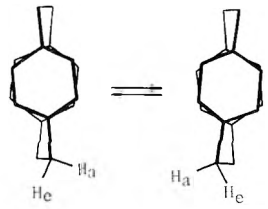


Figure 4. Conformation change of 2°-PCP.

3), $\Delta\delta$ was 0 ppm, and for freely rotating benzene rings, $\Delta\delta$ was ca. 0.12 ppm. The present observed value (0.51 ppm) suggests that the benzene rings still vibrate or rotate (around a C_{α}–C_1–C_4–$C_{\alpha'}$ axis) to produce a statistically averaged shielding effect; however, "face" conformation is much favored in a statistical sense under the condition investigated. This is consistent with the fact that aromatic protons showed only small line broadening.

(2) E_a of the axial–equatorial change was estimated to be 3.8 kcal/mol for 4°-PCP and this value suggests a reasonable connection between present barrier and the usual ethane barrier.[11]

The smaller $\Delta G^{\ddagger}$ value of 5°-PCP or 6°-PCP than 4°-PCP may be due to greater flexibility of 5°-PCP or 6°-PCP than 4°-PCP, but the unexpectedly small $\Delta G^{\ddagger}$ value of 3°-PCP is interesting to note. According to our calculation of energy of 3°-PCP by means of π approximation (VI/1 method[12]), the transannular distance of 3°-PCP seems to be somewhat in a slightly repulsive region.[13] This forces benzene rings to be apart, making the conformation nearly eclipsed and raising the bottom of the energy surface (the gauche conformation). Actually, 2°-PCP, where much larger π–π repulsion is involved, was reported to have a very low transition region, at near 55 K, from the measurement of heat capacity of crystals and the ΔH of the transition to be only 51 cal/mol.[14] This transition was presumed to be due to the conformational exchange of H_a and H_e as shown in Figure 4. X-Ray analysis of 2°-PCP at 93 K also indicated that this conformation change did take place even at this very low temperature.[15] This small energy barrier of the axial–equatorial change of 2°-PCP may be ascribed to the increasing π–π repulsion in the gauche conformation. This situation seems to be similar to that in 3°-PCP. Therefore, the expected order of the activation energy for the conformation change of n°-PCPs is 4°-PCP > 5°-PCP $\simeq$ 6°-PCP > 3°-PCP > 2°-PCP, just consistent with the observed order.

Other Spectral Properties of n°-PCPs. Table III shows the uv spectra of n°-PCPs together with that of p-xylene. A considerable bathochromic shift for 2°-PCP is reported where benzene rings are not planar as shown by X-ray analysis. However, uv spectra of higher paracyclophanes were very similar to that of p-xylene. Therefore, it should be concluded that benzene rings of these paracyclophanes, except 2°-PCP, are "normal" (i.e., not appreciably distorted).

In the region from 400 to 1000 cm^{-1} of ir spectra, p-xylene showed only two sharp absorptions at 796 and 482 cm^{-1}. Every paracyclophane showed an additional sharp absorption at near 600 cm^{-1} and near 800 and 500 cm^{-1} (Table IV). This may be characteristic of paracyclophane, although details are not yet known.

Table IV
Moderately Intense Absorptions of Ir Spectra of n°-PCPs at Near 800, 600, and 500 cm^{-1} [a]

2°-PCP	3°-PCP	4°-PCP	5°-PCP	6°-PCP	8°-PCP
807	804, 787	822, 813	816, 806	819	829
623	588	587, 569	594	595	576
509	469	459,[b] 452[b]	537[b]	546,[b] 463[b]	546,[b] 506[b]

[a] KBr, cm^{-1}. [b] Moderately weak absorption.

Experimental Section

Materials. 3°-PCP and 4°-PCP were prepared by the modified Wurtz condensation of p-xylylene chloride in the presence of a catalytic amount of tetraphenylethylene as described elsewhere.[1,2] Combined mixture of several reactions, from which 3°-PCP 4°-PCP had been already separated,[1,2] were chromatographed on silica gel. Early elution product with 15% benzene–n-hexane solution mainly consisted of 5°-PCP. Repeated fractional crystallizations from benzene–n-hexane gave pure 5°-PCP as colorless prisms in about 2% yield, based on p-xylylene chloride used: mp 170–172° (from benzene–n-hexane); mass spectrum m/e (rel intensity) 520 (M^+, 0.37), 168 (13), 167 (100), 165 (19), 152 (13); ir (KBr) 3075, 3040, 2995, 2915, 2845, 1511, 1438, 1415, 1310, 1200, 1142, 1093, 1022, 920, 905, 816, 806, 594, 537 cm^{-1}. Anal. Calcd for $C_{40}H_{40}$: C, 92.26; H, 7.74. Found: C, 92.02; H, 7.72.

Further elution with 15% benzene–n-hexane solution contained 6°-PCP mainly, which was purified by means of repeated fractional crystallizations. Thus 6°-PCP was obtained as white plates in about 2% yield based on p-xylylene chloride: mp 200–202° (from benzene–n-hexane); mass spectrum m/e (rel intensity) 624 (M^+, small), 168 (14), 167 (100), 165 (20), 152 (14); ir (KBr) 3070, 3025, 2995, 2845, 1510, 1440, 1415, 1338, 1200, 1096, 1021, 920, 819, 595 cm^{-1}. Anal. Calcd for $C_{48}H_{48}$: C, 92.26; H, 7.74. Found: C, 92.00; H, 7.64.

Then elution with 50% benzene–n-hexane gave mainly 8°-PCP, which was purified similarly. 8°-PCP was obtained as scale-like crystals and melted at 273–275° (from benzene–n-hexane): mass spectrum m/e (rel intensity) 832 (M^+, very small), 415 (13), 311 (18), 156 (31), 119 (41), 118 (18), 117 (25), 103 (95), 102 (100); ir (KB) 3080, 3030, 3010, 2990, 2915, 2835, 1512, 1438, 1414, 1341, 1200, 1142, 1094, 1023, 924, 825, 576, 546, 506 cm^{-1}. Anal. Calcd for $C_{64}H_{64}$: C, 92.26; H, 7.74. Found: C, 92.36; H, 7.73.

6°-PCP and 8°-PCP were also prepared by the modified Wurtz condensation of p,p'-di(chloromethyl)-1,2-diphenylethane using a catalytic amount of tetraphenylethylene.

Measurements. NMR spectra were measured by using Varian T-60 and HA-100 spectrometers. Temperature was determined by the NMR chemical shift difference between hydroxyl and methyl protons of methanol.

Uv spectra were measured with a Hitachi Model EPS-3T spectrophotometer in hexane.

Ir spectra were measured with a Hitachi Model 285 ir spectrophotometer.

The activation energy of the conformation change of 4°-PCP was calculated from the slope of the plots of log $*2\pi(\nu_A - \nu_B)\tau$ vs. $1/T$ according to the reported procedure,[16] where ν_A and ν_B are corresponding separate chemical shifts of protons A and B and $\frac{1}{2}\tau$ is the exchange rate between A and B (cf. Figure 2).

Registry No.—2°-PCP, 1633-22-3; 3°-PCP, 283-80-7; 4°-PCP, 283-81-8; 5°-PCP, 43082-13-9; 6°-PCP, 43082-14-0; 8°-PCP, 54823-92-6; tetraphenylethylene, 632-51-9; p-xylylene chloride, 623-25-6; p,p'-di(chloromethyl)-1,2-diphenylethane, 38058-86-5.

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Stereochemistry of Deuteron Attack on the 3α,5α-Cycloandrost-6-ene System[1]

James C. Orr* and Janet M. Broughton

John Collins Warren Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University at the Massachusetts General Hospital and the Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts 02115

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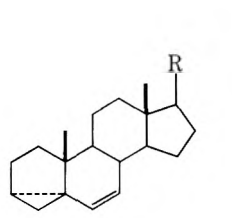
Acid-catalyzed hydration of the 3α,5α-cycloandrost-6-ene system gives the 3β-hydroxyandrost-5-ene system in high yield. In the presence of D_2O, irreversible deuteron attack at the 7 position occurs equally from the α and β faces of the steroid. Elimination of methanol from 7β-deuterio-6β-methoxy-3α,5α-cycloandrostan-17β-ol occurs by pyrolysis with 70% loss of the 7β-deuterium (cis elimination), by alumina catalysis with 48% loss of the 7β-deuterium, and by electron impact in the mass spectrometer with no loss of the 7β-deuterium.

Although it had been observed in 1946[2] that acid-catalyzed hydration of 3α,5α-cyclocholest-6-ene (**1**, R = C_8H_{17}) gives rise to cholesterol, no further study of this reaction had been reported. Acid-catalyzed rearrangements of related vinyl cyclopropanes have, however, been examined in considerable depth.[3,4] Since this hydration appeared to offer a useful method for the introduction of deuterium at the 7 position of the biologically important 3β-hydroxy-Δ^5-steroids, we have determined the direction of addition of the proton (deuteron) to the 3α,5α-cyclo-Δ^6 system.



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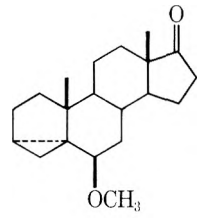

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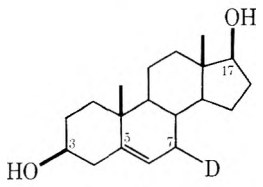

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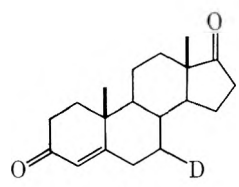

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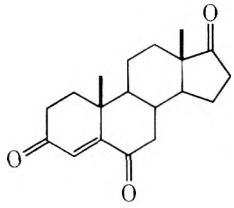

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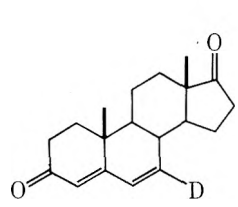

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3α,5α-Cycloandrost-6-en-17-one[5] (**1**, R = O) was prepared by the standard procedure of converting 3β-hydroxyandrost-5-en-17-one *p*-toluenesulfonate to 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**), which on treatment with alumina in refluxing xylene gave **1**, R = O, in 14% yield. Attempts to convert the 3-*p*-toluenesulfonate directly to the 3α,5α-cycloandrost-6-ene system with potassium *tert*-butoxide in *tert*-butyl alcohol, or treatment with alumina or barium oxide in refluxing xylene, led instead to the formation of the 3,5-diene.

Hydration of 3α,5α-cycloandrost-6-en-17-one (**1**, R = O) with D_2SO_4 and D_2O in dimethyl sulfoxide at 90°, followed by acid-catalyzed exchange of the 16-deuterium, gave 3β-hydroxyandrost-5-en-17-one with incorporation of 94% of one nonexchangeable deuterium atom per molecule.

With bis(2-methoxyethyl) ether (diglyme) which had been distilled from a mixture with D_2O, 3α,5α-cycloandrost-6-en-17β-ol (**1**, R = OH) was converted by D_2SO_4–D_2O to androst-5-ene-3β,17β-diol (**3**, 87% d_1, 13% d_2), which crystallized on cooling the sealed tube. Chromium trioxide oxidation[6] and isomerization with dilute hydrochloric acid gave androst-4-ene-3,17-dione (**4**, 100% d_1, 0% d_2). Unlabeled androst-5-ene-3β,17β-diol was recovered essentially unlabeled after treatment with D_2SO_4–D_2O–diglyme under the conditions of the hydration reaction, and in experiments in which 3α,5α-cycloandrost-6-en-17β-ol was recovered, it too was unlabeled. The additional 13% of deuterium is therefore incorporated at positions 2, 3, 4, or 6 during the ring-opening hydration reactions.

That the deuteron attack on the vinyl cyclopropane (**1**, R = OH) had occurred at the 7 position was established since no loss of label occurred from the derived androst-4-ene-3,17-dione (100% d_1) under conditions (D_2SO_4–D_2O–diglyme) which caused incorporation of five deuterium atoms into testosterone at carbons 2, 2, 4, 6, and 6. A by-product in the chromium trioxide oxidation of deuterated androst-5-ene-3β,17β-diol (**3**) is androst-4-ene-3,6,17-trione (**5**).

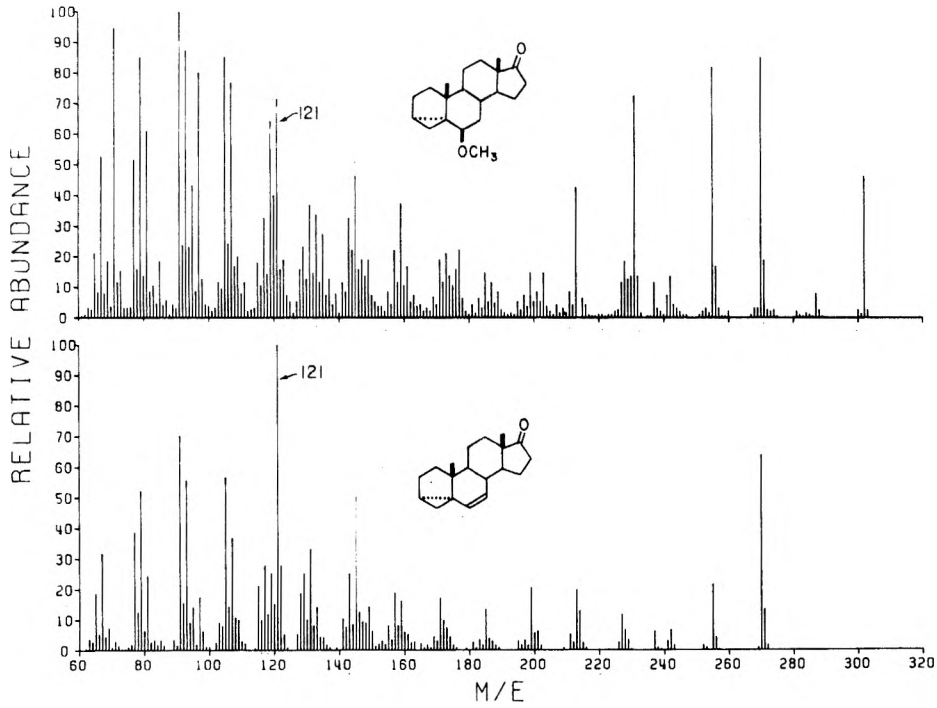

Figure 1. Mass spectra of 6β-methoxy-3α,5α-cycloandrostan-17-one and 3α,5α-cycloandrost-6-en-17-one.

This enetrione contained no excess deuterium; the presence of the 6-ketone had allowed exchange of hydrogen at the 7 position presumably during the acid treatment. The mass spectrum of the deuterated androst-4-ene-3,17-dione (4) showed an abundant peak at *m/e* 124 characteristic of steroid-4-en-3-ones.[7] This peak would have been at *m/e* 125, had the introduced label been attached to a ring A or positions 6 or 8. In the 3α,5α-cyclo-Δ^6 system, the geometry of the rings is such that the trigonal C-6 is very close to the bisected conformation found most favorable[8] for overlap of a 6-carbonium with the cyclopropane ring, and indeed the protonation giving a tetrahedral C-7 causes C-6 to move from this optimal orientation. This cyclopropyl carbonium ion is clearly preferred to the less stable[9] allyl carbonium ion which would be formed by attack of the proton (deuteron) on the cyclopropane ring. Conjugated vinyl cyclopropanes[3,4] are thus an exception to the rule[10] that cyclopropanes are more reactive toward the addition of acid than are olefins.

The stereochemistry of deuterium substitution at the 7 position was not immediately clear. The ir spectrum of 7-deuterio-3β-hydroxyandrost-5-en-17-one showed the presence of bands indicative of both axial α (2102, 2132 cm^{-1}) and equatorial β (2143 cm^{-1}) deuterium.[11] The NMR spectrum of a vinyl 6 proton coupled only to 7α-H (7β-D) is known to be a sharp singlet, while vinyl 6-H coupled to 7β-H (7α-βr) gives a sharp doublet, J = 5 Hz.[12] The 7-deuterio-3β-hydroxyandrost-5-en-17-one and 7-deuterioandrost-5-en-3β,17β-diol diacetate derived from the ring opening–hydration reactions had 6-H as a broad singlet or indistinct doublet of half-band width 8 Hz indicating that the products were mixtures of 7α- and 7β-D.

The orientation of the deuterium at the 7 position was established by chloranil dehydrogenation, which has been shown to remove the 7α hydrogen atom in the conversion of steroid Δ^4-3-ketones to the 4,6-dien-3-ones.[12] Androst-4-ene-3,17-dione-7ξ-*d* (4, 100% d_1), prepared as described, gave on chloranil dehydrogenation androsta-4,6-diene-3,17-dione (6, 46% ± 2% d_1) under conditions where dehydrogenation had progressed to the extent of 70%, and 49 ± 2% when the reaction was 87% complete. Further reaction caused appreciable formation of the 1,4,6-trien-3-one. The unreacted androst-4-ene-3,17-dione had lost no deuterium. The ring-opening hydration reaction therefore occurs with hydrogen attack on the 7 position equally from the α and β directions. Since no more than one deuterium atom is incorporated at the 7 position during the hydration, and since this step is not stereospecific, the addition of the deuteron at the 7 position is not reversible under these reaction conditions.

The hydration reaction was also carried out on 3α,5α-cyclocholest-6-ene (1, R = C_8H_{17}) and gave 7-deuteriocholesterol (90% d_1). With 3α,5α-cyclopregn-6-en-20-one (1, R = $COCH_3$),[5] the 7-deuteriopregnenolone formed was contaminated with the 17 epimer and contained four additional deuterium atoms due to the exchange at the 17 and 21 positions; on treatment with acid, only the 7 deuterium (84% d_1) remained; the mixture of the 17 epimers was separated by column chromatography to give pregnenolone-7-*d*.

3α,5α-Cycloandrost-6-en-17-one (1, R = O) and its precursor, 3α,5α-cyclo-6β-methoxyandrostan-17-one (2), were examined by combined GLC–mass spectrometry using the stainless steel gauze, solid injection technique.[12,13] During GLC of the 6β-methoxy compound (2) partial pyrolytic decomposition occurred in the flash heater (245°) to give a GLC peak well separated from that of the methyl ether. The retention time and mass spectrum of this product (M^+ 270) are identical with those of 3α,5α-cycloandrost-6-en-17-one (1, R = O), and different from those of androsta-3,5-dien-17-one, though the 3,5-dien-17-one itself differs only slightly, but significantly, in mass spectrum from 3α,5α-cycloandrost-6-en-17-one. In addition, the mass spectrum of 6β-methoxy-3α,5α-cycloandrostan-17-one (2) (Figure 1) shows a strong *m/e* 270 corresponding to loss of the elements of methanol; the fragmentation pattern below *m/e* 270 is not that of 3α,5α-cycloandrost-6-en-17-one.

Since 7β-deuterio-3β-hydroxyandrost-5-en-17-one[12] was available, it was possible to determine if cis elimination occurred with loss of the 7β-hydrogen during loss of methanol from 6β-methoxy-3α,5α-cycloandrostan-17-one by (a) pyrolysis, (b) electron impact, and (c) alumina catalysis. 7β-Deuterio-3β-hydroxyandrost-5-en-17-one (99% d_1) was

converted to the 3-*p*-toluenesulfonate and thence to 7β-deuterio-6β-methoxy-3α,5α-cycloandrostan-17-one (99% d_1).

(a) The ions at *m/e* 271 (M − CH_4O), and 256 (M − CH_4O-CH_3) showed complete retention of the deuterium; loss of methanol on electron impact involves no loss of 7β-hydrogen, and hence no 1,2-cis elimination.

(b) The product M^+ 270, formed by pyrolytic loss of methanol from the methyl ether in the flash heater, contained only 31% d_1 indicating approximately 70% cis elimination of deuteriomethanol.

(c) On refluxing with xylene and alumina as before, the 7β-deuterio-6β-methyl ether was converted to 3α,5α-cycloandrost-6-en-17-one containing 52% d_1. Although cis elimination is important in both cases, neither pyrolysis nor alumina-catalyzed removal of methanol appears to be stereospecific. It is not known if there is an isotope effect operating in these processes.

The stereochemistry of alumina-catalyzed elimination of methanol in solution has not been studied previously; the dehydration of 1-decalols on passage of the vapor over alumina at 280–400° has been rationalized[14] in terms of a predominantly trans mechanism.

The mass spectra of 3α,5α-cyclosteroids with a 6 double bond or 6β-hydroxy or 6β-methoxy substituents (Figure 1) all show *m/e* 121 as a prominent ion. Since the weight of this fragment does not depend upon the nature of the 17 substituent, it probably corresponds to ring A and part of ring B with cleavage of C-7/8 and C-9/10. The presence of deuterium at C-7 causes this ion of 3α,5α-cycloandrost-6-en-17-one (**1**, R = O) and of 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**) to become *m/e* 122. The relative abundance of *m/e* 121 and 122 indicates 90% retention of deuterium in the ion from **1**, R = O, and 60% from **2**.

Experimental Section

Combined gas–liquid chromatography–mass spectrometry was carried out on an LKB 9000 instrument with helium carrier gas, and OV-1 on Gas-Chrom Q (Applied Science Laboratories, State College, Pa.) as the stationary phase. Samples in the solid state, adsorbed on stainless steel gauze,[13] were injected into the flash heater at 230°, and the chromatographic column was kept at 200° except where otherwise noted. The molecular separator was maintained at 250°, and the ion source at 270°. Melting points were determined on a Kofler block. NMR spectra were measured on a Varian A-60 spectrometer in deuteriochloroform solution. Chemical shifts are reported in parts per million downfield from tetramethylsilane.

3β-Hydroxyandrost-5-en-17-one-*7,16,16-d*$_3$. A solution of 3α,5α-cycloandrost-6-en-17-one (**1**, R = O, 300 mg, 1.11 mmol) in dimethyl sulfoxide (25 ml) with 4 *N* D_2SO_4 in D_2O (5 ml) in a sealed tube was kept at 90° for 24 hr. On cooling, crystals formed in the tube. The solution was diluted with water, when further crystallization occurred. The product was filtered off and washed with water, giving 298 mg (1.03 mmol, 93% yield). Thin layer chromatography and GLC–MS showed the product to be greater than 95% 3β-hydroxyandrost-5-en-17-one (76% d_3, 24% d_2). The NMR spectrum differed from that of authentic nondeuterated material only in the broad singlet at 5.40 ppm (C-6 H); in the nondeuterated steroid this is an ill-defined doublet. Recrystallization from methanol raised the melting point from 131–138° to 147–150°, undepressed on mixing with an authentic sample of 3β-hydroxyandrost-5-en-17-one of mp 149–151°.

3β-Hydroxyandrost-5-en-17-one-*7-d*$_1$. 3β-Hydroxyandrost-5-en-17-one-7(αβ),*16,16-d*$_3$ (240 mg, 0.83 mmol) in methanol (15 ml), water (1.3 ml), and KOH (270 mg) was left at room temperature under N_2 for 5 hr. Extraction (EtOAc), washing (H_2O), and crystallization from methanol gave 3β-hydroxyandrost-5-en-17-one-7-d_1 (215 mg, 90% yield), mp 149–151°. GLC–MS and TLC showed the product to be homogeneous and to contain 94% d_1 and 6% d_0 species. The ir spectrum (CCl_4) showed bands at 2102, 2132 (axial C–D), and 2143 cm^{-1} (equatorial C–D).

Androst-5-ene-3β,17β-diol-*7-d*$_1$ (3). Diglyme was left over a molecular sieve (Linde 4A) for 1 week. Of this, 150 ml and D_2O (15 ml) were mixed and distilled and the fraction boiling at 161–163° was collected and stored in sealed ampoules. 3α,5α-Cycloandrost-6-en-17β-ol (**1**, R = β-OH, 350 mg, 1.30 mmol) in the diglyme (5 ml) and 4 *N* D_2SO_4 in D_2O (5 ml) in a sealed tube was heated to 75°. The crystals of steroid changed rapidly to an oil, but on leaving for 18 hr at 75°, crystals had again appeared. On cooling, the contents of the tube became a crystalline mass. Two recrystallizations of the solid from methanol gave the diol (**3**) (330 mg, 88% yield), mp 175°, undepressed on mixing with authentic material of mp 176–177°. TLC and GLC–MS showed the diol to be >98% pure and to consist of 87 ± 3% d_1 and 13% d_2 species. In a similar run in which some starting material was recovered after 3 hr of reaction, deuterium had been incorporated in the diol, **3**, but not in the recovered starting material.

Chromium trioxide oxidation[6] and conjugation of the diol with 4 *N* hydrochloric acid–acetone (1:5) gave androst-4-ene-3,17-dione (100 ± 3% d_1), together with a minor product, androst-4-ene-3,6,17-trione (0% d_1). The two products were readily separable by GLC and identified by retention time and mass spectrum.

Treatment of androst-5-ene-3β,17β-diol with D_2SO_4–diglyme at 90° for 68 hr, followed by dilution with a large excess of water, and filtration gave crystals of the starting material containing, in two separate runs, 0 and 4% of one excess deuterium atom per molecule.

Chloranil dehydrogenation of the deuterated androst-4-ene-3,17-dione (**4**) was performed as described previously[12] under benzene reflux for 24 hr. The product by GLC–MS showed approximately 87% conversion to the 4,6-dien-3-one (**6**), and contained 49 ± 2% d_1. It was later found convenient to perform the dehydrogenation with 1 mg or less of enone in a sealed tube, and to apply a portion of the reaction solution directly to the stainless steel gauze for injection into the GLC–MS instrument.

6β-Methoxy-3α,5α-cycloandrostan-17-one-*7β-d*$_1$ (2). 3β-Hydroxyandrost-5-en-17-one-7α-$d_{0.04}$-7β-$d_{0.95}$ (100 mg), obtained via reduction of the 7α-bromide-17-ketal with lithium aluminum deuteride,[12] was converted to the 3-*p*-toluenesulfonate, and thence to 6β-methoxy-3α,5α-cycloandrostan-17-one-7β-d_1 (**2**). Chromatography on alumina allowed removal of a minor contaminant of the same molecular weight (M^+ 303), presumably 3β-methoxyandrost-5-en-17-one. Although **2** has not yet been obtained crystalline in this laboratory even after careful chromatography, TLC and NMR evidence indicated that it is homogeneous. GLC–MS (flash heater, 254°) showed peaks for both 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**), retention time 10.8 min, and 3α,5α-cycloandrost-6-en-17-one (**1**, R = O), retention time 8.2 min. The retention times and mass spectra were consistent with the assigned structures on comparison with unlabeled standards. On reducing the GLC flash-heater temperature to 170°, the proportion of 3α,5α-cycloandrost-6-en-17-one decreased. The mass spectrum of the 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**) had M^+ 303, 96% d_1, and prominent fragment peaks at *m/e* 271 (M − 32, M − CH_4O) and 256 (M − 32 − 15, M − CH_4O − CH_3), both of which also correspond to the retention of 96% d_1. The GLC peak corresponding to 3α,5α-cycloandrost-6-en-17-one had molecular ions at *m/e* 270 and 271, 31% d_1.

3α,5α-Cycloandrost-6-en-17-one-*7-d*. 6β-Methoxy-3α,5α-cycloandrostan-17-one-7β-$d_{0.96}$ (5 mg) in xylene (10 ml) with alumina (Brinkmann, activity I, 500 mg) was refluxed for 1 hr. GLC–MS showed 3α,5α-cycloandrost-6-en-17-one to be the major product, but with some remaining starting material (M^+ 303). Chromatography on alumina (1.5 g, activity I) and elution with carbon tetrachloride gave 3α,5α-cycloandrost-6-en-17-one-7-*d*, homogeneous on TLC, mp 124–132°, undepressed on mixing with authentic unlabeled steroid of mp 133–139°. GLC–MS gave a single peak corresponding in retention time and MS to the authentic material; four mass spectral scans were taken approximately evenly spaced over the peak; the ratios of M^+ 270 to 271 showed the presence of successively 59, 54, 51, and 46% d_1 in excess of natural abundance, evidence of isotope separation of GLC; the average of all four, or of the central two scans, gives 52% d_1. In a repeat of the above sequence there was obtained 3α,5α-cycloandrost-6-en-17-one containing 51% d_1.

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trometer was purchased through a special grant from the American Cancer Society (Massachusetts Division).

Registry No.—1 (R = O), 1224-07-03; 1 (R = OH), 55058-89-4; **2**, 55102-65-3; α isomer **3**, 55102-66-4; β isomer **3**, 55058-90-7; 3β-hydroxyandrost-5-en-17-one-7α,16,16-d_3, 55058-91-8; 3β-hydroxyandrost-5-en-17-one-7β,16,16-d_3, 55102-67-5; 3β-hydroxyandrost-5-en-17-one-7α-d_1, 55058-92-9; 3β-hydroxyandrost-5-en-17-one-7β-d_1, 55102-68-6; 3α,5α-cycloandrost-6-en-17-one-7-d, 55058-93-0.

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Interpretation of the Pseudocontact Model for Nuclear Magnetic Shift Reagents. VI. Determination of the Stereoisomeric Relationships of Four Structurally Isomeric Methylbicyclooctenols[1]

M. Robert Willcott, III,*[2] Raymond E. Davis, and Richard W. Holder[3]

Departments of Chemistry, University of Houston, Houston, Texas 77004, University of Texas, Austin, Texas 78712, and Yale University, New Haven, Connecticut 06520

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Assignment of stereochemistry to the four isomeric 5-hydroxy-6-methylbicyclo[2.2.2]oct-2-enes was accomplished by both qualitative and quantitative analyses of lanthanide induced shift (LIS) NMR data. The chemical relationships between these isomers and their epimeric precursors, *endo*- and *exo*-6-methylbicyclo[2.2.2]-oct-2-ene-5-ones, allowed assignment of stereochemical features to these as well. Since some LIS indices could not be assigned accurately, a computer program was designed to use indices of low precision. The combination of auto-assignment (signal assignment by computer) and the ordinary LIS computation distinguished the four isomers by the *R*-factor ratio test. Statistical analysis shows that the distinction is at the 98% or greater confidence level.

The utility of lanthanide shift reagents for clarification of complex nuclear magnetic resonance spectra (LIS–NMR) and the consequent simplification of structural assignments is well established.[4] Quantitative treatment of the lanthanide-induced chemical shift has led to important decisions about the validity of the pseudocontact model,[5] structure verification,[6] and the statistical basis for the evaluations of the agreement factor.[7] Many examples of the properly judicious application of qualitative techniques for structural resolutions also have appeared.[8] We wish to document a technique of serial addition using europium(III) *tris*(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) [Eu(fod)$_3$] which makes possible a convincing qualitative assignment of stereochemistry to four isomeric methylbicyclooctenols. The same data then are treated quantitatively in a useful extension of the *R*-factor method to confirm the stereochemical assignments. The good agreement between the two methods contributes to the literature of corroboration which must be constructed before the *R*-factor method can be trusted in cases where qualitative approaches fail.

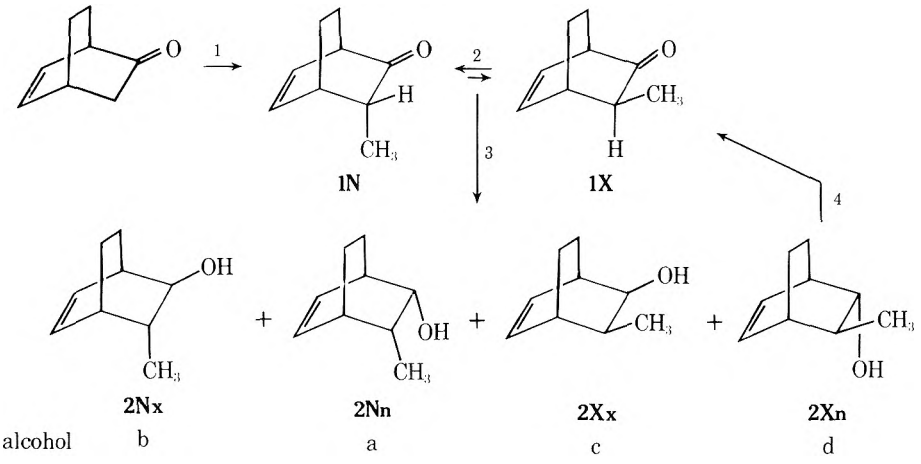
Results

The isomeric ketones *endo*- and *exo*-6-methylbicyclo[2.2.2]oct-2-en-5-one (**1N** and **1X**) and the four isomeric 6-methylbicyclo[2.2.2]oct-2-en-5-ols *endo*-CH$_3$, *endo*-OH (**2Nn**); *endo*-CH$_3$, *exo*-OH (**2Nx**); *exo*-CH$_3$, *exo*-OH (**2Xx**); and *exo*-CH$_3$, *endo*-OH (**2Xn**) were required to identify the thermolysis products in other studies.[10] Scheme I outlines the synthetic procedures used to prepare the required compounds. Prompt work-up of the product of step 1 afforded one of the epimeric ketones (later shown to be **1N**) in pure form. Delayed work-up, or subsequent treatment of **1N** by base, afforded a 65:35 mixture of **1N** and **1X**. Although analytical gas–liquid chromatography (GLC) was adequate to analyze the ketone mixture, all attempts at preparative separation failed.

Reduction of **1N** and the **1N–1X** mixture provided the four isomeric alcohols as shown. These were separated readily and purified by preparative GLC into alcohols a (mp 30–31°), b (mp 67–68°), c (mp 43–44°), and d (mp 82–84°). Jones oxidation of alcohol d, after identification as **2Xn**, afforded ketone **1X** nearly free of epimer **1N**, and proved the only feasible route to this material.

The usual spectroscopic techniques served to confirm the gross structures of compounds **1** and **2** as shown, but except for observation of intramolecular H bonding in alcohols a and d (identifying them[11] as the **2Xn, 2Nn** pair) and notation of the common methyl relationships (**1N**, a + b; **1X**, c + d), definitive stereochemical assignments were not possible. The NMR spectra of alcohols a–d then were run in $CDCl_3$ with both tetramethylsilane (Me_4Si) and $CHCl_3$ internal standards. Each sample was serially treated with successive additions of Eu(fod)$_3$ such that (1) each sample had ca. twice as much Eu(fod)$_3$ as the preceding one, and (2) the final mole ratio of alcohol:Eu(fod)$_3$ was ca. 4:1 (see Experimental Section). NMR spectra were recorded after

Scheme I[a]



[a] Reagents: 1, NaH, CH_3I, glyme; 2, NaH or NaOH; 3, $LiAlH_4$; 4, CrO_3.

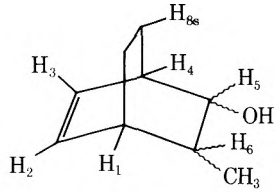
each doping, and decoupling was utilized with the most heavily doped sample to confirm signal assignments. The set of spectra measured for alcohol a is presented as Figure 1; the data for all four alcohols are contained in Table I.

Discussion

Qualitative Approach. The data for each alcohol were plotted as $\Delta\delta$ (LIS shift in parts per million measured from internal Me_4Si or $CHCl_3$) vs. the concentration ratio of alcohol to $Eu(fod)_3$ for each assignable hydrogen. Figure 2 presents the plot for alcohol a. Extrapolation of the shift values to a 1:1 alcohol:$Eu(fod)_3$ molar ratio (line broadening complicates actual measurement of the spectra at this ratio), and selecting the values for the methyl group, H_6, and vinyl protons H_2 and H_3 allows the ready assignment of stereochemistry to the four isomeric alcohols shown in Table II.

These assignments follow from the pattern of extrapolated shifts if the reasonable assumption is made that the Eu atom responsible for the shift perturbations lies spatially

Table I
NMR Chemical Shift Values for Alcohols 2Nn, 2Nx, 2Xx, and 2Xn Doped with Successive Amounts of $Eu(fod)_3$



Alcohol	Ratio alcohol:$Eu(fod)_3$	NMR, δ, ppm							
		H_1	H_2	H_3	H_4	H_5	H_6	H_{8s}	$-CH_3$
2Nn	No doping	2.34	6.56	6.25	2.80	3.96	1.97	*a*	0.88
(a)	64.8:1.0	2.48	6.66	6.42	3.06	4.38	2.16	*a*	1.20
	32.4:1.0	2.64	6.84	6.64	3.34	4.83	2.37	*a*	1.52
	16.2:1.0	2.88	7.12	7.08	3.82	5.60	2.72	*a*	2.12
	8.1:1.0	3.4	7.76	7.76	4.83	7.24	3.4	*a*	3.32
	4.1:1.0	4.44[b]	8.92[b]	9.32[b]	8.84[b]	10.48[b]	4.93[b]	*a*	5.64[b]
2Nx	No doping	2.28	6.30	6.26	2.54	3.30	1.99[c]	1.35[c]	0.93
(b)	61.8:1.0	2.36	6.36	6.32	2.72	3.64	2.20[c]	1.60[c]	1.04
	30.9:1.0	2.44	6.42	6.38	2.90	3.96	2.40	1.84	1.12
	15.4:1.0	2.59	6.52	6.48	3.30	4.64	2.84	2.30	1.33
	7.7:1.0	2.92	6.72	6.71	4.05	5.97	3.70	3.32	1.72
	3.9:1.0	3.56[b]	7.13[b]	7.13[b]	5.64[b]	8.69[b]	5.40[b]	5.30	2.52[b]
2Xn	No doping	2.34	6.80	6.34	2.72	3.40	1.15[c]	*a*	1.12
(d)	62.0:1.0	2.42	6.88	6.46	2.92	3.76	1.45[c]	*a*	1.20
	31.0:1.0	2.52	6.97	6.60	3.16	4.12	1.74[c]	*a*	1.28
	15.5:1.0	2.70	7.16	6.87	3.60	4.82	2.25[c]	*a*	1.46
	7.8:1.0	3.10	7.48	7.48	4.52	6.30	3.46	*a*	1.83
	3.9:1.0	3.85[b]	8.36[b]	8.60[b]	6.24[b]	9.38[b]	5.74[b]	*a*	2.64[b]
2Xx	No doping	2.30	6.61	6.40	2.60	3.88	1.77[c]	*a*	0.97
(c)	68.2:1.0	2.41	6.68	6.46	2.88	4.34	1.96	*a*	1.33
	34.1:1.0	2.54	6.79	6.54	3.22	4.88	2.12	2.77	1.71
	17.1:1.0	2.82	6.98	6.68	3.83	5.92	2.68	3.54	2.41
	8.5:1.0	3.40	7.36	6.95	5.04	7.85	3.56	5.16	3.70
	5.1:1.0	4.04[b]	7.77[b]	7.34[b]	6.41[b]	10.25[b]	4.74[b]	*a*	5.32[b]

[a] Not identified. [b] Identified by double irradiation. [c] Located by extrapolation.

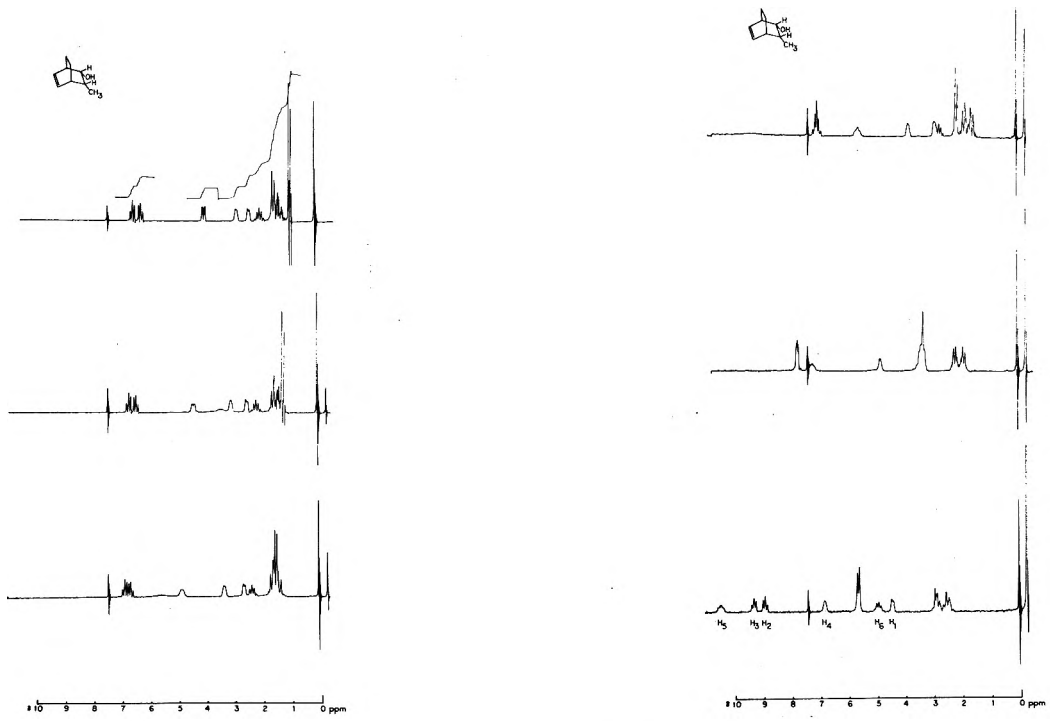
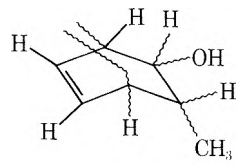


Figure 1. LIS NMR sequence for alcohol a (**2Nn**): a, no Eu(fod)$_3$; b, Eu(fod)$_3$:alcohol = 64.8:1.0; c, 32.4:1.0; d, 16.2:1.0; e, 8.1:1.0; f, 4.1:1.0.

near the oxygen with which it is complexed. Thus the shift magnitudes show that alcohols a and c have OH and CH_3 cis with OH and H_6 trans, alcohols b and d have OH and CH_3 trans with OH and H_6 cis, alcohols a and d have OH endo (near vinyl protons H_2 and H_3), and alcohols b and c have the OH exo (far from the vinyl protons). This pattern, together with the confirming indication from the ir spectra that alcohols a and d are *endo*-OH, and the aforementioned common methyl relationships, completes the stereochemical assignments deduced from the qualitative approach.

Quantitative Approach. For quantitative analysis we have selected to use the more convenient representation of the data in Table I which results from normalizing $\Delta\delta$ for H_5 = 10.0 and forcing the Eu-frequency plot[12] to be linear for each alcohol. These data are contained in Table III.[13] Seven easily assigned resonances, discrete in nearly every experimental spectrum, are shown in partial structure **3** below. The LIS indices for these signals are accurate to 3%.



3

The remaining four resonances, protons 7 and 8 of the ethano bridge, were determined by integration of the spectra and estimation of the possible locations. These four indices are of poor precision (±20%), and cannot be assigned reliably.

We have been investigating local stereochemistry by using partial sets of assigned LIS indices on a routine basis; in this instance we tested four data sets consisting of the seven LIS values for structure **3** vs. each of the four possible geometrical arrangements (**2Nn, 2Nx, 2Xn, 2Xx**). *R* values were obtained for all reasonable locations of the europium relative to the alcohol by a systematic search procedure.[6c] Our experience with the analysis of LIS spectra of

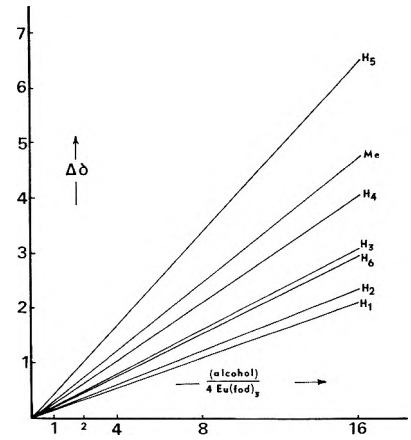


Figure 2. $\Delta\delta$ vs. ratio of added Eu(fod)$_3$ for LIS NMR spectra of alcohol a (**2Nn**).

alcohols led us to select the region in which the C–O–Eu bond angle was 120 ± 20°, the disposition of the europium was away from the steric bulk of the substrate, and the oxygen–europium distance was 2.6 ± 0.4 Å as the "reasonable" locations to investigate. The minimum *R* values obtained in this way for the 16 combinations of data vs. isomer are in Table IV.

Even before applying statistical criteria it is clear that alcohol a accords best with isomer **2Nn** and alcohol d less reliably with isomer **2Xx.** Matching of the two remaining isomers (**2Nx, 2Xn**) with alcohols b and c from *R* factors is not possible at this stage. We were not surprised that isomers **2Nx** and **2Xn** were confused after we realized that the flattened partial structure **3** is enantiomeric for this pair. Note also that an inordinate emphasis is placed on the correct identification of **2Nn.**

A more thorough analysis of the data indicated that inclusion of the poorly determined resonances of the ethano bridge could define all of the structures. We devised a computational feature, auto-assign, to incorporate this additional information. For each lanthanide location during the

Table II
$\Delta\delta$ Extrapolated to 1.0:1.0 Alcohol:Eu(fod)$_3$ Ratio

Alcohol	$-CH_3$	H_6	H_2	H_3	Assignment
a	14.0	8.9	7.0	9.3	**2Nn**
b	4.8	10.2	2.5	2.6	**2Nx**
c	10.8	7.7	2.8	2.5	**2Xx**
d	4.8	13.7	5.1	6.7	**2Xn**

Table III
Chemical Shift Perturbations of Compounds 2

	a	b	c	d
	Assigned Resonances			
H_1	3.22	2.52	2.38	2.73
H_2	3.62	2.61	1.54	1.48
H_3	4.71	3.78	1.61	1.82
H_4	6.18	5.88	5.76	5.97
H_5	10.00	10.00	10.00	10.00
H_6	4.54	7.66	6.30	4.66
CH_3	7.60	2.52	2.95	6.83
	Unassigned Resonances			
H_8	2.3	2.5	7.4	8.0
H_8	2.0	2.0	3.3	4.5
H_7	2.0	2.0	2.2	3.9
H_7	1.7	?	2.2	3.5

systematic search we compute a hypothetical spectrum, match the seven assigned resonances, and select by computer the arrangement of the remaining ethano resonances which produce the lowest overall R factor.[14]

The effect of including the ethano resonances and using auto-assign for the signals due to H_7 and H_8 completes the stereochemical assignments as displayed in Table V. The paired combinations of structure and data omitted from Table V had R factors much larger than those reported in Table IV. The Hamilton statistical tests were carried out as previously described.[7,15] In this testing method, pairwise comparison of four possible structures vs. each data set was made. In this study any one data set points to a single structure, and excludes the other three possibilities. The fact that we found four different structures for the four data set assures the integrity of the PDIGM approach, and encourages the continued use of the LIS method to assess topology.

Conclusions

When all possible stereoisomers of a given set are available it would appear that in many favorable cases qualitative evaluation of NMR data generated by serial additions of a lanthanide shift reagent will allow confident assignment of all stereochemical features. Partial LIS information can be adequate to define the stereochemistry of rigid molecules (such as partial structure **3** vs. **2Nn** and **2Xx** models) even where some members of the stereoisomeric set are absent. Two similar partial sets of experimental data (alcohols b and c) when matched with similar structures (**3**, flattened, makes **2Xn** and **2Nx** enantiomeric) require that less certain LIS indices be introduced to remove the ambiguities.

We are aware that the simplified pseudocontact computational model we have used may be incorrect in several respects. Nevertheless, this interpretation of substrate structure from these LIS data is self-consistent and in complete agreement with the chemical evidence. We will continue to use the pseudocontact model for the interpretation of structure from lanthanide induced shifts until it is shown to give erroneous results.

Table IV
Minimum R Factors for All Structure-Data Pairs. Partial Structure 3

	2Nn	2Nx	2Xn	2Xx
a	4.7	33	38	15.6
b	21.5	5.0	9.0	20.8
c	11.6	5.2	7.8	12.9
d	5.3	30	31	4.1

Table V
Critical Decisions Using Partial Structure 3 and Ethano Bridge Data

	2Nn	2Nx	2Xn	2Xx
a	4.8			
b		6.4	14.0	
c		28	9.2	
d	30.4			5.8

Experimental Section

Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., and by Alfred Bernhardt Microanalytisches Laboratories, Elbach, West Germany. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer as dilute solutions in CCl_4. All reported absorptions were corrected with reference to polystyrene bands in the appropriate spectral regions. Nuclear magnetic resonance spectra were obtained on a Jeolco Minimar 100-MHz instrument. Preparative gas–liquid chromatography (GLC) separations were obtained with a Varian Aerograph Model A-90 instrument equipped with a thermal conductivity detector with helium as the carrier gas. Analytical GLC determinations were carried out using a Perkin-Elmer Model 900 gas chromatograph equipped with flame ionization detectors with nitrogen as the carrier gas. Quantitative GLC analyses resulted from automatic integration of peak areas performed by a Hewlett-Packard digital integrator, Model 3370A. The GLC columns utilized are identified as follows: A, 234-ft capillary TCEP; B, 20 ft × 0.375 in., 20% TCEP on 60–80 Chromosorb P; C, 5 ft × 0.125 in., 5% FFAP on 100–120 Chromosorb P (AW, DMCS); D, 20 ft × 0.375 in., 20% FFAP on 60–80 Chromosorb W.

***endo*-6-Methylbicyclo[2.2.2]oct-2-en-5-one (1N).**[16] A well-stirred mixture of 1.94 g (0.081 mol) of oil-free sodium hydride, 285.0 g (2.0 mol) of methyl iodide (washed with sodium bisulfite, dried, and redistilled), and 400 ml of glyme (distilled from lithium aluminum hydride) was heated to 55°. A solution of 4.25 g (0.035 mol) of bicyclo[2.2.2]oct-2-en-5-one[17] in 20 ml of glyme was added in one portion. From time to time 3-μl aliquots were withdrawn and analyzed by GLC (column A, 115°). After 3.0 hr the analysis showed 10.0% 6,6-dimethylbicyclo[2.2.2]oct-2-en-5-one, 74.7% **1N**, 3.7% *exo*-6-methylbicyclo[2.2.2]oct-2-en-5-one (**1X**), and 11.6% unreacted bicyclo[2.2.2]oct-2-en-5-one. The reaction was quenched by adding 100 ml of water and cooling to 25°. The resulting mixture was poured into 200 ml of water and extracted with petroleum ether, and the extracts were washed thoroughly with water. After drying over magnesium sulfate, flash distillation provided 12 g of material, which was concentrated further to 4.66 g by distilling ca. 8 ml of glyme away. Preparative GLC (column B, 170°) was utilized to obtain pure **1N**. The endo configuration was assigned on the basis of the alcohols derived from it by lithium aluminum hydride reduction (vide infra and Discussion). The following spectral properties were observed: ir (CCl_4) 3050, 2950, 2910, 2865, 1740 (C=O), 760 cm^{-1}; NMR ($CDCl_3$) δ 6.2–5.8 (m, 2, vinyl), 3.04 (m, 1), 2.80 (m, 1), 2.1–1.4 (m, 5), 0.99 (d, J = 7.3 Hz, $-CH_3$). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.83. Found: C, 79.40; H, 8.93.

endo-6-Methylbicyclo[2.2.2]oct-2-en-5-one (1N) and exo-6-Methylbicyclo[2.2.2]oct-2-en-5-one (1X). When quenching and work-up of the product mixture from methylation of bicyclo[2.2.2]oct-2-en-5-one was delayed for an additional 3.0 hr, GLC (column A, 115°) showed that isomerization of the kinetic product (**1N**) had occurred to form a 64.6:35.4 mixture of **1N** and epimer

1X. Alternatively, treatment of pure **1N** with sodium hydroxide in methanol provided the same 64.6:35.4 mixture of **1N:1X**. Although capillary GLC was adequate to analyze these two epimers, attempts at preparative resolution failed.[18] Pure **1X** was obtained only from oxidation of an exo-methyl alcohol as described below.

***endo*-6-Methylbicyclo[2.2.2]oct-2-en-*endo*-5-ol (2Nn) and *endo*-6-Methylbicyclo[2.2.2]oct-2-en-*exo*-5-ol (2Nx).** To a well-stirred slurry of 169 mg (4.5 mmol) of lithium aluminum hydride in 35 mg of dry ether, contained in a dry reaction vessel under a nitrogen atmosphere, was added dropwise a solution of 202 mg (1.5 mmol) of **1N** in 12 ml of ether over a 1-hr period. The resulting gray, heterogeneous mixture was stirred for 16 hr and then worked up by successive dropwise additions of 0.169 ml of water, 0.169 ml of 15% sodium hydroxide, and 0.507 ml of water.[19] After a further 1.5 hr of stirring, during which time the solids turned white and granular, the reaction mixture was filtered. The solids were washed with ether, and the combined filtrate was dried over magnesium sulfate, refiltered, and concentrated by flash distillation through a 10-cm Vigreux column to afford 192 mg (93%) of cloudy, colorless oil. Analysis by GLC (column C, 120°) showed the presence of two components in the ratio 69.2:30.8 in the order of their elution times. The two products were separated preparatively by GLC (column D, 135°).

The major, first-eluting, component was a white, waxy solid, mp 30–31°, and was identified as **2Nn** (alcohol a) on the basis of the following spectroscopic properties (see Discussion): ir (CCl_4) 3630 (O–H), 3595 (intramolecular H bond,[11] remains upon dilution), 3050, 2945, 2870, 1615 (C=C), 1060, 715 cm^{-1}; NMR ($CDCl_3$) δ 6.56 (d of d, $J_{12} = J_{23} = 7.8$ Hz, 1, H_2), 6.25 (d of d, $J_{23} = J_{34} = 7.8$ Hz, 1, H_3), 3.96 (d of d, $J_{56} = 8.0$, $J_{45} = 4.0$ Hz, 1, H_5), 2.80 (broad s, 1, H_4), 2.34 (broad s, 1, H_1), 1.97 (m, 1, H_6), 1.60–1.12 (m, 5), 0.88 (d, $J = 7.0$ Hz, 3, $-CH_3$); the NMR run with sequential additions of Eu(fod)$_3$ is summarized in Table I. Anal. Calcd for $C_9H_{14}O$: C, 78.02; H, 10.21. Found: C, 78.09; H, 10.16.

The minor, second-eluting component was also a white, waxy solid, mp 67–68°. It was identified as **2Nx** (alcohol b) on the basis of its spectroscopic characteristics (see Discussion): ir (CCl_4) 3620 (O–H), 3440 (intermolecular H bond), 3040, 2950, 2940, 2910, 2870, 1630 (C=O), 1010, 710 cm^{-1}; NMR ($CDCl_3$) δ 6.4–6.2 (m, 2, H_2 + H_3), 3.30 (broad s, 1, H_5), 2.53 (broad s, 1, H_4), 2.28 (broad s, 1, H_1), 1.96 (s, 1, OH), 2.0–1.0 (m, 5), 0.93 (d, $J = 6.5$ Hz, 3, $-CH_3$); the NMR run with sequential additions of Eu(fod)$_3$ is summarized in Table I. Anal. Calcd for $C_9H_{14}O$: C, 78.02; H, 10.21. Found: C, 77.97; H, 10.26.

***exo*-6-Methylbicyclo[2.2.2]oct-2-en-*endo*-5-ol (2Xn) and *exo*-6-Methylbicyclo[2.2.2]oct-2-en-*exo*-5-ol (2Xx).** Using 708 mg (5.2 mmol) of an equilibrium mixture of **1N:1X** (66.4:33.6, obtained by base-catalyzed epimerization of **1N**, vide supra) and 590 mg (15.6 mmol) of lithium aluminum hydride, the above-described reduction procedure and work-up provided 680 mg (94%) of milky-white semisolid. Analysis by GLC (column C, 120°) showed four components in the ratio 46.0:16.8:20.4:16.8 (order of elution times). All four products were obtained pure by preparative GLC (column D, 135°). The first-eluting component proved to be **2Nn** and the third-eluting component was **2Nx**. The second-eluting component, a white solid, mp 82–84°, was identified as **2Xn** (alcohol d) by the following spectroscopic properties (see Discussion): ir (CCl_4) 3600 (O–H), 3580 (intramolecular H bond,[11] remains upon dilution), 3360 (intermolecular H bond, disappears upon dilution), 3027, 2930, 2860, 1635 (w), 1050, 715 cm^{-1}; NMR ($CDCl_3$) δ 6.80 (d of d, $J_{12} = J_{23} = 7.5$ Hz, 1, H_2), 6.34 (d of d, $J_{23} = J_{34} = 7.5$ Hz, 1, H_3), 3.40 (slightly broadened s, 1, H_5), 2.72 (broad s, 1, H_4) 2.34 (broad s, 1, H_1), 1.8–0.8 (m, 6), 1.12 (s, 3, $-CH_3$, coincident with H_6); the NMR run with sequential additions of Eu(fod)$_3$ is summarized in Table I. Anal. Calcd for $C_9H_{14}O$: C, 78.02; H, 10.21. Found: C, 78.24; H, 10.12.

The fourth-eluting component, a white solid, mp 43–44°, was assigned the structure of the only remaining isomer, **2Xx** (alcohol c), on the basis of its spectroscopic properties (see Discussion): ir (CCl_4) 3610 (O–H), 3450 (intermolecular H bond, disappears upon dilution), 3027, 2930, 2870, 1625 (w), 1020, 705 cm^{-1}; NMR ($CDCl_3$) δ 6.61 (d of d, $J_{12} = J_{23} = 7.5$ Hz, 1, H_2), 6.40 (d of d, $J_{23} = J_{34} = 7.5$ Hz, 1, H_3), 3.88 (d of d, $J_{56} = 8.3$, $J_{45} = 4.0$ Hz, 1, H_5), 2.60 (broad s, 1, H_4), 2.30 (broad s, 1, H_1), 2.0–1.0 (m, 5), 1.67 (s, 1, OH), 0.97 (d, $J = 7.5$ Hz, 3, $-CH_3$); the NMR run with sequential additions of Eu(fod)$_3$ is summarized in Table I. Anal. Calcd for $C_9H_{14}O$: C, 78.02; H, 10.21. Found: C, 78.11; H, 10.12.

***exo*-6-Methylbicyclo[2.2.2]oct-2-en-5-one (1X).** A solution of 47.1 mg (0.34 mmol) of **2Xn** in 30 ml of acetone over 250 mg of sodium sulfate was cooled to −5° in an ice–acetone bath. Jones reagent[20] was added dropwise with stirring until a pale orange color persisted for 5 min. Two drops of 2-propanol was added to discharge the orange color. The reaction solution was filtered and the solids were washed with acetone. The combined filtrates were concentrated by rotatory evaporation to a pale blue-green oil which was taken up in 50 ml of ether, washed once with saturated sodium chloride, and dried over sodium sulfate. Filtration and concentration afforded a yellow oil (35.2 mg) which upon GLC analysis (column A, 95°) proved to be a 75:25 mixture of **1X:2Xn**. Purification by GLC (column B, 140°) provided 12.6 mg (36%) of **1X**, contaminated by <3% **1N** from epimerization under the mild Jones conditions. The structure was assigned by the method of synthesis and the following spectral properties: ir (CCl_4) 3050, 2980, 2960, 1730 (C=O), 1120, 720, 715, 675 cm^{-1}; NMR ($CDCl_3$) δ 6.58 (d of d, J = 7.5 Hz, 1, H_3 or H_2), 3.08 (broad s, 1, H_4 or H_1), 2.76 (broad s, 1, H_1 or H_4), 2.2–0.8 (m, 5), 1.08 (d, $J = 8.0$ Hz, 3, $-CH_3$). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.83. Found: C, 79.10, H, 8.97.

Reduction of 1X. The stereochemical integrity of the Jones oxidation used to isolate **1X** was demonstrated further by reducing 7.7 mg (0.06 mmol) of **1X** with lithium aluminum hydride according to the procedure described above. Work-up provided an ethereal solution which GLC analysis (column C, 115°) showed to contain only **2Xn** and **2Xx** in the ratio 53:47. No trace of **2Nn** or **2Nx** was present.

Procedure for Measuring Eu(fod)$_3$-Doped NMR Spectra. Using the case of **2Nn** for an example, 32.1 mg (0.232 mmol) of pure **2Nn** was dissolved in the minimum amount of $CDCl_3$, which contained 3% tetramethylsilane and 3% $CHCl_3$ as a double internal standard,[21] and the spectrum was run. Enough Eu(fod)$_3$ was dissolved in a second portion of solvent to ensure a final doping ratio of 4:1 alcohol:Eu(fod)$_3$; in this case 59.3 mg (0.057 mmol) was used. An aliquot of the Eu(fod)$_3$ solution was added to the NMR tube, and the spectrum was run again.[22] The process was repeated, with aliquot sizes calculated so that each doping ratio was twice the preceding one. In this case the ratios were **2Nn**:Eu(fod)$_3$ = 64.8:1.0, 32.4:1.0, 16.2:1.0, 8.1:1.0, and 4.1:1.0. Signal assignments were made on the most highly doped sample with the aid of extensive decoupling experiments, and then each resonance was tracked back as described in the Discussion section using such plots as Figure 2. The data generated for the four alcohols are summarized in Table I.

Acknowledgment. The authors are grateful to Professor Jerome A. Berson for advice and encouragement.

Registry No.—**1N**, 53626-33-8; **1X**, 53626-32-7; **2Nn**, 54446-71-8; **2Nx**, 54515-25-2; **2Xn**, 54515-26-3; **2Xx**, 54515-27-4; bicyclo[2.2.2]oct-2-en-5-one, 2220-40-8; Eu(fod)$_3$, 17631-68-4.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of R. W. Holder, Yale University, 1972. Financial support of this investigation under National Science Foundation Grant GP-33909x and the Robert A. Welch Foundation Grants E-183 and F-233 is gratefully acknowledged.
(2) John Simon Guggenheim Memorial Fellow, 1972–1973, University of Houston.
(3) National Science Foundation Graduate Fellow No. 8700-35-45821, 1968–1972. Address comments regarding the synthetic aspects of this work to this author at Chemistry Department, University of New Mexico, Albuquerque, N Mex. 87131.
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(14) We have observed repeatedly that the algorithm auto-assignment[23] finds an L-S complex which has the smallest possible *R* factor for that data set under investigation. In the event that we auto-assign all resonances in a molecule whose resonances were independently identified, we recover the correct L-S array. In one or two cases we find a second L-S array, with some assignments differing, which was characterized by a smaller *R* factor. In general, we find that it is an excellent screening device since poor structures give large minimum *R* values and these can be rejected with confidence.
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(16) We thank Dr. Guilford Jones, II, for details of this procedure.
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(18) Methods tried included a number of preparative GLC columns, washing ethereal solutions with aqueous silver nitrate or sodium bisulfite, and column chromatography on silver nitrate–silica gel.
(19) Procedure of C. K. Steinhardt as described by L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 584.
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(21) These two markers are shifted upfield due to a bulk susceptibility effect, but they maintain the same 7.26-ppm relationship and thus serve as reference points for the measurement of all the signals. This is useful, especially since $Eu(fod)_3$ itself has a strong absorption near tetramethylsilane.
(22) The instrument often needs retuning for each new doping ratio. A delay of several minutes between placing the doped sample in the probe and running the spectrum minimizes the retuning problem.
(23) The program PDIGM includes the autoassign algorithm. Copies of the program are available on request from R.E.D. or M.R.W.

Synthesis and Properties of Some Heterocirculenes[1]

J. H. Dopper and Hans Wynberg*

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

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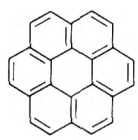
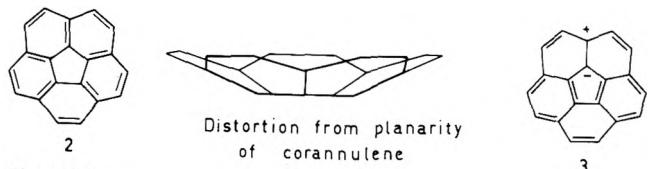
The synthesis of some heterocirculenes is reported. Based on a model study, we recognize two classes of circulenes, namely planar and nonplanar ones. Depending on the ratio of the outer and inner radii, bowl-shaped and corrugated nonplanar circulenes may exist. Attempts to prove that [7]-heterocirculenes belonged to the corrugated type of circulenes failed. The spectral characteristics of heterocirculenes are reported in detail.

Coronene and Corannulene. Coronene (1) is unique in the family of polycyclic aromatic compounds.[2] It has been of interest for many years not only because of its symmetric graphite-like structure but also because its synthesis continues to present a challenge to the ingenuity of the organic chemist. Scholl and Meyer announced in 1932 the first synthesis of **1**.[3a] Since then others have reported improved



1

syntheses of **1**.[3bc] The high symmetry of the coronene molecule is of great value in the interpretation of spectroscopic results and their mathematical treatment. Coronene is an alternant hydrocarbon. According to the Hückel approximation there is no net charge on any atom in the system and the energy levels are symmetrically placed about the value of the α integral.[4] A complete determination of the coronene structure has been obtained by X-ray analysis.[5] It is a completely flat molecule. The carbon–carbon length varies in different parts of the molecule. The central ring and the "spokes" connecting it to the outer edges have bond lengths of 1.43 Å. The outer bonds are of two types measuring 1.41 and 1.38 Å. The planarity of coronene—and its many benzoid homologs—is an obvious consequence of the angular fusion of six benzene rings in the manner indicated (see **1**). When the number of aromatic rings—angularly annulated to form a "coronene"—deviates from six, the possibility of nonplanarity arises. A classical example of this type of molecules is corannulene (**2**), first prepared and studied by Barth and Lawton.[6] It has attracted much interest because despite its coronene-like structure it differs from the latter in two essential features. (a) Corannulene is a nonplanar, highly strained molecule. X-Ray analysis[6] demonstrates that it has a bowl-like shape (Figure 1). (b) Corannulene is a nonalternant hydrocarbon.[4] According



2 3

Figure 1.

to the Hückel theory, the electronic charge on each carbon atom differs in the ground state from one. An attractive way to accommodate this charge separation is found in structure **3**, in which two concentric annulene systems are formed. Both the cyclopentadienyl anion as well as the cyclopentadecaheptaenyl cation obey the well-known Hückel $4n + 2$ rule. SCF–MO calculations carried out by Gleicher[7] support the idea that **3** contributes to the stability of the ground state. However, no experimental data have been presented which substantiate any contribution from **3**.

Results of a Model Study. The structural differences between **1** and **2** (planarity vs. nonplanarity) can be made clearer by the following considerations. It is assumed that there are two circles of fixed diameter both of which are (within moderate limits) flexible. These circles (radii $r1$ and $r2$, $r1 < r2$) are connected by spokes of a constant length a (Figure 2).

The optimal geometry will be determined by the following factors.

(a) If $r1 + a = r2$ then both circles will lie in a common plane (Figure 2a), as in coronene (**1**).

(b) If $r1 + a > r2$ then a likely geometry is one in which

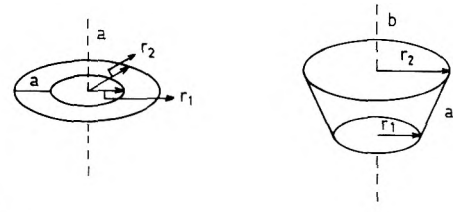


Figure 2.

the two circles lie in parallel planes (Figure 2b), as in corannulene (2).

(c) If $r1 + a < r2$ then the "extra" diameter of the outer circle is taken up by forming an unending wave; in other words, the system becomes corrugated. Molecular models indicate that this can be exemplified by the conformation of the hitherto unknown compound 4 (Figure 3).

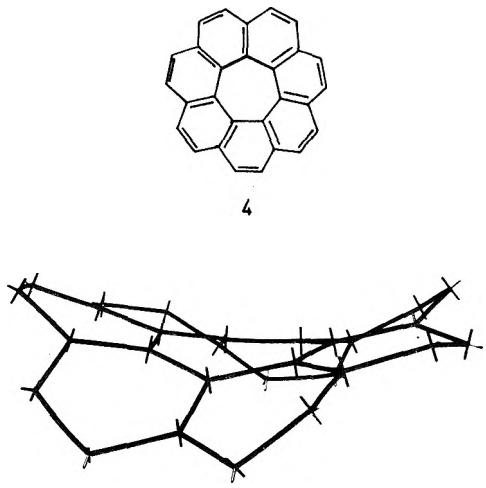
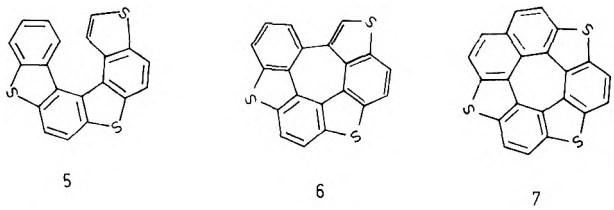


Figure 3.

$r1$ and $r2$ can be varied endlessly. Consequently the number of possible molecules which conform to these restraints is almost unlimited. Since the term "coronene" is firmly established to one compound and because of their circular arrangement of aromatic rings, it is proposed that this class of molecules be called *circulenes*.[8] A [m]-circulene is then a circulene constructed out of m aromatic rings. A circulene in which one or more aromatic rings are replaced by a heterocyclic ring will be called a heterocirculene.

Heterocirculenes. A study of the preparation of heterohelicenes was started around 1966 by Groen and Wynberg.[10,11] By 1971, the synthetic pathways leading to heterohelicenes were improved in such a way that these helicenes were "available" for a further study.

Among the many points of interest was the question of transannular effects. This led to the preparation of **6**, a compound in which the two helical termini of **5** are connected by a σ bond. Molecules like **6** were called dehydrohelicenes.[12] This compound was of particular interest to us because in its structure a great deal of that of the [7]-heterocirculene **7** was realized. Moreover, simple models



suggested that this circulene **7** could have the nonplanar corrugated structure proposed above. (The limits of bond length adjustments which might keep a "corrugated" circulene planar are not known, of course.) One other early example of a heterocirculene exists. Erdtman and Högberg[13] cyclized a number of quinones under the influence of acids. The [8]-heterocirculene **8** is obtained in low yield when *p*-benzoquinone is treated with a mixture of sulfuric acid, acetic acid, and water (Figure 4). The authors expect **8** to be planar or nearly planar. The structure of **8** has not yet been determined by X-ray analysis.

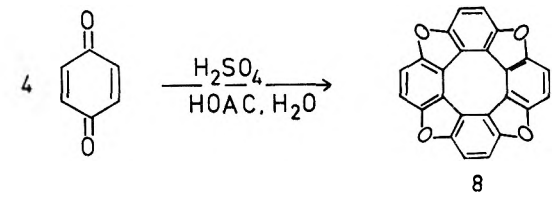


Figure 4.

The Preparation of Heterocirculenes. Patterned after the Diels–Alder addition of maleic anhydride to perylene,[3b] we found that when the dehydrohelicene **6** was allowed to react with maleic anhydride in the presence of chloranil as

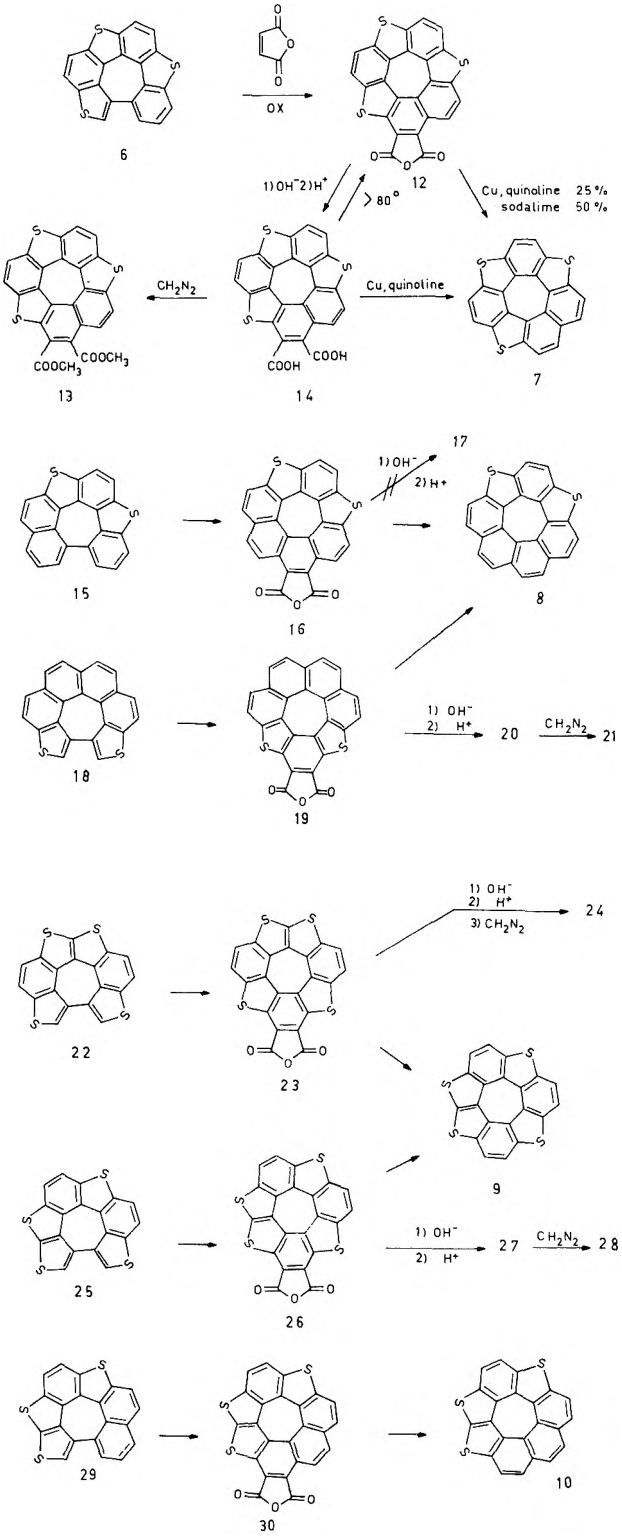


Figure 5.

oxidizing agent, the red anhydride **12** (mp above 400°) was obtained in 65% yield (Figure 5). When the reaction was carried out without an oxidizing agent no reaction was observed and the starting materials were recovered completely. Chloranil was superior to sulfur, nitrobenzene, or oxygen as an oxidizing agent. The anhydride **12** was only slightly soluble in nitrobenzene and quinoline whereas it was almost completely insoluble in common organic solvents. From **12** no NMR, uv, and MS could be obtained. Its ir spectrum showed the principal absorptions at 1825 and 1722 cm^{-1}, absorptions characteristic for the anhydride moiety.

The anhydrides **16, 19, 23, 26,** and **30** were prepared by the same method and are shown in Figure 5.

In Diels–Alder reactions of this type maleic anhydride has some distinct advantages. It is a reactive but stable dienophile which can withstand high temperatures for long reaction periods. This in contradistinction to dienophiles like dicyanoacetylene, which is known to polymerize at higher temperatures.[14] An additional important factor is the insolubility of the obtained anhydrides, which makes them easy to isolate from the reaction mixtures. When instead of maleic anhydride, dicyanoacetylene or dimethyl acetylenedicarboxylate were used as dienophiles, very complex reaction mixtures were obtained from which no definite products could be isolated. With acrylonitrile no reaction was observed. Somewhat better results were obtained when methyl propiolate was used. The addition product **31** was obtained in 34% yield when **18** was allowed to react with methyl propiolate at 130° for 48 hr (Figure 6). When **31** was hydrolyzed an acid **32** was obtained which upon decarboxylation gave the heterocirculene **8** in 40% yield.

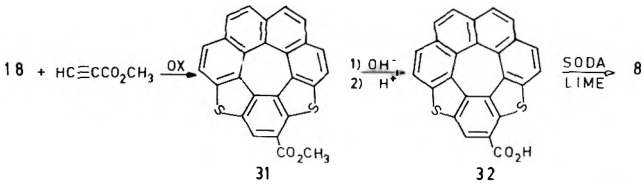
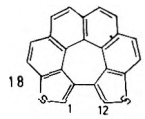
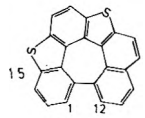
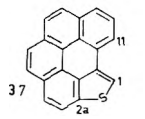


Figure 6.

The Para-Localization Energies.[15,16] The yields in which the anhydrides are formed from the corresponding dehydrohelicenes vary from 17 to 70%. This indicates that the dehydrohelicenes differ from one another in their reactivity toward Diels–Alder additions. For the two isomeric dehydrohelicenes **15** and **18** we calculated the para-localization energies for the positions indicated in Table I using HMO methods.[4,17] The results are in agreement with the experimental data.

Table I

Compd	Diels–Alder yield, %	Para-localization energies (Dewar) in β units	Positions	Para-localization energies (Brown) in β units
	60	3.712	1.12	3.120
	17	4.624	1.12	4.140
		4.053	1.11	3.640
		4.392	1.2[a]	3.777

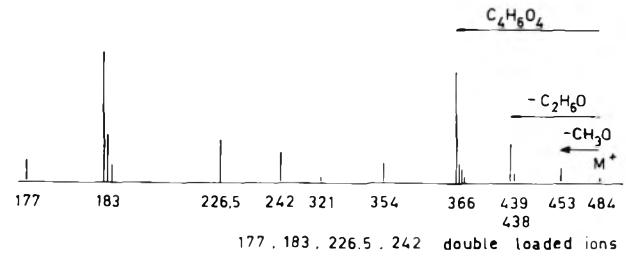


Figure 7. Mass spectrum of **13**.

Hydrolysis of the Anhydrides. A. Results. The anhydrides described in the preceding section were further identified by conversion into the corresponding dimethyl esters (Figure 5). A case in point was **12**, which, when treated with dilute base for 30 min, gave a pale yellow salt which furnished the diacid **14** upon acidification. This acid was rather unstable. As soon as it was formed it started to revert into **12.** Consequently **14** was isolated as quickly as possible and transformed directly into the dimethyl ester **13** by treatment with diazomethane. Relative to **12** the dimethyl ester was easier to handle and it could be chromatographed and recrystallized as in normal working-up procedures. However, its solubility was still too low to allow a well-resolved NMR spectrum to be obtained. Its mass spectrum is shown in Figure 7. The main features of this spectrum are typical for compounds related to dimethyl phthalate. Above its melting point or by treatment with 48% HBr **13** is transformed again into **12.** When **16** was treated with a dilute NaOH solution the corresponding disodium salt was easily obtained. Upon careful acidification a dark yellow compound, presumably the dibasic acid **17,** was obtained but before it could be filtered and dried it had reverted completely into **16.** The diacids **20** and **27** were much more stable. They can be stored for hours and are thermally stable to at least 100°. Clearly the stability of these diacids is of the following order (Figure 8).

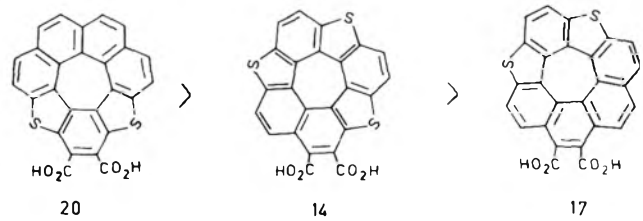


Figure 8.

B. Discussion. Phenanthrene-9,10-dicarboxylic acid (**33**) is unknown to date.[18] The instability of this compound is ascribed to the presence of β hydrogen atoms next to the carboxyl groups. These atoms are believed to bring the carboxyl groups closer together than, for instance, in phthalic acid. The angle between the C–COOH bond and the plane of the C=C bond is decreased to less than 123° (the corresponding angle in phthalic acid). The result is an increased interaction between the two carboxyl groups and consequently anhydride formation will be preferred. Bruice and Pandit[19] reported that the rate of anhydride formation is greatly enhanced when the free rotation of the reacting carboxyl groups is restricted. Molecular models show clearly that the β hydrogen atoms in **33** (Figure 9) indeed cause a

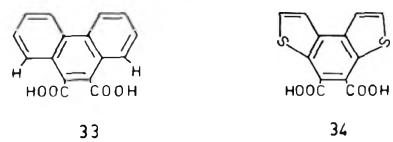


Figure 9.

Table II
Mass Spectra of the Heterocirculenes

Compd	M^+	M - S	M - H_2S	M - CHS	M - CH_3S	M - C_2S_2	M^{2+}
7	100	2	2	2	4		40
9	100			8		3	80
8	100	2	4	3	3		35
10	100	2	2	2	2		50
11	100	2		2	2		32

restricted rotation of the carboxyl groups. However, these β hydrogen atoms are no longer present in **34**, where the two outer benzene rings are replaced by thiophene rings. In this compound rotation is no longer restricted and as a result this acid is expected to be much more stable than **33**. This is in full accordance with the experimental results presented in this section.

Decarbonylation of the Anhydrides. The Heterocirculenes. The heterocirculenes were obtained by decarbonylation of the corresponding anhydrides (Figure 5). The decarbonylation could be effected either by prolonged boiling with copper powder in quinoline or by pyrolysis with soda lime. The first method gave poor results. The anhydrides were only partially decarbonylated and the heterocirculenes were not obtained in a yield higher than 20%. Decarbonylation with soda lime is a method used frequently in the synthesis of polyaromatics.[3b] Normally the anhydride is heated together with the soda lime at 400° for several hours and from the reaction mixture the hydrocarbon is removed by sublimation. The heterocirculenes described in this paper were stable enough to survive 400° and they were isolated by this method in about 50% yield.

The heterocirculenes crystallized from *p*-xylene in long, thin needles. They have a green-yellow color and show a weak fluorescence in solution. They do not melt but decompose very slowly above 350°. They are sparingly soluble in common organic solvents, making CAT NMR spectroscopy mandatory. From the circulene 8 a picrate (anthracite colored) was obtained which did not melt but instead decomposed over a wide range. The heterocirculenes show in their mass spectra as the only significant peaks the singly and doubly charged molecular ions. Low-intensity fragments $M - S^+$, $M - H_2S^+$, and $M - CHS^+$ could be detected. The mass spectral data of the heterocirculenes are collected in Table II.

Structure Proof of the Heterocirculenes. The conversion helicene → circulene represents in effect the addition of two carbon atoms to the helicene to form a new cyclic system containing an extra benzene ring. This means that identical circulenes can be prepared from different helicenes as indicated below (Figure 10). Based on this approach the circulene **9** was prepared from both the helicenes **35** and **36**. This two-way synthesis of **9** verifies unambiguously the structures of the heterocirculenes as well as the structures of the intermediate dehydrohelicenes.

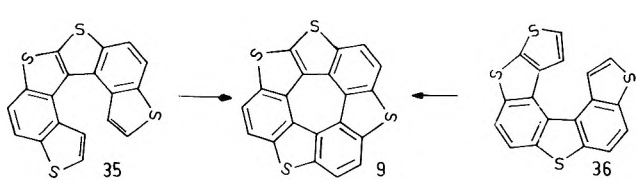


Figure 10.

Synthesis of Thiacoronene. Boekelheide[20] has recently reported the isolation of the heterocirculene **11**, called thiacoronene. It should be noted that **11** belongs theoretically

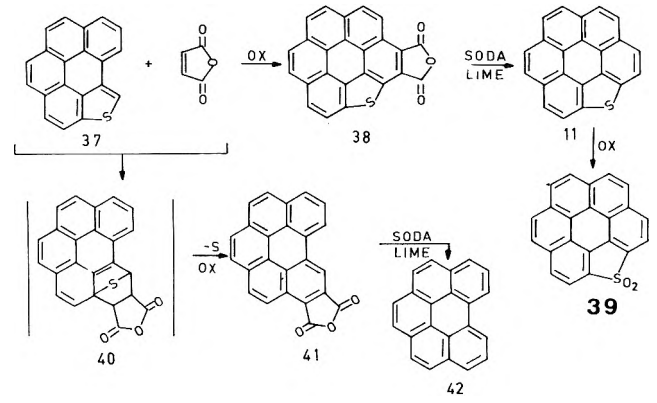


Figure 11.

to the corannulene class of circulenes, that is, it might be bowl shaped. It appeared that our route to thiacoronene, namely via the dehydrohelicene **37**, would allow **11** to be readily prepared. Nevertheless this apparently straightforward synthesis deserves some comment.

The Diels–Alder addition of maleic anhydride to the dehydrohelicene **37** furnished a mixture of anhydrides (Figure 11). The presence of anhydride functions was demonstrated by ir spectroscopy. The mixture showed absorptions at 1820 and 1760 cm^{-1}. Elemental analysis of the purified anhydrides gave a lower sulfur percentage than calculated for **38**. The anhydride mixture was not purified any further, but was directly decarboxylated with soda lime. A careful analysis of the reaction mixture showed the presence of at least five products. Mass spectral analysis of the mixture showed molecular ions at *m/e* 350, 306, and 276. The compound with M^+ *m/e* 350 could not be isolated or identified. The compounds with M^+ *m/e* 306 and 276 could be obtained pure and were identified as **11** and **42**. The uv spectrum of thiacoronene was found to be identical with that recorded by Boekelheide[20] et al. The reason for the formation of more than two different anhydrides during the Diels–Alder addition is not understood at the moment. The presence of **42** as a reaction product can be explained by assuming a 1,4 addition of maleic anhydride to the thiophene ring of **37**.[21] From the intermediate **40** sulfur is lost and the resulting anhydride **41** is decarboxylated to **42**.

The values of the para-localization energies for the different sites of adduct formation in **37** are shown in Table I. These values support the possibility of a Diels–Alder addition to the thiophene ring of **37**. However, the very low yield in which **11** is formed cannot be blamed on this side reaction, because the calculations predict additions to take place almost exclusively at the 1,11 position. Thiacoronene sulfone (**39**) was obtained by oxidation of **11** with *m*-chloroperbenzoic acid in methylene chloride. Only 0.8 mg of **39** was obtained and from this material only a mass spectrum was taken. The spectrum is shown in Figure 12. This spectrum has an interesting feature. The sulfone loses little or no oxygen directly [1% relative abundance for (M − 16) peak, 3% for the (M − 32) peak]. Instead the most predominant peak in the spectrum, *m/e* 290, appears to be due to the formation of an oxacoronene ion **46** (Figure 13). A similar fragmentation has been observed in sulfones of a related structure.[22] However, the intensity of the fragmentation

Figure 12. Mass spectrum of **46**.

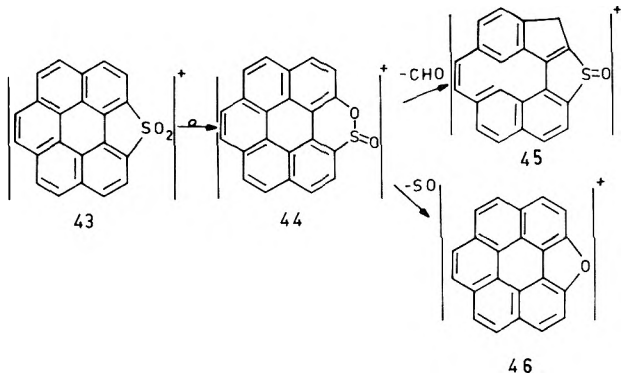
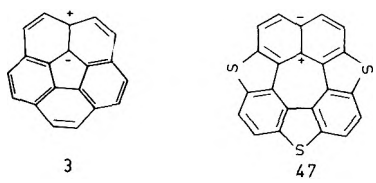


Figure 13.

representing **46** is unusually large, demonstrating the greater stability of the latter. The formation of the oxacoronene ion can best be explained[23] by a rearrangement of **43** to the cyclic sulfinate ester **44**, which either eliminates HCO or SO.

Spectral Properties of the Heterocirculenes. NMR Spectra. Charged structures like **3** and **47** may contribute



respectively to the ground state of **2** and **7**. If they do so, a direct influence of this charge distribution on the ^1H and ^{13}C chemical shifts in the NMR spectra is predicted.[24] However, Barth and Lawton[6] did not publish the ^{13}C NMR spectrum of **2** and because of the limited solubility of the heterocirculenes in NMR solvents, no ^{13}C NMR spectra of these molecules could be obtained. The ^1H signal of **2** is found at δ 7.80 ppm, a value little changed from that of benzene. The ^1H NMR spectra of the heterocirculenes are given in Figure 14. They all consist of multiplets centered about δ 7.6 ppm. These are normal values for condensed sulfur heterocycles. Hence, the ^1H chemical shifts in the NMR spectra of the heterocirculenes give no significant indication for a polarization in the ground state.

Uv Spectra. The uv spectra of the heterocirculenes are drawn in Figure 15. The uv spectra of the [7]-heterocirculenes show resolved bands with much vibrational structure. They resemble the uv spectra of the corresponding dehydrohelicenes.[12] Relative to those dehydrohelicenes a 10–20-mμ red shift of the longest wavelength band is observed. A much larger red shift is observed when the longest wavelength band of a thiophthene[25] containing heterocirculene is compared with those of its corresponding dehydrohelicene.[12] Red shifts up to 62 mμ were found. The uv spectrum of **9** does not differ essentially from that of **7**![12] To account for these results the uv spectra of **7** and **9** were calculated[26] by PPP type of semiempirical SCF–MO calculations.[27] In these calculations, limited configuration interaction was employed by taking into account all singly excited states corresponding to excitation of an electron from the four highest occupied orbitals into the four lowest vacant orbitals. In the calculations the molecules were assumed to be flat and the geometry was based on the known bond lengths and bond angles of thiophene[28] and benzene.[29] Electron repulsion integrals were evaluated with the aid of the Nishimoto and Mataga[30] approximation. The variable β modification of the PPP method[31] has been employed, using the following parameters:[32] I_c = 11.22, γ_{cc} = 10.53 and $\beta_{cc} = -0.51p - 1.84$ eV; I_s = 20.00, γ_{ss} = 10.84 and $\beta_{cs} = -1.625$ eV. The results are given in Tables III and IV.

As can be seen from the results in Table IV, the calculations predict the general features of the uv spectra very well. The uv spectrum of thiacoronene (**11**) corresponds very closely to that of coronene[2] itself. It is almost identical with respect to the nature and position of the absorption bands. The intensity of the absorption bands differs somewhat. Relative to coronene the α band has a higher and the β band a lower intensity.

ESR Spectra. Radical anions of the heterocirculenes **7** and **9** were obtained by electrolysis in DMF. They were generated in a 10^{-3} *M* solution at a constant current of 10 μA. Using this procedure 10^{-2} *M* supporting electrolyte

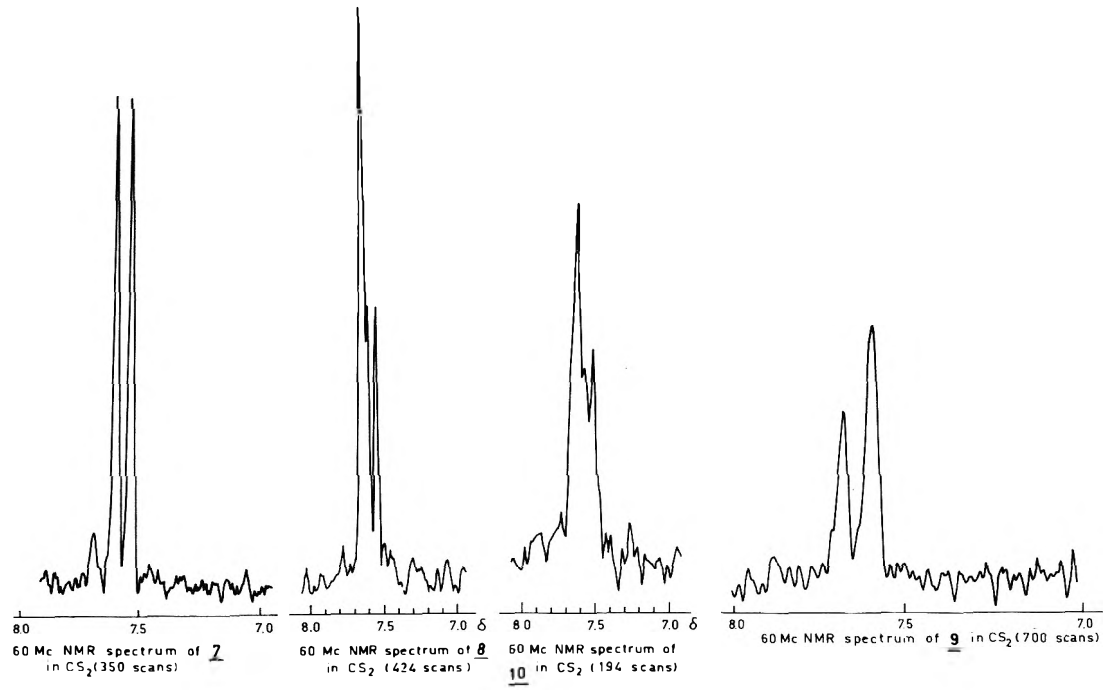


Figure 14.

Table III
Experimental and Calculated Transitions of the Heterocirculenes 7 and 9 (λ_{max}, mμ)

Compd	Experimental nm (log ε)	Calculated nm (f)
9	425 (2.92), 399 (3.14), 383 (3.60), 363 (3.55), 233 (4.32), 318 (4.20), 288 (4.47), 275 (4.65)	390 (0.05), 348 (0.06), 336 (0.29), 323 (0.72), 292 (0.01), 283 (0.48), 280 (1.61), 274 (0.29), 264 (0.53), 257 (0.00), 256 (0.05), 252 (0.04), 230 (0.07), 226 (0.15)
7	431 (2.40), 408 (2.90), 387 (3.25), 369 (3.35), 357 (3.54), 311 (3.82), 289 (4.10), 258 (4.40), 240 (4.20)	390 (0.04), 366 (0.16), 359 (0.38), 352 (0.14), 299 (0.83), 287 (0.54), 286 (0.24), 282 (0.18), 276 (0.04), 275 (0.47), 257 (0.98), 254 (0.70), 238 (0.17), 233 (0.11)

Table IV
The Red Shift Δλ of the Longest Wavelength Absorption of the Heterocirculenes Relative to the Corresponding Dehydrohelicenes

Compds	Δλ obsd, mμ	Δλ calcd, mμ
6 → 7	18	6
25 → 9	49	30
22 → 9	62	40

tetraethylammonium perchlorate (TEAP) was suitable. The resulting ESR spectra of the radical anions of **7** and **9** are shown in Figure 16. The assignment of the different hyperfine splitting constants was made by comparing them with the theoretical values obtained by McLachlan's approximate SCF method[33] and the McConnell relationship.[34] The results are summarized in Table V.

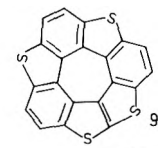
Correlation between Nonplanarity and Optical Activity. Preparation of a Methylated Circulene. Optical activity of a suitable circulene would be prima facie evidence for nonplanarity. Nonplanar circulenes can be bowl shaped or corrugated and a qualitative way to discriminate

Table V
Splitting Constants of the Circulene Radical Anions

Compd	Splitting constants, G a_{H1}	a_{H2}	a_{H3}	a_{H4}	
7	2.0	0.2	1.25	3.35	obsd
	1.494	−0.348	1.316	5.959	calcd
9	2.6	0.5	3.8		obsd
	3.071	0.420	3.289		calcd

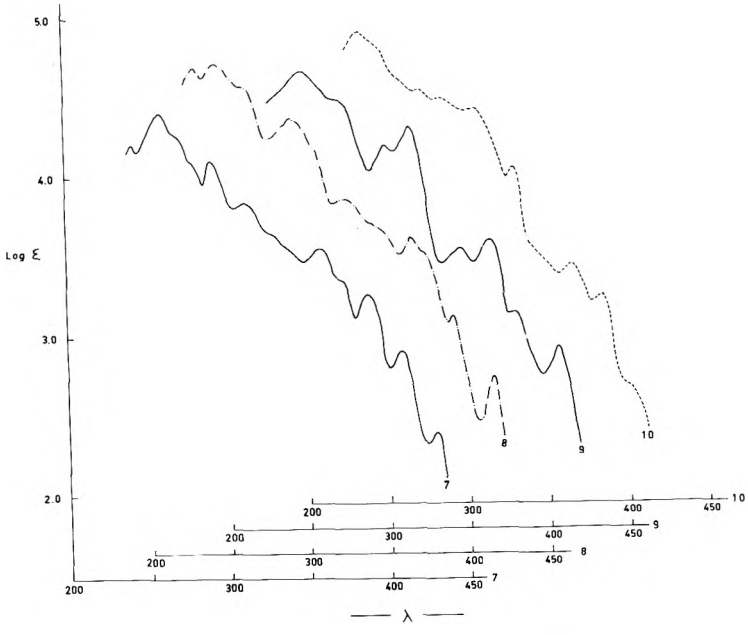
between these molecules is based on the geometry of the aromatic rings from which the circulene is constructed. The internal angle (the angle between two carbon–carbon double bonds) of a benzene ring is 60°, whereas those for thiophene[35a] and furan[35b] are 45 and 30°, respectively (Figure 17). In order to obtain a circulene which is approximately strain-free the sum of these angles need to be 360°. This is the case in coronene (**1**) and in the heterocirculene **9**. We

360° = 6 × 60°



360° = 3 × 60° + 4 × 45°

know from coronene that it is a planar molecule[5] and most probably **9** is also planar. When the sum of the individual internal angles differs from 360° the construction of a circulene will be attended with introduction of additional strain energy. The difference between bowl-shaped and corrugated circulenes is that in the former the sum of these angles is less than 360° and in the latter more than 360°. In corannulene (**2**) this sum is 300° (5 × 60°), whereas in the [7]-circulene **4** it is 420° (7 × 60°). For obvious reasons in our attempts to demonstrate nonplanarity of the heterocirculenes we concentrated our attention on the heterocirculene **8**, in which the sum of the internal angles (390°) deviates most from 360°. However, **8** had to be substituted in order to make it dissymetric. A substitution reaction of this type had to conform to the following requirements: (a) result in a compound which had an unequivocal substitution pattern, (b) furnish the substituted compound in high yield. A compound with an unequivocal substitution pat-



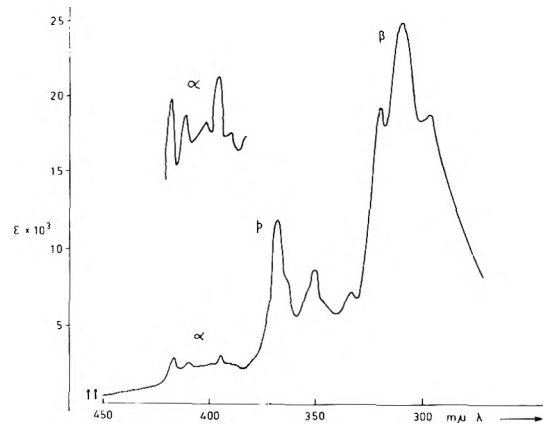


Figure 15. The uv spectra of the heterocirculenes in $CHCl_3$.

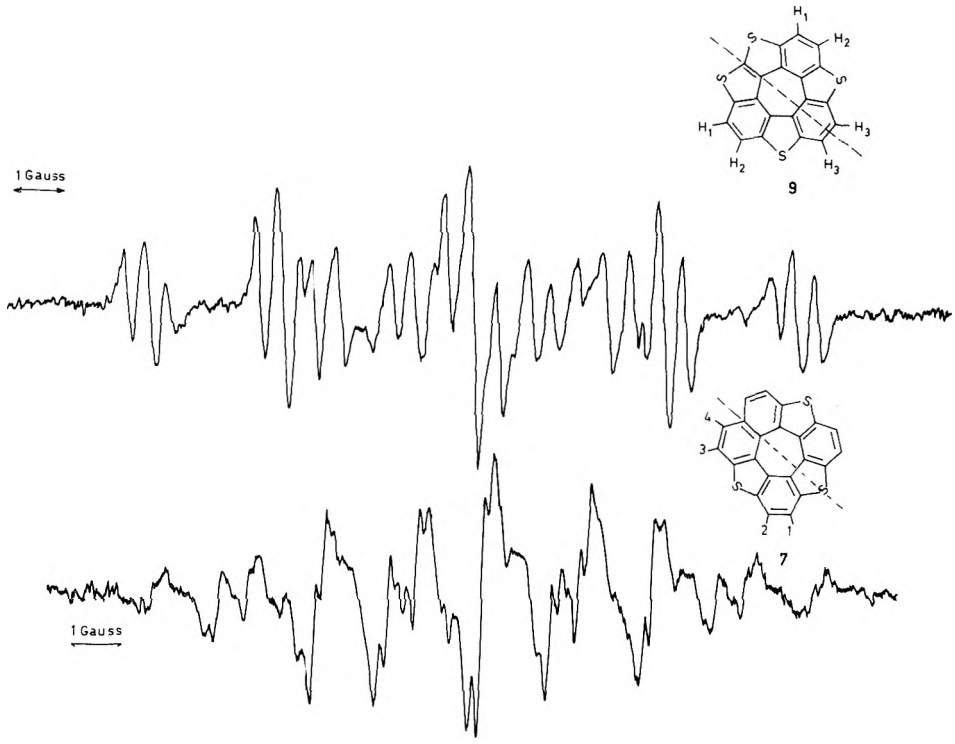


Figure 16. ESR spectra of the radical anions of **7** and **9**.

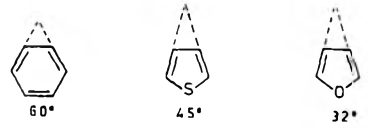


Figure 17.

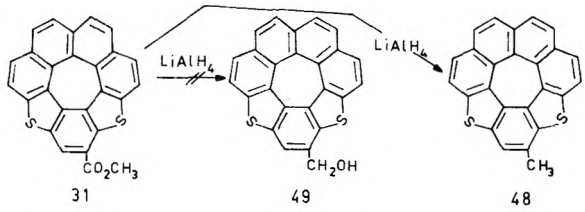
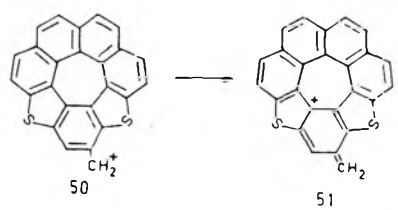
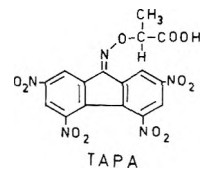


Figure 18.

tern had been realized in the synthesis of **31**. The methylated circulene **48** was a suitable compound for the resolution experiments. Therefore we directed our attention to the conversion of **31** into **48**. This could be achieved in a very simple one-step reduction. Treatment of **31** with $LiAlH_4$ under normal reaction conditions did not furnish **49** (as expected), but yielded almost quantitatively **48** (Figure 18). This reaction is thus a rare example of a one-step reduction of an ester to the corresponding hydrocarbon initiated by a metal hydride only.[36] Closely related reactions are found in reports of reductions with $LiAlH_4$–$AlCl_3$.[37] The reduction procedure is believed to involve carbonium ion intermediates. Thus, the reaction described above provides an indication of the relatively great stability of the intermediate carbonium ion **50**. The aromatization to the inner seven-membered ring in structure **51** might explain this.



Diastereomeric Complex Formation. In the attempted resolution of **48** we followed the procedure which had been developed by Newman for the resolution of hexahelicene.[38] When a solution of the circulene **48** in benzene was treated with 1 equiv of (+)-TAPA, $[\alpha]^{20}_{436}$ +432°, the solu-



tion became green. The uv spectrum of the resulting solution was recorded and the spectrum shown in Figure 19 was obtained. A broad absorption band with a maximum at 570 mμ was observed. Neither **48** nor TAPA separately exhibit an absorption above 450 mμ, a clear indication for the pres-

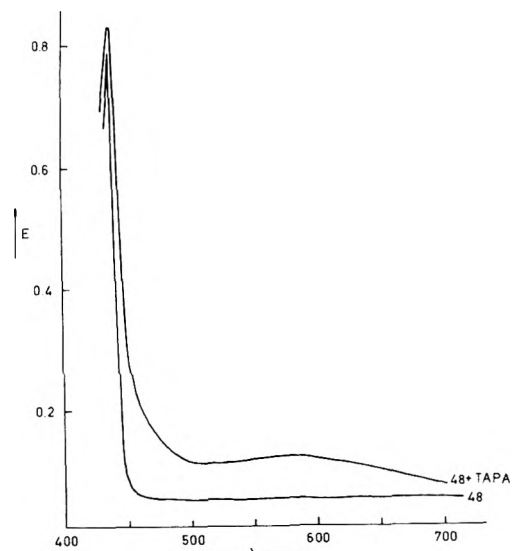


Figure 19. Uv spectra of **48** and of **48** + TAPA (1:1 molar) in C_6H_6.

ence of a charge-transfer complex. In the actual resolution experiment 48 was treated with 0.5 equiv of (+)-TAPA. Upon the addition of ethanol some of the circulene separated as yellow needles. A further application of this treatment afforded a small quantity of 48, which showed no optical rotation (measured at 436, 546, and 578 mμ). We repeated the experiments at lower temperature. Both the circulene and TAPA were soluble in 1,2-dichloroethane at −30°. Solutions of 48 and (+)-TAPA were mixed at 25° and some ethanol was added. The solution was cooled carefully to −30°, after which the circulene started to crystallize. The circulene crystals were isolated and then redissolved in CS_2 at −30°. Again no optical rotation was observed. A small quantity (0.9 mg) of the circulene TAPA complex could be obtained in crystalline form when the experiments were carried out in chloroform. The measured rotation of this complex was α^{20}_{436} +0.025°. From this complex the circulene could be regained by addition of ethanol, but again no optical rotation was observed. The experiments described above were repeated with the circulene 10. The same negative results were obtained.

Discussion

A few comments about these negative results are in order.

Three particular factors may be invoked to explain the failure of the resolution experiments:

(1) adjustments of bond lengths and bond angles keep a circulene planar;

(2) the circulenes are nonplanar, but inversions occur at such a rate that resolution is prevented;

(3) the method used for the resolution was not the appropriate one.

Inversions of a corrugated circulene can proceed via a planar transition state or via an undulating motion which passes through the whole molecule. It is very difficult to differentiate between these two modes of inversion and until experimental proof concerning possible nonplanarity of our heterocirculenes is available further predictions about this subject seem useless.[40] Concerning the resolution method: [7]-heterocirculenes readily form charge-transfer complexes in which the former function as donor molecules (see Experimental Section). This may be ascribed to a partial aromatization of the inner seven-membered ring which of course promotes planarity of the molecule. Moreover, it is known that in some cases formation of charge-transfer complexes enhances greatly the rate of racemization.[41] This diminishes to some extent the importance of our resolution experiments with TAPA.

Experimental Section

All reagents were purified where necessary by standard methods. For column chromatography neutral alumina (Merck A_1) or silica gel (B. D. H.) was used. Melting points (corrected) up to 300° were determined on a Mettler FP_1 microscope and between 300 and 350° (uncorrected) on a Reichert hot-stage apparatus. Uv spectra were measured on a Zeiss PMQ II or recorded with a Beckman DB-G grating spectrophotometer. NMR spectra were obtained with a Varian A-60D instrument, using tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values (parts per million). Mass spectra were obtained with a AEI MS 902 instrument and recorded by Mr. A. Kiewiet. The ESR spectra were recorded on a Varian E_4 spectrometer. Elemental analyses were carried out by Mr. H. Draayer, Mr. J. Ebels, and Mr. J. Vos in the microanalytical department of this laboratory. Optical activity was measured on a Zeiss Lichtelektrisches Präzisionspolarimeter 005 using 5- or 10-cm cells.

9,10-Epithio-3,6-dithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,7,6-*cdef*]fluorene-1,2-dicarboxylic Anhydride (12). The dehydrohelicene **6** (50 mg, 0.15 mmol), chloranil (125 mg, 0.51 mmol), and maleic anhydride (750 mg, 7.7 mmol) were mixed together in a 50-ml reaction flask. The flask was equipped with an air condenser and the flask contents were brought under a nitrogen atmosphere. The flask was put into a molten metal bath of 220° and the reaction mixture was refluxed for 2 hr. After cooling, 20 ml of *p*-xylene was added and the resulting suspension was refluxed for an additional 10 min. After cooling, the orange-red anhydride was filtered, washed thoroughly with *p*-xylene and ether, and dried in vacuo. The analytically pure anhydride **12** (mp >400°) was obtained by sublimation (350–400°, 10^{-4} mm). The yield of **12** was 43 mg (65%).

Anal. Calcd for $C_{24}H_6S_3O_3$: C, 65.74; H, 1.38; S, 21.93. Found: C, 65.8; H, 1.6; S, 21.9.

Ir (KBr) 1825, 1772, 1220, 1149, 895, and 790 cm^{-1}.

9,10-Epithio-3,6-dithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,7,6-*cdef*]fluorene-1,2-dicarboxylic Acid Dimethyl Ester (13). To 15 ml of a 10% sodium hydroxide solution was added 15 mg (3.4×10^{-2} mmol) of the anhydride **12**. The mixture was boiled for 30 min. After cooling, the pale yellow salt was hydrolyzed by acidification with dilute hydrochloric acid. The pale yellow diacid **14** was filtered, washed with water until neutral, and dried quickly in vacuo. After drying, the acid was transferred into a 50-ml reaction flask and a solution of an excess of diazomethane in ether was added. After 30 min of stirring excess of diazomethane was destroyed with some acetic acid, after which the solvent was removed at reduced pressure. The ester was taken up in a minimum of hot chloroform and chromatographed on alumina with chloroform. After removal of the solvent, the residue was recrystallized from carbon tetrachloride, yielding 12 mg (73%) of the pure diester **13** (mp 308–309°).

Anal. Calcd for $C_{26}H_{12}S_3O_4$: C, 64.45; H, 2.49. Found: C, 64.3; H, 2.6.

Ir (KBr) carbonyl absorptions at 1711, 1720 cm^{-1}; NMR (CD_2Cl_2, CAT) 3 H δ 4.06 (s), 3 H 4.08 (s), 4 H 7.41 (m), 2 H 7.54 ppm (m); uv ($CHCl_3$) λ_{max} (log ε) 450 (2.88), 384 (3.68), 332 (3.83), 318 (s) (3.90), 304 (4.23), 294 (4.29) 288 (4.28), 262 (4.51).

The other anhydrides and diesters were obtained by an analogous procedure to that described for the preparation of **12** and **13**.

9,10-Etheno-3,6-dithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,7,6-*cdef*]fluorene-9,10-dicarboxylic Anhydride (16). The anhydride **16** (mp >400°) was obtained from the dehydrohelicene **15** (50 mg, 0.15 mmol). The yield of **16** was 11 mg (17%).

Anal. Calcd for $C_{26}H_8O_3S_2$: C, 72.21; H, 1.87. Found: C, 72.2; H, 2.0.

Ir (KBr) 1824, 1763, 1220, 1156, 918, 828, and 801 cm^{-1}.

When the anhydride **16** was boiled with dilute sodium hydroxide solution a yellow disodium salt was readily formed. However, after careful acidification **16** was reformed immediately.

9,10-Etheno-3,6-dithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,7,6-*cdef*]fluorene-4,5-dicarboxylic Anhydride (19). The anhydride **19** (mp >400°) was obtained from the dehydrohelicene **18** (40 mg, 0.12 mmol). The yield of **19** was 31.2 mg (60%).

Anal. Calcd for $C_{26}H_8O_3S_2$: C, 72.21; H, 1.87; S, 14.83. Found: C, 72.2; H, 2.0; S, 14.4.

Ir (KBr) 1824, 1769, 1221, 1186, 888, 852, 741, and 550 cm^{-1}.

9,10-Etheno-3,6-dithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,7,6-*cdef*]fluorene-4,5-dicarboxylic Acid Dimethyl Ester (21). The dimethyl ester **21** (mp 320–322°) was obtained from the anhydride **19** (5 mg, 1.2×10^{-2} mmol). The yield of **21** was 4.4 mg (76%): calcd mol wt 478.033 (found by mass spectrometry, M 478.035); ir (Nujol) carbonyl absorptions at 1722, 1710 cm^{-1}.

1,11-Etheno-6,7-epithio-2,5,8-trithiabenz[3.4]azuleno[5,6,-7,8-*jkl*]-*as*-indacene-1,2-dicarboxylic Anhydride (26). The anhydride **26** (mp >400°) was obtained from the dehydrohelicene **25** (30 mg, 8.5×10^{-2} mmol). The yield of **26** was 23 mg (61%).

Anal. Calcd for $C_{22}H_4S_4O_3$: C, 59.44; H, 0.91; S, 28.85. Found: C, 60.0; H, 1.2; S, 28.3.

Ir (KBr) 1830, 1772, 1233, 1186, 905, and 802 cm^{-1}.

1,11-Etheno-6,7-epithio-2,5,8-trithiabenz[3.4]azuleno[5,6,-7,8-*jkl*]-*as*-indacene-1,2-dicarboxylic Acid Dimethyl Ester (28). The dimethyl ester **28** (mp 338–342° dec) was obtained from the anhydride **26** (7.4 mg, 1.7×10^{-2} mmol). The yield of **28** was 5.7 mg (68%): calcd mol wt for $C_{24}H_{10}O_4S_4$, M 489.946 (found by mass spectrometry, M 490); ir (Nujol) carbonyl absorptions at 1733, 1714 cm^{-1}.

1,11-Etheno-6,7-epithio-2,5,8-trithiabenz[3.4]azuleno[5,6,-7,8-*jkl*]-*as*-indacene-8,9-dicarboxylic Anhydride (23). The anhydride **23** (mp >400°) was obtained from the dehydrohelicene **22** (70 mg, 2.10^{-1} mmol). The yield of **23** was 65 mg (73%).

Anal. Calcd for $C_{22}H_4S_4O_3$: C, 59.44; H, 0.91; S, 28.85. Found: C, 59.5; H, 0.9; S, 28.9.

Ir (KBr) 1829, 1773, 1276, 1207, 1182, 1172, 920, 891, 794, and 746 cm^{-1}.

1,11-Etheno-6,7-epithio-2,5,8-trithiabenz[3.4]azuleno[5,6,-7,8-*jkl*]-*as*-indacene-8,9-dicarboxylic Acid Dimethyl Ester (24). The dimethyl ester **24** (mp 320–324°) was obtained from the anhydride **23** (4.5 mg, 1.10^{-1} mmol). The yield of **24** was 4.0 mg (82%): calcd mol wt for $C_{24}H_{10}O_4S_4$, M 489.946 (found by mass spectrometry, M 489.947); ir (Nujol) carbonyl absorptions at 1718 and 1703 cm^{-1}.

1,11-Etheno-2,5,6-trithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,-7,6-*ijkl*]-*as*-indacene-1,2-dicarboxylic Anhydride (30). The anhydride **30** (mp >400°) was obtained from the dehydrohelicene **29** (70 mg, 0.2 mmol). The yield of **30** was 42 mg (48%).

Anal. Calcd for $C_{24}H_6S_3O_3$: C, 65.74; H, 1.38; S, 21.93. Found: C, 66.3; H, 1.7; S, 21.1.

Ir (KBr) 1825, 1769, 1231, 1171, 904, and 812 cm^{-1}.

9,10-Epithio-3,6-dithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,-7,6-*cdef*]fluorene (7). A. By Soda Lime Decarboxylation. The anhydride **12** (50 mg, 0.11 mmol) and soda lime (700 mg) were ground together and transferred into a sublimation apparatus. The reaction mixture was brought carefully under a nitrogen atmosphere and heated to 350° for 45 min. After cooling the sublimation apparatus was evacuated (2×10^{-3} mm) and heated again to 380–420° for 4 hr. The circulene (22 mg, 6.0×10^{-2} mmol) sublimed in yellow-green needles. Analytically pure **9** (mp 400–410° dec) was obtained by recrystallization from *p*-xylene.

Anal. Calcd for $C_{22}H_8S_3$: C, 71.71; H, 2.19. Found: C, 71.8; H, 2.2.

B. By Cu–Quinoline Decarboxylation. The anhydride **12** (40 mg, 9×10^{-2} mmol) was added to a suspension of 50 mg of Cu powder in 10 ml of quinoline. The mixture was heated at 240° for 24 hr. After cooling the reaction mixture was diluted with chloroform (50 ml). The organic solution was extracted with 2 *N* hydrochloric acid (6 × 20 ml), water, and sodium bicarbonate solution. After drying, filtering, and evaporation of the solvent, the residue was chromatographed on alumina with benzene. The eluate gave upon concentration 12 mg (36%) of the circulene **9.**

The circulenes **8, 9,** and **10** were obtained by a similar procedure as that described for the preparation of **7.**

1,11-Etheno-6,7-epithio-2,5,8-trithiabenz[3.4]azuleno[5,6,-7,8-*jkl*]-*as*-indacene (9). A. By Soda Lime Decarboxylation of the Anhydride 23 (50 mg, 0.11 mmol). The yield of the circulene **9** (mp 460° dec) was 21.1 mg (51%).

B. By Cu–Quinoline Decarboxylation of the Anhydride 23 (70 mg, 0.16 mmol). The yield of the circulene **9** was 8 mg (13.3%).

C. By Soda Lime Decarboxylation of the Anhydride 26 (33 mg, 7.4×10^{-2} mmol). The yield of the circulene **7** was 12 mg (42.9%).

D. By Cu–Quinoline Decarboxylation of the Anhydride 26 (150 mg, 0.34 mmol). The yield of the circulene **7** was 16.5 (13%).

Anal. Calcd for $C_{20}H_6S_4$: C, 64.14; H, 1.61. Found: C, 64.1; H, 1.6.

9,10-Etheno-3,6-dithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,7,6-*cdef*]fluorene (8). A. By Soda Lime Decarboxylation of the Anhydride 16 (9.2 mg, 2.1×10^{-2} mmol). The yield of the circulene **8** was 2.3 mg (23%).

B. By Soda Lime Decarboxylation of the Anhydride 19 (80 mg, 0.18 mmol). The yield of the circulene **8** (mp 410° dec) was 35 mg (54%).

Anal. Calcd for $C_{24}H_{10}S_2$: C, 79.51; H, 2.78; S, 17.69. Found: C, 79.4; H, 2.8; S, 17.7.

Picrate of Circulene 8. To a stirred solution of **8** (10 mg) in *p*-xylene (10 ml) was added dropwise a solution of picric acid (10 mg) in absolute ethanol (3 ml); the solution was refluxed for 10 min, cooled, and allowed to stand overnight. The almost black colored needles were filtered, washed with ethanol, and dried in vacuo. The crystals decomposed above 238°.

Anal. Calcd for $C_{30}H_{13}N_3O_7S_2$: N, 7.10. Found: N, 6.6.

1,11-Etheno-2,5,6-trithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,7,6-*ijkl*]-*as*-indacene (10). By Soda Lime Decarboxylation of the Anhydride 30 (49 mg, 0.11 mmol). The yield of the circulene **10** (mp 390° dec) was 20 mg (50%).

Anal. Calcd for $C_{22}H_8S_3$: C, 71.71; H, 2.19; S, 26.10. Found: C, 71.8; H, 2.3; S, 25.9.

Thiacoronene (11). The Diels–Alder reaction was carried out with the dehydrohelicene **37** (70 mg, 0.25 mmol), chloranil (160 mg), and maleic anhydride (950 mg). At the end of the reaction a dark-brown mixture of anhydrides was obtained, which were not identified at that stage. The crude mixture was used for the soda lime decarboxylation.

The anhydrides (72 mg) and soda lime (1 g) were ground together and transferred to a sublimation apparatus. The mixture was brought under a nitrogen atmosphere and heated at 370° for 1 hr. After evacuation of the apparatus (10^{-2} mm) the mixture of polyaromatics started to sublime over a long range of bath temperatures (300–460°). The reaction products were dissolved in benzene and chromatographed on alumina with benzene. This yielded 18 mg of yellow-green material and TLC analysis of this mixture showed the presence of at least four different products. These products could be separated using preparative thick layer chromatography on alumina with benzene–cyclohexane (1:5) as eluting agent. The compound with the highest R_f value could be identified as thiacoronene. Pure **11** (3 mg) was obtained by recrystallization from methylcyclohexane. Thiacoronene starts to sublime at 262°. The crystals soften at 326° and melt above 350°: calcd mol wt for $C_{22}H_{10}S$, M 306.050 (obtained by mass spectrometry, M 306.051).

Thiacoronene 3,3-Dioxide (39). To a stirred solution of thiacoronene (1 mg) in CH_2Cl_2 (2 ml) was added excess *m*-chloroperbenzoic acid (6 mg). Stirring was continued for 5 hr, after which the solution was filtered and 10 ml of cold methanol was added. The precipitated sulfone **39** (0.7 mg) was collected and dried. From this material only a mass spectrum was taken.

9,10-Etheno-3,6-dithianaphth[2′.1′.8′:3.4.5]azuleno[1,8,7,6-*cdef*]fluorene-4-carboxylic Acid Methyl Ester (31). To a solution of **18** (58 mg, 0.21 mmol) in hot *p*-xylene (10 ml) was added methyl propiolate (5 ml) and chloranil (60 mg). After the addition the solution was refluxed for 3 days and after cooling the precipitate was filtered, washed with benzene and ether, and dried in vacuo. The solid was taken up in a minimum of hot *p*-xylene and chromatographed on alumina with chloroform. After removal of the solvent the residue was recrystallized from *p*-xylene. This yielded 43 mg (60%) of the pure ester **31** (mp 309–311°): calcd mol wt for $C_{26}H_{12}O_2S_2$, M 420.0279 (found by mass spectrometry, M 420.0289); ir (Nujol) most important absorptions at 1696, 1292, 1249, 1202, and 845 cm^{-1}.

Decarboxylation of the acid **32** with soda lime according to the general procedure yielded the circulene **18** in 45% yield.

ESR Spectra. Electrolytic Reduction. The spectra were recorded in a flat cell with a platinium gauze cathode at the bottom of the flat area and a platinum anode in the middle of the cell. The cell was provided with a variable direct current supply. After degassing with dry nitrogen, radical anions could be detected at 10-μA solutions in DMF with TEAP as the supporting electrolyte.

Reduction of 31 with $LiAlH_4$. To a suspension of 500 mg of $LiAlH_4$ in dry THF (15 ml) was added dropwise with vigorous magnetic stirring 21.8 mg (5.2×10^{-2} mmol) of the methyl ester **31** in 125 ml of dry THF. After the addition was complete the reaction mixture was refluxed for 18 hr. The reaction flask was cooled in an ice bath and the $LiAlH_4$ was destroyed by the careful addition of some water. Subsequently 10 ml of a 4*N* HCl solution and 50 ml of benzene were added. After extraction the benzene layer was separated and washed with water and $NaHCO_3$ solution. After drying ($MgSO_4$), filtering, and evaporation of the solvent the residue was taken up in a minimum of hot *p*-xylene and chromatographed on alumina with benzene. After removal of the solvent the residue was recrystallized from benzene. The yield of **48** (mp 335° dec) (17.2 mg) was 88%.

Anal. Calcd for $C_{25}H_{12}S$: C, 79.74; H, 3.21. Found: C, 79.9; H, 3.4.

Uv ($CHCl_3$) λ_{max} (log ϵ) 436 (2.72), 412 (3.06), 384 (3.51), 363 (3.51), 342 (3.64), 323 (4.10), 312 (4.30), 296 (4.18), 281 (4.52), 264 (4.68), 249 (4.65).

Attempted Resolution of 48. A. To a refluxing solution of **48** (7.951 mg, 2.1×10^{-2} mmol) in 2 ml of benzene was added (+)-TAPA (4.271 mg, 9.5×10^{-3} mmol) in 4 ml of benzene. The solution became directly green colored. Refluxing was continued for an additional 10 min and after cooling 3 drops of ethanol was added to the solution. After standing for 2 days at room temperature the precipitated circulene (4.312 mg) was filtered, washed with benzene and ethanol, and dried in vacuo. This material (dissolved in 4 ml of $CHCl_3$) showed no optical rotation. To the mother liquor was added an additional 3 ml of ethanol. The precipitated circulene (2.013 mg) was collected and washed as before. This material showed also no optical rotation.

B. To a suspension of **48** (11.0 mg, 2.9×10^{-2} mmol) in dichloroethane (5 ml) was added a solution of (+)-TAPA (9.3 mg, 2.1×10^{-2} mmol) in 6 ml of dichloroethane. The resulting green-colored solution was cooled at −30° for 24 hr. Ethanol (4 ml) was added and cooling was continued for an additional 3 days. The crystallized circulene (4.23 mg) was separated from the solution by decantation, thoroughly washed with ethanol, and then redissolved in carbon disulfide (6 ml) which was previously cooled to −50°. The solution was transported to a thermostated cell in which the

temperature was kept at −30°. Again no optical rotation was observed.

C. To a solution of **48** (4.651 mg, 12.5×10^{-3} mmol) in chloroform (10 ml) was added (+)-TAPA (3.578 mg, 8×10^{-3} mmol) in chloroform (2 ml). The resulting solution was refluxed for 5 min and half of the chloroform (6 ml) was removed by distillation. After cooling and standing for 48 hr, the precipitated complex (0.988 mg) was separated from the solution by decantation and washed with 1 ml of cold chloroform. The solid was dried and then dissolved in 4 ml of chloroform and the rotation was measured. The observed values were α_{436} 0.025°, α_{546} 0.005°, and α_{578} <0.005°. After removal of the chloroform and addition of 5 ml of ethanol the resulting circulene (0.314 mg) was filtered and washed with benzene–ethanol. This material showed no optical rotation.

Registry No.—**6**, 30689-70-4; **7**, 35817-61-9; **8**, 54844-47-2; **8** picrate, 54844-48-3; **9**, 54844-49-4; **10**, 54844-50-7; **11**, 40516-55-0; **12**, 35817-59-5; **13**, 35817-60-8; **15**, 30689-69-1; **16**, 54844-51-8; **18**, 54844-52-9; **19**, 54844-53-0; **21**, 54869-88-4; **22**, 54844-54-1; **23**, 54844-55-2; **24**, 54844-56-3; **25**, 54844-57-4; **26**, 54844-58-5; **28**, 54844-59-6; **29**, 54844-60-9; **30**, 54844-61-0; **31**, 54844-62-1; **37**, 54844-63-2; **39**, 54844-64-3; **48**, 54869-87-3; maleic anhydride, 108-31-6; methyl propiolate, 922-67-8; $LiAlH_4$, 16853-85-3.

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Polymeric Reagents. IV.[1] Synthesis and Utilization of an Insoluble Polymeric Organotin Dihydride Reagent

Ned M. Weinshenker, Guy A. Crosby,* and Jack Y. Wong[2]

Chemical Synthesis Laboratories, Dynapol, Palo Alto, California 94304

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The preparation of an insoluble polymeric hydride reagent has been achieved by the incorporation of *n*-butyltin dihydride functional groups onto a macroreticular polystyrene matrix. Reaction of the polymeric organotin dihydride reagent with iodooctane indicated the minimum hydride content to average 2.0 mmol/g of polymer. Utilization of the reagent for the reduction of aldehydes and ketones to alcohols and the reduction of halides to hydrocarbons is discussed. The selective reduction of only one functional group of a symmetrical difunctional aldehyde (terephthaldehyde) is also demonstrated. The regeneration and stability of the reagent are also discussed.

The chemical industry is being faced with the ever-increasing problems of pollution control and a scarcity of raw materials. Recent developments[1,3] in the area of insoluble, regeneratable reactive polymers has resulted in the availability of many new reagents with unique properties that are capable of providing solutions to these problems. Despite the growing list of polymers that have been used to effect oxidation, hydrogenation, alkylation, etc., there has been no report of a general reducing agent possessing a wide range of applications. We now describe our efforts di-

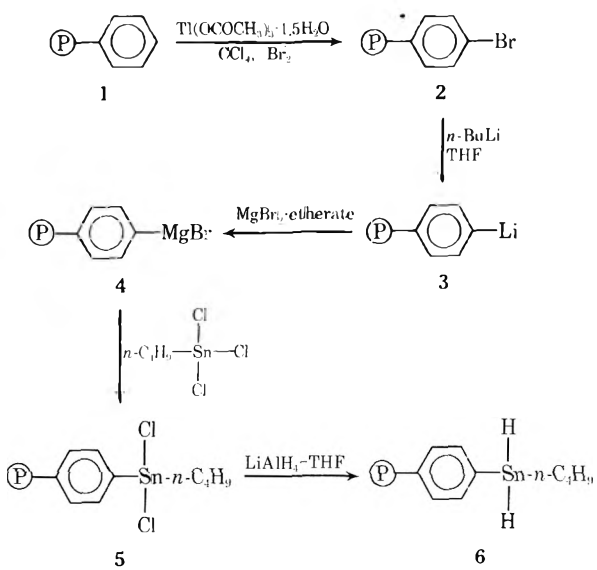
rected at the synthesis and utilization of an insoluble polymeric tin dihydride reagent.

The versatility and selectivity of organotin hydrides as reducing agents is well documented,[4] with the dihydrides generally being more reactive but less stable than the corresponding monohydrides. Kuivila[4c] attributed these special characteristics to the fact that the tin–hydrogen bond is weaker and less polar than both the boron–hydrogen and aluminum–hydrogen bonds. As a consequence, reduction with organotin hydrides can proceed by either free-radical chain or polar mechanisms depending on the substrate, catalysts, or reaction conditions. Thus, one might expect that an insoluble polymeric organotin dihydride reagent would include the advantages of monomeric organotin hydrides plus the advantages of a typical polymeric reagent: ease of operation and reaction work-up, avoidance of malodors and toxic vapors characteristic of tin hydrides,[4d] and capability of regeneration. In principle a polymeric tin monohydride or trihydride can be made in the same manner as the dihydride described in this paper. The latter was chosen for study because it appeared to offer a combination of reasonable stability and sufficient chemical reactivity.

Results and Discussion

Preparation. Macroreticular polystyrene (1), Amberlite XE-305 (Rohm & Haas),[5] was used as starting material in the preparation of polymeric organotin dihydride reagent **6** as outlined in Scheme I. A major consideration in using a

Scheme I

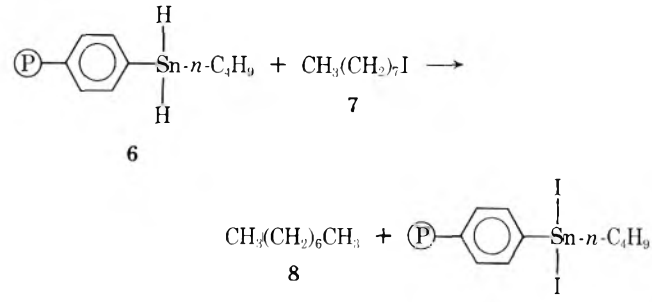


macroreticular instead of a microreticular resin is that the macroporosity and rigidity of the beads give certain advantages[6] over the ordinary gel-type polymers such as (a) greater number of accessible reactive sites and (b) nominal shrinking and swelling properties allowing the use of a wide variety of solvents and temperatures.

Bromination of the macroreticular polystyrene 1 with bromine and ferric chloride[7] in carbon tetrachloride proceeded to give a product containing 4.02 mmol of bromine/g of polymer.[8] However, using thallic acetate sesquihydrate [$Tl(OAc)_3 \cdot 1.5H_2O$][9] in place of ferric chloride as catalyst gave a visually cleaner, more homogenous product containing 3.62 mmol of bromine/g. The literature[10] indicates that this product should be exclusively the para-substituted bromo isomer **2**. The bromo resin **2** was treated twice with *n*-butyllithium in anhydrous tetrahydrofuran under an inert atmosphere to give the lithiated resin **3**. This material was not isolated, but immediately treated with freshly prepared magnesium bromide–ether solution (1.5 equiv) at 0° to give the Grignard resin **4**. The magnesium bromide etherate solution can be prepared according to Bachmann's[11] or House's method.[12] However, it was found that House's method of treating ethylene dibromide with magnesium gave a much cleaner product. Treatment of the Grignard resin **4** with excess (1.5 equiv) *n*-butyltin trichloride gave the polymeric tin dichloride **5**. Elemental analysis indicated 1.2 mmol of Sn and 2.34 mmol of chlorine per gram of polymer. The final product **6** was obtained by treating the tin dichloride beads **5** with either diisobutylaluminum hydride in benzene or a solution of lithium aluminum hydride in tetrahydrofuran at room temperature. Isolation of the product was conducted under an inert atmosphere. The ir spectrum of **6** displayed a strong band at 1850 cm^{-1} which is characteristic of a Sn–H absorption. Elemental analysis (14.80% Sn, 1.25 mmol/g, ~0% Cl) indicated a maximum of 2.50 mmol of active hydride/g of polymer.

The reaction of tin dihydride resin **6** with iodooctane (**7**) (Scheme II) was used as a measure of the minimum hydride content of the polymer **6**. Conversion of iodooctane to octane (**8**) was followed by gas chromatography (4% FFAP, 7 ft × 0.25 in., on Chromosorb G, 80–100 mesh, 100°) using ethylbenzene as internal standard. The resin **6** (1.00 g) was treated with an excess of iodooctane (5 mmol) in 25 ml of anhydrous benzene to yield 1.98 mmol of octane (**8**), indicating a minimum of 1.98 mmol of active hydride/g of polymer.

Scheme II



We have found that the reaction conditions described in the Experimental Section are critical to the optimal preparation of the polymeric tin dihydride reagent. Our initial attempt resulted in the incorporation of only 0.22 mmol of tin/g of polymer based on elemental analysis. However, by paying careful attention to experimental conditions we have been able to repeatedly incorporate an average of 2.0 mmol of hydride/g of reagent.

Stability. The literature does not give a clear indication of the stability of monomeric *n*-butylphenyltin dihydride. However, it has been reported that diphenyltin dihydride decomposes slowly to diphenyltin in liquid ammonia (−33°)[13] and to tetraphenyltin and metallic tin when heated above 100° in vacuo.[14] Di-*n*-butyltin dihydride was observed by van der Kerk[14] to be stable for up to 4 months if kept at 0° in a sealed tube. Hence, the stability of monomeric *n*-butylphenyltin dihydride should be intermediate between the conditions indicated above.

From the outset, the polymeric organotin dihydride **6** was expected to be more stable than its corresponding monomer owing to a restriction of intermolecular crosslinking and interactions created by the polymeric matrix.[15] The data given in Table I give an indication of the stability of the hydride reagent **6** and surprisingly reveal that there is little difference between samples stored under an inert atmosphere at 0° and room temperature. The data also suggest that for long-term use, the reagent is best stored in

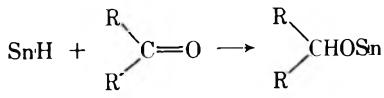
Table I
Stability Studies on the Polymeric Organotin Dihydride Reagent

Storage time, months	Storage temp, °C	Active hydride,[a] mmol/g
Fresh		2.01
1	Room	1.37
1	0	1.42
2	Room	0.80
2	0	0.76
3	Room	0.36
3	0	0.53

[a] Active hydride determined by reduction of octyl iodide.

the form of its polymeric tin dichloride precursor **5** and converted to the desired hydride reagent in batches.

Reduction of Aldehydes and Ketones. The general application of monomeric organotin hydrides as reducing agents for aldehydes and ketones has received only limited attention.[16] Kuivila[4c] has reported that the reductions proceed by a two-step mechanism. Depending upon condi-



(A)

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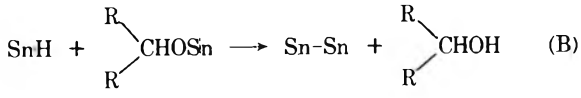

(B)

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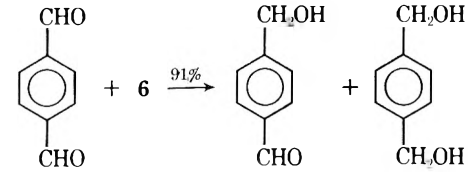
tions, only reaction A, or both A and B, may occur. The first step can be catalyzed by light, free-radical sources, Lewis acids, or heat. The second step represents an example of a general reaction between organotin hydrides and organotins containing electronegative groups bonded to tin. It should be pointed out, however, that reaction B cannot occur to any significant extent with the polymeric tin hydride because of the restricted mobility of the polymer matrix.[15] Hence, hydrolysis of the polymeric tin alkoxide **9** is necessary to obtain maximum yields of alcohol.[17]

Table II contains a summary of the results obtained from the reduction of a selected group of aldehydes and ketones with the polymeric hydride reagent **6**. In the reduction of a typical ketone, such as acetophenone, the best yields of alcohol were obtained by performing the reduction at the reflux temperature of toluene and adding the reagent **6** (3 equiv) in three separate portions.[18] This suggests that some decomposition of the tin reagent occurs during the reaction.

The dramatic catalytic effect of platinum tetrachloride was illustrated by the reduction of 4-phenylcyclohexanone. In the presence of 5 mol % of catalyst this reaction was >50% complete in 4 hr at room temperature in tetrahydrofuran (compare with entry 4, Table II).

The need to hydrolyze the intermediate tin alkoxide **9** in order to isolate the reduction product can be used to advantage. Thus, reduction of an excess of the symmetrical dialdehyde terephthaldehyde (1 g, 7.5 mmol, 44% molar excess) with a limiting amount of the polymeric tin dihydride reagent **6** (4 g, 5.2 mmol of hydride) resulted in the isolation of a 91% yield of products composed of an 86:14 ratio of the monoalcohol to dialcohol, respectively. Isolation of the two products simply involved removal of the excess aldehyde by filtration, followed by hydrolysis, extraction, and purification by preparative TLC. The increase in selec-



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tivity over the statistical 2:1 ratio of products is undoubtedly a result of the restricted accessibility of the remaining aldehyde group after formation of the initial tin alkoxide

Table II
Reduction of Aldehydes and Ketones via the Polymeric Tin Hydride Reagent 6[h]

Entry	Aldehyde or ketone	Registry no.	Reaction time, hr	Product(s)	Registry no.	Isolated product(s) Weight, g	Isolated product(s) Yield, %	VPC analysis of distilled products
1	Acetophenone 0.12 g (1 mmol)	98-86-2	45	1-Phenylethanol[a]	98-85-1	0.112	92	95% alcohol 4% ketone
2	*tert*-Butyl methyl ketone 0.10 g (1 mmol)	75-97-8	41	3,3-Dimethylbutan-2-ol[a]	464-07-3	0.093	91	91% alcohol 8% ketone
3	Benzaldehyde 0.106 g (1 mmol)	100-52-7	40	Benzyl alcohol[b]	100-51-6	0.102	91	99+% alcohol
4	4-Phenylcyclohexanone 0.174 g (1 mmol)	4894-75-1	42	4-Phenylcyclohexanol[b,c]	5437-46-7	0.108	61	
5	Heptanal 0.114 g (1 mmol)	111-71-7	38	*n*-Heptanol[a]	111-70-6	0.100	86	99% alcohol 0.5% ketone
6	Benzophenone 0.182 g (1 mmol)	119-61-9	44	Benzhydrol[b,d]	91-01-0	0.099	54	
7	Terephthaldehyde[e]	623-27-8	24	*p*-Hydroxymethylbenzaldehyde[b,f] + 1,4-Benzenedimethanol[b]	52010-97-6 589-29-7	0.556 0.091	91[g]	

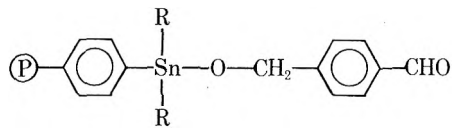
[a] Product isolated by bulb-to-bulb evaporative distillation. [b] Product isolated by preparative TLC. [c] Mp 109–112°. [d] Mp 68–69°. [e] Polymeric hydride reagent added in one portion. [f] Mp 37–46°. [g] Yield based on hydride as limiting reagent (4 g, 5.2 mmol); ratio of monoalcohol to dialcohol 86:14. [h] All products were characterized by NMR and ir. All reductions were conducted in refluxing toluene with 2.5 g (1.25 mmol hydride/g, 3 equiv) of resin **6** added in three portions at 0, 18, and 30 hr unless noted otherwise.

Table III
Reduction of Alkyl and Aryl Halides via the Polymeric Tin Hydride Reagent 6[i]

Halide	Registry no.	Solvent	Time, hr	Temp, °C	Product	Registry no.	Product(s) weight, g	% yield	VPC analysis of product(s)
1-Iodooctane 0.240 g (1 mmol)		THF	1.5	Room	Octane[a]		0.111	98[a]	99+%
1-Bromooctane[b] 0.193 g (1 mmol)	111-83-1	Benzene	30	80	Octane[a]		0.107	94[a]	99+%
1-Bromoadamantane 0.215 g (1 mmol)	768-90-1	Benzene	18	80	Adamantane[c,d]	281-23-2	0.126	93	
α-Bromoacetophenone[e] 0.199 g (1 mmol)	70-11-1	Benzene	2	80	Acetophenone[f]	98-86-2	0.108	90	99
9-Bromoanthracene 0.257 g (1 mmol)	1564-64-3	Toluene	51	111	Anthracene[g,h]	120-72-7	0.143	80	
Benzyl bromide 0.171 g (1 mmol)	100-39-0	Benzene	8	80	Toluene[i]	108-88-3		98[i]	
(2-Bromoethyl)-benzene 0.185 g (1 mmol)	103-63-9	Benzene	17	80	Ethylbenzene[f]	100-41-4	0.105	99	95[j]
d-3-Bromocamphor 0.231 g (1 mmol)	55057-87-9	Benzene	6	80	Camphor[g,k]	464-49-3	0.117	84	
Prostaglandin iodide intermediate (**11**) 0.492 g (1 mmol)		THF	80	Room	Prostaglandin intermediate (**12**)[g]		0.315	86	

[a] Solvent removed by distillation; product not purified further. [b] Four grams of resin added in two portions. [c] Product purified by sublimation (180°, 0.5 mm). [d] Mp 209–213°. [e] One gram of resin used (1.25 mequiv of hydride). [f] Product isolated by evaporative distillation. [g] Product isolated by preparative TLC. [h] Mp 216–217°. [i] Product not isolated; percent of product determined by VPC analysis. [j] Remainder is solvent. [k] Mp 168–173°. [l] All products were characterized by NMR and ir unless otherwise noted. Three grams of resin containing 1.25 mmol of hydride/g were used, added in one portion, unless otherwise noted.

bond (see **10**), as well as restricted mobility of the polymer-bound tin hydride groups.[1]



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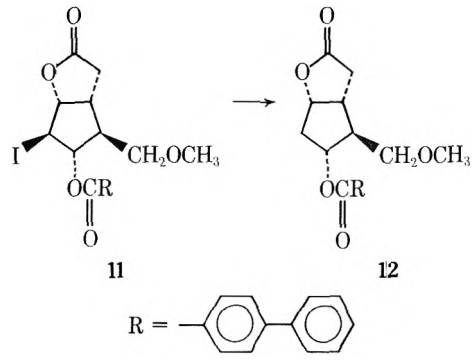
Reduction of Halides. The use of organotin hydrides for the reduction[4c] of alkyl and aryl halides in the presence of other functional groups is generally superior to lithium aluminum hydride[19] or more recently introduced procedures.[20] As additional advantages, the polymeric tin hydride **6** offers a reagent which is free from toxic vapors and malodors and completely avoids contamination of products with residual organotin impurities.

Table III represents the scope of this method to date and illustrates the reagent's ability to reduce a halide in the presence of other functional groups. The reaction can be carried out by simply stirring the halide with the polymeric tin dihydride reagent (1.25–3.75 equiv) in an appropriate solvent at room temperature or reflux temperature (depending on halide) until the reaction is complete as determined by VPC or TLC. The solution of products is separated from the insoluble beads by filtration, combined with solvent washings of the beads, and concentrated by removal of solvent. In the majority of cases the purity of the resulting product is sufficiently high that additional purification is unnecessary. The procedure can also be applied to labile compounds such as the iodide **11** (a prostaglandin intermediate),[21] which is reduced at room temperature in high yield to give a product, **12**, free of organotin impurities.

Regeneration. One of the major advantages of an insoluble polymeric reagent is its potential capacity to be regenerated. The principal by-products formed during the reduction of aldehydes, ketones, and halides with the polymeric tin hydride reagent should be the polymeric tin halides, alkoxides, and hydroxides. Lithium aluminum hydride is reported[14,22] to be an excellent reagent for reduction of the corresponding monomeric tin derivatives to tin hydrides. However, treatment of spent tin resin **6** (combined from reduction of aldehydes and ketones) with lithium aluminum hydride in THF at room temperature for 16 hr gave a material that was devoid of Sn–H absorption in the infrared spectrum and inert to iodooctane. Further exposure of this same material to $LiAlH_4$–THF for 3 hr at refluxing temperature (65°) resulted in beads that displayed a weak ir absorption at 1850 cm^{-1} and only 30% of the original hydride content (iodooctane standardization). Elemental analysis indicated that there had been no loss in tin content. The low content of regenerated hydride suggests that the formation of tin oxide, Sn–Sn, Sn–O–Sn, or divalent tin derivatives has occurred during the reduction–hydrolysis sequence.



11 **12**

Since the reduction of alkyl and aryl halides by organotin hydrides involves only free-radical hydrogen–halogen exchanges,[23] the used resin from halide reductions should be readily converted back to the polymeric organotin dihydride **6** with no loss in hydride content. Surprisingly, we have been able to regenerate only 60% of the original active hydride content in reagent **6** that has been utilized for halide reductions. Elemental analysis again indicated that there had been no loss in tin content. In addition, we have found it possible to regenerate only 10% of the active hydride that is lost in unused resin during storage. This is another strong indication that conversion of **6** to divalent tin compounds is occurring.

Experimental Section

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer as KBr pellets. NMR spectra were recorded with a Varian T-60A instrument using tetramethylsilane as the internal standard (δ 0, $CDCl_3$ was the solvent). GLC analyses were carried out on a Varian Aerograph Model 920 instrument equipped with a thermal conductivity detector. The columns used were commercially available (Varian) 4% FFAP (7 ft × 0.25 in.) on Chromosorb G (80–100 mesh). Evaporative distillation refers to bulb-to-bulb distillation under reduced pressure using a Büchi Kugelrohr oven. All solvents used were reagent grade unless specified otherwise. Anhydrous solvents were obtained by distillation from lithium aluminum hydride. Elemental analyses were performed by the Microanalytical Laboratory, Stanford University, Stanford, Calif.

Preparation of Poly(*p*-bromostyrene) (2).[7,9] Method A. Crosslinked macroreticular resin (2% crosslinked, Amberlite XE-305) (**1**, 50 g) was slurried in 350 ml of carbon tetrachloride in a 2-l. three-neck round-bottom flask equipped with a dropping funnel, a condenser, and an overhead stirrer.[24] After stirring for 0.5 hr at room temperature, thallic acetate sesquihydrate (100 g) was added, and stirring was continued for another 0.5 hr. Then bromine (18 ml) was added dropwise and the mixture was refluxed with stirring for 2 hr, during which time the solvent color changed from deep brown to yellow. After cooling the beads were filtered and washed with concentrated HCl–dioxane (1:1, three times), water–dioxane (1:1, three times), water (six times), dilute NH_3–dioxane (1:1, three times), dioxane (three times), THF (three times), and dry ether (three times). It was desirable to allow each of the solvents used in the washing procedure to be in contact with the beads for a 3–5-min period before filtration to allow complete penetration. The weight of the polymer after drying over calcium chloride in vacuo at 50° for 48 hr was 77 g.

Anal. Found: C, 58.11; H, 4.78; Br, 32.14.

The bromine content from elemental analysis was therefore 32.14%, which is equivalent to 4.02 mmol of bromine/g of polymer.

Method B. To a suspension of 10 g (96 mmol) of macroreticular polystyrene (Amberlite XE-305, Rohm & Haas) (**1**) and 0.1 g of anhydrous ferric chloride in 100 ml of carbon tetrachloride was added at room temperature a solution of 6 ml (112 mmol) of bromine (as Br_2) in 25 ml of carbon tetrachloride. The resulting mixture was stirred[24] at ambient temperature for 24 hr and filtered. The beads were washed with acetone until no brown filtrate was obtained, then with dioxane–H_2O (1:1), followed by dioxane. The brominated polymer was extracted overnight in a Soxhlet apparatus equipped with a Dean-Stark water separator using a 2:1 mixture of benzene and dioxane, then dried in vacuo at 50° for 24 hr. Elemental analysis of the product indicated the incorporation of 3.62 mmol of bromine/g of beads.

Anal. Calcd for $(C_8H_7Br)_n$: Br, 43.70. Found: Br, 28.83.

Preparation of the Polystyrene Tin Dichloride Resin 5 from the Bromo Resin 2. The brominated crosslinked polystyrene **2** from above (67 g, 4.0 mmol/g) was suspended in 450 ml of anhydrous tetrahydrofuran in a 2-l. three-necked round-bottomed flask equipped with a mechanical stirrer,[24] a dropping funnel, and a condenser connected to an argon source such that the reaction flask was set up in an atmosphere of argon. After the mixture had cooled to −55° in an acetone–Dry Ice bath, commercial *n*-butyllithium in hexane (350 mmol) was added by way of a syringe with continuous stirring. After the addition was completed, the mixture was allowed to warm to room temperature and stirring was continued for an additional 30 min. The solvent was then siphoned off after a second treatment with *n*-butyllithium in fresh THF, 500 ml of fresh tetrahydrofuran was added,[25] and the suspension was cooled by means of an ice–water bath. Magnesium bromide etherate (350 mmol), freshly prepared from ethylene dibromide and magnesium,[12] was next added dropwise followed immediately by the slow addition of *n*-butyltin trichloride (150 g). Stirring[24] was continued for 24 hr at room temperature under an argon atmosphere. The beads were collected by filtration and washed with dioxane–water (1:1, six times), water (six times), THF–water (1:1, three times), THF (three times), and dry ether (three times). After drying in vacuo at 50° for 24 hr, 78 g of the tin dichloride polymer was obtained.

Anal. Found: C, 63.47; H, 5.04; Br, 0; Cl, 8.20; Sn, 13.15.

The chloride content (8.20%) was thus 2.34 mmol/g of polymer and the tin (13.15%) 1.12 mmol/g.

Generation of the Polymeric Organotin Dihydride Reagent 6. A mechanically stirred[24] slurry of the polymeric tin dichloride beads prepared above (77 g), in 400 ml of anhydrous tetrahydrofuran, was cooled to −55° under an argon atmosphere and treated dropwise with an excess of lithium aluminum hydride (200 ml, 1.6 *M* solution) in tetrahydrofuran.[26] After the addition was completed the mixture was allowed to warm to room temperature and stirring was continued for another 1 hr. The resulting beads were collected by filtration under a stream of argon[27] and washed[27] rapidly with anhydrous tetrahydrofuran (ten times) followed by anhydrous ether (ten times), and finally evacuated in a desiccator at room temperature for 24 hr to give 62 g of material.

Anal. Found: C, 68.34; H, 6.02, Al, 0; Cl, 0; Sn, 14.80.

The tin content (14.80%) corresponds to 1.25 mmol/g. The *maximum* hydride content is therefore 2.50 mmol/g. The *minimum* hydride content (1.98 mmol/g) was determined as described below. The final product displayed a strong absorption at 1850 cm^{-1} (Sn–H) in the infrared spectrum (KBr pellet).

Standardization of the Polymeric Organotin Dihydride Reagent 6 with Iodooctane. One gram of accurately weighed polymeric tin dihydride reagent **6** was suspended in 25 ml of anhydrous tetrahydrofuran (dried and redistilled over lithium aluminum hydride) under an argon atmosphere and treated with a mixture of excess iodooctane (1.2 g, 5 mmol) and ethylbenzene (1 mmol) as an internal standard. The slurry was stirred at room temperature for 3 hr and the conversion of iodooctane to octane was determined by gas chromatography using a 4% FFAP column (7 ft × 0.25 in., 100°).

As determined by VPC analysis, 1.98 mmol of iodooctane was converted to octane. Hence, reagent **6** must contain a minimum of 1.98 mmol of active hydride/g of resin.

Reduction of Acetophenone with the Polymeric Organotin Dihydride Reagent 6. One millimole of acetophenone (0.12 g) was dissolved in 40 ml of anhydrous toluene (dried over Na). To this solution was added 1.5 g of the polymeric organotin resin containing 1.25 mmol H/g. The mixture was refluxed with stirring (overhead mechanical stirrer)[24] for 18 hr under an argon atmosphere. After this period of time, fresh tin resin **6** (0.5 g) was added and the reaction was continued as before. After 30 hr another batch of fresh resin **6** (0.5 g) was added and the reaction was allowed to proceed for an additional 15 hr. The resulting mixture was then cooled and beads were separated by filtration, and the filtrate was saved. The beads were then suspended in 1 *N* HCl–THF (1:1, 40 ml), and stirred for 1 hr at room temperature, then separated by filtration and washed with water, THF, and ether. The combined filtrates and washings were extracted with ether and the combined ether extracts were washed with water, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure to give a yellow oil. The product was purified by evaporative distillation under reduced pressure using a Buchi distillation oven to yield 0.112 g of product (92% of the theoretical). VPC analysis of this distilled product indicated the presence of 95% alcohol and 4% starting material. The product was verified by NMR, ir, and VPC retention time to be 1-phenylethanol.

The reduction of *tert*-butyl methyl ketone, benzaldehyde, 4-phenylcyclohexanone, heptanal, and benzophenone were all carried out in a similar manner. The appropriate isolation procedure is indicated in Table II.

Reduction of 4-Phenylcyclohexanone with Polymer Reagent 6 in the Presence of Platinum Tetrachloride. One millimole of 4-phenylcyclohexanone (0.174 g) and 3 g of tin resin **1** (1.25 mmol H^-/g) in 40 ml of dry tetrahydrofuran were treated with 5 mol % of platinum tetrachloride added in one portion. The mixture was stirred at room temperature for 3 hr, after which time the used beads and catalyst were separated by filtration and washed with

dilute acid, THF, methanol, and ether. The combined filtrates were collected and extracted with three aliquots of ether. The combined ether extracts were washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to give a crude oil. Purification by preparative TLC (silica gel, 5% ether–95% $CHCl_3$ as eluent) afforded 0.132 g (75% of the theoretical) of 4-phenylcyclohexanol along with 19% recovered starting material.

Selective Reduction of Terephthaldehyde. A mixture of 4.0 g (5.2 mmol of active hydride) of the polymeric hydride reagent **6** and 1.0 g (7.5 mmol) of terephthaldehyde in 25 ml of dry toluene was heated overnight at reflux temperature with stirring[24] under an atmosphere of argon. After cooling, the beads were collected by filtration and washed first with anhydrous THF (six times), then dry ether (six times), and the washings were discarded. The insoluble beads were suspended in 1 *N* HCl–THF (1:1, 50 ml) and the mixture was stirred for 2 hr and then filtered. The filtrates were extracted with ether (three times), the combined extracts were dried ($MgSO_4$), and the solvent was removed by evaporation under reduced pressure to yield 1.02 g of crude product. Isolation by preparative TLC on silica gel (1:1 methanol–ethyl acetate) provided the desired *p*-hydroxymethylbenzaldehyde[28] (556 mg, mp 37–46°, 79% yield) along with 1,4-benzenedimethanol (91 mg, 13%). Both products were confirmed by NMR and ir.

Reduction of a Sensitive Alkyl Halide, Iodide 12, Utilizing the Polymeric Organotin Dihydride Reagent 6. In a reaction vessel equipped with an overhead mechanical stirrer[24] was placed 0.492 g (1 mmol) of the iodide **11** (prostaglandin intermediate)[21] in 30 ml of anhydrous tetrahydrofuran. To this solution was added the polymeric organotin dihydride reagent **6** (3 g, 3.75 mmol of hydride) in one portion and the mixture was stirred at room temperature for 80 hr. The beads were separated by filtration and washed with benzene (three times), THF (three times), and dry ether (three times). The combined filtrates were collected and the solvent was removed by evaporation under reduced pressure to yield 0.376 g of a yellow oil. Purification by preparative TLC on silica gel (2:1 benzene–ethyl acetate) afforded 0.315 g (86%) of the desired product, as determined by NMR and ir comparison with an authentic sample,[21] along with 0.022 g (4.5%) of recovered starting material.

The reductions of iodooctane, bromooctane, 1-bromoadamantane, 2-bromoacetophenone, 9-bromoanthracene, benzyl bromide, 2-bromoethylbenzene, and *d*-3-bromocamphor were also investigated. Specific reaction conditions and methods of isolation are indicated in Table III.

Attempted Regeneration of Resin 6 Recovered from Aldehyde and Ketone Reductions. The used resin **6** (25 g) was suspended in 150 ml of anhydrous tetrahydrofuran under an argon atmosphere in a 500-ml three-necked round-bottom flask equipped with a condenser, a mechanical stirrer,[24] and a dropping funnel. The mixture was cooled to −55° in an acetone–Dry Ice bath and treated dropwise with a solution of lithium aluminum hydride in tetrahydrofuran[26] (100 ml, 1 *M*). The mixture was stirred at room temperature for 16 hr and refluxed for an additional 3 hr. After cooling, the beads were separated by filtration under argon[27] and washed with anhydrous THF (three times) and dry ether (six times). Drying under vacuum (ca. 0.1 mmHg, at 20°) afforded 23 g of product. The ir of the regenerated product displayed a weaker absorption at 1850 cm^{-1} (Sn–H absorption) than the fresh resin. Standardization with iodooctane (ethylbenzene used as VPC internal standard) indicated 0.35 mmol of active hydride/g of polymer (1.25 mmol H/g for fresh resin).

Regeneration of the Used Polymeric Reagent 6 Recovered from Halide Reductions. A suspension of the spent hydride reagent **6** (7g) in 80 ml of anhydrous tetrahydrofuran under an argon atmosphere was treated at −30° with a solution of lithium aluminum hydride in THF[26] (40 ml, 0.90 *M*). The mixture was warmed to room temperature and stirred[24] overnight. After heating at the reflux temperature for 3 hr the resin was isolated as described above to yield 6.5 g of beads. Standardization of the regenerated resin with excess iodooctane (followed by VPC analysis using ethylbenzene as the internal standard) indicated that the polymer contained 0.75 mmol of active hydride/g (fresh resin contained 1.25 mmol/g).

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Registry No.—**1**, 39464-91-0; **7**, 629-27-6; **8**, 111-65-9; **11**, 38361-03-4; **12**, 38361-00-1.

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(25) It is important to avoid contact of the lithiated beads with air.
(26) A freshly opened bottle of commercial material or a freshly prepared solution is satisfactory.
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Dilution Effects on the Reaction of Carbethoxynitrene with *trans*-1,2-Dimethylcyclohexane with Hexafluorobenzene and Reactive Solvents

Robert C. Belloli* and Valerie A. LaBahn

Department of Chemistry, California State University, Fullerton, Fullerton, California 92634

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Absolute yields, stereospecificity, and selectivity of reaction are reported for the thermal decomposition of ethyl azidoformate in *trans*-1,2-dimethylcyclohexane using hexafluorobenzene as an inert diluent. Hexafluorobenzene is shown to have a stabilizing interaction on the singlet state of the resulting carbethoxynitrene as manifested by increased absolute yields with increasing dilution. Comparisons are made with previous results using dichloromethane to illustrate the generality of this theoretically predicted singlet stabilization. The absolute yield but not the selectivity or stereospecificity is shown to be very dependent on azide molarity (extent of dilution) even without inert, singlet-stabilizing solvents present.

In a previous communication, we reported on the ability of dichloromethane to stabilize the singlet state of carbethoxynitrene as manifested by an increase in absolute yield of insertion products with *trans*-1,2-dimethylcyclohexane upon dilution with dichloromethane and a reduction in the selectivity (tertiary–secondary–primary insertion products) of the reaction with dilution as progressively more of the nitrene exists as a nitrene–solvent complex.[1] A similar reduction of selectivity in the presence of halogenated solvents has been recently reported by Tardella et al., based on a study of the insertion reaction of carbethoxynitrene with bicyclo[4.*n*.0.]alkanes.[2]

An increase in absolute yield for the insertion reaction of carbalkoxynitrenes with hydrocarbons upon dilution with hexafluorobenzene has also been observed.[3] Hexafluorobenzene is an inert solvent which has the symmetrical lone pairs of electrons necessary for stabilization of singlet nitrenes according to the proposal of Gleiter and Hoffmann.[4] Since insertion yields from the singlet nitrene have been observed to increase in the presence of radical (triplet nitrene) traps,[5] some question has existed whether the effect of C_6F_6 is that of singlet stabilizing by complex formation as with CH_2Cl_2 or whether it is functioning as a radical trap. A related question arising from the use of CH_2Cl_2 and C_6F_6 as solvents is whether the singlet stabilizing phenomenon is limited to the reactions of alkanoylnitrenes (ROCN) or includes carbalkoxynitrenes (ROCON) as well.[6,7] In the first part of this paper, we will report our results of a study of the effect on stereochemistry, selectivity, and absolute yield of dilution with hexafluorobenzene of the reaction between thermally generated carbethoxynitrene and *trans*-1,2-dimethylcyclohexane (eq 1). The results in Table I are based on triplicate runs with an error of ±1.0% for the stereospecificity, ±1.0% for the selectivity (percent tertiary), and ±2.0% for the absolute yield. The data in Table I which deal with the effect of dilution on absolute yields are presented in graphical form in Figure 1. The absolute yield of C–H insertion products is shown to increase dramatically upon initial dilution of the azide–hydrocarbon reaction mixture with C_6F_6 with an eventual leveling off at high dilution. The range of absolute yields agrees with our previous results[1] using CH_2Cl_2 as the diluent, although C_6F_6 shows a smooth increasing trend and a higher final absolute yield whereas CH_2Cl_2 showed an initial increase with no noticeable trend thereafter.

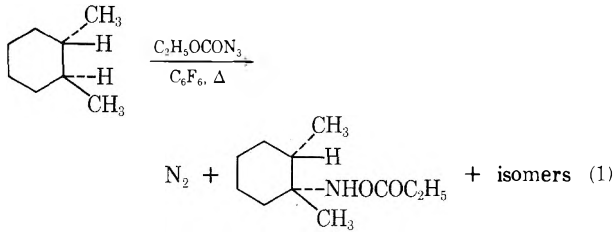

Table I
Thermal Decomposition of Ethyl Azidoformate in Hexafluorobenzene–*trans*-1,2-Dimethylcyclohexane (TDCH) Solutions[a]

Concn TDCH, mol %[b]	Azidoformate, *M*	Stereospecificity (% trans insertion product)	Selectivity (% tertiary product)[c]	Absolute yield, %[d]
100.0	0.660	96.9	40.6	26.0
89.2	0.602	97.0	41.4	33.3
74.7	0.510	98.2	40.1	41.2
50.1	0.344	96.9	36.3	42.7
25.0	0.170	95.3	36.2	44.2
10.7	0.078	90.9	35.1	44.8

[a] Reaction mixtures were carefully degassed and azide decomposition was carried out in evacuated, sealed tubes at 120° for 90 hr; analysis by BPC. [b] The mol % TDCH is computed from the number of moles of TDCH and C_6F_6 present and does not include the azidoformate concentration. [c] Percent tertiary C–H insertion product of other isomers combined: (tertiary)/(tertiary + secondary + primary) × 100. [d] Total absolute yield of all insertion isomers.

Based on our selectivity data, we conclude that CH_2Cl_2 forms a stronger complex with carbethoxynitrene than C_6F_6, since at high dilution the percent tertiary product is substantially less with CH_2Cl_2 as solvent than with C_6F_6. The stereospecificity data is in accord with many observations that only the singlet carbethoxynitrene (complexed or not) inserts into inactivated C–H bonds.[8] It is noteworthy that at the highest dilution with both CH_2Cl_2 and C_6F_6, the stereospecificity is somewhat lower than for the other concentrations whereas with TDCH (a reactive diluent) Table II shows no decrease at high dilution. It is conceivable that at very high dilution with inert solvent, collisional deactivation of singlet to triplet nitrene begins to compete with singlet insertion or complex formation. There is evidence for some radical character (CH_3CH_2OCONH formed from the triplet nitrene) in thermal reactions of ethyl azidoformate with hydrocarbons and this could be responsible for a small amount of nonstereospecifically formed insertion product or for cis–trans isomerization of the tertiary insertion product.[9] If the small decrease in stereospecificity were due to partial radical character, then this would be evidence against C_6F_6 acting as a radical trap in these reac-

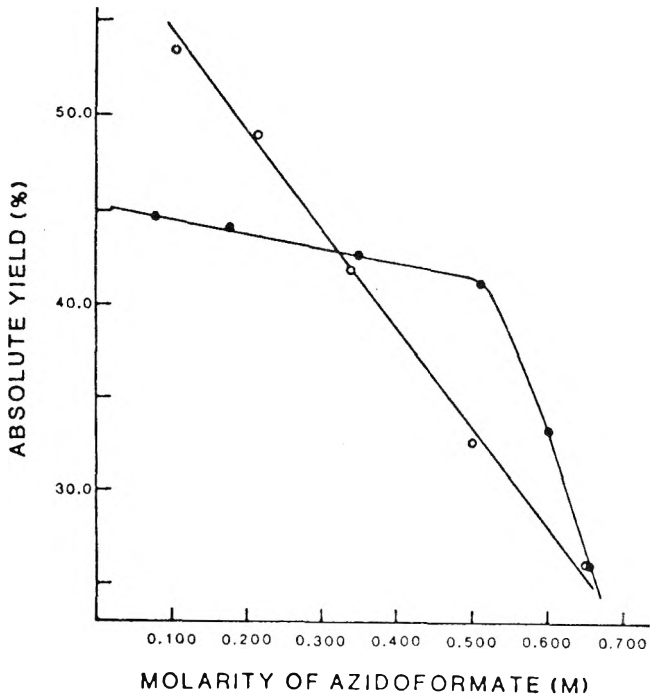

Figure 1. Absolute yield of TDCH insertion products as a function of azidoformate molarity: ●, dilution with C_6F_6; ○, dilution with TDCH.

tions, since the stereospecificity should remain high or should increase with increasing dilution with C_6F_6. Moreover, the hexafluorobenzene even for the initial dilution experiment (89.2 mol % TDCH and 10.8 mol % C_6F_6) is present in much greater concentration than the azidoformate. Therefore, although the initial increase in absolute yield might be explained by C_6F_6 acting as a radical trap, the steady increase in yield with subsequent dilution is not explicable on this basis.

In these studies the weight ratio of azidoformate to hydrocarbon was kept the same at about 1:10. This is an excess of hydrocarbon similar to that employed by Lwowski in his studies of dichloromethane dilution effects on the reaction of ethyl azidoformate with 3-methylhexane[10] to which our results were compared. Suitable volumes of CH_2Cl_2 or C_6F_6 are then added to give solutions of lower mole percent TDCH and lower molarity of azidoformate. Although the absolute yields we presented in our previous paper[1] and in Table I agreed with those of Lwowski,[10] these yields are low (25–45%) compared to those obtained by other workers studying carbalkoxynitrene-saturated hydrocarbon reactions, e.g., Breslow (50–75%).[3]

Table II presents the results of a series of experiments designed to test the assumption that a 10:1 ratio of hydrocarbon to azide constitutes a sufficiently great excess of hydrocarbon to ensure reaction between the nitrene and hydrocarbon uncomplicated by yield-reducing side reactions. Figure 1 shows the dependence of absolute yield of insertion products of TDCH on the molarity of the azidoformate with TDCH itself as the diluent. It is evident that a hydrocarbon–azide ratio of 10:1 (approximately 0.66 *M*) is not a sufficiently great excess of hydrocarbon to ensure maximum yields of insertion products. However, the absolute yield appears to be the only result which is noticeably affected by dilution with the reacting hydrocarbon itself; the selectivity and stereochemistry remain about the same through the dilution range. Figure 1 shows that dilution with hexafluorobenzene causes a considerably greater initial increase in absolute yield than does dilution with the reacting hydrocarbon itself.

The decrease in absolute yield of insertion products with

Table II
Thermal Decomposition of Ethyl Azidoformate in *trans*-1,2-Dimethylcyclohexane[a]

Azidoformate, *M*	Stereospecificity (% trans insertion product)	Selectivity (% tertiary product)	Absolute yield, %
0.665	96.9	40.6	26.0
0.501	97.5	39.7	32.4
0.341	99.1	39.9	41.8
0.228	97.8	39.0	49.0
0.100	98.2	37.0	53.8

[a] See Table I for definition of terms and reaction conditions.

increasing molarity of the azidoformate in the saturated hydrocarbon (Table II) is not compensated for by an increase in yield of the ethyl carbamate (triplet abstraction) product. In our study, the ethyl carbamate (urethane) yield decreased slightly as the molarity of azidoformate increased and in another study[10] involving thermolysis of ethyl azidoformate in saturated hydrocarbon solutions the insertion yields but not the ethyl carbamate yields were changed by dilution experiment.

Ethyl azidoformate was thermally decomposed in solutions (approximately 0.6 *M*) of dichloromethane and of carbon tetrachloride under conditions exactly the same as those employed to obtain the data in Tables I and II. For both solvents gas chromatographic analysis showed only solvent, a small amount of unreacted azide, and a trace amount of urethane. Slightly more urethane was observed using CH_2Cl_2 as inert solvent. Some polymeric material was deposited in the tubes and the solutions were light yellow after reaction using either solvent.

The conclusion based on the evidence accumulated in these and other experiments is that the side reaction responsible for reducing the insertion yields is the decomposition of the nitrene itself.

Experimental Section

The general reaction procedure for these sealed-tube reactions and the analysis and characterization of the insertion products have been previously described.[1] It was subsequently determined that reaction times as short as 48 hr are sufficient to ensure complete decomposition of the azide without changing the yield, stereospecificity, or selectivity.

The source and purity of the ethyl azidoformate, dichloromethane, and *trans*-1,2-dimethylcyclohexane reagents has also been given in a previous work.[1]

Hexafluorobenzene (Aldrich) was found to be >99% pure by VPC analysis and was used without further purification.

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Registry No.—*trans*-1,2-Dimethylcyclohexane, 6876-23-9; hexafluorobenzene, 392-56-3; ethyl azidoformate, 817-87-8.

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Spiro[5.5]undeca-5,11-(propan-2′-one)-2,8-dione—a Possible Precursor of the Benzo[*d*]naphthalene Cation

Charles F. Wilcox, Jr.,* and G. D. Grantham

Department of Chemistry, Cornell University, Ithaca, New York, 14853

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The synthesis of two stereoisomers of the title compound is described and their stereochemistries assigned using a combination of high-field NMR and lanthanide shift reagents. These results are applied to the stereochemical assignment of the previously synthesized spiro[5.5]undeca-5,11-propano-2,8-dione.

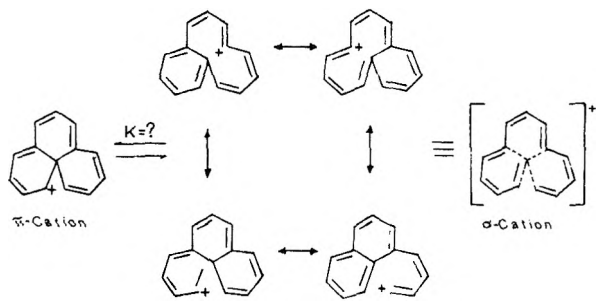
The tetrahedral carbon atom is the cornerstone of organic structural theory, although very few compounds possess pure tetrahedral geometry.[1] The question naturally arises as to how much the tetrahedral geometry may be distorted, the ultimate distortion being represented by a square planar geometry.

Extended Hückel calculations[2] predict that tetrahedral methane is more stable than the planar geometry by 127 kcal/mol, while a CNDO[3] calculation yields 187 kcal/mol for the same quantity. An ab initio calculation using a minimal basis set[4] predicts the energy of planar methane to be 250 kcal/mol greater than that of tetrahedral methane. More recently Wiberg and Ellison[5] found that an ab initio calculation using a larger basis set which included 3d functions on carbon and 2p functions on the hydrogens reduced the total energy of planar methane to 160 kcal/mol; if the bond angle was reduced from 180° (planar) to 140° the total energy using the larger basis set was only 37 kcal/mol above that of tetrahedral methane.

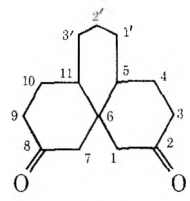
Clearly the energy requirements are high, and in order to be accessible the planar geometry must be stabilized or the tetrahedral geometry destabilized. Recently Hoffmann, Alder, and Wilcox[6] have outlined several ways in which this problem might be solved. One of the more promising approaches for stabilizing the planar geometry involves incorporation of the lone pair of the planar tetracoordinate carbon into an annulene perimeter.

One such possibility is the benzo[*d*]naphthalene cation system (Chart I). In this system the planar σ cation is an aromatic (i.e., $4n + 2$) [14]annulene with a Hückel π energy of 19.3β. The nonplanar π cation (fully conjugated, positive charge in the π network) has a π energy of 15.8β. The 3.5β difference is therefore available to provide the driving force for promotion of a pair of σ electrons into the π system to create the planar σ cation.

Chart I
The Benzo[*d*]naphthalene Cation System



In order to test this approach a suitable precursor having the correct carbon skeleton and with sufficient functionality to permit subsequent introduction of the required unsaturation is necessary. Entry into the desired carbon skeleton can be attained through a novel reaction between 1-(1-pyrrolidino)cyclohexene and methyl vinyl ketone originally discovered by House and coworkers.[7] This paper describes an elaboration of this reaction that provides such an appropriately functionalized precursor. The product of the House reaction, spiro[5.5]undeca-5,11-propano-2,8-dione[8] (**1**), already has appropriate functionality in two of its three



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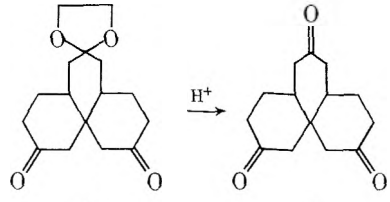
rings. The original plan was to introduce a third carbonyl group at the 2′ position by employing the analogous reaction between the pyrrolidine enamine of 1,4-cyclohexanedione monoethylene ketal[9] and methyl vinyl ketone to afford **2**, which could then be converted to spiro[5.5]undeca-5,11-(propan-2′-one)-2,8-dione (**3**). Unfortunately, **2**



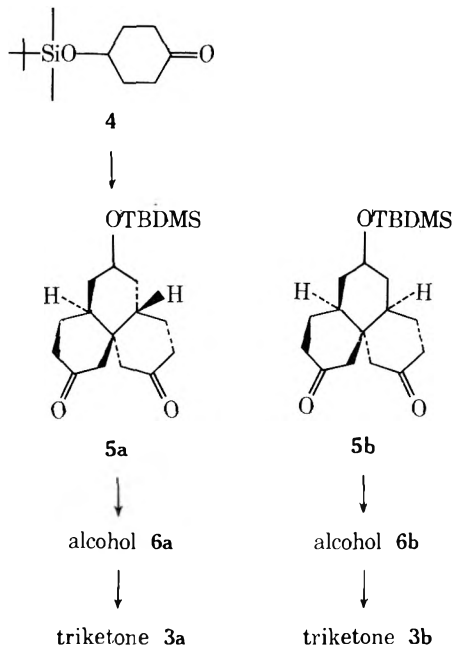
2 **3**

could be obtained in only 1.4% yield. This low yield is presumably due to the acid lability of the ketal protecting group, which fails to survive under the conditions necessary to hydrolyze the intermediate enamine. As a result, an alternate approach utilizing a protected hydroxyl function (Scheme I) was employed. Corey's[10] work utilizing *tert*-butyldimethylchlorosilane as a hydroxyl protecting group suggested that this silyl ether would survive a mild acid hydrolysis yet be removable under conditions which would not affect the integrity of the ring system.

4-*tert*-Butyldimethylsiloxycyclohexanone (**4**, Scheme I) could be prepared in high yield using Corey's[10] imidazole-catalyzed procedure. The enamine was prepared using standard[9] procedures and reacted with methyl vinyl ketone. Work-up of this reaction followed by column chromatography afforded a white, amorphous powder, **5**, in 16% yield based on 4 together with a viscous resin which NMR indicated consisted primarily of a mixture of 6-*tert*-butyldimethylsiloxy-$\Delta^{1,9}$- and -$\Delta^{9,10}$-octal-2-one epimers. Careful examination of this amorphous powder by thin layer chromatography revealed the presence of two components. The two compounds, later identified as isomers **5a** and **5b** (vide infra), were separated as outlined below.

Isomer **5a** could be obtained in pure form (mp 113.5–114.4°) by careful column chromatography on alumina

Scheme I



using chloroform as the eluent. Once isolated in pure form it was easily hydrolyzed to the alcohol **6a** (mp 163.5–164.5°), which in turn was converted in high yield to the triketone **3a** (mp 155–157°) via Jones oxidation. Unfortunately, isomer **5b** could not be freed entirely of isomer **5a** by column chromatography. However, in the course of hydrolyzing a mixture of isomers **5a** and **5b** it was observed that **5b** hydrolyzed much more slowly than isomer **5a**. By exploiting this observation it was possible to obtain isomer **5b** in pure form (mp 129–130°) by subjecting the mixture to a short hydrolysis followed by column chromatography to separate **5b** from the mixture of isomeric alcohols **6a** and **6b**. Isomer **5b** was then converted to the alcohol **6b** (mp 182–184°), which in turn was oxidized to the triketone **3b** (mp 215–218°).

Stereochemistry of Isomers 3a and 3b. There are three possible geometrical arrangements for the triketone **3**. Isomer **3a**, in which there are two cis ring fusions, is a very flexible configuration. In the all-chair conformation **3a** is unsymmetrical; however, a slight distortion of the all-chair conformation would result in a potential twofold rotational axis (Chart II). Isomer **3b**, in which there is one cis and one

Chart II
Stereoisomer of Triketone 3

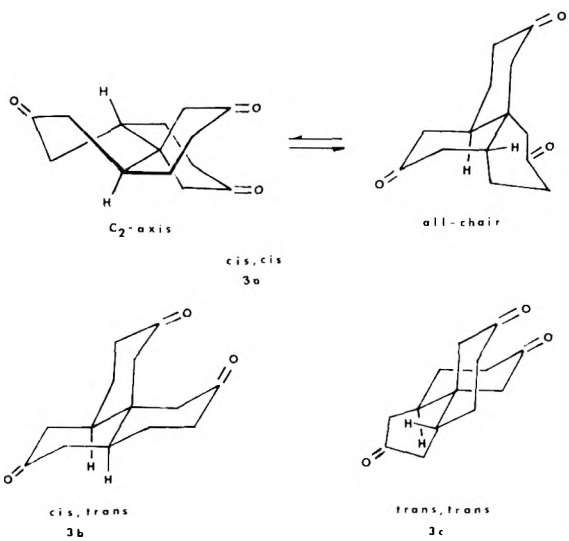


Table I
Chemical Shifts and Coupling Constants for Isomer 3a[a]

Chemical shifts (Hz from external Me_4Si)		Coupling constants, Hz	
H_8, H_9	869.0[b], 1040.6[b]	$J_{1,2} = -7.56$	$J_{4,6} = 6.65$
		$J_{1,3} = 7.68$	$J_{4,7} = 7.46$
H_1, H_2	963.3, 962.7	$J_{2,3} = 4.50$	$J_{5,6} = 6.40$
		$J_{3,4} = 7.09$	$J_{5,7} = 7.97$
H_6, H_7	846.1, 841.8	$J_{3,5} = 4.63$	$J_{6,7} = -13.68$
H_3	814.8	$J_{4,5} = -14.42$	$J_{8,9} = -14.0$[b]
H_5	732.8		
H_4	657.1		

[a] The chemical shifts and coupling constants were extracted from the 220-MHz Eu(thd)$_3$-shifted spectrum of **3a** (Figure 1) using a LAOCOON III computer program on an IBM 370/168 computer. [b] H_8 and H_9 were not included in the LAOCOON III calculation; these values were measured directly from the spectrum.

trans ring fusion, is a relatively rigid all-chair conformation in which there is no C_2 axis. Isomer **3c**, in which there are two trans ring fusions, is locked into a conformation which requires a C_2 axis.

The usual 60-MHz proton NMR spectra were of little use in assigning the structures of isomers **3a** and **3b**: both spectra consist of a broad envelope in which there are no recognizable structural features. However, more stereochemical information could be obtained with the use of high field strength 220-MHz instrumentation in conjunction with the lanthanide shift reagent Eu(thd)$_3$.

Upon addition of successive increments of Eu(thd)$_3$ to a solution of **3a** in deuteriochloroform several resonances are progressively shifted downfield until at saturation the 220-MHz spectrum appears as in Figure 1. Most strongly affected was a two-proton doublet which was shown by double resonance to be one half of an isolated four-proton AB system (δ_{Eu} 4.73, 3.95, $J \simeq 14$ Hz).[11] The observation that this system was not coupled to any other protons in the spectrum permitted the assignment of these resonances to the methylene protons isolated between the quaternary carbon and the adjacent carbonyl groups (H_8 and H_9 in Figure 1). Somewhat less strongly affected was a four-proton doublet (δ_{Eu} 4.38) which was shown to be coupled ($J \simeq 7$ Hz) solely to H_3 by irradiation of the latter signal. This observation permitted the assignment of this resonance to H_1 and H_2. A four-proton triplet (actually a pair of overlapping doublets, δ_{Eu} 3.85, 3.83) was shown to be coupled to H_4 and H_5 by irradiation of the latter two signals and can therefore be assigned to H_6 and H_7. The four coupling constants in this system are all approximately 7 Hz. Finally, protons H_4 and H_5 were shown to be coupled to H_3 as well as to H_6 and H_7. The measured coupling constants and chemical shifts were then used as input for an iterative LAOCOON III calculation which gave the refined values in Table I. The bottom portion of Figure 1 is a computer simulation of the NMR spectrum of **3a** using these calculated values.

The proton NMR results clearly demand a C_2 axis (either static or dynamic) for the lower melting triketone isomer (**3a**). Consistent with this requirement, the ^{13}C NMR spectrum of this isomer (without shift reagent) shows only eight absorptions, whereas the precursor alcohol (**6a**) in which the C_2 axis is destroyed shows all 14 individual carbon resonances. The requirement of a C_2 axis is sufficient to eliminate isomer **3b** from consideration as the correct stereochemistry for the lower melting triketone isomer.

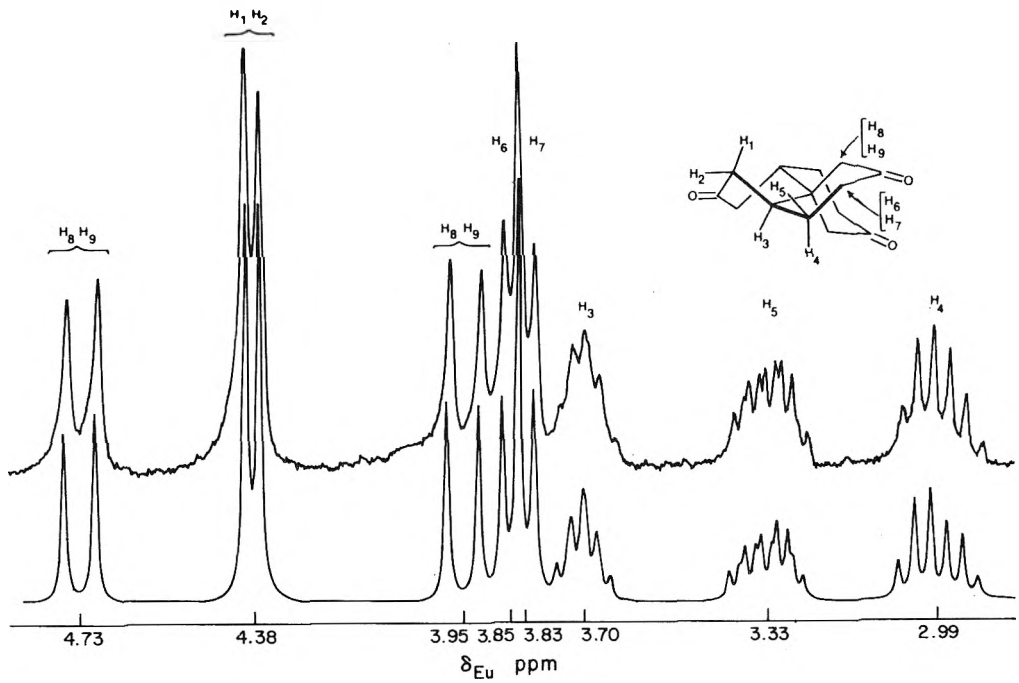
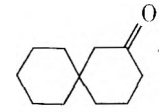


Figure 1. Top: observed Eu(thd)$_3$-shifted 220-MHz proton NMR spectrum of **3a**. Bottom: computer-simulated NMR spectrum using the chemical shifts and coupling constants in Table I.

However, the presence of a C_2 axis does not distinguish between **3a** and **3c**. In order to distinguish between these two possibilities one must be able to detect the presence of either cis or trans ring fusions. Crucial to this distinction are the magnitudes of the coupling constants $J_{3,4}$ and $J_{3,5}$ between the methine proton (H_3) and the adjacent methylene protons (H_4 and H_5). In the isomer having two trans fusions (**3c**) one would expect one trans diaxial interaction (typically J = 8–10 Hz) and one axial–equatorial interaction (typically J = 2–3 Hz). In the isomer having two cis ring fusions (**3a**) the relationship between the methine and methylene protons is nearly gauche and there should therefore be a tendency for the coupling constants to equalize. Since **3a** is conformationally mobile, the observed coupling constants will be a weighted average of the coupling constants over all the conformations of the molecule. Examination of models suggests that these coupling constants should fall in the range $J_{3,4}$ = 6–7 and $J_{3,5}$ = 3–4 Hz. Thus, the observed values, $J_{3,4}$ = 7.09 and $J_{3,5}$ = 4.63 Hz, are suggestive of cis ring fusions in the lower melting ketone isomer. However, since the vicinal coupling constant–dihedral angle correlation is approximate at best, these results do not rigorously exclude isomer **3c**. It may be argued that the fact that the triketones are formed under relatively mild conditions via a series of presumably reversible reactions mitigates against the formation of the trans,trans isomer (**3c**) in which the two trans fusions introduce a substantial amount of strain.[7] While we cannot rigorously exclude isomer **3c**, we feel that this argument, coupled with the foregoing NMR evidence, makes the cis,cis geometry (**3a**) most probable for the lower melting ketone isomer.

The foregoing discussion leaves **3b** as the only possible stereochemistry for the higher melting triketone isomer. The required absence of a C_2 axis is confirmed by the ^{13}C NMR spectrum, in which 12 separate carbon resonances appear. Unfortunately, this isomer proved too insoluble in deuteriochloroform to obtain high-field continuous wave lanthanide shifted proton NMR spectra. However, we were able to obtain a pulsed Fourier transform proton NMR (90 MHz) in the presence of Eu(fod)$_3$.[13] It seems reasonable to assume that the protons in this isomer shift in the same order that was observed for **3a**. The extra splitting which would be expected based on the absence of a C_2 axis and the presence of both a cis and a trans ring fusion is readily apparent in this spectrum. The NMR results are therefore consistent with the required assignment of stereochemistry **3b** to the higher melting triketone isomer.

In the course of isolating **3a** and **3b**, we obtained the mass spectra of these isomers. Weringa[14] has extensively studied the mass spectra of spiroalkanones with five- and six-membered rings. In particular, he has found that two of the principal peaks in the mass spectrum of spiro[5.5]undecan-2-one (**7**) arise from the loss of C_3H_6O (P − 58, rel intensity 92) and C_3H_5O (P −57, rel intensity 23) fragments. As might be expected, these two modes of decomposition are also important in the triketone isomers **3a** and **3b**. More interesting, however, are the marked differences in the relative amounts of the two decomposition modes observed for these isomers. In the cis,cis isomer (**3a**) the relative intensity of the peak resulting from the loss of C_3H_6O (*m/e* 176) is nearly four times the relative intensity of the peak resulting from the loss of C_3H_5O (*m/e* 177), whereas in isomer **3b** the relative intensities of the peaks resulting from these two modes of decomposition are nearly equal.



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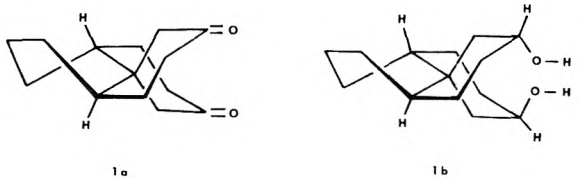
The same three stereochemical arrangements are of course possible for the diketone **1**. House et al.[7] eliminated the trans,trans diketone from consideration on the grounds that the formation of the strained trans,trans ring fusions was unlikely in a series of reversible reactions. Furthermore, the all-chair conformation for the cis,cis isomer was assumed. The diketone was assigned the cis,trans structure on the grounds that the diol resulting from reduction of the diketone with sodium borohydride showed evidence of an *intramolecular* hydrogen bond in its infrared spectrum; the formation of an intramolecular hydrogen bond in the diol which would result from reduction of the all-chair form of cis,cis diketone being deemed impossible since the oxygens would be too far apart. Our results, however, indicate

that the possibility of the stereochemistry **1a** cannot be ignored (this stereochemistry being accessible in triketone **3a**). Examination of models indicates that if the diketone were to assume this conformation the distance between the carbonyl groups would be precisely the same as that in cis-,trans isomer. Furthermore, even if the diketone itself did not prefer the stereochemistry **1a**, it could be argued that the formation of an intramolecular hydrogen bond might provide the impetus for a change in this conformation in the corresponding diol (**1b**). Thus, the formation of such a



1a 1b

hydrogen bond does not itself provide enough evidence to distinguish between the cis,cis isomer and the cis,trans isomer. In an effort to clarify this point we obtained ^{13}C and lanthanide-shifted 60-MHz proton NMR spectra of diketone **1**. Fourteen individual carbon resonances are visible in the ^{13}C spectrum of diketone **1**, indicating the absence of a C_2 axis. This absence of a C_2 axis is consistent with either the all-chair cis,cis stereochemistry or the cis,trans stereochemistry and indicates that if the diketone prepared by House et al.[7] is the cis,cis isomer, the conformation **1a** is not accessible under the same conditions as it was for the corresponding triketone conformer **3a**. The ^{13}C NMR spectrum therefore does not offer a means of distinguishing between these two possibilities; it does, however, exclude the trans,trans stereochemistry.

Efforts to assign either the cis,cis or the cis,trans stereochemistry on the basis of coupling constants between the methine proton and the adjacent methylene protons were thwarted because the methine resonances could not be shifted out of the broad envelope of resonances arising from the saturated three-carbon bridge in **1**. One piece of evidence in favor of the cis,trans stereochemistry is provided by the mass spectrum, which resembles the mass spectrum of triketone isomer **3b** in that the loss of C_3H_6O (P − 58) is not the major fragmentation mode. Thus, while we are unable to offer any positive evidence for the assignment of the cis,trans stereochemistry to the diketone prepared by House and coworkers,[7] failure to observe a C_2 axis, particularly in the light of the findings for the triketone isomers, constitutes strong presumptive evidence that the diketone **1** has the cis,trans stereochemistry.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The continuous wave 60-MHz proton NMR spectra were obtained on a Varian A-60A spectrometer in the solvent indicated using tetramethylsilane as an internal reference. ^{13}C NMR spectra were obtained at 22.6 MHz in $CDCl_3$ on a Bruker HFX-90 spectrometer equipped with a Digilab Fourier transform accessory; chemical shifts are reported in parts per million relative to internal tetramethylsilane. Mass spectra were obtained on an AEI MS902 spectrometer at 70 eV. Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Spiro[5.5]undeca-5,11-propano-2,8-dione (1) was prepared as described by House et al.:[7] mp 159–160° (lit.[7] mp 161–162°); ^{13}C NMR 25.7, 26.3, 26.5, 27.4, 27.9, 36.7, 40.0, 41.2, 41.6, 43.4, 44.7, 50.9, 208.0, 208.8 ppm; MS m/e (rel intensity) 221 (16), 220 (100), 163 (45), 162 (26), 156 (68), 149 (61), 141 (61).

4-Hydroxycyclohexanone was first prepared by the method of Jones and Sondheimer,[15] and later by a shorter route developed by Radlick and Crawford.[16]

Preparation of 4-*tert*-Butyldimethylsiloxycyclohexanone (4). A solution of 4-hydroxycyclohexanone (6.13 g, 0.053 mol), *tert*-butyldimethylchlorosilane (9.70 g, 0.064 mol, Willowbrook Labs), and imidazole (9.00 g, 0.132 mol, Aldrich) in 13 ml of dry (distilled from CaH_2) dimethylformamide was stirred for 48 hr at room temperature under a silica gel drying tube.[12] The mixture was then poured into water and extracted several times with diethyl ether. The ether extracts were back extracted with distilled water, dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford 12.6 g of the crude silyl ether. Distillation afforded 10.01 g (84%) of 4-*tert*-butyldimethylsiloxycyclohexanone as a clear, viscous liquid: bp 71–72° (0.45 Torr); ir (neat) 1710, 1260, 1110, and 1050 cm^{-1}; NMR ($CDCl_3$) δ 4.15 (multiplet, 1 H), 3.0–1.7 (complex multiplet, 8 H), 0.95 (singlet, 9 H), 0.15 (singlet, 6 H).

Reaction of 1-(1-Pyrrolidino)-4-*tert*-butyldimethylsiloxycyclohexene with Methyl Vinyl Ketone (Preparation of 5). The pyrrolidine enamine of 4-*tert*-butyldimethylsiloxycyclohexanone was prepared by refluxing a solution of the ketone (22.80 g, 0.10 mol) and pyrrolidine (16.1 ml, 0.20 mol, Aldrich) in 150 ml of benzene under a Dean-Stark trap until water ceased to separate (about 8 hr). The benzene and excess pyrrolidine were removed under vacuum on a rotary evaporator. The crude enamine was used without further purification (the crude material gave spectra consistent with the desired product): ir (neat) 1640, 1260, and 1110 cm^{-1}; NMR ($CDCl_3$) δ 4.2–3.5 (multiplet, 2 H), 3.2–1.5 (complex multiplet, 6 H), 0.95 (singlet, 9 H), 0.15 (singlet, 6 H).

The crude enamine was placed under a nitrogen atmosphere and dissolved in 35 ml of absolute ethanol (dried over 3-Å molecular sieves). Freshly distilled methyl vinyl ketone (18.0 g, 0.30 mol, Aldrich) was added (exothermic reaction!) with stirring at a rate sufficient to maintain a gentle reflux. After the addition of methyl vinyl ketone was complete the solution was refluxed for 4 hr. Acetate buffer solution (15 ml, prepared by dissolving 12.5 g of sodium acetate in 25.0 ml of distilled water and 25.0 ml of glacial acetic acid) was added, and the solution was refluxed for an additional 2 hr. The reaction mixture was cooled, most of the solvent was removed under vacuum on the rotary evaporator, and the residue was taken up in CH_2Cl_2 and washed with several portions of water. The organic extracts were filtered through a 2 × 5.5 cm column of Woelm Activity Grade I alumina (100–200 mesh) to afford 44.1 g of an orange resin.

The products were isolated by chromatography on 1200 g of Woelm Dry Column Grade alumina (100–200 mesh). The fractions eluted with anhydrous ether afforded 22.0 g of a reddish liquid which NMR indicates is predominantly a mixture of 6-*tert*-butyldimethylsiloxy-$\Delta^{1,9}$-octal-2-one and 6-*tert*-butyldimethylsiloxy-$\Delta^{9,10}$-octal-2-one: NMR ($CDCl_3$) δ 5.85 (singlet), 4.25 (broad multiplet), 3.0–1.2 (complex multiplet), 0.95 (singlet), 0.15 (singlet). When the eluent was changed to 50:50 (v/v) ethyl acetate–diethyl ether, the desired products were obtained as a yellow, resinous material which crystallized on trituration with pentane to afford 5.78 g (16%) of the mixed isomers **15** as a white, amorphous powder: mp 90–110°; ir (Nujol) 1705, 1110, and 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.15 (broad multiplet, 1 H), 3.2–1.5 (complex multiplet, 18 H), 0.95 (singlet, 9 H), 0.15 (singlet, 6 H).

In several runs of this reaction on a similar scale yields ranged from 8–20% of the theoretical (based on 4-*tert*-butyldimethylsiloxycyclohexanone). The remainder of the starting material was always accounted for in the yield of 6-*tert*-butyldimethylsiloxy-$\Delta^{1,9}$- and -$\Delta^{9,10}$-octal-2-one epimers.

Separation of *cis,cis*-Spiro[5.5]undeca-5,11-(2'-*tert*-butyldimethylsiloxypropane)-2,8-dione (5a). In a typical separation 1.38 g of the mixed isomers 15 was chromatographed on 500 g of Woelm Dry Column Grade alumina (100–200 mesh) using chloroform as the eluent. Forty 25-ml fractions were collected. Fractions 1–5 gave 106 mg of the cis,cis isomer (**5a**), mp 113–114°. Fractions 6–19 gave 840 mg of mixed isomers, mp 90–110°. Fractions 20–40 afforded 357 mg of mixed isomers, mp 104–108°. The middle fractions could be rechromatographed to yield additional pure cis,cis isomer. Treatment of 5.00 g of the mixed isomers in this manner followed by crystallization from Fisher "hexanes" gave 1.38 g of the cis,cis isomer (**5a**), mp 113.5–114.5°, ir (KBr) 2850, 1690, 1440, 1240, 1050, 865, 830, and 770 cm^{-1}, NMR ($CDCl_3$) δ 4.15 (broad multiplet, 1 H), 3.2–1.6 (complex multiplet, 18 H), 0.95 (singlet, 9 H), 0.15 (singlet, 6 H), and 2.75 g of the mixed isomers, mp 104–107°. Attempts to improve the melting point of this latter mixture by further chromatography were not successful.

Preparation of *cis,cis*-Spiro[5.5]undeca-5,11-(propan-2'-ol)-2,8-dione (6a). A solution of 710 mg of *cis,cis*-spiro[5.5]undeca-5,11-(2'-*tert*-butyldimethylsiloxypropane)-2,8-dione (**5a**) in 15 ml of 3:1:1 acetic acid–tetrahydrofuran–water was stirred at

room temperature for 24 hr. The reaction mixture was then diluted to 100 ml with distilled water and most of the acetic acid was neutralized by addition of solid $NaHCO_3$. The resulting solution was extracted twice with 25-ml portions of $CHCl_3$, and the aqueous layer was saturated with NaCl and then reextracted with a total of 100 ml of $CHCl_3$. The combined organic extracts were dried over anhydrous K_2CO_3 and concentrated under vacuum to afford an oily residue. Trituration with pentane and filtration afforded 400 mg (84%) of the alcohol **6a** as a white powder, mp 163–164°. Crystallization from ethyl acetate gave white plates: mp 163.5–164.5°; ir (KBr) 3350, 2900, 1690, 1420, 1315, 1290, 1140, 1080, 1040, and 1010 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (broad multiplet, 1 H) 3.15–170 (complex multiplet, 19 H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.54; O, 20.31. Found: C, 71.17; H, 8.51; O, 20.32.

Preparation of *cis,cis*-Spiro[5.5]undeca-5,11-(propan-2′-one)-2,8-dione (3a). A solution of 313 mg of *cis,cis*-spiro[5.5]undeca-5,11-(propan-2′-ol)-2,8-dione (**6a**) in 25 ml of acetone (Mallinkrodt, reagent grade) was titrated at room temperature with a total of 0.67 ml of Jones reagent (prepared by dissolving 100.00 g of CrO_3 in 84 ml of concentrated H_2SO_4 and diluting to 500 ml with water). After addition was complete, the reaction mixture was stirred for 15 min at room temperature and a few drops of ethanol were added to destroy any excess reagent. The precipitated chromium salts were filtered off and washed with acetone. The combined acetone fractions were concentrated and the residue was taken up in $CHCl_3$ and washed with water to remove a faint green tinge. The $CHCl_3$ solution was dried over K_2CO_3 and concentrated. Crystallization of the residue from 50:50 ethyl acetate–cyclohexane gave 250 mg (90%) of *cis,cis*-spiro[5.5]undeca-5,11-(propan-2′-one)-2,8-dione as fine, white needles: mp 155–157°; ir (KBr) 2900, 1690, 1430, 1310, and 1220 cm^{-1}; NMR ($CDCl_3$) δ 3.0–1.5 (complex multiplet), see also Figure 1 and Table I; ^{13}C NMR 27.9, 37.8, 38.3, 42.6, 45.4, 49.1, 209.3, 209.6 ppm; MS m/e (rel intensity) 235 (13.0), 234 (75.8), 177 (16.3), 176 (63.0), 163 (13.6), 149 (8.9).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; O, 20.49. Found: C, 71.68; H, 7.52; O, 20.80.

Separation of *cis,trans*-Spiro[5.5]undeca-5,11-(2′-*tert*-butyldimethylsiloxypropane)-2,8-dione (5b). The cis,trans isomer (**5b**) could be obtained in pure form by exploiting the faster rate of hydrolysis of the cis,cis isomer (**5a**). In a typical separation 5.56 g of the mixed isomers (mp 104–108° obtained from the chromatography described above) was hydrolyzed in 120 ml of a 3:1:1 mixture of acetic acid–tetrahydrofuran–water at room temperature. After 24 hr the reaction mixture was diluted with water and most of the acetic acid was neutralized by addition of solid $NaHCO_3$. The resulting solution was extracted several times with $CHCl_3$, and the aqueous layer was saturated with NaCl and reextracted with $CHCl_3$. The combined organic extracts were dried over anhydrous K_2CO_3 and concentrated to afford 4.78 g of waxy semisolid material which was chromatographed on 200 g of Woelm Dry Column Grade alumina (100–200 mesh) using $CHCl_3$ as the eluent. A total of 13 125-ml fractions was collected. Fractions 3–9 gave 2.24 g of the pure *cis,trans*-spiro[5.5]undeca-5,11-(2′-*tert*-butyldimethylsiloxypropane)-2,8-dione: mp 129–130°; ir (KBr) 2850, 1710, 1460, 1420, 1240, 1050, 880, 840, and 770 cm^{-1}; NMR ($CDCl_3$) δ 4.25 (broad multiplet, 1 H), 2.7–1.3 (complex multiplet, 18 H), 0.95 (singlet, 9 H), 0.15 (singlet, 6 H).

Elution with ethyl acetate afforded 1.36 g of mixed *cis,cis*- and *cis,trans*-spiro[5.5]undeca-5,11-(propan-2′-ol)-2,8-dione isomers, mp 140–170°.

Preparation of *cis,trans*-Spiro[5.5]undeca-5,11-(propan-2′-ol)-2,8-dione (6b). A solution of 2.00 g of *cis,trans*-spiro[5.5]undeca-5,11-(2′-*tert*-butyldimethylsiloxypropane)-2,8-dione in 50 ml of 3:1:1 acetic acid–tetrahydrofuran–water was stirred at room temperature for 142 hr. Distilled water (100 ml) was added to the reaction mixture and the solution was neutralized by addition of solid Na_2CO_3. The resulting solution was extracted with a total of 200 ml of ethyl acetate. The organic extracts were given a preliminary drying with anhydrous Na_2SO_4 followed by final drying with anhydrous $MgSO_4$. Concentration under vacuum gave a residue which was crystallized from ethyl acetate to afford 1.04 g (74%) of the alcohol **6b**: mp 182–184°C; ir (KBr) 3400, 2850, 1690, 1410, 1240, and 1030 cm^{-1}; NMR ($CDCl_3$) δ 4.30 (broad multiplet, 1 H), 2.70–1.20 (complex multiplet, 19 H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.54; O, 20.31. Found: C, 71.08; H, 8.63; O, 20.29.

Preparation of *cis,trans*-Spiro[5.5]undeca-5,11-(propan-2′-one)-2,8-dione (3b). A solution of 504 mg (2.13 mmol) of *cis,trans*-spiro[5.5]undeca-5,11-(propan-2′-ol)-2,8-dione (**6b**) in 50 ml of acetone (Mallinkrodt, reagent grade) was titrated with a total of 1.07 ml of Jones reagent (prepared by dissolving 100.00 g of CrO_3 in 84 ml of concentrated H_2SO_4 and diluting to 500 ml with H_2O). After addition was complete, the solution was stirred for approximately 15 min at room temperature and then a few drops of ethanol were added to destroy any excess reagent. The insoluble chromium salts were filtered off and washed with acetone. The combined acetone fractions were concentrated under vacuum and the residue was taken up in CH_2Cl_2 and washed with water to remove a faint green coloration. The CH_2Cl_2 was dried over K_2CO_3 and concentrated under vacuum to afford a white, crystalline residue. One crystallization from ethyl acetate gave 444 mg (89%) of *cis,trans*-spiro[5.5]undeca-5,11-(propan-2′-one)-2,8-dione as small, white crystals: mp 215–218°; ir (KBr) 2900, 1690, 1450, 1420, 1310, and 1210 cm^{-1}; NMR ($CDCl_3$) δ 2.9–1.5 (complex multiplet); ^{13}C NMR 25.8, 27.4, 35.9, 39.6, 40.6, 42.0, 43.9, 48.6, 50.0, 204.8, 206.7, 207.2; MS *m/e* (rel intensity) 235 (6.9), 234 (54.4), 177 (11.4), 176 (10.8), 163 (1.5), 149 (15.2).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; O, 20.49. Found: C, 71.74; H, 7.87; O, 20.39.

Acknowledgment. The authors wish to thank Mr. James Howard for his assistance in obtaining the 220-MHz NMR spectra. The partial support of the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No.—**1**, 3284-28-4; **3a**, 55176-82-4; **3b**, 55145-53-4; **4**, 55145-45-4; **5a**, 55145-46-5; **6a**, 55145-47-6; 4-hydroxycyclohexanone, 13482-22-9; *tert*-butyldimethylchlorosilane, 18162-48-6; 1-(1-pyrrolidino)-4-*tert*-butyldimethylsiloxycyclohexene, 55145-48-7; methyl vinyl ketone, 107-25-5; 6-*tert*-butyldimethylsiloxy-$\Delta^{1,9}$-octal-2-one, 55145-49-8; 6-*tert*-butyldimethylsiloxy-$\Delta^{9,10}$-octal-2-one, 55145-50-1; benzo[*d*]napthalene cation, 55145-43-2.

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α-Phosphoryl Sulfoxides. II. Synthesis of α,β-Unsaturated Sulfoxides and Configurational Assignments to Geometrical Isomers[1]

Marian Mikolajczyk,* Slawomir Grzejszczak, and Andrzej Zatorski

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, 90-362 Lodz, Boczna 5, Poland

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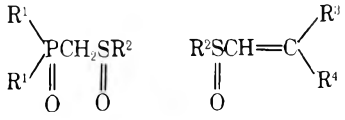
A new synthesis of α,β-unsaturated sulfoxides which involves the reaction of carbonyl compounds with 1-diethylphosphoryl-1-methylsulfinylmethyllithium (4) is described. The reaction was found to be nonstereoselective, mixtures of *E* and *Z* isomers being formed from aldehydes and unsymmetrical ketones. The geometry of mono- and disubstituted vinyl sulfoxides so formed was assigned with the aid of NMR spectroscopic methods (INDOR, NOE) and chemical correlations.

We have recently described[2] the synthesis of α-phosphoryl sulfoxides (**1**) arising from selective oxidation of corresponding α-phosphoryl sulfides using sodium metaperiodate. Other synthetic routes to **1**, which include the reaction of phosphonate carbanions with sulfinic esters and dialkyl phosphite anions with α-halogeno sulfoxides, are now being investigated in this laboratory.[3] This new class of compounds is of considerable interest for both synthetic and stereochemical studies. Owing to the presence of an asymmetric center at the sulfur atom, the α-phosphoryl sulfoxides **1** are chiral. Two additional centers of chirality may be created at the phosphorus and α-carbon atoms either by varying the substituents R^1 at phosphorus or by substitution of one of the two diastereotopic protons of the methylene group. In the latter case, owing to the presence of highly electron-withdrawing phosphoryl and sulfinyl groups, proton elimination may readily occur on treatment with a strong base, yielding the appropriate carbanion. This anion may be used in the same way as related anions generated from α-phosphoryl sulfides[4] and α-phosphoryl sulfones[4b,c,5] in the Horner–Wittig olefination to afford α,β-unsaturated sulfoxides (**2**).



1 **2**

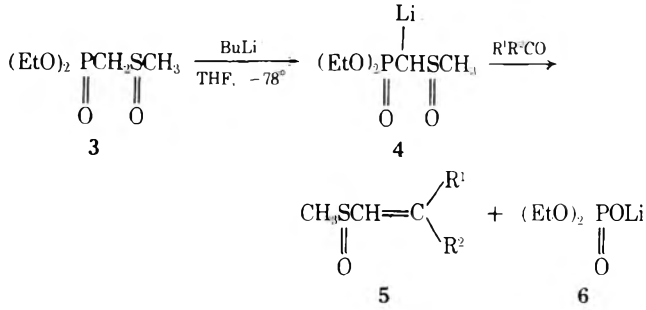
Although a number of synthetic methods for α,β-unsaturated sulfoxides are known, they are not general and do not lead to arbitrarily substituted systems. So far, α,β-unsaturated sulfoxides have usually been obtained by oxidation of appropriate α,β-unsaturated sulfides,[6] the oxidizing agents being hydrogen peroxide,[6a] peracids,[6b,c] hypochlorites,[6d] fuming nitric acid,[6e] iodobenzene dichloride,[6f] and sodium metaperiodate.[6c,6g] They are formed in elimination reactions from suitably β-substituted sulfoxides.[7] The sulfoxides **2** also arise from a reaction of vinyl Grignard reagents with sulfinic esters[8] and by addition to alkynes of sulfenic acids formed as a result of thiolsulfinate and sulfoxide decomposition.[9]

The synthesis of vinyl sulfoxides in a Peterson-type reaction of α-trimethylsilyl sulfoxides with carbonyl compounds, described recently by Carey and Hernandez,[10] has a more general character, but the relatively low thermal stability of the starting α-silyl substituted sulfoxides constitutes a serious limitation to this method.

In the present paper we describe a general and highly efficient synthesis of α,β-unsaturated sulfoxides (**2**) using diethylphosphorylmethyl methyl sulfoxide (**3**)[2] as a key compound for the Horner–Wittig reaction with carbonyl compounds. We also report studies on geometric isomerism is some suitably substituted sulfoxides (**2**).

Results and Discussion

Metalation of sulfoxide **3** was carried out in tetrahydrofuran solution at −78° using a small molar excess of *n*-butyllithium. It was found that raising of the temperature to above −50° after formation of lithium derivative **4** leads to its partial decomposition. For this reason attempts to prepare **3** by reaction with sodium hydride in boiling dimethoxyethane or tetrahydrofuran failed, even in the presence of the carbonyl component. Thus, in order to obtain high yields of α,β-unsaturated sulfoxides (**5**) it is necessary to add carbonyl compounds to **4** at ca. −70°. The adduct formed probably undergoes decomposition to **5** and the lithium salt of diethylphosphoric acid (**6**) at ca. −20°, which is evidenced by distinct turbidity of the reaction mixture brought about by precipitation of **6** from solution.



3 **4** **5** **6**

Representative aldehydes and ketones react with **4** giving in all cases sulfoxides **5** in good yields. These results are summarized in Table I.

The good yield (over 50%) of sulfoxides **5b, 5i,** and **5k** from cyclopentanone and acetophenones is noteworthy, since in the Horner–Wittig reaction these ketones undergo aldol condensation either exclusively or to a large extent.[4d] Crude sulfoxides **5** were in most cases purified by column chromatography on silica gel or by crystallization. The structure of the products obtained was established by elemental analysis and the usual spectroscopic techniques (NMR, ir) and in some cases by comparison of physical properties with those previously reported.

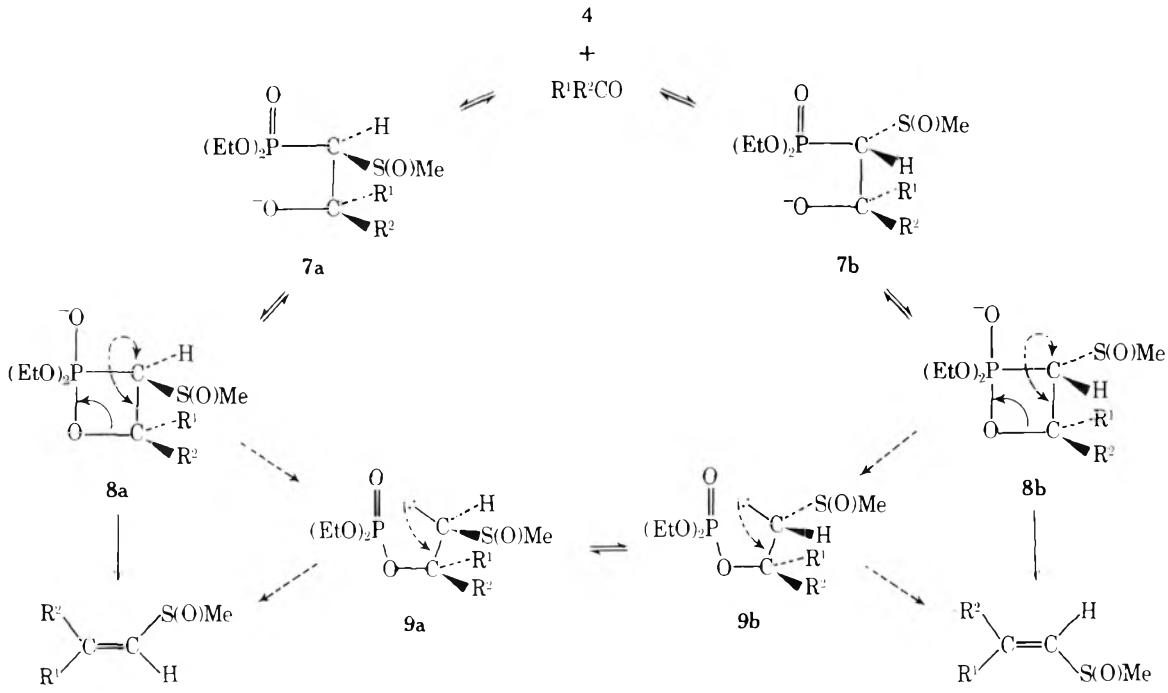
If aldehydes and unsymmetrical ketones were used, sulfoxides **5** were obtained as mixtures of *E* and *Z* geometrical isomers. Since geometrical isomers of sulfoxides **5** have been found to be configurationally stable under the reaction conditions used, this result shows that the Horner–Wittig type of olefination we employed is not stereoselective. The observed stereochemistry can be rationalized on the basis of the previously proposed mechanism of the Horner–Wittig reaction.[11] It appears that anion **4** reacts with

Table I
Preparation of α,β-Unsaturated Sulfoxides (5)

Registry no.	Aldehyde or ketone	Product	R^1	R^2	Yield,[a] %	E:Z ratio
119-61-9	Benzophenone	**5a**	C_6H_5	C_6H_5	84	
120-92-3	Cyclopentanone	**5b**	$-(CH_2)_4-$		50	
108-94-1	Cyclohexanone	**5c**	$-(CH_2)_5-$		81	
502-42-1	Cycloheptanone	**5d**	$-(CH_2)_6-$		81	
100-52-7	Benzaldehyde	**5e**	H	C_6H_5	70	58:42
874-42-0	2,4-Dichlorobenzaldehyde	**5f**	H	$Cl_2C_6H_3$	80	45:55
104-87-0	4-Methylbenzaldehyde	**5g**	H	$CH_3C_6H_4$	72	54:46
100-10-7	4-Dimethylaminobenzaldehyde	**5h**	H	$(CH_3)_2NC_6H_4$	75	82:18
98-86-2	Acetophenone	**5i**	CH_3	C_6H_5	70	45:55
2234-16-4	2,4-Dichloroacetophenone	**5k**	CH_3	$Cl_2C_6H_3$	51	27:73

[a] Isolated yield of purified product.

Scheme I



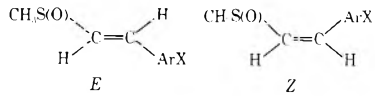
the carbonyl compound in a reversible step to afford diastereomeric alkoxides **7a** and **7b**, which in turn form corresponding five-coordinated phosphorus intermediates **8a** and **8b** (Scheme I). Formation of similar oxaphosphetanes in the Wittig reaction has recently been demonstrated by Vedejs and Snoble[12] with the aid of FT ^{31}P NMR spectroscopy. Compounds **8a** and **8b** then undergo fragmentation to vinyl sulfoxides and the phosphate anion by a concerted, four-center mechanism involving the phosphorus–carbon and carbon–oxygen bond breaking. However, recent CNDO–MO calculations carried out by Trindle, Hwang, and Carey[13] on the decomposition of species of the type $XCH_2CH_2O^-$ (X = H_3P^+, H_3Si) typical for the Wittig and Peterson reaction led us to consider the formation of final reaction products via diastereomeric carbanions **9a** and **9b** formed as a result of carbon–phosphorus bond cleavage. This latter process may be favored over scission of the carbon–oxygen bond in **8**, owing to the presence of the sulfinyl group, which is known to effectively stabilize adjacent carbanion centers.[14] In this context it is noteworthy that the Horner–Wittig reaction proceeds much faster with α-phosphoryl sulfones and sulfoxides than with α-phosphoryl sulfides.

The ratio of isomeric vinyl sulfoxides would then be expected to depend on the degree of reversibility of the formation of the two alkoxides **7a** and **7b** and on the rate of epimerization and stability of the oxy- and carbanions **7** and **9**. This point needs further study.

The isomeric compositions of vinyl sulfoxides **5** were determined from ^1H NMR spectra of crude products (see Table I). For all *E* and *Z* isomers distinct differences in chemical shifts of methylsulfinyl group protons as well as corresponding vinyl protons were observed. The isomer ratio was estimated by integration of the methylsulfinyl signals and in the case of sulfoxides **5i** and **5k** by also integrating signals for the vinyl protons.

Assignment of configuration *E* and *Z* to respective isomers of sulfoxides **5e–h** was based on the well-established geometrical dependence of vicinal proton coupling constants in olefins.[15] The ^1H NMR spectra of the above-mentioned sulfoxides reveal AB systems for trans and cis vinyl protons with $^3J_{H-H}$ of ca. 15.5 and 11.0 Hz, respectively. Another fact is that the singlet of the methylsulfinyl group for the *E* isomers appears at higher field than that for *Z* isomers. If examination of a greater number of examples shows this to be a general rule the methylsulfinyl chemical shift might allow a rapid assignment of configuration to geometrical isomers of α,β-unsaturated sulfoxides. The chemical shift and coupling constant values for *E* and *Z* isomers of the sulfoxides **5e–h** are collected in Table II.

Table II
Chemical Shifts and Coupling Constants of Monosubstituted Vinyl Sulfoxides 5

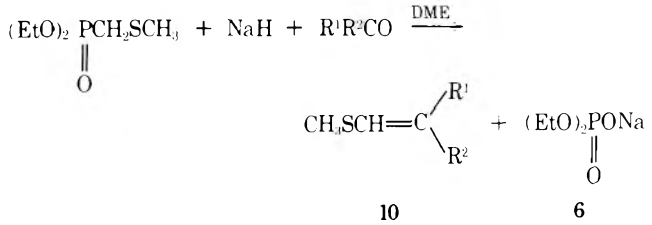


	Product, ArX	δ CH3, ppm	3J H-H, Hz	δ CH3, ppm	3J H-H, Hz
5e,	C_6H_5	2.69	15.6	2.72	11.0
5f,	$Cl_2C_6H_3$	2.61	15.5	2.64	10.5
5g,	$CH_3C_6H_4$	2.62	15.6	2.66	11.0
5h,	$(CH_3)_2NC_6H_4$	2.61	16.0	2.64	11.2

By fractional crystallization we were able to isolate isomerically pure samples of (*E*)-**5e**, (*E*)-**5h**, (*Z*)-**5f**, and (2)-**5g** from the initially obtained isomeric mixture of sulfoxides. Physical constants and spectroscopic data for the isomers (*E*)-**5e** and (*E*)-**5h** were identical with those reported in the literature.

As expected, the NMR spectrum of the isomeric mixture of sulfoxide **5i** revealed two singlets for the methylsulfinyl group and two quartets and two doublets for the olefinic proton and methyl group, respectively. Moreover, *E* and *Z* isomers of **5i** differ in allylic coupling constants $^4J_{H-CH_3}$, which are 1.5 and 1.0 Hz, respectively. However, in contradistinction to the vicinal coupling constant $^3J_{H-H}$ discussed above, the value of the allylic coupling constant does not constitute a sure criterion for the configurational assignments of the geometrical isomers.[16]

In view of the fact that Vermeer, de Graaf. and Meijer[17] recently obtained pure *E* and *Z* isomers of 1-thiomethyl-2-methyl-2-phenylethylene (**10c**) by stereoselective addition of the Grignard reagents to suitable alkynyl sulfides in the presence of cuprous halides, it was expected that their oxidation to isomeric sulfoxides (*E*)-**5i** and (*Z*)-**5i** would allow the configuration of the latter to be rigorously established. To this end a series of α,β-unsaturated sulfides **10** was obtained from diethylphosphoryl dimethyl sulfide and several carbonyl compounds following Green's procedure,[4a] which,



10 **6**

in accordance with recent results of Shahak and Almog,[4b,c] should give pure *E* isomers of **10**, at least in the case of aldehydes. However, a detailed analysis of the ^{1}H NMR and GLC spectra of the crude reaction products showed that sulfides **10** are a mixture of isomers *E* and *Z*, though the former clearly predominate. Yields and isomeric ratios of sulfides **10** thus obtained are listed in Table III.

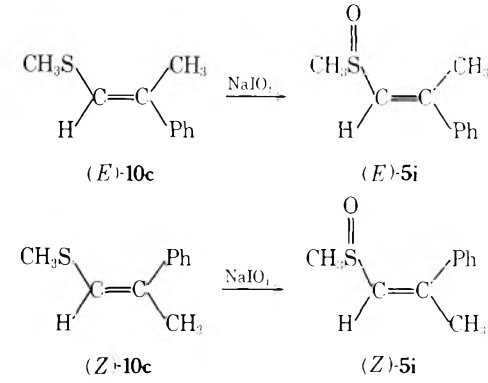
By means of preparative gas chromatography the sulfide **10c** was separated into pure *E* and *Z* isomers whose physical and spectroscopic constants were in perfect agreement with those reported by Vermeer et al. In addition, by using the INDOR technique we determined the sign of the allylic coupling constant, $^4J_{H-CH_3}$. Thus, in the isomer (*E*)-**10c** one can observe a trans allylic coupling constant equal to −1.0 Hz while for the isomer (*Z*)-**10c** it is a cis allylic coupling constant of −1.4 Hz. This result coincides with the theretical calculations of Barfield,[18] according to whom the trans $^4J_{H-CH_3}$ should be greater (i.e., less negative) than the cis $^4J_{H-CH_3}$. The correctness of the configurational assignment to sulfides (*E*)-**10c** and (*Z*)-**10c** is additionally confirmed by the agreement of experimental values of the chemical shift for the vinyl proton with those calculated on the basis of Pascual-Simon's table[19] (for isomer *E* δ_{obsd} 6.21 ppm, δ_{calcd} 6.33 ppm; for isomer *Z* δ_{obsd} 5.95 ppm, δ_{calcd} 5.96 ppm).

Table III
Preparation of α,β-Unsaturated Sulfides 10

Aldehyde or ketone	Product	R^1	R^2	Yield, [a] %	*E*:*Z* ratio
Benzaldehyde	**10a**	H	C_6H_5	66	88:12
4-Methylbenzaldehyde	**10b**	H	$CH_3C_6H_4$	63	87:13
Acetophenone	**10c**	CH_3	C_6H_5	45	82:18
2,4-Dichloroacetophenone	**10d**	CH_3	$Cl_2C_6H_3$	41	63:37

[a] Isolated yield of purified product.

Selective oxidation of sulfide (*E*)-**10c** yielded a pure isomer of sulfoxide **5i** as a crystalline compound having mp 70–71°. The same isomer with identical physical and spectroscopic properties was isolated from the crude product of the reaction of **4** with acetophenone. Oxidation of sulfide (*Z*)-**10c** gave the second pure isomer of **5i** in the form of a colorless oil. Since the configuration about the double bond



(*E*)-**10c** (*E*)-**5i**

(*Z*)-**10c** (*Z*)-**5i**

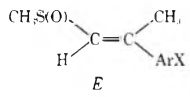
does not undergo change during oxidation, the sulfoxide obtained from (*E*)-**10c** should possess the *E* configuration while the one obtained from (*Z*)-**10c** should have the *Z* configuration.

The excellent agreement between the observed and calculated[20] vinyl proton resonance positions provides independent proof of this assignment [for the isomer (*E*)-**5i** δ_{obsd} 6.54 ppm, δ_{calcd} 6.60 ppm; for the isomer (*Z*)-**5i** δ_{obsd} 6.30 ppm, δ_{calcd} 6.23 ppm].

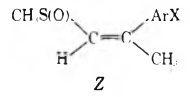
In view of the above results the configurational assignments to the geometrical isomers of sulfoxide **5i** and sulfide **10c** given by Russell et al.[6c,21] need correction. It is interesting to point out that, as in the case of the corresponding sulfides **10c**, the trans allylic coupling constant $^4J_{H-CH_3}$ for isomer (*E*)-**5i** is greater (−1.0 Hz) than the cis $^4J_{H-CH_3}$ (−1.5 Hz) for isomer (*Z*)-**5i**. All the proton NMR data for the above-mentioned sulfoxide **5i** are collected in Table IV.

We have also been successful in preparing and purifying both sulfoxide isomers of **5k**, which exhibit distinct differences in the ^{1}H NMR spectra (see Table IV). Their geometry has been established on the basis of the allylic coupling constant values discussed above and on nuclear Overhauser effect (NOE) studies.[22] Thus, the isomer with $^4J_{H-CH_3}$ = −1.5 Hz was assigned the *Z* configuration whereas the configuration *E* was given to the isomer with $^4J_{H-CH_3}$ = −1.3 Hz. In accord with this are the results of NOE experiments.

Table IV
Chemical Shifts and Coupling Constants of Disubstituted Vinyl Sulfoxides 5



E



Z

	5i (E)	5k (E)	5i (Z)	5k (Z)
δ_{CH_3SO}, ppm	2.65	2.66	2.50	2.59
δ_{CH_3C}, ppm	2.34	2.27	2.16	2.16
δ_H, ppm	6.54	6.24	6.30	6.48
$^4J_{H-CH_3}$, Hz	−1.0	−1.3	−1.5	−1.5

Saturation of *C*-methyl protons in the isomer with a greater $^4J_{H-CH_3}$ value (−1.3 Hz) gave no observable enhancement of the vinyl proton resonance while in the isomer with the lower allylic coupling constant (−1.5 Hz) the resonance of the vinyl proton was enhanced by 11%. As the largest enhancement would be expected from the methyl group closest to the vinyl proton, these findings confirm our assignment that the methyl group is cis to the vinyl proton in the isomer with the lower allylic coupling (configuration *Z*).

Oxidation of isomeric vinyl sulfides **10d** to sulfoxides (*E*)-**5k** and (*Z*)-**5k** (63:37) enabled us to assign their *E* and *Z* geometry. It is worth stressing, however, that the major isomer obtained after oxidation was (*E*)-**5k**, whereas the Horner–Wittig reaction of **4** with 2,4-dichloroacetophenone afforded (*Z*)-**5k** as a predominant product. This clearly shows that the Horner–Wittig reaction of α-phosphoryl sulfide and α-phosphoryl sulfoxide with 2,4-dichloroacetophenone resulted in preferable formation of isomers possessing the sulfur and methyl group in reverse geometrical positions.

Experimental Section

All melting and boiling points are uncorrected. NMR spectra were recorded on a Tesla BS-487C 80-MHz spectrometer using Me_4Si as an internal standard. Ir spectra were measured on a Spektromom 2000 spectrophotometer as KBr disks for solids and pressed films for liquids. GLC analysis was carried out with a Varian Aerograph Model 1520 flame ionization gas chromatograph using a 20-ft column of 10% diethylene glycol adipate (DEGA) on Chromosorb W 60/80 at a column temperature of 190°, an injector temperature of 240°, and a detector temperature of 225°. Preparative gas chromatographic analyses were effected using a 50-ft column containing 10% Carbowax 20M at a column temperature of 180°, an injector temperature of 220°, and a detector temperature of 220°. Column chromatography was done on silica gel Merck 100–200 mesh. Commercially available aldehydes and ketones were purified by distillation or recrystallization immediately before use. All solvents used were purified according to standard procedures; tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride.

General Procedure for Synthesis of α,β-Unsaturated Sulfoxides (5). To a solution of diethylphosphorylmethyl methyl sulfoxide (**3**, 3.21 g, 0.015 mol) in 25 ml of THF a solution of *n*-butyllithium (16 ml, 0.016 mol) in ether was added at −78° under a nitrogen atmosphere. After 1 hr a clear and colorless solution of **4** was obtained. A solution of the carbonyl compound (0.015 mol) in 20 ml of THF was then added dropwise at −78° and the reaction mixture was stirred for 30 min at this temperature. The mixture was warmed slowly to room temperature and stirred for an additional 2 hr. At −20° the reaction mixture becomes turbid and in some cases an appearance of the yellow-orange color was observed. After removal of solvents the residue was treated with water (50 ml) and extracted with chloroform (3 × 25 ml). The chloroform solution was washed with water (25 ml), dried, and evaporated to afford the crude sulfoxide (**3**).

1-(Methylsulfinyl)-2,2-diphenylethylene (5a). The crude product (mp 102–105°) obtained from benzophenone (2.73 g, 0.015 mol) according to the procedure described above was recrystallized from *n*-hexane–ether (1:1), giving 3.05 g (84%) of **5a**, mp 106–107° (lit.[6c] mp 106–107°). Anal. Calcd for $C_{15}H_{14}OS$: C, 74.36; H, 5.83. Found: C, 74.34; H, 5.90.

1-[(Methylsulfinyl)methylene]cyclopentane (5b). Cyclopentanone (1.26 g, 0.015 mol) and **4** gave, after the usual work-up, crude **5b** as a dark-brown oil. Chromatography [elution with benzene–acetone–ethyl acetate (18:1:1)] afforded 1.08 g (50%) of pure sulfoxide **5b** as a yellow oil: $n^{20}D$ 1.5108; ^1H NMR ($CDCl_3$) δ 1.78 (m, 4, $-CH_2CH_2-$), 2.34 [m, 4, $(-CH_2)_2C=$], 2.49 (s, 3, CH_3SO), 6.12 (m, 1, $-CH=C<$); ir (film) 2850 s, 1710 m, 1430 w, 1405 m, 1310 w, 1280 w, 1200 w, 1090 w, 1010 vs (SO), 940 s, 530 w, 790 m, 710 w, 670 cm^{-1} w. Anal. Calcd for $C_7H_{12}OS$: C, 58.33; H, 8.33. Found: C, 58.22; H, 8.37.

1-[(Methylsulfinyl)methylene]cyclohexane (5c). The reaction of cyclohexanone (1.47 g, 0.015 mol) and **4** carried out according to the general procedure yielded crude **5c** as a yellow oil. Chromatography [benzene–acetone–ethyl acetate (18:1:1)] afforded 1.93 g (81%) of analytically pure **5c**: $n^{20}D$ 1.5138; ^1H NMR ($CDCl_3$) δ 1.61 [m, 6, $CH_2(CH_2-)_2$], 2.23 [m, 4, $(CH_2)_2C=$], 2.49 (s, 3, CH_3SO), 6.01 (s, 1, $-CH=C$); ir (film) 2900 s, 2850 s, 1610 m, 1440 s, 1420 m, 1400 w, 1340 w, 1300 w, 1270 w, 1155 w, 1105 w, 1030 s (SO), 970 m, 950 m, 925 m, 900 m, 820 m, 800 m, 750 m, 980 cm^{-1} w. Anal. Calcd for $C_8H_{14}OS$: C, 60.75; H, 8.86. Found: C, 60.68; H, 8.85.

1-[(Methylsulfinyl)methylene]cycloheptane (5d). Column chromatography [benzene–acetone (18:1)] of the crude product from cycloheptanone (1.68 g, 0.015 mol) gave 2.09 g (81%) of **5d** as a colorless oil: $n^{20}D$ 1.5245; ^1H NMR ($CDCl_3$) δ 1.58 (m, 8, $-CH_2CH_2CH_2CH_2-$), 2.40 [m, 4, $(-CH_2)_2C=C$], 2.49 (s, 3, CH_3SO), 6.01 (s, 1, $-CH=C<$); ir (film) 2900 s, 2800 s, 1680 w, 1600 w, 1440 m, 1420 w, 1340 w, 1240 w, 1180 m, 1120 w, 1030 vs (SO), 950 m, 860 w, 760 w, 740 w, 680 cm^{-1} w. Anal. Calcd for $C_9H_{16}OS$: C, 62.73; H, 9.30. Found: 62.29; H, 9.41.

Methyl Styryl Sulfoxide (5e). Benzaldehyde (1.51 g, 0.015 mol) and **4** gave crude product as a mixture of *E* and *Z* isomers in a ratio of 58:42 (^1H NMR assay). Column chromatography using benzene–acetone–ethyl acetate (18:1:1) as the solvent afforded 2.48 g (70%) of a pure isomeric mixture. Recrystallization from *n*-hexane–ether afforded the pure isomer (*E*)-**5e**: mp 64–65° (lit.[7e] mp 61–62°); ^1H NMR ($CDCl_3$) δ 2.69 (s, 3, CH_3SO), 6.88 and 7.23 (AB system, 2, J_{AB} = 15.6 Hz), 7.36 (m, 5, aromatic); ir (KBr) 2960 m, 2870 m, 1620 w, 1605 w, 1580 w, 1500 m, 1460 m, 1420 w, 1300 w, 1295 m, 1210 w, 1190 w, 1170 w, 1050 vs (SO), 1000 s, 960 s, 940 m, 820 w, 760 s, 740 vs, 700 s, 680 cm^{-1} w. Anal. Calcd for $C_9H_{10}OS$: C, 65.05; H, 6.07. Found: C, 65.04; H, 6.07. ^1H NMR ($CDCl_3$) for (*Z*)-**5e**: 2.72 (s, 3, CH_3SO), 6.44 and 7.02 (AB system, 2, J_{AB} = 11.0 Hz).

1-(Methylsulfinyl)-2-(2,4-dichlorophenyl)ethylene (5f). The crude product obtained from 2,4-dichlorobenzaldehyde (2.55 g, 0.015 mol) was a mixture of *E* and *Z* isomers in a ratio of 45:55 as determined by ^1H NMR ($CDCl_3$). (*E*)-**5f**: δ 2.61 (s, 3, CH_3SO), 7.02 and 7.45 (AB system, 2, J_{AB} = 15.5 Hz), 7.38 (m, 3, aromatic). (*Z*)-**5f**: δ 2.64 (s, 3, CH_3SO), 6.62 and 7.07 (AB system, 2, J_{AB} = 10.5 Hz), 7.38 (m, 3, aromatic). The pure mixture of isomers (2.81 g, 80%) was obtained as a syrupy oil after column chromatography using benzene–ethyl acetate (18:2) as the eluent. Crystallization from *n*-hexane–ether (1:1) afforded the pure isomer (*Z*)-**5f**: mp 87–88°; ir (KBr) 2960 m, 2870 m, 1700 w, 1600 w, 1570 s, 1540 w, 1460 s, 1450 s, 1400 m, 1380 s, 1295 w, 1200 w, 1120 w, 1100 s, 1040 s, 1020 vs (SO), 970 s, 960 s, 900 m, 850 s, 830 s, 800 s, 755 s, 720 w, 705 s, 699 w, 960 cm^{-1} w. Anal. Calcd for $C_9H_8OSCl_2$: C, 45.96; H, 3.40. Found: C, 46.06; H, 3.85.

1-(Methylsulfinyl)-2-(4-methylphenyl)ethylene (5g). The crude product obtained from 4-methylbenzaldehyde consisted of 54 and 46% of *E* and *Z* isomers, respectively. ^1H NMR ($CDCl_3$) for (*E*)-**5g**: δ 2.32 (s, 3, $CH_3C_6H_4$), 2.62 (s, 3, CH_3SO), 6.83 and 7.24 (AB system, 2, J_{AB} = 15.6 Hz), 7.14 and 7.32 (AB system, 4, aromatic, J_{AB} = 8.6 Hz). (*Z*)-**5g**: δ 2.35 (s, 3, $CH_3C_6H_4$), 2.66 (s, 3, CH_3SO), 6.37 and 6.97 (AB system, 2, J_{AB} = 11.0 Hz), 7.11 and 7.26 (AB system, 4, aromatic, J_{AB} = 8.6 Hz). After column chromatography [benzene–ethyl acetate–acetone (18:1:1)] a pure isomeric mixture (1.94 g, 72%) was obtained from which pure isomer (*Z*)-**5g** was isolated by crystallization from *n*-hexane–ether (1:1): mp 109–110°; ir (KBr) 2800 m, 1700 w, 1600 w, 1560 w, 1480 w, 1435 m, 1405 w, 1370 w, 1290 w, 1240 w, 1200 w, 1180 w, 1030 s (SO), 960 w, 780 m, 750 s, 700 cm^{-1} s. Anal. Calcd for $C_{10}H_{12}SO$: C, 66.67; H, 6.67. Found: C, 66.80; H, 7.00.

1-(Methylsulfinyl)-2-(4-dimethylaminophenyl)ethylene (5h). The crude product obtained from *p*-dimethylaminobenzaldehyde (2.24 g, 0.015 mol) was a yellow solid. Analysis of the ^1H NMR spectrum permitted the determination of the *E*:*Z* ratio as

82:18. After crystallization from *n*-hexane–ether (1:1) the pure isomer (*E*)-**5h** was obtained: 2.35 g (75%); mp 136–137° (lit.[23] mp 135–137°); ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3, CH_2SO), 2.98 [s, 6, $(CH_3)_2N$–], 6.65 and 7.14 (AB system, 2, J_{AB} = 16.0 Hz), 6.67 and 7.32 (AB system, 4, aromatic, J_{AB} = 9.0 Hz); ir (KBr) 2900 m, 2800 m, 1600 vs, 1520 s, 1445 m, 1430 m, 1360 s, 1320 w, 1300 w, 1210 m, 1190 s, 1160 s, 1110 w, 1040 vs (SO), 965 s, 940 m, 825 m, 760 w, 710 s, 670 cm^{-1} w. Anal. Calcd for $C_{11}H_{15}OSN$: C, 63.12; H, 7.22. Found: C, 63.40; H, 7.24.

1-(Methylsulfinyl)-2-methyl-2-phenylethylene (5i). Reaction of acetophenone (1.80 g, 0.015 mol) and **4** according to the general procedure gave crude product as an brown oil. The product composition was determined by ^{1}H NMR ($CDCl_3$) to be *E*:*Z* = 45:55. (*Z*)-**5i:** δ 2.16 (d, 3, CH_3C=C, J = −1.5 Hz), 2.50 (s, 3, CH_3SO), 6.30 (q, 1, C=CH, J = −1.5 Hz), 7.24 (m, 5, aromatic). (*E*)-**5i:** δ 2.34 (d, 3, CH_3C=C, J = −1.0 Hz), 2.65 (s, 3, CH_3SO), 6.54 (q, 1, C=CH, J = −1.0 Hz), 7.38 (m, 5, aromatic). Column chromatography [benzene–ethyl acetate (18:1)] afforded 1.89 g (70%) of pure sulfoxide **5i** from which after crystallization [*n*-hexane–ether (1:1)] pure isomer (*E*)-**5i** was obtained: mp 70–71°; ir (KBr) 2960 m, 2870 m, 1600 m, 1500 m, 1430 w, 1400 w, 1380 w, 1240 w, 1040 s (SO), 960 s, 940 m, 850 w, 830 m, 785 s, 740 w, 705 w, 680 cm^{-1} w. Anal. Calcd for $C_{10}H_{12}OS$: C, 66.67; H, 6.67. Found: C, 66.45; H, 6.96.

1-(Methylsulfinyl)-2-methyl-2-(2,4-dichlorophenyl)ethylene (5k). A mixture of *Z* and *E* isomers (73:27) was obtained from 2,4-dichloroacetophenone (2.84 g, 0.015 mol). Analysis of ^{1}H NMR spectra ($CDCl_3$) led to the following assignments. (*Z*)-**5k:** δ 2.16 (d, 3, CH_3C=C, J = −1.5 Hz), 2.59 (s, 3, CH_3SO), 6.48 (q, 1, HC=C, J = −1.5 Hz), 7.26 (m, 3, aromatic). (*E*)-**5k:** δ 2.27 (d, 3, CH_3C=C–, J = −1.3 Hz), 2.66 (s, 3, CH_3SO), 6.24 (q, 1, HC=C, J = −1.3 Hz), 7.26 (m, 3, aromatic). Column chromatography [benzene–ethyl acetate (10:1)] gave 1.92 g (51.5%) of the pure product. Rechromatography using benzene–ethyl acetate–acetone (20:1:1) as the eluent afforded the pure prodominant sulfoxide (*Z*)-**5k** as a colorless oil: n^{20}D 1.5748; ir (film) 2960 w, 2850 w, 1700 w, 1610 w, 1570 m, 1540 w, 1460 s, 1420 w, 1360 m, 1280 w, 1100 m, 1080 m, 1030 s (SO), 960 w, 860 w, 810 s, 810 s, 680 cm^{-1} w. Anal. Calcd for $C_{10}H_{10}OSCl_2$: C, 48.10; H, 4.02. Found: C, 48.32; H, 4.02.

Synthesis of α,β-Unsaturated Sulfides (10). All the sulfides (**10**) listed in Table III were obtained according to Green's procedure[4a] from α-phosphoryldimethyl sulfide and carbonyl compounds. The physical and spectral data of the products follow.

10a: a colorless oil; n^{20}D 1.6320 (lit.[4a] n^{20}D 1.6325); yield 66%; *E*:*Z* ratio 88:12. ^{1}H NMR ($CDCl_3$) (*E*)-**10a:** δ 2.28 (s, 3, CH_3S), 6.22 and 6.67 (AB system, 2, J_{AB} = 15.5 Hz), 7.20 (m, 5, aromatic). (*Z*)-**10a:** δ 6.07 and 6.30 (AB system, 2, J_{AB} = 11.0 Hz). Anal. Calcd for $C_9H_{10}S$: C, 71.94; H, 6.69. Found: C, 71.96; H, 6.81.

10b: a colorless oil; n^{20}D 1.6030; yield 63%; *E*:*Z* ratio 87:13. ^{1}H NMR ($CDCl_3$) (*E*)-**10b:** δ 2.27 and 2.29 (two s, 6, CH_3S and $CH_3C_6H_4$–), 6.20 and 6.62 (AB system, 2, J_{AB} = 15.6 Hz), 6.97 and 7.13 (AB system, 2, J_{AB} = 8.6 Hz, aromatic). (*Z*)-**10b:** δ 6.28 and 6.45 (AB system, 2, J_{AB} = 11.2 Hz).

The pure geometrical isomers of sulfide **10c** were obtained by gas chromatography of the crude reaction product (45% yield) which consisted of 82% of *E* and 18% of *Z* isomers. (*E*)-**10c:** mp 29–30° (lit.[21] mp 29–30°); ^{1}H NMR ($CDCl_3$) δ 2.08 (d, 3, CH_3C=, J = −1.0 Hz), 2.28 (s, 3, CH_3S), 6.21 (q, 1, HC=, J = −1.0 Hz), 7.20 (m, 5, aromatic). Anal. Calcd for $C_{10}H_{12}S$: C, 73.12; H, 7.36. Found: C, 72.76; H, 7.35. (*Z*)-**10c:** a colorless oil; n^{20}D 1.6130 (lit.[17] n^{20}D 1.6130); ^{1}H NMR ($CDCl_3$) δ 2.11 (d, 3, CH_3C=, J = −1.4 Hz), 2.20 (s, 3, CH_3S), 5.95 (q, 1, HC=, J = −1.4 Hz), 7.29 (m, 5, aromatic). Anal. Calcd for $C_{10}H_{12}S$: C, 73.12; H, 7.36. Found: C, 72.78; H, 7.32.

10d: a colorless oil; n^{20}D 1.5825; yield 41%; *E*:*Z* ratio 63:37. ^{1}H NMR ($CDCl_3$) (*E*)-**10d:** δ 2.01 (d, 3, CH_3C=, J = −1.1 Hz), 2.31 (s, 3, CH_3S), 5.91 (q, 1, HC=, J = −1.1 Hz), 7.18 (m, 3, aromatic). (*Z*)-**10d:** δ 2.30 (d, 3, CH_3C=, J = −1.4 Hz), 2.18 (s, 3, CH_3S), 5.99 (q, 1, HC=, J = −1.4 Hz), 7.18 (m, 3, aromatic). Anal. Calcd for $C_{10}H_{10}SCl_2$: C, 51.52; H, 4.32. Found: C, 51.48; H, 4.32.

Oxidation of (*E*)-10c to (*E*)-5i. To a mixture of 200 mg (1.22 mmol) of (*E*)-**10c**, 10 ml of acetone, and 10 ml of water was added dropwise 280 mg (1.3 mmol) of sodium metaperiodate in water at −10°. The reaction mixture was stirred at this temperature for an additional 6 hr and allowed to stand at 5° for 4 days. The precipitated sodium iodate was filtered off. After removal of the solvents at reduced pressure the residue was dissolved in acetone and dried over anhydrous $MgSO_4$. Removal of the acetone left 211 mg (96%) of (*E*)-**5i**, mp 70–71°. Anal. Calcd for $C_{10}H_{12}OS$: C, 66.67; H, 6.67. Found: C, 66.44; H, 6.31.

Oxidation of (*Z*)-10c to (*Z*)-5i. Oxidation of (*Z*)-**10c** (77 mg, 0.47 mmol) according to the procedure described above gave 79 mg (93.5%) of (*Z*)-**5i** as a pale yellow oil. Anal. Calcd for $C_{10}H_{12}OS$: C, 66.67; H, 6.67. Found: C, 66.41; H, 6.40.

Oxidation of 10d to 5k. A 932-mg (4 mmol) sample of **10d** (isomeric content 63:37) in 50 ml of chloroform was treated with an equimolar amount of *m*-chloroperbenzoic acid in chloroform solution at −10°. The reaction mixture was stirred at this temperature for an additional 10 hr and allowed to stand at −10° overnight. The precipitated acid was filtered off and chloroform solution was washed with a 5% aqueous solution of Na_2CO_3 and then with water. The chloroform layer was dried over anhydrous $MgSO_4$ and evaporated to give 945 mg (95%) of the sulfoxide **5k** which consisted of 63% *E* and 37% *Z* isomers. Anal. Calcd for $C_{10}H_{10}OSCl_2$: C, 48.20; H, 4.02. Found: C, 48.21; H, 4.23.

Column chromatography using benzene–ethyl acetate (9:1) as the eluent afforded the pure predominant isomer (*E*)-**5k** as a colorless oil, n^{20}D 1.5649. Anal. Calcd for $C_{10}H_{10}OSCl_2$: C, 48.20; H, 4.02. Found: C, 48.20; H, 4.04.

Oxidation of 10b to 5g. The oxidation of **10b** was performed in the same manner as the oxidation of **10c**. From 410 mg (2.5 mmol) of **10b** (87% of *E* and 13% of *Z* isomer) 420 mg (93.5%) of **5g** (*E*:*Z* ratio 87:13) was obtained. The product was crystallized from ether–hexane (2:1) to afford pure sulfoxide (*E*)-**5g**, mp 78–79°. Anal. Calcd for $C_{10}H_{12}SO$: C, 66.67; H, 6.67. Found: C, 66.60; H, 6.75.

Configurational Stability of Sulfoxide 5i under the Reaction Conditions. Control Experiments. A. To a solution of **4** (0.5 mmol) obtained as described above a solution of sulfoxide (*E*)-**5i** (0.5 mmol) in 5 ml of THF was added at −78° under the nitrogen atmosphere. The mixture was stirred at this temperature for 1 hr and then at room temperature for an additional 2 hr. After addition of water and the usual work-up starting sulfoxide (*E*)-**5i** was recovered.

B. Under the same conditions a mixture of *E* and *Z* isomers of sulfoxide **5i** in a ratio of 45:55 has been found to be unchanged.

C. To a solution of the lithium salt of diethylphosphoric acid (0.5 mmol) in 5 ml of THF a solution of sulfoxide (*E*)-**5i** in 5 ml of THF was added at −78°. The mixture was stirred at −78° for 1 hr. Then it was warmed slowly to room temperature and stirred for an additional 2 hr. After the usual work-up sulfoxide (*E*)-**5i** was recovered.

D. Under the same conditions a mixture of (*E*)-**5i** and (*Z*)-**5i** (45:53) has been found to undergo no changes.

Registry No.—**3,** 50746-61-7; **4,** 55059-02-4; **5a,** 21147-11-5; **5b,** 55059-03-5; **5c,** 55059-04-6; **5d,** 55059-05-7; (*E*)-**5e,** 7715-00-6; (*Z*)-**5e,** 53165-40-5; (*E*)-**5f,** 55059 06-8; (*Z*)-**5f,** 55059-07-9; (*E*)-**5g,** 55059-08-0; (*Z*)-**5g,** 55059-09-1; (*E*)-**5h,** 41411-19-2; (*Z*)-**5h,** 55059-10-4; (*E*)-**5i,** 24377-98-8; (*Z*)-**5i,** 24377-97-7; (*E*)-**5k,** 55059-11-5; (*Z*)-**5k,** 55059-12-6; (*E*)-**10a,** 15436-06-3; (*Z*)-**10a,** 35822-50-5; (*E*)-**10b,** 55059-13-7; (*Z*)-**10b,** 55059-14-8; (*E*)-**10c,** 25650-53-7; (*Z*)-**10c,** 22950-86-3; (*E*)-**10d,** 55059-15-9; (*Z*)-**10d,** 55059-16-0.

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On Conformation–Reactivity Correlations

Donald C. Best, Gary M. Underwood, and Charles A. Kingsbury*

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

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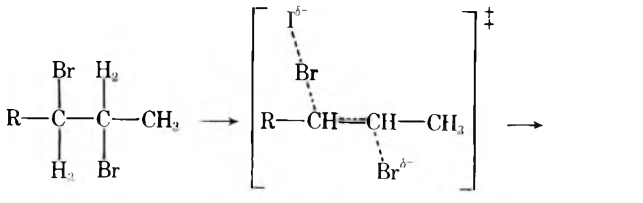
The kinetics and product studies of the reaction of 2,3-dibromo-4-methylpentanes and 2,3-dibromo-4,4-dimethylpentanes with iodide ion are reported. ^{13}C NMR studies, in conjunction with previous ^{1}H and dipole moment studies, strongly suggest that the erythro isomer of the *tert*-butyl compound occupies a different conformation than the erythro isomer of the isopropyl compound; yet the rates of reactions are not divergent. The bases for the frequently observed correlation between a favorable ground-state conformation and a rapid reaction rate are discussed.

A number of recent papers have commented upon the fact that substrates in which the reactive groups exist in the correct steric relationship for a given reaction frequently undergo rapid reaction.[1-16] Other studies have considered the obverse, namely, that a slow reaction is found where the preferred ground-state conformation is unfavorable for reaction. Occasionally, the suggestion is made that the ground-state conformation affects or determines reactivity. We wish to show a case in which a compound with an unfavorable ground-state conformation reacts more rapidly than a compound with a favorable conformation.[17]

The reaction in question is the iodide-catalyzed debromination of certain acyclic dibromides **1** and **2**. Earlier work on similar debrominations showed a preference for a trans elimination of the elements of bromine (Scheme I).[18]

Scheme I

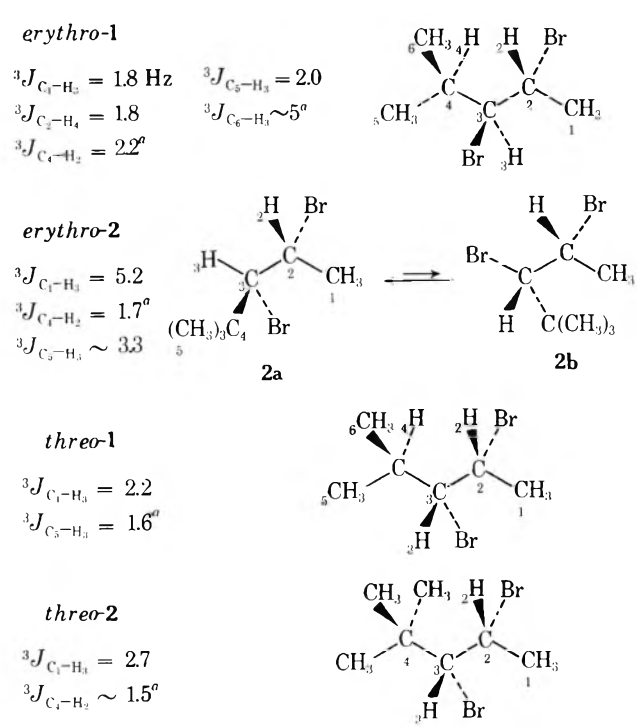


1, R = *i*-C_3H_7
2, R = *t*-C_4H_9

The ground-state conformations of *threo*-**1** and -**2** are quite similar.[19] For these threo isomers, very low ^{1}H NMR J_{23} values were observed, which implies a predominance of conformation(s) having gauche vicinal hydrogens. The dipole moment studies showed high resultant moments ($\mu \simeq$ 2.5 D) due to vectorially additive group moments for bromine such as expected for gauche vicinal bromines. Both lines of evidence suggest a preference for the conformers shown in Scheme II.

erythro-**1** shows a high J_{23} value (10.6 Hz) and a low dipole moment (0.9 D). In contrast, *erythro*-**2** shows a lower

Scheme II



[a] Approximate value.

J_{23} (2.0 Hz) and a much higher dipole moment (2.6 D). Thus, the preferred conformations of these two substrates appear quite different (Scheme II). Others have noted divergent conformations for compounds containing *tert*-butyl groups compared to compounds having isopropyl or phenyl groups.[20-24] In particular, Bodot and coworkers were able to suggest numerical weights for the different conformers in certain halohydrins analogous to **1** and **2**.[23] Reasons for the divergence in conformation have been suggested in earlier work.[21,25]

A third method of conformational analysis of these sub-

Table I
Iodide-Catalyzed Debromination Rates and Activation Parameters

Registry no.	Compd	R	Isomer	$k \times 10^5$, l./mol sec, 60°	70°	80°	85°	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
		CH_3[a]	meso	0.291					
			dl	0.151					
		C_2H_5[a]	erythro	0.496					
			threo	0.272					
7694-00-0	1	i-C_3H_7	erythro	0.78 ± 0.03	2.73 ± 0.07	6.8 ± 0.3	12 ± 1	24.7 ± 0.7	−8 ± 2
7694-01-1	1		threo	0.22 ± 0.02	0.61 ± 0.02	1.80 ± 0.09	3.0 ± 0.3	24 ± 1	−12 ± 3
7694-04-4	2	t-C_4H_9	erythro	3.13 ± 0.02	11.8 ± 0.1	34.3 ± 0.6	62 ± 2	26.7 ± 0.5	−0.8 ± 1.3
7694-05-5	2		threo	0.210 ± 0.001	0.572 ± 0.004	1.51 ± 0.02	2.6 ± 0.2	22.7 ± 0.9	−18 ± 3

[a] These data are taken from ref 27. [b] Adjusted to the temperatures indicated from slightly lower temperatures for 1 and 2.

strates has recently become available, i.e., ^{13}C–H coupling constants. Lemieux and coworkers have suggested that a correlation exists between the dihedral angel described by the ^{13}C–C–C–H nuclei and the magnitude of $^3J_{CH}$ similar to the well-known Karplus relationship.[26] However, they caution that electronegativity effects, steric effects, and other internal factors were of concern regarding the magnitude of $^3J_{CH}$. In this work,[26] trans ^{13}C and H nuclei were found to have a ^3J value of ca. 8 Hz, whereas gauche nuclei have a ^3J value of ca. 1 Hz.

Scheme II shows certain $^3J_{CH}$ values found for the compounds of this study. Other $^3J_{CH}$ values could not be determined with precision, and these are not listed. The $^3J_{CH}$ values are in qualitative agreement with the results of previous methods of conformational determination. Thus, for *threo*-**1** and -**2**, C_1 is predominantly gauche to H_3, as shown by the quite low $^3J_{CH}$ values in question.

More important is the check upon the previous data which suggested divergent conformations for *erythro*-**1** and -**2**. For *erythro*-**1**, C_1 and H_3 are predominantly gauche as indicated by the low $^3J_{CH}$ value. The larger $^3J_{CH}$ for C_6 and H_3 is qualitatively in agreement with their predominant trans geometry. In *erythro*-**2**, the ^1H NMR data do not distinguish between conformers **2a** and **2b** (Scheme II). However, the fairly high ^{13}C coupling constant for C_1 and H_3 suggests a predominant trans relationship as found in **2a** (the low $^3J_{C_4-H_2}$ is in agreement with the preference for **2a**). It is quite reasonable that **2a** should predominate over **2b** as *tert*-butyl would be very hindered in the latter.

Thus, the combination of three lines of evidence indicates that *erythro*-**1** has an ideal conformation for iodide-catalyzed debromination (trans bromines) whereas *erythro*-**2** predominately occupies an unfavorable conformation (gauche bromines). The rates of reaction are listed in Table I. These data show that *erythro*-**2** reacts ca. 4 times *faster* than *erythro*-**1**. Using literature values[27] for similar compounds (e.g., R = CH_3 and R = C_2H_5), a reasonably linear plot of log k vs. E_s[c] (Taft's steric substituent constants) can be made.[28,29] Thus, it appears that the size of R affects reactivity through steric acceleration of debromination that is unrelated to any particular ground-state conformation. The products of reaction were >96% *trans*-4-methyl-2-pentene from **1**, and 100% *trans*-4,4-dimethyl-2-pentene from **2**.

The various threo isomers are similar in reactivity. With increasing size of R, the destabilization of the ground state apparently parallels the destabilization of the transition state resulting in little net change in rate as R varies. *threo*-**1** formed >90% *cis*-4-methyl-2-pentene, but *threo*-**2** formed 87 ± 3 *cis*- and 13% *trans*-4,4-dimethyl-2-pentene at 85°. In the latter case, the trans alkene probably resulted from a small amount of cis elimination. We were not able to detect any isomerization of the cis alkene under the reaction conditions. Interruption of the reaction after 1 half-life revealed only the presence of *threo*-**2** and alkene. However, any isomerization to *erythro*-**2** would be difficult to detect owing to the greater reactivity of this isomer. An SN2 displacement by iodide, followed by an iodide-catalyzed debromoiodination, is also possible,[30–32] although steric hindrance to SN2 attack militates against this alternative.[30]

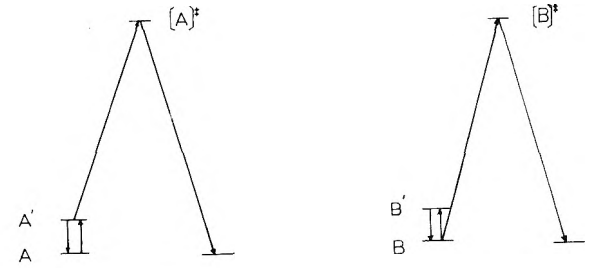


Figure 1.

As background for discussion of these findings and literature data, the Curtin–Hammett principle deserves special note.[33,34] This principle refers to a starting material that can form two separate products in parallel reactions. The principle states that the relative population of the various ground-state conformations in no way affects the proportions of the two products. The product ratio is dominated by the relative transition state energies. This principle assumes that the barrier to conformational interconversion (commonly a few kilocalories) is small compared to the transition state barrier (15–30 kcal). In common usage, the principle is accorded a somewhat wide range of applicability.

In a situation more directly relevant to this study, *two* hypothetical substrates A and B might be considered (Figure 1). These substrates, which have equal internal energy, form products by way of transition states of the same energy. However, substrate A must undergo internal rotation to form a less stable conformer A′ before reacting, whereas B (although it partly exists as B′) can react directly from the most stable conformer. It is easily shown by application of rate and equilibrium laws that the rates of reaction of A and B will be identical. Thus, ground-state conformation in this hypothetical case will also be irrelevant.

One might then question why so many reactions show a parallelism between preference for a particular ground-state conformation (which appears to be ideal for rapid reaction) and a high rate of reaction (or unfavorable conformation and slow reaction). In our estimation, the answer lies in the fact that if a ground state conformation is stable and highly populated, nonbonded repulsions and other internal strain factors are minimized. The transition state is even more sensitive, in many cases, to the same nonbonded repulsions and the transition state orientation in which

these repulsions are minimized will also be more stable. The ground-state molecule will undergo many thousands of internal rotations, however, before the transition state is reached. Thus, the correlation between ground-state conformation and reaction rate may mean only that both phenomena are related to the same underlying factors, not that conformation per se determines reaction rate.[35] Even so, as this work indicates, the preference for an "unfavorable" conformation does not necessarily mean that the reaction rate will be slow.[36]

Experimental Section

The compounds of this study were available from a previous study. The kinetics of reaction were determined by an ampoule technique in a manner as closely as possible approximating that of Young, Pressman, and Coryell and of Dillon.[27] The rate equation of the former group of workers was used. The solvent was 99% methanol. Rate constants were calculated by computer techniques. The average of at least two runs is reported in Table I. The observed rate constant was corrected for solvent expansion, but it was not corrected for salt effects, since the concentration of KI was virtually constant from run to run (ca. 0.22 *M*). The concentration of substate was ca. 0.038 *M* at room temperature. To check the closeness of our data to that of previous workers, the rates of reaction of *meso*-2,3-dibromobutane and *erythro*-2,3-dibromopentane were determined. The rates were within 12 and 6%, respectively, of the values reported by Young, Pressman, and Coryell.[27] The activation parameters were calculated by standard means. The kinetic data reported in Table I were actually determined at 0.1–0.2° lower temperature than those indicated. Corrections were made to the temperatures indicated using the activation enthalpy. The plot (Figure 2) uses the raw data of Young et al. in part, which were determined at slightly lower temperatures than 60 and 75°.

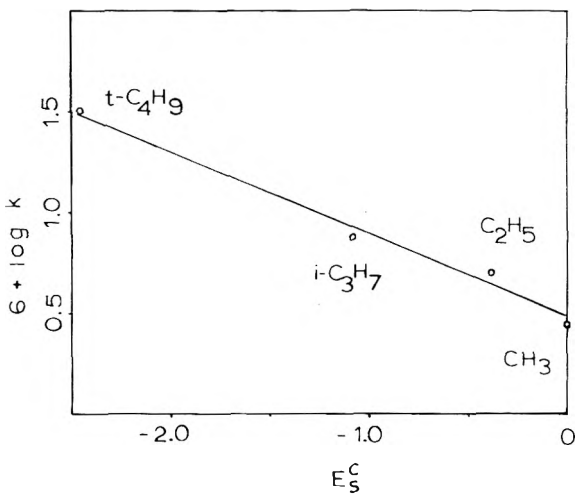


Figure 2. Plot of the logarithm of the rate of iodide-catalyzed debromination vs. corrected steric substituent constants (E_s^c) for the substituents indicated.

In a typical product study, 2.040 g of KI and 0.4791 g of *threo*-2 were dissolved in 25 ml of 99% methanol and heated at 85° for 59 hr in a pressure bottle. The reaction mixture was added to a large quantity of water containing a little bisulfite. This was extracted with small amounts (ca. 3 ml) of a high-boiling organic solvent (various were used). Various VPC columns adequately separated the components; an example is 7% bis(2-ethylhexyl)tetrachlorophthalate on HMDS-treated Chromosorb W (a ca. 10-ft column). At a column temperature of 50°, and a helium flow of 50 ml/min, the retention times of the *trans*- and *cis*-4,4-dimethyl-2-pentenes were 2.3 and 3.0 min, respectively. The VPC data were corrected for different thermal response factors for the two isomers determined with a mixture of known proportions. Subsequent extraction fractions of the aqueous layer showed decreasing amounts of olefins in the same ratio as the initial extract.

It was not possible to separate the *cis*- and *trans*-4-methyl-2-pentenes. The product olefins were rebrominated in cold CCl_4, protected from light. The rebromination was between 90 and 95% stereospecific. The resulting mixtures of I were analyzed on a 5% SE-30 on Var-Fort A column (5-ft stainless steel) at a column temperature of 90° and a flow of 100 ml/min. *erythro*-I showed a retention time of 2.3 min and *threo*-I showed a time of 3.4 min.

The ^{13}C NMR data was taken on ca. 1.0 g of substrate dissolved in 3 ml of $CDCl_3$. In a typical run a 1500-Hz spectral width was used along with a 2.65-sec acquisition time and a 2-sec pulse delay using the gated mode of operation of the decoupler; 4K of transient were collected. The coupling constants were taken from 100-Hz expansions or else the computer-generated listing of peak frequencies was used. The ^{13}C spectra were simulated using the LAOCOON III program adapted to provide a computer-generated plot of the spectrum.[37] The spectral parameters were varied until the computer simulation was superimposable on the original spectrum. In some cases, the computer program could not accommodate the number of spins required for the calculation, and a first-order analysis of the spectrum was necessary. These cases are appropriately indicated in Scheme II. The error in the $^{13}J_{CH}$ values is ±0.4 Hz.

Registry No.—Iodide, 20461-54-5.

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fraction, and k_i is the rate constant for reaction of this conformation. For the compounds of this study, $k_{gauche} = 0$; thus $k_{obsd} = n_{anti} k_{anti}$. However, it should be noted that reservations have been expressed concerning this approach; e.g., E. L. Eliel, and J. Biros, *J. Am. Chem. Soc.*, **88**, 3334 (1966). For this approach to be valid in the case of *erythro*-**2**, the low n_{anti} would require a compensatory effect in the form of a higher k_{anti}. This is possible if exceptional steric strains are present in the ground state that are relieved in the transition state. However, the observation of a (roughly) successful log k vs. E_s correlation in two cases[17] would demand an extremely fortuitous balancing of n and k factors.

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Notes

Determination of the Enantiomeric Purity of Isoquinoline Alkaloids by the Use of Chiral Lanthanide Nuclear Magnetic Resonance Shift Reagents

Nadim A. Shaath and Taito O. Soine*

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

Received February 25, 1975

Since the discovery[1] that lanthanide shift reagents[2] are capable of inducing simplification and enhancement of resolution in NMR spectra of various Lewis bases, many new developments and refinements have been introduced. Whitesides and coworkers[3-5] and others[6-10] have reported that chiral lanthanide shift reagents shift the resonances of many enantiomeric organic substances to different extents. This finding provides a simpler method for the determination of enantiomeric purity than others presently employed.[11-16] On the other hand, the usual procedure of adding the shift reagent incrementally to the substrate in amounts approximating an equimolar ratio to maximize the shifts results in problems. The principal ones are loss of resolution, precipitation, peak broadening, and complexity of the spectrum (especially in polyfunctional compounds) because of signal overlap due to large shifts. In addition, the significant amount of time consumed in such a method led us to investigate the reliability and reproducibility of a simpler procedure.

In essence, the method consists of the addition of the shift reagent in an approximately 1:15 molar ratio directly to the compound dissolved in a suitable solvent in an NMR tube. The procedure utilizes low-frequency NMR spectrometers, only about 25 mg of reagent, and requires less than 0.5 hr for the analysis. Because most of these alkaloids[17] are polyfunctional in nature,[18] it has been determined that, by the use of a relatively small amount of chiral shift reagent as mentioned above, the resolution of the enantiomeric signals is sufficient to permit complete analysis with a high degree of precision even at these low reagent concentrations (see Figure 1). Any signal that meets the requirement of being sufficiently separated from the others and which will respond to the chiral shift reagent is satisfactory. Thus, in one case, it was the methoxyl and/or the aromatic proton signal (glaucine, laudanosine, *N*-methylpavine, tetrahydropalmatine) and, in the other, the methyl signal (the C_1 methyl of salsolidine). For any specific application, the investigator can quickly determine the appropriate signal to be used.

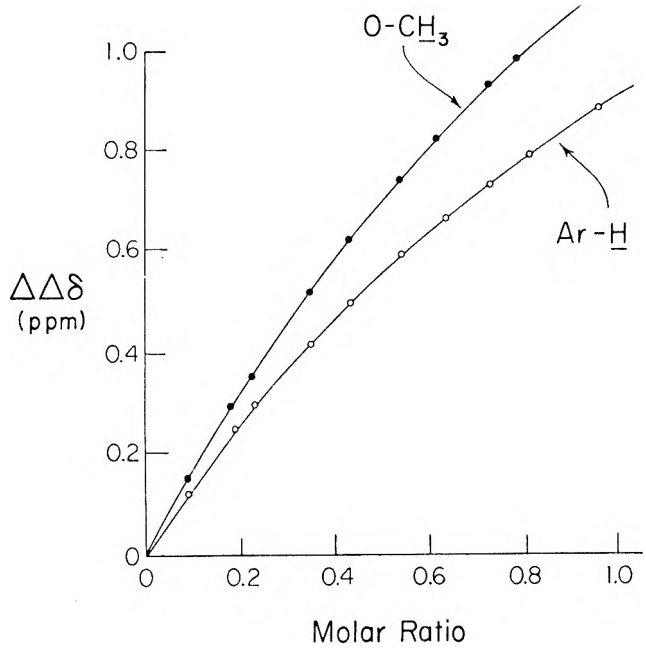

Figure 1. Plots of $\Delta\Delta\delta$ (parts per million) vs. molar ratio of Eu(facam)$_3$ chiral shift reagent to compound.

Five enantiomeric pairs were studied by this method with each representing a different class of isoquinoline alkaloids: (−)-(*S*)- and (+)-(*R*)-salsolidine (a simple tetrahydroisoquinoline alkaloid), (−)-(*R*)- and (+)-(*S*)-glaucine (an aporphine alkaloid), (−)-(*S*)- and (+)-(*R*)-tetrahydropalmatine (a protoberberine alkaloid), (−)-(*S,S*)- and (+)-(*R,R*)-*N*-methylpavine (a pavine alkaloid), and (−)-(*R*)- and (+)-(*S*)-laudanosine (a benzylisoquinoline alkaloid). Because both enantiomers were available to us for each compound, several mixtures (90:10, 80:20, 70:30, 60:40, and the racemic mixture of 50:50) were made up by weighing the two enantiomers in their respective proportions and then tested by the chiral NMR shift reagent procedure. These analyses agree very well with the expected results for the weighed mixtures of enantiomers. For the cases studied, the method accurately detects an enantiomeric mixture of 95:5.

The NMR spectrum of glaucine is well known[19-22] and serves as an example of the analysis (Figure 2a). Two characteristic signals were used for the determination of its enantiomeric composition: (a) the methoxyl singlet resonance at 3.68 ppm (upfield from the three remaining methoxyl singlets) and (b) the strongly deshielded C_{11} aromatic proton at 8.11 ppm. Addition of Eu(facam)$_3$ to a solution of

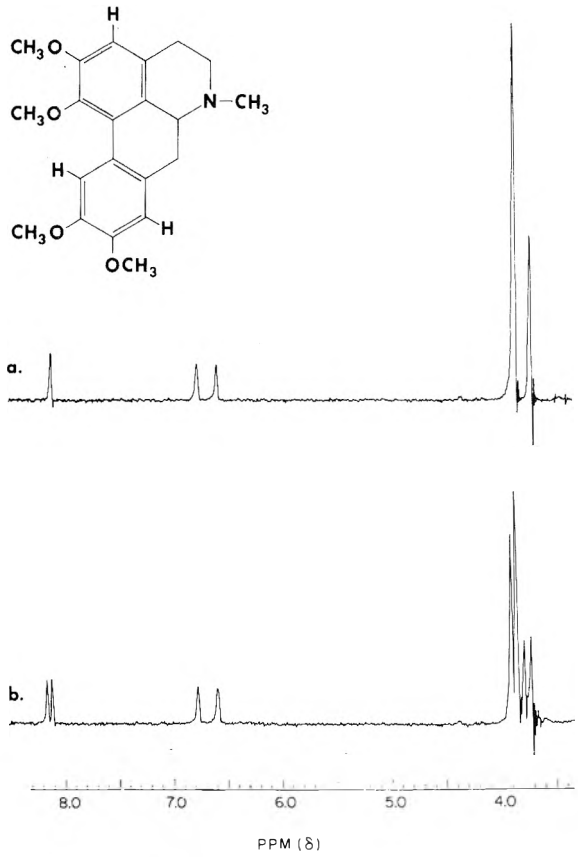

Figure 2. (a) The NMR spectrum of a 0.5 *M* solution of (±)- (*S*)-glaucine in $CDCl_3$ using an A-60D Varian Associates NMR spectrometer; (b) the NMR spectrum after the addition of a 0.033 *M* solution of Eu(facam)$_3$ in $CDCl_3$.[28]

(±)-glaucine in $CDCl_3$ caused both of the singlet resonances for the C_{11} aromatic and the C_1 methoxyl protons to be split into two equal signals (Figure 2b), with the *S* enantiomer shifting 0.05 ppm in each case. Several integrations, as well as actual weighings of the tracings of the expanded area below the signals, showed the expected 50:50 ratio of the enantiomers.

The determination of enantiomeric purity is a concern of all natural product chemists but has been exceptionally useful to us in following the progress of resolutions of racemic mixtures and/or the racemization of enantiomers frequently used in our laboratories. Since the method does not require the possession of both, or even one, of the enantiomers in pure form, direct determination of the relative enantiomeric concentrations is thus possible with a single scan NMR spectrum of any aliquot without resorting to the tedious procedures of separation and identification.

It is our hope that this report will demonstrate the remarkable simplicity and reliability inherent in the use of small amounts of chiral lanthanide NMR shift reagents for the determination of the enantiomeric purity of many optically active isoquinoline and related alkaloids.

Experimental Section

The NMR spectra were determined on a Varian A-60D spectrometer. Several mixtures were made up by weighing the two enantiomers in their respective proportions (50:50, 60:40, 70:30, 80:20, and 90:10) and dissolving them in $CDCl_3$ to form a 0.5 *M* solution. The shift reagent, Eu(facam)$_3$,[23] was weighed and added to the enantiomeric mixture to give a reagent concentration of 0.033 *M*. This ratio of substrate to reagent (1 :1) effected the desired separation of signals in almost all cases. Occasionally, in specific areas, this ratio was altered slightly to achieve the best separation. Several machine integrations of the area below each separated enantiomeric peak are adequate for a reasonably precise analysis. Other integration procedures have been performed and are recommended for more accurate analyses (e.g., weighing of the tracings of the expanded area below the signals, use of a compensating polar planimeter, etc.), although the simpler method usually supplies the experimentally needed information.

All of the enantiomers tested by this procedure are known compounds, a few of which were commercially available. Synthesis, spectral, and analytical data for the others are reported elsewhere.[24]

Salsolidine. The (±) form was obtained by the Bischler–Napieralski cyclization of *N*-acetylhomoveratrylamide and resolution with the appropriate *O,O*-dibenzoyltartaric acids via the bitartrates provided the required enantiomers.[24a]

Glaucine. The (+) form was obtained from Pierce Chemical Co. The (−) form was obtained by racemizing the (+) form under catalytic hydrogenation conditions described by Kametani et al.[25] and applied by Genenah.[24a] Resolution by bitartrate formation using L-tartaric acid provided the (−) isomer.

Tetrahydropalmatine. Both enantiomers of this base were available as the hydrochlorides from Pierce Chemical Co.

***N*-Methylpavine.** The racemic form was prepared by the method of Battersby and Binks[26] and the enantiomeric forms were obtained by the use of the enantiomeric tartaric acids to provide the appropriate bitartrates.

Laudanosine. The method of Mirza[27] was used to obtain the racemic form from papaverine methiodide. The enantiomers were obtained through bitartrate formation with the appropriate *O,O*-dibenzoyltartaric acids.[24a]

Registry No.—(−)-(*S*)-Salsolidine, 493-48-1; (+)-(*R*)-salsolidine, 54193-08-7; (−)-(*R*)-glaucine, 38325-02-9; (+)-(*S*)-glaucine, 475-81-0; (−)-(*S*)-tetrahydropalmatine, 483-14-7; (+)-(*R*)-tetrahydropalmatine, 3520-14-7; (−)-(*S,S*)-*N*-methylpavine, 6901-16-2; (+)-(*R,R,*)-*N*-methylpavine, 16584-62-6; (−)-(*R*)-laudanosine, 85-63-2; (+)-(*S*)-laudanosine, 2688-77-9.

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(24) The preparation of the enantiomers is described in two Ph.D. Dissertations from the University of Minnesota: (a) A. A. Genenah, 1972; (b) P. W. Erhardt, 1974.
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(28) Note also the enhancement in resolution of the remaining methoxyl resonances that accompanied the split of the C_1 methoxyl singlet.

Conversion of Androstenolone to Pregnenolone

Samuel Danishefsky,* Kazuo Nagasawa, and Nai Wang

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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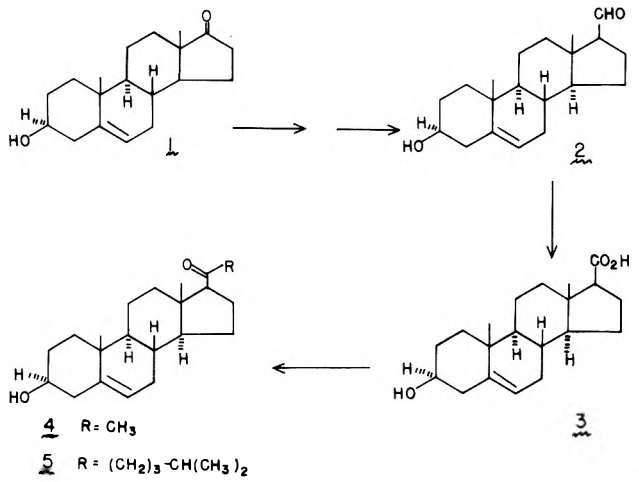
The Butenandt group developed the original methodology for the transformation of androstenolone (**1**) to pregnenolone (**4**).[1] Their route involves the reaction of methyl Grignard reagent with a Δ^{16}-17 cyano steroid, which arises from the dehydration ($POCl_3$) of a 17-cyanohydrin. Selective saturation of the Δ^{16} double bond completes the sequence.



The formation of 20-keto steroids has also been achieved[2] via reductive cleavage of a 17α-acetoxy-20-ketone, in turn, derivable from a sequence starting with ethynylation of a 17-ketone. Another route involves the reaction of an etianyl chloride with dimethylcadmium.[3] Oliveto and coworkers have applied ethylidenation (via a Wittig reaction) toward this objective. Oxygen is introduced at C_{20} either through hydroboration[4] or photoxygenation.[5]

As part of our synthetic efforts in steroids, we had need for a short, efficient sequence of reactions which allows for the transformation of a 17- to a 20-keto steroid. An important condition was that the process be compatible with isolated and conjugated double bonds[6] and unprotected alcohols.

We describe below an efficient conversion of **1** to **4**. We feel that this route constitutes the simplest way of achieving the objective. Furthermore, considerable synthetic flexibility for the synthesis of steroid side chain analogs is available.

The reaction of **1** with methoxymethylenetriphenylphosphorane[7] in dimethyl sulfoxide[8] followed by acidic hydrolysis via aqueous perchloric acid[9] gives 20β-formylandrost-5-en-3β-ol (**2**) in 70% yield. The aldehyde was oxidized to a carboxyl group, without protection of the 3β-ol through the action of silver oxide in aqueous methanol. The etianic acid, **3**, reacts smoothly with excess methyllithium[10] to afford pregnenolone (80%). The ability to produce the alkyl ketone directly from the alcohol–acid with alkyllithium is an important simplification in that it allows for the avoidance of the blocking and deblocking of the alcohol and activation of the carboxyl involved in the acid chloride routes.[3]

Curiously, the alkyllithium reactions with steroidal carboxylic acids have been conducted only in the *D*-nor series.[11,12] We find that reaction of **3** with excess isohexyllithium gives 20-oxo-21-norcholesterol (**5**)[13] in 94% yield. The reaction of etianic acids with alkyllithium reagents has considerable utility in the elaboration of sterol side chains.

Experimental Section[13]

Conversion of Androstenolone (1) to 20β-Formylandrost-5-en-3β-ol (2). Sodium hydride (308 mg of a 50% dispersion, 6.4 mmol) was suspended in 5 ml of dry DMSO. Upon warming to 55° and stirring under a nitrogen atmosphere for 40 min, gas was evolved and a pale yellow-green solution resulted. To this solution was slowly added a solution of 2.2 g (6.4 mmol) of methoxymethylenetriphenylphosphonium chloride in 10 ml of DMSO. A deep red coloration developed upon mixing. After 30 min, a solution of 350 mg (1.2 mmol) of androstenolone (**1**) in 10 ml of DMSO was added. The temperature was raised to 70° and stirring was continued for 10 hr at the same temperature. The reaction mixture was poured into water and the aqueous system was extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and the volatiles were evaporated at the water pump. To the brown residue was added 20 ml of ether and 5 ml of 70% aqueous perchloric acid. After being stirred at room temperature for 10 hr, the reaction mixture was poured into ice–water. The aqueous system was thoroughly extracted with ethyl acetate. After drying over $MgSO_4$, the organic extracts were evaporated and the residue was chromatographed on silica gel. Elution with 3:1 *n*-hexane–ethyl acetate gave 254 mg of **2** (70%). Recrystallization from EtOH–H_2O gave plates: mp 155–157°; $[\alpha]D$ (room temperature) −21.0° (*c* 0.1, $CHCl_3$) [lit.[14] mp 148–153°, $[\alpha]^{21}D$ 14.5° ($CHCl_3$)]; $\bar{\nu}$ 3450, 1710 cm^{-1}; *m/e* 302 (parent); NMR δ ($CDCl_3$) 0.80 (s, 3, C_{13} Me), 1.05 (s, 3, C_{10} Me), 3.45 (m, 1, CHOH), 9.80 [s (broad), 1, CHO].

Oxidation of 2. Formation of 3β-Hydroxyeti-5-enoic Acid (3). Silver nitrate (3.4 g, 20 mmol) was dissolved in 60 ml of deionized water. To this was added 30 ml of 10% aqueous sodium hydroxide. A brown precipitate formed immediately. To this system was slowly added 75 ml of dilute ammonia, thus giving a clear solution. To this was added a solution of aldehyde **2** (1 g, 3.3 mmol) in 25 ml of methanol and the system was stirred at 80–90° for 6 hr. The reaction mixture was poured into ice–water, acidified with 10% aqueous HCl, and extracted with ethyl acetate. After the organic extract was dried over magnesium sulfate, the volatiles were removed at the water pump. The residual yellow powder was recrystallized from ethanol–water to give 800 mg (76% yield) of **3**. Recrystallization from ethanol gave **3** as needles, mp 282–283° dec, $[\alpha]D$ (room temperature) −20° (*c* 0.2, EtOH) (lit.[15] mp 280–281°, no reported rotation).

Conversion of 3 to Pregnenolone (4). To 100 mg (0.32 mmol) of acid **3** was added via syringe 4 ml of 1.0 *M* methyllithium in hexane. The reaction mixture was maintained under a nitrogen atmosphere and allowed to stir for 15 hr at room temperature. The contents were poured into ice–water and the aqueous system was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated at the water pump. The residue was chromatographed on silica gel. Elution with 3:1 *n*-hexane–ethyl acetate gave 81 mg (81%) of pregnenolone (**4**), mp 190–192°, $[\alpha]D$ (room temperature) (*c* 0.15, EtOH) [lit.[16] mp 193°, $[\alpha]D$ +28° (EtOH)].

Reaction of Hydroxy Acid 3 with Isohexyllithium. Formation of 21-Nor-20-oxochlesterol (5). A solution of isohexyllithium in ether was prepared by dropwise addition of a solution of isohexyl bromide (10 g) in 10 ml of anhydrous ether to lithium wire (1.3 g) covered with 40 ml of ether. The temperature was maintained at 10–15° and stirring was continued for 3 hr. The titer (0.8 *M*) was established according to Gilman.[17]

To compound **3** (700 mg, 2.2 mmol), under nitrogen and with rigorous exclusion of moisture, was added via syringe a solution of isohexyllithium (22 mmol) in ether. The system was stirred at room temperature for 50 hr.

The reaction mixture was poured into ice and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the volatiles left a crystalline residue (840 mg, 99%). Recrystallization from 3-hexane gave **5** (800 mg, 94%): mp 138–139° (lit.[18] mp 139–140°); $[\alpha]D$ (room temperature) +20° ($CHCl_3$, *c* 0.2) [lit. $[\alpha]^{25}D$ +20° ($CHCl_3$, *c* 1.22)]; $\bar{\nu}$ (Nujol) 1710 cm^{-1}; *m/e* 386 (parent).

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Registry No.—**1**, 53-43-0; **2**, 55029-99-7; **3**, 10325-79-8; **4**, 145-13-1; **5**, 38673-20-0.

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Iodide Catalysis of Oxidations with Dimethyl Sulfoxide. A Convenient Two-Step Synthesis of α Diketones from α-Methylene Ketones

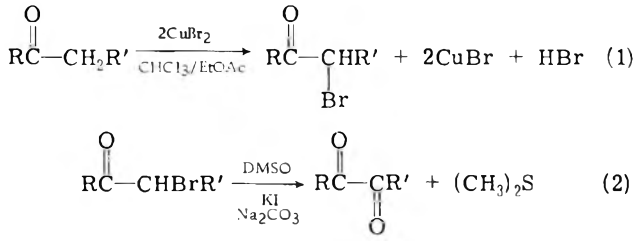
Dennis P. Bauer and Roger S. Macomber*

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221

Received January 24, 1975

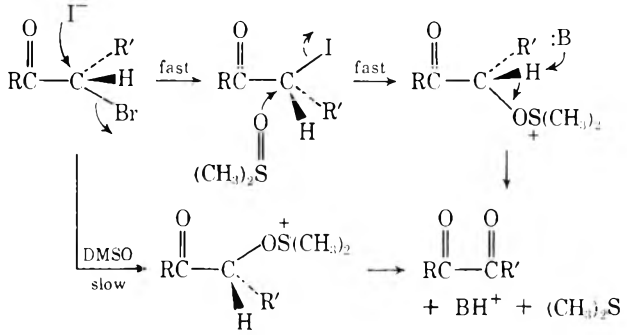
α diketones are not only interesting with regard to conformational analysis,[1] electronic spectroscopy,[2] and photochemistry,[3] but also because they are versatile synthetic intermediates and they undergo a variety of unique reactions, including the benzil–benzilic acid rearrangement[4] and dioxaphospholene formation.[5]

In connection with our synthesis of macrotricyclic hydrocarbons, we needed large amounts of several cyclic α diketones, including 1,2-cyclooctanedione and 1,2-cyclododecanedione. One synthesis involved an acyloin condensation, followed by oxidation with cupric acetate;[6,7] another was the selenium dioxide oxidation of the corresponding cyclic ketones.[7] Our attempts to reproduce the selenium dioxide oxidations led to products in moderate yields, but these products were contaminated with selenium which proved extremely difficult to remove.[8] The acyloin condensation, while providing higher purity, was much more difficult to carry out and gave frustratingly low yields. The observation that primary and secondary halides and sulfonate esters could be oxidized to aldehydes and ketones with dimethyl sulfoxide (DMSO)[9] led several groups to prepare α diketones via the DMSO oxidation of α-bromo ketones.[10] Unfortunately, the DMSO oxidation, because it requires SN2 attack by the sulfoxide oxygen at the brominated carbon, is sensitive to the steric environment of that center. Thus, while primary halides and tosylates provide aldehydes in decent yields, oxidation of secondary systems, as required to make diketones, is often sluggish. This low reactivity can be partially overcome by promoting the oxidation with silver salts such as silver perchlorate[11] or silver nitrate,[12] but such reagents are not economical on the mole scale. We wish to report a convenient, high-yield process for conversion of α-methylene ketones to α diketones, using only inexpensive, common reagents.



Of the many ways to α-brominate ketones, we have had uniformly excellent results with cupric bromide in refluxing chloroform–ethyl acetate.[13] For the five ketones listed in Table I, the isolated yield of α-bromo ketone ranged from 90 to 97%, and the slowest reaction required 8 hr (2,2,5,5-tetramethyl-3-hexanone). The success of the sequence thus depended only on the oxidation step. Our attempts to oxidize these α-bromo ketones directly with DMSO gave only slow reactions in the cases of the third and fourth entries in Table I, and essentially no reaction in the first, second, and fifth cases.

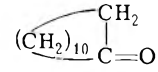
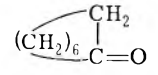
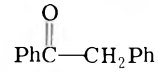
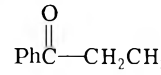
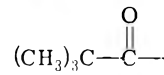
It has been noted[14] that DMSO is a weaker nucleophile than even bicarbonate in at least one instance. It seemed reasonable that the oxidation step could be catalyzed by a species that was a better nucleophile than DMSO and a better leaving group than bromide. Iodide ion fits this description well, for it is not only a powerful nucleophile (by virtue of high polarizability and low solvation), but also a highly reactive leaving group in nucleophilic displacements (because of the weakness of the C–I bond).[15] Thus, the slow direct attack by DMSO on the α-bromo ketone could be circumvented by two faster displacements involving iodide.



The catalytic effect of iodide was dramatic. The second, third, and fourth entries in Table I reacted completely within 10 min at ambient temperature. The first entry, for reasons that are not clear, required 60 min at 120°, but still gave a reasonable yield. Not unexpectedly the 4-bromo-2,2,5,5-tetramethyl-3-hexanone (a new compound, entry 5) failed to react even after 25 hr at 150°. Although there was evidence that attack by iodide occurred (see Experimental Section), attack by DMSO was apparently precluded by the neopentyl nature of the reaction center.[16] We *were* able to oxidize 4-bromo-2,2,5,5-tetramethyl-3-hexanone in 47% yield using silver nitrate in DMSO.[12] This is probably the method of choice when dealing with highly hindered α-halo ketones.

With the exception of the above compound, overall yields of the α diketones ranged from 65 to 92%. Both reactions are simple to perform and the required reagents and solvents are economical to use. The only disadvantages of this procedure are (1) certain α-bromo ketones (Table I, entries 1 and 2) are somewhat unstable and should not be stored for long periods before carrying out the oxidation, (2) some α-bromo ketones and α diketones undergo side reactions such as aldol condensations in DMSO, so the oxi-

Table I
Two-Step Conversion of Ketones to α Diketones

Entry	Starting ketone	Registry no.	Step 1 Time, hr	Step 1 Yield, %	Step 2 Time, min.	Step 2 Yield, %	Overall yield, %	Registry no.
1		830-13-7	3.5	90	60[a]	71	65	3008-41-1
2		502-49-8	5.0	90	4–5[b]	65	59	3008-37-5
3		451-40-1	5.0	97	5–10[b]	95	92	134-81-6
4		93-55-0	5.0	95	5–10[b]	90	86	579-07-7
5		868-91-7	8.0	93	*c*	*c*	*c*	

[a] 120°. [b] Ambient temperature. [c] No reaction, even after 25 hr at 150°; see text.

dation step should be monitored with TLC and stopped when complete, and (3) ketones with nonidentical α-methylene groups will give mixtures of monobromo derivatives, and hence mixtures of isomeric diketones. Only if the isomers are separable at one stage or the other will this synthesis be of use.

Experimental Section

The following instruments were employed: Beckman IR-12 (calibrated with polystyrene); Varian A-60 (δ, parts per million downfield from internal Me_4Si); Bruker HFX-90 (^{13}C data are given in parts per million upfield from CS_2); Hitachi RMU-7 (70 eV unless otherwise noted). All starting materials, reagents, and solvents were obtained from Aldrich Chemical Co. or Matheson Scientific unless otherwise noted. Melting and boiling points are not corrected. The elemental analysis was performed by Chemalytics, Inc., Tempe, Ariz.

2-Bromocyclododecanone. Cyclododecanone (9.1 g, 0.050 mol), chloroform (50 ml), and ethyl acetate (50 ml) were placed in a 250-ml three-necked flask equipped with magnetic stirrer, nitrogen inlet tube, and reflux condenser. Powdered cupric bromide (22.3 g, 0.10 mol) was added in small portions over a 2-hr period, with the reaction mixture maintained at 75–80° while a constant stream of nitrogen gas was bubbled through the reaction solution.[13] The green color from each portion was allowed to disappear before the next portion was added. After the addition was completed, the solution was heated for 1.5 hr until the green color and dark cupric bromide disappeared, cooled, and filtered, and the colorless solid cuprous bromide was washed with 25 ml of chloroform. The combined filtrate and washings were rotary evaporated and the oily residue was redissolved in 200 ml of diethyl ether, washed with water (50 ml), 5% sodium bicarbonate (2 × 50 ml), and brine (50 ml), then dried over sodium sulfate. After filtration, rotary evaporation of solvent, and cooling (−10°), the resulting oil solidified to give cream-colored crystals (11.8 g, 90%) of 2-bromocyclododecanone, mp 52–53° (lit.[17] mp 53–54°). The product could also be recrystallized from pentane at −78°.

Spectral data for 2-bromocyclododecanone[18] include: ir ($CHCl_3$) 1713 cm^{-1}; ^1H NMR ($CDCl_3$) 1.33 (s, $\Delta\nu_{1/2}$ = 4.5 Hz, 14 H), 1.65–2.25 (br m, 4 H), 2.76 (m, 2 H), 4.43 (d of d, J = 4 Hz, 1 H); ^{13}C NMR (CS_2) −10.1, 155.2, 156.2, 164.2, 165.5, 167.1 ppm; mass spectrum *m/e* (rel intensity) 262/260 (M^+, 33/33), 180 (100).

1,2-Cyclododecanedione. To a stirred mixture of potassium iodide (8.3 g, 0.05 mol), sodium carbonate (5.3 g, 0.05 mol), and dimethyl sulfoxide (170 ml) at 120° under nitrogen was added 2-bromocyclododecanone (13.05 g, 0.05 mol) at once. After stirring for 1 hr, the mixture was rapidly cooled and then poured into ice-cold brine (300 ml), and the mixture was extracted with diethyl ether (2 × 100 ml). The combined extracts were washed with water (100 ml), brine (100 ml), 5% sodium bicarbonate (100 ml), and brine (100 ml), then dried (Na_2SO_4) and filtered. Rotary evaporation left an oil which was chromatographed through alumina (Alcoa), using benzene–diethyl ether (2:1 v/v) as the eluent, to yield 7.0 g (71%) of bright yellow 1,2-cyclododecanedione, which crystallized upon removal of the solvent: mp 43° (lit.[6,7] mp 44°); ir (cyclohexane) 1708 cm^{-1}; ^1H NMR ($CDCl_3$) 1.29 (s, $\Delta\nu_{1/2}$ = 3.5 Hz, 12 H), 1.53–1.93 (br m, 4 H), 2.75 ppm (t of t, J = 6 Hz, 4 H); ^{13}C NMR (CS_2) −8.0, 153.9, 163.4, 164.5, 166.0, 167.3 ppm; mass spectrum *m/e* (rel intensity) 196 (M^+, 100).

2-Bromocyclooctanone. The preceding method was employed on the 0.10-mol scale to prepare 2-bromocyclooctanone, bp 54–55° (0.1 mm) [lit.[19] bp 79–81° (1 mm)], yield 18.4 g (90%), from cyclooctanone. Addition required 3.5 hr, and this was followed by stirring for 1.5 hr.

Spectral data[18,19] include: ir (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) 1.67 (m, 8 H), 2.10–2.90 (m, 4 H), 4.36 ppm (t, 1 H); mass spectrum *m/e* (rel abundance) 206/204 (M^+, 30/30), 98 (100).

1,2-Cyclooctanedione was prepared on the 20-mmol scale from 2-bromocyclooctanone. Reaction time was ~4–5 min at 20–23°. The work-up procedure was the same as described in the previous example: yield 2.0 g (74%); bp 44–45° (0.4 mm) [lit.[7] bp 59–60° (1.5 mm)].

Spectral data include: ir (CCl_4) 1701 cm^{-1}; ^1H NMR ($CDCl_3$) 1.70 (s, $\Delta\nu_{1/2}$ = 7.0 Hz, 8 H), 2.30–2.71 ppm (m, 4 H); mass spectrum *m/e* (rel abundance) 140 (M^+, 100).

2-Bromo-2-phenylacetophenone was prepared on the 50-mmol scale from deoxybenzoin. Addition required 3.5 hr, with 1.5 hr of additional stirring. After the usual work-up, 13.4 g (97%) of opaque product was isolated, mp 55–56° (lit.[20] mp 54–55°). The ir [(CCl_4) 1701 cm^{-1}], ^1H NMR [($CDCl_3$) 6.45 (s, 1 H), 7.30–8.15 ppm (m, 10 H)], and TLC of the purified product were identical with those of an authentic sample of 2-bromo-2-phenylacetophenone (Eastman Organic Chemical Co.).

Benzil was prepared on the 10-mmol scale from 2-bromo-2-phenylacetophenone at ambient temperature for 5–10 min. After the usual work-up, 2.0 g (95%) of benzil was isolated, mp 95–96° (lit.[21] mp 95–96°).

The ir [(CCl_4) 1677, 1684 cm^{-1}], ^1H NMR [($CDCl_3$) 7.50–8.15 ppm (m, 10 H)], and TLC of the purified product were identical with those of an authentic sample of benzil (Eastman Organic Chemical Co.).

α-Bromopropiophenone was prepared on the 100-mmol scale (addition 1.5 hr, stirring 1.5 hr): yield 95%; bp 64–66° (1 mmHg) [lit.[22] bp 110–111° (3 mmHg)].

The ir [(neat) 1710 cm^{-1}], ^1H NMR [($CDCl_3$) 1.88 (d, J = 6 Hz, 3 H), 5.20 (q, J = 6 Hz, 1 H), 7.36–8.15 ppm (m, 5 H)], and TLC of the purified product match the data obtained from an authentic sample (Aldrich Chemical Co.).

1-Phenyl-1,2-propanedione was prepared on the 20-mmol scale exactly as in the preparation of benzil: yield 90%; bp 60–62° (0.5 mmHg) [lit.[23] bp 101° (12 mm)].

The ir [(neat) 1673, 1712 cm^{-1}], ^1H NMR [($CDCl_3$) 2.53 (s, 3 H), 7.35–8.15 ppm (m, 5 H)], and TLC of the purified product match those data obtained on an authentic sample (Eastman Chemical Co.).

2,2,5,5-Tetramethyl-3-hexanone was prepared by the "Jones reagent"[24] oxidation of 2,2,5,5-tetramethyl-3-hexanol (Chemical

Samples Co.): bp 160–161° (lit.[16] bp 161°); ir ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) 1.05 (s, 9 H), 1.10 (s, 9 H), 2.40 ppm (2 H); mass spectrum *m/e* (rel abundance) 156 (M^+, 40), 57 (100).

4-Bromo-2,2,5,5-tetramethyl-3-hexanone was prepared from the above ketone on the 50-mmol scale. The reaction was notably slower than the other reactions, with addition requiring 8 hr. Work-up as usual gave 10.9 g (93%) of the bromo ketone as clear, colorless oil: bp 31° (0.10 mm); ir ($CHCl_3$) 1709 cm^{-1}; ^1H NMR ($CDCl_3$) 1.16 (s, 9 H), 1.25 (s, 9 H), 4.53 ppm (s, 1 H); mass spectrum *m/e* (rel abundance) 236/234 (M^+, 60/60), 151/149 ($M - C_4H_9CO$, 70/70), 57 (100).

Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.07; H, 8.14; Br, 33.98. Found: C, 51.04; H, 8.11; Br, 34.04.

Attempted Preparation of 2,2,5,5-Tetramethyl-3,4-hexanedione via Iodide-Catalyzed Oxidation. When the usual reaction was attempted on the above bromo ketone, even after reaction times of up to 25 hr at 150°, no diketone could be isolated, although there was development of some yellow color. The liquid reisolated from the reaction (105% based on mass of starting bromo ketone), which had an NMR identical with that of starting material, was shown by GLC (12% Carbowax 20M) to be a 55:45 mixture of α-bromo and α-iodo ketone: mass spectrum *m/e* 282 (RI), 236/234 (RBr), 197 (RI − C_4H_9CO), 151/149 (RBr − C_4H_9CO).

2,2,5,5-Tetramethyl-3,4-hexanedione was prepared by Kornblum's method;[12] 4-bromo-2,2,5,5-tetramethyl-3-hexanone (2.35 g, 10 mmol) was dissolved in 15 ml of acetonitrile, and a solution of silver nitrate (1.87 g, 11 mmol) in 15 ml of acetonitrile was added. After stirring for 60 hr at ambient temperature the mixture was filtered, the silver bromide was washed with diethyl ether, and the combined filtrate and washing were rotary evaporated (water aspirator, 30°). The residue was taken up in ether, washed with water, and dried, and the solvent was removed. The crude nitrate ester was dissolved in 70 ml of DMSO and then a suspension of sodium acetate trihydrate (0.20 g) in 20 ml of DMSO was added. After stirring for 5–10 min at room temperature, the reaction mixture was worked up in a similar manner to the previously mentioned DMSO oxidation reactions: yield 0.80 g (47%); bp 38–40° (5 mm) [lit.[1] bp 59–62° (14 mm)]; ir (neat) 1700 cm^{-1}; NMR (CCl_4) 1.18 ppm (s); mass spectrum *m/e* (rel abundance) 170 (M^+, 6), 57 (100).

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Registry No.—2-Bromocyclododecanone, 31236-94-9; 2-bromocyclooctanone, 39261-18-2; 2-bromo-2-phenylacetophenone, 1484-50-0; α-bromopropiophenone, 2114-00-3; 2,2,5,5-tetramethyl-3-hexanol, 55073-86-4; 4-bromo-2,2,5,5-tetramethyl-3-hexanone, 55073-87-5; 4-iodo-2,2,5,5-tetramethyl-3-hexanone, 55073-88-6; 2,2,5,5-tetramethyl-3,4-hexanedione, 4388-88-9.

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Oxidation of Alcohols with Acetyl Hypoiodite

Thomas R. Beebe* Beverly A. Barnes, Keith A. Bender, Allan D. Halbert, Robert D. Miller, Martin L. Ramsay, and Michael W. Ridenour

Department of Chemistry, Berea College, Berea, Kentucky 40403

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This report covers the reaction of a variety of alcohols with acetyl hypoiodite and the subsequent decomposition of the alkyl hypoiodite that was formed. The formation and decomposition of the alkyl hypoiodite product was done in the absence of metal salts. Previous reported reactions of steroid alcohols with acetyl hypoiodite involved the preparation and decomposition of the products in the presence of mercury, silver, or lead salts.[1] These salts very likely have a direct effect on the product composition.

To determine the generality of preparing alkyl hypoiodites from acetyl hypoiodite and alcohols, we have treated several alcohols with acetic acid solutions of acetyl hypoiodite. Solutions of acetyl hypoiodite were prepared by treating silver acetate with a 5% molar excess of iodine in glacial acetic acid.[2] The molar amount of precipitated silver iodide accounted for more than 99% of the starting silver acetate.

The alcohols to be oxidized were selected so that the proposed alkyl hypoiodite intermediates would break down to products in a variety of ways. Good yields of products were obtained by irradiating the cooled (20–25°) reaction mixtures immediately after the alcohols were mixed with the acetyl hypoiodite solutions. The product yields were cut approximately in half when the reaction mixtures were irradiated and heated (90–100°), and yields were very low (10–20%) when the reaction mixtures were run in the dark at ambient temperatures.

A general sequence for the reaction between acetyl hypoiodite and an alcohol is suggested below. The acetyl hypoiodite reacts with the alcohol to give an equilibrium with the alkyl hypoiodite and acetic acid. The O–I bond of the alkyl hypoiodite then is cleaved homolytically by visible light to produce alkoxy radicals. The alkoxy radicals have several decomposition pathways available to them.

$$CH_3COOI + ROH \rightleftharpoons CH_3COOH + ROI$$

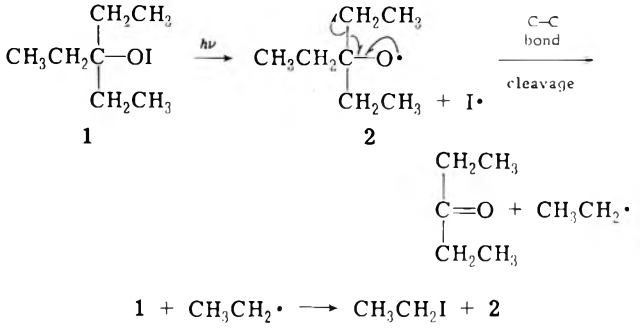
$$ROI \xrightarrow{h\nu} I\cdot + RO\cdot \longrightarrow \text{products}$$

The oxidations of 3-ethyl-3-pentanol, 1-pentanol, and benzyl alcohol with acetyl hypoiodite will be discussed in some detail. The only detectable products from the reaction of 3-ethyl-3-pentanol with acetyl hypoiodite were 3-pentanone and iodoethane. The 3-pentanone is formed from β-scission[3] of the intermediate alkoxy radical **2**, while the iodoethane is produced when the ethyl radical and the hypoiodite **1** collide.

Table I
Oxidations[a] of Alcohols with Acetyl Hypoiodite

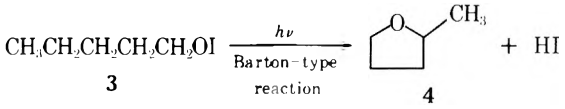
Registry no.	Alcohol	Products (% yield[b])	Irradiation time, hr
597-49-9	3-Ethyl-3-pentanol	3-Pentanone (90) Ethyl iodide (84)	1
6032-29-7	2-Pentanol	2-Methyltetrahydrofuran (30) 2-Pentanone (60[c])	24
71-41-0	1-Pentanol	2-Methyltetrahydrofuran (80)	24
100-51-6	Benzyl alcohol	Benzaldehyde (85[c]) Iodobenzene (0)	4
611-69-8	2-Methyl-1-phenyl-1-propanol	Benzaldehyde (61[c]) 2-Iodopropane (>15[d]) 2-Methyl-1-phenyl-1-propanone (40[c])	17

[a] The oxidations were performed at 20–25° with irradiation. [b] The percent yields were an average of three runs. [c] The yield was based on a 50% maximum because of a presumed disproportionation reaction of the alkoxy radical. [d] The 2-iodopropane was not stable under our GLC conditions and more than 15% was probably formed.

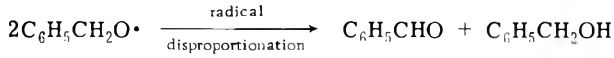


$$1 + CH_3CH_2\cdot \longrightarrow CH_3CH_2I + 2$$

Reaction of 1-pentanol with acetyl hypoiodite produces 80% yields of 2-methyltetrahydrofuran (**4**). The furan product gives evidence that a Barton-type[4] decomposition is the preferred pathway for the intermediate hypoiodite **3**.



Benzaldehyde is the major product when benzyl alcohol and acetyl hypoiodite are mixed and irradiated. The benzoxy radical **6** forms benzaldehyde and presumably benzyl alcohol, by a radical disproportionation reaction.



Two products, 2-pentanone (60%) and 2-methyltetrahydrofuran (30%), were formed when 2-pentanol and acetyl hypoiodite were mixed together with irradiation. The 2-pentanone was probably formed by a disproportionation reaction of the 2-pentoxy radical while the 2-methyltetrahydrofuran was produced by a Barton-type reaction.

The decomposition of the hypoiodite obtained from 2-methyl-1-phenyl-1-propanol gave benzaldehyde (61%) and 2-iodopropane (>15%) from a β-scission of the alkoxy radical and produced 2-methyl-1-phenyl-1-propanone (40%) by radical disproportionation of the alkoxy radical.

A list of alcohols oxidized with acetyl hypoiodite, the percentage yields of the products, and the reaction times are given in Table I.

The reactions of some alcohols with acetyl hypoiodite other than those listed in Table I were tried. 1-Phenyl-1-ethanol and *tert*-butyl alcohol dehydrated too rapidly in the acetic acid solution before any substantial hypoiodite formation could take place. Diphenylcarbinol and triphenylcarbinol acetylated before an oxidation could occur.

In summary, the acetyl hypoiodite converted several alcohols to their corresponding alkyl hypoiodites in good yields. The reaction of acetyl hypoiodite with alcohols provides an excellent source of the not easily accessible primary and secondary alkoxy radicals. With no metal ions present the alkyl hypoiodites gave products that indicated light-induced homolytic decomposition. We are presently looking for an inert solvent in which the acetyl hypoiodite is stable so that the reaction of alcohols with acetyl hypoiodite would be more general.

Experimental Section

Analyses were performed on a Perkin-Elmer 810 GLC and a Varian Aerograph Model 700 GLC. Irradiation of the reaction mixtures was effected with a G. E. projector spot 150-W, 130-V tungsten lamp. Liquid chemicals used in reaction mixtures and standard GLC mixtures all had greater than 99.5% purity as determined on the gas chromatograph. The silver acetate was dried under vacuum in the dark at 64°. The iodine was sublimed. The acetic acid was refluxed for 24 hr with 2% acetic anhydride and was fractionally distilled. GLC analyses of the acetic acid solutions were performed using a 6 ft × 0.25-in. copper column of 20% FFAP (modified Carbowax 20M from Varian) adsorbed on 60–80 mesh base-washed Chromosorb P. All oxidations were run between 20 and 25° with irradiation. The oxidations were monitored frequently and the time for maximum yields of products ranged from 1 to 24 hr. Descriptions of the preparation of acetyl hypoiodite and of the oxidation of 3-ethyl-3-pentanol with acetyl hypoiodite are given in detail. The other oxidations were performed in a similar manner.

Preparation of Acetyl Hypoiodite. Dry silver acetate (4.09 mmol) was placed in an aluminum foil covered 100-ml round-bottomed flask containing a small magnetic stirrer. Forty milliliters of acetic acid containing iodine (4.3 mmol) was added dropwise into the flask with stirring. The mixture was stirred for 1 hr at room temperature and was filtered through a fine sintered-glass funnel. The precipitate contained 4.08 mmol of silver iodide. The liquid filtrate contained 2.5 mmol of acetyl hypoiodite. Analysis was done by adding aliquot portions of the acetyl hypoiodite to aqueous potassium iodide solutions. The liberated iodine was titrated with standard thiosulfate solutions.

Oxidation of 3-Ethyl-3-pentanol with Acetyl Hypoiodite. Five milliliters of an acetic acid solution containing 3-ethyl-3-pentanol (1.0 mmol) and chlorobenzene (0.25 mmol) was added to a 25-ml round-bottomed flask. To this solution was added 5 ml of acetic acid solution containing acetyl hypoiodite (0.25 mmol). The combined solutions were placed in a cooling bath (20–25°) and irradiated. GLC analysis showed 50% iodoethane and 53% 3-pentanone within 19 min and a maximum of 84% iodoethane and 90% 3-pentanone in 1 hr.

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Registry No.—Acetyl hypoiodite, 6540-76-7.

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Vinyl Cations. 19.[1] Preparation and Solvolysis of (1-Bromo-1-arylmethylene)cyclopropanes. Effect of *p*-Aryl Substituents on the Generation of Stabilized Vinyl Cations

J. Salaun and M. Hanack*

Fachbereich 14, Organische Chemie, Universität des Saarlandes, D 6600 Saarbrücken, Germany

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Vinyl cation intermediates are now readily available in solvolysis reactions either through heterolysis of vinyl substrates or triple bond participations.[2] Although vinyl cations are generally less stable than the corresponding saturated carbenium ions,[3] recent studies have given evidence for their formation.

Thus, in the solvolysis of simple alkyl vinyl derivatives the choice of a more reactive leaving group (e.g., arylsulfonates[4] or, even better, the "super leaving groups" triflate[5] and nonaflate[6]), or the stabilization of the positive charge by electron-releasing neighboring groups (e.g., vinyl,[7] aryl,[7,8] cyclopropane[9]) have favored the generation of this challenging intermediate.

In the particular case of a cyclopropane ring, it appears possible to stabilize a positive charge in two ways.

In the vinyl cation **1** the cyclopropane ring is directly attached to the positive center. In the vinyl cation **2**, the β carbon atom of the vinyl double bond is in the cyclopropyl ring.

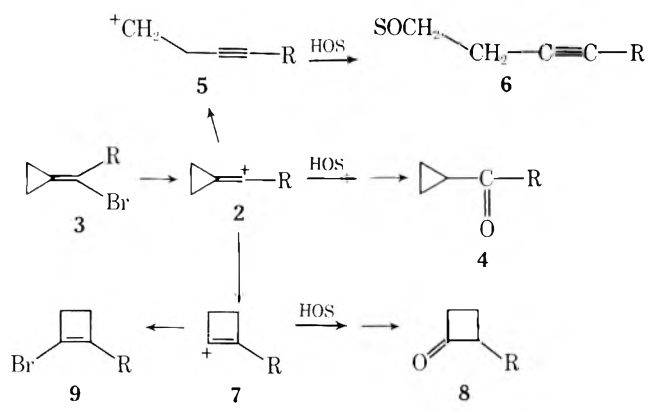
1 **2**

Vinyl cation **1** appears analogous to the cyclopropyl carbinyl cation, where the stabilizing effect of the cyclopropyl group is well established.[10] Vinyl cation **2** was first proposed by us as an intermediate in the homopropargyl rearrangement;[11] its high stability, arising from its special geometry (favorable overlapping of the vacant p orbital with the cyclopropane bonds and short C–C distance of the double bond), was confirmed by MO calculations.[12] If we consider now the generation of the vinyl cation **2** by the solvolysis of (halomethylene)cyclopropanes **3**, the reaction products given in Scheme I are possible.

Besides direct substitution by solvent leading to the cyclopropyl ketone **4**, the cyclopropylidenemethyl cation **2** is able to undergo either a homopropargylic rearrangement to give the homopropargyl cation **5** and then **6**, or a ring enlargement to the cyclobutenyl cation **7** and formation of the cyclobutanone **8**.

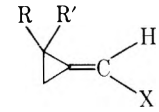
We have previously reported the generation of primary cyclopropylidene methyl cations **2** (R = H) through the solvolysis reactions of vinyl halides **10.** If the cyclopropane ring is substituted by one or two methyl groups (**10a, 10b**)

Scheme I



5 **6** **3** **2** **4** **9** **7** **8**

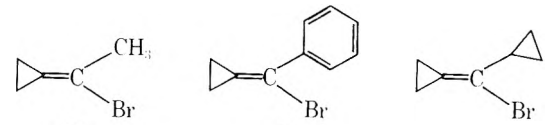
the corresponding primary vinyl cations undergo partial rearrangement to the corresponding homopropargyl cat-



10a. R = R′ = CH_3; X = Cl
b. R = CH_3; R′ = H; X = Br
c. R = R′ = H; X = Br

ions (secondary and tertiary derivative of ion **5**).[13,14] The (1-bromomethylene)cyclopropane **10c** solvolyzes to cyclobutanone as the only solvolysis product,[15] involving a rearrangement of the labile primary vinyl cation **2** into a nonclassical stabilized cyclobutenyl cation **7.**[12]

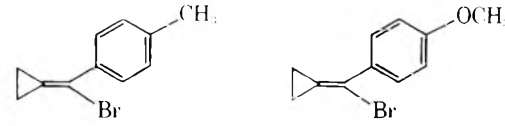
Further work has led to the generation of secondary vinyl cations **2** (R ≠ H) through the solvolysis of the (bromomethylene)cyclopropanes **11, 12,** and **13** in order to ob-



11 **12** **13**

tain additional stabilization of the positive charge by electron-releasing substituents.[16,17] As expected, the kinetic data and product analysis have evidenced the formation of stabilized cyclopropylidenemethyl cation intermediates such as **2.**[17]

We report here the syntheses and the solvolysis reactions of the (1-bromo-1-arylmethylene)cyclopropanes **14** and **15**



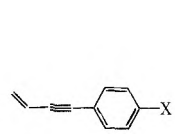
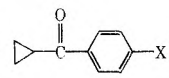
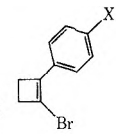
14 **15**

in which the phenyl ring is substituted by a *p*-methyl and a *p*-methoxy group, respectively, in order to study the increase in the stabilization of the intermediate vinyl cations induced by the increased electron-releasing effect of such para substituents.

Syntheses. The syntheses of the vinyl bromides **14** and **15** were carried out via the methylenecyclopropanes **16** and **20.**

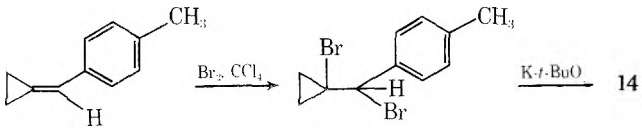
(1-*p*-Tolylmethylene)cyclopropane (**16**) was prepared in 70% yield by the Wittig reaction of *p*-methylbenzaldehyde with cyclopropyltriphenylphosphonium bromide (from 1,3 dibromopropane and triphenylphosphine), as recently reported for the synthesis of benzylidenecyclopropane.[16,18]

Table I
Solvolysis Products (Percent) of (1-Bromoarylmethylene)cyclopropanes 12, 14, and 15[d]

	Solvent	Reaction time, hr	 22	 23	 24	Others
12[16]	EtOH–H_2O (80:20)	24	48	52		
	Trifluoroethanol	4	55			Seven unknown compounds
14	EtOH–H_2O (80:20)	48	31	49	8	12[c]
	Acetone–H_2O (60:40)	24		84	4	12[c]
	Trifluoroethanol	4	64	23[a]		13[b]
15	EtOH–H_2O (80:20)	48	34	54	4	8[c]
	Acetone–H_2O (60:40)	48	51	37	6	6[c]
	Trifluoroethanol	4	29	58[a]	8	5[c]

[a] As trifluoroethanol ketal. [b] As trifluoroethyl enol ether. [c] Brominated derivatives of 23 from ir and mass spectra. [d] Temperature 80°, buffered with 1.1 equiv of triethylamine.

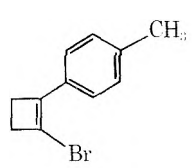
The bromination of **16** in carbon tetrachloride at −5° gave the dibromide **17**. The dehydrobromination with KOH and



16 17

sea sand was successful for the preparation of **12**;[16] treated under the same conditions the dibromide **17** underwent ring opening to form olefinic derivatives. The addition of the dibromide **17** to potassium *tert*-butoxide in dimethyl sulfoxide gave, after hydrolysis and pentane extraction, the expected vinyl bromide **14** in 15% yield as shown by NMR spectroscopy. However, attempted purification by distillation or sublimation in vacuo led to a rearranged product.

The vinyl bromide **14** was finally obtained in 76% yield by stirring a mixture of the dibromide **17** and 1.5 equiv of potassium *tert*-butoxide in pentane for 10 min at 0°. After the usual work-up, **14** was purified by several recrystallizations from pentane. Unlike the (1-bromo-1-phenylmethylene)cyclopropane **12**, the vinyl bromide **14** cannot be purified by gas chromatography; on heating to 100° for 15 min **14** undergoes a quantitative ring enlargement, probably into 1-bromo-2-*p*-tolylcyclobutene (**18**) from mass spectra and NMR evidence. In the same way, on heating to 150° for 60 min the dibromide **17** undergoes a nearly quantitative ring enlargement into the 1,1-dibromo-2-*p*-tolylcyclobutane (**19**).



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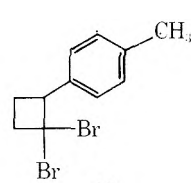
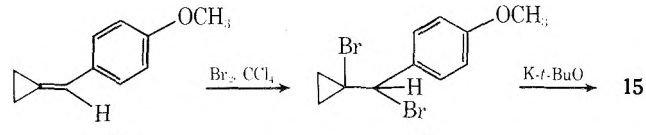


19

(1-*p*-Anisylmethylene)cyclopropane (**20**) was prepared from 1,3-dibromopropane, triphenylphosphine, and *p*-anisaldehyde in 60% yield. The bromination of **20** in carbon tetrachloride at −5° gave the labile dibromide **21**, which without further purification was readily dehydrobrominated by stirring it for 10 min at 0° with 1.5 equiv of potassium *tert*-butoxide in pentane. The vinyl bromide **15** was obtained in 82% yield; although attempts at crystallization were unsuccessful, NMR examination and gas chromatographic analysis show it to be more than 95% pure, contaminated only by the rearrangement product 1-bromo-2-*p*-anisylcyclobutene.



20 21

Results and Discussion

The (bromomethylene)cyclopropanes **14** and **15** were solvolyzed in solvents of different ionizing power and nucleophilicity. For each run, the products were separated by gas chromatography and their structures unequivocally proven by ir, NMR, and mass spectroscopy. The solvolysis rates were measured by automatic continuous titration, and compared with the reaction rates of the parent vinyl bromide **10c**.

The vinyl bromides **12**, **14**, and **15**, as shown in Table I, solvolyze mainly with formation of the cyclopropylaryl ketones **23** and the but-3-en-1-yne derivatives **22**, as well as a few percent of the four-membered ring vinyl bromides **24**.

A secondary vinyl cation **25**, stabilized by both the adjacent cyclopropane and aryl rings, can explain the results of the solvolyses as shown in Scheme II.

Trapping of **25** by the solvent led to the expected cyclopropyl ketones **23**. However, an astonishing result in this case was the formation of the 3-buten-1-yne derivative **22**. Such a rearrangement would imply the homopropargylic rearrangement of a highly stabilized secondary vinyl cation **25** into the less stable primary cation **26**, followed by the formation of the eneyne **22**.

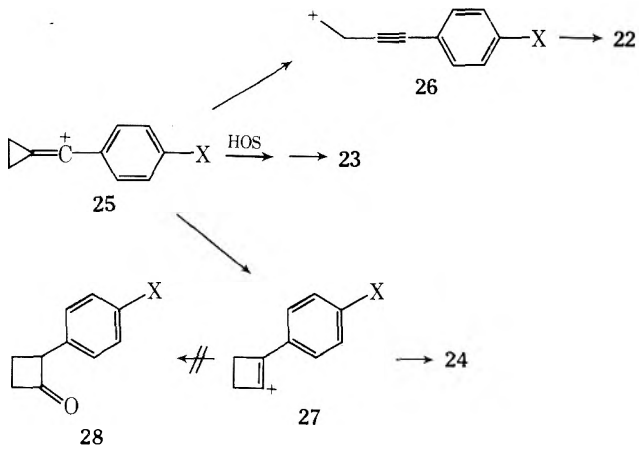
It must be noted that the eneynes **22** were not detected in the products of unbuffered solvolysis. Thus, for example, the solvolysis of the vinyl bromide **15** in aqueous EtOH (80:20) at 80° for 48 hr, without any buffer (NEt_3), led

Table II
Solvolysis Rates of the Vinyl Bromides 12, 14, and 15 in 80% Aqueous Ethanol at pH 6.88[a]

	Temp, °C		$10^5 k$, sec^{-1}	k_{rel}
12[16]	80		2.60 ± 0.09	1
14	80	(extrapolated)	11.95	4.60
	74.5		6.91 ± 0.02	
	60		1.49 ± 0.04	
15	80	(extrapolated)	658	253
	38.7		8.68 ± 0.11	
	17.7		2.72 ± 0.15	
29a	100.0		4.2×10^{-4}	1
29b	100.1		3.60	8.5×10^3

[a] For 12 at 120°, E_a = 25.9 kcal/mol; for 14 and 15 at 80°, E_a = 24.42 and 23.05 kcal/mol; for 29a and 29b at 100°, E_a = 34.1 and 27.8 kcal/mol, respectively.

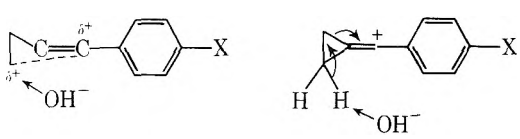
Scheme II



mainly to the ketone **23**, besides the rearranged derivatives **24** and some unknown compounds. We have determined that the vinyl bromides **14** and **15** do not undergo ring opening by the direct action of bases (K-*t*-BuO in pentane, NEt_3, etc.) implying, then, that this base-induced rearrangement occurs during the heterolysis of the C–Br bond of the initial vinyl bromides.

The direct attack by base on the delocalized positive charge at one of the cyclopropyl carbons as envisaged by Bergman and Kelsey to take into account the ring opening of the 1-cyclopropyl propenyl cation[19] or the base-induced proton elimination at one of the cyclopropyl carbons, and concurrent ring opening as shown in Scheme III appears likely in this case.

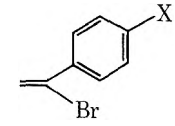
Scheme III



The fact that 2-aryl cyclobutanones **28** are not observed among the products of the solvolysis of the vinyl bromides **12, 14,** and **15** would imply that the ring enlargement **25** → **27** is also unlikely. However, we have found that the rearranged 1-bromo-2-methylcyclobutene (65–70%), along with 2-methylcyclobutanone (15–30%), were the main products from the solvolysis of (1-bromo-1-methylmethylene)cyclopropane.[17] On the other hand, considering the thermal behavior of the vinyl bromides **14** and **15**, which undergo, on simple heating, ring enlargement with simultaneous internal return (vide supra), the formation of larger amounts of 1-bromo-2-aryl cyclobutenes **24** could be expected in this case.

Finally, the total absence of cyclobutanone derivatives in the solvolysis products of vinyl bromides **12, 14,** and **15** (it must be remembered that 1-bromomethylenecyclopropane itself led to cyclobutanone as the sole solvolysis product[15]) illustrates clearly here the importance of the classical stabilizing effect of the aromatic ring (phenyl, *p*-tolyl, *p*-anisyl) on the positive charge of the secondary vinyl cations **25**.

The solvolysis rates of the vinyl bromides **12, 14,** and **15** are given in Table II. As expected, the rates increase with the increasing electron-releasing ability of the substituent in the para position of the aromatic ring: the vinyl bromide **14** reacted 4.6 times faster than the nonsubstituted compound **12** owing to the inductive effect of the para methyl group. The effect of a para methoxy group was strongly marked, **15** reacting 253 times faster than the parent compound **12** under the same conditions. Such a substituent effect on the solvolysis rates strongly suggests a unimolecular ionization process and the formation of an intermediate vinyl cation (i.e., **25**). In comparison, the solvolysis rates of the α-bromostyrenes **29** at 100° in 80% aqueous ethanol are



29a, X = H
b, X = OCH_3

shown in Table II as previously reported by Grob and Cseh.[7a]

The contribution of the three-membered ring to the stabilization of the intermediate vinyl cation **25** is reflected by the higher reactivity of the vinyl bromide **12** compared to α-bromostyrene (**29a**) (at 100°, k_{12}/k_{29a} = 3.6 × 10^4) and also by a relatively less marked rate enhancement due to the added effect of a para methoxy group (compare k_{15}/k_{12} = 253 and k_{29b}/k_{29a} = 8.500). The kinetic data for the solvolyses of various 1-substituted (1-bromomethylene)cyclopropanes are given in Table III. An increase in the solvolysis rates (implying an increase in the stabilization of the intermediate vinyl cation) is clearly observed when the carbon of the vinyl bromide which will become positively charged is successively substituted by a more powerful electron-releasing group. Changing from a methyl (**11**) to a phenyl (**12**) to a *p*-tolyl (**14**) or to a *p*-anisyl (**15**) and most markedly when changing from a primary vinyl bromide (**10c**) to a secondary vinyl bromide with suitable electron-donating substituents, a rate increase of five powers of ten is observed.

It must be mentioned that the high rate enhancement we

Table III
Comparison of the Solvolysis Rates of (1-Bromomethylene)cyclopropane Derivatives in 80% Aqueous Ethanol at 100°

	k, sec^{-1}	k_{rel}	m
10c[17]	7.1×10^{-8} [a]	1	0.53[b]
11[17]	6.6×10^{-5}	10^3	0.64[c]
12[16]	1.54×10^{-4}	2.2×10^3	
14	7.65×10^{-4} [a]	1.08×10^4	0.85[d]
15	3.78×10^{-2} [a]	5.32×10^5	
13[9c,17]	6.4×10^{-3} [a]	1.11×10^5	0.89[e]

[a] Extrapolated. [b] At 130°. [c] At 90°. [d] At 74.5°. [e] At 48.8°.

expected for (1-bromo-1-cyclopropylmethylene)cyclopropane (**13**[9c,17]) is of the same order (10^5 times faster than the parent compound **10c**) as that gained with the vinyl bromide **15** (effect of an added *p*-anisyl substituent).

Finally the intermediate formation of the vinyl cation **25** was supported by two other findings. A criterion for the occurrence of **25** was the high sensitivity of the reaction rates to the ionizing power of the solvent; e.g., at 74.5°, the vinyl bromide **14**, reacted 26 times faster in 50% aqueous ethanol ($k = 1.77 \pm 0.02 \times 10^{-3}$ sec^{-1}) than in 80% ethanol, corresponding to a Winstein–Grunwald m value of 0.85, which, together with that for **13** ($m = 0.89$[9c,17]), is one of the highest m values determined up to now for a reaction involving a vinyl cation. (See Table III.)

For the vinyl bromides **12**, **14**, and **15**, the plots of log k_x/k_H correlated linearly with Brown σ^+ substituent constants with a ρ value of −2.8. Compared to the values obtained in the solvolysis of α-arylvinyl substrates such as **29a**, and **29b** ($\rho = -6.6$[7d]) this value appears small. However, it is normal when one considers the delocalization of the positive charge of the vinyl cation **25** over the adjacent cyclopropane ring.

Experimental Section

A. Synthesis of (1-Bromo-1-*p*-tolylmethylene)cyclopropane (14). (1-*p*-Tolylmethylene)cyclopropane (16). A suspension of 108.4 g (0.4 mol) of triphenylphosphine in 70 ml of absolute xylene was treated with 80.8 g (0.4 mol) of 1,3-dibromopropane. The mixture was heated at reflux for 16 hr and left at room temperature overnight. The precipitated salt was removed by filtration, washed three times with 50 ml of dry ether, and dried at 50° under vacuum. The salt, 180 g (mp 217°), was obtained in 95% yield.[18c]

A suspension of 47.3 g (0.1 mol) of the phosphonium salt in 200 ml of dry 1,2-dimethoxyethane was treated with 9.6 g of NaH (50% in suspension in oil, 0.2 mol). The mixture was stirred at room temperature for 8 hr, and then was treated dropwise with 12.02 g (0.1 mol) of *p*-methylbenzaldehyde (freshly distilled) and 5 drops of absolute ethanol. The mixture was stirred for 5 hr at room temperature and then 8 hr at 60°. After cooling, the triphenylphosphine oxide was removed by filtration and the filtrate was concentrated by distillation of the solvent followed by a short-path vacuum distillation of the product. Fractional distillation of the crude distillate yielded 9.9 g (68.5%) of **16** (liquid): bp 58° (0.2 mm); NMR (CCl_4) δ 1.13 (m, 4 H), 2.30 (s, 3 H), 6.60 (m, 1 H), 6.90–7.35 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 144 (19, 5), 143 (13), 129 (100).

(1,2-Dibromo-1-*p*-tolylmethylene)cyclopropane (17). A solution of 4.32 g (0.03 mol) of **16** in 40 ml of carbon tetrachloride was cooled to −5°, then treated dropwise with 4.8 g (0.03 mol) of bromine. The mixture was washed with aqueous Na_2SO_3 solution and with NaCl-saturated water and dried over $CaCl_2$. The solvent was removed under vacuum, followed by a short-path distillation, yielding 8.65 g (95%) of the liquid dibromide **17**: bp 94° (0.5 mm); NMR (CCl_4) δ 1.30 (s, 4 H), 2.32 (s, 3 H), 5.06 (s, 1 H), 7.05–7.45 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 302 (6), 304 (12), 306 (5), and 105 (100).

1,1-Dibromo-2-*p*-tolylcyclobutane (19). The dibromide **17** (1 g, 3.3×10^{-3} mol) was placed in a 5-ml flask and heated at 150° for 60 min. After cooling, the pale yellow liquid product was examined spectroscopically: NMR (CCl_4) δ 2.42 (s, 3 H), 3.10 (t, 2 H) 3.63 (t, 2 H) (J_{AB} = 6.5 Hz), 6.80 (s, 1 H), 7.0–7.6 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 302 (24), 304 (37), 306 (24), and 130 (100).

Analytical gas chromatography (2 m, 10% SE-30, 150°, N_2 30 ml/min) showed only a single product.

(1-Bromo-1-*p*-tolylmethylene)cyclopropane (14). A mixture of 2 g (6.6×10^{-3} mol) of the dibromide **17**, 1 g of finely powdered KOH, and 1 g of sea sand was heated to 100° with stirring, under vacuum (0.1 Torr). No reaction was observed. The mixture became black, and under higher vacuum a distillate was collected, bp 63° (0.025 mm). The NMR of the distillate showed the complete disappearance of the cyclopropane proton signals and the formation of some olefinic derivatives.

To a mixture of 2.24 g (0.02 mol) of K-*t*-BuO in 20 ml of dry dimethyl sulfoxide (freshly distilled over calcium hydride) was added with stirring 3.04 g (0.01 mol) of the dibromide **17**. During the addition the mixture was cooled by immersion of the flask in ice water. Then the mixture was stirred at room temperature for 2 hr, hydrolyzed with 160 ml of water, and extracted with pentane. The pentane phase was washed three times with 20 ml of water, dried over $CaCl_2$, and concentrated under vacuum. From the residue, cooled in the freezer (−20°) overnight, 0.33 g (15% yield) of pure crystalline **14** was isolated by filtration.

To a solution of 3.04 g (0.010 mol) of the dibromide **17** in 10 ml of pentane was added at 0° a suspension of 1.68 g (0.015 mol) of K-*t*-BuO in 20 ml of pentane. The mixture was stirred at room temperature for 10 min and quickly hydrolyzed with 20 ml of water and extracted with pentane. The pentane phase was washed three times with 10 ml of water and dried over Na_2SO_4. Removing the solvent on a rotary evaporator gave 1.7 g (76%) of a pale yellow solid. Two recrystallizations from pentane gave the pure (1-bromo-1-*p*-tolylmethylene)cyclopropane (**14**): mp 53.4°; NMR (CCl_4) δ 1.18–1.88 (m, 4 H), 2.35 (s, 3 H), 7.04–7.68 ppm (q, 4 H); MS: M^+ *m/e* (rel intensity) 224 (9), 222 (9), and 128 (100).

Anal. Calcd for $C_{11}H_{11}Br$: C, 59.21; H, 4.96; Br, 35.81. Found: C, 57.87; H, 4.96; Br, 34.97.

1-Bromo-2-*p*-tolylcyclobutene (18). The vinyl bromide **14** (10 mg) was placed in a NMR tube and heated at 100° for 15 min. After cooling, CCl_4 was added. The NMR spectrum showed δ 2.35 (s, 3 H), 2.98 (t, 2 H), 3.48 (t, 2 H) (J_{AB} = 6.5 Hz), 6.85–7.65 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 224 (30), 222 (30), and 128 (100).

B. Synthesis of (1-Bromo-1-*p*-anisylmethylene)cyclopropane (15). (1-*p*-Anisylmethylene)cyclopropane (20). **20** can be prepared analogously to **16** by the Wittig reaction of cyclopropyltriphenylphosphonium bromide[18] with *p*-anisaldehyde. After the usual work-up **20** was obtained in 60% yield (liquid): bp 72–74° (0.1 mm); NMR (CCl_4) δ 0.9–1.50 (m, 4 H), 3.72 (s, 3 H), 6.60 (s, 1 H), 6.65–7.35 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 160 (83), 159 (100), 145 (83), 129 (75).

(1,2-Dibromo-1-*p*-anisylmethylene)cyclopropane (21). The bromination of **20** gave, after work-up, the dibromide **21** (for the procedure, see **17**): NMR (CCl_4) δ 1.28 (m, 4 H), 3.75 (s, 3 H), 3.82 (s, 0.4 H) and 5.08 (s, 0.6 H) (two isomers), 6.75–7.50 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 318 (18), 320 (26), 322 (18), and 57 (100).

(1-Bromo-1-*p*-anisylmethylene)cyclopropane (15). To a solution of 3.2 g (0.010 mol) of the dibromide **21** in 20 ml of pentane was added at 0° a suspension of 1.68 g (0.015 mol) of K-*t*-BuO in 20 ml of pentane. The mixture was stirred at room temperature for 10 min. After work-up (see **14**) and removal of the solvent on a rotary evaporator 1.95 g (82%) of a pale yellow liquid was obtained which was shown to be practically pure by NMR: NMR (CCl_4) δ 1.10–1.90 (m, 4 H), 3.80 (s, 3 H), 6.70–7.75 (q, 4 H); MS M^+ *m/e* (rel intensity) 240 (10), 238 (12), and 135 (100).

Several attempts to crystallize **15** in different solvent systems were unsuccessful. The purification of **15** was achieved by preparative gas chromatography (on 1 m × 0.25 in. 10% SE-30 at 100°) and was obtained 96% pure.

Anal. Calcd for $C_{11}H_{11}OBr$: C, 55.25; H, 4.63; Br, 33.42. Found: C, 54.07; H, 4.65; Br, 32.97.

On heating over 100°, the vinyl bromide **15** underwent a rearrangement into the isomeric 2-*p*-anisyl-1-bromocyclobutene: NMR δ 3.08 (t, 2 H), 3.58 (t, 2 H), 3.75 (s, 3 H), 6.70–7.40 (q, 4 H); MS M^+ m/e (rel intensity) 240 (13), 238 (13), and 159 (100).

C. Solvolyses. Description of a Typical Product Analysis. The vinyl bromide **14** (300 mg, 1.34 mmol) was dissolved in 5 ml of EtOH–H_2O (80:20) mixture containing 135 mg (1.1 equiv) of triethylamine as buffer. The mixture was heated in a sealed tube for

48 hr at 80°. After cooling, the tube was opened and the solvent was removed on a rotary evaporator. The residue was mixed with concentrated aqueous NaCl solution and extracted three times with pentane. The pentane extract was dried over $CaCl_2$ and concentrated on a rotary evaporator. The remainder of the pentane phase was worked up by preparative gas chromatography, and each product was identified by combined GC and MS analysis.

The other solvolysis reactions were run in the same way, under the conditions reported in Table I.

Cyclopropyl *p*-tolyl ketone (23, X = CH_3):[20] NMR (CCl_4) δ 0.80–1.40 (m, 4 H), 2.25–2.85 (m, 1 H), 2.35 (s, 3 H), 7.15–7.95 (q, 4 H); MS M^+ *m/e* (rel intensity) 160 (57) and 119 (100); ir $\nu_{C=O}$ 1680 cm^{-1}.

1-*p*-Tolyl-3-buten-1-yne (22, X = CH_3): NMR (CCl_4) δ 2.40 (s, 3 H), 5.35–6.28 (m, 3 H), 7.0–7.90 (q, 4 H); MS M^+ *m/e* (rel intensity) 142 (100) and 116 (70); ir ν_{C-H} 915 and 970 cm^{-1}, $\nu_{C=C}$ 1600 and 1665 cm^{-1}, $\nu_{C\equiv C}$ 2200 cm^{-1}. The brominated derivative of **22** (X = CH_3) has been characterized by its mass spectra: M^+ *m/e* (rel intensity) 238 (8), 240 (8), and 119 (100) (p-$CH_3C_6H_4C{\equiv}O^+$) and by ir, $\nu_{C=O}$ 1710 cm^{-1}.

The trifluoroethanol ketal derivative of **23** (X = CH_3) was identified from spectroscopic data: MS M^+ *m/e* (rel intensity) 342 (4) and 243 (100); NMR (CCl_4) δ 1.25 (m, 4 H), 235 (s, 3 H), 2.30–2.50 (m, 1 H), 3.55–4.10 (q, 4 H), 7.0–7.5 (q, 4 H); ir ν[C (OCH_2CF_3)$_2$] 1160 and 1280 cm^{-1}.

Cyclopropyl *p*-anisyl ketone (23, X = OCH_3):[21] NMR (CCl_4) δ 0.75–1.40 (m, 4 H), 2.25–2.85 (m, 1 H), 3.85 (s, 3 H), 6.75–7.95 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 176 (36) and 135 (100); ir $\nu_{C=O}$ 1680 cm^{-1}.

1-*p*-Anisyl-3-buten-1-yne (22, X = OCH_3): NMR (CCl_4) δ 3.75 (s, 3 H), 5.20–5.95 (m, 3 H), 6.60–6.80 (m, 4 H); MS M^+ *m/e* (rel intensity) 158 (100) and 142 (80); ir ν_{C-H} 915 and 990 cm^{-1}, $\nu_{C=C}$ 1600 and 1635 cm^{-1}, $\nu_{C\equiv C}$ 2200 cm^{-1}. The brominated derivative of **22** (X = OCH_3) was characterized from its mass spectra, M^+ *m/e* (rel intensity) 254 (5), 256 (5), and 135 (100) (p-CH_3O-$C_6H_4C{\equiv}O^+$) and from ir, $\nu_{C=O}$ 1715 cm^{-1}.

The trifluoroethanol ketal derivative of **23** (X = OCH_3) has been identified from spectroscopic data: MS M^+ *m/e* (rel intensity) 358 (40) and 259 (100); NMR (CCl_4) δ 1.30 (m, 4 H), 2.35–2.60 (m, 1 H), 3.50–4.20 (m, 7 H), 6.60–7.70 (q, 4 H); ir ν_{C-O} 1170, 1250, and 1280 cm^{-1}.

D. Kinetic Procedures. The solutions used during the kinetic runs were prepared with absolute ethanol (Fluka) and with triply distilled water. The solvolysis rates were measured by means of a Combi titrator 3 D (Metrohm AG CH-9100, Herisau, Switzerland). The pH of the solution was adjusted to 6.88. About 30 ml of solvent was transferred to the reaction vessel, which was placed in a constant-temperature bath adjusted to the appropriate temperature within a range of ±0.01°. After the stirred solution had reached thermal equilibrium, 5 mg of reactant (**14** or **15**) were added to it. The solvolysis proceeded with continual stirring. The HBr liberated during the solvolysis was automatically neutralized with 0.015 *N* NaOH solution prepared with the same aqueous ethanol solvent used for the solvolysis mixture. The titer was registered automatically on a graph, and the data were gathered in such a way that the Guggenheim method[22] could be employed for calculation of the rate constants. The errors reported were determined by means of a least-squares computer program.

Acknowledgment. The authors gratefully acknowledge the financial support of the Centre National de la Recherche Scientifique of France (J.S.).

Registry No.—**10c,** 33745-37-8; **11,** 53968-63-1; **12,** 41893-65-6; **13,** 41886-92-4; **14,** 55088-78-3; **15,** 55088-79-4; **16,** 55088-80-7; **17,** 55088-81-8; **18,** 55088-82-9; **19,** 55088-83-0; **20,** 55088-84-1; **21,** 55088-85-2; **22** (X = H), 13633-26-6; **22** (X = CH_3), 30011-66-6; **22** (X = OCH_3), 55088-86-3; **23** (X = CH_3), 7143-76-2; **23** (X = CH_3) trifluoroethanol ketal derivative, 55088-87-4; **23** (X = OCH_3), 7152-03-6; **23** (X = H), 3481-02-5; **24** (X = CH_3), 55088-82-9; **24** (X = OCH_3), 55088-88-5; triphenylphosphine, 603-35-0; 1,3-dibromopropane, 109-64-8; cyclopropyltriphenylphosphonium bromide, 14114-05-7; *p*-methylbenzaldehyde, 104-87-0; K-*t*-BuO, 865-47-4; *p*-anisaldehyde, 123-11-5.

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Biological Spin Labels as Organic Reagents. Oxidation of Alcohols to Carbonyl Compounds Using Nitroxyls

Bruce Ganem

Department of Chemistry, Cornell University, Ithaca, New York 14853

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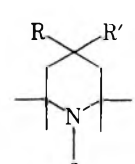
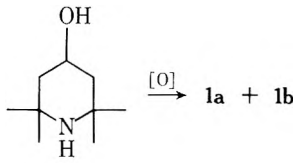
Stable nitroxyl radicals such as 4-oxotetramethylpiperidinooxy (**1,** TEMPO) are widely employed as spectroscopic probes for observing binding sites and molecular motion in macromolecules.[1,2] We report here that as a result of their remarkable redox properties, nitroxyl radicals in conjunction with an added oxidizing agent can conveniently convert a variety of alcohols to carbonyl compounds.



1a. R, R′ = =O
b. R = H; R′ = OH
c. R, R′ = H

Our interest in nitroxyls was first aroused by a report[3] that ketone **1a** was formed during the peracid oxidation of 4-hydroxy-2,2,6,6-tetramethylpiperidine (**2**) to the nitroxyl alcohol **1b.** No mechanism was proposed to account for this



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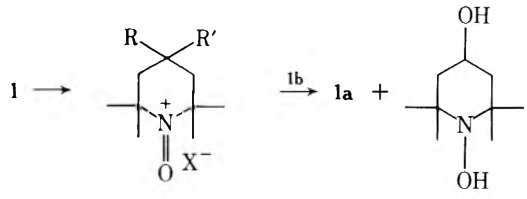
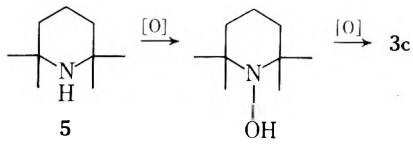
unexpected by-product. We reasoned that peracid might transform **1b** to the immonium oxide salt **3b**,[4] and that in-



3a, R, R′ = =O
b, R = H; R′ = OH
c, R, R′ = H

4

termolecular oxidation of **1b** by the reactive $^{+}N{=}O$ electrophile of **3b** would give rise to **1a.** The reported isolation by Russian workers[4c] of acetaldehyde as its 2,4-dinitrophenylhydrazone when **3b** (X = Br) is heated in ethanol supports this hypothesis. In fact, when 1 equiv each of 2,2,6,6-tetramethylpiperidinooxy[5] **1c** and *m*-chloroperoxybenzoic acid are stirred in CH_2Cl_2 at 0° and then treated with an equimolar amount of 4-*tert*-butylcyclohexanol and warmed to room temperature for 2 hr, a 70% yield of 4-*tert*-butylcyclohexanone is obtained. Since the nitroxyl component is itself derived from the corresponding amine, a much simpler and more convenient procedure employs commercially available 2,2,6,6-tetramethylpiperidine and 2 molar equiv of peracid.[6] Generation of the immonium oxide salt undoubtedly occurs by an overall four-electron oxidation, initially involving the hydroxylamine **6.** Table I summa-



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rizes the oxidation of representative alcohols by this modified technique. Yields, which are generally respectable, can be improved 5–10% by using the 1:1 nitroxyl–peracid reagent mentioned above. The method, however, is not adaptable to primary aliphatic alcohols since the aldehydes produced undergo further, as yet unelucidated, reactions in the oxidizing medium.

We can substantiate no one mechanism for this oxidation, but the results with 3-pentanol and 2-undecanol do provide a valuable clue. In these instances starting alcohol is consumed after 3.5 hr at room temperature, yet no pentanone or undecanone is formed, as is evident from infrared spectroscopic analysis in the OH and C=O regions. Refluxing the reaction mixtures eventually affords the desired ketones. One mechanism consistent with these observations may involve addition of the alcohol across the $^{+}N{=}O$ bond followed by Cope-like elimination of **7.** Unfortunately, any attempted purification of the reaction intermediate(s) also results in their rapid decomposition to ketone.

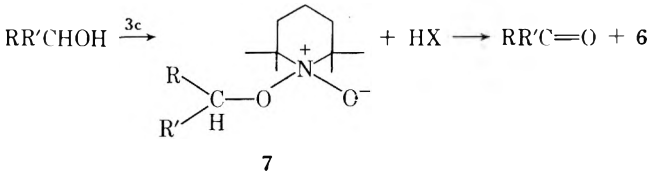

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Table I

Alcohol	Time, hr[a]	Product	Yield,[c] %
4-*tert*-Butylcyclohexanol	3	4-*tert*-Butylcyclohexanone[d]	70 (70% conversion)
Cyclooctanol	2	Cyclooctanone	69 (70% conversion)
Piperonyl alcohol	0.25	Piperonal	60
3-Pentanol	3.5[b]	3-Pentanone	45[e]
2-Undecanol	3.5[b]	2-Undecanone	50
3β-Cholestanol	10	Cholestanone	52

[a] Alcohol and oxidizing agent were mixed at 0°, then slowly warmed to room temperature over 15 min; reactions were continued at room temperature except as noted. [b] Reaction subsequently refluxed for 5 hr before work-up. [c] Yields are reported for chromatographed products, and are *not* optimized. [d] A small amount of 4-*tert*-butylcaprolactone was also formed. [e] This yield was determined by VPC.

We are currently exploring other aspects of nitroxyl-mediated oxidation, including remote control, site-specific oxidation, as well as the design of a catalytic process (perhaps electrochemical) based on the hydroxylamine–nitroxyl–immonium oxide redox cycle.

Experimental Section

Using Tetramethylpiperidine and *m*-Chloroperoxybenzoic Acid (1:2) for the Oxidation of Cyclooctanol. A mixture of *m*-chloroperoxybenzoic acid (Aldrich Chemical Co., 85% pure, 0.564 g, 2.8 mmol) in CH_2Cl_2 (8 ml) in a flask fitted with a $CaCl_2$ drying tube was cooled in an ice bath during the dropwise addition of tetramethylpiperidine (Aldrich, 1.4 mmol, 0.234 ml). After stirring for 30 min at room temperature the solution was recooled to 0° and cyclooctanol was added (0.178 g, 1.4 mmol) dissolved in CH_2Cl_2 (4 ml). The ice bath was removed and stirring was continued for 2 hr. Extraction with 5% aqueous $NaHCO_3$ then 5% HCl, drying of the organic layer ($MgSO_4$), and concentration afforded 0.363 g of red oil. Column chromatography over silica gel using 1:99 ether–hexane furnished 85 mg (0.68 mmol) of cyclooctanone having infrared and NMR spectra identical with those of an authentic sample. Continued elution afforded 54 mg (0.42 mmol) of starting alcohol.

Using Tetramethylpiperidinooxy and *m*-Chloroperoxybenzoic Acid (1:1) for the Oxidation of 4-*tert*-Butylcyclohexanol. To a 0° solution of the nitroxyl **1c** (0.206 g, 1.32 mmol) in CH_2Cl_2 (15 ml) was added solid *m*-chloroperoxybenzoic acid (Aldrich, 85% pure, 0.260 g, 1.32 mmol). The mixture was stirred under N_2 for 10 min, then treated with a solution of 4-*tert*-butylcyclohexanol (0.206 g, 1.32 mmol) in CH_2Cl_2 (4 ml). The orange color faded slightly and after 2 hr at room temperature, the crude product (0.404 g) was isolated as described above. Column chromatography over silica gel using hexane, then ether–hexane mixtures afforded 100 mg (0.65 mmol) of 4-*tert*-butylcyclohexanone which was identical with an authentic sample. Further elution yielded 60 mg (0.39 mmol) of 4-*tert*-butylcyclohexanol and a small amount (15 mg) of 4-*tert*-butylcaprolactone, as identified by its infrared spectrum.

Acknowledgment. The author acknowledges a particularly helpful discussion about this work with Professor Jerrold Meinwald. Thanks are due to the Research Corporation and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this research.

Registry No.—**1c,** 2564-83-2; tetramethylpiperidine, 768-66-1; *m*-chloroperoxybenzoic acid, 937-14-4; 4-*tert*-butylcyclohexanol, 98-52-2; cyclooctanol, 696-71-9; piperonyl alcohol, 495-76-1; 3-pentanol, 584-02-1; 2-undecanol, 1653-30-1; 3β-cholestanol, 17608-41-2.

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2-Amino-2-thiazoline. VIII.[1] A Nonregioselective Reaction of 2-Amino-2-thiazoline with Benzoyl Isothiocyanate to Give a Thermally Unstable Thiourea and a Thiazolotriazine

Daniel L. Klayman* and Thomas S. Woods

Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Washington, D.C. 20012

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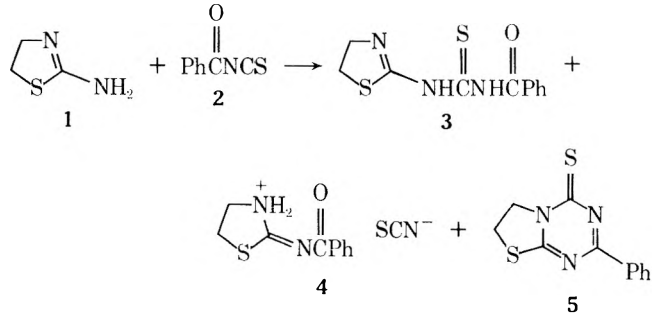
The reactions of 2-amino-2-thiazoline (**1**) with electrophiles giving products resulting from attack on either or both nitrogen atoms have been recently summarized.[2] Although the interaction of **1** with a given electrophile usually gives rise to a product resulting from a regioselective attack, behavior within a family of electrophiles cannot be predicted with certainty. The isothiocyanate family has provided a particularly perplexing series of examples in this regard. Yamamoto and Yoda,[3] for example, have reported that alkyl isothiocyanates react with **1** to give thiocarbamoyl derivatives resulting from nonregioselective attack on both nitrogen atoms. Phenyl isothiocyanate, on the other hand, exhibits regioselective attack on the exocyclic nitrogen atom of **1**[4] whereas carbethoxy isothiocyanate undergoes the opposite mode of reaction and interacts with the ring nitrogen of **1**.[1] These examples demonstrate that reactions of **1** with isothiocyanates are characterized by lack of predictability as to regioselectivity.

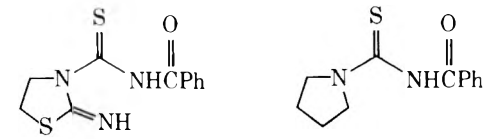
We report here the investigation of the reaction of **1** with another acyl isothiocyanate, namely, benzoyl isothiocyanate (**2**). If **2** were to behave as does carbethoxy isothiocyanate, regioselective attack of **2** on the ring nitrogen atom of **1** would produce a single derivative.

Results and Discussion

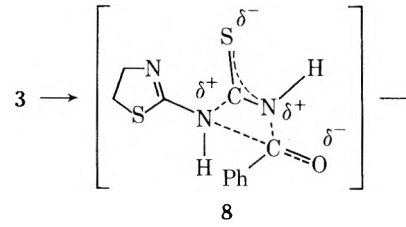
The reaction of 2-amino-2-thiazoline (**1**) with benzoyl isothiocyanate (**2**) was found to give three products: 1-benzoyl-3-(2-thiazolin-2-yl)-2-thiourea (**3**), 2-benzamido-2-thiazoline thiocyanic acid salt (**4**), and 6,7-dihydro-2-phenyl-4*H*-thiazolo[3,2-*a*]triazine-4-thione (**5**). The structural assignments of the products follow from their elemental analyses, chemical behavior, and spectral properties.



The ir spectrum of **3** shows diagnostic absorptions at 3280 and 1639 cm^{-1} in KBr and at 3440 and 1645 cm^{-1} in $CHCl_3$ solution, observations consistent with values reported for conjugated amides.[5] The alternate structure **6**, which would have resulted from attack of **2** on the ring nitrogen atom of **1**, may be ruled out on the following bases: the NMR spectrum of **3** shows NH signals at δ 10.12 and 11.35 (the imino NH of **6** would be expected to appear at much higher field[6]); the chemical behavior of **3** is also consistent with that of a disubstituted thiourea in that **3** gives a positive ammoniacal silver nitrate test, which **6** would not be expected to exhibit;[7] furthermore, the *S*-methyl derivative of **3**, generated in situ from **3** and iodomethane, proved to be stable to alkali at room temperature, but liberated methyl mercaptan after being heated at 100° for 30 sec. This latter test is diagnostic of 1,3-disubstituted thioureas.[7] A model compound, 1-(*N*-benzoylthiocarbamoyl)pyrrolidine (**7**), prepared from **2** and pyrrolidine, which would have been expected to behave similarly to **6**, gave negative results in both the ammoniacal silver nitrate and *S*-methyl tests mentioned above.

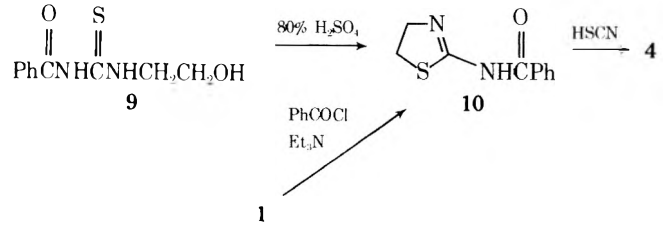


Compound **3** undergoes facile thermal conversion to **4** on being heated at the boiling point of common solvents for a short time. The phenomenon, first noted on attempted recrystallization of **3** from CH_3CN, probably proceeds through the transition state **8**. The alternate process, i.e., thermal retroreaction of **3** to give **1** and **2**, followed by benzoylation of **1** to give **4**, is untenable, since no **5** is produced. Qualitatively, the rate of thermolysis of **3** in boiling solvents to give **4** was shown to proceed as follows: very slowly in methylene chloride, slowly in chloroform or methanol, moderately rapidly in 1,2-dichloroethane, and very rapidly in dioxane. Also **3** undergoes rearrangement to **4** near its melting point as evidenced by the strong $FeCl_3$ test exhibited by the cooled melt of **3** as well as by its ir spectrum.



The structure of **4** was elucidated by its unequivocal synthesis as outlined in Scheme I. 1-Benzoyl-3-(2-hydroxyethyl)-2-thiourea (**9**) was prepared and cyclized to **10** as previously described.[8] The free base **10** was also prepared

Scheme I

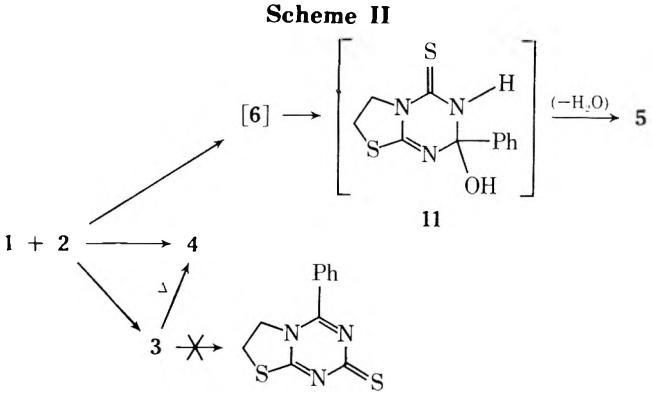


by treatment of 1 with benzoyl chloride and triethylamine. The thiocyanic acid salt of 10 was found to be identical with the sample produced in the reaction of 1 and 2. Crucial to the structure assignment of 4 as a thiocyanic acid salt is the strong peak in the ir spectrum of 4 at 2040 cm^{-1} and the intense $FeCl_3$ test.

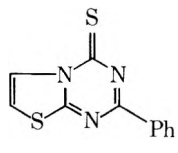
Reactions of 2 and amines giving benzoylated products are well documented.[9-12] These authors do not report having considered, however, that the amide products could have been formed via thermally unstable thiourea intermediates. As might be expected, none of these workers report the isolation of thiocyanic acid salts of their benzamide products; however, Durant[10] obtained 1-benzoyl-2-alkylthiosemicarbazide products from the reaction of 2 and substituted hydrazines, apparently resulting from reaction of intermediate benzhydrazides with concomitantly produced thiocyanic acid.

The structure of the cyclized product 5 follows from its elemental analysis, indicating loss of water from the elements of 1 and 2. Initial attack of 2 on the ring nitrogen atom of 1 would give the imino compound 6, following which cyclization to the carbinolamine intermediate 11 with subsequent loss of water would lead to 5 (Scheme II).

Scheme II



That the thiocarbonyl group of 5 is located at the 4 position rather than at the 2 position as indicated in the alternate structure 12 is shown by the chemical behavior of 3. If the product had structure 12, then of necessity 3 would have been an intermediate in its formation. Maintaining pure 3 under the reaction conditions, including in the presence of excess 2, produced no 12. Heating the reaction mixture caused only the conversion of 3 to 4, indicating by exclusion that 5 is the proper structure of the compound. Further evidence is provided by comparison of the uv spectrum of 5 [λ_{max} 286 nm (ϵ 42,000) and 360 (3190)] with that of the corresponding product from 2-aminothiazole, namely 13 [λ_{max} 301 nm (ϵ 41,000) and 376 (6500)], reported by Barnikow and Bödeker.[12] The bathochromic shift of ~15 nm of the maxima in the spectrum of 13 relative to that of 5 would be expected considering the additional conjugation provided by the 6,7 double bond of 13. Thus, evidence indicates that 5 is structured similarly to 13.



13

The reaction of 1 and 2 is therefore very similar to that reported[12] earlier for the reaction of 2-aminothiazole and 2, which produces the thiourea corresponding to 3, the thiazolotriazine 13, and, in slight contrast, the free base form of 2-benzamidothiazole. The latter is probably due to the reduced basicity of the ring nitrogen of the thiazole relative to that of the thiazoline ring.

The formation of the thermally unstable 3 leading to the amide product 4 could indicate that other less stable thioureas are intermediates in reactions of 2 leading to amide products. The lack of regioselectivity in the reaction of 1 with 2 further indicates that predictions of sites of reaction of 1 with electrophiles cannot be made as yet with any degree of certainty.

Experimental Section[13]

Reaction of 2-Amino-2-thiazoline (1) with Benzoyl Isothiocyanate (2). To a magnetically stirred solution of 4.08 g (0.04 mol) of 1 in 40 ml of CH_3CN was added 6.53 g (0.04 mol) of 2, causing a slightly exothermic reaction. Crystals precipitated from the solution very shortly; however, stirring was continued for an additional 10 hr at room temperature. The crystals, 2.97 g (28%), were collected and proved to be 1-benzoyl-3-(2-thiazolin-2-yl)-2-thiourea (3): mp 137–138° (from CH_2Cl_2); ir 3280 (NH), 3080 (CH), 1639 (C=O), 1613, 1593, 1571, and 1499 cm^{-1}; ir ($CHCl_3$) 3440 (NH), 3020 (CH), 1645 (C=O), and 1602 cm^{-1}; NMR (DMSO-d_6) δ 3.23 (t, J = 8 Hz, 2, CH_2S), 4.63 (t, J = 8 Hz, 2, CH_2N), 7.63 (m, 3, o- and p-ArH), 8.00 (m, 2, m-ArH), 10.0 (s, 1, NH), and 11.3 (s, 1, NH); uv (EtOH) λ_{max} 206 nm (ϵ 8410), 246 (sh, 9680), 294 (21,700); mass spectrum m/e (rel intensity) 265 (1), 247 (1), 205 (100), 177 (28), 129 (30), 105 (31), 77 (87), 59 (64), and 51 (44).

Anal. Calcd for $C_{11}H_{11}N_3OS_2$: C, 49.79; H, 4.18; N, 15.84; S, 24.17. Found: C, 49.69; H, 4.28; N, 15.48; S, 23.48.

The filtrate was reduced to about one-half volume under reduced pressure and cooled. The yellow material which separated was treated with a minimum of boiling $CHCl_3$ to give 1.44 g (14%) of an insoluble, essentially colorless solid, 2-benzamido-2-thiazoline thiocyanic acid salt (4), mp 150–153° (from CH_3CN). Further small quantities of 4 were obtained from work-up of the balance of the reaction product: ir 3120–2650 (broad, NH^+), 2040 ($SC{\equiv}N^-$), 1701 (C=O), 1590, and 1525 cm^{-1}; NMR (DMSO-d_6) δ 3.67 (m, 2, CH_2S), 4.20 (m, 2, CH_2N), 7.75 (m, 3, o- and p-ArH), 8.02 (m, 2, m-ArH), and 11.0 (s, 2, NH_2^+); uv (EtOH) λ_{max} 304 nm (ϵ 1920); mass spectrum m/e (rel intensity) 205 (42), 177 (13), 129 (14), 105 (100), 77 (61), 59 (40), and 51 (24).

Anal. Calcd for $C_{11}H_{11}N_3OS_2$: C, 49.79; H, 4.18; N, 15.84; S, 24.17. Found: C, 49.89; H, 4.26; N, 15.59; S, 23.51.

The CH_3CN mother liquor was evaporated to dryness under reduced pressure and the residue was dissolved in 30 ml of hot $CHCl_3$. The cooled solution yielded 0.97 g (10%) of 6,7-dihydro-2-phenyl-4H-thiazolo[3,2-a]triazine-4-thione (5) as fine yellow crystals: mp 242° (from $CHCl_3$); ir 1585, 1548, 1458, and 1425 cm^{-1}; NMR (CF_3COOH) δ 3.83 (t, J = 8 Hz, 2, CH_2S), 5.00 (t, J = 8 Hz, 2, CH_2N), 7.80 (m, 3, m- and p-ArH), 8.37 (m, 2, m-ArH); uv (EtOH) λ_{max} 207 nm (ϵ 9900), 227 (sh, 6840), 245 (sh, 9110), 286 (42,000), and 360 (3185); mass spectrum m/e (rel intensity) 249 (10), 248 (14), 247 (78), 214 (16), 188 (18), 128 (20), 104 (25), 103 (27), 85 (100), 77 (27), 60 (21), and 59 (16).

Anal. Calcd for $C_{11}H_9N_3S_2$: C, 53.42; H, 3.67; N, 16.99; S, 25.93. Found: C, 53.51; H, 3.82; N, 17.01; S, 25.59.

Alternative Synthesis of 4. The compound 2-benzamido-2-thiazoline was prepared by cyclization of 1-benzoyl-3-(2-hydroxyethyl)-2-thiourea with 80% H_2SO_4 in the manner described by Douglass and Dains[8] and by the direct benzoylation of 1. To a magnetically stirred solution of 5.1 g (0.05 mol) of 1 and 5.1 g (0.05 mol) of triethylamine in 60 ml of $CHCl_3$ was added dropwise 7.0 g (0.05 mol) of benzoyl chloride. After 0.4 hr, the solution was evaporated to dryness and the residue was washed three times with H_2O. The H_2O-insoluble residue was recrystallized from CH_3CN to give 5.06 g (49%) of 2-benzamido-2-thiazoline, mp 167–169° (lit.[8] mp 168°).

2-Benzamido-2-thiazoline (0.206 g, 1.0 mmol) was dissolved in 1.2 ml of 1 N HCl. To the solution was added 0.81 g (1.0 mmol) of sodium thiocyanate in 1 ml of H_2O. The two solutions were combined and cooled, causing the slow separation of 4. The latter, after collection and recrystallization from CH_3CN, melted at 149–150°, ir identical with that of 4 described earlier.

Thermolysis of 3. A. In Acetonitrile. A sample of 500 mg (1.89 mmol) of 3 was heated in 50 ml of boiling CH_3CN for approximately 30 min, i.e., until no remaining 3 was detectable by TLC (silica gel–benzene). The solution, which gave a strong $FeCl_3$ test for thio-

cyanate ion, was evaporated to dryness, yielding 485 mg (97%) of **4**, mp 149–152°.

B. In Other Solvents. The thermal stability of **3** was examined at the boiling point of common organic solvents as follows. A sample of 5 mg of **3** was heated in 1 ml of boiling solvent. At intervals of 1, 2, 5, 15, and 30 min, after adjusting the volume of the solution for evaporation, 2 drops of the solution were removed and tested for the presence of thiocyanate ion with 1 drop of 5% $FeCl_3$ solution. The results are summarized as follows: in methylene chloride (bp 42°), no conversion was noted after 30 min; in chloroform (bp 61°) and in methanol (bp 65°) only trace conversion of **3** to **4** was noted after 30 min; in CH_3CN (bp 81°) and in ethylene chloride (bp 83°) maximum intensity was noted after 5 min (no **3** detectable by TLC); and in dioxane (bp 102°) maximum intensity was noted after 1 min (no **3** detectable by TLC).

C. At Its Melting Point. A 5-ml beaker containing 100 mg of **3** was slowly increased in temperature on a hot stage. Samples (~1 mg) were removed at 60, 80, 100, and 120° and were tested for the presence of thiocyanate ion with 5% $FeCl_3$ solution, all giving negative results. At 135–140°, the sample melted and was completely converted to **4** as indicated by ir, TLC, and a positive $FeCl_3$ test.

1-(*N*-Benzoylthiocarbamoyl)pyrrolidine (7). To 1.00 g (6.13 mmol) of **2** in 5 ml of CH_3CN was added dropwise with cooling and stirring 0.88 g (12.4 mmol) of pyrrolidine. The mixture was stirred in an ice bath for 0.5 hr, filtered, and washed with CH_3CN. The colorless solid was collected and recrystallized from CH_3CN to give 0.48 g (34%) of 1-(*N*-benzoylthiocarbamoyl)pyrrolidine as colorless needles: mp 133–134°; ir 3100 (NH), 2960 (CH), 1642 (C=O), 1603, and 1530 cm^{-1}; NMR (DMSO-d_6) δ 1.93 (m, 4, 2 CCH_2), 3.67 (m, 5, 2 CH_2N + NH), 7.63 (m, 3, *o*- and *p*-ArH), and 8.00 (m, 2, *m*-ArH).

Anal. Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96; S, 13.68. Found: C, 61.55; H, 6.02; N, 12.06; S, 13.55).

As anticipated,[7] the compound failed to react with ammoniacal silver nitrate solution to give a black precipitate of silver sulfide and its *S*-methyl derivative did not release methyl mercaptan on attempted hot alkaline hydrolysis.

Registry No.—**1**, 1779-81-3; **2**, 532-55-8; **3**, 55103-06-5; **4**, 55103-07-6; **5**, 55103-08-7; **7**, 55103-09-8; **9**, 29146-60-9; **10**, 6558-36-7.

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(13) Infrared spectra were taken on a Beckman IR-5 spectrophotometer in KBr pellets unless otherwise indicated, and NMR spectra were determined on a Varian Associates T-60A spectrometer. Mass spectra were obtained at 70 eV and 290° on an LKB spectrometer. Uv spectra were taken on a Beckman DB-G recording spectrophotometer. Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

Reduction of the 1,3-Dithiolium Cation with Hexacarbonylvanadate(1−)

A. R. Siedle* and R. B. Johannesen

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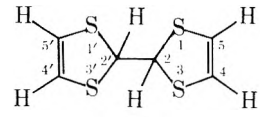
Received April 4, 1975

While the reduction of 1,2-dithiolium cations has been extensively studied,[1-4] less information is available concerning the isomeric 1,3-dithiolium salts. An electrochemical reduction of the 2-thioethoxy-4,5-dithiomethoxy-1,3-dithiolium cation to the orthothiooxalate has been reported.[5] We wish to report a reductive coupling of the unsubstituted 1,3-dithiolium cation using sodium (bisdiglyme) hexacarbonylvanadate(1−) as the reducing agent. This is, to our knowledge, the first example of the use of $V(CO)_6^-$ as a reducing agent for organic compounds.

When solutions of 1,3-dithiolium hexafluorophosphate[6] and $Na(diglyme)_2V(CO)_6$ in acetone–tetrahydrofuran were mixed and the resulting solution diluted with water, white, crystalline 2,2′-bi(1,3-dithiolyl) (**1**) separated; the very air-sensitive $V(CO)_6$ was not isolated in this procedure.[7] The mass spectrum of **1** was characterized by strong M^+ and $M^+/2$ peaks. The 220-MHz ^1H NMR spectrum of **1** in acetone-d_6 consisted of two singlets at δ 4.73 and 6.20 in a 1:2 ratio. At 60 MHz, with a resolution better than 0.4 Hz, these signals showed unresolved fine structure.[8] Examination of the ^{13}C satellites in the ^1H NMR spectrum of **1** revealed $^3J_{H(4)H(5)} = 5.4 \pm 1$ Hz and $^3J_{H(2)H(2')} = 10.5 \pm 1$ Hz. The former value is similar to $^3J_{H(3)H(4)}$ in aromatic derivatives such as pyrrole and furan.[9] The latter coupling constant is larger than might be expected for vicinal protons but might be modified by the presence of the electronegative sulfur atoms or by a preference by **1** for a specific conformation. The ^{13}C NMR spectrum of **1** in carbon tetrachloride consisted of two doublets at 115.6 (J_{CH} = 184 Hz) and 60.3 ppm (J_{CH} = 160 Hz) [relative to internal $(CH_3)_4Si$] in a 2:1 intensity ratio.

The formation of **1** presumably proceeds through a one-electron reduction by $V(CO)_6^-$ of the 1,3-dithiolium cation to form the free radical **2**. Subsequent dimerization of **2** would then lead to **1**.



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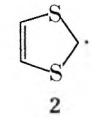

2

Experimental Section

A solution of 0.33 g (1.44 mmol) of $C_3H_3S_2^+PF_6^-$ in 10 ml of 1:1 acetone–tetrahydrofuran was added with stirring to 0.75 g (1.44 mmol) of $Na(C_6H_{14}O_3)_2V(CO)_6$[10,11] in 15 ml of the same solvent. The solution turned dark and a small amount of gas was evolved. The mixture was evaporated to ca. 5 ml on a rotary evaporator. Slow addition of water caused the product to separate as white flakes which were further purified by sublimation (90°, 10^{-3}mm). The yield was 0.09 g (59%), mp 150–151°. Anal. Calcd for $C_6H_6S_4$: C, 34.95; H, 2.91; S, 62.14. Found: C, 35.18; H, 3.04; S, 61.95. Ir (KBr) 3030 (w), 2950 (w), 1580 (w), 1525 (m), 1500 (w), 1245 (m), 1165 (s), 1075 (w), 855 (w), 780 (s), 730 (m), 695 (m), 435 (w), and 315 cm^{-1} (m); uv (C_2H_5OH) λ_{max} (log ϵ) 290 (3.23) and 309 nm (3.22); mass spectrum (70 eV) *m/e* (assignment, rel abundance) 208 ($^{12}C_6{}^1H_6{}^{32}S_3{}^{34}S$, 4.9), 206 ($M^+$, 27), 103 ($M^+/2$, 100), 45 ($HCS^+$, 25).

A mixture of 0.05 g of 2,2′-bi(1,3-dithiolyl), 0.1 g of active manganese dioxide, and 3 ml of acetonitrile was gently refluxed for 3 hr to give a yellow solution. Preparative thin layer chromatography (1:1 benzene–hexane, silica gel) afforded 0.013 g (26%) of tetrathiafulvalene, identified by its R_f and ultraviolet spectrum.

Acknowledgments. We are grateful to Dr. J. N. Lyerla and Mr. R. Bradley for obtaining the ^{13}C and ^1H satellite spectra and to Dr. A. Fatiadi for a sample of active manganese dioxide. One of us (A.R.S.) is grateful for a NRC Postdoctoral Research Associateship.

Registry No.—**1**, 51187-35-0; hexacarbonylvanadate(1−), 20644-87-5; 1,3-dithiolium cation, 288-75-5; 1,3-dithiolium hexafluorophosphate, 55298-73-2.

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(7) If the reaction is run in water, **1** and $V(CO)_6$, identified by its infrared spectrum, precipitate. However, the yield of **1** under these conditions is only 25%.
(8) The ^1H NMR spectrum of **1** should be an $A_2XX'A'_2$ pattern. The ^1H NMR spectrum of $C_3H_3S_2^+PF_6^-$ in acetone shows resonances at δ 11.72 (t, 1 H, $^4J_{HCSCH}$ = 2 Hz) and 9.58 (d, 2 H, J = 2 Hz). This suggests that J_{AX} in **1** will be ~2 Hz and that $J_{AA'}$ will be $\ll$2 Hz. In fact, the ^{13}C satellite spectrum indicates that all long-range couplings are <0.5 Hz.
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(10) This material was obtained from Pressure Chemical Co., Pittsburgh, Pa.
(11) Certain commercial equipment or materials are identified in this paper in order to adequately specify the experimental procedure. In no case does such identification imply recommendation or endorsement by the National Bureau of Standards nor does it imply that the material or equipment identified is necessarily the best available for the purpose.

Internal Rotation of Charge-Transfer Complexes[1]

F. M. Menger*[2] and G. Saito

Department of Chemistry, Emory University, Atlanta, Georgia 30322

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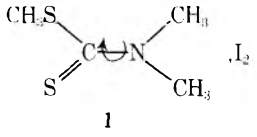
We report here a study of torsional barriers to rotation *about single bonds of charge-transfer complexes.* Despite wide theoretical[3] and biological[4] interest in charge-transfer complexes, there have been few previous measurements of the effect of such association on internal rotation.[5] Two systems were investigated. Internal rotation rates were determined about the central nitrogen–carbon bond of *N,N*-dimethyldithiocarbamic acid methyl ester (**1**) in the presence and absence of an *acceptor*, I_2. Rotation rates were also determined about the nitrogen–aryl bond of *N*-methyl-2,4,6-trinitroaniline (**2**) in the presence and absence of a *donor*, *N,N*-dimethylaniline. Charge-transfer complexes of **1** with I_2 and **2** with *N,N*-dimethylaniline fall into the "n–aσ" [3,6] and "bπ–aπ" [3] classifications, respectively.



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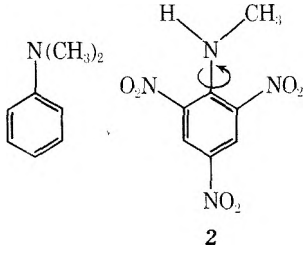


2

Rotation rates of **1** were evaluated by ^1H NMR lineshape analysis of the singlet-to-doublet transition of the *N*-methyl signal. Selection of **1** for this work was based on two considerations. First, the *N*-methyl signal coalesces near room temperature (38°). This precluded the need to attain high temperatures (where complexes dissociate) or low temperatures (where evaluation of the static NMR parameters is difficult). An even more important reason for choosing **1** stemmed from the sizable association constant found for **1** and I_2 (K_{assoc} = 222 M^{-1} at 25.0° in chlorobenzene). Favorable binding is necessary to obtain kinetic effects sufficiently large to interpret meaningfully. There is evidence that I_2 complexes with **1** at the thiocarbonyl site[7].

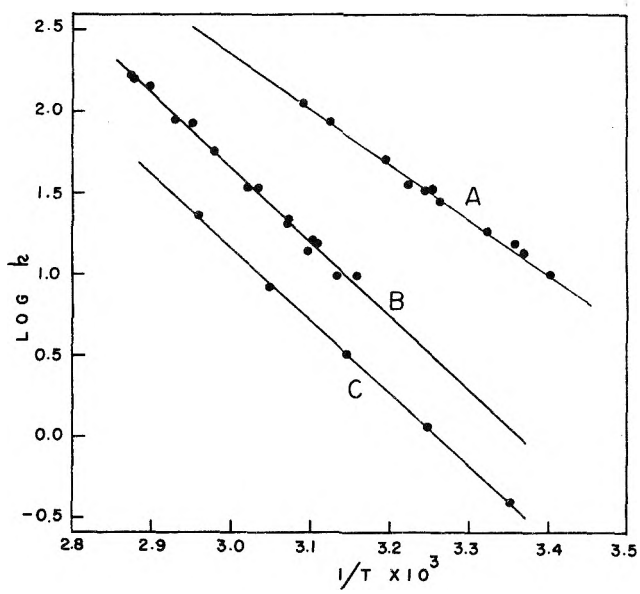
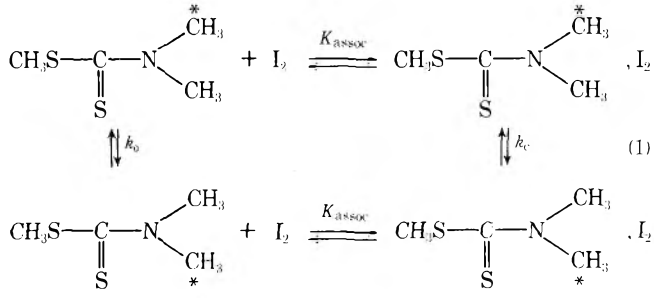


Figure 1. Line A: Arrhenius plot of log k_{obsd} (sec^{-1}) vs. the reciprocal of the temperature (K) for rotation of **1** in chlorobenzene in the absence of I_2. Line B: Arrhenius plot of log k_{obsd} vs. $1/T$ for rotation of 0.100 M **1** and 0.208 M I_2 in chlorobenzene. Line C: Arrhenius plot of log k_c (see eq 1) vs. $1/T$.

Rates of internal rotation of 0.100 M **1** in chlorobenzene at several temperatures between 21 and 51° (Figure 1, line A) afforded the following activation parameters: $\Delta G^{\ddagger}_{298}$ = 15.88 kcal/mol,[8] $\Delta H^{\ddagger}$ = 15.1 kcal/mol, and $\Delta S^{\ddagger}$ = −1.4 eu. Doubling the concentration of **1** had no effect on the rate constants. When 0.208 M I_2 was added to the solution, the rate of internal rotation[9] decreased (as manifested, for example, by elevation of the coalescence temperature from 38 to 61°). A plot of log k_{obsd} vs. $1/T$ is given in Figure 1, line B. The observed rate data could also be analyzed in terms of the scheme shown in eq 1. In order to extract k_c (the rate



(1)

of internal rotation of the complex itself), it was necessary to evaluate K_{assoc} using a spectrophotometric method based on the Ketelaar equation.[10,11] K_{assoc} was found to equal 222 ± 1 M^{-1} at 25.0° and 62.9 ± 1 M^{-1} at 55.0°.[12] Thus, 96.1% of **1** exists in the complexed state at 0.100 M **1** and 0.208 M I_2 at 25.0°. Values of C (the concentration of complex) and k_0 (the rotation rate in the absence of I_2) were inserted into eq 2 to obtain k_c values at several temperatures.[13] We find that k_0 is 37 times greater than k_c at 25.0°, indicating that complexation with I_2 retards rotation. An Arrhenius plot of k_c is shown in Figure 1, line C. From this plot we estimate that $\Delta G^{\ddagger}_{298}$ = 18.1 ± 0.1 kcal/mol; *this is 2.2 kcal/mol greater than that of the uncomplexed substrate.*[14]

$$k_{obsd} = k_0\left(\frac{[1]_0 - [C]}{[1]_0}\right) + k_c\left(\frac{[C]}{[1]_0}\right) \qquad (2)$$

Rotation rates about the bond joining the amine nitrogen to the aryl group in *N*-methyl-2,4,6-trinitroaniline (**2**) were

determined from the NMR line shape of the aryl proton signals. Two experimental problems hampered the study of rotation of **2** when complexed with *N,N*-dimethylaniline: (1) low temperatures were necessary to bring rotation of **2** within the NMR time scale (T_c of aryl protons = −55° in acetone) and (2) the complex has a relatively small association constant (K_{assoc} = 2 M^{-1} at −60° in acetone). It was therefore not possible to analyze the kinetics in terms of eq 1. However, we did establish that the effect of π–π complexation is small. When 57% of **2** is complexed, the rotation rate increases only twofold (barely larger than the experimental error).

In summary, we have found that n–σ complexation of **1** to an acceptor decreases its rate of rotation, whereas π–π complexation of **2** to a donor causes only a small rate perturbation. These findings bear on the controversial question of whether weak donor–acceptor complexes are primarily stabilized by electron transfer ("charge-transfer" model[15]) or by van der Waals forces ("electrostatic" model[16–18]). On the basis of our results with the π–π complex of **2**, we can conclude that either electron transfer between the π donor and π acceptor is insignificant or else electron transfer does not appreciably affect internal rotation in the acceptor. The latter appears unlikely, especially in view of the claim that a small degree of charge transfer can have a large effect on vibrational spectra and other properties.[19] A firm decision between the possibilities must, of course, await theoretical calculations. Electron transfer is more probable in the complex between **1** and I_2, because, according to the parameters of Drago and Wayland,[20] both the donor and acceptor possess strong charge-transfer properties. Since $\Delta G^{\ddagger}$ for rotation of **1** is insensitive to a wide range of protic and aprotic solvents,[8] nonspecific medium effects (including hydrogen bonding) have little affect on rotation. Therefore, actual electron transfer is a likely cause of the modified rotational barrier.

Experimental Section

Materials. *N,N*-Dimethyldithiocarbamic acid methyl ester (**1**) and *N*-methyl-2,4,6-trinitroaniline (**2**) were preppared according to published procedures.[21,22] Chlorobenzene was distilled over P_2O_5 and again over K_2CO_3.

Kinetics. Rate constants for rotation were calculated with the aid of an RCA Spectra 70/55 computer which adjusts τ (the reciprocal of $2k_{obsd}$) so as to minimize deviations between experimental and theoretical spectral parameters.[23] NMR spectra were recorded with a Jeol JNM-MH-100 spectrometer equipped with a variable-temperature probe. Temperatures, calculated by the equation of Van Geet,[24] were measured before and after each run and are believed to be accurate to ±0.5°. Six to eight spectra were traced in both directions at each temperature, and the resulting rate constants were averaged. An optimum constant homogeneity was achieved by adjusting the resolution control prior to each run while observing the SCH_3 signal. This peak also provided an estimate of the effective relaxation times (T_2's). Spectra were obtained using a sweep width of 54 or 108 Hz, sweep time of 250 sec, filter band width of 10 Hz, and radiofrequency field of 0.1 mG.

Registry No.—**1**, 3735-92-0; **2**, 1022-07-7; I_2, 7553-56-2; *N,N*-dimethylaniline, 121-69-7.

References and Notes

(1) This work was supported by grants from the National Science Foundation and the National Institutes of Health.
(2) Recipient of a Camille and Henry Dreyfus Foundation Teacher Scholar Grant and a National Institutes of Health Research Career Development Award.
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(10) J. A. A. Ketelaar, C. Van De Stolpe, A. Goudsmit, and W. Dzcubas, *Recl. Trav. Chim. Pays-Bas*, **71**, 1104 (1952).
(11) The values of the forward and reverse rate constants comprising k_{assoc} would be expected to be orders of magnitude larger than the rates of rotation about the central C–N bond of **1**. See A. H. Price in "Spectroscopy and Structure of Molecular Complexes", J. Yarwood, Ed., Plenum Press, New York, N.Y., 1973, Chapter 7.
(12) These values correspond to $-\Delta H$ = 8.2 kcal/mol and $-\Delta S$ = 16.7 eu. The thermodynamic parameters in another solvent, CCl_4, are reported to be $-\Delta H$ = 7.53 kcal/mol and $-\Delta S$ = 15.3 eu.[7]
(13) We also performed a series of runs using 0.198 *M* **1** and 0.301 *M* I_2 with no significant difference in results.
(14) The rate data were not considered sufficiently precise to calculate $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (which are difficult to obtain by NMR methods even in simple systems).
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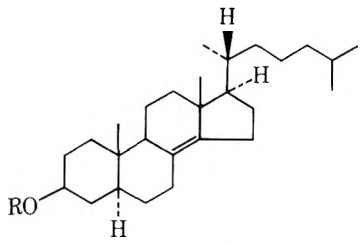
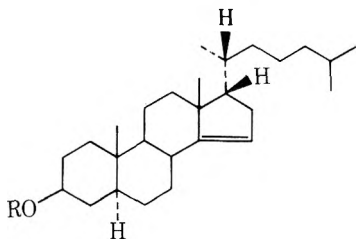
An Unusual Backbone Rearrangement. The Formation of 5α,17α-Cholest-14-en-3β-ol Acetate from 5α-Cholest-8(14)-en-3β-ol Acetate[1]

Summary: The acid-catalyzed isomerization of 5α-cholest-8(14)-en-3β-ol acetate (and 3β-benzoate) at −78° results in 5α,17α-cholest-14-en-3β-ol acetate (or 3β-benzoate); hydrogenation ($^1H_2$, $^2H_2$) gave a product which on the basis of ^{13}C NMR was tentatively assigned as 5α,14β,17α-cholestan-3β-ol.

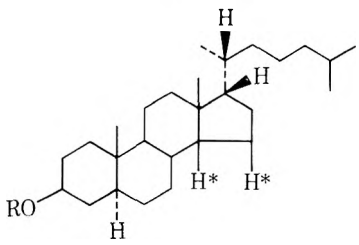
Sir: The preparation of 5α-cholest-14-en-3β-ol acetate (**1a**) requires the treatment of a chloroform solution of 5α-cholest-8(14)-en-3β-ol acetate (**2a**) first with a stream of dry HCl at −30° and then with aqueous $NaHCO_3$.[2] In our hands the obtained **1a** is usually accompanied by variable amounts of an unknown product, now characterized as **3a.**



2a. R = CH_3CO
b. R = C_6H_5CO



3a. R = CH_3CO
b. R = H
c. R = *p*-BrC_6H_4CO



4a. R = CH_3CO; H* = ^1H
b. R = CH_3CO; H* = ^2H
c. R = H; H* = ^1H
d. R = H; H* = ^2H

We present proof of structure and efficient methods of synthesis of the rather inaccessible 5α,17α-cholest-14-en-3β-ol acetate (**3a**) and 5α,14β,17α-cholestan-3β-ol acetate (**4a**). It is worthy of note that the unusual isomerization at C-17 occurred at a center remote from the reaction site.

When the reaction was carried out by treating a solution of **2a** (1500 mg) in dry chloroform (2 ml) with HCl at −78° for 7 hr, and then with aqueous $NaHCO_3$ for 8 hr, the main product (80–90% yield) was[3] **3a.** The mass spectrum [*m/e* 428 (M^+), −15, −60, −173, etc.] and NMR [δ 5.07 (m, 1 H, vinylic), 0.90 (s, 3 H, C-10 methyl), 1.13 (s, 3 H, C-13 methyl), 0.89 (d, *J* = 7 Hz, 9 H, C-25 and C-20 methyls] were consistent with a C_{27} structure having a trisubstituted double bond. Hydrogenation ($^1H_2$ or $^2H_2$) of **3a** gave saturated **4a** (^1H) or **4b** (^2H), which differed from cholestanol acetate (**5a**). These results were consistent with the hypothesis that **3a** was obtained via a structural rearrangement of the cholestenol skeleton, which very likely involved rings C and/or D.

The natural abundance, noise-decoupled ^{13}C NMR spectra of the 3β-hydroxy compounds [**1b, 3b, 4c** (^1H), **4d** (^2H), and **5b**] were obtained from dioxane solutions.[4] Each spectrum consisted of 27 peaks, clearly establishing the C_{27} nature of the unknown. Both **1b** and **3b** showed two peaks in the olefinic region, one carbinol peak, five methyl peaks, and peaks for two quaternary aliphatic carbons, presumably C-10 and C-13. The remaining peaks arose from secondary or tertiary carbons.

The mass spectrum of **3a** had pronounced peaks at *m/e* 255 [$M^+ - (C_8H_{17} + CH_3COOH)$] and 240 [$M^+ - (C_8H_{17} + CH_3COOH + CH_3)$]. These results were consistent with the view that **3a** has a tetracyclic steroidal structure with a C_8H_{17} moiety at C-17.[5] On this basis we assigned peaks corresponding to C-1 through C-10, C-19, and C-24 through C-27 in the ^{13}C spectrum of the 3β-hydroxy **3b.** The signals for these carbons in the spectrum of **3b** showed little displacement from the corresponding peaks in the spectrum of **1b.** This reinforced the view that **1b** and **3b** differ only in rings C and/or D.

The chemical shift of the protons of the C-10 methyl and the presence of a single vinylic *hydrogen* in the ^1H NMR spectrum of **3b** established that the double bond is trisubstituted and cannot be located in rings A or B or at C-9 (11). This, together with the mass spectral data narrowed the choice of the likely structures of **3** to the following: **a,** Δ^{12}-14β-methyl; **b,** 14ξ(H)-Δ^{16}; and **c,** Δ^{14}-17α side chain. The influence of the Δ^{14} on the chemical shifts of ^{13}C atoms of **5b** was deduced from a comparison of its spectrum with that of **1b.** The effects of epimerization at C-17 on the chemical shifts of ^{13}C atoms of the tetracyclic nucleus of **5b** were estimated from a comparison of the spectra of estra-1,3,5(10)-triene-3,17α-diol and estra-1,3,5(10)-triene-3,17β-diol.[6] Based on these considerations it was inferred that the most likely structure of **3b** is 5α,17α-cholest-14-en-3β-ol. This conclusion was confirmed by X-ray structure determination carried out on *p*-bromobenzoate (**3c**, mp 101.5–103.5°).

Cell dimensions of a small (0.3 mm on edge) crystal of the *p*-bromobenzoate derivative of the rearranged product (**3c**) were determined by a least-squares procedure of the 2θ values of 15 well-centered reflections. Cell data: *a* = 22.125 Å, *b* = 51.859 Å, *c* = 11.072 Å, *V* = 12703 Å^3, orthorhombic, $P2_12_12_1$, *Z* = 16. Three-dimensional data were collected on an Enraf-Nonius Kappa automated diffractometer with Cu Kα radiation. Of the 11278 data collected, 3591 were classed as observed. The structure was solved by Patterson techniques and subsequent Fourier synthesis to an *R* factor of 25%. Least-squares refinement of the bromine positions with anisotropic thermal parameters and

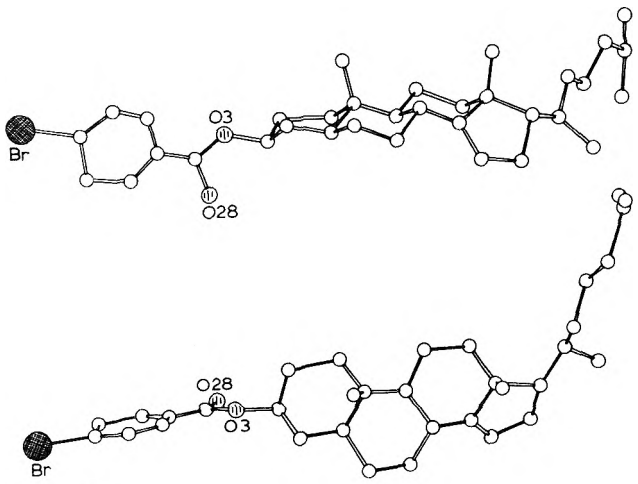


Figure 1.

the carbon and oxygen positions with isotropic thermal parameters is continuing. The R factor is 11.8% at the present time. The data revealed the presence of four crystallographically independent molecules of **3c** in the cell.[7] ORTEP views (50% probability thermal ellipsoids) of molecule 2 are seen in Figure 1. The structure of **3c** is unequivocally 5α,17α-cholest-14-en-3β-ol p-bromobenzoate. Molecules 1, 2, and 4 have the same D ring conformation, 17β envelope, and similar side chain orientation; C-21 is anti to C-13 and gauche to C-16. In molecule 3 tlhe D-ring conformation appears to be a 17α envelope and C-21 is gauche to C-13 and C-16. The end of the cholestane side chain, C-25, C-26, C-27, is probably disordered in at least two of the molecules. Other interesting conformational details which vary in the four molecules will be discussed in a future paper.

The saturated derivative **4** obtained by hydrogenation of **3** could have either the 14α or 14β stereochemistry. From ^{13}C NMR studies[4] of **4c** and **4d**, it was tentatively concluded that **4** is 5α,14β,17α-cholestan-3β-ol.

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Supplementary Material Available. Tables of ^{13}C chemical shifts and bond distances and angles will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2005.

References and Notes

(1) Professor A. Fiecchi and his associates at the University of Milano have obtained similar results. It was agreed to publish the results of both groups simultaneously.
(2) J. W. Cornforth, I. Y. Gore, and G. Popjak. *Biochem. J.*, **65**, 94 (1957). These authors have carried out the referred to transformation on the $\Delta^{8(14)}$-benzoate. We have carried out the reactions described in this communication on both $\Delta^{8(14)}$-acetate and the benzoate. In both instances analogous products were obtained which were interrelated as the free C-3 alcohol. At present we report the results for the acetate.
(3) All new compounds were fully characterized. ^{1}H NMR spectra were recorded on a Varian DA-60 instrument. ^{13}C NMR spectra were obtained on a Varian HA 100-15 instrument equipped with a Varian time-averaging computer (C-1024) and were recorded at 25.1 MHz. Mass spectra were obtained on a Du Pont 21-491 instrument.
(4) A table of ^{13}C chemical shifts of these compounds is published in the microfilm edition of the journal immediately following these pages.
(5) C. Djerassi, *Pure Appl. Chem.*, **21**, 205 (1970).
(6) T. A. Wittstruck and K. I. Williams, *J. Org. Chem.*, **38**, 1542 (1973).
(7) A table of bond distances and angles averaged over the four molecules is published in the microfilm edition of the journal immediately following these pages.
(8) (a) Worcester Foundation for Experimental Biology, Shrewsbury, Mass. 01545. (b) Medical Foundation of Buffalo Research Laboratories, Buffalo, N.Y. 14203. (c) Extracted in part from the Ph.D. Thesis of J. P. Moreau to be submitted to the University of Orleans, France.

The Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts 01545

Eliahu Caspi[*8a]
William L. Duax[8b]
Jane F. Griffin[8b]
Jacques P. Moreau[8a,c]
Thomas A. Wittstruck[8a]

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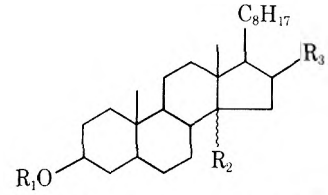
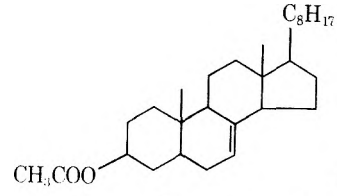
A Ready Synthesis of 17α Steroids[1,2]

Summary: Reaction of sterol acetates with a Δ^7, $\Delta^{8(14)}$, and Δ^{14} double bond with hydrogen chloride yields 3β-acetyloxy-14-chloro-5α,14β,17α-cholestane (structure determined by X-ray analysis), which is easily dehydrohalogenated to 3β-acetyloxy-5α,17α-cholest-14-ene.

Sir: Anhydrous hydrogen chloride in chloroform has been described to promote the isomerization of Δ^7, Δ^8, and $\Delta^{8(14)}$ double bonds to the 14 position in sterols.[3,4] Compound **1a** (mp 104–106°) was obtained as the single reaction product by bubbling hydrogen chloride for 3 hr at −60° in a 20–25 mM solution of 3β-acetyloxy-5α-cholest-7-ene (**2**) in diethyl ether. The ^{1}H NMR spectrum showed signals at δ



1a, R_1 = CH_3CO; R_2 = β-Cl; R_3 = β-H
b, R_1 = C_6H_5CO; R_2 = ξ-Cl; R_3 = α-H
c, R_1 = CH_3CO; R_2 = ξ-Cl; R_3 = α-H



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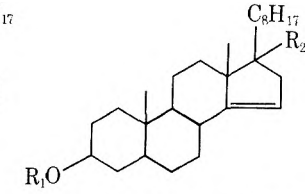
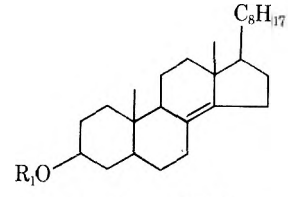
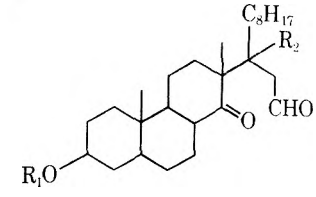


3a, R_1 = CH_3CO; R_2 = α-H
b, R_1 = C_6H_5CO; R_2 = α-H
c, R_1 = CH_3CO; R_2 = β-H
d, R_1 = p-BrC_6H_4CO; R_2 = β-H



4a, R_1 = CH_3CO
b, R_1 = C_6H_5CO



5a, R_1 = CH_3CO; R_2 = (*S*)-H
b, R_1 = C_6H_5CO; R_2 = (*R*)-H

$C_8H_{17}CH{=}CHCHO$

6

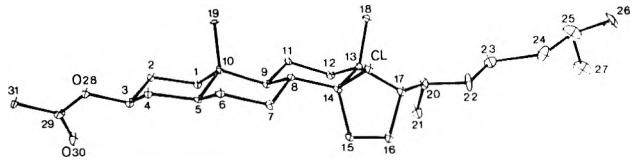


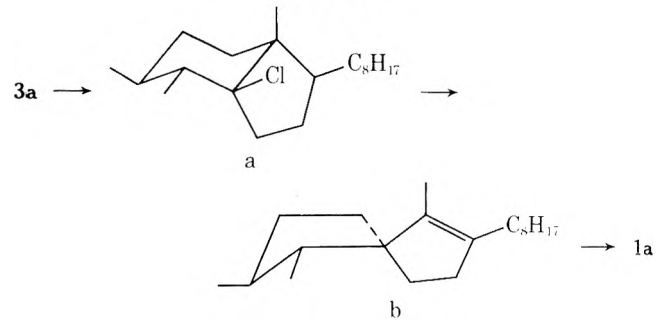
Figure 1. ORTEP plot of 3β-acetoxy-14-chloro-5α,14β,17α-cholestane.

0.81 (C_{19} CH_3, s) and 1.18 (C_{18} CH_3, s). The molecular ion was absent in the mass spectrum which differed from that of **3a** only in the relative intensity of fragmentation peaks. By X-ray diffraction analysis the compound was shown to give orthorombic crystals with cell dimensions: a = 34.148 (10), b = 12.538 (2), c = 6.641 (2) Å; space group $P2_12_12_1$, Z = 4. A total of 1371 reflections was measured up to ϑ = 45°. The structure was solved by direct methods employing the program MULTAN.[5] The final R index was 0.091 for the 1125 reflections with Int. > 2σ Int. The crystal structure analysis showed that the examined compound is 3β-acetyloxy-14-chloro-5α,14β,17α-cholestane (**1a**). The ORTEP plot of the molecule is reported in Figure 1.[6]

Formation of **1b** in the reaction of 3β-benzoyloxy-5α-cholest-8(14)-ene (**4b**) with hydrogen chloride has been reported by Cornforth et al.[4] According to these authors the compound is transformed into 3β-benzoyloxy-5α-cholest-14-ene (**3b**) by shaking the reaction mixture with a saturated solution of sodium hydrogen carbonate. Treatment of **1a** under these conditions failed to transform the compound into **3a,** whereas **1a** with excess triethylamine in methanol at 50° gave the acetate **3c,** which showed ^{1}H NMR signals at δ 0.87 (C_{19} CH_3, s), 1.09 (C_{18} CH_3, s), and 5.08 (H_{15}, m). The mass spectrum showed differences only in the relative intensity of the peaks when compared with that of compound **3a.** Compound **3c** failed to crystallize but a crystalline 3β-*p*-bromobenzoyloxy derivative (**3d,** mp 101–102°) was obtained (orthorombic with cell dimensions: a = 22.15, b = 51.87, c = 11.05 Å; space group $P2_12_12_1$; Z = 16; automatic diffractometer data).[7] From the above reported spectral data, the structure of 3β-acetyloxy-5α,17α-cholest-14-ene was considered the most probable for compound **3c.** To confirm this hypothesis, reductive ozonolysis of compound **3c** was performed. The oily ketoaldehyde **5a** was obtained from the reaction. It showed ^{1}H NMR signals at δ 0.88 (C_{19} CH_3, s), 1.2 (C_{18} CH_3, s), and 9.67 (H_{15}, t, J ~ 1,5 H). The mass spectrum of **5a** showed an intense peak at *m/e* 292 corresponding to the loss of a $C_{11}H_{20}O$ fragment from the molecular ion. The structure either of aldehyde **6** or of an isomer of this aldehyde might be assigned to this fragment, since 4,8-dimethylnon-2-en-1-al (**6**), isolated as the semicarbazone, was obtained by pyrolysis of **5a.** On the other hand pyrolysis of **5b** was described by Cornforth et al.[4] to give **6,** thus confirming the presence of a Δ^{14} double bond in **3c.**

Acetate **1a** was obtained with hydrogen chloride at low temperature also from **3a, 3c,** and **4a.** On the basis of these experimental evidences, the mechanism shown in Scheme I may be hypothesized for this reaction. Dilution and low temperature seem to promote the formation of **3a** instead of **1c** which is obtained under the conditions reported by Cornforth et al.[4] Trans addition of HCl to the Δ^{14} double bond starting with the attack of a proton at carbon 15 from the less hindered α side of the molecule would yield 3β-acetyloxy-14-chloro-5α,14β-cholestane (a). From the molecular model it is apparent that the 14β-Cl, 13β-CH_3, and 17β side chains strongly interact and that these interactions can be avoided by elimination of chloride ion, followed by ring C contraction and formation of the spiranic olefin b with loss of the 17α hydrogen.[8] Reaction of the spiranic olefin b with hydrogen chloride formally reverses the rearrangement starting from the attack of a proton at 17β position and with the final introduction of chloride ion at position 14β.[9]

Scheme I



Supplementary Material Available. A table of atomic coordinates and equivalent temperature factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2006.

References and Notes

(1) This investigation was supported by the Italian National Research Council.
(2) Dr. E. Caspi and his associates at the Worcester Foundation have obtained similar results. It was agreed to publish the results of both groups simultaneously.
(3) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, pp 113, 260, 354, 400, and references cited therein.
(4) J. W. Cornforth, I. Y. Gore, and G. Popjak. *Biochem. J.*, **65,** 84 (1957).
(5) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.*, **A27,** 368 (1971).
(6) The reflections were measured with a Philips PW 1100 automatic diffractometer (Cu Kα radiation monochromatized with a flat graphite crystal; ϑ–2ϑ scan mode; scan rate 0.03°/min; scan width 1.2° ϑ). The positional and anisotropic thermal parameters of nonhydrogen atoms were refined by full matrix least-squares calculations. The hydrogen atoms could not be discerned on the difference Fourier map; so they were placed at their theoretically expected positions and held fixed during refinement. Bond distances and angles are all within the range of the expected values except three C–C distances involving atoms belonging to the side chain in 17; these atoms exhibit very high thermal vibrations. The average of the absolute values of the torsion angles inside rings A, B, and C are 58.1, 58.4, and 54.2°, respectively. The D ring is a slightly distorted 13β-envelope conformation. The angle between the least-squares plane of rings C and D is 68°. The only intermolecular distance less than 3.6 Å occurs between C_4 and O_{28} and is 3.41 Å.
(7) When the X-ray analysis was in progress Dr. Caspi informed us that he and his associates had already determined the structure oi this compound.
(8) A transposition of this type has been reported by A. Lardon and T. Reichstein, *Helv. Chim. Acta,* **45,** 943 (1962). It is caused by $SOCl_2$ in pyridine on methyl 5β,14β-androstane-3β,14-dihydroxy-15-oxo-17β-carboxylate and similar compounds.
(9) A carbonium ion formed from **3a** or directly from **4a** at C_{14} seems unlikely since there is no conformation of the molecule in which the C_{12}–C_{13} bond is aligned with the vacant p orbital at C_{14} as it appears from molecular models. This assumption is supported by the evidence that the transposition of the 10β-methyl group pf 5α-cholestane-4α,5-diol-4α-acetate occurs owing to the alignment of the C_{10}–C_{19} bond with the vacant p orbital at C_5. Cf. E. T. J. Bathurst, J. M. Coxon, and M. P. Hartshorn, *Aust. J. Chem.,* **27,** 1505 (1974).

Institute of Chemistry
Faculty of Medicine
University of Milan
Milan, Italy
Centro Studio Cristallografia strutturale C.N.R. and Institute of Crystallography
University of Pavia
Pavia, Italy

Mario Anastasia*
Martino Bolognesi
Alberto Fiecchi
Giuseppe Rossi
Antonio Scala

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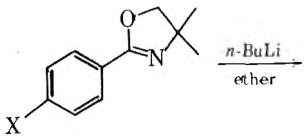
Ortho-Lithiation of Aryloxazolines

Summary: A method is described to convert aryloxazolines directly into their ortho-lithio and ortho-lithiomethyl derivatives which react with a variety of electrophiles in high yields.

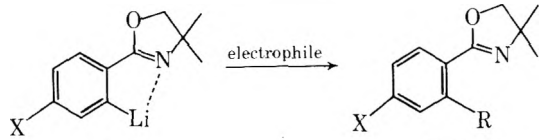
Sir: The heteroatom-facilitated ortho-lithiation has become a powerful tool in synthetic aromatic chemistry. The preparation of an appropriately functionalized 1,2-disubstituted derivative of benzene is often the starting point for the subsequent elaboration of bi- or multicyclic ring systems. Some drawbacks of the currently available ortho-lithiation of N-monosubstituted benzamides, developed by Hauser et al.,[1,2] are the varying yields, strongly dependent upon strict temperature control,[3,4] the use of 2 mol of BuLi/mol of amide coupled with the insolubility of the dilithio species and the relatively poor versatility of the secondary amide group for further transformation. A recently reported method by Meyers[5] makes use of the inertness of an oxazoline derived from *o*-bromobenzoic acid in the formation of a Grignard reagent. Although the yields are high, the method is limited by the availability of substituted *o*-bromobenzoic acids. We wish to report the direct ortho-lithiation of aryloxazolines, which proceeds with extreme ease, regiospecifically and nearly quantitatively.

The aryloxazolines **1** were prepared according to Meyers[5] and distilled under reduced pressure. All lithiations were performed in dry ether at ice-bath temperature with *n*-BuLi in hexane (cf. footnote *e*, Table I). In a typical example a solution of **1c** (3.07 g, 15 mmol) in 65 ml of ether was cooled under a N_2 atmosphere in an ice bath. Then 10.3 ml of a 1.6 *m* solution of *n*-BuLi/hexane (16.5 mmol) was added. After stirring at ice-bath temperature for 4 hr, a solution of 3.65 g of $(C_6H_5S)_2$ (16.5 mmol) in 30 ml of ether was added at once and the mixture stirred at room temperature for 16 hr. After work-up (H_2O, brine, Na_2SO_4), the residue (5.6 g) was crystallized from ether–hexane to give 4.2 g of **8**, mp 51° (89%).

Surprisingly, when the standard lithiation conditions were applied to the unsubstituted **1b**, **5** was obtained only to the extent of 80% with 15% of the product mixture being derived from addition of *n*-BuLi to the oxazoline (product isolated and identified after hydrolysis as valerophenone). While this competing reaction was essentially undetectable in the substituted cases (**1a** and **1c**), it could be suppressed by the use of sec BuLi at −70°.



1a, X = Cl
b, X = H[6]
c, X = OCH_3



2 **3-9** (see Table I)

The lithiation of **1a** proceeds extremely rapidly and reaches 40% after 1 hr at −78° when quenched with D_2O. The stability of **2**, however, permits lithiation to be carried out at the more practical ice-bath temperature. Although no quantitative studies have been carried out, it can be assumed that the rate-enhancing effect of the substituent X on the ortho-lithiation follows earlier observations with *p*-benzamides[3] and benzylamines and decreases in the order Cl > H > OCH_3. It is furthermore noteworthy that in **1c**, whose OCH_3 group could also give rise to ortho-metalation,[7] lithiation occurs regiospecifically ortho to the oxazoline group, as no isomeric products were detected. The variety of substrates which react with **2** accentuates the generality and versatility of this method.[8]

As has been demonstrated with *o*-toluamides[9,10] and *o*-toluic acid itself,[11] the analogous deprotonation of the aromatic CH_3 group can be observed with the oxazoline **10**. Again, lithiation proceeds rapidly (20 min at 0°) after the addition of 1.1 equiv of *n*-BuLi to an ethereal solution of **10** and produces the deep red anion **11**. The completion of its reaction with an electrophilic substrate is clearly evident by the disappearance of the red color.

Table I[a]

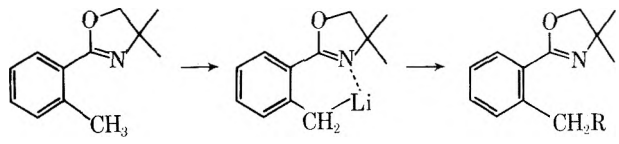
Compd	Lithiation time 2, hr	Electrophile	X	R	Yield,[b] % GC	Yield,[b] % Isold	Mp, °C
3	1	CH_3I[c]	Cl	CH_3	95	71[d]	135
4	1	I_2	Cl	I	94	66[d]	85
5	*e*	D_2O	H	D	92	86[f] (94% D)	
6	*e*	*t*-BuNCO	H	CONHtBu		81	103
7	4	$HCON(CH_3)_2$[g]	OCH_3	CHO	98	70	37
8	4	$(C_6H_5S)_2$	OCH_3	SC_6H_5		89	51
9	4	CH_3NCS	OCH_3	$CSNHCH_3$		77	115

[a] All compounds reported are new (with the exception of 5[5]) and show satisfactory analytical data. [b] With the exception of **5** and **6** no attempts were made to optimize the yields. [c] 5 molar excess of CH_3I added. [d] HCl salt. [e] Addition of 1.1 molar equiv of *sec*-BuLi at −70°, warm up to 0°, quench with electrophile. [f] 2-D-Benzoic acid. [g] Two molar equivalents of DMF added.

Table II

Compd	Lithiation time, min	Electrophile	R	Yield,[a] % GC	Yield,[a] % Isold	Mp or distillin point, °C
12	20	$(CH_3S)_2$	SCH_3	88	85[b]	109
13	20	$CH_2{=}CHCH_2Br$	$CH_2CH{=}CH_2$	83	78	60 (0.1 mmHg)

[a] Yields were not optimized. [b] HCl salt.



10 11 12, 13 (see Table II)

One of the attractive and useful aspects of this new method of ortho-lithiation is the possibility for further modifications and transformations of the oxazoline group under mild conditions: (i) into ketones *via* N-alkylation and addition of an organometallic reagent,[12] (ii) into aldehydes by reduction,[13,14] (iii) into ester or acids by solvolysis.[5]

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Supplementary Material Available. Full experimental details and analytical data on compounds **3–9** and **12, 13** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy, or $2.50 for microfiche referring to code number JOC-75-2008.

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(8) Ketones and aldehydes react, of course, equally well with **2**. However, because of the propensity of internal nucleophilic attack of the OH group at the trigonal oxazoline carbon, the primary product is usually obtained as a mixture and thus better carried on to the corresponding phthalides as described by Meyers.[5]
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Research Department **Heinz W. Gschwend***
Pharmaceuticals Division **Ali Hamdan**
CIBA-GEIGY Corporation
Summit, New Jersey 07901

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Synthetic Studies on Histrionicotoxins. I. A Stereocontrolled Synthesis of (±)-Perhydrohistrionicotoxin

Summary: A stereocontrolled synthesis of (±)-perhydrohistrionicotoxin (**18**) was achieved by using a reaction of acylaziridine **11** with dibutylcopper lithium as a key step.

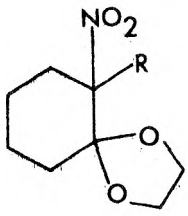
Sir: Histrionicotoxins,[1] the toxic principles isolated from the venom of the Columbian frog *Dendrobates histrionicus*, are remarkably useful neurophysiological tools which selectively inhibit the ion transport mechanism of the cholinergic receptor.[2] Recent communication[3] on a synthesis of perhydrohistrionicotoxin prompted us to report our synthetic studies in this field.

The spiro ketolactam **4** was synthesized by the following simple procedures in 60% overall yield from **1**. Treatment of 2-nitrocyclohexanone ketal[4,5] **1** [bp 125–127° (7mmHg)] with methyl acrylate in *tert*-butyl alcohol containing Triton B, followed by hydrolysis (NaOH in aqueous methyl alcohol at room temperature), afforded the nitro acid[5] **2** (mp 130–131°). The nitro acid **2** was homologated to the nitro ester[5] **3** (oil) by Arndt–Eistert reactions, i.e., (1) $SOCl_2$ in C_6H_6 at 50°, (2) CH_2N_2 in Et_2O at room temperature, (3) $AgBF_4$–Et_3N in methyl alcohol at 0°. Catalytic hydrogenation of **3** (Raney Ni in methyl alcohol at 50°), followed by deketallization (aqueous TFA at 75°), afforded the spiro ketolactam[5] **4** (mp 150–152°).

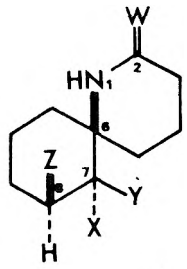
A possibility to control the stereochemistry at the 6 and 7 positions was first examined. Namely, sodium borohydride reduction of **4** in methyl alcohol gave in 85% yield the alcohol[5] **5** (mp 160–162°), which was converted to the mesylate[5] **6** (mp 157–158°). The stereochemistry of the alcohol **5** was assigned based on the fact that sodium hydride treatment of **6** in wet THF yielded cleanly the acylaziridine[5] **7** (oil). Acetic acid treatment of **7** gave exclusively the acetate[5] **8** (mp 143–144°),[6] identical with the acetate obtained by acetylation of the alcohol **5**. This acetolysis result suggested that the required functionality with the desired stereochemistry could be introduced by opening the acylaziridine system in **7**. Thus, **7** was allowed to react with dibutylcopper lithium in THF at room temperature, to give exclusively the lactam **9** (oil) in ~65% yield.[5,6] On the other hand, butyllithium or butylmagnesium bromide reacted with **7** in a 1,2-addition fashion.[7]

In order to apply the described method to the real synthesis, the mesylate[5] **10** (melting point of the corresponding alcohol, i.e., X = OH in **10**, 134–135°) was stereospecifically synthesized from **4** in 35% overall yield by six successive operations [(1) $(EtO)_3CH$–H^+, (2) Δ,[8] (3) Br_2, (4) $NaBH_4$,[9] (5) *i*-PrONa–*i*-PrOH,[10] (6) MsCl–Py]. Sodium hydride treatment of **10** in wet benzene at room temperature yielded cleanly the acylaziridine[5] **11** (oil), which was allowed to react with dibutylcopper lithium in THF at room temperature to afford the lactam[5] **12** (oil) in 15% yield from **10**. One of the undesired products (~30%) in this reaction was the *olefin*[5] **13** (*mp 115–117°*); **13** was possibly derived from the halo intermediate **14**.[7]

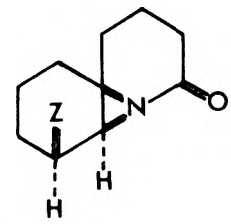
The lactam **12** was converted to the thiolactam[5] **15** (melting point unrecorded) by P_2S_5 in refluxing benzene. The thiolactam **15** was converted to the imine[5] **16** (oil) by two steps, i.e., thioimino ether formation with Meerwein reagent and alkylation with pentyllithium in hexane–ether containing diisobutylaluminum hydride. In the last alkylation process, the activation of the carbon–nitrogen double bond and solvent system are critical.[11] Boron tribromide treatment of **16** in methylene chloride (i.e., **16** → **17**), followed by aluminum hydride reduction in cyclohexane, afforded a mixture of (±)-perhydrohistrionicotoxin (**18**) [six parts, melting point (in a sealed tube) as its hydrochloride, 159–161°] and (±)-*epi*-perhydrohistrionicotoxin (**19**) [one part, melting point (in a sealed tube) as its hydrochloride, 199–201°], which could be separated by preparative TLC or by direct crystallization and recrystallization as the hydrochloride. Stereochemistry of the aluminum hydride reduction is obviously controlled by a complex formation of the reducing reagent with the alcoholic function in **17**, because aluminum hydride reduction of **16** in THF or sodium borohydride reduction of **17** in methyl alcohol gave the



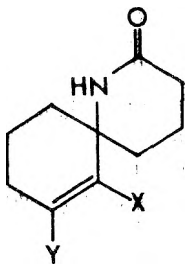
1 R=H
2 R=$(CH_2)_2CO_2H$
3 R=$(CH_2)_3CO_2CH_3$



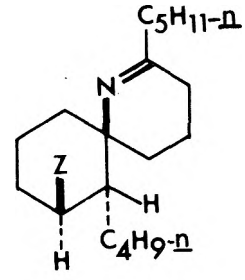
4 X,Y=O, Z=H, W=O
5 X=OH, Y=H, Z=H, W=O
6 X=OMs, Y=H, Z=H, W=O
8 X=OAc, Y=H, Z=H, W=O
9 X=n-Bu, Y=H, Z=H, W=O
10 X=OMs, Y=H, Z=OPr^i, W=O
12 X=n-Bu, Y=H, Z=OPr^i, W=O
14 X=hal, Y=H, Z=OPr^i, W=O
15 X=n-Bu, Y=H, Z=OPr^i, W=S
20 X=n-Bu, Y=H, Z=OH, W=O



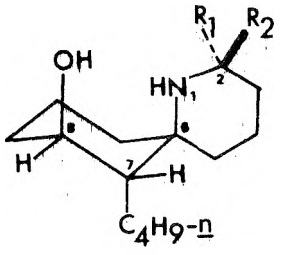
7 Z=H
11 Z=OPr^i



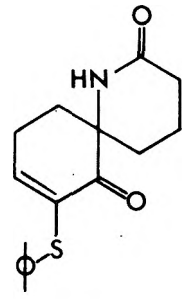
13 X=Y=H
21 X=OEt, Y=H



16 Z=OPr^i
17 Z=OH



18 R_1=n-C_5H_{11}, R_2=H
19 R_1=H, R_2=n-C_5H_{11}



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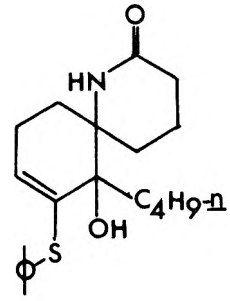
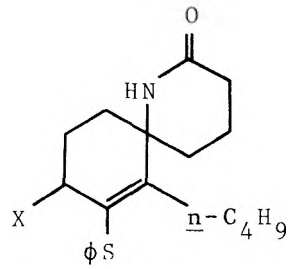


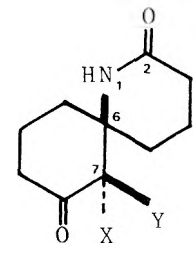
23

product belonging to the epi series as the major product. The best overall yield from the lactam **12** to (±)-perhydrohistrionicotoxin (**18**) was ~55%. Synthetic perhydrohistrionicotoxin (**18**) [melting point (in a sealed tube) as its hydrochloride, 159–161°] was identical with the authentic substance[12] by comparison of spectroscopic data (MS, NMR, ir), chromatographic behavior (silca gel and aluminum oxide TLC), and physiological activity.[13]

For the practical purposes, a more efficient route to the spiro lactam alcohol **20** was sought. Phenylsulfenyl chloride treatment of the enol ether[5,8] **21** (mp 126–127°) in methylene chloride gave thiophenylenone[5] **22** (mp 170–171°), which reacted with butylmagnesium chloride in THF to give the carbinol[5] **23** (mp 201–202°) in 80% overall yield. Thionyl chloride treatment of **23** gave the chloride[5] **24** (oil), which was reduced to the thiophenylenol[5] **25** (oil) with zinc–hydrogen chloride. Hydrolysis of **25** with concentrated hydrobromic acid yielded a mixture of the epimeric spiro ketolactams[5,14] **26** (one part) and **27** (three parts).[15] Equilibration of the mixture of **26** and **27** in methylene chloride containing sodium methoxide gave a new mixture composed of four parts **27** and one part **26**. Lithium or calcium ammonia reduction[16] of **27** at −78° gave exclusively the desired alcohol[5] **20** (mp 133–134°), which was identified with the authentic alcohol synthesized by hydrolysis of **12** (BBr_3 in CH_2Cl_2). Conventionally, the equilibrated mixture of **26** and **27** was subjected to the lithium or calcium reduction and the desired alcohol **20** was easily isolated in 50% yield by a short silica gel column chromatography. The fraction containing the undesired alcohols (epimers at the 7 position) could be recycled by Jones oxidation, equilibration,



24 X=Cl
25 X=H



26 X=H, Y=n-C_4H_9
27 X=n-C_4H_9, Y=H

and reduction. The overall yield from the spiro ketolactam **4** to the alcohol **29** was ~20% (the conditions have *not* been optimized; the recycle procedure is *not* counted).

The alcohol **20** could be converted to (±)-perhydrohistrionicotoxin (**18**) in ~65% overall yield by following the method established before.[17,18]

Supplementary Material Available. Experimental details will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfilm (105 × 148mm, 24× reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street, N.W. Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfilm, referring to code number JOC-75-2009.

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(4) The ketal **1** was synthesized from 2-nitrocyclohexanone [C. Bischoff and E. Schröder, *J. Prakt. Chem.*, **314**, 891 (1972)].
(5) Satisfactory spectroscopic data (MS, NMR, ir, and uv) were obtained on this compound.
(6) The precise yield could not be obtained on this reaction because of the high volatility of **7**.
(7) Detailed results on the reaction of acylaziridine with dialkylcopper lithium and with alkyllithium and Grignard reagents will be reported elsewhere.
(8) Product at this stage is the enol ether[5] **21**.
(9) Product at this stage is the bromohydrin[5] (mp 156–158°; i.e., X = OH, Y = H, Z = Br, and W = O in structure **5**), which yield "α" epoxide upon basic treatment.
(10) Stereochemistry of the mesylate **10** is controlled by opening "α" epoxide by isopropoxide. Epoxidation of the olefin **13** with *m*-chloroperbenzoic acid gave "β" epoxide as the major product, which is opened again at the 8 position by isopropoxide; dibutylcopper lithium opened the "β" epoxide also at the 8 position.
(11) We had studied independently a method converting **12** into perhydrohistrionicotoxin similar to the reported method,[3] but the results were less satisfactory than the present method.
(12) Generously supplied by Dr. B. Witkop and Dr. T. Tokuyama.
(13) Kindly carried out by Professor E. X. Albuquerque.
(14) The ratio (**26**:**27**) depends on the acidic work-up conditions. Sterochemical assignments of **26** and **27** were made on the basis that **27** yielded the alcohol **20** upon reduction, but **26** did not.
(15) In addition a minor product (~5%) was identified as the α,β-unsaturated ketoamide **3a** in the succeeding paper.[17] Since **26** and **27** are stable under the reaction conditions, **3a** probably arises directly from **25**.
(16) Sodium borohydride reduction of **27** gave exclusively the undesired alcohol.
(17) Part II following by T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi.
(18) We (M.A., L.V.D., T.F., and Y.K.) thank Harvard University and Hoffmann-La Roche Co. for their financial assistance.

Department of Chemistry **M. Aratani**
Harvard University **L. V. Dunkerton**
Cambridge, Massachusetts 02138 **T. Fukuyama**
Y. Kishi*

Faculty of Pharmacy **H. Kakoi**
Meijo University **S. Sugiura**
Showa, Nagoya, Japan **S. Inoue**

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Synthetic Studies on Histrionicotoxins. II.[1] A Practical Synthetic Route to (±)-Perhydro- and (±)-Octahydrohistrionicotoxin

Summary: The first total synthesis of (±)-octahydrohistrionicotoxin (**9b**), one of the actual naturally occurring histrionicotoxins, and a practical synthesis of (±)-perhydrohistrionicotoxin (**9a**) have been achieved by using cyclization of the α,β-unsaturated ketoamide **3** to the spiro ketolactam **5** as a key reaction.

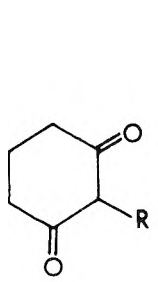
Sir: In the preceding paper[1] we reported a stereocontrolled synthesis of perhydrohistrionicotoxin (**9a**). However, this route is still unsatisfactory from the practical point of view, because of too many steps required and its low overall yield from the commercially available starting material. In this communication we describe a practical synthetic route to (±)-perhydrohistrionicotoxin (**9a**) and the first total synthesis of (±)-octahydrohistrionicotoxin (**9b**), one of the actual naturally occurring histrionicotoxins.[2,3] The key step of this new route was developed based on our previous observation[1] that the spiro ketolactam **5a** is stable under strong acidic and basic conditions, which would suggest a possibility to cyclize the α,β-unsaturated ketoamide **3a** to the spiro ketolactam **5a**.

2-Butylcyclohexane-1,3-dione[4,5] (**1a**) (mp 112–113°, lit.[4] mp 115–116°) was synthesized from methyl 4-(chloroformyl)butyrate by two operations [(1) $(C_5H_{11})_2Cd$ in benzene, (2) KO-*t*-Bu in ether]. The cyclohexanedione **1a** was converted to the vinylcyclohexenone[5] **2a** (oil) by two operations [(1) EtOH–H^+, (2) CH_2=$CHMgBr$ in THF]. Michael addition of methyl malonamate to **2a** ($NaOCH_3$ in CH_3OH), followed by hydrolysis of the ester group (aqueous NaOH), neutralization (aqueous HCl), and decarboxylation (100° in dioxane), yielded the α,β-unsaturated ketoamide[5] **3a** (viscous oil) in 45% overall yield from methyl 4-(chloroformyl)butyrate.

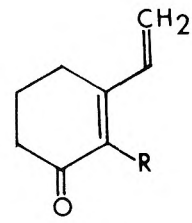
The expected cyclization of **3a** was most efficiently achieved by treatment with ethyl orthoformate in ethyl alcohol containing camphorsulfonic acid, followed by aqueous acetic acid work-up, and a mixture of the epimeric ketolactams[5,6] **4a** (two parts) and **5a** (one part) was isolated in almost quantitative yield.

Parallel experiments, starting from methyl 4-(chloroformyl)butyrate and dipentenylcadmium, gave the corresponding 2-(Δ³-butenyl)cyclohexane-1,3-dione[5] (**1b**) (mp 92.5–93.5°, lit.[7] mp 95–97.5°), the vinylcyclohexenone[5] **2b** (oil), the α,β-unsaturated ketoamide[5] **3b** (viscous oil), and then an epimeric mixture of the spiro ketolactam[5,6] **4b** (two parts) and **5b** (one part) in 45% overall yield.

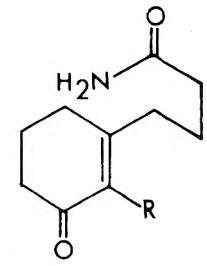
The epimeric mixture of the spiro ketolactams **4a** and **5a** was converted to (±)-perhydrohistrionicotoxin (**9a**) by the established method.[1] Parallel experiments allowed the conversion of the epimeric mixture of the spiro ketolactams **4b** and **5b** to (±)-octahydrohistrionicotoxin (**9b**). Namely, equilibration of the mixture in methylene chloride containing sodium methoxide at room temperature gave a new mixture of **5b** (four parts) and **4b** (one part), which was reduced to the alcohol[5] **6b** (mp 181–183°) by lithium in ammonia at −78° in 50% yield. The undesired alcohols (epimers at the 7 position), easily separated by a short silica gel column chromatography, can be recycled by Jones oxidation, equilibration, and reduction. The structure of the alcohol **6b** was confirmed by spectroscopic data as well as by reducing and identifying the product with the authentic **6a**.[1] The lactam alcohol **6b** was converted into the corresponding thiolactam alcohol[5] **7b** (mp 171–172°) in 90% yield by three operations [(1) Ac_2O–Py, (2) P_2S_5, (3) OH^-]. Protection of the alcoholic function of **7b** as the THP derivative, thioimino ether formation with Meerwein reagent, $AlH(i\text{-}Bu)_2$-catalyzed alkylation with pentenyllithium,[1] and deprotection of the alcoholic function yielded the ketimine[5] **8b**, which was immediately reduced with AlH_3 in cyclohexane to yield a mixture of (±)-octahydrohistrionicotoxin (**9b**, six parts) and *epi*-octahydrohistrionicotoxin (one part). The (±)-octahydrohistrionicotoxin (**9b**) can be



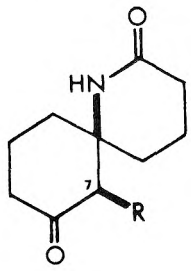
1a,b



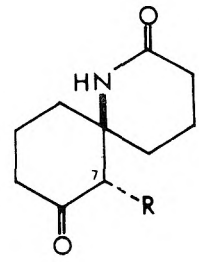
2a,b



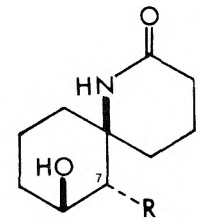
3a,b



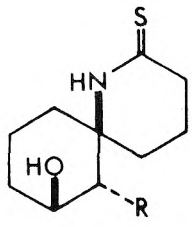
4a,b



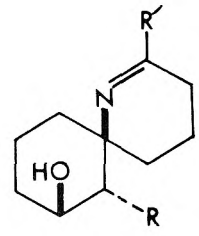
5a,b



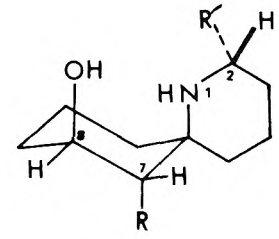
6a,b



7a,b



8a,b



9a,b

a series : R=$CH_2CH_2CH_2CH_3$, R'=$CH_2CH_2CH_2CH_2CH_3$

b series : R=$CH_2CH_2CH=CH_2$, R'=$CH_2CH_2CH_2CH=CH_2$

separated by silica gel TLC or by direct recrystallization as its hydrochloride. The overall yield of **9b** from **7b** was ~70%. The structure of the synthetic octahydrohistrionicotoxin[5] **9b** (melting point in a sealed tube, 151–154° as its hydrochloride) was confirmed by spectroscopic data (MS, NMR, ir) and also by reducing and identifying it with authentic perhydrohistrionicotoxin (**9a**).[1]

Thus, racemic octahydro- and perhydrohistrionicotoxin can be synthesized in ~14% overall yield (the conditions have *not* been optimized; the recycle of the undesired alcohols is *not* counted) from the commercially available methyl 4-(chloroformyl)butyrate by simple operations. It is also possible to apply the procedure for the synthesis of octahydro- and perhydrohistrionicotoxin analogs and of decahydrohistrionicotoxins. The detailed results of the physiological tests of these synthetic materials will be reported elsewhere. Further extension of the present procedure for the synthesis of additional histrionicotoxins is in progress in our laboratories.[8]

Supplementary Material Available. Experimental details will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfilm (105 × 148 mm, 24× reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfilm, referring to code number JOC-75-2011.

References and Footnotes

(1) Part I of this series by M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue.
(2) T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, and B. Witkop, *Helv. Chim. Acta*, **57**, 2597 (1974), and references therein.
(3) Although octahydrohistrionicotoxin is one of the *minor* alkaloids of the Columbian "arrow poison frog", *Dendrobates histrionicus*,[2] a population of this frog in northern Ecuador was recently found by Dr. J. W. Daly and Dr. C. W. Myers to contain octahydrohistrionicotoxin as a *major* alkaloid (private communication from Dr. B. Witkop).
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(5) Satisfactory spectroscopic data (MS, NMR, ir, and uv) were obtained on this compound.
(6) The ratio (**5:4**) depends on the acidic work-up conditions.
(7) W. S. Johnson, W. H. Lunn, and K. Fitzi, *J. Am. Chem. Soc.*, **86**, 1972 (1964).

(8) We thank Harvard University and Hoffmann-La Roche Co. for generous financial assistance.

Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138

T. Fukuyama
L. V. Dunkerton
M. Aratani
Y. Kishi*

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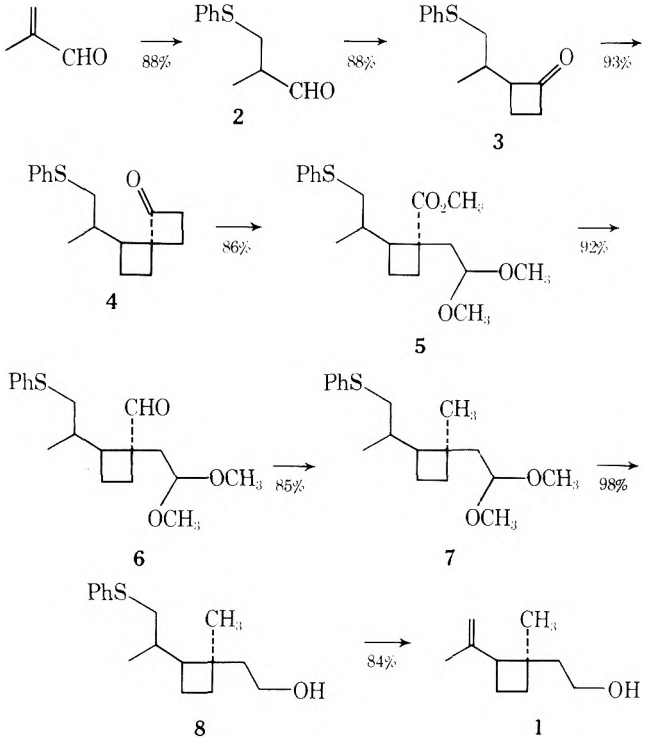
New Synthetic Methods. Secoalkylative Approach to Grandisol

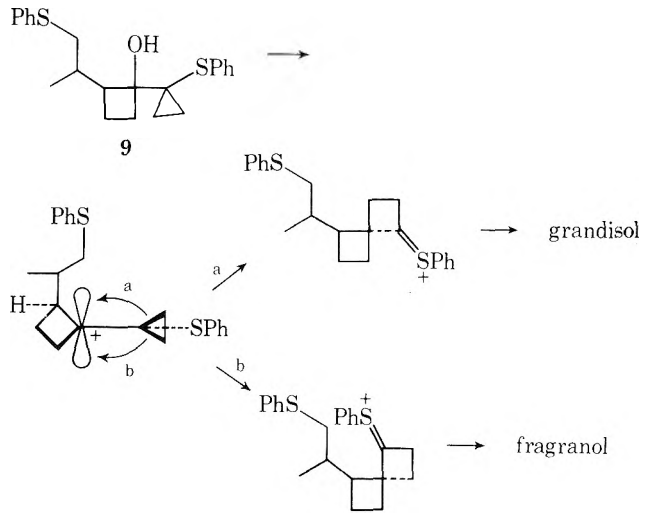
Summary: A stereoselective synthesis of a constituent of the boll weevil sex pheromone using a double cyclobutyl annelation and a new isopropenylation procedure is reported.

Sir: We wish to report a flexible synthesis of racemic grandisol (**1**), one of the four components of the sex attractant released by the male boll weevil.[1,2] This approach illustrates the new cyclobutyl annelation using 1-lithiocyclopropyl phenyl sulfide[3,4] in secoalkylation[5,6] and develops a new way for the introduction of an isopropenyl group based on the sulfoxide elimination.[7]

Scheme I outlines the sequence. Conjugate addition of thiophenol to methacrolein (triethylamine, neat, 0°) gave aldehyde **2**:[8] bp 103° (0.1 mm); ir 1720 cm^{-1}; NMR δ 9.6 (s, 1 H), 1.05 (d, J = 6 Hz, 3 H). Addition of 1-lithiocyclopropyl phenyl sulfide (THF, −78°) followed by acid-catalyzed rearrangement (TsOH, PhH, water, reflux) gave cyclobutanone **3**:[8] bp 109° (0.1 mm); ir 1777 cm^{-1}; NMR, two doublets for diasteromeric methyl group, δ 1.05 (d, J = 6 Hz), 1.15 (d, J = 6 Hz). Repetition of the sequence led to the spiro[3.3]heptan-1-one **4**:[8] bp 115° (0.05 mm); ir 1772 cm^{-1}; NMR, two doublets centered at δ 1.0 (J = 8 Hz, 3 H). Bromination of **4** (pyridinium bromide perbromide, HOAc, 50°), ring cleavage (sodium methoxide, methanol, 25°), and silver ion assisted solvolysis (silver nitrate, methanol, 25°) gave **5**[8] without purification of any intermediates [**5**: ir 1731 cm^{-1}; NMR δ 3.18, 3.22 (6 H), 3.62 (s, 3 H), 4.26 (m, 1 H)]. Reduction of the ester to the alcohol ($LiAlH_4$, THF, reflux) followed by Moffatt oxidation[9] (pyridine–sulfur trioxide, DMSO, triethylamine, 25°) gave the aldehyde **6**[8] [ir 1720 cm^{-1}; NMR δ 9.45 (s, 1 H), 3.19, 3.21 (6 H), 0.95 (d, J = 6 Hz, 3 H), 4.25 (d of d, J = 7 Hz, 1 H)] which, in turn, was subjected to the Wolff–Kishner reduction (hydrazine hydrate, ethylene glycol, KOH, 210°) to produce the methylcyclobutane **7**[8] [NMR δ 0.95 (m, 3 H, 1.16 (s, 3 H), 3.35 (s, 6 H), 4.3 (d of d, J = 6 Hz, 1 H)]. Acetal hydrolysis (1:1 THF–water, HCl) and reduction ($LiAlH_4$, ether, 25°) gave the requisite precursor **8**:[8] ir 3620 cm^{-1}, 3410 cm^{-1}; NMR δ 1.05 (s, 3 H), 1.15 (s, 3 H), 3.6 (m, 2 H). The creation of the isopropenyl substituent involved oxidation of sulfur to the sulfoxide (MCPBA, methylene chloride, −78°) followed by thermolysis (decalin, calcium carbonate, 180°).[7] It is important to note that no isomerization of the double bond occurred—a fact that makes this method a useful one for introduction of an isopropenyl unit. The ir, NMR, and mass spectra of **1** correspond to the published data.[2]

Scheme I
Secoalkylative Approach to Grandisol





The saturated methyl region in the NMR spectrum (δ 1.17 and 0.92) revealed that the product was an 80:20 mixture of grandisol[1] and fragranol.[10] The stereoselectivity is determined in the rearrangement of the cyclopropylcarbinol **9**.[4] Ring expansion of the presumed carbonium ion intermediate by path a involves less steric crowding of the largest groups than the alternative, path b. This route provided grandisol in ~32% overall yield from α-methylacrolein.

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health for their generous support of our programs.

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(8) All new compounds had spectral properties and analytical data in complete accord with the assigned structure.
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(10) F. Bohlmann, C. Zdero, and U. Faass, *Chem. Ber.*, **106**, 2904 (1973).
(11) Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1970–1975.

Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706

Barry M. Trost*[11]
Donald E. Keeley

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Alkylative Eliminations. Scope of the Activating Group

Summary: Reaction of alkyl, allyl, and benzyl halides with the anions from benzyl, 3,4-methylenedioxybenzyl, phenylthiomethyl, phenylsulfinylmethyl, and cyanomethyl phenyl sulfoxide leads directly to the corresponding alkylated and eliminated products in a convenient one-pot olefin synthesis

Sir: The observation that the rate of elimination of sulfoxides is appreciably affected by (1) the presence of substituents on the carbon bearing the sulfinyl group, (2) the leaving group ability of sulfur, and (3) the acidity of the hydrogen being abstracted makes this olefin-forming reaction much more synthetically useful.[1,2] In our previous work, we noted that a carbonyl group lowers the activation energy so that eliminations occur between room temperature and 110° at reasonable rates.[2,3] We have been able to combine this mild olefin-forming reaction with the alkylation of the anion of methyl 2-phenylsulfinylacetate to generate a counterpart to the Wittig olefination.[4] In this paper, we explore the generality of this alkylative elimination as a function of activating group.

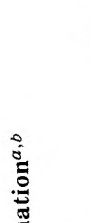
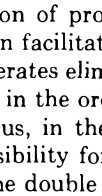
The sulfoxides **1–5** form the corresponding anions on treatment with lithium *N*-isopropylcyclohexylamide; the anions from **4** and **5** were also generated using sodium hydride. In most cases, the alkylation was performed at room temperature in dry THF or DME and the elimination effected by raising the temperature to reflux. The results are summarized in Table I.

The alkylation proceeds smoothly in every case[6,8,9] except the nitrile in which dialkylation was a severe problem.[10] It is quite interesting to note that a single stereoisomer, assigned the *Z* stereochemistry depicted in **7** (entry 13), results from this dialkylation–elimination. This assignment is based upon comparison of the chemical shifts of H_b (δ 6.69) and H_c (δ 6.11) compared to the corresponding shifts in the *E* and *Z* isomers of **6**. In particular, (*E*)-**6** shows H_b downfield and H_c upfield (δ 5.93) from the absorptions for the corresponding protons in (*Z*)-**6** (H_c, δ 6.32). Furthermore, dialkylation was suppressed by adding the anion inversely to warm geranyl bromide. The sluggishness of alkylation of the anion from **4** with an unactivated alkylating agent dictated the use of elevated temperatures (~80°), although no complications were encountered.

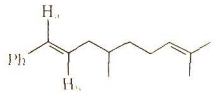
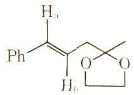
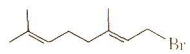
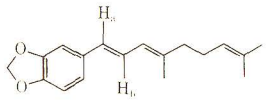
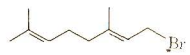
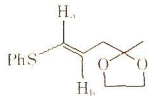
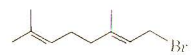
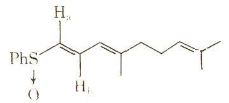
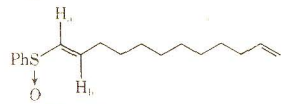
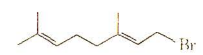
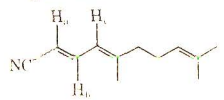
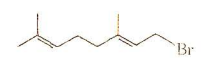
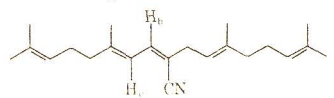
The temperatures for elimination in several instances were determined by pyrolyzing the isolated sulfoxides. The conditions determined in this way were incorporated into the one-pot alkylative elimination and are summarized in Table I. In some cases, a scavenger of phenylsulfenic acid, trimethyl phosphite,[11] was employed to avoid decomposition and facilitate isolation of product. Aryl, phenylthio, and cyano on the α carbon facilitate the elimination; however, phenylsulfinyl decelerates elimination. Ease of hydrogen abstraction decreases in the order allylic > benzylic > secondary > tertiary. Thus, in the absence of conformational restraints, the possibility for regioselectivity exists. The stereochemistry of the double bonds is *E* in the reactions using the anions from **1**, **2**, and **4** as determined by NMR (see Table I). As indicated above, monoalkylation of the anion of **5** gave, on elimination, a 1:1 *E*:*Z* mixture[12] in contrast to the corresponding alkylation of the carboxylic ester.[2–4] Alkylation with the anion of **3** gives predominantly the *E* isomer.

These results demonstrate the utility of the method for making a variety of olefins (aryl ethylenes and butadienes, vinyl thioethers, α,β-unsaturated sulfoxides, and α,β-un-

Table I
Alkylative Elimination[a,b]

Entry	Sulfoxide	Halide	Reaction conditions, temp, °C (time, hr)	Solvent	Product	% yield[c]	δ_{H_a}	δ_{H_b}	J_{AB}, Hz
1[d,e]	1	$PhCH_2Br$	0 (1), 20 (1), 85 (1)	DME		79	7.10		
2[d]	1		20 (1), 65 (8)	THF		87	6.35	6.93	15

1,[5] mp 120–122° | 2, mp 85–86° | 3[6] | 4[5] | 5,[7] mp 63–64°

3[d,e]	1		20 (3), 85 (16)	DME		65	6.35	6.19	16
4[d]	1		20 (4), 85 (16)	DME		57	6.45	6.22	16
5[d]	1		20 (20), 180 (10 min)[g]	THF		41	6.25		
6[d,e]	2		0 (1), 20 (1), 85 (1)	DME		67	6.32	*i*	16
7[d,e]	3		0 (1), 20 (1), 85 (2)	DME		66	*j*	*j*	*j*
8[d,e]	3		20 (4), 85 (16)	DME		67	6.12	*k*	15
9[d]	3		20 (4), 85 (16)	DME		47	(*Z*) 6.44 (*E*) 6.32	5.98 6.04	9.5 15
10[e,f]	4		20 (2), 140 (3.5)	Diglyme		60	6.15	7.13	15
11[e,f]	4		80 (6), 165 (3)	HMPA		45	6.12	6.48	16
12[d,e]	5		65 (4)[h]	THF	 6	49	(*Z*) 5.05 (*E*) 5.18	7.06 7.24	11 15
13[e,f]	5	 (2 equiv)	20 (2), 85 (2)	HMPA	 7	42		6.69	

[a] All new compounds have satisfactory spectral properties. [b] All experiments were performed on a 1-mmol scale. [c] Isolated yields of pure materials. No attempts were made to optimize yields. [d] Anion generated with lithium *N*-isopropylcyclohexylamide. [e] Trimethyl phosphite added just prior to raising temperature for elimination. [f] Anion generated with sodium hydride. [g] Intermediate sulfoxide was pyrolyzed dry with olefin being distilled as formed. In decalin, pyrolysis of sulfoxide required 3 hr at 135°. [h] Carbanion generated in THF added *to* alkylating agent in refluxing THF. [i] H_b coincident with aromatic multiplet. [j] Multiplet of vinyl region in the NMR spectrum precludes interpretation. [k] Mainly *E*. H_b not discernible from terminal vinyl protons.

saturated nitriles) even without optimization of reaction conditions. The gentleness of the method is illustrated both by the sensitive nature of the systems that can be formed, as well as its compatibility with various functionality. Several of the compounds formed using geranyl bromide and citronellyl iodide have interest as juvenile hormone mimics.[13]

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(14) Camille and Henry Dreyfus Teacher Scholar Grant Recipient, 1970–1975.

Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706

Barry M. Trost*[14]
Alex J. Bridges

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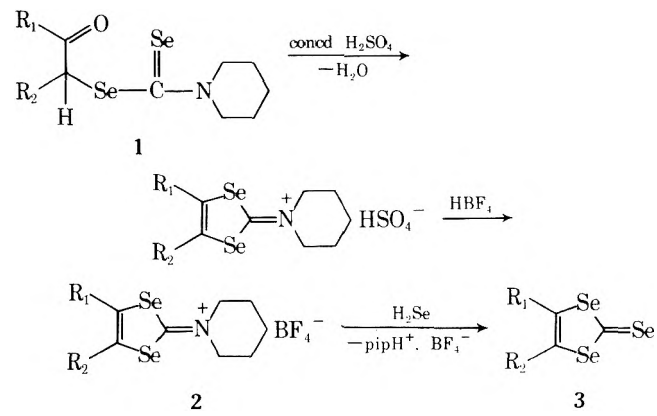
A Safe Preparation of Mono- and Disubstituted 1,3-Diselenole-2-selones

Summary: The preparation of 2-(*N,N*-pentamethylenimino)-1,3-diselenolium fluoroborate as nonhazardous intermediates in the synthesis of 1,3-diselenole-2-selones and tetraselenafulvalenes is described.

Sir: 1,3-Diselenole-2-selones[1-4] have recently gained in interest as intermediates in the synthesis of certain tetraselenafulvalenes, which form highly conducting organic solids with 7,7′,8,8′-tetracyanoquinodimethane.[2,5,6] Two different synthetic routes to 1,3-diselenole-2-selones have been

Scheme I

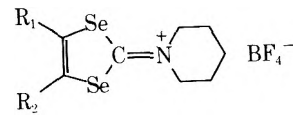


reported. The first[2,4] involves the reaction of selenium and carbon diselenide with sodium acetylides leading to unsubstituted or monosubstituted selones. In the second[1,3] mono- and disubstituted 1,3-diselenole-2-selones are obtained by passing hydrogen selenide through a methanolic solution of 2-(*N,N*-pentamethylenimino)-1,3-diselenolium perchlorates. These salts do, however, detonate upon ignition, heating, and shock and, although we have not so far observed any spontaneous detonations as reported for related systems,[7] their handling in larger quantities constitutes a potential hazard. In spite of this, the use of perchlorates as intermediates was justified by their ready isolation in high yield and purity.

Previous attempts to prepare the fluoroborates (2) by treating the hydrosulfates, obtained by ring closure of 2-oxoalkyl piperidinodiselenocarbamates (1),[1,3] in concentrated H_2SO_4 with an excess of an ethanolic solution of 48% aqueous HBF_4 resulted in a rather poor yield of a deliquescent product.[8]

We have now found that addition of the reaction mixture containing the hydrosulfate to a stirred ethanolic solution containing a 2–3-fold molar excess of HBF_4, prepared from an etheral solution of HBF_4 (54%, Merck-Schuchardt, Munich), gives well-defined, nonhygroscopic fluoroborates in excellent yields (Table I). This procedure makes the corresponding selones available in large quantities without the safety hazards of the earlier procedure.

Table I
2-(*N,N*-Pentamethylenimino)-1,3-diselenolium Tetrafluoroborates



2

R_1	R_2	Yield, %[a]	Mp, °C
CH_3	H	90[b]	111–112
CH_3	CH_3	91	178–179
Ph	H	93	176–177
$-CH_2CH_2CH_2-$		89	210–212 dec

[a] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds listed in the table. [b] A crystalline product was obtained by addition of ether until turbidity, followed by storage overnight at −30°.

In the general procedure, 0.05 mol of the 2-oxoalkyl piperidinodiselenocarbamate (1)[1,3] (Scheme I) was dissolved slowly in 50 g of concentrated H_2SO_4 over 1 hr. Enough ethyl acetate to cause starting precipitation of the hydrosulfate was added cautiously to the now cooled reaction mixture, which was then filtered through a

coarse glass filter funnel into a vigorously stirred, cooled solution of 0.15 mol of HBF_4 (54% in ether) in 500 ml of absolute ethanol. The fluoroborate **2** was precipitated by addition of dry ether, filtered off, washed with dry ether, and dried in vacuo. If necessary the product may be purified by dissolving it in a minimum amount of methanol, filtering, and reprecipitating with dry ether.

The fluoroborates were converted to the corresponding selones **3** by a procedure identical with that earlier reported for the perchlorates.[1,3] This step is facilitated by the fact that the fluoroborates are more readily soluble in methanol than are the perchlorates.

Melting points are uncorrected. Elemental analyses were performed by Mr. Preben Hansen, Department of General and Organic Chemistry.

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Department of Chemistry **Jan R. Andersen**
Danish Atomic Energy Commission
Research Establishment Risø
DK-4000 Roskilde, Denmark

Department of General and Organic Chemistry **Klaus Bechgaard***
H. C. Ørsted Institute
DK-2100 Copenhagen, Denmark

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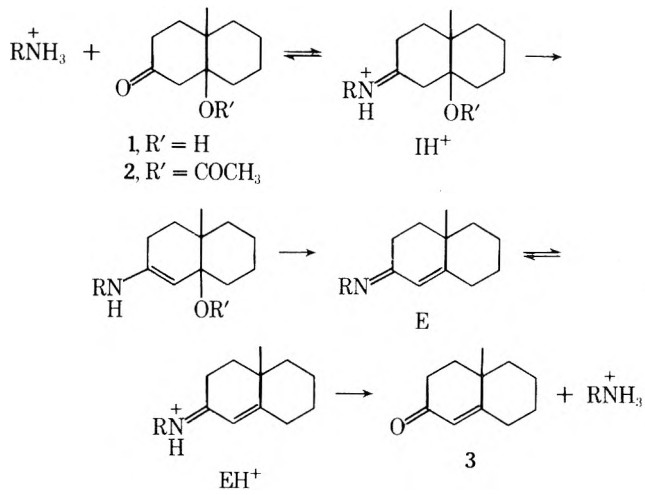
Detection and Characterization of Eniminium Ion Intermediates in Nucleophilic Amine Catalyzed β-Ketol Dehydration

Summary: Previously undetected chromophoric ($\lambda_{max}^{H_2O}$ ~270 nm, ϵ ~16,000) intermediates in nucleophilic amine catalyzed dehydration of β-ketol **1** have been detected (when a large concentration of catalyst is used), isolated, and characterized as eniminium ions (e.g., **4**).

Sir: Nucleophilic amine catalysis of the conversions of β-ketol **1** and β-acetoxy ketone **2** to enone **3** in aqueous solution has been reported by us[1] to proceed without appreciable accumulation of intermediate species according to the mechanism shown in Scheme I, with α-deprotonation of iminium ion IH^+ as the rate-limiting step. We have now found that under appropriate conditions eniminium ion EH^+ is formed in significant concentrations. Since, as discussed below, this species is an intermediate in the sequence **1** → EH^+ → **3**, its detection constitutes important corroboration that catalysis is occurring via amine-carbonyl condensation.[2]

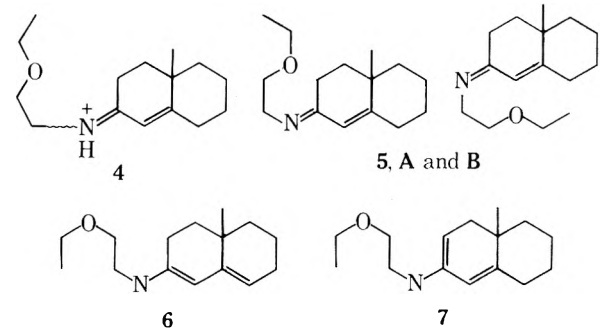
Intermediate EH^+ is characterized by an ultraviolet absorption maximum at ~270 nm. Our failure to detect this species earlier resulted from the use of conditions (low substrate and catalyst concentrations) which tend not to lead to appreciable accumulation of EH^+.[3] Absorption at ~270 nm is readily detectable, however, when relatively high concentrations of reactant and catalyst (pseudo-zero-order conditions) are used at pH ≤ catalyst pK_a. For example, an

Scheme I



aqueous solution of **1** (5.85×10^{-3} *M*) and ethoxyethylamine (pK_a = 9.44; 0.52 *M*) at pH 8.65 develops absorption predominantly at 270 nm through approximately the first 10% of consumption of **1**.

Identification of this chromophoric species as **4** was accomplished by extraction of the reaction mixture with deuteriochloroform and determination of the mass spectrum [*m/e* 235.1938 (calcd for $C_{15}H_{15}NO$ 235.1936)] and the NMR spectrum of the extract. In addition to a peak at δ 5.70 in the latter due to the vinyl proton peak of **3**, two peaks appeared at δ 5.92 and 6.09 (area ratio of ~2:1) which can only reasonably be assigned to the vinyl protons of the geometrical isomers **5A** and **5B** of the neutral enimine derived from **4**.[4,5]



If the extracted species were dienamine **6**,[6] the olefinic protons should appear at ~5 ppm,[7,8] and a mixture of **5** and **6** prepared by the method of Malhotra[9] did indeed show the expected additional resonances of equal intensity at δ 4.89 and 5.06.[10] If the species were dienamine **7**, it should have an NMR peak at about δ 4.25.[7] The vinyl proton of **4** itself would be expected to appear well below 6 ppm,[8,11] and, when DCl was added to a CD_3OD solution of the synthesized mixture of **5** and **6**, peaks at δ 5.85 and 6.18 were replaced by ones at δ 6.30 and 6.55. The ir spectrum of the extract showed ν 1630 and 1615 cm^{-1}, consistent with the postulated imine structure.[12]

The fact that **4** is observed in reactions run at a pH near the pK_a of the catalyst means that this species must be at least comparable in basicity to ethoxyethylamine. This is not unreasonable. Although imines are generally believed to be ~10^3 less basic than the corresponding amines,[13-16] the additional double bond in the enimine should help to stabilize its protonated form.[17] Unsaturated ketones are ~10^3 more basic than saturated ketones.[18]

The pH-dependent equilibrium between **4** and neutral enimine can be easily demonstrated. A chloroform solution of **5**, prepared in the manner described above, was extract-

ed with strongly acidic D_2O, and the extract had λ_{max} 270 nm. When excess KOH solution was added, the peak at 270 was replaced by one of equal intensity at 245 nm.[12,1] Reacidification returned the peak to 270 nm, but with somewhat diminished intensity, presumably owing to partial hydrolysis to **3**.[20]

An extinction coefficient for **4** was determined in the following manner. As previously demonstrated,[1] dehydration of **1** occurs predominantly by a third-order process at pH's near the pK_a (rate proportional to $[1][RNH_2][RNH_3^+]$). Dilution about thirtyfold of a reaction mixture displaying a peak at 270 nm slows the production of **4** sufficiently so that the hydrolysis of **4** to **3** ($\epsilon_{247}^{H_2O}$ 15,500) could readily be followed. An isosbestic point was observed, and a value for **4** of $\epsilon_{max}^{H_2O}$ 16,000 was calculated.[21]

Other EH^+ species analogous to **4** have been observed under appropriate conditions with the following catalysts for **1** → **3**: pyrrolidine, proline, ethyl glycinate, methyl alanate, cyanomethylamine, histamine,[22] histidine,[22] and histidine methyl ester.[22] A value of $\epsilon_{max}^{H_2O}$ 17,000 was obtained by the method described for EH^+ incorporating histamine.

That EH^+ ($\rightleftarrows E$) is an intermediate in the formation of **3** from **1** is supported by the following facts: (1) when EH^+ appears it appears before **3** and (2) only **3** is present at the end of reaction, despite typical catalyst/substrate ratios of ~100.[23] In addition, the rate data for appearance and disappearance of EH^+ can be fitted successfully to a nonlinear least-squares consecutive first-order kinetics program.[24] For the reaction of 2.97×10^{-3} *M* **1** with 0.40 *M* ethoxyethylamine buffer at pH 9.16, this program yielded the following values for the pseudo-first-order rate constants in eq 1: $k_1 = 7.14 \times 10^{-5}$ sec^{-1} and $k_2 = 6.26 \times 10^{-4}$ sec^{-1}

$$1 \xrightarrow{k_1} EH^+ \xrightarrow{k_2} 3 \qquad (1)$$

($k_2/k_1 = 9$). With 0.40 *M* cyanomethylamine buffer at pH 5.47, the values were $k_1 = 9.92 \times 10^{-5}$ sec^{-1} and $k_2 = 1.92 \times 10^{-3}$ sec^{-1} ($k_2/k_1 = 19$). The third-order rate constants for the conversion of **1** to EH^+ calculated from these values of k_1 are in good agreement with the rate constants (k_{AB}'s) previously determined[1b] for nucleophilic amine catalyzed dehydration of **1**.

The detection of these chromophoric eniminium ion intermediates in amine catalyzed β-ketol dehydration suggests that a search for analogous species in other model, as well as enzymic,[25] reactions would be worthwhile, and we are exploring some of these possibilities.

Acknowledgment. This research was supported by Research Grants GP-34390 and MPS75-02737 from the National Science Foundation.

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(19) It should be noted that in our monitoring of reactions of **1** and **2** at 247 nm we may have been registering absorption caused by species E as well as by **3** during the early part of some reactions. The ε of E at 247 nm, based on $\epsilon_{max}^5 \geq \epsilon_{max}^4 = \epsilon_{max}^3 + 500$ (vide infra), is not very different from ϵ_{max}^3.
(20) At pH <3, **4** appears to be stable indefinitely, but conversion to **3** is rapid at pH ≥ pK_a of **4**. See P. Bolla and M. Legrand, *Bull. Soc. Chim. Fr.*, 2143 (1973), for a study of dienamine hydrolysis in which eniminium ions figure prominently and for pertinent references.
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(22) A study of intramolecular bifunctional nucleophilic amine catalysis using this compound will be the subject of a subsequent publication.
(23) The absence of E is easily demonstrated by addition of acid, which does not affect the uv spectrum.
(24) We thank Professor M. V. Olson for lending us this program and we thank him and Professor R. Ditchfield for generous assistance in using it.
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Department of Chemistry **H. E. Ferran, Jr.**
Dartmouth College **D. A. Drake**
Hanover, New Hampshire 03755 **T. A. Spencer***

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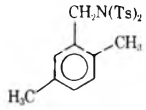
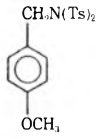
Reductive Deamination of Primary Amines. Sodium Borohydride Reduction of *N,N*-Disulfonimides in Hexamethylphosphoramide

Summary: Sodium borohydride in hexamethylphosphoramide provides a convenient and efficient reagent system for the reductive deamination of unhindered primary amines via initial conversion to *N,N*-disulfonimides and reduction at 150–175°.

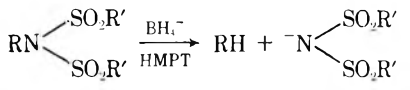
Sir: Although procedures for the activation of hydroxyl groups for displacement or elimination are numerous and

Table I
Reduction of Disulfonimides with Borohydride in HMPT

Entry	Compd [a, b]	Ratio of MBH_4^-/M compd	Temp, °C	Time, hr	% yield of hydrocarbon [c] (isold)
1	$CH_3(CH_2)_9N(Ts)_2$	2	25	48	30
2		2	110	46	43
3		2	150	4.0	80
4		2	175	4.0	84
5		2	175	8.0	88
6		2	175	8.0	91
7		4 ($NaBH_3CN$)	175	26.5	23
8		3 ($LiBHEt_3$) [d]	Reflux	8.0	0 [e]
9	$CH_3(CH_2)_9N(Bs)_2$	2	150	4.0	73
10	$CH_3(CH_2)_{11}N(Ts)_2$	2	175	4.0	68
11		2	150	4.0	(78)
12		2	175	4.0	(78)
13	$CH_3(CH_2)_6CH(CH_3)N(Bs)_2$	4	175	8.0	66
				19.0	73
14	Cyclododecyl-$N(Ts)_2$	4	175	20	Trace [f]

[a] All new disulfonimides gave satisfactory elemental analysis, a copy of which was furnished to the Editor. [b] Solutions were 0.2 *M*. [c] Yields were determined by GLC using internal standards and corrected for detector response. [d] Solvent was a 1:1 mixture of THF and HMPT. [e] A 96% yield of *n*-decyl-*p*-toluenesulfonamide was isolated. [f] A 71% yield of cyclododecyl-*p*-toluenesulfonamide was isolated.

well documented, analogous functionalization of amines is considerably more difficult primarily because most nitrogen anions are relatively strong bases and, consequently, poor leaving groups. Recently, De Christopher and Baumgarten[1] and others[2] have successfully approached this problem using the anion of disulfonimides (i.e., 1) as the departing group, although competing substitution and elimination occurs with most nucleophiles.[1,2]



1

Along this line, we wish to disclose our preliminary observations that borohydride anion in the SN2 enhancing solvent hexamethylphosphoramide (HMPT)[3] functions as an effective hydride source for the reductive deamination of unhindered primary amines[4] *via* initial conversion to disulfonimides.

The general synthetic procedure developed by Baumgarten and De Christopher[5] was employed to convert a variety of primary amines successively to the sulfonamides and disulfonimides. Initial experimentation with *N*-(*n*-decyl)-*N*,*N*-di(*p*-toluene)sulfonimide established that effective conversion to decane (80–91%) in reasonable reaction times (4–8 hr) was obtainable at 150–175° using a 2-fold excess of borohydride (entries 3–5, 9–12, Table I). The progress of the reductions were conveniently monitored by GLC (using internal standards) and the products were obtained simply by dilution with water and extraction with cyclohexane. In this fashion good to excellent yields of hydrocarbons were obtained with primary (entries 3–6, 9, 10), benzyl (entries 11, 12), and unhindered secondary alkyl groups (entry 13). The relatively congested cyclododecyl disulfonimide gave almost exclusive attack at nitrogen (entry 14), presumably because of the reluctance of this system to undergo SN2 displacements.[6] The following reduction is presented as a representative example of the procedure. A solution of *N*-(2,5-dimethylbenzyl)-*N*,*N*-di(*p*-toluene)sulfonimide (3.55 g, 8 mmol) and $NaBH_4$ (605 mg, 16 mmol) in 40 ml of HMPT was heated for 4 hr at 150°, then diluted with water and extracted three times with cyclohexane. The cyclohexane solution was washed three times with water, dried, and concentrated on a rotary evaporator to give 852 mg of colorless oil. Flash distillation at reduced pressure (Kugelrohr apparatus) afforded 747 mg (78%) of 1,2,5-trimethylbenzene product.

Predictably,[7] cyanoborohydride was much less potent as a hydride source (entry 7). Surprisingly, lithium triethylborohydride ("Super-Hydride"),[8] normally an exceptional nucleophile, afforded only *N*-decyl-*p*-toluenesulfonamide resulting from attack at nitrogen (entry 8). The reduction of *N*-(*n*-decyl)-*N*,*N*-d(*p*-toluene)sulfonimide with $LiBD(C_2H_5)_3$ gave the corresponding sulfonamide which showed no deuterium incorporation at the carbon adjacent to nitrogen. This excludes the possibility that the product was formed by initial hydride induced elimination of *p*-toluenesulfinic acid and subsequent reduction of the resulting *N*-tosylimine (2).

$$CH_3(CH_2)_8CH{=}N{-}Ts$$

2

Apparently, the steric requirement of the bulky triethylborohydride anion precludes attack at even a primary carbon next to a large *N*,*N*-disulfonimide group. Attack at nitrogen by borohydride seems to compete favorably only when carbon approach is slow as in *N*-cyclododecyl-*N*,*N*-di(*p*-toluene)sulfonimide (entry 14, Table I).[6]

We are currently exploring the possibility of enhancing the leaving capacity of the sulfonomide by incorporating more powerful electron-withdrawing sulfonyl derivatives such as trifluoromethyl[1,2a] and 2,4-dinitrophenyl groups.[9]

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(6) This sluggish behavior of 12-membered rings toward SN2 reactions has been previously noted; see, for example, P. J. C. Fierens and P. Verschelden, *Bull. Soc. Chim. Belges.*, **61**, 427, 609 (1952); L. Schotsmans, P. J. C. Fierens, and T. Verlie, *ibid.*, **68**, 580 (1959).

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(10) Undergraduate research participant, 1974–1975.

Department of Chemistry
Drexel University
Philadelphia, PA 19104

Robert O. Hutchins*
Frank Cistone[10]
Barry Goldsmith[10]
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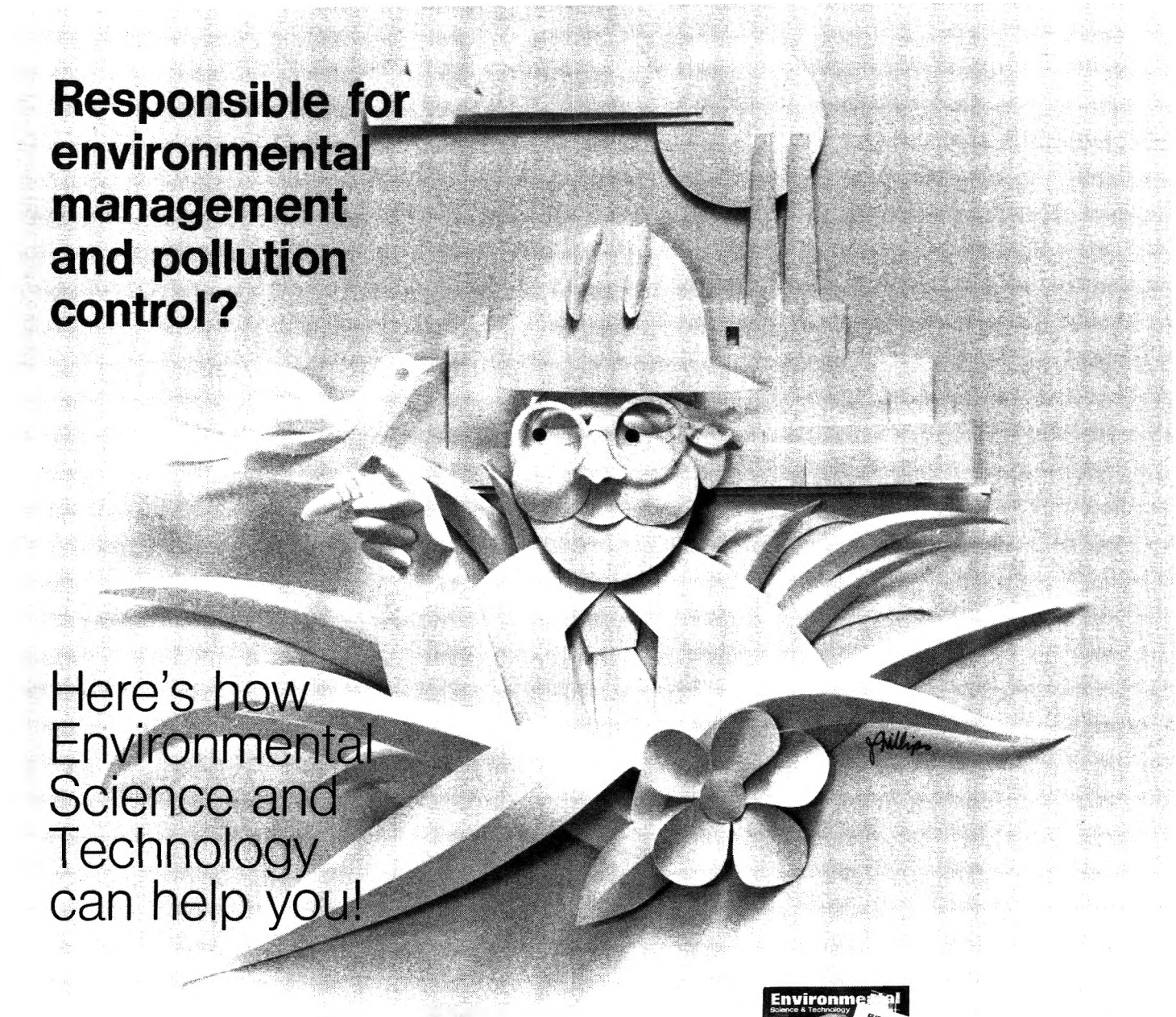

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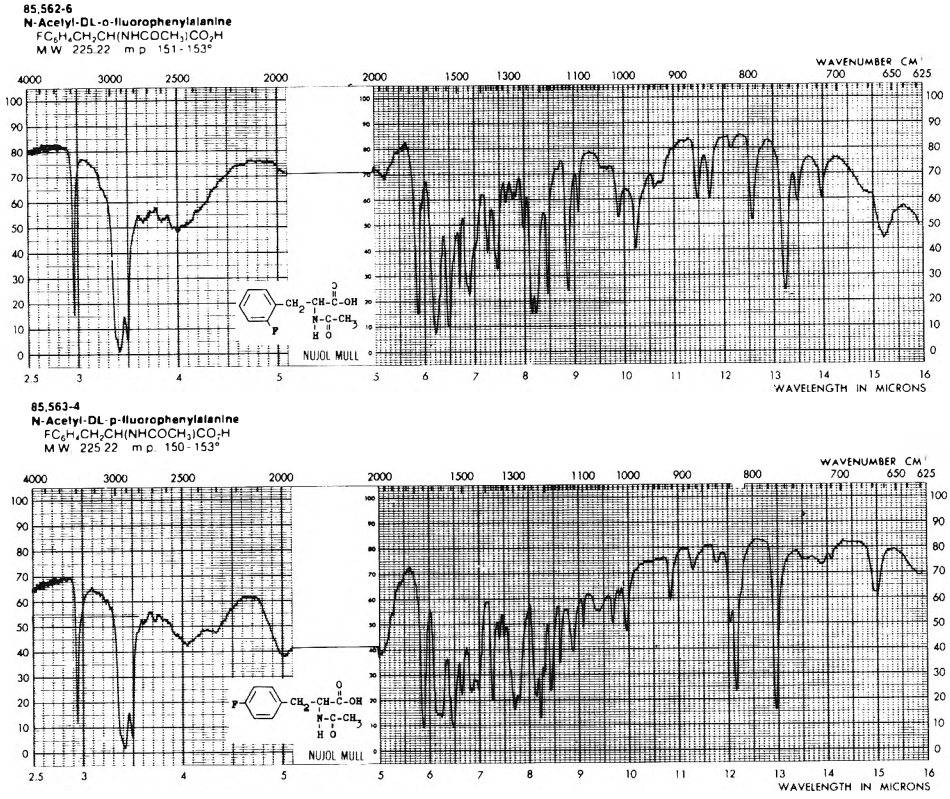

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