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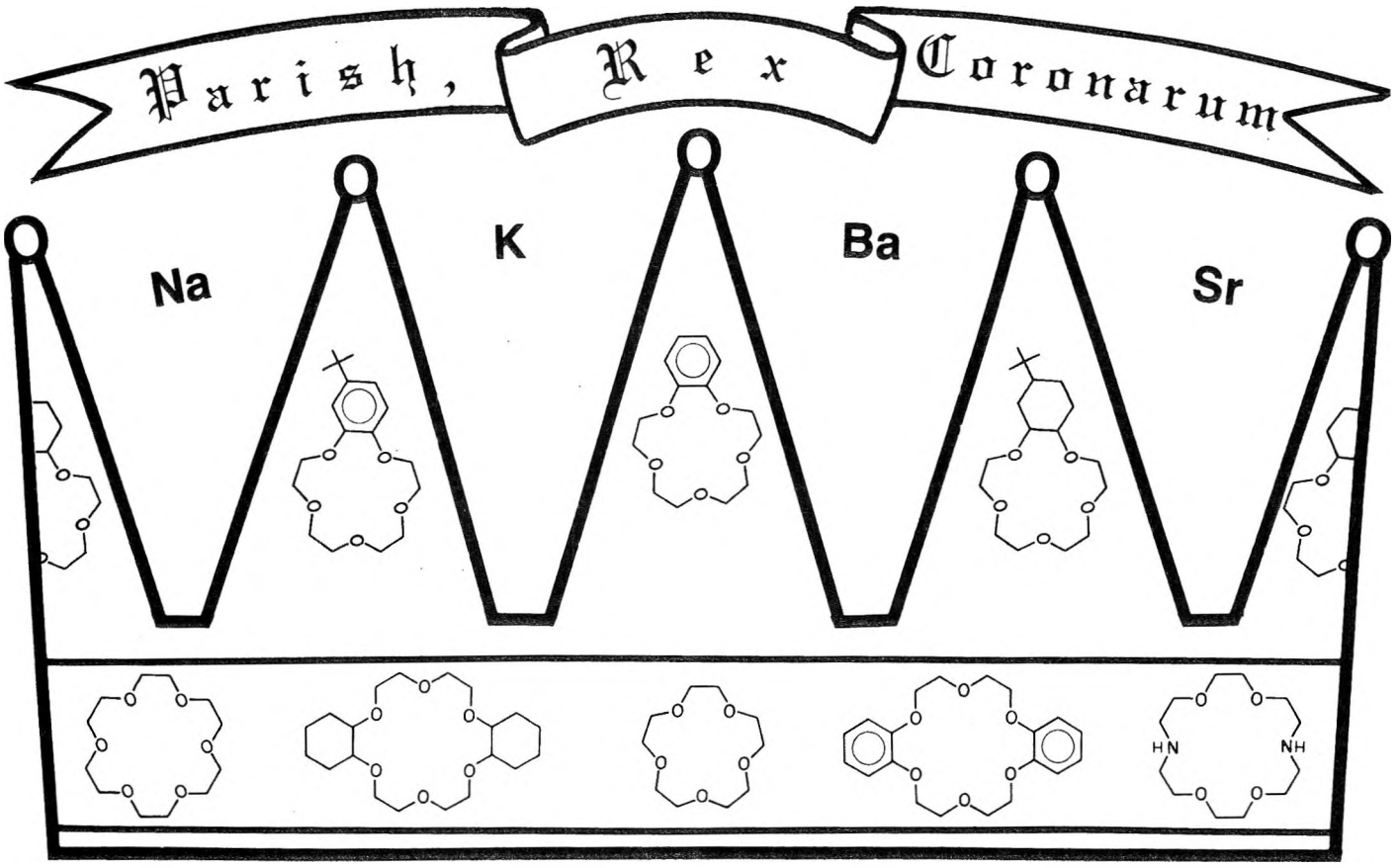


CROWN ETHERS

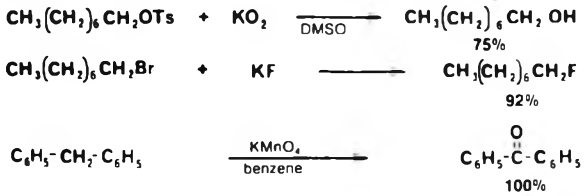
The crown ethers are probably some of the most fascinating compounds investigated in recent years. Their remarkable ability to form stable cation complexes, particularly with the alkali or alkaline earth cations, has led to some truly amazing chemistry.[1] Stability constants of selected cations with 18-crown-6 and 15-crown-5 at 25° in water are illustrated in table I.[2]

Table I

Ligand	Log_{10}Ks for Cations									
	Na	K	Rb	Cs	NH_4	Ag	Sr	Ba	Pb	Tl
15 crown 5	0.70	0.74	0.62	0.8	1.71	0.94	1.95	1.71	1 85	1.23
18 crown 6	0.80	2.03	1.56	0.99	1.23	1.50	2.72	3.87	4 27	2.27

With the exception of the ammonium catcn 18-crown-6 invariably forms more stable complexes than 15-crown-5. Benzo substitution on the crowns leads to more rigid structures with lower solubility and lower stability constants whereas Cyclohexo substitution generally gives increased solubility in nonpolar organics with stability constants about the same as the unsubstituted parent crown. Less polar nonaqueous solvents also give much higher stability constants than aqueous systems. Larger crown ring sizes show increased selectivity for the larger cations.

The crown ethers have shown great utility as catalysts for promoting reactions which would otherwise be impractical or impossible. A few of these reactions are illustrated below: [1]



The improved yields and enchanced reactivity are probably due to a combination of phenomena such as increased reagent solubility, liquid-liquid and solid-liquid phase-transfer, ligand separated ion activation, altered reagent geometry and altered conformation of the transition state or activated complex.

Potential applications exist in such exciting fields as selective decorporation of radioactive or toxic elements such as strontium, thallium and lead from living organisms[3]; models for studies of biological membranes and biological cation transport mechanisms[4]; trace metal carriers in nutrition experiments; construction of ion selective membrane electrodes[5]; studies of the solvated electron in the non-amine solutions[6]; solubilization of photosensitizing dye salts in synthetic applications[7]; solubilization of cationic and anionic dyes for tunable dye laser applications; selective concentration and separation of alkali, alkaline earth, rare earth, actinide, and lanthanide cations[8]; isotope separations; homogeneous base catalyzed polymerizations[9]; homogeneous hindered Lewis acid catalysts for polymerizations and oligimerizations; homogeneous transition metal and noble metal catalysts for oxidations, reductions and carbonylations; starting materials for novel types of drugs and pharmaceuticals[8]. Perhaps a crown ether is the answer to your research problem.

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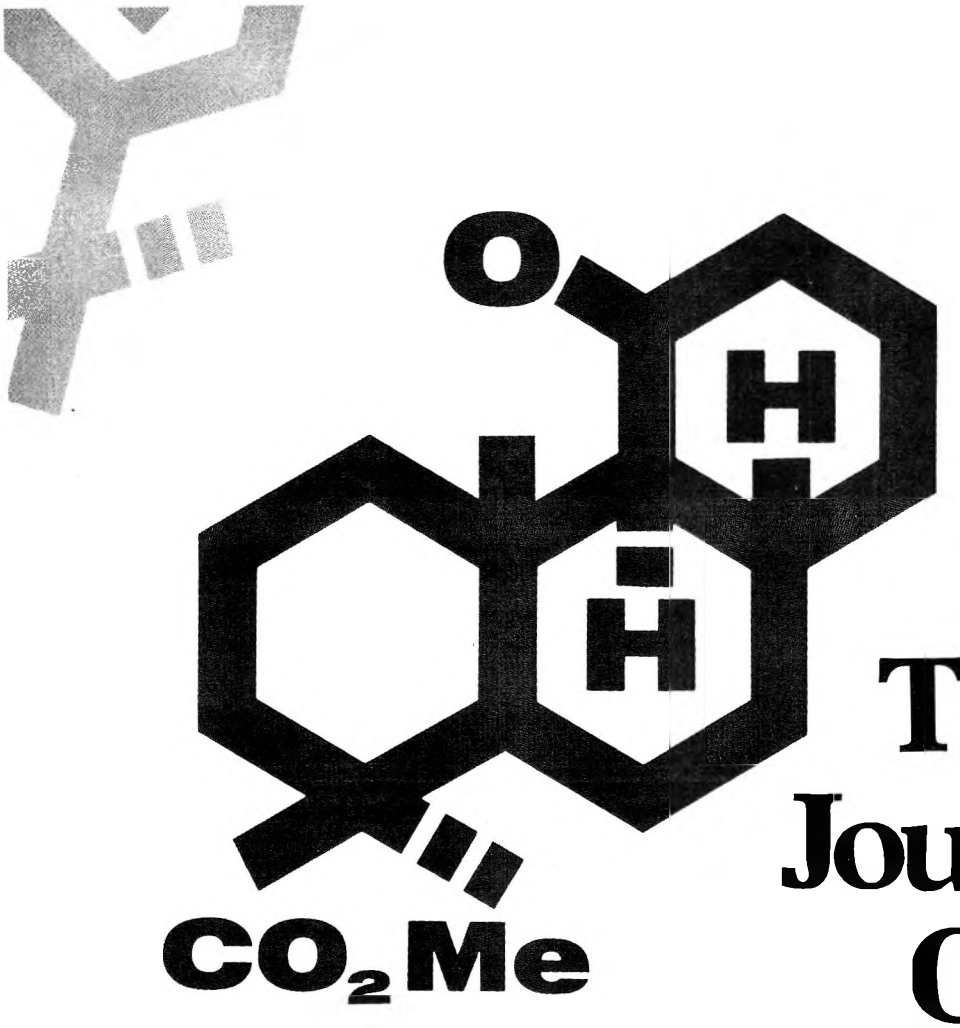

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Trifluoromethanesulfonic Acid Catalyzed Rearrangement of 2- and 4-Homoprotoadamantane to Methyladamantanes and the Existence of Methylprotoadamantane Route. Empirical Force Field Calculations

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Brief treatment of 2-homoprotoadamantane (**10**) with trifluoromethanesulfonic acid gave 4-homoisotwistane (**4**), homoadamantane (**7**), and 2-methyladamantane (**6**), while similar treatment of 4-homoprotoadamantane (**11**) afforded **4**, **6**, 1-methyladamantane (**5**), 2,4-bishomobrendane (**15**), and *endo*-2,8-trimethylene-*cis*-bicyclo[3.3.0]octane (**14**), but no trace of **7**. The absence of **7** in the latter reaction mixture precludes the possibility of intermediacy of **7** as the source of **6**. Instead, methylprotoadamantanes (**9**) are suggested to form transiently and directly from **11** by ring contraction and give rise to **5** and **6**. Reaction mixture composition from **10** can be rationally explained by assuming the intermediacy of 2-homoadamantyl cation (**7a**), the product of one 1,2-alkyl shift in **10**, but the possibility of intermediacy of 3-methylprotoadamantane (3-Me-**9**) as the direct source of **6** cannot be excluded. Proposed mechanisms agree well with empirical force field calculations on the enthalpies of formation and geometry of cations.

In the course of the study on acid-catalyzed multistep rearrangement of tricycloundecanes, it has been established[1,2] that isomers such as *cis-exo-* and *cis-endo*-2,3-tetramethylenenorbornane (**1**), *cis*-2,3-trimethylenebicyclo[2.2.2]octane (**2**), and *cis-endo*-6,7-trimethylenebicyclo[3.2.1]octane (**3**) first isomerize to a stable intermediate, 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane, **4**), which then rearranges to the final equilibrium mixture of 1- and 2-methyladamantane (**5** and **6**) upon prolonged treatment with catalyst (Scheme I).

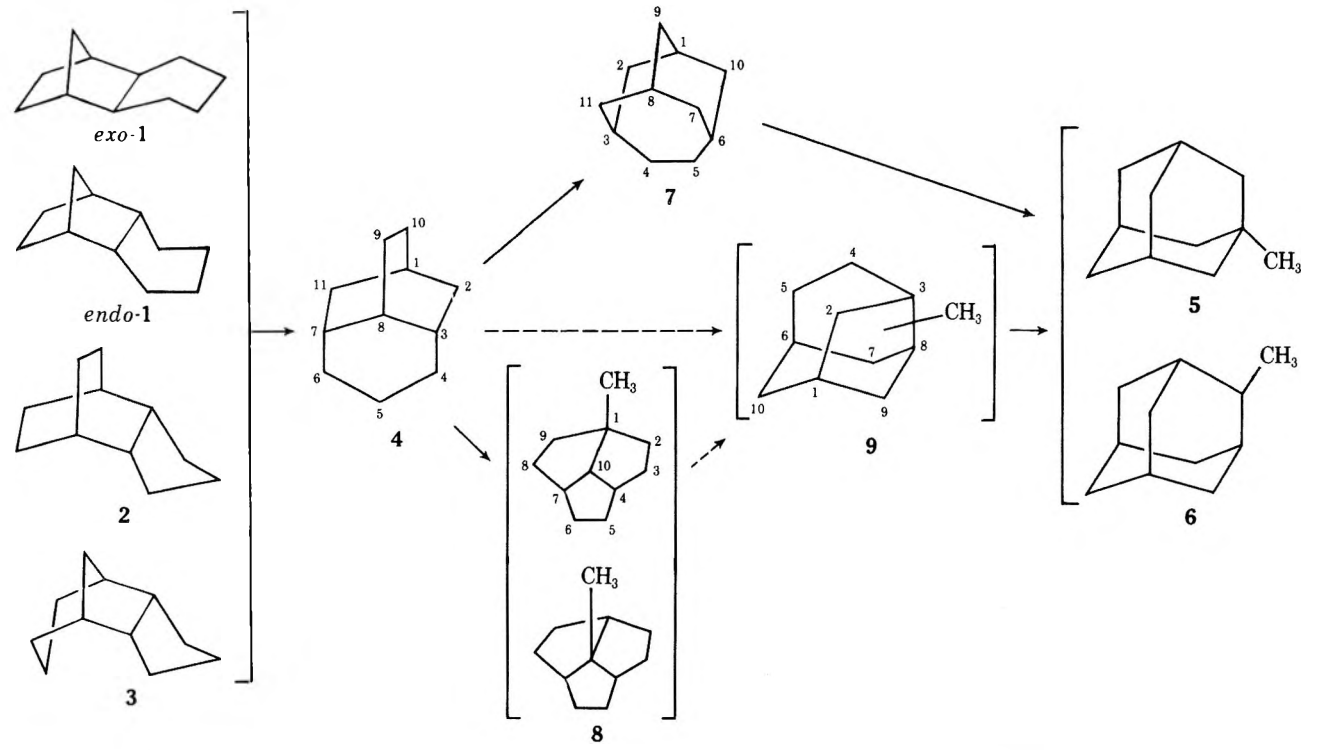
Complex pathways connecting **1**[2d,3] and **2**[2e] to **4** were recently elucidated experimentally[2d,e] as well as theoretically.[3] However, there remains much to be clarified on the reaction sequence from **4** to methyladamantanes. One of the most intriguing problems associated with the "later" rearrangement paths that start from **4** is at which stage of the rearrangement the methyl group is extruded out of the ring system. Thermodynamically, the extrusion of a methyl group should be slightly exothermic.[4] The activation energy of the methyl extrusion step is, however, supposed to be relatively high because of the primary carbonium ion character of the transition state,[3] and for this reason the step is kinetically unfavorable. As a consequence, the methyl extrusion process is postponed until very late stages of the multistep rearrangement sequence unless especially favorable conditions are provided.

Homoadamantane (**7**) has long been known to participate in such methyl extrusion steps.[5] 4-Homoadamantyl cation (**7b**, Scheme V) rearranges directly into **6**[5a,6] and 3-homoadamantyl cation into **5**.[5b,c] However, homoadamantane does not seem to be the only entrance into methyladamantanes, because two methyl-bearing intermediates, 1- and 10-methylperhydrotriquinacene (**8**, Scheme I), have recently been isolated from the rearrangement mixture.[6]

In analogy with the tricyclodecane rearrangement sequence, where protoadamantane is the last intermediate before adamantane,[7,8] methylprotoadamantanes (**9**, Scheme I)[9] appear to be potential penultimate isomers in the tricycloundecane rearrangement. Schleyer[1a] has already indicated this possibility on intuitive grounds. Methylprotoadamantanes (**9**) are also claimed to be the most plausible intermediates in the conversion between 1- and 2-methyladamantane.[10] However, none of the ten isomers of **9** has ever been detected in the tricycloundecane rearrangement,[1-3] and this situation prompted us to design some experiments to clarify the expected role of **9**.

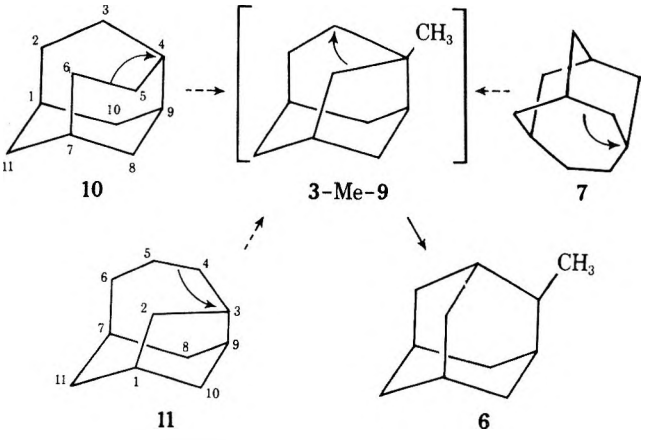
We chose 3-methylprotoadamantane (3-Me-**9**) as the target molecule because of two related reasons (Scheme II). Firstly, it is predicted to be the most stable of the six methylprotoadamantane isomers that lead to 2-methyladamantane (**6**) in single protoadamantane–adamantane rearrangement.[9] Secondly, 2-methyladamantane, rather than the 1-methyl

Scheme I



isomer (**5**), is considered a major entrance into the methyladamantane mixture, since **6** usually accumulates faster than **5** in the initial phases of many tricycloundecane rearrangements.[2,5] Three tricycloundecane isomers may give rise to 3-Me-**9** in one methyl extrusion process (Scheme II). They are **7**, 2-homoprotoadamantane (tricyclo[5.3.1.0^{4,9}]undecane, **10**),[11] and 4-homoprotoadamantane (tricyclo[5.3.1.0^{3,9}]undecane, **11**).

Scheme II



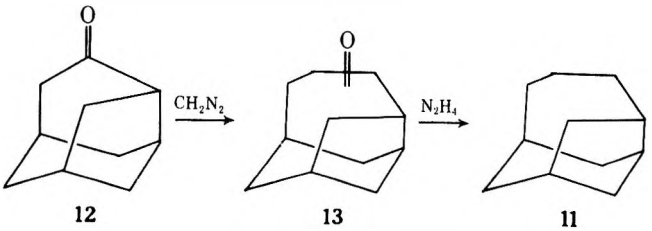
Rearrangement of **7** and related derivatives has already been studied extensively, but no trace of **9** was detected.[5] We describe here the rearrangement of **10** and **11**. However, any methyl extrusion in these compounds, if it occurs, may not necessarily represent the process actually occurring in the overall rearrangement, since **10** and **11** were not found among intermediates.[1,2] Nevertheless, the reaction is considered worth studying because it is a good probe for the process which has never been realized experimentally.

Results

Rearrangement of 2-Homoprotoadamantane (10). **10** was isomerized in methylene chloride solvent in the presence of trifluoromethanesulfonic acid to produce **4**, **6**, and **7** (Table I), as analyzed on Golay GC/MS.[2] No sign was seen of the formation of **9** in this rearrangement. Monotonous increase in the amount of the products suggests that they are formed almost directly from **10**. Other products and their distributions detected in minor amounts in later periods of the reaction were similar to those obtained in the rearrangement of **4**.[2d] These minor products, therefore, most probably originate in the once-formed **4**.

Rearrangement of 4-Homoprotoadamantane (11). **11** was prepared from protoadamantan-4-one (**12**)[12,13] through ring enlargement with diazomethane[14] followed by Wolff–Kishner reduction of the resulting ketone mixture (**13**, Scheme III). Structure **11** of the reduction product was confirmed by

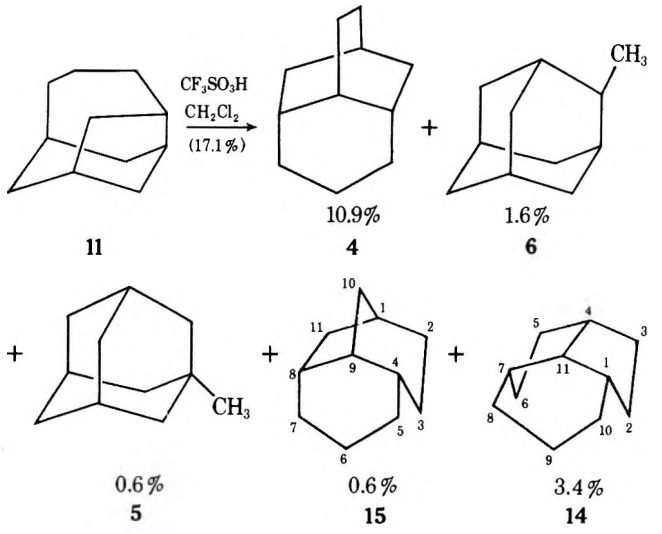
Scheme III



mass (*m/e* 150) and ^{13}C NMR spectra (no element of molecular symmetry).

11 was refluxed in methylene chloride with 1 molar equiv of trifluoromethanesulfonic acid for 3 min. Under these conditions, only 17.1% of the starting **11** isomerized to a mixture of **4**, **5**, **6**, *endo*-2,8-trimethylene-*cis*-bicyclo[3.3.0]octane (**14**),[2e] and 2,4-bishomobrendane (**15**)[15] (Scheme IV). Other isomers which should be produced from and equilibrated with the once formed **4** under prolonged treatment with the catalyst[2] were not detected in this reaction mixture. Therefore, the reaction conditions employed can be considered mild enough to render little possibility of the secondary conversion of the immediate isomerization products. In sharp contrast to the rearrangement of **10**, **7** was not detected at all. We believe that the *absence* of **7** in the reaction mixture is noteworthy in connection with the rearrangement mechanism discussed below.

Scheme IV



Discussion

No methylprotoadamantane (**9**) was actually detected in the present experiments. However, the formation of **6** in the rearrangement of **11** under essentially kinetically controlled conditions seems to indicate the intermediacy of 3-Me-**9** as shown in path b of Scheme V. The possibility of the formation of **6** by way of **4** can be excluded by the fact that no other product of the secondary conversion of **4**[2d] was detected except for **14** (see below). On the other hand, if **6** were formed from **7** (Scheme V), **7** should also have been detected in the reaction, as it *was* detected in the rearrangement of **10** under similar reaction conditions (Table I). Thus we speculate that the path a, which would have led to 2-homoadamantyl cation (**7a**),[5b] never took place in the present reaction of **11**. 3-Me-**9** is then the most plausible intermediate in the proposed two-step isomerization of **11** to **6**.

The small amount of **5** is likely to have formed along a similar pathway as that to **6**, namely, via either 6-Me-**9** along path c or *endo*-4-Me-**9** along path d, or both. An alternative possibility for the formation of **5**, that by a secondary conversion of once-formed **6**, should be negligible, since **5** was entirely absent in the reaction mixtures from **10** which contain **6** (Table I). Indeed slow interconversion between **5** and **6** under trifluoromethanesulfonic acid catalysis has been well established.[2]

Since path a is crossed out in the rearrangement of **11**, at least under the present reaction conditions, the observed formation of **4** cannot be explained by way of **7**,[5b] and an alternative path e from **11**-8-yl cation may be invoked. The same cation seems to explain also the formation of **15** (path f), as discussed below.

14, formally designated as unknown D,[2] has been frequently observed in many of the tricycloundecane rearrangements and considered to belong to one of those "dead end" intermediates which equilibrate with the stable intermediate **4**.[2,3] However, the ratio of **14** to **4** observed in the present study (1:3) is much larger than the equilibrium ratio (1:10),[2] and this is one of the reasons why the route to **14** via **4** is neglected in Scheme V. We suggest path g by way of **15a** to be the major route to **14** by taking advantage of the likelihood that the last of the observed products, **15**,[15] may well be the result of one-step isomerization of **11** along path f.

The product distribution in the rearrangement of **10** (Table I) indicates that this isomerization is rather simple and straightforward, giving 2-homoadamantyl cation (**7a**) as the major intermediate (according to path h). The observed products can be explained fully by this cation, since the behavior of **7** and its various cations in the rearrangement is well understood.[5] Thus **7a** leads to **4** via path i. **7a** readily gives 4-homoadamantyl cation (**7b**) by 1,3-intramolecular hydride shift,[5b,c] and the ring contraction path j from **7b** to **6** is well established by isotope experiments.[5a] Path k, an alternative route to **6**, may not be excluded in view of the intermediacy of 3-Me-**9** in the reaction of **11**, as inferred above.

3-Homoadamantyl cation is considered to be the major precursor of **5** in the rearrangement of **7**.[5b,c] The absence of **5** in the reaction mixture from **10**, therefore, may be taken to indicate that the formation of 3-homoadamantyl cation[5c] either by 1,2-intramolecular hydride shift[16] in **7a** or by hydride abstraction from neutral **7**[5b] is slow compared to other competing processes mentioned above.[17]

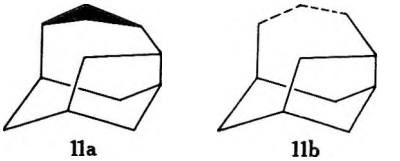
Table I. Products of the Rearrangement of 2-Homoprotoadamantane (10)[a]

Reaction time, min	Product,[b] %[c] 4	6	7	10[d]	Others[e]
5	3.7	1.2	18.7	76.4	
20	7.5	2.3	35.8	53.3	1.1
270	11.6	4.4	68.1	13.6	2.3

[a] 7 mg (0.05 mmol) of **10**, 25.2 μL (0.3 mmol) of CF_3SO_3H, and 5 mL of CH_2Cl_2. [b] Identified on Golay GC/MS. [c] Calculated from Golay VPC peak area. [d] Unreacted starting material. [e] Secondary rearrangement products. See text.

Molecular Mechanics Calculations. One of the key issues emerged from the present experiments is the fact that 2-homoadamantyl cation (**7a**) does *not* form from **11** (path a, Scheme V), a puzzling observation which can hardly be rationalized by merely examining conventional molecular models. No less intriguing is the detection of only a few products of rearrangement from both **10** and **11** despite many other, formally possible paths from these two starting materials (Chart I and II). We therefore performed extensive molecular mechanics calculations in order to gain insight into these puzzles.

Among two conformers of **11**, the endo form (**11a**) is calculated to be of about 2 kcal/mol lower enthalpy than the exo

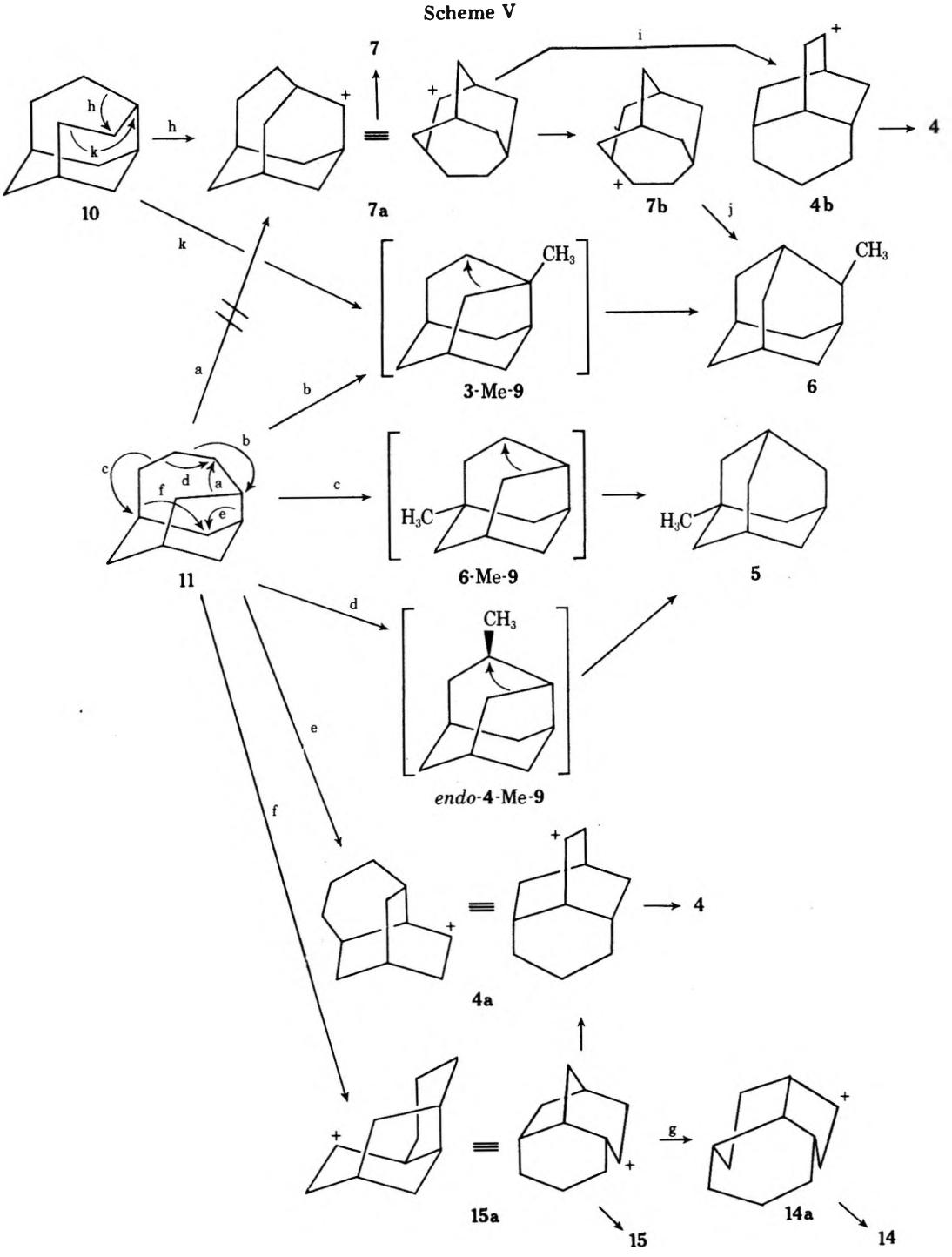


	11a	**11b**
ΔH_f° (calcd), kcal/mol E'[8a]	−21.61	−19.16
A'[8b]	−20.35	−18.65

form (**11b**). Although the calculated energy difference is barely outside the accuracy of the calculation,[18a] it is large enough to shift the conformational population largely to **11a** around room temperature and the subsequent analysis of **11** is based on the endo form **11a**. Chart I and II summarize energetic and geometric conditions for all the possible 1,2-alkyl shifts that start from various cations of **11a** and **10**. Energy terms considered are enthalpies of formation ($\Delta\Delta H_f^\circ$) of both starting and product cations relative to *tert*-butyl cation.[19,21] For "methyl extrusion" processes, $\Delta\Delta H_f^\circ$ could not be calculated, as force field parameters for the bridged ion intermediate or the transition state corresponding to concerted mechanism[3] are unknown. The available energetic criterion of the methyl extrusion process is the calculated heats of formation of methylprotoadamantanes.[3,9]

It has been recognized[3] that a geometric factor, the dihedral angle between the vacant orbital of carbonium ion center and the adjacent σ orbital about to migrate, is as important as

Scheme V

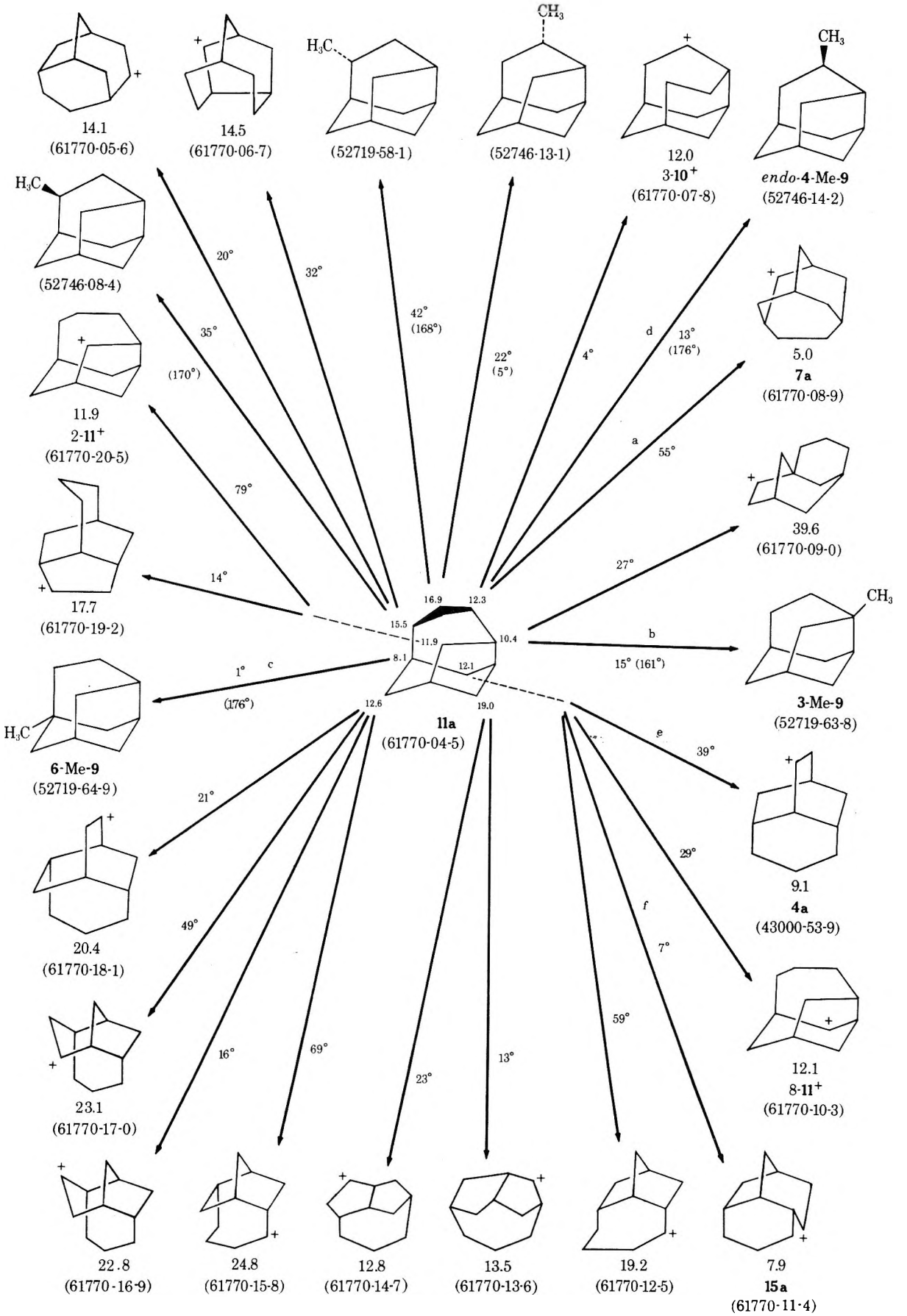


$\Delta\Delta H_f°$ in determining the course of the alkyl shift. The closer the angle to zero, the less will be the strain increase in the transition state of the 1,2-alkyl shift. These angles were estimated from the energy minimum structure of appropriate cations of **11a** and **10**. For the possible concerted mechanism of "methyl extrusion" process,[3] the dihedral angle between leaving and migrating bond should favorably be 180° as in the ideal trans-periplanar orbital disposition. The "trans" dihedral angles were estimated from calculated energy minimum structure of **11a** and **10** and given in Charts I and II in parentheses.

The analysis provides truly useful information related to the experimental observations presented above. Most of the 1,2-alkyl shift possibilities involve either too large an interorbital angle or too unstable a cation (or both). They are unlikely to occur,[3,7] and consequently only a few paths remain available to the first steps of rearrangement, in accordance with the observation of only six kinds of products in the initial phases of both reactions.

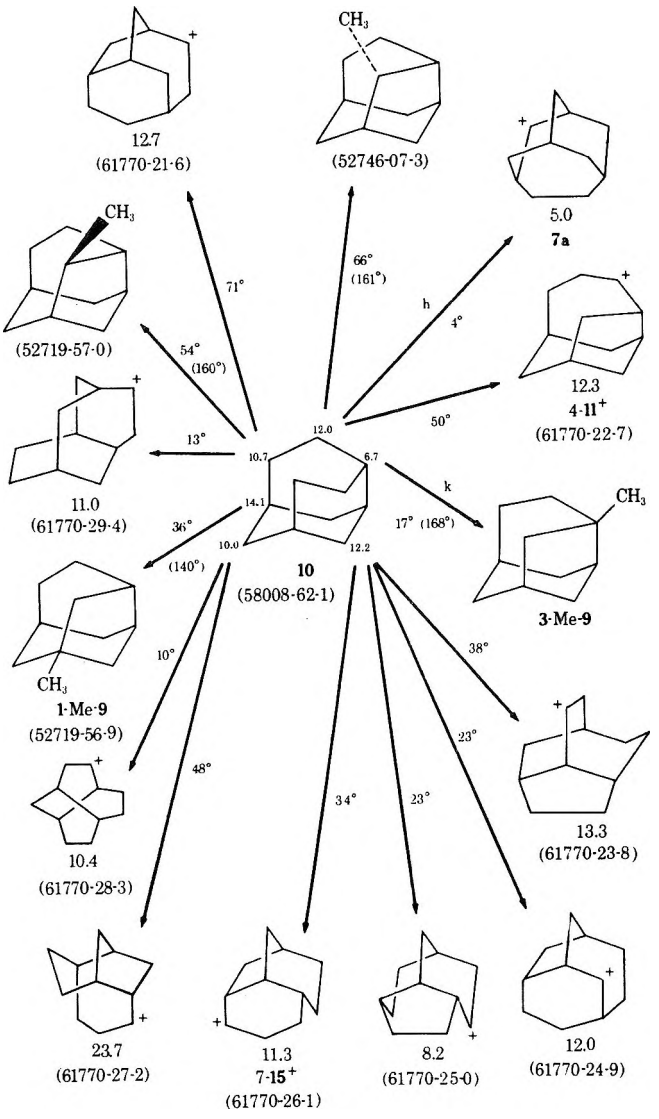
Concerning the rearrangement of **11a**, we first note that 2-homoadamantyl cation (**7a**) is energetically the most favorable ($\Delta\Delta H_f°$, 5 kcal/mol) among all the possible isomerization products, but this ion must be arrived at through an extremely unfavorable interorbital angle of 55° between the vacant orbital at C_4 and the C_2–C_3 bond of 4-**11a**$^+$. The barrier is high enough to exclude the possibility of reaching **7a** by path a in view of the fact that a 60° interorbital angle is regarded as an unsurmountable obstacle in the 1,2-alkyl shift on a rigid cage molecule.[10,16] The most favorable path as judged by the three criteria given in Chart I is e leading to **15a**, and thus this path is very likely the one which gave **15**. Other paths as theoretically feasible as e are b and c leading to 3-Me-**9** and 6-Me-**9**, respectively. Ready formation of bridgehead carbonium ions at C_3 and C_7 of **11a** ($\Delta\Delta H_f°$ = 10.4 and 8.1 kcal/mol, respectively) certainly assists the processes along these paths, in addition to favorable interorbital angles. We think that

Chart I



[a] Calculated heats of formation of cations $\Delta\Delta H_f^\circ$ (kcal/mol, 25 °C, relative to *tert*-butyl cation) and dihedral angle between vacant orbital of cationic center and adjacent, migrating σ bond in all possible 1,2-alkyl shifts on 4-homoprotoadamantane (11a) by Engler force field.[18a,19,21] Angles in parentheses correspond to concerted mechanism of methyl extrusion, for which trans-periplanar disposition (180° dihedral angle) between leaving and migrating orbitals in ideal. [b] Registry no. are in parentheses.

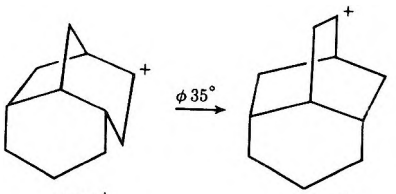
Chart II



[a] Calculated heats of formation $\Delta\Delta H_f°$ and interorbital angles of cations in all possible 1,2-alkyl shifts on 2-homoprotoadamantane (10) by Engler force field. See Chart I for explanation. [b] Registry no. are in parentheses.

these computational results lend further support to the methylprotoadamantane route.

Somewhat annoying in relation to the proposed reaction scheme (Scheme V) is the relatively large interorbital angle (39°) calculated for path e, which we expected to lead to the most abundant product 4 in one step, even though $\Delta\Delta H_f°$ values of both starting and product cations for path e are certainly favorable. An alternative way of obtaining 4 is suggested in eq 1. $\Delta\Delta H_f°$ values are satisfactorily low. The interorbital angle (35°) cannot be regarded as very favorable; nevertheless one may expect some lowering in activation energy from the neighboring methylene assistance similar to that observed in 2-bicyclo[3.2.1]octyl cation.[22]



(1)

	2-15+	10-4+
$\Delta\Delta H_f°$ (calcd), kcal/mol	11.2	9.1

The path g suggested in Scheme V to give the second most abundant product 14 is confirmed to involve a fairly favorable interorbital angle (13°) in 10-15+ ($\Delta\Delta H_f°$, 8.4 kcal/mol).

Among various possibilities of first steps in the rearrangement of 10, the formation of 7a by path h is clearly proved to be very favorable by our steric criteria. With the lowest interorbital angle (4°) and the lowest enthalpy of cation formation (5 kcal/mol), this path is most likely to represent the major source of observed 4 and 6. Force field calculations further support the suggested possibilities of the intermediacy of 3-Me-9 by path k as an alternative source of 6. Namely, 4-10+ is calculated to have the lowest enthalpy of formation (6.7 kcal/mol) among various 10 cations and the interorbital angle for methyl extrusion leading to 3-Me-9 to be in favorable range. 1-Me-9, the only potential intermediate from 10 leading to 1-methyladamantane (5), is less likely to form because of high $\Delta\Delta H_f°$ and a large interorbital angle in 11-10+. These results do not contradict the observed absence of 5 in the reaction of 10.

Conclusion

The failure to detect any methylprotoadamantanes in this study appears to have nullified the attempt to obtain direct evidence on their intermediacy in the rearrangement. However, absence of homoadamantane (7) in the reaction of 11 and presence of potentially favorable paths going through methylprotoadamantanes constitute indirect evidence that supports strongly the hypothetical intermediacy of methylprotoadamantanes. This evidence should be understood to suggest, but not to demonstrate, the role of methylprotoadamantanes as the last intermediate of the overall C_{11} rearrangement, since the inference was made on the basis of the isomerization of 11 which was not found among intermediates of the overall rearrangement. Further efforts will be concentrated on the study of the role of recently identified methylperhydrotriquinacenes (8) in the rearrangement, in order to clarify other aspects of the methyl extrusion process.

Experimental Section

Conventional VPC, Golay column GC/MS, ^1H and ^{13}C NMR, and mass spectrometry were made with the same instruments as in the previous works.[2] Rearrangement reactions of homoprotoadamantanes with 1 molar equiv of CF_3SO_3H and product analyses were conducted similarly as before.[2]

Computer calculations with program STRAIN[18a] were done on UNIVAC 1100 (Kao Soap Co.) and FACOM 230-75 (Hokkaido University).

4-Homoprotoadamantane (11). A solution of 6.0 g of potassium hydroxide in 30 mL of 50% aqueous methanol was added dropwise with efficient stirring to a mixture consisting of 15.0 g (0.1 mol) of protoadamantan-4-one, 51.4 g (0.24 mol) of *N*-nitroso-*p*-toluenesulfonamide, 150 mL of methanol, and 6 mL of water, while the reaction temperature was kept between 10 and 20 °C. The reaction mixture was stirred at the same temperature for an additional 3 h. The mixture was made acidic by the addition of 2 N hydrochloric acid. Methanol was distilled off from the mixture, and the residue was diluted with 100 mL of water. The mixture was extracted with three 200-mL portions of petroleum ether. Combined extracts were washed with 1% sodium hydrogen carbonate and then with water, and dried over anhydrous sodium sulfate. Solvent was evaporated off, and the residue was passed through an alumina column (eluted with benzene). The eluent was further purified on preparative VPC to give two fractions (ca. 3:2 area ratio) corresponding to homoprotoadamantanone (*m/e* 164).

The earlier eluted fraction: IR (Nujol) 1695, 1250, 1140, 1040, 980, 920 cm^{-1}; mass spectrum *m/e* (rel intensity) 164 (60, M^+), 108 (75), 107 (47), 95 (100), 93 (68), 81 (59), 80 (47), 79 (100), 68 (74), 67 (57), 41 (86).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.6; H, 9.7.

The later eluted fraction: IR (Nujol) 1695, 1320, 1310, 1260, 1200,

1130, 1050, 1020, 810 cm^{-1}; mass spectrum *m/e* (rel intensity) 164 (46, M^+), 109 (42), 96 (100), 83 (58), 80 (50), 79 (98), 67 (96), 66 (75), 41 (50).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.6; H, 9.8.

A mixture of 3.3 g (0.02 mol) of the combined VPC fractions of homoprotoadamantanone obtained above, 93 g (0.165 mol) of potassium hydroxide, 10 mL (0.207 mol) of 100% hydrazine hydrate, and 100 mL of diethylene glycol was heated under gentle reflux (ca. 160 °C) for 3 h. The reaction temperature was elevated gradually to 220 °C while water formed was distilled off, and the mixture was refluxed for an additional 2 h at that temperature. Combined reaction mixture and distillate were diluted with 100 mL of a saturated sodium chloride solution and extracted with three 50-mL portions of *n*-hexane. Combined hexane extracts were washed with two 50-mL portions of water and dried over anhydrous magnesium sulfate. Evaporation of the solvent and purification of the residue by sublimation under slightly diminished pressure gave 1.3 g (42% yield) of a pure sample of 4-homoprotoadamantane (**11**): mp 129–130 °C; IR (neat) 2910, 2850, 1460, 1230, 1100, 1020, 920, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.4 (complex m); ^{13}C NMR ($CDCl_3$) δ_C 21.0 (t), 27.3 (t), 29.3 (d), 32.8 (t), 34.1 (d), 34.7 (t), 35.9 (d), 37.2 (t), 37.5 (t), 37.7 (d), 40.8 (t); mass spectrum *m/e* (rel intensity) 150 (86, M^+), 135 (44), 107 (44), 94 (54), 93 (65), 81 (62), 80 (68), 79 (100), 67 (86), 55 (46), 41 (78).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 88.1; H, 12.0.

Acknowledgment. We thank Professor P. v. R. Schleyer for a copy of program STRAIN, and Dr. E. M. Engler for instruction on the carbonium ion calculations.

Registry No.—**4**, 43000-53-9; **6**, 700-56-1; **7**, 281-46-9; 12, 27567-85-7; **13** isomer 1, 61770-30-7; **13** isomer 2, 61770-31-8; trifluoromethanesulfonic acid, 1493-13-6.

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Selective Formation of Biaryls via Interaction of Polynuclear Arylcopper Compounds with Copper(I) Trifluoromethanesulfonate [Copper(I) Triflate][1]

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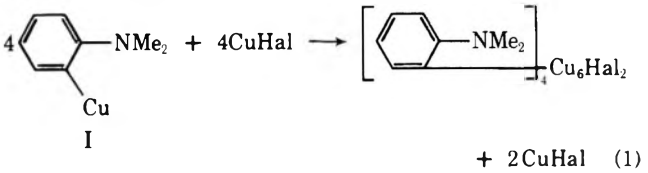
Selective formation of biaryls is observed upon interacting well-defined arylcopper cluster compounds (2-$Me_2NCH_2C_6H_4)_4Cu_4$, (4-$MeC_6H_4)_4Cu_4$, (2-$Me_2NC_6H_4)_4Cu_6Br_2$, and (2-$Me_2NC_6H_4)_4Cu_6OTf_2$ with equimolar amounts of CuOTf in benzene. It is shown that complex formation of the arylcopper cluster with CuOTf precedes the C–C-coupling process. In some cases these complexes are sufficiently stable to be isolated, e.g., (2-$Me_2NC_6H_4)_4$-Cu_6OTf_2 (from the 2/1 reaction of 2-$Me_2NC_6H_4Cu$ with CuOTf). Decomposition of the 2-MeC_6H_4Cu/CuOTf complex with NH_3/H_2O in the presence of oxygen affords, in addition to toluene and 2,2′-bitolyl, 2-$H_2NC_6H_4Me$ and 2-HOC_6H_4Me. The formation of the arylcopper–CuOTf complexes and hence biaryl formation can be inhibited by suitable ligands such as PPh_3. In the absence of built-in ligands in the arylcopper compound, e.g., (4-$MeC_6H_4)_4Cu_4$, the reaction with CuOTf can be made catalytic in CuOTf. The selective C–C-coupling reaction has been explained in terms of intraaggregate electron-transfer processes occurring in the intermediate arylcopper–copper triflate complexes. A mechanism is proposed based on valence disproportionation inside the copper core induced by charge transfer from the core to the electron-accepting OTf anions.

The 1/1 reaction of polymeric 2-(dimethylamino)phenylcopper[3] (I) with cuprous halides affords stable hexanuclear copper complexes which have $R_4Cu_6Hal_2$ stoichiometry.[4] The interaction of 2-[(dimethylamino)methyl]phenylcopper[5] (II) with cuprous halides gives rise to the formation of polymeric complexes with $(R'Cu{\cdot}CuHal)_n$ stoichiometry.[6] Both types

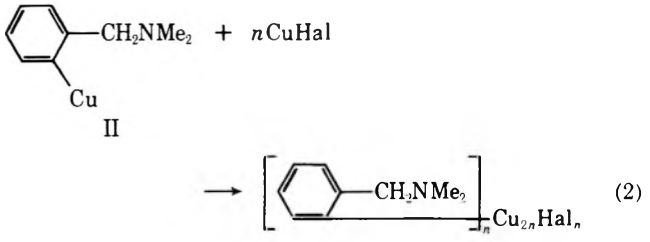
Table I. Interaction of 2-$Me_2NCH_2C_6H_4Cu$ and 2-$Me_2NC_6H_4Cu$ with $(CuO_3SCF_3)_2 \cdot C_6H_6$ in Benzene

Reagents[a]	Added ligands	Reaction time, h	Products[b] RR	RH	Others
R = 2-$Me_2NC_6H_4$					
RCu/CuOTf[c] (2/1)		48	0	0	$R_4Cu_6OTf_2$ 80
$R_4Cu_6OTf_2$/CuOTf (1/2)		24	91	9	*d*
RCu/CuOTf (1/1)		48	85	15	*d*
RCu/CuOTf (1/0.1)		288	*e*	*e*	$R_4Cu_6OTf_2$/RCu
RCu (1/4)	PPh_3	24			
CuOTf (2)		72	0	0	RCu·3CuOTf·6PPh_3[f]
RCu (1/3)	PPh_3	48	0	0	No reaction
$R_4Cu_6Br_2$/CuOTf (1/4)		48	97	Trace	CuBr[d]
R' = 2-$CH_2NMe_2C_6H_4$			R'R'	R'H	Others
R'Cu/CuOTf (1/1)		48	100	N.D.[g]	
R'Cu/CuOTf (2/1)		3[h]	0	0	*i*

[a] Molar ratio of the reagents are given in parentheses. [b] Yield (%) calculated on the total amount of R (or R') in the starting organocopper. [c] Pure benzene complex of CuOTf, $(CuOTf)_2 \cdot C_6H_6$, has been used. [d] Quantitative amounts of Cu^0 were formed. After the reaction the total amount of CuOTf was present in the form of a complex with RR and RH. [e] Small amount of RH (< 10%) was present in solution. Heating of the reaction mixture at 80 °C for 12 h afforded 75% R as RH and 25% R as RR (for comparison: the thermal decomposition of pure I in DMF gives 60% R as RH and 40% R as RR[8e]). [f] Composition of the solid isolated (18% yield) from the reaction mixture; see Experimental Section. [g] Not detectable by NMR or by GC/MS. [h] CuOTf was added to II at −20 °C. [i] Yellow solid with 3R'Cu·2CuOTf stoichiometry (elemental analysis; NMR in pyridine confirmed 3/2 molar ratio) was isolated.



+ 2CuHal (1)

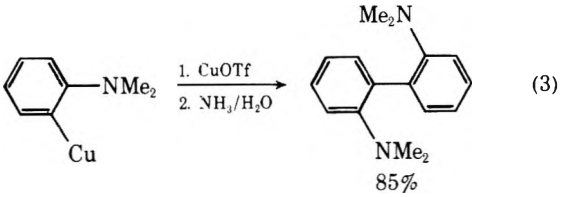


(2)

of complexes are stable in the presence of an excess of cuprous halide.

During a study of the interaction of I with copper triflate (CuOTf)[7] we noted that depending on the I/CuOTf molar ratio either stable complexes of the type $R_4Cu_6OTf_2$ were formed (2/1 molar ratio) or decomposition of the arylcopper with formation of metallic copper occurred (1/1 molar ratio). The results of a study of the 2/1 reaction have been published elsewhere.[2] The high stability of $R_4Cu_6OTf_2$ has been ascribed to the geometry of the 2-(dimethylamino)phenyl ligands which each are capable of spanning three copper atoms of the octahedral copper core thus stabilizing the $R_4Cu_6^{2+}$ unit.[2]

A study of the products formed in the 1/1 reaction of 2-$Me_2NC_6H_4Cu$ with CuOTf revealed that a selective coupling of the 2-(dimethylamino)phenyl ligands had taken place. While studies concerning carbon–carbon bond formation via interaction of organocopper intermediates with *divalent* copper salts have recently been reported,[6,8] to our knowledge



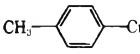
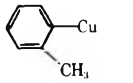
(3)

this is the first example of selective coupling of organic groups achieved by interaction of organocopper compounds with a *monovalent* copper salt. In view of the scant knowledge about the relation between reactivity and structure of organocopper intermediates we have studied this reaction in greater detail. Three other, structurally different, arylcopper compounds, 2-$Me_2NCH_2C_6H_4Cu$ (II), 4-MeC_6H_4Cu[9] (III), and 2-Me-C_6H_4Cu[9] (IV), have been included in this study.

Results

The results of the reaction of 2-$Me_2NC_6H_4Cu$ (I) and 2-$Me_2NCH_2C_6H_4Cu$ (II) with CuOTf are presented in Table I. The reaction of I with CuOTf afforded well-defined $R_4Cu_6OTf_2$ (V)[2] in 80% yield. At I/CuOTf molar ratios between 2/1 and 1/1 metallic copper was formed during the reaction. NMR spectra of a 1/2 reaction mixture of $R_4Cu_6OTf_2$ with CuOTf in benzene-d_6 revealed that in addition to metallic copper 2,2'-bis(dimethylamino)biphenyl (VI) and *N,N*-dimethylaniline (VII) had formed. The chemical shift data as well as the broadening of the NMe_2 proton resonances of VI and VII indicated that these products were present in solution as their complexes with CuOTf.[10] Decomposition of these complexes by workup procedures involving extraction of the reaction mixture with NH_3/H_2O solution afforded a mixture of uncomplexed VI and VII. GC/MS analysis revealed that the dimer VI was formed in 91% and the arene VII in 9%

Table II. Interaction of *o*- and *p*-Tolylcopper with CuOTf in Benzene

Reagents[a]	Workup conditions	Products[b]			
		x,x'-Bitolyl	Toluene	Other	
		*x* = *x'* = para			
p-TolCu/CuOTf[c] (1/1)		95[d]	0	0	
p-TolCu/CuOTf (1/0.1)		100[d]	0	0	
		*x* = *x'* = ortho		*o*-H_2NTol	*o*-HOTol
o-TolCu/CuOTf (1/1)	$NH_3/H_2O/O_2$[e]	20	40	10	17[f]
o-TolCu/CuOTf (1/1)	$NH_3/H_2O/N_2$[g]	±20	±80	<1	<1

[a] Molar ratio of the reagents given in parentheses. [b] Yield (%) calculated on the total amount of tolyl in the starting tolylcopper. [c] $(CuOTf)_2 \cdot C_6H_6$ has been used. [d] Quantitative amount of Cu^0 is formed. [e] Reaction time 5 h; workup in the presence of air oxygen. [f] Minor amounts of ditolyl ether (most probably the 2,2' isomer) were detected by GC/MS. [g] NH_3/H_2O solution added under N_2 atmosphere; reaction mixture stirred for 1.5 h before the final workup procedure in air was carried out.

yield (calculated on the amount of R in I).

$$4\ \underset{\text{I}}{2\text{-Me}_2\text{NC}_6\text{H}_4\text{Cu}} + 2\text{CuOTf} \xrightarrow{C_6H_6} \underset{\text{V}}{(2\text{-Me}_2\text{NC}_6\text{H}_4)_4\text{Cu}_6\text{OTf}_2} \quad (4)$$

$$\text{V} + 2\text{CuOTf} \xrightarrow{C_6H_6} 4\text{Cu}^0 + 4\text{CuOTf} \cdot [(2\text{-Me}_2\text{NC}_6\text{H}_4)_2 \text{ and } \text{Me}_2\text{NC}_6\text{H}_5] \quad (5)$$

The different reactivity of CuOTf toward arylcopper–copper halide compounds is clearly demonstrated by the formation of the dimer VI in 97% yield in the 1/4 reaction of $(2\text{-Me}_2\text{NC}_6\text{H}_4)_4\text{Cu}_6\text{Br}_2$ with CuOTf in benzene [cf. eq 1, which shows that $(2\text{-Me}_2\text{NC}_6\text{H}_4)_4\text{Cu}_6\text{Br}_2$ is stable toward CuBr[4]]. Most probably this reaction involves ligand displacement with retention of the hexanuclear cluster structure [11] followed by the irreversible interaction of $(2\text{-Me}_2\text{NC}_6\text{H}_4)_4\text{Cu}_6\text{OTf}_2$ with CuOTf.[12]

$$(2\text{-Me}_2\text{NC}_6\text{H}_4)_4\text{Cu}_6\text{Br}_2 + 2\text{CuOTf} \rightleftarrows \underset{\text{V}}{(2\text{-Me}_2\text{NC}_6\text{H}_4)_4\text{Cu}_6\text{OTf}_2} + 2\text{CuBr} \quad (6)$$

$$\text{V} + 2\text{CuOTf} \rightarrow 2(2\text{-Me}_2\text{NC}_6\text{H}_4)_2 \cdot \text{CuOTf} + 4\text{Cu}^0 \quad (7)$$

The interaction of I with CuOTf in a 1/1 molar ratio afforded the dimer VI in a significantly lower yield (85%) while the arene VII was formed in 15% yield.

$$\underset{\text{polymer}}{2\text{-Me}_2\text{NC}_6\text{H}_4\text{Cu}} \xrightarrow[-\text{Cu}^0]{\text{CuOTf}} (\text{VI} + \text{VII}) \cdot \text{CuOTf} \xrightarrow[-\text{CuOTf}]{\text{NH}_3/\text{H}_2\text{O}} \text{VI (85\%)} + \text{VII (15\%)} \quad (8)$$

$$\underset{\text{tetramer}}{2\text{-Me}_2\text{NCH}_2\text{C}_6\text{H}_4\text{Cu}} \xrightarrow[-\text{Cu}^0]{\text{CuOTf}} \text{VIII} \cdot \text{CuOTf} \xrightarrow[-\text{CuOTf}]{\text{NH}_3/\text{H}_2\text{O}} \text{VIII (100\%)} \quad (9)$$

The corresponding 1/1 reaction of tetrameric 2-[(dimethylamino)methyl]phenylcopper (II) with CuOTf resulted in the formation of a 1/2 complex of the dimer with CuOTf. Not a trace of the arene could be detected. Hydrolytic workup of the reaction mixture afforded exclusively the dimer 2,2'-bis-[(dimethylamino)methyl]biphenyl (VIII) (100% yield). Accordingly, reaction sequence 9 provides an excellent synthetic route for the synthesis of pure VIII.[13] It is worthy of note that complexes with well-defined $2\text{-Me}_2\text{NCH}_2\text{C}_6\text{H}_4\text{Cu}$/CuOTf ratios are not formed. Insoluble yellow solids with varying II/CuOTf ratios were obtained starting from reaction mixtures with II/CuOTf molar ratios greater than 1.

As is seen from eq 8 and 9, CuOTf is not consumed in the reaction of the arylcopper compounds. Therefore, in principle reactions of this type might proceed in a catalytic fashion. However, complex formation between CuOTf and the biaryl coupling products VI and VIII (cf. ref 10) may account for the fact that this is not observed. Indeed, the reactions of arylcopper compounds I and II with CuOTf were effectively blocked by the presence of other complexing ligands such as triphenylphosphine (see Table I). In separate experiments it was established that this was not due to the formation of arylcopper triphenylphosphine complexes. Surprisingly, both I and II do not interact with triphenylphosphine.[14] In contrast, CuOTf does form a stable 2/1 complex with triphenylphosphine.[10] It is this complex formation which blocks the interaction of CuOTf with the arylcopper compounds.[15]

These observations strongly suggest that in the absence of external or of built-in ligands ($-NMe_2$ or $-CH_2NMe_2$) only catalytic amounts of CuOTf are required to effect the coupling reaction. In order to confirm this hypothesis the interaction of *o*- and *p*-tolylcopper with catalytic amounts of CuOTf was studied. The results are compiled in Table II.

The reaction of *p*-tolylcopper (III) with both stoichiometric and catalytic amounts of CuOTf resulted in the quantitative formation of *p,p'*-bitolyl (IX).

$$4\text{-CH}_3\text{C}_6\text{H}_4\text{Cu} + n\text{CuOTf} \xrightarrow{C_6H_6} \underset{\text{IX, 100\%}}{\tfrac{1}{2}(4\text{-CH}_3\text{C}_6\text{H}_4)_2} + \text{Cu}^0 + n\text{CuOTf} \quad (10)$$

n = 1 or 0.1

NMR spectroscopy unambiguously showed that this reaction involves the intermediate formation of an insoluble $4\text{-CH}_3\text{C}_6\text{H}_4\text{Cu}$/CuOTf complex. Addition of CuOTf to a solution of *p*-tolylcopper in benzene-d_6 causes a complete disappearance of the resonances due to the methyl and the aromatic protons when the CuOTf/III ratio reaches 1/4. NMR spectroscopy further reveals that this insoluble complex decomposes in about 2 h to give *p,p'*-bitolyl as the only product.

Interestingly, using *o*- instead of *p*-tolylcopper different results were obtained. Insoluble purple-colored complexes $(o\text{-CH}_3\text{C}_6\text{H}_4\text{Cu})_x(\text{CuOTf})_4$ were isolated from the reactions of *o*-tolylcopper (IV) with CuOTf in benzene (see Table II).

Attempts to purify these complexes failed. Essentially, no reaction leading to *o,o'*-bitolyl (X) or toluene was observed. An NMR spectrum of a 1/1 mixture of *o*-tolylcopper with CuOTf showed that these complexes are stable at room temperature. After 28 h only minor amounts (<5%) of o,o'-bitolyl were present in solution. It is worthy of note that decomposition of this complex with a NH_3/H_2O solution in the presence of oxygen afforded not only toluene arising from hydrolysis of the organocopper, but also o,o'-bitolyl, 2-aminotoluene (XI), and 2-hydroxytoluene (XII).[16] As shown in Table II the solvolysis products XI and XII are only formed in the presence of oxygen.[17] Addition of NH_3/H_2O to the reaction mixture in a nitrogen atmosphere afforded toluene (80%) and *o,o'*-bitolyl (20%), but not XI and XII.

$$2\text{-}MeC_6H_4Cu + CuOTf \longrightarrow [complex] \xrightarrow[O_2]{NH_3/H_2O} \text{toluene} + \text{o,o'-bitolyl} + 2\text{-}HOC_6H_4Me + 2\text{-}H_2NC_6H_4Me \quad (11)$$

Discussion

Earlier we had observed that interaction of arylcopper compounds Ar_nCu_n with copper halides CuHal results in the formation of complexes $Ar_nCu_{m+n}Hal_m$ which have equal or higher stability as compared with the parent compound. However, the present study reveals that complex formation of ArCu with copper(I) salts of anions with strong electron acceptor properties gives rise to less stable complexes. This observation establishes for the first time that the nature of the counterion has a great influence on the stability of the arylcopper–copper(I) salt complex. A better understanding of this effect is important in view of the interpretation of reactions involving organocopper compounds as intermediates, e.g., the Ullmann biaryl synthesis.

The elucidation of the mode of interaction of CuOTf with arylcopper compounds[20] requires a discussion of the following factors: (1) the structure of the arylcopper compounds before reaction; (2) the nature of the arylcopper–copper triflate interaction including the nature of the electron-transfer processes resulting in product formation.

The Structure before Reaction. The structures of $(2\text{-}Me_2NCH_2C_6H_4)_4Cu_4$[21] as well as of $(2\text{-}Me_2NC_6H_4)_4Cu_6X_2$, X = halide[4] or triflate,[2] in the solid and in solution are well-documented main structural featurs of these compounds being central tetra- or hexanuclear copper cores to which aryl groups are bound via 2e–3c bonds.

Camus and Marsich[9] have reported that the results of molecular weight determinations of *o*- and *p*-tolylcopper were in agreement with low aggregation states (monomers or dimers), but structural details were not given.[22] However, the extreme air sensitivity of *o*- and *p*-tolylcopper as well as the fact that $HCCl_3$[24] and CCl_4 had been used as solvents for the osmometric molecular weight determinations led us to redetermine the molecular weight of these compounds. Cryoscopic molecular weight determinations show that *p*-tolylcopper exists as a tetramer, $(4\text{-}MeC_6H_4)_4Cu_4$, in benzene. In contrast, *o*-tolylcopper exists directly after dissolution in benzene as an apparent hexanuclear species, which equilibrates in about 2 h to a tetranuclear aggregate $(2\text{-}MeC_6H_4)_4Cu_4$. Obviously, in solution the $(2\text{-}MeC_6H_4)_4Cu_4$ aggregate is thermodynamically the most stable. Other examples of tetranuclear copper cluster species are $(Me_3SiCH_2)_4Cu_4$,[25] $(C_6F_5)_4Cu_4$,[26] and $(2\text{-}CF_3C_6H_4)_4Cu_4$.[26] The copper atoms in these compounds are two-coordinate by participating in two 2e–3c C–Cu interactions, whereas in arylcopper compounds containing built-in ligands, such as $(2\text{-}Me_2NCH_2C_6H_4)_4Cu_4$ the copper atoms become three-coordinate by an extra Cu–N coordination bond.[21]

$2\text{-}Me_2NC_6H_4Cu$ is the only arylcopper compound used in this study of which the structure is not known with certainty. The available spectroscopic data[27] strongly support a polymeric structure consisting of 2-(dimethylamino)phenyl groups bridging Cu atoms of one copper chain via 2e–3c Cu–C bonds and coordinating to a copper atom of a second chain via a Cu–N bond.[3]

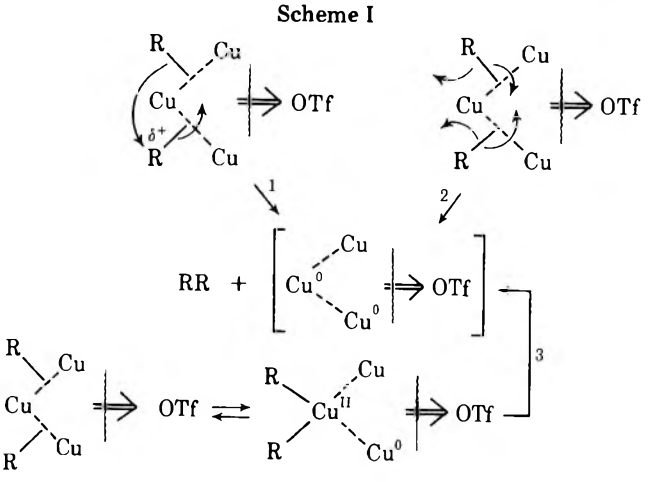
The C–C Coupling. Interaction of CuOTf with organocopper compounds which have a discrete cluster structure $[(4\text{-}MeC_6H_4)_4Cu_4$, $(2\text{-}Me_2NC_6H_4)_4Cu_6Br_2$, $(2\text{-}Me_2NC_6H_4)_4Cu_6OTf_2$, and $(2\text{-}Me_2NCH_2C_6H_4)_4Cu_4]$ results in almost quantitative formation of biaryls. The fact that arenes are formed in less than 9% yield excludes decomposition pathways involving free radicals, but instead points to the occurrence of intramolecular processes leading to pairwise release of aryl groups. It therefore would seem plausible to propose that these processes take place in an arylcopper–copper triflate precursor complex formed by extension of the copper core of the parent organocopper with one or more copper atoms of copper triflate. A representative example of such a complex is $(2\text{-}Me_2NC_6H_4)_4Cu_6OTf_2$. This complex, which has been isolated and characterized, has a structure consisting of an octahedral copper core to which both aryl groups and anions are bound in a well-defined way.[2]

$$Ar_nCu_n + mCuOTf \longrightarrow \underset{\text{precursor complex XIII}}{Ar_nCu_{m+n}OTf_m} \longrightarrow ArAr + 2Cu^0 + Ar_{n-2}Cu_{m+n-2}OTf_{m-2}$$

The driving force in the coupling reaction is charge transfer in the precursor complex XIII from the Ar_nCu_{m+n} skeleton to the strongly electron accepting OTf groups, which reduces the electron density in the Cu_n–C region and thus the kinetic stability of the Cu_n–C bond. The occurrence of Cu_n–C bond weakening as a result of electron transfer can be concluded from the mass spectral fragmentation pattern of $(2\text{-}Me_2NCH_2C_6H_4)_4Cu_4$. The parent ion $R_4Cu_4^{+\cdot}$ undergoes fragmentation to $R_3Cu_4^+$ (most abundant Cu-containing ion) by cleavage of a Cu_4–C bond indicating that an electron from the bridge-bond MO has been removed rather than from the Cu_4 core.[21] This is also illustrated by the formation of biaryl and aryl halide in the reaction of $(2\text{-}Me_2NCH_2C_6H_4)_4Cu_4$ with $Cu^{II}X_2$ which involves inner-sphere-redox reaction in activated complexes of the type $(2\text{-}Me_2NCH_2C_6H_4)_4Cu_4\cdots X\cdots Cu^{II}X(Cu^{II}X_2)_n$.[6]

In the precursor complex XIII aryl groups are at close proximity so that concerted or consecutive Cu–C bond cleavage and C–C bond formation can occur. Three different mechanisms for pairwise release of aryl groups from Cu_n clusters can be envisaged (see Scheme I): (1) two-electron

Scheme I



transfer from one Cu–C bond to the Cu_n cluster resulting in reduction of two Cu^I atoms in the metal core and development of a high degree of carbonium ion character at C(bridge) fol-

lowed by intraaggregate nucleophilic attack of a second Cu–C bond; (2) simultaneous one-electron transfer from two Cu–C bonds to the Cu_n cluster and concomitant coupling of the two aryl radicals or one-electron transfer followed by intraaggregate trapping of the aryl radical by a second Cu–C bond; (3) valence disproportionation inside the metal core followed by reductive elimination of R–R.

Process 3 seems to provide a rationale for the large influence of the type of the anion on the occurrence of coupling reactions because the anions attached to the copper core will affect the potentials of the various copper couples.[28,29] The strong electron-accepting properties of the OTf anion favor the Cu^{II} oxidation state, whereas, for example, the electron-donating halide anions favor the Cu^{I} state. As regards the influence of the type of aryl group on the coupling process the kinetic stability of the Cu_n–C bonding will be optimal when the aryl nucleus is oriented about perpendicular to the Cu–Cu axis thus allowing maximum back-bonding to the aryl nucleus.[21] This orientation is favored for steric reasons[30] in the *o*-methyl substituted aryl derivative whereas in the 2-Me_2N- and 2-Me_2NCH_2-substituted compounds the occurrence of Cu–N coordination further reduces the number of possible rotamers. The lower stability of the precursor complex containing the 2-Me_2NCH_2 grouping as compared with the *o*-methyl substituted complex can be ascribed to coordination of the hard nitrogen ligand to the copper core which favors valence disproportionation by stabilizing the Cu^{II} oxidation state.

Finally, selective biaryl formation can only be expected for precursor complexes $Ar_nCu_{n+m}OTf_m$ in which n equals 2, 4, 6, etc.[31] In case of polymeric or oligomeric arylcopper compounds chains containing both odd and even numbers of aryl groups will be present. Accordingly, for these compounds the formation of a small amount of arene originating from decomposition of chains with n = 3, 5, 7, etc., must be expected. Indeed, interaction of polymeric 2-$Me_2NC_6H_4Cu$ with CuOTf yields in addition to 85% of the dimer 15% of the arene $Me_2NC_6H_5$.

Experimental Section

General. CuOTf·½C_6H_6 was prepared according to the directions given by Salomon and Kochi.[7] *o*- and *p*-tolylcopper and 2-dimethylamino- and 2-dimethylaminomethyl-substituted phenylcopper compounds were prepared by published methods.[3,5,9] The reactions were carried out under dry, oxygen-free nitrogen. Solvents were carefully purified, dried, and distilled before use under nitrogen.

IR spectra were recorded on a Perkin-Elmer 577 grating IR spectrometer. ^1H NMR spectra were recorded on a Varian Associates HA-100 NMR spectrometer. Molecular weight determinations were carried out in benzene using a cryoscopic method. The spectra and the molecular weight data were obtained by Mrs. G. M. Bijlsma-Krüger and Mrs. T. van Montfort-Volp. GC/MS analyses were recorded on a Finnigan 3100D by Mrs. G. G. Versluis-De Haan. Elemental analyses were carried out under the supervision of Mr. W. J. Buis in the Analytical Department of this Institute.

Interaction of 2-(Dimethylamino)phenylcopper with CuOTf. Synthesis of (2-$Me_2NC_6H_4$)$_4Cu_6OTf_2$ (V). Solid CuOTf·½C_6H_6 (2.45 mmol) was added at room temperature to a well-stirred suspension of 2-(dimethylamino)phenylcopper (I) in benzene (25 mL). The resulting brown-yellow colored reaction mixture was stirred for 48 h. The yellow precipitate was filtered off and extracted twice with benzene (20 mL) and with pentane (2 × 20 mL). The yellow residue (80%) was dried in vacuo. Anal. Calcd for $C_{17}H_{20}Cu_3F_3O_3N_2S$: C, 35.20; H, 3.48; N, 4.83; Cu, 32.86; F, 9.83. Found: C, 34.2; H, 3.5; N, 4.4; Cu, 32.0; F, 9.6. IR (OTf vibrations[2]) ν_4, 1315 s, 1298 (sh), 1230 m, 1199 m; ν_1 1010 s; ν_5 632 s; ν_3 521 m. NMR (in toluene-d_8) δ (10 °C) 1.92 and 2.96 (2 s, br, 6 H, NMe_2, coalescence at room temperature to one singlet at 2.50), 6.50 (m, J = 8 Hz, H_3), and 8.84 (m, $J \simeq$ 6 Hz, H_6). Decomposition (under N_2, 5 °C/min) started at 118 °C; explosion occurs at 123 °C.

Reactions of 2-$Me_2NC_6H_4Cu$, (2-$Me_2NC_6H_4$)$_4Cu_6OTf_2$, and (2-$Me_2NC_6H_4$)$_4Cu_6Br_2$ with CuOTf. A typical experiment involving the reaction of I with CuOTf in a 1/1 molar ratio is described. The respective reaction conditions and results of the other reactions are in Table I.

Solid CuOTf·½C_6H_6 (2.36 mmol) was added at room temperature to a suspension of I (2.36 mmol) in benzene (25 mL). This mixture was stirred for 48 h. NMR spectroscopy of the solution showed two broad NMe resonances at δ 2.46 and 2.54 ppm [NMR in benzene-d_6 of (2-$Me_2NC_6H_4$)$_2$·2CuOTf, NCH_3, 2.52 ppm broad,[10] and of pure VI, NCH_3, δ 2.40 ppm[3]]. A 6 N NH_3/H_2O solution (25 mL) was added to the reaction mixture. The benzene layer was extracted with NH_3/H_2O solution (removal of copper). The benzene layer was extracted with 4 N HCl solution. The acidic water layer was made basic with NaOH solution and extracted with diethyl ether. The ether layer was dried over Na_2SO_4 and concentrated, affording a yellow oil. NMR spectroscopy showed this oil to be a mixture of 2,2′-bis(dimethylamino)-biphenyl (VI) and *N,N*-dimethylaniline (VII). NMR (C_6D_6) VI, δ 2.40 (12 H, s, NCH_3), 7.52 (m, 2 H, H_3 or H_6), 7.15 (m, 2 H, H_6 or H_3 partly masked by $C_6D_{6-x}H_x$ resonances), and 6.94 (m, 4 H, $H_{4,5}$); VII, 2.50 (3, 6 H, NCH_3). Total recovery of R as VI and VII amounts to 98%, 85% as RR and 15% as RH.

Reaction of 2-(dimethylamino)phenylcopper with Triphenylphosphine. Solid triphenylphosphine (8.17 mmol) was added to a suspension of I (2.72 mmol) in benzene (20 mL). The resulting yellow colored suspension was stirred at room temperature for 48 h. The solid was filtered off and extracted with benzene (2 × 10 mL). NMR and IR spectroscopy revealed that this solid consisted of pure I. The spectra were identical with those of an analytically pure sample of I (see ref 3). I was recovered in 96% yield.

Reaction of I with PPh_3 and CuOTf. A mixture of I (3.3 mmol) and PPh_3 (13.1 mmol) in benzene (25 mL) was stirred at room temperature for 24 h. Subsequently, solid CuOTf·½C_6H_6 (5.68 mmol) was added and the reaction mixture stirred for another 72 h. The yellow precipitate was separated by centrifugation and extracted with benzene (3 × 25 mL). The benzene extract was concentrated, which afforded a yellow solid. Extraction of this solid with pentane (2 × 20 mL) and with ether (3 × 20 mL; removal of PPh_3) afforded an ochre solid which had 2-$Me_2NC_6H_4Cu$·3CuOTf·6PPh_3 stoichiometry (18% yield calculated on the starting amount of I). Decomposition occurred at 140–160 °C. Anal. Calcd for $C_{119}H_{100}NO_9P_6S_3F_9Cu_4$: C, 59.66; H, 4.2; N, 0.58; P, 7.76; F, 7.14; Cu, 10.61. Found: C, 59.2; H, 4.6; N, 0.6; P, 7.5; F, 7.1; Cu, 11.7. NMR (pyridine-d_5) δ 2.90 (br, NCH_3), 7.15–7.60 and 6.4–7.0 (m, br, complexed PPh_3); addition of H_2O afforded VII and PPh_3 in 1/5.7 molar ratio (elemental analysis, 1/6).

Reaction of I with CuO_2CCF_3 in DMF. Solid copper(I) trifluoroacetate[19] (3.6 mmol) was added to a suspension of I (3.6 mmol) in DMF. This mixture was stirred for 96 h. Workup with NH_3 solution (vide supra) afforded a colorless solid which according to NMR spectroscopy was 2,2′-bis(dimethylamino)biphenyl and *N,N*-dimethylaniline in 9/1 molar ratio. The recovery of R in these products was 70%.

Interaction of 2-[(Dimethylamino)methyl]phenylcopper (II) with CuOTf. Reaction of II with CuOTf. Solid CuOTf·½C_6H_6 (1.62 mmol) was slowly added at room temperature to a solution of II (1.62 mmol) in benzene (20 mL). The color of the solution turned immediately to red upon the addition of the first amount of CuOTf. At 2/1 molar ratios a yellow precipitate was formed which upon continued addition of CuOTf dissolved. Finally, a green solution containing metallic copper was obtained. After 48 h the reaction mixture was worked up following the procedure described above for the I/CuOTf reactions. A yellow oil was isolated which according to NMR spectroscopy consisted of pure 2,2′-bis[(dimethylamino)methyl]biphenyl (VIII). Thus R was quantitatively recovered as the dimer VIII: NMR (C_6H_6) δ 2.01 (s, 2 H, NCH_3), 3.07 (d, 2 H) and 3.28 (d, 2 H, $J_{gem} \simeq$ 13 Hz, NCH_2) (cf. ref 5). *N,N*-Dimethylbenzylamine was absent.

In a separate experiment the NMR spectrum of the reaction mixture after stirring for 48 h, but before hydrolysis, was recorded: NMR (C_6D_6) δ 2.30 and 2.14 (2 s, br, 12 H, NMe), 3.78 and 2.34 (2 d, br, 4 H, J_{gem} = 12 Hz, NCH_2), identical with the spectrum obtained by mixing VIII and CuOTf in an exact 1/2 molar ratio.

Synthesis of VIII. Crude 2-[(dimethylamino)methyl]phenylcopper (II), isolated by filtration of the reaction mixture of 2-[(dimethylamino)methyl]phenyllithium (59.7 mmol) with an equimolar amount of CuBr,[5] was mixed with 120 g of naphthalene and subsequently heated at 165 °C for 6 h. Crude VIII was isolated by an acid/base workup procedure and purified by fractional distillation. The overall yield, calculated on the amount of the aryllithium, was 63%, bp 135–140 °C (0.1 mm), NMR spectrum vide supra.

Attempted Synthesis of II/CuOTf Complexes. A solution of II in toluene (3.29 mmol in 20 mL) was cooled to −20 °C. Under vigorous stirring solid CuOTf (1.65 mmol) was added. The resulting orange-brown suspension was stirred at −45 °C for 1 h and for another 1 h

at room temperature. The orange solution was filtered and concentrated affording a yellow solid. This solid was extracted with pentane (2 × 10 mL) and dried in vacuo. Elemental analysis pointed to the isolation of a complex which had 3(2-$Me_2NCH_2C_6H_4Cu$)·2CuOTf stoichiometry. Anal. Calcd for $C_{29}H_{36}N_2Cu_5O_6S_2F_2$: C, 34.19; H, 3.54; Cu, 31.21; N, 4.13; F, 11.20. Found: C, 35.2; H, 3.9; Cu, 28.3; N, 3.7; F, 10.8. This solid decomposed slowly at room temperature.

Interaction of *p*-Tolylcopper with CuOTf. Pure *p*-tolylcopper was prepared following the directions of Camus and Marsich.[9] Anal. Calcd for C_7H_7Cu: C, 54.36; H, 4.56; Cu, 41.08. Found: C, 52.8; H, 4.6; Cu, 40.8. Mol wt (cryometry in C_6H_6) 604 ($\bar{n}$ = 3.9) concentration independent (calcd for C_7H_7Cu, 154.7). NMR (C_6D_5N) δ 2.15 (s, 3, CH_3), 7.03 (m, 2, $J_{2,3}$ 7 Hz, H_3) and 8.09 (m, 2, H_2); (in C_6D_6) 1.96 (CH_3), 6.84 (H_3), and 7.98 (H_2).

Reaction of *p*-Tolylcopper with CuOTf. Solid CuOTf (3.24 mmol) was added to a solution of *p*-tolylcopper (3.24 mmol) in benzene (40 mL). The color of the solution turned red and a black solid precipitated. A 6 N NH_3/H_2O solution was added. The benzene layer was extracted with NH_3/H_2O solution and with H_2O and dried over $MgSO_4$. The NMR spectrum indicated that *p,p'*-bitolyl was formed in 95% yield. NMR (CCl_4) δ 2.32 (3, s, CH_3), 7.08 and 7.34 (2 d, J = 8 Hz, $H_{2,3}$). Concentration of the benzene solution afforded white solid *p,p'*-bitolyl, mp 115–119 °C (lit.[20] 121 °C).

Interaction of CuOTf with *p*-Tolylcopper/2-[(Dimethylamino)methyl]phenylcopper Aggregates. *p*-Tolylcopper (0.8 mmol) and II (2.4 mmol) were dissolved in toluene-d_8 (3 mL). NMR (toluene-d_8) δ (100 °C) H_6 (II), 8.40 (d, br); H_2 (4-TolCu), 7.74 (d); NCH_2 (II), 3.08 (s, br); NMe (II), 1.84 (s, br); CH_3 (4-TolCu), 1.90 (s, br). Solid CuOTf (3.2 mmol) was added to this solution which was then stirred at room temperature for 2 h. NH_3/H_2O solution (10 mL, 6 N) was added. Workup as described above resulted in the isolation of a white solid. NMR spectroscopy indicated that (2-$Me_2NCH_2C_6H_4$)$_2$ (VIII) (64 mol %), 2-$Me_2NCH_2C_6H_4C_6H_4CH_3$-*p* (15 mol %), *p,p'*-bitolyl (15 mol %), and *N,N*-dimethylbenzylamine (6 mol %) were present. NMR (C_6D_6) δ VIII, 2.01 (NCH_3), 3.07 and 3.28 (NCH_2, J_{gem} = 13 Hz); 2-$Me_2NCH_2C_6H_4C_6H_4CH_3$-*p*, 2.06 ($NCH_3$), 2.18 (*p*-$CH_3$), 3.36 ($NCH_2$); *p,p'*-bitolyl, 2.18 (CH_3); *N,N*-dimethylbenzylamine, 2.08 (NCH_3), 3.26 (NCH_2).

The corresponding reaction but now using *p*-tolylcopper/II/CuOTf in a 1/0.8/2 molar ratio afforded VIII (34 mol %), 2-$Me_2NCH_2C_6H_4C_6H_4CH_3$-*p* (16 mol %), and *p,p'*-bitolyl (51 mol %). GC/MS: VIII, *m/e* 268; 2-$Me_2NCH_2C_6H_4C_6H_4CH_3$-*p*, *m/e* 225; *p,p'*-bitolyl, *m/e* 182.

Interaction of o-Tolylcopper with CuOTF. Pure o-tolylcopper was prepared according to ref 9. NMR (C_5D_5N) δ 2.39 (s, 3, CH_3), 7.0–7.4 (m, $H_{3,4,\text{ and }5}$), 8.42 (m, 1, H_6); (in C_6D_6) 2.62 (CH_3), 6.7–7.1 (other H_{arom}), 7.97 (d, br, J = 6 Hz, H_6). Upon heating (75 °C, 1 h) of the benzene-d_6 solution in the NMR tube o,*o'*-bitolyl was formed exclusively [δ (CH_3) 1.96 ppm]. Mol wt (cryometry in C_6H_6) $\bar{n}_{0h}$ 6.1, $\bar{n}_{3/4h}$ 4.9, $\bar{n}_{2h}$ 4.1; second run $\bar{n}_{1h}$ 4.5, $\bar{n}_{2h}$ 4.0, concentration independent.

Reaction of o-Tolylcopper with CuOTf. Solid CuOTf (1.2 mmol) was added to a solution of o-tolylcopper (1.2 mmol) in benzene (10 mL). A purple colored product precipitated during 5 h of stirring. Workup with NH_3/H_2O solution *in air* afforded a colorless oil which consisted of o,*o'*-bitolyl, *o*-hydroxytoluene, and *o*-aminotoluene. The recovery of tolyl group in these products amounted to 46%. These compounds were identified by NMR and GC/MS techniques. NMR (benzene-d_6) o,*o'*-bitolyl, δ 1.95 (CH_3); *o*-aminotoluene, 1.80 (CH_3) and 2.84 (br, NH_2); o-hydroxytoluene, 2.08 (CH_3). Mol % 43/37/21. Their identity was further established by GC/MS analysis. A trace amount of a compound with $C_{14}H_{24}O$ (*m/e* 198) was identified to be bis(*o*-methylphenyl) ether (very intensive *m/e* 107).

Exactly the same result was obtained when after the addition of NH_3/H_2O solution O_2 gas was bubbled through the reaction mixture.

Complex Formation of o-Tolylcopper with CuOTf. An equimolar mixture of CuOTf and *o*-tolylcopper (CuOTf added to o-tolylcopper) which was dissolved in benzene (50 mL) was stirred for 0.5 h. The purple colored precipitate was filtered off, washed with benzene (3 × 40 mL, removal of uncomplexed CuOTf) and with pentane (2 × 10 mL), and dried in vacuo. Elemental analysis of this solid pointed to the isolation of a CuOTf·1.1 o-tolylcopper complex contaminated with metallic copper. NMR (pyridine-d_5) δ 2.5 (br, NCH_3) and 8.4 (br, H_6).

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Registry No.—I, 32691-15-9; II, 38286-29-2; III, 5588-74-9; IV, 20854-03-9; V, 61966-49-2; VI, 20627-78-5; VII, 121-69-7; VIII, 38286-37-2; IX, 613-33-2; X, 605-39-0; XI, 95-53-4; XII, 95-48-7; CuOTf, 42152-44-3; (2-$Me_2NC_6H_4)_4Cu_6Br_2$, 58616-70-9; (2-$Me_2NC_6H_4$)$_2$·2CuOTf, 61966-46-9; triphenylphosphine, 603-35-0; 2-$Me_2NC_6H_4Cu$·3CuOTf·6PPh_3, 61966-50-5; CuO_2CCF_3, 25535-55-1; 3(2-$Me_2NCH_2C_6H_4Cu$)·2CuOTf, 61966-48-1; bis(*o*-methylphenyl) ether, 4731-34-4; (2-$Me_2NCH_2C_6H_4)_4Cu_4$, 37185-48-1; (4-$MeC_6H_4)_4Cu_4$, 61966-47-0; 2-$Me_2NCH_2C_6H_4C_6H_4CH_3$-*p*, 61846-68-2.

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(9) The synthesis of *o*- and *p*-tolylcopper has been described by A. Camus and N. Marsich, *J. Organomet. Chem.*, **14**, 441 (1968). For a redetermination of the aggregation state of these arylcopper compounds in solution, see Discussion and Experimental Section of this paper.
(10) G. van Koten, J. T. B. H. Jastrzebski, and J. G. Noltes, *Inorg. Chim. Acta*, **21**, Lg (1977).
(11) Ligand displacement with retention of the cluster structure has been observed in the 2/1 reaction of LiI with (2-$Me_2NC_6H_4)_4Cu_6Cl_2$ in benzene. The iodide cluster 2-$Me_2NC_6H_4Cu_6I_2$ and LiCl were isolated quantitatively (cf. ref 4).
(12) The solubility of CuOTf in benzene (cuprous halides are insoluble) favors this equilibrium in spite of the fact that OTf is a weaker bridging ligand than bromide.[2]
(13) Thermal decomposition of 2-$Me_2NCH_2C_6H_4Cu$ (II) in naphthalene at 165 °C for 6 h, which affords a 9/1 mixture of VIII and the arene (63% overall yield starting from in situ prepared II, see Experimental Section), provides an alternative route to the dimer VIII. Oxidation of II with O_2 gives rise to a mixture of VIII, the arene, and 2-hydroxybenzyldimethylamine [NMR (CCl_4) δ 2.27 (s, 6 H, NCH_3), 3.53 ppm (s, 2 H, NCH_2); in C_6D_6, δ 1.72 (s, 6 H, NCH_3), 3.15 (s, 2 H, NCH_2)].
(14) In general organocopper compounds form complexes with triphenylphosphine [cf. A. Camus and N. Marsich, *J. Organomet. Chem.*, **21**, 249 (1970); A. Miyashita and A. Yamamoto, *ibid.*, **113**, 187 (1976)]. However, the tetranuclear structure of II as well as the polymeric structure of I are not broken down by triphenylphosphine. The fact that in these compounds each copper atom has already trigonal coordination symmetry as a result of intraaggregate N–Cu coordination may account for this observation [cf. G. van Koten and J. G. Noltes, *J. Chem. Soc., Chem. Commun.*, 452 (1972)].
(15) That, however, CuOTf·2PPh_3 is capable of interacting with arylcopper compounds is substantiated by the precipitation of insoluble yellow solids which contain both the arylcopper, CuOTf and PPh_3 (elemental analysis, IR) from homogeneous solutions of I and II and CuOTf·2PPh_3 (see Experimental Section). This is illustrated by the isolation of (2-$Me_2NC_6H_4Cu$)·3CuOTf·6PPh_3.
(16) The 1/1 reaction of 2,6-dimethoxyphenylcopper[3] with CuOTf in benzene affords a stable insoluble complex 2,6-$(MeO)_2C_6H_3Cu$·CuOTf. Decomposition of this complex with NH_3/H_2O in the presence of oxygen affords the arene in 50% yield together with about 12% of 2,6-$(MeO)_2C_6H_3NH_2$ and 37% of [2,6-$MeO)_2C_6H_3$]$_2$ (calculated on R).
(17) This reaction can be viewed as an electron transfer oxidation of *o*-tolyl radicals (formed by homolytic cleavage of the Cu–C bonds) by the highly electrophilic $Cu(NH_3)_x^{2+}$ cation. Oxidative solvolysis[18] of the intermediate [2-$MeC_6H_4Cu(NH_3)_x^{2+}$] affords XI and XII. Oxidative elimination pathways are not important in view of the constraints of the aromatic nucleus. This route is important in the case of oxidation of alkyl radicals by copper(II) complexes.[18]
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(20) The use of copper(I) trifluoroacetate instead of copper(I) triflate gives similar results, e.g., the reaction of I with CuO_2CCF_3 in DMF affords the dimer VI in 63% yield and only a minor amount of the arene VII (see Experimental Section).
(21) G. van Koten and J. G. Noltes, *J. Organomet. Chem.*, **84**, 129 (1975).
(22) Camus et al. prefer to describe the bonding in *o*- and *p*-tolylcopper in terms of 2e–2c Cu–C bonding. Their NMR spectroscopic data seem to justify this conclusion.[23] However, the symmetry of this bonding does not change on going from 2e–2c to 2e–3c Cu–C interaction. Moreover, the occurrence of rapid interaggregate exchange phenomena can often result in deceptively simple NMR spectra: G. van Koten and J. G. Noltes, to be published.
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(31) The formation of asymmetric biaryls in the reaction of CuOTf with premixed benzene solutions of (2-$Me_2NCH_2C_6H_4$)$_4Cu_4$ (Ar_4Cu_4) and (4-MeC_6H_4)$_4Cu_4$ (Ar'_4Cu_4) (see Experimental Section) indicates that (1) interaggregate exchange between these tetranuclear species takes place resulting in the formation of a mixed arylcopper–copper triflate precursor complex $Ar_xAr'_yCu_{x+y+z}OTf_z$, and (2) an even number of aryl groups ($x + y$) is present in the precursor complex because arenes are formed in very low yields.

A Simple Preparation of Phenols from Diazonium Ions via the Generation and Oxidation of Aryl Radicals by Copper Salts[1a]

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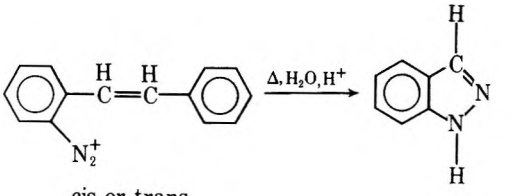
The standard method of preparation of phenols from diazonium salts consists of heating the latter in highly acidic aqueous solution; the high temperature and acidity often cause a variety of unwanted side reactions. We advocate an entirely different procedure which can be performed in a few minutes in neutral solution at room temperature, or below. The method is based on our previous observation that aryl radicals can be oxidized to phenols by cupric ion and it consists of adding cuprous oxide to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of cupric nitrate. In one case the presence of silver(I) appeared to accelerate the radical oxidation. Not only is the redox procedure simpler than the thermal method, but in all cases studied to date, the yields are equivalent or superior to those obtained by the thermal procedure. In four cases in which the latter is unsatisfactory, the redox method is quite successful and it is considered the method of choice for new cases.

As indicated in all textbooks in organic chemistry the standard method for the conversion of an aromatic diazonium ion to a phenol is thermal decomposition of the diazonium ion in a highly acidic aqueous medium. The great deal of controversy concerning the mechanism of this reaction[2] has apparently been resolved recently in favor of a substantially free, singlet, aryl cation intermediate (eq 1).[3]

$$ArN_2^+ \longrightarrow N_2 + Ar^+ \xrightarrow{H_2O} ArO^+H_2 \longrightarrow ArOH + H^+ \quad (1)$$

The high acidity is required in order to suppress the ionization of the product phenol to phenoxide ion which couples readily with unreacted diazonium ion to produce an azo compound.[4,5] In order to obtain high yields of phenol uncontaminated with azo compound, it is frequently necessary to add a solution of the diazonium salt to a boiling sulfuric acid solution,[6] if possible with simultaneous removal of the phenol by steam distillation.[7]

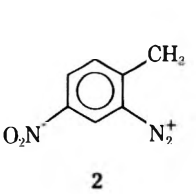
The coupling reaction is only one of a variety of competing reactions which plague the synthesis of phenols by this route. Intramolecular nucleophiles or potential nucleophiles can also attack the diazonium group. For example, an ortho carboxamido group reacts with a diazonium function to yield a benzo-1,2,3-triazene.[8] Similarly, an ortho hydroxyl group leads to the production of a diazoxazole,[9] while an ortho thiol group leads to a benzothiadiazole.[10] Intramolecular diazo coupling with a suitably placed electron-rich ring has also been observed.[11] Nucleophilic attack on the diazonium function by an ortho vinyl group to form an indazole (1) is also common (eq 2).[12]



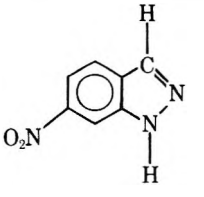
cis or trans 1

+ PhCHO + H^+ (2)

Even a saturated carbon atom in the ortho position to a diazonium function can serve as a nucleophile, presumably after deprotonation.[13-15] For example, the diazonium ion 2



2



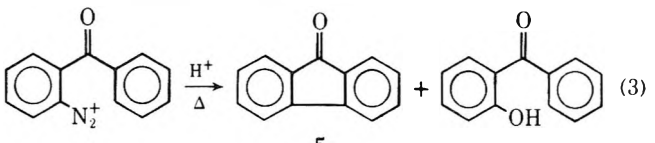
3

yields 85% of the indazole 3 when heated in acid solution,[13] although the phenol can be produced instead by adding the diazonium solution to a boiling sulfuric acid solution.[14]

Another problem sometimes encountered during thermal decomposition of a diazonium ion is replacement of an ortho or para substituent with a hydroxyl group.[16]

In addition to these competing reactions in which the two nitrogen atoms are retained in the product, several reactions in which nitrogen is lost are known to occur in place of phenol

production. One of these involves attack of the aryl cation on the phenolic product to yield arylphenol and diaryl ether.[17] A more serious and widespread competing reaction of this type is intramolecular attack of the aryl cation intermediate upon a suitably placed aromatic ring;[11,18-20] the most common of these is the thermal Pschorr[18-20] reaction as illustrated in eq 3.[18-20] Two types of nitrogen-free products are frequently

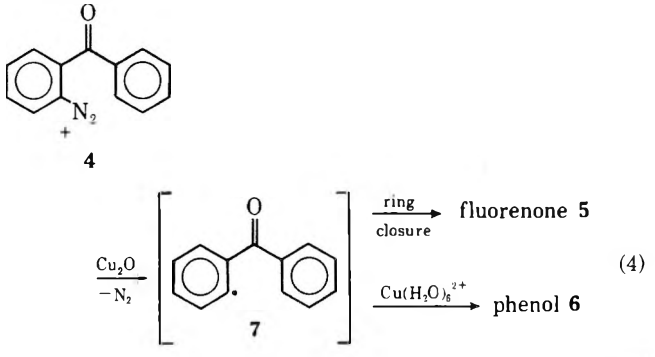


4 5 65-68% 6 32-35% (3)

observed involving saturated carbon atoms four atoms removed from the carbon atom bearing the diazonium function. One of these is direct carbon–carbon bond formation leading to a five-membered ring[21-23] and the other involves a 1,5-hydrogen transfer to the carbon bearing the diazonium function.[22,24]

Finally, the high acidity and temperature required in the conventional conversion of diazonium salt to phenol would obviously be detrimental to acid-sensitive functions such as acetals, phenol or enol esters, and lactones. Examples are given below.

In this paper we indicate the details and something of the scope of a procedure which does not require high temperatures, extreme acidities, and long reaction times. It is based upon a previous observation from this laboratory that aryl radicals, produced by cuprous oxide induced diazonium decomposition, could be oxidized to phenols by hydrated cupric ion.[20] Whereas diazonium ion 4 is converted mainly to fluorenone (5) by heating in acid (eq 3) and almost entirely to 5 by radical decomposition induced by cuprous oxide, 88% of the product is phenol when the latter reaction is conducted in the presence of a high concentration of cupric nitrate (eq 4). Formally, the process is a Sandmeyer reaction[25] with the



4 7 fluorenone 5 phenol 6 (4)

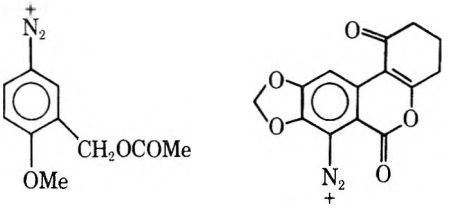
transfer to the radical site of $H_2O^+\cdot$ instead of a halogen atom or CN radical from the ligand shell of copper(II). A reasonable mechanism involves the attack of cupric ion on the radical 7 and reductive elimination of copper(I) from the resulting arylcopper(III) hydrate (eq 5).[26]

$$Ar\cdot + Cu(H_2O)_n^{2+} \longrightarrow ArCu(H_2O)_m^{2+} \longrightarrow ArO^+H_2 + Cu(H_2O)_{m-1}^{+} \quad (5)$$

A closely related reaction in which a vinyl radical is apparently oxidized to an aldehyde by hydrated cupric ion has recently been described by Walling.[27]

The conversion of diazonium ions to phenols by the generation and oxidation of aryl radicals is, of course, fundamentally different from the thermal method proceeding via aryl cations and it has been suggested as a new phenol synthesis.[20] It was also demonstrated that *p*-bromophenol could be generated in 87% yield by the radical procedure from *p*-bromobenzenediazonium ion whereas a simple thermal decomposition in acid solution resulted in only 53% of phenol contaminated with "diazo resins".[20]

Since this early publication,[20] several groups have successfully utilized our procedure.[28-30] Two interesting cases which did not yield to the traditional hydrolysis procedure are 8[29] and 9,[30] which produced the corresponding phenols in 79



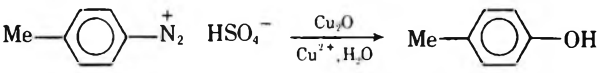
8 9

and 95% yield, respectively; it is of interest that both possess acid-sensitive functions, 8 an ester and 9 both acetal and enol lactone groups.

In order to provide information concerning the scope and utility of the copper-catalyzed conversion of diazonium ions to phenols, five diazonium salts in aqueous solutions containing cupric nitrate were subjected to the action of solid cuprous oxide. The facility of the procedure and the yields of phenol were then compared with those for the noncatalytic (thermal) method. A limited number of optimization experiments were also conducted.

Results

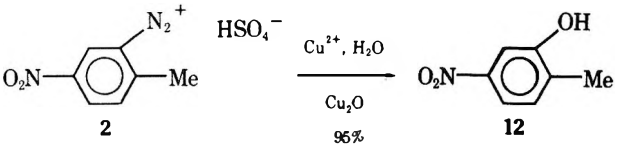
Although the thermal conversion of *p*-toluenediazonium bisulfate (10) to *p*-cresol (11) proceeds in 89% yield,[7] the procedure is cumbersome, as indicated above. The copper-



10 93% 11

catalyzed reaction occurred in 93% yield (GLC) and was performed at room temperature over a period of less than 1 min. In a larger scale experiment, 88% of *p*-cresol could be isolated. The only two drawbacks to this procedure are that large quantities of cupric nitrate are required and that the concentration of diazonium salt must be maintained very low; both of these requirements have the same basis, that the rate of oxidation of the radical by cupric ion should be high compared to the rate of reaction of the radical with substrate or product. At a constant concentration of cupric nitrate (41 mmol/100 mL of water), the yield of *p*-cresol increased from 66% to 93% as the concentration of diazonium salt was lowered from 8.1 mmol to 2.6 mmol in 100 mL of water (1.8 mmol of cuprous oxide was used). Inspection of the gas chromatograms for a number of experiments in which the cupric nitrate concentration was varied indicate that the yields of phenol decreased when the concentration of copper(II) decreased much below about 41 mmol/100 mL of water.

As indicated above, thermal decomposition of 5-nitro-2-methylbenzenediazonium bisulfate (2) gives mainly the indazole 3 if it is heated in aqueous acid;[13] phenol could be produced, however, by adding the cold solution of diazonium salt to a boiling solution of concentrated sulfuric acid–water (1:2).[14] We have obtained a 95% yield (GLC) of the phenol (12) in a 1-min reaction at 0 °C. A higher concentration of cupric ion (205 mmol/100 mL of water) than in the case of *p*-cresol

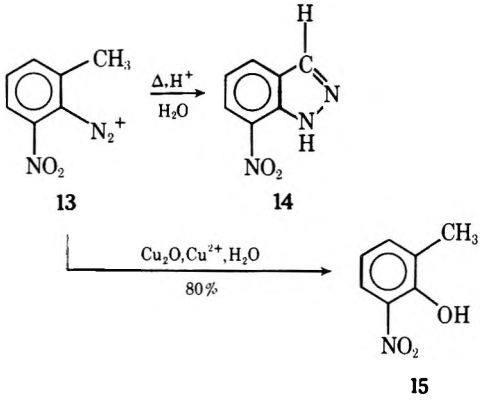


2 95% 12

formation was required to obtain this yield (concentration of diazonium salt, 2.1 mmol/100 mL). The lower concentration of 123 mmol of Cu^{II}/100 mL gave an only slightly inferior yield (90%), but still lower concentrations of copper(II) caused substantial reduction in the yield of phenol and an increase in that of by-products as indicated by gas chromatograms of the reaction mixture. The by-products consisted of *p*-nitrotoluene, an aryl chloride thought to be 5-nitro-2-methylchlorobenzene (undoubtedly due to a Sandmeyer reaction involving adventitious traces of chloride ion, probably contaminating the cupric nitrate), and a biaryl (molecular ion 272 amu).

The next substrate submitted to the redox procedure for phenol formation was 6-nitro-2-methylbenzenediazonium ion (**13**). Although the amine precursor is commercially available, a careful search of the literature revealed that there are no reports of the conversion of this diazonium ion to the phenol (**15**). The reason became clear when it was discovered that the major product (42% yield) of thermal decomposition is the indazole **14**, even when the diazonium solution was added to a boiling solution of extremely strong acid (concentrated sulfuric acid–water, 2:1); the yield of phenol in this thermal decomposition was only 10% and 9% of *m*-nitrotoluene was also produced.

Several redox conversions of **13** to phenol (**15**) were performed. In all cases 0.50 mmol of diazonium salt was decomposed by 1.4 mmol of cuprous oxide in a solution containing



13 **14** **15**

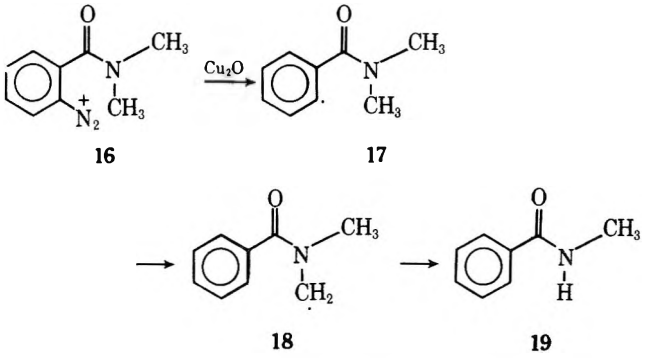
210 mmol of cupric nitrate in 50 mL of water. The poorest isolated yield (55% from the amine) was obtained when the diazonium bisulfate was not isolated but decomposed in situ in the still acidic solution. The yield improved to 60% (average of two experiments) when the diazonium tetrafluoroborate was decomposed in situ, also in an acidic solution. In the latter case, 14% of *m*-nitrotoluene and 8% of a biaryl were also produced. The best yields of phenol (80% based on diazonium ion, 74% based on amine) were obtained when the isolated diazonium fluoroborate was decomposed in neutral solution; in this case the yields of the two by-products were reduced to about 2% each. As in the other examples the reaction was over in 1–2 min.

Since aryl radicals are produced very rapidly from diazonium ions in the presence of cuprous oxide, it is clear that the phenol yield would be determined by the competition between oxidation of this radical and other reactions available to it. In order to simplify the interpretation of the data, this type of competition was studied in a system in which only a single nonoxidative reaction is available to the radical. Previous work in this laboratory[22,31,32] has established that the radical **17**, formed by the reaction of diazonium ion **16** with cuprous oxide, undergoes an extremely efficient 1,5-hydrogen atom transfer to produce the new radical **18** which, in the presence of cupric ion, is converted to *N*-methylbenzamide (**19**) and formaldehyde. Yields of **19** in excess of 95% can be obtained when cupric ion is not purposely added to the solution; the

Table I. Cuprous Oxide Induced Decomposition of *N,N*-Dimethylbenzamide-*o*-diazonium Tetrafluoroborate at Room Temperature in the Presence of Cupric Nitrate and Silver Nitrate[a]

Reagents, mmol			Phenol[b]/ *N*-methyl-benzamide	Phenol[b]/ *N,N*-dimethyl-benzamide
ArN_2^+	$Cu(NO_3)_2$	$AgNO_3$		
2.3	4.1		0.17	v large
2.5	20		0.39	v large
2.3	20	30	2.8	5.0
2.3	40	15	3.6	1.2
2.5	40	30	5.8	8.2
2.4	40	30	5.5	9.2
2.3	40	60	7.1	6.6
2.1	60	30	9.8	11
2.4	60[c]	60[c]	12	7.5
2.4	80[c]	60[c]	12	7.5
2.4	100[c]	60[c]	12	7.5

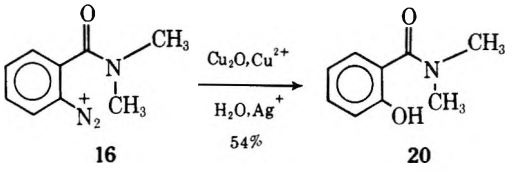
[a] 100 mg of Cu_2O in 10 mL of H_2O used in each case except run 3, in which 540 mg was used. [b] Ratios determined by gas chromatography. [c] The cupric and silver nitrates were not completely soluble at these concentrations.



16 **17** **18** **19**

only other detected product is reduced material, *N,N*-dimethylbenzamide.

It was found that the aryl radical **17** can be intercepted and converted to phenol (**20**), although inefficiently, by high concentrations of cupric ion (Table I). However, the interception becomes far more efficient when silver nitrate is also present in the solution and, at a given concentration of cupric ion, the ratio of phenol (**20**) to *N*-methylbenzamide (**19**)

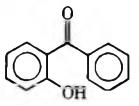
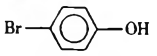
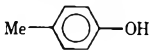
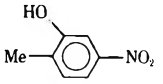
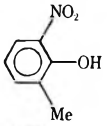
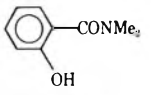
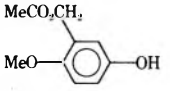
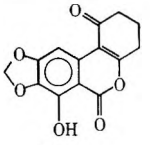
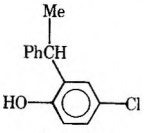
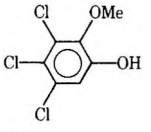
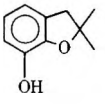


16 **20**

produced increases with increasing concentration of silver(I) (Table I). Unfortunately, the yield of reduced material, *N,N*-dimethylbenzamide, also has a tendency to increase when the silver ion concentration is increased, particularly at high concentrations of the latter. Nevertheless, a yield of 54% of *N,N*-dimethylsalicylamide could be obtained in the three runs at the bottom of Table I; this represents a fairly efficient diversion of the aryl radical when it is considered that no detectable phenol is produced without the deliberate addition of copper(II) and silver(I). The thermal decomposition of the diazonium ion gives about the same yield of phenol accompanied by *N*-methylbenzamide and *N*-methylphthalimidine.[22]

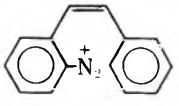
Finally, the redox procedure was applied to *cis*-stilbene-2-diazonium ion (**21**). As indicated in eq 2, DeTar and Chu[12] reported that thermolysis in aqueous acid yielded indazole (**1**, 62% yield) and benzaldehyde as the major products. However,

Table II. Yields in the Conversion of Diazonium Ions to Phenols by the Redox Method

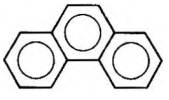
Entry	Phenol prepared	Yield, %[a]	Ref
1		76–85	20
2		87	20
3		93	*b*
4		95	*b*
5		80	*b*
6		54	*b*
7		79	29
8		95	30
9		38[c]	28a
10		*d*	28b
11		88–93	28c

[a] Yields are the maximum obtained if more than one set of conditions was tried. [b] Present work. [c] No attempt was made to improve this yield. [d] Yield not reported.

at higher temperatures, the isomerized olefin, *trans*-2-hydroxystilbene, and the product of Pschorr ring closure, phenanthrene (**22**), predominated; no *cis*-2-hydroxystilbene was produced. Treatment of this diazonium ion (**21**), as its



21



22

tetrafluoroborate salt, with cuprous oxide in a solution containing cupric nitrate gave 64% (GLC yield) of phenanthrene and a trace of stilbene. Apparently, the radical undergoes such rapid ring closure that it is not intercepted by cupric ion. Supplementation of the cupric nitrate with silver nitrate did not lead to the cis phenol; phenanthrene was produced in 86% yield.

Conclusions

The redox procedure is the method of choice for the conversion of diazonium salts to the corresponding phenols. Table II is a compilation of all of the examples of its successful use of which we are aware. The only unsuccessful case of which we know is that of the *cis*-stilbene-2-diazonium ion (**21**); the thermal method is also unsuccessful in this case. It may be that other metal ions would lead to a successful phenol synthe from **21**. We are unaware of any example in which the thermal method is significantly more successful than the redox procedure and the latter has been successful in at least four cases in which the thermal method gives extremely poor yields or fails entirely (entries 1, 5, 7, and 8, Table II). The redox method should be especially advantageous in the case of diazonium ions which undergo indazole formation readily or those which bear groups which are sensitive to the strong acid or high temperatures ordinarily required in the thermal method. However, even in cases in which the latter gives satisfactory yields of phenol, the redox procedure is very much preferable owing to its great ease and rapidity. The major disadvantage of the procedure is that fairly high dilutions are necessary for optimum results.[33] However, it appears likely that the use of silver nitrate will permit higher concentrations to be used since in the case of diazonium ion **16** this salt apparently increases the rate of radical oxidation.

Experimental Section

Melting points were determined on a Thomas-Kofler micro hot stage and are corrected. Infrared spectra were determined on a Beckman Model IR-8 spectrophotometer. Mass spectra were obtained on an LKB-9000 combined gas chromatograph–mass spectrometer at 70 eV. Gas–liquid chromatography (GLC) was performed on Varian Associates Model 1860-3 and Hewlett-Packard Model 5750 gas chromatographs equipped with flame ionization detectors and either a Disc or an electronic integrator.

***p*-Cresol (11).** *p*-Toluidine (0.213 g, 1.98 mmol) was dissolved in 2 mL of hot 35% sulfuric acid and then allowed to cool to below 15 °C. Ice (2 g) was added and the amine bisulfate precipitated. A solution of 0.176 g (2.55 mmol) of sodium nitrite in 2 mL of ice water was added dropwise under the surface of the ice-cooled solution with stirring at such a rate as to maintain the temperature at 0–5 °C. After the solution had been stirred for an additional 5 min, a few crystals of urea were added to decompose any excess sodium nitrite.

To the cold (0 °C) solution of *p*-methylbenzenediazonium bisulfate was added a solution of 7.5 g (31 mmol) of cupric nitrate trihydrate in 70 mL of water (total volume 76 mL of H_2O) at room temperature. With vigorous stirring, 0.265 g (1.82 mmol) of cuprous oxide was added to the solution. The liquid became dark blue and rapidly changed to green. About 1 min after the addition of cuprous oxide the nitrogen evolution ceased and a negative test with alkaline β-naphthol indicated that the reaction was complete. The mixture was extracted with ether and this extract was used for the GLC analysis.

p-Cresol was identified by comparison of its GLC retention times with those of an authentic sample via the coinjection technique and by its combined GLC–mass spectrum:[34] *m/e* (rel intensity, assignment) 109 (7, P + 1), 108 (90, P), 107 (base, P − H), 90 (8, P − OH_2), 79 (15), 77 (20). The yield of *p*-cresol by GLC (hexadecane as internal standard) was 93%. An isolated yield of 88% for this phenol was realized from 5.34 g (50.0 mmol) of the amine by base extraction of the organic extract, reacidification of the aqueous solution, and extraction with ether.

5-Nitro-2-methylphenol (12). By a similar procedure, using 0.319 g (2.08 mmol) of 5-nitro-2-methylaniline (Matheson Coleman and Bell), 5 mL of sulfuric acid, 5 g of ice, 2.5 mmol of sodium nitrite in 2 mL of ice water, 205 mmol of cupric nitrate trihydrate in 90 mL of water, and 1.96 mmol of cuprous oxide, a 95% (GLC) yield of 5-nitro-2-methylphenol was obtained. It was identified by the melting point of an isolated sample, 115–117 °C (after recrystallization from petroleum ether–benzene) (lit.[14] mp 118 °C), and by its combined GLC–MS: *m/e* (rel intensity, assignment) 154 (10, P + 1), 153 (base, P), 107 (30, P − NO_2), 95 (7, P − NO, CO), 79 (17, P − NO_2, CO), 77 (52). Three very minor peaks had mass spectra which were consistent with those expected for *p*-nitrotoluene,[35] 5-nitro-2-methylchlorobenzene, and a biaryl (molecular ion 272).

2-Methyl-6-nitrobenzenediazonium Tetrafluoroborate. A solution of 2-methyl-6-nitroaniline (2.00 g, 13.2 mmol, Aldrich) and 5.4 g (30 mmol) of fluoroboric acid (48–50%) in 100 mL of absolute ethanol was stirred and cooled to 0 °C. To the resulting solution was

added, dropwise over a 15-min period, 2.12 g (18.0 mmol) of freshly distilled *n*-amyl nitrite. The resulting solution was stirred for 30 min at 0 °C and poured into 100 mL of cold ether causing precipitation of 3.0 g (92% yield) of 2-methyl-6-nitrobenzenediazonium tetrafluoroborate: mp 117.5–118.0 °C dec; IR (Nujol) 2300 (s, N≡N$^+$), 1560 (s, NO_2), and 1050 cm^{-1} (s, broad, BF).

2-Methyl-6-nitrophenol (15). A. From Isolated 2-Methyl-6-nitrobenzenediazonium Tetrafluoroborate. The reaction was performed using 0.125 g (0.50 mmol) of the diazonium salt, 75 g (0.31 mol) of cupric nitrate trihydrate, 67 mg (1.4 mmol) of cuprous oxide, and 50 mL of water at room temperature. The decomposition seemed to be complete within a matter of minutes, but stirring was continued for an additional 30 min. The mixture was filtered free of cuprous oxide. The filtrate was made basic by the addition of 10 mL of 1 N sodium hydroxide and the resulting solution was extracted with methylene chloride. The base extract was reacidified with dilute hydrochloric acid and extracted with methylene chloride. The extract was dried (sodium carbonate) and filtered, and the solvent evaporated to leave 59 mg (0.38 mmol, 77% yield) of light yellow crystals of 2-methyl-6-nitrophenol: mp 68.0–68.5 °C (lit.[14] mp 69.5 °C); *m/e* (rel intensity, assignment) 154 (8, P + 1), 153 (base, P), 136 (8, P − OH), 107 (14, P − NO_2), 105 (9, P − NO, H_2O), 79 (11, P − NO_2, CO), 77 (32). GLC analysis of the organic extract from the basic solution indicated the presence of *m*-nitrotoluene, a biaryl (base peak 226 for P − NO_2), and a trace of 2-chloro-3-nitrotoluene.

B. From 2-Nitro-6-methylbenzenediazonium Bisulfate Prepared in Situ. The procedure was identical with that used for *p*-toluidine described above. The quantities used were 0.50 mmol of amine, 2.5 mL of sulfuric acid, 2 g of ice, 0.64 mmol of sodium nitrite in 2.5 mL of water, 21 mmol of cupric nitrate trihydrate in 50 mL of water, and 1.4 mmol of cuprous oxide. The 2-methyl-6-nitrophenol prepared (55% yield) in this manner was not as clean (dull yellow crystals, broad mp range, 59–64 °C) as that produced from the isolated 2-methyl-6-nitrobenzenediazonium tetrafluoroborate. Analysis of the neutral fraction by GLC indicated that *m*-nitrotoluene (13% yield), the biaryl (5%), and a trace of aryl chloride were also produced.

C. From 6-Nitro-2-methylbenzenediazonium Tetrafluoroborate Prepared in Situ. A solution of 76 mg (0.50 mmol) of 2-methyl-6-nitroaniline and 10.4 mL (60 mmol) of fluoroboric acid (48–50%) was magnetically stirred at room temperature for 0.5 h. The solution was cooled to 0 °C and treated dropwise over a 15-min period with 2 mL of an aqueous solution of sodium nitrite (44 mg, 0.64 mmol). The decomposition procedure and workup were identical with those described above. The yield of phenol was 62%; *m*-nitrotoluene (14%), the biaryl (8%), and a trace of aryl chloride were also formed.

Thermal Decomposition of 2-Nitro-6-methylbenzenediazonium Tetrafluoroborate. An aqueous solution containing 125 mg (0.500 mmol) of 2-methyl-6-nitrobenzenediazonium tetrafluoroborate in 25 mL of water was added dropwise to a boiling solution of aqueous sulfuric acid and sodium sulfate [25 g of concentrated sulfuric acid, 12.5 mL of water, and 18.7 g (157 mmol) of sodium sulfate].[6b] The resulting solution was heated at reflux for 2 h, cooled to room temperature, and extracted with methylene chloride. A GLC analysis indicated the presence of 3-nitrotoluene (9.2%) and 2-methyl-6-nitrophenol (9.7%), as well as a major component of longer retention time. The solution was extracted with 10 mL of a 1 N sodium hydroxide solution. The aqueous layer was made slightly acidic (pH 6, litmus) by the addition of 1 N hydrochloric acid; the resulting solution was extracted with methylene chloride, and the combined extracts were dried (magnesium sulfate), filtered, and concentrated, leaving 34 mg (42% yield) of a light yellow crystalline compound, mp of 7-nitro-1*H*-indazole 184–185 °C (lit. mp[36] 187 °C). The mass spectrum was also consistent with this structure: *m/e* (rel intensity, assignment) 164 (9, P + 1), 163 (base, P), 117 (22, P − NO_2), 90 (46), 63 (21).

o-Amino-*N,N*-dimethylbenzamide. A mixture containing 1.01 g (5.15 mmol) of *o*-nitro-*N,N*-dimethylbenzamide[22a] and 0.101 g of 10% palladium on charcoal in 25 mL of absolute ethanol was hydrogenated at room temperature and atmospheric pressure. The hydrogen uptake was approximately 400 mL. The solution was filtered free of catalyst and the solvent was evaporated leaving an almost colorless oil that was induced to crystallize to give 0.80 g (95% yield) of white amine: mp 61.0–61.5 °C (lit.[37] mp 61–62 °C); IR ($CHCl_3$) 3480 (w), 3370 (w), and 1610 cm^1 (C=O).

***N,N*-Dimethylbenzamide-*o*-diazonium Tetrafluoroborate.** The procedure was the same as that used for the preparation of 2-methyl-6-nitrobenzenediazonium tetrafluoroborate. From 0.800 g (4.87 mmol) of *o*-amino-*N,N*-dimethylbenzamide, there was obtained 1.17 g (92% yield) of *N,N*-dimethylbenzamide-*o*-diazonium tetrafluoroborate, after recrystallization from cold acetone–ether: mp 96–97 °C dec; IR (Nujol) 2280 (s, N≡N$^+$), 1620 (s, C=O), and 1050 cm^{-1} (s, broad, BF).

Decomposition of *N,N*-Dimethylbenzamide-*o*-diazonium Tetrafluoroborate. The following representative procedure is the one that gives the optimum yield of the phenol; in other experiments the quantities of copper(II) and silver(I) salts were varied as indicated in Table I. The diazonium salt (62.4 mg, 0.237 mmol) was added to a stirred suspension of 100.0 ± 2 mg of cuprous oxide in 10 mL of distilled water containing 15 g (60 mmol) of cupric nitrate trihydrate and 10 g (59 mmol) of silver nitrate at room temperature, under a positive pressure of prepurified nitrogen. As the diazonium salt was added to the suspension an immediate evolution of nitrogen gas was observed. The reaction was over almost immediately and was considered complete when a negative β-naphthol test was obtained; stirring was continued for an additional 30 min. The reaction mixture was filtered free of cuprous oxide and other inorganic salts, the reaction vessel being rinsed well first with water and then with methylene chloride. The aqueous layer was extracted with four 15-mL portions of methylene chloride and the combined extracts were dried (sodium carbonate) and concentrated. The residue was taken up in 3 mL of acetone, the GLC standard, *p*-tolyl benzoate, was added, and the solution was analyzed by GLC. The chromatogram exhibited three peaks which were identified by a comparison of retention times with those of authentic samples of *N,N*-dimethylbenzamide (Eastman Organic Chemicals), *N*-methylbenzamide,[22d] and *N,N*-dimethylsalicylamide.[22c] Coinjection with authentic samples caused peak enhancements for each of the three compounds.

***cis*-2-Nitrostilbene.** *trans*-*o*-Nitro-α-phenylcinnamic acid was decarboxylated by the method of Cohen and Schambach.[38] In a 500-mL, three-neck, round-bottom flask fitted with a nitrogen inlet which entered below the surface of the liquid and a thermometer that was immersed in the liquid were placed 11 g (40 mmol) of *trans*-*o*-nitro-α-phenylcinnamic acid,[12] 2.9 g (20 mmol) of cuprous oxide, and 250 mL of quinoline. The mixture was then heated slowly until the rate of carbon dioxide evolution (noted via a change in weight of an Ascarite tube) reached a maximum (155 °C). Carbon dioxide evolution was monitored until the reaction was nearly complete (97% yield of CO_2) after which time the reaction mixture was allowed to cool to room temperature. Cuprous oxide and other inorganics were removed by filtration, the quinoline was removed by vacuum distillation (55 °C at 0.1 mmHg), and the residue was chromatographed on a 4-ft glass column packed with neutral alumina. The *cis*- and *trans*-2-nitrostilbene isomers were eluted with a 5% ether–95% *n*-hexane mixture, the cis isomer eluting first and yielding bright yellow needles, mp 63.0–63.5 °C (lit.[12] mp 63.0–63.5 °C), in a 55% yield.

***cis*-Stilbene-2-diazonium Tetrafluoroborate.**[12] Reduction of 3.0 g of the nitrostilbene to the hydrochloride (mp 203–204 °C lit.[12] mp 202–203 °C) of *cis*-2-aminostilbene was accomplished in 60% yield by the method of Ruggli and Staub.[39] This hydrochloride (1.85 g, 8.0 mmol) was dissolved in 50 mL of a 10% aqueous sodium hydroxide solution, shaken vigorously, and extracted four times with 10-mL portions of methylene chloride. The combined extracts were dried over sodium carbonate and concentrated, leaving 1.54 g (7.9 mmol) of a colorless oil, presumed to be *cis*-2-aminostilbene, which showed one peak via a GLC analysis. To a stirred solution of this oil in 50 mL of absolute ethanol at 0 °C was added 5.4 g (30 mmol) of fluoroboric acid (48–50%) and the resulting solution was allowed to stir for 15 min. Freshly distilled *n*-amyl nitrite (1.42 g, 12.0 mmol) was then added dropwise over a 15-min period, whereupon the reaction mixture changed from colorless to bright yellow. After the solution had been stirred for 2 h at 0 °C, 200 mL of cold anhydrous ether was added to precipitate the bright yellow diazonium salt. The material was then filtered and purified by solution in a mixture of 40 mL of methanol–10 mL of dimethylformamide followed by precipitation with about 250 mL of anhydrous ether. The yield of reprecipitated fluoroborate (yellow crystals) was 1.45 g (65%): mp 87.0–87.5 °C dec; IR (Nujol) 2240 (s, N≡N$^+$), 1470 (s), and 1050 cm^{-1} (s, broad, BF).

Decomposition of *cis*-Stilbene-2-diazonium Tetrafluoroborate. The procedure was nearly identical with that for the decomposition of *N,N*-dimethylbenzamide-*o*-diazonium tetrafluoroborate except that the cupric nitrate trihydrate (15 g, 62 mmol) and silver nitrate (10 g, 59 mmol) were added to a solution of the diazonium salt in 50 mL of water. This mode of addition was used in order to ensure the complete dissolution of the diazonium salt prior to adding the catalyst, cuprous oxide. GLC analysis showed one peak which was identified by comparison of retention times and peak enhancement via the dual injection technique with an authentic sample (Aldrich), as phenanthrene. Based on the internal standard, *p*-tolyl benzoate, the yield of phenanthrene was 88% for duplicate runs. No *cis*-2-hydroxystilbene was formed.

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Registry No.—**10** bisulfate, 32066-79-8; **11**, 106-44-5; **12**, 5428-54-6; **13** BF_4, 1427-01-6; **13** HSO_4, 62058-61-1; **15**, 13073-29-5; **16** BF_4, 54616-48-7; **21** BF_4, 62058-63-3; *p*-toluidine, 106-49-0; 5-nitro-2-methylaniline, 99-55-8; 2-methyl-6-nitroaniline, 570-24-1; fluoroboric acid, 16872-11-0; 7-nitro-1*H*-indazole, 2942-42-9; *o*-amino-*N,N*-dimethylbenzamide, 6526-66-5; *o*-nitro-*N,N*-dimethylbenzamide, 2018-71-5; *cis*-2-nitrostilbene, 52208-62-5; *trans*-*o*-nitro-α-phenylcinnamic acid, 19319-35-8; *cis*-2-aminostilbene, 62058-64-4.

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Protonated Cyclopropanes. 9. Protonated Methylcyclopropane Intermediates in the Trifluoroacetolysis of 1-Butyl-*1*-^{14}C-mercuric Perchlorate

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The trifluoroacetolysis of 1-butyl-*1*-^{14}C-mercuric perchlorate was carried out at 35, 50, and 72 °C. At 35 °C, ^{14}C was scrambled only between C-1 and C-4 in the major 2-butyl product and there was no isotopic scrambling in the minor 1-butyl product. At 50 or 72 °C, all four isomeric butyl products were obtained. In the major product, 2-butyl-^{14}C trifluoroacetate, the label was scrambled over all four carbon positions. There was a small amount of ^{14}C scrambling from C-1 to C-2 in the 1-butyl product, while in the isobutyl ester, a 50:50 split of the label between C-1 and the rest of the molecule was observed. These results indicated that at 35 °C, the only scrambling processes were successive 1,2-hydride shifts involving classical 1-butyl and 2-butyl cations. At 50 or 72 °C, however, the scrambling data could be explained only by invoking some involvement (about 8–14%) of equilibrating protonated methylcyclopropanes in the overall reaction.

Work on protonated cyclopropanes has been the subject of a number of reviews,[1] and much of the evidence implicating such species as reaction intermediates has been derived from studies using isotopes as labels. In contrast to the unsubstituted protonated cyclopropane intermediates, definitive evidence from isotopic scrambling for protonated methylcyclopropane has been rather limited. Deno et al.[2] have reported that according to NMR studies, the addition of DCl to

Table I. Yields (%) of Isomeric Butyl Alcohols Derived from the Ester Products in the Trifluoroacetolysis of 1-Butyl-*1*-^{14}C-mercuric Perchlorate as Determined by Isotopic Dilution Calculations

Reaction conditions	1-BuOH		2-BuOH		*i*-BuOH		*t*-BuOH	
	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2
35 °C, 10 days	2.5	2.4	26.8	26.5	Trace	Trace	0	0
50 °C, 4 days	3.0	3.2	63.5	59.5	2.5	2.8	0.1	0.1
72 °C, 1 h	2.8	2.7	51.0	50.7	0.4	0.4	0.9	0.9

methylcyclopropane (1) gave only $CH_3CHClCH_2CH_2D$, and it was suggested that addition of D^+ to 1 gave rise to the 2-butyl cation either directly or via a short-lived, nonisomerizing protonated methylcyclopropane. On the other hand, Deno and Billup[3] noted that the ionic addition of Cl_2 to 1 gave a mixture of 1,3-, 1,2-, and 2,3-dichlorobutanes which were interpreted as arising, at least partially, from protonated methylcyclopropane intermediates.

From the mass spectral analysis and NMR examination of the alcohols derived from the aqueous acid deamination of a number of D-labeled 1-butyl- and isobutylamines, Karabatsos, Meyerson, and co-workers[4] failed to obtain any scrambling data in support of protonated methylcyclopropanes as important intermediates. It was stated, however, that this did not exclude a minor degree of intervention by such intermediates, since small extents of rearrangements might be within the experimental errors of the method of measurement. Small amounts of 1 were detected among the products from these reactions, and it was concluded that the only evidence for the intermediacy of protonated methylcyclopropane in aqueous acid deamination of 1-butylamine or isobutylamine was the formation of 1.

Considerably greater amounts of 1 were observed among the hydrocarbon products by Friedman et al.[5] from the deamination of 1-butyl- and isobutylamines under aprotic conditions. The D contents of 1 from the diazotization of several D-labeled isobutyl- and 2-butylamines in protic and aprotic solvents also led to the conclusion that a minor amount of the methylcyclopropane (1) did arise via partially equilibrated protonated methylcyclopropanes.[5c] In superacids, extensive scramblings via protonated methylcyclopropanes have been proposed. Thus the scrambling of all the protons in the 2-butyl cation observed by NMR in SbF_5–SO_2ClF solution,[1e,6] and the HF-SbF_5 catalyzed isomerization of butane-*1*-^{13}C to butane-*2*-^{13}C,[7] have been interpreted as proceeding via protonated methylcyclopropane intermediates.

Lee and Zea Ponce[8] have reported the observation of extensive and complex rearrangements when 1-butyl-*1*-^{14}C chloride was treated with $AlCl_3$, but no definitive evidence for protonated methylcyclopropanes could be deduced. Support for equilibrating protonated methylcyclopropane intermediates was obtained in the trifluoroacetolysis of 1-butyl-*1*-^{14}C tosylate (2-OTs-*1*-^{14}C).[9] The 2-butyl product from this reaction was found to contain some of the ^{14}C label in all four carbon positions. Since 1,2-hydride shifts in the 2-butyl cation would only scramble the label over C-1 and C-4, and after eliminating a mechanism solely involving 1,2 shifts in classical ions, it was proposed[9] that a minor pathway involving equilibrating protonated methylcyclopropane intermediates could account for the overall ^{14}C distribution in the 2-butyl product. In the same investigation,[9] it was also found that the trifluoroacetolysis of 1-propyl-*1*-^{14}C-mercuric perchlorate gave a 1-propyl product with more of the label scrambled to C-3 than C-2. This result agreed with the prediction of Collins[1a] for product formation from equilibrating edge-protonated cyclopropane intermediates. Even if corner-protonated cyclopropane were more stable than the edge-protonated species,[1e,10] the observed result could arise from kinetically controlled processes. In the trifluoroacetolysis of $RHgClO_4$, since the loss of Hg^0 from RHg^+ gave no counterion for ion pair formation, and since the low nucleophilic character of CF_3COOH would render the solvent poorly solvating, it was suggested[9] that the carbocation formed in such a reaction more likely would give rise to a kinetically controlled rather than a thermodynamically controlled product. In the present work, the trifluoroacetolysis of 2-OTs-*1*-^{14}C was extended to include a study on the trifluoroacetolysis of 1-butyl-*1*-^{14}C-mercuric perchlorate (2-$HgClO_4$-*1*-^{14}C) in an attempt to obtain further scrambling data in support of protonated methylcyclopropane intermediates.

Results

1-Butyl-*1*-^{14}C-mercuric acetate (2-HgOAc-*1*-^{14}C) was prepared by the method of Ouellette,[11] which involved the conversion of 2-Cl-*1*-^{14}C[8] to the Grignard reagent, followed by reaction with $HgCl_2$ to give 2-HgCl-*1*-^{14}C and then treatment with AgOAc to give 2-HgOAc-*1*-^{14}C. As was done in the preparation of 1-propyl-*1*-^{14}C-mercuric acetate,[12] the 2-HgOAc-*1*-^{14}C was hydrolyzed in aqueous dioxane containing NaOH to give 1-butyl-*1*-^{14}C alcohol (2-OH-*1*-^{14}C), the degradation of which showed that all of the ^{14}C label was located at C-1.

The solvolytic demercuration reaction is generally carried out by treatment of RHgOAc in the appropriate solvent in the presence of $HClO_4$.[13] The present solvolysis studies were effected by treating 2-HgOAc-*1*-^{14}C in CF_3COOH in the presence of $HClO_4$ at 35 °C for 10 days, at 50 °C for 4 days, and at 72 °C (the reflux temperature) for 1 h. The various reaction times were chosen so as to give about the maximum yield of the major product, 2-butyl trifluoroacetate (3-$OAcF_3$). These reaction times were determined in preliminary experiments by NMR examination of the reaction mixture using nonlabeled 2-HgOAc. At 35 and 50 °C, reaction times longer than 10 and 4 days, respectively, gave only very slight increases in yields of 3-$OAcF_3$, while at 72 °C, reaction times longer than 1 h caused a sharp decrease in yield, presumably because of decomposition. In the experiments with active 2-HgOAc-*1*-^{14}C, the isomeric butyl ester products were hydrolyzed directly to give a mixture of the isomeric butyl alcohols (1-butyl-^{14}C, 2-butyl-^{14}C, isobutyl-^{14}C, and *tert*-butyl-^{14}C alcohols, 2-OH-^{14}C, 3-OH-^{14}C, 4-OH-^{14}C, and 5-OH-^{14}C, respectively). The yields of these alcohols were determined by isotopic dilution,[8,9] and the results are given in Table I.

After the separation of the isomeric butyl alcohols by preparative VPC in the isotopic dilution experiments, additional carriers were added to 2-OH-^{14}C, 3-OH-^{14}C, and 4-OH-$^{14}C$and these three alcohols were then degraded in order to give the ^{14}C distributions. Degradations of 2-OH-^{14}C and 3-OH-^{14}C were carried out as previously described,[8,9] involving the conversion of 2-OH-^{14}C to butyric acid, propylamine, propionic acid, and acetic acid, and the conversion of 3-OH-^{14}C to CBr_4 and propionic acid, and the latter in turn was converted to acetic acid and methylamine. 4-OH-^{14}C, which was not degraded in the previous studies,[8,9] was oxidized to isobutyric acid and then converted to isopropylamine. The relevant ac-

Table II. ^{14}C Distributions in the 1-Butyl-^{14}C Alcohol (2-OH-^{14}C) Derived from the Trifluoroacetolysis of 1-Butyl-*1*-^{14}C-mercuric Perchlorate

Reaction conditions		Specific activity, dpm/mmol[a]			^{14}C distribution, %		
		1-BuOH[b]	CH_3CH_2COOH[c]	CH_3COOH[c]	C-1	C-2	C-3,4
35 °C, 10 days	Run 1	32 700	0	0	100	0	0
	Run 2	39 400	0	0	100	0	0
50 °C, 4 days	Run 1	61 800	2530	0	95.9	4.1	0
	Run 2	56 500	2330	0	95.9	4.0	0
72 °C, 1 h	Run 1	39 800	917	0	97.7	2.3	0
	Run 2	42 400	1020	0	97.6	2.4	0

[a] ^{14}C activities in this and other tables were measured by a liquid scintillation counter. Statistical counting errors were ±1% or less. [b] Assayed as the α-naphthylurethane. [c] Assayed as the *S*-benzylisothiouronium salt.

Table III. ^{14}C Distribution in the 2-Butyl-^{14}C Alcohol (3-OH-^{14}C) Derived from the Trifluoroacetolysis of 1-Butyl-*1*-^{14}C-mercuric Perchlorate

Reaction conditions		Specific activity, dpm/mmol					^{14}C distribution, %			
		2-BuOH[a]	CBr_4	CH_3CH_2COOH[b]	CH_3COOH[b]	CH_3NH_2[c]	C-1	C-2	C-3	C-4
35 °C, 10 days	Run 1	382 000	241 000	141 000	141 000	141 000	63.1	0	0	36.9
	Run 2	449 000	274 000	175 000	175 000	175 000	61.0	0	0	39.0
50 °C, 4 days	Run 1	843 000	504 000	339 000	336 000	278 000	59.8	0.3	6.9	33.0
	Run 2	906 000	544 000	362 000	359 000	295 000	60.1	0.3	6.9	32.6
72 °C, 1 h	Run 1	664 000	335 000	329 000	318 000	303 000	50.5	1.7	2.3	45.6
	Run 2	690 000	348 000	342 000	331 000	316 000	50.4	1.6	2.3	45.8

[a] Assayed as the α-naphthylurethane. [b] Assayed as the *S*-benzylisothiouronium salt. [c] Assayed as the *p*-toluenesulfonamide.

Table IV. ^{14}C Distribution in the Isobutyl-^{14}C Alcohol (4-OH-^{14}C) Derived from the Trifluoroacetolysis of 1-Butyl-*1*-^{14}C-mercuric Perchlorate

Reaction conditions		Specific activity, dpm/mmol		^{14}C distribution, %	
		i-BuOH[a]	$(CH_3)_2CHNH_2$[b]	C-1	Rest of molecule
50 °C, 4 days	Run 1	44 900	21 200	52.6	47.4
	Run 2	45 700	22 900	49.8	50.1
72 °C, 1 h	Run 1	6 770	3 460	48.9	51.1
	Run 2	7 510	3 810	49.3	50.7

[a] Assayed as the α-naphthylurethane. [b] Assayed as the *p*-toluenesulfonamide.

tivity data and the ^{14}C distributions are summarized in Tables II–IV.

Discussion

Hydrolysis of the products from the trifluoroacetolysis of 2-$HgClO_4$-*1*-^{14}C at 35 °C for 10 days gave 2-butyl-^{14}C alcohol (3-OH-^{14}C) as the major product, with a minor amount of 1-butyl-^{14}C alcohol (2-OH-^{14}C) and essentially no isobutyl and *tert*-butyl alcohols (Table I). The 2-OH-^{14}C was the isotopically unrearranged 2-OH-*1*-^{14}C (Table II), while in the 3-OH-^{14}C, the label was scrambled only between C-1 and C-4 (Table III). These results indicate no involvement of protonated methylcyclopropane in the reaction at 35 °C. The unrearranged 2-OH-*1*-^{14}C could be derived from a direct displacement and/or the trapping of the 1-butyl-*1*-^{14}C cation from the demercuration of 2-Hg^+-*1*-^{14}C. Successive 1,2-hydride shifts involving only classical butyl cations also would account for the scrambling of ^{14}C over C-1 and C-4 in the 2-butyl product (Scheme I). The fact that more 2-butyl-*1*-^{14}C than 2-butyl-*4*-^{14}C product was formed would suggest that under the reaction conditions employed, trapping of the 2-butyl cation to give product was more rapid than the 1,2-hydride shifts that interconverted the degenerate 2-butyl cations.

Scheme I

$$CH_3CH_2CH_2{}^{14}CH_2^+ \longrightarrow CH_3CH_2\overset{+}{C}H{}^{14}CH_3 \rightleftharpoons CH_3\overset{+}{C}HCH_2{}^{14}CH_3$$

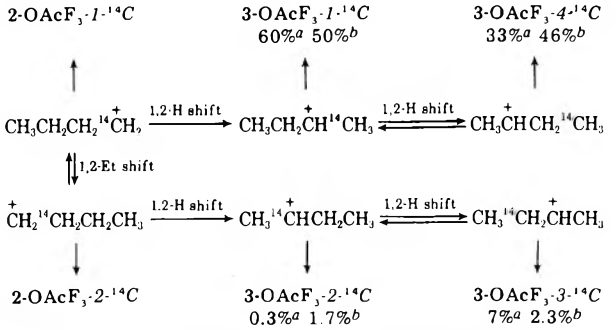
$$\downarrow \qquad\qquad \downarrow$$

3-$OAcF_3$-*1*-^{14}C (62%) 3-$OAcF_3$-*4*-^{14}C (38%)

From the reaction at 50 °C for 4 days or at 72 °C for 1 h, all four isomeric butyl products were detected (Table I) and scramblings of the label were more extensive. In the major 2-butyl product, ^{14}C was found in all four carbon positions (Table III), while in the 1-butyl product, there was some scrambling to C-2 (Table II). As discussed in previous studies,[8,9] if one were to invoke only classical ions to explain these results, the processes depicted in Scheme II may be proposed. Since the 2-butyl-*1*-^{14}C cation and the 2-butyl-*2*-^{14}C cation differ only in the position of the label, one would expect these ions to give the same subsequent reactions. Thus according to Scheme II, the ratio of 3-$OAcF_3$-*4*-^{14}C/3-$OAcF_3$-*1*-^{14}C should be equal to the ratio of 3-$OAcF_3$-*3*-^{14}C/3-$OAcF_3$-*2*-^{14}C. Clearly this is not the case since 33/60 and 7/0.3, or 46/50 and 2.2/1.7, are not equal. Scheme II, involving only classical ions, therefore, is not adequate in accounting for the scrambling results.

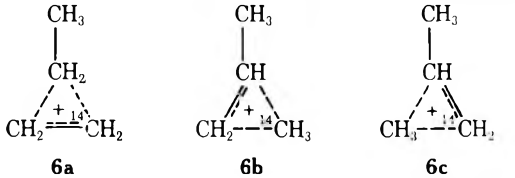
In order to scramble the ^{14}C label to the C-2 and C-3 positions of the 2-butyl product, as an alternative to the 1,2-ethyl shift, equilibrating protonated methylcyclopropanes could be involved. Analogous to the mechanism proposed for the

Scheme II

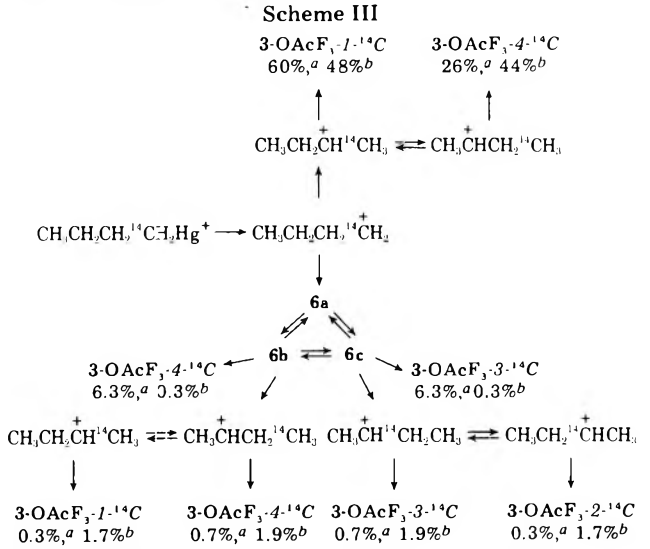


[a] Mean values from Table III for reaction at 50 °C for 4 days. [b] Mean values from Table III for reaction at 72 °C for 1 h.

trifluoroacetolysis of 2-OTs-*1*-^{14}C,[9] in the present solvolytic demercuration, besides the successive hydride shifts as depicted in Scheme I, which were the only processes observed at 35 °C, it is suggested that at 50 or 72 °C, part of the reaction would proceed via equilibrating methylcyclopropane intermediates (corner-protonated **6a–c** or edge-protonated **7a–c**). Scheme III shows the partitioning of the various routes (utilizing corner-protonated **6a–c**) leading to the ^{14}C scrambling in the 2-butyl product, 3-OAcF$_3$-^{14}C. In this scheme it is proposed that **6b** and **6c** could give the 2-butyl ester without further scrambling, or give rise to the more stable 2-butyl cation which subsequently would undergo degenerate hydride shifts. Moreover, in the various routes leading to 3-OAcF$_3$-^{14}C, the equality of the product ratios derived from equilibrating degenerate 2-butyl cations was maintained (26/60 = 0.3/0.7 at 50 °C and 44/48 = 1.7/1.9 at 72 °C). The net ^{14}C contents



Scheme III

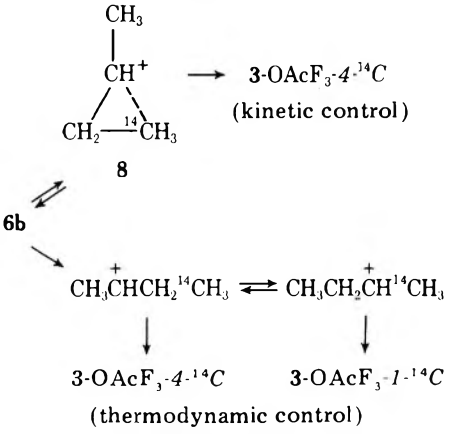


[a] Reaction at 50 °C for 4 days. [b] Reaction at 72 °C for 1 h.

would be 60 + 0.3, 0.3, 6.3 + 0.7, and 26 + 6.3 + 0.7, or 60, 0.3, 7.0, and 33%, respectively, at C-1, C-2, C-3, and C-4 for the reaction at 50 °C; and 48 + 1.7, 1.7, 0.3 + 1.9, and 44 + 0.3 + 1.9, or 50, 1.7, 2.2, and 46%, respectively, at C-1, C-2, C-3, and C-4 for the reaction at 72 °C. These calculated ^{14}C distributions are in good agreement with the mean observed values recorded in Table III.

According to Scheme III, at 50 °C, there was more 2-butyl ester formation from **6b** or **6c** without further scrambling (6.3%) than the formation of 2-butyl cation which subsequently could undergo degenerate hydride shifts (0.7 + 0.3%), while at 72 °C, the reverse was true (0.3% and 1.9 + 1.7%). These findings could be rationalized by the assumption that the more stable 2-butyl cation was formed under thermodynamic control, and at 50 °C protonated methylcyclopropanes gave rise to more kinetically controlled product. A possible formulation of such processes could be as illustrated for **6b** in Scheme IV, utilizing a partially bridged ion **8**. Calculations for

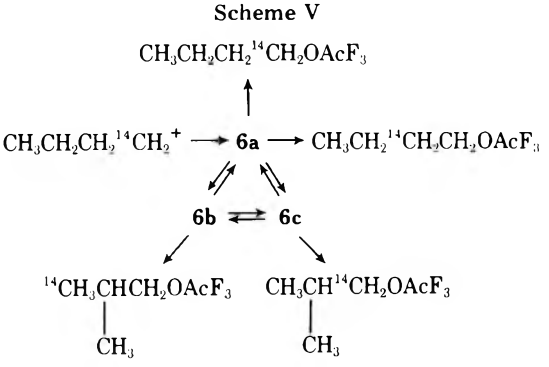
Scheme IV



the unsubstituted protonated cyclopropane intermediates indicated that a partially bridged ion analogous to 8 is of comparable stability to corner-protonated cyclopropane.[10] Thus at 50 °C, more kinetically controlled product was formed from **6b** via **8**, while at 72 °C, more thermodynamically controlled product derived from the degenerate 2-butyl cations was obtained. It is also of interest to note that, as expected, there were more extensive degenerate hydride shifts in the 2-butyl cation at 72 °C (44/48 and 1.7/1.9) than at 50 °C (26/60 and 0.3/0.7).

Equilibrating protonated methylcyclopropanes could also account for the isotopic scramblings observed in the minor products given in Tables II and IV. As shown in Scheme V, the

Scheme V



small amount of scrambling to C-2 in the 1-butyl product (Table II) could be derived from **6a**, while the isobutyl product derived from **6b** and **6c** would result in a 50% scrambling of the label between C-1 and the rest of the molecule, and this was as observed (Table IV). The minor amounts of *tert*-butyl product, as recorded in Table I, presumably was derived from

the facile rearrangement of the isobutyl to the *tert*-butyl cation. Interestingly, reaction at 50 °C, which favored kinetic control of product formation from protonated methylcyclopropanes, gave only 0.1% *t*-BuOH compared to 2.5–2.8% *i*-BuOH, while in the reaction at 72 °C, which was more favorable to thermodynamic control, 0.9% *t*-BuOH compared to 0.4% *i*-BuOH was obtained (Table I). From these considerations and from the discussion on the ^{14}C scrambling processes leading to the 2-butyl product, the conclusion may be made that the present data gave support to some involvement of equilibrating protonated methylcyclopropanes in the trifluoroacetolysis of 2-$HgClO_4$-*1*-^{14}C. While the only scrambling processes occurring at 35 °C were successive 1,2-hydride shifts in classical 1-butyl and 2-butyl cations (Scheme I), besides these classical processes, reaction at 50 and 72 °C, respectively, apparently resulted in about 14 and 8% of the overall reaction (Scheme III) proceeding via equilibrating protonated methylcyclopropanes.

Experimental Section

1-Butyl-*1*-^{14}C-mercuric Acetate (2-HgOAc-*1*-^{14}C). Following the method of Ouellette,[11] 1-butyl-*1*-^{14}C chloride (2-Cl-*1*-^{14}C)[8] was converted successively to 2-MgCl-*1*-^{14}C, 2-HgCl-*1*-^{14}C, and 2-HgOAc-*1*-^{14}C, mp 52–53 °C (lit.[11,14] mp 53.8–54.4, 52.5–53.2 °C). Hydrolysis of 2-HgOAc-*1*-^{14}C in 10% dioxane–90% H_2O containing 10% NaOH[12] gave a 40% yield of 2-OH-*1*-^{14}C, which upon oxidation to butyric acid followed by a Schmidt reaction gave 1-propylamine[8] which contained essentially no ^{14}C activity.

Trifluoroacetolysis Reactions. A solution of 5.0 g (16 mmol) of 2-HgOAc-*1*-^{14}C and 3.6 g (25 mmol) of 70% $HClO_4$ in 50 mL of CF_3COOH was placed in a 250-mL flask equipped with a reflux condenser. The material was heated at 35 °C for 10 days, 50 °C for 4 days, or 72 °C for 1 h. After cooling, the reaction mixture was neutralized with 25% NaOH solution. After the addition of a further 60 mL of 25% NaOH solution, the mixture was heated under reflux overnight to hydrolyze the ester products. Ordinary 1-butyl, 2-butyl, isobutyl, and *tert*-butyl alcohols (2-OH, 3-OH, 4-OH, and 5-OH, respectively) were added as carriers. The mixture of diluted isomeric butyl-^{14}C alcohols were recovered by continuous extraction with ether and then separated and purified by preparative VPC.[8] From the known amount of carriers added and their specific activities before and after dilution, the yields of the four isomeric butyl alcohols (Table I) were calculated as previously described.[8]

The recovered 2-OH-^{14}C, 3-OH-^{14}C, and 4-OH-^{14}C were further diluted with appropriate amounts of inactive carriers before being subjected to degradation.

Degradation of the Butyl Alcohols. The degradation of 2-OH-^{14}C and 3-OH-^{14}C were carried out as described in previous work.[8,9] 4-OH-^{14}C was oxidized to isobutyric acid by $KMnO_4$ in Na_2CO_3 solution.[15] The isobutyric acid was converted to isopropylamine by the Schmidt reaction analogous to the conversion of butyric acid to 1-propylamine.[8]

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Registry No.—2-HgOAc-*i*-^{14}C, 61990-71-4; 2-$HgClO_4$-*1*-^{14}C, 61990-72-5; 2-OH-*1*-^{14}C, 61990-73-6; 2-OH-*2*-^{14}C, 19836-38-5; 2-$OAcF_3$-*1*-^{14}C, 61990-74-7; 2-$OAcF_3$-*2*-^{14}C, 61990-75-8; 3-OH-*1*-^{14}C, 61990-76-9; 3-OH-*2*-^{14}C, 61990-77-0; 3-OH-*3*-^{14}C, 61990-78-1; 3-OH-*4*-^{14}C, 61990-79-2; 3-$OAcF_3$-*1*-^{14}C, 61990-80-5; 3-$OAcF_3$-*2*-^{14}C, 61990-81-6; 3-$OAcF_3$-*3*-^{14}C, 61990-82-7; 3-$OAcF_3$-*4*-^{14}C, 61990-83-8; 4-OH-*1*-^{14}C, 41871-35-6; 4-OH-*2*-^{14}C, 61990-84-9; 4-OH-*3*-^{14}C, 19836-37-4; 4-$OAcF_3$-*1*-^{14}C, 61990-85-0; 4-$OAcF_3$-*2*-^{14}C, 61990-86-1; 4-$OAcF_3$-*3*-^{14}C, 61990-87-2; 5-OH, 61990-88-3; 5-$OAcF_3$-^{14}C, 61990-89-4; 6, 61990-90-7.

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Metal-Ion Oxidative Decarboxylations. 9.[1] Reaction of Benzilic Acid with Cerium(IV) in Acidic Perchlorate and Sulfate Media

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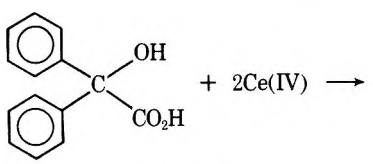
The kinetics of oxidation of benzilic acid (HLH) to benzophenone by cerium(IV) has been studied in several media using the stopped-flow technique. In $HClO_4$–Na_2SO_4–$NaClO_4$ media, which allow for the variation and control of the concentrations of the various Ce(IV) species at constant $[H^+]$ and ionic strength, the rate data suggest $CeSO_4^{2+}$ as the kinetically relevant species. In $HClO_4$ the observed first-order rate constants, k^I_{obsd}, first increase with increasing HLH concentration, then decrease slightly at higher substrate concentrations suggesting the intermediacy of two complexes: a reactive [Ce(IV)HL] and a [Ce(IV)$(HL)_2$] which resists reaction. The rate law which best describes the observed kinetics in $HClO_4$ media is given by $-d[Ce^{IV}]_T/dt = k^I_{obsd}[Ce(IV)]_T$, $k^I_{obsd} = (k_\alpha K_7'[HLH] + k_\beta K_7' K_8'[HLH]^2)/(1 + K_7'[HLH] + K_7'K_8'[HLH]^2)$, where K_7' and K_8' are H^+-dependent equilibrium constants for the formation of the 1:1 and 1:2 complexes, respectively. The kinetic parameters k_α and k_β are the rate constants for the intramolecular redox reaction of the 1:1 and 1:2 complexes, respectively. The rates in H_2SO_4 are much slower than those in $HClO_4$ and do not reflect strong complex formation before electron transfer. Whereas H^+ had an inhibiting effect in the above-mentioned media, catalysis by H^+ was manifest in $HClO_4$–HOAc media, possibly through decreasing acetato complexation of Ce(IV).

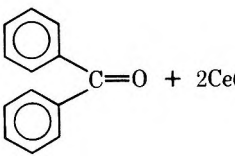
In spite of the multitude and variety of reports on the uses of cerium(IV) in mechanistic and synthetic studies,[2,3] the investigations frequently refer to the oxidant as "Ce(IV)" without specifying the particular cerium(IV) species involved in the oxidation. In sulfuric acid, where many kinetic investigations are conducted,[4] cerium(IV) exists mainly as a mixture of several sulfato complexes: $CeSO_4^{2+}$, $Ce(SO_4)_2$, and $Ce(SO_4)_3^{2-}$.[5] On the other hand, in acidic perchlorate media, cerium(IV) is not complexed, although the following species have been reported:[6,7] Ce^{4+}, $CeOH^{3+}$, $Ce(OH)_2^{2+}$, $(CeOCe)^{6+}$, and $(HOCeOCeOH)^{4+}$. In perchloric acid, evidence for polymeric species with molecular weight up to 40 000 has been recently reported.[8] The presence of such species would certainly lead to complications in the kinetic analyses of rate data.[9] Their presence can be tested for by reaction with H_2O_2 which, owing to complex formation, gives a red color that fades only slowly.[9] Polymeric species can be avoided, however, by reduction of Ce(IV) to Ce(III) with excess H_2O_2 followed by electrochemical oxidation.[9,10] Freshly electrolyzed cerium solutions in $HClO_4$ thus contain only monomeric species whose concentrations are governed by a set of hydrolysis constants.

Recently, we proposed the system $HClO_4$–Na_2SO_4–$NaClO_4$ as an ideal acidic sulfate medium in which the various concentrations of all the cerium(IV) species, governed by known equilibrium constants, can be calculated and varied at will.[11] At a specified $[H^+]$ and constant ionic strength, one introduces calculated amounts of Na_2SO_4 to generate controllable concentrations of the various cerium(IV) species and then studies the rate of a redox reaction as a function of variations in such species.[11]

The oxidative decarboxylation of benzilic acid to benzophenone (eq 1) was chosen as a model reaction to test the proposed idea of pinpointing the kinetically significant species



$$+ 2Ce(IV) \longrightarrow$$



$$+ 2Ce(III) + 2H^+ + CO_2 \quad (1)$$

of cerium(IV). Although the said decarboxylation has been studied previously in some detail,[12,13] the medium was not defined clearly with respect to either $[H^+]$ or the ionic strength. In 1–2.5 M H_2SO_4, $Ce(OH)_2^{2+}$ was suggested as the main reactive species.[12] In the present paper we report the results of a spectrophotometric study, mainly by the stopped-flow technique, of the cerium(IV) oxidation of benzilic acid to benzophenone in acidic perchlorate and sulfate media.

Experimental Section

Materials. Cerium(IV) in perchloric acid was prepared by the electrolytic oxidation of cerium(III) perchlorate solutions.[9-13] The latter were obtained either from ammonium cerium(IV) nitrate (Fisher, Certified A. C. S.) or from cerium(IV) perchlorate solution (G. Frederick Smith Chemical Co.) by reduction with excess H_2O_2. The electrolyses were carried out in perchloric acid [ca. 0.02 M Ce(IV) in 4 M $HClO_4$] with a spinning cylindrical Pt-gauze anode and a Pt-wire cathode for 2.5 h. The steps involved in the preparations are summarized in Scheme I. Electrolytically reoxidized cerium solutions in perchloric acid were titrated against ammonium iron(II) sulfate for their Ce(IV) content,[14] and against standardized NaOH for their acid content.

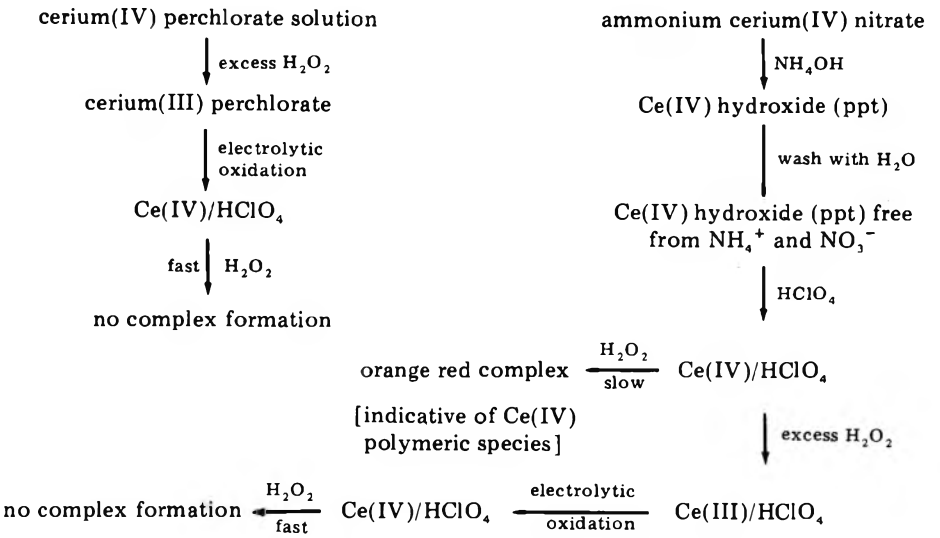
Cerium(IV) in H_2SO_4 solutions were prepared freshly before each series of kinetic runs by dissolving cerium(IV) sulfate or ammonium cerium(IV) sulfate (Merck, p.a.) in sulfuric acid solutions; these solutions were standardized by the same method used for cerium(IV) perchlorate and were double checked spectrophotometrically.[15]

Benzilic acid, acrylamide, *N,N'*-methylenebisacrylamide, *N,N,N',N'*-tetramethylenediamine (TEMED), and diphenylacetic acid were Eastman, White Label chemicals. Lead-free double vacuum-distilled 70% perchloric acid, sodium perchlorate, and ammonium iron(II) sulfate (A. C. S.) were from G. Frederick Smith Chemical Co. Sulfuric acid and sodium sulfate were from Fisher.

Stoichiometry. The stoichiometry was determined, under the conditions of kinetic runs, from the absorbance of benzophenone (monitored at 256 nm) produced on the oxidation of a slight excess of benzilic acid by a known amount of Ce(IV). The results point to the consumption of 2 mol of Ce(IV) (monitored at 300 nm) per mol of benzophenone produced (Figure 1). This confirms the stoichiometry previously reported[12,13] and depicted in eq 1.

Kinetics. The majority of rate measurements were done on a Durrum-Gibson stopped-flow apparatus equipped with a photometric log amplifier. The signal from the spectrophotometer's photomultiplier was fed into a Biomation transient recorder, Model 802, which was interfaced with a Tektronix storage oscilloscope, a Bausch and Lomb plotter, and a Data Cap tape perforator, Model 820. The digitized data were retrieved from the transient recorder through the tape perforator and were processed by a linear least-squares program of polynomial fit on an IBM 370/168. A typical computer-drawn second-order plot of the data output is shown in Figure 2; the uncertainty

Scheme I



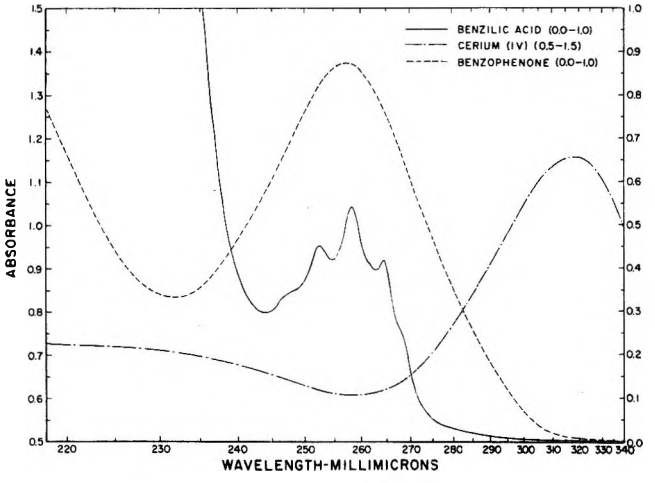


Figure 1. Absorption spectra of 2×10^{-4} M cerium(IV) in sulfuric acid, 1×10^{-3} M benzilic acid, and 5×10^{-5} M benzophenone.

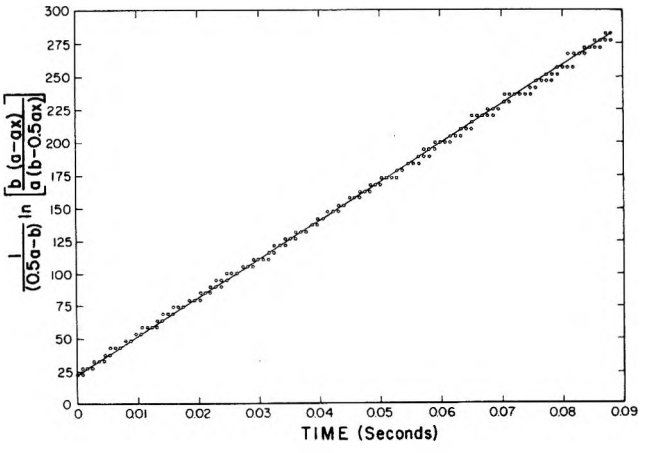


Figure 2. Second-order computer plot of cerium(IV) reaction with benzilic acid.

in the slopes of such plots was calculated to be 0.5–1.2%. Straight lines were obtained routinely over 80% reaction and the rate constants were reproducible to better than ±3%. For the slower runs, a Beckman DK-2A spectrophotometer equipped with a time-drive attachment and a thermostated cell holder was used.

For most runs, the benzilic acid concentration was 10–20 times the initial concentration of cerium(IV). The reactions were followed by observing the change in absorbance at 300–320 nm, characteristic of cerium(IV). In several experiments, the rates were followed by monitoring the production of benzophenone at 256 nm.

Tests for Free Radicals. Tests for polymerization,[16] as indicated by gel formation, of several monomers were conducted for mixtures of cerium(IV) with benzilic acid, EDTA, malic acid, and oxalic acid. While immediate gel formation was observed with EDTA, neither benzilic acid nor the other acids initiated visible polymerization except after long periods. Mercuric chloride, which has been used as a free-radical trap in similar systems,[17] gave no visible precipitate of Hg^0 during the cerium(IV) oxidation of benzilic acid.

Results and Discussion

We studied the oxidation of benzilic acid with cerium(IV) in four media. Employing electrolytically generated Ce(IV), we used an acidic sulfate medium which consisted of $HClO_4$–Na_2SO_4–$NaClO_4$ and an acidic perchlorate medium. The two other media consisted of either cerium(IV) sulfate or ammonium cerium(IV) sulfate in H_2SO_4 solutions, and of perchloric–acetic acids mixtures.

A. Kinetic Identification of the Reactive Cerium(IV) Species in Acidic Sulfate Media. We chose the system $HClO_4$–Na_2SO_4–$NaClO_4$ as an acidic sulfate medium to define $[H^+]$, $[HSO_4^-]$, $[SO_4^{2-}]$, and the ionic strength μ. This system is preferred to sulfuric acid because it has the distinct advantages of ensuring (1) an $[H^+]$ which can be varied independently of the sulfate concentration, while maintaining a defined and constant μ, and (2) a defined and controllable distribution of Ce(IV) species. If one defines $[H^+] = c$, and the formal concentrations of Na_2SO_4 and $HClO_4$ as m and s, respectively, then $s = c + [HSO_4^-]$, and $[HSO_4^-] = cm/c + K_a$ where K_a is the second dissociation constant for sulfuric acid. Using eq 2 of Reynolds and Fukushima[18]

$$\log K_a = -1.991 + \frac{2.04\sqrt{\mu}}{1 + 1.7\sqrt{\mu}} + 0.0314\mu \qquad (2)$$

to compute the dependence of K_a on μ in conjunction with the accepted definition of ionic strength, $\mu = \frac{1}{2} \Sigma_i c_i z_i^2$, one calculates the amount of $NaClO_4$ necessary to attain a certain ionic strength in the system $HClO_4$–Na_2SO_4–$NaClO_4$ from

$$\mu = \tfrac{1}{2}(c + [HSO_4^-] + 4[SO_4^{2-}] + 2m + s + 2[NaClO_4]) \qquad (3)$$

$$[NaClO_4] = \mu - 3m + s - 2c \qquad (4)$$

Hardwick and Robertson deterined the equilibrium constants, eq 5–7, at $[H^+] = 1$ M and $\mu = 2$ in a range of sulfate ion concentrations from 10^{-3} to 0.7 M.[19]

Table I. First-Order Rate Constants for the Ce(IV) [a]–Benzilic Acid [b] Reaction at 25 °C, μ = 1.00 ($NaClO_4$)

Run	Na_2SO_4 [c]	$[H^+]$	$HClO_4$ [c]	$NaClO_4$ [c]	$Ce(OH)^{3+}$ [d]	$Ce(OH)_2^{2+}$ [d]	Ce^{4+} [d]	CeX [d,e]	CeX_2 [d,e]	CeX_3 [d,e]	k^I_{obsd}, s^{-1}
1	0.002	0.75	0.75	0.246	9.3720	1.5000	1.0980	67.767	20.017	0.246	19.2
2	0.004		0.75	0.242	4.0830	0.6530	0.4790	59.045	34.882	0.859	17.6
3	0.010		0.76	0.229	1.0630	0.1700	0.1250	38.415	56.736	3.491	6.4
4	0.020		0.77	0.209	0.3190	0.0510	0.0370	23.068	68.138	8.386	1.85
5	0.040		0.79	0.168	0.0830	0.0130	0.0100	11.947	70.576	17.372	0.65
6	0.100		0.85	0.044	0.0110	0.0020	0.0010	4.022	59.406	36.557	0.14
7	0.002	0.50	0.50	0.496	5.9600	1.4300	0.4660	64.246	27.411	0.487	26.1
8	0.004		0.50	0.492	2.3850	0.5720	0.1860	51.419	43.877	1.560	19.4
9	0.010		0.51	0.479	0.5540	0.1330	0.0430	29.874	63.730	5.665	5.2
10	0.025		0.52	0.448	0.0990	0.0240	0.0080	13.284	70.844	15.743	1.42
11	0.100		0.59	0.290	0.0050	0.0010	0.0004	2.421	51.657	45.916	0.09
12	0.003	0.40	0.40	0.594	2.6300	0.7890	0.1640	53.458	41.609	1.350	21.0
13	0.010		0.41	0.579	0.3790	0.1140	0.0240	25.673	66.610	7.201	8.1
14	0.030		0.43	0.537	0.0440	0.0130	0.0030	8.838	68.792	22.311	1.34
15	0.100		0.54	0.286	0.0010	0.0003	0.0001	0.971	37.774	61.254	0.05
16	0.001	0.30	0.30	0.698	7.2950	2.9180	0.3420	66.970	22.169	0.306	44.
17	0.003		0.30	0.694	1.7400	0.6960	0.0820	47.923	47.591	1.970	28.
18	0.010		0.31	0.678	0.2280	0.0910	0.0110	20.909	69.215	9.547	9.0
19	0.030		0.32	0.636	0.0240	0.0100	0.0010	6.647	66.006	27.312	1.61
20	0.100		0.39	0.488	0.0014	0.0005	0.0001	1.254	41.502	57.242	0.14
21	0.0005	0.20	0.20	0.799	9.5910	5.7540	0.2990	68.539	15.665	0.149	55.
22	0.002		0.20	0.795	1.7440	1.0460	0.0540	49.847	45.572	1.736	42.
23	0.005		0.20	0.788	0.3970	0.2380	0.0124	28.359	64.819	6.173	25.6
24	0.020		0.22	0.755	0.0257	0.0154	0.0008	7.336	67.071	25.550	3.9
25	0.100		0.28	0.576	0.0005	0.0003	0.0000	0.748	34.170	65.082	0.17

[a] $[Ce(IV)]_0 = 2.5 \times 10^{-5}$ M. [b] $[\text{Benzilic acid}]_0 = 5 \times 10^{-4}$ M. [c] Formal concentrations. [d] Percent of total [Ce(IV)]. [e] X = SO_4^{2-}.

$$Ce(4) + HSO_4^- \overset{K_1}{\rightleftharpoons} CeSO_4^{2+} + H^+ \quad (5)$$

$$CeSO_4^{2+} + HSO_4^- \overset{K_2}{\rightleftharpoons} Ce(SO_4)_2 + H^+ \quad (6)$$

$$Ce(SO_4)_2 + HSO_4^- \overset{K_3}{\rightleftharpoons} Ce(SO_4)_3^{2-} + H^+ \quad (7)$$

The values of K_1, K_2, and K_3 are 3500, 200, and 20, respectively. Another set of equilibrium constants for the Ce(IV) sulfato complexation was determined by Bächmann and Lieser[20] at μ = 5.9. We calculated their values to be about 8600, 500, and 10, respectively.[21] The symbol Ce(4) in eq 5 represents the nonsulfated Ce(IV) species, Ce^{4+}, $CeOH^{3+}$, and $Ce(OH)_2^{2+}$, whose concentrations can be estimated from the hydrolysis constants given by Everett and Skoog,[22] eq 8 and 9. The values of the hydrolysis constants, K_4 and K_5, determined spectrophotometrically at μ = 1, are 6.4 and 0.12, respectively.[22]

$$Ce^{4+} + H_2O \overset{K_4}{\rightleftharpoons} CeOH^{3+} + H^+ \quad (8)$$

$$CeOH^{3+} + H_2O \overset{K_5}{\rightleftharpoons} Ce(OH)_2^{2+} + H^+ \quad (9)$$

For our work, we needed K_1, K_2, and K_3 at μ = 1. We evaluated these equilibrium constants at μ = 1 in acidic sulfate media ($HClO_4$–Na_2SO_4–$NaClO_4$) from spectrophotometric measurements at 400 nm by using the method of Hardwick and Robertson.[19] The values are 2300, 120, and 5, respectively.

The above equilibria, eq 5–9, were solved simultaneously, and the concentration distribution of the different sulfato and hydroxo complexes, as well as Ce^{4+}, was computed for a 10^{-3} to 0.6 M range of Na_2SO_4 concentrations and $[H^+] = 10^{-2}$ to 1.0 M at a fixed ionic strength, μ = 1.

The results of rate measurements on the Ce(IV)–benzilic acid reaction in $HClO_4$–Na_2SO_4–$NaClO_4$ media, for which the concentration distribution of the various Ce(IV) species has been computed, are summarized in Table I. The observed first-order rate constants, in s^{-1}, were calculated according to

$$k^I_{obsd}t = \ln\left(\frac{A_\infty - A_0}{A_\infty - A_t}\right) \quad (10)$$

by least-squares analysis, from spectrophotometric data collected by observing the formation of benzophenone at 256 nm using the stopped-flow technique; A_0, A_t, and A_∞ refer to the absorbances at the start of reaction, at time t, and at infinity, respectively. Inspection of Table I reveals the following facts. (1) At fixed $[H^+]$ and μ, the rate constant decreases steadily with increasing sulfate concentration. This is to be expected in view of the increase in sulfato complexation. The oxidations of organic and inorganic substrates by Ce(IV) are usually much faster in perchlorate than in sulfate media.[10,23,24] This is a reflection of the competition between the SO_4^{2-} and the substrates' ligands for positions in the coordination sphere around the metal ion, particularly if substitution is a necessary prerequisite for electron transfer.[25] An exception to this expectation is found in Adamson, Dainton, and Glentworth's report on the Ce(IV)–Fe(II) redox reaction where catalysis by small concentrations of sulfate was reported.[26] (2) The decreases in the concentrations of $CeOH^{3+}$, $Ce(OH)_2^{2+}$, and Ce^{4+} which accompany the addition of Na_2SO_4 are very much greater than the corresponding decreases in k^I_{obsd}. (3) At any fixed $[H^+]$ the increases in the concentration of $Ce(SO_4)_3^{2-}$ are accompanied by decreases in k^I_{obsd}. (4) Of all the species, whose concentrations are calculable by known equilibrium constants, the monosulfato complex, $CeSO_4^{2+}$, shows the closest parallelism to k^I_{obsd}.

The data in Table I were subjected to statistical analysis by a stepwise regression technique.[27] The correlation coefficients for k^I_{obsd} vs. the concentrations of the six Ce(IV) species are listed in Table II. It is evident that the best correlation exists between k^I_{obsd} and $[CeSO_4^{2+}]$. We wish, therefore, to propose the monosulfato complex as the kinetically relevant Ce(IV) species under our experimental conditions. This is to be contrasted with the results of the earlier investigation[12] which portrayed the dihydroxy species, $Ce(OH)_2^{2+}$, as the reactive

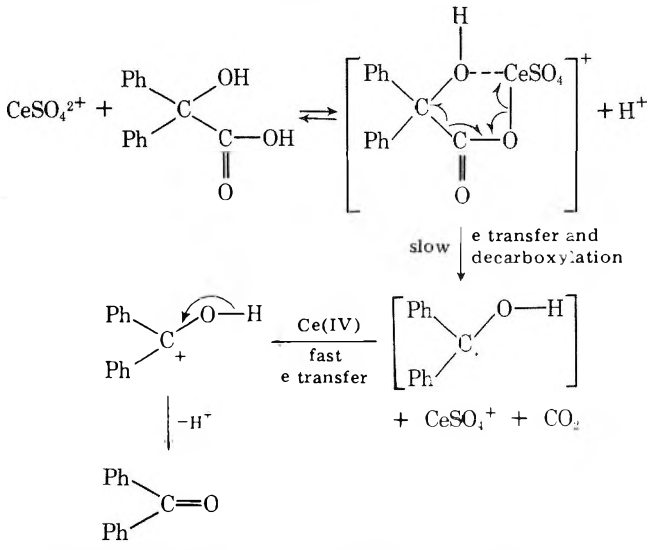
Table II. Correlation Coefficients for the Observed Rate Constants' Dependence on Ce(IV) Species at Various [H⁺]

	Correlation coefficients for k^{I}_{obsd} vs.					
[H⁺], M	$Ce(OH)^{3+}$	$Ce(OH)_2^{2+}$	Ce^{4+}	$CeSO_4^{2+}$	$Ce(SO_4)_2$	$Ce(SO_4)_3^{2-}$
0.20	0.80212	0.80209	0.80156	0.99713	−0.51502	−0.83096
0.30	0.92180	0.92178	0.92234	0.99472	−0.71337	−0.77033
0.40	0.97142	0.97153	0.97182	0.99411	−0.27878	−0.74953
0.50	0.94644	0.94639	0.94605	0.97311	−0.86448	−0.71084
0.75	0.90823	0.90809	0.90853	0.97147	−0.95585	−0.72417

species in 1–2.5 M H_2SO_4. We must emphasize at this point that the poor correlation coefficient for k^{I}_{obsd} vs. $[Ce(OH)_2^{2+}]$ indicates a very minor role, if any, for the participation of the dihydroxy species in the oxidative pathway under our conditions. It is much more unlikely that $Ce(OH)_2^{2+}$ could be a kinetically significant participant in 1–2.5 M H_2SO_4. One calculates that over 99.99% of Ce(IV) in the latter media exists as the trisulfato complex, which is expected to be relatively unreactive toward oxidizable ligands. The rates of oxidation of benzilic acid by Ce(IV) in 1–2.5 M H_2SO_4 are quite slow[12] in comparison to the rates reported in this work.

Stepwise regression analysis of the data in Table I gives the following values for the rate constant specific of the monosulfato species: k_{CeX} = 30, 42, 41, 67, and 95 at 0.75, 0.5, 0.4, 0.3, and 0.2 M H⁺, respectively. The direct and logarithmic relationships of these kinetic parameters to the hydrogen ion concentration in the reaction media are shown in Figure 3. The plot of log k_{CeX} against −log [H⁺] is a straight line with a slope of 1.03 ± 0.17. This inverse dependence on [H⁺] may be explained in terms of a transition state which contains the reactants minus an H⁺.[28] This is compatible with the mechanism shown in Scheme II which portrays preliminary

Scheme II



Ce(IV)–benzilic acid complex formation followed by a rate-determining intramolecular electron transfer simultaneous with C–C bond fission and liberation of CO_2. The produced radical is expected to be unstable and to lose an electron in a fast step to a second Ce(IV). The proposed mechanism is summarized (HLH = benzilic acid and L′ = benzophenone) in eq 11–14.

$$CeX^{2+} + HLH \underset{\text{fast}}{\overset{K_6}{\rightleftharpoons}} [HLCeX]^+ + H^+ \qquad (11)$$

$$[HLCeX] \xrightarrow{\text{slow}} HL'\cdot + CeX^+ + CO_2 \qquad (12)$$

$$HL'\cdot + Ce(IV) \xrightarrow{\text{fast}} [HL']^+ + Ce(III) \qquad (13)$$

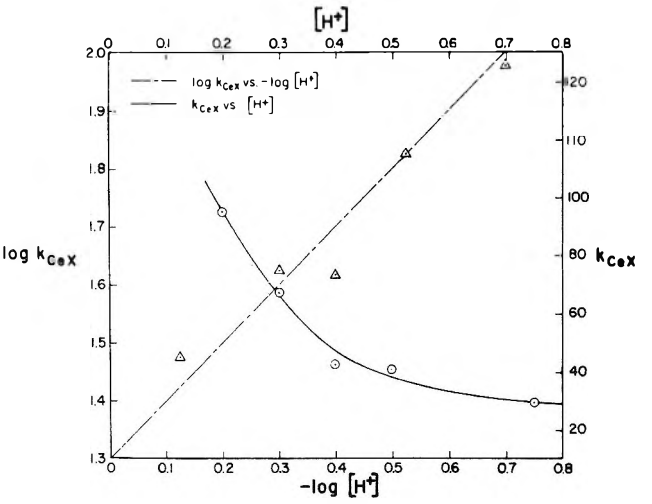


Figure 3. Plots of log k_{CeX} against − log [H⁺] and of k_{CeX} against [H⁺] in $HClO_4$–Na_2SO_4–$NaClO_4$ media.

$$[HL']^+ \xrightarrow{\text{fast}} L' + H^+ \qquad (14)$$

B. Kinetics in Sulfuric and in Perchloric Acids. The observed pseudo-first-order and second-order rate constants, k^{I}_{obsd} and k^{II}_{obsd}, calculated by eq 10 and 15, respectively, for the reaction of Ce(IV) in aqueous H_2SO_4, are listed in Table III.

$$k^{II}_{obsd}t = \frac{1}{(0.5a - b)} \ln\left[\frac{b(a - ax)}{a(b - 0.5ax)}\right] \qquad (15)$$

$$x = (A_0 - A_t)/(A_0 - A_\infty)$$

For a fixed initial concentration of Ce(IV) and at constant acidity, k^{I}_{obsd} increases linearly with increasing $[HLH]_0$. The slope of the straight-line plot of k^{I}_{obsd} against $[HLH]_0$ was found to be 4.63 ± 0.04 M^{-1} s^{-1} by least squares. An average k^{II}_{obsd}, calculated by eq 15, is 5.13 M^{-1} s^{-1}. By comparison with other organic substrates' oxidations, one might expect a Ce(IV)–benzilic acid complex as an intermediate. Cerium(IV)–organic ligand complex formation appears to depend on the anion associated with Ce(IV). It is generally believed that the presence of sulfate is not conducive to Ce(IV)–organic ligand complex formation. However, there are several cases [ethylene glycol,[29] malonic acid,[2,30,31] mandelic acid,[32] oxalic acid,[33] and diethylenetriaminepentaacetic acid (DTPA)[34]] where such complexation in acidic sulfate media has been documented. A plot of $1/k^{I}_{obsd}$ against $1/[HLH]_0$ (Table III) gives a straight line; the slope and intercept yield a value of 45 for the acid-dependent equilibrium constant K_6' of Ce(IV)–benzilic acid complex formation at 1.45 M H⁺.

By contrast, inspection of the rate data in Table IV for the oxidations carried out in $HClO_4$ media reveals that k^{II}_{obsd} is not constant and that k^{I}_{obsd} changes in a nonlinear fashion with changes in $[HLH]_0$. A similar behavior, namely, a difference in the response of k^{I}_{obsd} to changing the concentration

Table III. Observed Rate Constants in Sulfuric Acid for Different Initial Concentrations of Benzilic Acid at 25 °C, [H⁺] = 1.45 M, λ = 320 nm, [Ce(IV)] = 1.25 × 10⁻⁴ M

Run	10³[benzilic], M	$10^2 k^{I}_{obsd}$, s^{-1}	k^{II}_{obsd}, M^{-1} s^{-1}
254	1.25	0.68	5.71
255	2.50	1.24	5.07
258	3.12	1.54	5.15
256	3.75	1.90	5.03
257	4.37	2.17	5.02
259	5.00	2.37	4.79

Table IV. Observed First- and Second-Order Rate Constants and Calculated First-Order Rate Constants in Perchloric Acid for Different Initial Concentrations of Benzilic Acid at 25 °C, λ = 295 nm at 0.195 and 0.5 M H⁺[a]

Run	[H⁺], M	10³[benzilic], M	k^{I}_{obsd}, s^{-1}	k_{calcd}, s^{-1}	$10^{-3}k^{II}_{obsd}$, M^{-1} s^{-1}
342	0.195	0.50	55	66	126
343		1.25	77	84	66
337		2.50	92	82	38
338		3.13	87	82	25
339		3.75	86	82	23
340		4.38	84	80	20
242		5.00	80	81	16
353	0.50	0.50	42	42	91
354		2.50	72	73	29
355		3.75	73	77	20
356		5.00	66	78	13

[a] [Ce(IV)] = 2.5 × 10⁻⁴ M at [H⁺] = 0.195 M, and 1.25 × 10⁻⁴ M at [H⁺] = 0.50 M.

of the reducing substrate in sulfate and perchlorate media, was observed in a study of the oxidation of glycerol by cerium(IV),[35] and is probably due to the greater availability of Ce(IV) in perchlorate than in sulfate media for complex formation with reducing substrates.

The nonlinear behavior of k^{I}_{obsd} as a function of changing the initial concentration of benzilic acid in $HClO_4$ media is suggestive of extensive Ce(IV)–HLH complex formation. A plot of the data in Table IV, at 0.195 M $HClO_4$, as $1/k^{I}_{obsd}$ against $1/[HLH]_0$ is shown in Figure 4. Linearity is obtained only at the lower benzilic acid concentrations. Actually, an increase in $[HLH]_0$ beyond 0.0025 M leads to a decrease in the reaction rate. This behavior may be explained in terms of a Ce(IV)–substrate complex which either resists oxidation or does so very slowly. Since we assume that the 1:1 complex is that which is involved in the observed oxidation (cf. Scheme II), the inert or relatively unreactive complex is probably a 1:2 Ce(IV)–benzilic acid complex. Similar behavior, namely, a decrease in the reaction rate with increasing substrate concentration, has been reported by Littler and Waters for the oxidation of ethanol,[36] by Duke and Forist for the oxidation of butane-2,3-diol,[37] and by Wiberg and Ford for the oxidation of benzaldehyde.[38]

The data in $HClO_4$ then suggest the mechanism summarized in eq 16–19.

$$\text{Ce(IV)} + \text{HLH} \underset{}{\overset{K_7}{\rightleftharpoons}} \text{[Ce(IV)HL]} + \text{H}^+ \quad (16)$$

$$\text{[Ce(IV)HL]} + \text{HLH} \overset{K_8}{\rightleftharpoons} \text{[Ce(IV)(HL)}_2\text{]} + \text{H}^+ \quad (17)$$

$$\text{[Ce(IV)HL]} \xrightarrow[\text{rate determining}]{k_\alpha} \text{HL}'\cdot + \text{Ce(III)} + \text{CO}_2 \quad (18)$$

$$\text{[Ce(IV)(HL)}_2\text{]} \xrightarrow[\text{very slow}]{k_\beta} \text{HL}'\cdot + \text{[Ce(III)HL]} + \text{CO}_2 \quad (19)$$

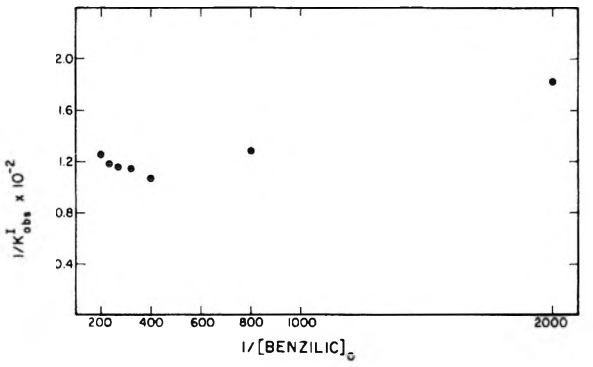


Figure 4. Plot of $1/k^{I}_{obsd}$ against 1/[benzilic] at 0.195 M H⁺.

From the above equations, the rate of loss of total cerium(IV) in the presence of excess benzilic acid may be expressed as

$$\text{rate} = -\frac{d[\text{Ce(IV)}]_T}{dt} = k^{I}_{obsd}[\text{Ce(IV)}]_T = k_\alpha[\text{CeHL}] + k_\beta[\text{Ce(HL)}_2] \quad (20)$$

$$[\text{Ce(IV)}]_T = [\text{Ce(IV)}]_{free} + [\text{CeHL}] + [\text{Ce(HL)}_2] = [\text{Ce(IV)}]_{free}\{1 + K_7'[\text{HLH}] + K_7'K_8'[\text{HLH}]^2\} \quad (21)$$

where

$$K_7' = K_7/[\text{H}^+] \quad \text{and} \quad K_8' = K_8/[\text{H}^+]$$

$$k^{I}_{obsd} = \frac{k_\alpha K_7'[\text{HLH}] + k_\beta K_7'K_8'[\text{HLH}]^2}{1 + K_7'[\text{HLH}] + K_7'K_8'[\text{HLH}]^2} \quad (22)$$

With the assumption that $K_7' \ll K_8'$, $k_\alpha \gg k_\beta$, and that at relatively low benzilic acid concentrations only the 1:1 complex need be considered, eq 22 may be simplified to

$$k^{I}_{obsd} = \frac{k_\alpha K_7'[\text{HLH}]}{1 + K_7'[\text{HLH}]} \quad (23)$$

Evaluation of the rate and equilibrium parameters in eq 23 from the linear portions of the plots of $1/k^{I}_{obsd}$ against $1/[HLH]_0$ is not recommended when the plots are not linear (cf. Figure 4). We, therefore, employed eq 24

$$1/k^{II}_{obsd} = \frac{[\text{HLH}]}{k_\alpha} + \frac{1}{k_\alpha K_7'} \quad (24)$$

for processing the data at 0.195 M H⁺. A plot of $1/k^{II}_{obsd}$ against $[HLH]_0$ yields a straight line. From the slope and intercept, values of about 4500 for K_7' and 95 s^{-1} for k_α are obtained. Whereas k_α should be independent of the acidity, K_7' is not a true equilibrium constant and should vary with [H⁺]. This is a consequence of the fact that any of the Ce(IV) species, Ce^{4+}, $CeOH^{3+}$, or $Ce(OH)_2^{2+}$, may be involved in the complex formation. The concentrations of such species are governed by [H⁺] as shown in eq 8 and 9.

The true equilibrium constant, K_7, may be obtained by multiplying K_7' with [H⁺] = 0.195. This yields a value of about 870. Furthermore, differentiation of eq 23, $\partial k^{I}_{obsd}/\partial[HLH]_0$, yields an expression, eq 25, from which $K_8 \approx 7$.

$$K_7'K_8' = \frac{1}{[\text{HLH}]^2_{max}} \quad (25)$$

$[HLH]_{max}$ = benzilic acid concentration which corresponds to a maximum in the observed reaction rate

Substitution in eq 22 with $K_7 = 870$, $K_8 = 7$, $k_\alpha = 95$, and $k_\beta = 20$ yields the k^{I}_{calcd} listed in Table IV. The agreement with k^{I}_{obsd} is far better at 0.195 M H⁺ than at 0.5 M H⁺. It is noteworthy that better agreement between k^{I}_{calcd} and k^{I}_{obsd} is obtained when the rate and equilibrium parameters, extracted from the plots of $1/k^{I}_{obsd}$ against $1/[HLH]_0$, are used.

Table V. Observed Rate Constants in Various Perchloric Acid Concentrations at 25 °C, [Ce(IV)] = 2.5×10^{-5} M, [Benzilic] = 5×10^{-4} M, λ = 256 nm

Run	$[HClO_4]$, M	k_{obsd}, s^{-1}
92	0.25	51
93	0.50	48
94	1.00	33
95	2.00	26

Table VI. Rate Constants in 49.5 wt % Acetic Acid–Perchloric Acid at 25 °C, [Benzilic] = 5×10^{-3} M, [Ce(IV)] = 2.5×10^{-4} M, λ = 310 nm

Run	$[HClO_4]$, M	k_{obsd}, s^{-1}	$10^{-2}k_2$, M^{-1} s^{-1}
222	0.195	15.8	32
223	0.425	26.3	53
224	0.660	38	77
225	0.890	40	81

The large value of K_7 obtained in this work, in comparison to $K = 20$ for the Ce(IV)–glycerol complex in 0.5 M $HClO_4$,[35] and to $K = 18$ and 29 for Ce(IV)–*cis*-1,2-cyclohexanediol and Ce(IV)–*trans*-1,2-cyclohexanediol complexes, respectively,[39] and to our own value of $K_6' = 45$ in 1.45 M H^+ in sulfuric acid, indicates very strong complexation in $HClO_4$ media. It is noteworthy that our attempts to detect complex formation in $HClO_4$ by stopped-flow techniques and by rapid scan spectrometry were not successful. The overall reduction of Ce(IV) by benzilic acid in $HClO_4$ media is quite fast, with half-lives in the millisecond region. Presumably, complex formation is even faster than that. Amjad and McAuley report that the Ce(IV)–malic acid complex was formed on mixing (2 ms).[24] This prompts us to question the validity of the spectral information about a presumed 1:1 Ce(IV)–HLH complex which was reported by Grover and Gupta.[12] The presumed complex was shown to have a maximum at 255 nm 10 s after mixing the reactants. The spectrum reported by Grover and Gupta has all the characteristics of benzophenone (Figure 1).

C. Influence of Acidity. In $HClO_4$–Na_2SO_4–$NaClO_4$ (Table I), H_2SO_4,[12,40] and $HClO_4$ (Table V) media, k^I_{obsd} decreases with increasing acidity. The order in $[H^+]$ is medium dependent. In the media where $CeSO_4^{2+}$ is clearly the predominantly reactive species, an order of about −1 is observed. In H_2SO_4 media doped with $HClO_4$, inverse first-order dependence on $[H^+]$ is reported.[12] In H_2SO_4 media, an order of −1.83 is observed.[40] This is possibly due to the interplay of several factors, of which the acid-dependent concentration of the sulfato species is an important one. In $HClO_4$, an order of about −0.34 is calculated from the data in Table V. The inhibiting effect of H^+ in all these media can be understood in terms of the mechanism depicted in Scheme II, where complex formation, which is attended by H^+ release, would be checked by increasing $[H^+]$. The fractional negative order observed in $HClO_4$ could be due to opposing factors. On the one hand, there is the inhibition of complex formation. On the other, increasing acidity should produce less hydrolyzed, and presumably more reactive, Ce(IV) species.[23] This is tantamount to catalysis by H^+.

A case of clear-cut catalysis by H^+ is presented in Table VI which contains the rate data obtained in 49.5 wt % acetic acid–perchloric acid solvent mixture. Here, increasing acidity brings about an enhancement in k^I_{obsd}; the order in $[H^+]$ is about 0.64. We believe that this rate enhancement is again concordant with the mechanism depicted in Scheme II. Cerium(IV) is expected to form relatively stable acetato complexes;[41] their tendency to form [Ce(IV)–HLH] is likely to be lower than that of noncomplexed Ce(IV). When formed, the complex is likely to be a mixed-ligand complex which again may retard electron transfer from HL to Ce(IV) because of stabilization of the latter by the acetate ligands. Increasing acidity would provide H^+ to compete with Ce(IV) for the acetate ligands, thereby freeing the complex of their stabilizing influence and hence the rate enhancement.

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Registry No.—Cerium(IV) perchlorate, 14338-93-3; cerium(IV) sulfate, 13590-82-4; benzilic acid, 76-93-7.

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Metal-Ion Oxidative Decarboxylations. 10.[1] Substituent Effects in the Cerium(IV)–Benzilic Acids Reaction

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The rates of oxidation by cerium(IV) of several substituted benzilic acids (unsubstituted, 2,2′-dichloro, 4,4′-dichloro, 4,4′-dimethyl, 4,4′-dimethoxy, and 4,4′-dinitro) to the corresponding benzophenones have been studied spectrophotometrically in aqueous H_2SO_4, aqueous $HClO_4$–HOAc, and acetonitrile. The rates are much slower in H_2SO_4 than in the other two media, probably because of heavy sulfato complexation of cerium(IV). The pK_as of the various acids were determined potentiometrically. The Hammett ρ values in acetonitrile and $HClO_4$–HOAc media, derived from correlations with several sets of σ constants and with the newly determined pK_as, are about −0.7 and −0.35 in the two media, respectively. These values rule out the possibility of positive charge development at the benzhydrilic carbon, at or prior to the rate-determining step. Instead, a mechanism involving free (?) radicals is proposed.

Many substituted benzilic acids and their esters are known for their analgesic and physiological activities and have, accordingly, been subjected to detailed pharmacological studies.[2] The ethyl and isopropyl esters of 4,4′-dichlorobenzilic acid are used as pesticides and their degradation products are believed to contribute to water pollution and to increasing environmental hazards.[3,4] Aside from these and similar studies, the literature on the chemistry of substituted benzilic acids is scarce. On the other hand, unsubstituted benzilic acid itself has been, alone or included with other α-hydroxy acids, the subject of several studies involving metal-ion oxidations.[5–7] In the preceding paper, we reported on the cerium(IV) oxidation of benzilic acid in acidic perchlorate and sulfate media,[8] and realized the need for information regarding the effect of substituents on the oxidative decarboxylations of substituted benzilic acids. Such information is expected to yield valuable clues pertaining to the structure of the transition state (free-radical vs. carbocationic character) and to the mode of action of the oxidizing agent (one-electron vs. two-electron oxidation).[9] In this paper, we report the results of a kinetic and mechanistic study of the cerium(IV) oxidation of benzilic, 2,2′-dichloro-, 4,4′-dichloro-, 4,4′-dimethyl-, 4,4′-dimethoxy-, and 4,4′-dinitrobenzilic acids in several media.

Experimental Section

Materials. Aniline, 4,4′-dimethylbenzil, 4,4′-dimethoxybenzil (anisil), and 4,4′-dichlorobenzophenone were obtained from Aldrich Chemical Co. Benzil was from Matheson Coleman and Bell Co. Benzilic acid, *p*-chlorobenzaldehyde, and bis(*p*-nitrophenyl)methane were Eastman White Label; 2,2′-dichlorobenzilic acid was from ICN-K & K Laboratories; nitric acid (90%, *d* 1.5) was from J. T. Baker Chemical Co. Cerium(IV) perchlorate (0.5 M in 6 M perchloric acid), iron(II) ammonium sulfate, perchloric acid (70%, lead-free, double vacuum distilled) and sodium perchlorate were from G. Frederick Smith Chemical Co. Cerium(IV) sulfate was from Merck, and cerium(IV) ammonium nitrate (CAN) was from Fisher Scientific Co. Glacial acetic acid was from Mallinckrodt.

Syntheses. 4,4′-Dimethylbenzilic acid was prepared by reacting the corresponding benzil with potassium ethoxide (metallic potassium in ethanol) in EtOH–Et_2O mixture for 24 h at 0 °C with exclusion of air.[10] Acidification of the reaction mixture to pH 4 gave a precipitate which, after recrystallization from benzene–petroleum ether, was identified as *p*-toluic acid, mp 177–179 °C, λ_{max} (MeOH) 237 nm.[11] Lowering the acidity of the filtrate to pH 2 brought about a second precipitate which, after recrystallization from hot water and drying under vacuum, had mp 132–134 °C.[12] 4,4′-Dimethoxybenzilic (anisilic) acid was prepared by the benzilic acid rearrangement of anisil effected by potassium hydroxide in refluxing *n*-butyl alcohol[13] After purification and recrystallization from *n*-heptane–ethyl acetate, anisilic acid had mp 156–158 °C[14] 4,4′-Dichlorobenzilic acid was prepared from *p*-chlorobenzaldehyde via the benzoin condensation. The corresponding benzil, obtained by oxidation of the benzoin with nitric acid (*d* 1.38) in glacial acetic acid and recrystallized from benzene, had mp 198–199 °C.[15] The benzilic acid rearrangement was effected by a refluxing solution of KOH in *n*-butyl alcohol. The potassium salt of the acid was acidified; redissolution in $NaHCO_3$ solution and reprecipitation gave the desired acid which, after recrystallization from *n*-heptane, had mp 101–102 °C.[16] 4,4′-Dinitrobenzilic acid was prepared by nitration of benzilic acid with white fuming nitric acid (*d* 1.5).[17] The material was purified through the formation of the anilinium salt (mp 140–142 °C dec) and reliberation of the acid which, after recrystallization from *n*-heptane–ethyl acetate, gave colorless crystals, mp 170–173 °C dec.[18]

Spectral analyses of the benzilic acids were conducted on a JEOL-D100 mass spectrometer, Perkin-Elmer 180 and 137 infrared spectrometers, Varian EM-360 NMR, and Beckman DK-2A UV–visible spectrophotometer. The spectral characteristics are summarized in Table I.

pK_a Measurements. These were done by potentiometric titrations of the benzilic acids (mostly in 1% EtOH–H_2O) with $Ba(OH)_2$ which had been standardized against potassium hydrogen phthalate. A Corning Digital-112 research pH meter equipped with a Fisher combination electrode was used for the determinations which were carried out at 25 °C. Neutralization equivalents and pK_a values were first evaluated graphically. The pK_a values were further checked by computation using the equation[19]

$$pK_a = pH + \log \frac{C_a - C_s - [H^+]}{C_s + [H^+]} + \frac{0.509\sqrt{C_a}}{1 + \sqrt{C_a}}$$

where

$$C_a = n_A/(V_A + X)$$
$$C_s = XC_b/(V_A + X)$$
$$[H^+] = 10^{-pH}$$

n_A: moles of benzilic acid
V_A: initial volume of the benzilic acid solution
X: volume of added base solution
C_b: initial normality of base
C_a: concentration of acid
C_s: concentration of base

A summary of the pK_a values and the neutralization equivalents appears in Table II.

Solutions. Electrolytically prepared cerium(IV) perchlorate solutions were prepared as described previously.[8,20] They were mixed with the appropriate amounts of glacial acetic to obtain 49.5% (wt) solutions. The Ce(IV) concentration was determined by titration with iron(II) ammonium sulfate. The benzilic acids were first dissolved in glacial acetic acid and then diluted with water to 49.5% (wt) acetic acid.

In experiments where CAN was used, the oxidizing agent and the benzilic acids were dissolved separately in acetonitrile. Only freshly prepared solutions were used for rate measurements.

Kinetics. Rate measurements were conducted spectrophotometrically under conditions where the benzilic acid's concentration was in excess of the cerium(IV) concentration. With the exception of a few slow runs which were carried out on a Beckman DK-2A most of the kinetic runs were performed on a Durrum-Gibson stopped-flow apparatus equipped with a photometric log amplifier and interfaced with

Table I. Spectral Data for Benzilic Acids

Registry no.	Acid	UV λ, nm[a]	UV Medium	UV ϵ_{max}	Mass spectrum, m/e	Infrared[b] Wavenumbers, cm^{-1}	NMR[b] ArH chem shift, δ
76-93-7	Benzilic	252, *258*, 264	OH^-/H_2O	540	184, 183, 105, 77, 76, 51, 44	3340, 3100–2400 (b), 1720, 133, 1240, 1050	7.36
3152-12-3	2,2′-Di-Cl	*263*, *267*, 274	OH^-/H_2O	460	253, 251, 141, 139, 111, 76, 75	3500–2400 (b), 1720, 760	7.35
23851-49-9	4,4′-Di-Cl	*259*, 266, 275	OH^-/H_2O	680	253, 251, 141, 139, 111, 76, 75, 44, 40	3450–2400 (b), 1720, 825, 760	7.44
		259, *266*, 275	MeOH	605			
2695-79-6	4,4′-Di-Me	257, *264*, 273	OH^-/H_2O	880	211, 119, 91, 65, 44	3350, 3100–2400 (b), 1720, 820	7.24
		257, *264*, 273	MeOH				
639-61-2	4,4′-Di-OMe	*273*, 280	OH^-/H_2O	2950	243, 135, 119,107, 77, 45, 44	3600–2700 (b), 1725, 835	7.12
62058-71-3	4,4′-Di-NO_2	*282*	OH^-/H_2O	16 200	272, 256, 150, 120, 104, 76, 44	3350, 3100–2400 (b), 1720, 1510, 1345, 855, 845	8.01
		280	MeOH				

[a] Wavelength in italics denotes peak of maximum absorbance. [b] Full spectra are available from the authors upon request.

Table II. pK_a Values and Neutralization Equivalents for Benzilic Acids

Acid	Mol wt (calcd)	Neut equiv, potentiometric	pK_a
Benzilic	228.24	225.03	3.04
2,2′-Dichloro-	297.13	291.68	2.54
4,4′-Dichloro-	297.13	302.02	2.96
4,4′-Dimethyl-	256.30	259.92	3.30
4,4′-Dimethoxy-	288.30	287.41	3.93
4,4′-Dinitro-	318.23	317.72	2.47

a Tektronix storage oscilloscope, a Bausch and Lomb recorder, and a Data Cap tape perforator Model 820, through a Biomation transient recorder, Model 802. The digitized data were processed by a linear least-squares program of polynomial fit on an IBM 370/168. A typical computer-drawn plot of data processed as first-order kinetics (uncertainty in slope is less than 0.5%) showing linearity over 80% of reaction appears as Figure 1. The rate constants were reproducible to ±3%.

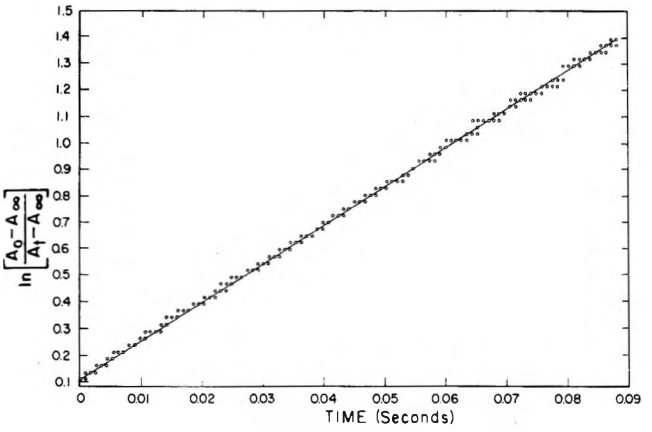
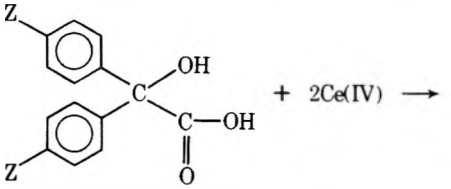


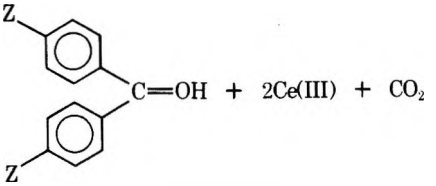
Figure 1. Plot of first-order kinetics of benzilic acid oxidation with Ce(IV).

Results and Discussion

Stoichiometry and Products. The oxidation of each of the benzilic acids by cerium(IV) leads to the formation of the corresponding benzophenone in quantitative yield. From a comparison of the decrease in absorbance at 300–320 nm, characteristic of cerium(IV), with increase in absorbance at the wavelength characteristic of the benzophenone produced on oxidation, the following stoichiometry was established:



p-Z = H, Cl, CH_3, OCH_3, NO_2
o-Z = Cl



The products' identities were established by comparison with the characteristics of benzophenones produced by other routes. The results are summarized in Table III.

pK_a Values. The influence of substituents on the dissociation of benzilic acids was evaluated by measuring the pK_as by potentiometric titration. The results are shown in Table II. The trends are as expected; the dinitro compound is the strongest acid whereas the dimethoxy is the weakest in the series. However, the pK_a values determined in this work do not agree with those already reported in the literature for benzilic and the 4,4′-dichloro acid.[30a] We, therefore, determined the pK_a for another α-hydroxy acid, viz., mandelic acid, to assess the dependability of our measurements. Our value of 3.41 for mandelic acid agrees within 0.02 pK_a units of literature values.[30b] This strengthens the credibility of our measurements and we will, accordingly, use our own pK_a values in preference to the literature values for benzilic acid and 4,4′-dichlorobenzilic acids.[30a]

Relative Reactivities. The rates of oxidation of the benzilic acids were conducted with the concentration of the α-hydroxy acid in excess. Pseudo-first-order kinetics were observed for the consumption of cerium(IV). Preliminary measurements were conducted with cerium(IV) sulfate in aqueous sulfuric acid solutions where the disappearance of Ce(IV) could be followed at 319 nm. It was realized, however, that because of solubility problems, particularly with the produced benzophenones, a different medium is needed. The results in H_2SO_4 solutions were limited accordingly to those benzilic acids which did not pose solubility problems. The results, summarized in Table IV, for four different H_2SO_4 concentrations, reveal two features. First, anisilic acid is far more reactive than benzilic acid which, in turn, is more reactive than 2,2′-dichlorobenzilic acid. At 1 N H_2SO_4, for example, $k_{benzilic}:k_{anisilic}:k_{2,2'\text{-diCl}}$ = 1:9:0.4. It seems that high

Table III. Characteristics of Benzophenones Produced on Oxidation of Benzilic Acids

Registry no.	Benzilic acid	Mp of benzophenone derived from benzilic acid oxidation, °C	Ref for other routes of benzophenone production and mp, °C
5293-97-0	2,2′-Dichloro-	45	45–46,[21] 50–51.5[22]
90-98-2	4,4′-Dichloro-	147–148	144–145[23]
611-97-2	4,4′-Dimethyl-	94–95	97,[24] 90–91[25]
90-96-0	4,4′-Dimethoxy-	145–146	144–145[26]
1033-26-7	4,4′-Dinitro-	188–191	189,[27] 190–191,[28] 188.6–189.4[29]

Table IV. Observed Pseudo-First-Order Rate Constants[a] for the Oxidation of Benzilic Acids[b] with Cerium(IV)[c] in H_2SO_4 Solutions

H_2SO_4, N	10^2k_1, s^{-1}		
	Benzilic	Anisilic	2,2′-Dichlorobenzilic
0.5	1.84		0.804
1.0	0.55	4.95	0.235
1.5	0.22	3.88	0.124
2.0	0.15	3.52	0.064

[a] Measured at 319 nm. [b] [Benzilic acid] = 5×10^{-4} M. [c] [Ce(IV)] = 5×10^{-5} M.

Table V. Rate Constants[a] for the Reaction of CAN[b] with Substituted Benzilic Acids[c] in Acetonitrile at 25 °C

Hydroxy acid	k_1, s^{-1}	k_1 (rel)
Benzilic	29.6	1.00
2,2′-Dichlorobenzilic	10.3	0.35
4,4′-Dichlorobenzilic	28.8	0.97
4,4′-Dimethylbenzilic	37.5	1.27
4,4′-Dimethoxybenzilic	53.1	1.79
4,4′-Dinitrobenzilic[d]	7.57	0.26

[a] Measured at 325 nm. [b] [CAN] = 2.5×10^{-4} M. [c] [Benzilic acid] = 2×10^{-3} M. [d] Measured at 400 nm.

Table VI. Rate Constants[a] for the Reaction of Cerium(IV)[b] with Substituted Benzilic Acids[c] in Perchloric Acid[d]–Acetic Acid (49.5 wt %) at 25 °C

Hydroxy acid	k_1, s^{-1}	k_1 (rel)
Benzilic	14.9	1.00
2,2′-Dichlorobenzilic	11.6	0.78
4,4′-Dichlorobenzilic	15.2	1.03
4,4′-Dimethylbenzilic	21.0	1.41
4,4′-Dimethoxybenzilic[e]	41.0	2.76
4,4′-Dinitrobenzilic[f]	12.7	0.85

[a] Measured at 305 nm. [b] [Ce(IV)] = 2.5×10^{-4} M. [c] [Benzilic acid] = 5×10^{-3} M. [d] [$HClO_4$] = 0.195 M. [e] Measured at 390 nm. [f] Measured at 400 nm.

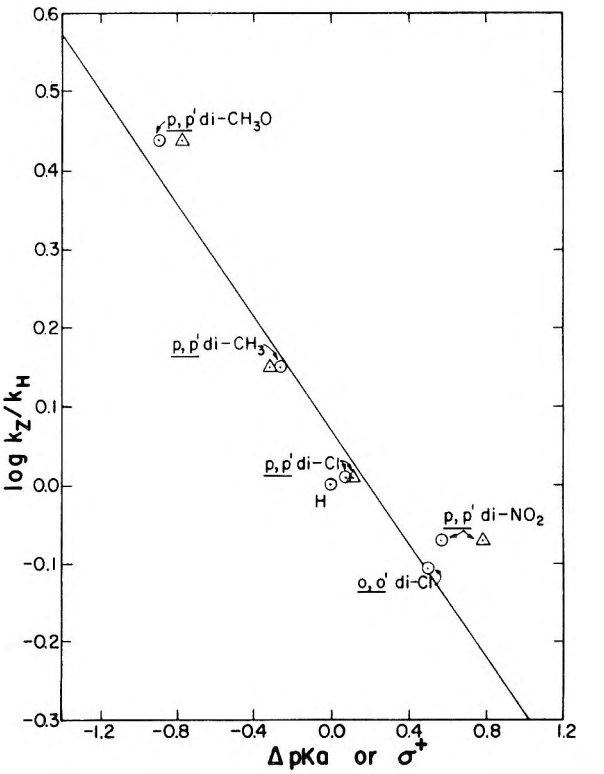


Figure 2. Hammett plot for the substituent effects on the Ce(IV) oxidation of benzilic acids in $HClO_4$–HOAc.

electron density facilitates oxidative decarboxylation by Ce(IV). This is to be expected for a reaction of an electrophile with the reductant. Among the various cerium(IV)–sulfato species,[31] $CeSO_4^{2+}$, $Ce(SO_4)_2$, $Ce(SO_4)_3^{2-}$, only the monosulfato species qualifies as an electrophile and is expected to be the most reactive species.[8,32] Second, for any of the three benzilic acids studied in H_2SO_4, the rate decreases with increasing acidity. However, whereas the decrease in $k_{benzilic}$ parallels the decrease in $k_{2,2'\text{-di-Cl}}$ (about 12-fold for a 4-fold increase in acidity), anisilic acid is far less sensitive to changing the concentration of H_2SO_4 in the range studied. It is possible that anisilic acid, because of the electron-supplying OCH_3 groups, is already so heavily protonated at 1 N H_2SO_4 when compared to the other two α-hydroxy acids that further increases in acidity are not effective in bringing about a significant change in the amount of protonated species.

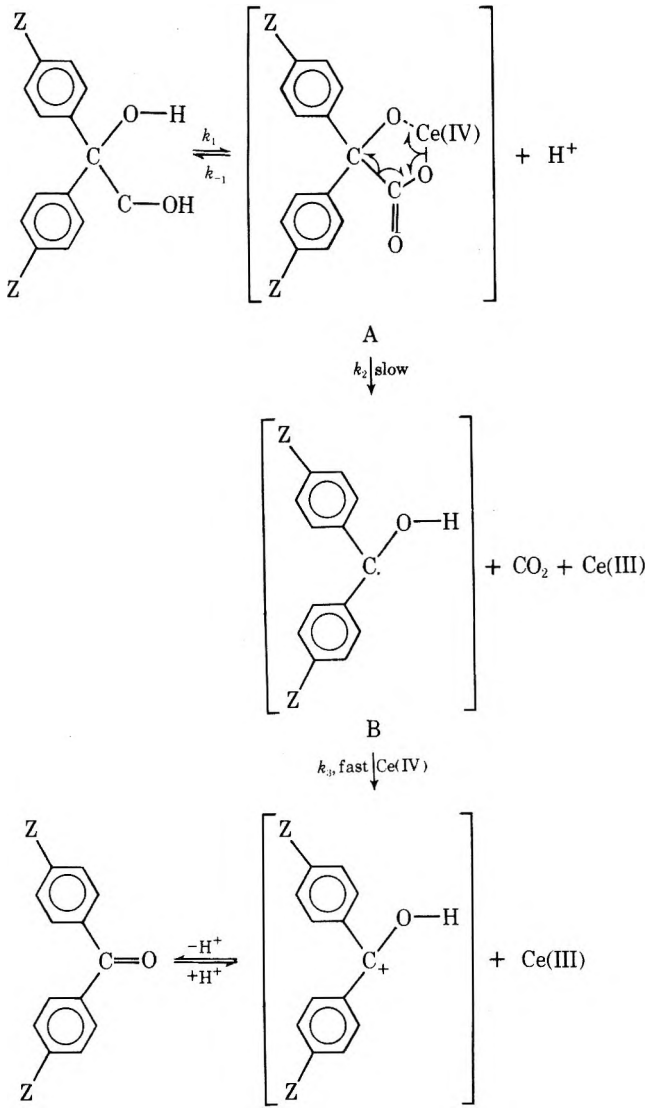
In Tables V and VI are presented the rate constants for the oxidation of substituted benzilic acids by cerium(IV) in acetonitrile and in perchloric–acetic acids mixtures, respectively. The relative rates indicate that in both media, electron-supplying groups facilitate the reaction whereas electron-withdrawing groups slow down the rate of oxidation. This may be taken as an indication of development of some carbocationic character in the transition state which would be stabilized by electron-releasing groups and hence the enhancement of rate by CH_3 and OCH_3 groups. To test for the development of charge at the reaction site, various Hammett substituent correlations were tried. Different sets of σ[33-35] and σ^+ [36,37] were used. The Hammett correlation, obtained with the σ_p^+ values of Brown and Okamoto,[36] gave $\rho = -0.317$ (±0.100) in the acetic–perchloric acids medium (Figure 2). With the σ_p^+ values, calculated by Swain and Lupton,[37] $\rho = -0.617$ (±0.084) in acetonitrile. A summary of the ρ values obtained in the Hammett correlations of the observed rate constants with different sets of literature-available substituent constants appears in Table VII. Inspection reveals several features. (1) The ρ values for either medium are negative but less than 1. (2) The ρs for the reaction in acetonitrile are approximately twice as negative as the corresponding ρs for the reaction in $HClO_4$–HOAc. (3) The magnitude of ρ is not very sensitive to the set of σ values used. These features are to be viewed in the light of the following information. The ρ values reported for reactions which involve cationic character at benzylic or benzhydrilic center lie in the vicinity of −5.0.[38] On the other hand, whereas most radical reactions display better correla-

Table VII. Substituent Constants' Correlations in Acetonitrile and in Perchloric–Acetic Acids Media

Origin of σ values	ρ in acetonitrile	ρ in $HClO_4$–HOAc
Brown and Okamoto[36] σ^+	−0.541 (±0.091)	−0.317 (±0.100)
Swain and Lupton[37] σ^+	−0.617 (±0.084)	−0.350 (±0.113)
Sjostrom and Wold[34] σ	−0.779 (±0.100)	−0.337 (±0.176)
McDaniel and Brown[35] σ	−0.752 (±0.086)	−0.368 (±0.153)
Taft[30] σ^0	−0.763 (±0.115)	−0.341 (±0.174)

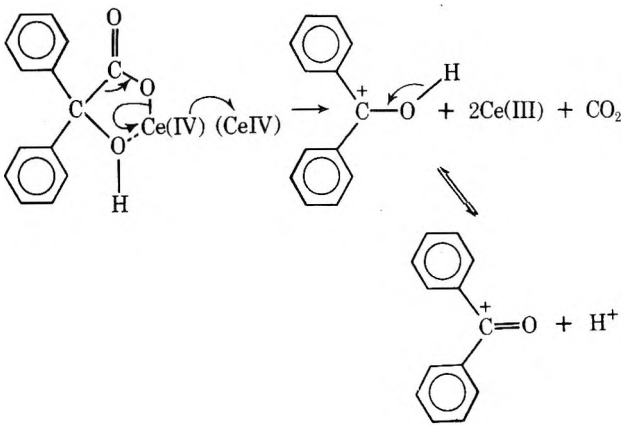
tions with σ^+ than with σ,[39] the ρs lie in the range of −0.3 to −1.5.[40] In some cases, ρ is as high as −2.0, or even −2.9.[9a] In the oxidative decarboxylation of benzilic acids (Scheme I), one might expect little, if any, development of cationic charge at the benzhydrilic carbon. For the development of positive charge character at that carbon, which would interact with

Scheme I



substituents in the aromatic rings, the decarboxylation will have to have proceeded to such an extent that the incipient free radical is already interacting with a second Ce(IV). This would necessitate second-order kinetics with respect to Ce(IV), which is not the case. An alternative mechanism (Scheme II) which portrays development of carbocationic character in the rate-determining step would, again, necessitate second-order kinetics in Ce(IV). This alternative, however, is termolecular in nature because a divalent cerium

Scheme II



≈ 2-electron transfer
≈ 1-electron transfer

species, Ce(II), which would result from a two-electron transfer, is highly unlikely.

Because the σ constants developed by Sjostrom and Wold,[31] in connection with phenylacetic and phenylpropionic acids, are different from the generally used Hammett σ values (benzoic acids), we sought a correlation with ΔpK_a determined in this work for the investigated benzilic acids. The plot of log k_{rel} vs. ΔpK_a [pK_a (benzilic) − pK_a (substituted benzilic)] is shown in Figure 2; ρ = −0.362 (±0.056) for the reaction in acetic acid.

In summary, the ρs are negative and lie within the range characteristic of free-radical reactions. The higher sensitivity of the reaction to substituent effects in acetonitrile as compared to $HClO_4$–HOAc may very well reflect the difference in the solvation abilities of the two media. The developing charge, or the change in electron density, at the benzhydrilic carbon which accompanies the C–C bond cleavage is expected to be better dispersed with $HClO_4$–HOAc than with acetonitrile. This would lead to a greater interaction between substituent and reaction site in acetonitrile (higher ρ) than in $HClO_4$–HOAc.

Although we have no direct evidence for the intermediacy of free radicals, the substituent effects reported in this work are compatible with the mechanism proposed in Scheme I. The mechanism involves the rapid formation of a coordination complex (A) between Ce(IV) and the benzilic acid characterized by the equilibrium constant K. This disproportionates unimolecularly in the rate-determining step (k_d) by a one-electron transfer from the carboxyl group to Ce(IV), thereby generating the benzophenone ketyl radical (B) and Ce(III). The free radical is rapidly oxidized by a second Ce(IV).

Registry No.—Cerium(IV) perchlorate, 14338-93-3; cerium(IV) sulfate, 13590-82-4; cerium(IV) ammonium nitrate, 16593-75-2; 4,4′-benzil, 3457-48-5; potassium ethoxide, 917-58-8; *p*-toluic acid, 99-94-5; *p*-chlorobenzaldehyde, 104-88-1; 4,4′-dinitrobenzilic acid anilinium salt, 62058-72-4.

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Asymmetric Reduction of Acetophenone with Lithium Aluminum Hydride Complexes of Terpenic Glycols†

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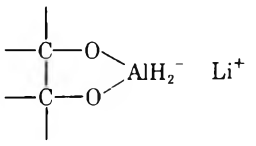
Optically active 1,2-glycols derived from (+)-1-menthene, (+)-α-terpineol, and (+)-α- and (−)-β-pinene formed chiral complexes with lithium aluminum hydride. The complexes were used to reduce acetophenone in different solvents and at various temperatures. The solvents included dioxane, diethyl ether, ethylene glycol dimethyl ether, and tetrahydrofuran, and temperatures ranged from −50 to 66 °C. Enantiomeric excess was maximum when the solvent was diethyl ether and the temperature was 15–20 °C. Various glycol complexes reduced the ketone in enantiomeric excesses ranging from 15% negative rotation to 30% positive rotation.

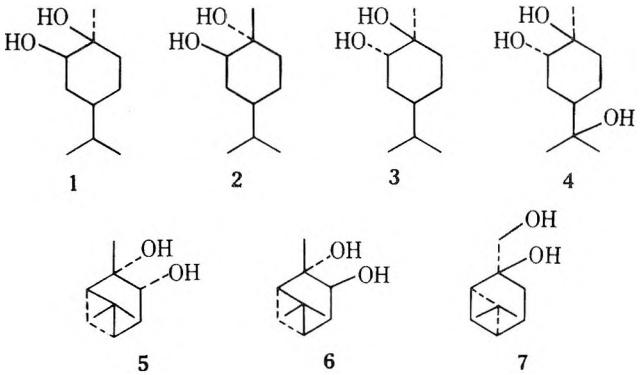
Conversion of abundant optically active terpenes such as limonene and pinene to useful optically active products has been the focus of much research effort. One approach is to synthesize asymmetric reagents from the terpenes.

In previous studies,[1] glycol–lithium aluminum hydride complexes were prepared from monosaccharide derivatives[2] and diol derivatives of tartaric acid[3] and α-pinene.[4,5] In one case, use of a monosaccharide derivative resulted in an enantiomeric excess (optical yield) of 70%.[2c] Enantiomeric excess has been found to depend on the glycol structure, whether ethanol or benzyl alcohol is added to the complex, and other variables, such as temperature and solvent.[1]

We converted glycols **1**–**7** to hydride complexes



and used them to reduce acetophenone under various conditions. Five of the glycols were prepared from (+)-limonene and (+)-α and (−)-β-pinene by oxidation with $KMnO_4$ (compounds **1** and **4**–**7**); two other glycols (**2** and **3**) were donated to us. Since (+)-limonene could not be converted directly to a simple 1,2-glycol, it was first converted to (+)-1-menthene and (+)-α-terpineol by procedures which preserved the optical activity.[6,12] The respective products were then oxidized to the 1,2-glycol **1**, and the 1,2,8-triol **4**. The pinane glycols (**5**, **6**, and **7**) were synthesized by the oxidation of α- or β-pinene according to published procedures.[3–6] Acetophenone was chosen as the test ketone because it is frequently so used in the evaluation of asymmetric hydride reducing agents.[1]



Results and Discussion

Tables I and II show that the yields of α-methylbenzyl alcohol from the reduction of acetophenone under various conditions were generally high but that the optical yields were

† Mention of a brand name is for identification only and does not imply its endorsement by the U.S. Department of Agriculture over others which may also be suitable.
‡ One of the laboratories of the Southern Region, U.S. Department of Agriculture, Agricultural Research Service.

Table I. Reduction of Acetophenone with Glycol 1–Lithium Aluminum Hydride Complex

Run	Molar reactant ratio[a] Glycol	Alcohol	$LiAlH_4$	Solvent	Temp, °C Reag prepn	Reaction	Alcohol yield, %[b]	Product rotation, $[\alpha]_D$, deg	Optical yield, %[c]
A	1.1		1.1	Diethyl ether	0	25	99	+6.98	20
B	1.1		1.1	Glyme[d]	0	25	99	+6.42	18
C	1.1		1.1	Dioxane	10	25	99	+2.15	6
D	1.1		1.1	THF	0	25	98	+4.95	14
E	1.1		1.1	THF	0	−50	86	+3.70	11
F	1.1		1.1	THF	0	66	99	+5.99	17
G	1.1		1.1	THF	20	25	99	+6.42	18
H	1.1		1.1	THF	20	66	99	+4.33	12
I	1.1		1.1	THF	66	66	98	+3.89	11
J	1.1		1.1	THF	−50	−50	94	+1.58	4
K	1.1		1.1	Diethyl ether	20	25	99	+8.42	24
L	0.55		0.55	Diethyl ether	20	25	67	+7.56	21
M	1.1	Ethanol 1.0	1.1	THF	20	25	45	−1.99	(−)6
N	1.1	Ethanol 1.1	1.1	THF	20	66	57	+0.64	2
O	1.1	Benzyl alcohol 1.1	1.1	THF	20	66	59	+0.98	3
P	2.0	Ethanol 8.7	4.6	Diethyl ether	20	25	99	+10.7	30

[a] Based on 1.0 ratio for acetophenone. [b] Based on relative peak areas of acetophenone and α-methylbenzyl alcohol in GC trace of crude product mixture. [c] Corrected for optical purity of starting glycol. For most glycols, optical purity was based on that of the starting hydrocarbon, assuming no change in optical composition during the subsequent transformations. In some cases, the optical purity of the glycols was actually higher than that of starting material, because of purification during recrystallization. Rotations of the pure hydrocarbons were taken from the literature as follows: 1-menthene, 86°;[6b] limonene, 127°;[16b] α-pinene, 51°;[16b] β-pinene, 21°.[16b] The purity of glycols 2 and 3 was based on the reported rotation of 3.[10b,11b] On the basis of these data, glycols and optical purities (%) were 1, 79; 2 and 3, 86; 4, 79; 5 and 6, 76; 7, 95. [d] Ethylene glycol dimethyl ether.

Table II. Reduction of Acetophenone with Glycol (2–7)–Lithium Aluminum Hydride Complex[a]

Molar reactant ratio[b] Glycol	$LiAlH_4$	Solvent	Alcohol yield, %[c]	Product rotation, $[\alpha]_D$, deg	Optical yield, %[d]
(2) 1.1	1.1	Diethyl ether	99	−5.29	(−)14
(3) 1.1	1.1	Diethyl ether	99	+3.78	10
(3) 1.7	1.1	Diethyl ether	48	+0.90	2
(3) 0.5	1.0	Diethyl ether	99	+2.21	6
(4) 1.1	1.1	THF	55	+1.27	4
(5) 1.1	1.1	Diethyl ether	99	−1.23	(−)4
(6) 1.1	1.1	THF	94	+3.30	10
(6) 1.7	1.1	THF	73	+4.63	14
(6) 0.5	1.0	THF	98	+1.29	4
(7) 1.1	1.1	Diethyl ether	99	−0.98	(−)2

[a] Reaction temperature 25 °C, reagent preparation 20 °C. [b] Based on 1.0 ratio for acetophenone. [c] See footnote *b*, Table I. [d] Corrected for optical purity of starting glycol; see footnote *c*, Table I.

not (maximum was 30%). Optical yield was little affected by variations of solvent and/or reaction temperature. It was noticeably affected by the addition of alcohol to the reagent and variation of the glycol structure.

Data in Table I are for the reduction of acetophenone under various conditions with the complex of glycol 1. This glycol was one of the easiest to synthesize, and relatively large amounts of the pure starting compound were available. Runs A–D were carried out in solvents representing four different types of ethers. Temperatures for the reagent preparation and reaction steps were arbitrarily kept at 0 and 25 °C, respectively, for three of these runs. Run C required a slightly elevated temperature for the reagent preparation to prevent crystallization of the solvent. The last column shows that optical yield of the alcohol was highest for diethyl ether and glyme (ethylene glycol dimethyl ether). The cyclic ethers THF (tetrahydrofuran) and 1,4-dioxane were less effective.

The effect of varying both reagent preparation and reaction temperature was studied with THF rather than ether or glyme. Tetrahydrofuran was used because its boiling point is higher than that of ether and because of possible interference of glyme during the workup.

Runs D–F showed that raising the reaction temperature increased optical yield, but not greatly. The decrease observed with run H as compared with run G is anomalous for the reasons cited below. This behavior is the reverse of that observed for oxazoline carbinol–lithium aluminum hydride reagents, whose asymmetric reduction yields increase with temperature.[7]

A separate temperature effect was found for the reagent preparation step. The reagent was prepared by dropwise addition of the glycol to the lithium aluminum hydride solution so that disproportionation of the complex to lithium aluminum hydride and a lithium aluminum tetraalkoxide[8] would

be minimized. For runs D and G with the reaction temperature at 25 °C and the reagent prepared at 0 and 20 °C, respectively, optical yields increased from 14 to 18%. Similarly, runs E and J showed that an increase in temperature of reagent preparation (−50 to 0 °C) increased optical yield (4 to 11%). However, for runs F, H, and I, with reagent preparation temperatures of 0, 20, and 66 °C, optical yields at 66 °C reaction temperature were 17, 12, and 11%. It seems likely that high reagent preparation temperatures increase the extent of disproportionation and hence reduce optical purity. On the other hand low temperatures appear to result in incomplete reactions and hence reduced optical yields. The similar results from runs H and I suggest that by the time the reagent had been heated to reaction temperature from 20 °C, disproportionation had already occurred to a great extent. At −50 °C, evolution of hydrogen during reagent preparation was not measured, but at 20 °C, the reagent preparation step was completed almost immediately, as indicated by the volume of hydrogen evolved. Thus, for this step, a temperature of about 20 °C was judged optimum for maximum optical yield. In run K, the optical yield was 24%, one of the highest in this series, as expected on the basis of the temperature and solvent effects discussed. In run L, half the amount of reagent relative to ketone was used, so that both active hydrogens in the reagent would have had to be consumed for complete reduction. The optical yield dropped slightly and the alcohol yield went down considerably, as compared to the yields for run K. Apparently, the second hydride hydrogen is not as reactive or as effective in inducing asymmetry as the first.

The addition of 1 equiv of a primary alcohol to the complex has been reported to increase optical yield in some cases.[2c,4] The addition of ethanol at two different reaction temperatures (runs M and N) and of benzyl alcohol (run O) markedly reduced optical yield. The product rotation was a negative value in run M and was a small positive value in run N. Product rotation in run O, with benzyl alcohol, was not significantly different from that of run N. Although the sign reversal associated with removal of one of the hydride atoms has been previously reported,[2c] reversal due to temperature has not. The effect of alcohol addition is preferential conversion of the more reactive hydride to alkoxide. The decrease in alcohol yield for runs M–O is consistent with this theory. In these complexes, the optical yield was also decreased in all three cases.

The final run in Table I, run P, was carried out with the most effective ethanol modified complex described in the monosaccharide study.[2c] The glycol complex was prepared by dropwise addition of glycol solution to a large excess of hydride, and sufficient ethanol was then added dropwise to react with excess hydride. This approach considerably improved optical yield.

Although the reducing agents derived from glycols other than **1** produced generally low optical yields (Table II), the effect of glycol structure was observable. Product rotation was negative for several runs (glycols **2**, **5**, and **7**). None of the glycols listed in Table II were as effective as glycol **1**. The effect of glycol to hydride ratio on optical yields was determined with trans glycols **3** and **6**. Diethyl ether was the solvent in most of the runs, but THF was used for glycols **4** and **6**, because of their insolubility in diethyl ether. The effect of this substitution on optical yield was assumed to be relatively small. To eliminate extraneous effects, we did not use alcohol-modified complexes in evaluating glycols **2–7**.

We attempted to correlate glycol structure with the sign and magnitude of rotation assuming that the hydride complexes of all the glycols except trans glycol **3** were cyclic. A cyclic complex of this glycol would be unlikely because of the diaxial orientation of the hydroxyl groups. In all of the cyclic complexes the bulky part of the glycol group would be held away from the hydride hydrogens. Relatively little interference from groups on the ketone would be expected. This was apparently the reason for the generally low optical yields. In view of the small differences involved, interpretation of the results in terms of asymmetric steric hindrance is difficult.

Experimental Section

Melting points were measured on a capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Optical rotation were taken with a Rudolph Model 62 visual polarimeter: all samples were dissolved in ethanol and placed in an end-filled 0.5-dm cell, unless otherwise noted; values ± standard deviation are reported. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Ether solvents, except diethyl ether, were purified by passage through a column of activity I basic alumina. Diethyl ether (Fisher E-138) was used directly as received. Acetophenone (Fisher A-22) was purified by distillation at 90 °C (15 mm) and stored over $CaSO_4$. The purity of all reagents was checked by GC and infrared spectrometric analyses. Solutions were concentrated by distillation with a rotary evaporator at 40 mmHg, unless otherwise noted.

GC Analysis. GC analyses were performed on a Hewlett-Packard 7620A instrument with a flame ionization detector and helium carrier gas. Injection port, detector, and heated collector temperatures were 220 °C. Oven temperature was programmed from 80 to 220 °C at 2 °C/min. Two columns were used: a 0.125 in. × 15 ft stainless steel analytical column packed with 5% Carbowax 20M on 70/80 mesh Anakrom ABS (Analabs, Inc., North Haven, Conn.), and a 0.25 in. × 9 ft stainless steel preparative column packed with 20% Carbowax 20M on 60/80 mesh Anakrom ABS. The carrier gas flow rates were 33 mL/min for the analytical and 220 mL/min for the preparative column. Peak areas were determined with a Hewlett-Packard 3380A integrator.

TLC and Column Chromatographic Analyses. Analtech silica gel GF plates of 250- or 500-μ thickness were used. The 250-μ (analytical) plates were sprayed with anisaldehyde–phosphomolybdic acid reagent[9] for detection of spots. The 500-μ (preparative) plates were sprayed with 0.1% Rhodamine B in isopropyl alcohol followed by irradiation from beneath the plate with 366-nm light for visualization of bands. They appeared as alternate light and dark zones, which were scraped off and eluted with ether or ethanol. Ether was the developing solvent, unless otherwise noted. For column chromatography, Fisher F-101 Florisil deactivated with water (6%) was used.

(+)-1-Hydroxycarvomenthol (1). A solution of 28 g (0.20 mol) of (+)-1-menthene, $[\alpha]^{25}_D$ +86° (neat), n^{27}_D 1.4528, bp 181–182 °C (763 mm), 300 mg (0.054 mol) of KOH, and 40 ml of H_2O in 160 mL of 2-propanol was cooled to 3 °C with an ice bath, then stirred vigorously while 64 g (0.41 mol) of $KMnO_4$ was added, portionwise, over a 2-h period. The reaction mixture was maintained at 3–5 °C during this period and then stirred for an additional 1 h at 3–5 °C. The product was filtered through a Celite pad, and the pad washed several times with a 1:1 mixture of ice-cold 2-propanol and water (total of 300 mL). The combined filtrates were diluted with 500 mL of water, saturated with Na_2SO_4, and extracted with 1 L of CH_2Cl_2. Removal of solvent at 30–50 °C left 22 g of low-melting solid. The product was recrystallized twice from hexane. After drying overnight in an evacuated desiccator over $CaSO_4$, the product weighed 7.9 g and had mp 77–78 °C; $[\alpha]^{29}_D$ +8.2 ± 0.6° (c 42.0, acetone); IR (Nujol mull) 3.02 (s), 6.95 (s), 7.32 (s), 7.53 (m), 8.60 (s), 9.38 (s), 9.97 (m), 10.64 (m), 10.78 (s), 13.60 μ (m) (lit.[11] $[\alpha]_D$ + 14°, mp 77.5 °C). Attempts to recover additional product **1** from the mother liquor by recrystallization or bisulfite washing were unsuccessful.

(+)-1-Hydroxyneoisocarvomenthol (2). Compound **2** was obtained from Newhall[6] as a mixture with **3** (TLC showed green spots with R_f 0.3 for **2** and 0.6 for **3**). A 430-mg sample of the mixture was chromatographed on a 2.5 × 57 cm column (40 g) of Florisil packed in benzene and eluted with CH_2Cl_2 and CH_2Cl_2–EtOH. Elution with 1% EtOH in CH_2Cl_2 afforded 260 mg of **2**, $[\alpha]^{29}_D$ +1.49 ± 0.4° (c 20.2, acetone) (lit.[10,11] $[\alpha]_D$ + 2°). A sample of **2** isolated by preparative GC of the mixture (retention times 67 and 68 min for **3** and **2**, respectively, 40% of **3** and 60% of **2** by peak areas) after crystallization from hexane afforded colorless needles: mp 85–87 °C (lit.[10,11] 85–86 °C); IR (Nujol mull) 3.04 (s), 7.48, 8.66 (s), 8.91 (s), 9.31 (s), 9.81, 9.98, 10.44 (m), 10.81, 11.87, 12.00, 13.75 μ.

(+)-1-Hydroxyneocarvomenthol (3). Compound **3**[6] obtained from Newhall had mp 87–89 °C; $[\alpha]^{29}_D$ +41.4 ± 1.2° (lit.[10,11] mp 90 °C, $[\alpha]_D$ 48°); IR (Nujol mull) 2.96 (s), 7.73, 8.53 (m), 9.06, 9.70 (s), 10.40, 10.96, 11.65, 13.80 μ; TLC R_f 0.6 (dark green) and GC t_R 67 min (>99% of total peak area).

Hydration of (+)-Limonene to (+)-α-Terpineol. The solvomercuration–demercuration procedure of Brown et al.[12] was applied to the hydration of 42 g (0.31 mol) of (+)-limonene (Glidden P and F grade, $[\alpha]^{25}_D$ +100°). After saturation of the aqueous layer with K_2CO_3 and separation of the upper layer, the lower layer was extracted with 150 mL of THF. The upper layer combined with the THF extract of the lower layer was filtered (Whatman no. 1 filter paper, then phase separating paper), and the filtrate dried over Na_2SO_4, filtered, and concentrated by distillation to about 300 mL to afford a mixture of two liquid phases and a white solid. The mixture of lower layer and white solid was extracted with ether, and the extract was dried over Na_2SO_4, filtered, and concentrated at 30–50 °C to give 39 g of liquid. The crude product was distilled at 8–10 mmHg to give three fractions of the following boiling points and weights (g): 63–95 °C, 6 (fraction 1); 95–103 °C, 25 (fraction 2); 95–103 °C, 2 (fraction 3). The pot residue weighed 2.5 g. The second and third fractions had IR spectra identical with that of α-terpineol. The second fraction was a colorless liquid, $[\alpha]^{27}_D$ +96.0° (neat) (lit. $[\alpha]_D$ +95°[16]), and the third fraction was a yellow liquid, $[\alpha]^{27}_D$ +82°. Yield, based on the second fraction, was 53%.

Permanganate Oxidation of α-Terpineol to 4. A mixture of 16 g (0.104 mol) of (+)-α-terpineol (fraction 2 above), 95 mL of 2-propanol, 20 mL of water, and 130 mg (0.0023 mol) of KOH was cooled in an ice bath under nitrogen to 1–4 °C and stirred rapidly while 15 g (0.095 mol) of $KMnO_4$ was added, in portions, over a period of 0.5 h. The mixture was stirred under nitrogen at 1–6 °C for an additional 2 h. The product was filtered through a Celite pad and the pad washed with 150 mL of CH_2Cl_2. The lower layer of the filtrate was extracted with 300 mL of water in a separatory funnel, and the aqueous (upper) layer, with two 150-mL portions of ether. The combined aqueous material contained most the desired product and was neutralized to pH 6.8 with HCl. Distillation at 30 °C (15 mmHg) gave 4.2 g of glassy liquid; TLC with 16% ethanol in ether showed a large purple spot at R_4 0.5 and a smaller purple spot at R_f 0.4. A 1.3-g sample of the crude product was crystallized from ether, then recrystallized from ethanol–ether to afford 0.3 g of **4**, mp 80–81 °C, and 0.3 g, mp 79–81 °C, from the mother liquor on standing in a refrigerator, TLC R_f 0.5 (purple spot), $[\alpha]^{27}_D$ +16.6 ± 0.8° (*c* 19.1). The IR spectrum (Nujol mull) had bands at 3.03 (s), 7.37 (s), 8.60 (m), 9.39 (s), 9.49 (m), 10.92 (s), 12.30, 12.91, 13.70 μ. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.64; H, 10.90. A sample was dissolved in ethanol and a glassy film deposited on an NaCl IR plate: IR 3.00 (s), 6.10, 6.93, 7.35 (m), 8.48 (m), 8.97 (m), 9.56 (s), 10.25, 10.60, 11.03 (s), 11.40, 11.50, 12.29 (m), 12.99, 13.70 μ.

For confirmation of the identity of **4**, a sample of the racemic compound was synthesized by permanganate oxidation of (±)-α-terpineol.[13] The racemate had mp 99–102 °C (lit.[13] mp 120.5 °C), and analytical TLC under the above conditions revealed a single spot at R_f 0.5. Films deposited from ethanolic (±)-**4** and (+)-**4** gave identical IR spectra. The IR spectrum of (±)-**4** (Nujol mull) had bands at 3.00 (s), 7.50 (s), 8.39 (s), 8.48 (s), 9.40 (s), 9.50 (s), 10.26 (s), 11.05 (s), 12.30 (s), 13.00 (m), 13.67 μ (s). The substantial differences between (+)-**4** and (±)-**4** in melting point and IR of their crystalline mulls were attributed to differences in crystalline form.

[1*S*-(1α,2β,3β,5α)]-2,6,6-Trimethylbicyclo[3.1.1]heptane-2,3-diol (5) and [1*S*-(1α,2β,3α,5α)]-2,6,6-Trimethylbicyclo-[3.1.1]heptane-2,3-diol (6). The cis and trans glycols **5** and **6** were synthesized according to published procedures.[4,14] The melting point of **5** was 55–57 °C, $[\alpha]^{27}_D$ +2.4 ± 0.4° (c 39.0). Compound **6** had mp 161–162 °C, $[\alpha]^{30}_D$ +42.8 ± 2° (c 5.70). The literature values[4,14] for **5** were mp 55–56 °C, $[\alpha]^{25}_D$ −0.71° (*c* 2, $CHCl_3$). For **6** the values were mp 169–170 °C, $[\alpha]^{20}_D$ 49°. The TLC R_fs (purple spots) and GC retention times were 0.6 and 67 min for **5**, and 0.3 and 71 min for **6**.

2,10-Pinanediol (7). By a published procedure,[15] 28 g of (−)-β-pinene (Aldrich Chemical, $[\alpha]^{30}_D$-20°) was oxidized in 2-propanol–water with 30 g of $KMnO_4$. The product (10.5 g) was a low-melting solid. Recrystallization from hexane twice gave 6.0 g, mp 60–65 °C. Analytical GC produced a peak pattern indicative of instability. Analytical TLC showed a major blue-purple spot at R_f 0.4 and two minor spots at R_f 0.7. The product was further purified by column chromatography. An 800-mg sample was separated on a 1.9 × 20 cm column (43 g) of adsorbent packed in hexane and eluted with mixtures of hexane, methylene chloride, and ether. The desired product **7**[15] was eluted in the ether fractions, wt 500 mg, mp 82–84 °C, $[\alpha]^{27}_D$ −29 ± 3° (c 4.45) (lit.[15] mp 83.5 °C). Analytical TLC showed a single blue-purple spot at R_f 0.4.

Procedure for Acetophenone Reduction. A. General Procedure. A mixture of 80 mg (2.1 mmol) of $LiAlH_4$ (PCR Inc., Gainesville, Fla.) and 8 mL of ether was stirred under nitrogen and cooled to 20 °C with an ice water bath. A solution of 360 mg of glycol (2.1 mmol) in 3 mL of ether was added over a period of 15 min, while the temperature was maintained at 20 °C. A solution of 230 mg (1.9 mmol) of acetophenone in 1 mL of ether was added to the resultant mixture over a 2-min period. The temperature was allowed to rise to 25 °C and the mixture was stirred under nitrogen at 25 °C for 1 h. Since a precipitate was present from undissolved impurities in the hydride, it was not possible to determine whether the reaction was homogeneous or not. For decomposition of excess hydride, the mixture was cooled in an ice bath, and a solution of 75 mg (4.2 mmol) of H_2O dissolved in 1 mL of THF was added with vigorous stirring. Hydrogen evolution was measured by water displacement for both reagent preparation and reaction steps. The above reactant ratios were varied, and THF was substituted for ether in some runs. The temperature of either reagent preparation or reaction steps was also varied (see Tables I and II). Reaction time was decreased for those runs carried out at 66 °C: 2 min for runs F, H, and I; 5 min for run L; and 15 min for run M.

In the workup, the reaction mixture was filtered with a Celite pad, and the pad washed with ether. One to four filtrations were required. The filtrate was concentrated at 30–50 °C, placed in a volumetric flask, and diluted to 25 mL with ether. A 2-μL aliquot was analyzed by GC. Peak areas were compared to those of a standard sample of acetophenone and α-methylbenzyl alcohol at known concentrations (retention times 40 and 48 min, respectively).

The ether solution was concentrated to 1–2 mL at 30–50 °C, and the residue was transferred to a distilling bulb and distilled at 25–60 °C (0.3–1 mmHg). The distillate was diluted with CH_2Cl_2 to 200–500 μL. The diluted sample was injected into a preparative GC column, and the α-methylbenzyl alcohol collected. Optical rotations were measured at 26–29 °C. Precision of measurement was ±0.06°.

The extent of racemization during workup was evaluated. A 230-mg sample of (+)-α-methylbenzyl alcohol (K & K Chemicals, Plainview, N.Y., $[\alpha]^{27}_D$ +41.4°) was added to the distillation residue from one of the runs, and the sample subjected to the normal workup procedure. The rotation of the α-methylbenzyl alcohol sample collected, $[\alpha]^{28}_D$ +39.3°, indicated that over 98% of the original optical activity was retained.

B. Procedure with Added Alcohol. The general procedure (A) was followed, except that after glycol addition, a solution of the alcohol in 1 mL of ether or THF was added over 2 min, and the mixture was stirred for 10 min at 20 °C.

Hydrogen evolution for both steps was measured for runs H, M, and P and runs with glycols **3** (ratio 0.5) through **7** (Table II). For run O and runs with glycols **2** and **3** (ratios 1.1 and 1.7, Table II), hydrogen evolved from the reagent preparation step only was measured. Hydrogen evolution was not measured for the remaining runs. The ratio of actual to theoretical hydrogen evolved was 1.04 ± 0.13 std dev for the reagent preparation and 0.87 ± 0.11 for the total.

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Registry No.—**1**, 5729-92-0; **1** hydride complex, 62006-55-7; **2**, 20688-46-4; **2** hydride complex, 62057-38-9; **3**, 4031-57-6; **3** hydride complex, 62057-39-0; **4**, 62014-81-7; **4** hydride complex, 62006-56-8; **5**, 18680-27-8; **5** hydride complex, 62006-57-9; **6**, 21803-49-6; **6** hydride complex, 62057-40-3; **7**, 62015-66-1; **7** hydride complex, 62006-58-0; (+)-1-menthene, 1195-31-9; (+)-limonene, 5989-27-5; (+)-α-terpineol, 7785-53-7; (+)-α-pinene, 7785-70-8; (−)-β-pinene, 127-91-3; acetophenone, 98-86-2; $LiAlH_4$, 16853-85-3.

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Applications of the Peracid-Mediated Oxidation of Alcohols

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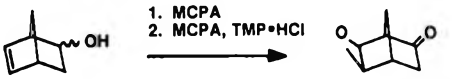
An efficient, general, one-pot procedure for the preparation of epoxy ketones from olefinic alcohols is described. Epoxidation of olefinic alcohols with *m*-chloroperbenzoic acid followed by oxidation of the alcohol with the same reagent in the presence of catalytic amounts of 2,2,6,6-tetramethylpiperidine hydrochloride affords epoxy ketones in excellent yield. Application of this procedure to allylic alcohols bearing bulky substituents in the β position followed by reduction of the resulting epoxy ketones with hydrazine yields the rearranged allylic isomer of the starting alcohol. Epoxy ketones of unhindered allylic alcohols yield diazoles on treatment with hydrazine. Oxidation of secondary alcohols using a large excess of *m*-chloroperbenzoic acid in the presence of 2,2,6,6-tetramethylpiperidine hydrochloride affords esters or lactones via a Baeyer–Villiger oxidation of initially generated ketones.

Alcohols are rapidly and efficiently oxidized to carbonyl compounds by *m*-chloroperbenzoic acid (MCPA) in the presence of catalytic amounts of nitroxide radicals and mineral acids.[2,3] The value of this convenient procedure is amplified when it is combined with the ability of peracids to effect epoxidations and Baeyer–Villiger reactions. This paper describes a number of these applications.

Preparation of Epoxy Ketones. The utility of epoxy ketones in preparative organic chemistry derives from the multitude of predictable transformations achievable when these compounds are manipulated under various conditions.[4] For example, the rearrangement of epoxy ketones can be induced thermally,[5] photochemically,[5,6] and by treatment with acids and bases.[7] Rearrangement products vary with the reaction conditions. Reaction of α,β-epoxy ketones with hydrazine yields allylic alcohols.[8] Fragmentation of the hydrazones from α,β-epoxy ketones and *N*-aminoaziridines affords carbonyl compounds and acetylenes.[9] The oximes of α,β-epoxy ketones are alkylated at the α position by dialkylcopper lithium reagents to yield α-alkylated β-hydroxy ketones.[10] Finally, epoxy ketones can be reduced to diols or β-hydroxy ketones.[11]

In spite of this versatility, no generally applicable method exists for the preparation of epoxy ketones. Direct epoxidation of olefinic ketones with peracids gives rise to complex mixtures of products due to competing Baeyer–Villiger and subsequent epoxidation and/or rearrangement reactions[12]. Epoxidation with basic hydrogen peroxide[13] or *tert*-butyl hydroperoxide[14] is applicable only to the preparation of α,β-epoxy ketones. Moreover, Baeyer–Villiger type cleavage can occur in these reactions in some cases[15] and the stereochemistry of the products is often less predictable than for peracid epoxidations. A third method which can, in principle, be used to prepare any epoxy ketone is epoxidation of an olefinic alcohol followed by oxidation of the resultant epoxy alcohol. A problem with this sequence is the instability of intermediate epoxy alcohols or epoxy ketone products to the conditions of oxidation. This problem is sometimes avoided by use of the chromium trioxide-pyridine complex to oxidize the epoxy alcohol,[16] although epoxide cleavage can occur even under these conditions and low yields have been reported in some cases.[17]

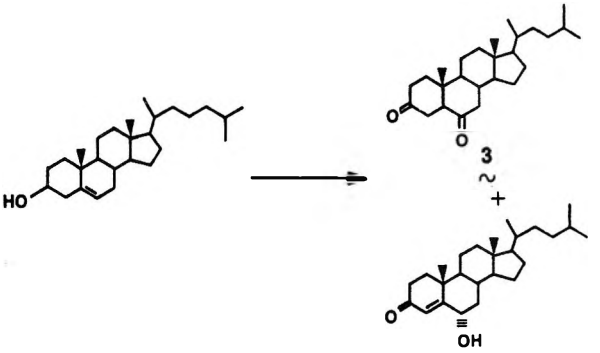
The nitroxide catalyzed oxidation of secondary alcohols by *m*-chloroperbenzoic acid offers a number of advantages for the preparation of epoxy ketones from olefinic alcohols. First, the conditions are mild enough so that epoxide cleavage should not occur. Second, since the peracid used in the oxidation can also be employed in the initial epoxidation, the entire sequence from an olefinic alcohol to an epoxy ketone can be accomplished in a single operation without isolation of the intermediate epoxy alcohol! The feasibility of this process was demonstrated by the one-pot conversion of olefinic alcohol, **1**, to epoxy ketone, **2**.[2] We now report that this method is generally applicable to the preparation of α,β-, β,γ-, and other epoxy ketones.



1 **2**

Experimentally, the epoxidation–oxidation sequence is conducted by addition of MCPA (1 equiv) to a cold solution of an olefinic alcohol in methylene chloride or tetrahydrofuran. When epoxidation is complete (usually 1–2 h), a catalytic amount (2–4 mol %) of 2,2,6,6-tetramethylpiperidine hydrochloride (TMP·HCl) is added followed by a second portion of MCPA (1.5–2.0 equiv). Oxidation is generally complete in 1–2 h at ambient temperature. An extractive workup removes *m*-chlorobenzoic acid and affords the epoxy ketone in excellent yield. Results of application of this sequence to a number of olefinic alcohols are given in Table I.

Application of the epoxidation–oxidation sequence to cholesterol afforded a mixture of diketone, **3**, and keto alcohol, **4**. Presumably, the epoxy ketone is formed, but undergoes acid-catalyzed rearrangement to **3** and **4**. Keto alcohol **4** rearranges to **3** on treatment with acid,[18] so that **3** is the principal product of the reaction if the mixture is allowed to stand for some time prior to workup.



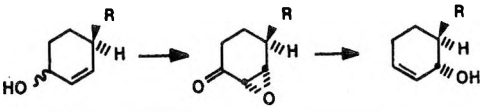
In general, this one-pot epoxidation–oxidation sequence is a convenient, efficient procedure for the preparation of epoxy ketones. The epoxidation–oxidation of allylic alcohols by this procedure affords α,β-epoxy ketones which can undergo reductive cleavage on treatment with hydrazine (Wharton reaction).[8] Since the allylic alcohol derived from this reaction is the isomer of the starting allylic alcohol, the two-step sequence of epoxidation–oxidation followed by the Wharton reaction constitutes a method for the rearrangement of allylic alcohols. Most methods for effecting this transfor-

Table I. Epoxidation–Oxidation of Olefinic Alcohols

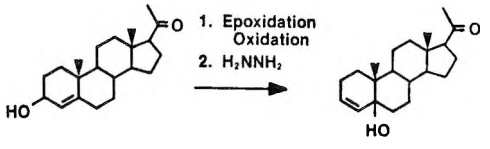
Olefinic alcohol	Epoxy ketone	% yield[a]
5-Norbornen-2-ol	5,6-Epoxy-2-norbornanone	86[b]
2-Cyclohexenol	2,3-Epoxycyclohexanone	61
4-Phenyl-3-buten-2-ol	3,4-Epoxy-4-phenyl-2-butanone	93
1,3-Diphenylpropenol	2,3-Epoxy-3-phenylpropiophenone	81
1-Hexen-3-ol	1,2-Epoxy-3-hexanone	90
2,6-Dimethyl-2-nonen-8-ol	2,3-Epoxy-2,6-dimethyl-8-nonanone	73
4-Pregnen-20-on-3-ol	(α- + β-)4,5-Epoxypregna-3,20-dione	50[c]
4-Methyl-3-penten-2-ol	3,4-Epoxy-4-methyl-2-pentanone	89

[a] Yields are of isolated products. No attempt was made to optimize individual yields. The physical and spectral properties of all products were in accord with their structures (see Experimental Section). [b] Taken from ref 2. [c] Yield determined gas chromatographically.

mation are less direct and rely on the thermodynamic or kinetic properties of the system to determine the predominant isomer.[19] The present method should yield the allylic isomer of the starting alcohol regiospecifically, regardless of the relative stabilities of the two isomers. In rigid systems, moreover, an additional feature of stereochemical control is introduced since the stereochemistry of the alcohol in the final product will be determined by the stereochemistry of the epoxide in the intermediate epoxy ketone.



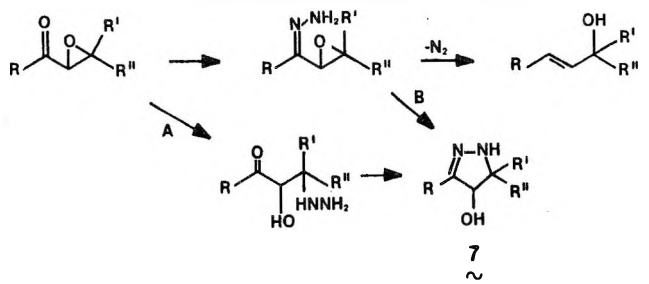
The feasibility of this two-step sequence for the rearrangement of an allylic alcohol is demonstrated for the alcohol derived from the selective reduction of progesterone (pregn-4-en-20-on-3-ol)[20] (5 → 6). While in this case the allylic



5 6

transposition proceeded in reasonable yield, results with other systems were disappointing. In most cases, little or no allylic alcohol could be isolated from the reaction of various epoxy ketones with hydrazine.

The proposed mechanism for the Wharton reaction[8] involves hydrazone formation followed by a Wolff–Kishner type elimination of nitrogen with cleavage of the epoxide. An alternate pathway can be envisaged involving attack at the β carbon of the epoxy ketone by hydrazine itself (path A) or intramolecularly, via the hydrazone (path B). In either case, an intermediate, 7, is produced which does not lose nitrogen,



7

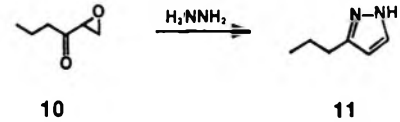
Table II. Hydrazine Reduction of Epoxy Ketones

Epoxy ketone	Method[a]	Yield of N_2 evolved
Isophorone oxide	B[b]	89
4,5-Epoxypregna-3,20-dione	A	90
2,3-Epoxycyclohexanone	B[b]	75
4-Phenyl-3,4-epoxy-2-butanone	A	60
1,2-Epoxy-3-hexanone	A	50
2,3-Epoxy-3-phenylpropiophenone	A	27
Glycidaldehyde	B[b]	20

[a] See Experimental Section for details. In each case, the method reported is that which gave the best yield. [b] Taken from ref 8.

hence does not produce an allylic alcohol. Table II reveals the yield of nitrogen evolved when several epoxy ketones are subjected to the Wharton reaction. These results indicate that as the degree of substitution at the β carbon increases, the yield of gas evolved increases. This is consistent with the proposed formation of **7** as a competitive process in those cases where attack at the β carbon is unencumbered. This postulate is further substantiated by the isolation of diazoles **9** and **11** from the Wharton reaction of epoxy ketones **8** and **10**. These derivatives presumably arise via loss of water from intermediate **7**.

8 9



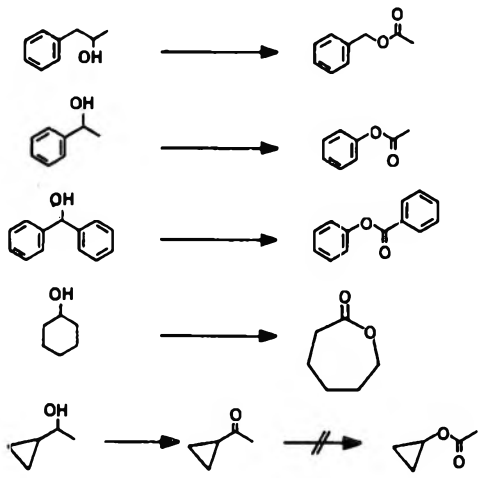
10 11

This two-step allylic transposition is thus limited to those allylic alcohols having a highly substituted β carbon.

Preparation of Esters and Lactones from Secondary Alcohols. The Baeyer–Villiger cleavage of ketones by peracids finds importance both as a preparative method and as a degradative reaction for the identification of unknowns.[21] While under ordinary conditions this reaction does not interfere with the nitroxide catalyzed oxidation of alcohols, more forcing conditions will enable both processes to occur.[2] This combination of alcohol oxidation followed by Baeyer–Villiger reaction constitutes a method for the degradation of secondary alcohols, since the net result of the process is cleavage of a carbon–carbon bond at the site of the initial alcohol function.[22] Moreover, since both reactions employ peracid as the oxidant, the overall cleavage can be effected as a one-pot operation.

Since the Baeyer–Villiger reaction requires more severe conditions than those employed in the alcohol oxidation, an attempt was made to optimize the two-step sequence by employing more reactive peracids such as trifluoroperacetic[23] and permaleic[24] acids, which are known for their efficacy in the Baeyer–Villiger reaction. Unfortunately, these peracids are rapidly decomposed by the nitroxide catalyst and are ineffective in the alcohol oxidation.[25] The sequence can be conducted using MCPA, provided that a large excess (3.5–4.0 equiv) is employed. Thus, treatment of phenyl-2-propanol with 4 equiv of MCPA and a catalytic amount (3 mol %) of TMP·HCl in methylene chloride for 5 h afforded benzyl acetate in 90% yield. In some cases these conditions were insuf-

ficient and longer reaction times, higher temperatures, or both were required to effect the oxidation. For example, the conversion of diphenylcarbinol to phenyl benzoate required heating the reactants at 90 °C for 18 h in a sealed bottle. Even under these forcing conditions, cyclopropylmethylcarbinol was oxidized only as far as the ketone.[26] Typical results for this process are given below. These results demonstrate the feasibility of this one-pot procedure for the degradation of secondary alcohols.



Experimental Section[27]

The starting alcohols used in this study were obtained as follows: 5-norbornen-2-ol, 2-cyclohexen-1-ol, hexen-3-ol, 4-methyl-3-penten-2-ol, and cholesterol were obtained commercially. Cyclohexanol, benzhydrol, 1-phenylethanol, and phenyl-2-propanol were obtained by lithium aluminum hydride reduction of the corresponding ketones. 4-Pregnen-20-on-3-ol was obtained by the selective reduction of progesterone with diborane.[20] 4-Phenyl-3-buten-2-ol was obtained from the reaction of methyllithium with *trans*-cinnamaldehyde. 1,4-Diphenyl-2-propen-1-ol was obtained from the reaction of phenylmagnesium bromide with *trans*-cinnamaldedyde. 2,6-Dimethyl-2-nonen-8-ol was prepared by the reaction of methyllithium with citronellal.

Representative Procedure for the Preparation of Epoxy Ketones. exo-5,6-Epoxy-2-norbornanone (2). To a stirred, ice-chilled solution of 2.20 g (20 mmol) of 5-norbornen-2-ol (1) in 5 mL of methylene chloride was added a solution of 4.3 g (21 mmol) of 85% *m*-chloroperbenzoic acid in 50 mL of methylene chloride. Analysis of the reaction mixture after 2 h revealed that all of the starting material had reacted. To the resultant mixture was added 1 mL (0.2 mmol) of a 0.2 M solution of TMP·HCl in methylene chloride, followed by an additional 5.3 g (26 mmol) of MCPA in 50 mL of methylene chloride. After 1.5 h the mixture was transferred to a separatory funnel and worked up as usual. The residue was sublimed to afford 2.1 g (86%) of pure 2 whose melting point and infrared spectrum correlate with those reported:[17b] mass spectrum *m/e* (rel intensity) 124 (M^+, 24.4), 106 (2.6), 96 (24.0), 95 (43.0), 82 (77.6), 81 (100), 68 (52.8), 67 (57.1). 41 (38.9), 39 (56.4).

The following epoxy ketones were prepared using the above procedure.

2,3-Epoxycyclohexanone was obtained as an oil, bp 87 °C (15 mm), IR 5.85 μ (ν C=O).

3,4-Epoxy-4-phenyl-2-butanone was obtained as an oil which crystallized on standing. Recrystallization from hexane afforded the pure epoxy ketone: mp 52–54 °C; NMR (CCl_4) δ 2.03 (s, 3, $COCH_3$), 3.28 (d, 1, J = 1 Hz, COCH), 3.90 (d, 1, J = 1 Hz, COCH), and 7.19 ppm (s, 5, ArH); mass spectrum *m/e* (rel intensity) 162 (M^+, 32.7), 120 (41.3), 91 (100), 90 (28.7), 89 (36.4).

2,3-Epoxy-3-phenylpropiophenone was obtained as an oil which crystallized on standing: NMR (CCl_4) δ 3.98 (d, 1, COCH), 4.10 (d, 1, CCH), 7.32 and 7.90 ppm (m, 10, ArH); mass spectrum *m/e* (rel intensity) 224 (M^+, 12.3), 208 (26.9), 207 (42.1), 131 (10.6), 105 (100), 89 (15.2), 77 (57.1).

1,2-Epoxy-3-hexanone was obtained as an oil: NMR (CCl_4) δ 0.92 (t, 3, CH_2CH_3), 1.55 and 2.31 (m, 4, CH_2CH_2), 2.90 (m, 2, $COCH_2$), and 3.35 ppm (m, 1, $RCHOCH_2$).

2,3-Epoxy-2,6-dimethyl-8-nonanone was obtained as an oil: NMR (CCl_4) δ 0.90 (d, 3, $CHCH_3$), 1.20 and 1.23 [s, 3, $COC(CH_3)_2$], and 2.08 ppm (s, 3, $COCH_3$), no vinyl Hs.

4,5-Epoxypregna-3,20-dione was obtained as a white solid after chromatography over silica gel, mp 120–123 °C. This material was identical with the epoxy ketone obtained from the reaction of progesterone with basic hydrogen peroxide.[28]

3,4-Epoxy-4-methyl-2-pentanone was obtained as a colorless liquid: bp 60–65 °C (20 mm); NMR (CCl_4) δ 1.27 (s, 3, $COCCH_3$), 1.40 (s, 3, $COCCH_3$), 2.14 (s, 3, $COCH_3$), and 3.22 ppm (s, 1, COCHOC).

Epoxidation–Oxidation of Cholesterol. To a stirred, ice-chilled mixture of 1.17 g (3 mmol) of cholesterol and 10 mL of methylene chloride was added a solution of 0.66 g (3.14 mmol) of MCPA in 6 mL of methylene chloride. After 2 h an additional 0.90 g (4.28 mmol) of MCPA in 9 mL of methylene chloride plus 0.3 mL of 0.1 M solution of TMP·HCl in methylene chloride were added. The resultant mixture was stirred for 18 h at room temperature, then worked up in the usual fashion to yield 1.0 g of a viscous residue which was chromatographed on 40 g of alumina (elution with chloroform) to afford 0.43 g of a white solid whose infrared spectrum exhibited two carbonyl absorptions. Fractional crystallization of this material (acetone–water) afforded pure 3 [mp (acetone–H_2O) 168–170 °C (lit.[18] mp 169–170 °C); IR 5.84 μ (ν C=O); mass spectrum *m/e* (rel intensity) 400 (M^+, 95.5), 385 (12.4), 287 (50.6), 245 (100), 231 (32.6)] and 4 [mp (CH_2Cl_2–ligroin) 154–155 °C (lit.[29] mp 156 °C); IR 2.98 (ν OH) and 6.00 (ν C=O); UV λ_{EtOH} (max) 237 nm; mass spectrum *m/e* (rel intensity) 400 (M^+, 80.4), 385 (17.1), 382 (13.7), 331 (100), 287 (18.0), 245 (32.7), 231 (11.5)].

Hydrazine Reduction of Epoxy Ketones. The epoxy ketones were allowed to react with hydrazine according to the procedures of Wharton et al.[8] Two techniques were employed. Method A. Hydrazine hydrate was added to a solution of the epoxy ketone, neat, and the mixture was heated (60–90 °C) until gas evolution ceased. Method B. Hydrazine hydrate was added to a solution of the epoxy ketone in ethanol containing 10–15% acetic acid by weight. The yield of gas evolved in each case is given in Table II.

Reduction of 4,5-Epoxypregna-3,20-dione. 4,5-Epoxypregna-3,20-dione (1.1 g, 3.3 mmol) was treated neat with 4 mL of 85% hydrazine hydrate at 90 °C. Gas evolution was 90% complete in 10 min. Following an extractive workup, the crude product was chromatographed on silica gel (hexane–ethyl acetate). The major component was crystallized from aqueous ethanol to yield pure 6: mp 220–224 °C; mass spectrum *m/e* (rel intensity) 316 (M^+, 2.4), 298 (74.0), 254 (34.8).

Reduction of 3,4-Epoxy-4-phenyl-2-butanone. 3,4-Epoxy-4-phenyl-2-butanone (2.43 g, 15 mmol) in 20 mL of ethanol plus 0.12 mL of acetic acid was treated with 2.0 g of hydrazine hydrate (35 mmol). Gas evolution was complete in 5 min. Following an extractive workup, the crude residue (0.8 g) was purified by preparative thin layer chromatography (silica gel G, 4:2:1 C_6H_6–$CHCl_3$–EtOAc). The major component was identified as diazole 9: NMR (CCl_4) δ 2.20 (s, 3, $ArCH_3$), 6.23 (s, 1, ArH), 7.30 and 7.60 (m, 5, PhH), and 10.33 ppm (s, 1, NH); mass spectrum *m/e* (rel intensity) 158 (M^+, 100), 157 (44.4), 130 (13.5), 128 (21.6), 77 (32.2).

Reduction of 1,2-Epoxy-3-hexanone. 1,2-Epoxy-3-hexanone (0.57 g, 5 mmol) in 0.5 mL of ethanol was treated with 2.0 mL of hydrazine hydrate at room temperature. Gas evolution was complete in 5 min and was not increased by further heating. The residue obtained after an extractive workup was a mixture of at least two major components (TLC). The gas chromatogram (10% Carbowax 1540 on 40/60 mesh Chromosorb T) of this mixture exhibited only one peak. This component was identified by its mass spectrum as the diazole 11. The crude product is apparently a mixture of the diazole, 11, and its hydrated analogue (7, R = C_3H_7; R′ = R″ = H). Loss of water from the hydrated analogue occurs in the injector port to produce 11 as the only eluted peak. The mass spectrum of the eluted peak exhibited a fragmentation pattern analogous to that of diazole 9: mass spectrum *m/e* (rel intensity) 110 (M^+, 30.8), 95 ($M - CH_3$, 21.1), 82 (96.2), 81 (100), 68 (5.0).

Oxidation. Baeyer–Villiger Reactions. Method A. Preparation of Benzyl Acetate. A solution of 2.72 g (20 mmol) of phenyl-2-propanol, 16.0 g (80 mmol) of MCPA, and 4.0 mL of 0.1 M TMP·HCl in 150 mL of methylene chloride was stirred for 5 h at room temperature (the reaction was slightly exothermic at first). The usual workup afforded 2.7 g (90%) of pure benzyl acetate: NMR (CCl_4) δ 2.00 (s, 3, O_2CCH_3), 5.02 (s, 2, $ArCH_2O$), and 7.27 ppm (s, 5, ArH).

ϵ-Caprolactone was prepared similarly from cyclohexanol.

Method B. A solution of 0.92 g (5 mmol) of diphenylcarbinol, 4.2 g (20 mmol) of MCPA, and 1.0 mL of 0.1 M TMP·HCl in 40 mL of methylene chloride was stirred at room temperature for 1 h to oxidize the alcohol to the ketone. The vial was then sealed and immersed in

an oil bath at 100 °C. After 18 h the vial was removed from the bath and allowed to reach room temperature. The usual workup afforded, after chromatography (silica gel, 2:1 C_6H_6–hexane), 0.53 g (53.5%) of pheryl benzoate, crystals from hexane, mp 68–69 °C (lit.[29] mp 71 °C).

Phenyl acetate was prepared in a similar fashion from 1-phenylethanol.

Registry No.—**1**, 13080-90-5; **2**, 55044-07-0; **3**, 13492-22-3; **4**, 570-90-1; **5**, 566-66-5; 5β-**6**, 61990-52-1; 5α-**6**, 61990-53-2; **8**, 6249-79-2; **9**, 3347-62-4; **10**, 61990-54-3; **11**, 7231-31-4; 2,3-epoxycyclohexanone, 6705-49-3; 2,3-epoxy-3-phenylpropiophenone, 5411-12-1; 2,3-epoxy-2,6-dimethyl-8-nonanone, 61990-55-4; α-4,5-epoxy-3,20-dione, 17503-05-8; β-4,5-epoxy-3,20-dione, 17597-24-9; 3,4-epoxy-4-methyl-2-pentanone, 4478-63-1; cholesterol, 57-88-5; benzyl acetate, 140-11-4; phenyl-2-propanol, 698-87-3; diphenylcarbinol, 91-01-0; phenyl benzoate, 93-99-2; 2-cyclohexenol, 822-67-3; 4-phenyl-3-buten-2-ol, 17488-65-2; 1,3-diphenylpropenol, 4663-33-6; 1-hexen-3-ol, 4798-44-1; 2,6-dimethyl-2-nonen-8-ol, 40596-76-7; 4-methyl-3-penten-2-ol, 4325-82-0.

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(1) Address to which correspondence should be sent: General Electric Co., Research & Development Center, P.O. Box 8, Bldg. K-1, Room 5A20, Schenectady, N.Y. 12301.
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(25) *m*-Chloroperbenzoic acid is also decomposed by the nitroxide catalyst (ref 1); however, the rate of this decomposition is slower than the alcohol oxidation, thus does not interfere with it.
(26) Cyclopropyl methyl ketone is particularly unreactive in the Baeyer–Villiger reaction, but can be oxidized by trifluoroperacetic acid (ref 23).
(27) Melting points were determined on a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer using sodium chloride disks or potassium chloride pellets. Mass spectra were determined on an LKB 9000 gas chromatograph–mass spectrometer system operated with an accelerating voltage of 3.5 kV, an ionizing current of 60 μA, an electron energy of 70 eV, and an ion source temperature of 250 °C or on a Hewlett-Packard 5982 A gas chromatograph–mass spectrometer system with an ion source temperature of 180 °C, ionizing current 0.15 μA, and an electron energy of 70 eV. Aliquots of crude reaction and isolated products were monitored using gas chromatographic columns described below. Gas chromatography was performed on a Varian 2700 gas chromatograph equipped with a FID detector using 6 ft × 0.25 in. glass columns: column A, 3% OV-1 on 80/100 mesh Supelcoport; column B, 5% Carbowax 1540 on 40/60 mesh Chromosorb T. The phrase "worked up in the usual fashion" means that the organic phase was washed successively with 1.0 M NaOH, water, and brine, then dried by passage through a cone of anhydrous sodium sulfate.
(28) H. J. Ringold, E. Bates, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956). These authors report a melting point of 122–124 °C for the mixed (α + β) epoxide.
(29) R. C. Weast, Ed., "Handbook of Chemistry and Physics", 49th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p C-182.

Reevaluation of the Use of Peroxycamphoric Acid as an Asymmetric Oxidizing Agent

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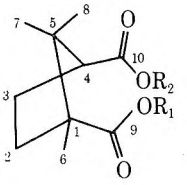
The usual method for preparation of monopercamphoric acid for asymmetric synthesis is shown to afford significant quantities of two isomers giving opposite stereochemical senses of asymmetric induction. One of the isomers can be obtained crystalline and use of this single isomer for asymmetric induction leads to optical yields of chiral sulfoxides, epoxides, and oxaziridines 50–100% greater than previously reported to result from use of the mixed isomers. In one of the more favorable cases, 2-*tert*-butyl-3-(*p*-bromophenyl)oxaziridine (**4**) was obtained in 60% enantiomeric excess using the crystalline peracid.

In recent years, a monoperoxycamphoric acid (MPCA) ascribed structure **1** has found use as a chiral oxidant for the asymmetric syntheses of chiral sulfoxides,[1-3] epoxides,[3-6] and oxaziridines.[3,7-9] In most instances, the degree of asymmetric induction afforded by MPCA is rather low. In this paper, we report an experimental modification that substantially increases the optical yields of products afforded by oxidation with MPCA.

Ordinarily, MPCA is prepared by reaction of camphoric anhydride with hydroperoxide ion, as originally described by Milas and McAlevy.[10] So far as can be ascertained from most published procedures ,the MPCA used for asymmetric synthesis is isolated via an extractive workup and does not appear to be purified further (apart from drying and iodometric standardization) before use *even though Milas and McAlevy originally reported it to be a crystalline solid.* Use of the unpurified extract is tantamount to a general de facto assumption that MPCA **1** is the only significant peracid in the

Table I. ^{13}C Chemical Shifts[a] of Camphoric Acid and Percamphoric Acid Isomers



Carbon atom	Camphoric acid,[b] R_1 = R_2 = H	1,[c] R_1 = H; R_2 = OH	2,[c] R_1 = OH; R_2 = H	3,[c] R_1' = R_2' = OH
1	56.66	56.07	55.39	56.20
2	33.19	32.29	31.87	32.16
3	23.12	22.58	22.58	22.58
4	53.04	50.16	52.34	52.79
5	46.63	47.30	47.63	46.88
6	21.99	21.67	21.38	21.60
7	21.51	21.18	21.08	21.08
8	23.12	22.58	22.58	22.58
9	175.66	175.17	179.71	180.26
10	177.55	181.79	176.66	182.25

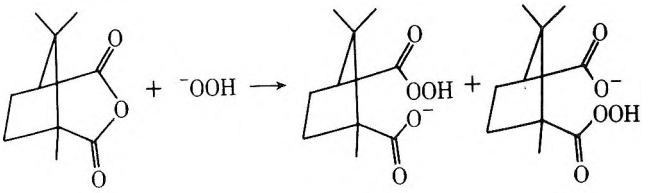
[a] All chemical shifts ± 0.06 ppm. Single-frequency off-resonance decoupling was used to assist in spectral assignments. [b] In acetone-d_6, ~ 250 mg/2 mL. [c] In chloroform-d, ~ 500 mg/2 mL.

Table II. Oxidation of *p*-Bromobenzylidene-*N*-*tert*-butylamine with MPCA at −78 °C[a]

Entry	Solvent	Ratio of oxidants[b] 1	2	3	Enantiomeric excess, % (±1%)[c]
1	CH_2Cl_2[d]	15	1	~0	40
2	CH_2Cl_2[d]	2	1	1	<1
3	CH_2Cl_2[d]	4	2	1	24
4	$CHCl_3$/CH_2Cl_2 (4:1)	15	1	~0	60

[a] The reaction mixture was kept at this temperature for 12 h, then allowed to warm to room temperature over a 5–6 h period. [b] Estimated from the intensities of ^{13}C NMR peroxycarbonyl resonances. [c] An excess of the (−) isomer[12] was obtained in each instance, in an overall yield of >80%. [d] 95% of the theoretical amount of camphoric acid had precipitated at the conclusion of the reaction.

extract. It is logical to expect that MPCA isomer **2** might also be present (eq 1); the question is, to what extent?



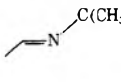
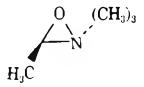
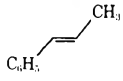
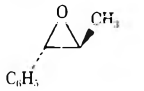
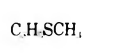
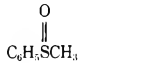
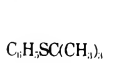
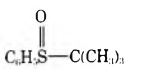
1 **2**

Using the usual procedure and workup, we obtained a solution that, by iodometry, contained essentially only MPCA. However, six signals (three pairs) are evident in the carbonyl region of the ^{13}C NMR spectrum of this material (Table I). None of these signals arise from the anhydride or diacid. By means of ^{13}C NMR, it was ascertained that monoperacids **1** and **2** were both present as was a small amount of bisperacid **3**, presumably formed by exchange. In our hands, the proportion of monoperacid **1** varies (50–80% of total) depending upon the care taken in regulating reaction temperature and the rate of anhydride addition. Although hardly astonishing, this observation has considerable impact in terms of asymmetric induction. By concentrating the crude ethereal extract under vacuum, diluting with CH_2Cl_2, and storing at −30 °C for several days, colorless prisms (ca. 50%, mp 65–68 °C) were obtained. The ^{13}C NMR spectrum of this material is consistent with its being a 15:1 mixture of monoperacids **1** and **2**. One additional recrystallization raises the melting point to 70–71 °C.[11] Crystalline **1** shows no demonstrable decomposition after storage at −30 °C for 1 month. However, when crystalline **1** is dissolved in CH_2Cl_2 and stored for several days at 25 °C, or 2 weeks at −30 °C, noticeable conversion of **1** to **2**, **3**, and camphoric acid occurs. Monoperacid **2** has not been isolated although the mother liquors from the crystallization of **1** are substantially enriched in **2**.

From the results of asymmetric synthesis of 2-*tert*-butyl-3-(*p*-bromophenyl)oxaziridine (**4**) using MPCA of different isomeric compositions, it may be inferred that peracids **1** and **2** have opposite stereochemical preferences. Oxidation with a fresh solution of crystalline **1** affords **4** in 40% ee (Table II, entry 1), use of the crude extract affords **4** in 24% ee (entry 3), and use of the mother liquors affords essentially racemic oxaziridine (entry 2).

These results raise the possibility that, in prior reports of the use of MPCA, optical yields might have been significantly

Table III. Asymmetric Oxidations of Various Substrates with MPCA

Starting material[a]	Product[b]	Solvent	Temp, °C	Enantiomeric excess, % Lit. or crude extract	Crystalline
		CH_2Cl_2	−78	10 (−)	14 (−)[13]
		$CHCl_3$	0	4.6 (*S*)[5]	7.8 (*S*)
		$CHCl_3$	0	5.1 (1*S*,2*S*)[5]	9.2 (1*S*,2*S*)
		$CHCl_3$	0 4 −50	3.8 (*R*)[1] 6.4 (*R*)[2]	 6.4 (*R*) 9.0 (*R*)
		$CHCl_3$	0 4 −30	1.3 (*S*)[1] 1.6 (*S*)[2]	 4.4 (*S*)

[a] Registry no. are, respectively, 62058-77-9, 100-42-5, 873-66-5, 100-68-5, 3019-19-0. [b] Registry no. are, respectively, 62107-41-9, 20780-54-5, 4518-66-5, 4850-71-9, 62076-10-2.

higher (and possibly sometimes of the opposite sense) had crystalline MPCA been used instead of crude extract. To check upon the generality of this hypothesis, several previously reported MPCA asymmetric oxidations were repeated using crystalline **1**. The results of these comparisons and of the asymmetric synthesis of several other oxaziridines, again using different compositions of the MPCA isomers, appear in Table III. In general, the use of crystalline **1**, rather than the crude extract, increases optical yield by 50–100%. In some instances, optical yields are still fairly low. However, the 60% optical yield obtained in the case of oxaziridine **4** (Table II) demonstrates that crystalline **1** sometimes functions as quite an efficient chiral oxidant.

Acknowledgment. This work has been partially supported by grants from the National Institutes of Health and the National Science Foundation.

Registry No.—**1**, 16211-85-1; **2**, 62058-73-5; **3**, 39923-07-4; (−)-**4**, 62058-74-6; (±)-**4**, 62058-75-7; camphoric acid, 5394-83-2; *p*-bromobenzylidene-*N*-*tert*-butylamine, 62058-76-8.

References and Notes

(1) U. Folli, D. Iarossi, F. Montanari, and G. Torre, *J. Chem. Soc. C*, 1317 (1968).
(2) U. Folli, D. Iarossi, and F. Montanari, *J. Chem. Soc. C*, 1372 (1968).
(3) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", American Chemical Society, Washington, D.C., 1971, pp 336–344.
(4) R. C. Ewins, H. B. Henbest, and M. A. McKervey, *Chem. Commun.*, 1085 (1967).
(5) F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 135 (1969).
(6) F. Montanari, I. Moretti, and G. Torre, *Gazz. Chim. Ital.*, **104**, 7 (1974).
(7) D. R. Boyd and R. Graham, *J. Chem. Soc. C*, 2648 (1969).
(8) (a) F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 1694 (1968); (b) *Gazz. Chim. Ital.*, **103**, 681 (1973).
(9) C. Belzecki and D. Mostowicz, *J. Chem. Soc., Chem. Commun.*, 244 (1975).
(10) N. A. Milas and A. McAlevy, *J. Am. Chem. Soc.*, **55**, 349 (1933).
(11) The originally reported melting point of 49–50 °C may indicate that Milas and McAlevy had in hand a mixture of **1** and **2**.
(12) A sample of this material with 39.6% ee had $[\alpha]^{23}_{D}$ −29.7° (tentatively assigned the 2*S*,3*R* configuration).[13]
(13) An NMR method for the determination of absolute configuration and enantiomeric composition of oxaziridines is being reported elsewhere.

Reduction of Amides and Lactams to Amines by Reactions with Phosphorus Oxychloride and Sodium Borohydride[1]

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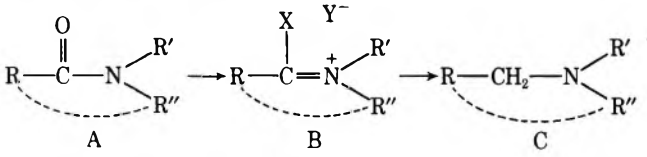
Practical and convenient procedures were developed for the reduction of carboxamides and lactams to corresponding secondary and tertiary amines by reactions with $POCl_3$ and $NaBH_4$. Optimum conditions for formation of *O*-phosphoryl (or chloroimonium) intermediates and their reductions are structure dependent. Selective reductions of amide esters and amide nitriles to amino esters and amino nitriles were obtained.

The reduction of amides and lactams to amines with lithium aluminum hydride[2] sometimes proceeds with difficulty, particularly where secondary amines are to be generated, due to NH proton acidity and formation of insoluble complexes. The use of forcing reaction conditions such as reduction in refluxing *N*-ethylmorpholine[3] does not always overcome this barrier. Alternatively, diborane may be used for such reductions but other susceptible groups, such as double bonds, can then also react. Selective reduction of amido esters to amino esters[4] with diborane usually requires a deactivated pentachlorophenyl or an aromatic acid ester. The recently developed reduction of amides to amines by a sodium borohydride–carboxylic acid complex[6] could also not be used for selective reduction of the lactam ester **18**, with both carbonyl groups lost in the reduction product. However, selective reduction of lactams in the presence of ester functions can be achieved by conversion to thiolactams and desulfurization with Raney nickel[7,8] or by formation of alkoxyimonium intermediates with triethyloxonium fluoroborate and subsequent reduction with sodium borohydride.[9,10]

Since the latter procedures suffer from being either cumbersome, experimentally difficult, or costly, a more practical preparative method for reduction of N-mono- and disubstituted amides and lactams was required, preferably with selectivity for these functional groups. This was found in the reactions of lactams and amides with $POCl_3$ followed by $NaBH_4$.[11] While a previous report of the reaction of *N*-benzylpiperidone with $POCl_3$ and subsequent borohydride reduction had indicated only dimeric amine products,[12] we found that good yields of the monomeric amine could be obtained from this lactam as well as from other examples listed in Table I.

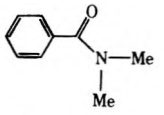
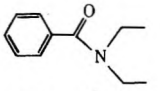
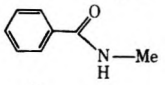
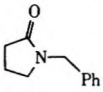
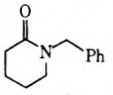
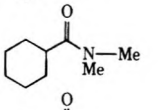
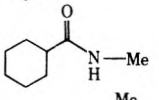
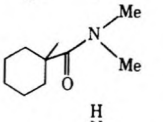
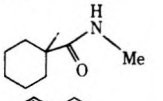
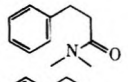
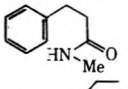
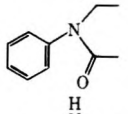
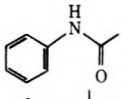
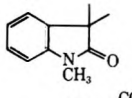
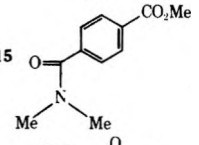
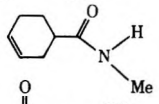
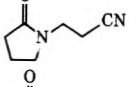
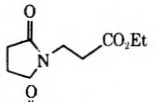
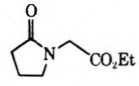
The reaction sequence proceeds from an amide or lactam A to an imino derivative B where X and/or Y can be $OPOCl_2$



and/or Cl. While an *O*-phosphoryl derivative may be favored over the corresponding imino chloride, in analogy to observations in related studies,[13–16] either or both types of derivatives may be produced in the reaction medium. Formation of the imonium derivatives was followed by NMR spectra which showed a downfield shift of 0.8–1.0 ppm for protons α to nitrogen in tertiary amides and 0.4–0.6 ppm in secondary amides. It was also noted that alkyl groups in *N*,*N*-dialkylamides, usually nonequivalent in $CDCl_3$ solutions, became equivalent in $POCl_3$ solutions (owing to amide protonation by HCl, which could be suppressed by addition of pyridine). This equivalence was lost as the amide A was converted to the imino derivative B in *N*,*N*-dimethyl- and -diethylbenzamide and in *N*,*N*-dimethylcyclohexanecarboxamide, but not in the other examples shown in Table I. Observation of these conversions provided minimal reaction times for the first step of the reaction sequence.

Table I lists the times necessary for complete reaction of amides with $POCl_3$, plus 20–30%. A dependence of the reaction rate on steric and electronic structural parameters may be

Table I

Amide	Conditions for complexation[a] Time, h	Amide concn, M	Conditions for reduction[b] Equiv of $NaBH_4$	Time, h	Yield,[c] %
1 	3	0.5	2.7	1	89
2 	2	0.5	3.2	1.25	88
3 	4.5	0.5	3.2	1	87
4 	0.25 0.33	1.0 1.0	3.2[d] 2.8[d]	1.0 0.25	84 72[e,f]
5 	0.25	1.0	3.0[d]	1.0	70[e]
6 	3.5	1.0	3.1	1.5	86
7 	0.5	1.0	3.1	1.0	83
8 	5.0[g]	1.1	3.0[d]	1.0	80
9 	2.5[h]	1.0	3.9	1.25	85
10 	0.33 0.33 1.0[g]	1.0 1.0 1.0	3.0[d] 2.0[d] 2.0[d]	1.0 0.25 0.25	78[e] 71[e,f] 38[e,f]
11 	0.25 0.33 2.0[g]	1.0 1.0 1.0	3.0[d] 2.0[d] 2.0[d]	1.0 0.25 0.25	72[e] 74[e,f] 51[e,f]
12 	6.0	1.0	3.1	1.0	41[m]
13 	10.0	1.0	3.0	1.0	68[f]
14 	24.0[i]	1.0			
15 	3.0[j]	1.0	3.0	1.0	75[k]
16 	0.75	1.0	2.0[d,l]	0.25	76
17 	0.33	1.0	2.0[d,l]	0.25	66
18 	0.33 0.33	1.0 1.0	2.0[d,l] 1.5[d,l]	0.25 0.25	71 59
19 	0.33	1.0	2.0[d,l]	0.25	50

[a] Reaction at room temperature. [b] Reaction at room temperature, about 0.25 M in glyme. [c] Determined by gas chromatographic analysis. [d] Recrystallized $NaBH_4$ used. [e] Dimer also isolated; see text. [f] Isolated yield. [g] At 69–72 °C. [h] At 50–55 °C. [i] Reaction at reflux with no substantial complexation being observed. [j] At 45–40 °C. [k] This selective reduction could be carried out in glyme. The amine–borane complex is difficult to decompose; refluxing in methanolic HCl for 8 h was required. [l] Reaction with about 0.7 M $NaBH_4$ in ethanol. [m] Transalkylation–dealkylation products also isolated.

noted. Increasing substitution α to the carbonyl group decreases the reaction rate and secondary amides generally react faster than corresponding tertiary amides (**6** vs. **7**; **8** vs **9**). Aliphatic amides react faster than benzamides, which in turn react more rapidly than anilides. Addition of pyridine increased the rates of imonium derivative formation considerably over those shown in Table I (see Table II). This is of particular value for systems lacking protons α to the carbonyl group which generally react slowly (i.e,, **1–3, 8**) but pyridine addition should be chosen with caution for others owing to the possibility of increased dimerization reactions (see below).

Evaporation of excess phosphorus oxychloride and addition of glyme and sodium borohydride resulted in reduction of the imino derivatives B to amines C. This reduction could also be achieved with diborane. Since it was found in a control experiment that diborane is generated by addition of sodium borohydride to phosphorus oxychloride and the crude imonium derivatives were suspect of containing residual $POCl_3$, or of generating HCl, reduction of the imino intermediates by diborane had to be considered as a possible general reaction course in the amide reduction sequence.

Diborane was also generated from excess sodium borohydride on workup of the reduction reactions with aqueous hydrochloric acid and resulted in formation of amine borane adducts. These adducts, which are stable in aqueous solution, were readily decomposed by heating for 20 min in aqueous acid.[17,18] In order to establish direct reduction of the imino derivatives by sodium borohydride and to optimize selective reductions of amides and lactams with preservation of ester, nitrile, and olefinic groups, it was desirable to avoid the presence of diborane. This was achieved by addition of sodium borohydride, as an ethanolic solution, to the imino derivatives in glyme. Examples **16–19**, Table I, showed no reduction of the second functional group and only traces of aminoboranes when this procedure was used. It may also be noted that reduction of the imonium derivative of *N,N*-dimethylbenzamide in glyme by a limited amount of diborane was not affected by a severalfold excess of cyclopentene (a 92% yield of amine was obtained), but that no reduction of the corresponding amide was found under those conditions, owing to exclusive hydroboration of the olefin.

Amides or lactams with protons α to the carbonyl carbon can be expected to show equilibrium of an initially generated imonium intermediate B with a corresponding heterosubstituted enamine D[19] or imine E. Formation of enamines D is increased by addition of pyridine and can then be readily seen in NMR spectra (see Table II, **6**[b,f]). The enamines D and imines E are subject to electrophilic alkylation by the imonium intermediate B, thus giving rise to dimeric products F–H[20] which are then subject to reduction by sodium borohydride. While addition of pyridine was found to increase the rate of imonium derivative formation, such addition may thus also lead to lower yields of monomeric amines, depending on the structure of the amide or lactam.

Even without pyridine this initial dimerization accounts for a decreased yield of some monomeric amines. Thus *N*-benzylpyrrolidone gave 7% of the dimeric amine **20a**, *N*-benzylpiperidone gave 8% of the homologue **20b**, *N,N*-dimethyl-3-phenylpropionamide gave 9% of the three dimers **21–23** in ratios of 81:17:2, and *N*-methyl-3-phenylpropionamide gave a 7% yield of amine **24**.

20a, $n = 1$

b, $n = 2$

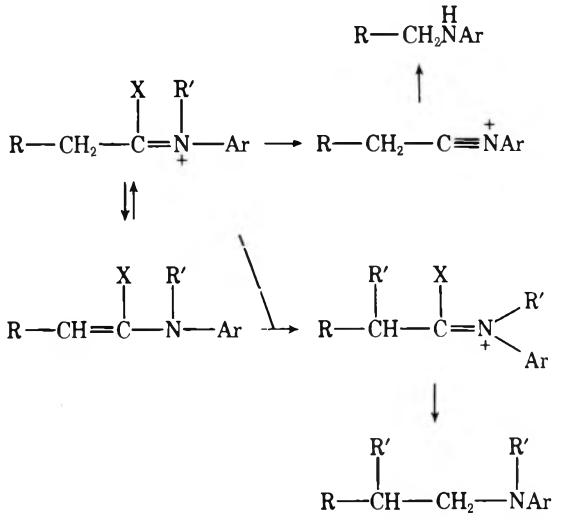
21

22 **23**

24

The dimerization can be observed during reaction of the amides with $POCl_3$ by the increased complexity of NMR spectra of the crude imonium intermediates B and by isolation of *N,N*[1]-dibenzyl-3-(4-aminovaleryl)-2-piperidone[12] when the *N*-benzylpiperidone reaction is quenched with water rather than reduced with sodium borohydride. Heating *N,N*-dimethylphenylpropionamide in $POCl_3$ for 1 h and subsequent reduction changed the ratio of monomeric to dimeric products (**21–23**) from 70:9% to 39:40%. Dimerization may also take place during the reduction, i.e., following the known reaction of piperideins[21] in the piperidone reduction. In any event dimerization is inhibited by a second substituent α to the carbonyl group (e.g., in cyclohexanecarboxamides).

A further limit to the $POCl_3$–$NaBH_4$ reduction sequence is found in amides with *N*-aryl substituents. Stabilization of charge on nitrogen promotes dealkylation[22–24] and transalkylation reactions. Thus *N*-ethylacetanilide (**12**) gave only 39% of *N,N*-diethylaniline, 52% of *N*-ethylaniline, and 6% of *N*-butyl *N*-ethylaniline.



Experimental Section

Imonium Derivative Formation. The conditions necessary for imonium derivative formation were determined in separate experiments. In most cases room temperature gave practical reaction rates. The most notable feature observed with the NMR spectra was a downfield shift of protons α to nitrogen upon complexation. Table II lists the observed NMR data for several amides and lactams and their imonium derivatives, from which one can judge the progress of the reaction.[25] As seen in Table II, addition of pyridine gave a large increase in reaction rates. The following procedure for the complexation of *N,N*-dimethylcyclohexanecarboxamide (**6**) is representative. To 2 mL of phosphoryl chloride was added 304 mg (2 mmol) of amide **6**. The reaction mixture was sealed and stirred at room temperature. At appropriate intervals aliquots were withdrawn for NMR spectra.

Reduction of *N*-Benzylpyrrolidone (4). The following procedure for the reduction of *N*-benzylpyrrolidone (**4**) is representative of the general procedure followed for reduction of amides and lactams in *glyme*.

A. *N*-Benzylpyrrolidone (0.81 g, 4.7 mmol) was added to 5 mL of phosphoryl chloride at room temperature. The solution was stirred for 15 min and excess phosphoryl chloride then removed at 20 °C (10 mm). The resultant oil was placed under high vacuum for 20 min to remove residual phosphoryl chloride and then dissolved in 20 mL of glyme. The solution was cooled in ice and sodium borohydride[26] (0.56 g, 15 mmol) was added with vigorous stirring. The reaction mixture was warmed to 20 °C, stirred for 1 h, and cooled in ice and 10 mL of 10% hydrochloric acid was added dropwise. The glyme was evaporated, water added to bring the volume to 30 mL, and the mixture refluxed for 20 min. After extraction with ether, sodium hydroxide (3.0 g) was added to the aqueous solution followed by extraction with ether. The basic extracts were dried over potassium carbonate and concentrated. Addition of benzene and a measured amount of dimethylaniline (internal standard) allowed for determination of the yield by GC analysis. One component corresponding to an 84% yield of *N*-benzylpyrrolidine was found.

B. In a similar experiment starting with 0.91 g (5.2 mmol) of *N*-benzylpyrrolidone the basic extract was distilled to 70 °C (0.005 mm) to give 0.61 g (72%) of *N*-benzylpyrrolidine. A residual 0.13 g of oil was tube distilled (160–200 °C block temperature, 0.005 mm) to give 0.10 g of colorless oil. Preparative TLC of the oil on alumina (chloroform–ethyl acetate, 7:2) and elution of the first major band (R_f 0.7) gave 0.06 g of oil which displayed the spectral characteristics of **20a**: IR 2785 cm^{-1}, no carbonyl; NMR δ 7.30 (m, 10 H), 4.1–3.1 (m, 4 H), 3.0–1.5 (m, 14 H); mass spectrum *m/e* (rel intensity) 320 M^+ (72), 229 (100), 186 (81), 172 (62), 160 (94), 91 (90). Picrate (ethanol) mp 151–153 °C.

Anal. Calcd for $C_{34}H_{34}N_8O_{14}$: C, 52.44; H, 4.40; N, 14.39. Found: C, 52.30; H, 4.47; N, 14.26.

Reduction of *N*-Ethyl-β-carboethoxypyrrolidone (18). The following procedure is representative of the general procedure followed to effect selective reductions using *ethanolic* sodium borohydride solution. The imonium derivative prepared from 1.03 g (5.50 mmol) of lactam ester and 5 mL of phosphoryl chloride, as described in the general procedure, was taken up in 3 mL of glyme at room temperature and cooled to 0 °C. To the glyme solution was added 16 mL of 0.7 M sodium borohydride in ethanol (11.0 mmol) at such a rate as to maintain a vigorous reaction. After stirring for 15 min at room temperature 10 mL of 2% hydrochloric acid was added. The ethanol was evaporated, water added, and the solution extracted with ether. The ether extracts were dried over magnesium sulfate and concentrated to give 0.37 g of oil: IR 2360, 2250, 1735 cm^{-1}; weak bands indicative of the presence of small quantities of amine borane adduct. Most of the extract consisted of ethyl esters of phosphoric acid: IR 3500–3200, 1000–1100 cm^{-1}; NMR strong quartets δ 4.3–4.0. The aqueous acidic solution was brought to pH 10.5–11.0 by addition of 30 mL of 20% potassium carbonate while cooling in an ice–salt bath at 0 °C. The cold aqueous solution was extracted with ether and the extracts dried over magnesium sulfate and concentrated at 1 atm. Addition of toluene and *N*-ethylaniline (internal standard) allowed determination of the yield by GC analysis. One component corresponding to a 71% yield of *N*-ethyl-β-carboethoxypyrrolidine was found. GC comparison of the reaction mixture with the corresponding amino alcohol indicated that negligible reduction of the ester had occurred. The determination of dimerization products was not undertaken in this case.

Reduction of *N*-Benzylpiperidone (5). Reduction of 0.95 g (5.0 mmol) of *N*-benzylpiperidone using the general procedure described above gave a 70% yield of *N*-benzylpiperidine by GC analysis. No other volatile products were evident. Distillation of the reaction mixture under high vacuum left a residual solid, 0.13 g, which was recrystallized from ethanol to give 0.07 g of dimeric amine **20b**: mp 116–118 °C (lit. 117–118 °C);[12] IR (KBr) 2790, 2750 cm^{-1}; NMR δ 7.26 (m, 10 H), 4.20, 3.98, 3.22, 3.0 (dd, 2 H), 3.50 (s, 2 H), 3.2–2.6 (m, 4 H), 2.2–1.3 (m, 14 H); mass spectrum *m/e* (rel intensity) 348 M^+ (23), 257 (43), 186 (17), 174 (100). Picrate (ethanol) mp 194–195 °C (lit. mp 194–195 °C).[12]

Reduction of *N,N*-Dimethyl-β-phenylpropionamide (10). A. The amide (1.85 g, 10.5 mmol) was added to 10 mL of phosphoryl chloride and heated to 69–72 °C for 1 h. Excess phosphoryl chloride was removed as described in the general procedure. The imonium derivative was taken up in 20 mL of glyme and cooled to 0 °C, and 0.79

Table II. NMR Signals of Protons α to Nitrogen during Imonium Derivative Formation

Compd	Chemical shift, ppm: Amide	Chemical shift, ppm: Imonium derivative	Δδ, ppm	Reaction time, h[a]
1	(s) 3.14	(bd) 4.0	0.86	2.25
1[b]	(s) 3.0	(s) 3.94	0.94	0.5
1[c]	(s) 3.0	(bs) 3.92	0.92	0.8
2	(q) 3.4	(d/q) 4.3	0.90	1.5
3	(s) 3.16	(s) 3.68	0.52	2.0
3[b]	(d) 3.02	(s) 3.52	0.50	0.25
4[d]	(s) 4.5[e]	(s) 5.48	0.98	0.2
5[d,f]	(s) 4.6[e]	(s) 5.60	1.0	0.2
6	(s) 3.0	(d) 3.92	0.92	2.0
6[b,f]	(d) 3.14	(s) 2.84	−0.30	2.0
7	(s) 3.02	(s) 3.42	0.40	0.5
8[g]	(s) 2.96	(s) 3.92	0.96	4.0
8	(s) 2.98	(s) 3.94	0.96	24.0[h]
8[b]	(s) 3.0	(s) 4.08	1.08	25.0
9	(s) 3.0	(s) 3.40	0.40	9.0
9[i]	(s) 3.0	(s) 3.40	0.40	2.0
9[b]	(d) 2.94	(s) 3.52	0.58	0.15
10[f]	(s) 3.0	(s) 3.92	0.92	0.3
11	(d) 2.8[e]	(s) 3.35	0.55	<0.25
12[f]	(q) 3.82	(q) 4.58	0.76	~3.5
13[f]	(s) 2.38	(s) 2.68	0.30	~4–5
13[b]	(s) 2.12	(s) 2.52	0.40	0.2
14	(s) 3.26			24.0[j]
14[b]	(s) 3.26			15.0[j]
15	(bs) 2.92	(s) 3.80	0.88	4.5
15[i]	(bs) 3.00	(s) 3.90	0.90	2.0
16	(s) 2.90	(s) 3.30	0.40	0.5

[a] For completion of complexation at room temperature. [b] 1 equiv of pyridine added. [c] 0.1 equiv of pyridine added. [d] Value for benzyl protons. [e] Taken from NMR spectra of sample run in $CDCl_3$. [f] Spectra became more complex over extended period. [g] Run at 69–72 °C. [h] 30% completion by integration. [i] At 45–50 °C. [j] Run at reflux with no substantial complexation observed.

g (21.0 mmol) of sodium borohydride was added. After the mixture was stirred at room temperature for 15 min it was worked up as described in the general procedure. Tube distillation of the basic extract up to 70 °C (0.1 mm), with the collector cooled to −78 °C, gave 0.64 g (38%) of monomeric amine. The residue was distilled at 140–160 °C (0.01 mm) to give 0.57 g of distillate. This distillate was chromatographed on a 20 g silica gel column. Elution with 60 mL of ethyl acetate gave 0.04 g (3.3%) of **22:** IR no carbonyl, N–H, or O–H stretch; NMR δ 7.30 (m, 10 H), 4.88 (d, 2 H), 3.40 (s, 2 H), 2.60 (t, 2 H), 2.1–1.5 (m, 4 H); mass spectrum *m/e* (rel intensity) 236 M^+ (44), 145 (85), 132 (57), 117 (92), 105 (74), 104 (100), 92 (40), 91 (85).

Elution with 90 mL of ethyl acetate–ethanol (10:1) gave 0.51 g (35%) of **21:** IR 3090, 3060, 2820, 2765, 1600 cm^{-1}; NMR δ 7.30 (m, 10 H), 5.60 (t, 1 H), 3.44 (bs, 2 H), 2.8–2.4 (m, 6 H), 2.1 (bs, 6 H); mass spectrum *m/e* (rel intensity) 279 M^+ (100), 188 (86), 174 (45), 143 (83), 128 (48), 91 (67), 58 (65); picrate (ethanol) mp 105–106 °C.

Anal. Calcd for $C_{26}H_{28}N_4O_7$: C, 61.4; H, 5.5; N, 11.0. Found: C, 61.2; H, 5.5; N, 10.8.

Further elution with ethyl acetate–ethanol (10:1) gave 0.03 g of oil consisting of a mixture of **21** and **23.** Ethyl acetate–ethanol (10:2) gave 0.02 g of the third product **23:** mass spectrum *m/e* (rel intensity) 324 M^+ (3), 279 (8), 188 (90), 163 (62), 162 (100), 91 (72), 58 (64). Elution with ethyl acetate–ethanol (1:1) gave 15 mg of a mixture of third product **23** and a fourth product. Preparative TLC of this mixture (ethyl acetate–ethanol, 1:1) gave 8 mg of the fourth component. Identical mass spectra for the third and fourth reaction products indicate stereoisomeric structures **23.**

B. The imonium derivative was prepared from 1.81 g (10.2 mmol) of amide at room temperature as described in the general procedure. It was reduced under the conditions described in part A. Distillation gave 1.19 g (71%) of monomeric amine. The residue, upon distillation, gave 0.13 g of oil, which upon chromatography as described in part A gave 20 mg of **22,** 96 mg of **21,** and 2 g of **23,** as a mixture of isomers.

Reduction of *N*-Methyl-β-phenylpropionamide (11). A. The imonium derivative was prepared from 1.62 g (9.9 mmol) of amide by the general procedure. Its reduction in glyme with 0.75 g (19.8 mmol) of sodium borohydride for 15 min at room temperature was followed by normal workup. Tube distillation of the basic extract (up to 80 °C, 0.1 mm) with cooling of the collector to −78 °C gave 1.10 g (74%) of monomeric amine. Tube distillation of the residue (130–155 °C, 0.1 mm) gave 0.13 g of oil consisting of one major component by TLC. Preparative TLC (ethyl acetate–ethanol, 10:1.5) gave 96 mg (7.2%) of **24:** IR 2750–2800 cm^{-1}; NMR δ 7.48 (m, 10 H), 2.72 (t, 4 H), 2.42 (t, 4 H), 2.28 (s, 3 H), 1.84 (m, 4 H); mass spectrum *m/e* (rel intensity) 267 M^+ (50), 162 (100), 91 (77), 58 (77), metastable ion at ~20.5 and 98.3. Spectra obtained with a sample of **24** prepared by lithium aluminum hydride reduction of *N*-methyl *N*-3-phenylpropyl-β-phenylpropionamide were found to be identical with those described above.

B. The amide (1.63 g, 10.0 mmol) was added to 10 mL of phosphoryl chloride and heated to 60–72 °C for 1 h. Excess phosphoryl chloride was removed as described in the general procedure. The imonium derivative was reduced as described in part A. Distillation gave 0.76 g (51%) of monomeric amine. Tube distillation of the residue gave 0.18 g of oil which upon chromatography gave 0.14 g (10%) of **24.**

Reduction of *N*-Ethylacetanilide (12). Reduction of 0.80 g (4.9 mmol) of amide was carried out as described in the general procedure. GC analysis of the crude product on a Carbowax 20M column at 150 °C indicated two volatile components, one of which corresponded to *N,N*-diethylaniline. The basic mixture was chromatographed on a 15-g silica gel column. Elution with 60 mL of petroleum ether (bp 60–90 °C)–chloroform (10:2) gave 0.28 g of oil, which was a mixture of two components. The oil was applied to three preparative TLC plates and developed four times in petroleum ether–chloroform (10:1). Elution of the topmost band afforded 0.04 g of *N*-butyl-*N*-ethylaniline: NMR δ 7.5–6.5 (m, 5 H), 3.57–3.10 (m, 4 H), 1.75–0.90 (m, 10 H); mass spectrum *m/e* (rel intensity) 177 M^+ (90), 135 (60), 134 (100), 106 (89), 77 (73), metastable ion at 101.5. The second component of the mixture was *N,N*-diethylaniline. Elution with 30 mL of petroleum ether–chloroform (10:2) gave 0.12 g of a mixture of *N,N*-diethylaniline and a third component. Elution with another 120 mL of the same solvent mixture provided 0.25 g of the third component, which was found to be identical with *N*-ethylaniline by comparison of NMR spectra and GC retention times.

Reduction of *N,N*-Dimethyl-*p*-carbomethoxybenzamide (15). The amido ester (0.62 g, 3.0 mmol) was added to 3 mL of phosphoryl chloride and heated to 45–50 °C for 3 h. Excess phosphoryl chloride was removed and the imonium derivative reduced as described in the general procedure. The reduction was stopped by addition of 5 mL of methanolic hydrogen chloride, concentration of the solution, addition of a further 20 mL of methanolic hydrogen chloride, and heating to reflux for 8 h. Further workup as described in the general procedure gave methyl *p*-(*N,N*-dimethylaminomethyl)benzoate in 75% yield, as determined by GC analysis. A trace of the amino alcohol could be detected by TLC.

Imonium Derivative Reduction in Presence of Cyclopentene. *N,N*-Dimethylbenzamide (0.76 g, 5.0 mmol) was treated with phosphoryl chloride in the usual manner. A solution containing the imonium derivative, 20 mL of tetrahydrofuran, and 2.20 g (32.3 mmol) of cyclopentene was cooled in an ice bath. Borane (10 mL, 1.0 M) solution in tetrahydrofuran was added over 2 min. The mixture was warmed to room temperature and allowed to stir for 1 h. Workup according to the general procedure and GC analysis of the extract indicated a 92% yield of *N,N*-dimethylbenzylamine. Borane and *N,N*-dimethylbenzamide under the same conditions, and without initial reaction with phosphoryl chloride, gave no amine.

Borane Adduct of *N,N*-Dimethylbenzylamine. A. To *N,N*-dimethylbenzylamine (1.74 g, 12.9 mmol) in 30 mL of glyme was added 13 mL of 1 M borane solution in tetrahydrofuran at 0 °C. The mixture was allowed to stir for 20 min at room temperature, followed by addition of 10 mL of 2% hydrochloric acid, and evaporation of the ethereal solvents. The aqueous solution was extracted three times with ether. The ether extracts were washed with brine, dried over magnesium sulfate, and concentrated to give 1.93 g of amine borane adduct: IR 2460, 2410, 2365 cm^{-1}; NMR δ 7.26 (m, 5 H), 3.94 (s, 2 H), 2.50 (s, 6 H); mp 101–102 °C (lit. mp 104–105 °C).[28]

B. To a solution of *N,N*-dimethylbenzylamine (0.80 g, 5.9 mmol) 20 mL of glyme, and 0.57 g (15 mmol) of sodium borohydride cooled in an ice bath was added dropwise 10 mL of 10% hydrochloric acid. The mixture was worked up as described in part A to give 0.62 g of amine borane adduct.

***N*,1-Dimethylcyclohexanecarboxamide (9).** To 275 mL of benzene saturated with methylamine at 0 °C was added dropwise a solution of 22.6 g (0.14 mmol) of 1-methylcyclohexanecarbonyl chloride[29] in 25 mL of benzene. The mixture was stirred for 2 h at room temperature. Water was added and the layers separated. The benzene layer was washed with brine, dried over magnesium sulfate, and concentrated to give a colorless oil which crystallized upon standing. The solid was recrystallized from ether–hexane to give 20.0 g (92%) of **9:** mp 74–75 °C; IR 3456, 1645 cm^{-1}; NMR δ 5.98 (b, 1 H), 2.82 (d, 3 H), 1.90 (m, 2 H), 1.6–1.2 (m, 8 H), 1.14 (s, 3 H).

Anal. Calcd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.8; H, 11.3; N, 9.1.

***N*-methyl-1-methylcyclohexylmethylamine.** To 7.3 g (0.19 mol) of lithium aluminum hydride in 300 mL of ether was dropped a suspension of 15.0 g (0.1 mol) of *N*,1-dimethylcyclohexanecarboxamide (**9**) in 50 mL of ether. The mixture was refluxed for 20 h. Excess lithium aluminum hydride was destroyed by consecutive addition of 7 mL of water, 7 mL of 15% sodium hydroxide, and 21 mL of water with vigorous stirring. The white suspension was filtered and washed with ether. The ether solution was concentrated, taken up in 70 mL of 10% hydrochloric acid, and extracted with ether. The aqueous solution was basified with 12.0 g of sodium hydroxide and extracted four times with ether. The latter ether extracts were dried over potassium carbonate, concentrated, and distilled to give 12.0 g (88%) of oil: bp 76–78 °C (17 mm); IR 2790 cm^{-1}; NMR δ 2.56 (s, 3 H), 2.48 (s, 2 H), 1.7–1.2 (m, 10 H), 1.08 (bs, 1 H), 0.96 (s, 3 H). Benzoyl derivative, mp 75–76 °C.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.3; H, 9.5; N, 5.7. Found: C, 78.5; H, 9.5; N, 5.5.

Formation of *N,N*-Dimethyl-*p*-carbomethoxybenzamide (15). To 200 mL of benzene saturated with dimethylamine at 0 °C was added dropwise a solution of 30 mL of benzene and *p*-carbomethoxybenzenecarbonyl chloride prepared from 21.8 g (0.1 mol) of potassium methyl terephthalate.[30] The mixture was stirred for 1 h at 0 °C followed by addition of 5% hydrochloric acid. The benzene layer was washed with water, 5% sodium carbonate, and brine, dried over magnesium sulfate, and concentrated to give 20 g of solid. Recrystallization from ether–methanol gave 12.6 g (61%) of **15:**[31] IR 1712, 1625 cm^{-1}; NMR δ 8.0–7.4 (dd, 4 H), 3.90 (s, 3 H), 3.1–2.9 (bd, 6 H).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8. Found: C, 63.7; H, 6.4; N, 6.6.

***N*-Methyl-*N*-3-phenylpropyl-β-phenylpropionamide.** A solution of 3.0 g (20 mmol) of β-phenylpropionic acid in 40 mL of benzene was cooled to 0 °C, and 2.8 g (22 mmol) of oxalyl chloride was added slowly with stirring. After 10 h at room temperature the benzene and excess oxalyl chloride were evaporated. The crude acid chloride in 10 mL of toluene was added slowly with stirring to a solution of 3.0 g (20 mmol) of *N*-methyl-3-phenylpropylamine, 2.0 g (20

mmol) of triethylamine, and 70 mL of toluene, cooled to 0 °C. After 12 h at room temperature water was added and the layers separated. The toluene layer was washed with 2% hydrochloric acid, 5% sodium hydroxide, and brine, dried over magnesium sulfate, and concentrated to give 5.4 g (96%) of yellow oil. This oil was used without further purification in the preparation of *N*-methyl-*N*-3-phenylpropyl-3-phenylpropylamine (**24**). An analytical sample was prepared by tube distillation (0.003 mm, 175–185 °C): IR 1640 cm^{-1}; NMR δ 7.24 (m, 10 H), 3.44 (t), 3.20 (t), 2.90 (d) (7 H total), 2.7–2.40 (m, 4 H), 1.90 (m, 2 H).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.83; H, 8.33; N, 4.72.

Reduction of Acetanilide (13). Acetanilide (1.35 g, 10 mmol) was reduced according to the general procedure. Tube distillation of the basic extracts (up to 70 °C, 0.005 mm) gave 0.81 g (68%) of monomeric amine. GC analysis (Carbowax 20M, 150 °C) indicated the presence of a trace of diethylaniline and another unidentified component. Tube distillation of the residue (160–180 °C, 0.005 mm) gave 0.15 g of oil. Preparative TLC of the oil on alumina (hexane–chloroform–ethyl acetate, 10:2:1) gave 0.10 g (8.2%) of 2,3-di-*N*-phenylaminobutane (R_f 0.5): IR 3390, 1600 cm^{-1}; NMR δ 7.2 (m, 4 H), 6.7 (m, 6 H), 3.8–3.4 (m, 4 H), 1.12 (dd, 6 H), two protons in the 3.8–3.4 region would be exchanged with deuterium oxide; mass spectrum *m/e* (rel intensity) 240 M^+ (50), 121 (92), 120 (100), 77 (69). Benzamide, mp 254–255 °C.

Anal. Calcd for $C_{30}H_{28}N_2O_2$: C, 80.32; H, 6.29; N, 6.24. Found: C, 79.95; H, 6.38; N, 6.04.

A second component (R_f 0.2), 7 mg (<1%), had spectral data identical with that of *N*,*N*^{1}-diphenylacetamidine: IR (KBr) 3275–3200, 1630, 1585 cm^{-1}; mass spectrum *m/e* (rel intensity) 210 M^+ (92), 118 (100), 77 (84), 51 (92); mp 131–132 °C (lit. mp 134–135 °C).[32]

Registry No.—**1,** 611-74-5; **2,** 1696-17-9; **3,** 613-93-4; **4,** 5291-77-0; **5,** 4783-65-7; **6,** 17566-51-7; **7,** 6830-84-8; **8,** 61930-85-6; **9,** 61930-86-7; **10,** 5830-31-9; **11,** 940-43-2; **12,** 529-65-7; **13,** 103-84-4; **14,** 20200-86-6; **15,** 21928-11-0; **16,** 54385-24-9; **17,** 7663-76-5; **18,** 61930-87-8; **19,** 61516-73-2; **20a,** 61930-88-9; **20a** picrate, 61930-89-0; **20b,** 24333-47-9; **20b** picrate, 61930-90-3; **21,** 61930-91-4; **21** picrate, 61930-92-5; **22,** 61930-93-6; *R**,*R**-**23,** 61930-94-7; *R**,*S**-**23,** 61930-95-8; **24,** 61930-96-9; phosphoryl chloride, 10025-87-3; *N*-butyl-*N*-ethylaniline, 13206-64-9; *N*,*N*-dimethylbenzylamine, 121-69-7; borane, 13283-31-3; *N*,*N*-dimethylbenzylamine borane adduct, 61967-06-4; 1-methylcyclohexanecarbonyl chloride, 2890-61-1; *N*-methyl-1-methylcyclohexylmethylamine, 61930-97-0; *N*-methyl-1-methylcyclohexylmethylamine benzoyl derivative, 61930-98-1; *p*-carbomethoxybenzenecarbonyl chloride, 7377-26-6; *N*-methyl-*N*-3-phenylpropyl-β-phenylpropionamide, 61930-99-2; β-phenylpropionic acid, 501-52-0; *N*-methyl-3-phenylpropylamine, 23580-89-4; 2,3-di-*N*-phenylaminobutane, 59540-56-6; 2,3-di-*N*-phenylaminobutane benzamide derivative, 61931-00-8; *N*,*N*′-diphenylacetamidine, 621-09-0.

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(26) The reduction is dependent upon the quality of the sodium borohydride. Since sodium borohydride has a limited solubility in glyme (0.8 g/100 mL of solvent at 20 °C) and tends to cake on exposure to moist air, variance in its surface area may affect reaction rates. As entries **10** and **11** indicate, recrystallized sodium borohydride[27] gave fast reductions even when 2 equiv was used.
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Formation of α,β-Unsaturated Schiff Bases from β,γ-Unsaturated Ketones. A Change in Rate-Determining Step in the Reactions of 3-Methyl-3-cyclohexenone with Glycinamide and Ethylenediamine

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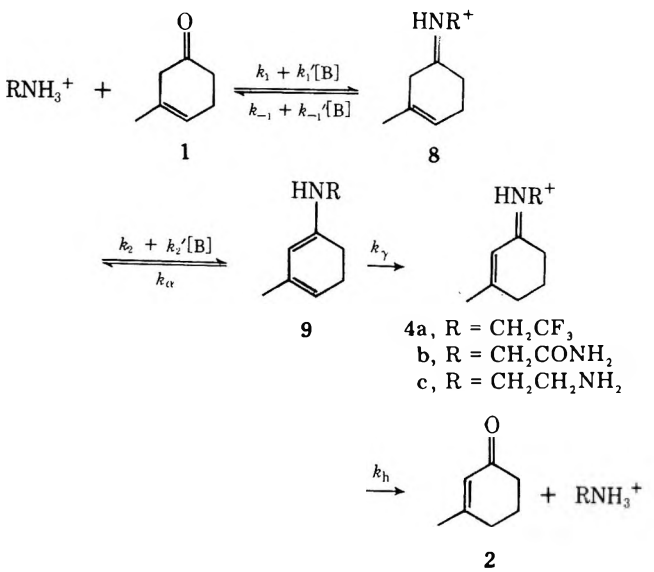
The isomerization of 3-methyl-3-cyclohexenone (1) to 3-methyl-2-cyclohexenone (2) is catalyzed by glycinamide (GA) and ethylenediamine (EDA) through the intermediate formation of an α,β-unsaturated Schiff base (4). The formation of 4 (k_i) was investigated in detail. A mechanism is proposed which involves formation of a β,γ-unsaturated Schiff base (8) followed by isomerization through a dienamine (9) to the α,β-unsaturated Schiff base. Nonlinear plots of $k_i/[RNH_2]$ vs. $[RNH_3^+]$ are interpreted in terms of a change in rate-determining step from breakdown of 8 at low $[RNH_2]$ to formation of 8 at high $[RNH_2]$.

We have previously shown[1,2] that the isomerizations of 3-methyl-3-cyclohexenone and 1-acetyl-2-cyclohexene to the corresponding α,β-unsaturated isomers are efficiently catalyzed by 2,2,2-trifluoroethylamine (TFEA). The isomerization of 3-methyl-3-cyclohexenone (1) proceeds through the formation of an α,β-unsaturated Schiff base (4a) which is produced by protonation of a dienamine intermediate (9), analogous to the dienol in the corresponding acid-catalyzed[3] isomerization (Scheme I). The hydrolysis of 4a is relatively

Scheme I



slow and has been discussed elsewhere.[4] The overall catalytic efficiency of TFEA in the isomerization of 1 is limited by the rate of hydrolysis of 4a (k_h). Even so, the TFEA-catalyzed reaction shows a rate enhancement of $>10^6$- and $>10^5$-fold over the corresponding acid- and base-catalyzed processes, respectively.

In this paper we report on the kinetics of the formation of the corresponding α,β-unsaturated Schiff bases (4b and 4c) from two more basic amines, glycinamide (pK 8.31) and ethylenediamine (pK 7.52). The formation of the α,β-unsaturated Schiff bases from these two amines shows kinetics which suggest a change in rate-determining step with changing amine concentration.

Results

Both glycinamide (GA) and ethylenediamine (EDA) are efficient catalysts for the isomerization of 1 to 2. For catalysis by each amine, ultraviolet spectroscopy showed rapid formation of an intermediate ($\lambda_{max} \sim 268$ nm) which then slowly decomposed to 2 ($\lambda_{max} \sim 240$ nm). By analogy to the corresponding reaction of 1 with trifluoroethylamine (TFEA), this intermediate is considered to be the α,β-unsaturated Schiff base (4) from the amine (GA or EDA) and 3-methyl-2-cyclohexenone.

Since our interest in this study is in the mechanism of the conversion of the β,γ-unsaturated ketone (1) to an α,β-unsaturated Schiff base (4), we monitored the reaction at the isosbestic point for the subsequent hydrolysis of 4 to 2. This procedure allows rate constants for the reaction 1 → 4 to be obtained directly. Rate constants for the hydrolysis of the α,β-unsaturated Schiff bases were not determined. Using this procedure, values for the pseudo-first-order rate constants for the formation of 4 (k_i) were evaluated at 25.0 ± 0.2°C and constant ionic strength (μ = 1.0, maintained with NaCl). Good first-order kinetics were obtained at all concentrations of amine.

In our previous investigation of this reaction with TFEA,[1,2] it was found that k_i could be expressed by an equation of the form

$$k_i = k^B[RNH_2] + k^{AB}[RNH_2][RNH_3^+]$$

so that a plot of $k_i/[RNH_2]$ vs. $[RNH_3^+]$ was linear. In contrast, similar plots for EDA and GA are not linear. The reaction with GA was studied in detail to determine the reason for the curvature in the buffer plots. Figure 1 shows plots of $k_i/[GA]$ vs. $[GAH^+]$ at constant pH for three buffer ratios. Concave buffer plots such as these are indicative of a change in rate-determining step with changing buffer concentration. At low $[GAH^+]$, k_i is largely second order in amine, while at high $[GAH^+]$, k_i becomes predominantly first order in amine. In addition, the first-order term at high amine concentration decreases with increasing pH, giving rise to more pronounced curvature of these plots at high pH.

These results may be analyzed in terms of Scheme I. Application of the steady-state equation to Scheme I gives eq 1 for the conversion of 1 to 4 in the absence of external buffer (i.e., $[B] = [RNH_2]$)

$$k_i = \frac{(k_1[RNH_3^+] + k_1'[RNH_3^+][RNH_2])(k_2 + k_2'[RNH_2])R}{(k_{-1} + k_{-1}'[RNH_2]) + (k_2 + k_2'[RNH_2])R} \quad (1)$$

where $R = k_\gamma/(k_\alpha + k_\gamma)$. Dividing eq 1 by $[RNH_2]$ and rearranging gives eq 2, where $K_1 = [8]/[1][RNH_3^+] = (k_1 + k_1'[RNH_2])/(k_{-1} + k_{-1}'[RNH_2])$, $k_1^0 = k_1[RNH_3^+]/[RNH_2]$, and $k_2^0 = k_2[RNH_3^+]/[RNH_2]$.

$$\frac{k_i}{[RNH_2]} = \frac{K_1(k_1^0 + k_1'[RNH_3^+])(k_2^0 + k_2'[RNH_3^+])R}{(k_1^0 + k_1'[RNH_3^+]) + K_1(k_2^0 + k_2'[RNH_3^+])R} \quad (2)$$

Table I. Calculated Rate Constants for the Formation of α,β-Unsaturated Schiff Bases from 3-Methyl-3-cyclohexenone[a]

Amine	pH	10^2k_1, $M^{-1}\,s^{-1}$	$10^2k_1'$, $M^{-2}\,s^{-1}$	$10^3K_1k_2R$, $M^{-1}\,s^{-1}$	$K_1k_2'R$, $M^{-2}\,s^{-1}$
GA	7.71	2.90 ± 0.13	3.2 ± 1.4	*b*	0.55 ± 0.03
	8.31	3.18 ± 0.18	3.5 ± 1.0	4.9 ± 1.6	0.54 ± 0.05
	8.89	4.36 ± 0.16	4.5 ± 0.7	12 ± 1.0	0.57 ± 0.02
	Av		3.7 ± 0.7		0.56 ± 0.02
EDA	7.02	8.2 ± 0.8	*b*	1.3 ± 0.3	1.10 ± 0.04
	7.52	15 ± 3	*b*	5.6 ± 3.9	1.05 ± 0.13
	Av				1.08 ± 0.07

[a] Errors are standard deviations obtained from linear plots according to eq 3 (see text). [b] Could not be determined.

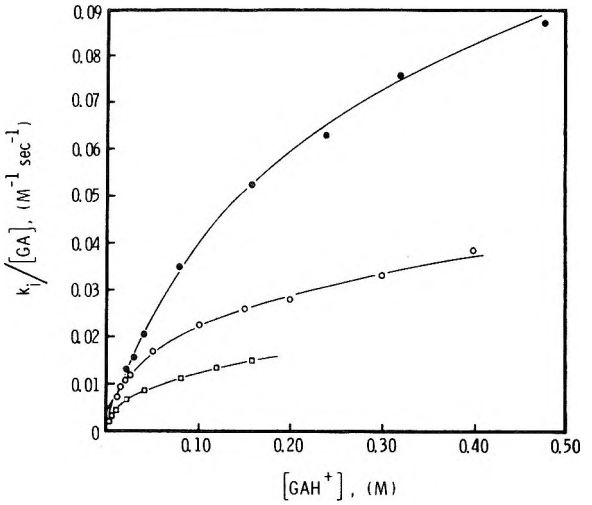


Figure 1. The variation of $k_i/[GA]$ with $[GAH^+]$ for the GA catalyzed formation of 4; (●), pH 7.71; (○), pH 8.31; and (□), pH 8.89. Theoretical curves were calculated from the parameters in Table I.

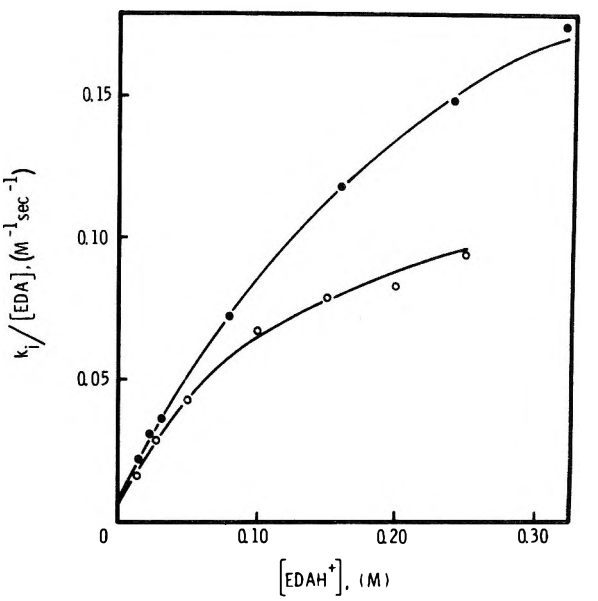


Figure 2. The variation of $k_i/[EDA]$ with $[EDAH^+]$ for the EDA catalyzed formation of 4: (●), pH 7.02; (○), pH 7.52. Theoretical curves were calculated from the parameters in Table I.

This rearrangement facilitates fitting the data to the experimental buffer curves.

Initial values of the parameters k_1^0, k_1', $K_1k_2^0R$, and $K_1k_2'R$ were obtained at each pH by assuming that the rate-limiting step at low $[RNH_2]$ is the decomposition of 8 (i.e., $k_1^0 + k_1'[RNH_3^+] \gg K_1(k_2^0 + k_2'[RNH_3^+])R$), and at high $[RNH_2]$, the rate-limiting step is the formation of 8 (i.e., $k_1^0 + k_1'[RNH_3^+] \ll K_1(k_2^0 + k_2'[RNH_3^+])R$). Under this assumption, the limiting slope of a plot of $k_i/[RNH_2]$ vs. $[RNH_3^+]$ at low $[RNH_3^+]$ corresponds to $K_1k_2'R$ and the intercept is $K_1k_2^0R$. At high concentration of amine, the slope is k_1' and the extrapolated intercept k_1^0. Although these limiting cases were not actually observed, estimates of these values could be obtained in this way. Successive approximations enabled a reasonably good fit to the experimental points to be realized. In order to improve the fit, eq 2 was inverted to give

$$\frac{[RNH_2]}{k_i} = \frac{1}{K_1(k_2^0 + k_2'[RNH_3^+])R} + \frac{1}{k_1^0 + k_1'[RNH_3^+]} \quad (3)$$

and the values for k_1^0 and k_1' were substituted into eq 3 leading to values for the quantity $K_1(k_2^0 + k_2'[RNH_3^+])R$ as a function of $[RNH_3^+]$. A plot of this quantity vs. $[RNH_3^+]$ should then yield a straight line with slope = $K_1k_2'R$ and intercept $K_1k_2^0R$. The parameters k_1^0 and k_1' were varied slightly to give the best least-squares fit for this linear relationship. The new values of $K_1k_2'R$ and $K_1k_2^0R$ thus generated were then used in conjunction with eq 3 to recalculate k_1^0 and k_1' in a similar manner. This method was repeated until further iterations showed no change in the parameters. An identical procedure was followed for the reaction with EDA.

With EDA, the curvature in the buffer plots is not as pronounced as with GA, resulting in both relatively large errors for k_1^0 and in k_1' values indistinguishable from zero. Calculated values of k_1, k_1', K_1k_2R, and $K_1k_2'R$ for both amines are given in Table I. These values, when used in conjunction with eq 1, give excellent fits to the experimental data (Figures 1 and 2).

For both GA and EDA, the rate constant corresponding to the uncatalyzed rate of formation of 8 (k_1) increases with increasing pH. This suggests that these rate constants are composed of a term in hydroxide ion as well as a term independent of pH ($k_1 = k_1^{H_2O} + k_1^{OH^-}[OH^-]$). A plot of k_1 vs. $[OH^-]$ for GA is linear with a slope ($k_1^{OH^-}$) of $2.0 \times 10^3\ M^{-2}\ s^{-1}$ and an intercept ($k_1^{H_2O}$) of $2.8 \times 10^{-2}\ M^{-1}\ s^{-1}$. For EDA, only two pHs were used and the values for k_1 are less reliable, but estimates of $k_1^{OH^-}$ ($3.0 \times 10^5\ M^{-2}\ s^{-1}$) and $k_1^{H_2O}$($4.5 \times 10^{-2}\ M^{-1}\ s^{-1}$) may be obtained. For both amines, the rate of breakdown of 8 (k_2) appears to be linearly dependent on the hydroxide ion concentration with no discernible contribution from a water rate ($k_2 = k_2^{OH^-}[OH^-]$). Although the precision in these numbers is not high, values of $K_1k_2^{OH^-}R$ may be obtained for both GA ($1.9 \times 10^3\ M^{-2}\ s^{-1}$) and EDA ($15 \times 10^3\ M^{-2}\ s^{-1}$).

Discussion

The complex kinetics for the formation of α,β-unsaturated Schiff bases from 3-methyl-3-cyclohexenone and either glycinamide or ethylenediamine may be rationalized in terms of the mechanism proposed previously[2] for the corresponding

Table II. Rate Constants for Formation of 4 for Various Amines[a]

Amine	pK_a[b]	k^{AB}, $M^{-2}\ s^{-1}$	$10^3 k^B$, $M^{-1}\ s^{-1}$	$10^4 K_1 k_2^{OH^-} R$,[c] $M^{-2}\ s^{-1}$
TFEA[d]	5.77	0.22 ± 0.02	0.19 ± 0.03	3.3 ± 0.3
EDA[e]	7.52 (7.82)[f]	0.54 ± 0.04	2.8 ± 1.2	0.85 ± 0.30
GA	8.31	0.56 ± 0.02	3.8 ± 0.8	0.19 ± 0.04

[a] Errors are standard deviations. [b] pH of 1:1 buffer at μ = 1.0; the pK_a for EDA is the first dissociation constant of $EDAH_2^{2+}$. [c] Calculated from identity, $k^B = (K_1 k_2^{OH^-} R)\ K_w/K_a$. [d] Rate constants from ref 2. [e] All rate constants for EDA have been halved due to the presence of two reactive sites in the diamine. [f] Corrected for statistical effects.

reaction with trifluoroethylamine (Scheme I). Initial formation of a protonated β,γ-unsaturated Schiff base (8) is followed by loss of a proton from the α carbon to give a dienamine (9), which upon protonation at the γ carbon gives the protonated α,β-unsaturated Schiff base (4). Although the curved buffer plots for GA and EDA as reactants show that a change in rate-determining step is occurring as the amine concentration is increased, they do not indicate which steps are rate determining at various amine concentrations. The steady-state equation for Scheme I (eq 2) does not by itself allow a unique solution to this problem. Although we assumed that the change in rate-determining step is from decomposition of 8 at low $[RNH_2]$ to formation of 8 at high $[RNH_2]$, the kinetics alone do not require that this be so. The reverse situation (rate-determining formation of 8 at low $[RNH_2]$ and rate-determining breakdown of 8 at high $[RNH_2]$) can accommodate the kinetic results equally well. Consequently, it is imperative that other criteria be used to justify our assignment.

At low concentrations of amine, k_i is dominated by a large second-order term $(K_1 k_2' R)$ which we assign to abstraction of the α proton from 8, followed by partitioning of the dienamine, analogous to the reaction with TFEA $[(k_{-1} + k_{-1}'[RNH_2]) > (k_\gamma/(k_\gamma + k_\alpha))(k_2 + k_2'[RNH_2])]$. As the amine concentration is increased, the rate-determining step then becomes formation of 8 $[(k_\gamma/(k_\gamma + k_\alpha))(k_2 + k_2'[RNH_2]) > (k_{-1} + k_{-1}'[RNH_2])]$. For this explanation to be reasonable, it is necessary that k_{-1} be greater than $k_2(k_\gamma)/(k_\gamma + k_\alpha)$ but that $k_2'(k_\gamma)/(k_\gamma + k_\alpha)$ be greater than k_{-1}'. In other words, abstraction of the α proton from 8 must be more sensitive to general base catalysis than the hydrolysis of the Schiff base. In the pH region examined (7.7–8.9) the rate-determining step in the hydrolysis of 8 should be attack of either water or hydroxide ion on the protonated Schiff base.[5] Although general base catalysis of protonated Schiff base hydrolysis is often observed, the sensitivity of the rate to external general bases is low ($\beta \leq 0.25$ for saturated Schiff bases).[5-8] Deprotonation of iminium ions, on the other hand, generally shows a greater sensitivity to the presence of external general bases in the solution. For example, a β of 0.4 has been observed for the abstraction of a proton from the protonated Schiff base of acetone and methylamine[9] and a β of ca. 0.5 may be calculated from the data of Hine et al.[10] for the deprotonation of the *N*-methyliminium ion of isobutyraldehyde. If the change in rate-determining step with increasing amine concentration were in the opposite direction (i.e., formation of 8 at low $[RNH_2]$ and decomposition of 8 at high $[RNH_2]$), then this would require that the hydrolysis of a protonated Schiff base be *more* sensitive to general base catalysis than its deprotonation, contrary to what is observed in other systems.

Further evidence for our assignment can be seen by the fact that a change in rate-determining step is only observable with the more basic amines GA and EDA and not with TFEA. Since the rates of hydrolysis of protonated Schiff bases (under conditions where attack of water is rate determining) increase markedly with decreasing amine pK_a ($\beta \sim -1.0$)[7] it is to be expected that the rate of hydrolysis of 8 would be much greater for TFEA than either GA or EDA. The rate of breakdown of 8 to products, however, is expected to show a much smaller dependence on amine pK_a, for both $k_2^{OH^-}(\beta \sim -0.5)$ and $k_2'(\beta \sim 0)$.[11] Consequently, the partitioning of 8 should favor return to reactants as the amine pK_a decreases. Since breakdown of 8 is rate determining for TFEA,[1,2] a change in the rate-determining step would be favored by raising the amine basicity, as is observed.

An alternate explanation is that the curved buffer plots are due to a change in rate-determining step from k_α at low amine concentration to k_γ at high $[RNH_2]$. We consider that any appreciable variation in the ratio of k_α to k_γ is unlikely since the corresponding ratio in the TFEA reaction is invariant with changes in both pH and amine concentration.[1,2]

The derived rate constants for GA and EDA may be compared with those for TFEA in the following way. At very low amine concentration, the slow step is breakdown of the intermediate [i.e., $k_{-1} + k_{-1}'[RNH_2] \gg (k_2 + k_2'[RNH_2])[R]$, and the overall rate constant k_i can be expressed simply by

$$k_i = K_1 R k_2^{OH^-}[RNH_3^+][OH^-] + K_1 R k_2'[RNH_3^+][RNH_2] \quad (4)$$

$$= k^B[RNH_2] + k^{AB}[RNH_3^+][RNH_2] \quad (4a)$$

Values for k^B and k^{AB} can then be calculated and compared with the corresponding values for TFEA (Table II).[1,2] The rate constants for EDA have been halved to correct for the presence of two reactive sites in the diamine. The k^{AB} terms reflect proton abstraction by free amine from the iminium ion (8) derived from the same amine; in terms of Scheme I $k^{AB} = K_1 k_2' k_\gamma/(k_\gamma + k_\alpha)$. Several investigations[9,13] have shown that the equilibrium concentration of Schiff base depends only slightly on the amine pK_a. If the partitioning ratio of the dienamine 9, $k_\gamma/(k_\alpha + k_\gamma)$, does not vary significantly with the identity of the amine, then the relative invariance of k^{AB} with amine pK_a reflects two compensating trends in k_2'. Increasing the pK_a should increase the efficiency of the amine in proton abstraction from 8. However, as the amine pK_a increases, 8 becomes less susceptible to α-proton removal, thus causing little change in k^{AB} for amines of varying base strength.

Evidence that the iminium ion 8 does become less susceptible to α-proton removal with increasing amine pK_a is available from Table II. The sensitivity of the rate of proton abstraction from 8 to the amine pK_a may be estimated from a plot of the statistically corrected values of log $(K_1 k_2^{OH^-} R)$ vs. amine pK_a (not shown). A reasonable linear correlation with slope of ca. −0.5 is obtained. Since this term corresponds to proton abstraction from 8 by hydroxide ion, this result suggests that for the same base (OH^- or, presumably, any general base), an increase in pK_a of the amine forming 8 results in a decrease in the rate of abstraction of the α proton. An analogous plot of k^{AB} vs. the pK_a of the base which is abstracting the proton from 8 in the reaction with TFEA shows a slope of $\beta = 0.55$.[2] These two trends then balance each other

in the k^{AB} terms, making the effect of amine pK_a on k^{AB} very small. Similar conclusions have been reached previously by Spencer et al.[11] for simple α-proton abstractions of Schiff base by the corresponding amine. These authors have extensively discussed the implications of this finding for the mechanism of action of enzymes which function via Schiff base intermediates.

Experimental Section

Materials. 3-Methyl-3-cyclohexenone (1) was prepared and purified as previously described.[2] Gycinamide hydrochloride was purified by recrystallization from absolute ethanol, and ethylenediamine by distillation of the free amine. Distilled water was used for all kinetic runs.

Kinetic Methods. The kinetics were monitored at 25.0 ± 0.2°C with an ionic strength of 1.0 maintained by NaCl. Spectra were obtained on a Cary 16K spectrophotometer and rates were followed on either a Gilford 2000 or 2400 spectrophotometer. All first-order rate constants were calculated by a nonlinear least-squares regression analysis. pH values for each series of buffer runs were constant to ±0.02 pH unit.

The rate constant k_i was measured at the isosbestic point for the subsequent hydrolysis as described previously.[2] Good first-order kinetics were obtained for 6–8 half-lives in most cases and yielded stable infinity points. Buffer plots of $k_i/[RNH_2]$ were fit to the steady-state equation (eq 3) by successive approximations as described in the text.

Acknowledgment. This work was supported by Grant GM 20188 from the National Institutes of Health.

Registry No.—1, 31883-98-4; 2, 1193-18-6; 4b, 61915-53-5; 4c, 61915-54-6; GA, 598-41-4; EDA, 107-15-3.

Supplementary Material Available. Observed rate constants for formation of the α,β-saturated Schiff base intermediate (4) from ethylenediamine and glycinamide (Table III) (2 pages). Ordering information is given on any current masthead page.

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(12) This treatment assumes that proton abstraction from **8** by water makes no contribution to k_2 for GA and EDA. The neglect of any terms in protonated amine in eq 4a (i.e., $k^A[RNH_3^+]$) cannot be rigorously justified because of the uncertainty in most k_2 values for GA and EDA. However, the k^A term for TFEA is small (7.9×10^{-4} s^{-1})[2] and k^A values for GA and EDA should be significantly less ($\lesssim 10^{-4}$ s^{-1}) if k^A decreases with increasing amine pK_a as expected.
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Reactions of α-Nitroarylidene Phenylhydrazines in Acid and Basic Media

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The reaction of α-nitrobenzylidene phenylhydrazine (1) in absolute ether with hydrogen chloride, methanesulfonic acid, and periodic acid affords diprotonated salts which have been proposed as one of the intermediates in the conversion in acidic medium of primary and secondary nitroalkanes to carbonyl compounds (Nef reaction). These salts are rapidly hydrolyzed to 1-nitroso-2-benzoylphenylhydrazine (4). The reaction of 1 with secondary amines gives rise to amidrazones.

In continuation of our studies of α-nitroarylidene phenylhydrazines, which recently have become readily available by the direct alkyl nitration of arylidene phenylhydrazines,[1] we are now reporting on their reactions in acidic and basic media. Although this class of compounds has been known for a long time, very little is known about their reactivity. Bamberger[2,3] reported that α-nitroarylidene phenylhydrazines were converted to the corresponding aroyl phenylhydrazines on treatment with aqueous base, and to tetrazines on treatment with methanolic sodium methoxide.

Reaction with Acids. The reaction of α-nitrobenzylidene phenylhydrazine (1) in absolute ether with hydrogen chloride, methanesulfonic acid, and periodic acid afforded α-nitrobenzylidene phenylhydrazine dihydrochloride (**2a**), α-nitrobenzylidene phenylhydrazine dimethanesulfonate (**2b**), and α-nitrobenzylidene phenylhydrazine diperiodate (**2c**) in yields of 78, 70, and 90%, respectively (Scheme I). The spectral properties of these salts are in accord with a diprotonated structure.[4] As shown in Table I, the infrared spectra of **2a–c** showed weak ammonium absorption in the range 3500–2200 cm^{-1} and strong nitronate bands[5] at 1550 and 1335 cm^{-1}. The NMR spectra[6] of **2a,b** in Me_2SO-d_6 exhibited, respectively, absorptions of OH at δ 14.05 and 13.50 and of NH^+ at δ 11.95 and 12.10, which integrated to three protons in a ratio of 2:1. Although structure **2** is well supported by the nitronate bands in the infrared and the low field absorptions of OH in the NMR spectra, the presence of the tautomeric structure **3** (Scheme I) cannot be excluded. It is of interest that in Me_2SO-d_6 the NMR signals of $^+NH_3$ in anilinium chloride and of $^+NH_2$ in phenylhydrazinium chloride occur at δ 9.78 and 9.51, respectively.[7]

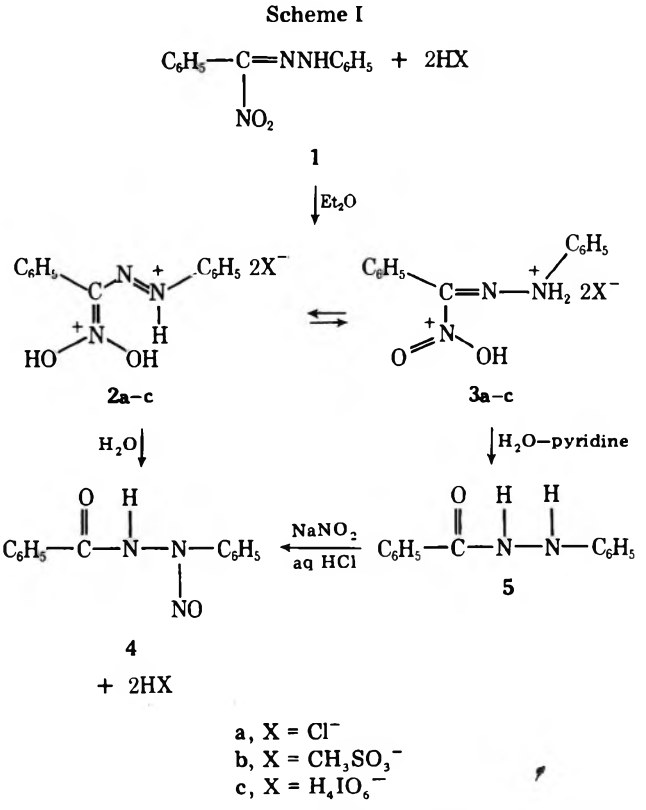
Tautomer **2** can be considered as one of the proposed intermediates in the conversion of primary and secondary nitro compounds to carbonyl compounds in acidic media.[8,9] This viewpoint is supported by the observation that the salts underwent rapid hydrolysis at room temperature to 1-nitroso-2-benzoylphenylhydrazine[10] (**4**) in quantitative yield (Scheme I). It is believed that compound **4** was formed from the reaction of 2-benzoylphenylhydrazine (**5**) with nitrous acid, these being possible intermediates in the hydrolysis of **2**. In fact, compound **5** was isolated when the hydrolysis of **2a** was carried out in the presence of pyridine, which scavenged the nitrous

Table I. Spectral Data of $C_6H_5C[=^+N(OH)_2]N=^+NHNHC_6H_5$ $2X^-$(2)

X	Infrared spectra, cm^{-1} [a]			NMR spectra, ppm [b]	
	$C=NO_2H_2$	$-N=NH-$	$=^+NH$	$C=NO_2H_2$	$N=NH^+$
Cl^- (2a)	1550, 1335	1605	3300–2500	14.05 s [e]	11.95 s
$CH_3SO_3^-$ (2b) [c]	1550, 1335	1600	3200–2200	13.50 s	12.10 s
$H_4IO_6^-$ (2c) [d]	1550, 1325	1605	3500–2750		

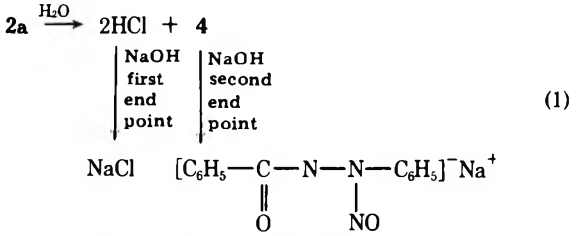
[a] Spectra were run as potassium bromide wafers. [b] The solvent was Me_2SO-d_6. [c] A $CH_3SO_3^-$ band was present at 1150 and 1060 cm^{-1}. [d] A $H_4IO_6^-$ band was present at 844 cm^{-1}. [e] s = singlet.

Scheme I



acid. In a control test, **5** was readily converted to **4** on treatment with sodium nitrite and hydrochloric acid (Scheme I).

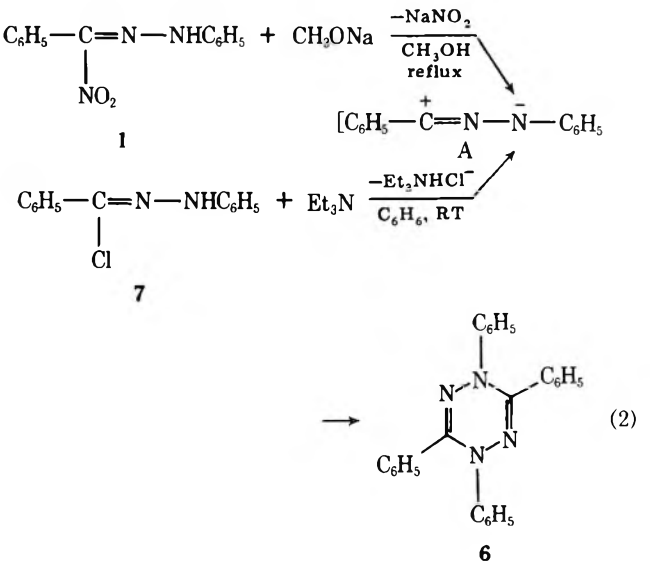
The results of the neutral equivalent determinations of **2a–c** are in agreement with these observations. Titrations with base gave curves exhibiting two end points. The first at pK_a 2.65 corresponded to the neutralization of acid liberated in the hydrolysis and the second at pK_a 8.60 resulted from the neutralization of the acidic proton in the nitroso compound **4** (eq 1). Direct titration of authentic **4** gave a pK_a of 8.90.[11]



(1)

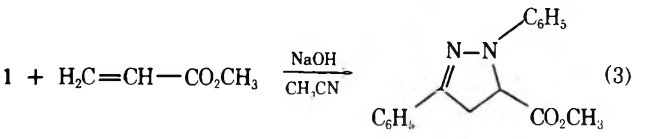
Reactions in Basic Medium. As reported by Bamberger[2] the reaction of **1** with sodium methoxide in methanol gave 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (**6**) (eq 2). More recently, Huisgen[12] reported that **6** is also formed when the hydrazidic chloride **7** was treated with triethylamine in benzene at room temperature (eq 2). He considered that the formation of **6** occurred by a 1,3-dipolar head to tail coupling of the diphenyliminonitrile A. Evidence for the intermediacy of A was found when **7** in the presence of triethylamine reacted with dipolarophiles to give 1,3-dipolar adducts.[13]

It was established that **1** could replace **7** as a source of a



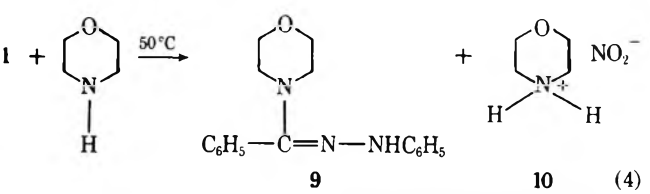
(2)

nitrilimine synthon. Treatment of **1** with sodium hydroxide and methyl acrylate in acetonitrile afforded a 75% yield of 5-carboxymethyl-4,5-dihydro-1,3-diphenyl-2-pyrazoline (**8**) (eq 3). Compound **8** was previously prepared by the thermolysis of 1,3-diphenyltetrazole in the presence of methyl acrylate.[14]



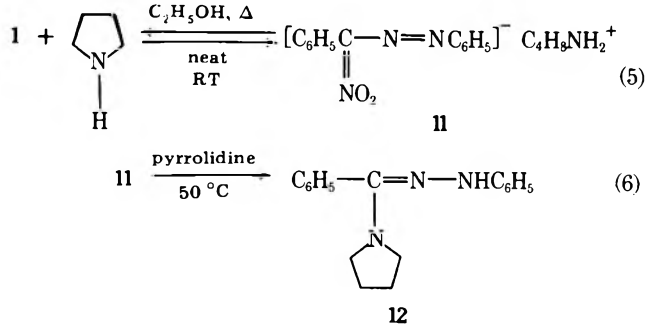
(3)

In contrast to **7**, compound **1** did not react with triethylamine in refluxing benzene and was recovered unchanged. However, reactions did take place with secondary amines to give amidrazones. The reaction of **1** with morpholine afforded α-*N*-morpholinobenzylidene phenylhydrazine (**9**) and morpholinium nitrite (**10**), each in 85% yield (eq 4). The spectral properties of **9** and **10** were in agreement with their assigned structures.



(4)

When compound **1** was treated with pyrrolidine at room temperature, a quantitative yield of orange-red pyrrolidinium phenylazophenylmethanenitronate (**11**) was isolated (eq 5). The infrared spectrum of **11** showed a strong ammonium band at 3100–2300 cm^{-1} and nitronate bands at 1465 and 1210 cm^{-1}. The NMR spectrum indicated pyrrolidinium absorptions at δ 1.6 and 2.9 and ammonium absorptions at δ 6.1. The ultraviolet spectrum in 95% ethanol showed a maximum at 403 nm with a large extinction coefficient (log ϵ 4.10), similar to

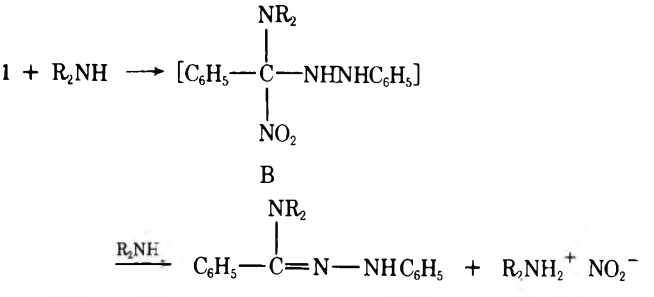


that reported[1] for compound 1. Apparently the extended conjugation in 1 was not changed in salt 11.

Compound 11 reverted to starting materials when placed in refluxing absolute ethanol or when kept in vacuo for several days. The instability of ammonium salts of nitro compounds is well documented in the literature.[15] Upon heating in pyrrolidine at 50 °C, 11 was converted in high yield to α-*N*-pyrrolidinobenzylidene phenylhydrazine (12) (eq 6). However, 12 was unstable and could not be purified. Its infrared and NMR spectra agreed with the proposed structure.

The formation of compounds 9 and 12 might occur by an addition-elimination type reaction as shown in Scheme II.

Scheme II



The formation of the adduct B is very likely preceded by salt formation which is a reversible step as observed in the reaction between compound 1 with pyrrolidine. Our observation that triethylamine, a stronger base than morpholine and slightly weaker than pyrrolidine, did not react with 1 (no formation of tetrazine 6) renders a 1,3-dipolar reaction very unlikely. Moreover, salt 11 underwent dissociation (eq 5) rather then elimination of pyrrolidinium nitrite.

Experimental Section

α-Nitrobenzylidene Phenylhydrazine Dihydrochloride (2a). A 150-mL solution of absolute ether containing 2.41 g (0.01 mol) of α-nitrobenzylidene phenylhydrazine (1) was cooled to 10 °C. Hydrogen chloride was introduced slowly with stirring in 30 min as the temperature rose to 20 °C. A white precipitate formed and the suspension was kept at 0 °C overnight. Filtration and repeated washings with absolute ether gave 2.5 g (78%) of α-nitrobenzylidene phenylhydrazine dihydrochloride (**2a**): mp 70–75 °C dec; IR (KBr) 3100–2500 (N=NHC$_6$H$_5$), 1605 (N=NH), and 1550 and 1335 cm^{-1} (NO$_2$); NMR (Me$_2$SO-d_6) δ 7.2–8.0 (m, 10, ring H), 11.95 (s, 1, N=$^+$NHC$_6$H$_5$), and 14.05 (s, 2, C=NO$_2$H$_2$).

Anal. Calcd for $C_{13}H_{13}Cl_2N_3O_2$: Cl, 21.58; neut equiv, 314. Found: Cl, 21.50; neut equiv, 320.

α-Nitrobenzylidene Phenylhydrazine Dimethanesulfonate (2b). To 25 mL of absolute ether containing 1.0 g (0.004 mol) of 1 was added with stirring 1.48 g (0.05 mol) of methanesulfonic acid at room temperature. After 2 h, a yellow precipitate formed. The suspension was cooled to 0 °C, filtered, and dried in vacuo to give 1.2 g (70%) of α-nitrobenzylidene phenylhydrazine dimethanesulfonate (**2b**): mp >80 °C dec; IR (KBr) 3100–2200 (N=NHC$_6$H$_5$), 1605 (N=NH), 1550 and 1335 (NO$_2$), and 1150 and 1060 cm^{-1} (CH$_3$SO$_3^-$); NMR (Me$_2$SO-d_6) δ 2.5 (s, 6, CH$_3$SO$_3^-$), 7.2–8.0 (m, 10, ring H), 12.1 (s, 1, N=$^+$NHC$_6$H$_5$), and 13.50 (s, 2, C=NO$_2$H$_2$).

Anal. Calcd for $C_{15}H_{19}N_3O_8S_2$: C, 41.55; H, 4.38; N, 9.69; S, 14.77; neut equiv, 433. Found: C, 42.61; H, 4.39; N, 9.78; S, 15.00; neut equiv, 441.

α-Nitrobenzylidene Phenylhydrazine Diperiodate (2c). A similar procedure was used as described in the preparation of **2b** except that 1.0 g (0.004 mol) of 1 and 2.3 g (0.01 mol) of periodic acid were employed in 25 mL of absolute ether. Filtration gave 2.5 g (90%) of α-nitrobenzylidene phenylhydrazine diperiodate (**2c**): mp 155–160 °C dec; IR (KBr) 3500–2750 (N=NHC$_6$H$_5$), 1605 (N=NH), 1550 and 1325 (NO$_2$), and 844 cm^{-1} (H$_4$IO$_6^-$).

Anal. Calcd for $C_{13}H_{21}I_2N_3O_{14}$: I, 36.41; neut equiv, 697. Found: I, 36.13; neut equiv, 681.

1-Nitroso-2-benzoylphenylhydrazine (4). A. Employing Compound 2a. To 25 mL of water was added with stirring 1.0 g (3 mmol) of compound **2a** at room temperature. The solution rapidly turned cloudy with the formation of a white precipitate. The suspension was filtered, dried, and recrystallized (50 °C) from 75% ethanol to give 0.6 g (80%) of 1-nitroso-2-benzoylphenylhydrazine (**4**): mp 105–110 °C dec (lit.[10] mp 108–110 °C); IR (KBr) 3180 (OH) and 1680 cm^{-1} (C=O); NMR (Me$_2$SO-d_6) δ 7.1–7.8 (m, 10, ring H) and 11.2 (s, 1, NH).

Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.32; H, 4.60; N, 17.42. Found: C, 64.50; H, 4.83; N, 17.29.

B. Employing Compound 5. To a suspension of **5** (5.0 g, 0.023 mol) in absolute ethanol (100 mL) and 12 M hydrochloric acid (5.5 mL) was added at 0 °C a 10-mL aqueous solution of sodium nitrite (1.72 g, 0.025 mol). A yellow color developed with the formation of a homogeneous solution. Addition of 50 mL of water gave a yellow precipitate which after drying and recrystallization from 95% ethanol afforded compound **4** (66% yield), mp 106 °C dec.[16]

Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.32; H, 4.60; N, 17.42; neut equiv, 241.2. Found: C, 64.58; H, 4.78; N, 17.30; neut equiv, 250.2.

5-Carbomethoxy-1,3-diphenyl-4,5-dihydro-2-pyrazoline (8). Compound 1 (1 g, 4 mmol), sodium hydroxide (0.5 g, 12 mmol), and methyl acrylate (1.6 g, 10 mmol) were added to 50 mL of acetonitrile and the mixture refluxed for 30 min. Cooling, filtering, and concentrating the filtrate in vacuo gave 0.8 g (75%) of 5-carbomethoxy-1,3-diphenyl-4,5-dihydro-2-pyrazoline (**8**) (absolute CH$_3$OH): mp 108–109 °C (lit.[14] mp 107 °C); IR (KBr) 1650 (C=O) and 1600 cm^{-1} (C=N); NMR (CDCl$_3$) δ 3.5 (m, 2, CH$_2$CH), 3.75 (s, 3, CH$_3$), 4.8 (m, 1, CHCH$_2$), and 6.8–7.9 (m, 10, ring H).

α-*N*-Morpholinobenzylidene Phenylhydrazine (9). To 10 mL of morpholine was added with stirring 0.65 g (3 mmol) of compound 1 at room temperature. The deep red solution turned bright yellow upon heating for 30 min at 50 °C. Then excess morpholine was removed in vacuo and the residual yellow oil dissolved in 30 mL of ethyl ether. A white precipitate formed which was filtered and dried to give 0.30 g (85%) of morpholinium nitrite (**10**): IR (KBr) 3400–2200 (NH$_2$), 1235 and 860 (NO$_2^-$), and 1185 cm^{-1} (C–NH$_2$).

The ethereal solution was concentrated in vacuo and the remaining white solid recrystallized from 80% ethanol to afford 0.65 g (85%) of α-*N*-morpholinobenzylidene phenylhydrazine (**9**): mp 137.5–139 °C; IR (KBr) 3257 (NH), 1597 (C=N), 1269 (>NC=N), 1252 (NC$_6$H$_5$), and 1112 cm^{-1} (COC); NMR (CDCl$_3$) δ 3.10 (t, 4, CH$_2$NCH$_2$), 3.75 (t, 4, CH$_2$OCH$_2$), and 6.6–7.5 (m, 11, ring H and NH).

Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.80; N, 14.93. Found: C, 72.31; H, 6.70; N, 14.85.

Pyrrolidinium Phenylazophenylmethanenitronate (11). To 10 mL of pyrrolidine was added 1.0 g (4 mmol) of compound 1 at room temperature. An orange-red precipitate formed immediately which after drying and recrystallization from hexane gave 1.25 g (100%) of pyrrolidinium phenylazophenylmethanenitronate (**11**): mp 103 °C; UV max (95% C$_2$H$_5$OH) 403 nm (log ε 4.10); IR (KBr) 3100–2300 (NH$_2$) and 1465 and 1210 cm^{-1} (C=NO$_2$); NMR (Me$_2$SO-d_6) δ 1.5 (m, 4, CH$_2$CH$_2$), 2.9 (m, 4, CH$_2$NCH$_2$), 6.1 (s, 2, >NH$_2^+$), and 6.6–7.2 (m, 10, ring H).

Anal. Calcd for $C_{17}H_{20}N_4O_2$: C, 65.36; H, 6.45; N, 17.95. Found: C, 65.25; H, 6.32; N, 17.71.

When compound 11 was either refluxed in absolute ethanol or placed in a vacuum desiccator for 1 week, a quantitative yield of 1 was obtained.

α-*N*-Pyrrolidinobenzylidene Phenylhydrazine (12). To 10 mL of pyrrolidine was added with stirring 1.0 g (3 mmol) of salt 11 at room temperature. The solution was heated to 50 °C for 30 min, the excess pyrrolidine removed in vacuo, and the residual yellow oil dissolved in 30 mL of ether. The ethereal solution was washed with 3 × 50 mL of water and dried (MgSO$_4$), and the solvent removed in vacuo to give 0.75 g (95%) of α-*N*-pyrrolidinobenzylidene phenylhydrazine (**12**) as a brown-yellow oil: IR (neat) 3250 (NH) and 1595 cm^{-1} (C=N); NMR (CDCl$_3$) δ 1.4–1.9 (m, 4, CH$_2$CH$_2$), 3.0–3.3 (m, 4, CH$_2$NCH$_2$), and 6.6–7.5 (m, 11, ring H and NH).

Determination of Neutralization Equivalents of Salts 2a–c. Samples (0.1 g) of salts **2a–c** were dissolved with stirring in 40 mL of

50% ethanol and titrated with 0.09 M sodium hydroxide. The end points were determined by plotting the volume of titrant against the millivolts which were read directly from a Beckman Zeromatic pH meter.

Registry No.—**1**, 23157-59-7; **2a**, 62076-89-5; **2b**, 62076-90-8; **2c**, 62076-91-9; **4**, 62076-92-0; **5**, 532-96-7; **8**, 17660-82-1; **9**, 36584-22-2; **10**, 62076-93-1; **11**, 62076-95-3; **12**, 62076-96-4; HCl, 7647-01-0; methanesulfonic acid, 75-75-2; periodic acid, 10450-60-9; morpholine, 110-91-8; pyrrolidine, 123-75-1.

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(11) We should like to thank Mr. S. W. Heinzman for carrying out this experiment.
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(16) Compound **4** decolorized at about 80 °C and then decomposed at about 106 °C.

Synthesis and Configurational Assignment of Some 1-*tert*-Butyl-2-aryl 3-Substituted Azetidines[1]

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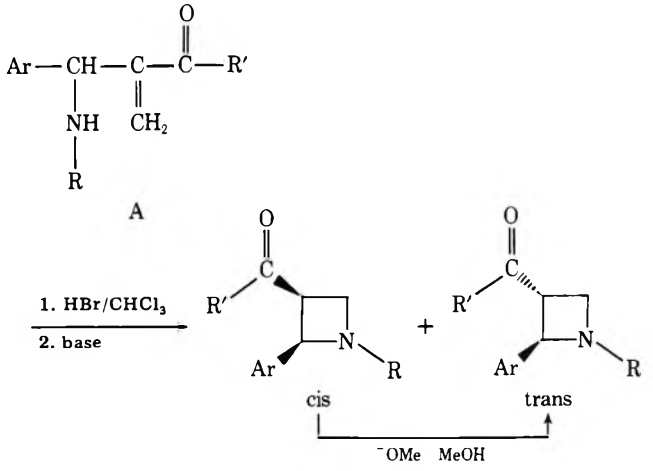
The kinetically favored products, methyl α-(α-*tert*-butylaminobenzyl)acrylates (**2**), from the reaction of *tert*-butylamine with methyl α-(bromomethyl)cinnamates (**1**), upon treatment with hydrogen bromide in chloroform and then triethylamine gave *trans*-1-*tert*-butyl-2-aryl-3-carbomethoxyazetidine (**7**). Similar treatment of the kinetically favored α-(α-*tert*-butylaminobenzyl)acrylonitrile (**5**), of the reaction of *tert*-butylamine with α-(bromomethyl)cinnamonitrile (**4**) gave a mixture of *cis*- and *trans*-1-*tert*-butyl-2-phenyl-3-carbamoylazetidine (**9** and **10**) and *trans*-1-*tert*-butyl-2-phenyl-3-cyanoazetidine (**11**). ^1H NMR spectroscopic studies, base-catalyzed epimerization, deuterium exchange studies, and chemical correlation of the azetidines were employed to assign the configurations. The mechanism and stereochemistry of the reactions leading to these cyclizations to produce the 1-*tert*-butyl-2-aryl 3-substituted azetidines are discussed.

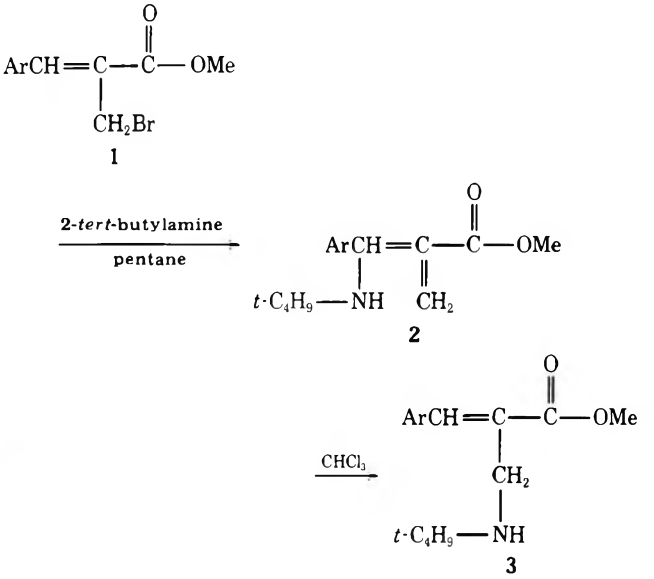
It has been reported[2] that β-carboallylamines A are precursors for the high-yield synthesis of 1-alkyl-2-aryl-3-carboazetidines. The *cis*-azetidine was usually the exclusive or major product, and readily epimerized to the thermodynamically more stable trans isomer in methanol in the presence of sodium methoxide.



R = alkyl
R′ = Ar or CH_3

The cis and trans isomers of the azetidines can be distinguished readily from each other by the ^1H NMR spectra.[2b] Compared to that of the trans isomer, the benzylic (C-2) proton of the cis isomer usually resonates as a doublet at a higher frequency.

In a previous publication,[3] it was reported that the reaction of 2 molar equiv of *tert*-butylamine with β-carbomethoxyallyl bromides **1** gave the substitution–rearrangement products **2**

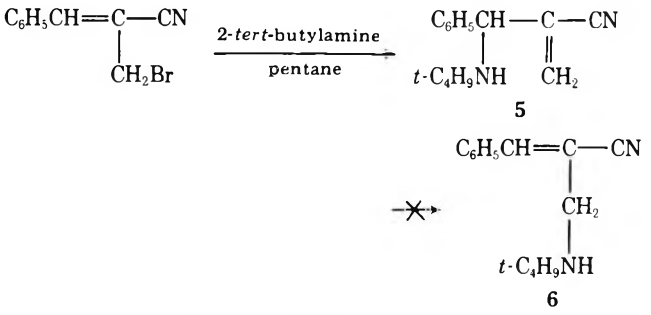


a, Ar = C_6H_5
b, *p*-ClC_6H_4

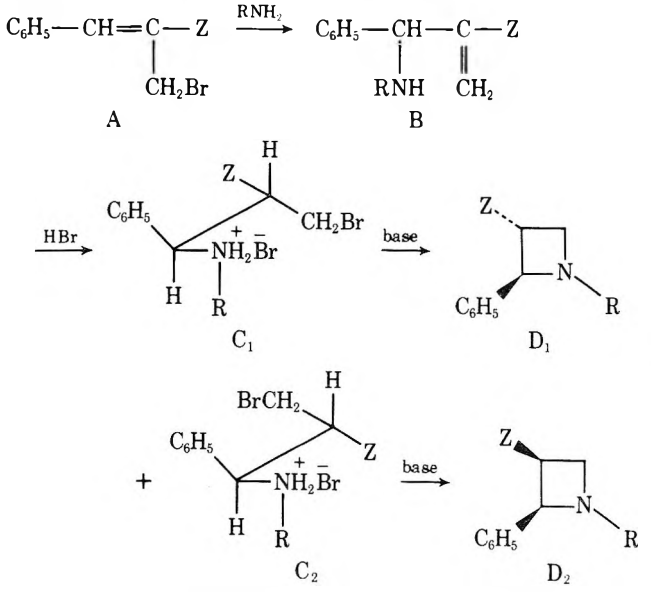
exclusively. Compounds **2** isomerized to **3** autocatalytically on prolonged standing in a polar solvent.

It has also been reported[4] that the reaction of *tert*-butylamine with α-(bromomethyl)cinnamonitrile (**4**) yielded the

substitution rearrangement product **5** exclusively. Conversion of **5** to **6** either autocatalytically or in the presence of excess amine was too slow to be detectable in chloroform.



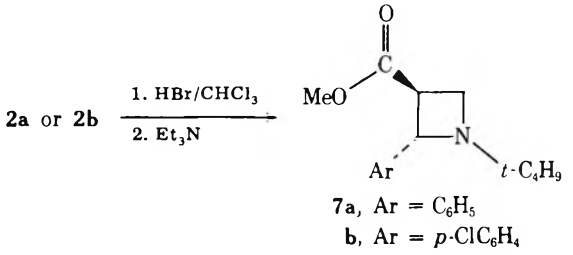
In conjunction with our integrated program of comparative studies of the chemistry of aziridines and azetidines, synthesis of azetidines with different substituents at various positions is under investigation. It seemed important to explore fully the steric controls[2b] operating during the addition of hydrogen bromide to the allylamines B to form the threo (C_1) and



erythro (C_2) γ-bromoamines when the activating group Z in A is varied from benzoyl to acetyl to carbomethoxy to cyano. Ring closures of the γ-bromoamines are stereospecific processes to produce the trans (D_1) and cis (D_2) substituted azetidines.[2] It is premature to attempt to discuss the various factors of asymmetric induction involved in the addition of hydrogen bromide to these several systems. Previously brief mention was made of this matter when Z is the benzoyl group.[2b] In this publication we wish to report the cyclization of **2** and **5** by a method developed for the synthesis of 1-alkyl-2-aryl-3-carboazetidines,[2] and to discuss in a preliminary manner the stereochemistry and mechanism for the reactions involved in the synthesis of these stereoisomeric substituted azetidines.

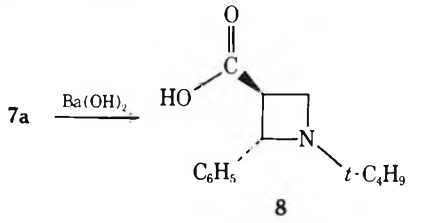
Results

The syntheses of 1-*tert*-butyl-2-phenyl-3-carbomethoxyazetidine (**7a**) and 1-*tert*-butyl-2-*p*-chlorophenyl-3-carbomethoxyazetidine (**7b**) were accomplished in excellent yield by treatment of **2a** and **2b** with hydrogen bromide in chloroform, followed by neutralization with triethylamine.

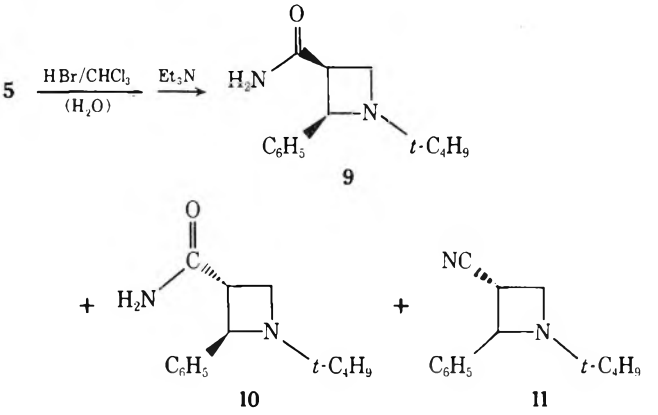


The existence of the azetidine ring in **7** was readily determined by the typical ^1H NMR absorption of benzylic, C-3, and C-4 protons.[2] The azetidinyl esters **7** were found to be exclusively of one configuration, which were later shown to be trans. Treatment of azetidinyl esters **7** with strong base did not effect epimerization, and no deuterium exchange could be observed when the reaction was carried out in methanol-d_1.

Base-catalyzed hydrolysis of azetidinyl ester **7a** with barium hydroxide yielded azetidinyl acid **8**, which later was assigned the trans configuration. The ^1H NMR spectrum displayed the benzylic proton as a doublet (J_{HH} = 8.4 Hz) at δ 5.31 in D_2O. The mass spectrum showed a weak molecular ion at *m/e* 233 (calcd 233). The M + 1/M ratio corresponded to C/N ratio of 14:1, which is in agreement with the structure of **8**.

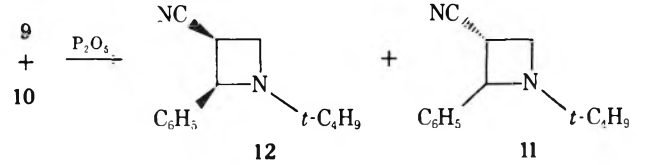


Treatment of aminonitrile **5** with hydrogen bromide in chloroform and then triethylamine yielded three products. Apparently small amounts of moisture were present in these solutions.



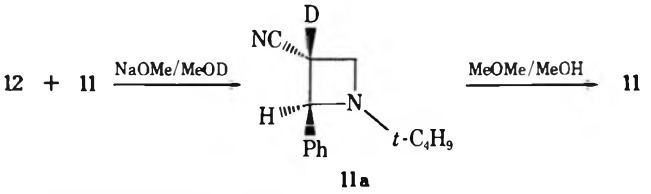
Carbamoylazetidines **9** and **10** crystallized together as a 60:40 (**9**/**10**) mixture from the pentane solution. Chromatography of the mother liquor yielded in addition to **9** and **10**, cyanoazetidine **11**. The ^1H NMR spectrum of the mixture of **9** and **10** displayed the benzylic protons as two doublets, respectively, at δ 4.72 (J_{HH} = 8 Hz) and 4.43 (J_{HH} = 8 Hz).

Dehydration of amidoazetidines **9** and **10** with phosphorus pentoxide yielded a mixture of *cis*- and *trans*-1-*tert*-butyl-2-phenyl-3-cyanoazetidine (**12**/**11**, 50:50). The ^1H NMR spectrum of the mixture displayed the benzylic protons of the two isomers as two doublets at δ 4.55 (J_{HH} = 7 Hz) and 4.45 (J_{HH} = 8 Hz). The unreacted amidoazetidine was found to consist of only the trans isomer **10**.



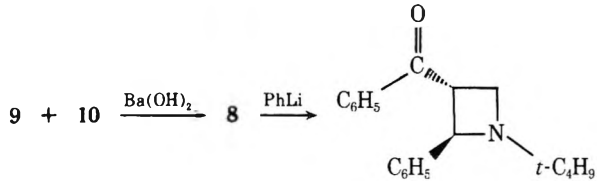
Cyanoazetidine mixture **12** and **11** was refluxed with sodium methoxide in methanol-d_1. The ^1H NMR spectrum of the product **11a** after working up indicated that deuterium had become incorporated into the compound. Refluxing com-

pound **11a** with sodium methoxide in methanol yielded *trans*-1-*tert*-butyl-2-phenyl-3-cyanoazetidine **11**.



11a

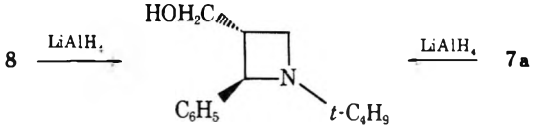
Base-catalyzed hydrolysis of amidoazetidine mixture **9** and **10** with barium hydroxide produced the azetidinylcarboxylic acid, which was spectrally identical with **8**. The ^{1}H NMR spectrum of the crude product did not reveal the presence of any other isomer of the acid.



13

Reaction of azetidinyl acid **8** with phenyllithium yielded *trans*-1-*tert*-butyl-2-phenyl-3-benzoylazetidine **13**, which was spectrally equivalent to an authentic sample.[2b] This result, however, is of no use in assigning the configuration of **8**, since phenyllithium is itself a strong base.[5]

Reaction of azetidinyl acid **8** with lithium aluminum hydride gave the corresponding alcohol **14**. The ^{1}H NMR spectrum of alcohol **14** displayed the benzylic signal at δ 4.13 as a doublet (J_{HH} = 7 Hz). The same alcohol **14** was also obtained by the reaction of ester **7a** with lithium aluminum hydride. Lithium aluminum hydride is not expected to catalyze epimerization in the azetidine nucleus in either case,[6] so azetidinyl ester **7a** and azetidinyl acid **8** are expected to have the same configuration.



14

X-ray crystallographic studies of the picrate of **7b**[7] showed that azetidinyl esters **7** have a trans configuration. Therefore, azetidinyl acid **8** and azetidinyl alcohol **14** are also assigned a trans configuration.

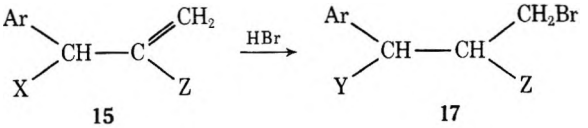
Discussion

Treatment of aminoester **2** or aminonitrile **5** with hydrogen bromide followed by triethylamine yielded the appropriate azetidine. The conversion can be rationalized as a two-step process. The first involves a hydrobromination of the alkenes and the second is the cyclization of the γ-haloamines.[8]

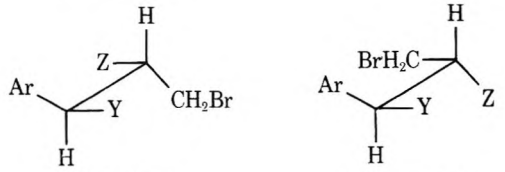
The addition of hydrogen bromide to **15** gives **17**, which can exist in two diastereomeric forms, **17a** for the threo, and **17b** for the erythro.

As pointed out by Grob,[9] Vaughan,[10] and later by Cromwell,[2b] the cyclization of these γ-haloamines should be treated as a conformational problem. Therefore **17a** would give *trans*-azetidine **18a** and **17b** would give *cis*-azetidine **18b**. When Z is carbomethoxy, the reaction sequence goes through **15** → **17a** → **18a**. For the case when Z is cyano, **15** goes to **17a** and **17b**, giving **18a** and **18b** rather nonselectively.

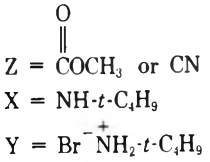
Epimerization of the *cis*-2-carbomethoxyazetidine to its trans isomer is unlikely in an acidic medium. In one experiment, the reaction of **2a** with HBr/$CHCl_3$ was interrupted purposely before it went to completion, and was then treated with triethylamine. However, no signal corresponding to the

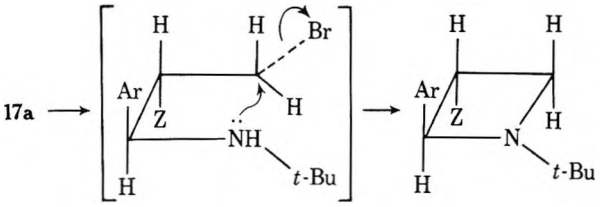


15 **17**

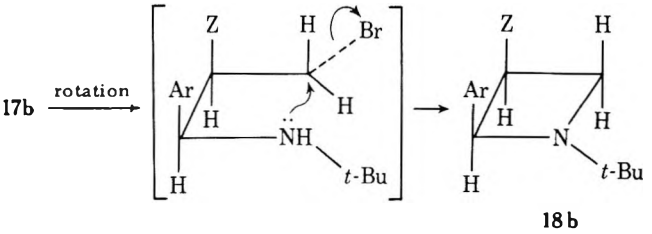


17a, threo **17b**, erythro





18a



18b

cis-arylcarbomethoxyazetidine could be observed in the ^{1}H NMR spectrum of the reaction mixture, thus it seems improbable that **2a** produced any of the cis product in this reaction sequence.

Experimental Section

Melting points were determined from a Mel-Temp apparatus, and were uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 621 Spectrophotometer. The proton magnetic resonance spectra were determined on a Varian Model A-60 spectrometer, utilizing tetramethylsilane as an internal standard. Elementary analyses were performed by Micro-Tech Laboratories, Skokie, Ill. The low-resolution mass spectra were obtained from a Hitachi RMU-60 spectrometer, and the high-resolution spectra from a AEI MS-50 spectrometer.

1-*tert*-Butyl-2-phenyl-3-carbomethoxyazetidine (7a). A 5.10-g (0.02 mol) sample of methyl α-(bromomethyl)cinnamate[3] (**1a**) dissolved in 250 mL of pentane was treated with 2.92 g (0.04 mol) of *tert*-butylamine in a closed vessel. The tightly stoppered contents were stirred magnetically at room temperature for 76.5 h. The *tert*-butylamine hydrobromide thus produced was removed by filtration. The filtrate was subjected to rotary evaporation at reduced pressure to leave an oil which was taken up in ca. 100 mL of chloroform saturated with hydrogen bromide gas at 0 °C. The reactants were kept tightly stoppered in a flask while warmed to room temperature over a period of 15 days. The chloroform and excess hydrogen bromide were evaporated under reduced pressure with warming and the residue was taken up in another 100 mL of chloroform. To this solution was added excess triethylamine and the contents stirred for 1 h. Evaporation of the solvent and excess triethylamine left a solid residue, which was extracted with boiling hexane. After being subjected to filtration, the hexane was evaporated to leave an oil (quantitative) which was shown to be **7a**: IR ν (C=O) ($CHCl_3$) 1723 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.10–7.70 (m, 5 H, aromatic), 4.51 (d, J_{HH} = 7.2 Hz, 1 H, PhC**H**), 3.50 (s, 3 H, CH_3) 2.70–3.50 (m, 3 H, other azetidine ring protons), 1.06 (s, 9 H, *tert*-butyl). The compound was analyzed as its picrate, mp 160.5–162 °C.

Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.14; H, 5.12; N, 11.63.

Attempted Deuterium Exchange with 7a. (1) A 0.025-g sample of **7a** was dissolved in 1 mL of methanol-d_1, to which was added a catalytic amount of sodium methoxide. The contents were allowed to stand at room temperature for 46 h. Evaporation of the solvent under reduced pressure with warming left an oil which was analyzed by ^{1}H NMR spectroscopy to be unchanged starting material.

(2) A 0.95-g sample of **7a** was dissolved in 4 mL of methanol-d_1, to which was added 0.21 g of sodium methoxide. The mixture was refluxed for 88 h. Evaporation of the solvent gave a residue, the ^{1}H NMR spectrum of which indicated the presence of unchanged starting material together with a small amount of unidentifiable impurities.

(3) A 0.025-g sample of **7a** was dissolved in 2 mL of *tert*-butyl alcohol containing a catalytic amount of potassium *tert*-butoxide. The mixture was allowed to stand at room temperature for 40 h, followed by the addition of 1 mL of deuterium oxide. The mixture was allowed to stand for several minutes, and the solvent evaporated under reduced pressure to leave a residue which was taken up in ether. The ethereal solution was filtered and subjected to rotary evaporation. The residue was analyzed by ^{1}H NMR spectroscopy, indicating the complete destruction of the starting material.

1-*tert*-Butyl-2-(4-chlorophenyl)-3-carbomethoxyazetidine (7b). A 4.0-g (0.011 mol) sample of the hydrobromide of methyl α-(α-*tert*-butylamino-4-chlorobenzyl)acrylate (**2b**)[3] was dissolved in 500 mL of chloroform saturated with anhydrous hydrogen bromide at 0 °C. The reaction mixture was tightly stoppered in a flask while warming to room temperature, and allowed to stand for 14 days. The solvent and excess hydrogen bromide were removed under reduced pressure to leave a solid residue, which was taken up in 75 mL of chloroform. The solution was treated with excess triethylamine. The mixture was allowed to stand for another 6 h and the solution then filtered. Excess triethylamine and the solvent were evaporated under reduced pressure. The residue was taken up in boiling hexane and the hexane solution again filtered. Rotary evaporation under reduced pressure yielded an oil (quantitative), which was identified to be **7b**: IR ν (C=O) ($CHCl_3$) 1726 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.15–7.65 (m, 4 H, aromatic), 4.53 (d, J = 7.0 Hz, 1 H, ArCH), 3.66 (s, 3 H, OCH_3), 2.60–3.60 (m, 3 H, the remaining azetidine ring protons), 0.90 (s, 9 H, *tert*-butyl). The compound was analyzed as its picrate, mp 181–182.5 °C.

Anal. Calcd for $C_{21}H_{23}ClN_4O_9$: C, 49.37; H, 4.52; Cl, 6.94; N, 10.97. Found: C, 49.15; H, 4.42; Cl, 6.94; N, 10.79.

Attempted Deuterium Exchange with 7b. A small amount of **7b** was dissolved in methanol-d_1 which contained a catalytic amount of sodium methoxide. The contents were allowed to stand at room temperature for 19 h. Evaporation of the solvent under reduced pressure with mild warming gave a residue, which was analyzed by ^{1}H NMR spectroscopy to be unchanged starting material.

1-*tert*-Butyl-2-phenylazetidine-3-carboxylic Acid (8). A 2.0-g (8.1 mmol) sample of **7a** was dissolved in 40 mL of dioxane/water mixture (v/v, 1:1) to which was added 1.5 g (4.0 mmol) of barium hydroxide octahydrate. The mixture was refluxed for 8 h. Carbon dioxide was bubbled through the reaction mixture to precipitate barium carbonate, which was removed by filtration. Evaporation of the solvents under reduced pressure with heating gave a solid residue. Recrystallization from an ethanol/ether mixture yielded 1 g (53%) of a white flaky solid, which was identified to be **8**: mp 156–157 °C; IR ν (C=O) (Nujol) 1590 cm^{-1}; ^{1}H NMR δ (D_2O with acetone as internal standard at 125 Hz), 7.40–7.75 (m, 5 H, aromatic), 5.31 (d, J = 8.4 Hz, 1 H, PhC**H**), 3.50–4.10 (m, 3 H, other azetidine ring protons), 1.12 (s, 9 H, *tert*-butyl); MS M$^+$ 233.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.05; H, 8.21; N, 6.01. Found: C, 72.03; H, 8.31; N, 6.02.

***cis*- and *trans*-1-*tert*-Butyl-2-phenyl-3-amidoazetidine (9 and 10).** To a solution of 11.9 g (0.0536 mol) of α-(bromomethyl)cinnamonitrile (**4**)[4] in 900 mL of pentane was added 7.89 g (0.11 mol) of *tert*-butylamine. The solution was allowed to stand for 41.5 h. The amine salt thus produced was removed by filtration. Removal of the solvent yielded an oil, dissolved in 125 mL of chloroform. The solution was then saturated with hydrogen bromide gas. After standing for 7 days at room temperature, the hydrogen bromide in excess and the solvent were evaporated. To the residue was added another 125 mL of chloroform. The solution was neutralized by excess triethylamine. The amine salt produced upon replacement of chloroform with ether was removed by filtration. The residue was washed well with ether, and the combined washings were subjected to rotary evaporation. The residual oil was extracted with hot pentane. The pentane extract was collected and the solvent evaporated. Recrystallization of the residue yielded 2.4 g (20%) of a white solid, which was identified to be a 60:40 mixture of *cis*- and *trans*-1-*tert*-butyl-2-phenyl-3-amidoazetidine (**9** and **10**): IR (Nujol) ν (NH) 3360, 3191 (hydrogen bending), ν (C=O) 1660 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.20–7.60 (m, 5 H, aromatic), 4.72, 4.43 (2 d, J_{HH} = 8 Hz, 1 H, benzylic proton of the cis and trans epimers), 2.37–3.50 (m, 3 H, the remaining azetidine ring protons), 0.92, 0.90 (2 s, 9 H, *tert*-butyl protons of the two epimers).

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.41; H, 8.62; N, 12.06. Found: C, 72.21; H, 8.74; N, 12.03.

The mother liquor of the previously described recrystallization yielded a residual oil upon evaporation of the solvent. Preparative thin-layer chromatographic separation of the residual oil gave three compounds. The first (30 mg) was identified to be the unreacted starting material by ^{1}H NMR spectroscopy. The second (100 mg, 0.9%) was identified to be *trans*-1-*tert*-butyl-2-phenyl-3-cyanoazetidine (**11**). (Identification was made by comparing the ^{1}H NMR spectrum with that of an authentic sample obtained by an independent route.) A third compound (250 mg) was identified to be a 10:90 mixture of the **9** and **10**.

1-*tert*-Butyl-2-phenylazetidine-3-carboxylic Acid (8) from a Mixture of 9 and 10. To a solution of 750 mg of barium hydroxide octahydrate in 20 mL of 1:1 (v/v) mixture of dioxane and distilled water was added 700 mg (0.003 mol) of a 60:40 mixture of **9** and **10**. The mixture was refluxed for 11 h. Excess carbon dioxide was added to precipitate barium carbonate, which was removed by filtration. Evaporation of the solvent yielded 580 mg (83%) of a white solid. Recrystallization from methanol/ether mixture gave flaky white crystals, spectrally equivalent to 1-*tert*-butyl-2-phenylazetidine-3-carboxylic acid (**8**) prepared by the previously described independent route.

***trans*-1-*tert*-Butyl-2-phenyl-3-benzoylazetidine (13).** To a solution of 220 mg (0.0009 mol) of **8** in 10 mL of dry tetrahydrofuran at the temperature of ice was added 2.6 mL of 1.72 M phenyllithium in benzene. The solution was stirred for 2.75 h while warming to room temperature. Aqueous ammonium chloride solution was added. The mixture was then extracted with ether. After being dried over anhydrous magnesium sulfate, the solution was subjected to rotary evaporation. The ^{1}H NMR spectrum of the residual oil showed that in the region of the benzylic protons, only one doublet was present. Preparative thin-layer chromatography on the residual oil yielded two compounds. The first was a polyphenyl compound which was not further investigated. The second (80 mg, 30%) was a yellow oil, which was identified to be **13**:[2b] ^{1}H NMR δ ($CDCl_3$) 7.10–7.72 (m, 5 H, aromatic), 4.67 (d, 1 H, J_{HH} = 7.8 Hz, benzylic), 3.33–4.00 (m, 3 H, the other azetidine ring protons), 0.92 (s, 9 H, *tert*-butyl).

An 80-mg sample of **13** was refluxed in a solution of 50 mg of sodium methoxide in 10 mL of methanol-d_1 for 12 h. The solvent was evaporated in vacuo and the residue was extracted with hot pentane. The hot extract was evaporated in vacuo. The solid residue left was identified to be **13** deuterated at C-3: ^{1}H NMR δ ($CDCl_3$) 7.10–7.72 (m, 10 H, aromatic), 4.66 (s, 1 H, benzylic), 3.52 (s, 2 H, NCH_2–), 0.92 (s, 9 H, *tert*-butyl).

***cis*- and *trans*-1-*tert*-Butyl-2-phenyl-3-cyanoazetidine (12 and 11).** A 200-mg (0.00086 mol) sample of a 60:40 mixture of **9** and **10** was refluxed in a suspension of 1.97 g of phosphorus pentoxide in 70 mL of benzene for 48 h. The P_2O_5 in excess was destroyed by adding water and the solution was neutralized with sodium bicarbonate solution. The organic layer was separated and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo yielded a yellow oil, preparative thin-layer chromatography of which gave three compounds. The first was a carbonyl compound: IR ν_{max} 1745 cm^{-1}, which was not further investigated due to the small quantity obtained. The second was a 50:50 mixture of **12** and **11** (100 mg, 54.6%): IR (CCl_4) ν (CN) 2242 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.16–7.64 (m, 5 H, aromatic), 4.55, 4.45 (2 d, 1 H, J_{HH} = 7, 8 Hz, benzylic proton of respectively the cis and trans epimers), 2.50–3.53 (m, 3 H, the remaining azetidine ring protons), 0.89 (s, 9 H, *tert*-butyl). The third compound was **10**: ^{1}H NMR δ ($CDCl_3$) 7.15–7.76 (m, 5 H, aromatic), 4.43 (d, 1 H, J_{HH} = 8 Hz, benzylic), 2.50–3.50 (m, 3 H, remaining azetidine ring protons), 0.90 (s, 9 H, *tert*-butyl).

A 100-mg sample of the mixture of **12** and **11** (50:50) was refluxed in a solution of 200 mg of sodium methoxide in 10 mL of methanol-d_1 for 18 h. The solvent was then evaporated in vacuo. The solid residue was extracted with boiling pentane, and the organic solution was separated from the inorganic residue. Evaporation of the solvent in vacuo yielded a yellow solid: ^{1}H NMR δ ($CDCl_3$) 7.20–7.62 (m, 5 H, aromatic), 4.33–4.59 (1 H, m, benzylic), 3.37 (br s, 2 H, NCH_2–), 0.89 (s, 9 H, *tert*-butyl). The deuterium incorporated compound was refluxed in a solution of 200 mg of sodium methoxide in 10 mL of methanol. Similar workup as above yielded a yellow solid (100 mg,

quantitative). Recrystallization from pentane gave a yellow crystalline solid, which was identified to be **11**: mp 119–119.5 °C; IR (CCl_4) ν (CN) 2242 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.20–7.62 (m, 5 H, aromatic), 4.45 (d, 1 H, J_{HH} = 8 Hz, benzylic), 2.70–3.55 (m, 3 H, remaining azetidine ring protons), 0.89 (s, 9 H, *tert*-butyl).

The compound was analyzed as its picrate derivative, mp 181–181.5 °C.

Anal. Calcd for $C_{20}H_{21}N_5O_7$: C, 54.18; H, 4.74; N, 15.80. Found: C, 53.98; H, 4.70; N, 15.57.

***trans*-1-*tert*-Butyl-2-phenyl-3-hydroxymethylazetidine (14).** A 0.6-g (0.0025 mol) sample of 8 was refluxed in a suspension of 1 g of lithium aluminum hydride in a mixture of 15 mL of dioxane and 60 mL of ether for 57 h. The $LiAlH_4$ in excess was destroyed by adding water to it. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic extract was dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo yielded 490 mg (89%) of a slightly yellow oil, which was identified to be **14**: IR ν (OH) 3400 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.10–7.58 (m, 5 H, aromatic), 4.13 (d, 1 H, J_{HH} = 7 Hz, benzylic), 3.66 (d, 2 H, J_{HH} = 5.5 Hz, $-CH_2OH$), 2.20–3.50 (m, 3 H, remaining azetidine ring protons), 0.89 (s, 9 H, *tert*-butyl); high-resolution MS M^+ 219.1620; molecular weight, calcd for $C_{14}H_{21}NO$ = 219.1623.

Azetidine 14 from 7a. A 500-mg (0.0021 mol) sample of **7a** was stirred in a suspension of 350 mg of lithium aluminum hydride in 75 mL of anhydrous ether for 46.5 h at room temperature. The $LiAlH_4$ in excess was destroyed by adding water to the mixture. The organic layer was separated and the aqueous layer was extracted several times with ether. The combined ethereal extract was dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 300 mg (65.2%) of a light yellow oil, which was spectrally equivalent to **14** prepared by a different method as described in the previous section.

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Registry No.—**1a**, 53059-43-1; **2b** HBr, 62029-87-2; **4**, 59728-94-8; **7a**, 62029-88-3; **7a** picrate, 62029-89-4; **7b**, 62029-90-7; **7b** picrate, 62029-91-8; **8**, 62029-92-9; **9**, 62029-93-0; **10**, 62029-94-1; **11**, 62029-95-2; **11** picrate, 62029-96-3; **11a**, 62059-32-9; **12**, 62029-97-4; **13**, 10235-75-3; **13-*d***, 13943-11-8; **14**, 62029-98-5; *tert*-butylamine, 75-64-9.

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(5) Under basic condition *cis*-1-*tert*-butyl-2-phenyl-3-benzoylazetidine epimerizes to its trans isomer.[2b]
(6) Compared to sodium methoxide and potassium *tert*-butoxide in the appropriate alcohol which fail to catalyze epimerization or deuterium exchange of azetidinyl ester **7**, lithium aluminum hydride and the bases produced during hydrolysis are much weaker. Therefore, under the condition described, base-catalyzed epimerization of azetidinyl ester 7a, acid **8**, and alcohol **14** is unlikely.
(7) A report on the x-ray crystallographic studies of the picrates of the series of 1-*tert*-butyl-2-phenyl 3-substituted azetidines is under preparation and will be published elsewhere. A preliminary report was presented at the 12th Midwest Regional Meeting (Organic) of the American Chemical Society, University of Missouri, Kansas City, Mo., October 1976.
(8) The ring closure of a γ-haloamine in the presence of base is one of the most commonly used methods for the synthesis of azetidines. This reaction involves an internal nucleophilic displacement by an amino group of the halogen atom at the γ position of a three-carbon chain. For a review, see J. A. Moore in "Heterocyclic Compounds with Three and Four-Membered Rings", Part II, A. Weissberger, Ed., Interscience, New York, N.Y., 1964, p 885.
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Excess Azide Method of Peptide Synthesis

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A new procedure of peptide synthesis using a large excess of protected amino acid azide is described. The azide solution in CH_2Cl_2 (or DMF) is added to the amino component dissolved in DMF. Methylene chloride (if used) can then be evaporated in vacuo at low temperatures. The excess azide is subsequently hydrolyzed at 0 °C by treatment of the DMF solution with $KHCO_3/H_2O$ *in a homogenous phase.* The procedure permits isolation of analytically pure peptides in high yields. Syntheses of several dipeptides and Z-Gly-Gly-Gly-OEt are reported.

Summary

Analytically pure peptides were synthesized in excellent yields by a procedure employing a large excess of the amino acid azide component. Two equivalents of the protected amino acid azides were reacted with the amino group of a carboxyl protected amino acid or peptide in DMF. Consistent 85–90% yields of the coupled peptide were obtained. The excess azide components were eliminated during product isolation by rapid hydrolysis in a homogeneous potassium bicarbonate/H_2O/DMF solution. The large excess may reduce side reactions by permitting a low reaction temperature (0 °C or lower) during a relatively short time period (27 h). The relative freedom from racemization, an outstanding feature of azide couplings, was retained in this procedure. Additional purification steps were generally not required after the simple isolation of the product. Hydroxyl protective groups for serine and threonine were not needed, but side reactions occurred with the unprotected phenolic group of tyrosine. This procedure offers a convenient approach to the stepwise synthesis of many peptide sequences and may be of help in optimizing the yields of longer peptides.

Discussion

There have been recent successful applications of the excess mixed anhydride method[1,2] for the synthesis of peptides, such as secretin.[3] This has encouraged us to extend the advantages of the excess amino acid derivative concept to the development of new peptide synthesis procedures. The acid azide method of peptide synthesis has proven to be adaptable to procedural modifications, similar to the excess mixed anhydride method.

The azide method of peptide synthesis, in use for over 70 years, is held in high regard by peptide chemists due to several advantages. The starting materials (hydrazides) are easy to

prepare, racemization during coupling is minimal, and in many cases side chain protection is not required. The relative freedom from racemization, which is so important in peptide synthesis, has been repeatedly confirmed[4,5,10] during azide couplings. Some disadvantages of the azide method include frequent low yields, amide formation during the conversion of hydrazides to azides, and isocyanate formation via the Curtius rearrangement.[6] The excess azide method described below employs a significant excess of the acid azide to ensure a relatively quick, quantitative coupling. Azide preparations, reaction conditions, and other procedural details are designed to reduce potential side reactions to a minimum. This azide procedure, somewhat analogous to the excess mixed anhydride method, affords excellent yields of analytically pure peptides and can obviously be applied repetitively to the synthesis of larger peptides.

The carbobenzyloxy amino acid hydrazides were prepared from the methyl esters by the procedure of Zahn and Schnabel.[7] However, we found that good yields (72–94%) of the analytically pure hydrazides could be obtained by using 3 molar equiv of 85% hydrazine hydrate in the reaction.

Of key importance to the success of the excess azide procedure is the rapid and total elimination of the large excess of N-protected amino acid azide used in the reaction. This is demonstrated to be successful by treatment of the reaction mixture with a homogeneous $KHCO_3/DMF/H_2O$ solution. A solution of Z-Ala-N_3 dissolved in chloroform/methanol was treated for 45 min at 0 °C with a 50% saturated $KHCO_3/H_2O$ solution and water. As a control, an identical sample was treated with a 50% saturated $NaCl/H_2O$ solution and water. The azide remaining in these homogeneous solutions was extracted into chloroform. The infrared spectra of these extracts showed that the azide band (2140 cm^{-1}) was eliminated by the $KHCO_3$ treatment, but it was retained when treated with $NaCl/H_2O$. The azide hydrolysis product was further identified as the potassium salt of Z-Ala, which could be eliminated from coupling products by washing with water.

To enable incorporation of this alkaline hydrolysis into a generalized peptide synthesis procedure, solvent changes were required. DMF was chosen as a reaction solvent, since it would easily dissolve the acid azides and amino components, yet would be fully miscible with the $KHCO_3/H_2O$ treatment and so permit precipitation and easy isolation of the product. Methylene chloride (CH_2Cl_2) was chosen as the Z-amino acid azide extraction solvent because it is a good solvent for azides[8,9,13,14] and has a low boiling point. Even in the presence of DMF, CH_2Cl_2 can be quickly and totally removed (in vacuo) at temperatures lower than 0 °C.

Use of 1 equiv excess of the azide enables this sluggish reaction to proceed to completion in only 27 h at temperatures of 0 °C or lower. Further experimentation using the coupling of Z-Thr-N_3 to Phe-OMe as a model indicated that both 0.75 and 0.50 molar equiv excesses of the azide under identical reaction conditions gave complete reactions, but the time involved was considerably longer (51 and 96 h, respectively). To reduce possible side reactions in azide couplings we maintained the low temperature, the large 2:1 azide excess, and short reaction times in the remaining peptide syntheses.

To ensure complete conversion of the hydrazide to azide and eliminate amide formation,[11] excesses of both $NaNO_2$ and HCl at low temperatures were employed. Azide extracts in CH_2Cl_2 were washed extensively with water and the usual $NaHCO_3/H_2O$ washes were omitted to minimize possible racemization.[12]

The product isolated following the coupling of Z-Ser-N_3 and Phe-OMe using the excess azide method described below was examined for the presence of 4-carbobenzoxyaminooxazolidone-2, a cyclic urethane formed from the isocyanate of Z-Ser-N_3.[15] The cyclic urethane carbonyl stretch (1770 cm^{-1}) of this compound could not be detected during infrared analysis of this product. A parallel synthesis using excess Z-Ser-N_3 in an alternate azide procedure[16] gave a product in which IR, NMR, and other analyses showed a significant quantity of the cyclic urethane. Hence, the precise reaction conditions and rapid hydrolysis of the excess azide in the method described here seem to be significant in reducing side reactions and affording analytically pure peptides.

The excess azide method, however, does appear to preclude the use of tyrosine derivatives without phenolic protection. Dipeptide syntheses using unprotected tyrosine either as Z-Tyr-N_3 in excess or as the amino component, TyrOMe, all resulted in colored impurities in the products. The excess nitrite/HCl during azide formation as well as excess azide during the coupling itself may be leading to the nitration of the tyrosine aromatic ring or to other side reactions previously reported.[17] There were no problems, however, associated with synthesis of the hydrazide, Z-Tyr-NH-NH_2, in the usual manner.

The following examples outline the procedural details of the excess azide method of peptide synthesis. The only real variations involved are the occasional use of acetic acid in dissolving the N-protected amino acid hydrazide and the methods of isolating the product. Small, simple peptides appear to be synthesized in consistently good yields and purity. The excess azide method could also conceivably be used in a repetitive manner for the stepwise synthesis of larger peptides.

Experimental Section

All melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. The compounds reported in this paper in most cases were precipitated by the addition of water to the DMF solutions of the compounds. This method of precipitation, while providing analytically pure peptides, yields amorphous substances whose melting points differ appreciably from those reported previously[18] in crystalline form by crystallization. Elemental analyses were performed on a Perkin-Elmer 240 analyzer. Thin layer chromatographic (TLC) results were obtained on 5 × 20 cm plates of silica gel F-254 (E. Merck, Darmstadt, Germany). The four different solvent systems used were A, 93:7:10 THF/cyclohexane/H_2O; B, 75:24:1 ether/MeOH/H_2O; C, 75:24:1 $CHCl_3$/MeOH/H_2O; D, 75:24:1 $CHCl_3$/BuOH/H_2O. Amino acid analyses were performed in a Beckman Model 120 C automatic amino acid analyzer. Optical rotations were measured in 5-cm tubes with a Perkin-Elmer Model 241 polarimeter. All the amino acids used were of the L configuration. The following abbreviations were employed: Z, benzyloxycarbonyl; DMF, *N,N*-dimethylformamide

Z-Thr-Phe-OMe.[18] A solution of Z-Thr-NH-NH_2 (2.1383 g, 8.0 mmol) dissolved in 32 mL of 1 N HCl and 30 mL of H_2O was cooled to 0 °C. $NaNO_2$ (0.828 g, 12 mmol), dissolved in 20 mL of H_2O and chilled, was added. After stirring for 50 min in an ice bath, the azide was extracted into 100 mL of CH_2Cl_2. The dichloromethane solution was washed six times with cold H_2O, dried over Na_2SO_4, and cooled to −15 °C. It was then added to a −15 °C solution of Phe-OMe, prepared by neutralizing HCl·Phe-OMe (0.863 g, 4 mmol) in 25 mL of DMF with *N*-methylmorpholine (0.49 mL, 4 mmol). The final reaction mixture was stirred for 3.5 h at −15 °C under strong vacuum, collecting the CH_2Cl_2 in a dry ice/methanol trap. The solution was stirred under vacuum at 0 °C for an additional 23.5 h.

A saturated $KHCO_3/H_2O$ solution of 25 mL at 0 °C was added. The homogeneous, pH 8 solution was stirred for 45 min at 0 °C under vacuum; 50 mL of a chilled 50% saturated $NaCl/H_2O$ solution was added. Stirring at 0 °C under vacuum continued for an additional 70 min. The precipitate was filtered, washed thoroughly with H_2O, and dried in vacuo. This procedure gave 1.6071 g (97%) of product, mp 99–101 °C.

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32, N, 6.76, O, 23.16. Found: C, 63.72; H, 6.35; N, 6.76; O, 23.08.

TLC: one spot in all four solvent systems.

$[\alpha]^{25}_D$ +5.2° (c 10 mg/mL, DMF), $[\alpha]^{25}_D$ −8.2° (c 10 mg/mL, MeOH).

Amino Acid Anal. Thr, 0.97; Phe, 1.03.

Z-Ser-Phe-OMe.[18] This compound was prepared in 95% yield by the exact method described for the synthesis of Z-Thr-Phe-OMe; 1.5182 g of product was obtained, mp 75–76 °C.

Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.84; H, 6.14; N, 6.80.

TLC: one spot in all four solvent systems.

$[\alpha]^{25}_D$ +3.8° (c 3.5 mg/mL, DMF), $[\alpha]^{25}_D$ −5.1° (c 3.7 mg/mL, MeOH).

Amino Acid Anal. Ser, 0.83; Phe, 1.00.

Z-Phe-Phe-OMe.[18] Z-Phe-NH-NH_2 (2.5069 g, 8 mmol) was dissolved in a solution of 32 mL of 1 N HCl and 20 mL of acetic acid; 30 mL of H_2O was added and the solution cooled to 0 °C. $NaNO_2$ (0.828 g, 12 mmol), dissolved in 20 mL of H_2O and chilled, was added. The reaction proceeded for 25 min while cooled in an ice bath. Added was 100 mL of CH_2Cl_2. After mixing, the organic layer was washed six times with cold water, dried over Na_2SO_4, and cooled to −15 °C. The organic layer was then added to a −15 °C solution of Phe-OMe, prepared by neutralizing HCl·Phe-OMe (0.863 g, 4 mmol) in 15 mL of DMF with *N*-methylmorpholine (0.49 mL, 4 mmol). After stirring for 6 h at −15 °C under vacuum, the reaction proceeded for an additional 21 h at 0 °C.

Approximately 10–15 mL of a saturated $KHCO_3/H_2O$ solution at 0 °C was added. The homogeneous solution remained at pH 8 through 45 min of stirring at 0 °C under vacuum. A solution of 50% saturated $NaCl/H_2O$ (50 mL) at 0 °C was added. Stirring at 0 °C under vacuum continued for an additional 70 min, during which time chilled water (25 mL or less) was periodically added. The solution was then filtered and the precipitate washed well with copious amounts of H_2O. After drying in vacuo, the entire sample was reprecipitated from EtOH with water to give 1.7241 g (93.6%) of product, mp 138–140 °C.

Anal. Calcd for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.39; H, 6.25; N, 6.35.

TLC: one spot in all four solvent systems.

$[\alpha]^{25}_D$ −20.0° (c 2.5 mg/mL, DMF), $[\alpha]^{25}_D$ −20.0° (c 2.6 mg/mL, MeOH).

Z-Phe-Ala-OMe.[18] This peptide was synthesized in a manner identical with the preparation of Z-Phe-Phe-OMe described above. An additional reprecipitation from MeOH with water yielded 1.4356 g (93.5%) of product, mp 118–120 °C.

Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.40; H, 6.08; N, 7.40.

TLC: one spot in all four solvent systems. $[\alpha]^{25}_D$ −11.5° (c 3.2 mg/mL, DMF), $[\alpha]^{25}_D$ −19.6° (c 3.4 mg/mL, MeOH).

Amino Acid Anal. Phe, 1.04; Ala, 0.96.

Z-Gly-Gly-OEt. A solution of Z-Gly-NH-NH_2 (4.4647 g, 20 mmol) dissolved in 80 mL of 1 N HCl was cooled to 0 °C. A chilled solution of $NaNO_2$ (2.066 g, 30 mmol) in 50 mL of H_2O was added. Stirring the solution for 30 min at 0 °C led to the appearance of a white precipitate (Z-Gly-N_3). The azide was extracted into 200 mL of CH_2Cl_2, washed six times with cold H_2O, dried over Na_2SO_4, and cooled to −15 °C. The CH_2Cl_2 extract was then added to a −15 °C solution of Gly-OEt, prepared by neutralizing HCl·Gly-OEt (1.3959 g, 10 mmol) in 100 mL of DMF with *N*-methylmorpholine (1.25 mL, 10 mmol). The reaction mixture was stirred at −15 °C under strong vacuum for 6 h plus an additional 21 h at 0 °C.

A chilled, saturated $KHCO_3/H_2O$ solution of 60 mL was slowly added. After stirring for 45 min under vacuum in an ice bath, 100 mL of a 50% saturated $NaCl/H_2O$ solution at 0 °C was added. Cold water was occasionally added during 90 min of additional stirring at 0 °C under vacuum. The solution was then filtered and the precipitated material washed extensively with water and dried in vacuo.

Due to the expected partial solubility of the peptide in a homogeneous DMF/H_2O solution, examination of the above filtrate for additional product was undertaken. The dry residue resulting from lyophilization of the filtrate was triturated well in absolute ethyl acetate and the insoluble salts were removed by filtration. After drying over Na_2SO_4, the EtoAc solution was treated with decolorizing carbon. The carbon was filtered off and the solution was evaporated to dryness on a Büchi rotary evaporator. Following trituration of the residue with water, the crystalline product was filtered, washed well with water, and dried in vacuo. Both identical fractions were combined to give 2.7051 g (92%) of Z-Gly-Gly-OEt, mp 78–80 °C.

Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57-04; H, 6.01; N, 9.30.

TLC: one spot in all four solvent systems.

Z-Gly-Gly-Gly-OEt. The amino component for this reaction, HCl·Gly-Gly-OEt, was prepared by dissolving Z-Gly-Gly-OEt (1.1772 g, 4 mmol) in 50 mL of absolute methanol. Palladium, 5% on activated carbon and wetted with acetic acid, was added, followed by 4 mL of 1 N HCl and 5 mL of DMF. After flushing with nitrogen, hydrogen gas was bubbled through the vigorously shaking solution for 4.5 h at room temperature. The carbon was filtered off and washed well with methanol. The filtrate was evaporated to an oily residue on a Büchi and redissolved in 20 mL of DMF. The compound Gly-Gly-OEt (4 mmol) was prepared by neutralizing this solution with *N*-methylmorpholine (0.49 mL, 4 mmol).

The remainder of the tripeptide synthesis was completed in a manner identical with the preparation of Z-Gly-Gly-OEt already described to yield 1.2128 g (87%) of product, mp 164–166 °C.

Anal. Calcd for $C_{16}H_{21}N_3O_6$: C, 54.70; H, 6.02; N, 11.96; O, 27.32. Found: C, 54.55; H, 5.94; N, 11.71; O, 27.71.

TLC: one spot in all four solvent systems.

Registry No.—Z-Thr-Phe-OMe, 19649-01-5; Z-Thr-Phe-NH-NH_2, 49706-30-1; Z-Thr-Phe-N_3, 41446-42-8; Phe-OMe, 2577-90-4; HCl·Phe-OMe, 7524-50-7; Z-Ser-Phe-OMe, 40290-58-2; Z-Ser-NH-NH_2, 26582-86-5; Z-Ser-N_3, 41446-15-5; Z-Phe-Phe-OMe, 4892-10-8; Z-Phe-NH-NH_2, 21887-86-5; Z-Phe-N_3, 62067-14-5; Z-Phe-Ala-OMe, 25422-44-0; Ala-OMe, 10065-72-2; HCl·Ala-OMe, 2491-20-5; Z-Gly-Gly-OEt, 3005-87-6; Z-Gly-NH-NH_2, 5680-83-1; Z-Gly-N_3, 50622-95-2; Gly-OEt, 459-73-4; HCl·Gly-OEt, 623-33-6; Z-Gly-Gly-Gly-OEt, 2503-35-7; HCl·Gly-Gly-OEt, 2087-41-4; Gly-Gly-OEt, 627-74-7.

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Beckmann Fragmentation Reaction of 3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one Oxime

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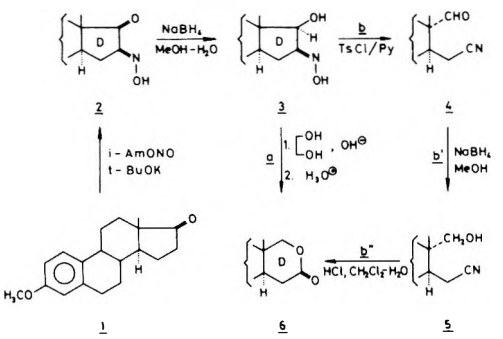
The Beckmann fragmentation reaction of 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (**3**), achieved with *p*-toluenesulfonyl chloride in pyridine at room temperature, gave 3-methoxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**4**) in a high yield. The structure of the fragmentation product **4** was proved on the basis of spectral data and by its conversion into the corresponding lactone **6**. The same lactone **6** was prepared by a simple and novel synthetic procedure, directly from the 17β-hydroxy-16-one oxime (**3**) and potassium hydroxide in boiling ethylene glycol. The first step of this transformation was assumed to be the formation of **4** by the Beckmann fragmentation reaction of **3** under basic conditions, followed by a reduction of the aldehyde group of **4** with ethylene glycol catalyzed by potassium hydroxide.

The Beckmann fragmentation reaction of steroidal α-hydroxy oximes has not been extensively studied. A few characteristic examples of this reaction were given in our previous paper.[1] A recent example of the same reaction was described by Paisley and Weiler,[2] who converted 2β-hydroxy-17β-acetoxy-5β-androstan-3-one oxime into the corresponding 2,3-seco-2-oxo-3-nitrile. Our preliminary studies in estrone series and the fact that certain ring D seco derivatives of estrone show a hypocholesterolemic activity[3] prompted us to investigate the Beckmann fragmentation reaction in the estrone series.

We selected as a starting material 3-methoxyestra-1,3,5(10)-triene-16,17-dione 16-oxime (**2**), prepared according to the procedure of Litvan and Robinson.[4] We noticed a significant difference in melting points for the compound **2** (Litvan and Robinson claimed mp 161–162 °C; in our case mp was 212–214 °C), which was attributed to the presence of a certain amount of the syn isomer in Litvan and Robinson's case.[5] Further chemical transformations of **2** are given in Scheme I.

Scheme I



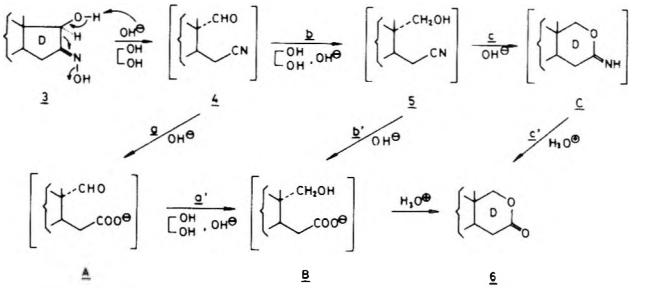
The reduction of the hydroxyimino ketone **2** with $NaBH_4$ in aqueous methanol afforded 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (**3**) in a high yield. The anti configurations of oximes **2** and **3** were assumed for the reasons cited in our previous paper.[1]

The Beckmann cleveage of **3** (pathway b) was carried out under similar reaction conditions as earlier,[1] but in this case, the primary fragmentation product **4**, mp 158–160 °C, was easily isolated and purified by direct crystallization from methylene chloride–hexane. The spectral data proved the proposed structure of **4**.

Seco cyanoaldehyde **4** has been converted, in a high yield, by $NaBH_4$ reduction into the corresponding seco cyano alcohol **5** (b′), whose structure was also proved by spectral data. By the action of gaseous hydrogen chloride on the solution of **5** in methylene chloride, saturated with water, 3-methoxy-17-oxa-*D*-homoestra-1,3,5(10)-trien-16-one (**6**) was obtained[7] (b″). The intermediary formation of the six-membered iminolactone C (see Scheme II) has been assumed. The hydrochloride of the intermediate C was isolated, when the reaction was carried out under anhydrous conditions, but we did not succeed in getting an analytically pure sample, since the compound C·HCl hydrolyzed very readily in air to the corresponding lactone **6**.

The lactone **6** has been independently prepared by a simple procedure directly from the α-hydroxy oxime **3** and potassium hydroxide in boiling ethylene glycol, in a stream of nitrogen. The assumed mechanism of this interesting transformation is given in Scheme II.

Scheme II



In the first step the Beckmann fragmentation reaction, catalyzed by OH^-, is supposed, followed by two equally possible reaction pathways: aa′ and bb′, in which, regardless of sequence, reduction of the aldehyde into the alcohol and the hydrolysis of the nitrile into the carboxylic acid take place. There exists another possibility, cc′, including an intermediary formation of the iminolactone C, which in turn, by hydrolysis, gives the lactone **6**. This transformation (**3** → **6**) presents a novel and simple procedure for a direct preparation of steroidal lactones of the type **6** from the easily accessible compounds of the type **3**.

The Beckmann fragmentation reaction under basic conditions is quite unusual and we could not find any similar example in the chemical literature. The assumed reduction of an aldehyde into an alcohol, by means of ethylene glycol in the presence of OH^-, presents an interesting case which should be studied further.

Experimental Section

The melting points are uncorrected. The IR spectra were recorded in KBr pellets with a Perkin-Elmer infrared spectrophotometer, Model 457, and NMR spectra with a Varian 60A spectrometer with tetramethylsilane as the internal standard. Chemical shifts (δ) are expressed in parts per million. Mass spectra were recorded with a Varian CH-5 spectrometer.

3-Methoxyestra-1,3,5(10)-triene-16,17-dione 16-Oxime (2). Metallic potassium (1 g, 25.5 mmol) was dissolved in *tert*-butyl alcohol (40 mL), 3-methoxyestra-1,3,5(10)-trien-17-one (**1**, 2 g, 7.0 mmol) was added, and the mixture stirred for 1 h at room temperature. Isoamyl nitrite (2 mL, 14.9 mmol) was then introduced and the stirring continued for 3 h, and for another 2 h at 50 °C. The mixture was left overnight, and then diluted with 1% aqueous KOH (200 mL) and extracted with $CHCl_3$. The aqueous layer was acidified with 2 N HCl to pH 5, and the pale yellow crystals of 3-methoxyestra-1,3,5(10)-triene-16,17-dione 16-oxime (**2**) were collected, washed with water, and dried (1.29 g, 59% yield, mp 176–180 °C dec). The crude **2** was recrystallized from ethyl acetate, giving white crystals: 0.60 g; 27% yield; mp 212–214 °C dec; IR 3500–3300, 1740, 1630, 1605, 1500, 1260, and 945 cm^{-1}; mass spectrum *m/e* 313 (71, M^+), 297 (63), 268 (71), 257 (100), 147 (52), and 121 (54).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.98; H, 7.41; N, 4.36.

3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one Oxime (3). To an aqueous methanolic solution (30 mL of H_2O and 130 mL of methanol) of 3-methoxyestra-1,3,5(10)-triene-16,17-dione 16-oxime (**2**, 1 g, 3.19 mmol), $NaBH_4$ (1 g, 26.4 mmol) was added portionwise at room temperature. The solution was then refluxed for 5 min, cooled, and diluted with water (100 mL). The separated crystals were collected, washed thoroughly with 50% aqueous methanol, and dried (0.93 g, 93% yield, mp 203–206 °C dec). Recrystallization from methanol (100 mL) afforded analytically pure 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (**3**): 0.77 g; 77% yield; mp 215 °C dec; IR 3500–3260, 1610, 1500, 1260, and 950 cm^{-1}; NMR (Py-d_5) 1.05 (18 methyl), 3.80 (C-3 methoxy), 4.55 (17α proton, d, J = 2 Hz), 5.50 (two OH groups, m), 6.80 (C-4 proton, d, $J_{2,4}$ = 3 Hz), 6.95 (C-2 proton, quartet, $J_{1,2}$ = 10, $J_{2,4}$ = 3 Hz), and 7.50 (C-1 proton, d, $J_{1,2}$ = 10 Hz); mass spectrum *m/e* 315 (90, M^+), 297 (60), 257 (85), 227 (100), 121 (84), 91 (51), and 29 (55).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.23; H, 8.02; N, 4.45.

3-Methoxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (4). α-Hydroxy oxime **3** (1 g, 3.17 mmol, finely ground and dried for 3 h at 120 °C) and *p*-toluenesulfonyl chloride (1 g, 5.25 mmol) were dissolved in absolute pyridine (20 mL). The reaction mixture was kept at room temperature for 3 h, and then poured in an excess of cold diluted HCl. The separated precipitate of the crude 3-methoxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**4**) was collected, washed with water, and dried (0.94 g; 98% yield, mp 142 °C). Recrystallization from methylene chloride–hexane afforded pure **4**: 0.78 g; 82% yield; mp 158–160 °C; IR 2240, 1715, 1605, 1500, 1260, 1030, and 860 cm^{-1}; NMR ($CDCl_3$) 1.20 (18 methyl), 2.80 (C-15 protons, m), 3.65 (C-3 methoxy), 6.45 (C-4 proton, d, $J_{2,4}$ = 3 Hz), 6.90 (C-2 proton, quartet, $J_{1,2}$ = 10, $J_{2,4}$ = 3 Hz), 7.20 (C-1 proton, d, $J_{1,2}$ = 10 Hz), and 9.40 (C-17 aldehydic proton, s); mass spectrum *m/e* 297 (75, M^+), 257 (100), 121 (68), and 29 (41).

Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 77.10; H, 7.72; N, 4.52.

3-Methoxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (5). 3-Methoxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**4**, 1 g, 3.37 mmol) was dissolved in methanol (60 mL). $NaBH_4$ (1 g, 26.4 mmol) was added portionwise to this solution at room temperature, and after 30 min the reaction mixture was diluted with water (60 mL). The white precipitate was filtered off, washed with water, and dried (0.91 g, 90% yield, mp 90 °C). Recrystallization from methylene chloride–hexane afforded analytically pure **5**: 0.86 g; 86% yield; mp 95 °C; IR 3480, 2255, 1605, 1500, 1260, and 865 cm^{-1}; NMR ($CDCl_3$) 0.92 (18 methyl), 2.80 (C-15 protons, m), 3.35 (C-17 protons, AB system, J_{AB} = 6 Hz), 3.68 (C-3 methoxy), 6.45 (C-4 proton, d, $J_{2,4}$ = 3 Hz), 6.60 (C-2 proton, quartet, $J_{1,2}$ = 10, $J_{2,4}$ = 3 Hz), and 7.08 (C-1 proton, d, $J_{1,2}$ = 10 Hz);[8] mass spectrum *m/e* 299 (58, M^+), 241 (52), 91 (51), 57 (89), 43 (83), 31 (88), and 29 (100).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.19; H, 8.49; N, 4.74.

3-Methoxy-17-oxa-*D*-homoestra-1,3,5(10)-trien-16-one (6) from 5. Through a solution of 3-methoxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**5**, 1 g, 3.34 mmol) in methylene chloride (50 mL), saturated with water, an excess of gaseous HCl was bubbled. The reaction mixture was left overnight at room temperature, and then washed with water (3 × 100 mL) in a separatory funnel. The organic layer was dried and the solvent evaporated in vacuo, affording 0.93 g (93% yield) of the crude **6**, mp 161–162 °C. Recrystallization from methylene chloride–hexane gave analytically pure **6**: 0.70 g; 70% yield; mp 189 °C dec; IR 1720, 1610, 1500, 1260, 1240, 1195, and 1030 cm^{-1}; NMR ($CDCl_3$) 1.02 (18 methyl), 2.80 (C-15 protons, m), 3.85 (C-3 methoxy), 3.95 (C-17 protons, s), 6.55 (C-4 proton, d, $J_{2,4}$ = 3 Hz), 6.75 (C-2 proton, quartet, $J_{1,2}$ = 10, $J_{2,4}$ = 3 Hz), and 7.20 (C-1 proton, d, $J_{1,2}$ = 10 Hz); mass spectrum *m/e* 300 (100, M^+), and 186 (66).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.85; H, 8.01.

3-Methoxy-17-oxa-*D*-homoestra-1,3,5(10)-trien-16-one (6) from 3. To a solution of 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (**3**, 1 g, 3.17 mmol) in ethylene glycol (50 mL), KOH (1 g, 17.8 mmol) was added. The reaction mixture was refluxed for 10 h in a stream of nitrogen; after cooling, the solution was acidified with 2 N HCl and extracted with $CHCl_3$. After drying the extract, $CHCl_3$ was removed in vacuo, affording an oily product, which was further purified by column chromatography on silica gel (100 g, benzene–ethyl acetate, 4:1); the yield of the pure **6** was 0.60 g (63%), mp 185–187 °C dec.

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Registry No.—**1**, 1624-62-0; **2**, 61949-13-1; **3**, 61949-14-2; **4**, 59642-11-4; **5**, 61886-13-3; **6**, 61949-15-3.

References and Notes

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(2) J. K. Paisley and L. Weiler, *Tetrahedron Lett.*, 261 (1972).
(3) J. S. Baran, *J. Med. Chem.*, **10**, 1039 (1967).
(4) F. Litvan and R. Robinson, *J. Chem. Soc.*, 1997 (1938).
(5) In the mass spectrum of **2** there was a noticeable M − 16 peak, characteristic for α-hydroxyimino ketone function; see D. Goldsmith, D. Becher, S. Sample, and C. Djerassi, *Tetrahedron, Suppl.*, **7**, 145 (1966).
(6) We noticed a characteristic fragmentation pattern of **3** under the conditions of mass spectrometry, which includes an intensive M − 18 peak, showing that under given conditions a Beckmann fission takes place readily, similar to our previous findings.[1]
(7) The lactone **6** has been prepared by Huffman et al., starting from 3-methoxy-17α-hydroxyestra-1,3,5(10)-trien-16-one in two distinct steps; mp of their sample was 176–177 °C. See M. N. Huffman, M. H. Lott, and J. Ashmore *J. Am. Chem. Soc.*, **70**, 4268 (1948).
(8) The appearance of the AB quartet in the NMR spectrum at about 3.35 ppm (2 H), corresponding to C_{17} protons, indicates a probable intramolecular hydrogen bond between the C_{17} hydroxyl group and the C_{16} nitrile function, i.e., a prevented rotation about the C_{13}–C_{17} bond; the same conclusion could be made from a shifted position of –C≡N stretching vibration at 2255 cm^{-1}, in contrast to the position of the cyano group (2240 cm^{-1}) in the IR spectrum of **4**.

Synthesis of 11-Deoxy-13,14-dihydro-8-azaprostaglandin E_1

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The synthesis of 11-deoxy-13,14-dihydro-8-azaprostaglandin E_1 is reported. The synthetic sequence to 11-deoxy-8-aza-13,14-dihydroprostaglandin E_1 involves the construction of a 5-substituted 2-pyrrolidinone containing an intact C_8 side chain.

Recently Bolliger and Muchowski[2] and DeKoning and co-workers[3] reported the synthesis of 11-deoxy-8-azaprostaglandin E_1. In this paper we would like to communicate our synthesis of 11-deoxy-8-aza-13,14-dihydroprostaglandin E_1 (**9**). The synthetic approach to **9** involves the construction of a 5-substituted 2-pyrrolidinone nucleus containing an intact C_8 side chain as outlined below (Scheme I).

Reaction of *n*-hexanoyl chloride (**1**) with ethylene[4] in the presence of $AlCl_3$ in chloroform at 0°C yielded a 42:58 mixture of 1-chloro-3-octanone (**2**) and 3-oxo-1-octene (**3**) as determined by NMR. The mixture of chloro ketone **2** and vinyl ketone **3** was reacted with excess nitromethane in the presence of sodium methoxide in methanol at room temperature to afford 1-nitro-4-nonanone (**4**) in 42% yield. Ketalization of **4** with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid gave 1-nitro-4,4-ethylenedioxononane (**5**, 89%). Reaction of **5** with methyl acrylate[5] in the presence of Triton B at 90–95°C for 5 h and subsequent chromatography on silica gel G and elution with an ether–hexane solution afforded methyl 4-nitro-7,7-ethylenedioxydodecanoate in 45% yield.

Catalytic reduction of 4-nitro-7,7-ethylenedioxydodecanoate in the presence of R(Ni)W-4[6] in ethanol with hydrogen at 47 psi yielded a mixture of the ketal lactam **6** and uncyclized ketal amino ester. This mixture was refluxed in benzene for 5 h and chromatography of the crude reaction product on silica gel G afforded the pure ketal lactam **6** in 54% yield.

Reaction of **6** with sodium hydride in refluxing THF and subsequent alkylation with methyl 7-bromoheptanoate followed by chromatography on silica gel G gave the lactam ketal ester **7** (59%).

Hydrolysis of the lactam ketal ester **7** with an aqueous methanolic sodium hydroxide solution at room temperature followed by acidification and concomitant hydrolysis of the ketal moiety with an aqueous HCl–THF solution at room temperature and subsequent chromatography on silica gel G yielded the keto acid **8** in 56% yield. Reduction of the keto acid **8** with sodium borohydride[7] in an aqueous sodium bicarbonate solution between 0 and 20°C afforded a C_{15} epimeric mixture of the acid alcohols **9** in 76% yield. An attempt to separate the epimeric acid alcohols **9** by preparative TLC using analytical silica gel plates and employing different solvent systems failed. In each case the alcohols appeared as one elongated spot. The epimeric mixture of acid alcohols[8] **9** was found to be active in inhibiting gastric acid secretion.

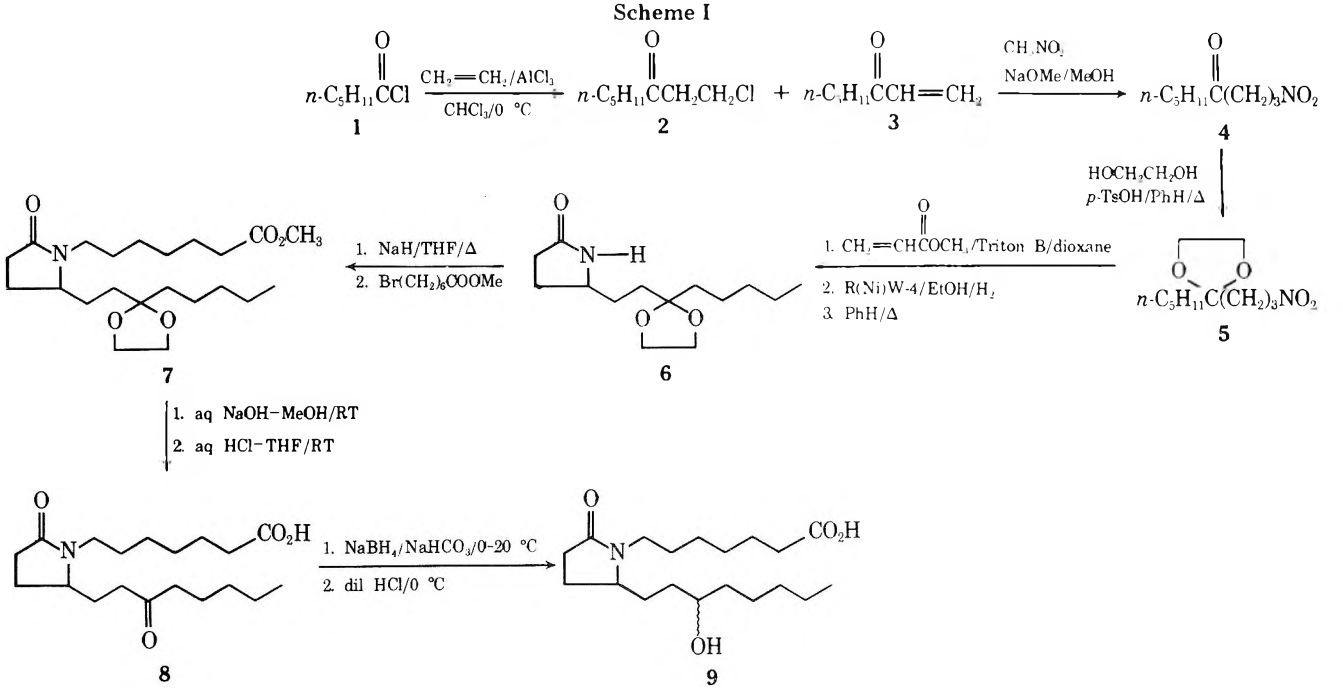
Experimental Section

1-Chloro-3-octanone (2) and 3-Oxo-1-octene (3). Chloroform (400 mL) was placed in a 1-L three-neck flask fitted with an addition funnel, mechanical stirrer, and inlet tube. A mercury bubbler was connected to the addition funnel and the chloroform was deaerated with nitrogen. Aluminum chloride (94.5 g, 0.71 mol) was added all at once to the chloroform under nitrogen. To this heterogeneous mixture, hexanoyl chloride (96 g, 0.71 mol) was added over a 5-min period. A homogeneous solution was obtained after addition of the hexanoyl chloride.

The reaction mixture was cooled to 0 °C with an ice bath and ethylene was bubbled into the reaction mixture at a rate so that excess ethylene was not escaping from the reaction vessel. Ethylene was allowed to bubble through the reaction mixture at 0 °C for 5.5 h, and the reaction mixture was allowed to stand overnight at 0 °C.

The reaction mixture was poured into a cold aqueous HCl solution (10% HCl, 700 mL, and 700 mL of ice) and extracted with chloroform

Scheme I



(500 mL). The chloroform layer was washed with a 10% HCl solution (2 × 700 mL), water (1 L), a 10% $NaHCO_3$ solution (700 mL), 5% $NaHCO_3$ solution (500 mL), and water.

The chloroform layer was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving a yellow oil. Distillation of the oil afforded 82.1 g of a mixture of 1-chloro-3-octanone (**2**) and 3-oxo-1-octene (**3**): bp 52–65 °C (12 mm); NMR (CCl_4) δ 3.77 ($ClCH_2$, t), 2.85 ($ClCH_2CH_2CO$–, t), 2.42 ($ClCH_2CH_2COCH_2$– and CH_2=$CHCOCH_2$–, t), 0.96 (t), 6.18–6.38 (m), 5.60–5.90 (m); IR (neat) 1780 and 1695 cm^{-1}. NMR analysis indicated that the mixture consisted of 42% of **2** and 58% of **3**. The reaction mixture was utilized directly in the synthesis of **4**.

1-Nitro-4-nonanone (4). Methanol (1 L) was placed in a 3-L three-neck flask fitted with a mechanical stirrer, water condenser, and nitrogen inlet tube, and was deaerated with nitrogen. Sodium methylate (54.0 g, 1.0 mol) was added under nitrogen and the resulting solution was allowed to cool to room temperature.

To this solution, nitromethane (335 g, 5.5 mol) was added all at once under nitrogen and the reaction mixture was stirred for 10 min. During this time period, a turbid solution resulted. A mixture of 1-chloro-3-octanone (**2**) and 3-oxo-1-octene (**3**) (75.1 g) was added all at once to the turbid solution under nitrogen. After addition, the reaction mixture became warm and a yellow color resulted. The reaction mixture was stirred for 14.5 h at room temperature. During the stirring period, the reaction mixture developed a deep orange juice color.

Ice-cold 10% HCl (800 mL) was added to the reaction mixture and the resulting solution was divided into four equal portions. To each portion, 700 mL of H_2O was added and the resulting mixture was extracted twice with 350 mL of chloroform. The chloroform extracts were combined and washed with water, and dried over anhydrous magnesium sulfate. Concentration of the chloroform solution and distillation of the yellow oil afforded 42.5 g (42%) of 1-nitro-4-nonanone (**4**): bp 108 °C (0.45 mm); NMR (CCl_4) δ 4.42 (t, 2 H), 2.06–2.62 (m, 6 H), 1.14–1.77 (m, 6 H), 0.97 (t, 3 H); IR (neat) 1715, 1550, and 1375 cm^{-1}.

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.54; H, 9.24; N, 7.28.

1-Nitro-4,4-ethylenedioxynonane (5). A mixture of 1-nitro-4-nonanone (**4**, 135.0 g, 0.722 mol), ethylene glycol (216 g, 3.48 mol), *p*-toluenesulfonic acid (2.0 g, 0.011 mol), and 700 mL of benzene was placed in a 2-L flask fitted with a Dean-Stark trap, condenser, and drying tube. The resulting mixture was refluxed for 24 h. During this period of time 18 mL of water was collected. The reaction mixture was allowed to cool to room temperature and was poured into a 2% $NaHCO_3$ solution (1 L). Ethyl ether (200 mL) was added and the organic layer was separated and washed with two 1-L portions of a 2% $NaHCO_3$ solution and twice with 1 L of water. The organic layer was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving 186 g of an oil. Distillation of the oil afforded 148.7 g (89%) of 1-nitro-4,4-ethylenedioxynonane (**5**): bp 110–117 °C (0.2 mm); NMR (CCl_4) δ 4.50 (t, 2 H), 3.90 (s, 4 H), 1.20–2.80 (m, 12 H), and 0.93 (t, 3 H); IR (neat) 1560 and 1375 cm^{-1}.

Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.24; H, 9.25; N, 6.00.

8-[5′-Oxo-(2′-pyrrolidinyl)]-6,6-ethylenedioxyoctane (6). A solution of 1-nitro-4,4-ethylenedioxynonane (**5**, 144.0 g, 0.623 mol) dissolved in 600 mL of dioxane was placed in a 1-L three-neck flask fitted with an addition funnel, condenser, and nitrogen inlet tube. The apparatus was connected to a mercury bubbler and the solution was deaerated with nitrogen. A 40% solution of Triton B (0.0623 mol, 26.2 mL) was added under nitrogen and the resulting solution was stirred for 10 min. During this time period the reaction mixture became yellow-orange. Methyl acrylate (58.9 g, 0.685 mol) was added all at once under nitrogen and the resulting mixture was stirred at 90–95 °C for 5 h.

The reaction mixture was cooled to room temperature and poured into a 3% oxalic acid solution (600 mL). Water (1 L) was added and the resulting mixture was extracted with three 800-mL portions of chloroform. The chloroform extracts were combined and washed with water, twice with 500 mL of a 1.5% sodium bicarbonate solution, and then water. The chloroform solution was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving 204 g of a dark yellow oil. Distillation of the oil afforded 121 g (61%) of crude methyl 4-nitro-7,7-ethylenedioxydodecanoate, bp 155–185 °C (0.6–1.0 mm). During the distillation some decomposition was observed.

The crude methyl 4-nitro-7,7-ethylenedioxydodecanoate was chromatographed using silica gel G and elution with an ether–hexane solution afforded 89.1 g (45%) of pure 4-nitro-7,7-ethylenedioxydodecanoate: NMR (CCl_4) δ 4.50 (m, 1 H), 3.88 (s, 4 H), 3.66 (s, 3 H), 1.10–2.50 (m, 16 H), and 0.90 (t, 3 H); IR (neat) 1745, 1555, and 1375 cm^{-1}.

Methyl 4-nitro-7,7-ethylenedioxydodecanoate (21.5 g, 0.068 mol) was dissolved in 150 mL of absolute ethanol and placed in a Parr shaker bottle. Raney nickel W-4 (approximately 20 g) was added and the resulting mixture was reduced at 47 psi on a Parr shaker. Hydrogen (13 psi) was taken up over a 43.5-h period. The reaction mixture was filtered through Celite 545 with suction and the residue was washed with chloroform. The filtrate was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, affording 17.4 g of an oil.

The oil (17.4 g) was dissolved in 75 mL of benzene and was refluxed for 5 h. The reaction mixture was allowed to cool to room temperature and the benzene solution was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving 17 g of an oil.

The oil was chromatographed on silica gel G and elution with chloroform and methanol–chloroform solutions afforded 13 g of an oil. The oil was dissolved in ether. The ether solution was extracted with a dilute solution of oxalic acid and then washed with a 1.5% $NaHCO_3$ solution and water. The ether layer was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving 9.4 g (54%) of the lactam ketal **6**: NMR (CCl_4) δ 8.53 (s, 1 H), 3.84 (s, 4 H), 3.50 (m, 1 H), 1.10–2.50 (m, 16 H), and 0.90 (t, 3 H); IR (neat) 1680 and 3220 cm^{-1}.

Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.47; H, 9.82; N, 5.39.

Methyl 8-Aza-9-oxo-15,15-ethylenedioxyprostanoate (7). A 300-mL three-neck flask fitted with a nitrogen inlet tube, condenser, and glass stopper was deaerated with nitrogen. A 50% sodium hydride–mineral oil suspension (1.3 g, 0.027 mol) and dry THF (130 mL) were placed in the flask under nitrogen. A solution of the lactam ketal **6** (6.2 g, 0.024 mol) dissolved in 20 mL of THF was added all at once under nitrogen and the resulting mixture was refluxed for 4.5 h. A solution of methyl 7-bromoheptanoate (6.3 g, 0.028 mol) dissolved in 10 mL of THF was then added all at once under nitrogen and the reaction mixture was refluxed for 18.5 h.

The reaction mixture was cooled to room temperature and poured into 400 mL of water. The resulting milky-white suspension was extracted with five 200-mL portions of chloroform. The chloroform extracts were combined and dried over anhydrous magnesium sulfate. Concentration of the chloroform solution afforded 10.7 g of an oil. Chromatography of the oil using silica gel G and elution with ether–hexane solutions afforded 5.7 g (60%) of the lactam ketal ester **7**: NMR (CCl_4) δ 3.88 (s, 4 H), 3.60 (s, 3 H), 3.15–3.58 [m, 1 H (–NCH)], 2.55–3.15 [m, 2 H (>$NCCH_2$–)], 2.18–2.50 [m, 4 H (–CH_2–C(=O)O and –CH_2C(=O)N<)], 1.1–2.10 (m, 24 H), and 0.90 (t, 3 H); IR (neat) 1740 and 1690 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_5$: C, 66.47; H, 9.89; N, 3.52. Found: C, 66.14; H, 9.83; N, 3.23.

8-Aza-13,14-dihydro-9,9-dioxoprostanoic Acid (8). The lactam ketal ester **7** (2.5 g, 0.0063 mol) was dissolved in an aqueous methanolic sodium hydroxide solution [NaOH (284 mg, 0.0071 mol), 24 mL of MeOH, and 10 mL of H_2O] and stirred at room temperature for 22 h.

The reaction mixture was poured into 150 mL of H_2O and extracted with an ether–chloroform solution. The ether–chloroform extracts contained a negligible amount of ester.

The aqueous layer was acidified and extracted with chloroform. The chloroform extracts were combined and dried over anhydrous magnesium sulfate and filtered, and concentration of the chloroform solution on a rotary evaporator afforded 2.4 g of an oil.

The oil (2.4 g) was dissolved in an aqueous HCl–THF solution (25 mL of THF and 25 mL of 10% HCl) and stirred at room temperature for 5 h. The reaction mixture was poured into H_2O and extracted with 2 × 125 mL of chloroform. The combined chloroform extracts were washed with H_2O, dried, and filtered, and concentration on a rotary evaporator afforded 2.0 g of the crude lactam keto acid **8**. Crude **8** was chromatographed using silica gel G and elution with a methanol–ether solution afforded 1.2 g (56%) of pure **8**: NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.10–2.04 (m), 2.10–2.55 (m) [26 H], 2.60–3.10 (m) and 3.11–3.90 (m) [3 H], and 7.60 (s, broad 1 H); on addition of D_2O the resonance peak at δ 7.6 disappeared; IR (neat) 1640 and 1750–1700 cm^{-1} (shoulder).

Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 66.87; H, 9.65; N, 4.08.

15α- and 15β-11-Deoxy-8-aza-13,14-dihydroprostaglandin E_1 (9). The lactam keto acid **8** (4.0 g, 0.012 mol) was dissolved in a 5% $NaHCO_3$ solution (60 mL) and cooled to 0 °C with an ice bath. $NaBH_4$ (760 mg, 0.02 mol) was added in small portions over a 1.5-h period. The reaction mixture was allowed to warm to 20 °C over a 1.25-h pe-

riod, and then cooled to 0 °C. At 0 °C the reaction mixture was acidified with 10% HCl and extracted immediately with 2 × 200 mL of chloroform. The chloroform extracts were combined, washed with H_2O, and dried over anhydrous magnesium sulfate and concentration of the chloroform solution on a rotary evaporator yielded 5.0 g of an oil. The oil was chromatographed using silica gel G and elution with a methanol–ether solution afforded 3.1 g (76%) of an epimeric mixture of 15α- and 15β-11-deoxy-8-aza-13,14-dihydroprostaglandin E_1 (**9**): NMR ($CDCl_3$) δ 0.91 (t), 1.05–1.93 (m) [23 H], 1.95–2.63 (m, 6 H), 2.65–3.95 (m, 4 H), and 7.10 [s (broad, CO_2H and OH), 2 H]; IR (neat) 1725 and 1665 cm^{-1}.

Anal. Calcd for $C_{19}H_{35}NO_4$: C, 66.82; H, 10.33; N, 4.10. Found: C, 66.84; H, 10.11; N, 4.03.

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Registry No.—**1**, 142-61-0; **2**, 62005-96-3; **3**, 4312-99-6; **4**, 62005-97-4; **5**, 62005-98-5; **6**, 62005-99-6; **7**, 62006-00-2; **8**, 62006-01-3; 15α-**9**, 62006-02-4; 15β-**9**, 62006-03-5; nitromethane, 75-52-5; ethylene glycol, 107-21-1; methyl 4-nitro-7,7-ethylenedioxydodecanoate, 62006-04-6; methyl 7-bromoheptanoate, 54049-24-0.

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Synthesis of L-Prolyl-L-leucylglycine Alkylamides[1]

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The synthesis of H-Pro-Leu-Gly-$NHCH_3$ and related alkylamido derivatives by a new general approach is described. The preferred conformation of H-Pro-Leu-Gly-$NHCH_3$ is assumed to be identical with that of H-Pro-Leu-Gly-NH_2. Also α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate β-methylamide and α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-glutamate β-methylamide were synthesized.

The C-terminal tripeptide of oxytocin, H-Pro-Leu-Gly-NH_2, has been suggested to be the natural factor inhibiting the release of melanocyte-stimulating hormone (MRIF). Indeed there exists an enzymic system in rat hypothalamic extracts which can form MRIF activity on using oxytocin as a substrate.[2,3] On the other hand, the replacement of a carboxamide proton in position 9 of oxytocin by a methyl group (a) eliminates the agonistic properties of the hormone, but not its binding capacity, and (b) exerts potent inhibitory oxytocin-induced avian vasodepressor response.[4] In view of these considerations, we thought it of interest to synthesize H-Pro-Leu-Gly-$NHCH_3$ and its analogues with enhanced lipophilicity (Table II) as possible agents of potent and selective clinical value. This paper provides experimental details on the synthesis of certain L-prolyl-L-leucylglycine alkylamides by a new general approach and some information concerning the conformation of H-Pro-Leu-Gly-$NHCH_3$.

Results and Discussion

Firstly, the tripeptide derivative, Z-Pro-Leu-Gly-$NHCH_3$, was synthesized in a stepwise manner using *N*-Trt-glycine[5] as the starting material. This compound was condensed via the mixed-anhydride method[6] with methyl-, ethyl-, and propylamine, respectively, yielding the corresponding *N*-alkylamido derivatives in good yields (Table I). Since methylamide has a very low boiling point, its hydrochloride salt, dissolved in tetrahydrofuran–water (6:4), was used alternatively. Liberation of the amine in situ was brought about by addition of triethylamine. In fact the latter modification enabled us also to prepare α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate β-methylamide and its L-glutamic analogue in satisfactory yield. On the contrary, prolonged reaction time of methylamine under anhydrous conditions facilitated the formation of the cyclic aspartoyl methylimide derivative. Its structure is based on elemental analysis and spectral data (see Experimental Section). As expected the ^1H NMR spectrum in Me_2SO-d_6 lacks aromatic protons. Since the NCH_3 protons are located under the large $(CH_3)_2SO$ peak, this solvent was replaced with CD_3OD and the NCH_3 protons were shown then clearly as a singlet in the region of δ 2.7. In contrast, the ^1H NMR spectrum of the noncyclic product (a) displays a doublet at δ 2.7 due to coupling with the amide proton and a singlet at δ 7.35 attributed to the aromatic protons.

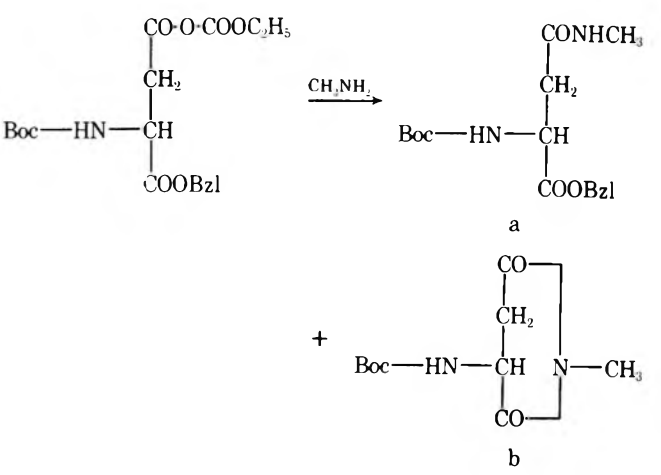


Table I. *N*-Tritylglycine Alkylamides and Deprotected Derivatives

Compd	Formula[a]	Mp, °C	Yield, %
Trt-Gly-NHCH$_2$CH$_3$[b]	$C_{23}H_{24}N_2O$	144–145	70
Trt-Gly-NH(CH$_2$)$_2$-CH$_3$[b]	$C_{24}H_{26}N_2O$	148–150	85
H-Gly-NHCH$_2$CH$_3$[c,d]	$C_{11}H_{18}N_2SO_4$	174–175	85
H-Gly-NH(CH$_2$)$_2$-CH$_3$[c,d]	$C_{12}H_{20}N_2SO_4$	140–141	82

[a] Analytical data were within ±0.4% for C, H, N. [b] Recrystallized from ethyl acetate–petroleum ether. [c] Isolated as the *p*-toluenesulfonate. [d] Recrystallized from ethanol.

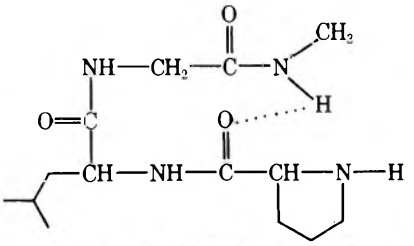
The tendency of aspartic acid amides and esters to imide formation is well known[7]. As the amide nitrogen of (a) becomes more nucleophilic, due to the methyl group, its cyclization to (b) proceeds in analogy to the proposed mechanism by Ondetti et al.[8] more readily.

Detritylation[5] of *N*-Trt-Gly-NHCH$_3$ (I) with *p*-toluenesulfonic acid afforded crystalline glycine methylamide *p-toluenesulfonate* (II). Similarly prepared Z-Gly-NHCH$_3$ was decarbobenzoxylated with HBr/AcOH to give glycine methylamide hydrobromide in high yield. Coupling of II with Z-Leu-OH by the *p*-nitrophenyl ester[9] produced Z-Leu-Gly-NHCH$_3$ (III) in crystalline form. The ^{1}H NMR spectrum shows characteristically a singlet at δ 7.15 for aromatic protons, a broad doublet at δ 0.9 for the methyl groups of the leucine residue, and a sharp doublet at δ 2.65 due to the methyl group coupled to the amide proton of the glycine residue. Compound III after deprotection with catalytic hydrogenolysis provided L-leucylglycine methylamide, which was isolated as the *p*-toluenesulfonate (IV). The latter was condensed in turn with Z-Pro-OH by the mixed-anhydride method[6] to give crystalline Z-Pro-Leu-Gly-NHCH$_3$ (V).

Besides the stepwise synthesis of III and V (procedure A), a more convenient route to these compounds is by condensation of Z-Leu-Gly-OH[10] and Z-Pro-Leu-Gly-OH,[11] respectively, with methylamine hydrochloride as described above (procedure B). Both peptide derivatives, Z-Leu-Gly-NHCH$_3$ and Z-Pro-Leu-Gly-NHCH$_3$, obtained either by procedure A or B had identical melting points and optical values. Analogously, the coupling of Z-Pro-Leu-Gly-OH with ammonium chloride afforded Z-Pro-Leu-Gly-NH$_2$ identical with that prepared by another method.[11]

Finally, the desired H-Pro-Leu-Gly-NHCH$_3$ (VI) was obtained by catalytic deprotection of V and crystallized from ethyl acetate–petroleum ether as needles. Its structure (VI) was confirmed by spectral data. The mass spectrum displays a molecular ion at *m/e* 298 (M^+) corresponding to the molecular formula $C_{14}H_{26}O_3N_4$ (requires *m/e* 298). The ^{1}H NMR spectrum shows a sharp doublet methyl signal at δ 2.75 due to coupling with the glycine amide proton which shows up as a quartet at δ 7.25.

The IR spectrum (CHCl$_3$) displays a strong, broad band at 3340 cm^{-1} and a weak one at 3440 cm^{-1}. It is known that the 3300–3380-cm^{-1} region corresponds to hydrogen-bonded NH groups whereas the presence of NH bands in the 3430–3480-cm^{-1} region is evidence of the presence of free NH groups.[12] In this connection it should be mentioned that unpublished experiments at that time showed that Z-Pro-Leu-Gly-N(CH$_3$)$_2$ and its deprotected derivative show very weak absorption at the region of 3300–3380 cm^{-1}. Provided that secondary amides exist in the trans configuration the above findings suggest that the trans orientation of H-Pro-Leu-Gly-NHCH$_3$ agrees best with a hydrogen bonding between the trans carboxamide proton and the C=O of proline to form a



ten-membered β turn. This is in line with the proposed conformation of H-Pro-Leu-Gly-NH$_2$ by Walter et al.[13]

Experimental Section

Melting points were taken on a Buchi SMP-20 capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Laboratory of Microanalysis of National Hellenic Research Foundation, Athens, Greece. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6MG spectrometer. NMR spectra were obtained with a Hitachi Perkin-Elmer R-24 (60-MHz) spectrometer in CDCl$_3$. Chemical shifts are reported in δ units using tetramethylsilane as the internal standard. Infrared spectra were recorded with a Perkin-Elmer 457 grating infrared spectrophotometer. Thin layer chromatography (TLC) was carried out on silica gel Si F chromatogram sheets with the solvent system I (BAWP), 1-butanol–acetic acid–water–pyridine (30:6:24:20), and the solvent system II (BE), benzene–ethanol (8:2), and visualized by UV, ninhydrin, and chlorine–tolidine reagent.

***N*-Tritylglycine Methylamide.** The following procedure is typical for the preparation of certain tritylglycine alkylamides which are listed in Table I.

To a solution of Trt-Gly-OH (12.98 g, 40 mmol) in 100 mL of THF, cooled to −10 °C, were added triethylamine (4.04 g, 40 mmol) and ethyl chlorocarbonate (4.34 g, 40 mmol). After 3 min a solution of 8.1 g (200% excess) of methylamine hydrochloride in 20 mL of THF–H$_2$O (6:4) was neutralized with 12.12 g of triethylamine and added immediately with vigorous shaking. Half an hour later the solvent was evaporated to dryness and the residue was taken up in CH$_2$Cl$_2$ (100 mL). This solution was washed with 3 × 50 mL of 5% NaHCO$_3$, then with water and dried (Na$_2$SO$_4$). After removal of the solvent, a residue of 10 g (80%) was obtained, mp 187–188 °C. This was recrystallized from ethanol–water (9:3) or ethyl acetate–petroleum ether (9:2) to give 9.4 g (75%) of the desired product,[14] mp 188–189 °C.

Anal. Calcd for $C_{22}H_{22}N_2O$: C, 80.00; H, 6.66; N, 8.48. Found: C, 80.32; H, 6.85; N, 8.17.

Glycine Methylamide *p*-Toluenesulfonate. A mixture of tritylglycine methylamide (3.8 g, 20 mmol) and *p*-toluenesulfonic acid monohydrate (3.8 g, 20 mmol) in 60 mL of ethanol was heated for 5 min under reflux. The solvent was then evaporated to dryness and the solid residue was collected by filtration, repeatedly washed with ether, and finally recrystallized from 2-propanol–ether to give 5 g (96%) of product, mp 180–181 °C.

Anal. Calcd for $C_{10}H_{16}N_2O_4S$: C, 46.15; H, 6.15; N, 10.76. Found: C, 46.18; H, 6.41; N, 10.47.

Carbobenzoxy-L-leucylglycine Methylamide. To a magnetically stirred solution of glycine methylamide *p*-toluenesulfonate (1.93 g, 5 mmol) and *N*-methylmorpholine (0.5 g, 5 mmol) in DMF (12 mL) was added Z-Leu-ONp (1.93 g, 5 mmol). After 24 h the solvent was evaporated in vacuo and the remaining oily residue solidified by addition of water (60 mL) while cooling. The solid product was filtered and washed with 1 N HCl (50 mL), 5% NaHCO$_3$ (50 mL), and water. Crystallization from ethyl acetate–petroleum ether (7:3) gave 1.75 g (75%) of product, mp 124–125 °C, $[\alpha]^{24}_D$ −12.5° (c 1, DMF).

Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.89; H, 7.46; N, 12.53. Found: C, 60.42; H, 7.31; N, 12.24.

L-Leucylglycine Methylamide *p*-Toluenesulfonate. A solution of Z-Leu-Gly-NHCH$_3$ (1.45 g, 5 mmol) in ethanol (50 mL) was subjected to catalytic hydrogenolysis over 250 mg of PdO. The evolution of CO$_2$ ceased after 3 h, the reaction mixture was filtered, and the solvent was evaporated to dryness yielding an oily product (0.86 g) homogeneous to TLC. The oil was then dissolved in dry ether (10 mL) and added *p*-toluenesulfonic acid *monohydrate* (0.96 g). After about 10 min the solvent was evaporated under vacuum and the remaining residue crystallized by addition of THF (10 mL), yield 1.3 g (68%), mp 172–175 °C.

Anal. Calcd for $C_{16}H_{27}N_3O_5S \cdot \frac{1}{2}H_2O$: C, 50.26; H, 7.32; N, 10.99. Found: C, 50.62; H, 6.96; N, 10.69.

Carbobenzoxy-L-prolyl-L-leucylglycine Methylamide. Procedure A. To a solution of Z-Pro-OH (0.78 g, 3.2 mmol) and trieth-

Table II. L-Prolyl-L-leucylglycine Alkylamide Derivatives

Peptide	Formula[a]	$[\alpha]^{24}D$[b]	Mp, °C	Yield, %
Z-Pro-Leu-Gly-$NHCH_2CH_3$[c,d]	$C_{23}H_{34}N_4O_5$	−49.85°	163–165	64
Z-Pro-Leu-Gly-$NHCH_2CH_2CH_3$[c,d]	$C_{24}H_{36}N_4O_5$	−46.2°	110–111	55
H-Pro-Leu-Gly-$NHCH_2CH_3$[d]	$C_{15}H_{28}N_4O_3$	−41.4°	101–102	79
H-Pro-Leu-Gly-$NHCH_2CH_2CH_3$[d]	$C_{16}H_{30}N_4O_3$	−40.2°	112–113	84

[a] Analytical data were within ±0.4% for C, H, N. [b] As 1% solution in DMF. [c] By procedure B. [d] Recrystallized from ethyl acetate–petroleum ether.

ylamine (0.32 g, mmol) in THF (10 mL), cooled to −10 °C, was added ethyl chlorocarbonate (0.35 g, 3.2 mmol). After 3 min a mixture of L-leucylglycine methylamide *p*-toluenesulfonate (1.2 g, 3.2 mmol), *N*-methylmorpholine (0.44 mL), and water (1 mL) in THF (10 mL) was added with shaking. The reaction mixture was permitted to remain for 1 h at room temperature. Then the solvent was evaporated under vacuum and the residue was taken up in CH_2Cl_2, washed with 5% $NaHCO_3$ and H_2O, and dried (Na_2SO_4). The solvent was removed leaving an oil, which was crystallized (needles) from ethyl acetate–petroleum ether: yield 0.95 g (75%); mp 155–156 °C; $[\alpha]^{24}D$ −52.6° (*c* 1, DMF).

Procedure B. To a chilled solution of Z-Pro-Leu-Gly-OH (4.19 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in THF (20 mL) was added ethyl chlorocarbonate (1.1 g, 10 mmol). After 3 min a solution of methylamine hydrochloride (2.02 g, 30 mmol) in 10 mL of THF–H_2O (6:4) was neutralized with triethylamine (3.03 g, 30 mmol) and mixed immediately with the anhydride. After 5 min the solvent was evaporated under vacuum and residue was taken up in CH_2Cl_2 and treated as described above: yield 2.76 g (64%); mp 155–156 °C; $[\alpha]^{24}D$ −52.2° (c 1, DMF); IR (KBr) 3320, 3280, 1690, 1660, 1560 cm^{-1}; NMR ($CDCl_3$) δ 0.9 [br d, $(CH_3)_2C$], 1.6–2.3 (br signal, 9 H, 3 CH_2, $CHCH_2$), 2.7 (d, J = 6 Hz, 3 H, NCH_3), 3.5 (poorly resolved triplet, 1 H, α-CHPro), 3.8 (d, J = 6 Hz, 2 H, α-CH_2Gly, collapsed to a singlet on exchange with D_2O), 4.25 (br signal, 1 H, α-CHLeu), 5 (s, 2 H, $ArCH_2$), 7.2 (s, 5 H, C_6H_5), 7–7.8 (br signal, 3 H, 3 CONH, D_2O exchangeable); mass spectrum *m/e* 432 (molecular ion), 417, 402, 401, 389, 375, 344, 343, 317.

Anal. Calcd for $C_{22}H_{32}N_4O_5$: C, 61.11; H, 7.40; N, 12.96. Found: C, 60.76; H, 7.18; N, 12.63.

L-Prolyl-L-leucylglycine Methylamide. A solution of Z-Pro-Leu-Gly-$NHCH_3$ (0.71 g, 1.6 mmol) in ethanol (50 mL) was hydrogenolyzed over 100 mg of PdO and the resulting oily product crystallized (needles) from ethyl acetate–petroleum ether: yield 250 mg (58%); mp 117–118 °C; $[\alpha]^{24}D$ −45.4° (*c* 1, DMF); IR (KBr) 3290, 2950, 1650–1630, 1560–1540 cm^{-1}; NMR ($CDCl_3$) δ 0.9 [br d, 6 H, $(CH_3)_2C$], 1.5–2.2 (br, 9 H, 3 CH_2, $CHCH_2$), 2.75 (d, J = 6 Hz, 3 H, CH_3), 3.6–3.9 (br s, 3 H, α-CHPro, α-CH_2Gly), 4.3 (poorly resolved signal, 1 H, α-CHLeu, on exchange with D_2O becomes apparent triplet), 7.25 (q, J = 6 Hz, 1 H, $CONHCH_3$), 7.75 (br t, 1 H, α-CH_2GlyNH), 8.1 (br d, J ~7 Hz, 1 H, α-CHLeuNH); mass spectrum *m/e* 298 (molecular ion), 283, 281. 268, 266, 265, 242, 211, 210, 186, 183, 155.

Anal. Calcd for $C_{14}H_{26}N_4O_3$: C, 56.37; H, 8.72; N, 18.79. Found: C, 56.10; H, 8.71; N, 18.76.

Carbobenzoxyglycine Methylamide. This compound was prepared from carbobenzoxyglycine (2.1 g, 10 mmol) by exactly the same procedure described for the tritylglycine analogue, yield 1.44 g (65%), mp 107–108 °C.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.30; N, 12.61. Found: C, 59.10; H, 6.12; N, 12.42.

Glycine Methylamide Hydrobromide. The above product, Z-Gly-$NHCH_3$ (2.22 g, 10 mmol), was stirred for 1 h with 10 mL of 2 N HBr in glacial acetic acid. During this time most of the hydrobromide precipitated. The precipitation was completed by addition of 60 mL of anhydrous ether. The solid material was collected by filtration, repeatedly washed with ether, and finally recrystallized from 2-propanol–ether, yield 1.6 g (95%), mp 126–128 °C.

Anal. Calcd for $C_3H_9N_2OBr$: C, 28.91; H, 7.22; N, 22.48. Found: C, 28.80; H, 7.19; N, 22.40.

α-Benzyl N^{α}-*tert*-Butyloxycarbonyl-L-aspartate β-Methylamide. To a chilled solution of α-benzyl Boc-L-asparate[15] (1.61 g, 5 mmol) and triethylamine (0.5 g, 5 mmol) was added 0.55 g (5 mmol) of ethyl chlorocarbonate. After 2 min a solution of methylamine hydrochloride (1.01 g, 200% excess) and triethylamine (2.1 mL) in 10 mL of THF–H_2O (6:4) was added with vigorous shaking. The reaction mixture remained at room temperature for 2 min and the solvent was evaporated under vacuum. The remaining residue was solidified from ethanol–water (2:10) and cooled for 24 h. Then it was filtered and washed with 5% $NaHCO_3$ and water: yield 1.4 g (40%); mp 108–109 °C; $[\alpha]^{24}D$ −16.1° (c 1, CH_3OH); NMR ($CDCl_3$) δ 1.4 [s, 9 H, $(CH_3)_3C$], 2.7 (br d, 5 H, NCH_3, CH_2), 4.6 (complex m, 1 H, COCHN), 5.15 (s, 2 H, $ArCH_2$), 5.7 (br d, 1 H, OCONH), 6.3 (br signal, 1 H, CONH), 7.35 (s, 5 H, C_6H_5).

Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.71; H, 7.14; N, 8.33. Found: C, 60.45; H, 7.11; N, 8.29.

When dry methylamine (300% excess) was used and the reaction mixture permitted to remain at room temperature for 1 h the main product was found to be the Boc-aspartoylmethylimide derivative (b): yield 66%; mp 195–197 °C; $[\alpha]^{24}D$ +2.9° (c 1, CH_3OH); NMR spectrum of the cyclic product in $(CD_3)_2SO$ does not exhibit absorption for aromatic protons, δ 1.4 [s, 9 H, $(CH_3)_3C$], 4.25 (complex m, 1 H, NCOCHN), 6.65 (br d, 1 H, OCONH).

Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 56.60; H, 7.54; N, 13.20. Found: C, 56.49; H, 7.51; N, 13.10.

α-Benzyl N^{α}-*tert*-Butyloxycarbonyl-L-glutamate-β-methylamide. This compound was prepared in a manner similar to that used in the synthesis of α-benzyl Boc-L-aspartate-β-methylamide: yield 77%; mp 89–90 °C; $[\alpha]^{24}D$ −24.2° (*c* 1, CH_3OH).

Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.71; H, 7.42; N, 8.00. Found: C, 61.20; H, 7.39; N, 7.92.

Carbobenzoxy-L-prolyl-L-leucylglycinamide. Coupling of Z-Pro-Leu-Gly-OH (629 mg, 1.5 mmol) with ammonium chloride (240 mg, 4.5 mmol) was done by the same reactions described above. The solid product resulting from the evaporation of THF was collected by addition of 5% $NaHCO_3$ solution and washed with water. It was dried over P_2O_5 and triturated with ethyl acetate: yield 0.4 g (64%); mp 162–163 °C; $[\alpha]^{24}D$ −74.1° (c 2, 95% C_2H_5OH); reported[11] mp 163–163.5 °C; $[\alpha]^{24}D$ −73.3° (c 2, 95% C_2H_5OH).

Registry No.—*N*-Trityl-Gly methylamide, 62029-66-7; Trt-Gly-OH, 5893-05-0; methylamine HCl, 593-51-1; Gly methylamide *p*-toluenesulfonate, 62029-67-8; carbobenzoxy-L-Leu-Gly methylamide, 62029-68-9; Z-Leu-ONp, 1738-87-0; L-Leu-Gly methylamide *p*-toluenesulfonate, 62029-70-3; Z-L-Pro-L-Leu-Gly methylamide, 62029-71-4; Z-Pro-OH, 1148-11-4; Z-Pro-Leu-Gly-OH, 7801-38-9; L-Pro-L-Leu-Gly-$NHCH_3$, 62029-72-5; Z-Gly-$NHCH_3$, 21855-72-1; Z-Gly-OH, 1138-80-3; Gly-$NHCH_3$ HBr, 62029-73-6; α-benzyl N^{α}-Boc-L-Asp-β-$NHCH_3$, 62029-74-7; α-benzyl Boc-L-Asp, 30925-18-9; Boc-aspartoyl methylimide derivative, 62029-75-8; α-benzyl N^{α}-Boc-L-Glu-$NHCH_3$, 62029-76-9; Z-L-Pro-L-Leu-Gly-NH_2, 14485-80-4; Trt-Gly-$NHCH_2CH_3$, 62029-77-0; Trt-Gly-$NH(CH_2)_2CH_3$, 62029-78-1; H-Gly-$NHCH_2CH_3$ *p*-toluenesulfonate, 62029-80-5; H-Gly-$NH(CH_2)_2CH_3$ *p*-toluenesulfonate, 62029-82-7; Z-Pro-Leu-Gly-$NHCH_2CH_3$, 62029-83-8; Z-Pro-Leu-Gly-$NH(CH_2)_2CH_3$, 62029-84-9; H-Pro-Leu-Gly-$NHCH_2CH_3$, 62029-85-0; H-Pro-Leu-Gly-$NH(CH_2)_2CH_3$, 62029-86-1; ethylamine, 75-04-7; propylamine, 107-10-8.

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A Synthesis of (±)-*trans*-Chrysanthemic Acid

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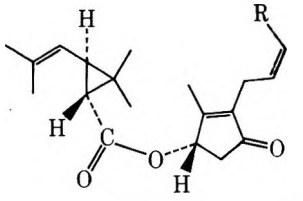
A synthesis of (±)-*trans*-chrysanthemic acid (8) from eucarvone (1) is described. Ozonolysis of 3-methylcar-4-en-2-one (2) in methanol at −78 °C followed by reduction with dimethyl sulfide and treatment with methanolic hydrogen chloride effects cleavage of the alkene, decarbonylation, and formation of acetal 3 in a single synthetic stage.

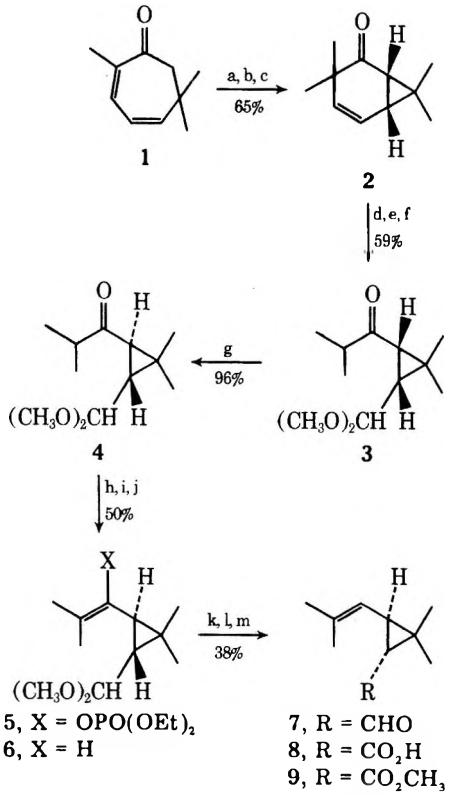
Pyrethrins are a family of naturally occurring insecticides from *Chrysanthemum cineriaefolium* (pyrethrum daises) which exhibit low mammalian toxicity and ready biodegradability.[1] Pyrethrins, such as pyrethrin I, are esters of *trans*-



pyrethrin I, R = CH_3, C_2H_5, or $CH{=}CH_2$

chrysanthemic acid (8) and various rethrolone alcohols.[2] A number of syntheses of *trans*-chrysanthemic acid (8) have been reported[3] presumably because of the usefulness of this substance in the preparation of commercial pyrethrins for pest insect control. We wish to report herein a synthesis of (±)-*trans*-chrysanthemic acid (8) from eucarvone (1).

Eucarvone (1), readily available from carvone,[4] upon alkylation using sodium amide in 1,2-dimethoxyethane (DME) followed by methyl iodide affords a 4:1 mixture of 3-methylcar-4-en-2-one (2) and 2,6,6,7-tetramethylcyclohepta-2,4-dienone, respectively.[5] These two ketones can be separated by preparative gas chromatography;[5] however, while investigating various methods of cleaving the alkenes in this mixture we discovered that the cycloheptadienone could be oxidized at an appreciably faster rate than ketone 2. Therefore, if this mixture of enones is stirred in a homogeneous solution of osmium tetroxide (catalytic amount) and sodium chlorate (2.62 equiv) in aqueous *tert*-butyl alcohol for 18 h,[6] followed by workup and simple bulb-to-bulb distillation, 3-methylcar-4-en-2-one (2) is then obtained pure in 65% overall yield from eucarvone (1). Ozonolysis of ketone 2 in methanol at −78 °C followed by reduction of the ozonide with dimethyl sulfide[7] and treatment with methanolic hydrogen chloride over anhydrous calcium sulfate affords keto acetal 3 in 59% yield. Methanolic hydrogen chloride not only converts the aldehyde group to an acetal, but it also affects decarbonylation of the intermediate nonenolizable β-keto aldehyde. Epimerization of keto acetal 3 using potassium *tert*-butoxide in dry *tert*-butyl alcohol gives keto acetal 4 in 96% yield. Treatment of keto acetal 4 with lithium diisopropylamide (1.1 equiv) in anhydrous tetrahydrofuran (THF) at −78 °C followed by diethyl chlorophosphate (1.1 equiv) at 0–25 °C produces enol phosphate 5 in 62% yield.[8] Reduction of enol phosphate 5 utilizing lithium metal (16 equiv) in anhydrous ethylamine in the presence of dry *tert*-butyl alcohol affords alkene 6 in 81% yield.[9] Hydrolysis of acetal 6 by simply stirring in aqueous acetone for 12 h gives aldehyde 7 in 98% yield. Oxidation of aldehyde 7 with chromium trioxide in wet pyridine for 78 h according to the procedure of Raphael and co-workers[3] produces (±)-*trans*-chrysanthemic acid (8) in 42% yield.[3] Other



a, $NaNH_2$, DME; b, CH_3I; c, OsO_4 cat., $NaClO_3$, H_2O, *t*-BuOH; d, O_3, CH_3OH, −78°C; e, $(CH_3)_2S$; f, CH_3OH, HCl cat., $CaSO_4$; g, KO-*t*-Bu, *t*-BuOH; h, $LiN(i\text{-}Pr)_2$, THF; i, $(EtO)_2POCl$; j, Li, $EtNH_2$, *t*-BuOH; k, acetone, H_2O; l, CrO_3, pyridine, H_2O; m, CH_2N_2, Et_2O.

oxidizing agents were tried including Jones reagent[10] and silver oxide;[12] however, these latter methods proved to be less efficient than chromium trioxide in wet pyridine. Synthetic *trans*-chrysanthemic acid (8) was esterified to (±)-methyl

trans-crysanthemate (**9**) in 92% yield with ethereal diazomethane. Both acid **8** and ester **9** were found to be identical with respect to IR, NMR, TLC, and GLC with authentic samples obtained by epimerization (KO-*t*-Bu, *t*-BuOH), saponification (KOH, H_2O, EtOH), and esterification (CH_2N_2, Et_2O) of ethyl chrysanthemate (Aldrich 12,819-8).

Experimental Section

Melting points were determined on a Nalge No. 500 and/or Büchi melting point apparatus and are uncorrected. All boiling points are uncorrected. Analyses were performed by P.C.R. Laboratories, Inc., Gainsville, Fla., and Spang Microanalytical Laboratory, Ann Arbor, Mich. Analytical gas phase chromatography (GLC) was performed using the following types of columns and flow rates: (a) 6 ft, stainless steel, 0.125 in. column, packed with 3% SE-30 on Varaport 30, 100/120 mesh (Varian); (b) 6 ft, stainless steel, 0.125 in. column, packed with 5% FFAP on Varaport 30, 80/100 mesh (Varian); (c) 6-ft, stainless steel, 0.125 in. column, packed with 5% OV-17 on Varaport 30, 80/100 mesh (Varian); (d) 6 ft, stainless steel, 0.125 in. column, packed with 20% OV-101 on Chromosorb G, 80/100; (e) 6 ft, stainless steel, 0.125 in. column, packed with 5% SE-30 on Chromosorb W, 60/80 mesh; (f) 5 ft, stainless steel, 0.125 in. column, packed with 1.5% OV-101 on Chromosorb G, 100/120 mesh, all columns with a flow rate 15 mL/min at ambient temperature. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer. High-resolution mass spectra (HRMS) were obtained on a CEC Model 21-110-B spectrometer under the supervision of Dr. R. Grigsby, Department of Chemistry, Texas A & M University, College Station, Texas. Medium-resolution mass spectra (MRMS) were obtained on a Perkin-Elmer RMU-6H. Finally, for all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120 °C for several hours, then allowed to cool in an atmosphere of dry nitrogen using an apparatus designed by Johnson and Schneider.[10] The term "petroleum ether" refers to Baker "Analyzed Reagent", bp 30–60 °C. The general workup procedure was as follows: the aqueous layer was extracted with ether (three times), and the combined ethereal extracts were washed with water (four times) and saturated sodium chloride solution (once), and then dried (Na_2SO_4), filtered (through Na_2SO_4 or $MgSO_4$), and concentrated in vacuo.

3-Methylcar-4-en-2-one (2).[4,5] Ketone **2** was prepared according to the procedures in ref 4 and 5 starting with eucarvone (9.90 g, 65.9 mmol) and substituing 1,2-dimethoxyethane for 1,4-dioxane as the solvent. Distillation of the crude product gave 9.95 g (92%) of a pale yellow mixture of 3-methylcar-4-en-2-one (**2**) and 2,6,6,7-tetramethylcyclohepta-2,4-dienone in a 4:1 ratio, respectively, by GLC analysis on column a (column temperature 115 °C), retention times 6.8 and 8.9 min, respectively, bp 82–84 °C (0.8 mm) [lit. 86–90 °C (12 mm)].[3] The cycloheptadienone impurity was removed by the following procedure.[6] A solution of the distilled mixture (10.0 g, 60.9 mmol), water (400 mL), *tert*-butyl alcohol (200 mL), sodium chlorate (34.20 g, 159.8 mmol), and a catalytic amount of osmium tetroxide (0.005 g/mL, 4 mL) was allowed to stir at room temperature. The selective cleavage of the cycloheptadienone impurity was monitored by GLC analysis on column a (column temperature 115 °C). After 18 h the resulting pale yellow solution was taken up in an equal volume of water (600 mL) and extracted with dichloromethane (6 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL) and saturated sodium chloride solution (150 mL), and then dried ($MgSO_4$) and concentrated in vacuo to yield 9.84 g of a dark yellow liquid. Distillation gave 7.04 g (70.4%) of pure 3-methylcar-4-en-2-one (**2**): bp 66–70 °C (6 mm) [lit. 70 °C (5 mm)];[3] IR (film) 1695 (CO), 3020, and 995 cm^{-1} (cyclopropyl); NMR (CCl_4) δ 5.74 (2 q, 5-H) as the X part of an ABX system, $J_{4,5}$ = 10 Hz), 5.46 (d, 4-H), 1.66 (m, 2-H, 1- and 6-H as the AB parts of an ABX system, $J_{1,6}$ = 7, $J_{5,6}$ = 4, $J_{1,5}$ = 1 Hz), 1.26, 1.06, 1.03, and 0.95 ppm (4 s, 3,3-7, and 7-CH_3); GLC analysis on column a (column temperature 80 °C, retention time 6.8 min) and spectroscopic evidence show ketone **2** to have less than 0.4% impurity.

(±)-*cis*-3-Isobutyryl-2,2-dimethylcyclopropanecarboxyaldehyde Dimethyl Acetal (3).[7] Ozone was bubbled through a solution of ketone **2** (6.34 g, 38.7 mmol) in absolute methanol (150 mL) at −78 °C for 35 min. Nitrogen was bubbled through the blue purple solution for 15 min to remove any excess ozone. The solution was transferred to a 1-L round-bottomed flask, stirred, and allowed to warm to room temperature while methyl sulfide (2 equiv or until it gave a negative potassium starch–iodide test) was added. This reaction mixture was concentrated in vacuo to approximately one-third its original volume and a catalytic amount of methanolic hydrogen chloride was added (1 mL) with a few crystals of anhydrous calcium sulfate (white Drierite, 8 mesh), then allowed to stand in a refrigerator at 3 °C for 48 h. The solution was diluted with ether (100 mL), shaken with a small amount of solid sodium bicarbonate to remove any traces of acid, washed with water (3 × 40 mL), and then dried (Na_2SO_4, 1 drop of pyridine), filtered (Na_2SO_4), and concentrated in vacuo to give 7.85 g (95%) of a crude product. A portion of the crude product (9.265 g) was chromatographed immediately before use on silica gel (30 g, 70–230 mesh, E. Merck) in a 2.5-cm diameter column. A solution of 30% ether–70% petroleum ether (with a few drops of pyridine) was used to develop the column, taking 15-mL sized fractions. Fractions 12–18 gave 0.211 g (62.5%) of pure keto acetal **3** as a colorless oil: by 40–42 °C (6 mm); IR (film) 1690 (CO), 1370, 1380 (*gem*-CH_3), 3020 (cyclopropyl), 1115, 1090, 1055, and 1020 cm^{-1} (acetal); NMR (CCl_4) δ 4.77 [d, 1, J = 8 Hz, $CH(OCH_3)_2$], 3.28 and 3.23 [2 s, 6, $-CH(OCH_3)_2$], 1.07 (d, 6, J = 7.6 Hz, isopropyl), 1.22 (bs, 6, *gem*-CH_3), and 1.83 ppm (d, 1, J = 8 Hz, –COCH); mass spectrum, HRMS (70 eV) *m/e* (rel intensity) 214 (1), 183 (18), 139 (89), 112 (23), 111 (19), 97 (34), 75 (100), 73 (94), 71 (89), 79 (20), 57 (25), 47 (23), 43 (88), 41 (55), 39 (19), 27 (23).

Anal. Calcd for $C_{12}H_{22}O_3$ ($M^+ - OCH_3$, peak at 214 too weak for high-resolution measurement): 183.139309. Found: 183.138495 (MS), 4.4 ppm error.

(±)-*trans*-3-Isobutyryl-2,2-dimethylcyclopropanecarboxaldehyde Dimethyl Acetal (4). Keto acetal **3** (250 mg, 1.17 mmol) in dry *tert*-butyl alcohol (3 mL) was added to a solution of potassium *tert*-butoxide (26.2 mg, 0.233 mmol) in dry *tert*-butyl alcohol (10 mL, freshly distilled from calcium hydrid)). The resulting light yellow solution was allowed to stir at gentle reflux (90 ± 5 °C) for 48 h. The resulting yellow solution was taken up in water (40 mL) and worked up in the usual way. The remaining traces of *tert*-butyl alcohol were removed by codistillation in vacuo with benzene (3 × 40 mL containing a trace of pyridine) to give 248.4 mg of pale yellow crude oil. Distillation of the crude product afforded 241 mg (96%) of colorless epimerized keto acetal **4**: bp 40 °C (5 mm, bulb to bulb, external temperature); IR (film) 1690 (CO), 1370, 1380 (*gem*-CH_3), 1140, 1100, 1055, 1035 cm^{-1} (acetal); NMR (CCl_4) δ 4.16 [d, 1, J = 5 Hz, $CH(OCH_3)_2$], 3.26, 3.23 [2 s, 6, $-CH(OCH_3)_2$], 1.20 (d, 6, J = 6 Hz, isopropyl), and 1.07 ppm (bs, 6, *gem*-CH_3); mass spectrum, MRMS (70 eV) 214 (4) 183 (40), 139 (100), 113 (39), 112 (39), 108 (60), 100 (32), 98 (48), 126 (19), 90 (47), 89 (95), 82 (30), 80 (33), 77 (19), 76 (96), 74 (90), 72 (85), 71 (41), 70 (25), 67 (23), 61 (21), 59 (20), 58 (37), 55 (37), 53 (19), 47 (25), 45 (41), 44 (21), 43 (81), 41 (86), 39 (29), 32 (56), 31 (51).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.25. Found: C, 67.64; H, 10.62.

(±)-*trans*-3-(1-Hydroxy-2-methylpropenyl)-2,2-dimethylcyclopropanecarboxaldehyde Dimethyl Acetal Diethyl Phosphate (5).[8] To a solution of methyllithium (0.372 mL, 0.770 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (5 mL, freshly distilled from lithium aluminum hydride) containing a few crystals of bipyridine (used as an indicator) at −40 °C was added freshly distilled diisopropylamine (0.113 mL, 1.15 equiv, 0.806 mmol, distilled from calcium hydride). Stirring was continued for 0.5 h and the temperature allowed to rise to 0 °C. The solution was again cooled to −78 °C and a solution of keto acetal **4** (0.150 g, 0.700 mmol) in anhydrous tetrahydrofuran (3 mL) was added all at once. The resulting yellow orange solution was stirred for an additional 0.75 h and the temperature was allowed to rise to 0 °C. Diethyl chlorophosphate (0.094 mL, 1.1 equiv, 0.771 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, and the solution turned a pale yellow color. The reaction mixture was poured into ice–water (40 mL) and worked up in the usual way to give 0.172 g of a colorless oil. Preparative thin layer chromatography on a 20 × 20 cm silica gel plate using 90% ether–10% petroleum ether eluent (with a drop of pyridine) gave 0.152 g (62%) of enol phosphate **5** (R_f 0.34): bp 90–94 °C (2 mm); IR (film) 1680 (C=C), 1370, 1380 (*gem*-CH_3), 1135, 1095, 1035 (acetal), and 1260 cm^{-1} [$P(OC)_2$]; NMR (CCl_4) δ 4.08 [m, 5, $CH(OCH_3)_2$ and $P(OCH_2-)_2$], 3.28 and 3.26 [s, s, 6, $CH(OCH_3)_2$], 1.70 [bs, 6, $(CH_3)_2C{=}C$], 1.35 [t, 6, J = 7.6 Hz, $P(OCH_2CH_3)_2$], 1.17 and 1.03 ppm (s, s, 6, *gem*-CH_3); mass spectrum, HRMS (70 eV) *m/e* (rel intensity) 350 (2), 319 (17), 318 (43), 169 (32), 165 (44), 164 (95), 155 (32), 150 (26), 149 (94), 133 (31), 124 (89), 122 (26), 121 (29), 109 (46), 107 (83), 105 (25), 99 (45), 91 (38), 75 (100), 73 (56), 41 (41).

Anal. Calcd for $C_{16}H_{31}O_6P$ ($M^+ - OCH_3$, peak at 350 too weak for high-resolution measurement): 319.167414. Found: 319.168674 (MS), 3.9 ppm error.

(±)-*trans*-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarboxaldehyde Dimethyl Acetal (6).[9] Freshly cut lithium wire (80 mg, 11 mg-atoms, 16 equiv) was introduced into anhydrous

monoethylamine (25 mL, distilled from lithium metal) with stirring, and stirring continued for 20 min to allow dissolution of the metal. While stirring was continued a solution of enol phosphate (256 mg, 0.731 mmol) in dry *tert*-butyl alcohol (0.27 mL, freshly distilled from calcium hydride) was added all at once. The blue-colored solution was stirred for 10 min and then carefully quenched with ethyl alcohol (2–5 mL). The monoethylamine was then allowed to evaporate. The reaction mixture was transferred to a separatory funnel with a mixture of ether (50 mL) and water (50 mL), and worked up in the usual way to give 0.1245 g of a colorless oil. This crude product was chromatographed on silica gel (14 g, 70–230 mesh, E. Merck) in a 1.0-cm diameter column using 15% ether–85% petroleum ether to develop the column, taking 7-mL sized fractions. Fractions 5–7 gave 0.118 g (81%) of pure olefin acetal **6**: bp 48–51 °C (4 mm, external temperature); IR (film) 1660 (C=C), 1375, 1360 (*gem*-CH_3), 1190, 1125, 1085, 1050 (acetal), 970 cm^{-1} (C=CH); NMR (CCl_4) δ 4.81 (dm, 1, J = 7 Hz, C=CH), 4.05 [d, 1, J = 6 Hz, $CHC(CH_3)_2$], 3.21 [s, 6, $(OCH_3)_2$], 1.70 [s, 6, $(CH_3)_2C$=C], 1.12, 1.03 ppm (s, s, 6, *gem*-CH_3); mass spectrum, MRMS (70 eV) *m/e* (rel intensity) 198 (2), 75 (100), 74 (62), 73 (53), 59 (79), 45 (77), 43 (76), 41 (68), 31 (57), 30 (97).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.68; H, 11.24.

(±)-*trans*-2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarboxaldehyde (7).[3] A solution of olefin acetal **6** (100 mg, 0.50 mmol) in reagent acetone (5 mL) and water (about 2 drops) was allowed to stir at room temperature while the progress of the acetal hydrolysis was monitored by TLC [R_f 0.63 (acetal)–9.39 (aldehyde) using 5% ether–95% petroleum ether to develop the slides].

After 12 h the reaction mixture was taken up in water (20 mL) and worked up in the usual way to give 79.4 mg (98%) of colorless olefin aldehyde **7**; bp 38–40 °C (5 mm, external temperature); IR (CCl_4) 2720 (-CHO), 1700 (-CHO), 1375 (*gem*-CH_3), and 975 cm^{-1} (C=CH); NMR (CCl_4) δ 9.5 (d, 1, J = 5 Hz, -CHO), 4.88 (dm, 1, J = 7 Hz, HC=C), 1.72 [s, 6, $(CH_3)_2C$=C], 1.28, 1.18 ppm (s, s, 6, *gem*-CH_3); mass spectrum, HRMS (70 eV) *m/e* (rel intensity) 152 (12), 123 (100), 81 (73), 69 (26), 67 (36), 55 (32), 43 (39), 41 (64), 39 (40).

Anal. Calcd for $C_{10}H_{16}O$: 152.120110. Found: 152.119776 (2.9 ppm error).

(±)-*trans*-Chrysanthemic Acid (8) and (±)-Methyl *trans*-Chrysanthemate (9).[3] **Method A.** Chromium trioxide (1.0 g, 10 mmol) was added carefully to pyridine (10 mL) at 0 °C. The olefin aldehyde **7** (380 mg, 2.50 mmol) in pyridine (3 mL) was added in one portion, followed by water (5 drops). The mixture was stirred at room temperature. The slow oxidation of aldehyde **7** to the acid **8** was monitored by thin layer chromatography, by taking small aliquots of the mixture and diluting it in ether–water (3:1) prior to spotting the plate. Ether–petroleum ether (70:30, respectively) was used to develop the silica gel slides (R_f 0.89, aldehyde; 0.32, acid). After 78 h the mixture was poured into water (25 mL) and ether (5 mL). The reaction mixture was acidified with 10% hydrochloric acid solution until the pH reached 3–4 (approximated by litmus paper), and this mixture was worked up in the usual way to give 189 mg of the crude product as a viscous, colorless oil. Bulb to bulb distillation afforded 178 mg (42.3%) of pure acid **8**, bp 97–99 °C (6 mm, external temperature). The product failed to crystallize even after storing in the refrigerator (3 °C) overnight. Crystallization was induced by taking up a simple sample (50 mg) of the above distilled product in an ethyl acetate–petroleum ether (5 mL, 10:1 ratio, respectively). Removal of the solvent afforded 48 mg of a white, crystalline solid, which was further recrystallized from the same ethyl acetate–petroleum ether solvent system: mp 47–49 °C (lit. 46–48 °C);[3] IR (CCl_4) 2960 (COOH), 1690 (CO), 1740 weak shoulder (H bonding of dimer), 1375 (*gem*-CH_3), 850 cm^{-1} (C=CH); NMR (CCl_4) δ 4.86 (dm, 1, J = 8 Hz, HC=C), 1.95 (dd, 1, J = 8, 5 Hz, -C=CHCH), 1.73 [s, 6, $(CH_3)_2C$=C], 1.31, 1.17 (s, s, 6, *gem*-CH_3), 1.33 ppm (d, 1, J = 5 Hz).

Method B. Excess Jones reagent[11] (0.3 mL) was added dropwise to a solution of olefin aldehyde **58** (51.14 mg, 0.337 mmol) in anhydrous reagent acetone (3 mL) at 0 °C (ice bath). After 30 min the reaction mixture was checked by TLC (silica gel slides) developed using 30% ether–70% petroleum ether eluent. The presence of a spot with a high R_f of 0.83 indicated the presence of unoxidized aldehyde. There was also one other unidentified spot of R_f 0.45 besides the acid spot (R_f 0.3). Additional Jones reagent (0.1 mL) was added and the stirring continued at 0 °C. After 30 min the ice bath was removed and the solution stirred at room temperature for an additional 30 min. At this time the excess Jones reagent was quenched with 2-propanol (1 mL) added dropwise. The mixture was poured into water (10 mL) and worked up in the usual way to give 40.4 mg of a colorless, viscous oil. Preparative thin layer chromatography on a 10 × 20 cm silica gel plate using 30% ether–70% petroleum ether eluent gave 16 mg of the acid **8** (28%) and 16.4 mg of an unidentified material (R_f 0.3, acid; 0.41, other product), NMR spectrum of which lacked the doublet at δ 4.8 and the singlet at δ 1.73, characteristic signals of the vinyl H (C=CH) and the isopropylidene 6 H [$(CH_3)_2C$=C], respectively. The pure acid fraction 1 was crystallized from ethyl acetate–petroleum ether (10:1) solvent system, mp 45–47 °C.

Method C.[12] A solution of silver nitrate (1.7 g, 0.1 mol) in water (50 mL) was treated dropwise, with stirring, with a solution of 80% sodium hydroxide solution [prepared from 4 g (0.1 mol) of NaOH and 5.0 mL of H_2O]. The mixture was stirred for 10 min and the brown precipitate (silver oxide) was collected by decantation and washed free of nitrates with distilled water (3 × 20 mL). The wet, freshly precipitated silver oxide was covered with water (2 mL) and stirred while olefin aldehyde **7** (224 mg, 1.47 mmol) in tetrahydrofuran (20 mL) was added all at once followed by addition of a 50% solution of sodium hydroxide (4 drops). After stirring for 36 h the raction mixture was taken up in ether (50 mL) and the aqueous layer separated. The ether portion was washed with 10% sodium hydroxide solution (5 × 20 mL), then worked up in the usual way to give 118 mg of a crude product. The combined aqueous layers were cooled to 0 °C, acidified with concentrated hydrochloric acid (2–4 drops), and worked up in the usual way to give 95.4 mg of a viscous, colorless oil. Distillation of the crude product afforded 83.4 mg (34%) of the pure acid, bp 96–99 °C (6 mm, external temperature). The other 118.2 mg of crude product obtained from the neutral fraction comprised 48% of the theoretical yield and was recognized by the NMR doublet at δ 9.5 as a mixture of unoxidized aldehyde **7** and an unidentified third product. The pure acid **1** obtained by this method was crystallized by ethyl acetate–petroleum ether (10:1) solvent system, mp 47–49 °C. The spectral data of this acid sample are identical with those observed for the other samples obtained via method A and B.

Synthetic *trans*-chrysanthemic acid (**8**, 80 mg, 0.476 mmol) was transformed to its methyl ester by dissolving in ether (10 mL) and adding an ethereal solution of diazomethane at 0 °C in small increments until the yellow color persisted. The solution was maintained at 0 °C for 30 min, then allowed to rise to room temperature. Excess of diazomethane was quenched with glacial acetic acid (2 drops), then the solution was added to an equal volume of ether (15 mL) and washed with water (2 × 10 mL). The ether layer was separated and then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 82 mg of a slightly yellow oil. Distillation of this crude product gave 79 mg (92%) of methyl ester **9**: bp 86–90 °C (12 mm, external temperature) [lit. 90–92 °C (12 mm)];[3] IR (film) 1730 (CO), 3020 (cyclopropyl), 1375, 1350 cm^{-1} (*gem*-CH_3); NMR (CCl_4) δ 4.86 (dm, 1, J = 8 Hz, HC=C), 3.62 (s, 3, CO_2CH_3), 1.73 [s, 6, $(CH_3)_2C$=], 1.93 (dd, 1, J = 7, 8 Hz, C=CHCH), 1.25, 1.14 (s, s, 6, *gem*-CH_3) 1.26 ppm (d, 1, J = 7 Hz).

Synthetic (±)-*trans*-chrysanthemic acid (**8**) was found to have identical retention times and R_f values with a sample of authentic *trans*-chrysanthemic acid which was obtained by the epimerization and saponification of ethyl chrysanthemumate[13] (Aldrich 12,819-8). The methyl esters were also found to be identical with respect to IR, NMR, TLC, and GLC.[2,3]

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Registry No.—**1**, 503-93-5; **2**, 62057-37-8; **3**, 62006-18-2; **4**, 62005-88-3; **5**, 62005-89-4; **6**, 62005-90-7; **7**, 62057-35-6; **8**, 705-16-8; **9**, 15543-70-1; 2,6,6,7-tetramethylcyclohepta-2,4-dienone, 62005-91-8; diethyl chlorophosphate, 814-49-3.

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Vinylketenes. Synthesis of (+)-Actinidine‡

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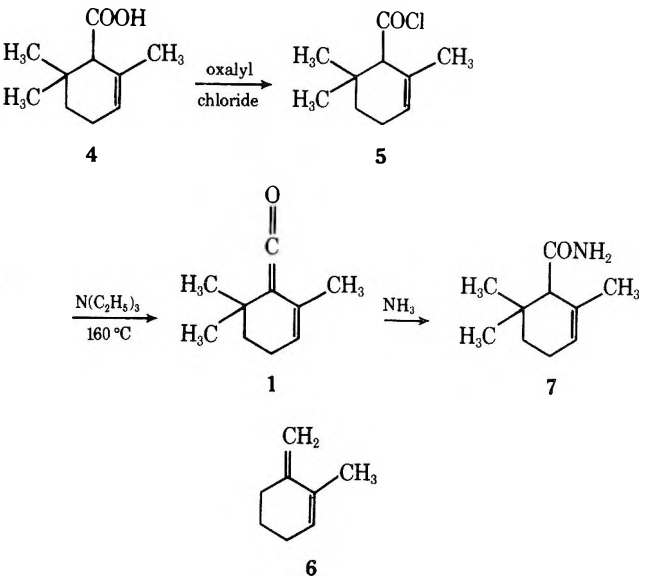
Dehydrochlorination of 2,6,6-trimethylcyclohex-2-ene-1-carbonyl chloride (**5**) yielded 2,6,6-trimethyl-1-carbonylcyclohex-2-ene (**1**), a vinylketene which could be isolated and characterized. Dehydrochlorination of (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carbonyl chloride (**9**) led presumably to (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**), but this vinylketene quickly rearranged by a [1,5] migration of hydrogen into (*R*)-5-methyl-2-(1-methylethenyl)cyclopent-1-ene-1-carboxaldehyde (**10**). Aldehyde **10** could be converted directly into (+)-actinidine (**12**).

Valence isomerizations of cyclobutenones[1a] and cyclohexadienones,[1b] [1,5] sigmatropic migrations of hydrogen in α,β-γ,δ-unsaturated aldehydes,[2] and pyrolyses of β,γ-unsaturated acid chlorides[2] apparently produce vinylketenes. Although these reactive intermediates have been detected spectroscopically and trapped chemically, the isolation and complete characterization of a vinylketene has not yet been reported. We therefore would like to describe the synthesis and physical properties of 2,6,6-trimethyl-1-carbonylcyclohex-2-ene (**1**), the behavior of (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**), and an application of our observations in a synthesis of the enantiomer of (−)-actinidine (**3**), a natural product of *Actinidia polygama*[3] and *Valeriana officinalis*.[4] Actinidine, first synthesized by Sakan,[5] has received some special attention since it is one of the rare monoterpenoid alkaloids,[6] since it has been reported to be an attractant of cats,[3] and since it is a close structural relative of the principal alkaloid of the medicinal plant *Valeriana officinalis* L.[7]

Results and Discussion

Vinylketene **1** was synthesized by the sequence of reactions described in Scheme I. 2,6,6-Trimethylcyclohex-2-ene-1-carboxylic acid (**4**) was prepared from geranic acid[8] and converted into 2,6,6-trimethylcyclohex-2-ene-1-carbonyl chloride (**5**). This acid chloride strongly resisted dehydrochlorination but was transformed by the action of triethylamine in benzene at 160 °C into compound **1**, which could be isolated and purified by molecular distillation. The infrared spectrum contained bands at 2115 and 1645 cm^{-1}, and the ultraviolet spectrum, which consisted of absorptions at 234 (ϵ 10 100) and 404 nm (ϵ 33), was simply the sum of the spectra expected for the butadiene **6** (λ_{max} 236 nm)[9] and the ketene portion of a diarylketene (λ_{max} 405 nm).[10] In the ^1H NMR spectrum of compound **1**, a sharp singlet replaced the doublet attributable to the diastereotopic methyl groups at C_6 in compounds **4** and **5**. In addition, treatment with ethereal ammonia converted

Scheme I

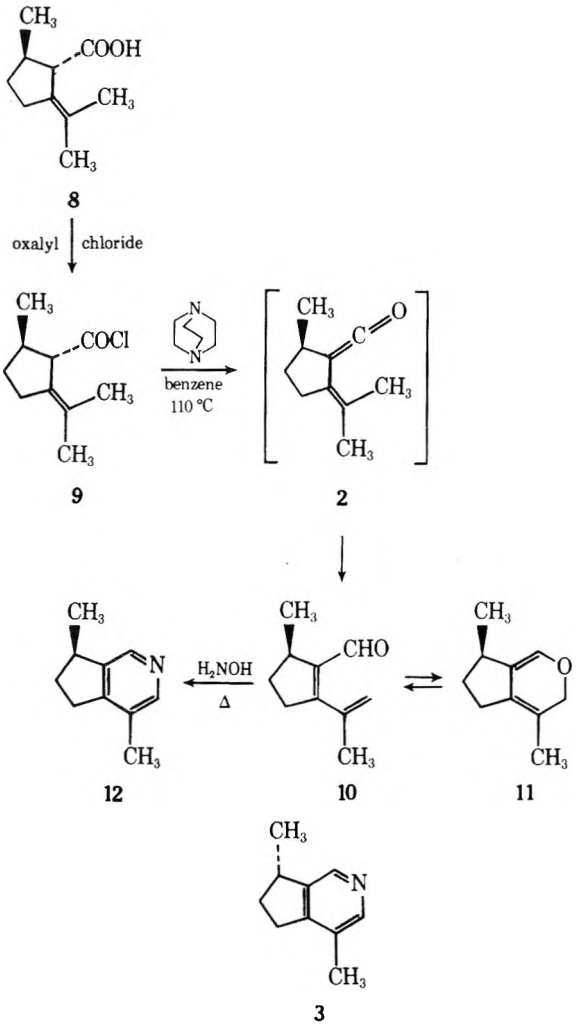


the ketene into 2,6,6-trimethylcyclohex-2-ene-1-carboxamide (**7**), which was identical with a sample of the amide prepared by the method of Bouveault.[11]

Applied to (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carboxylic acid (**8**), derived from (+)-pulegone by the procedure of Achmad and Cavill,[12] a similar sequence of reactions did not lead to (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**). Instead, (*R*)-5-methyl-2-(1-methylethenyl)cyclopent-1-ene-1-carboxaldehyde (**10**) was isolated. A [1,5] sigmatropic migration of hydrogen in ketene **2**, a rearrangement which has been observed recently by others,[1,2] accounts for the formation of aldehyde **10**; and, in fact, when the dehydrochlorination was interrupted, a ketene was detected spectroscopically by an absorption at 2090 cm^{-1} which vanished slowly at 25 °C. However, no bases, including tetramethylethylenediamine, triethylamine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-bis(dimethylamino)-naphthalene, pyridine, lithium diisopropylamide, and po-

‡ Dedicated to Professor Robert Burns Woodward on the occasion of his sixtieth birthday.

Scheme II



tassium hydride, converted compound **9** to ketene **2** or aldehyde **10** under milder conditions, and ketene **2** could not be isolated and characterized.

No evidence for the formation of valence isomer **11** appeared in the spectra of aldehyde **10**,[13] but its reaction with hot ethanolic hydroxylamine[14] efficiently yielded (+)-actinidine (**12**). Comparison of the IR, UV, ^{1}H NMR, and mass spectra, the optical rotations, and the melting points of the picrates of compound **12** and natural (−)-actinidine (**3**) showed that the substances were enantiomers.

Experimental Section

All infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Varian T-60, A-60, HA-100, and XL-100 spectrometers were used to obtain ^{1}H nuclear magnetic resonance (NMR) spectra. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ). Ultraviolet (UV) spectra were recorded on a Cary 14 spectrophotometer. The wavelength (λ) and molar extinction coefficient (ϵ) of absorption maxima are reported in the form λ (ϵ). An AEI MS-9 double-focusing spectrometer was used to obtain mass spectra at 70 eV. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were measured on a Thomas-Hoover capillary apparatus and are uncorrected. Vapor phase chromatographic analyses were performed on columns of SE-30 on Chromosorb W (6 ft × 0.25 in.) and Carbowax 20M on Chromosorb W (6 ft × 0.25 in.) in a Varian Aerograph Model 1420 instrument. Benzene was dried over sodium wire and triethylamine was distilled twice from 1-naphthyl isocyanate and once from lithium aluminum hydride before use.

Preparation of 2,6,6-Trimethylcyclohex-2-ene-1-carbonyl Chloride (5). Under dry N_2 a stirred solution of 2,6,6-trimethylcyclohex-2-ene-1-carboxylic acid[8] (**4**, 6.62 g, 39.4 mmol) in benzene (70 mL) at 5 °C was treated dropwise during 24 min with a solution of oxalyl chloride (6.27 g, 49.4 mmol) in benzene (30 mL). The mixture was stored at 27 °C for 14 h and then solvent and excess oxalyl chloride were removed by evaporation under reduced pressure. Distillation of the residue yielded acid chloride **5** (6.05 g, 32.5 mmol, 82%) as a colorless liquid: bp 44–47 °C at 0.6 Torr (reported[15] bp 103–108 °C at 13 Torr; reported[16] bp 87–88 °C at 12 Torr); IR (liquid film) 1800 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.97 (s, 3 H), 1.10 (s, 3 H), 1.1–1.4 (m, 2 H), 1.7–1.9 (m, 3 H), 1.9–2.3 (m, 2 H), 3.06 (broad s, 1 H), 5.5–5.7 (m, 1 H); mass spectrum *m/e* (rel intensity) 186 (1), 150 (49), 135 (72), 123 (100), 122 (43), 107 (97), 91 (89), 81 (76), 79 (68).

Preparation of 2,6,6-Trimethyl-1-carbonylcyclohex-2-ene (1). A solution of acid chloride **5** (2.24 g, 12.0 mmol) and triethylamine (1.45 g, 14.3 mmol) in benzene (9 mL) was heated at 160 °C for 8.3 h under dry N_2 in a sealed Pyrex tube. The mixture was filtered under dry N_2 and the filtrate was concentrated by evaporation under reduced pressure. Molecular distillation of the concentrate (24 °C at 0.01 Torr) yielded ketene **1** (1.12 g, 7.46 mmol, 62.2%) as a yellow-orange liquid: IR (liquid film) 2115, 1645, 1380, 1360 cm^{-1}; UV (hexane) 234 nm (ϵ 10 100), 404 (33); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.14 (s, 6 H), 1.42 (t of d, 2 H, J = 6.3, 1.0 Hz), 1.73 (d of t, 3 H, J = 1.3, 1.8 Hz), 1.98–2.22 (m, 2 H), 5.13 (t of q, 1 H, J = 1.3, 3.5 Hz); mass spectrum *m/e* (rel intensity) 150 (62), 135 (95), 107 (100), 79 (68); high-resolution mass spectrum *m/e* 150.1062 (calcd for $C_{10}H_{14}O$, 150.1045).

Preparation of 2,6,6-Trimethylcyclohex-2-ene-1-carboxamide (7). At 0 °C under dry N_2 a stirred solution of ketene **1** (74 mg, 0.49 mmol) in anhydrous ether (1.0 mL) was treated dropwise during 3 min with a saturated ethereal solution of anhydrous ammonia (5 mL). The orange color was not discharged instantaneously, so the mixture was stored at 26 °C for 30 h. Removal of solvent by evaporation left the amide **7** (67 mg, 0.41 mmol, 84%) as a colorless solid: mp 121.0–122.0 °C (reported[11] mp 120–121 °C); IR (KBr) 3450, 3250, 1650 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.97 (s, 3 H), 1.03 (s, 3 H), 1.0–1.4 (m, 2 H), 1.6–1.8 (m, 3 H), 1.9–2.3 (m, 2 H), 2.40 (s, 1 H), 5.69 (broad s, 1 H), 5.8–6.1 and 6.4–6.9 (broad s, 2 H).

Preparation of (1*S*,5*R*)-5-Methyl-2-(1-methylethylidene)-cyclopentane-1-carbonyl Chloride (9). Under dry N_2 a stirred solution of (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carboxylic acid[12,17] (**8**, 7.3 g, 43 mmol) in benzene (85 mL) at 5 °C was treated dropwise during 30 min with a solution of oxalyl chloride (6.2 g, 49 mmol) in benzene (27 mL). The mixture was stirred at 27 °C for 14 h and then solvent and excess oxalyl chloride were removed by evaporation under reduced pressure. Distillation of the residue yielded acid chloride **9** (6.8 g, 36 mmol, 85%) as a colorless liquid: bp 47–50 °C at 0.55 Torr; IR (liquid film) 1795 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.14 (d, 3 H, J = 7 Hz), 1.2–1.5 (m, 1 H), 1.6–1.7 (m, 6 H), 1.8–2.1 (m, 1 H), 2.2–2.6 (m, 3 H), 3.34 (broad d, 1 H); mass spectrum *m/e* (rel intensity) 186 (2), 123 (100), 107 (20), 81 (75), 79 (21), 69 (20), 67 (22), 55 (20).

Preparation of (*R*)-5-Methyl-2-(1-methylethenyl)cyclopent-1-ene-1-carboxaldehyde (10). A solution of acid chloride **9** (394 mg, 2.11 mmol) and 1,4-diazabicyclo[2.2.2]octane (239 mg, 2.13 mmol) in benzene (3.0 mL) was heated at 110 °C for 8 h under dry N_2 in a sealed Pyrex tube. The mixture was filtered and benzene was removed by evaporation under reduced pressure. Distillation of the residue yielded aldehyde **10** (128 mg, 0.85 mmol, 40.5%), the only volatile component, as a chromatographically pure, yellow liquid: bp 52–57 °C at 1.5 Torr; IR (liquid film) 2730, 1665, 1605 cm^{-1}; UV (95% ethanol) 233 nm (ϵ 3550); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.13 (d, 3 H, J = 7.0 Hz), 1.3–1.7 (m, 1 H), 1.9 (m, 3 H), 2.0–2.3 (m, 1 H), 2.6–2.8 (m, 2 H), 3.0–3.3 (m, 1 H), 5.06 (qn, 1 H), 5.21 (qn, 1 H), 9.81 (s, 1 H); mass spectrum *m/e* (rel intensity) 150 (88), 149 (71), 135 (100), 121 (27), 107 (66), 105 (24), 93 (41), 91 (66), 79 (73), 77 (49), 65 (24), 53 (27), 51 (27). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39; O, 10.65. Found: C, 80.21; H, 9.12; O, 10.67.

Synthesis of (+)-Actinidine (12). A solution of aldehyde **10** (150 mg, 1.00 mmol) and hydroxylamine hydrochloride (145 mg, 2.08 mmol) in a mixture of ethanol (6.0 mL) and water (1.5 mL) was stirred at 0 °C and treated with aqueous NaOH (1.5 mL, 1.7 N). The mixture then was heated at reflux for 25 h, diluted with water, and extracted with dichloromethane. After solvent had been removed by evaporation under reduced pressure, distillation of the residue yielded (+)-actinidine (**12**, 133 mg, 0.90 mmol, 90.5%), the only volatile component, as a chromatographically pure, colorless liquid. The IR, UV, ^{1}H NMR, and mass spectra of this substance were identical with those of natural (−)-actinidine, but the sample proved to be dextrorotatory: $[\alpha]^{20}_D$ +10.8° (c 0.360, $CHCl_3$).

The picrate of (+)-actinidine (**12**) was prepared in the usual manner and crystallized from ethanol to constant melting point: mp 146.0–

146.3 °C (reported[5b] mp 146–147 °C); $[\alpha]^{20}_D$ −34.6° (c 0.940, $CHCl_3$).

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Registry No.—**1**, 61899-98-7; **4**, 564-24-9; **5**, 61899-99-8; **7**, 61900-00-3; **8**, 7712-68-7; **9**, 61900-01-4; **10**, 61900-02-5; **12**, 15524-81-9; **12** picrate, 61900-03-6; oxalyl chloride, 79-37-8.

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(17) The (+)-pulegone from which acid **8** was derived had $[\alpha]^{20}_D$ +22° (neat).

A Stereocontrolled Synthesis of (±)-Anhydronupharamine. The ^{1}H and ^{13}C Nuclear Magnetic Resonance of Piperidine Nuphar Alkaloids[1]

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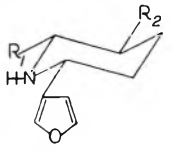
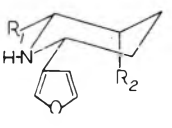
(±)-Anhydronupharamine is prepared in 11 steps starting from 6-methyl-5-hepten-2-one and proceeding through key intermediates *trans*-3-methyl-2-(3-methyl-2-butenyl)cyclopentanone, *trans*-6-(3-methyl-2-butenyl)-5-methyl-2-piperidone, and *trans*-2-(3-methyl-2-butenyl)-3-methyl-6-(3-furyl)-2,3,4,5-tetrahydropyridine. Stereocontrol is based on the greater stability of trans substituents in a 2,3-disubstituted cyclopentanone and the more favorable reduction of a C-2 substituted 2,3,4,5-tetrahydropyridine from the direction opposite the C-2 substituent. The ^{1}H and ^{13}C NMR characteristics of the various 3-furyl-substituted piperidines obtained in the course of synthesis are given and briefly discussed with regard to conformation.

The structures of (−)-anhydronupharamine (**1**) and (−)-nuphenine (**2**) exemplify the two stereochemical types of Nuphar piperidine alkaloids. The trans disposition of C-2 and C-3 hydrogen atoms in **1** similarly occurs in the Nuphar quinolizidine alkaloids where the carbons of the second ring might be considered constituted by those of the C-2 side chain in **1**. This trans arrangement appeared, until recently, to be the only one in the quinolizidine Nuphar alkaloids. However, the results of new isolation work show that the C-2 and C-3 cis arrangement of hydrogen atoms in **2** also presents itself in the C_{15} quinolizidine 1-*epi*-deoxynupharidine[2] and in some C_{30} thiaspiranes such as 1-*epi*,1′-*epi*-thiobinupharidine.[3] Regardless of the steric disposition of the C-2 and C-3 substituents, the 3-furyl group at C-6 always assumes an equatorial conformation and is cis to the C-2 substituent in the naturally occurring Nuphar piperidines and quinolizidines.



1, $R_1=(CH_3)_2C{=}CHCH_2$; $R_2=CH_3$
20, $R_1=R_2=H$
21, $R_1=CH_3$; $R_2=H$
28, $R_1=(CH_3)_2C(OH)CH_2CH_2$; $R_2=CH_3$

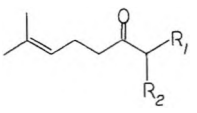


2, $R_1=(CH_3)_2C{=}CHCH_2$; $R_2=CH_3$
29, $R_1=(CH_3)_2C(OH)CH_2CH_2$; $R_2=CH_3$

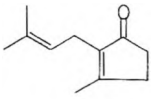
We sought to prepare the piperidine Nuphar alkaloids by routes which would offer control over the C-2, C-3, and C-6 stereochemistry and which appeared to hold some promise for appropriate elaboration of the C-2 side chain in order that the route could be extended later to the Nuphar quinolizidines. We report here the synthesis[4] of (±)-anhydronupharamine by a route through which the stereocontrol of C-2 and C-3 substituents rests on the far greater stability of trans C-2, C-3 alkyl substituents in a cyclopentanone.[5] As results were to demonstrate, the basis for the C-2, C-6 cis arrangement of substituents is the more favorable reduction of a C-2 substituted 2,3,4,5-tetrahydropyridine from the side opposite the C-2 substituent. In addition we report on the results of the ^{1}H and ^{13}C NMR investigations of the stereochemistry of the new piperidine compounds which have arisen in the course of the synthesis.

Results and Discussion

Synthesis. The cyclopentenone **6**, substituted by γ,γ-dimethylallyl and methyl groups at C-2 and C-3, was prepared by starting from the 6-methyl-5-hepten-2-one (**3**) and proceeding through **4** and **5** according to an established sequence[6] for preparing 2,3-disubstituted cyclopentenones. Thereafter the key intermediate cyclopentanone **7** possessing C-2 and C-3 trans substituents was prepared through lithium/liquid ammonia reduction of the cyclopentenone. None of the cis isomer



3, $R_1=R_2=H$
4, $R_1=COOCH_3$; $R_2=H$
5, $R_1=COOCH_3$; $R_2=CH_2COCH_3$



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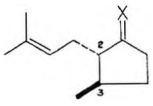
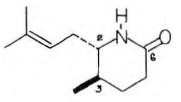


7, X=O
8, X=NOH

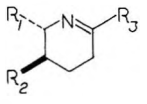
could be detected by ^1H NMR or GLC. The yields for these steps and all subsequent ones are given in the Experimental Section.

The conversion of ketone **7** to the oxime **8** with hydroxylamine hydrochloride in refluxing pyridine and subsequent Beckmann rearrangement of the oxime, by treatment of the latter with phosphorus pentachloride, achieved nitrogen incorporation in a six-membered lactam, **9**, in the desired position relative to C-2 and C-3 as indicated by the ^1H NMR. The trans disposition of substituents was largely preserved, but some loss of stereochemical integrity occurred in oxime formation. The presence of 8.5% of the cis oxime was detected by ^1H NMR observation of the C-3 methyl doublet which appeared at δ 0.82 ppm, while the methyl doublet from the predominant trans isomer appeared slightly downfield at δ 1.00 ppm. This cis isomer was carried through the remainder of the synthesis.



9

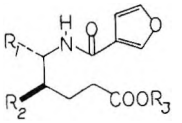
The major obstacle to the completion of the synthesis was the attachment of a 3-furyl group to the carbon present as the lactam carbonyl carbon in **9**. Alkylation of a lactam carbonyl carbon has been achieved through conversion of the lactam to a thioimidate ester followed by treatment of the latter with a lithium alkyl in the presence of diisopropylaluminum hydride (DIBAH).[7] Similarly the treatment of the *S*-methylthiolactim **10** with phenyllithium in the presence of DIBAH or diphenylmercury gave the imine **11** in yields up to 50%. The *O*-methyllactim **12** and phenyllithium also produced **11** in the



10, $R_1=R_2=H$; $R_3=SCH_3$
11, $R_1=R_2=H$; $R_3=C_6H_5$
12, $R_1=R_2=H$; $R_3=OCH_3$
13, $R_1=R_2=H$; $R_3=3$-furyl
14, $R_1=CH_3$; $R_2=H$; $R_3=OCH_3$
19, $R_1=CH_3$; $R_2=H$; $R_3=3$-furyl
23, $R_1=(CH_3)_2C=CHCH_2$; $R_2=CH_3$; $R_3=OCH_3$
26, $R_1=(CH_3)_2C=CHCH_2$; $R_2=CH_3$; $R_3=3$-furyl

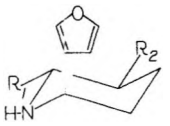
presence or absence of DIBAH, though in better yield when DIBAH was present.[8] However when 3-furyllithium and DIBAH or bis(3-furyl)mercury replaced the phenyl counterparts, the corresponding 3-furyl-substituted imine **13** was not obtained.

Since the direct attachment of the 3-furyl portion of the molecule seemed frustrated, the indirect incorporation of this group was attempted and achieved through N-acylation of an *O*-methyllactim with 3-furoyl chloride followed by decarboxylation and simultaneous nitrogen–carbon bond formation to reestablish the six-membered heterocyclic ring. Thus treatment of the *O*-methyllactims **12** and **14** with lithium hydride and 3-furoyl chloride produced the amido esters **15** and **16**, respectively,[9] which after ester hydrolysis and pyrolysis of the resulting amidocarboxylic acids, **17** and **18**, in the



15, $R_1=R_2=H$; $R_3=CH_3$
16, $R_1=R_3=CH_3$; $R_2=H$
17, $R_1=R_2=R_3=H$
18, $R_1=CH_3$; $R_2=R_3=H$
24, $R_1=(CH_3)_2C=CHCH_2$; $R_2=R_3=CH_3$
25, $R_1=(CH_3)_2C=CHCH_2$; $R_2=CH_3$; $R_3=H$

presence of calcium oxide gave the imines **13** and **19** in 52 and 60% yields, respectively, in the last step. Sodium borohydride reduction of **13** gave 2-(3-furyl)piperidine, **20**, while imine **19** led to a mixture of *cis*- (**21**, 91%) and *trans*-6-methyl-2-(3-furyl)piperidine (**22**, 9%). The sequence of transformations



22, $R_1=CH_3$; $R_2=H$
27, $R_1=(CH_3)_2C=CHCH_2$; $R_2=CH_3$

was applied thereafter to the lactam **9**. Conversion of the latter to the *O*-methyllactim **23**, N-acylation and ring opening to amido ester **24**, hydrolysis to the amido acid **25**, pyrolysis with calcium oxide to imine **26**, and reduction with sodium borohydride produced a mixture of piperidines. According to GLC analysis, this mixture consisted of 85% anhydronupharamine (**1**) and 15% of the stereoisomers nuphenine (**2**) and the 2,6-trans isomer, **27**. Each of the three was separated by elution chromatography and the samples of anhydronupharamine and nuphenine possessed chromatographic and spectrometric properties identical with those of the naturally occurring alkaloids.

^1H and ^{13}C NMR. (−)-Anhydronupharamine has been correlated[10] with (−)-nupharamine (**28**), which in turn has been correlated[11] with (−)-deoxynupharidine, whose stereochemistry is secure.[12] Therefore there is no question regarding the relative configuration of anhydronupharamine. The relative configurations of nuphenine[13] and the closely related tertiary alcohol 3-*epi*-nupharamine[14] (**29**) rest on the ^1H NMR spectra, which indicate the C-3 methyl groups are axial. The same spectra are consistent with the C-2 side chains being equatorial, though the axial disposition of these side chains is not necessarily ruled out. We have found that a comparison of the ^1H and ^{13}C NMR of the various 3-furyl-substituted piperidines has been useful in confirming and assigning conformation and configuration to the various 3-furyl-substituted piperidines.

The ^1H doublets exhibited by the C-3 methyls in anhydronupharamine, **1**, and the 2,6-trans isomer, **27**, are at nearly the same field strength (δ 0.91 and 0.89 ppm, respectively) and have the same coupling constants (6.0 Hz), but are upfield from and have slightly smaller coupling constants than the δ 0.98 ppm methyl doublet (J = 7.2 Hz) shown by nuphenine **2**. These ^1H NMR properties of the C-3 methyl-substituted piperidines parallel those of the corresponding quinolizidines where axial methyl groups, substituted at C-1 or C-3 in chair

Table I. ^{13}C Chemical Shift Values[a] of Selected Carbons in 3-Furyl-Substituted Piperidines

Compd	Substituted	Carbon no.[b] 2 (6)	3 (5)	4	5 (3)	6 (2)	CH_2	CH_3
Piperidine[c]		47.7 (t)	27.5 (t)	26.1 (t)	27.5 (t)	47.7 (t)		
20	Mono	53.1 (d)	33.7 (t)	24.7 (t)[d]	25.9 (t)[d]	47.0 (t)		
21	Di	53.6 (d)	33.9 (t)[e]	24.9 (t)	33.2 (t)[e]	52.8 (d)		22.9
22	Di	46.9 (d)	31.0 (t)	20.0 (t)	33.0 (t)	45.5 (d)		21.3
1	Tri	53.8 (d)	34.7 (t)[f]	34.3 (t)[f]	35.9 (d)	64.1 (d)	32.4 (t)	18.2[g] (18.5) (q)[g]
2	Tri	54.4 (d)	28.6 (t)	33.2 (t)	30.7 (d)	60.5 (d)	32.6 (t)	11.8 (q)
27	Tri	43.6 (d)	29.4 (t)[h]	29.2 (t)[h]	35.6 (d)	57.2 (d)	32.3 (t)	18.2[i] (18.8) (q)[i]

[a] Given in parts per million from δ 0.0 ppm from Me_4Si with multiplicity in parentheses. [b] The carbon to which the 3-furyl group is attached is C-2 in the mono- and disubstituted piperidines but C-6 in the trisubstituted piperidines. The remaining carbons in the ring are numbered in sequence accordingly. [c] Values taken from ref 16. [d-i] Assignments may be interchanged where the same superscript letter appears.

form rings, appear downfield with slightly larger coupling constants than equatorial methyls.[15] Thus our analysis of the piperidines points to an equatorial C-3 methyl in anhydronupharamine and the 2,6-trans isomer, but an axial C-3 methyl in nuphenine.

The resonance of the proton attached to the 3-furyl bearing carbon appears in the region of δ 3.57–3.60 ppm as a doublet of doublets (J = 8.0–10.9 and 2.1–5.5 Hz) in the spectra of anhydronupharamine, nuphenine, and *cis*-2-(3-furyl)-6-methylpiperidine (**21**), while the corresponding resonance appears at lower field, δ 4.11 and 4.00, as a triplet (J = 4.0 Hz) in the spectra of the trans-2,6 compounds, **22** and **27**. The higher field doublet of doublet resonance indicates an axial proton (3-furyl equatorial) split by vicinal axial and equatorial protons, but the lower field triplet indicates an equatorial proton (3-furyl axial) split by vicinal axial and equatorial protons having equal coupling constants.

The ^1H resonance of the second carbinyl proton adjacent to nitrogen is less straightforward in providing useful stereochemical information. This proton appears as a quintet of doublets at 2.78 and 3.04 ppm, respectively, in the spectra of the *cis*- and *trans*-2-(3-furyl)-6-methylpiperidines. The splitting pattern is best rationalized for both spectra by the proton in question being axial and split by each of the three methyl protons and the vicinal axial proton by the same amount, 6.4 Hz, and split again by the vicinal equatorial proton by 2.3 Hz. The lower field shift value of this proton in the 2,6-trans isomer **22** would seem to reflect the conformation of the 3-furyl group. In the nuphenine case, the proton appears as a triplet of doublets (J = 7.4 and 2.2 Hz) at δ 2.77 ppm. The splitting with the vicinal C-3 equatorial proton is ambiguous regarding the question whether the C-2 proton is axial or equatorial. However the chemical shift value of the proton in question agrees with that of the corresponding proton in the cis-2,6 model compound **21**, and therefore suggests that the C-2 proton is axial and the side chain equatorial. In the case of anhydronupharamine and its trans-2,6 isomer **27**, the chemical shift value of the C-2 proton is anomalously low, occurring coincidentally with the allyl methylene in the δ 2.0–2.6 ppm region. This anomalous chemical shift is occurring only when an equatorial methyl group is attached to C-3, but the nature of the influence which this group has on the C-2 proton is not clear.

The ^{13}C chemical shifts, excluding the values for the 3-furyl, the vinyl, and the vinylmethyl carbons are given in Table I for the six 3-furyl-substituted piperidines. The chemical shifts excluded from Table I appear at the expected values.[17] Assignments were made with the assistance of ^1H off-resonance decoupled spectra and the chemical shift comparison within the series. Assignments for the ring carbons of the cis- and trans-2,6 model compounds **21** and **22** were given additional support by the agreement of observed chemical shifts with those calculated from parameters of Booth and Griffiths determined from a study of several methylpiperidines.[18] Carbons adjacent to nitrogen in all compounds except the mono-substituted piperidine were distinguished by ^1H single frequency decoupling experiments.

A comparison of the ^{13}C chemical shift values for the disubstituted piperidines **21** and **22** shows that all ring carbons, except C-5, are at higher field in **22** than in **21**. In addition the C-6 methyl group chemical shift values are very nearly the same, although the one for **22** is slightly higher, by 1.6 ppm. These observations, along with the ^1H NMR splitting patterns and chemical shift values for C-6, are consistent with the predominant conformer of the trans-2,6 isomer **22** being the one possessing an axial 3-furyl group and an equatorial methyl group. The axial–equatorial chemical shift increment for a C-1 or C-3 methyl group in quinolizidines is about 6 ppm. Assuming that this increment can be applied to the 2-methylpiperidine case and using the 1.6-ppm value of the methyl chemical shift difference in **21** and **22**, we estimate that the ratio of axial methyl conformer to axial 3-furyl conformer in the equilibrium mixture of the two is about 1:4.

The presence of the C-3 axial methyl in nuphenine is indicated by the lower chemical shift value of this group relative to the corresponding group in anhydronupharamine.[19] Also consistent with this stereochemistry is the observation that all ring carbon chemical shift values, except that for C-6, are lower for nuphenine than anhydronupharamine. Similarly in comparing **27** with **1**, both methyl chemical shift values are the same and the values for all ring carbons, except C-3, are lower in **27** than **1**. These observations are consistent with the C-3 methyl group in **27** being equatorial and the C-6 3-furyl group being axial.

Experimental Section

Spectra were determined as follows: infrared (IR) neat on a Perkin-Elmer 137 spectrometer; ^1H NMR in $CDCl_3$ solution in 5-mm tubes (1% Me_4Si; δ 0.00) on Varian A60 A and XL 100-15 spectrometers, the latter operating at 100 MHz in the FT absorption mode, lock being established on $CDCl_3$ (m, s, d, t, q, q′, and br refer to multiplet, singlet, doublet, triplet, quartet, quintet, and broad, respectively); ^{13}C NMR on a XL 100-15 spectrometer operating in the FT absorption mode at 25.2 MHz employing 8192 data points, using 5–69-mg samples in 5-mm tubes, the $CDCl_3$ also furnishing the secondary reference signal (77.2 ppm from Me_4Si at δ 0.0 ppm) and the deuterium resonance for field-frequency lock. Fully ^1H noise decoupled, selective ^1H decoupled, and ^1H off-resonance decoupled ^{13}C NMR spectra were obtained from 6 to 272 K transients, the number of transients for off-resonance decoupled spectra being at the higher end of the range. In all cases ^{13}C spectral widths were 5000 Hz and acquisition times were 0.8 s. Pulse angles for ^{13}C determinations ranged from 20 to 45 °C. Gas–liquid chromatography (GLC) is given as retention time (R_t) in minutes and was performed at the column temperature and flow rate or back pressure indicated on: a 5 ft × ¼ in. stainless steel column packed with 1.5% OV101 on 100/120 Chromo-

sorb G HP (column A); a 5 ft × ¼ in. stainless steel column packed with 20% SE 30 on 60/80 Chromosorb W (column B); 5 ft × ¼ in. stainless steel column packed with 10% Carbowax 20M on Chromosorb G (column C); 5 ft × ¼ in. stainless steel packed with 2% OV101 on 100/120 Chromosorb G HP (column D); 10 ft × ⅛ in. stainless steel column packed with 1.5% OV101 on 100/120 Chromosorb G (column E). Thin layer chromatography was performed on: A, Analtech precoated silica gel G (250-μm thickness) developed with hexane–ether (4:1), or with the solvent system indicated, and visualized with I_2 vapor; B, Merck Alumina (250-μm thickness) developed with hexane–ether (4:1) and visualized with Dragendorff–Munier reagent; C, Merck Alumina (250-μm thickness) developed with 5% EtOAc in benzene and visualized with Dragendorff–Munier reagent. Elemental analyses were performed by Galbraith Analytical Laboratories, Knoxville, Tenn.; melting points (mp) were taken on a Mel-temp apparatus and are uncorrected.

Methyl 7-Methyl-3-oxo-6-octenoate (4). To a suspension of 38 g of NaH (1.58 mol) in 250 mL of dry ether under N_2 was added 142.75 g of dimethyl carbonate (1.58 mol), the resulting mixture was heated to reflux, and 100 g of 6-methyl-5-hepten-2-one (0.79 mol) (purchased from the Aldrich Chemical Co.) was added over 5 h to the heated mixture. The mixture was heated to reflux another 2 h, cooled to 25 °C, and poured onto crushed ice containing 99 mL of acetic acid. The ether solution was separated, washed with dilute aqueous $NaHCO_3$ and dried ($MgSO_4$). Removal of the ether at reduced pressure left an oil which was distilled to give 112 g of **4** (77%): bp 84–85 °C (0.5 mm); IR (neat) 1742 ($COOCH_3$), 1715 cm^{-1} (RCOR); ^1H NMR δ 5.08 (m, 1 H, C-6 H), 3.70 (s, OCH_3), 3.41 (s, 2 H, C-2 H), 2.00–2.83 (m, 4 H, C-4 and C-5 H), 1.65 (d, J = 1.2 Hz, 3 H, CH_3), 1.60 (s, 3 H, CH_3); GLC (column A, 125 °C, back pressure 16 psi) R_t 6.9; TLC (A) R_f 0.39. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.77. Found: C, 65.30; H, 8.87.

4-Carbomethoxy-9-methyl-8-decene-2,5-dione (5). To a stirred suspension of 5.72 g of NaH (0.237 mol) in 300 mL of ether under N_2 was added dropwise a solution of 44 g of **4** (0.237 mol) in 100 mL of ether. The resulting slurry was stirred until no effervescence was observed. Ether (200 mL) was added to facilitate stirring, the slurry was cooled to −25 °C, and a solution of 32.7 g of bromoacetone (0.238 mol) in 50 mL of ether was added with vigorous stirring. The mixture was heated to reflux for 30 min, cooled to 25 °C, and poured into crushed ice. The pH was adjusted to 5 with 25% aqueous H_2SO_4, the ether solution was separated, and the aqueous phase was extracted repeatedly with ether. The extracts were combined with the ether solution and the resulting solution was dried ($MgSO_4$). Removal of the ether at reduced pressure yielded 51 g of **5** (94%), 46 g of which was used in the next step without further purification and 1 g of which was distilled by short-path distillation to afford **5**: bp 104–106 °C (0.1 mm); IR (neat) 1742 ($COOCH_3$), 1720 (RCOR), 1715 cm^{-1} (RCOR); ^1H NMR δ 5.08 (m, 1 H, C-6 H), 4.00 (t, 1 H, C-2 H), 3.69 (s, 3 H, OCH_3), 3.50–2.00 (m, 6 H, C-4, C-5, and C-2 H), 2.14 (s, 3 H, CH_3), 1.65 (d, 3 H, CH_3), 1.60 (d, 3 H, CH_3); GLC (column B, 175 °C, 60 ml/min) R_t 9.4; GLC (column A, 150 °C, back pressure 18 psi) R_t 11.2; TLC (A) R_f 0.16. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.96; H, 8.40. Found: C, 65.05; H, 8.50.

3-Methyl-2-(3-methyl-2-butenyl)-2-cyclopentenone (6). A solution of 50 g of **5** in 800 mL of 3% aqueous NaOH was stirred at 70 ± 2 °C for 3 h and thereafter cooled to 25 °C. The pH was adjusted to 4.0 with 25% aqueous H_2SO_4 and the liberated ketone was extracted repeatedly with 100 mL of ether. The combined extracts were washed with brine and dried ($MgSO_4$). Removal of the ether at reduced pressure and distillation of the residue gave 28 g of **6** (78%): bp 76–77 °C (0.2 mm); IR (neat) 1691 (RCOR), 1640 cm^{-1} (C=C); ^1H NMR δ 5.05 (m, 1 H, C-7 H), 2.86 (d, 2 H, C-6 H), 2.44 (m, 4 H, C-4 and C-5 H), 2.03 (s, 3 H, CH_3), 1.66 (s, 6 H, C-9 and C-10 H); GLC (column B, 175 °C, 60 ml/min) R_t 3.9; GLC (column C, 210 °C, 60 ml/min) R_t 13.3; GLC (column A, 125 °C, back pressure 16 psi) R_t 9.3; TLC (A) R_f 0.19. Anal. Calcd for $C_{11}H_{16}O$: C, 80.42; H, 9.83. Found: C, 78.46; H, 9.92.

***trans*-3-Methyl-2-(3-methyl-2-butenyl)cyclopentanone (7).** A solution of 5 g of **6** in 50 mL of ether was added to 400 mL of liquid NH_3 in a flask at −78 °C. Small pieces of lithium wire totaling 1.7 g (0.24 g atom) were added over a period of 3 min with vigorous stirring. The blue reaction mixture was stirred an additional 10 min, solid NH_4Cl was added, vigorous stirring was continued for 15 min, and to the resulting white slurry was added slowly 100 mL of water. The flask was removed from the cooling bath and kept at 35–40 °C until the bulk of the NH_3 had evaporated. The ether layer was separated, the aqueous layer was extracted repeatedly with ether, and the combined extract and original ether layer was dried ($MgSO_4$). Removal of the ether at reduced pressure gave an oil which was distilled to yield 3.7 g of **7** (73%): bp 83–84 °C (3.5 mm); IR (neat) 1740 cm^{-1} (RCOR); ^1H NMR δ 5.08 (m, 1 H, C-7 H), 1.25–2.50 (m, 8 H, $(C)_3CH$ and $(C)_2CH_2$), 1.62 (d, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.11 (d, 3 H, C-3 CH_3); GLC (column B, 170 °C, 60 ml/min) R_t 2.8; GLC (column A, 125 °C, back pressure 15 psi) R_t 5.0; TLC (A) R_f 0.52. Anal. Calcd for $C_{11}H_{18}O$: C, 79.44, H, 10.93. Found: C, 79.25; H, 10.84.

***trans*-3-Methyl-2-(3-methyl-2-butenyl)cyclopentanone Oxime (8).** A solution of 2.5 g of hydroxylamine hydrochloride (0.035 mol) in 10 mL of 50% EtOH was added to a solution of 5 g of **7** in 10 mL of pyridine. The mixture was heated to reflux for 15 min, cooled to 25 °C, and the reaction flask was evacuated at 60 °C to form an oil which was treated with 50-mL portions of ether. The combined ether solution was dried ($MgSO_4$) and the ether was removed at reduced pressure to give an oil which when distilled afforded 5.3 g of **8** (98%): bp 90–91 °C (0.2 mm); IR (neat) 3300 (OH), 1670 cm^{-1} (C=N); ^1H NMR δ 5.20 (m, 1 H, C-7 H); 1.16–3.00 (m, 8 H, $(C)_3CH$ and $(C)_2CH_2$), 1.66 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.01 (d, 3 H, CH_3); GLC (column A, 150 °C, back pressure 17 psi) R_t 5.6; TLC (A) R_f 0.37. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.86; H, 10.58; N, 7.72. Found: C, 72.92; H, 10.50; N, 7.73.

***trans*-6-(3-Methyl-2-butenyl)-5-methyl-2-piperidone (9).** A 6.9-g quantity of PCl_5 (0.032 mol) was added to 4 g of **8** (0.022 mol) in ether and the resulting slurry was stirred at 25 °C for 20 h. The reaction flask was evacuated at 25 °C to obtain an oil which was dissolved in 150 mL of CH_2Cl_2 and the resulting solution was poured onto crushed ice containing 100 mL of 10 N NaOH. The mixture was stirred and additional NaOH was added to pH 10–12. The phases were separated and the aqueous phase was extracted repeatedly with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to obtain an oil which was chromatographed on silica gel (grade 62) using hexane–ether–methanol (80:15:5) to obtain 2.6 g of **9** (65%): IR (neat) 1645 cm^{-1} (amide); ^1H NMR δ 5.11 (m, 1 H, C-8 H), 3.75 (m, 1 H, C-6 H), 1.16–2.66 (m, 7 H, $(C)_3CH$ and $(C)_2CH_2$), 1.68 (d, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.03 (d, 3 H, CH_3); GLC (column A, 175 °C, back pressure, 18 psi) R_t 5.8; TLC (A, hexane–ether–methanol, 80:15:5) (A) R_f 0.20. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.86; H, 10.58; N, 7.72. Found: C, 72.69; H, 10.64; N, 7.80.

***trans*-2-(3-Methyl-2-butenyl)-3-methyl-6-methoxy-2,3,4,5-tetrahydropyridine (23).** To a mixture of 2 g of **9** (0.011 mol) and 0.344 g of dimethyl sulfate (0.0027 mol) at 80 °C was added dropwise over a period of 15 min 1.049 g (0.79 mL, 0.0083 mol) of dimethyl sulfate. The resulting mixture was kept at 80 °C 3 h, 2.5 mL of benzene was added, and then the mixture was cooled to 25 °C. A solution of 0.493 g of NaOH (0.012 mol) in 1 mL of water was slowly added with stirring; thereupon the temperature rose to 55 °C. The mixture was stirred at 55–60 °C for 15 min. After cooling, the two phases were separated. The aqueous phase was extracted repeatedly with benzene, the combined extracts were dried ($MgSO_4$), the benzene was distilled off at 760 mm, and the residue was distilled. The fraction collected at 45–46 °C (0.1 mm) consisted of 1.48 g of **23** (69%): IR (neat) 1680 (C=N), 1210 cm^{-1} (OCH_3); ^1H NMR δ 5.27 (m, 1 H, C-8 H), 3.62 (s, 3 H, OCH_3), 2.83–3.57 (m, 1 H, C-6 H), 1.17–2.55 (m, 7 H, $(C)_3CH$ and $(C)_2CH_2$), 1.72 (d, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 1.00 (d, 3 H, CH_3); GLC (column A, 150 °C, back pressure 18 psi) R_t 3.4. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.77; H, 10.85; N, 7.17. Found: C, 73.55; H, 10.93; N, 7.23.

Methyl *erythro*-5-(3-Furamido)-4,8-dimethyl-7-nonenoate (24). A solution of 1.0 g of **23** (0.0051 mol) in 12 mL of THF was added to a suspension of 0.035 g of LiH (0.005 mol) in 10 mL of THF under N_2. After the mixture had been heated to reflux for 3 h and cooled to 25 °C, a solution of 0.668 g of 3-furoyl chloride (0.0051 mol) in 12 mL of THF was added and the mixture was stirred for 7 days at 25 °C. A 12-mL quantity of 6 N aqueous HCl was added slowly with stirring. After continued stirring for 15 min, the mixture was extracted repeatedly with CH_2Cl_2. The combined extracts were dried ($MgSO_4$ and $NaHCO_3$) and the solvent was removed at reduced pressure to obtain an oil which was chromatographed on Alumina (activity 1) with ether and thereby was afforded 0.74 g of oily **24** (47%): ir (neat) 3300 (NH), 3120 (furan CH), 1735 ($COOCH_3$), 1630 (CONH), 871 cm^{-1} (furan); ^1H NMR δ 7.88 (m, 1 H, 3-furyl α-H), 7.36 (m, 1 H, 3-furyl α-H), 6.58 (m, 1 H, 3-furyl β-H), 5.85 (d, 1 H, NH), 5.10 (m, 1 H, C-7 H), 3.96 (m, 1 H, C-5 H), 3.64 (s, 3 H, OCH_3), 1.00–2.60 (m, 7 H, $(C)_3CH$ and $(C)_2CH_2$), 1.65 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 0.91 (d, 3 H, C-4 CH_3); GLC (column A, 200 °C, back pressure 20 psi) R_t 15.6; TLC (A, ether) R_f 0.73. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.41; H, 8.21; N, 4.55. Found: C, 66.16; H, 8.08; N, 4.30.

***erythro*-5-(3-Furamido)-4,8-dimethyl-7-nonenoic Acid (25).** A suspension of 0.75 g of **24** in 20 mL of 5% aqueous KOH was heated to reflux for 2 h. The mixture was cooled to 5 °C, the pH was adjusted to 2 with 6 N aqueous HCl, and the mixture was extracted with four 50-mL portions of methyl isobutyl ketone (MIBK). The combined

MIBK extracts were washed with 25 mL of brine, dried ($MgSO_4$), and the MIBK was removed at reduced pressure to afford an oily residue, which was dried over P_2O_5 at 60 °C (0.5 mm) to produce 0.70 g of **25** (98%): IR (neat) 3318 (NH), 3122 (furan CH), 1710 (COOH), 1630 (CONH), 872 cm^{-1} (furan); ^1H NMR δ 7.88 (m, 1 H, 3-furyl α-H), 7.36 (m, 1 H, 3-furyl α-H), 6.58 (m, 1 H 3-furyl β-H), 5.85 (d, 1 H, NH), 5.10 (m, 1 H, C-7 H), 3.96 (m, 1 H, C-5 H), 1.00–2.60 (m, 7 H, $(C)_3CH$ and $(C)_2CH_2$), 1.65 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 0.91 (d, 3 H, C-4 CH_3). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.45; H, 7.91; N, 4.77. Found: C, 65.52; H, 7.97; N, 4.87.

***trans*-2-(3-Methyl-2-butenyl)-3-methyl-*cis*-6-(3-furyl)piperidine (1).** A 0.5-g quantity of **25** was mixed thoroughly with 0.5 g of CaO and placed in a Pyrex tube fitted with a side arm which projected far into an Erlenmeyer flask cooled at 0 °C. The Pyrex tube was heated by the gentle application of a microburner flame until the enamine distilled. To the enamine in 20 mL of absolute ethanol was added 240 mg of $NaBH_4$ under N_2 and the resulting mixture was stirred 5 h at 25 °C. The solvent was removed at reduced pressure, the residue was dissolved in 25 mL of CH_2Cl_2, 5 mL of H_2O was added, the two phase system was stirred for 10 min, the phases separated, the aqueous extracted repeatedly with CH_2Cl_2, and all CH_2Cl_2 solutions combined and dried. Removal of the CH_2Cl_2 at reduced pressure afforded 225 mg of oil (57%) which according to GLC (column A, 150 °C, back pressure 17 psi) contained 85% **1** (R_t 13.2 min) and 15% of a mixture of what later proved to be **2** and **27** (R_t 14.8). A 140-mg portion of this oil was chromatographed on neutral Alumina (4% H_2O) in a 8 × 1 cm column packed in C_6H_6. Elution with the following solvents in the specified quantities produced the fractions and milligram amounts indicated in parentheses: 1 mL C_6H_6, Al (6); 70 mL C_6H_6, A2 (123); 30 mL C_6H_6, A3 (8); 30 mL CH_2Cl_2–C_6H_6 (1:1), A4 (3). Fraction A1, a brown oil, was the only one which was Dragendorff inactive and was discarded. Fraction A2 was chromatographed on neutral Alumina (3% H_2O) by eluting with 5% ether–hexane in the following amounts, constituting the fractions indicated in parentheses: 50 mL (B1), 100 drops (B2), 36 mL (B3), 30 mL (B4), 20 mL (B5), 220 mL (B6). Fractions B7 and B8 were eluted with 60 mL of chloroform each. Combined fractions B1–B3 consisted of a total of 12 mg of UV active but Dragendorff inactive material and were discarded. Combined fractions B4–B6 consisted of a total of 79 mg of pure **1**. Fraction B7 consisted of a 2-mg mixture of **1** and **2** and B8 consisted of a 16-mg mixture of **1** and **27**. The GLC (column A, 150 °C, back pressure 17 psi), the TLC (B and C), IR (CCl_4), ^1H NMR, and ^{13}C NMR of **1** were identical with those of (−)-anhydronupharamine and are as follows: GLC R_t 13.2; TLC (B) R_f 0.80; TLC (C) R_f 0.54; IR (CCl_4) 2770 (Bohlmann bands), 873 cm^{-1} (3-furyl); ^1H NMR δ 7.27–7.35 (3-furyl α-H), 6.36 (apparent t, J = 1.4 Hz, 1 H, 3-furyl β-H), 5.12 (t, J = 6 Hz, 1 H, CH=C), 3.57 (dd, J = 10.0 and 2.1 Hz, 1 H, C-6 ax H), 1.96–2.52 (m, 3 H), 1.70 (s, CH_3 C(C)=C), 1.64 (s, CH_3 C(C)=C), 0.91 (d, J = 6.0 Hz, 3 H, C-3 CH_3); ^{13}C NMR, see Table I; GLC (column E, 185 °C) R_t 10.15.

***cis*-2-(3-Methyl-2-butenyl)-3-methyl-*cis*-6-(3-furyl)piperidine (2).** Fraction B7 was chromatographed on neutral Alumina (4% H_2O) in a 0.6 × 24 cm column packed in hexane. Elution with 5% ether in hexane in 25-, 15-, and 40-mL volumes yielded fractions C1 (0 mg), C2 (1 mg), and C3 (0.5 mg). Fraction C2 contained pure **2**: TLC (B) R_f 0.82; TLC (C) R_f 0.50; GLC (column A, 150 °C, back pressure 17 psi) R_t 14.8; GLC (column E, 185 °C) R_t 11.04; ^1H NMR δ 7.28–7.36 (3-furyl α-H), 6.41 (apparent t, 1 H, 3-furyl β-H), 5.12 (t, J = 7 Hz, 1 H, C=CH), 3.60 (dd, J = 5.0 and 8.0 Hz, 1 H, C-6 H), 2.77 (td, J = 7.4 and 2.2 Hz, 1 H, C-2 H), 2.05 (br t, J = 7.4 Hz, 2 H, CH_2C=C), 1.63 (s, $CH_3C(C)$=C), 1.71 (d, J = 0.5 Hz, $CH_3C(C)$=C), 0.98 (d, J = 7.2 Hz, 3 H, C-3 CH_3), and whose TLC, GLC, and ^1H NMR were identical with those of naturally occurring (−)-nuphenine.

***trans*-2-(3-Methyl-2-butenyl)-3-methyl-*trans*-6-(3-furyl)-piperidine (27).** Fractions A3 and B8 were combined (24 mg) and chromatographed on neutral Alumina (4% H_2O) in a 1 × 10 cm column. Elution with 5% ether–hexane was carried out in the following volumes constituting the fractions indicated in parentheses: 100 mL (D1), 150 mL (D2), 100 mL (D3). Fraction D4 was eluted with 100 mL of $CHCl_3$. Fraction D2 contained 5 mg of pure **27**: TLC (B) R_f 0.39; GLC (column E, 185 °C) R_t 11.34; IR (CCl_4) 873 cm^{-1} (3-furyl); ^1H NMR δ 7.22–7.46 (m, 2 H, 3-furyl α-H), 6.28 (m, 1 H, 3-furyl α-H), 5.12 (apparent t, J = 7.2 Hz, 1 H, CH=C), 4.11 (t, J = 4 Hz, 1 H, C-6 H), 1.72 (s, CH_3 C(C)=C), 1.66 (s, $CH_3C(C)$=C), 0.89 (d, J = 6.0 Hz, 3 H, C-3 CH_3); ^{13}C NMR, see Table I.

Nuphenine and (−)-Anhydronupharamine. These two alkaloids had been isolated in these laboratories from *N. luteum* subsp. *variegatum* and *N. japonicum*, respectively, and were purified by elution chromatography on Alumina immediately before comparison with synthetic samples. Optical rotations, ^1H NMR, and IR of these samples agreed with those reported earlier for (−)-nuphenine (**2**) and (−)-anhydronupharamine (**1**). The ^{13}C NMR of these two compounds are reported in Table I.

5-(3-Furamido)pentanoic Acid (17). Procedure A. A suspension of 500 mg of methyl 5-(3-furamido)pentanoate, **15**,[9] in 10 mL of 2.25% aqueous KOH was heated to reflux for 2 h, during which time solution resulted. The mixture was cooled to 25 °C over the course of 1 h, the pH was adjusted to 2.0 with 25% aqueous H_2SO_4, and the mixture was repeatedly extracted with 50-mL quantities of methyl isobutyl ketone. The combined extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure to obtain an oil which was dissolved in 25 mL of ether. From this solution crystals were formed on inducement. Drying these crystals at 40 °C at reduced pressure gave 400 mg of **17** (85%): mp 118–119 °C.

Procedure B. To a solution of 5 g of 5-aminopentanoic acid (0.04 mol) in 150 mL of H_2O was added 250 mL of methyl isobutyl ketone (MIBK) and the pH of the mixture was adjusted to 8.5 with 10% aqueous KOH. A 6.68-g sample of 3-furoyl chloride (0.05 mol) in 75 mL of MIBK was added in one portion with vigorous stirring. As the pH dropped it was adjusted to 8.0–8.5 by dropwise addition of 10% aqueous KOH. The reaction mixture was stirred until the pH remained constant (about 1.5 h), at which point the pH was adjusted to 2.0 with 25% H_2SO_4 and two phases were separated. The aqueous phase was extracted repeatedly with MIBK and all the MIBK extracts and solutions were combined and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave an oil which, in the manner described in procedure A above, was transformed to 8.7 g of crystalline **17** (97%): mp 118–119 °C; IR (KBr) 3340 (NH), 1700 (COOH), 1620 (CONH), 875 cm^{-1} (3-furyl); ^1H NMR (Me_2SO-d_6) δ 8.15 (m, 2 H, 3-furyl α-H and COOH), 7.70 (m, 1 H, 3-furyl α-H), 6.85 (m, 1 H, 3-furyl β-H), 3.32 (m, 2 H, C-5 H), 2.25 (m, 2 H, C-2 H), 1.52 (m, 4 H, C-3 and C-4 H). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.85; H, 6.22; N, 6.63. Found: C, 57.00; H, 6.46; N, 6.56.

2-(3-Furyl)piperidine (20). A 1.5-g sample of **17** was mixed thoroughly with 1.5 g of CaO and the mixture was heated as described above in the preparation of **1**. The resulting distillate was collected in 25 mL of 10% aqueous HCl, the pyrolysis tube was rinsed with $CHCl_3$, and the solid residue was extracted with $CHCl_3$. The aqueous HCl solution and the combined $CHCl_3$ solutions were added to a separatory funnel. After shaking, the $CHCl_3$ layer was discarded, the aqueous layer was cooled to 5 °C, mixed with ether, and basified to pH 10 with 20% NaOH. The aqueous phase was extracted repeatedly and all ether extracts were combined and dried ($MgSO_4$). Removal of the ether at reduced pressure gave 550 mg of brown oily **13** (52%): GLC (column A, 150 °C, back pressure 12 psi) R_t 3.1. A 500-mg portion of **13** in 5 mL of dry EtOH under N_2 was mixed with 250 mg of $NaBH_4$ and the resulting heterogeneous mixture was stirred at 25 °C for 5 h. The EtOH was removed at reduced pressure, the residue was suspended in ether, water was added to the suspension, and the layers were separated. The aqueous layer was extracted with ether and all ether extracts were combined and dried ($MgSO_4$). Removal of the ether at reduced pressure gave 432 mg of brown oily **20** (85%): GLC (column A, 150 °C, back pressure 12 psi) R_t 2.1; IR 2920, 2840 (CH), 870 cm^{-1} (3-furyl); ^1H NMR δ 7.35 (m, 2 H, 3-furyl α-H), 6.45 (m, 1 H, 3-furyl β-H), 2.50–3.80 (m, C-2 and C-6 H), 1.75 (6 H, m, C-3, C-4, and C-5 H); ^{13}C NMR is given in Table I. Anal. Calcd for $C_9H_{14}NOCl$: C, 57.60; H, 7.52; N, 7.37. Found: C, 57.49; H, 7.71; N, 7.37.

5-(3-Furamido)hexanoic Acid (18). A suspension of 300 mg of methyl 5-(3-furamido)hexanoate[9] in 6 mL of 2.25% aqueous KOH was treated as **15** in the preparation of **17** (procedure A) described above. In that manner was obtained 242 mg of **18** (80%): mp 112–113 °C; IR (KBr) 3300 (NH), 1700 (COOH), 1630 (CONH), 875 cm^{-1} (3-furyl); ^1H NMR (Me_2SO-d_6) δ 8.31 (s, 1 H, COOH), 7.83 (m, 2 H, 3-furyl α-H), 6.97 (m, 1 H, 3-furyl β-H), 3.8–4.3 (m, 1 H, C-5 H), 2.00–2.45 (m, 2 H, C-2 H). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 56.85; H, 6.72; N, 6.21. Found: C, 58.52; H, 6.77; N, 6.47.

***cis*- and *trans*-6-Methyl-2-(3-furyl)piperidine (21 and 22).** A mixture containing 440 mg of **18** and 440 mg of CaO was treated as described above in the preparation of **1**. In this manner was obtained 191 mg of a light brown oily **19** (60%): GLC (column A, 150 °C, back pressure 16 psi) R_t 3.1. A 185-mg portion of **19** in 3 mL of dry EtOH under N_2 was mixed with 185 mg of $NaBH_4$ and the resulting suspension was treated as described above in the preparation of **1**. Thereby was obtained 150 mg of a light brown oily mixture of **21** and **22** (80%), GLC (column A, 150 °C, back pressure 16 psi), R_t 2.4 (91% **21**) and 3.1 (9% **22**), which was chromatographed on a neutral alumina (activity 2) column (1 × 11 cm) eluted with CH_2Cl_2, in 20 (E1), 7 (E2) and 170 mL (E3) fractions and with $CHCl_3$ in 75 (E4) and 100 mL (E5) fractions. Fraction E3, 69 mg, contained **21**: GLC (column E, 150 °C) R_t 5.27; TLC (Alumina, twice developed, once with CH_2Cl_2 then

$CHCl_3$) R_f 0.38; IR (CCl_4) 2778 (Bohlmann bands). 873 cm^{-1} (3-furyl); ^1H NMR δ 7.31 (m, 2 H, 3-furyl α-H), 6.36 (m, 1 , 3-furyl β-H), 3.60 (dd, J = 10.4 and 3.0 Hz, 1 H, C-2 H), 2.78 (q'd, 1 H, C-6 H), 1.05 (d, J , 6.6 Hz, 3 H, C-2 CH_3); ^{13}C NMR, see Table I; high-resolution MS, obsd/calcd mass (formula) 165.1151/165.1152 ($C_{10}H_{15}NO$).

Fraction E4 was chromatographed on a 1 × 11 cm column of neutral fractions and a 30-ml $CHCl_3$ fraction (F4). Fraction F4 was chromatographed on a 0.7 × 2-cm column of neutral Alumina (activity 2) with 150 mL of CH_2Cl_2 (G1) and two 75-mL portions of $CHCl_3$–CH_2Cl_2 (1:9) (G2 and G3). Fractions F3 (3 mg) and G3 (7 mg) were combined and consisted of pure **22**: GLC (column E, 150 °C) R_t 6.06; TLC (Alumina, twice developed, once with CH_2Cl_2 and then $CHCl_3$) R_f 0.31; IR (CCl_4) 2718 (very weak Bohlmann bands), 873 cm^{-1} (3-furyl); ^1H NMR δ 7.24–7.44 (m, 2 H, 3-furyl α-H), 6.36 (m, 1 H, 3-furyl β-H), 4.10 (t, J = 4 Hz, 1 H, C-2 H), 3.04 (q'd, J = 7.0 and 2.2 Hz, 1 H, C-6 H), 1.11 (d, J = 6.0 Hz, 3 H, C-6 CH_3); ^{13}C NMR, see Table I; high-resolution MS, obsd/calcd mass (formula) 165.1173/165.1152 ($C_{10}H_{15}NO$).

Registry No.—**1**, 61949-86-8; **2**, 61949-87-9; **3**, 110-93-0; **4**, 53067-23-5; **5**, 61900-43-4; **6**, 61900-44-5; **7**, 61900-45-6; **8**, 61900-46-7; **9**, 61900-47-8; **13**, 61900-48-9; **15**, 61586-90-1; **17**, 61900-30-9; **18**, 61900-31-0; **19**, 61900-32-1; **20**, 61900-33-2; **21**, 61900-34-3; **22**, 61900-35-4; **23**, 61900-36-5; **24**, 61900-37-6; **25**, 61900-38-7; **27**, 61949-85-7; dimethyl carbonate, 616-38-6; hydroxylamine HCl, 5470-11-1; dimethyl sulfate, 77-78-1; 3-furoyl chloride, 26214-65-3; 5-aminopentanoic acid, 660-88-8; 5-(3-furamido)hexanoate, 61900-39-8; (−)-nuphenine, 4850-01-5; (−)-anhydronupharamine, 4849-88-1.

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A Carbon-13 Nuclear Magnetic Resonance Study of Thiol Esters

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The ^{13}C NMR chemical shifts for each of the carbons of a number of simple thiol esters have been measured in Me_2SO-d_6 and $CDCl_3$ and the results related to known chemical properties of the thiol ester function. In general the chemical shift of the thiol ester carbonyl carbon occurs some 15–20 ppm further downfield than that found for all other carboxylic acid derivatives reported to date. The carbon α to the carbonyl function in thiol esters is also shifted downfield by about 10 ppm relative to the α carbon in acids, oxygen esters, or amides. The effect of carbon group and halogen substituents on thiol ester chemical shifts has been analyzed. A solvent study on β-hydroxy thiol esters shows that the carbonyl carbon is shielded in Me_2SO-d_6 relative to $CDCl_3$, which may be attributed to intramolecular hydrogen bonding in the latter solvent. Carbon-13 chemical shift changes resulting from conversion of mercaptans to thiol ester derivatives indicate relatively little difference between *S-tert*-butyl and other types of *S*-alkyl thiol esters in contrast to results obtained previously with *tert*-butyl oxygen esters.

The thiol ester group **1** is the ester function of choice in condensation and acyl transfer reactions occurring in biochemical systems.[1] In contrast to (oxygen) esters or amides, relatively little is known about the electronic structure of this group. As a result of our interest in the chemistry and properties of thiol esters, we have undertaken a ^{13}C NMR study of this class of compounds. A search of the literature has not produced any general ^{13}C NMR studies on the thiol ester function.[2] We have thus obtained natural abundance ^{13}C NMR spectra for some 30 different compounds. These results are discussed in connection with ^{13}C NMR data available for other carbonyl derivatives.[3,4] Substituent effects of the thiol ester group are analyzed and the effect of structure on thiol ester chemical shifts has been examined. Finally, we have focused attention on the relationship of these ^{13}C NMR results to the chemistry and biological properties of the thiol ester function.

1

Experimental Section

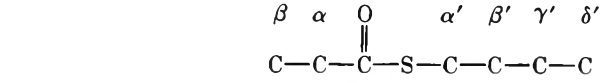
Spectra. The ^{13}C NMR spectra were obtained on ca. 20–25% (w/v) solutions in $DCCl_3$ or Me_2SO-d_6 using a Varian CFT-20 spectrometer

Table I. Carbon-13 Chemical Shifts for Thiol Ester Carbonyl Carbons[a]

R	R′							
	Methyl	Ethyl	*n*-Propyl	Isopropyl	*n*-Butyl	*tert*-Butyl	Benzyl	Phenyl
Methyl	195.4	195.0	194.9	195.0	194.9[b]	195.6	194.5	193.2
		195.3	*195.6*	*195.7*	*195.2*	*196.3*	*194.7*	*193.3*
Ethyl		199.3		199.2		199.9		
						200.8		
Isopropyl						203.5	202.3	
						204.7		
Cyclopropyl						198.6		
Phenyl		191.2			191.0			
					191.7			
Chloromethyl						193.2	193.3	
1-Chloroethyl						196.6		
Dichloromethyl					191.2			
Acetyl								*(189.2)*[c,d]

[a] δ_C ppm from Me_4Si (internal standard) in Me_2SO-d_6. Numbers in italics refer to chemical shifts recorded in $CDCl_3$. [b] The reported value[2] in dioxane is 194.1 ppm. [c] The other carbonyl carbon in *S*-phenyl thiolpyruvate had a value of 193.2 ppm. [d] Registry no., 13884-99-6.

Table II. Carbon-13 Alkyl Carbon Chemical Shifts for Thiol Ester Derivatives[a]



Registry no.	R	R′	α	β	α′	β′	γ′	δ′
1534-08-3	Methyl	Methyl	30.2		11.3			
625-60-5	Methyl	Ethyl	30.5[b]		23.1	14.7		
			30.5		*23.6*	*14.8*		
2307-10-0	Methyl	Propyl	30.5		30.5	22.7	13.1	
			30.6		*23.0*	*31.1*	*13.3*	
926-73-8	Methyl	Isopropyl	30.6[b]		34.4[b]	22.7		
			30.6		*34.8*	*23.0*		
928-47-2	Methyl	Butyl	30.5		28.3[c]	31.6	21.6	13.5
			30.5		*28.9*	*31.8*	*22.1*	*13.6*
999-90-6	Methyl	*tert*-Butyl	31.2		47.4	29.5		
			31.2		*47.8*	*29.8*		
32362-99-5	Methyl	Benzyl	30.1		32.7			
			30.2		*33.4*			
934-87-2	Methyl	Phenyl	30.1					
			30.0					
3232-39-1	Methyl	Acetyl	*32.6*					
2432-42-0	Ethyl	Ethyl	37.1	9.5	22.7	14.8		
2432-47-5	Ethyl	Isopropyl	37.0	9.4	34.1	22.8		
61540-13-4	Ethyl	*tert*-Butyl	37.3	9.2	47.1	29.4		
			37.9	*9.6*	*47.5*	*29.9*		
29786-94-5	Isopropyl	*tert*-Butyl	43.0[b]	19.2	46.9[b]	29.6		
			43.4	*19.4*	*47.3*	*29.9*		
61915-58-0	Isopropyl	Benzyl	42.4	19.1	32.2			
58058-56-3	Cyclopropyl	*tert*-Butyl	22.4	9.6	47.4	29.6		
1484-17-9	Phenyl	Ethyl			23.0	14.7		
7269-35-4	Phenyl	Butyl			28.3	31.4	21.7	13.5
					28.7	*31.8*	*22.1*	*13.6*
56377-45-8	Chloromethyl	*tert*-Butyl	48.1[b]		48.5[b]	29.3		
56377-58-3	Chloromethyl	Benzyl	48.1		33.0			
56377-47-0	1-Chloroethyl	*tert*-Butyl	59.7	21.5	48.8	29.5		
61915-59-1	Dichloromethyl	Butyl	70.1		(29.4)	(30.6)	21.3	13.4

[a] δ ppm from Me_4Si (internal standard) in Me_2SO-d_6. Chemical shifts recorded in italics refer to values obtained in $CDCl_3$. [b] Assignments based in part on off-resonance decoupled ^{13}C NMR spectra. [c] The reported values[2] in dioxane are 30.1 (α), 28.7 (α′), 32.1 (β′), 22.2 (γ′), and 13.6 (δ′).

with noise decoupling. The chemical shifts are referenced to internal Me_4Si. The precision of the chemical shift data is at least ±0.05 ppm (8K data points in the time domain for a 225 ppm spectral window).

Materials. *S*-Phenyl thiolacetate, γ-thiobutyrolactone, *S*-ethyl thiolpropionate, and diacetyl sulfide were obtained from Aldrich Chemical Co. *S*-Methyl thiolacetate, *S*-isopropyl thiolacetate, *S*-isopropyl thiolpropionate, and *S*-ethyl thiolbenzoate were purchased from Wateree Chemical Co. *S*-Propyl thiolacetate and *S*-butyl thiolacetate were obtained from Columbia and *S*-ethyl thiolacetate and *S*-butyl thiolbenzoate were purchased from Pfaltz and Bauer. The purity of these commercial samples was checked by ^1H NMR. They

Table III. Carbon-13 Chemical Shifts for Certain β-Hydroxy Thiol Esters in Me_2SO-d_6 and $CDCl_3$[a]

Registry no.	β-Hydroxy thiol ester				Solvent	C=O	α	β	R⁵	Δδ Me_2SO-d_6 relative to $CDCl_3$				
	R¹	R²	R³	R⁴	R⁵					R¹	C=O	α	β	R⁵	R¹
58058-57-4	Ph	Ph	H	H	$C(CH_3)_3$	Me_2SO-d_6	197.4	54.7	76.3	47.4[b]	29.3[c]	146.9[d]	−4.0	+0.6	−1.7	−1.5	−0.3	+1.0
						$CDCl_3$	*201.4*	*54.1*	*78.0*	*48.9*	*29.6*	*145.9*						
58058-60-9	Ph	Ph	H	H	CH_2Ph	Me_2SO-d_6	195.5	54.5	76.7	32.2[e]		147.0[d]	−4.0	+0.5	−1.2	−0.9		+1.4
						$CDCl_3$	*199.5*	*54.0*	*77.9*	*33.1*		*145.6*						
58058-61-0	Ph	Ph	H	H	Ph	Me_2SO-d_6	193.6	54.5	76.2			146.9[d]	−5.0	+0.6	−1.7			+1.3
						$CDCl_3$	*198.6*	*53.9*	*77.9*			*145.6*						
58105-75-2	Ph	H	CH_3[f]	CH_3[f]	$C(CH_3)_3$	Me_2SO-d_6	205.4	55.2	76.8	46.6[b]	29.5[c]	141.8[d]	−3.1	+0.3	−2.2	−1.0	0.0	+1.6
						$CDCl_3$	*208.5*	*54.9*	*79.0*	*47.6*	*29.5*	*140.2*						
41823-07-8	H	H	H	PH	Ph	Me_2SO-d_6	196.5	62.3[g]	63.4[g]				−1.8	+0.1	−1.1			
						$CDCl_3$	*198.3*	*62.2*	*64.5*									
42479-96-9	Ph	H	H	H	Ph	Me_2SO-d_6	194.2	52.9	69.6			144.2[d]	−2.5	+0.7	−1.1			+1.8
						$CDCl_3$	*196.7*	*52.2*	*70.7*			*142.4*						

[a] δ ppm from Me_4Si (internal standard) in Me_2SO-d_6. Numbers in italics refer to values obtained in $CDCl_3$. [b] Tertiary carbon of *tert*-butyl group. [c] Methyl of *tert*-butyl group. [d] Carbon one of the β-phenyl group. [e] Benzyl carbon. [f] The two α-methyl groups had chemical shifts of δ 20.0 and 21.5 in Me_2SO-d_6 and δ 19.5 and 23.5 in $CDCl_3$. [g] Assignments based in part on off-resonance decoupled spectra.

were all used without further purification. *S-tert*-Butyl thiolacetate,[5] *S*-benzyl thiolacetate,[6] *S-tert*-butyl thiolisobutyrate,[7] *S-tert*-butyl chlorothiolacetate,[8] *S*-phenyl thiolpyruvate,[9] *S-tert*-butyl cyclopropanecarbothioate,[10] *S-tert*-butyl α-chlorothiolpropionate,[11] *S*-benzyl chlorothiolacetate,[11] *S-tert*-butyl thiolpropionate,[12] α-methyl-γ-thiobutyrolactone,[12] *S-tert*-butyl β,β-diphenyl-β-hydroxythiolpropionate,[10] *S*-benzyl β,β-diphenyl-β-hydroxythiolpropionate,[10] *S*-phenyl β,β-diphenyl-β-hydroxythiolpropionate,[10] *S-tert*-butyl α,α-dimethyl-β-phenyl-β-hydroxythiolpropionate,[10] *S*-phenyl β-phenyl-β-hydroxythiolpropionate,[10] and *S*-phenyl α-phenyl-β-hydroxythiolpropionate[13] were prepared according to literature methods.

***S*-Benzyl thiolisobutyrate** was obtained from isobutyryl chloride, benzyl mercaptan, and pyridine according to the procedure described previously for the synthesis of *S-tert*-butyl bromothiolacetate.[11] The *S*-benzyl thiolisobutyrate was isolated as a colorless oil following distillation under reduced pressure: bp 150–152 °C (15 mm); $n^{23}D$ 1.5405; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.18 (d, 6 H, J = 7 Hz), 2.74 (septet, 1 H, J = 7 Hz) 4.13 (s, 2 H), 7.33 (s, 5 H); IR (film) 1680 cm^{-1}. Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26; S, 16.50. Found: C, 68.31; H, 7.25; S, 16.27.

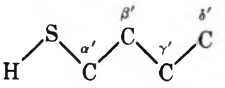
***S*-Butyl dichlorothiolacetate** was obtained in a similar way[11] from dichloroacetyl chloride, butyl mercaptan, and pyridine as a colorless oil: $n^{28}D$ 1.4975; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.75–1.15 (t, 3 H), 1.15–2.0 (m, 4 H), 3.03 (t, 2 H), 6.17 (s, 1 H); IR (film) 1675 cm^{-1}. Anal. Calcd for $C_6H_{10}OSCl_2$: C, 35.83; H, 5.01; S, 15.94. Found: C, 35.66; H, 5.13; S, 16.12.

Results and Discussion

The chemical shifts (δ_c, ppm from Me_4Si) for a series of simple thiol esters are recorded in Tables I–III. The signals corresponding to the carbonyl carbons as well as many of the carbons attached to halogen or oxygen heteroatoms are easily distinguished as a result of their low field chemical shifts. For other carbons, assignments were based on readily recognizable trends for a particular type of carbon observed within a series of similar structures. For example, eight different *S-tert*-butyl thiol esters were examined. In all of these spectra taken in Me_2SO-d_6 we observed a high intensity peak between δ 29.2 and 29.7 which was assigned to the methyl groups, and a low intensity peak between δ 46.6 and 48.5 which was assigned to the tertiary carbon of the *tert*-butyl group. Certain assignments were more difficult and are based solely on analogy with the corresponding carbon in the parent alkanes, alcohols, ethers, mercaptans, and/or oxygen esters reported previously.[3,4] In many cases it was possible to confirm these assignments by single frequency off-resonance decoupling experiments. Where uncertainty still exists with respect to a given assignment, the number is indicated in brackets in Tables I–V. However, possible ambiguities in these assignments are not of major significance for the conclusions that we have drawn in our discussion.

Of considerable interest is the result that the chemical shift of the carbonyl carbon in thiol esters generally occurs in the 193–203-ppm range for aliphatic thiol esters. This value is some 15–20 ppm further downfield than that found for the carbonyl carbon of all other carboxylic acid derivatives reported to date[3,4] including the parent acids,[14,15] esters,[14,16] amides,[4,14,17] acid chlorides,[4,14,18] anhydrides,[4,14a] carboxylate salts,[15b] and other derivatives.[4] γ-Thiobutyrolactone and α-methyl-γ-thiobutyrolactone have carbonyl chemical shifts of 209.4 and 210.5 ppm, respectively, compared to a value of 178.0 ppm for γ-butyrolactone.[14] This marked difference in chemical shift, characteristic of the thiol ester carbonyl carbon, may potentially be exploited in numerous ways including the use of the ^{13}C NMR method in biochemical studies on coenzyme A thiol ester derivatives insofar as the thiol ester carbonyl carbon should appear further downfield than any other carbon in the complex coenzyme A structure. Our results would suggest a value of 193–195 ppm for the thiol ester carbonyl of acetyl CoA.[19] The 193–203-ppm range found for thiol esters closely approaches that reported for aldehydes and

Table IV. Carbon-13 Chemical Shifts for Simple Mercaptans[a]



Registry no.	Mercaptan	α′	β′	γ′	δ′
107-03-9	Propyl mercaptan[b]	(26.0)	(26.8)	12.8	
75-33-2	Isopropyl mercaptan	29.9[d]	27.4[d]		
109-79-5	Butyl mercaptan[c]	23.6	35.6	21.0	13.4
		24.3	*36.2*	*21.5*	*13.5*
75-66-1	*tert*-Butyl mercaptan	40.7	34.7		
		41.1	*35.0*		
100-53-8	Benzyl mercaptan	27.8			

[a] δ_C ppm from Me_4Si (internal standard) in Me_2SO-d_6. Chemical shifts recorded in italics are values obtained in $CDCl_3$. [b] The reported[38] values in CD_3OD are 26.4 (α′), 27.6 (β′), and 12.6 (γ′). [c] The reported[38] values in CD_3OD are 24.6 (α′), 37.1 (β′), 22.3 (γ′), and 13.9 (δ′). [d] Assignments based in part on off-resonance decoupled ^{13}C NMR spectra.

Table V. Carbon-13 Chemical Shift Changes (Δδ, ppm) Associated with Formation of Thiol Ester Derivatives of Mercaptans[a]

Thiol ester	α′	β′	γ′	δ′
S-Propyl thiolacetate	(+4.5)	(−4.1)	+0.3	
S-Isopropyl thiolacetate	+4.4	−4.7		
S-Butyl thiolacetate	+4.8	−4.1	+0.6	+0.1
	+4.6	*−4.4*	*+0.5*	*+0.1*
S-*tert*-Butyl thiolacetate	+6.7	−5.2		
	+6.7	*−5.2*		
S-Benzyl thiolacetate	+4.9			
S-Isopropyl thiolpropionate	+4.2	−4.6		
S-*tert*-Butyl thiolpropionate	+6.4	−5.3		
	+6.5	*−5.1*		
S-*tert*-Butyl thiolisobutyrate	+6.2	−5.1		
	+6.3	*−5.1*		
S-Benzyl thiolisobutyrate	+4.3			
S-*tert*-Butyl cyclopropanecarbothioate	+6.7	−5.1		
S-*tert*-Butyl chlorothiolacetate	+7.8	−5.3		
S-Benzyl chlorothiolacetate	+5.1			
S-*tert*-Butyl α-chlorothiolpropionate	+7.5	−5.2		
S-Butyl thiolbenzoate	+4.7	−4.2	+0.6	+0.1
	+4.4	*−4.5*	*+0.6*	*+0.1*

[a] The data represent chemical shifts of the *S*-alkyl carbons of the indicated thiol ester relative to the analogous carbon in the corresponding mercaptans. Comparisons were made in Me_2SO-d_6 or $CDCl_3$ (italics). The values were calculated from data in Tables II and IV.

ketones.[3,4] In this connection it is noteworthy that in many ways thiol esters resemble ketones or aldehydes in their chemical properties. For example, unlike oxygen esters, acids, or amides, thiol esters are rapidly reduced by sodium borohydride.[20] We have also recently found that the migratory aptitude of the thiol ester group is comparable to the ketone in the boron trifluoride induced rearrangement of α,β-epoxy carbonyl systems. Both groups migrate more readily than the oxygen ester.[21]

Many of the substituent effects observed earlier in ^{13}C NMR studies of other carbonyl compounds were also found in our analysis of thiol esters. For example, as in the case of aldehydes, ketones, acids, esters, and amides,[3,4] replacement of an α hydrogen with a methyl group causes a substantial downfield shift for the thiol ester carbonyl carbon (cf. Table I and the values for *S*-*tert*-butyl thiolacetate, thiolpropionate, and thiolisobutyrate). It is interesting that in the case of thiol esters the shift (~4 ppm) is somewhat greater than noted earlier (2–3 ppm) for aldehydes, ketones, acids, and oxygen esters.[3] A relatively large increment (4.5 ppm) is found, however, in comparing acetamide with propionamide.[4b] Substitution at the α position with chlorine causes an upfield change (1–2 ppm) in the chemical shift of the carbonyl carbon in Me_2SO-d_6 (cf. *S*-*tert*-butyl thiolacetate and chlorothiolacetate). A similar effect due to α-chlorine substitution has been observed for ketones, carboxylic acids, and acid chlorides.[3,4] Attachment of a phenyl group or a cyclopropane ring to the thiol ester carbonyl carbon also causes a substantial upfield shift (cf. Table I. Compare *S*-butyl thiolbenzoate with *S*-butyl thiolacetate and *S*-*tert*-butyl cyclopropanecarbothioate with *S*-*tert*-butyl thiolisobutyrate). In contrast to the marked changes in the carbonyl chemical shift caused by modification of the acyl portion of the thiol ester, relatively little change occurs when the hydrocarbon group attached to sulfur is modified. Thus, the carbonyl resonance for *S*-methyl, *S*-ethyl, *S*-propyl, *S*-isopropyl, *S*-butyl, and *S*-*tert*-butyl thiolacetates all come between 194.4 and 195.6 ppm in Me_2SO-d_6. An upfield shift of approximately 2 ppm occurs in *S*-phenyl thiolacetate (193.2 ppm in Me_2SO-d_6) and the carbonyl carbon of diacetyl sulfide [$(CH_3CO)_2S$] comes at still higher field (191.8 ppm in $CDCl_3$). A chemical shift of 194.5 ppm found for thioacetic acid has been ascribed to the thiocarbonyl group in tautomer **2**.[4] However, the weight of experimental evidence argues against a thiocarbonyl group in thioacetic acid favoring instead a carbonyl group as in tautomer **3**.[1c,22] The 194.5-ppm value obtained for thioacetic acid is in good agreement with structure **3** in view of the result that

2 **3**

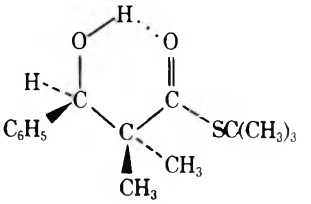
S-alkyl and *S*-aryl thiolacetates all fall in the 193–196-ppm range.

A semiempirical approach has been developed to relate carbonyl chemical shifts to the π bond polarity of the carbonyl function.[23] This π bond polarity depends to a considerable extent on the relative electron-withdrawing ability of attached groups as gauged by Taft's inductive parameter σ_I.[24] Based on this analysis the lower electron-attracting ability of sulfur compared to oxygen would result in greater shielding of the carbonyl carbon in oxygen esters relative to the corresponding thiol esters.[14,16] The effect of p–p π bonding in thiol esters on the chemical shift of the carbonyl carbon is less certain. Indeed the relative degree of resonance in thiol esters has recently been questioned by Noe[25] in a DNMR study of rotational barriers in thioacetic acid. This work suggests that there is considerably more resonance in thio acids than in the corresponding oxygen acids or esters in contradiction to conclusions reached in earlier studies.[1c,26,27]

The deshielding effect of the thiol ester function at the α carbon is very similar to that caused by a ketone or aldehyde group. Thus, the methyl carbon in *S*-alkyl and *S*-aryl thiolacetates occurs in the 30–31-ppm range (Table II) while the methyl carbon in acetaldehyde comes at 31 ppm and in aliphatic methyl ketones between 28 and 30 ppm.[3] In contrast, the methyl carbon in acetate esters[3,16f] or acetamides[17b] occurs at about 21 ppm.[3,16f] In this connection it is interesting to note

that the acidity of the α protons in thiol esters is comparable to that in ketones while both ketones and thiol esters are substantially more acidic than the corresponding oxygen esters.[28] Further, we have found recently that the nucleophilicity of thiol ester lithium enolates in substitution reactions with alkyl halides is considerably less than that of the corresponding oxygen ester lithium enolates.[12] Thus again in this instance we see a useful correlation of the ^{13}C NMR data with the chemical properties of thiol esters as compared to data available for ketones, esters, and amides.

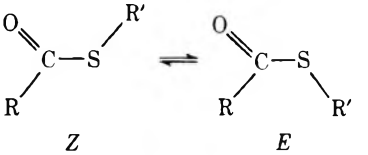
For simple thiol esters such as *S*-ethyl, *S*-phenyl, or *S*-butyl thiolacetates there is relatively little effect on chemical shift values as a result of a change in solvent from the very polar Me_2SO to the less polar chloroform. Generally we observed a slight downfield shift of between 0.1 and 0.6 ppm on going from Me_2SO-d_6 to $CDCl_3$ for the carbonyl carbon as well as most of the other carbons. This is consistent with earlier observations on the small effect of a change in solvent on the carbonyl chemical shift of acetone.[29] In contrast in a study of several β-hydroxy thiol esters we observed a marked downfield shift of the carbonyl carbon of between 1.8 and 5.0 ppm on going from Me_2SO-d_6 to $CDCl_3$ (Table III). It is likely that intramolecular hydrogen bonding is responsible for this solvent effect. Intramolecular hydrogen bonding would be relatively important in chloroform but less so in Me_2SO, where intermolecular hydrogen bonding with solvent molecules is expected to be more significant. Me_2SO has recently been used to rupture intramolecular hydrogen bonds in ^{13}C NMR studies of β-hydroxy (oxygen) esters and amides.[30,31] Hydrogen bonding interactions with ketone and ester carbonyl functions is reported to result in a downfield shift of the carbonyl carbon atom.[14a,29,32] Additional support for strong intramolecular hydrogen bonding in β-hydroxy thiol esters in $CDCl_3$ is seen in the relatively large chemical shift difference of the two α-methyl carbons in *S-tert*-butyl α,α-dimethyl-β-phenyl-β-hydroxythiolpropionate (**4**). The methyls occur at δ 20.0 and 21.5 in Me_2SO-d_6. One is shifted upfield (δ 19.5) and the other downfield (δ 23.5) in $CDCl_3$. Intramolecular hydrogen bonding in $CDCl_3$ would result in restricted rotation about the C_α–C_β and $C_{C=O}$–C_α bonds in **4** such that one methyl would be placed in close proximity to the phenyl group.



4

Also of interest is the result that the α carbon in the β-hydroxy thiol ester system is shielded (0.1–0.7 ppm) while the β carbon is deshielded (1.1–2.2 ppm) as a result of intramolecular hydrogen bonding in $CDCl_3$. This phenomenon was also seen in our analysis of 4-hydroxy-4-methylpentan-2-one [$CH_3COCH_2C(OH)(CH_3)_2$], which gave chemical shifts of 208.3 and 210.5 ppm for carbon 2, 55.8 and 54.2 ppm for carbon 3, and 68.6 and 69.6 ppm for carbon 4 in Me_2SO-d_6 and $CDCl_3$, respectively. Shielding of the α position is then due to increased importance of a fixed conformational state that is characteristic of the intramolecularly hydrogen bonded structure in $CDCl_3$ as opposed to the greater variety of conformations available to the β-hydroxy thiol ester in Me_2SO-d_6.

We have obtained ^{13}C NMR spectra of several simple mercaptans (Table IV) and with this information calculated α' and $\beta'\Delta\delta$ values for certain thiol ester derivatives (Table V). The $\beta'\Delta\delta$ values (C-2 esterification effect) found for thiol esters are in the same direction although somewhat larger than those found for oxygen esters.[16f,h] The fact that relatively little variation is seen in the $\beta'\Delta\delta$ values (5.2 ± 0.2 in Me_2SO-d_6) for a large number of *S-tert*-butyl esters would indicate that the C-2 esterification effect results primarily from interaction of the *S-tert*-butyl group with the carbonyl function rather than the R substituent in the acyl group. A similar pattern is seen for other types of *S*-alkyl thiol esters studied (Table V). This would support the conclusion that *Z* conformation **5** is the major conformation present in these thiol esters.



Z *E*

5 **6**

The origin of nonequivalence in the chemical shifts of syn and anti methyl groups in *N,N*-dimethylformamide has been attributed to electric field effects[33] as well as steric perturbations.[17a,34] An electric field argument has been suggested to account for the large $\alpha'\Delta\delta$ value (C-1 esterification effect) found for *tert*-butyl formate compared to a smaller value obtained for other formate esters.[16f] More recently chemical shifts have been evaluated for a large number of methyl, ethyl, isopropyl, and *tert*-butyl oxygen esters.[16h] A linear relationship was shown to exist between the ^{13}C chemical shifts of the α' carbon and the pK_a values of acids from which the esters were derived. This was explained as a consequence of the polar character of the $-C_{\alpha'}{}^{\delta+}-O_2{}^{\delta-}CR$ bond. With respect to variation of the *O*-alkyl group from primary to secondary and tertiary, the C-1 esterification effect ($\alpha'\Delta\delta$ values) can be correlated with increasing stability of the partial positive charge at the α' carbon.[16h] These results[16h] suggest that the electric field argument is not a major factor in determining this C-1 esterification effect. The results obtained with oxygen esters[16f,h] do not appear to be inconsistent with steric perturbation providing some contribution to the large $\alpha'\Delta\delta$ values found for *tert*-butyl oxygen esters. Steric perturbation resulting in greater deviation from coplanarity[35,36] for the ester function has recently been proposed to account for the large bathochromic shift in the ultraviolet found for *tert*-butyl acetate compared to other alkyl acetates.[37]

The $\alpha'\Delta\delta$ values for thiol esters (Table V) increase with increasing acidity of the acid from which the ester is derived in agreement with the conclusions of Pelletier.[16h] The C-1 esterification effect found for propyl, butyl, or isopropyl thiol esters is in the same direction and generally larger than that found for propyl, butyl, and isopropyl oxygen esters; however, the $\alpha'\Delta\delta$ value found for *S-tert*-butyl thiol esters is considerably smaller than that found for *tert*-butyl oxygen esters. The relatively small difference (~2 ppm) in $\alpha'\Delta\delta$ values between *S-tert*-butyl thiol esters and other types of *S*-alkyl thiol esters is of particular interest and should be contrasted with the very large difference (~10 ppm) found earlier for oxygen esters.[16f,h] In the thiol ester system we may expect some increase in the degree of polarization of the S–C_α' bond when comparing *S-tert*-butyl esters with other alkyl thiol esters, although this effect is expected to be smaller than in oxygen esters[16h] owing to the lower electronegativity of sulfur compared to oxygen. It would seem that this X–C_α' polarization explanation[16h] is sufficient to account for the variation in $\alpha'\delta$ values found for thiol esters without invoking steric perturbation in the *S-tert*-butyl thiol ester system. The larger size of sulfur compared to oxygen would leave the *tert*-butyl further removed from the acyl group in *S-tert*-butyl thiol esters relative to *tert*-butyl oxygen esters. The likelihood of steric perturbation is greater in the *tert*-butyl oxygen ester system.

To what extent this influences the $\alpha'\Delta\delta$ values in *tert*-butyl oxygen esters is not clear based on available information.

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Registry No.—Isobutyryl chloride, 79-30-1; dichloroacetyl chloride, 79-36-7.

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Phase-Transfer Catalyzed Syntheses. 5-Thiacyclohexenecarboxaldehydes and 3,4-Epoxy-2,5-dihydrothiophenes[1]

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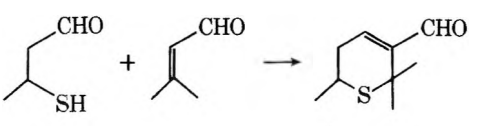
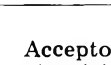
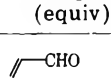
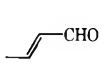
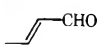
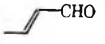
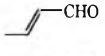
The phase-transfer catalyzed condensation of 3-thioacetoxyaldehydes with acrolein and crotonaldehyde leads to cyclized products **5–9**. Product distributions indicate that no equilibration of intermediates occurs as has been previously noted in pyridine solution. Condensations of α-mercaptocarbonyl compounds with 2-chloroacrylonitrile led to epoxides **11–14** in excellent yields. This reaction may be of some importance in biotin synthesis.

Recently, we have shown that the reaction of 3-mercaptoaldehydes (**1**) with conjugated carbonyl compounds affords, by a conjugate addition–aldol condensation sequence, an excellent route to substituted 5-thiacyclohexene-1-carboxaldehydes (**2**).[3] Compounds related to **2** have previously been shown[4] to be excellent synthons for stereospecific alkene synthesis. However, two drawbacks to the synthesis, as reported,[3] are evident. The first is the difficulty encountered in the purification of mercaptans **1**. Whereas the isomeric 2-mercaptoaldehydes exist largely as dimeric 2,5-dihydroxy-1,4-dithianes[5] which can be purified relatively easily, **1** are polymeric hemithioacetals which are uniformly evil-smelling, viscous oils that decompose (presumbly by dehydration) when distillation is attempted. This leads to complicated mixtures when the preparation of **2** is attempted. Although many examples of **1** are obtained pure enough for direct use in the cyclization, others are not and it was felt that an alternate preparation which avoided this difficulty would be desirable. Replacement of the thiol proton with a suitable protecting group which could be converted into the anion of **1** in situ would achieve this end. Furthermore, as the malodorous properties of most thiols are associated with the SH



1 **2**

Table I. Products and Yields from Crossed Condensations[a,b]

Ester (equiv)	Acceptor (equiv)	Temp, °C	Procedure[c]	Products (%)[d]		
3 (1)	 (1)	0	B	5 (13)	7 (8)	8 (79)
6 (1)	 (1)	0	A	5 (54)	7 (23)	9 (23)
6 (1)	 (1)	−10	A	5 (52)	7 (21)	9 (27)
6 (1)	 (2)	0	B	5 (60)	7 (7)	9 (33)
6 (1)	 (1)	20	B	5 (61)	7 (10)	9 (29)
6 (2)	 (1)	20	B	5 (42)	7 (27)	9 (31)

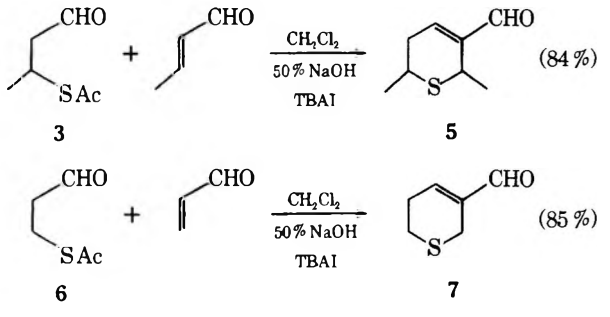
[a] Yields determined by GLC. [b] All reactions carried out using 2 equiv of 50% sodium hydroxide. [c] See Experimental Section. [d] Overall yield in each case was 60–62%.

group, the protected form held the distinctly attractive possibility of being much less noxious to handle. We report here our approach to this problem and some of the unforeseen results that were obtained.

Results and Discussion

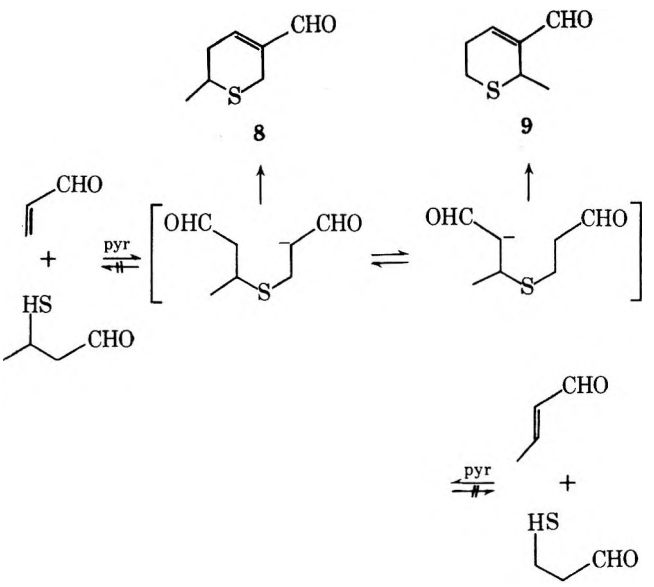
The thiolacetate was an obvious candidate for such a protecting group. 3-Thioacetoxycarbonyl compounds are readily prepared by addition of thiolacetic acid to unsaturated aldehydes and ketones[6] and are prevented from polymerization by virtue of the absence of a sulfhydryl proton. Basic hydrolysis should afford the thiolate ion required for the initiation of the cyclization reaction.

When 3-thioacetoxybutanal (**3**) was subjected to basic hydrolysis using alcoholic sodium hydroxide, neutralization afforded some 3-mercaptobutanol (**4**), but a considerable amount of crotonaldehyde was also formed. Acid-catalyzed methanolysis of **3** did afford **4** in good yield, but the problems previously alluded to regarding its purification arose and thus no advantage was gained. However, application of the phase-transfer technique[7] to the basic hydrolysis in the presence of crotonaldehyde as an acceptor molecule led directly to the formation of 4,6-dimethyl-3-thiacyclohexene-1-carboxaldehyde (**5**) in 84% yield.[8] Similar results were obtained in the condensation of 3-thioacetoxypropanal and acrolein.



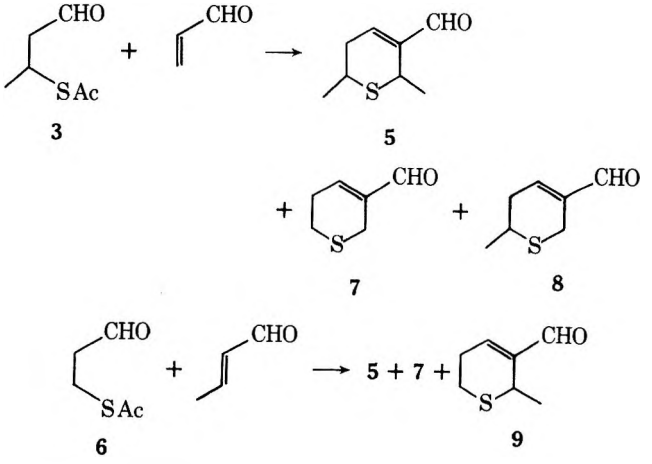
In our previous report,[3] the condensation of 3-mercaptobutanal and acrolein in pyridine solution led to two products—4-methyl-5-thiacyclohexene-1-carboxaldehyde (**8**) and its 6-methyl isomer (**9**). These results were rationalized on the basis of an anion equilibration (Scheme I). The absence of **5** and **7** from these reactions strongly suggested that reversal of the conjugate addition was not competing with ring closure in pyridine solution. It was of interest to determine if the same

Scheme I



results would be obtained under the phase-transfer conditions employed in this work. Evidence obtained previously in somewhat related systems[9] suggested that side reactions such as anion transposition are maximized when the rate of ring closure of the carbanionic intermediates is slow. In the system 50% aqueous sodium hydroxide–dichloromethane, the large amount of energy associated with removing water molecules from the strongly hydrogen-bonded aqueous phase suggests that the solvation of the anionic intermediates *in the organic phase* should be minimal and thus the rate of cyclization might increase dramatically. The near absence in these reactions of polymers of acrolein and crotonaldehyde which are usually formed in the presence of aqueous base[10] confirms that the reactions are in fact occurring in the organic phase.

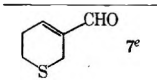
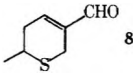
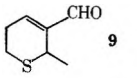
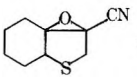
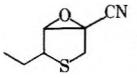
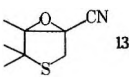
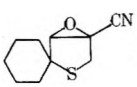
When **3** was condensed with acrolein under phase-transfer conditions, three products were formed, **5**, **7**, and **8**. No trace of **9** could be detected either by NMR or GLC analysis, confirming our hypothesis regarding anion transposition. When the reverse condensation was attempted, a mixture of three materials (**5**, **7**, and **9**) was again obtained, now to the exclusion



of **8**. Several different sets of reaction conditions were tried in an attempt to maximize the yields of **8** and **9** (Table I). As can be seen, these efforts met with limited success. However, the data obtained allow a possible rationalization of the observed results (Scheme II).

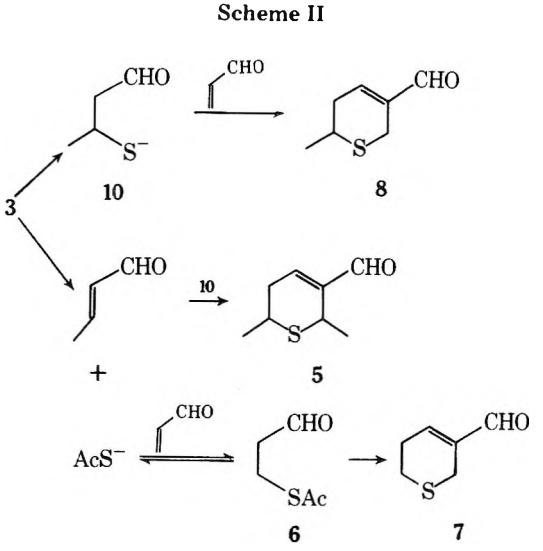
The formation of significant amounts of **5** and **7** and the absence of the products of alternate ring closure seem to exclude the possibility of direct anion equilibration. A more

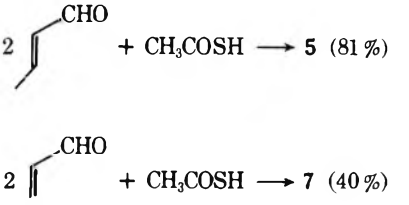
Table II. Spectral Data for Previously Unreported Compounds

Compd	n^{25}D or mp, °C	Infrared, cm^{-1} [a]	m/e (100%) [b]	^{1}H NMR [c,d]
 7 [e]	1.5365	2700 (w), 1690 (vs), 1648 (m)	128	9.33 (s, 1), 6.83 (m, 1), 3.26 (m, 2), 2.70 (m, 4)
 8	1.5316	2715 (w), 1688 (vs), 1647 (s) 1647 (s)	Found 142.0453 Calcd 142.0452	9.50 (s, 1), 6.88 (m, 1), 3.30 (m, 2) 2.95 (m, 1), 2.56 (m, 2), 1.28 (d, 3, J = 6.7 Hz)
 9	1.5413	2720 (w), 1690 (vs), 1649 (s)	Found 142.0453 Calcd 142.0452	9.40 (s, 1), 6.85 (m, 1), 3.70 (m, 1) 2.78 (m, 4), 1.45 (d, 3, J = 6.7 Hz)
 11	61–63	2244 (m), 1451 (vs), 1265 (s) 1250 (m), 944 (s), 912 (s), 870 (s)	Found 181.0561 Calcd 181.0561	3.23 (s, 2), 3.15 (m, 1), 1.75 (m, 8)
 12	1.5080	2240 (w), 910 (s), 855 (m)	Found 155.0405 Calcd 155.0405	3.86 (s, 1), 3.56 (m, 1), 3.27 (d, 2, J = 3 Hz), 1.6 (m, 2), 1.00 (t, 3, J = 7 Hz)
 13	36–37	2242 (w), 1463 (s), 1169 (s), 1137 (s), 941 (vs), 871 (s)	Found 169.0559 Calcd 169.0561	3.35 (s, 2), 1.58 (s, 3), 1.45 (s, 3) 1.40 (s, 3)
 14	110–112	2242 (w), 1450 (m), 1260 (w) 1165 (w), 1150 (w), 1110 (w), 970 (m), 950 (s), 910 (vs), 855 (m)	Found 195.0718 Calcd 195.0718	3.75 (s, 1), 3.48 and 3.32 (AB q, 2, J = 14 Hz), 1.70 (m, 10)

[a] In chloroform solution. [b] In all cases, the molecular ion is the base peak. [c] In deuteriochloroform solution. [d] Tabulation follows the order chemical shift (δ), multiplicity, number of protons, coupling constant. [e] Reference 3.

Scheme II





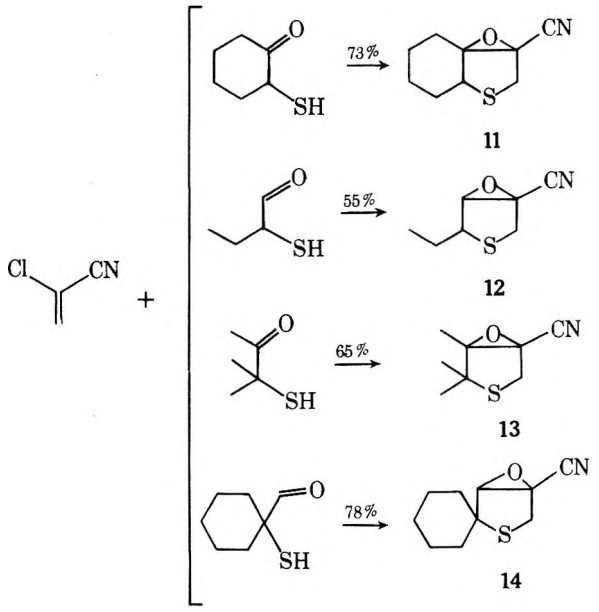
acceptable explanation assumes that the initial reaction between base and thiol ester **3** occurs in the organic phase and involves an elimination–hydrolysis competition leading to some crotonaldehyde and some of the desired anion **10**. Condensation of **10** with acrolein leads to **8** only, while condensation with the crotonaldehyde leads to **5**. Thiolacetate ion adds to acrolein forming **6** which then suffers hydrolysis and condensation with acrolein leading to **7**. Because of the relatively low concentrations of both **6** and crotonaldehyde, the rate of bimolecular reaction between these two would be expected to be very low, accounting for the absence of **9** from the mixture. Why the yield of **9** from the reaction of **6** and crotonaldehyde should be so much lower than that of **8** from **5** and acrolein is not immediately obvious.

In order that the above scheme can operate, it is necessary that the phase-transfer catalyzed addition of thiolacetic acid to crotonaldehyde and acrolein occur. In order to verify this, the reaction between 2 equiv of acceptor, 1 equiv of thiolacetic acid, and 2 equiv of 50% sodium hydroxide was carried out under the standard conditions. In each case, the expected condensation products were obtained. Unfortunately, neither cinnamaldehyde nor acrylonitrile could be induced to react.

Currently there is much interest in devising improved methods for the preparation of biotin and related molecules.[11] These contain a reduced thiophene ring, bearing heteroatom substituents at positions 3 and 4. An obvious possibility for the synthesis of these compounds involves the epoxidation of 2,5-dihydrothiophenes, but this route has proved abortive owing to the very facile oxidation of the sulfur atom.[12] It occurred to us that the incorporation of a leaving group adjacent to the anion-stabilizing group in the acceptor molecule might lead to an intramolecular Darzen's condensation and the desired epoxides. This type of reaction has been noted previously under non-phase-transfer conditions.[11]

In the event, reaction of a variety of α-mercaptocarbonyl compounds with 2-chloroacrylonitrile led to the ready formation of epoxides **11**, **12**, **13**, and **14**, in excellent yields.

The NMR spectra of epoxides **11**–**14** (Table II) require some comment. The spectra of **11** and **13** show a clean singlet for the diastereotopic methylene protons adjacent to sulfur, indicating an accidental degeneracy. The corresponding absorption for **12** appears to be a doublet. This doublet may be due to a long-range coupling through sulfur to the methine proton at C_5 or it may be the center two lines of an AB quartet of which the outer lines are too weak to be seen. In the case of **14**, a clear AB quartet is observable whose calculated coupling constant is 14 Hz. These differences may be ascribed to minor differences in the ring geometries in the four compounds. It should be noted that a similar complexity of the analogous protons in the dihydrothiophene related to **14** has been observed.[14]



Conclusion

To our knowledge, the results described constitute the first report of the successful condensation of reactive aliphatic aldehydes in the presence of strong aqueous base.[10] The application of the phase-transfer technique to these molecules will undoubtedly have considerable future use. Also, the consecutive liberation of a reactive functional group and its utilization under the same reaction conditions is an attractive feature which should find wide application in other systems. We are currently exploring some of these, as well as methods for improving the selectivity for hydrolysis of the thiol esters. These will form the basis of future reports.

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained on a Beckman IR-12 instrument; NMR spectra were run on a JEOLCO C60HL spectrometer and are reported in parts per million downfield from Me_4Si as an internal standard. Mass spectra were run on a Varian-MAT CH5-DF spectrometer under the control of an INCOS computer. Gas chromatographic analyses were performed on an F and M Model 720 instrument, using the following columns; column A, 10 ft × 0.375 in. 20% SE-30 on Chromosorb W; column B, 10 ft × 0.375 in. 20% Carbowax 20M on Chromosorb W; column C, 10 ft × 0.25 in. 20% SE-30 on Chromosorb W. Preparative TLC was performed on 2 mm thick silica gel G.F. plates using 5% ether in petroleum ether as the eluting solvent.

Materials. Crotonaldehyde and acrolein were distilled just prior to use. Compounds **3** and **6** were prepared as outlined in the literature.[6]

General Procedures for Phase-Transfer Catalyzed Reactions. Procedure A. In a 250-mL round-bottom flask fitted with a magnetic stirrer, reflux condenser, nitrogen inlet, and addition funnel were placed 15 mL (0.185 mol) of 50% aqueous sodium hydroxide solution, 100 mL of methylene chloride, and 100 mg of tetra-*n*-butylammonium iodide (TBAI). The system was purged with nitrogen and cooled to the desired temperature. The mixture was stirred vigorously while 0.1 mol of the thiol ester was added rapidly. A pale yellow color developed immediately. After 1–2 min, the acceptor molecule (0.1 mol) was added rapidly. (Note that when acrolein was the acceptor, the ensuing reaction was vigorously exothermic.) The solution was stirred for 3 h, and then allowed to warm to room temperature overnight. After 1 h at reflux (40 °C), the cooled solution was diluted with water, the organic layer separated, and the aqueous phase extracted twice with ether. The combined organic layers were washed with water until the washings were neutral and dried over sodium sulfate and the solvent was removed to give the product(s) which were treated as outlined below. Infrared and NMR spectral data are collected in Table II.

Procedure B. The same general procedure was used except that the thioester and acceptor were added simultaneously to the cooled, stirred mixture containing the base and ammonium salt.

4,6-Dimethyl-5-thiacyclohex-1-enecarboxaldehyde (5). Using procedure A, 84% of **5** was obtained from **3** and crotonaldehyde which was identical in all respects with an authentic sample[3,15] (GLC, column C, 180 °C).

5-Thiacyclohex-1-enecarboxaldehyde (7). Using procedure A, a yellow oil was obtained from **6** and acrolein which showed only one peak on GLC analysis (column C, 180 °C). An analytical sample showed $n^{25}D$ 1.5365; *m/e* 128 (100%); 2,4-DNP mp 250–251 °C (lit.[16] 247–248 °C). Spectral data are included in Table II. This compound should be stored in ether solution to avoid decomposition.

4-Methyl-5-thiacyclohex-1-enecarboxaldehyde (8). Using procedure B, a mixture of **5**, **7**, and **8** in 70% yield was obtained when **3** was condensed with acrolein. These were separated by GLC (column B, 180 °C) and identified by their spectral characteristics.

6-Methyl-5-thiacyclohex-1-enecarboxaldehyde (9). The series of experiments outlined in Table I were performed. In each case, the product mixture was separated into three components by GLC (columns A or B) and identified by their spectral characteristics.

Reaction of thiolacetic acid and crotonaldehyde. The reaction was carried out in the usual fashion by adding the acceptor to a vigorously stirred mixture of 2 equiv of 50% sodium hydroxide, 1 equiv of thiolacetic acid, TBAI, and methylene chloride over a period of 30 min at 0 °C. The mixture was stirred for an additional 2.5 h at 0 °C and then refluxed for 20 min. The organic layer was separated, diluted with ether, washed thoroughly with water, dried, and evaporated. Aldehyde **5** (81%) was obtained as the only product.

Reaction of Thiolacetic Acid and Acrolein. Substituting acrolein for the crotonaldehyde in the above experiment afforded aldehyde **7** (41%).

Synthesis of Epoxynitriles 11, 12, and 13. The following procedure is representative. Sodium hydroxide (50%, 10 mL), methylene chloride (40 mL), and TBAI (150 mg) were cooled (ice–salt bath) in a round-bottom flask fitted with magnetic stirrer, two addition funnels, and a reflux condenser with a nitrogen inlet. 3-Mercapto-3-methyl-2-butanone[17] (2.63 g) in 5 mL of methylene chloride and 2-chloroacrylonitrile (1.75 g) in 5 mL of the same solvent were added simultaneously from the two funnels over a period of 1 h while the mixture was vigorously stirred. The reaction mixture was worked up as usual and the product was purified by preparative TLC to give 65% of pure nitrile **13**.

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Registry No.—**3**, 54278-24-9; **6**, 53943-93-4; **7**, 30058-79-8; **8**, 61049-59-0; **9**, 61348-70-7; **11**, 61348-71-8; **12**, 61348-72-9; **13**, 61348-73-0; **14**, 61348-74-1; crotonaldehyde, 4170-30-3; acrolein, 107-02-8; thiolacetic acid, 68-11-1; 2-mercaptocyclohexanone, 42904-05-2; 2-mercaptobutanal, 53101-85-2; 3-mercapto-3-methyl-2-butanone, 42855-44-7; 1-mercaptocyclohexanecarboxaldehyde, 53101-87-4; 2-chloroacylonitrile, 920-37-6.

References and Notes

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Synthesis and X-Ray Crystal Structure of 1,3,3,4,5,6-Hexamethyl-7-thiabicyclo[2.2.1]hept-5-en-2-one 7-*anti*-Oxide

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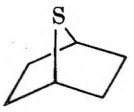
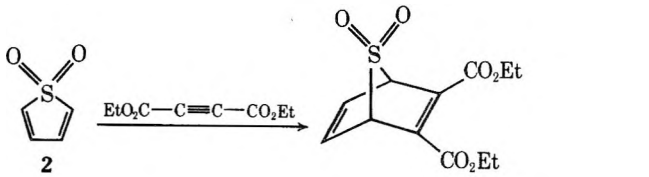
Refluxing a toluene solution containing equimolar quantities of hexamethyl-2,4-cyclohexadienone and ethylene episulfoxide under nitrogen affords hexamethyl-7-thiabicyclo[2.2.1]hept-5-en-2-one 7-*anti*-oxide (**10**) in nearly quantitative yield. The detailed molecular geometry of **10** follows from its x-ray crystal structure. Treatment of 3,4,6,6-tetramethyl-2,4-cyclohexadienone under identical conditions returns starting material.

Although 7-thiabicyclo[2.2.1]heptane (**1**) has been known for some time,[2] only one unsaturated derivative of **1** has been

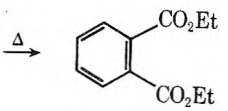


1

isolated.[3] Bailey and Cummins found that treatment of thiophene 1,1-dioxide (**2**) with diethyl acetylenedicarboxylate at 0 °C gave a crystalline compound of molecular formula $C_{12}H_{14}O_6S$ which lost sulfur dioxide upon gentle heating to give diethyl phthalate (**4**).[3] In view of these results, the intermediate was assigned structure **3**.[3]



2 **3**



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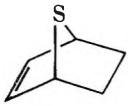
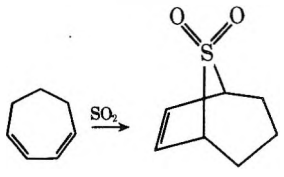
In principle, the 7-thiabicyclo[2.2.1]hept-2-ene skeleton (**5**) should be accessible by the Diels–Alder addition of sulfur



5

monoxide or sulfur dioxide to 1,3-cyclohexadiene (**6**). However, treatment of **6** with sulfur dioxide at −50 °C in the presence or absence of oxygen only leads to copolymerization.[4] Since 1,3-cycloheptadiene (**7**) reacts with sulfur dioxide to give a nearly quantitative yield of 8-thiabicyclo[3.2.1]oct-6-ene 8,8-dioxide (**8**),[5] it has been contended that isolation of the monoadduct of **6** with sulfur dioxide has not been achieved

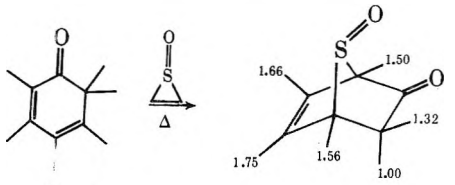


7 **8**

owing to the instability of the Diels–Alder product.[6] We now wish to report the synthesis of a stable derivative of **5**.

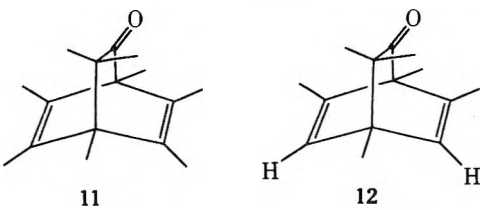
Results and Discussion

Refluxing a toluene solution containing equimolar quantities of hexamethyl-2,4-cyclohexadienone (**9**)[7] and ethylene episulfoxide (which is known to thermally decompose at ca. 100 °C to ethylene and sulfur monoxide[8]) under nitrogen for 5 h proceeded with a ca. 40% conversion of **9** to give a nearly quantitative yield of hexamethyl-7-thiabicyclo[2.2.1]hept-5-en-2-one 7-oxide (**10**).[9] Changing the molar ratio of the reacting species, the time of reaction, or not employing a nitrogen atmosphere all resulted in reduced yields of **10**. However, refluxing **10** in toluene for 1.5 h did not lead to its thermal decomposition.



9 **10**

Unreacted dienone **9** was readily removed from the product by vacuum distillation. Upon extended standing, sulfoxide **10** slowly crystallized from the distillation residue. Alternatively, **9** and **10** could be separated by chromatography on silica gel with benzene–methylene chloride as eluent. Repeated recrystallization of **10** from pentane gave white crystals of mp 84.5–85 °C. The preliminary structure assignment of **10** followed from its spectroscopic characteristics. The infrared spectrum of **10** contains a strong carbonyl absorption at 1738 cm^{-1}, indicative of a five-membered ring ketone, and a strong sulfoxide absorption at 1070 cm^{-1}. The ^1H NMR spectrum of **10** consists of aliphatic methyl singlets at δ 1.56, 1.50, 1.32, and 1.00 and allylic methyl quartets (J = 1 Hz) at δ 1.75 and 1.66. The ^1H NMR spectrum of **10** derived from dienone **9** with a CD_3 group at C-3 in **9**[10] lacks the quartet at δ 1.66 and the quartet at δ 1.75 has sharpened to a singlet. Similarly, the ^1H NMR spectrum of **10** prepared from dienone **9** with a CD_3 group at C-5 in **9**[10] is missing the singlet at δ 1.56. Since the *gem*-dimethyls in **11**[11] and **12**[12] appear at δ 0.82 and 0.90, respectively, the chemical shifts of all of the methyl groups in **10** can be confidently assigned as indicated in the figure.



11 **12**

In order to complete the structure assignment of **10**, it remained to define the stereochemistry at sulfur. Recrystallization of **10** ($C_{12}H_{18}O_2S$, mol wt 226.33) from heptane gave

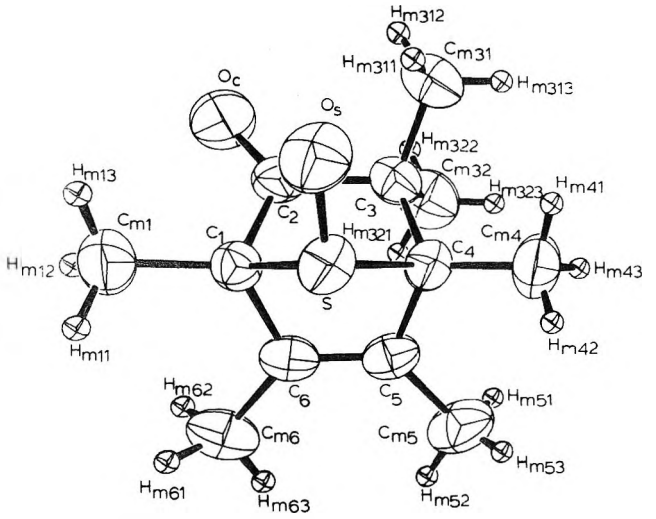


Figure 1. An ORTEP drawing showing the solid-state molecular structure of 1,3,3,4,5,6-hexamethyl-7-thiabicyclo[2.2.1]hept-5-en-2-one 7-*anti*-oxide (**10**). All atoms except hydrogen are represented by a (50% probability) ellipsoid having the shape, orientation, and relative size consistent with the refined anisotropic thermal parameters. Hydrogen atoms are represented by arbitrarily small spheres for purposes of clarity.

single crystals suitable for x-ray studies which were orthorhombic of space group P_{bca}-D_{2h}^{15} (no. 61)[13] with a = 9.494 ± 0.001 Å, b = 13.123 ± 0.001 Å, c = 20.012 ± 0.002 Å, and Z = 8 at 20 ± 1 °C [d_{calcd} = 1.207 g cm^{-3}, d_{measd} = 1.199 g cm^{-3} μ_a(Cu K$\bar{\alpha}$)[14] = 2.074 mm^{-1}]. Intensity measurements for a spherical specimen 0.48 mm in diameter (μr = 0.50) on a Syntex $P\bar{1}$ autodiffractometer with 1° wide ω scans and graphite-monochromated Cu K$\bar{\alpha}$ radiation gave a total of 1679 independent reflections having $2\theta_{CuK\bar{\alpha}} < 115°$ (the equivalent of 0.60 limiting Cu K$\bar{\alpha}$ spheres). For those reflections having $2\theta_{CuK\bar{\alpha}} < 84°$, a scanning rate of 3°/min was employed for the scan between ω settings 0.50° respectively above and below the calculated K$\bar{\alpha}$ doublet value ($\lambda_{K\bar{\alpha}}$ = 1.54178 Å). A scanning rate of 2°/min was used for the remaining reflections. Each 1° scan was divided into 19 equal (time) intervals and those 13 contiguous intervals which had the highest single accumulated count at their midpoint were used to calculate the net intensity from scanning. Background counts, each lasting for one-fourth the total time used for the net scan (13/19 of the total scan time), were measured at ω settings 1° above and below the calculated K$\bar{\alpha}$ doublet value for each reflection. The data were corrected for absorption as a strict function of the scattering angle.[15]

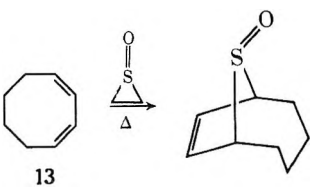
The 15 nonhydrogen atoms comprising the asymmetric unit appeared simultaneously on an E map which was calculated from a trial set of statistical direct methods (MULTAN) phases. All 18 chemically anticipated hydrogen atoms were located from a difference Fourier synthesis calculated from a full-matrix least-squares refined structural model [R (unweighted) = 0.084, r (weighted) = 0.104 for 1334 reflections having $2\theta_{CuK\bar{\alpha}} < 105°$ and $I > 3\sigma(I)$] which incorporated unit weighting and anisotropic thermal parameters for all nonhydrogen atoms. All structure factor calculations employed a least-squares refineable extinction correction[16] of the form $1/(1 + gI_c)^{1/2}$, the atomic form factors compiled by Cromer and Mann,[17] and an anomalous dispersion correction to the scattering factor of the sulfur atom.[18] The final cycles of empirically weighted full-matrix least-squares refinement which employed isotropic thermal parameters for hydrogen atoms and anisotropic thermal parameters for all others converged to values of 0.034 and 0.041 for R and r, respectively, for 1603 independent reflections having $2\theta_{CuK\bar{\alpha}} < 115°$ and $I > \sigma(I)$.

Figure 1 shows a computer-generated drawing of **10**.[19] The x-ray crystal structural analysis clearly indicates that the sulfoxide oxygen atom is anti to the C_5–C_6 double bond. Examination of the bond length and bond angle data in Tables I–III reveals that significant distortions from idealized geometries for certain atoms are present in **10**. As might be anticipated, the bond angles are affected considerably more than the bond lengths. The C_1SC_4 angle of 81.4 (1)°[20] is considerably smaller than that proposed in any normal hybridization scheme for sulfur and well outside the 95.2–98.2° range found for CSC angles in several sulfoxides in which the sulfur atom is not part of a small (<six atoms) ring.[21] Five of the six CCC bond angles within the six-membered ring are also significantly smaller than their respective idealized sp^2 or sp^3 hybridized values. Unfavorable intramolecular contacts of 2.41 (3) and 3.022 (3) Å for O_s with H_{m311} and C_2, respectively (the corresponding van der Waals contact values[22] are 2.60 and 3.10 Å) are probably responsible for the 0.22 Å elongation of the C_4–S bond relative to C_1–S and the 8.4° opening of the C_2C_1S and C_3C_4S pair of bond angles relative to the C_6C_1S and C_5C_4S pair.

Whereas many of the bond angles exhibit major departures from their idealized values, bond lengths of a given type show much less deviation from their generally accepted (x-ray) values. Average values for the five sp^3–sp^3 and the six sp^2–sp^3 C–C single bonds in **10** are 1.528 (3, 16, 21)[20] and 1.515 (3, 10, 17) Å, respectively. The C–H bonds have an average length of 0.96 (3, 3, 6) Å, which is in excellent agreement with values determined by x-ray studies of compounds containing similar bonds.[23] Intermolecular contacts for only two pairs of atoms (each pair contains one oxygen and one hydrogen atom) in the crystal are less than the sum of their respective van der Waals radii (2.60 Å in this case[22]). These short contacts include a 2.46 (3) Å $O_2 \cdots H_{m11}$ and a 2.57 (4) Å $O_c \cdots H_{m62}$ separation. Each atom of the following groups is coplanar to within 0.04 Å with Å $O_2 \cdots H_{m11}$ and a 2.57 (4) Å $O_c \cdots H_{m62}$ separation. Each atom of the following groups is coplanar to within 0.04 Å with all other members of the group: C_2, C_3, C_5, and C_6, group I; C_1, C_2, C_3, C_4, and O_c, group II; C_1, C_4, C_5, C_6, C_{m5}, and C_{m6}, group III; and C_{m1}, C_1, S, C_4, and C_{m4}, group IV. Angles between the normals to the least-square mean planes for these groupings follow (in pairs): I–II, 28.7°; I–III, 31.3°; I–IV, 85.1°; II–III, 60.0°; II–IV, 56.4°; and III–IV, 63.6°.

It appears that a trace amount of the 7-*syn*-oxide of **10** is also formed in the addition of sulfur monoxide to **9**. The ^{1}H NMR spectrum of the first fraction containing **10** (ca. 30 mg) eluted during the column chromatography of the reaction mixture obtained from treatment of 1.62 g of **9** with an equimolar quantity of ethylene episulfoxide shows in addition to the signals for the 7-*anti*-oxide of **10** what are presumably aliphatic methyl singlets at δ 1.40, 1.36, 1.27, and 0.93 and allylic methyl quartets (J = 1 Hz) at δ 1.84 and 1.74. Although the syn and anti isomers of **10** appear to be present in approximately equal amounts in this fraction, the material in all of the other fractions from the column chromatographic separation was isomerically pure.

The preponderance of the 7-*anti*-oxide of **10** formed in the addition of sulfur monoxide to **9** parallels the addition of sulfur monoxide to *cis,cis*-1,3-cyclooctadiene (**13**) which is reported to give "essentially exclusive formation of stereo-



13 **14**

Table I. Bond Lengths in Crystalline $C_{12}H_{18}O_2S$[a]

Type[b]	Bond length, Å	Type[b]	Bond length, Å	Type[b]	Bond length, Å
$S-C_1$	1.848 (2)	C_1-C_{m1}	1.507 (3)	$C_{m31}-H_{m313}$	0.95 (3)
$S-C_4$	1.870 (2)	C_4-C_{m4}	1.510 (3)	$C_{m32}-H_{m321}$	1.01 (3)
		C_3-C_{m31}	1.540 (4)	$C_{m32}-H_{m322}$	0.94 (3)
$S-O_s$	1.483 (2)	C_3-C_{m32}	1.536 (4)	$C_{m32}-H_{m323}$	0.95 (3)
		C_3-C_4	1.547 (3)	$C_{m4}-H_{m41}$	1.00 (3)
C_2-O_c	1.200 (3)			$C_{m4}-H_{m42}$	0.95 (4)
		C_5-C_6	1.329 (3)	$C_{m4}-H_{m43}$	1.02 (3)
C_1-C_2	1.526 (3)			$C_{m5}-H_{m51}$	0.91 (4)
C_1-C_6	1.523 (3)	$C_{m1}-H_{m11}$	1.01 (3)	$C_{m5}-H_{m52}$	0.98 (4)
C_2-C_3	1.525 (3)	$C_{m1}-H_{m12}$	0.91 (4)	$C_{m5}-H_{m53}$	0.90 (4)
C_4-C_5	1.515 (3)	$C_{m1}-H_{m13}$	0.99 (3)	$C_{m6}-H_{m61}$	0.95 (3)
C_5-C_{m5}	1.503 (4)	$C_{m31}-H_{m311}$	1.00 (3)	$C_{m6}-H_{m62}$	0.97 (4)
C_6-C_{m6}	1.498 (3)	$C_{m31}-H_{m312}$	0.97 (3)	$C_{m6}-H_{m63}$	0.91 (3)

[a] The number in parentheses following each entry is the least-squares estimate of the standard deviation of the last significant figure. [b] Atoms labeled to agree with Figure 1.

Table II. Bond Angles for Nonhydrogen Atoms in Crystalline $C_{12}H_{18}O_2S$[a]

Type[b]	Bond angle, deg	Type[b]	Bond angle, deg	Type[b]	Bond angle, deg
C_1SC_4	81.4 (1)	$C_1C_2C_3$	111.0 (2)	$C_{m4}C_4S$	111.2 (2)
C_1SO_s	111.2 (1)	$O_cC_2C_3$	125.6 (2)	$C_{m4}C_4C_3$	117.0 (2)
C_4SO_s	112.9 (1)	$C_2C_3C_4$	103.1 (2)	$C_{m4}C_4C_5$	117.4 (2)
C_2C_1S	101.0 (1)	$C_2C_3C_{m31}$	109.4 (2)	$C_3C_4C_5$	108.9 (2)
C_6C_1S	95.0 (1)	$C_2C_3C_{m32}$	109.6 (2)	$C_4C_5C_6$	111.2 (2)
$C_{m1}C_1S$	114.4 (2)	$C_4C_3C_{m31}$	113.8 (2)	$C_4C_5C_{m5}$	121.4 (2)
$C_{m1}C_1C_2$	115.4 (2)	$C_4C_3C_{m32}$	111.9 (2)	$C_6C_5C_{m5}$	127.4 (3)
$C_{m1}C_1C_6$	119.8 (2)	$C_{m31}C_3C_{m32}$	108.8 (2)	$C_5C_6C_1$	111.1 (2)
$C_2C_1C_6$	108.0 (2)	C_3C_4S	105.0 (1)	$C_1C_6C_{m6}$	120.2 (2)
$C_1C_2O_c$	123.4 (2)	C_5C_4S	94.3 (1)	$C_5C_6C_{m6}$	128.6 (2)

[a] The number in parentheses following each entry is the least-squares estimate of the standard deviation of the last significant figure. [b] Atoms labeled to agree with Figure 1.

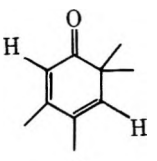
Table III. Bond Angles Involving Hydrogen Atoms in Crystalline $C_{12}H_{18}O_2S$[a]

Type[b]	Bond angle, deg	Type[b]	Bond angle, deg	Type[b]	Bond angle, deg
$C_1C_{m1}H_{m11}$	112 (2)	$C_3C_{m32}H_{m321}$	111 (2)	$C_5C_{m5}H_{m51}$	109 (2)
$C_1C_{m1}H_{m12}$	109 (2)	$C_3C_{m32}H_{m322}$	107 (2)	$C_5C_{m5}H_{m52}$	112 (2)
$C_1C_{m1}H_{m13}$	112 (2)	$C_3C_{m32}H_{m323}$	107 (2)	$C_5C_{m5}H_{m53}$	113 (2)
$H_{m11}C_{m1}H_{m12}$	105 (3)	$H_{m321}C_{m32}H_{m322}$	108 (3)	$H_{m51}C_{m5}H_{m52}$	105 (3)
$H_{m11}C_{m1}H_{m13}$	109 (2)	$H_{m321}C_{m32}H_{m323}$	116 (3)	$H_{m51}C_{m5}H_{m53}$	110 (3)
$H_{m12}C_{m1}H_{m13}$	109 (3)	$H_{m322}C_{m32}H_{m323}$	108 (3)	$H_{m52}C_{m5}H_{m53}$	108 (3)
$C_3C_{m31}H_{m311}$	112 (2)	$C_4C_{m4}H_{m41}$	110 (2)	$C_6C_{m6}H_{m61}$	112 (2)
$C_3C_{m31}H_{m312}$	108 (2)	$C_4C_{m4}H_{m42}$	111 (2)	$C_6C_{m6}H_{m62}$	111 (2)
$C_3C_{m31}H_{m313}$	109 (2)	$C_4C_{m4}H_{m43}$	110 (2)	$C_6C_{m6}H_{m63}$	111 (2)
$H_{m311}C_{m31}H_{m312}$	105 (3)	$H_{m41}C_{m4}H_{m42}$	111 (3)	$H_{m61}C_{m6}H_{m62}$	102 (3)
$H_{m311}C_{m31}H_{m313}$	113 (3)	$H_{m41}C_{m4}H_{m43}$	108 (2)	$H_{m61}C_{m6}H_{m63}$	110 (3)
$H_{m312}C_{m31}H_{m313}$	109 (3)	$H_{m42}C_{m4}H_{m43}$	108 (3)	$H_{m62}C_{m6}H_{m63}$	110 (3)

[a] The number in parentheses following each entry is the least-squares estimate of the standard deviation of the last significant figure. [b] Atoms labeled to agree with Figure 1.

isomer **14**".[9c] A rationale which accounts for these observations has already been presented.[9d]

The synthesis of 7-thiabicyclo[2.2.1]hept-5-en-2-one 7-oxides by Diels–Alder addition of sulfur monoxide to 2,4-cyclohexadienones does not seem to be general. For example, treatment of 3,4,6,6-tetramethyl-2,4-cyclohexadienone (**15**)[24] under the identical conditions employed for **9** → **10** gives only recovered starting material. Of course, this result may be a consequence of the instability of the Diels–Alder adduct of sulfur monoxide and **15** at 110 °C.



15

Experimental Section

Hexamethyl-7-thiabicyclo[2.2.1]hept-5-en-2-one 7-*anti*-Oxide (10). A solution of freshly distilled ethylene episulfoxide[8] (2.9 g, 37.8

mmol) and hexamethyl-2,4-cyclohexadienone[7] (6.7 g, 37.6 mmol) in 137 mL of toluene was heated at reflux under nitrogen for 5 h. After cooling, the solvent was evaporated at reduced pressure to give an oil. ^{1}H NMR analysis of the crude reaction mixture showed that the reaction had proceeded with a ca. 40% conversion of the starting dienone to give a quantitative yield of **10**. Most of the dienone was removed by distillation (55 °C, 0.03 mm). Upon extended standing, sulfoxide **10** slowly crystallized from the distillation residue. Repeated recrystallizations from pentane gave **10** as a white, crystalline solid: ν (CCl_4) 2970, 2935, 1738, 1475, 1455, 1435, 1385, 1375, 1290, 1190, 1110, 1100, 1070, and 1005 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02; S, 14.17. Found: C, 63.69; H, 7.85; S, 13.96.

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Registry No.—**9**, 3854-96-4; *anti*-**10**, 61966-92-5; *syn*-**10**, 61966-93-6; ethylene episulfoxide, 7117-41-1.

Supplementary Material Available. A listing of fractional coordinates for nonhydrogen atoms, anisotropic thermal parameters for nonhydrogen atoms, refined fractional coordinates and isotropic thermal parameters for hydrogen atoms, observed and calculated structure factor amplitudes, and a detailed description of the experimental conditions for the crystallographic study (15 pages). Ordering information is given on any current masthead page.

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(19) Tables of fractional coordinates for nonhydrogen atoms, anisotropic thermal parameters for nonhydrogen atoms, refined fractional coordinates and isotropic thermal parameters for hydrogen atoms, and observed and calculated structure factor amplitudes will be found in the microfilm edition.
(20) The first number in parentheses following a given bond length or angle is the root mean square estimated standard deviation of an individual datum. The second and third numbers, when included, are the average and maximum deviations from the average value, respectively.
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Synthesis of Methyl-Substituted Bisdehydro[13]annulenones. Conformational Isomerism and Ring Current Effects in Conjugated 13-Membered Cyclic Ketones[1]

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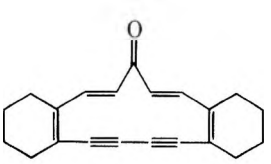
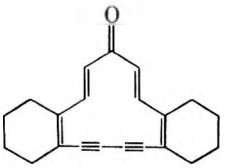
Syntheses of 5,10-dimethyl-6,8-bisdehydro[13]annulenone (**3**) and 2,5,10-trimethyl-6,8-bisdehydro[13]annulenone (**4**) are described. It was found that the extra methyl group in **4** causes a change of conformation as compared with **3**. The ^{1}H NMR spectrum of **4** proved to be temperature dependent, due to rotation of the trans double bond. Both **3** and **4** are weakly paratropic, and the paratropicity is increased by dissolution in deuteriotrifluoroacetic acid.

The synthesis of the bis(cyclohexene)-annelated bisdehydro[13]annulenone **1** in these laboratories has been described previously.[2] Although inspection of models suggested that the conformation **1a** would be the preferred one for this compound, ^{1}H NMR spectrometry [nuclear Overhauser experiments and Eu(fod)$_3$ shifts], combined with selective deuteration, pointed to conformation **1b**.[2]

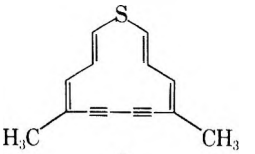


1a



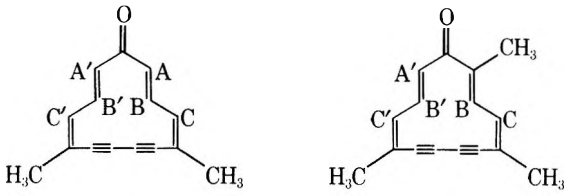
1b

Since this work was carried out, it has been shown that the related dimethylbisdehydrothia[13]annulene **2** is conforma-



2

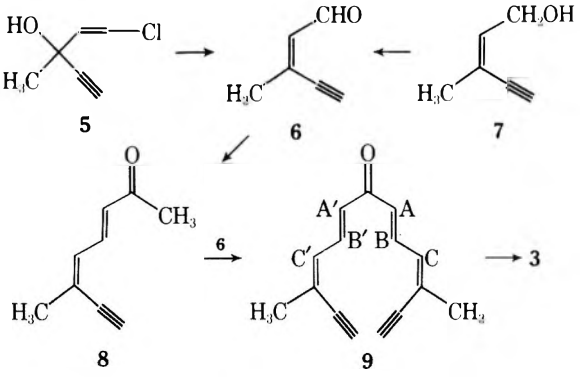
tionally mobile on the NMR time scale.[3] This suggested that the annulenone **1** might also be conformationally mobile, with **1b** predominating. In order to investigate this possibility, it was decided to synthesize dehydroannulenones related to **1** in which one of the trans double bonds is conformationally fixed. The target compounds were the potentially mobile 5,10-dimethyl-6,8-bisdehydro[13]annulenone (**3**)[4a] and 2,5,10-trimethyl-6,8-bisdehydro[13]annulenone (**4**),[4b] in which



3 **4**

the methyl group adjacent to the ketone must be external. This series of compounds was chosen instead of bis(cyclohexene)-annelated compounds of type **1**, since in other cases it has been found that methyl substituted dehydroannulenes are preferable for the study of conformational mobility and ring current effects.[5] We now describe the synthesis of **3**[6] and **4**, the first monocyclic large-ring annulenones to be obtained.[7]

(*Z*)-3-Methyl-2-penten-4-yn-1-al (**6**) has been prepared by acid treatment of 1-chloro-3-methyl-1-penten-4-yn-3-ol (**5**),[8,9] as well as by manganese dioxide oxidation of (*Z*)-3-methyl-2-penten-4-yn-1-ol (**7**).[10] We have found that the aldehyde **6** obtained by the first method is contaminated with ~5–10%



5 **6** **7** **8** **9**

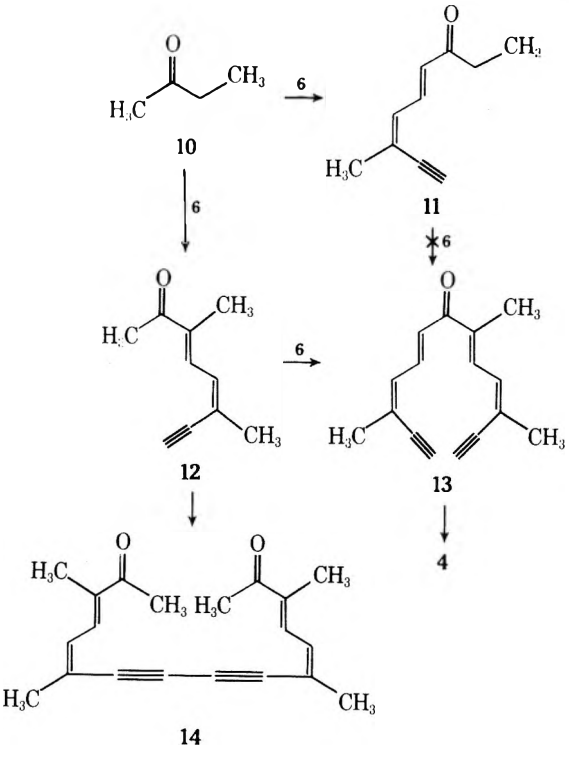
of the *E* isomer (as determined by the ^{1}H NMR spectrum), in agreement with the conclusion of Ojima et al.[8c] The second method was the preferred one, since **6** was obtained stereochemically pure in ~70% yield, and **7** was kindly made available to us by Hoffmann-La Roche, Basel.

Aldol condensation of **6** and acetone in the presence of aqueous ethanolic sodium hydroxide, essentially by the described[8c] modification of the method of Heilbron et al.,[8b] led to 6-methyl-3,5-octadien-7-yn-2-one (**8**) in 58% yield. A second aldol condensation of **8** and **6** in ether with methanolic potassium hydroxide then gave 42% of 3,11-dimethyl-3,5,8,10-tridecatetraene-1,12-diyn-7-one (**9**). The structure and stereochemistry of **9** were confirmed by the ^{1}H NMR spectrum determined in the presence of Eu(fod)$_3$ shift reagent.

Oxidative coupling of **9** with cupric acetate monohydrate in pyridine at 60 °C led to ~25% of the dimethylbisdehydro[13]annulenone **3** as orange needles, mp >170 °C dec. Subsequently it was found that oxidative couplings of this type proceed in higher yield when anhydrous cupric acetate in pyridine–ether at ~50 °C is employed,[11] and the yield of **3** from **9** could be improved to 80% under these conditions. The overall yield in the four-step sequence **7** → **6** → **8** → **9** → **3** is ~15%, and the dehydro[13]annulenone **3** has become a relatively readily available substance.

A suitable precursor of the trimethylbisdehydro[13]annulenone **4** appeared to be 3,6,11-trimethyl-3,5,8,10-tridecatetraene-1,12-diyn-7-one (**13**). It was expected that this ketone could be obtained by the aldol condensation between 2-butanone (**10**) and (*Z*)-3-methyl-2-penten-4-yn-1-al (**6**) to give the ketone **11** or **12**, followed by condensation with another molecule of the aldehyde **6**. In practice, reaction of **10** with **6** in the presence of methanolic sodium methoxide[12] led to 7-methyl-4,6-nonadien-8-yn-3-one (**11**) in 43% yield. Unfortunately, all attempts to condense this ketone with another molecule of the aldehyde **6** to give **13** failed.

The alternative approach to **13** was therefore investigated. Reaction of **10** with **6** under acidic conditions (sulfuric acid–acetic acid)[12] yielded 59% of 3,6-dimethyl-3,5-octadien-7-yn-2-one (**12**). Condensation of this ketone with the aldehyde



10 **11** **12** **13** **14**

6 in the presence of ethanolic potassium hydroxide then gave the required ketone **13**, admixed with unchanged **12**. The separation between **12** and **13** proved to be inefficient, and it was found most convenient to proceed with the mixture.

Oxidative coupling of the mixture of **12** and **13** with cupric acetate monohydrate in dimethylformamide at 60 °C gave rise to a mixture of the diketone **14** (derived from **12**) and the dehydroannulenone **4** (derived from **13**), which were readily separated by chromatography. The dehydroannulenone **4**, isolated in 4% yield (based on **12**), formed orange crystals, mp 83–84 °C.

The electronic absorption maxima (in ether) of the dimethylbisdehydro[13]annulenone **3** and trimethylbisdehydro[13]annulenone **4**, as well as of the bis(cyclohexene)-annelated bisdehydro[13]annulenone **1**,[2] are given in Table I. As expected, the spectra are similar, the maxima exhibiting small bathochromic shifts as the degree of alkyl substitution increases. The electronic absorption maxima of **3**, **4**, and **1** in trifluoroacetic acid are given in Table II, and it is evident that protonation with this acid causes the main maxima to shift to higher wavelengths.

The ^{1}H NMR chemical shifts of the bisdehydro[13]annulenones **3** and **4** are given in Table III. The individual assignments were made on the basis of the multiplicity and coupling constants, given in the Experimental Section. The spectrum

Table I. Electronic Absorption Maxima of Bisdehydro[13]-annulenones in Ether [λ_{max} (ϵ_{max})]

3	4	1[a]
~250 sh (25 800)	~250 sh (24 700)	~250 sh (16 000)
262 (37 900)	265 (48 300)	~270 sh (26 800)
273 (39 900)	276 (50 300)	279 (31 000)
387 (990)	390 sh (1400)	394 (1160)

[a] See ref 2.

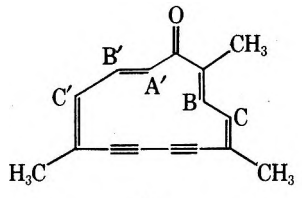
Table II. Electronic Absorption Maxima of Bisdehydro[13]-annulenones in Trifluoroacetic Acid [λ_{max} (Relative Extinction Coefficients)][a]

3	4	1[b]
~269 sh (0.82)	~271 sh (0.90)	~275 sh (0.89)
281 (1.00)	282 (1.00)	288 (1.00)
~350 sh (0.12)	~350 sh (0.12)	~350 sh (0.15)

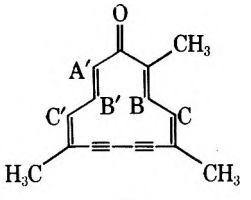
[a] All the spectra showed tailing to ~700 nm. [b] See ref 2.

of the dimethyl compound **3** (Figure 1) proved to be essentially temperature independent in the range −60 to 80 °C. On the other hand, the spectrum of the trimethyl compound **4** was temperature dependent, as indicated in Figure 2. At 27 °C (and above), the $H^{A'}$, $H^{B'}$, and $H^{C'}$ resonances are unresolved multiplets. On cooling, these bands become resolved, and the expected first-order pattern is observed at −60 °C. Further cooling results in increased separation of the $H^{A'}$ and the $H^{B'}$ bands.

Two facts indicate that the trimethylbisdehydro[13]annulenone **4** exists as conformer **4a**, and not **4b**. Firstly, H^B and



4a



4b

$H^{B'}$ resonate at very different field (τ 0.27 and 2.60, respectively, at −60 °C), indicative of their different environments. Secondly, the low $J_{B'C'}$ value (6 Hz) points to the s-cis relationship of $H^{B'}$ and $H^{C'}$, and is in contrast to the s-trans $J_{B,C}$ value (11 Hz). The reason for the temperature dependence of the spectrum of **4** must be due to rotation of the $H^{A'}$, $H^{B'}$ double bond.

Comparison of the ^1H NMR spectrum of the dimethylbisdehydro[13]annulenone **3** with that of **4** shows that **3** exists essentially in the indicated conformation. This follows from

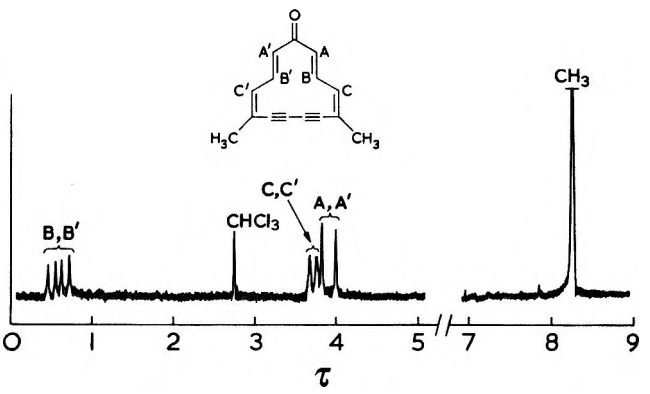
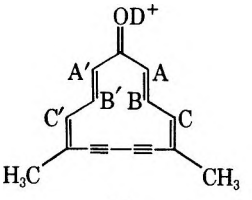


Figure 1. ^1H NMR spectrum of the dimethylbisdehydro[13]annulenone **3** in $CDCl_3$ at 27 °C (100 MHz, τ values, internal standard Me_4Si).

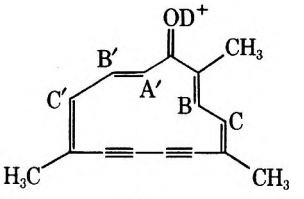
the similarity of the H^B resonance in **3** (τ 0.61) to that in **4** (τ 0.45),[13] and the difference of the $H^{A'}$ resonance in **3** (τ 3.90) from that in **4** (τ 2.10, at −60 °C). It is interesting that the perturbation caused by introduction of the extra methyl group into **3** to give **4** is sufficient to effect a conformational change in the other trans double bond.

Comparison of the NMR chemical shifts of the various protons of the bisdehydro[13]annulenones **3** and **4** with those of the corresponding acyclic model **9** (Table III) indicates that **3** and **4** are weakly paratropic, as might be expected of 12π-electron systems. This follows from the fact that essentially all the outer protons in **3** and **4** (especially the methyl protons) resonate at higher field than the corresponding protons in **9**, whereas the inner protons in **3** and **4** resonate at lower field. The bis(cyclohexene)-annelated bisdehydro[13]annulenone **1** is presumably also paratropic, but no conclusion could be made, since the "open" model in this series is even less satisfactory than in the presently described methyl substituted series.

The ^1H NMR chemical shifts of the deuteronated species **15** and **16**, obtained by dissolving **3** and **4** in deuteriotrifluo-



15



16

roacetic acid, are also given in Table III. It is evident that the conformations are unchanged. The positive charge is expected to cause a downfield shift of all of the proton resonances (~−0.8 ppm for the olefinic protons if the charge were equally

Table III. ^1H NMR Chemical Shifts of 3, 4, 9 (in $CDCl_3$) and 15, 16 (in CF_3COOD) at 100 MHz, Determined at 27 °C Unless Otherwise Stated (τ Values, Internal Standard Me_4Si)

Compd	H^A	H^B	H^C	$H^{A'}$	$H^{B'}$	$H^{C'}$	CH_3
3	3.90	0.61	3.71	3.90	0.61	3.71	8.26
4		0.45	3.46	2.10[a]	2.51[a]	3.82	8.20
9	3.55	2.32	3.54	3.55	2.32	3.54	7.98
Δ (3 − 9)	+0.35	−1.71	+0.17	+0.35	−1.71	+0.17	+0.28
Δ (4 − 9)		−1.87	−0.08	−1.45	+0.19	+0.28	+0.22
15	3.85	−0.79	3.88	3.85	−0.79	3.88	8.33
16		−0.50	3.50	*b*	*b*	3.84	8.28
Δ (15 − 3)	−0.05	−1.40	+0.17	−0.05	−1.40	+0.17	+0.07
Δ (16 − 4)		−0.95	+0.04			+0.02	+0.08

[a] At −60 °C. [b] The $H^{A'}$ and $H^{B'}$ chemical shifts of **16** appeared as a multiplet at τ 1.74–2.18, due to conformational mobility.

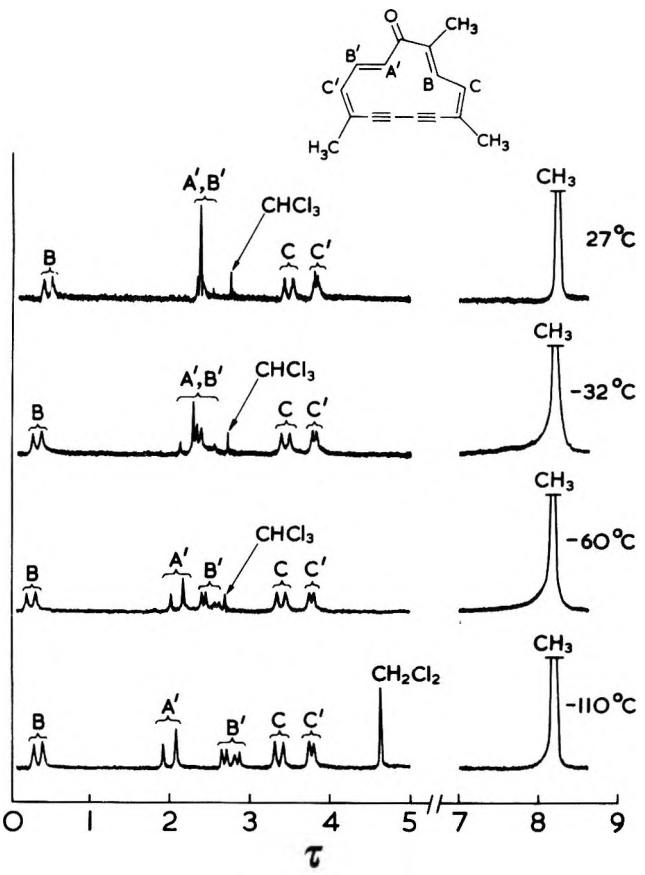


Figure 2. ^{1}H NMR spectra of the trimethylbisdehydro[13]annulenone **4** in $CDCl_3$ or $CDCl_2$–CS_2 (−110 °C) at different temperatures (100 MHz, τ values, internal standard Me_4Si).

distributed over the 13-membered ring). The observation that deuteronation of **3** and **4** caused a considerable downfield shift of the inner proton bands, but only little change of the outer ones (see Table III), indicates **15** and **16** to be more paratropic than **3** and **4**.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were measured on a Unicam SP 200 spectrophotometer (s = strong, m = medium, w = weak); only significant maxima are reported. Electronic spectra were determined on a Unicam SP 800 spectrophotometer (sh = shoulder). ^{1}H NMR spectra were measured on a Varian T60 (60 MHz) or a Varian HA 100 (100 MHz) spectrometer, tetramethylsilane being used as an internal standard. Assignments were assisted by nuclear Overhauser experiments and $Eu(fod)_3$ shifts where necessary. Proton decoupled ^{13}C NMR spectra were measured on a Varian CFT 20 spectrometer, tetramethylsilane being used as an internal standard. Mass spectra were determined on an AEI MS-12 or (for accurate mass measurements) on an AEI MS-9 spectrometer, both operating at 70 eV. Alumina for column chromatography refers to Woelm neutral alumina activity III. Compounds were preadsorbed from ether or dichloromethane solution onto alumina before being applied to the column. Pyridine and dimethylformamide were Analar grade that had been stored for a prolonged period over 4Å molecular sieves. Petrol refers to light petroleum (bp 40–60 °C) which had been distilled from phosphorus pentoxide. Organic extracts were washed with saturated aqueous sodium chloride and dried over magnesium sulfate immediately prior to solvent removal. All reactions were conducted under a purified nitrogen flow.

(*Z*)-3-Methyl-2-penten-4-yn-1-al (6) from (*Z*)-3-Methyl-2-penten-4-yn-1-ol (7).[10] A solution of the alcohol **7** (20 g) in methylene chloride (300 ml) was stirred with activated manganese dioxide[14] (100 g) at ambient temperature for 3 h. A further quantity of activated manganese dioxide (30 g) was added, and stirring was continued for 2 h. The mixture was filtered, the solid was washed well with methylene chloride, and the solvent was evaporated. Examination of the residue (14.1 g, 72%) by ^{1}H NMR spectrometry showed it to be essentially pure *Z* aldehyde **6**.

6-Methyl-3,5-octadien-7-yn-2-one (8). An ice-cold solution of aqueous sodium hydroxide (0.65 N, 4.1 mL) and ethanol (4.1 mL) was added over 10 min to an ice-cooled stirred solution of the *Z* aldehyde **6** (1.41 g) in acetone (8.1 mL). The solution was stirred for a further 1 h at 0 °C and aqueous sulfuric acid (2 N, 1.6 mL) was then added. The solution was diluted with water (100 mL) and extracted with ether, and the extracts were washed with saturated aqueous sodium bicarbonate. The residue after solvent removal was chromatographed on a column of alumina (5 × 4 cm). Fractions eluted with 5% ether–petrol on evaporation afforded the ketone **8**[8b,c] (1.16 g, 58%) as a pale yellow oil: UV (Et_2O) λ_{max} 288 nm (ϵ 21 400), ~300 sh (18 800); IR (film) 3260 m (C≡CH), 2100 w (C≡C), 1660 s (C=O), 1610 m and 1600 m (C=C), 985 cm^{-1} m (trans HC=CH); ^{1}H NMR (60 MHz, $CDCl_3$) τ 2.50 (dd, $J_{4,3}$ = 16, $J_{4,5}$ = 11 Hz, H-4), 3.62 [d (b), $J_{5,4}$ = 11 Hz, H-5], 3.92 (d, $J_{3,4}$ = 16 Hz, H-3), 6.53 (s, H-8), 7.74 (s, H-1), 8.00 [s (b), CH_3-6].

3,11-Dimethyl-3,5,8,10-tridecatetraene-1,12-diyn-7-one (9). Methanolic potassium hydroxide (3.6 N, 2 mL) was added to a stirred solution of the ketone **8** (2.0 g, 15 mmol) and the aldehyde **6** (1.41 g, 15 mmol) in ether (60 mL, previously passed through basic alumina and flushed with nitrogen). After 1.5 h at ambient temperature, acetic acid (3 mL) was added, followed by stirring for 15 min and then dilution with water (100 mL). The separated aqueous layer was extracted with ether and the combined ethereal extracts were washed with saturated aqueous sodium bicarbonate. The residue after solvent removal was chromatographed on a column of alumina (5 × 4 cm). Fractions eluted with 15% ether–petrol on evaporation yielded the ketone **9** (1.31 g, 42%) as a yellow solid. It formed yellow cubes, mp 100–101 °C dec (sealed and evaporated tube, Buchi melting point apparatus) from ether–petrol: mass spectrum *m/e* 210.104 (M^+, calcd 210.104), 209 ($M^+ - 1$), 195 ($M^+ - 15$), 181 ($M^+ - 29$); UV (Et_2O) λ_{max} 250 nm (ϵ 13 800), 338 (28 300); IR ($CHCl_3$) 3280 m (C≡CH), 2100 w (C≡C), 1640 s (C=O), 1600 s (C=C), 995 cm^{-1} m (trans HC=CH); ^{1}H NMR (100 MHz, $CDCl_3$) τ 2.32 (dd, $J_{5,6}$ = $J_{9,8}$ = 16, $J_{5,4}$ = $J_{9,10}$ = 11 Hz, H-5, H-9), 3.54 (d, $J_{4,5}$ = $J_{10,9}$ = 11 Hz, H-4, H-10), 3.55 (d, $J_{6,5}$ = $J_{8,9}$ = 16 Hz, H-6, H-8), 6.54 (s, H-1, H-13), 7.98 (s, CH_3-3, CH_3-11). Addition of $Eu(fod)_3$ shift reagent effected complete separation of the overlapping bands at τ 3.54 and 3.55.

5,10-Dimethyl-6,8-bisdehydro[13]annulenone[4a] (3) (with L. Lombardo). A solution of the ketone **9** (500 mg) in pyridine and dry ether (3:1, 50 mL) was added dropwise during 4.5 h to a stirred solution of anhydrous cupric acetate[15] (3.0 g) in pyridine and dry ether (3:1, 110 mL) at 45–50 °C (bath). The solution was stirred at 45 °C for a further 1.5 h and was then cooled. The residue after solvent removal was extracted thoroughly with ether, the solid removed by filtration, and the filtrate evaporated. Chromatography on a column of alumina (8 × 4 cm), elution with 25% ether–petrol, evaporation, and trituration with petrol yielded the annulenone **3** as orange needles (395 mg, 80%). The substance could be crystallized from benzene–pentane or from ethanol, mp >170 °C dec: mass spectrum *m/e* 208 (M^+), 180 ($M^+ - 28$), 178 ($M^+ - 30$), 165 ($M^+ - 43$); UV (Et_2O) see Table I; UV (CF_3COOH) see Table II; IR (KBr) 2180 w and 2120 w (C≡C), 1620 s and 1605 s (C=O, C=C), 985 cm^{-1} s (trans HC=CH); ^{1}H NMR (100 MHz, $CDCl_3$, see Figure 1 and Table III) τ 0.61 (dd, $J_{3,2}$ = $J_{12,13}$ = 16.5, $J_{3,4}$ = $J_{12,11}$ = 9.5 Hz, H-3, H-12), 3.71 [d (b), $J_{4,3}$ = $J_{11,12}$ = 9.5 Hz, H-4, H-11], 3.90 (d, $J_{2,3}$ = $J_{13,12}$ = 16.5 Hz, H-2, H-13), 8.26 [s (b), CH_3-5, CH_3-10]; ^{1}H NMR (100 MHz, CF_3COOD, see Table III) τ −0.79 (dd, $J_{3,2}$ = $J_{12,13}$ = 16, $J_{3,4}$ = $J_{12,11}$ = 10 Hz, H-3, H-12), 3.85 (d, $J_{2,3}$ = $J_{13,12}$ = 16 Hz, H-2, H-13), 3.88 (d, $J_{4,3}$ = $J_{11,12}$ = 10 Hz, H-4, H-11), 8.33 (s, CH_3-5, CH_3-10); ^{13}C NMR (20 MHz, $CDCl_3$) δ 194.9 (C-1), 142.5 (C-3, C-12), 140.1, 129.8 (C-4, C-5, C-10, C-11), 127.3 (C-2, C-13), 98.5 (C-6, C-9), 86.0 (C-7, C-8), 20.1 (CH_3-5, CH_3-10).

Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.80; H, 5.84.

The yield of **3** was only ~25% when the coupling of **9** was carried out with cupric acetate monohydrate in pyridine at 60 °C for 3 h.

7-Methyl-4,6-nonadien-8-yn-3-one (11). A solution of the aldehyde **6** (470 mg, 5 mmol) in ether (5 mL) was added dropwise over 30 min to a stirred solution of 2-butanone (**10**, 720 mg, 10 mmol) in dry ether (30 mL) containing methanolic sodium methoxide [from sodium (7.6 mg) and methanol (2 mL)]. After a further 1 h, the reaction was quenched by addition of aqueous oxalic acid. The ethereal layer was evaporated and the residue chromatographed on a column of alumina (6 × 3.5 cm) with 10% ethyl acetate–petrol as eluent. Early fractions afforded the ketone **11** (320 mg, 43%) as a yellow oil: mass spectrum *m/e* 148.088 (M^+, calcd 148.089); UV (Et_2O) λ_{max} 291 nm (ϵ 19 800), ~300 sh (18 700), ~345 sh (1700); ^{1}H NMR (60 MHz, $CDCl_3$) τ 2.40 (dd, $J_{5,4}$ = 16, $J_{5,6}$ = 11 Hz, H-5), 3.58 [d (b), $J_{6,5}$ = 11

Hz, H-6], 3.83 (d, $J_{4,5}$ = 16 Hz, H-4), 6.47 (s, H-9), 7.37 (q, H-2), 7.97 [s (b), CH_3-7], 8.88 (t, H-1).

3,6-Dimethyl-3,5-octadien-7-yn-2-one (12). A solution of the aldehyde **6** (2.43 g, 0.026 mol) in acetic acid (8 mL) was added dropwise over 15 min to a stirred solution of 2-butanone (**10**, 8.0 g, 0.11 mol) and concentrated sulfuric acid (2 mL) in acetic acid (100 mL). The resultant dark solution was stirred for a further 18 h, and then cautiously poured into saturated aqueous potassium carbonate. The residue after solvent removal was chromatographed on a column of alumina (11 × 4 cm) with 5% ethyl acetate–petrol as eluent. Early fractions afforded the ketone **12** (2.24 g, 59%) as a yellow solid. It formed yellow prisms, mp 41–43 °C from pentane: mass spectrum *m/e* 148.089 (M^+, calcd 148.089), 133 ($M^+ - 15$), 119 ($M^+ - 29$), 105 ($M^+ - 43$), 103 ($M^+ - 45$); UV (Et_2O) λ_{max} ~277 nm sh (ϵ 17 000), 295 (26 600), ~307 sh (22 200); IR (CCl_4) 3250 m (C≡CH), 2100 w (C≡C), 1660 s (C=O), 1620 cm^{-1} m (C=C); ^1H NMR (60 MHz, $CDCl_3$) τ 2.47 [d (b), $J_{4,5}$ = 11 Hz, H-4], 3.30 [d (b), $J_{5,4}$ = 11 Hz, H-5], 6.40 (s, H-8), 7.62 (s, H-1), 7.93 [s (b), CH_3-6], 8.10 [s (b), CH_3-3].

2,5,10-Trimethyl-6,8-bisdehydro[13]annulenone[4b] (4) and 3,6,11,14-Tetramethyl-3,5,11,13-hexadecatetraene-7,9-diyne-2,15-dione (14) from 12. A solution of potassium hydroxide (0.4 g) in ethanol (5 mL) was added to a solution of the ketone **12** (2.15 g, 0.015 mol) in dry tetrahydrofuran (45 mL), and a solution of the aldehyde **6** (2.15 g, 0.023 mol) in dry tetrahydrofuran (15 mL) was then added during 30 min, with stirring. After 3 h, the reaction was quenched by the addition of acetic acid (3 mL), the resulting solution was poured into water (500 mL), and the mixture was extracted with ether. Chromatography of the residue after solvent removal on a column of alumina (10 × 4 cm), with 5% ethyl acetate–petrol as eluent, afforded a yellow gum (2.34 g). Spectroscopic examination of this material showed that it was a mixture of **12** and **13**.

A solution of the mixture of **12** and **13** (2.34 g) in dimethylformamide (40 mL) was added dropwise during 1 h to a stirred mixture of cupric acetate monohydrate (18.9 g) in dimethylformamide (100 mL) at 60 °C (bath). After a further 0.5 h at 60 °C, the mixture was cooled, diluted with water (1 L), and extracted with ether, and the extracts were washed with water. The residue after solvent removal was chromatographed on a column of alumina (6 × 4 cm), with 5–15% ethyl acetate–petrol as eluent.

Early fractions gave the annulenone **4** (136 mg, 4% based on **12**) as an orange solid. It formed orange rods, mp 83–84 °C, from petrol: mass spectrum *m/e* 222.105 (M^+, calcd 222.105), 207 ($M^+ - 15$), 194 ($M^+ - 28$), 179 ($M^+ - 43$); UV (Et_2O) see Table I; UV (CF_3COOH) see Table II; IR (KBr) 2165 w and 2100 w (C≡C), 1640 s, 1620 m and 1600 s (C=O, C=C), 980 cm^{-1} m (trans HC=CH); ^1H NMR (100 MHz, $CDCl_3$ 27 °C, see Figure 2 and Table III) τ 0.45 (d, $J_{3,4}$ = 11 Hz, H-3), 2.37 (m, H-12, H-13), 3.46 (d, $J_{4,3}$ = 11 Hz, H-4), 3.82 (m, H-11), 8.20 [s (b) CH_3-2, CH_3-5, CH_3-10]; ^1H NMR (100 MHz, $CDCl_3$ −60 °C, see Figure 2) τ 0.27 (d, $J_{3,4}$ = 11 Hz, H-3), 2.10 (d, $J_{13,12}$ = 16 Hz, H-13), 2.51 (dd, $J_{12,13}$ = 16, $J_{12,11}$ = 6 Hz, H-12), 3.39 [d (b), $J_{4,3}$ = 11 Hz, H-4], 3.76 [d (b), $J_{11,12}$ = 6 Hz, H-11], 8.17 [s (b), CH_3-2, CH_3-5, CH_3-10]; ^1H NMR (100 MHz, CF_3COOD, see Table III) τ −0.50 (d, $J_{3,4}$ = 11 Hz, H-3), 1.74–2.18 (m, H-12, H-13), 3.50 (d, $J_{4,3}$ = 11 Hz, H-4), 3.84 [d (b), $J_{11,12}$ = 7 Hz, H-11], 8.18 [s (b), CH_3-2], 8.28 [s (b), CH_3-5, CH_3-10]; ^{13}C NMR (20 MHz, $CDCl_3$) δ 195.5 (C-1), 139.8, 139.6, 138.6, 138.2, 137.4, 129.2, 127.2, 123.5 (C-2, C-3, C-4, C-5, C-10, C-11, C-12, C-13), 97.6, 97.1 (C-6, C-9), 88.3 (C-7, C-8), 21.2, 20.0 (CH_3-5, CH_3-10), 12.20 (CH_3-2).

Later fractions afforded the diketone **14** (442 mg, 21%) as a yellow solid. It formed yellow needles, mp 110–112 °C, from ethanol: UV (Et_2O) λ_{max} 248 nm sh (ϵ 11 800), 259 (14 000), 286 sh (31 700), 325 sh (30 000), 342 (34 600), 366 (32 100), 393 (22 400); IR (KBr) 2180 w (C≡C), 1660 s (C=O), 1610 m (C=C); ^1H NMR (100 MHz, $CDCl_3$) τ 2.53 [d (b), $J_{4,5}$ = $J_{13,12}$ = 11 Hz, H-4, H-13], 3.23 [d (b), $J_{5,4}$ = $J_{12,13}$ = 11 Hz, H-5, H-12], 7.60 (s, H-1, H-16), 7.90 [s (b), CH_3-6, CH_3-11], 8.10 [s (b), CH_3-3, CH_3-14].

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.62; H, 7.54.

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Registry No.—**3**, 55338-03-9; **4**, 61966-94-7; **6**, 52421-93-9; **7**, 6153-05-5; **8**, 58964-85-5; **9**, 61966-95-8; **10**, 78-93-3; **11**, 61966-96-9; **12**, 61966-97-0; **13**, 61966-98-1; **14**, 61966-99-2; **15**, 61967-00-8; **16**, 61967-01-9.

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Crystal Structure of Tetrahymanol Hemihydrate

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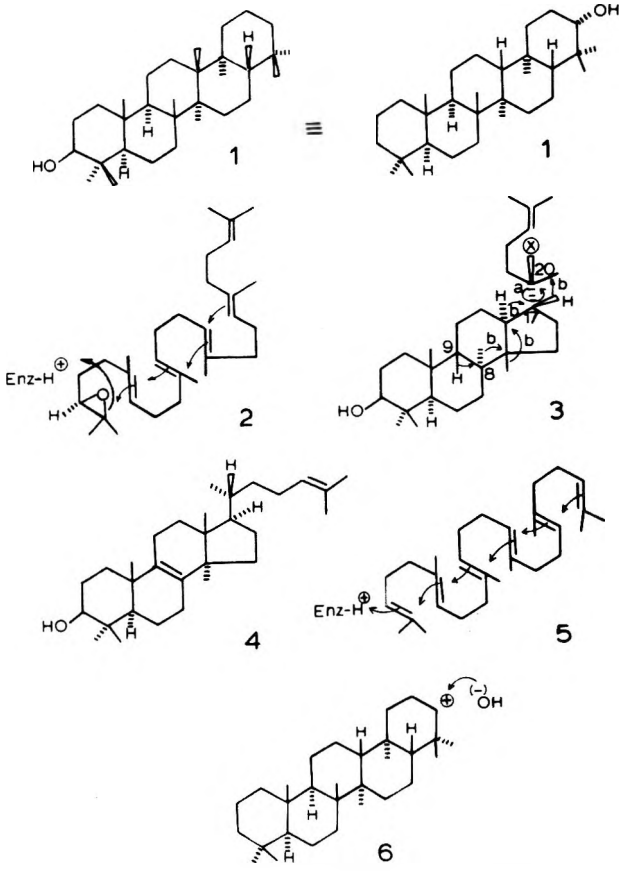
The crystal structure of a hemihydrate of the pentacyclic triterpenoid tetrahymanol, $C_{30}H_{52}O \cdot \frac{1}{2}H_2O$ [monoclinic, $P2_1$, a = 7.417 (1) Å, b = 11.438 (2), c = 30.248 (4), β = 91.95°, Z = 4, R = 0.076] has been determined. Steric overcrowding warps the gross conformation of the two molecules in the asymmetric unit and generates unusually long carbon–carbon single bonds. The observed weakening of the C8–C14 bond, whose average length is 1.61 Å, is consistent with its scission observed in mass spectral experiments. Although the molecular skeleton possesses rotational symmetry, the observed conformations are markedly asymmetric, appear to be independent of the hydroxyl moiety, and suggest the presence of conformational isomers in solution.

The pentacyclic triterpene tetrahymanol (**1**) was first isolated from the protozoan *Tetrahymena pyriformis*.[2] Later, it was also obtained from the fern *Oleandra walichii*.[3] Initially, tetrahymanol (**1**) was thought to be an "isomer of cho-

lesterol",[2] but, subsequently, it was recognized that the product is a triterpene.[4] Its structure was finally determined by interrelating tetrahymanol with known triterpenes of the gammacerane type.[5]

The available evidence indicates that the biosynthesis of C-3 oxygenated triterpenes and sterols requires molecular oxygen[6] and proceeds via 2,3(*S*)-oxidosqualene[7-9] (**2**). It is assumed that an enzymatic "cationic" cleavage of the epoxide (**2**) will generate an electron deficiency at C-3 and initiate the cyclization process. In many species (rat, yeast, *F. coccineum*, *D. lanata*, etc.) a free[10] or transiently stabilized[11] C-20 cation[12] (**3**) is thought to be formed. In rat livers (and in yeasts), following the rotation of the side chain around the C17–C20 bond (**3a**), the indicated backbone rearrangement (**3b**) takes place to yield a C8 cation.[13] Finally, elimination of the 9β hydrogen from the C8 cation results in lanosterol (**4**).[14] Accordingly, it was found that the oxygen atom of the hydroxyl of lanosterol (**4**) originates from *molecular oxygen* and not from the *water of the medium*.[15]



In contrast, we have proven that the biosynthesis of tetrahymanol (**1**) is *not oxygen dependent* and proceeds under *anaerobic conditions*.[16,17] Most likely, the biosynthesis involves a proton attack on a terminal double bond of squalene (**5**) which initiates the cyclization and results in the formation of the cation (**6**). Acquisition by the cation (**6**) of a hydroxyl moiety from the medium will yield tetrahymanol[17] (**1**). In fact, when a mixture of [^{3}H][2,3]oxidosqualene and [$^{14}C_6$]squalene was incubated with *T. pyriformis*[18] or an enzyme preparation of *T. pyriformis*,[16,17] the obtained tetrahymanol (**1**) contained only ^{14}C. However, when [$^{14}C_6$]squalene was incubated with an enzyme preparation suspended in deuterium oxide or $^{18}OH_2$, the biosynthesized tetrahymanol (**1**) contained one atom of deuterium[17,19] or one atom of oxygen-18,[17,20] respectively.

It is apparent that the biosynthesis of tetrahymanol (**1**) involves a nonoxidative cyclization of squalene. The overall process is equivalent to the acquisition of a molecule of water by squalene.[17]

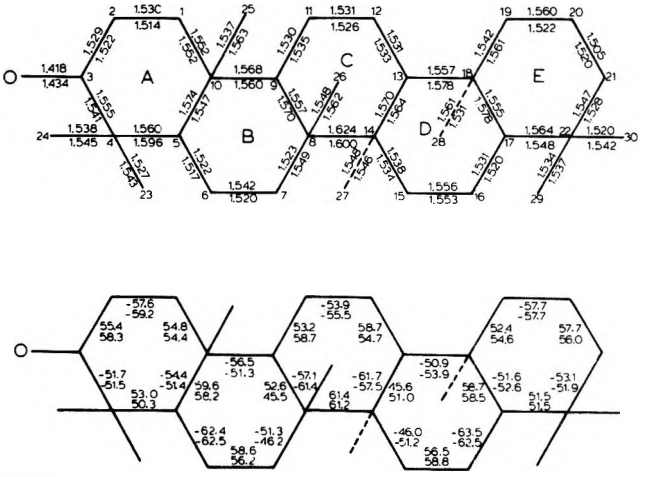


Figure 1. Observed bond lengths and endocyclic torsion angles in molecules I (above) and II of tetrahymanol. The average estimated standard deviation in the bond lengths and angles are 0.008 Å and 0.4°, respectively.

At present, it is considered likely that the biosynthesis of all 3-deoxytriterpenes proceeds via the nonoxidative mechanism of squalene cyclization.[3,21]

For the extension of studies on the mechanism of nonoxidative squalene cyclization, we required an x-ray crystal structure of tetrahymanol. The results of the crystallographic studies are reported in this paper.

Experimental Section

Tetrahymena pyriformis was grown in 15-L batches for 48–60 h and the organisms were harvested at 4 °C by continuous flow centrifugation.[16] The packed cells (ca. 20–30 g per 15-L batch) were freeze dried and extracted and the recovered lipids saponified under nitrogen.[18] The isolated tetrahymanol was extensively purified by thin layer chromatography,[17] sublimed, and crystallized.[18]

Cell dimensions of a crystal were determined by a least-squares procedure of 15 well-centered reflections. Cell data: a = 7.417 (1) Å, b = 11.438 (2) Å, c = 30.248 (4) Å, β = 91.95°, V = 2564.6 Å^3, monoclinic, $P2_1$, Z = 4. Three-dimensional data were collected on a Syntex $P\bar{1}$ automated diffractometer in a θ–2θ scan mode with Cu Kα radiation to a 2θ value of 137°. Of the 5020 data collected, 3134 were classified as observed (>1.5σ).

Structure Solution and Refinement. Although Patterson interpretation readily yielded the correct orientations of the two independent molecules in the asymmetric unit, attempts to achieve a solution by use of translation functions were not successful. Initial direct methods results obtained through the program MULTAN[22] were also discouraging and the structure was finally solved by a global fixed point phase refinement procedure, QTAN.[23] A structure factor calculation based on the 60-atom model located in the E map having the best figures of merit[24,25] produced a residual of 0.30.

After isotropic full-matrix least-squares refinement to a residual of 0.17, a single water of hydration was detected in a difference electron density synthesis. Hydrogen atoms, excluding methyl protons, were introduced in fixed theoretical positions with isothermal temperature factors of 5.0 Å^2. The positions of methyl protons were determined by difference electron density syntheses. The maximum coordinate shift in the last least-squares cycle (R = 0.076, wR = 0.087) corresponded to less than three-quarters of its estimated standard deviation. The estimated standard deviation in an observation of unit weight was 0.97

The final atomic corrdinates and anisotropic thermal parameters for the nonhydrogen atoms and the positional coordinates of the hydrogen atoms appear in the microfilm edition.

Discussion

Intramolecular bond distances and torsion angles derived from the refined atomic coordinates of the crystal structure are presented in Figure 1 for the two crystallographically in-

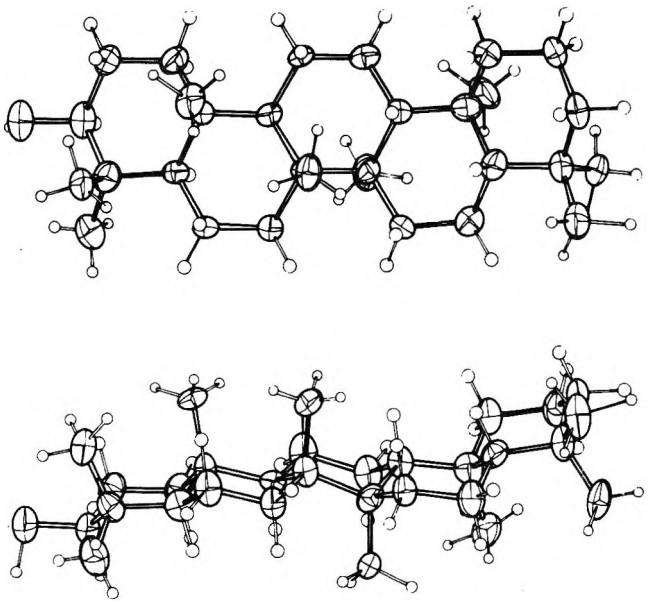


Figure 2. Observed conformation of molecule I of tetrahymanol with 50% probability thermal vibrational ellipsoids.

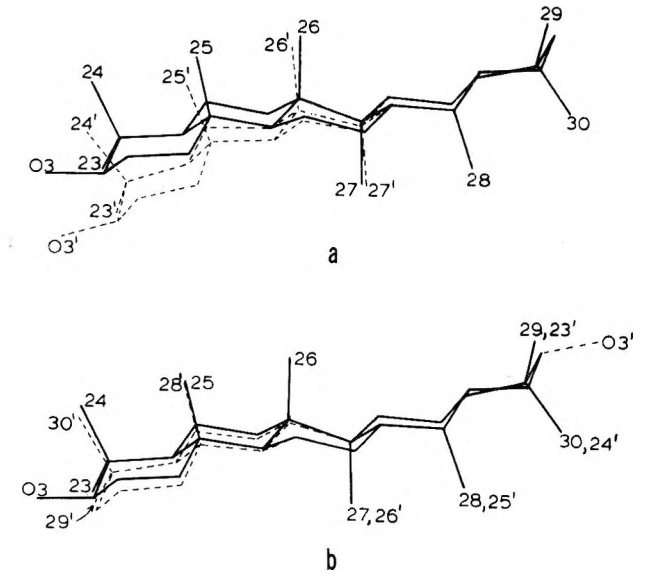


Figure 3. (a) Relative conformations of molecules I and II contrasted by superimposing the D and E rings of each as a reference element. (b) Similarity of conformations of molecule I and II illustrated by superimposing rings D and E of molecule I on rings B and A of molecule II.

dependent tetrahymanol molecules. The average carbon–carbon bond length is 1.546 (16) Å.

Observations of note include the relative lengthening of the endocyclic carbon–carbon single bonds which directly link the 1,3-diaxial methyl groups [average 1.565 (12) Å], and the abnormal lengthening of the C8–C14 bond to the average value of 1.612 Å.[27] Apparently bond angle and torsion angle deformations are insufficient to relieve steric overcrowding of the methyl groups and consequently bond lengths are also distorted from commonly observed values. In the structure of zeorin[26] the 1,3-diaxial methyl groups cause a similar lengthening of the C8–C14 bond to 1.63 Å. This bond lengthening is consistent with mass spectal data on tetrahymanol suggesting a scission of the C8–C14 bond.[17]

The tetrahymanol molecule possesses an approximate twofold axis which passes through the midpoints of the C8–C14 and C11–C12 bonds. This intramolecular symmetry extends to include the observed conformations of the methyl groups (Figure 2) and is broken only by the hydroxyl substituent. The axial methyl groups on carbons 4, 8, 14, and 22 are rotated by as much as 30° counterclockwise with respect to a staggered conformation with the molecular skeleton, and the axial groups on 10 and 18 are rotated clockwise so that all adjacent methyl groups have two symmetrical hydrogen contacts between them. Although the tetrahymanol backbone possesses compositional symmetry, the observed conformation is not symmetric as indicated in the torsion angles (Figure 1). An overlap of the chemically equivalent portions of molecule I with molecule II illustrates the conformational differences between the two molecules in the asymmetric unit (Figure 3a). However, if molecule II is rotated 180° about the axis through the midpoints of the C8–C14 and the C11–C12 bonds, the overlap of the polycyclic portions is almost exact (Figure 3b).

These observations are consistent with the hypotheses that (a) the most stable conformation of the symmetric portion of the molecule is in fact the asymmetric form observed, (b) the hydroxyl substituent does not alter this conformational asymmetry but permits the detection of two conformational isomers, and (c) in solution, tetrahymanol molecules oscillate between the two conformers that have been cocrystallized.

The polar ends of the molecules and the water of hydration form a left-handed helical hydrogen-bonding arrangement about one of the screw axes. Although the gross packing of the molecules in the unit cell is such that molecule I is approximately related to molecule II by pseudoorthorhombic symmetry operators, strict orthorhombic symmetry would require that either molecule I or II be rotated to exchange the polar and nonpolar ends, and as such the hydrogen bonding structure observed in the hemihydrate would be destroyed.

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Registry No.—Tetrahymanol hemihydrate, 61899-97-6.

Supplementary Material Available. The final atomic coordinates and anisotropic thermal parameters for the nonhydrogen atoms and the positional coordinates of the hydrogen atoms (2 pages). Ordering information is given on any current masthead page.

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γ-Alkylation of α,β-Unsaturated Carbonyl Compounds

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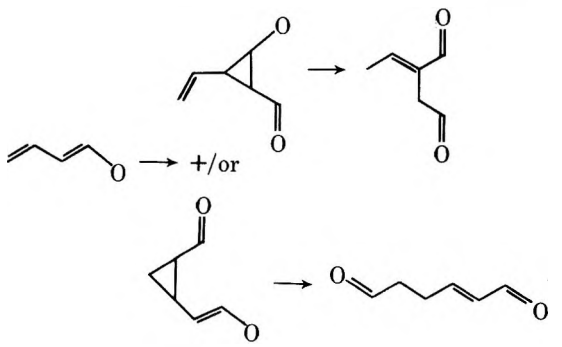
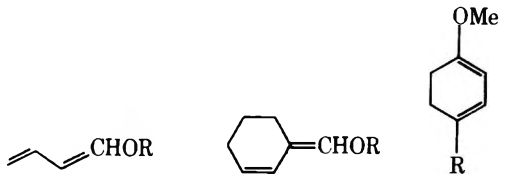
The copper-catalyzed reactions of ethyl diazoacetate and diazoacetone with the dienol derivatives 1-methoxy- and 1-trimethylsilyloxy-1,3-butadiene, 3-acetoxymethylene- and 3-trimethylsilyloxymethylenecyclohexene, and 1-methoxy-1,3-cyclohexadiene and its 4-methyl analogue are described. Hydrolysis of the olefinic cyclopropane adducts is shown to lead to α- and γ-alkylated α,β-unsaturated aldehydes and ketones.

The simple, three-step scheme of conversion of aldehydes or ketones into enol ethers or esters, cyclopropanation of these olefinic intermediates with α-diazocarbonyl reagents over copper, and aqueous acid cleavage of the resultant β-oxycyclopropylketo compounds has been shown to be the equivalent of α-alkylation of aldehydo and keto substances as well as a useful procedure for the synthesis of 1,4-dicarbonyl compounds.[1-4] As part of an attempt to broaden the scope of this method of synthesis it became of interest to explore the behavior of more highly functionalized enol derivatives and α-diazoketo systems in the cyclopropanation step. In this connection one study involved the copper-catalyzed interaction of ethyl diazoacetate as well as diazoacetone with conjugated dienyl ethers and esters, derived from α,β-unsaturated aldehydes and ketones. As the following equations indicate, it was assumed that, were the cyclopropanation to take place



on the unoxygenated double bond, the new three-step scheme would be the equivalent of a γ-alkylation of α,β-unsaturated keto systems,[5] leading to 1,6-dicarbonyl compounds.[6]

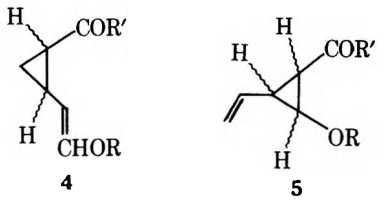
The crotonaldehyde-based dienyl ethers 1-methoxy-1,3-butadiene (**1a**) and 1-trimethylsilyloxy-1,3-butadiene (**1b**),[7,8] the enol acetate and trimethylsilyl ether from 1-cyclohexenecarboxaldehyde[9] (**2a** and **2b**, respectively), and the 1-methoxy-1,3-cyclohexadienes[10] **3a** and **3b** served as starting materials for this investigation. Diene **2a** was prepared by the acid-induced acetylation of 1-cyclohexenecarboxaldehyde with isopropenyl acetate, while diene **2b** was the result of the



1a, R = Me; **b**, R = $SiMe_3$ **2a**, R = Ac; **b**, R = $SiMe_3$ **3a**, R = H; **b**, R = Me

O-alkylation of the aldehyde with trimethylsilyl chloride in the presence of triethylamine.[7,11]

The decomposition of ethyl diazoacetate in cyclohexane or neat solutions of each of the six dienes over copper bronze at 65–85 °C led to 55–80% yields of stereo- and regioisomer mixtures of olefinic cyclopropanecarboxylates, i.e., **1a → 4a + 5a, 1b → 4b + 5b, 2a → 6a + 7a, 2b → 6b + 7b, 3a → 8a + 9a**, and **3b → 8b + 9b.** With the exception of the silyl ethers

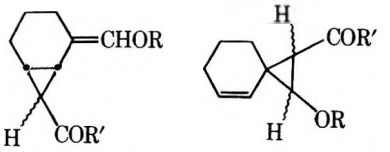


4 **5**

a, R = Me; R' = OEt
b, R = $SiMe_3$; R' = OEt
c, R = R' = Me
d, R = $SiMe_3$; R' = Me

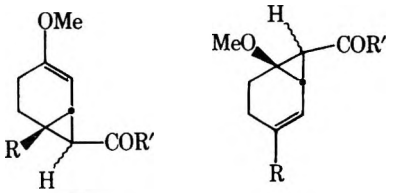
the regioisomers were separated into stereoisomer mixtures, no attempt having been made to fractionate the latter. Interaction of diazoacetone with each of the starting dienes under conditions similar to those of the diazoacetic ester reactions produced difficultly separable isomer mixtures of the ketone pairs **4c–5c, 4d–5d, 6c–7c, 6d–7d, 8c–9c**, and **8d–9d**, respectively.

Mild treatment of cyclopropane **4a** with aqueous acid caused the hydrolysis of its enol ether moiety leading to the aldehydo ester **10**, whereas oxycyclopropane **5a** remains un-



6 7

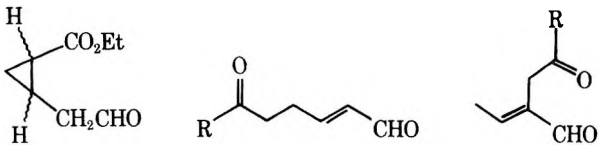
a, R = Ac; R′ = OEt
b, R = $SiMe_3$; R′ = OEt
c, R = Ac; R′ = Me
d, R = $SiMe_3$; R′ = Me



8 9

a, R = H; R′ = OEt
b, R = Me; R′ = OEt
c, R = H; R′ = Me
d, R = R′ = Me

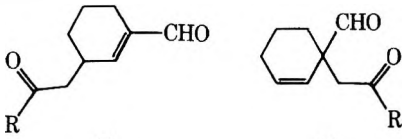
perturbed under these conditions. Hydrolyses of **4a** and **5a** at elevated temperature produced the acyclic substances **11a** and **12a**, respectively.[12] The same products result from the hydrolysis of the silyl ether mixture, **4b** and **5b**, on heating. Finally, mild, aqueous acid hydrolysis of either the ketone mixture **4c** and **5c** or the **4d–5d** mixture led to keto aldehydes **11b** and **12b**.



10 11 12

a, R = OEt
b, R = Me

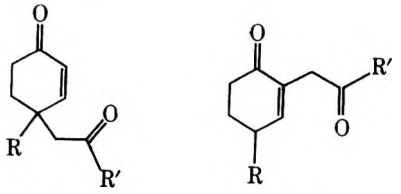
Cyclopropanes **6** and **7** were hydrolyzable in both acid and base. Cleavage of the three-membered rings of **6a** and **6b** with alcoholic base yielded ester **13a**, while **7a** and **7b** gave ester **14a**. Similarly, compounds **6c** and **6d** produced aldehydo ketone **13b**, while **7c** and **7d** led to **14b**.



13 14

a, R = OEt
b, R = Me

Acid hydrolysis of esters **8a**, **8b**, **9a**, and **9b** afforded cyclohexenone esters **15a**, **15b**, **16a**, and **16b**, respectively.



15 16

a, R = H; R′ = OEt
b, R = Me; R′ = OEt
c, R = H; R′ = Me
d, R = R′ = Me

Similar treatment of ketones **8c**, **8d**, **9c**, and **9d** produced diketones **15c**, **15d**, **16c**, and **16d** (in addition to its β,γ-unsaturated ketone isomer).

The isolation of 1,6-diketo compounds **11**, **13**, and **15** at the end of a two-step reaction scheme emanating from masked α,β-unsaturated keto systems makes the procedure a new γ-alkylation method. Furthermore, the ratios of cyclopropanation products (50–90% total yields) favoring nonoxygenated cyclopropanes (2:1 to 5:1) in most instances and the 1,6-diketo substances being the more preponderant, final products, irrespective of the O substituent of the initial conjugated diene, bodes well for this γ-alkylation concept. More work will be necessary to improve the regioselectivity of the cyclopropanation process.

Experimental Section

Boiling and melting points are uncorrected. Infrared spectra of neat liquids were recorded on a Perkin-Elmer 167 spectrophotometer and mass spectra obtained on a CEC 21-110 spectrometer. ^1H NMR spectra were run on $CDCl_3$ solutions with Me_4Si as internal standard (δ 0 ppm) on a Varian A-60 spectrometer and the ^{13}C NMR spectrum was recorded on a Varian XL-100-15 spectrometer operating at 25.02 MHz in the Fourier transform mode. GPC runs were performed on a 10-ft 20% Carbowax on Chromosorb W column in a Varian Autoprep A-700 chromatograph, while preparative TLC utilized Merck silica gel HF 254 as adsorbant.

3-Acetoxymethylenecyclohexene (2a). A stirring solution of 1.52 g of 1-cyclohexenecarboxaldehyde[9] [^1H NMR δ 1.65 (m, 4, methylenes), 2.21 (m, 4, allyl methylenes), 6.66 (m, 1, olefinic H), 9.35 (s, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 21.06 (C-4, C-5), 21.78 (C-6), 26.19 (C-3), 141.12 (C-1), 150.95 (C-2), 193.72 (CO)] and 19 mg of *p*-toluenesulfonic acid in 12 mL of isopropenyl acetate was refluxed under nitrogen with slow removal of the solvent for 5.5 h. Fractional, vacuum distillation yielded 2.09 g of colorless, liquid diene **2a**: bp 55–58 °C (1.25 Torr); IR C=O 1752 cm^{-1} (s); ^1H NMR δ 1.61 (m, 2, CH_2), 2.06, 2.39 (m, 2 each, allyl methylenes), 2.12 (s, 3, Me) 5.68 (dt, 1, J = 10, 3 Hz, H-1), 5.93 (dt, 1, J = 10, 1 Hz, H-2), 6.92 (broad s, 1, OCH); mass spectrum *m/e* 152 (M^+), 110 (base), 95, 81, 79; exact mass *m/e* 152.0842 (calcd for $C_9H_{12}O_2$, 152.0836).

3-Trimethylsilyloxymethylenecyclohexene (2b). A stirring solution of 1.78 g of 1-cyclohexenecarboxaldehyde,[9] 2.71 g of trimethylsilyl chloride, and 3.28 g of triethylamine in 7 mL of dimethylformamide was refluxed under nitrogen for 21 h. After cooling the brown solution was diluted with 50 mL of hexane, washed with 30 mL of 5% sodium bicarbonate solution, 30 mL of water, and 30 mL of saturated brine solution, and dried (Na_2SO_4). Upon removal of the solvent the liquid was distilled, yielding 1.73 g of liquid diene **2b**: bp 33–34 °C (0.25 Torr); IR C=C 1643 (m), 1609 cm^{-1} (m); ^1H NMR δ 0.19 (s, 9 Me_3), 1.56 (m, 2, CH_2), 2.04, 2.35 (m, 2 each, allyl methylenes), 5.48 (dt, 1, J = 10, 4 Hz, H-1), 5.98 (dt, 1, J = 10, 2 Hz, H-2), 6.12 (broad s, 1, OCH); mass spectrum *m/e* 182 (M^+), 167, 93, 92, 75, 73 (base); exact mass *m/e* 182.1132 (calcd for $C_{10}H_{18}OSi$, 182.1126).

1-Dimethoxymethylcyclohexene. A stirring mixture of 1.20 g of 1-cyclohexenecarboxaldehyde,[9] 0.60 g of Amberlite IR-120-H ion exchange resin (medium porosity, washed three times with methanol), and 5 mL of trimethyl orthoformate in 5 mL of methanol was refluxed under nitrogen for 5 h. Sodium sulfate was added and the cooled mixture filtered through Celite and evaporated. An ether solution (50 mL) of the residue was washed with 100 mL of 5% sodium bicarbonate solution and 50 mL of brine solution, dried (Na_2SO_4), and evaporated. Distillation (0.2 Torr, bath temperature 31 °C) of the residue (1.45 g) on a Vigreux column (1.7 × 13 mm) yielded 1.21 g of colorless, liquid 1-cyclohexenecarboxaldehyde dimethyl acetal: ^1H NMR δ 1.58 (m, 4, methylenes), 1.96 (m, 4, allyl methylenes), 3.23 [s, 6, $(OMe)_2$], 4.40 (s, 1, O_2CH), 5.75 (broad s, 1, olefinic H); mass spectrum *m/e* 156 (M^+), 128 (base), 94, 78; exact mass *m/e* 156.1146 (calcd for $C_9H_{16}O_2$, 156.1149).

Ethyl 2-(β-Methoxyvinyl)cyclopropanecarboxylate (4a) and Ethyl 2-Methoxy-3-vinylcyclopropanecarboxylate (5a). All cyclopropanations followed an earlier procedure.[1,2] Ethyl diazoacetate (3.15 g) was added dropwise over a 4-h period to a stirring suspension of 300 mg of copper bronze[13] and 2.10 g of 1-methoxy-1,3-butadiene (**1a**) in 10 mL of cyclohexane kept at 80 °C under nitrogen. Thereafter the mixture was stirred at 80 °C for an additional 0.5 h and filtered. The catalyst was washed with 15 mL of ether and the combined filtrate and washings evaporated. Distillation of the residue gave 2.60

g of an ester mixture, bp 50–55 °C (0.1 Torr), which was separated by GPC (column temperature 120 °C) and led to two fractions of 10 and 20 min retention times. The first fraction consisted of 350 mg of **5a:** IR C=O 1730 (s), C=C 1640 cm^{-1} (m); ^1H NMR δ 1.25 (t, 3, J = 7 Hz, Me), 1.7–2.6 (m, 2, c-Pr H), 3.31 (s, 3, OMe), 3.4–3.6 (m, 1, OCH), 4.18 (q, 2, J = 7 Hz, OCH_2), 4.8–6.0 (m, 3, olefinic H); mass spectrum m/e 170 (M^+), 169, 131, 119, 97 (base), 69; exact mass m/e 170.0942 (calcd for $C_9H_{14}O_3$, 170.0943).

The second fraction contained 1.60 g of **4a:** IR C=O 1730 (s), C=C 1670 (s), 1655 cm^{-1} (s); ^1H NMR δ 0.7–2.1 (m, 4, c-Pr H), 1.22 (t, 3, J = 7 Hz, Me), 3.45, 3.59 (s, 3 total, OMe), 4.12 (q, 2, J = 7 Hz, OCH_2), 4.4–4.9 (m, 1, olefinic H), 6.41 (dd, 1, J = 13, 3 Hz, OCH); mass spectrum m/e 170 (M^+), 169, 131, 119, 97 (base), 69; exact mass m/e 170.0943 (calcd for $C_9H_{14}O_3$, 170.0943).

Ethyl 2-(β-Trimethylsilyloxyvinyl)cyclopropanecarboxylate (4b) and Ethyl 2-Trimethylsilyloxy-3-vinylcyclopropanecarboxylate (5b). A mixture of 2.25 g of ethyl diazoacetate, 500 mg of copper bronze, and 4.70 g of 1-trimethylsilyloxy-1,3-butadiene (**1b**) was treated and worked up as above. Distillation of the crude product yielded 3.00 g of starting diene (**1b**) and 2.80 g of a mixture of **4b** and **5b:** bp 57–62 °C (0.25 Torr); IR C=O 1730 (s), C=C 1695 (m), 1655 cm^{-1} (m); ^1H NMR δ 0.19 (s, 9, $SiMe_3$), 1.24, 1.29 (t, 3 total, J = 7 Hz, Me), 0.7–2.4 (m, 3–4, c-Pr H), 4.08, 4.13 (q, 2, J = 7 Hz, OCH_2), 4.3–6.5 (m, 2–3, olefinic H); exact mass m/e 228.1185 (calcd for $C_{11}H_{20}O_3Si$, 228.1181).

Ethyl 2-Acetoxymethylenebicyclo[4.1.0]heptane-7-carboxylate (6a) and Ethyl 2-Acetoxyspiro[2.5]oct-4-ene-1-carboxylate (7a). A mixture of 6.31 g of ethyl diazoacetate, 970 mg of copper bronze, and 4.27 g of dienol acetate **2a** in 20 mL of cyclohexane was treated and worked up as above. Distillation of the crude product yielded 4.76 g of a mixture of **6a** and **7a** (3.5:1 ratio by ^1H NMR spectral integration of the olefinic H peaks), bp 125–145 °C (0.35 Torr), and 751 mg of a mixture, bp >145 °C (0.5 Torr), predominating in the biscyclopropanation product: IR C=O 1760–1700 cm^{-1} (s); ^1H NMR δ 1.24 (t, 6, J = 7 Hz, Me_2), 2.03 (s, 3, COMe), 3.8–4.3 [m, 4, $(OCH_2)_2$], 4.48 (d, <1, J = 4 Hz, OCH); mass spectrum m/e 324 (M^+), 282, 238, 207, 196, 167, 123, 122, 121, 43 (base); exact mass m/e 324.1558 (calcd for $C_{17}H_{24}O_6$; 324.1571).

GPC of the ester mixture (**6a** and **7a**) on a 10-ft column of 10% SE-30 on Chromosorb W at 195 °C yielded **6a** [IR C=O 1720 (s), 1750 (s), C=C 1660 cm^{-1} (m); ^1H NMR δ 1.22 (t, 3, J = 7 Hz, Me), 2.08 (s, 3, COMe), 4.06 (dd, 2, J = 7 Hz, OCH_2), 6.96 (t, 1, J = 2 Hz, olefinic H); mass spectrum m/e 238 (M^+), 196 (base), 167, 150, 123, 122, 121; exact mass m/e 238.1217 (calcd for $C_{13}H_{18}O_4$, 238.1205)] and **7a** (1.2:1 mixture of trans and cis isomers, respectively) [IR C=O 1725 (s), 1755 (s), C=C 1640 cm^{-1} (m); ^1H NMR δ 1.23 (t, 6, Me_2), 2.05 (s, 3, trans COMe), 2.07 (s, 3, cis COMe), 4.02 (q, 2, J = 7 Hz, cis OCH_2), 4.06 (q, 2, J = 7 Hz, trans OCH_2), 4.45 (d, 1, J = 4 Hz, trans OCH), 4.84 (dt, 1, J = 10, 2 Hz, cis OCH), 5.3–6.2 (m, 4, olefinic H); mass spectrum m/e 238 (M^+), 196, 192, 178, 167, 151, 139, 123, 122, 121, 43 (base); exact mass m/e 238.1210 (calcd for $C_{13}H_{18}O_4$, 238.1205).

Ethyl 2-Trimethylsilyloxymethylenebicyclo[4.1.0]heptane-7-carboxylate (6b) and Ethyl 2-Trimethylsilyloxyspiro[2.5]-oct-4-ene-1-carboxylate (7b). A mixture of 1.36 g of ethyl diazoacetate, 215 mg of copper bronze, and 1.12 g of dienol ether **2b** in 10 mL of cyclohexane was treated (2 h) and worked up as above. Distillation of the crude product [bp 83–100 °C (0.1 Torr)] yielded a 2.7:1 mixture of **6b** and **7b**, respectively: IR C=O 1722 (s), C=C 1655 cm^{-1} (m); ^1H NMR δ 0.18 (s, 9, $SiMe_3$), 1.23 (t, 3, J = 7 Hz, Me), 4.04 (q, 2, J = 7 Hz, OCH_2), 5.3–5.9 (m, <2, olefinic H), 6.18 (t, <1, J = 2 Hz, OCH of **6b**); exact mass m/e 268.1502 (calcd for $C_{14}H_{24}O_3Si$, 268.1494).

Ethyl 3-Methoxybicyclo[4.1.0]hept-2-ene-7-carboxylate (8a) and Ethyl 1-Methoxybicyclo[4.1.0]hept-4-ene-7-carboxylate (9a). A mixture of 2.28 g of ethyl diazoacetate, 500 mg of copper bronze, and 4.40 g of dienol ether **3a** was treated (3 h) and worked up as above. Distillation of the crude product gave 2.10 g of starting diene (**3a**) and 2.80 g of a mixture of **8a** and **9a**, bp 85 °C (0.5 Torr). Preparative TLC of the latter and elution with 4:1 hexane–ether yielded 1.70 g of **9a** [IR C=O 1730 (s), C=C 1650 cm^{-1} (m); ^1H NMR δ 1.25 (t, 3, J = 7 Hz, Me), 1.5–2.8 [m, 6, $(CH_2)_2$, $(CH)_2$], 3.29, 3.32 (s, 3 total, OMe), 4.15 (q, 2, J = 7 Hz, OCH_2), 5.4–6.1 (m, 2, olefinic H); mass spectrum m/e 196 (M^+), 123 (base), 91; exact mass m/e 196.1104 (calcd for $C_{11}H_{16}O_3$, 196.1099)] and 700 mg of **8a** [IR C=O 1725 (s), C=C 1658 cm^{-1} (m); ^1H NMR δ 0.8–2.5 [m, 7, $(CH_2)_2$, $(CH)_3$], 1.26 (t, 3, J = 7 Hz, Me), 3.48 (s, 3, OMe), 4.13 (q, 2, J = 7 Hz, OCH_2), 4.8–5.0 (m, 1, olefinic H); mass spectrum m/e 196 (M^+), 131, 119 (base); exact mass m/e 196.1103 (calcd for $C_{11}H_{16}O_3$, 196.1099)].

Ethyl 3-Methoxy-6-methylbicyclo[4.1.0]hept-2-ene-7-carboxylate (8b) and Ethyl 6-Methoxy-3-methylbicyclo[4.1.0]-hept-2-ene-7-carboxylate (9b). A mixture of 3.30 g of ethyl diazoacetate, 500 mg of copper bronze, and 6.30 g of dienol ether **3b** was treated and worked up as above. Distillation of the crude product gave 3.50 g of starting diene (**3b**) and 3.70 g of a mixture of **8b** and **9b**, bp 83–90 °C (0.4 Torr). Preparative TLC of the latter and elution with 3:1 hexane–ether led to 1.32 g of **9b** [IR C=O 1730 cm^{-1} (s); ^1H NMR δ 1.26 (t, 3, J = 7 Hz, Me of Et), 1.61 (d, 3, J = 1 Hz, olefinic Me), 1.7–2.4 [m, 6, $(CH_2)_2$, $(CH)_2$], 3.27 (s, 3, OMe), 4.13 (q, 2, J = 7 Hz, OCH_2), 5.63 (dd, 1, J = 5, 1 Hz, olefinic H); mass spectrum m/e 210 (M^+), 137 (base), 124, 105; exact mass m/e 210.1256 (calcd for $C_{12}H_{18}O_3$, 210.1256)] and 310 mg of **8b** [IR C=O 1725 (s), C=C 1658 cm^{-1} (m); ^1H NMR δ 1.25 (t, 3, J = 7 Hz, Me of Et), 1.30 (s, 3, Me), 1.5–2.5 [m, 6, $(CH_2)_2$, $(CH)_2$], 3.47 (s, 3, OMe), 4.12 (q, 2, J = 7 Hz, OCH_2), 4.7–5.0 (m, 1, olefinic H); mass spectrum m/e 210 (M^+), 132, 120, 69 (base); exact mass m/e 210.1254 (calcd for $C_{12}H_{18}O_3$, 210.1256)].

2-Acetyl-1-(β-methoxyvinyl)cyclopropane (4c) and 3-Acetyl-2-methoxy-1-vinylcyclopropane (5c). A mixture of 3.60 g of diazoacetone, 500 mg of copper bronze, and 3.60 g of dienol ether **1a** in 10 mL of cyclohexane was treated (70 °C) and worked up as above. Distillation of the crude product afforded 2.75 g of a mixture of **4c** and **5c:** bp 45–50 °C (0.25 Torr); IR C=O 1690 (s), C=C 1650 (m), 1640 cm^{-1} (m); ^1H NMR δ 0.7–2.0 (m, 3–4, CH_2, methines), 2.21, 2.22 (s, 3 total, Me), 3.45, 3.50 (s, 3 total, OMe), 4.4–5.4 (m, ca. 29% of 3, olefinic H of **5c**), 5.9–6.9 (m, ca. 71% of 2, olefinic H of **4c**); exact mass m/e 180.0838 (calcd for $C_8H_{12}O_2$, 180.0834).

2-Acetyl-1-(β-trimethylsilyloxyvinyl)cyclopropane (4d) and 3-Acetyl-2-trimethylsilyloxy-1-vinylcyclopropane (5d). A mixture of 2.10 g of diazoacetone, 500 mg of copper bronze, and 7.00 g of dienol ether **1b** was treated (70 °C) and worked up as above. The crude product was distilled yielding 4.30 g of starting diene (**1b**) and 2.15 g of a liquid mixture of **4d** and **5d:** bp 50–54 °C (0.25 Torr); IR C=O 1695 (s), C=C 1640 cm^{-1} (m); ^1H NMR δ 0.19 (s, 9, $SiMe_3$), 2.21, 2.18 (s, 3 total, Me); exact mass m/e 198.1058 (calcd for $C_{10}H_{18}O_2Si$, 198.1054).

7-Acetyl-2-acetoxymethylenebicyclo[4.1.0]heptane (6c) and 1-Acetoxy-2-acetylspiro[2.5]oct-4-ene (7c). A mixture of 3.95 g of diazoacetone, 1.30 g of copper bronze, and 6.68 g of dienol acetate **2a** in 50 mL of cyclohexane was treated (5 h) and worked up as above. Distillation of the crude product provided 5.00 g of starting diene (**2a**) and 2.40 g of a 3.2:1 mixture (by integration of the olefinic hydrogen NMR signals) of **6c** and **7c**, respectively, bp 108–130 °C (0.35–0.40 Torr). Redistillation afforded 2.09 g of the mixture: IR C=O 1755 (s), 1695 cm^{-1} (s); ^1H NMR δ 2.08, 2.18 (s, 6 total, Me), 4.49 (d, <1, J = 4 Hz, c-Pr H of *trans*-**7c**), 5.2–5.9 (m, <2, olefinic H of **7c**), 6.93 (t, <1, J = 2 Hz, olefinic H of **6c**); exact mass m/e 208.1091 (calcd for $C_{12}H_{16}O_3$, 208.1099).

7-Acetyl-2-trimethylsilyloxymethylenebicyclo[4.1.0]heptane (6d) and 2-Acetyl-1-trimethylsilyloxyspiro[2.5]oct-4-ene (7d). A mixture of 1.32 g of diazoacetone, 370 mg of copper bronze, and 1.91 g of dienol ether **2b** in 10 mL of cyclohexane was treated (2 h) and worked up as above. Distillation of the crude product gave 1.26 g of a 1.7:1 mixture of starting diene (**2b**) and 3-hexene-2,5-dione [bp 26–40 °C (0.25–0.35 Torr)], respectively, and 825 mg of a 2.3:1.8:1 mixture of **6d, 7d,** and **13b,** respectively. Redistillation of the latter gave an oil: bp 65–79 °C (0.1–0.15 Torr); IR C=O 1720 (s), 1688 cm^{-1} (s); ^1H NMR δ 0.18 (s, 9, $SiMe_3$), 2.15 (s, 3, Me), 3.92 (d, <1, J = 4 Hz, OCH of *trans*-**7d**), 5.2–5.9 (m, <2, olefinic H of **7d**), 6.19 (t, <1, J = 2 Hz, olefinic H of **6d**); exact mass m/e 238.1399 (calcd for $C_{13}H_{22}O_2Si$, 238.1388).

7-Acetyl-3-methoxybicyclo[4.1.0]hept-2-ene (8c) and 7-Acetyl-6-methoxybicyclo[4.1.0]hept-2-ene (9c). A mixture of 1.68 g of diazoacetone, 500 mg of copper bronze, and 4.40 g of dienol ether **3a** was treated (2 h) and worked up as above. Distillation of the crude product yielded 2.20 g of starting diene (**3a**) and 2.20 g of a colorless, liquid mixture of **8c** and **9c:** bp 61–65 °C (0.15 Torr); IR C=O 1690 (s), C=C 1655 (m), 1604 (w), 1585 cm^{-1} (w); ^1H NMR δ 2.15, 2.20 (s, 3 total, Me), 3.35, 3.51, 3.54 (s, 3 total, OMe), 4.89 (t, <1, J = 2 Hz, olefinic H of **8c**), 5.6–6.0 (m, <2, olefinic H of **9c**).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.34; H, 8.28.

7-Acetyl-3-methoxy-6-methylbicyclo[4.1.0]hept-2-ene (8d) and 7-Acetyl-6-methoxy-3-methylbicyclo[4.1.0]hept-2-ene (9d). A mixture of 2.20 g of diazoacetone, 500 mg of copper bronze, and 8.80 g of dienol ether **3b** was treated (3 h) and worked up as above. Distillation of the crude product yielded 7.90 g of starting diene (**3b**) and 1.17 g of a colorless, liquid mixture of **8d** and **9d:** bp 50–60 °C (0.1 Torr); IR C=O 1685 (s), C=C 1650 (m), 1605 cm^{-1} (w); ^1H NMR δ 1.67 (m, <3, olefinic Me of **9d**), 1.78, 1.81 (s, <3, Me of **8d**), 2.09, 2.18 (s, 3 total, Me of Ac), 3.29 (s, <3, OMe of **9d**), 3.48 (s, <3, OMe of **8d**),

4.58 (m, <1, olefinic H of **8d**), 5.25 (m, <1, olefinic H of **9d**).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.12; H, 8.81.

Ethyl 2-(β-Oxoethyl)-1-cyclopropanecarboxylate (10). A mixture of 100 mg of ester **4a** and 10 mL of 2 N hydrochloric acid was stirred under nitrogen at room temperature for 4 h. It was diluted with 15 mL of water, saturated with sodium chloride, and extracted with 75 mL of ether. The extract was washed with 5% sodium bicarbonate solution and brine, dried (Na_2SO_4), and evaporated, leaving 70 mg of colorless, liquid aldehydo ester **10:** IR aldehyde CH 2725 (w), C=O 1725 cm^{-1} (s); ^1H NMR δ 1.27 (t, 3, J = 7 Hz, Me), 2.46 (dd, <2, J = 6, 2 Hz, $COCH_2$ of one isomer), 2.82 (dd, <2, J = 6, 1 Hz, $COCH_2$ of other isomer), 4.15 (q, 2, J = 7 Hz, OCH_2), 9.76 (t, 1, J = 2 Hz, CHO); exact mass m/e 156.0790 (calcd for $C_8H_{12}O_3$, 156.0786).

Ethyl 6-Oxo-4-hexenoate (11a). A solution of 430 mg of ester **4a** and 4 mL of 5 N hydrochloric acid in 12 mL of ethanol was refluxed for 1.5 h. Workup as for aldehyde **10** (vide supra) led to 300 mg of product whose preparative TLC yielded liquid aldehydo ester **11a:** IR aldehyde CH 2725 (w), C=O 1731 (s), 1688 (s), C=C 1631 cm^{-1} (m); ^1H NMR δ 1.30 (t, 3, J = 7 Hz, Me), 2.3–3.0 [m, 4, $(CH_2)_2$], 4.20 (q, 2, J = 7 Hz, OCH_2), 6.18 (dd, 1, J = 15, 7 Hz, H-5), 6.93 (dt, 1, J = 15, 8 Hz, H-4), 9.52 (d, 1, J = 7 Hz, H-6); mass spectrum m/e 156 (M^+), 83 (base); exact mass m/e 156.0790 (calcd for $C_8H_{12}O_3$, 156.0786).

Ethyl 3-Formyl-3-pentenoate (12a). A solution of 100 mg of ester **5a** and 1 mL of concentrated hydrochloric acid in 8 mL of ethanol was refluxed under nitrogen for 2 h. Upon workup as for **10** (vide supra) there was obtained 80 mg of oil whose microdistillation gave liquid aldehydo ester **12a:** IR aldehyde CH 2770 (w), C=O 1730 (s), 1685 (s), C=C 1646 cm^{-1} (m); ^1H NMR δ 1.23 (t, 3, J = 7 Hz, Me of Et), 2.01 (d, 3, J = 7 Hz, Me), 3.33 (s, 2, CH_2), 4.15 (q, 2, J = 7 Hz, OCH_2), 6.82 (q, 1, J = 7 Hz, H-4), 9.48 (s, 1, CHO); mass spectrum m/e 156 (M^+), 111, 110, 83, 55, 45, 43, 29, 27 (base), 26, 25; exact mass m/e 156.0791 (calcd for $C_8H_{12}O_3$, 156.0786).

Hydrolysis of 4b and 5b. A 3.00-g mixture of **4b** and **5b** was poured onto a silica gel column, 40 g, and kept thereon for 24 h. Elution with benzene and evaporation gave 1.80 g of colorless oil whose preparative TLC separated the 2:2:1 mixture of aldehydes **10**, **11a**, and **12a**, respectively.

A solution of 890 mg of a **4b–5b** mixture and 1 mL of concentrated hydrochloric acid in 10 mL of ethanol was refluxed under nitrogen for 2 h. Workup as for **10** (vide supra) gave 492 mg of an oil whose preparative TLC separated the 4:1 mixture of **11a** and **12a**, respectively.

6-Oxo-2-heptenal (11b) and 4-Formyl-4-hexen-2-one (12b). A mixture of 500 mg of the **4c–5c** mixture and 30 mL of 1 N hydrochloric acid was stirred under nitrogen at room temperature for 2 h. Workup as for **10** above gave 350 mg of oil whose GPC separation (135 °C) led to 195 mg of **11b** [4 min retention time; IR aldehyde CH 2720 (w), C=O 1715 (s), 1685 (s), C=C 1632 cm^{-1} (m); ^1H NMR δ 2.19 (s, 3, Me), 2.58 (m, 2, H_2-4), 2.68 (s, 2, H_2-5), 6.08 (dd, 1, J = 15, 7 Hz, H-2), 6.88 (dt, 1, J = 15, 6 Hz, H-3), 9.48 (d, 1, J = 7 Hz, H-1); mass spectrum m/e 126 (M^+), 83, 68, 57, 55, 44 (base), 42, 40; exact mass m/e 126.0676 (calcd for $C_7H_{10}O_2$, 126.0680)] and to 80 mg of **12b** [11 min retention time; IR aldehyde CH 2720 (w), C=O 1715 (s), 1680 (s), C=C 1644 cm^{-1} (m); ^1H NMR δ 1.95 (d, 3, J = 7 Hz, Me), 2.18 (s, 3, COMe), 3.38 (s, 2, $COCH_2$), 6.80 (q, 1, J = 7 Hz, olefinic H), 9.46 (s, 1, CHO); mass spectrum m/e 126 (M^+), 83, 55, 43 (base); exact mass m/e 126.0683 (calcd for $C_7H_{10}O_2$, 126.0680).

Keeping 1.90 g of a **4c–5c** mixture on a silica gel column (30 g) and elution with benzene led to 1.40 g of a 2.5:1 mixture of **11b** and **12b**, respectively.

Hydrolysis of 4d and 5d. A 1.00-g mixture of **4d** and **5d** was kept on a silica column, 20 g, for 24 h and then eluted with benzene. The eluates yielded 700 mg of colorless oil whose GPC separated it into keto aldehydes **11b** and **12b** in 2.5:1 ratio.

A mixture of 1.20 g of the **4d–5d** mixture and 10 mL of 1 N hydrochloric acid in 20 mL of ether was stirred under nitrogen at room temperature for 1 h. Workup as for **10** above gave 900 mg of a 2.5:1 mixture of **11b** and **12b**, respectively, separated by GPC.

Ethyl (3-Formyl-2-cyclohexenyl)acetate (13a). A mixture of 103 mg of ester **6a** and 30 mg of anhydrous potassium carbonate in 3 mL of ethanol was stirred at 27 °C for 4 h. It then was diluted with 30 mL of brine solution and extracted with 40 mL of chloroform. The extract was dried ($MgSO_4$) and evaporated. Distillation [81–83 °C (0.2 Torr)] of the residue, 77 mg, yielded the ester **13a:** IR aldehyde CH 2710 (w), C=O 1730 (s), 1682 (s), C=C 1642 cm^{-1} (m); ^1H NMR δ 1.28 (t, 3, J = 7 Hz, Me), 2.26 (d, 1, J = 2 Hz, H of $COCH_2$), 2.39 (s, 1, other H of $COCH_2$), 4.08 (q, 2, J = 7 Hz, OCH_2), 6.52 (m, 1, olefinic H), 9.21 (s, 1, CHO); mass spectrum m/e 196 (M^+, base), 151, 123, 122, 109; exact mass m/e 196.1092 (calcd for $C_{11}H_{16}O_3$, 196.1099); semicarbazone mp 148–149 °C (crystallized from aqueous ethanol).

Anal. Calcd for $C_{12}H_{19}O_3N_3$: C, 56.90; H, 7.56; N, 16.59. Found: C, 57.05; H, 7.54; N, 16.48.

Ethyl (1-Formyl-2-cyclohexenyl)acetate (14a). A mixture of 86 mg of ester **7a** and 24 mg of anhydrous potassium carbonate in 2 mL of ethanol was stirred at 27 °C for 4 h. Workup as for **13a** above led to 66 mg of a liquid mixture of aldehydo ester **14a** (minor component) [IR aldehyde CH 2720 (w), C=O 1750 (s), 1730 (s), C=C 1635 cm^{-1} (w); ^1H NMR δ 9.33 (s, 1, CHO)] and its isomer, the ethyl lactol ether of (1-formyl-2-cyclohexenyl)acetic acid [IR C=O 1790 (s), C=C 1610 cm^{-1} (w); ^1H NMR δ 1.23 (t, 3, J = 7 Hz, Me), 4.06 (q, 2, J = 7 Hz, OCH_2), 4.95 (s, <1, OCH of one isomer), 5.01 (s, <1, OCH of the other isomer), 5.42 (d, 1, J = 10 Hz, c-hex H-2), 5.82 (dt, 1, J = 10, 3 Hz, c-hex H-3); mass spectrum m/e 196 (M^+)].

A mixture of 107 mg of the **6b–7b** mixture and 25 mg of anhydrous potassium carbonate in 2.5 mL of ethanol was stirred at 25 °C for 4 h. Workup as above gave 79 mg of a mixture of **13a**, **14a**, and the lactol ethyl ether isomer of the latter.

3-Acetonyl-1-cyclohexenecarboxaldehyde (13b) and 1-Acetonyl-2-cyclohexenecarboxaldehyde (14b). A mixture of 1.27 g of a 1.6:1 **6c–7c** mixture and 318 mg of anhydrous potassium carbonate in 35 mL of ethanol was stirred at room temperature for 3 h. Workup as for **14a** above gave 920 mg of oil whose distillation [75–85 °C (0.15 Torr)] yielded 637 mg of a 4:1 mixture of **13b** and **14b**, respectively, which was separated by GPC (180 °C) into **13b** [IR aldehyde CH 2730 (w), C=O 1712 (s), 1680 (s), C=C 1640 cm^{-1} (m); ^1H NMR δ 2.08 (s, 3, Me), 2.48 (d, 1, J = 2 Hz, H of $COCH_2$), 2.58 (s, 1, other H of $COCH_2$), 6.53 (m, 1, olefinic H), 9.26 (s, 1, CHO); mass spectrum m/e 166 (M^+), 124, 123 (base), 79, 43; exact mass m/e 166.1000 (calcd for $C_{10}H_{14}O_2$, 166.0993); bissemicarbazone (from aqueous ethanol), mp 218–226 °C (Anal. Calcd for $C_{12}H_{20}O_2N_6$: C, 51.41; H, 7.19; N, 29.98. Found: C, 51.47; H, 7.21; N, 29.94)] and **14b** [IR aldehyde CH 2740 (w), C=O 1725 (s), 1715 (s), C=C 1605 cm^{-1} (w); ^1H NMR δ 2.11 (s, 3, Me), 2.80 (s, 2, $COCH_2$), 5.42 (dt, 1, J = 10, 2 Hz, olefinic H), 5.88 (dt, 1, J = 10, 3 Hz, olefinic H), 9.45 (s, 1, CHO); mass spectrum m/e 166 (M^+), 138, 137, 123, 95, 81, 80, 79, 77, 69, 67, 43 (base); exact mass m/e 166.0997 (calcd for $C_{10}H_{14}O_2$, 166.0993).

A combination of 584 mg of the **6d–7d** mixture and 157 mg of anhydrous potassium carbonate in 10 mL of ethanol was stirred at 25 °C for 4 h. Workup as for **14a** above yielded 446 mg of an oil, identified by ^1H NMR spectral analysis as a mixture of **13b** and **14b**.

Ethyl (4-Oxo-2-cyclohexenyl)acetate (15a). A solution of 350 mg of ester **8a** and 1.5 mL of concentrated hydrochloric acid in 15 mL of ethanol was refluxed under nitrogen for 2 h. It then was diluted with 100 mL of water, saturated with sodium chloride, and extracted with 100 mL of ether. The extract was washed with 35 mL of 5% sodium bicarbonate solution and 20 mL of saturated brine solution, dried (Na_2SO_4), and evaporated. Microdistillation of the residue, 300 mg, yielded **15a:** IR C=O 1727 (s), 1679 (s), C=C 1606 cm^{-1} (w); ^1H NMR δ 1.27 (t, 3, J = 7 Hz, Me), 4.16 (q, 2, J = 7 Hz, OCH_2), 5.95 (dd, 1, J = 10, 2 Hz, H-3), 6.82 (ddd, 1, J = 10, 3, 1 Hz, H-2). [The substance contains a minor amount of the β,γ-unsaturated isomer, as revealed by the extra signals at 1.25 (t, 3, J = 7 Hz, Me), 4.14 (q, 2, J = 7 Hz, OCH_2), 5.60 (m, 1, olefinic H).]

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.78; H, 7.68.

Ethyl (1-Methyl-4-oxo-2-cyclohexenyl)acetate (15b). A solution of 125 mg of ester **8b** and 0.5 mL of concentrated hydrochloric acid in 8 mL of ethanol was refluxed under nitrogen for 2 h. Workup as for **15a** above yielded 95 mg of liquid **15b:** IR C=O 1735 (s), 1675 (s), C=C 1605 cm^{-1} (w); ^1H NMR δ 1.25 (t, 3, J = 7 Hz, Me), 2.45 (s, 2, $COCH_2$), 4.15 (q, 2, J = 7 Hz, OCH_2), 5.90 (d, 1, J = 10 Hz, H-3), 6.85 (dd, 1, J = 10, 1 Hz, H-2).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.11; H, 8.21.

Ethyl (6-Oxo-1-cyclohexenyl)acetate (16a). A solution of 150 mg of ester **9a** and 0.5 mL of concentrated hydrochloric acid in 8 mL of ethanol was refluxed under nitrogen for 2 h. Workup as for **15a** above yielded 120 mg of liquid **16a:** IR C=O 1735 (s), 1670 cm^{-1} (s); ^1H NMR δ 1.25 (t, 3, J = 7 Hz, Me), 3.28 (broad s, 2, $COCH_2$), 4.13 (q, 2, J = 7 Hz, OCH_2), 6.85 (t, 1, J = 4 Hz, olefinic H).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.77; H, 7.58.

Ethyl (3-Methyl-6-oxo-1-cyclohexenyl)acetate (16b). A solution of 150 mg of ester **9b** and 0.6 mL of concentrated hydrochloric acid in 10 mL of ethanol was refluxed under nitrogen for 2 h. Workup as for **15a** above afforded 120 mg of oily **16b:** IR C=O 1735 (s), 1675 (s), C=C 1608 cm^{-1} (w); ^1H NMR δ 1.20 (d, 3, J = 6 Hz, Me), 1.25 (t, 3, J = 7 Hz, Me of Et), 3.20 (broad s, 2, $COCH_2$), 4.15 (q, 2, J = 7 Hz,

OCH_2), 6.70 (m, 1, olefinic H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.11; H, 8.26.

4-Acetonyl-2-cyclohexenone (15c) and 2-Acetonyl-2-cyclohexenone (16c). A combination of 1.00 g of a **8c–9c** mixture and 15 mL of 2 N hydrochloric acid in 15 mL of ether was stirred at 25 °C for 1 h. The ether layer was separated, the aqueous solution saturated with sodium chloride and extracted with ether, and the combined organic solutions worked up as for **15a** above. Preparative TLC of the crude product, 750 mg, and elution with 4:1 ether–hexane yielded 110 mg of diketone **16c** [IR C=O 1710 (s), 1670 cm^{-1} (s); ^1H NMR δ 2.17 (s, 3, Me), 3.25 (broad s, 2, $COCH_2$), 6.78 (t, 1, J = 3 Hz, H-3); mass spectrum m/e 152 (M^+), 54, 37 (base); exact mass m/e 152.0837 (calcd for $C_9H_{12}O_2$, 152.0833)] and 565 mg of diketone **15c** [IR C=O 1715 (s), 1675 (s), C=C 1616 cm^{-1} (w); ^1H NMR δ 2.22 (s, 3, Me), 5.95 (dd, 1, J = 10, 2 Hz, H-2), 6.81 (ddd, 1, J = 10, 3, 1 Hz, H-3); mass spectrum m/e 152 (M^+), 95, 55, 43 (base); exact mass m/e 152.0830 (calcd for $C_9H_{12}O_2$, 152.0836)].

4-Acetonyl-4-methyl-2-cyclohexenone (15d) and 2-Acetonyl-4-methyl-2-cyclohexenone (16d). A combination of 1.30 g of a **8d–9d** mixture and 25 mL of 2 N hydrochloric acid in 25 mL of ether was stirred at 25 °C for 1 h. Workup as for **15c–16c** above yielded 850 mg of oil, bp 70 °C (0.15 Torr), whose preparative GPC (180 °C) yielded 477 mg of a mixture of **16d** and its isomer, **2-acetonyl-4-methyl-3-cyclohexenone (16d′)** [10 min retention time; IR C=O 1710 (s), 1675 cm^{-1} (s); ^1H NMR δ 1.16 (d, <3, J = 7 Hz, Me of **16d′**), 1.72 (broad s, <3, Me of **16d**), 2.15 (s, <3, COMe of **16d′**), 2.45 (s, <3, COMe of **16d**), 5.17 (m, <1, H-3 of **16d′**), 6.51 (m, <1, H-3 of **16d**); exact mass m/e 166.0989 (calcd for $C_{10}H_{14}O_2$, 166.0993)] and 190 mg of **15d** [14 min retention time; IR C=O 1720 (s), 1675 (s), C=C 1607 cm^{-1} (w); ^1H NMR δ 1.25 (s, 3, Me), 2.13 (s, 3, COMe), 2.58 (s, 2, $COCH_2$), 5.78 (d, 1, J = 10 Hz, H-2), 6.80 (broad d, 1, J = 10 Hz, H-3); mass spectrum m/e 166 (M^+), 109, 108 (base), 95, 43; exact mass m/e 166.0986 (calcd for $C_{10}H_{14}O_2$, 166.0993)].

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Registry No.—**1a,** 3036-66-6; **1b,** 6651-43-0; **2a,** 61967-78-0; **2a** biscyclopropanation product, 61967-79-1; **2b,** 61967-80-4; **3a,** 2161-90-2; **3b,** 2161-94-6; **4a,** 61967-81-5; **4b,** 61967-82-6; **4c,** 61967-83-7; **4d,** 61967-84-8; **5a,** 61967-85-9; **5b,** 61967-65-5; **5c,** 61967-66-6; **5d,** 61967-67-7; **6a,** 61967-68-8; **6b,** 61967-69-9; **6c,** 61967-70-2; **6d,** 61967-71-3; **7a,** 61967-72-4; **7b,** 61967-73-5; **7c,** 61967-74-6; **7d,** 61967-75-7; **8a,** 61967-76-8; **8b,** 61967-77-9; **8c,** 61967-31-5; **8d,** 61967-29-1; **9a,** 61967-30-4; **9b,** 61967-32-6; **9c,** 61967-33-7; **9d,** 61967-34-8; **10,** 61967-35-9; **11a,** 61967-36-0; **11b,** 61967-37-1; **12a,** 61967-38-2; **12b,** 61967-39-3; **13a,** 61967-40-6; **13a** semicarbazone, 61967-41-7; **13b.** 61967-42-8; **13b** bissemicarbazone, 61967-43-9; **14a,** 61967-44-0; **14a** ethyl ether lactol isomer, 61967-45-1; **14b,** 61967-46-2; **15a,** 16831-58-6; **15a** β,γ isomer, 61967-47-3; **15b,** 16831-59-7; **15c,** 56051-94-6; **15d,** 61967-48-4; **16a,** 24124-06-9; **16b,** 61967-49-5; **16c,** 33553-25-2; **16d,** 61967-19-9; **16d′,** 61967-20-2; 1-cyclohexenecarboxaldehyde, 1192-88-7; isopropenyl acetate, 108-22-5; trimethylsilyl chloride, 75-77-4; 1-dimethoxymethylcyclohexene, 61967-21-3; trimethyl orthoformate, 149-73-5; ethyl diazoacetate, 623-73-4; diazoacetone, 2684-62-0.

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Addition to 2,4-Dienes. Halogenation of Ethyl Sorbate

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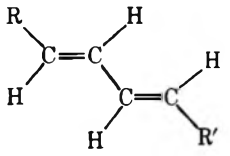
The addition of chlorine and bromine to ethyl sorbate (**1a**) gave 1,2- and 1,4-dihalo products derived from attack of the halogen across the γ,δ double bond. Chlorination of **1a** under ionic conditions proceeds through a tightly bridged chloronium ion intermediate, as indicated by the stereospecific formation of *erythro*-1,2-dichloride **3a**. Stereospecificity in **3a** is lost when chlorine is added to **1a** under radical conditions, indicating a molecule-induced homolysis for this reaction. Even under ionic conditions, bromine reacts with **1a** by a radical process unless an efficient radical scavenger is used.

The loss of stereospecificity in the ionic halogenation[2] of conjugated olefins such as β-methylstyrenes[3] and dienes[4] is ascribed to weakly bridged halonium ion intermediates. Apparently bromine bridges more tightly than chlorine, since 1,2-addition of bromine to *trans,trans*-2,4-hexadiene (**1b**) is more stereospecific (80%) than the 1,2-addition of chlorine (60%).[4] Halogenations of these dienes and olefins under radical conditions[2] involve nonbridged radical intermediates resulting in nonstereospecific products.[5]

We undertook this study to determine what effect a con-

jugated carbonyl group in a diene (see **1a**) would have on product formation when halogens are added to the diene. We anticipated that the carbonyl group should decrease the participation of both the α,β and γ,δ double bonds in electrophilic reactions because the inductive and resonance effects would reduce the basicity of the bonds. The effect of a conjugated carbonyl group on the addition of halogens to 2,4-dienes under radical conditions is not known.

A survey of the literature showed that the chlorinations of dienes such as **1a** and **2a,b** have not been reported. The



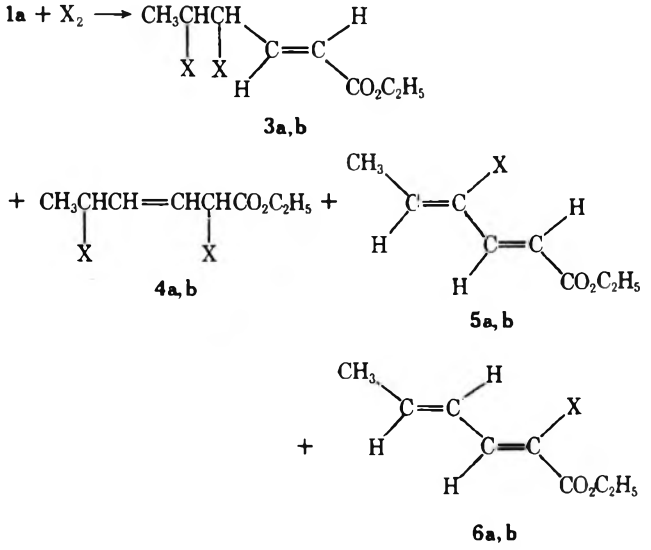
1a, R = CH_3; R′ = $CO_2C_2H_5$
b, R = R′ = CH_3
2a, R = CH_3; R′ = CO_2H
b, R = Ph; R′ = CO_2H

bromination of **2a** was reported to give a γ,δ-dibromide, but no 1,2 (α,β) or 1,4 products were isolated.[6a] However, only an α,β-dibromide was isolated when either **2b** or its methyl ester were treated with bromine,[6b] presumably because stable benzyl cations were involved. There is no indication whether these products were obtained by an ionic or radical process.

In this paper we report our findings on the halogenation of ethyl sorbate (**1a**) with bromine and chlorine under ionic and radical reaction conditions. Our purpose was to determine:)1) whether the reactions proceed by radical or ionic mechanisms; (2) if there are any additions to the α,β double bond; and (3) if any 1,4-dihalides are formed.

Results and Discussion

When ethyl sorbate (**1a**) was chlorinated under ionic conditions a mixture of 1,2- and 1,4-dichlorides (**3a** and **4a**, respectively) and substitution products **5a** and **6a** were obtained (Table I). Structural assignments for the dichlorides **3a** and

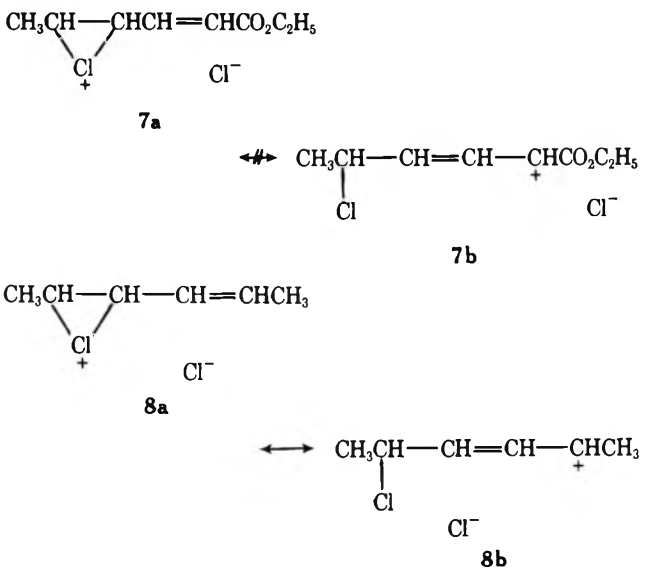


a, X = Cl
b, X = Br

4a were deduced from spectral data and by dehydrochlorinations to chlorodienes **5a** and **6a**. When a mixture of **3a** and **4a** was treated with an excess of triethylamine, **6a** was obtained in good yield from 1,4-dichloride (**4a**). Control experiments showed that the γ,δ-dichloride **3a** was stable under these reaction conditions. However, dehydrochlorination of **3a** did occur with sodium ethoxide in ethanol to give **5a**. Structures for **5a** and **6a** were assigned on the basis of their spectral data.

The γ,δ-dichloride **3a** was formed by a stereospecific anti 1,2-addition, whereas ionic chlorination of *trans*-2,4-hexadiene (**1a**) was shown previously[4b] to be nonstereospecific (ca. 60% anti). Stereospecific addition to **1a** implies that a tightly bridged chloronium ion intermediate was involved. Probably delocalization of the charge does not occur in **7a,b** as happens in **8a,b** because participation of **7b** as a resonance contributor would place a positive charge next to the carbonyl group, and the resonance stabilization of the α,β-bond with the ester carbonyl would be disrupted (Scheme I). Further support for

Scheme I



an ionic pathway comes from the insignificant change in the stereochemistry of **3a**, and in the product ratio of **3a** to **4a** when oxygen was used as a radical scavenger (compare entries 1 and 3 with 2 and 4).

These effects of the carbonyl group may also be responsible for the decrease in the amount of 1,4-dichlorides in the ionic chlorination of **1a** (ca. 30%) as compared to **1b** (ca. 60%) (compare entries 1 through 4 with 16 and 17). Presumably the 1,4-dichloride **4a** is formed[7] by a S_N2'-type attack of the chloride ion on the α-carbon of **7a,b**, since formation of **4a** via **9a,b** should give a significant amount of the α,β-dichloride **10** or the substitution product **6a** (Scheme II). Production of **6a** from intermediate **9a,b** should be favorable, since conjugation with the carbonyl group would be restored. We were unable to detect any **10** in the product mixture and only a trace of **6a** was obtained. Apparently there was little addition of chlorine to the α,β double bond in **1a** because of the resonance and inductive effects of the ester carbonyl.

The chlorination of **1a** under radical conditions involved nonbridged radical intermediates as indicated by the loss in stereochemistry of the 1,2 products (entry 5). Another characteristic of radical chlorination of dienes is an increase in the amount of 1,4-addition[8] (compare entries 1 through 4 with 5). Trichloramine, NCl_3, is known to react with dienes by a radical mechanism,[9] and results obtained with it and **1a** are similar to those obtained with chlorine under radical conditions[10] (compare entries 5 and 6).

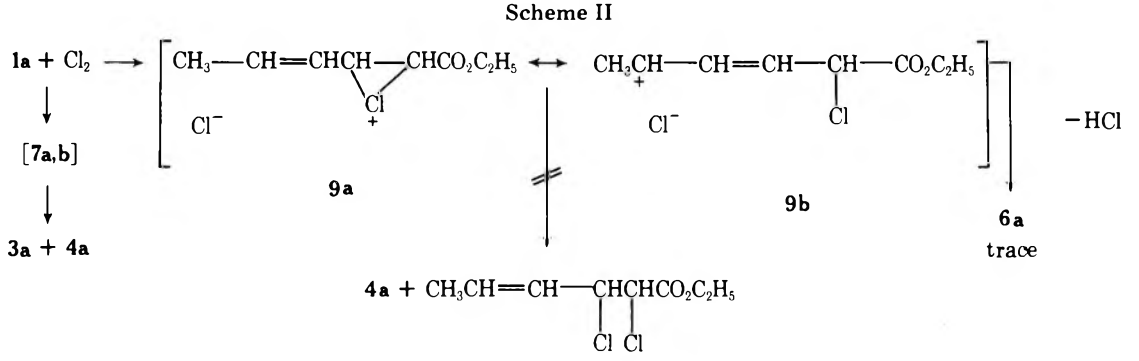
We were surprised to observe that bromine added to **1a** by a molecule-induced radical reaction as suggested by the loss of stereochemistry in **3b** (entries 8, 9, and 10). This is the first report of bromination of an olefinic system by a molecule-induced homolysis in a very dilute solution.[5a,11] Stereospecificity of the 1,2-dibromide increased significantly when luti-

Table I. Comparisons of the Chlorination and Bromination of Ethyl Sorbate and *trans,trans*-2,4-Hexadiene

Entry	Solvent	Diene[a]	Reaction conditions[b]	Halogenating reagent	Products, %[c] 1,2-[d]	1,4-[d]	5	6	Yields, %[c]	1,2-Addition, % anti[e]
1	CCl_4	**1a**	Dark	Cl_2	72	22	4	2	64	100
2	CCl_4	**1a**	Dark, O_2	Cl_2	77	19	3	1	50	100
3	CH_2Cl_2	**1a**	Dark	Cl_2	45	35	12	8	47	100
4	CH_2Cl_2	**1a**	Dark, O_2	Cl_2	45	35	12	8	49	100
5		**1a**[f]	$h\nu$	Cl_2 (g)	30	48	12	10	*g*	75
6	CH_2Cl_2	**1a**[h]	$h\nu$	NCl_3	44	45	9	2	42	53
7		**1a**[i]	$h\nu$	Br_2	91	5	4	0	85	70
8	CCl_4	**1a**	Dark	Br_2	91	7	2	0	85	70
9	CCl_4	**1a**	Dark, O_2	Br_2	89	4	7	0	76	75
10	CH_2Cl_2	**1a**	Dark	Br_2	83	14	3	0	72	70
11	CCl_4	**1a**	Inhibitor[j]	Br_2	*j*	*j*	*j*	*j*	*j*	90
12	CH_2Cl_2	**1a**	Dark	Lu·Br_2	82	4	14	0	78	90
13	CCl_4	**1b**[k]	Dark	Br_2	29	71			90	79
14	CH_2Cl_2	**1b**[k]	Dark	Br_2	27	73			90	85
15	CH_2Cl_2	**1b**[l]	Dark	Py·Br_2	95	5			72	99
16	CCl_4	**1b**[m]	Dark, O_2	Cl_2	35	65			71	63
17	CH_2Cl_2	**1b**[m]	Dark, O_2	Cl_2	48	52			71	56

[a] The diene was 0.02 mol fraction with respect to solvent. [b] The UV light was from a 275-W sunlamp. [c] Determined by VPC. [d] The 1,2- and 1,4-addition products of **1a** refer to addition across the γ,δ and α,δ carbons, respectively. [e] The percent erythro/threo for **1a** was determined by NMR analysis on the methyl and vinyl protons. [f] Chlorine gas was bubbled into neat diene. [g] The amount of chlorine gas bubbled into neat diene was not measured. [h] The diene was 0.1 mol fraction with respect to solvent. [i] Neat bromine was added to neat diene. [j] The inhibitor, 2,6-di-*tert*-butyl-4-methylphenol, has the same VPC retention time as **4b**, and it obscures **3b**, so that quantitative data could not be obtained. [k] Data from ref 4a. [l] Unpublished results. [m] Data from ref 4b.

Scheme II



dine dibromide (entry 12) was used as the brominating reagent.[12] Also the radical reaction can be decreased by using an inhibitor (2,6-di-*tert*-butyl-4-methylphenol) as indicated by an increase in the stereospecificity of **3b** (entry 11).[13] Apparently the ionic bromination of ethyl sorbate occurs so slowly that the radical process predominates unless an efficient inhibitor is used.

We were unable to isolate 1,4-dibromide **4b**, but its presence was confirmed by the same procedure that was used to establish the structure of the 1,4-dichloride (**4a**): When a mixture of **3b** and **4b** was treated with triethylamine the bromodiene (**6b**) was obtained in good yield. The 1,2-dibromide **3b** was stable under these reaction conditions.

Experimental Section

General. All of the reagents and solvents were obtained commercially except trichloramine, which was prepared as described in "Organic Syntheses." [14] Ethyl sorbate was distilled prior to use. IR and NMR were obtained on a Beckman IR-10 spectrophotometer and a Varian T-60 or EM-360-A, respectively. Vapor phase chromatographic analyses were done with a Hewlett Packard 5706A flame ionization chromatograph, and an F&M 700 chromatograph. The following columns (SS) were used: Column A, 6 ft × ⅛ in. of 2.5% SE-30 on 80/100 Chromosorb W; Column B, 10 ft × ¼ in. 2.5% SE-30 on 60/80 Chromosorb W; Column C, same as B, but 6 ft.

Halogenation Procedure. Chlorinations were done in the dark at 0 °C. The ethyl sorbate concentrations were 0.02 mol fraction with respect to the solvent. Chlorine was added as a 1.0 M solution in carbon tetrachloride. The amount of chlorine added was 20–25% of the amount of ethyl sorbate. Sunlamps (225 W) were used to generate the ultraviolet light. When oxygen was used as an inhibitor, it was bubbled into the reaction solution for ca. 3 min before the addition of the halogen, and continued during the reaction until the color of the halogen disappeared. Bromination of ethyl sorbate was carried out as above except that neat bromine was weighed into ca. 2–3 mL of carbon tetrachloride. The yields and product ratios were obtained by VPC analysis on corrected peak areas. Response factors were obtained by analysis of known mixtures prepared from pure products and the following internal standard: *p*-dibromobenzene for chlorinations, and 1,4-dichloro-2-nitrobenzene for brominations.

Reaction of Chlorine with 1a. Ionic Conditions. To 700 mg (5.0 mmol) of ethyl sorbate in 23.8 mL of carbon tetrachloride was added dropwise 1.0 mL of a 1.0 M chlorine solution in carbon tetrachloride. The reaction mixture was stirred for ca. 90 min. Analysis by VPC of this mixture on column A at 70 °C gave products **5a, 6a, 4a,** and **3a** with the retention times of 9, 10, 14, and 18 min, respectively. Products **3a** and **4a** were isolated by preparative VPC on column B, and the following spectral properties were recorded. **3a:** IR (CCl_4) 2980 (C–H), 1725 (C=O), 1660 (C=C),[15] 1450, 1365, and 1310 (C–H), 1260, and 1165 (C–O), 965 (C=CH), and 850 cm^{-1}; NMR (CCl_4) δ 1.30 (t, J = 6.8 Hz, 3 H), 1.66 (d, J = 6.2 Hz, 3 H), 4.16 (q, J = 6.8 Hz, 2 H), 4.0–4.6 (m, 2 H), 5.92 (dd, J = 15.2 and 0.8 Hz, 1 H), 6.8 (dd, J = 15.2 and 7.2 Hz, 1 H). **4a:** IR (CCl_4) 2990 (C–H), 1750 (C=O), 1445, 1365, and 1310 (C–H), 1260 and 1160 (C–O), 1020, 960, (C=CH), and 860 cm^{-1}; NMR (CCl_4) δ 1.31 (t, J = 6.8 Hz, 3 H), 1.60 (d, J = 6.5 Hz, 3 H), 4.16 (q, J = 6.8 Hz, 2 H), 4.0–4.8 (m, 2 H), 5.86 (m, 2 H). Compounds **5a** and **6a** had the same VPC retention time and spectra of those products obtained from the dehydrochlorination below.

Radical Conditions. Chlorine gas was bubbled into neat ethyl sorbate illuminated by UV light. Analysis by VPC on column B at 70 °C gave **3a, 4a, 5a,** and **6a** in a ratio of 1.2:1:3:4.8, respectively. Product **4a** was treated with triethylamine in pentane as described below, which gave **6a.** This mixture was distilled to obtain **3a** [bp 95–100 °C (0.02 mm)]. Analysis by NMR (vinyl hydrogens at δ −6.8 and the methyl at δ −1.66) showed the erythro/threo mixture to be 75:25, respectively. An NMR of this mixture gave the following spectra for *threo*-**3a:** NMR (CCl_4) δ 1.30 (t, J = 6.8 Hz, 3 H), 1.60 (d, J = 6.2 Hz, 3 H), 4.16 (q, J = 6.8 Hz, 2 H), 4.0–4.6 (m, 2 H), 5.97 (dd, J = 15.2 and 0.8 Hz, 1 H), 6.87 (dd, J = 15.2 and 7.2 Hz, 1 H).

Reaction of Trichloroamine with 1a. To 0.83 g (5.93 mmol) of ethyl sorbate in 4.54 g of methylene chloride (0.10 mol fraction) was added 1 mL of NCl_3 in methylene chloride (0.79 M), Analysis by VPC on column B revealed that products **3a, 4a, 5a,** and **6a** were formed in 42% yield with a product ratio of 44:45:9:2, respectively. Product **4a** was dehydrochlorinated with triethylamine as described below. Distillation gave **3a,** which upon analysis by NMR showed the erythro/threo ratio to be 53:47, respectively.

Dehydrochlorination of 4a. To 3.40 g (0.0161 mol) of a 40:60 mixture of **3a** and **4a** and 200 mg of *p*-dibromobenzene (internal standard) in 200 mL of pentane was added 1.63 g (0.0161 mol) of triethylamine. A white precipitate formed and analysis of the solution by VPC showed that **4a** had reacted to form **6a** in 80% yield. Analysis of the reaction mixture by VPC after 1 h at 25 °C demonstrated that **3a** was stable to triethylamine under these conditions. The reaction mixture was poured into 100 mL of water, and the organic layer was washed with two 50-mL portions of 1 N HCl, 50 mL of saturated $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was removed, and **6a** was isolated by preparative VPC on column B at 70 °C. The following spectral data were obtained for **6a:** IR (CCl_4) 3010 and 2850 (C–H), 1725 and 1715 (C=O), 1640 and 1600 (C=CC=C), 1445 and 1360 (C–H), 1260 (C–O), 1230, 1160, 1085, 1035, 970 (C=CH), and 850 cm^{-1}; NMR (CCl_4) δ 1.30 (t, J = 6.8 Hz, 3 H), 1.93 (d, J = 5.6 Hz, 3 H), 4.21 (q, J = 6.8 Hz, 2 H), 5.9–6.6 (m, 2 H), 7.27 (d, J = 9.2 Hz, 1 H).

Dehydrochlorination of 3a. To 1.5 g (0.022 mol) of sodium ethoxide in 10 mL of anhydrous ethanol at 20 °C was slowly added 1.00 g (4.74 mmol) of **3a.** The reaction mixture was stirred for ca. 3 min and worked up as described for the dehydrochlorination of **4a** above. Distillation gave 0.55 g (66%) of **5a** [bp 70–71 °C (0.12 mm)] with the following spectral properties: IR (CCl_4) 3010 and 2980 (C–H), 1720 (C=O), 1635 and 1595 (C=CC=C), 1445 and 1360 (C–H), 1300, 1255 (C–O), 1155, 1080, 1040, 955 (C=CH), and 855 cm^{-1}; NMR (CCl_4) δ 1.29 (t, J = 6 8 Hz, 3 H), 1.94 (d, J = 6.5 Hz, 3 H), 4.17 (q, J = 6.8 Hz, 2 H), 6.13 (dd, J = 14.2 and 0.8 Hz, 1 H), 6.23 (dq, J = 0.8 and 6.5 Hz, 1 H),[16] 7.27 (d, J = 14.2 Hz, 1 H).

Reaction of Bromine with 1a. To 2.11 g (15.1 mmol) of ethyl sorbate and 190 mg of internal standard in 113 g of carbon tetrachloride was added 2.0 mL (3.08 mmol) of a bromine–carbon tetrachloride (247 mg/mL) solution. The reaction was stirred at 0 °C for 60 min. Analysis by VPC revealed **3b, 4b,** and **5b** to be formed in a ratio of 91:7:2, respectively (86% yield), with retention times of 16, 12, and 9 min, respectively. Product **3b** was obtained by preparative VPC on column C at 90 °C as a 70:30 erythro/threo mixture indicated by NMR spectra on vinyl and methyl hydrogens listed below. The following data were recorded: IR (CCl_4) 2970 (C–H), 1720 (C=O), 1650 (C=C),[15] 1440, 1360, and 1310 (C–H), 1250 (C–O), 1200, 1155, 1040, 975 (C=CH), and 860 cm^{-1}; NMR (CCl_4) erythro δ 1.30 (t, J = 6.8 Hz, 3 H), 1.87 (d, J = 6.2 Hz, 3 H), 4.20 (q, J = 6.8 Hz, 2 H), 4.2–5.0 (m, 2 H), 5.98 (d, J = 14.4 Hz, 1 H), 6.93 (dd, J = 14.4 and 0.8 Hz, 1 H); threo δ 1.30 (t, J = 6.8 Hz, 3 H), 1.80 (d, J = 6.2 Hz, 3 H), 4.20 (q, J = 6.8 Hz, 2 H), 4.2–5.0 (m, 2 H), 6.06 (dd, J = 14.4 and 0.8 Hz, 1 H), 7.00 (dd, J = 14.4 and 8.4 Hz, 1 H). All attempts to isolate **4b** failed, but its structure was deduced from dehydrobrominating **4b** with triethylamine to **6b** as described above for the dehydrochlorination of **4a.** The bromodiene (**6b**) was isolated by preparative VPC on column C at 95 °C and gave the following spectral properties: IR (CCl_4) 3030 and 2980 (C–H), 1730 (C=O), 1630 and 1580 (C=CC=C), 1450 and 1366 (C–H), 1250 (C–O), 1139, 1095, 1044, 998, 972 (C=CH), 923, and 825 cm^{-1}; NMR (CCl_4) δ 1.33 (t, J = 6.8 Hz, 3 H), 1.92 (d, J = 5.2 Hz, 3 H), 4.22 (q, J = 6.8 Hz, 2 H), 6.0–6.6 (m, 2 H), 7.57 (d, J = 9.2 Hz, 1 H).

Dehydrobromination of 3b. The reaction was accomplished with 0.53 g (7.3 mmol) of sodium ethoxide and 1.8 g (6.0 mmol) of **3b** in 10 mL of anhydrous ethanol as described above for the dehydrochlorination of **3a.** After the mixture was worked up as described for **3a,** distillation gave 1.0 g (77%) of **5b** [bp 60–65 °C (0.40 mm)] with the following spectral properties: IR (CCl_4) 3030 and 2990 (C–H), 1720 (C=O), 1630 and 1600 (C=CC=C), 1450 and 1365 (C–H), 1300, 1260 (C–O), 1177, 1045, 963 (C=CH), and 869 cm^{-1}; NMR (CCl_4) δ 1.30 (t, J = 6.8 Hz, 3 H), 1.99 (d, J = 7.2 Hz, 3 H), 4.21 (q, J = 6.8 Hz, 2 H), 6.22 (dd, J = 14.6 and 0.8 Hz, 1 H),[16] 6.44 (dq, J = 0.8 and 7.2 Hz, 1 H), 7.52 (d, J = 14.6 Hz, 1 H).

Bromination of 1a in the Presence of an Inhibitor. When **1a** was treated with bromine as described above, but O_2 was bubbled through the reaction mixture a product ratio of 89:4:7 was recorded by VPC analysis for **3b, 4b,** and **5b,** respectively. Distillation [bp 95–105 °C (0.05 mm)] gave **3b,** which was a 75:25 erythro/threo mixture as determined by NMR.[13] The reaction was carried out with 2.8 g (0.020 mol) of **1a** in carbon tetrachloride (0.02 mol fraction diene) and 2.2 g (0.010 mol) of 2,6-di-*tert*-butyl-4-methylphenol was added to the mixture. The product ratios and yields could not be determined, since the inhibitor interfered with the VPC analysis. Distillation gave **3b** and inhibitor. Analysis by NMR as described above showed an erythro/threo ratio for **3b** to be 90:10, respectively. Product **4b** does not survive the distillation.

Radical Reaction of Bromine with 1a. To 5.0 g (35.7 mmol) of neat **1a** with stirring at 0 °C and illumination was added dropwise 1.14 g (1.74 mmol) of neat bromine. Analysis by VPC showed **3b, 4b,** and **5b** to be obtained (85% yield) in a ratio of 91:5:4, respectively. Distillation [bp 95–105 °C (0.05 mm)] gave **3b,** which was a 70:30 erythro/threo mixture by NMR analysis.

Reaction of Lutidine Dibromide with 1a. To 4.42 g (0.0316 mol) of ethyl sorbate in 24.2 g of methylene chloride with stirring at 0 °C was added 4.0 g (0.0158 mol) of lutidine dibromide. The reaction mixture was stirred for 3 h. Analysis by VPC showed **3b, 4b,** and **5b** in a ratio 82:4:14, respectively, formed in 78% yield. Distillation [bp 95–110 °C (0.05 mm)] followed by NMR analysis of the distillate displayed an erythro/threo product ratio of 90:10, respectively.

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Registry No.—**1a,** 5941-48-0; **1b,** 5194-51-4; *erythro*-**3a,** 62006-40-0; *threo*-**3a,** 62006-41-1; *erythro*-**3b,** 62006-42-2; *threo*-**3b,** 62006-43-3; **4a,** 62006-44-4; **4b,** 62006-45-5; **5a,** 62006-46-6; **5b,** 62006-47-7; **6a,** 62006-48-8; **6b,** 62006-49-9.

References and Notes

(1) (a) Point Loma College; (b) Bethany Nazarene College.
(2) Ionic conditions are defined as: low mole fraction olefin, absence of light, and presence of an inhibitor. Radical reactions are favored by neat olefin (molecule-induced homolysis), a nitrogen atmosphere, and ultraviolet illumination. See ref 5.
(3) R. C. Fahey and H. J. Schneider, *J. Am. Chem. Soc.*, **90,** 4429 (1968).
(4) (a) G. E. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, D. A. Redfield, T. L. Rold, and D. E. Williamson, *J. Org. Chem.*, **38,** 4109 (1973); (b) G. E. Heasley, D. C. Hayse, G. R. McClung, D. K. Strickland, V. L. Heasley, P. D. Davis, D. M. Ingle, K. D. Rold, and T. S. Ungermann, *ibid.*, **41,** 334 (1976).
(5) (a) V. L. Heasley, G. E. Heasley, and S. K. Taylor, *J. Org. Chem.*, **35,** 2967 (1970); V. L. Heasley and S. K. Taylor, *ibid.*, **34,** 2779 (1969); (b) M. L. Poutsma, *ibid.*, **31,** 4167 (1966); M. L. Poutsma and J. L. Kartch, *Tetrahedron*, **22,** 2167 (1966); M. L. Poutsma, *J. Am. Chem. Soc.*, **87,** 4293 (1965).
(6) (a) K. V. Auwers and J. Heyna, *Justus Lubigs Ann. Chem.*, **434,** 140 (1923); (b) K. V. Auwers and W. Muller, *ibid.*, **434,** 165 (1923).
(7) The stereochemistry of **4a** could not be determined by spectral methods.
(8) 1,4-Products are also favored when butadiene is treated with chlorine and bromine under radical conditions. See for chlorinations M. L. Poutsma, *J. Org. Chem.*, **31,** 4167 (1966); and for brominations V. L. Heasley and S. K. Taylor, *ibid.*, **34,** 2779 (1969).
(9) V. L. Heasley, G. E. Heasley, and B. T. Gipe, *J. Org. Chem.*, submitted for publication.
(10) The difference in product ratios for the addition of chlorine and trichloramine to **1a** indicates that these radical chlorinating reagents have different steric and/or electronic requirements in the chain-transfer step (compare entries 5 and 6).
(11) This suggests that the addition of bromine to other carbonyl conjugated olefins may also react by a radical process. Bromination of diethyl malonate and diethyl fumarate were reported to react by an ionic mechanism. See R. P. Bell and M. Pring, *J. Chem. Soc. B,* 119 (1966).
(12) The stereospecificity increases significantly when other dienes are treated with amine–halogen complexes and probably represents an ionic process for these reactions: V. L. Heasley, C. N. Griffith, and G. E. Heasley, *J. Org. Chem.*, **40,** 1358 (1975), and unpublished work.
(13) Although oxygen is an effective scavanger for chlorine radicals, it is not effective with bromine radicals (compare entries 8, 10, and 11 with 9). We observed that oxygen did not inhibit radical bromination of butadiene in a previous study.

(14) P. Kovacic and S. S. Chudhary, "Organic Syntheses", Collect. Vol. 5, Wiley, New York, N.Y., 1973, p 35.
(15) The IR stretching frequency of a double bond in conjugation with a carbonyl is very strong. See R. T. Conley, "Infrared Spectroscopy", Allyn and Bacon, Boston, Mass., 1966, p 99. The double bond stretching frequency was too weak to be observed at normal concentration in the 1,4-products where the carbonyl is not in conjugation.
(16) Bothner-By has investigated long-range coupling in a large number of butadienes and found that 1,4-vinyl protons in the trans,trans configuration show coupling constants ranging between 1.3 and 1.9 Hz, while cis,trans and cis,cis 1,4-vinyl protons show coupling between 0.5 and 0.9 Hz. Since the protons on the α,β carbons of **5** show a trans coupling (J = 14.2 Hz), the long range coupling of 0.6 Hz on the vinyl proton at δ 6.23 indicates a 1,4-cis,trans coupling in the trans,trans diene (**5**). See A. A. Bothner-By and R. K. Harris, *J. Am. Chem. Soc.*, **87**, 3445, 3451 (1965); A. A. Bothner-By and D. Jung, *Ibid.*, **90**, 2342 (1968); A. A. Bothner-By and E. Moser, *Ibid.*, **90**, 2347 (1968); A. A. Bothner-By and D. F. Koster, *Ibid.*, **90**, 2351 (1968).

Liquid-Phase Photolysis of Dioxane

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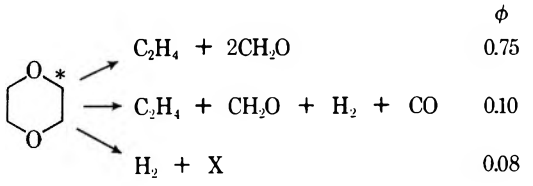
The photolysis of neat liquid-phase dioxane with a medium-pressure mercury lamp has been shown to give, in addition to gaseous products, a complicated mixture of liquid and solid products. The liquid product mixture has been partially separated, and evidence for the structures of nine previously unreported hydroxy ether and carbonyl containing components is presented. The products are postulated to result from initial CO bond scission followed by subsequent reactions of the radicals produced and from secondary photolyses. The photoproducts are not formed in any significant amount when either dioxane or dioxyldioxane is irradiated in ethanolic solution.

The photochemistry of simple aliphatic ethers in the gas phase has been studied by numerous workers, and a combination of radical and molecular processes reported.[1] In particular, the gas-phase photolysis of dioxane has been studied by Parrish and co-workers, both at 1470 Å[2] and with a megawatt ruby laser.[3] At 1470 Å, three processes were observed, and are given with their quantum yields in Scheme I. The laser-

Scheme I

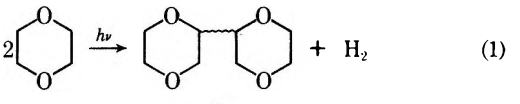


promoted decomposition yielded ethylene, CO, and H_2 in the ratio 1:2:2. It was postulated that these products were formed from a vibrationally excited ground state of dioxane, and that the hydrogen resulted from a molecular elimination, rather than via radical abstraction.

Considerably less attention has been given to the solution or neat liquid-phase photolysis of ethers, probably owing to the greater experimental difficulty of irradiating in the 200-nm region or below, where alcohols and ethers have their principal absorption band ($n \rightarrow \sigma^*$). This is unfortunate because these compounds have often been used as solvents for photochemical reactions using low- and medium-pressure mercury lamps capable of emitting small to moderate amounts of radiation in this region.

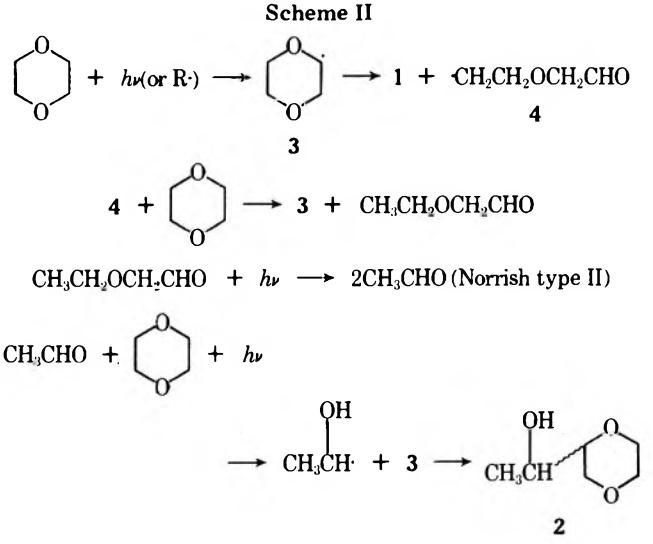
Pfordte studied the neat liquid-phase photolysis of several aliphatic ethers,[4] and reported that dioxane, after irradiation for 24 h with a medium-pressure mercury lamp, yields gaseous, liquid, and solid products. The major gaseous products were identified as H_2, CO, CH_4, C_2H_4, and C_2H_6. Minor amounts of other saturated and unsaturated hydrocarbon gases were also detected. The liquid product was not analyzed, but the solids were shown to be the racemic and meso forms of dioxyldioxane (**1**), for which the following mechanism of formation was advanced (eq 1).

Mazzocchi and Bowen have recently reported[5] two additional products from the 200-h photolysis of neat dioxane, the meso and racemic forms of 1-hydroxyethyldioxane (**2**), which they rationalize as forming via Scheme II. There is precedent



1

Scheme II



2

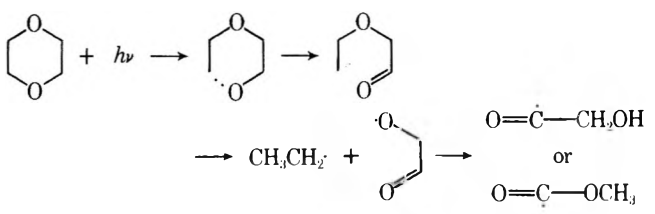
for the third step in Srinivasan's photolysis of methoxyacetone[6] which efficiently yields formaldehyde and acetone. The photoreduction of acetaldehyde in dioxane was demonstrated by Mazzocchi and Bowen to occur readily.

Both Pfordte and these later workers used medium-pressure mercury lamps which have an approximate lower wavelength limit of 190 nm. It seemed to us unlikely that a CH bond, which normally does not absorb above 150 nm (considering the absorption spectra of simple alkanes), could be broken in the primary step of this photolysis, as claimed, particularly since rupture of a CO bond in an $n \rightarrow \sigma^*$ process, occurring at slightly below 200 nm, is well documented.[7] Direct photochemical CH bond scission, in contrast to H *abstraction*,

as occurs in the Norrish type II process or in Hg-sensitized decompositions, is usually limited to gas-phase or low-temperature matrix photoreactions where collisional deactivation of vibrationally excited species is less efficient.[8] Yang[9] has reported the cleavage of the α-CH bond in simple alcohols on photolysis at 185 nm with a low-pressure mercury lamp, through high-purity fused silica. We will discuss this report in more detail presently.

In an experiment very relevant to our work, McIntosh and Wan[10] conducted ESR studies on UV-irradiated dioxane and THF at 77 K. The resulting spectra showed none of the prominent triplet patterns which would have been attributable to splitting by the protons of the methylene group in a diradical derived from ring opening at the carbon–oxygen bond, but rather they suggest that both THF and dioxane produce ethyl radicals during photolysis. The sequence shown in Scheme III was proposed to account for the formation of

Scheme III



ethyl radicals from dioxane. Subsequent abstraction of H· from dioxane by the ethyl radical could account for the ethane observed by Pfordte among the gaseous photoproducts. This scheme also provides an alternative, and, we think, preferable,[11] pathway for the formation of Mazzocchi and Bowen's ethoxyacetaldehyde.

The previous work, then, on the dioxane photolysis strongly suggested that low steady-state concentrations of carbonyl compounds and various radicals could be present when dioxane is used as a solvent in a photochemical reaction. In view of the well-known tendency of carbonyl compounds to act as triplet transfer agents, we decided to undertake a reexamination of the neat dioxane photolysis with particular emphasis on the liquid photoproduct. We found this product to be an exceedingly complex mixture, but high-resolution mass spectroscopy and GC/MS allowed us to deduce the structures, with varying degrees of certitude, of nine hitherto unreported products. Authentic samples of four of these, ethylene glycol, glycolaldehyde, dioxanone, and hydroxymethyldioxane, were obtained, and their spectral properties were completely consistent with those of the corresponding photoproducts. Attempts to synthesize the remaining five compounds were unsuccessful. We suggest that the photoproducts arise from a combination of radical and/or molecular fragmentations and secondary photolyses. Interestingly, when dioxane was irradiated in ethanol, only insignificant amounts of photoproducts were formed.

Results

Neat dioxane was irradiated through quartz with a 450-W medium-pressure mercury lamp. The complexity of the product mixture was found to be greatly dependent on the duration of the photolysis. Thirty minutes appeared to be the minimum irradiation time that would allow us to recover, by preparative gas chromatography, enough material for mass spectroscopic analysis, and all of the products reported herein were obtained from 30-min photolysates. The yield of dioxyldioxane (henceforth called dimer) increased steadily with irradiation time, and after 24 h, the dimer was the major nongaseous product.

Fifteen hundred milliliters of purified and degassed dioxane was divided into 30-mL portions placed in quartz tubes under nitrogen. The filled tubes, which because of the formation of gaseous products could not be sealed, were then irradiated under nitrogen, five or six at a time. The combined photolysate was distilled at atmospheric pressure, under nitrogen, to remove unchanged dioxane and gaseous photoproducts. A gas chromatogram of the remaining liquid (1.74 g) showed six or seven major, and approximately 50 minor, components. This mixture was separated by preparative gas chromatography into six fractions, numbered 1 through 6 in order of their increasing retention time. Fractions 2, 4, 5, and 6 were of sufficient volume to be analyzed spectroscopically as follows.

Table I. Mass Spectrum of Fraction 2 at Two Ionizing Voltages

70 eV		10 eV	
m/e	Rel intensity	*m/e*	Rel intensity
62	3	62	46
61	11	61	10
60	8	60	61
45	100	45	27
43	50	44	25
31	44	43	38
30	8	33	74
29	36	32	29
28	25	31	100

Fraction 2. The infrared spectrum of fraction 2 exhibited a strong absorption at 3330 cm^{-1}, suggesting multiple OH groups, a weak band at 2940 cm^{-1}, a broad band (ca. 22 cm^{-1} wide at its minimum) of only moderate intensity centered at about 1705 cm^{-1}, and other weak bands at 1200, 1090, 1050, and 890 cm^{-1}. The 1125-cm^{-1} band normally associated with the dioxane ring was missing. The NMR spectrum ($CDCl_3$) showed strong singlets at δ 2.75 and 3.75 (area ratio ca. 1:1.4), a pair of multiplets centered at δ 3.9 and 4.3 (each about equal in area to the δ 3.75 peak), and a singlet at δ 8.14 having an area about one-quarter of that of the δ 3.75 peak. When the probe temperature was raised to 75 °C, the δ 2.75 peak moved upfield to δ 2.15, suggesting an OH resonance, while the other peaks remained in their original positions. The mass spectrum of fraction 2 was recorded at ionizing voltages of 70 and 10 eV (Table I). The low voltage scan suggests that at least two components having nominal molecular weights of 62 and 60 are present in fraction 2. Mass measurements on these two peaks gave 62.0397 and 60.0217. The theoretical values for $C_2H_6O_2$ and $C_2H_4O_2$ are 62.0368 and 60.0211, respectively, and these compounds are postulated to be ethylene glycol and glycolaldehyde (**5**), $HOCH_2CHO$. The intense peaks at *m/e* 45 and 43, then, result from the loss of OH from the parent ions,[12] and the largest peak, at *m/e* 31, is due to CH_2OH^+. The presence of ethylene glycol was confirmed by comparison of the IR and NMR spectra and GC retention time with those of an authentic sample. The structure assignment of compound **5** is based partly on negative evidence and chemical intuition and partly on the NMR and mass spectra of an authentic sample. The only other plausible structures for $C_2H_4O_2$ are methyl formate and acetic acid. The former might have been considered to arise via H abstraction by the $O{=}\dot{C}CH_3$ radical postulated in Scheme III. The NMR spectrum of methyl formate exhibits an aldehyde resonance at δ 8.08 and a methyl resonance at δ 3.77, very near the methylene resonance of ethylene glycol (ca. δ 3.7). The infrared spectrum[13] of methyl formate shows C=O absorption at 1727 cm^{-1} which should have been distinguishable from the 1705-cm^{-1} peak observed in the spectrum of fraction 2. Finally, a large doublet at 1212, 1163 cm^{-1} in the spectrum of methyl formate is missing from the spectrum of fraction 2.

Table II. Mass Spectrum of Fraction 4 at Two Ionizing Voltages

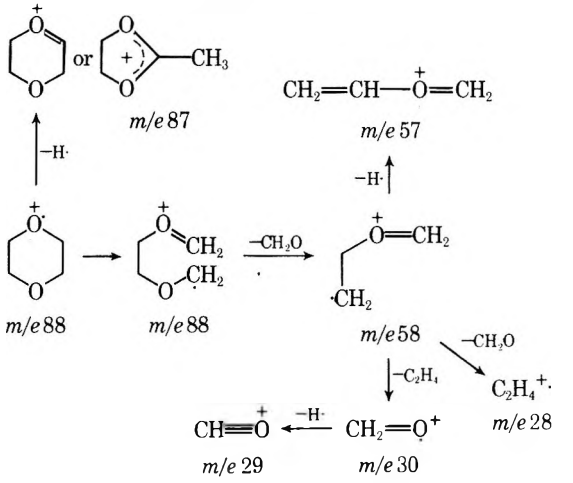
70 eV		8 eV	
m/e	Rel intensity	*m/e*	Rel intensity
130	4	172	5
118	11	148	5
104	37	130	14
102	17	118	31
87	86	104	43
86	17	102	33
74	41	87	69
73	92	86	18
60	17	74	45
59	47	73	29
58	100	58	100
45	72	45	18
44	50	30	6
43	85	28	20
31	85		
30	47		
29	59		
28	100		

Acetic acid is excluded as a major component on the basis of its NMR and IR spectra.

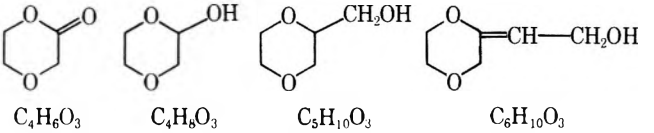
Collins and George[14] studied the NMR spectrum of glycolaldehyde and reviewed the previously reported behavior of this compound. The monomeric aldehyde exists only in the gas phase. The solid compound exhibits no carbonyl absorption[13] and is most likely the symmetrical dimer, 2,5-dihydroxydioxane. In solution, glycolaldehyde exists as a highly solvent- and temperature-dependent mixture of the monomer, the symmetrical dimer, and an unsymmetrical dimer, 2-hydroxymethyl-4-hydroxy-1,3-dioxolane. The NMR spectra[14] of glycolaldehyde in Me_2SO-d_6 and in D_2O show multiplets in the region δ 3–5.2, but the spectra are different from each other and from the spectrum of fraction 2. An authentic sample of solid "glycolaldehyde" (Aldrich), dissolved in ethylene glycol, was shaken with $CDCl_3$ and the NMR spectrum of the $CDCl_3$ layer taken repeatedly over a period of several days. When the sample had come to equilibrium, the spectrum resembled much more closely that of fraction 2. The mass spectrum of solid "glycolaldehyde" (ionizing voltage 45 eV) showed major peaks (with the indicated relative intensities) at *m/e* 61 (21), 44 (99), 43 (41), 32 (100), and 31 (62). The P + 1 peak (*m/e* 61) was about four times as intense as the parent peak. It is presumed that this is due to hydrogen abstraction from a neutral molecule by the parent radical ion, $P^{+}\cdot$, to give PH^{+}, a process with ample precedent in the literature.[15]

Fraction 4. The major features of the infrared spectrum of fraction 4 were a strong OH stretching band at 3380 cm^{-1}, CH stretching absorption at 2900 cm^{-1}, a large C=O stretching band centered at 1740 cm^{-1}, and several peaks in the region 1250–1050 cm^{-1}, assumed to be CO stretching bands. The NMR spectrum lacked detail, but showed two broad regions of absorption at δ 3.5–4.0 and 4.0–4.7. The mass spectral data for this fraction appear in Table II. From the appearance of the spectra, we deduced that there were at least four major components, the parent ions of which had *m/e* values of 102.0303, 104.0456, 118.0610, and 130.0608, corresponding to the molecular formulas $C_4H_6O_3$ (102.0317), $C_4H_8O_3$ (104.0473), $C_5H_{10}O_3$ (118.0630), and $C_6H_{10}O_3$ (130.0630). The ions with nominal *m/e* values of 172 and 148 were considered to be contaminants from fraction 6. Because the molecular formulas of the major components suggest that the dioxane ring might be intact in each of them, it is of some interest to consider the fragmentation pattern for dioxane itself (Scheme IV). With the exception of *m/e* 57, peaks with all of the above *m/e* values appear in the spectrum of fraction

Scheme IV



4. On the basis of the spectral data, then, the four major components of fraction 4 are presumed to be dioxanone (**6**), dioxanol (**7**), hydroxymethyldioxane (**8**), and hydroxyethylidenedioxane (**9**). The position of the double bond in **9** is not

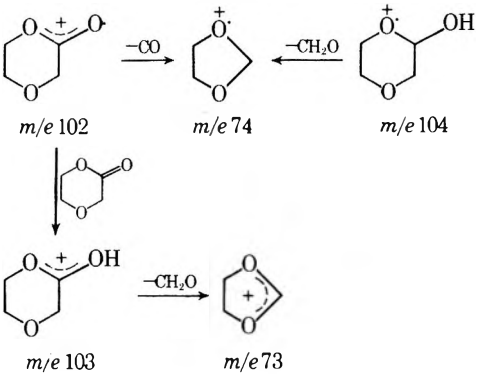


$C_4H_6O_3$ **6** $C_4H_8O_3$ **7** $C_5H_{10}O_3$ **8** $C_6H_{10}O_3$ **9**

certain, though the mass spectrum of the trifluoroacetic anhydride derivatized product, to be described shortly, strongly suggests that **9** is an alcohol, rather than an aldehyde or a ketone.

Authentic samples of **6** and **8** were prepared. The NMR spectrum of dioxanone exhibits a sharp singlet at δ 4.40 and two multiplets of equal intensity centered at δ 3.9 and 4.5. The infrared spectrum, taken neat, as was that of fraction 4, showed the following absorptions: CH stretching at 2900 cm^{-1}, C=O stretching at 1740 cm^{-1}, CH_2 bending at 1455 and 1432 cm^{-1}, CO stretching at 1200, 1130, and 1053 cm^{-1}, and other weaker bands at 876, 853, and 726 cm^{-1}. The mass spectrum of dioxanone, including parent, P + 1, and major peaks only, appears in Table III. The relatively large P + 1 peak is again attributed to hydrogen abstraction by the parent radical ion. The peaks at *m/e* 74 and 73 in the spectrum of fraction 4 can then be rationalized as shown in Scheme V.

Scheme V



The NMR spectrum of hydroxymethyldioxane shows only one very complex multiplet extending from δ 3.3 to 4.3. The major features of the infrared spectrum (neat) were absorptions attributable to OH stretching at 3378 cm^{-1}, CH

Table III. Mass Spectrum of Dioxanone at Two Ionizing Voltages

20 eV		45 eV	
m/e	Rel intensity	m/e	Rel intensity
103	18	103	6.6
102	18	102	9
101	12	101	10
87	22	87	18
86	12	75	12
75	12	73	34
73	31	61	11
58	10	60	11
57	16	59	10
45	44	58	10
44	16	57	30
43	29	55	11
42	10	45	75
32	100	44	21
		43	70
		42	21
		41	10
		40	11
		32	100
		31	33
		29	40

Table IV. Mass Spectrum of Hydroxymethyldioxane at 45 eV

m/e	Rel intensity	m/e	Rel intensity
118	8	57	27
87	100	45	27
86	12	44	15
75	15	43	47
74	12	41	12
73	11		
59	12		

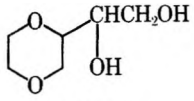
Table V. Mass Spectrum of Fraction 5 at Two Ionizing Voltages

70 eV		10 eV	
m/e	Rel intensity	m/e	Rel intensity
174	4	174	22
148	27	148	38
118	25	118	38
103	4	103	67
91	31	90	28
88	8	89	28
87	100	88	17
86	24	87	100
74	13	86	72
73	98	73	89
60	16	60	44
59	13	58	28
58	16	45	44
57	13	28	11
45	93		
44	26		
43	41		
31	48		
30	73		
29	28		
28	76		

stretching at 2875 cm^{-1}, CH_2 bending at 1451 cm^{-1}, and numerous CO stretching peaks from 1302 to 1040 cm^{-1}. Peaks were also present at 980, 962, 944, 896, 864, 814, 625, and 588 cm^{-1}. Finally, the infrared spectrum of a mixture of roughly equal parts of dioxanone and hydroxymethyldioxane, except for some differences in peak intensities, is quite close to that of fraction 4, suggesting that **7** and **9** may be only minor components of this fraction. The mass spectrum of hydroxymethyldioxane is presented in Table IV. The base peak is at *m/e* 87, representing loss of CH_2OH. The other major peaks are *m/e* 57, 45, and 43.

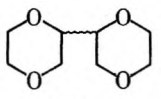
The most abundant ion in the mass spectrum of fraction 4 is that with *m/e* 58. This ion makes only a very minor contribution to the spectra of dioxanone and hydroxymethyldioxane, but a major one to the spectra of dioxane and dioxene. We are unable to explain this anomaly at present.[16]

Fraction 5. The infrared spectrum of fraction 5 shows a strong OH absorption at 3570 cm^{-1}, a weak to moderate C=O absorption at 1730 cm^{-1}, and strong C–O absorption in the 1163–1053-cm^{-1} region. The NMR spectrum shows peaks at δ 2.95 (broad singlet), 3.5–4.2 (broad multiplet), 4.5–4.7 (broad multiplet), and 8.1 (singlet), with the approximate area ratios 15:25:3:1. The mass spectral data (Table V) suggest at least three possible molecular ions at *m/e* 118.0617, 148.0750, and 174.0909, corresponding to $C_5H_{10}O_3$ (118.0630), $C_6H_{12}O_4$ (148.0736), and $C_8H_{14}O_4$ (174.0892). In the absence of evidence to the contrary, we have assumed that the $C_5H_{10}O_3$ component is the same as that found in fraction 4, namely, hydroxymethyldioxane (**8**). Owing to the large number of components in the photolysate, the separation into fractions was somewhat arbitrary, and some overlap of fractions on repeated collections probably was unavoidable. The NMR and IR spectra provide some evidence for the presence of an aldehyde in fraction 5, but as $C_5H_{10}O_3$, $C_6H_{12}O_4$, and $C_8H_{14}O_4$ all possess one degree of unsaturation, if the dioxane ring is intact in all three compounds as suggested by the fragmentation pattern, they must be alcohols or ethers. Thus, the aldehyde is regarded as a minor component, about which there is little structural information. Our postulated structures for the major components of fraction 5 are **10** and **1**. Structure **1**



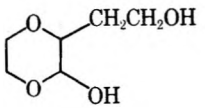
$C_6H_{12}O_4$

10



$C_8H_{14}O_4$

1



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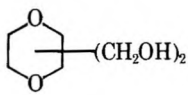


12

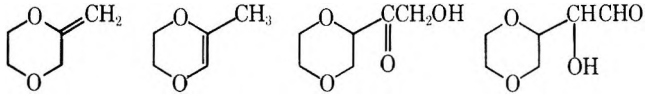
is advanced because it is a known reaction product. Structure **10** is chosen from among its possible isomers, such as **11** and **12**, on the grounds that the introduction of both a hydroxyl and a β- (or α-) hydroxyethyl group or two hydroxymethyl groups on the dioxane ring would involve further radical attacks on species such as **7**, **8**, or **9**. This we consider to be statistically improbable within an irradiation time of only 30 min.

Fraction 6. The infrared spectrum of fraction 6 is of rather low intensity, but shows absorption bands at 3390, 2857, 1724, 1136–1030, and 877–870 cm^{-1}, suggesting, in addition to CH, the presence of OH, C=O, and CO bonds. The NMR spectrum shows only two regions of absorption, a broad singlet at δ 2.8 and a broad multiplet at δ 3.5–4.0, with approximate relative areas of 2.3:1. The mass spectral data for fraction 6 are listed in Table VI. The spectrum at both ionizing voltages was quite weak, and only two peaks could be mass measured

Table VI. Mass Spectrum of Fraction 6 at Two Ionizing Voltages

70 eV		10 eV	
m/e	Rel intensity	*m/e*	Rel intensity
190	<1	190	5
148	2	186	7
146	2	161	10
145	2	159	13
131	2	149	10
119	15	148	3
117	10	146	7
101	8	145	10
100	1	131	13
89	5	119	10
88	6	117	51
87	100	103	30
86	33	101	20
73	31	100	20
60	3	89	15
59	9	88	20
58	9	87	100
57	16	86	48
45	53	73	70
44	9	60	5
43	25	59	10
41	13	58	15
31	26	57	20
29	13	45	25
28	10	44	8
		43	8
		31	3

with certainty, *m/e* 146.0572 and 100.0539. These correspond to $C_6H_{10}O_4$ (146.0579) and $C_5H_8O_2$ (100.0524). We have no evidence whatever to allow us to choose among the numerous isomers of $C_5H_8O_2$. Structures **13** and **14**, as well as various ring-opened and ring-contracted compounds are possibilities.



13 **14** **15** **16**

For the $C_6H_{10}O_4$ component, we propose either structure **15** or **16**, or a mixture of the two, since they may be interconverted through a common enediol. Here again, we prefer a structure with a single side chain over a multiply substituted dioxane or ring-opened product because these imply further attack on an initial photoproduct which is present only in low concentration. Attempts to synthesize authentic **15** or **16** met with failure.

GC/MS Analysis of Trifluoroacetate-Derivatized Photolysate. Because the mass spectral analysis of the dioxane photolysate suggested that the majority of the photoproducts are alcohols, and since alcohols are known to give weak, if any, molecular ion peaks, the product mixture was derivatized with trifluoroacetic anhydride. The crude photolysate, after removal of excess dioxane, was subjected to GC/MS analysis before and after treatment with trifluoroacetic anhydride. The mass spectrum of the underivatized photolysate exhibited all of the molecular ions discussed previously, except those at *m/e* 62 and 60, corresponding to ethylene glycol and glycolaldehyde. These two compounds had previously been separated from the other components using a Porapak Q column, whereas a Dexsil 300 column was employed in the GC/MS system. On this column, these two compounds show approximately the same retention time as dioxane itself, and were therefore eluted with the solvent and not leaked to the mass spectrometer. When the trifluoroacetate-derivatized photolysate was analyzed in the GC/MS system, it was found that the molecular ions previously attributed to the nonalcoholic components (**6** and **1**) were still present. On the other hand, the parent peaks attributed to the alcoholic components were either missing or greatly attenuated. New peaks, corresponding to the molecular ions of the trifluoroacetate esters of all of these alcohols, were observed with the exception of compound **7**. Since compound **7**, as postulated, is a hemiacetal, it may be that it did not survive the derivatization process.

Solution Photolysis of Dioxane and Dioxyldioxane. The previously described photoproducts were obtainable only when neat dioxane was photolyzed. When dioxane was irradiated for 30 min as 1.5, 3.0, and 6.0 M ethanolic solutions, only negligible amounts of photoproducts were formed. Furthermore, to investigate the possibility that the products were actually arising from secondary photoreactions of the dimer, dioxyldioxane was prepared and irradiated for 30 min as a 0.1 M ethanolic solution. Gas chromatographic analysis of the resulting photolysate again showed only minor amounts of photoproducts. Hirayama[17] has investigated the fluorescence of neat dioxane, and has found that dilution of the dioxane with isooctane causes a hypsochromic shift in the fluorescence, and reduces its quantum yield. In addition, the absorption spectrum of dioxane shows an inverse dependence of extinction coefficient on solvent viscosity. Finally, no fluorescence could be detected from dioxane in the gas phase. It was thus concluded that monomeric dioxane does not fluoresce, and that dioxane is strongly associated in the excited state. The lack of significant amounts of products from our solution photolysis of dioxane supports this conclusion.

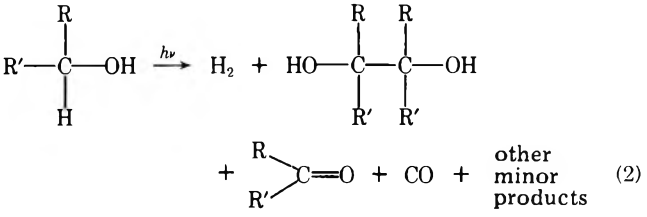
Discussion

We propose, then, that the dioxane photoproducts arise largely from the coupling of α-hydroxy and α-oxy radicals not produced in the primary step, though some, such as **2**, **8**, and **10**, could have resulted from the photoreduction of aldehydic intermediates. Plausible mechanisms for the formation of most of the products are detailed in Scheme VI.

An alternative explanation for the formation of **8**, **10**, and **15** has been proposed to us,[18] namely, that since the dioxyl radical would be expected to disproportionate to dioxane and dioxene, as well as to couple, **8**, **10**, and **15** could result from radical addition of, respectively, methanol, ethylene glycol, and glycolaldehyde to dioxene. To test this possibility, we refluxed mixtures of dioxene and benzoyl peroxide in methanol and in ethylene glycol. In neither case were detectable amounts of addition products obtained. It may be, however, that benzoyl peroxide is not the optimum initiator for these reactions, so they cannot be ruled out in the photolysis of dioxane.

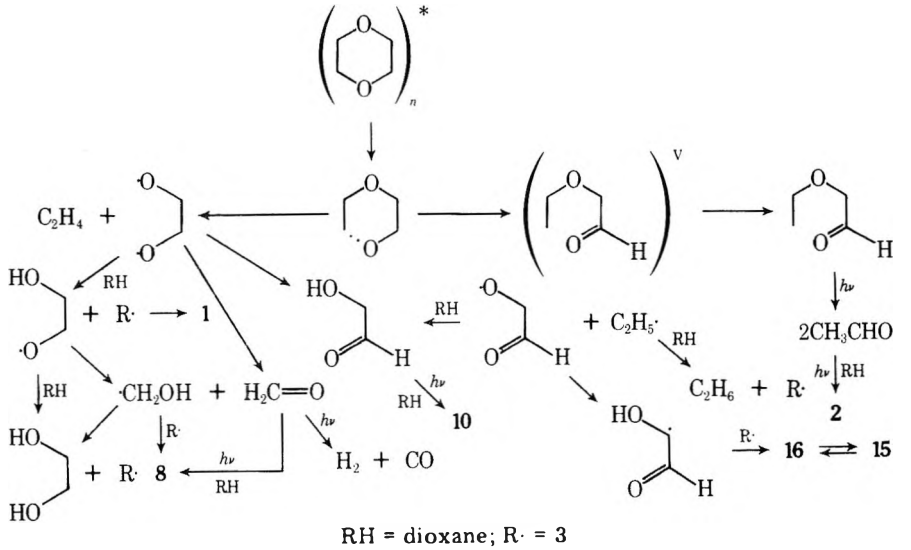
We still consider it unlikely that the primary process is the cleavage of a CH bond in dioxane, primarily because ethers, and dioxane in particular, have been shown in numerous cases to fragment on photolysis via CO bond scission.

As mentioned above, Yang has found[9] that methanol, ethanol, and 2-propanol, when irradiated neat at 185 nm, react according to eq 2. Hydrogen is the major gaseous product, and it is difficult to imagine a pathway, other than the cleavage of



(2)

Scheme VI



RH = dioxane; R· = 3

the α-CH bond of the alcohol, whereby it and the pinacol could be formed together. However, at 185 nm, it is likely that the chromophore responsible is the oxygen. Two facts are germane to the photolysis of dioxane with a medium-pressure lamp. First, with this lamp, the output in the region of 185 nm is blanked out due to self-absorption. Secondly, Yang reports that the impurities in ordinary quartz absorb strongly at 185 nm, and that high-purity fused silica is a requirement for studies at that wavelength.

We did not specifically observe the 1-hydroxyethyldioxane (**2**) reported by Mazzocchi and Bowen, though it is entirely possible—even likely—that it was present in one of our GC fractions, probably either 5 or 6. These workers reported that the mass spectra of the diastereomeric alcohols **2** showed a parent peak at *m/e* 132 (4 or 6% of base intensity), a base peak at *m/e* 87, and a peak at *m/e* 45 (52 or 98% of base intensity). The spectrum of each photolysate fraction, except fraction 2 which lacked the *m/e* 87 peak, contained intense peaks at *m/e* 87 and 45, and since the parent peak of **2** is so small, no special importance would be attached to it in the spectrum of a mixture of compounds which were also substituted dioxanes but ones having a higher molecular weight than that of **2**. Finally, Mazzocchi and Bowen isolated **2** after a 200-h photolysis of dioxane, so it is perhaps not to be expected that it would be a major component after only 30 min.

Three photoproducts are not obviously accommodated by our reaction scheme, namely, **6**, **7**, and **9**. The structure of compound **9** is known with less certainty from the experimental evidence than are the structures of the other photoproducts. However, traces of acid and water in the photolysate could catalyze the dehydration of compound **10** to yield **9**. Compounds **6** and **7** are not major components of the photolysate, and could have been formed by the reaction of dioxyl radicals with small amounts of oxygen not removed from the solution.

In summary, dioxane should be used with caution as a solvent in photochemical reactions in the 200-nm region, since even after relatively short periods of irradiation, it produces a multiplicity of products—including carbonyl compounds which can function as triplet transfer agents.

Experimental Section

Purification of Dioxane. Reagent grade dioxane was percolated through a column of acid-washed alumina into a flask containing KOH pellets, and the mixture stirred for 12 h. The upper layer was decanted, dried over fresh KOH pellets, filtered, and refluxed over sodium for 12 h. It was then distilled from the sodium and stored under nitrogen in an airtight amber bottle.

Photolysis of Dioxane. The dioxane, in 200-mL batches, was degassed in a round-bottom flask, using three freeze–pump–thaw cycles, and was transferred under nitrogen into a glove bag. Aliquots (30 mL) were transferred under nitrogen to 1 × 51 cm quartz tubes which were then closed with stopcocks. Five or six tubes were fastened with rubber bands to the outside of a Hanovia water-jacketed quartz dipping well, and were connected to a manifold which supplied a common nitrogen atmosphere to all tubes. Gaseous photoproducts and nitrogen were vented through a water bubbler. Irradiations were performed with a Hanovia 450-W medium-pressure mercury lamp.

Analysis of Photoproducts. Excess dioxane was distilled from the crude photolysate under nitrogen at atmospheric pressure, while the pot temperature was maintained at the boiling point of dioxane by means of an oil bath. The product mixture was analyzed and partially separated by gas chromatography on a Hewlett-Packard 5700A chromatograph, employing a 10 ft × 0.125 in. column packed with 10% Carbowax 20M on 60–80 mesh Gas Chrom W DCMS AW, maintained at a temperature of 180 °C, with an injection temperature of 250 °C, and a flow rate of 10 mL/min. The mass spectra of the four trapped fractions were recorded on a Du Pont 21-110C high-resolution mass spectrometer. Mass measurements were obtained using an electronic peak matching apparatus with perfluorokerosene as a reference. Low-resolution spectra were obtained on a Finnigan 1015 S/L quadrupole mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer 337 spectrometer, and NMR spectra on Varian A-60 and EM-360 instruments.

Preparation and Photolysis of Dioxyldioxane. Dioxyldioxane was recovered from the 24-h photolysis of dioxane, and the racemic and meso forms recrystallized from hexane and methanol, respectively, mp 131–134 °C (lit.[4] 131 °C); mp 153–156 °C (lit.[4] 157 °C). A 0.1 M solution of dioxyldioxane (24 mL) (mixture of diastereomers) was irradiated in a quartz tube under nitrogen for 30 min. The solvent was removed by distillation, and the photolysate analyzed by gas chromatography on a 6 ft × 0.125 in. column packed with 10% UCW 98 on 80–100 mesh Chromosorb W. The column temperature was programmed from 100 to 300 °C at 8 °C/min. The injection temperature was 250 °C, and the flow rate 70 mL/min.

The Solution Photolysis of Dioxane. Ethanolic dioxane solutions, 1.5, 3.0, and 6.0 M, were irradiated for 30 min in quartz tubes under nitrogen. After removal by distillation of most of the solvent, the remaining liquid was analyzed using the same column and conditions as for the dioxyldioxane photolysis.

Preparation of Dioxene and Dioxanone. Dioxene was prepared according to the method of Moss and Paige.[19] in which diethylene glycol is cyclodehydrated-dehydrogenated by refluxing with copper chromite and $NaHSO_4$. When the bisulfate is omitted, dioxanone is the major product. Physical constants: dioxene, bp 92–93 °C, reported 93–95 °C; dioxanone, bp 109–110 °C (22 mm) (ca. 220 °C at 760 Torr), reported (Beilstein) bp 213–214 °C (747 mm).

Preparation of Hydroxymethyldioxane. Using the method of Wojtowicz et al.,[20] allyl alcohol was chlorinated in ethylene glycol to give $ClCH_2CH(CH_2OH)OCH_2CH_2OH$, which yielded hydroxymethyldioxane on refluxing with aqueous NaOH, bp 98–99.5 °C (16 mm); reported[20] bp 100–105 °C (18 mm).

Acknowledgment. The authors are extremely grateful to the Goodyear Tire and Rubber Co. for the use of their high-resolution mass spectrometer and their GC/MS equipment, to Professor N. C. Deno for several helpful suggestions, and to Professor S. D. Darling for running some of the low-resolution mass spectra.

Registry No.—*dl*-**1**, 3333-27-5; *meso*-**1**, 3443-36-5; **5**, 141-46-8; **6**, 3041-16-5; **7**, 22347-47-3; **8**, 29908-11-0; **9**, 62005-92-9; **10**, 62005-93-0; **15**, 62005-94-1; **16**, 62005-95-2; dioxane, 123-91-1; ethylene glycol, 107-21-1.

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(11) This mechanism is completely analogous to that for the formation of *n*-butylketene in the photolysis of cyclohexanone.
(12) These ions were a constant and important feature of the mass spectra of the other fractions, as well as those of the authentic samples of dioxanone and hydroxymethyldioxane. They do not, however, appear in the spectra of dioxane and dioxene.
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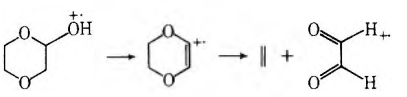
(15) See, for example, Hamming and Foster, "Interpretation of Mass Spectra of Organic Compounds", Academic Press, New York, N.Y., 1972, p 104.
(16) A referee has suggested the following scheme for the production of an ion with *m/e* 58.



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Stereoselectivity in Synthesis and Nucleophilic Displacement Reactions of *cis*- and *trans*-2,3-Dichlorotetrahydropyrans

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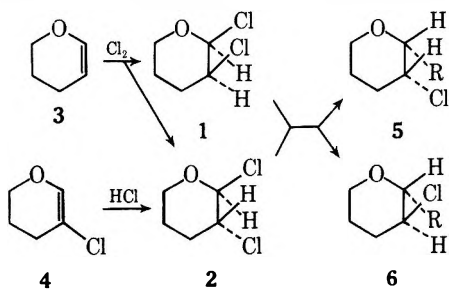
The stereochemistry of addition of chlorine to 3,4-dihydro-2*H*-pyran was reinvestigated and found to depend importantly on solvent polarity. In nonpolar solvents (e.g., pentane) stereoselective syn addition occurred yielding a mixture of *cis*- and *trans*-2,3-dichlorotetrahydropyrans in a ratio of 4:1. In polar solvents (e.g., dichloromethane) the cis:trans product ratio obtained was 1:2. Synthesis of *trans* 2,3-dichlorotetrahydropyran was accomplished by stereospecific syn addition of hydrogen chloride to 5-chloro-3,4-dihydro-2*H*-pyran. A general mechanism for the addition of chlorine to enol ethers which is consistent with the observed solvent dependence is discussed. The stereochemistry of nucleophilic displacement reactions at C-2 of *cis*- and *trans*-2,3-dichlorotetrahydropyrans and *trans*-2,3-dichlorotetrahydrofuran was studied using a variety of nucleophiles including NaSPh, NaOMe, NaN_3, and KOAc in dimethylformamide solution. *cis*-2,3-Dichlorotetrahydropyran yielded exclusively trans products with inversion at C-2. *trans*-2,3-Dichlorotetrahydropyran and -tetrahydrofuran yielded only cis products with C-2 inversion in reactions with NaSPh; with less effective nucleophiles mixtures of cis and trans products were obtained.

In connection with a synthetic program, we required *cis*- and *trans*-2,3-dichlorotetrahydropyran, **1** and **2**, respectively. It was thought by early workers[1] (owing to assumptions about the reaction mechanism) that addition of chlorine to 3,4-dihydro-2*H*-pyran (**3**) yielded only *trans*-2,3-dichlorotetrahydropyran (**2**). In 1965 Lemieux and Fraser-Reid[2] showed the product of this addition in carbon tetrachloride solution to be a 1:1 mixture of cis and trans dichloro compounds **1** and **2**. We have reinvestigated the addition reaction of chlorine to 3,4-dihydro-2*H*-pyran (**3**) and have found reaction conditions whereby the addition occurs with high (4:1) stereoselectivity, yielding largely *cis*-2,3-dichlorotetrahydropyran (**1**). The trans isomer[3] (**2**) was obtained by stereospecific syn addition of hydrogen chloride to 5-chloro-3,4-dihydro-2*H*-pyran (**4**). Using 2,3-dichlorotetrahydropyran and similar 2,3-dichlorotetrahydrofuran preparations of known stereochemical compositions, we have studied the stereochemical consequences of reactions of **1** and **2**, and those of *trans*-2,3-dichlorotetrahydrofuran (**7**), with selected nucleophiles.



Results

Chlorine Addition to 3,4-Dihydro-2*H*-pyran (3). Effects of variation of solvent and other reaction conditions on the stereoselectivity of addition of chlorine to 3,4-dihydro-2*H*-pyran (**3**) are recorded in Table I. When the addition reaction is carried out in polar solvents (e.g., dichloromethane or tetrahydrofuran) the product mixtures obtained exhibit a cis:trans isomer ratio little different from that observed at thermodynamic equilibrium,[2] i.e., 35% cis (**1**). As the reaction solvent polarity decreases the cis isomer (**1**) content of the product mixture increases to a maximum of about 80% when the addition reaction is carried out in pentane. Variation of reaction temperature from −78 to 25 °C has little effect; at higher temperatures equilibration of 1 and 2 occurs.[2] The concentration of 3,4-dihydro-2*H*-pyran (**3**) is important when nonpolar solvents are used; concentrations of **3** greater than

Table I. Stereoselectivity of Addition of Chlorine to 3,4-Dihydropyran (3)

Solvent	ϵ[a]	Temp, °C	% *cis*-2,3-dichlorotetrahydropyran (1)[b]
Pentane	1.8 (20 °C)	0	82
		−78	81
		0	73
		−78	75
Carbon tetrachloride	2.2 (20 °C)	0	65
Benzene	2.3	25	65
Diethyl ether	4.7	0	66
Chloroform	5.0	25	50
Ethyl acetate	6.4	0	44
Dichloromethane	9.1	25	38
Tetrahydrofuran		25	36
Nitromethane	45	0	44
Equilibration[c]		25	35

[a] Dielectric constant (at temperature of chlorination unless otherwise indicated) from "International Critical Tables", Vol. 6, E. W. Washburn, Ed., p 83. [b] See Experimental Section for methodology; reproducibility was <±3%. [c] By treatment with titanium tetrachloride in benzene or tetraethylammonium chloride in acetonitrile.

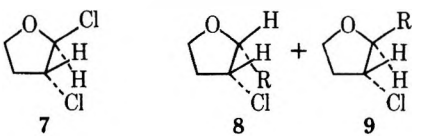
0.1 M increase the trans isomer (2) content of the 2.3-dichloro product. However, further dilution beyond 0.1 M 3 in pentane yields no measurable increase in formation of cis isomer 1.

Hydrogen chloride addition to 5-chloro-3,4-dihydro-2*H*-pyran (4). Synthesis of *trans*-2,3-dichlorotetrahydropyran[3] (2) was accomplished by stereospecific syn addition of hydrogen chloride to 5-chloro-3,4-dihydro-2*H*-pyran (4) in anhydrous benzene. We were unable to detect the presence of any cis isomer (1) in this preparation using ^{1}H NMR spectrometry.

^{1}H NMR Analyses and Molecular Conformation. Important to the present investigation was the direct determination of isomer content of mixtures of 1 and 2 from ^{1}H NMR spectra of benzene solutions. Previously, Lemieux and Fraser-Reid[2] used an indirect method of analysis.

Owing to the strong anomeric effect[4] operative in α-halo tetrahydropyrans[5] both *cis*- and *trans*-2,3-dichlorotetrahydropyrans (1 and 2) exist in conformations in which the C-2 chloro substituent is axial.[2] In trans 2,3-disubstituted tetrahydropyrans, when the atom bonded to C-2 is less electronegative than halogen, the anomeric effect is not totally dominating and other, presumably steric, effects are important in determining conformation. Steric effects are not as important in the analogous cis isomers and, for these compounds, even a relatively weak anomeric effect determines conformation. Assignments of the C-2 H resonances for the cis and trans 2,3-disubstituted tetrahydropyrans included in Table II were made using these considerations and the knowledge that in tetrahydropyrans the resonance for a C-2 equatorial hydrogen appears downfield of the corresponding axial hydrogen resonance.[6] Using these generalizations, stereochemical assignments for the various tetrahydropyrans (1, 2, 5, and 6) were straightforward and fully in accord with expectations based on their method of preparation (see Table III and following discussion), and previous literature assignments.[2,6,7]

In 2,3-disubstituted tetrahydrofurans 8 and 9 (R ≠ Ph)



7 8 9

Table II. Proton Magnetic Resonance Chemical Shifts (δ) and Coupling Constants (*J*) for C-2 H (Anomeric) Hydrogens of Cis and Trans 2,3-Disubstituted Tetrahydropyrans and -furans

	Cis		Trans	
Compd	δ (ppm)	$J_{C\text{-}2H,C\text{-}3H}$, Hz	δ (ppm)	$J_{C\text{-}2H,C\text{-}3H}$, Hz[b]
1, 2	5.86[a]	3	5.93	<1
7			6.16	s
5,6 R = SPh	5.33	3	5.21	4
8, 9[c] R = SPh	5.42	4	5.47	1
5, 6 R = OMe	4.49	3	4.35	4
8, 9 R = OMe	4.69	4	4.84	s
5, 6 R = N_3	5.12	3	4.82	6
8, 9 R = N_3	5.14	4	5.39	s
5, 6 R = OAc	6.02	3	5.66	5
8, 9 R = OAc	6.18	4	6.10	s
6 R = Ph			4.00	10
8 R = Ph	4.90	4		

[a] Spectra were obtained in carbon tetrachloride except for 1 and 2 for which benzene was used and 5, 6, R = SPh, for which dimethyl sulfoxide-d_6 was used. [b] s = singlet. [c] 9, R = SPh, was prepared by reaction of 3-chloro-4,5-dihydrofuran and thiophenol in liquid sulfur dioxide (see Experimental Section).

Table III. Stereochemistry of Products Formed by Reaction of *cis*- and *trans*-2,3-Dichlorotetrahydropyran (1 and 2) and *trans*-2,3-Dichlorotetrahydrofuran (7) with Selected Nucleophiles in Dimethylformamide at 25 °C

		Products		
Nucleophile (M^+Y^-)	α-Halo ether	% cis (5 or 8, R = Y)	% trans (6 or 9, R = Y)	% elimination (4)
NaSPh	1[a]	17	63	20
	2	100		
	7	100		
NaOMe	1[a]	16	62	22
	2	80	20	
	7	89	11	
NaN_3	1[a]	18	84	
	2	91	9	
	7	90	10	
KOAc	1[a]	12	88	
	2	69	31	
	7	61	39	
PhMgBr	1[a]		100	
	2		100	
	7	100		

[a] As prepared by addition of chlorine to 3 (0.1 M) in pentane at 0 °C (see Table I, Experimental Section), containing ~20% of 2.

assignments of stereochemistry are based on the magnitude of $J_{2,3}$. Trans compounds exhibit $J_{2,3} \leq 1$ Hz (eq,eq) and cis compounds exhibit $J_{2,3} \simeq 4$ Hz (eq,ax).[8,9]

3-Chloro-2-phenyltetrahydropyran[10] (6, R = Ph) exhibits $J_{2,3}$ = 10 Hz, which is indicative of trans diaxial hydrogens. 3-Chloro-2-phenyltetrahydrofuran (8, R = Ph) was assigned cis stereochemistry by comparison with assignments of *cis*- and *trans*-3-methyl-2-phenyltetrahydrofuran.[11]

Nucleophilic Displacement Reactions. For a study of the stereoselectivity achievable in nucleophilic displacement reactions of *cis*- and *trans*-2,3-dichlorotetrahydropyrans (1 and 2), dimethylformamide (DMF) was selected as reaction solvent because of its utility as an aprotic medium for S_N2 reactions.[12] Results of reactions of 1, 2, and 7 with selected nucleophiles in DMF are recorded in Table III. Evaluation of

results of reactions of *cis*-2,3-dichlorotetrahydropyran (**1**) required correction to remove the contribution of the trans isomer (**2**) present to the extent of 20% (Table I). Owing to the trans diaxial relationship of the C-3 hydrogen and the C-2 chloro substituent in the cis isomer (**1**) some elimination occurs with the more basic nucleophiles.

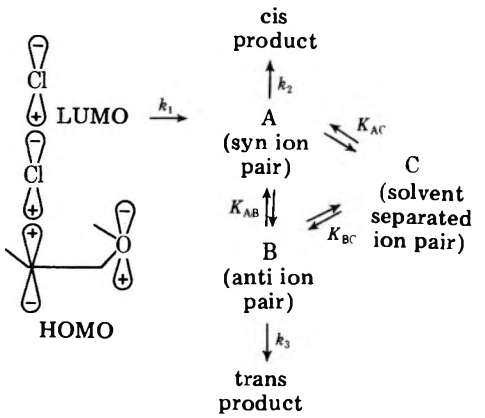
Reaction of phenylmagnesium bromide with either *cis*- or *trans*-2,3-dichlorotetrahydropyran (**1** or **2**) yields *trans*-2-phenyl-3-chlorotetrahydropyran (**6**, R = Ph).[10] In contrast, similar reaction of *trans*-2,3-dichlorotetrahydrofuran (**7**) with phenylmagnesium bromide yielded *cis*-2-phenyl-3-chlorotetrahydrofuran (**8**, R = Ph) analogous to the result obtained by reaction of phenylmagnesium bromide with *trans*-2,3-dichloro-3-methyltetrahydropyran.[8]

Discussion

Addition of Chlorine to Enol Ethers. Lemieux and Fraser-Reid[2] investigated the addition of halogens to several cyclic enol ethers in carbon tetrachloride solution and proposed as a general mechanism polar attack of halogen on the olefinic bond with formation of a carbonium ion (or ions) which, upon attack of halide ion, leads predominantly to thermodynamic products. Igarashi et al.[14] have extended this work by study of the addition of chlorine to tri-*O*-acetyl-D-glucal in a variety of solvents. They established that (a) product formation is under kinetic, not thermodynamic, control and (b) the stereoselectivity of addition is sensitive to solvent polarity.

Igarashi et al.[14] and later workers[15,16] have proposed modification to the mechanism of Lemieux and Fraser-Reid.[2] The results (Table I) of the present study are fully consistent with earlier findings.[14-16] However, we draw somewhat different conclusions concerning the implications of these data for those mechanistic parameters which determine the stereoselectivity of addition. Chlorine addition occurs in a bimolecular process (Ad_E2) in which the carbon–chlorine bonds are formed in separate steps.[17] Consideration of the initial step—formation of a carbonium ion intermediate—in frontier orbital terms[18] indicates a preferred reaction geometry in which the chlorine molecule is oriented perpendicular to the π system of the enol ether and leads to a "syn" ion pair in which the chloride ion is on the same face of the carbonium (oxonium) ion molecular backbone as the bonded chloro substituent. The net stereoselectivity of the chlorine addition reaction depends on the fate of this initially formed "syn" intimate ion pair (A, Scheme I). Direct collapse of A is the principal reaction pathway for

Scheme I. Addition of an Electrophile (e.g., Cl_2) to an Enol Ether



cyclic enol ethers in solvents with weak ion-solvating ability (Table I) and leads to a cis 2,3-dichloro ether product.[19]

As the ion-stabilizing ability of the reaction solvent increases other fates for ion pair A become increasingly probable. Separation of ion pair A results in solvated ions (C) which may recombine forming either "syn" intimate ion pair A or "anti" intimate ion pair B leading, upon collapse, to the observed (Table I) mixtures of cis and trans 2,3-dichloro ethers. In solvents of intermediate polarity (e.g. chloroform, ethyl acetate) the fate of A depends largely on the relative rates of ion collapse (k_2) and solvation (k_{AC}).

Interconversion of the syn and anti intimate alkoxycarbonium ion pairs A and B requires, in effect, migration of a chloride ion from one face of the cyclic alkoxycarbonium ion to the other. In contract, in acyclic analogues[20] interconversion between syn and anti isomers can occur by rotation of the carbonium ion center about the C–C bond (K_{AB}). Note that rotation of the C-3 carbon about this bond has no direct effect upon the stereochemistry of the product formed by intimate ion pair collapse although such rotation may be important in relieving steric or electronic strains.[21]

While any discussion of structural and conformational features of alkoxycarbonium ions (e.g., A, B, and C, Scheme I) is speculative,[2,14,15] results from both experimental[22] and theoretical[23] studies make clear that the dominant factor providing stabilization is π electron donation by oxygen. As a consequence, the C_2–O bond possesses substantial double bond character and bridged chloronium species are unimportant in alkoxycarbonium ion stabilization.

The more effective syn addition of hydrogen chloride to **4** (as compared with addition of chlorine to **3**) is readily accounted for by comparing the intermediate intimate ion pairs initially formed in the respective reactions. The total internuclear distance in the transition state for hydrogen chloride addition (Cl- - -H- - -C) is shorter than that for addition of chlorine (Cl- - -Cl- - -C). This and the lack of electronic repulsion between the chloro substituent in ion pair A and the chloride ion formed by hydrogen chloride addition to **4** (which in this case possess an anti relationship) predicts a "tighter" ion pair and greater reaction stereoselectivity.

Reactions of 1, 2, and 7 with Nucleophiles. Reaction of *cis*-2,3-dichlorotetrahydropyran (**1**) with five nucleophiles in dimethylformamide yielded, in each case, only trans (i.e., inverted) products (Table III). The results for reactions of the trans 2,3-dichloro ethers **2** and **7** are more complex. Both **2** and **7** yielded only products of inversion in reactions with sodium thiophenoxide; with weaker nuclephiles varying amounts of retention products were observed. With these trans 2,3-dichloro ethers the relative percentages of inversion products were of the order $PhS^- > N_3^- \simeq MeO^- > AcO^-$. This varies somewhat with a nucleophilicity scale ($PhS^- > AcO^- > N_3^-$) determined by relative rates of reaction with methyl iodide in DMF.[24] Since **1** reacted solely by inversion with all nucleophiles studied and acetate ion, the bulkiest nucleophile, was ineffective in achieving replacement with inversion when allowed to react with trans compounds **2** and **7**, it is probable that in these instances unfavorable steric interactions between the axial chloro substituent at C-3 and the incoming nucleophile are important.[27] The results of the present study extend and agree, only in part, with previous studies of displacement reactions of α-halo ethers.[25-30]

Experimental Section

Solvents used were commercial AR grade solvents and were not further purified unless otherwise noted. Mass spectra were obtained on CEC 21-110 and Du Pont 21-491B mass spectrometers. ^1H NMR spectra were obtained with a Varian HA-100 spectrometer. Chemical shifts are recorded in parts per million downfield from internal tetramethylsilane.

Chlorination of 3,4-Dihydro-2*H*-pyran (3). General Procedure. Chlorine was passed slowly through a stirred solution of 0.84 g (10 mmol) of 3,4-dihydro-2*H*-pyran in 100 mL of solvent (see Table I) until a yellow color persisted. The solvent and excess chlorine were then removed by distillation (<40 °C) in vacuo. The resulting residue

was dissolved in benzene and analyzed directly by ^{1}H NMR spectrometry. ^{1}H NMR spectra of all preparations (Table I) revealed the presence of only *cis*- and *trans*-2,3-dichlorotetrahydropyrans (1 and 2); in no instance was evidence for starting material or other transformation products observed. The ratios of 1 (cis) to 2 (trans) were determined by excision of the respective C-2 H resonances from photocopies of the strip chart-recorded spectra and comparison of their weights.

***trans*-2,3-Dichlorotetrahydropyran (2).** To 1.2 g (10 mmol) of 5-chloro-3,4-dihydro-2*H*-pyran (4)[31] in 160 mL of benzene (distilled from calcium hydride) was added anhydrous hydrogen chloride until the solution appeared saturated (as monitored by wet litmus paper). Gas addition was continued for an additional 10 min; the flask was then stoppered tightly and allowed to stand at room temperature for 2 h. The excess hydrogen chloride was removed by passing nitrogen through the solution and the solvent was removed. The ^{1}H NMR spectrum (benzene) of the residue revealed only one resonance assignable to C-2 H (δ 5.93). This material, essentially pure *trans*-2,3-dichlorotetrahydropyran (2), was used directly for nucleophilic displacement reactions.

Reactions of *cis*- and *trans*-2,3-Dichlorotetrahydropyrans (1 and 2) and *trans*-2,3-Dichlorotetrahydrofuran (7)[32] with Nucleophiles. General Procedure. To a vigorously stirred mixture of 10 mmol of a nucleophile (Table III) in 20 mL of dimethylformamide[33] was added 5 mmol of the appropriate dichloro ether (or dichloro ether mixture) in 10 mL of dimethylformamide.[33] With the exception of reactions involving potassium acetate and sodium azide the nucleophiles were soluble in dimethylformamide; for these nucleophiles suspensions were used. After 30 min (18 h for potassium acetate) the solution (mixture) was poured into 150 mL of water and extracted with benzene (two 75-mL portions). The combined benzene extracts were washed with 100 mL of water and dried with sodium sulfate and the benzene was removed in vacuo (<40 °C). ^{1}H NMR spectra (Table II) of the residues were obtained directly. Mass spectra of all previously unknown compounds (**5, 6, 8, 9,** R $\neq$ OMe or OAc) exhibited parent ions and fragment ions consistent with the assigned structures. Yields in all displacement reactions were high, although no attempt was made to determine them accurately owing to the difficulty in removing the last traces of dimethylformamide. Side products, as based on the appearance of extraneous doublets in the anomeric proton region of the ^{1}H NMR spectra, were visible only for the KOAc and NaOMe reactions of 1 and 2. In these instances the expected products constituted >95% of the isolated material. The side products were not identified but are thought to be *cis*- and *trans*-2,3-dimethoxy- and 2,3-diacetoxytetrahydropyrans.

Demonstration That the Product-Forming Step in the Reaction of Chlorine with 3,4-Dihydro-2*H*-pyran is Irreversible, i.e., under Kinetic Control. The chlorination of 0.84 g (10 mmol) of 3,4-dihydro-2*H*-pyran (3) was carried out in pentane by the general procedure yielding 82:18 *cis*-: *trans*-2,3-dichlorotetrahydropyrans. This mixture, free of solvent, was then added to 100 mL of dichloromethane containing 0.84 g of 3,4-dihydro-2*H*-pyran and the chlorination was repeated. Analysis of the ^{1}H NMR spectrum (benzene) of the resulting product mixture, as described in the general procedure, showed 57.4% cis (1) (predicted value 59.5% if under kinetic control, 38% if under thermodynamic equilibrium; see Table I).

***cis*- and *trans*-3-Chloro-2-thiophenyltetrahydrofurans (8, 9).** One gram (10 mmol) of 3-chloro-4,5-dihydrofuran[34] and 2.2 g (20 mmol) of thiophenol were added to 2 mL of liquid sulfur dioxide at −20 °C.[35] After 10 h at −20 °C the sulfur dioxide was allowed to evaporate at room temperature and the excess thiophenol was removed in vacuo. The ^{1}H NMR spectrum of this crude mixture (Table II) revealed that approximately equal amounts of *cis*- and *trans*-3-chloro-4,5-dihydrofurans (8 and 9, R = SPh) had been formed.

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Registry No.—1, 52809-66-2; 2, 7429-32-5; 3, 110-87-2; 4, 6581-49-3; 5 (R = SPh), 61900-17-2; 5 (R = OMe), 6559-29-1; 5 (R = N_3), 61900-18-3; 5 (R = OAc), 14750-43-7; 6 (R = SPh), 61900-19-4; 6 (R = OMe), 6559-30-4; 6 (R = N_3), 61900-20-7; 6 (R = OAc), 14750-42-6; 6 (R = Ph), 61900-21-8; 7, 13129-90-3; 8 (R = SPh), 61900-22-9; 8 (R = OMe), 29120-54-5; 8 (R = N_3), 61900-23-0; 8 (R = OAc), 61900-24-1; 8 (R = Ph), 61900-25-2; 9 (R = SPh), 61900-26-3; 9 (R = OMe), 29120-53-4; 9 (R = N_3), 61900-27-4; 9 (R = OAc), 61900-28-5; NaSPh, 930-69-8; NaOMe, 124-41-4; NaN_3, 26628-22-8; KOAc, 127-08-2; PhBr, 108-86-1; 3-chloro-4,5-dihydrofuran, 17557-40-3; thiophenol, 108-98-5.

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Perhydroindan Derivatives. 18. The Use of Indenone Ketals as Dienophiles[1]

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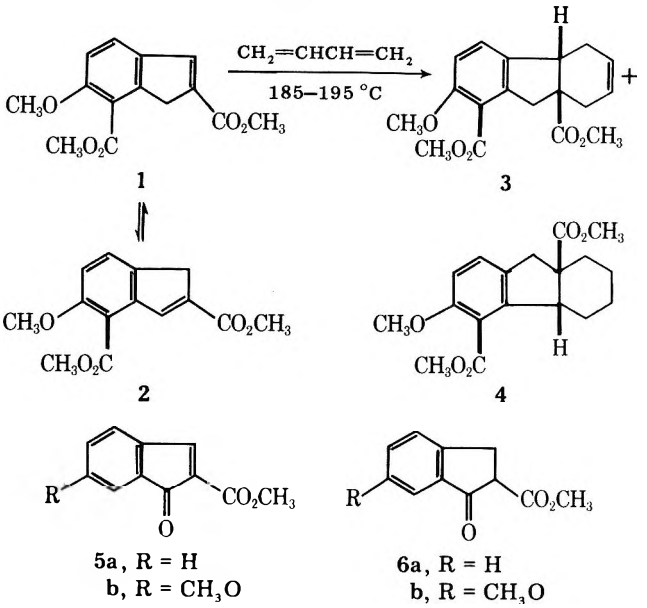
Synthetic routes to the indenone ketals **18, 19,** and **21** are described with the ketal acid derivatives **21** being formed by reaction with the α-lithio ketals **20.** Each of the ketals **18, 21b,** and **21d** has been shown to be a reasonably reactive dienophile in a Diels–Alder reaction with butadiene.

Previous study[2] of the Diels–Alder reaction of butadiene with the unsaturated ester **1** (Scheme I) established that the

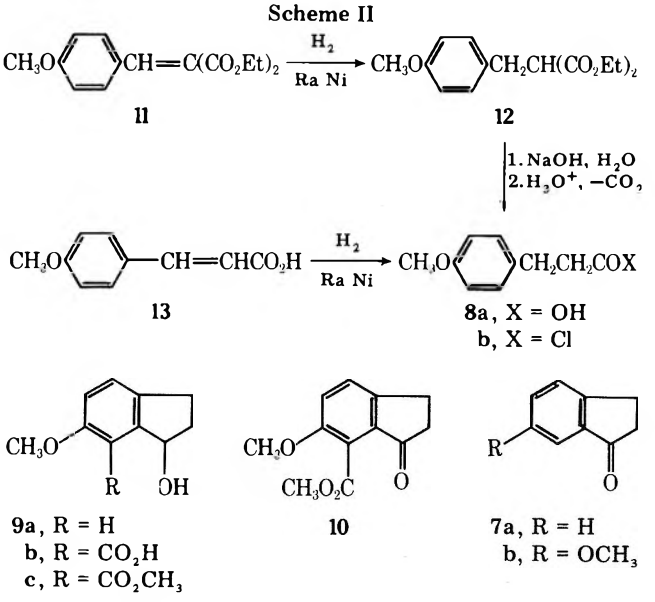
Scheme I



rather vigorous conditions required for successful reaction resulted in concurrent double bond isomerization **1** ⇌ **2** in the dienophile. Consequently, both the adduct **3,** desired as a gibberellin precursor, and the undesired structurally isomeric adduct **4** were produced in comparable amounts. It appeared that this synthetic problem might be solved by use of the indenone **5** as a dienophile since this ketone **5** would not only prevent double bond isomerization but should also be a more reactive dienophile.[3] However, a variety of attempts[4] to convert the readily available indanones **6** to the indenones **5** either by dehydrogenation or by a halogenation–dehydrohalogenation sequence were unsuccessful. Consequently, we were led to study alternative synthetic routes to the indenones **5** or synthetically equivalent structures; the results of this study are reported in this paper.

To obtain compounds synthetically equivalent to the indenone esters **5,** we chose the indanones **7** (Scheme II) as starting materials, the methoxy ketone **7b** being obtained by cyclization of the acid chloride **8b** under the special conditions described previously.[5] Previously described procedures[6] were also used to convert the indanone **7b** to the keto ester **10.** Each monobromo ketone **14** (prepared from the indanone **7,** Scheme III) was converted to its ketal **15** which could be further brominated with Br_2 in Et_2O containing a catalytic amount of HBr[7] to form the dibromo ketal **17.** Although the ketal **17a** was also successfully prepared from the dibromo ketone **16a,** we were unable to form ketal **17b** from the dibromo ketone **16b.** As had been observed previously with the bromo ketal **15a,**[3a] reaction of each of the bromo ketals **15** and **17** with

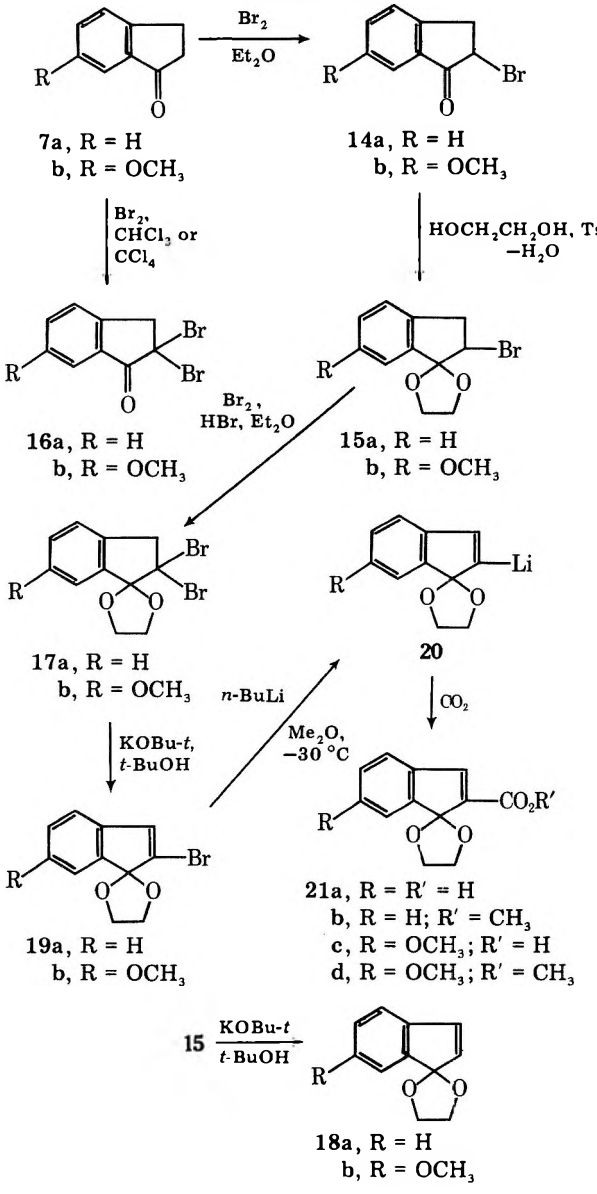
Scheme II



KOBu-*t* in *t*-BuOH afforded the indenone ketals **18** and **19** in good yield. Each of the vinyl bromides **19** could be converted to the corresponding organolithium derivative **20** by exchange with *n*-BuLi. Presumably, the stability of these β-alkoxy organolithium compounds **20** is attributable to the fact that elimination of lithium alkoxide in these cases would produce a highly strained cyclic allene.[8] The only problem we encountered in the formation of the lithium reagents **20** arose because the exchange of *n*-BuLi with the bromides **19** was very slow in hexane and addition of conventional ethereal cosolvents (Et_2O or THF) resulted in proton abstraction from these ethereal solvents converting an appreciable fraction of the lithium derivatives **20** to the protonated ketals **18.** This problem was largely overcome by the use of Me_2O (bp −24 °C) as an ethereal cosolvent that lacks β-hydrogen atoms and also served to control the temperature of the reaction. Carbonation of the lithio derivatives **20** produced the acids **21a** and **21c** that were converted to the corresponding esters **21b** and **21d** for further use.

Earlier study[3a,c] of the Diels–Alder reaction of butadiene with the indenone ketals **18a** and **18c** (Scheme IV) had indicated that the ketal **18a** could be used directly as a dienophile at 180 °C to form the ketal **22** that was subsequently hydrolyzed to the ketone **24a.** Alternatively, treatment of the ketal **18c** with aqueous acid generated at least a low concentration of a yellow-colored intermediate, thought to be either the indenone **23a** or the related oxonium ion **23b,** that reacted with butadiene at 25 °C to form the adduct **24b.** To explore these reaction conditions further, the ketal ester **21b** was allowed to react either with butadiene alone or with a mixture of butadiene, water, and 0.3 molar equiv of CH_3SO_3H to generate either the indenone **26** or the related oxonium ion (cf. **23b**). Although the reaction with butadiene under neutral condi-

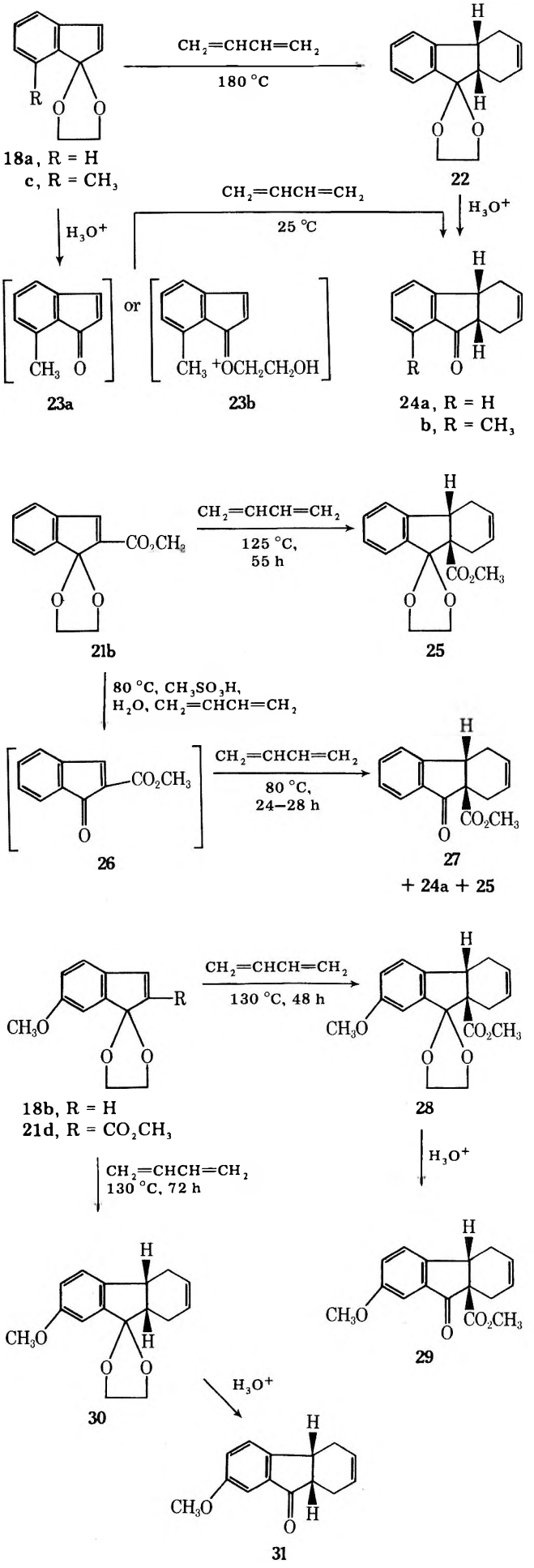
Scheme III



tions to form the ketal **25** required somewhat higher temperature and longer reaction time than the acid-catalyzed reaction to form ketone **27**, this advantage of the acid-catalyzed process was offset by the formation of the ketone **24a** (from hydrolysis and decarboxylation of the ester **27**) and a small amount of the ketal **25** as by-products in the acid-catalyzed reaction. Consequently, the reactions of the methoxy indenone ketals **18b** and **21d** with butadiene were effected under neutral conditions.

We were surprised to find that the reactivities of the two indenone ketals **18b** and **21d** as dienophiles were similar in spite of the fact that only one ketal, **21d**, has an electron-withdrawing carbomethoxyl group conjugated with the reacting double bond. From a series of reactions of these ketals with butadiene at 130 °C for various periods of time, we estimate that the rate of reaction of butadiene with the ketal **21d** is approximately twice the rate of the corresponding reaction with the ketal **18b**. Thus, the major factor responsible for the reactivity of these materials as dienophiles appears to be the presence of a strained C=C in the indene systems (cf. cyclopentadiene). It is likely that the 180 °C reaction temperature used in the earlier study[3a] with the indenone ketal **18a** was well above the minimum temperature required for reaction. In any case, the use of the indenone ketal **21d** as the dienophile in a reaction with butadiene provides a synthetically useful route

Scheme IV



to the tricyclic gibberellin intermediates **28** and **29** and avoids the problem of C=C isomerization encountered in our previous study of Diels–Alder reactions with the indene **1**.

Experimental Section[9]

Preparation of 6-Methoxy-1-indanone (7b). Condensation of anisaldehyde with diethyl malonate by a standard procedure[10] yielded 94% of the arylidene malonate **11** as a colorless liquid, bp 181–185 °C (0.85 mm), n^{25}_D 1.5578 [lit.[11] bp 130–147 °C (0.13 mm)]. An EtOH solution of this diester **11** was hydrogenated over Ra Ni[12] at 4 atm and 25 °C to yield 96.5% of the diester **12**, bp 186–190.5 °C (1.3 mm), n^{25}_D 1.4964 [lit.[11] bp 138–142 °C (0.2 mm), n^{27}_D 1.4928]. After saponification of the diester **12** and subsequent decarboxylation, reaction of the resulting crude acid **8a** with excess refluxing $SOCl_2$ yielded 76.5% of the acid chloride **8b** as a pale yellow liquid, bp 170–174 °C (15 mm), n^{25}_D 1.5323–1.5331 [lit.[11] bp 95–97 °C (0.2 mm)]. When intermediates were not isolated, the diester **11** could be converted to the acid chloride **8b**, bp 159–163 °C (10 mm), in an overall yield of 78.4%.

Alternatively, condensation of anisaldehyde with malonic acid yielded 83.2% of the cinnamic acid **13**, mp 171.4–173.3 °C (lit.[13] mp 173 °C). Hydrogenation of a slurry of this acid **13** in EtOH over Ra Ni at 4 atm and 25 °C yielded 94.8% of the crude acid **8a**, mp 95–102 °C (lit.[14] mp 103.5–104 °C). Reaction of this crude acid **8a** with excess refluxing $SOCl_2$ yielded 88.8% of the acid chloride **8b**, bp 120–122.8 °C (2.4–3.3 mm), n^{25}_D 1.5360. The same acid chloride **8b** was obtained in 87% yield by reaction of the crude acid **8a** with excess refluxing $(COCl)_2$. A previously described cyclization procedure[5] employing a dilute solution of the acid chloride **8b** and $AlCl_3$ in CH_2Cl_2 yielded 77.5% of the indanone **7b**, mp 104.3–107.3 °C (lit.[5] mp 109–110 °).

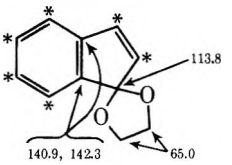
Preparation of the Keto Ester 9. After reduction of the ketone **7b** with $LiAlH_4$ in Et_2O to form 94.4% of the crude alcohol **9a**, mp 43.7–44.9 °C (lit.[6] mp 46–47.5 °C), use of the previously described[6] reaction of the alcohol **9a** with *n*-BuLi in hexane followed by carbonation on dry ice yielded 61.5% of the hydroxy acid **9b** mp 154.5–156.7 °C dec (lit.[6] mp 150–151 to 160–161 °C dec), accompanied by 16% recovery of the starting alcohol **9a**. Esterification with excess ethereal CH_2N_2 followed by recrystallization from pentane yielded 77% of the hydroxy ester **9c**, mp 53–56 °C (lit.[6] mp 55–55.5 °C). Oxidation of this alcohol yielded 85% of the keto ester **10**, mp 123–125 °C (lit.[6] mp 127–127.5 °C), that was identified with a previously described[6] sample by comparison of IR, NMR, and mass spectra.

Preparation of 1-Indanone (7a). Cyclization of hydrocinnamic acid with polyphosphoric acid at 70–85 °C yielded 83% of the ketone **7a**, bp 119–125 °C (10–15 mm), that solidified on standing, mp 36–38.7 °C (lit.[3a] mp 40–41 °C). When the same cyclization was effected with a mixture of P_2O_5 and CH_3SO_3H,[15] a 64% yield of ketone **7a** was obtained. Reaction of propiolactone and $AlCl_3$ with excess refluxing benzene[16] yielded 60% of the same ketone **7a**.

Preparation of the Dibromoindanone 16a and the Ketal 17a. Reaction of the indanone **7a** with 1 molar equiv of Br_2 in Et_2O at 3 °C yielded, after filtration through decolorizing carbon and removal of the solvent under vacuum, 86% of the crude bromo ketone **14a** as a cream-colored solid (lit.[3a] mp 37–38.5 °C). A solution of 16.2 g (76.7 mmol) of this crude bromo ketone **14a**, 4.76 g (76.7 mmol) of $HOCH_2CH_2OH$, and 0.15 g of *p*-TsOH in 125 mL of PhH was refluxed for 78 h with continuous separation of H_2O. During the reflux period two additional 1.54-g (24.8 mmol) portions of $HOCH_2CH_2OH$ were added. The resulting solution was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, and distilled to separate 15.39 g (78.6%) of the crude ketal **15a** as a pale yellow liquid, bp 93–97.5 °C (0.02–0.03 mm), n^{25}_D 1.5765–1.5779 [lit.[3a] bp 95–105 °C (3.5 mm)]; IR (CCl_4) weak absorption at 1745 and 1730 cm^{-1} (C=O of bromo ketone impurity); NMR (CCl_4) δ 6.9–7.5 (4 H, m, aryl CH), 3.9–4.7 (5 H, m, CH_2O and CHBr). and 2.8–3.7 (2 H, m, benzylic CH_2); mass spectrum *m/e* (rel intensity) 256 (M^+, 2), 254 (M^+, 2), 175 (100), 146 (44), 131 (60), 103 (47), 77 (28), and 51 (20).

After 7.60 g (29.8 mmol) of the bromo ketal **15a** had been stirred at 25 °C for 6 h with a solution of 43.5 mmol of KOBu-*t* in 50 mL of *t*-BuOH, the dark colored reaction mixture was partitioned between H_2O and Et_2O. The ethereal layer was washed with aqueous NaCl, dried, concentrated, and distilled to separate 3.27 g (63%) of the unsaturated ketal **18a** as a colorless liquid: bp 85–87 °C (0.1 mm); n^{25}_D 1.5717–1.5723 [lit.[3a] bp 78–80 °C (0.15 mm), n^{28}_D 1.5699]; IR (CCl_4) 1615 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity) 174 (M^+, 31), 118 (100), 115 (18), 102 (21), and 90 (24). The ^{13}C NMR spectrum of this ketal **18a** ($CDCl_3$ solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements.

(*121.0, 121.6, 126.1, 129.1, 132.4, 134.0 ppm)



After HBr gas had been passed through a cold (0 °C) solution of 39.09 g (153 mmol) of the bromo ketal **15a** in 600 mL of Et_2O, 24.5 g (153 mmol) of Br_2 was added, dropwise and with stirring during 15 min.[7] After the resulting mixture had been stirred for 2 h at 25 °C, it was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried (Na_2SO_4) and concentrated to leave 52.8 g of crude product as a pale yellow solid. Recrystallization of this material from CCl_4 separated 32.56 g (63.6%) of the dibromo ketal **17a** as fine, pale yellow crystals, mp 88–89.9 °C, as well as a 6.2-g fraction of less pure material, mp 67–84 °C, that contained (IR analysis) ketone impurities.

In an alternative preparation, a $CHCl_3$ solution of the indanone **7a** was treated with 2 molar equiv of Br_2 to yield the dibromo ketone **16a** as yellow prisms from EtOH: mp 131–133.8 °C (lit.[3a] mp 133–134 °C); IR (CCl_4) 1745 cm^{-1} (C=O); NMR (CCl_4) δ 7.2–8.1 (4 H, m, aryl CH) and 4.27 (2 H, s, benzylic CH_2). A solution of 8.12 g (28 mmol) of the dibromo ketone **16a**, 1.74 g (28 mmol) of the $HOCH_2CH_2OH$, and 0.15 g of *p*-TsOH in 50 mL of PhH was refluxed for 96 h with continuous separation of H_2O. During this reflux period two additional 0.58-g (9.3 mmol) portions of $HOCH_2CH_2OH$ were added. After the PhH solution had been washed successively with aqueous $NaHCO_3$, H_2O, and aqueous NaCl, it was concentrated to separate various crops of crystalline solid melting within the range 68–83 °C and containing (IR analysis) mixtures of the ketone **16a** and the ketal **17a**. Repeated recrystallization from CCl_4 and final sublimation (80 °C and 0.05 mm) separated a small sample of the pure ketal **17a** as a white solid: mp 86–87.8 °C; IR (CCl_4) no C=O absorption; NMR (CCl_4) δ 7.0–7.6 (4 H, m, aryl CH), 4.1–4.7 (4 H, m, CH_2O), and 3.85 (2 H, s, benzylic CH_2); UV max (95% EtOH) 258 nm (ϵ 750), 265 (990), and 272.5 (1050); mass spectrum *m/e* (rel intensity) 336 (M^+, 40), 334 (M^+, 81), 332 (M^+, 43), 255 (100), 253 (98), 211 (32), 209 (35), 148 (90), 118 (43), 115 (30), 104 (32), 102 (64), 101 (32), and 75 (32).

Anal. Calcd for $C_{11}H_{10}Br_2O_2$: C, 39.56; H, 3.02; Br, 47.84. Found: C, 39.66; H, 3.04; Br, 47.83.

Preparation of the Unsaturated Ketal 19a. A solution of 32.36 g (96.9 mmol) of the ketal **17a** and KOBu-*t* [from 5.3 g (136 mg-atoms) of K] in 127 mL of *t*-BuOH was stirred at 25–27 °C for 36 h and then partitioned between Et_2O and cold H_2O. The Et_2O solution was washed with aqueous NaCl, dried (Na_2SO_4), and concentrated to leave 23.67 g (96.5%) of the ketal **19a** as a cream-colored solid, mp 71.2–74 °C. Recrystallization from hexane afforded the pure ketal **19a** as colorless needles: mp 72.7–73.5 °C; IR (CCl_4) 1617 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 6.8–7.4 (4 H, m, aryl CH), 6.61 (1 H, s, vinyl CH), and 3.9–4.6 (4 H, m, CH_2O); UV max (95% EtOH) 217 nm (ϵ 35 700), 222 (32 200), 283 (4200), 294 (4100), and 311 (2900); mass spectrum *m/e* (rel intensity) 254 (M^+, 17), 252 (M^+, 17), 173 (100), 129 (32), 115 (22), 101 (29), and 89 (24).

Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58; Br, 31.58. Found: C, 52.21; H, 3.62; Br, 31.50.

Preparation of the Unsaturated Ester 21b. To a cold (−24 °C) solution of 3.68 g (14.5 mmol) of the bromide **19a** in 100 mL of Me_2O was added, dropwise and with stirring, 9.2 mL of a hexane solution containing 14.6 mmol of *n*-BuLi. After the resulting deep blue solution had been stirred at −25 °C for 10 min, it was siphoned onto crushed dry ice with accompanying change in the color of the solution from blue to red to orange. The resulting mixture was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. Concentration of the organic solution left 0.56 g of brown liquid with NMR absorption corresponding to the known[3a] ketal **18a** accompanied by a small amount of the starting bromo ketal **19a**. After the aqueous solution had been acidified to pH 2 with cold (5 °C) aqueous 6 M HCl, it was extracted with CH_2Cl_2 and the organic extract was washed with aqueous NaCl, dried (Na_2SO_4), and concentrated. The residual crude acid **21a** (2.46 g of tan solid) was recrystallized from CH_2Cl_2–hexane to separate 1.98 g (62.4%) of fractions of the acid **21a** as white solids melting within the range 185–189 °C dec; IR ($CHCl_3$) 2970 (broad, carboxyl OH), 1685 (carboxyl C=O), and 1612 cm^{-1} (conjugated C=C); UV max (95% EtOH) 224 nm (ϵ 24 900), 228 (24 000), and 313 (7500); NMR ($CDCl_3$) δ 11.16 (1 H, s, OH), 7.68 (1 H, s, vinyl CH), 7.1–7.4 (4 H, m, aryl CH), and 4.1–4.8 (4 H, m, CH_2O). Attempts to effect this same metalation, **19a** → **20**, with *n*-BuLi in hexane at 0 °C resulted in recovery of about half of the unchanged bromide **19a** and use of Et_2O at −35 °C as a reaction

solvent resulted in the formation of increased amounts of the crude olefin **18a**. A cold (−30 °C) solution of 2.2 g (0.79 mmol) of the bromide **19a** in 25 mL of THF was treated with 0.5 mL of a hexane solution containing 0.79 mmol of *n*-BuLi, stirred at −30 to −35 °C for 30 min, and then quenched by the dropwise addition of 0.25 mL of D_2O. The recovered crude product (a mixture of the olefin **18a** and a small amount of starting bromide, NMR analysis) was subjected to preparative TLC separation on silica gel to separate a sample of the pure olefin **18a** with NMR doublets (J = 5.6 Hz) of equal intensity at δ 6.46 and 5.98 corresponding to the vinyl CH groups of the nondeuterated olefin **18a**.

The acid **21a** (5.30 g, 24.3 mmol) was added to 235 mL of Et_2O containing 25.1 mmol of CH_2N_2. The resulting mixture was stirred at 25 °C for 5 min and then concentrated and partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal layer was dried and concentrated to leave 5.58 g (99%) of the ester **21b** (NMR analysis) as a pale yellow liquid that solidified on standing, mp 42.8–49 °C. Recrystallization from pentane separated the pure ester **21b** as a waxy, white solid: mp 47.8–50 °C; IR (CCl_4) 1722 (conjugated ester C=O) and 1615 cm^{-1} (conjugated C=C); UV max (95% EtOH) 225 nm (ϵ 21 900), 231 (21 600), and 315 (6900); NMR (CCl_4) δ 7.33 (1 H, s, vinyl CH), 7.0–7.3 (4 H, m, aryl CH), 3.9–4.6 (4 H, m, CH_2O), and 3.67 (3 H, s, OCH_3); mass spectrum *m/e* (rel intensity) 232 (M^+, 4), 189 (8), 173 (12), 157 (52), 101 (21), 85 (79), 83 (100), 48 (20), and 47 (31).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.95; H, 5.13.

In another experiment employing 12.66 g (50 mmol) of the bromide **19a**, the crude acid **21a** obtained (7.97 g, mp 183–187 °C dec) was directly esterified with ethereal CH_2N_2 to yield 7.96 g (69% overall yield) of the ester **21b**, mp 44–49 °C.

Preparation of the Bromo Ketone 14b. To a cold (0–5 °C) solution of 4.05 g (25 mmol) of the ketone **7b** in 400 mL of Et_2O was added, dropwise and with stirring during 8 min, 4.00 g (25 mmol) of Br_2. The resulting colorless solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl, and then dried and concentrated to leave 6.18 g of residual yellow liquid that solidified on standing. Recrystallization from hexane separated 3.17 g (53%) of the crude bromo ketone **14b** as various fractions of colorless to cream-colored plates melting within the range 45–60 °C. This material turned pink upon exposure to the air and light. Chromatography of a portion of this material on silica gel with an Et_2O–hexane eluent (1:9 v/v) followed by crystallization from hexane separated a sample of the pure bromo ketone **14b** as white plates: mp 60–62 °C; IR (CCl_4) 1720 cm^{-1} (C=O); UV max (95% EtOH) 220 nm (ϵ 21 200), 256 (8800), and 332 (3300); NMR (CCl_4) δ 6.9–7.4 (3 H, m, aryl CH), 4.4–4.7 (1 H, m, CHBr), and 3.0–4.0 (5 H, m, aliphatic CH including a CH_3O singlet at 3.78); mass spectrum *m/e* (rel intensity) 242 (M^+, 40), 240 (M^+, 44), 162 (22), 161 (100), 133 (26), 89 (22), and 63 (20).

Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76; Br, 33.14. Found: C, 49.80; H, 3.77; Br, 33.23.

Preparation of the Dibromo Ketone 16b. To a solution of 4.05 g (25 mmol) of the ketone **7b** in 400 mL of CCl_4 was added, dropwise and with stirring, 8.0 g (50 mmol) of Br_2. The resulting red solution was washed successively with H_2O, aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and aqueous NaCl and then dried and concentrated. Recrystallization of the residual orange solid from hexane separated 5.67 g (71%) of the crude ketone **16b** as orange plates melting within the range 103.6–107 °C. Recrystallization from hexane afforded the pure ketone **16b** as white prisms: mp 107.1–107.9 °C; IR (CCl_4) 1738 cm^{-1} (C=O); UV max (95% EtOH) 219 nm (ϵ 20 800), 263 (9400), and 344 (3300); NMR (CCl_4) δ 7.2–7.4 (3 H, m, aryl CH), 4.18 (2 H, s, benzylic CH_2), and 3.91 (3 H, s, OCH_3); mass spectrum *m/e* (rel intensity) 322 (M^+, 43), 320 (M^+, 86), 318 (M^+, 44), 242 (21), 241 (76), 240 (30), 239 (71), 161 (38), 160 (100), 132 (24), 89 (25), and 63 (20).

Anal. Calcd for $C_{10}H_8Br_2O_2$: C, 37.53; H, 2.52; Br, 49.95. Found: C, 37.56; H, 2.52; Br, 49.92.

Preparation of the Ketal 15b. A solution of 14.86 g (61.6 mmol) of the ketone **14b**, 3.82 g (61.5 mmol) of $HOCH_2CH_2OH$, and 20 mg of *p*-TsOH in 100 mL of PhH was refluxed for 3 days with continuous separation of H_2O; additional 2.0-g (32.2 mmol) quantities of $HOCH_2CH_2OH$ were added after 24 and 48 h. The resulting mixture was partitioned between PhH and aqueous $NaHCO_3$ and the organic layer was washed with H_2O and with aqueous NaCl and then dried and concentrated. The crude solid product (16.47 g) was recrystallized from hexane to separate 3.67 g (21%) of fractions of the ketal **15b** as tan prisms melting in the range 81.7–85 °C as well as 2.25 g of less pure product, mp 70.3–73.2 °C. A portion of this material was sublimed under reduced pressure to separate the pure ketal **15b** as a colorless solid: mp 83.2–83.7 °C; IR (CCl_4) 1282 and 1215 cm^{-1} (ketal C–O) with no absorption attributable to a C=O function; UV max (95% EtOH) 216 nm (shoulder, ϵ 9700), 285 (3000), and 292 (2700); NMR ($CDCl_3$) δ 6.7–7.3 (3 H, m, aryl CH), 4.53 (1 H, t, J = 7 Hz, CHBr), 4.1–4.4 (4 H, m, CH_2O), 3.78 (3 H, s, OCH_3), and 3.0–3.4 (2 H, m, benzylic CH_2); mass spectrum *m/e* (rel intensity) 286 (M^+, 6), 284 (M^+, 6), 206 (14), 205 (100), and 161 (25).

Anal. Calcd for $C_{12}H_{13}BrO_3$: C, 50.55; H, 4.60; Br, 28.02. Found: C, 50.58, H, 4.62; Br, 28.10.

Preparation of the Ketal 17b.[7] Bromine was added, dropwise and with stirring, to a solution (at 26 °C) of 1.37 g (4.8 mmol) of the ketal **15b** in 25 mL of Et_2O containing a catalytic amount of anhydrous HBr, until a red color persisted in the solution. The resulting red solution was stirred for 5 min with an aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ and then the colorless ethereal phase was washed with aqueous $NaHCO_3$ and aqueous NaCl, dried, and concentrated. The residual solid ketal **17b** (1.50 g or 86%, mp 131–136 °C) was recrystallized from hexane to separate 1.33 g (76%) of fractions melting within the range 130.1–138.8 °C. An additional recrystallization afforded the pure ketal **17b** as colorless prisms: mp 137.4–139.1 °C; IR (CCl_4) 1285 and 1220 cm^{-1} (ketal C–O); UV max (95% EtOH) 217 nm (shoulder, ϵ 10 700), 285 (3000), and 292 (2800); NMR ($CDCl_3$) δ 6.7–7.3 (3 H, m, aryl CH), 4.2–4.7 (4 H, m, CH_2O), 3.87 (2 H, s, benzylic CH_2), and 3.80 (3 H, s, OCH_3); mass spectrum *m/e* (rel intensity) 366 (M^+, 25), 364 (M^+, 48), 362 (M^+, 27), 285 (96), 283 (100), 178 (41), 160 (70), 148 (53), 120 (36), 89 (48), 63 (45), and 51 (32).

Anal. Calcd for $C_{12}H_{12}Br_2O_3$: C, 39.59; H, 3.32; Br, 43.90. Found: C, 39.54; H, 3.33; Br, 44.06.

An attempt to prepare the dibromo ketal **17b** by reaction of the dibromo ketone **16b** with $HOCH_2CH_2OH$ resulted in recovery of 97% of the starting ketone **16b**.

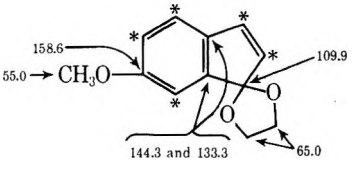
Preparation of the Unsaturated Ketal 19b. A slurry of 22.52 g (62 mmol) of the ketal **17b** in 100 g of *t*-BuOH was treated, portionwise and with stirring during 3 min, with *t*-BuOK, from 3.93 g (0.10 g-atom) of K and 78.6 g of *t*-BuOH. After the mixture had been stirred at 25–30 °C for 4 h, it was partitioned between H_2O and Et_2O. After the ethereal solution had been washed with aqueous NaCl and dried, concentration left 17.28 g (98.7%) of the crude ketal **19b** as a cream-colored solid, mp 91–93.7 °C. Recrystallization gave the pure ketal **19b** as a colorless powder: mp 93–93.9 °C; IR (CCl_4) 1605 (C=C), 1288, and 1211 cm^{-1} (ketal C–O); UV max (95% EtOH) 227 nm (ϵ 24 500), 287 (9300), 297 (8000), and 328 (3000); NMR ($CDCl_3$) δ 6.5–7.1 (4 H, m, vinyl and aryl CH), 4.1–4.5 (4 H, m, CH_2O), and 3.74 (3 H, s, OCH_3); mass spectrum *m/e* (rel intensity) 284 (M^+, 32), 282 (M^+, 32), 203 (100), 175 (21), 147 (48), 119 (26), and 116 (20).

Anal. Calcd for $C_{12}H_{11}BrO_3$: C, 50.91; H, 3.92; Br, 28.22. Found: C, 50.82; H, 3.96; Br, 28.31.

In a larger scale preparation, 40.54 g (0.25 mol) of the ketone **7b** was brominated in Et_2O and crude bromo ketone **14b** (56.98 g of yellow solid) was converted to the ketal **15b**. The crude ketal **15b** was brominated and the crude dibromo ketal **17b** (91.5 g, contains ca. 5% of the dibromo ketone **16b**) was treated with 0.358 mol of KOBu-*t* in *t*-BuOH. Application of the previously described isolation procedure afforded 56.8 g of the crude ketal **19b** as a tan solid. Recrystallization from hexane separated 44.75 g (63% based on the ketone **7b**) of the pure ketal **19b**, mp 90.7–93.8 °C, accompanied by 11.19 g (15%) of fractions containing less pure ketal **19b** (melting within the range 80–91 °C) that were also suitable for conversion to the ester **21d**.

Preparation of the Unsaturated Ketal 18b. A mixture of 5.70 g (20 mmol) of the bromo ketal **15b**, 28 mmol of KOBu-*t*, and 30 mL of *t*-BuOH was stirred at 25 °C for 18 h and then partitioned between H_2O and Et_2O. The ethereal layer was washed with aqueous NaCl, dried over Na_2SO_4, concentrated, and distilled to separate 3.64 g (89%) of the ketal **18b** as a colorless liquid: bp 110–115 °C (0.2 mm); n^{25}_D 1.5751–1.5753; IR (CCl_4) 1609 cm^{-1} (C=C); UV max (95% EtOH) 221 nm (ϵ 21 700), 280 (7200), 287 (shoulder, 6300), and 317 (1700); ^1H NMR (CCl_4) δ 6.5–7.0 (3 H, m, aryl CH), 6.47 (1 H, d, J = 6 Hz, vinyl CH), 5.93 (1 H, d, J = 6 Hz, vinyl CH), 3.8–4.2 (4 H, m, CH_2O), and 3.64 (3 H, s, OCH_3); mass spectrum *m/e* (rel intensity) 204 (M^+, 27), 148 (46), 120 (40), 58 (95), 43 (100), and 42 (22). The ^{13}C NMR spectrum of the product ($CDCl_3$ solution) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.

(*132.3, 132.1, 121.4, 113.6, and 112.6 ppm)



Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.66; H, 5.94.

The ketal **18b** was also obtained by reaction of 2.83 g (10 mmol) of the bromo ketal **19b** in 80 mL of Me_2O (at −30 °C) with 6.8 mL of a hexane solution containing 11 mmol of *n*-BuLi. After the solution had been stirred at −30 °C for 10 min, it was poured into a mixture of 100 mL of Et_2O and 30 mL of MeOH. After the reaction mixture had been partitioned between H_2O and Et_2O, the ethereal layer was dried, concentrated, and distilled to separate 1.65 g (81%) of the ketal **18b**, bp 115–120 °C (0.1 mm), $n^{25}D$ 1.5768, that was identified with the previously described sample by comparison of NMR and IR spectra.

Preparation of the Ketal Acid 21c. To a solution of 14.16 g (50 mmol) of the bromide **19b** in 400 mL of cold (−30 °C) Me_2O (bp −24 °C) was added, dropwise and with stirring during 5 min, 31.0 mL of a hexane solution containing 50.2 mmol of *n*-BuLi. After the resulting cold solution had been stirred for 10 min it was poured onto dry ice. The resulting mixture was partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O layer was washed with aqueous NaCl, dried, and concentrated to leave a pale yellow liquid with NMR absorption indicating it to be the crude ketal **18b**. The aqueous $NaHCO_3$ solution was cautiously acidified with cold aqueous HCl and extracted with Et_2O. The ethereal extract was washed with aqueous NaCl, dried, and concentrated, to leave 8.77 g (71%) of the acid **21c** as a white solid, mp 191–193 °C dec. Recrystallization from a $CHCl_3$–hexane mixture separated the acid **21c**, mp 195–198 °C dec. A subsequent recrystallization sharpened the decomposition point of the acid **21c** to mp 197–198 °C dec; IR ($CHCl_3$), 2950 (broad, associated OH), 1680 (carboxyl C=O), and 1608 cm^{-1} (C=C); UV max (95% EtOH) 237 nm (ε 17 000), 306 (7200), 315 (8400), and 341 (10 000); NMR (CD_3COCD_3) δ 7.57 (1 H, s, vinyl CH), 6.7–7.4 (3 H, m, aryl CH), 4.1–4.6 (4 H, m, CH_2O), and 3.84 (3 H, s, OCH_3); mass spectrum *m/e* (rel intensity) 248 (M^+, 61), 203 (34), 188 (24), 187 (100), 164 (38), 147 (23), 63 (20), and 44 (40).

Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.61; H, 4.81.

Preparation of the Unsaturated Ester 21d. The ketal acid **21c** (2.48 g, 10.0 mmol) was added, portionwise and with stirring during 10 min, to 300 mL of an Et_2O solution containing 11.7 mmol of CH_2N_2. The resulting solution was concentrated and the residual orange solid (2.708 g) was recrystallized from hexane to separate 1.998 g (76%) of the crude ester **21d**, mp 110–114 °C. Recrystallization afforded the pure ester **21d** as yellow prisms: mp 114.8–115.3 °C; IR (CCl_4) 1718 (conjugated ester C=O) and 1610 cm^{-1} (conjugated C=C); UV max (95% EtOH) 240 nm (ε 15 600), 303 (shoulder, 6100), 314 (7800), and 343 (10 400); NMR ($CDCl_3$) δ 7.46 (1 H, d, J = 0.9 Hz, vinyl CH), 6.6–7.3 (3 H, m, aryl CH), 4.0–4.7 (4 H, m, CH_2O), 3.77 (3 H, s, OCH_3), and 3.75 (3 H, s, OCH_3); mass spectrum *m/e* (rel intensity) 262 (M^+, 42), 203 (24), 187 (100), and 163 (24).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.20; H, 5.42.

Reaction of the Ketal Ester 21b with Butadiene. A. Neutral Conditions. A solution of 470 mg (2.02 mmol) of the ester **21b** in 1.71 g (31.6 mmol) of butadiene was heated to 125 °C for 55 h in a sealed tube and then cooled and concentrated. Distillation of the residual yellow, viscous liquid in a short-path still at 0.12 mm pressure separated 450 mg (78%) of the adduct **25** as a colorless, viscous liquid: $n^{25}D$ 1.5531; IR (CCl_4) 1735 (ester C=O) and 1662 cm^{-1} (weak, C=C); UV (95% EtOH) a series of weak maxima (ε 335–748) in the region 237–272 nm with an additional maximum at 306 nm (ε 399); NMR ($CDCl_3$) δ 7.0–7.4 (4 H, m, aryl CH), 5.3–6.0 (2 H, m, vinyl CH), 3.8–4.4 (5 H, m, CH_2O and benzylic CH), 3.70 (3 H, s, OCH_3), and 1.7–3.1 (4 H, m, allylic CH_2); mass spectrum *m/e* (rel intensity) 286 (M^+, 64), 227 (41), 183 (48), 182 (39), 181 (70), 165 (100), 162 (36), 157 (32), 155 (43), 153 (57), 152 (56), 141 (42), 128 (36), 115 (50), 105 (29), 104 (30), 77 (60), 76 (52), 51 (41), 45 (36), 43 (34), 41 (61), and 39 (40).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.32; H, 6.37.

In a preliminary experiment in which a solution of the ester **21b** in excess butadiene was heated to 80 °C for 28 h, the crude product contained (GLC, silicone SE-30 on Chromosorb P) a mixture of the starting ester **21b** (82% of the mixture, retention time 26.2 min) and the adduct **25** (18% of the mixture, 69.2 min).

B. Acidic Conditions. A series of small-scale reactions were run in which various mixtures of the ester **21b**, butadiene, H_2O, CH_3SO_3H, and either PhH or DME as a cosolvent were heated in sealed tubes, and then cooled, mixed with $PhCH_2CH_2Ph$ as an internal standard, and analyzed by GLC (silicone SE-30 on Chromosorb P, apparatus calibrated with known mixtures of authentic samples). The retention times of the various components follow: $PhCH_2CH_2Ph$, 3.5 min; ketone **24a**, 5.6 min; ester **21b**, 8.7 min; ketone **27**, 10.4 min; and ketal **25**, 18.3 min. In the presence of 1 molar equiv of H_2O and ca. 0.3 molar equiv of CH_3SO_3H, a reaction period of 24–28 h at 80 °C was sufficient to convert practically all of the starting ester **21b** to the ketone adduct **27** containing only small amounts of the previously described ketal **25** and the known[3a] ketone **24a** (from hydrolysis and decarboxylation of keto ester **27**). A collected (GLC) sample of the ketone **24a** was identified with the previously described[3a] material by comparison of IR spectra and from the mass spectrum of the material: *m/e* (rel intensity) 184 (M^+, 100), 169 (30), 165 (38), 155 (33), 141 (41), 130 (91), 128 (55), 115 (80), 102 (87), 78 (33), 77 (64), 76 (60), 75 (36), 63 (52), 51 (80), 50 (54), 41 (34), 40 (40), and 39 (88).

In a larger scale experiment, a solution of 1.11 g (20.5 mmol) of butadiene, 465 mg (2.0 mmol) of the ester **21b**, 0.035 mL (ca. 0.5 mmol) of CH_3SO_3H, and 0.035 mL (1.9 mmol) of H_2O in 1.5 mL of DME was heated to 80 °C for 31 h in a sealed tube and then cooled and concentrated. Distillation of the pale orange residue in a short-path still under reduced pressure separated 313 mg of colorless liquid distillate that contained (GLC) 93% of the keto ester **27** (60% yield), 5% of the ketone **24a**, and 2% of the ketal **25**. This material was chromatographed on silica gel with an Et_2O–hexane eluent to separate 208 mg (43%) of fractions of colorless liquid, $n^{25}D$ 1.5667, that contained (GLC) the pure keto ester **27**: IR (CCl_4) 1745 (ester C=O) and 1718 cm^{-1} (C=O); UV max (95% EtOH) 248 nm (ε 11 600), 292 (shoulder, 2160), and 296 (2210); NMR ($CDCl_3$) δ 7.2–7.9 (4 H, m, aryl CH), 5.6–6.0 (2 H, m, vinyl CH), 3.8–4.2 (1 H, m, benzylic CH), 3.65 (3 H, s, OCH_3), and 2.3–2.8 (4 H, m, allylic CH_2); mass spectrum *m/e* (rel intensity) 242 (M^+, 36), 183 (74), 182 (83), 181 (100), 165 (76), 156 (36), 155 (31), 154 (32), 153 (46), 152 (47), 128 (34), 115 (39), 77 (60), 76 (41), 75 (33), 63 (36), 51 (58), and 39 (52).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.18; H, 5.84.

Reaction of the Ketal Ester 21d with Butadiene. A solution of 4.16 g (15.9 mmol) of the ketal ester **21d** in 9.32 g (72 mmol) of cold (−5 °C) liquefied butadiene was heated to 130 °C in a sealed tube for 48 h. The reaction mixture was distilled in a short-path still at 0.8 mm pressure to separate 3.78 g (75%) of the adduct **28** as a viscous, pale yellow liquid, $n^{25}D$ 1.5538, that solidified on standing, mp 70.6–72.7 °C. Recrystallization from pentane afforded the pure ketal **28** as colorless crystals: mp 75.8–77 °C; IR (CCl_4) 1735 (ester C=O) and 1662 cm^{-1} (weak C=C); UV max (95% EtOH) 218 nm (shoulder, ε 7700), 225 (shoulder, 7200), 283 (2400), and 289 (shoulder, 2200); NMR (CCl_4) δ 6.6–7.1 (3 H, m, aryl CH), 5.4–5.7 (2 H, m, vinyl CH), 3.8–4.3 (5 H, m, CH_2O and benzylic CH), 3.75 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3) and 2.0–2.9 (4 H, m, allylic CH_2); mass spectrum *m/e* (rel intensity) 316 (M^+, 88), 257 (45), 254 (71), 213 (58), 212 (42), 211 (100), 195 (65), 187 (55), 163 (58), 141 (42), 115 (53), 77 (45), and 45 (48).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.19; H, 6.42.

A solution of 328 mg (1.00 mmol) of the ketal **28** and 7 mL of aqueous 5 M HCl in 14 mL of THF and 4 mL of MeOH was stirred at 26 °C for 24 h and then partitioned between H_2O and Et_2O. The organic phase was dried and concentrated to leave 331 mg of crude liquid product containing (NMR analysis) ca. 75% of the keto ester **29** and ca. 25% of the starting ketal **28**. Separation on a preparative TLC plate (coated with silica gel and eluted with Et_2O–hexane, 1:6 v/v) afforded 64 mg of the starting ketal **28**, 5 mg of the subsequently described ketone **31**, and 200 mg of the keto ester **29** that solidified on standing, mp 70–71.5 °C. Recrystallization from hexane afforded 143 mg (51%) of the pure keto ester **29** as colorless prisms: mp 73.6–74.9 °C; IR (CCl_4) 1742 (ester C=O), 1712 (C=O), and 1620 cm^{-1} (C=C); UV max (95% EtOH) 218 nm (ε 27 200), 250 (9800), and 323 (3900); NMR (CCl_4) δ 7.0–7.6 (3 H, m, aryl CH), 5.5–6.0 (2 H, m, vinyl CH), 3.7–4.1 (4 H, m, benzylic CH and a CH_3O singlet at 3.78), 3.58 (3 H, s, OCH_3), and 2.3–2.7 (4 H, m, allylic CH_2); mass spectrum *m/e* (rel intensity) 272 (M^+, 37), 254 (24), 213 (62), 212 (100), 211 (38), 195 (36), 187 (68), 141 (27), and 44 (38).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.51; H, 5.92.

Reaction of the Ketal 18b with Butadiene. After a solution of 4.28 g (21 mmol) of the ketal **18b** in 1.86 g (34.4 mmol) of cold (−5 °C), liquefied butadiene had been heated to 130 °C in a sealed tube for 72 h, the crude product was extracted with several portions of boiling $CHCl_3$. The extract was concentrated and distilled under reduced pressure in a short-path still to separate 4.205 g (78%) of the crude adduct **30** as a pale yellow liquid, $n^{25}D$ 1.5677, that darkened on standing: IR (CCl_4) 1660 and 1615 cm^{-1} (C=C); UV max (95% EtOH) 218 nm (ε 8800), 282 (2650), and 289 (2350); NMR (CCl_4) δ 6.6–7.2 (3 H, m, aryl CH), 5.5–5.8 (2 H, m, vinyl CH), 3.8–4.2 (4 H, m, CH_2O), 3.67 (3 H, s, OCH_3), and 1.8–3.4 (6 H, m, aliphatic CH); mass spectrum

m/e (rel intensity) 258 (M^+, 85), 214 (39), 213 (41), 205 (100), 204 (66), 196 (68), 161 (52), 160 (82), 149 (53), 148 (96), 77 (45), and 63 (43).

A solution of 1.30 g (5.0 mmol) of the crude ketal **30** and 12 mL of aqueous 6 M HCl in 28 mL of THF was stirred at 26 °C for 24 h and then partitioned between Et_2O and H_2O. After the organic extract had been washed with aqueous $NaHCO_3$, dried, and concentrated, the residual liquid was distilled (ca. 130 °C at 0.2 mm) in a short-path still to separate 913 mg (85%) of the crude ketone **31**, $n^{25}D$ 1.5825. The product contained (GLC, Apiezon M on Chromosorb P) mainly the ketone **31** (retention time 16.9 min) accompanied by several minor, unidentified impurities (2.6, 8.7, and 22.9 min). The ketone **31** was collected (GLC) as a yellow liquid that solidified on standing, mp 37–38.1 °C. Recrystallization from pentane afforded the pure ketone **31** as colorless prisms: mp 41–42.1 °C; IR (CCl_4) 1720, 1710 (C=O), and 1618 cm^{-1} (C=C); UV max (95% EtOH) 219 nm (ϵ 26 300), 249 (8400), and 322 (3500); NMR (CCl_4) δ 7.0–7.5 (3 H, m, aryl CH), 5.6–6.0 (2 H, m, vinyl CH), 3.77 (3 H, s, OCH_3), 3.3–3.7 (1 H, m, benzylic CH), and 1.8–3.0 (5 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 214 (M^+, 39), 161 (12), 160 (100), 145 (15), and 51 (14).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.38; H, 6.59.

To estimate the relative rates of reaction of the methoxyindenes **18b** and **21d** with butadiene, 0.92–0.98-mmol samples of these indenes were dissolved in 7.76-g (143 mmol) portions of cold (−5 °C) liquid butadiene and heated to 130 °C in sealed tubes for 8.5 or 12 h. After the tubes had been cooled and opened the crude product was dissolved in $CHCl_3$, concentrated, and extracted with several portions of boiling EtOH to separate the reactants **18b** and **21d** and products **28** and **30** from polymeric butadiene that was insoluble in EtOH. The EtOH extracts were diluted with EtOH to a known volume and subjected to UV analysis to measure the proportions of **18b** to **30** (using UV absorption at 317 nm) or **21d** to **28** (using UV absorption at 343 nm). After a reaction period of 8.5 h, the amounts of unchanged indenes remaining were 62% of **18b** and 40% of **21d**; after 12 h, the values were 40% of **18b** and 23% of **21d**. Consequently, we estimate that indene ester **21d** reacts with butadiene at 130 °C about twice as fast as the indene **18b**.

Registry No.—**7a**, 83-33-0; **7b**, 13623-25-1; **8a**, 1929-29-9; **8b**, 15893-42-2; **11**, 6768-23-6; **12**, 6335-37-1; **13**, 6099-04-3; **14a**, 1775-27-5; **14b**, 62015-79-6; **15a**, 58521-74-7; **15b**, 62015-80-9; **16a**, 7749-02-2; **16b**, 62015-81-0; **17a**, 62015-78-5; **17b**, 62046-07-5; **18a**, 6710-43-6; **18b**, 62015-82-1; **19a**, 62015-83-2; **19b**, 62015-84-3; **21a**, 62015-85-4; **21b**, 62015-86-5; **21c**, 62015-87-6; **21d**, 62015-88-7; **24a**, 62015-89-8; **25**, 62015-90-1; **27**, 62015-91-2; **28**, 62015-92-3; **29**, 62015-93-4; **30**, 62015-94-5; **31**, 62015-95-6; anisaldehyde, 123-11-5; malonic acid, 141-82-2; hydrocinnamic acid, 501-52-0; 1,2-ethanediol, 107-21-1; butadiene, 106-99-0.

References and Notes

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(9) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
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Thermal Decomposition of Bifunctional Peroxides[1]

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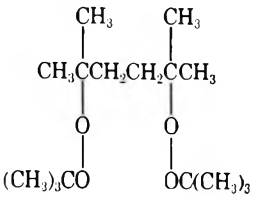
Quantitative determination of the products resulting from the thermal decomposition of 2,5-dimethyl-2,5-bis(*tert*-butylperoxy)hexane (**1**) in *m*-xylene and 2-octanol indicates extensive fragmentation of the 2,5-dimethylhexane moiety of **1**. A mechanism is proposed to account for the observed amounts of these fragmentation products in these solvents and the extent of self-induced decomposition of **1**. In contrast to **1**, 2,5-dimethyl-2,5-bis(*tert*-butylperoxy)-3-hexyne (**2**) undergoes thermal decomposition in *m*-xylene and in 2-butanol with no detectable amounts of fragmentation of the 2,5-dimethyl-3-hexyne moiety.

The bifunctional peroxide 2,5-dimethyl-2,5-bis(*tert*-butylperoxy)hexane (**1**)[2] is used as an initiator for free radical polymerizations and, presumably owing to its bifunctional character, for crosslinking of polyethylene and other polymers. Its value in this latter capacity depends at least in part on the ability of the two peroxide functionalities to react independently of each other when **1** undergoes thermal decomposition. Our investigations of the decomposition products of **1** in *m*-



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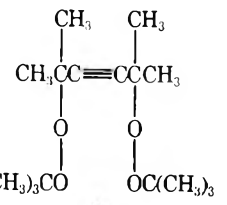

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Table I. Decomposition Products of 1 in *m*-Xylene at 125 °C

	Time[a]				
	205	530	840	1500	2940
1 consumed[b]	0.50	0.82	1.00	1.12	1.21
Products					
Acetone	0.54	0.99	1.31	1.90	2.00
tert-Butyl alcohol	0.46	0.80	1.07	1.54	1.64
tert-Amyl alcohol	0.04	0.08	0.15	0.71	0.82
tert-Amyl-*tert*-butyl peroxide (8)	0.28	0.37	0.31	0.15	0.00
2,5-Dimethyl-2-hydroxy-5-(*tert*-butylperoxy)hexane (5)	0.12	0.22	0.18	0.04	0.00
2,5-Dimethyl-2,5-dihydroxyhexane (11)	0.00	0.07	0.12	0.25	0.28

[a] Minutes. [b] Amounts in millimoles.

Table II. Product Distribution for Decomposition of 1 in *m*-Xylene at 125 °C

	Run 1	Run 2
Initial amount of 1[a]	12.76	12.60
Amount of 1 reacted	4.17	5.38
Products		
Acetone	4.21	6.13
tert-Butyl alcohol	3.66	5.24
tert-Amyl alcohol	0.32	0.49
tert-Amyl-*tert*-butyl peroxide (8)	2.30	2.70
Methane	1.05	1.62
Ethylene	0.10	0.16
Ethane	0.31	0.61
2,5-Dimethyl-2-hydroxy-5-*tert*-butylperoxyhexane (5)	0.98	1.09

[a] Amounts in millimoles.

xylene and in 2-octanol indicate that while there is extensive unimolecular fragmentation of the 2,5-dimethylhexane moiety of 1 there is little self-induced decomposition of one peroxide moiety by the other. Decomposition of 2,5-dimethyl-2,5-bis(*tert*-butylperoxy)-3-hexyne (2) in similar solvents yields radicals less prone to unimolecular fragmentation.

Results and Discussion

The nongaseous products resulting from the decomposition of 1 at 125 °C in *m*-xylene are listed in Table I. The presence of these products and the qualitative identification of methane, ethane, and ethylene as the gaseous decomposition products led to the proposed decomposition path for 1 shown in reaction Scheme I (RH = *m*-xylene, R· = 3-methylbenzyl). Support for this reaction scheme is found in the observed stoichiometric relationships among the decomposition products of 1. Table II lists both the gaseous and nongaseous decomposition products found after 1 has been allowed to undergo partial decomposition in *m*-xylene at 125 °C. The amount of 1 that has reacted in each run should equal the sum of the amounts of 2,5-dimethyl-2-hydroxy-5-(*tert*-butylperoxy)hexane (5), *tert*-amyl-*tert*-butyl peroxide (8), *tert*-amyl alcohol, ethane, and ethylene produced in the reaction (4.01 and 5.05 mmol for runs 1 and 2, respectively). Also, the amounts of acetone formed should equal the sum of the amounts of methane, 2 × ethane, 2 × ethylene, 8, and *tert*-

Scheme I

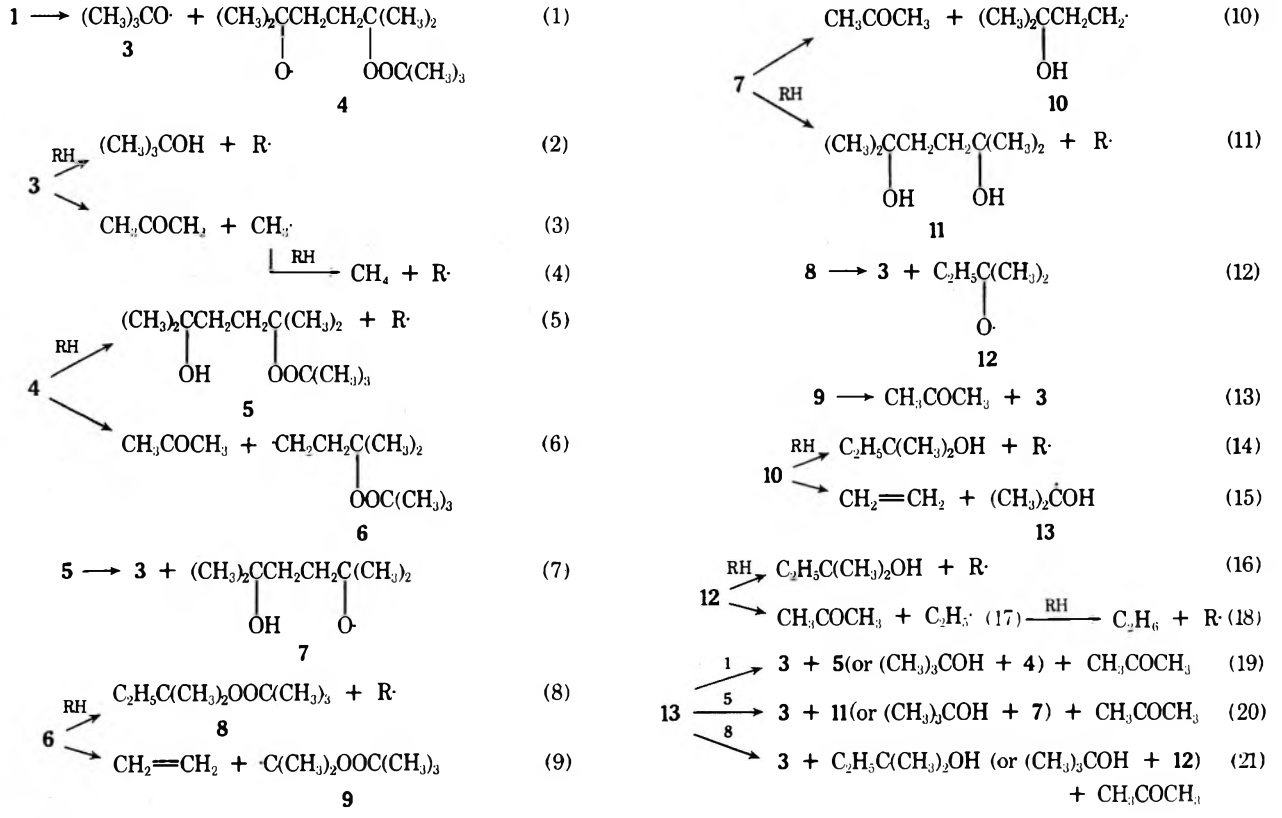


Table III. Product Distribution for Decomposition of 1 in 2-Octanol

	Run 3	Run 4
Initial amount of 1	10.48	12.65
Amount of 1 reacted	4.67	6.95
Products		
Acetone	5.09	9.05
tert-Butyl alcohol	4.74	8.07
tert-Amyl alcohol	0.71	1.59
8	1.61	2.31
Methane	1.44	2.18
Ethylene	0.16	0.20
Ethane	0.69	1.52
5	1.46	1.24
2-Octanone (14)	6.34	10.42

amyl alcohol (4.49 and 6.35 mmol for runs 1 and 2, respectively). A further relationship is that the sum of the amounts of *tert*-butoxyl-derived products, namely, *tert*-butyl alcohol, methane, 5, and 8 (7.99 mmol for run 1 and 10.65 mmol for run 2) should equal twice the amount of 1 that has reacted (8.34 and 10.76 mmol for runs 1 and 2, respectively). The agreement between these predicted and observed stoichiometric relationships is well within the experimental reliabilities of the gas chromatographic techniques employed for the quantitative determinations and support the unimolecular decomposition path for 1 outlined in reaction Scheme I.

The appearance of each of these products with the exception of acetone and ethylene results from hydrogen abstraction from the *m*-xylene by the radical precursor of the decomposition product (reactions 2, 4, 5, 8, 11, 14, 16, and 18), yielding in each case the 3-methylbenzyl radical (R·) along with the observed decomposition product. The 3-methylbenzyl radicals likely couple

$$2R\cdot \rightarrow R_2 \qquad (22)$$

and do not interact in any significant manner with either 1 or its decomposition products. This is not the case when 1 is allowed to decompose in 2-octanol (RH = n-$C_6H_{13}CHOHCH_3$). The hydrogen atom abstraction from 2-octanol yields an α-hydroxyalkyl radical (R· = n-$C_6H_{13}\dot{C}OHCH_3$), a species that reacts with the dialkyl peroxide functionalities as shown in reactions 23–25 in reaction Scheme II. That induced decom-

Scheme II

(RH = n-$C_6H_{13}CHOHCH_3$ and R· = n-$C_6H_{13}\dot{C}OHCH_3$)

(all reactions of Scheme I)

and

$$R\cdot + 1 \longrightarrow \underset{14}{n\text{-}C_6H_{13}\overset{O}{\overset{\|}{C}}CH_3} + 3\,(\text{or } 4) + 5\,(\text{or } (CH_3)_3COH) \qquad (23)$$

$$R\cdot + 5 \longrightarrow 14 + 11\,(\text{or } CH_3)_3COH) + 3\,(\text{or } 7) \qquad (24)$$

$$R\cdot + 8 \longrightarrow 14 + 3\,(\text{or } 12) + \underset{OH}{(CH_3)_2\overset{|}{C}C_2H_5}\ (\text{or } (CH_3)_3COH) \qquad (25)$$

positions of the dialkyl peroxide functionalities do occur is supported by the observation that the half-life of 1 at 125 °C in 2-octanol at 125 °C is about 90 min, in contrast to a half-life of about 300 min in toluene at 125 °C. The involvement of the α-hydroxyalkyl radical is also evidenced by the formation of 2-octanone as a reaction product. Not only should the stoichiometric relationships observed in the decompositions of

Table IV. Products of the Decomposition of 2 in *m*-Xylene and 2-Butanol

	m-Xylene (62.6 mmol)	2-Butanol (65.1 mmol)
Initial amount of 2	13.83	13.10
Amount of 2 reacted	5.33	9.48
Products		
Acetone	0.99	2.70
tert-Butyl alcohol	6.05	14.31
Methane	0.99	2.74
16	2.97	1.60
18	2.09	7.76
2-Butanone		17.56

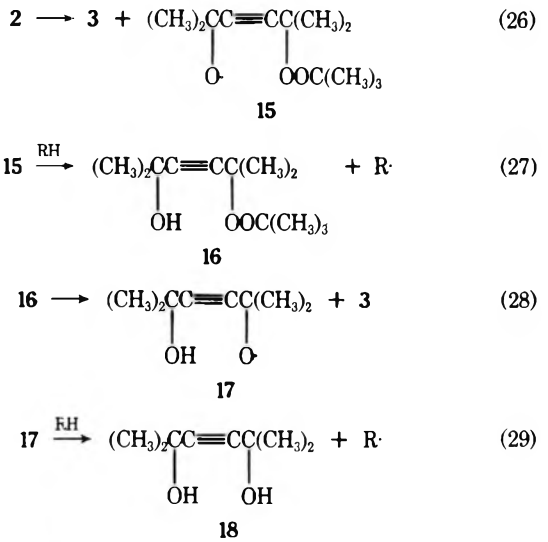
1 in *m*-xylene be observed in the decompositions of 1 in 2-octanol, but the amount of 2-octanone produced should be dependent on the extent of reduction of the peroxidic functionalities available (Table III). The amount of 1 that has reacted should equal the sum of the amounts of 5, 8, *tert*-amyl alcohol, ethane, and ethylene formed (4.63 and 6.86 mmol for runs 1 and 2, respectively). The calculated amounts of acetone formed should equal the sum of the amounts of methane, 2 × ethane, 2 × ethylene, *tert*-amyl alcohol, and 8 produced (5.46 and 9.52 mmol for runs 3 and 4, respectively); the calculated *tert*-butoxyl moieties involved in reaction based on the amounts of 1 that have reacted (9.34 mmol for run 3 and 13.9 mmol for run 4) correspond with the amounts of *tert*-butyl alcohol, methane, 5, and 8 found as reaction products (9.25 mmol for run 3 and 13.8 mmol for run 4). The amount of 2-octanone produced should equal the sum of 2 × 1 that has reacted minus the amounts of 5, 8, and ethylene found as reaction products (6.11 and 10.15 mmol for runs 3 and 4, respectively). Again, the agreement between the predicted and observed stoichiometric relationships is within the experimental reliability expected for the number of quantitative gas chromatographic determinations involved.

In marked contrast to the thermal decompositions of 1, the thermolysis of 2 in *m*-xylene shows no evidence of fragmentation of the main carbon skeleton of the molecule, namely the 2,5-dimethyl-3-hexyne moiety (Table IV). The amounts of methane, acetone, *tert*-butyl alcohol, 2,5-dimethyl-2-hydroxy-5-(*tert*-butylperoxy)-3-hexyne (16) and 2,5-dimethyl-2,5-dihydroxy-3-hexyne (18) found in the decomposition in both *m*-xylene and 2-butanol correspond to the stoichiometry expected on the basis of reaction Scheme III, namely, methane and acetone are formed in equal amounts, the sum of acetone, *tert*-butyl alcohol, and 16 equal 2 × 2 that has reacted and the sum of 16 and 18 equal the amount of 2 that has reacted. Furthermore, the amount of 2-butanone, the oxidation product of the secondary alcohol, corresponds to the extent of reduction of the available peroxide functionality.

The reactions outlined in Schemes I, II, and III are, for the most part, not unexpected for either the radical intermediates and the substrates available for reaction with these radicals. The fragmentation reactions of the alkoxyl radicals (reactions 3, 6, 10, and 17) follow the expected course in that the most stable radical is eliminated.[3] The interactions of the α-hydroxyalkyl radicals with dialkyl peroxide functions (reactions 19, 20, 21, 23, 24, 25, 30, and 31) are also known to occur with concurrent oxidation of the α-hydroxyalkyl radical to the corresponding carbonyl-containing compound.[4] Fragmentations similar to that encountered in the reaction of the α-(alkylperoxy)alkyl radical (reaction 13) have been proposed as chain propagating reactions in the self-induced decompositions of primary and secondary alkyl peroxides.[5]

The β-elimination of either the α-(alkylperoxy)alkyl radical 9 from radical 6 (reaction 9) or the α-hydroxyalkyl radical 13

Scheme III



If RH = *m*-xylene,

$$2R\cdot \longrightarrow R_2 \quad (22)$$

If RH = $C_2H_5CHOHCH_3$ and R· = $C_2H_5COHCH_3$,

$$R\cdot + 2 \longrightarrow C_2H_5COCH_3 + 16 + 3\,(\text{or } 15 + (CH_3)_3COH) \quad (30)$$

$$R\cdot + 16 \longrightarrow C_2H_5COCH_3 + 18 + 3\,(\text{or } 17 + (CH_3)_3COH) \quad (31)$$

from radical **10** (reaction 15) are the only sources of ethylene in the decompositions of **1**. The radicals formed along with ethylene in reactions 9 and 15, namely the 2-(*tert*-butylperoxy)propyl radical **9** and the 2-hydroxypropyl radical **13**, respectively, are the only radicals derived from **1** capable of effecting the induced decomposition of a peroxide functionality (reactions 13, 19, 20, and 21). The induced decomposition of a peroxide function by reaction 13 is an intramolecular route for the self-induced decomposition of **1**, whereas the reactions of radical **13** would be an intermolecular route for self-induced decomposition. The contributions of each route might possibly be ascertained by kinetic analysis of the rate of ethylene formation (the intramolecular route would be independent of the concentration of **1**, whereas the intermolecular route could show a kinetic order of 1 greater than unity).[6] The extent of the self-induced decomposition in both *m*-xylene and 2-octanol, however, was too small (~3%) to allow for such kinetic analysis.

Experimental Section

2,5-Dimethyl-2,5-bis(*tert*-butylperoxy)hexane (**1**) and 2,5-dimethyl-2,5-bis(*tert*-butylperoxy)-3-hexyne (**2**) were obtained from the Lucidol Division of Pennwalt Corp. The materials were redistilled [bp of **1** 87–90 °C (30 mm) and bp of **2** 81–83 °C (30 mm)] and gave a single peak on gas chromatographic analysis. An authentic sample of *tert*-amyl-*tert*-butyl peroxide [bp 40 °C (40 mm)] was prepared by interaction of *tert*-amyl alcohol and *tert*-butyl hydroperoxide (Lucidol) in the presence of sulfuric acid. Authentic samples of 2,5-dimethyl-2,5-dihydroxyhexane (**11**) and 2,5-dimethyl-2,5-dihydroxy-3-hexyne (**18**) were obtained from Aldrich. *m*-Xylene (Matheson, Coleman and Bell), 2-octanol (Fisher Scientific), and 2-butanol (Baker Analyzed) were distilled before using. All other liquid reagents used for gas chromatographic retention time comparisons were reagent grade materials, and, when necessary, redistilled until gas chromatographic analysis showed a single peak. The gaseous compounds were commercial materials (Matheson) and used without further purification.

Qualitative Identification of Decomposition Products of 1 and 2. All liquid and gaseous products with the exception of 2,5-dimethyl-2-hydroxy-5-(*tert*-butylperoxy)hexane (**5**) and 2,5-dimethyl-2-hydroxy-5-(*tert*-butylperoxy)-3-hexyne (**16**) were identified by comparison of their gas chromatographic retention time on two or more different columns with those of authentic samples. Attempts to prepare authentic samples of **5** and **16** by the acid-catalyzed reaction of *tert*-butyl hydroperoxide in excess of the corresponding diols **11** and **18**, respectively, led only to formation of the diperoxides **1** and **2**. The assignment of the structures **5** and **16** to the gas chromatographic peaks used to calculate the amounts of these materials as decomposition products **1** and **2**, respectively, was based on the facts that the retention times were between those of the diperoxide and the diol in each case and, as in the case of *tert*-amyl-*tert*-butyl peroxide, the peak areas decreased with time.

Quantitative Determinations. A reaction mixture consisting of the diperoxide in the appropriate solvent in a 1:5 molar ratio was heated in a 250-mL flask equipped with an efficient condenser by immersing the flask in an oil bath set at 125 °C. The gases evolved were collected in a gas buret that was connected to the end of the condenser. The composition of the gaseous products was determined by gas chromatographic analysis of a sample of the gas on a 6-ft column packed with Poropak Q. The amounts of diperoxides **1** and **2**, the hydroxymonoperoxides **5** and **16**,[7] and the diols **11** and **18** were determined by gas chromatographic analysis using a 5-ft column packed with DC-200 on Chromosorb W of a sample of the reaction mixture using dodecane as an internal standard. The amounts of 2-octanone formed in the reactions of **1** in 2-octanol were determined by gas chromatographic analysis of a sample of the reaction mixture on a 10-ft column packed with polyethyleneglycol succinate on Chromosorb W using isoamyl acetate as an internal standard. All other products were determined by gas chromatographic analysis on a 10-ft column packed with 10% dodecyl phthalate on Chromosorb W using either isoamyl acetate or ethyl propionate as the internal standards.

Kinetic Measurements. The rates of the decompositions of **1** and **2** were determined in toluene and in 2-octanol by the following general procedure: A master solution of the solvent and the peroxide in a molar ratio of approximately 10:1 was divided into seven 9-mm Pyrex tubes which were cooled to −80 °C and sealed. The tubes were warmed to room temperature and then immersed in a 125 °C oil bath. Tubes were removed periodically and the peroxide remaining determined by gas chromatographic analysis of a weighed portion of the reaction mixture with a weighed amount of dodecane, which served as the internal standard. The first-order rate constants for the decompositions of **1** and **2** in toluene were 2.41×10^{-3} ($t_{1/2}$ = 288 min) and 1.19×10^{-3} min^{-1} ($t_{1/2}$ = 583 min), respectively. The pseudo-first-order rate constants for the induced decompositions[4] of **1** and **2** in 2-octanol were 7.67×10^{-3} ($t_{1/2}$ = 90.3 min) and 2.73×10^{-3} min^{-1} ($t_{1/2}$ = 254 min), respectively.

Registry No.—**1**, 78-63-7; **2**, 1068-27-5.

References and Notes

(1) This work was supported in part by a Grant (GM AM18191) from the Department of Health, Education, and Welfare.

(2) The difunctional peroxides **1** and **2** are commercially available materials. The samples used in this work were supplied to us by the Lucidol Division of Pennwalt Corp. and the receipt of these materials is gratefully acknowledged.

(3) G. A. Schmidt and G. S. Fisher, *J. Am. Chem. Soc.*, **76**, 5426 (1954); F. D. Chattaway and O. G. Backeberg, *J. Chem. Soc.*, **123**, 2999 (1923); J. W. Wilt and J. W. Hill, *J. Org. Chem.*, **26**, 3523 (1961); T. L. Cairns and B. E. Englund, *ibid.*, **21**, 140 (1956); F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *ibid.*, **28**, 55 (1963).

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(7) Since authentic samples of the hydroxymonoperoxides **5** and **16** were not available, the correction factor required to relate their gas chromatographic peak areas and that of the internal standard to the amounts of **5** and **16** in the reaction mixtures were assumed in each case to be intermediate between those of the diperoxides **1** and **2** and the diols **11** and **18**, respectively.

Synthesis and Spectral Properties of Ethylmethylsulfonium 3,4-Dihydro-1,4-dioxo-3-(phenylimino)-2(1*H*)-naphthylenylide

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Sulfonium ylides are stabilized when the negative charge is delocalized by electron-withdrawing groups such as carbonyl,[1] cyano,[2,3] sulfonyl,[4] or an aromatic system.[5] It was of interest to determine the ability of the phenylimino (C_6H_5N=) group to delocalize the negative charge. The 3-ethylmethylsulfonium ylide **3** of 2-anilino-1,4-naphthoquinone was synthesized as a representative compound for this study.[6]

2-Anilino-3-(methylthio)-1,4-naphthoquinone[7] (**1**) was allowed to react with triethyloxonium tetrafluoroborate in anhydrous dichloromethane to give 85% of (3-anilino-1,4-dioxo-2-naphthyl)ethylmethylsulfonium tetrafluoroborate (**2**) as red crystals: λ_{max} (MeOH) 228, 268, 428 nm (ϵ 25 100, 23 800, 4100); λ_{max} (0.1 N HCl) 221, 260, 268 sh, 293 sh, 340, 420 nm (ϵ 19 300, 20 500, 18 900, 10 700, 3800, 3300); λ_{max} (0.1 N NaOH) 271, 438 nm (ϵ 23 800, 3300).

When a solution of the sulfonium tetrafluoroborate **2** in tetrahydrofuran was stirred with an aqueous solution of sodium bicarbonate, the initial red color changed to black. Dilution with water gave 77% of the stable ylide ethylmethylsulfonium 3,4-dihydro-1,4-dioxo-3-(phenylimino)-2-(1*H*)-naphthylenylide (**3**) as purple-black, monoclinic crystals:[8] λ_{max} (MeOH) 229, 269, 428 nm (ϵ 26 000, 24 900, 4530); λ_{max} (0.1 N HCl) 222, 260, 267 sh, 290 sh, 340, 415 nm (ϵ 20 200, 21 600, 20 200, 12 400, 4690, 4360); λ_{max} (0.1 N NaOH) 270, 437 nm (ϵ 23 900, 3270).

It is seen from the above that the electronic spectra of **2** and **3** are virtually identical, indicating that they produce the same chromophoric system in the same solvent. The spectra in methanol and in dilute alkali are superimposable if one corrects for solvent effect and absorption by carbonate in the alkali.

As was observed with diethylsulfonium 1,3-dihydro-1,3-dioxo-2*H*-inden-2-ylide[1] (**4**), the ^{1}H NMR spectrum (Figure 1) of sulfonium ylide **3** (in Me_2SO-d_6) exhibits magnetic nonequivalence of methylene protons. The ambient (32 °C) spectrum (Figures 1 and 2) displays the methyl protons of the ethylmethylsulfonium moiety as a somewhat broadened singlet at δ 3.15 and the methyl protons of the ethyl moiety appear as a rather broad triplet at δ 1.26 (J = 7.4 Hz). The methylene group of the ethyl moiety appears as two nonequivalent protons at δ 3.45 and 3.98. These protons form the AB portion of an ABX_3 spectrum (J_{AB} = 12 Hz, J_{AX} = J_{BX} = 7.4 Hz). The double quartet at δ 3.98 shows noticeable broadening due to what is presumed to be steric hindrance from the adjacent *N*-phenyl group. When the solution of **3** is heated to 60 °C [Figure 2 (b)] all peaks from the ethylmethylsulfonium moiety sharpen and the signals from the methylene protons, which now appear as a pair of double quartets similar to that reported for the methylene protons of **4**,[1] approach each other in chemical shift. Upon further heating to 80 °C the methylene resonance lines sharpen further and come closer together in chemical shift. The progressive shift towards each other ($\Delta\delta$ 0.52 at 32 °C to $\Delta\delta$ 0.45 at 100 °C) suggests that an extremely high temperature would be needed for coalescence. Decomposition was noted when the temperature was elevated to 190 °C (boiling solution) and no further information could be obtained.

The low-field region of the ^{1}H NMR spectrum of ylide **3**

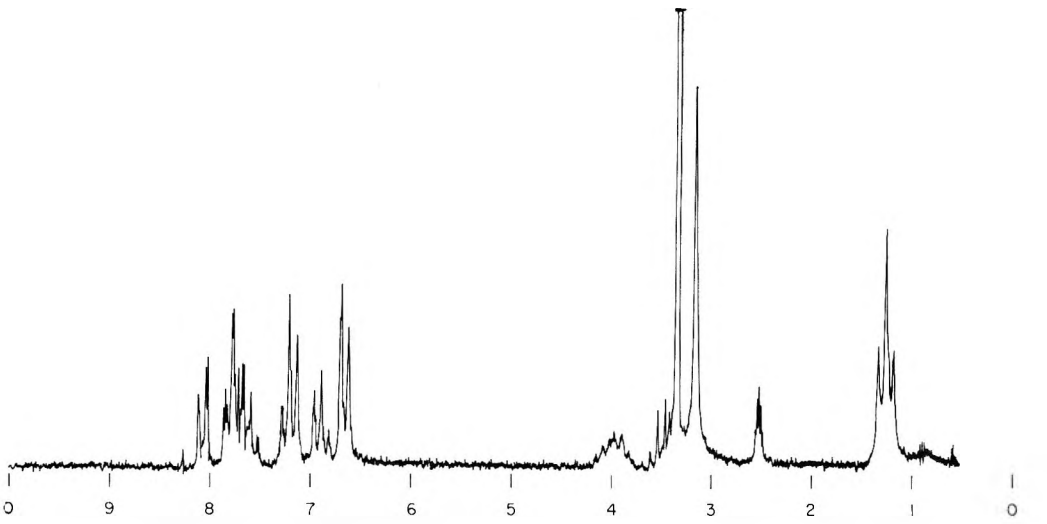

Figure 1. ^{1}H NMR spectrum (100 MHz) of ethylmethylsulfonium 3,4-dihydro-1,4-dioxo-3-(phenylimino)-2(1*H*)-naphthylenylide (**3**) in Me_2SO-d_6.

(Figure 1) shows distinct patterns for the two aromatic moieties. The *N*-phenyl protons appear as an A_2B_2C pattern which is typical for monosubstituted phenyl compounds substituted by a strong electron-donating group. A first-order analysis of the spectrum gives ortho protons at δ 6.66 (dd, J = 2 Hz, 8.5 Hz), meta protons at δ 7.19 (dd, J = 8.5, 8.5 Hz), and para proton at δ 6.90 (dt, J = 2, 8.5 Hz). The aromatic protons of the naphthoquinone moiety appear as a complex ABCD system. Here again a first-order analysis indicates protons at δ 7.61 (m, C_6 H), 7.70 (m, C_7 H), 7.80 (dd, J = 2, 8.5 Hz, C_5 H), and 8.07 (dd, J = 2, 8.5 Hz, C_8 H). The upfield shift of C_5 H($\Delta\delta$ 0.27) vs. C_8 H suggests that in solution there is less double bond character to the C_4 carbonyl than the C_1 carbonyl, in agreement with the negative charge of the ylide being partially delocalized by the C_4 carbonyl.

The ^{1}H NMR signal (δ 3.15) of the SCH_3 of ylide **3** is downfield from that (δ 3.05) of the SCH_3 of sulfonium salt **2**, and has the same chemical shift as the SCH_3 in ethylmethylsulfonium 3,4-dihydro-1,3,4-trioxo-2(1*H*)-naphthylenylide (**7**). It is evident that the negative charge of **3** is delocalized in degree similar to that of **7**. The phenylimino group, therefore, appears to behave like the carbonyl group in delocalizing the negative charge of a sulfonium ylide.

Ylide **7** was prepared by alkylating 2-hydroxy-3-(methylthio)-1,4-naphthoquinone (**6**) with ethyl iodide. Methylthio derivative **6** was obtained by pyridinium perchlorate demethylation[9] of dimethylsulfonium 3,4-dihydro-1,3,4-trioxo-2(1*H*)-naphthylenylide[10] (**5**).

The x-ray crystal structure of ylide **3** has been determined by Lovell and Cosulich.[11] The observed bond lengths and angles suggest that the four resonance forms depicted by a, b, c, and d are important and that the negative charge is delocalized through the bonds C(2)–N, C(2)–(3), C(3)–C(4), C(4)–O(4), and C(3)–S (Figure 3).

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Samples for analysis were dried in vacuo over P_2O_5 at 100 °C for 18–24 h. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). NMR spectra were determined on Varian A-60 and HA-100 spectrometers with tetramethylsilane as internal standard.

(3-Anilino-1,4-dihydro-1,4-dioxo-2-naphthyl)ethylmethylsulfonium Tetrafluoroborate (2). To a stirred solution of 5.90 g (0.02 mol) of 2-anilino-3-(methylthio)-1,4-naphthoquinone[7] (**1**) in 150 mL of dichloromethane was added a solution of 17.9 g (0.094 mol) of triethyloxonium tetrafluoroborate in 100 mL of dichloromethane. The solution was stirred at room temperature for 22 h and then evaporated in vacuo to give a red, crystalline residue. Recrystallization from methanol afforded 7.01 g (85%) of **2** as red crystals: mp 210–212 °C; ν_{max} (KBr) 1672, 3310 cm^{-1}.

Anal. Calcd for $C_{19}H_{18}NO_2SBF_4$: C, 55.5; H, 4.41; N, 3.41; S, 7.80; F, 18.5. Found: C, 55.4; H, 4.35; N, 3.33; S, 8.15; F, 18.3.

Ethylmethylsulfonium 3,4-Dihydro-1,4-dioxo-3-(phenylimino)-2(1*H*)-naphthylenylide (3). To a stirred solution of 5.00 g (0.012 mol) of **2** in 100 mL of tetrahydrofuran was added 25 mL of saturated aqueous $NaHCO_3$. The resulting mixture was stirred for 3 days at room temperature and then diluted further with water. The resulting suspension was chilled and filtered to give 3.10 g of **3** as purple-black crystals,[8] mp 183–185 °C, ν_{max} (KBr) 1688 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.6; H, 5.30; N, 4.33; S, 9.92. Found: C, 70.4; H, 5.53; N, 4.24; S, 9.94.

2-Hydroxy-3-(methylthio)-1,4-naphthoquinone (6). A mixture of 2.34 g (0.01 mol) of **5**,[10] 1.43 mL of 70–72% $HClO_4$, and 25 mL of pyridine was heated under reflux for 2 h and allowed to stand at room temperature overnight. The dark reddish-black solution was evaporated in vacuo to a reddish-black crystalline residue. The residue was extracted with four 35-mL portions of boiling ether and the combined ether extracts were evaporated in vacuo to give 1.80 g of red crystals, mp 116–119 °C. Recrystallization from ethyl acetate–petroleum ether (bp 30–60 °C) gave 1.46 g (66%) of **6** as blood-red needles: mp 127–129 °C; λ_{max} (0.1 N HCl) 243, 274, 339, 445 nm (ϵ 14 400, 20 400, 3520, 1540); λ_{max} (MeOH) 242, 274, 330, 460 nm (ϵ 15 400, 22 600, 3040, 2220); λ_{max} (0.1 NaOH) 280, 480 nm (ϵ 24 200, 2200); ν_{max} (KBr) 3320 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.62 (s, 3, SCH_3), 7.59–7.86 (m, 3, C_6 H,C_7 H.OH), 7.95–8.18 (m, 2, C_5 H,C_8 H).

Anal. Calcd for $C_{11}H_8O_3S$: C, 60.0; H, 3.66; S, 14.6. Found: C, 59.9; H, 3.61; S, 14.3.

Ethylmethylsulfonium 3,4-Dihydro-1,3,4-trioxo-2(1*H*)-naphthylenylide (7). A mixture of 6.80 g (0.031 mol) of **6**, 19.3 g (0.124 mol) of ethyl iodide, 4.40 g (0.034 mol) of diisopropylethylamine, and 100 mL of absolute ethanol was heated under reflux for 4.5 h. The dark-colored solution was evaporated in vacuo until crystallization occurred. The mixture was chilled and filtered and the yellow crystals were washed with absolute ethanol and absolute ethanol–ether (1:1) to give 8.11 g of yellow crystals, mp 130–145 °C. Two recrystallizations from absolute ethanol gave 4.72 g (61%) of **7** as yellow crystals: mp 181.5–184 °C; λ_{max} (0.1 N HCl) 225, 268, 326, 390 nm (ϵ 20 800, 25 300, 2730, 1980); λ_{max} (MeOH) 225, 271, 325, 383 nm (ϵ 21 100, 25 300, 2480, 1980); λ_{max} (0.1 N NaOH) 268, 287 (sh), 322, 383 nm (ϵ 23 300, 13 300, 2980, 1980); ν_{max} (KBr) 1695 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1 23 (t, 3, CH_2CH_3), 3.15 (s, 3, SCH_3), 3.16–4.17 (4 distinct quartets, 2, CH_2CH_3), 7.65–8.20 (m, 4, Ar).

Anal. Calcd for $C_{13}H_{12}O_3S$: C, 62.9; H, 4.87; S, 12.9. Found: C, 62.5; H, 4.82; S, 13.0.

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Registry No.—**1**, 61770-44-3; **2**, 61770-46-5; **3**, 61770-47-6; **5**,

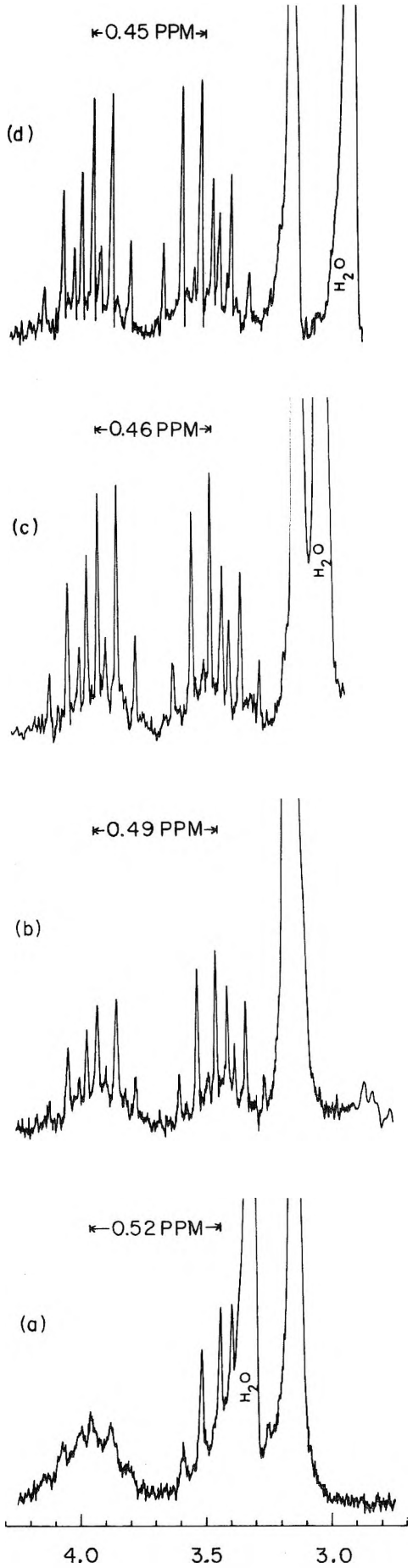

Figure 2. ^{1}H NMR spectra (100 MHz) of ethylmethylsulfonium 3,4-dihydro-1,4-dioxo-3-(phenylimino)-2(1*H*)-naphthylenylide (**3**) in Me_2SO-d_6 at various temperatures: (a) 32 °C, (b) 60 °C, (c) 80 °C, (d) 100 °C.

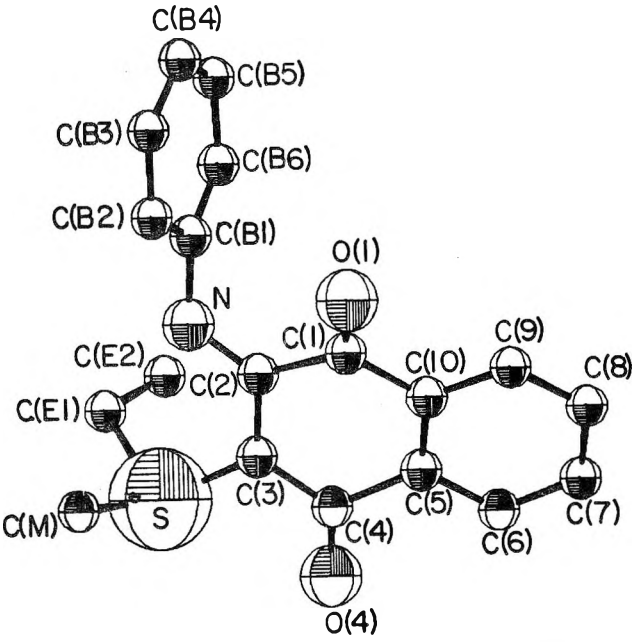

Figure 3. A perspective representation of the structure of ethylmethylsulfonium 3,4-dihydro-1,4-dioxo-3-(phenylimino)-2(1*H*)-naphthylenylide (**3**).

31914-13-3; **6**, 31914-17-7; **7**, 57893-97-7; triethyloxonium tetrafluoroborate, 368-39-8.

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Lithium Triethylborohydride Reduction of Alkyl Methanesulfonate Esters[1,2]

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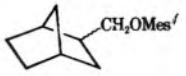
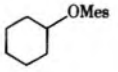
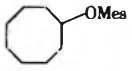
In the course of preparing some hydrocarbons for another study we required an efficient procedure for the transformation $>C{=}O \rightarrow >CH_2$ for cases in which the carbonyl group is in a sterically hindered neopentyl environment. A number of techniques are available for this reduction,[4] but after trying several of these with uncertain or unsatisfactory results, we decided to test lithium triethylborohydride ($LiEt_3BH$, or Super Hydride) on alkyl methanesulfonate esters (mesylates). This reagent is a powerful hydride donor toward alkyl halides,[9] and we reasoned that it might behave in an analogous fashion toward alkyl mesylates. Further, these esters are usually stable, easily handled compounds, and are ordinarily acces-

Table I. Reduction of Alkyl Methanesulfonates (ROMes) with Lithium Triethylborohydride[a]

Registry no.	Compd	Time, h[b]	Temp, °C	Product[c]	Yield, %[d]
16156-51-7	n-$C_7H_{15}OMes$	0.5	25	n-Heptane	90
16427-42-2	$(CH_3)_3C—CH_2OMes$	3.0	60	Neopentane	69[e]
62078-83-5	$CH_3(CH_2)_4CHOMes$ (CH$_3$)	0.5	25	n-Heptane	92
62078-84-6		4.0	60		96[f]
16156-56-2		4.0	60		68
					12
62078-85-7		24.0	25		93[g]
28627-77-2		4.0	75[h]		65
62107-93-1	$(PhCH_2CH_2)_2CHOMes$	6.0	25	$(PhCH_2CH_2)_2CH_2$	99

[a] The reactions, except where noted, were conducted in THF at either room temperature (25 °C) or reflux (60 °C) using a 2.1-fold excess of $LiEt_3BH$. [b] Not necessarily minimum times. [c] Except where noted no alkenes or alcohols were detected. All products are known compounds and in each case isolated samples had spectral properties corresponding to literature descriptions. [d] Except where noted these are VPC yields, utilizing an internal standard and corrected for detector response. [e] Yield calculated by measuring gas volume. [f] Mixture of endo and exo isomers. [g] Trace of cyclooctene noted. [h] Reaction run in benzene solution.

sible by two high-yield steps (>C=O → >CHOH → >CHO-SO_2CH_3). Finally, the desired reductive displacement does occur with the less powerful lithium aluminum hydride,[4,10] albeit in poor yields for sterically hindered cases.[11]

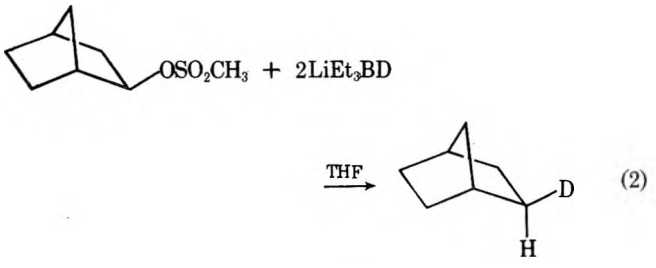
Treatment of the mesylates of the alcohols recorded in Table I with 2.1 equiv of $LiEt_3BH$ as a 1 M solution in tetrahydrofuran (THF) rapidly produced the corresponding alkanes in high yields (eq 1). An extra 1 equiv of the hydride

$$\begin{matrix} R' \\ | \\ R—CHOSO_2CH_3 \end{matrix} + 2LiEt_3BH \xrightarrow{THF} \begin{matrix} R' \\ | \\ R—CH_2 \end{matrix} + Et_6B_2H^-Li^+ + CH_3SO_3^-Li^+ \quad (1)$$

reagent proved necessary, evidently because initially formed triethylboron itself reacts readily to form a relatively unreactive complex of stoichiometry $Et_6B_2H^-$.[12]

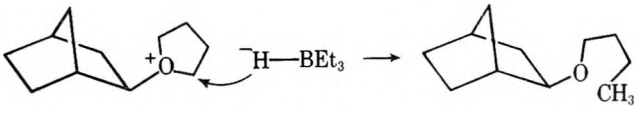
Rough kinetic studies in several cases established the enhanced reactivity of $LiEt_3BH$ relative to $LiAlH_4$. For example, for n-heptyl mesylate after 0.5 h at 25 °C the reaction was 90% complete with $LiEt_3BH$ but only 59% complete with $LiAlH_4$.

Although the attack of $LiEt_3BH$ on alkyl bromides was demonstrated to occur with configurational inversion, implicating an S_N2 mechanism for the displacement,[9] treatment of the mesylate of *exo*-2-norborneol with $LiEt_3BD$ (eq 2),



followed by NMR analysis of the VPC-purified norbornane,[16] showed essentially complete retention of configuration (95 ± 5% exo-2-D). Presumably the enhanced leaving group ability of the methanesulfonate anion relative to bromide[17] results in a transformation of the mechanism to S_N1 for this easily ionizable substrate.[18] A further indication of a possible S_N1 component in secondary systems is that the mesylates of both 1-heptanol and 2-heptanol react at comparable rates (Table I).

The intervention of the 2-norbornyl carbonium ion in eq 2 is also supported by the formation of 35% *exo*-2-*n*-butoxynorbornane when the reaction is run in THF. This unusual product could come from attack on a THF molecule involved in solvation, as shown below:



Lithium triethylborohydride cleaves epoxides easily,[19] and lithium tri-*tert*-butoxyaluminohydride in the presence of triethylboron rapidly opens the THF ring at 25 °C.[20] No analogous ethers were formed in any of our other experiments, however, and no formation of 1-butanol could be detected.

In any case, when the reaction was run in about 95:5 benzene–THF[21] to minimize ether formation the yield of norbornane was raised from 21% to 65%. Carrying out the experiment of eq 2 in benzene resulted in isolation of norbornane that contained 60 ± 5% exo-2-D. Thus the S_N1 component is less important in the less ionizing medium.

After submission of our preliminary results we became aware of the independently conceived and executed work of Krishnamurthy and Brown who have developed the reduction of alkyl *p*-toluenesulfonate esters (tosylates) with $LiEt_3BH$.[23,24] Our work presented in this note therefore corroborates and extends their recently published results. Although our preoccupation with the development of the reaction has kept us from applying it to the original synthetic targets, the combination of our results with those of Krishnamurthy and Brown make it clear that $LiEt_3BH$ reduction of both the mesylates and tosylates of a wide variety of ali-

phatic alcohols is a procedure of sufficient utility and generality to be added to those previously available for the reduction of carbonyl groups to methylene groups.

Experimental Section

Materials. $LiEt_3BH$ and $LiEt_3BD$ were purchased as 1 M solutions in THF from Aldrich Chemical Co. Reactant alcohols were either commercially available or prepared by unexceptional procedures. The mesylates were made by a standard literature method;[25] in all cases IR and NMR established the absence of reactant alcohol after the esterification.

General Procedure for Reductions. To a dry, N_2-flushed, round-bottom flask equipped with reflux condenser, magnetic stir bar, and rubber stopple was introduced by syringe x mmol of mesylate and x mL of dry THF. With stirring, $2.1x$ mL of a 1 M $LiEt_3BH$ solution in THF was added in one portion by syringe. The resulting reaction was stirred under N_2 for the time period and at the temperature recorded in Table I for each mesylate. A useful signal of reaction progress was found to be formation of lithium methanesulfonate, which precipitated.

After the reduction period, the vessel was cooled in an ice bath and excess hydride quenched by dropwise addition of water. The organoboranes were oxidized by adding $0.7x$ mL of 3 N NaOH, followed by the slow, dropwise addition of $0.7x$ mL of 30% H_2O_2. The ice bath was removed and the reaction mixture refluxed for 1 h. VPC analyses were measured from the THF layer of the cooled product mixture.[26]

Isolation of products was accomplished by pouring the reaction mixture into $10x$ mL of water, extraction with pentane, washing to remove dissolved THF, drying ($MgSO_4$), and concentration to the crude product by flash distillation. Final purification for structural studies was accomplished using standard preparative VPC techniques.

Acknowledgment. We are grateful to Dr. R. E. Williams and Professors H. C. Brown, R. O. Hutchins, and R. T. Paine for helpful suggestions.

Registry No.—Heptane, 142-82-5; neopentane, 463-82-1; *exo*-2-methylnorbornane, 872-78-6; *endo*-2-methylnorbornane, 765-90-2; cyclohexane, 110-82-7; cyclohexene, 110-83-8; cyclooctane, 292-64-8; norbornane, 279-23-2; 1,5-diphenylpentane, 1718-50-9.

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(2) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, and the University of New Mexico Research Allocations Committee for the support of this research.
(3) American Chemical Society Petroleum Research Fund Undergraduate Scholar, 1975–1976.
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The Basicity of Enones. Substituent Effects and the Correlation of Protonation with H_A

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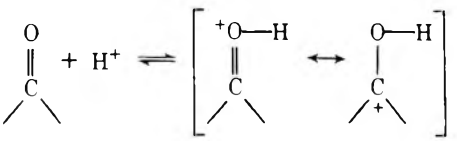
The basicity of carbonyl compounds is of considerable interest since most acid-catalyzed reactions proceed via a preequilibrium protonation of the carbonyl group, followed by some sort of nucleophilic attack.

Scheme I



Arnett has recently reported thermodynamic pK_as for 52 protonated carbonyl compounds, based on heats of ionization in fluorosulfonic acid.[1] Of particular interest to a kinetic study we carried out[2] are the basicities of α,β-unsaturated ketones. These compounds as a class are much more basic than other ketones by 3–5 pK_a units.[1] There have been several recent reports of basicity studies on a series of alicyclic α,β-unsaturated ketones.[3,4] However, the only reported pK_a value for a protonated noncyclic α,β-unsaturated ketone is 2.4 for 4-methyl-3-penten-2-one.[1,5] We wish to report pK_as for several α,β-unsaturated ketones demonstrating a sizable substituent effect on pK_a.

Acidity Dependence. Table I presents pK_a values measured in aqueous $HClO_4$ and H_2SO_4 solutions. Plots of log $[BH^+]/[B]$ vs. $-H_A$ gave straight lines of slope 1.0 for 3-methyl-3-penten-2-one and 4-methyl-3-penten-2-one; thus protonation of acyclic α,β-unsaturated ketones follows the acidity function based on amide protonation (H_A)[9] at least through 75% (12 M) H_2SO_4 and 65% (10.5 M) $HClO_4$. This result is consistent with previous studies on cyclopentenones and cyclohexenones.[4]

It is striking that protonation of 3-alkenones follows H_A so closely throughout such a broad range of acidity. This requires that the f_B/f_{BH^+} ratio for the protonation of amides and

Table I. pK_a Values for Protonated 3-Alkenones[a]

Compd	Acid	Method	pK_a
3-Buten-2-one	H_2SO_4	*b*	−4.8
3-Methyl-3-buten-2-one	H_2SO_4	*b*	−4.6
3-Penten-2-one	H_2SO_4	*b*	−3.8
	$HClO_4$	*b*	−3.4
3-Methyl-3-penten-2-one	H_2SO_4	*b*	−3.7
	H_2SO_4	*c*	−3.5
4-Methyl-3-penten-2-one	$HClO_4$	*b*	−2.9
	$HClO_4$	*c*	−2.9
	$HClO_4$	*d*	−2.6

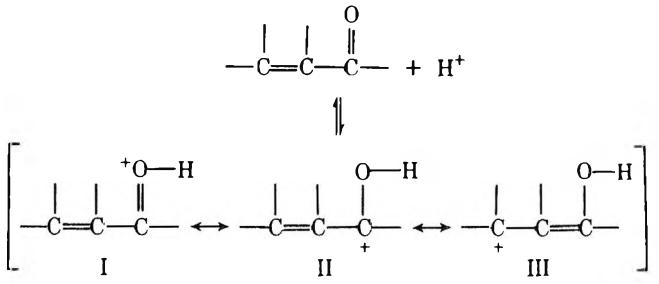
[a] Measured using a standard spectrophotometric method.[7] [b] pK_a was taken as the inflection point on the sigmoidal λ_{max} vs. $-H_A$ plot. [c] pK_a was taken as the point in the log $[BH^+]/[B]$ vs. $-H_A$ line where log $[BH^+]/[B] = 0$. The slope of the line was 1.0. [d] pK_a was calculated by the Bunnett–Olson method.[8]

Table II. Selected Values of H_A, H_E, H_B, and H_0 in H_2SO_4

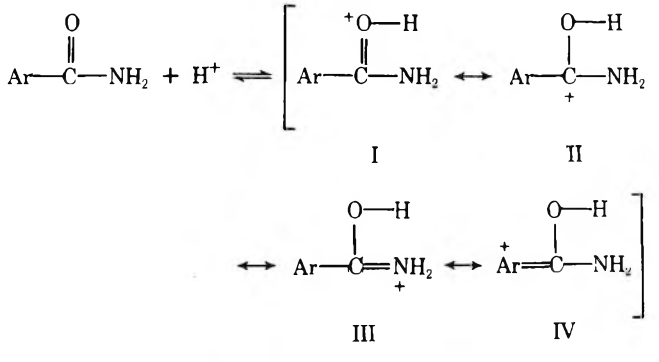
% H_2SO_4	$-H_A$[a]	$-H_E$[b]	$-H_B$[c]	$-H_0$[d]
40	2.00		2.44	2.41
50	2.51		3.49	3.38
60	3.07	2.2	4.46	4.46
70	3.77	2.8	5.38	5.80
80	4.59	3.5	6.35	7.34

[a] Reference 9. The amide protonation scale is anchored by the overlap method to 4-nitroaniline. [b] Reference 11. The ester protonation scale is based on the protonation of ethyl acetate. pK_{BH^+} for ethyl acetate was taken as −3.45 (obtained via Bunnett–Olson calculation). [c] Reference 10. The benzophenone protonation scale is anchored by the overlap method to H_0 scale[16] below 60% H_2SO_4. [d] Reference 12. Primary aniline protonation scale.

Scheme II



Scheme III



$$-H_A = \log a_{H^+} f_B / f_{BH^+}$$

α,β-unsaturated ketones be similarly affected by changes in medium (changes in solvation). This is a rather surprising result, since it would appear that protonation of 3-alkenones is more similar to protonation of benzophenones (H_B)[10] than to amide (H_A)[9] or ester (H_E)[11] protonation. Table II compiles values of these acidity functions over the range of 40–80% H_2SO_4; clearly $d(-H_A)/d(\%\ H_2SO_4) \simeq d(-H_E)/d(\%\ H_2SO_4) < d(-H_B)/d(\%\ H_2SO_4) < d(-H_0)/d(\%\ H_2SO_4)$. Thus it is certain that protonation of α,β-unsaturated ketones follows H_A and perhaps H_E, but not H_B or H_0.

It is interesting to note that the main difference between the H_A and H_E functions is the value at a given acidity *rather* than a difference in medium dependence. For example, if H_E had been anchored to the H_A scale at 60% H_2SO_4, $H_E = 4.4$ in 80% H_2SO_4 compared with $H_A = 4.6$ [i.e., $d(H_E)/d(\%\ H_2SO_4) = 0.9\ d(H_A)/d(\%\ H_2SO_4)$]. It is also interesting that Bunnett–Olson calculations for 3-alkenone protonation produce a pK_a value 0.3 pK_a units less than values calculated from H_A; this difference is in the same direction as the difference between the H_A and H_E acidity scales, but it is about one-half to one-third the magnitude. Evidently (a) the H_A and H_E scales could be commonly anchored and the differences in the absolute values would diminish,[13] or (b) protonation of 3-alkenones follows an acidity function with a medium dependence equal to that of H_A but of magnitude intermediate to H_E and H_A.

A brief rationale as to why Scheme I follows H_A rather than H_B: for the more basic 3-alkenones (e.g., 4-methyl-3-penten-2-one), canonical form III of Scheme II contributes much more to the hybrid structure than is the case for the less basic 3-alkenones (e.g., 3-buten-2-one). For the more basic benzamides, canonical form IV of Scheme III contributes much more to the hybrid structure than is the case for the less basic benzamides (ones with several nitro substituents in the aryl group). The net effect for both types of compounds is an increasing importance of canonical forms I and II (Schemes II and III) as the basicity diminishes. This trend is less pronounced for the amides than for the benzophenones because of the importance of canonical form III of Scheme III (i.e., the effect of several nitro groups in Ar is less important for benzamides because IV is less important overall). Thus the shallower acidity dependence of Schemes II and III compared with H_B or H_0 is attributable to f_B/f_{BH^+} decreasing for amide, ester, and 3-alkenone carbonyl protonation relative to f_B/f_{BH^+} changes for protonation of benzophenones or primary nitroanilines. This is consistent with the greater solvation of protonated benzamides, esters, and 3-alkenones. It is tempting to ascribe the relatively similar protonation behavior of esters, benzamides, and 3-alkenones to a common importance of canonical forms I and II in Schemes II and III; however, as discussed above in comparing the H_A and H_B functions, the situation is considerably more complex.

Substituent Effects on pK_{BH^+}. Two effects are evident from the pK_a values in Table I. First, methylation β to the carbonyl of an α,β-unsaturated ketone markedly enhances the basicity (e.g., 3-buten-2-one is half protonated in 14.5 M H_2SO_4 whereas 3-penten-2-one is half protonated in 11.5 M H_2SO_4). Second, methylation α to the carbonyl of an α,β-unsaturated ketone has little or no effect on the basicity. These two observations are discussed separately below.

4-Methyl-3-penten-2-one is a remarkably basic ketone: it is about 10% protonated in 4.5 M (35%) $HClO_4$ (cf. H_B, the acidity function based on benzophenone protonation, Table II). This large β-methylation effect is ascribable to a substituent effect. Two factors must be kept in mind: First, methylation of a carbon–carbon double bond stabilizes alkenes; e.g., for several classes of alkenes, trisubstituted are more stable than disubstituted by about 1 kcal mol^{-1}, disubstituted are more stable than monosubstituted by about 2.5 kcal mol^{-1}, and monosubstituted are more stable than ethylene by about 2.5 kcal mol^{-1}.[14] Of course, conjugation of a carbonyl group

with the alkene functionality also has a stabilizing effect (by about 2.4 kcal mol^{-1})[14] and it may be that the stabilization energies cited for mono-, di-, and trisubstituted alkenes are larger than the comparable values for 3-alkenones; however, it does not seem likely that the order would change. Secondly, β-methylation will stabilize the protonated 3-alkenone, particularly by increasing the contribution of resonance structure III, Scheme II. Since *both* the 3-alkenone and protonated 3-alkenone are stabilized by β-methylation, only a *difference* in the extent of stabilization will affect pK_a. Assuming that all the pK_a differences result from such a stabilization produces a net stabilization energy of the protonated 3-alkenones over the unprotonated of 0.7 and 1.4 kcal mol^{-1} on mono- and dimethylation, respectively. That is, the protonated–unprotonated energy difference for 4-methyl-3-penten-2-one is 0.7 kcal mol^{-1} less than that for 3-penten-2-one, which is 1.4 kcal mol^{-1} less than that for 3-buten-2-one. In general, then, protonated 3-alkenones are stabilized more than half again as much as unprotonated 3-alkenones on successive β-methylations.

It is tempting to invoke large solvation effects since a_W decreases from 0.5 to 10^{-3} over the range of acidity studied;[15] however, it must be remembered that plots of log $[BH^+]/[B]$ vs. $-H_A$ were linear and of slope 1.0. This requires that medium effects (including solvation) on f_B/f_{BH^+} ratios be similar for protonation of amides and 3-alkenones. Thus the use of the acidity function method has precluded a discussion of solvation effects on pK_a values.

Finally, the effect of α-methylation is diminishingly small; but provided that the differences in Table I are real, they are in a reasonable direction. It appears that α-methylation decreases the acidity by about 0.1 pK_a unit. In view of the substituent effects discussed above and Scheme II, this 0.1 pK_a difference means that α-methylation stabilizes a 3-alkenone just slightly more than a protonated 3-alkenone. This is consistent with a significant but not predominant contribution of resonance structure III in Scheme II.

Conclusions

Protonation of acyclic α,β-unsaturated ketones in aqueous H_2SO_4 and $HClO_4$ follows the acidity function based on amide protonation, H_A, through 75% (12 M) H_2SO_4; plots of log $[BH^+]/[B]$ vs. $-H_A$ produce straight lines of slope 1.0. This behavior differs from the protonation of benzophenones (H_B) or ethyl acetate (H_E) because of the way the changing nature of the conjugate acid resonance hybrid interacts with the changing medium.

Substitution of one methyl group for a hydrogen on the β carbon of the α,β-unsaturated carbonyl system increases pK_a by 1 unit; thus the conjugate acid of 3-buten-2-one has $pK_a = -4.8$, and the conjugate acid of 3-penten-2-one has $pK_a = -3.8$. 4-Methyl-3-penten-2-one is a remarkably basic ketone, being 10% protonated in 4.5 M (35%) $HClO_4$, $pK_a = -2.9$. The stabilization energies due to successive β-methyl substitution on the conjugate acids of homologues of 3-buten-2-one are estimated to be 1.4–3.9 and 0.7–1.7 kcal mol^{-1}. β-Methylation stabilizes the protonated 3-alkenones over the unprotonated by 1.4 and 0.7 kcal mol^{-1} for 3-buten-2-one/3-penten-2-one and 3-penten-2-one/4-methyl-3-penten-2-one, respectively.

Substitution of a methyl group for a hydrogen on the α carbon of the α,β-unsaturated carbonyl system has a barely discernible base-strengthening effect (0.2 pK_a unit).

α,β-Unsaturated ketones are remarkably basic, particularly when β-substituted; protonation is adequately described by the acidity function H_A.

Experimental Section

The compounds studied were purchased from Aldrich Chemical Co. and were purified by molecular distillation just prior to use. Ultraviolet spectra were obtained using a Cary Model 14 recording spectrophotometer. The general procedures used in determining pK_{BH^+} from the change in ultraviolet spectrum with changing acid concentration were similar to those used by us in a previous study of Hammett indicators.[7] The shift in λ_{max} on protonation of B to form BH^+ was 30–40 nm. At intermediate acidities where both B and BH^+ should be present, the characteristic "double humped" curve was observed. Solutions of BH^+ generated B quantitatively upon dilution. The general eq 1 was used to calculate $[BH^+]/[B]$ whenever ϵ_B or ϵ_{BH^+} could be ignored relative to ϵ_e (cf. Table I).

$$\frac{[BH^+]}{[B]} = \frac{\epsilon_e - \epsilon_B}{\epsilon_{BH^+} - \epsilon_e} \quad (1)$$

Values in brackets are molarities, ϵ represents molar absorptivity (e.g., ϵ_e is the molar absorptivity of an equilibrium mixture of B and BH^+ of comparable concentrations), and all values of ϵ are at the same wavelength.

Acknowledgments. Financial support from the Long Beach Heart Association and the California State University Long Beach Research Foundation is gratefully acknowledged.

Registry No.—3-Buten-2-one, 78-94-4; 3-methyl-3-buten-2-one, 814-78-8; 3-penten-2-one, 625-33-2; 3-methyl-3-penten-2-one, 565-62-8; 4-methyl-3-penten-2-one, 141-79-7.

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Medium Basicity Effects on the Transition State Structure of E2 Reactions. Kinetic Study of the Reaction of 1-Chloro-1-phenyl-2-arylethanes with Crown Ether Complexed Potassium *tert*-Butoxide in *tert*-Butyl Alcohol

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Lately[1] we have kinetically investigated the elimination reaction of 2-arylethyl bromides promoted by crown ether complexed *t*-BuOK in *t*-BuOH, and obtained data concerning the effect of base association on the transition state structure of this reaction.

Among others, two main observations have been made: (1) the reaction with complexed *t*-BuOK has an order in base significantly larger than one, (2) the transition state structure

Table I. Kinetic Data for the Elimination Reactions of 1-Phenyl-1-chloro-2-arylethanes Promoted by *t*-BuOK in *t*-BuOH in the Absence and in the Presence of 18-Crown-6 Ether at 30 °C

Registry no.	Substrate[a]	[*t*-BuOK], M	[18C6], M	k_1, s^{-1}	k_2, M^{-1} s^{-1}
4714-14-1	H	0.492		1.41×10^{-4}	2.86×10^{-4}
	H	0.665		2.00×10^{-4}	3.01×10^{-4}
22692-62-2	*p*-CH_3	0.501		6.56×10^{-5}	1.31×10^{-4}
	p-CH_3	0.665		8.78×10^{-5}	1.32×10^{-4}
4714-17-4	*p*-Cl	0.492		2.58×10^{-4}	5.23×10^{-4}
	p-Cl	0.665		3.49×10^{-4}	5.25×10^{-4}
4781-42-4	*p*-NO_2	0.095		1.71×10^{-2}	1.80×10^{-1}
	p-NO_2	0.376		6.53×10^{-2}	1.74×10^{-1}
	H	0.0105	0.0210	3.77×10^{-4}	0.0359
	p-CH_3	0.0105	0.0210	1.60×10^{-4}	0.0153
	p-Cl	0.0105	0.0210	3.83×10^{-3}	0.364
	p-NO_2	0.0105	0.0210	10.66	1016
	H	0.0442	0.0895	3.41×10^{-3}	0.0771
	p-CH_3	0.0442	0.0895	1.38×10^{-3}	0.0312
	p-Cl	0.0442	0.0895	3.37×10^{-2}	0.761
	H	0.0450	0.0905	3.96×10^{-3}	0.0880
	p-CH_3	0.0450	0.0905	1.51×10^{-3}	0.0337
	p-Cl	0.0450	0.0905	3.97×10^{-2}	0.883
	H	0.105	0.210	1.44×10^{-2}	0.137
	p-CH_3	0.105	0.210	5.85×10^{-3}	0.0557
	p-Cl	0.105	0.210	0.159	1.51

[a] H refers to 1-chloro-1,2-diphenylethane.

appears almost completely unaffected by the base association, the reaction with complexed *t*-BuOK exhibiting values of ρ, deuterium kinetic isotope effect, and leaving group effect very similar to those of the corresponding reaction carried out in the absence of crown ether.

In consideration of the interest of these results it seemed useful to obtain information on their degree of generality by studying a different series of substrates. In this note we report a kinetic study of the elimination from 1-chloro-1-phenyl-2-arylethanes promoted by *t*-BuOK and 18-crown-6 ether complexed *t*-BuOK in *t*-BuOH.

Results and Discussion

The reactions were followed by determining the formed *trans*-stilbene or substituted *trans*-stilbene spectrophotometrically, either in the presence or in the absence of 18-crown-6 ether (18C6). A stopped-flow spectrophotometer was used in the case of the reaction of 1-phenyl-1-chloro-2-*p*-nitrophenylethane with complexed *t*-BuOK. In each case, the UV spectrum, at infinity time, indicated a quantitative yield of olefin.

The concentration of *t*-BuOK was in the range 0.09–0.66 M in the experiments carried out without 18C6 and in the range 0.01–0.1 M when the crown ether was present. The base concentration was always in large excess with respect to that of the substrate (ca. 10^{-5} M) and first-order plots exhibited a satisfactory linearity. First-order and second-order rate constants (k_1 and k_2, respectively) are reported in Table I.

Also with this series of substrates the reaction with complexed *t*-BuOK exhibits an apparent order in base significantly larger than one. Accordingly, the data in Table I show that the k_2 values for eliminations carried out in the presence of 18C6 significantly increase by increasing base concentration. In contrast, no significant dependence on the base concentration is shown by the k_2 values for the reaction promoted by *t*-BuOK in the absence of 18C6. The apparent order in base for the reaction with complexed *t*-BuOK is ca. 1.5, a value very similar to that (1.4) determined for the reaction of 2-arylethyl bromides.[1] Thus, the peculiar kinetic aspect of eliminations promoted by crown ether complexed *t*-BuOK is fully confirmed.[2] Completely at variance with that observed in the reaction of 2-arylethyl bromides are, instead, the results concerning the effect of base association on the transition state structure, a very significant effect being observed in the eliminations from 1-chloro-1-phenyl-2-arylethanes. Accordingly, the Hammett reaction constant, ρ, is +2.20 (r = 0.996, S = 0.15) in the reaction promoted by *t*-BuOK in *t*-BuOH, and +3.40 (r = 0.999, S = 0.13) when the base is complexed *t*-BuOK. The latter value is evaluated using kinetic data obtained at the same base concentration (0.0105 M).[3,4] Thus, in going from associated to dissociated *t*-BuOK the elimination from 1-chloro-1-phenyl-2-arylethanes, unlike that from 2-arylethyl bromides, exhibits a substantial increase in the carbanion character of the transition state. A similar result has been recently found in the syn elimination from *trans*-2-arylcyclopentyl tosylates.[5] However, we feel that a syn mechanism of elimination is highly unlikely in our reaction, especially in the presence of a crown ether.

To explain the finding that the transition state of the eliminations from 2-arylethyl bromides promoted by *t*-BuOK is not significantly influenced by the medium basicity, it was suggested that in the transition state the base (whatever its state of association) is always the same species, partially neutralized *tert*-butoxide anion.[1,6] Clearly, the present results cast a serious doubt on the general validity of this suggestion.

According to recent work[7] it seems now well established that, in E2 reactions, structural changes can influence both the parallel and perpendicular modes of vibration of the transition state. In particular, the effects of structural changes which stabilize products or reactants are mainly felt along the parallel mode of vibration of the transition state (parallel effects) and lead to a transition state more "reactant-like" or "product-like", respectively. On the other hand, effects increasing the stability of the carbanion or the carbocation, which would be formed if the reaction were stepwise, manifest itself mainly along the perpendicular mode of vibration of the transition state (perpendicular effects) and make the transition state more "carbanion-like" or more "carbocation-like", respectively. When both parallel and perpendicular effects have to be taken into account it is very difficult to determine which effect will be the dominating one and, consequently, to

predict the changes in the transition state geometry. However, it has been recently suggested that perpendicular effects should prevail for "reactant-like" or "product-like" transition states whereas parallel effects should predominate when the transition state is "carbanion-like" or "carbocation-like".[7c]

In going from associated to dissociated *t*-BuOK there is a significant increase[8] in medium basicity and this structural change should favor both the product and the carbanion.[7b] Therefore, both parallel and perpendicular effects may play a role in determining the sensitivity of the transition state structure to changes in medium basicity. On this basis, the different behaviors of the reactions of 2-arylethyl bromides and 1-chloro-1-phenyl-2-arylethanes could be tentatively explained by suggesting a more "reactant-like" transition state for the latter reaction, owing to the much larger stability of the formed olefin,[9] and, consequently, a greater importance of the perpendicular effects. Thus, an increase in the medium basicity could increase the carbanion character of the transition state in the case of the eliminations from 1-chloro-1-phenyl-2-arylethanes and have practically no effect in the case of the eliminations from 2-arylethyl bromides.

Whatever the correct explanation, the present results clearly support the suggestion[7c,d] that the sensitivity of the transition state of an E2 reaction to structural changes can depend on the character of the transition state itself and its position in More O'Ferrall's potential energy diagram.[7b] It appears therefore particularly dangerous to draw general conclusions concerning this problem from the results of only one series of substrates.

The comparison of the data reported here with the corresponding ones relative to the reaction of 2-phenylethyl chloride[1] allow us to evaluate the kinetic effect of an α-phenyl group in these eliminations. It is interesting to note that the introduction of an α-phenyl group produces a significant rate-retarding effect (ca. two-fold, after consideration of the statistical factor[10]) in the reaction promoted by complexed *t*-BuOK, whereas no kinetic effect is found in the reaction carried out in the presence of crown ether. These findings compare with the six-fold accelerating effect observed (at 50°C) in the eliminations promoted by EtONa in EtOH.[11]

Experimental Section

Materials. 1-Chloro-1-phenyl-2-arylethanes were available from a previous study.[11]

18-Crown-6 ether (18C6) was a commercial product (Fluka) purified by crystallization from *n*-hexane, mp 38.5–39.5 °C (lit.[12] mp 39.5–40.5 °C).

Base–Solvent Solution. *tert*-Butyl alcohol was distilled after treatment with potassium metal. Solution of alkoxide was obtained by reaction, under nitrogen, of freshly cut potassium with *tert*-butyl alcohol.

Kinetic Studies. For all compounds but 1-chloro-1-phenyl-2-*p*-nitrophenylethane, kinetics were carried out in a stoppered two-limb silica cell, either in the presence or in the absence of 18C6. In one limb was placed the substrate solution (1 mL) and in the other the base solution (1 mL). The cell was placed in the thermostated compartment of a Beckman DB-GT spectrophotometer. After ca. 0.5 h the solutions were mixed thoroughly and the cell was rapidly placed again in the compartment of the spectrophotometer. Absorbances were measured at the following wavelengths (nm): 298 for *trans*-stilbene; 299 for *p*-chloro-*trans*-stilbene; 298 for *p*-methyl-*trans*-stilbene; and 348 for *p*-nitro-*trans*-stilbene.

In the experiments with complexed base the reference cell contained a solution of potassium *tert*-butoxide and 18C6 in *tert*-butyl alcohol at the same concentration used in the kinetic run, to compensate for the significant absorption by complexed *t*-BuOK. At the wavelengths used for measurements in this study, the compensation was effective in the range 0.01–0.1 M of *t*-BuOK–18C6 concentration.

The elimination from 1-chloro-1-phenyl-2-*p*-nitrophenylethane, in the presence of 18C6, was followed on a Durrum-Gibson D-110 stopped-flow spectrophotometer.

The yield of olefin was determined from the value of D_∞ (optical density at infinite time) and pseudo-first-order rate constants were determined from the slope of a plot of log $(D_\infty - D_t)$ against time. Second-order rate constants, k_2, were obtained by dividing the first-order rate constants by the base concentration.

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Registry No.—*trans*-Stilbene, 103-30-0; *p*-chloro-*trans*-stilbene, 1657-50-7; *p*-methyl-*trans*-stilbene, 1860-17-9; *p*-nitro-*trans*-stilbene, 1694-20-8; 18-crown-6 ether, 17455-13-9.

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(2) For the possible causes of this phenomenon see ref 1.
(3) For the *p*-NO_2 group the σ^- value was used.
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(9) The fact the two reactions have similar ρ values in *t*-BuOK–*t*-BuOH does not necessarily imply a similar location of the transition state in the potential energy surface, owing to the quite significant structural differences between the two reaction series.
(10) Only the trans olefin is formed from 1-chloro-1,2-diphenylethane.
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Acceleration of an Allylic Rearrangement by the Cyclopropyl Substituent. Reaction Conditions to Prevent Ring Opening[1]

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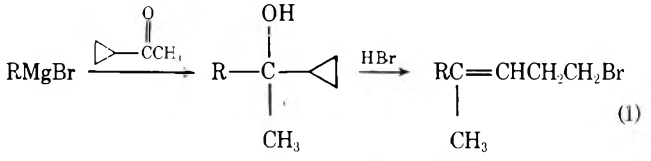
Although it is well known[2] that the cyclopropyl group has a remarkable ability to stabilize an α positive charge, there are conflicting data in the chemical literature as to whether the cyclopropyl or phenyl substituent is better able to delocalize a positive charge on an adjacent carbon. For example, it has been reported[3] that methyl cyclopropyl ketone is more basic than methyl isopropyl ketone and significantly more basic than acetophenone in H_2SO_4–H_2O or CF_3CO_2H–H_2SO_4 solutions, indicating that the cyclopropyl group is better able to delocalize an adjacent positive charge than is a phenyl group. On the other hand, Olah and White have demonstrated[4] that a phenyl group is considerably more effective than cyclopropyl in stabilizing an α carbonium ion by measuring the ^{13}C NMR chemical shifts of the sp^2 carbon in related cyclopropyl- and phenyl-substituted carbonium ions. This note discusses a series of experiments involving the acid-catalyzed rearrangement of tertiary vinyl carbinols (2) in acetic acid that not only demonstrates the remarkable ability of the cyclopropyl substituent to stabilize an adjacent cationic center but also provides some evidence concerning the nature of the reaction intermediate vs. the question of cyclopropane ring opening.

The acid-catalyzed ring opening of cyclopropanoids is a well-known reaction. For example, the Julia synthesis[5] of homoallylic halides is dependent on such cyclopropyl ring cleavage (eq 1). However, as Breslow has noted in his review of rearrangements of small ring compounds,[6] it is possible for

Table I. Allylic Rearrangement[a] of Tertiary Vinyl Carbinol 2a

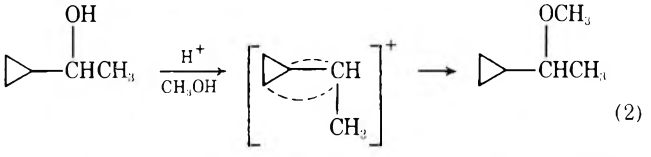
Entry	Solvent	Ratio[b] of 3a:3b:4c:4b:2a	Distilled yield, %	% yield[c] of tosylate 4d
1	Glacial HOAc[d]	25:1:1:0:0	68	8
2	Glacial HOAc	10:1.2:1:0:0	59	7
3	25:1 (v/v) HOAc–H_2O[e]	6:1:1:0:1	75	2
4	10:1 (v/v) HOAc–Ac_2O	8.3:3.3:1:0:0	68	8
5	Glacial HOAc containing sodium tosylate[f] (0.2 M solution)	56:40:3:1:0	64	8
6	Glacial HOAc[g]	1:0:20:0:0	12	17

[a] All reactions, unless indicated otherwise, were run for 30 s at 15 °C using *p*-toluenesulfonic acid (0.0125 M solution) as the catalyst, the solution being 0.1 M with respect to alcohol **2a**. [b] In the distilled product. Determined by NMR and VPC analysis. No other compounds could be detected in the distilled product. With longer reaction times (i.e., 1 or 2 min), the amount of alcohol **3a** diminished by its conversion to the corresponding acetate **3b**. The amount of ring-opened products remained constant, however. [c] Tosylate **4d** was isolated by chromatography of the distillation residue on silica gel (elution with hexane–8% ether). [d] The concentrations of alcohol **2a** and the catalyst were 0.02 and 0.0025 M, respectively, for this reaction. [e] This reaction was run for 60 s at 15 °C and evidently proceeded at a much slower rate, as indicated by the presence of approximately 10% starting material (**2a**) in the product mixture. [f] Prepared in situ by treatment of tosic acid with 1 equiv of anhydrous sodium acetate. [g] The concentration of *p*-toluenesulfonic acid was 0.50 M for this reaction.



(1)

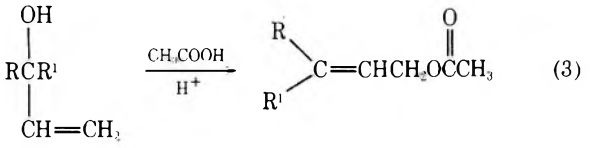
substituted cyclopropylcarbinyl derivatives to show very high reactivity and yet yield unrearranged derivatives. For example, the reaction[7] depicted in eq 2 proceeds quite rapidly and



(2)

is presumed to occur via protonation of the hydroxyl substituent followed by loss of water to form a nonclassical bicyclobutonium ion, which is subsequently attacked by the solvent at the center of maximum charge.

We decided to investigate the solvolysis of 2-cyclopropyl-3-buten-2-ol (**2a**) in acetic acid containing a strong acid catalyst. The latter conditions have recently been shown[8] to be useful for the rearrangement of tertiary vinyl carbinols to the corresponding primary allylic acetates (eq 3). Indeed, treat-

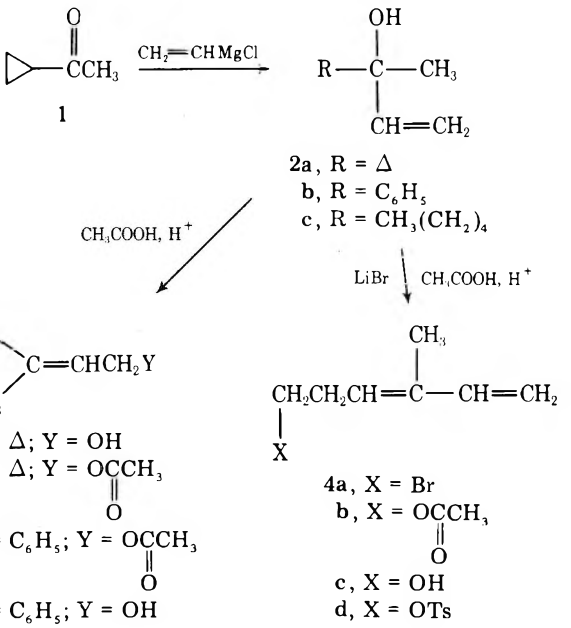


(3)

ment of alcohol **2a** (0.02 M solution) with glacial acetic acid containing *p*-toluenesulfonic acid (0.0025 M) at 15 °C for 30 s led to its facile rearrangement, without any appreciable ring opening,[9] to a 25:1 mixture of the corresponding primary allylic alcohol (**3a**) and its acetate derivative (**3b**) in 68% yield after evaporative distillation. The formation of alcohol **3a** as the major product[10] is remarkable in view of the nature of the solvent system and indicates that the reaction intermediate may be an intimate ion pair[11] which undergoes rapid rearrangement to afford the observed products. Such a hypothesis is also consistent with the structure of the only identifiable—and major—component of the nonvolatile portion of the reaction product. This latter substance was isolated in 8% yield by column chromatography on silica gel and identified as ring-opened tosylate **4d**.

The dramatic accelerating effect supplied by the cyclopropyl group in this allylic rearrangement was demonstrated

Scheme I



by running the reaction with 2-phenyl-3-buten-2-ol (**2b**)[8] under identical conditions. The product mixture in this latter reaction was determined by NMR analysis[12] to consist of a 16:1 mixture of unreacted starting material (**2b**) and the expected rearrangement product, 3-phenyl-2-buten-1-ol acetate (**3c**)[8] uncontaminated by any of the corresponding primary allylic alcohol (**3d**). Furthermore, using these same reaction conditions, 3-methyl-1-octen-3-ol (**2c**)[8] was recovered in almost quantitative yield.

Since the minor amount of products derived from cyclopropane ring opening is in direct contrast to an earlier report[13] that the same alcohol (**2a**) when treated with hydrobromic acid reacts with total ring cleavage to afford 6-bromo-3-methyl-1,3-hexadiene (**4a**) in 85% yield, a number of additional experiments were performed using different reaction conditions as outlined in Table I. In none of these reactions were significant amounts of other components detected in the *distilled* product.[14] The necessity of a catalyst was demonstrated by the observation that the starting tertiary vinyl carbinol (**2a**) could be recovered virtually unchanged from 10:1 (v/v) acetic acid–acetic anhydride after a period of 2 min.

Since the addition of lithium perchlorate or lithium bromide is known[11] to change the nature of the intermediate ion pair

in solvolyses by trapping the solvent-separated ion pair to give the unstable $R^+//Br^-$ (or ClO_4^-), two additional reactions were run using these salts as added reagents. In both cases NMR analysis of the reaction product indicated total cleavage of the cyclopropane ring. Using 5:1 (v/v) acetic acid–acetic anhydride as the solvent containing *p*-toluenesulfonic acid (0.025 M solution) and lithium bromide[15] (1 M solution), 2-cyclopropyl-3-buten-2-ol (**2a**) was converted[16] in 75% yield to 6-bromo-3-methyl-1,3-hexadiene (**4a**) as the only detectable reaction product.

An additional experiment (Table I, entry 6) involved treatment of alcohol **2a** (0.1 M solution) with glacial acetic acid containing a substantial amount of *p*-toluenesulfonic acid (0.50 M solution) at 15 °C for 30 s. In contrast to a similar experiment conducted in the presence of a large amount of sodium tosylate (Table I, entry 5), the major identifiable reaction product was ring opened tosylate **4d**, obtained in 17% yield after chromatography[17] on silica gel (elution with hexane–8% ether). Such results, together with an earlier study[13] of the same system (**2a**) using hydrobromic acid, seem to indicate that the presence of the lithium cation or a strong proton donor such as *p*-toluenesulfonic acid disrupts the intimate ion pair (R^+, ^-OTs, H_2O in a solvent cage) leading to cyclopropane ring opening.

Experimental Section[18]

2-Cyclopropyl-3-buten-2-ol (2a). A solution of 5.74 g (68 mmol) of ketone **1**[19] in 50 mL of anhydrous ether was added dropwise over a period of 10 min to 40 mL of 2.3 M vinylmagnesium chloride–tetrahydrofuran solution,[20] cooled to 0 °C in an ice water bath and maintained under a nitrogen atmosphere. After this mixture had been stirred at 0 °C for 10 min, the reaction was quenched by dropwise addition of saturated aqueous NH_4Cl solution. Extraction[18] of the product with ether, followed by short-path distillation, afforded 6.27 g (82%) of tertiary vinyl carbinol **2a**: bp 58–60 °C (35 mm) [lit.[21] bp 137 °C (760 mm)]; ν_{max} (film) 3450 (OH), 3100, 1645 (C=C), 1170, 1115, 1050, 1020, 1000, 920 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.82 (CH=CH_2, J_{AC} = 10, J_{BC} = 18 Hz), 5.31–4.83 (CH=CH_2, rest of ABC pattern[22]), 2.08 (s, OH), 1.23 (s, CH_3), 0.87 (multiplet, 1 cyclopropyl H, peaks at 1.03, 0.94, 0.92, 0.80, and 0.71), 0.36 and 0.25 ppm (4 cyclopropyl Hs).

Allylic Rearrangement of Tertiary Vinyl Carbinol 2a. A solution of 228 mg (2.03 mmol) of alcohol **2a** in 2.0 mL of glacial acetic acid was added rapidly to a well-stirred solution of 47 mg (0.25 mmol) of *p*-toluenesulfonic acid monohydrate in 18.0 mL of glacial acetic acid in a stoppered flask kept in a constant temperature bath at 15 °C. After 30 s, the reaction was quenched by quickly pouring the solution into a mixture of 100 mL of 4 N aqueous NaOH and 75 g of crushed ice. Extraction[18] of the product with ether, followed by evaporative distillation, afforded 136 mg (59% corrected yield) of colorless oil, bp 35–55 °C (bath temperature, 0.10 mm). VPC analysis[23] (oven temperature 155 °C, flow 15 mL/min) indicated that the product consisted almost exclusively of a mixture of three components: primary allylic acetate **3b** (retention time 7.6 min, 9.8% of the mixture), the corresponding alcohol **3a** (retention time 4.5 min, 82%), and homoallylic alcohol **4c**[24] (retention time 4.1 min, 8%). Only a trace (<0.3%) of ring-opened acetate (**4b**) (retention time 6.7 min) was detected in the product.[25]

An analytical sample of primary allylic acetate **3b** was obtained by chromatography on silica gel of the distilled product obtained using the conditions cited in Table I, entry 4. Elution with hexane–2% ether afforded the rearranged acetate **3b** as a mixture of *E*:*Z* stereoisomers: bp 77–94 °C (bath temperature, 2.0 mm); ν_{max} (film) 1745 (C=O), 1665 (C=C), 1240, 1025, 950 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.31 (broad triplet, J = 7 Hz, C=CH), 4.48 (doublet, J = 7 Hz, CH_2OAc), 1.97 [s, OC(=O)CH_3], 1.60 (s, vinyl CH_3), ~80% of the mixture), 1.48 (s, vinyl CH_3, ~20% of the mixture), 1.3 (complex multiplet, 1 cyclopropyl H), 0.55 ppm (complex multiplet, 4 cyclopropyl Hs). Anal. Calcd for $C_9H_{14}O_2$: C, 70.04; H, 9.16. Found: C, 70.01; H, 9.17.

An authentic sample of the corresponding primary allylic alcohol (**3a**) was obtained by chromatography of the distilled product obtained using the conditions cited in Table I, entry 1. Elution with hexane–20% ether afforded alcohol **3a**: bp 70–85 °C (bath temperature, 2.0 mm) [lit.[26] bp 88 °C (13 mm)]; ν_{max} (film) 3350 (OH), 1665 (C=C), 1085, 1045, 1000, 955, 895, 815 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.36 (triplet, J = 7 Hz, C=CH), 4.02 (doublet, J = 7 Hz, CH_2OH), 3.67 (s, OH), 1.56 (s, vinyl CH_3, ~80% of the mixture), 1.44 (broad s, vinyl CH_3, ~20% of the mixture), 1.25 (complex multiplet, 1 cyclopropyl H), 0.5 ppm (complex multiplet, 4 cyclopropyl Hs).

Preparation of 6-Bromo-3-methyl-1,3-hexadiene (4a). A solution of 439 mg (3.91 mmol) of tertiary vinyl carbinol **2a** in 5.0 mL of glacial acetic acid and 1.0 mL of acetic anhydride was added rapidly to a well-stirred mixture of 140 mg (0.74 mmol) of *p*-toluenesulfonic acid monohydrate and 2.46 g (28.8 mmol) of lithium bromide in 20 mL of glacial acetic acid–4.0 mL of acetic anhydride at 15 °C. After 2 min, the reaction was quenched by quickly pouring the solution into a mixture of 150 mL of 4 N aqueous NaOH and 100 g of crushed ice. Extraction[18] of the product with ether, followed by removal of the solvent via distillation at atmospheric pressure through a Vigreux column and subsequent evaporative distillation, afforded 509 mg (75%) of bromide **4a**: bp 65–70 °C (bath temperature, 7.5 mm) [lit.[26] bp 71–72 °C (12 mm)]; >99% pure by VPC analysis,[23] oven temperature 135 °C, retention time 4.1 min; ν_{max} (film) 3100, 1645, 1610, 1270, 1205, 1080, 985, 900 cm^{-1}; δ_{Me_4Si} (CCl_4) 6.91–4.87 (complex pattern, 4 vinyl Hs), 3.32 (triplet, J = 7 Hz, CH_2Br), 2.69 (quartet, J = 7 Hz, CH_2CH=C), 1.83 (broad s, "*Z*" vinyl methyl, ~30% of the mixture), 1.77 ppm (singlet, "*E*" vinyl methyl, ~70% of the mixture).

4-Methyl-3,5-hexadien-1-ol Acetate (4b). A mixture of 484 mg (2.77 mmol) of bromide **4a** and 1.13 g (13.8 mmol) of anhydrous sodium acetate in 10 mL of dry *N*,*N*-dimethylformamide was stirred at room temperature for 20 h and then at 95 °C (bath temperature) for 3 h. After cooling this mixture to room temperature, it was diluted with 80 mL of water and the product was isolated by extraction[18] with ether. Subsequent evaporative distillation afforded 257 mg (61%) of acetate **4b**:[13] bp 45–60 °C (bath temperature, 0.20 mm); >97% pure by VPC analysis,[23] oven temperature 155 °C, flow 15 mL/min, retention time 6.7 min; ν_{max} (film) 1740 (C=O), 1640 (C=C), 1605 (C=C), 1385, 1365, 1235, 1035, 985, 900 cm^{-1}; δ_{Me_4Si} (CCl_4) 6.98–4.87 (complex pattern, 4 vinyl Hs), 4.05 (triplet, J = 7 Hz, CH_2OAc), 2.46 (quartet, J = 7 Hz, CH_2CH=C), 1.98 [s, OC(=O)CH_3], 1.84 (broad s, "*Z*" vinyl methyl, ~30% of the mixture), 1.77 ppm (singlet, "*E*" vinyl methyl, ~70% of the mixture). Anal. Calcd for $C_9H_{14}O_2$: C, 70.04; H, 9.16. Found: C, 69.77; H, 8.95.

4-Methyl-3,5-hexadien-1-ol *p*-Toluenesulfonate (4d). A solution of 338 mg (3.01 mmol) of alcohol **2a** in 2.0 mL of glacial acetic acid was added rapidly to a well-stirred solution of 2.839 g (14.9 mmol) of *p*-toluenesulfonic acid monohydrate in 28.0 mL of glacial acetic acid and 1.50 mL (15.8 mmol) of acetic anhydride in a flask kept in a constant temperature bath at 15 °C. After 30 s, the reaction was quenched by quickly pouring the solution into a mixture of 175 mL of 4 N aqueous NaOH and 150 g of crushed ice. Extraction[18] of the product with ether, followed by evaporative distillation, afforded 40 mg (12% yield) of colorless oil, bp 40–55 °C (bath temperature, 0.20 mm). VPC analysis[23] (oven temperature 155 °C, flow 15 mL/min) indicated that >98% of the distillate consisted of a mixture of two components: ring-opened alcohol **4c** (retention time 4.1 min) and primary allylic alcohol **3a** (retention time 4.5 min) in a 20:1 ratio, respectively. Chromatography of the residue (384 mg) of 20 mL of silica gel (elution with hexane–8% ether) afforded 137 mg (17% yield)[17] of tosylate **4d** as a mixture of *E*:*Z* stereoisomers: ν_{max} (film) 1648, 1605, 1500, 1385, 1180, 1100, 975, 910, 815, 750, 660 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.52 (AB quartet, 4 aryl H, peaks at 7.82, 7.67, 7.37, 7.23), 6.84–4.85 (complex pattern, 4 vinyl Hs), 3.99 (triplet, J = 7 Hz, CH_2OTs), 2.48 (quartet, J = 7 Hz, CH_2CH=C), 2.44 (s, CH_3), 1.77 (broad s, vinyl CH_3, ~30% of the mixture), 1.69 ppm (broad s, vinyl CH_3, ~70% of the mixture). Anal. Calcd for $C_{14}H_{18}SO_3$: C, 63.11; H, 6.82; S, 12.04. Found: C, 62.84; H, 6.82; S, 12.26.

Acknowledgments. The authors wish to thank Dr. James W. Wilt and Dr. Harvey W. Posvic of Loyola University of Chicago for their helpful suggestions during the course of this project. The assistance of Nancy Casey and Peter Fries in some of the experimental work is also gratefully acknowledged.

Registry No.—**1**, 765-43-5; **2a**, 1072-76-0; (*E*)-**3a**, 61915-38-6; (*Z*)-**3a**, 61915-39-7; (*E*)-**3b**, 61915-40-0; (*Z*)-**3b**, 61915-41-1; (*E*)-**4a**, 61432-68-6; (*Z*)-**4a**, 61432-65-3; (*E*)-**4b**, 61915-42-2; (*Z*)-**4b**, 61915-43-3; (*E*)-**4d**, 61915-44-4; (*Z*)-**4d**, 61915-45-5; sodium acetate, 127-09-3.

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(9) As shown by the data in Table I, entry 1, >96% of the distilled product mixture consisted of cyclopropanoids **3a** and **3b**. In separate experiments, ring-opened acetate **4b** was shown to be stable to the conditions utilized for the reactions listed as entries 1 and 2 in Table I.
(10) Similar product ratios were obtained in an experiment using acetic acid that had been dried by treatment with triacetyl borate in the manner described by A. Pictet and A. Geleznoff, *Ber.*, **36**, 2219 (1903).
(11) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, N.Y., 1968, p 259.
(12) The rearranged acetate (3c)[8] was characterized by a doublet at δ 4.65 (J = 7 Hz, CH_2OAc), whereas the starting tertiary vinyl carbinol (**2b**) exhibited a sharp singlet at δ 1.57 (CH_3).
(13) M. Julia, S. Julia, and B. Stalla-Bourdillon, *C. R. Acad. Sci.*, **253**, 951 (1961). Acetate **4b** was prepared in this paper using a different procedure.
(14) The residue in the distillation contained ring-opened material, as determined by NMR analysis. Since most of this mixture was tosylate **4d**, sufficient catalyst must be used in the solvolysis or the reaction will cease prior to complete rearrangement of alcohol **2a**, due to depletion of the catalyst.
(15) When lithium perchlorate was used to replace the lithium bromide in this reaction, no product could be isolated, and it was presumed that an elimination reaction had occurred leading to the formation of volatile C-7 hydrocarbons. To substantiate this hypothesis, an additional experiment was run using lithium perchlorate (1 M solution) and *p*-toluenesulfonic acid (0.0125 M solution) in a more nucleophilic solvent system—25:1 (v/v) acetic acid–water. Under these conditions, alcohol **2a** was converted in 68% yield to a horrendous mixture of products, the NMR spectrum of which showed no cyclopropyl absorption. The yield of distilled product (bp 45–60 °C, 0.10 mm) in this reaction was only 10%. VPC analysis indicated a mixture of at least ten components, none in substantial amounts.
(16) Since this reaction was not complete after 30 s at 15 °C, a reaction time of 2 min was used.
(17) The remainder of the material on the column was not identified after it failed to be eluted with hexane–20% ether. Since the NMR spectrum of the distillation residue taken prior to this chromatography closely resembled the spectrum of purified tosylate **4d**, some decomposition may have occurred on the column.
(18) Unless indicated otherwise, the isolation of reaction products was accomplished by pouring the mixture into water or saturated brine and extracting thoroughly with the specified solvent. The combined extracts were washed with saturated aqueous sodium bicarbonate and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed from the dried extracts by using a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The NMR spectra were recorded with a Varian A-60 NMR spectrometer and infrared spectra were obtained using a Beckman Acculab 1 spectrophotometer. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.
(19) Available from Aldrich Chemical Co., Inc., Milwaukee, Wis.
(20) Available from Apache Chemicals, Inc., Seward, Ill.
(21) J. Kulesza, J. Gora, and K. Koseska, *Riechst., Aromen, Koerperpflegem.*, 192, 194, 199–200 (1969); *Chem. Abstr.*, **71**, 102020q (1969).
(22) Resolution of the signal peaks between δ 5.31 and 4.83 was not sufficient to allow a simple determination of J_{AB} and the chemical shifts for these two protons.
(23) A 6 ft × 0.125 in. SE-30 column was used for this analysis.
(24) This component was shown by NMR and VPC analysis to be identical with the alcohol (**4c**) obtained by saponification of ester **4b**. Alcohol **4c** was characterized by a triplet at δ 3.52 (J = 7 Hz, CH_2OH). This alcohol has previously been reported by M. Julia, S. Julia, and B. Stalla-Bourdillon (ref 13).
(25) Identified by coinjection of a mixture of the distilled product and an authentic sample of acetate **4b**.
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Regio- and Stereoselective Reactions of *trans*-5,6-Epoxy-*cis*-cyclodecene[1a]

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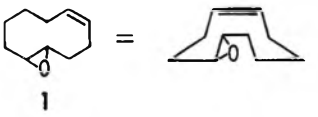
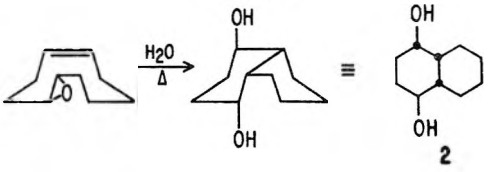
Recent reports on the reactions of acyclic and cyclic unsaturated epoxides with organometallic reagents[1–6] encouraged us to examine the less studied medium-ring congeners, which we felt would reveal novel pathways.[6–9] We found that products from one such epoxide, *trans*-5,6-epoxy-*cis*-cyclodecene[10] (1), differ strikingly in structure and selectivity from reaction with one organometallic reagent to another and also from those obtained in aqueous media[11] (see Scheme I). The



1

Scheme I



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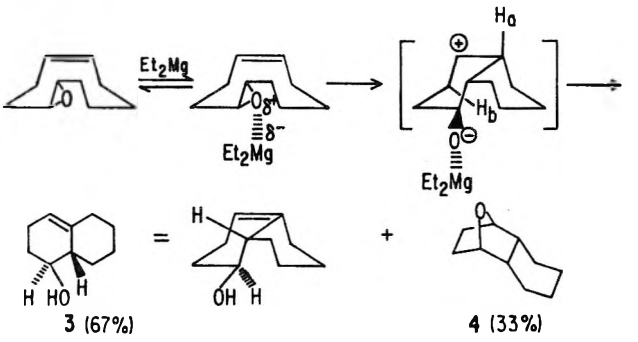
high selectivity of two pathways provides facile entry into two challenging ring functionalities of current interest.[9,12]

For example, when 1 is added to diethylmagnesium products 3 and 4 result (Scheme II). Ring opening is facilitated by

Scheme II



3 (67%) 4 (33%)

magnesium ion and occurs at the C_6 position most likely as a result of through-space interaction with the double bond in the transition state.[11,13]

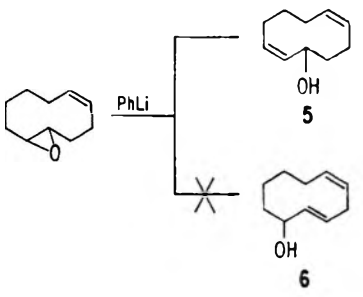
It is somewhat surprising that GC/mass spectrographic analyses failed to reveal addition products for all the Grignard-like reagents tested (ref 14–16 and vide infra). Also interesting is the effectiveness of the weak Lewis acid diethylmagnesium to effect a clean transannular ring closure. For example, reaction of 1 with BF_3·OEt_2 and Grignard reagents yielded synthetically less useful complex mixtures of products. Although 3 was the major product in these cases, additional products resulted from competing rearrangements. In retrospect, this is not unexpected since the magnesium halide in Grignards is known to give competing rearrangement[2–5,8] products, and BF_3·OEt_2 could ring open 4 and lead to carbonium-ion-like rearrangements.

The reaction was shown to be stereoselective for isomer 3 by comparison of physical and spectral constants with those of an authentic sample synthesized by an alternate route.[12] Some $\Delta^{3(4)}$-octalol, detected by NMR, resulted from elimination of a different hydrogen (H_b, Scheme II).[17]

Compound 4, 1,4-endoxodecalin,[18,19] was identified by establishing its symmetry in hydrogen-decoupled ^{13}C NMR [peaks at δ ^1H 80.1, 40.3, 24.3, and 19.6 ppm in a 1:1:1:2 ratio ($CDCl_3$)]. Also, the ^1H NMR of 4 was similar to that of a model compound, 7-oxabicyclo[2.2.1]heptane [δ 4.4 (CHOCH multiplet)] with multiplets at δ 4.4 (CHOC**H**) and 1.0–2.1 ppm (m, 14 H).

Whereas 1 underwent stereoselective ring closure with a dialkylmagnesium reagent, it reacted by a different pathway with an organolithium reagent. When freshly prepared phenyllithium was refluxed with 1 in ether, proton abstraction led to 5 in high yields (Scheme III). Bisallylic NMR peaks of

Scheme III



6 (Scheme III) were notably absent in all NMR spectra. Equilibration studies[21] and other considerations[22] indicate a strong conformational preference for the formation of **5**. However, ketonic products, whose presence would indicate rearrangement, were notably absent.[20]

These results complement other work with similar compounds[6,11] and help demonstrate the generality of the highly selective reaction pathways possible with unsaturated medium-ring epoxides.

Experimental Section

Reaction of Diethylmagnesium with *trans*-5,6-Epoxy-*cis*-cyclodecene. A solution of 1.52 g (10 mmol) of **1** in 20 mL of ether was added dropwise to 15 mL of an ice-cooled 0.6 M solution of diethylmagnesium.[23] After the solution was refluxed for 15 h, standard workup gave a mixture of **3** and **4** in an 85–90% yield. A sample of **3** was isolated by fractional distillation [bp 91–93 °C (20 mm); n^{25}_D 1.4885; NMR (CCl_4) δ 4.3 (multiplet, 2 H) and 1.0–2.1 (multiplet, 14 H); M^+ (calcd) 152.1200 for $C_{10}H_{16}O$, found 152.1188]. Compound **4** was crystallized out of the residue at low temperature from ether/pentane. Its melting point was 40–42 °C; IR and NMR spectra were identical with those of an authentic sample.[12]

Preparation of *cis,cis*-2,7-Cyclodecadienol. Under argon atmosphere, approximately 20 mmol of phenyllithium[24] was freshly prepared in 30 mL of ether. A solution containing 2.28 g (15 mmol) of **1** in 10 mL of ether was added dropwise to the phenyllithium. After 8–12 h reflux, normal workup gave an oil which crystallized after 2 days in the freezer. The crude solid (2.28 g) was recrystallized from 50–70 °C-boiling petroleum ether yielding 1.62 g (72%) of **5** [mp 89.8–90.7 °C; IR (CCl_4) 3200–3650 (OH) and 708 cm^{-1} (cis CH=CH); NMR (CCl_4) δ 5.0–5.6 (m, 4, –CH=CH–), 4.15–4.60 (m, 1, CHO), and 1.1–2.5 (m, 11 remaining H); mass spectrum (75 eV) *m/e* 152 M^+ (10), 55 (94), and 29 (100)].

Anal. Calcd for $C_{10}H_{16}O$; C, 78.89; H, 10.60. Found: C, 78.68; H, 10.72.

Acknowledgments. We wish to thank J. R. Olechowski for a generous sample of *cis,trans*-1,5-cyclodecadiene. P. S. Wharton kindly provided us with NMR and IR spectra of *syn*- and *anti*-$\Delta^{4(10)}$-octalol (**3**).

Registry No.—**1**, 24639-32-5; **3**, 41727-79-1; **4**, 61967-02-0; **5**, 61967-03-1; diethylmagnesium, 557-18-6; phenyllithium, 591-51-5.

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(17) A small vinyl peak at δ 5.5 in the NMR spectrum of **3** was essentially identical with that of the hydrocarbon analogue of $\Delta^{3(4)}$-octalol prepared by dehydration of *cis*-decahydronaphthol.
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(19) We prepared **2** by the reaction shown in Scheme I and dehydrated it after the method described in ref 18. This method gave the exo isomer of **4** in low yield [NMR (CCl_4) δ 4.0 (m, CHOCH) and 1.0–2.0 (m, 14 H)]. The exo isomer had a narrower CHOCH multiplet than endoxodecalin (the latter compound has exo hydrogens which couple more strongly than the endo hydrogens of the former compound).
(20) See J. K. Crandall and L. C. Lin, *J. Org. Chem.*, **33**, 2375 (1968), and references cited therein.
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Stereospecific Thallium(III) Nitrate Mediated Conversion of Bicyclo[3.2.1]-2-octanone to *exo*-2-Norbornanecarboxylic Acid Methyl Ester[1a,b]

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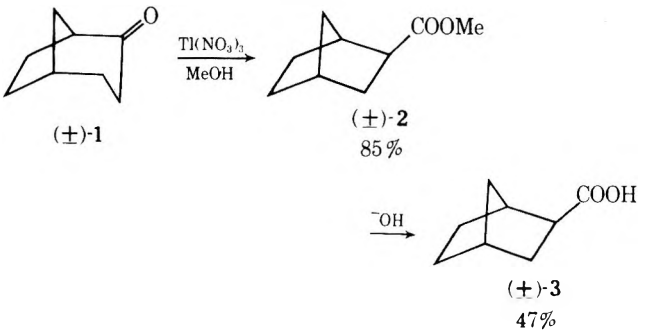
During absolute configuration assignments of bridged bicyclic products of some enzymic oxidoreduction reactions,[2] we carried out thallium(III) nitrate in methanol mediated homologation of (1*S*,4*R*)-2-methylenenorbornane to (1*S*,5*S*)-bicyclo[3.2.1]-2-octanone (**1**), a reaction similar to that first reported in the racemic series by Fărcaşiu and coworkers.[3] A methyl ester impurity was also formed in varying amounts during the reaction. This methyl ester, whose proportion we now find can reach as high as 31% under the homologation conditions, has been identified as *exo*-2-norbornanecarboxylic acid methyl ester (**2**).

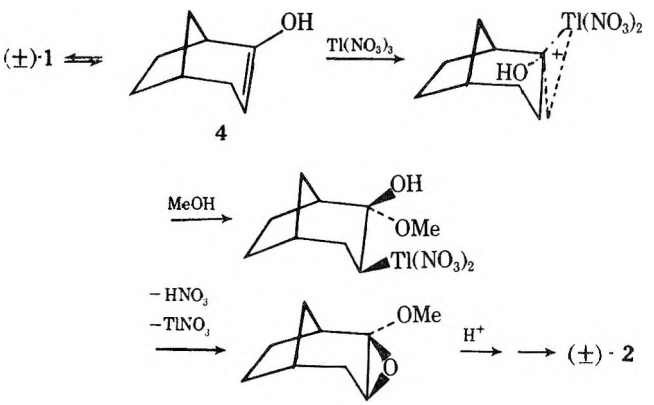
In view of the examples now available of ring contraction on treatment of six-membered cyclic ring ketones with thallium nitrate,[4–7] it seemed evident that **2** was formed from the initial homologation product **1**. This was confirmed by subjecting **1** itself to the thallium nitrate in methanol conditions. As shown in Scheme I, an 85% yield of **2**, characterized as the acid **3**, was obtained.

Scheme I



As in the steroid series,[6] the ring contraction is highly stereospecific, with none of the endo isomer of **2** being detected.[8] The exclusive formation of the exo ester **2** is consistent with the mechanism proposed by McKillop and Taylor,[5] with attack of the enol intermediate **4** by Tl^{3+} occurring from the exo direction as expected for electrophilic additions of this type.[9] The pathway envisaged is depicted in Scheme II.

Scheme II



Experimental Section[10]

Thallium(III) Nitrate Treatment of (±)-2-Methylenenorbornane. Thallium(III) nitrate[11] (2.67 g, 6 mmol) in methanol (20 mL) was added to (±)-2-methylenenorbornane [650 mg, 6 mmol, prepared as described for the (+) enantiomer[2]] in methanol (25 mL) at −10 °C. After being stirred for 30 min, the mixture was filtered and concentrated, and ether (50 mL) and 2 M hydrochloric acid (50 mL) were added. The mixture was shaken well and separated, and the aqueous phase was extracted three more times with ether. Evaporation of the dried ($MgSO_4$) ether extracts gave an oily product which contained (by GC analysis) 68% of 1 and 31% of 2. This mixture was treated directly with 15% ethanolic potassium hydroxide (30 mL) and warmed for 15 min on a steam bath. The mixture was then concentrated, diluted with water (100 mL), and washed four times with ether. The aqueous phase was acidified with concentrated hydrochloric acid and extracted four times with chloroform. The dried ($MgSO_4$) chloroform solution was evaporated to give a solid which after two sublimations gave *exo*-2-norbornanecarboxylic acid [(±)−3, 78 mg] as colorless crystals: mp 56–57 °C (lit.[12] mp 56–57 °C); IR 3330–2560 and 1725 cm^{-1}; NMR δ 1.0–2.0 (m, 8 H), 2.2–2.4 (m, 2 H), 2.5 (m, 1 H), and 11.2 ppm (br s, 1 H). No trace of *endo*-2-norbornanecarboxylic acid, NMR δ 1.1–1.8 (m, 8 H), 2.1–3.0 (overlapping m, 3 H), and 11.1 ppm (s, 1 H), could be detected.

Thallium(III) Nitrate Mediated Ring Contraction of Bicyclo[3.2.1]-2-octanone [(±)−1]. A solution of thallium(III) nitrate[11] (3.69 g, 8.3 mmol) in methanol (20 mL) was added to a stirred solution of the bicyclic ketone (±)−1 (1.03 g, 8.3 mmol) in methanol (30 mL) at 20 °C. After being stirred overnight the solution was filtered, concentrated, then diluted with water (50 mL), acidified with concentrated hydrochloric acid (2 mL), and finally extracted four times with ether. The combined ether phases were washed twice with brine, dried ($MgSO_4$), and then evaporated and distilled to give a colorless liquid [763 mg,bp 92–96 °C (12 Torr)] which contained (by GC analysis) unreacted ketone (±)−1 (15%) and the exo methyl ester (±)−2 (85%). This mixture was hydrolyzed with ethanolic potassium hydroxide and worked up as described above. The solid so obtained was sublimed twice to give colorless crystals of *exo*-2-norbornanecarboxylic acid [(±)−3, 544 mg, 48% yield], mp 55.0–56.5 °C, with spectral properties identical with those cited above.

Registry No.—(±)−1, 61242-42-0; (±)−2, 61967-04-2; (±)−3, 61967-05-3; thallium(III) nitrate, 13746-98-0; (±)-2-methylenenorbornane, 62014-79-3.

References and Notes

(1) (a) This work was supported by the National Research Council of Canada; (b) Abstracted from the Ph.D. Thesis of A. J. Irwin, University of Toronto, 1975; (c) Ontario Graduate Fellow, 1972–1973; National Research Council of Canada Scholar, 1973–1975.
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(8) A control experiment showed that no epimerization of *endo*-2 or 3 would have occurred during the hydrolysis step.
(9) Cf. R. R. Sauers, H. M. How, and H. Feilich, *Tetrahedron*, **21**, 983 (1965).
(10) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. NMR spectra (Me_4Si internal standard) were obtained on a Varian T-60 instrument, IR data on chloroform solutions with a Perkin-Elmer 141 spectrometer, and GC analyses at 125 °C on an F & M 400 chromatograph equipped with 3 mm × 1 m columns of 2% QF-1 on Chromosorb G.
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2,6-Di-*tert*-butyl-4,4-bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)-2,5-cyclohexadienone. A New Reaction Product of a Hindered Phenol

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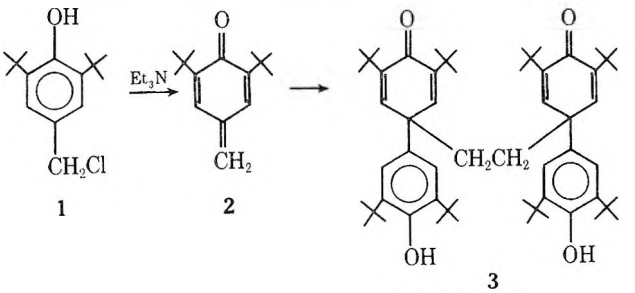
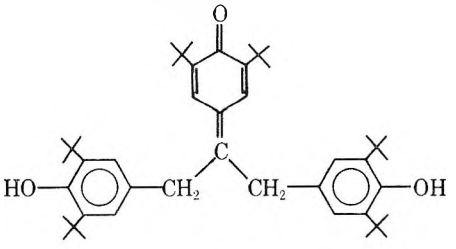
Received October 13, 1976

The fate of hindered phenols in their performance as antioxidants continues to attract the attention of chemists.[1,2] Neureiter[3] and Starnes and co-workers[4] have shown that the reaction of 3,5-di-*tert*-butyl-4-hydroxybenzyl chloride (1) with the base triethylamine gives the quinone methide (2), whose subsequent reactions with itself or added reagents affords a host of known and new compounds, e.g., 3. We found



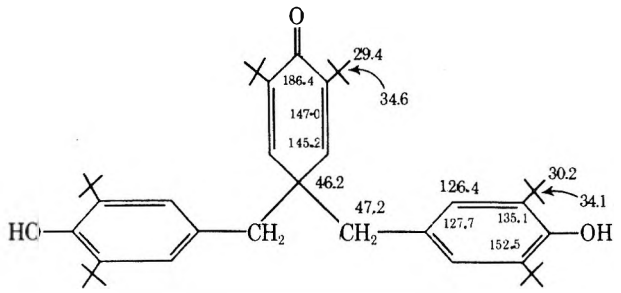
+ other products

that the reaction of the anion of dimethyl sulfoxide with 1 affords, along with other products, a heretofore unreported white, crystalline compound, mp 152–154 °C dec. The infrared spectrum (KBr) possesses absorptions at 3618 cm^{-1} (hindered phenol)[5] and at 1640 and 1655 cm^{-1} (conjugated carbonyl).[5] The ^1H NMR spectrum in deuteriochloroform has absorptions at 1.10 (9 H), 1.38 (18 H), 2.90 (2 H), 5.01 (1 H, exchangeable), 6.56 (1 H), and 6.81 ppm (2 H) downfield from internal Me_4Si.[6] All the absorptions were singlets. Structures 4 and 5 are consistent with these data.



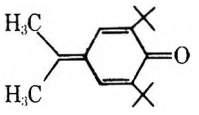
4

The proton decoupled ^{13}C NMR spectrum, run under conditions[7] where errors in peak areas due to differing relaxation times (T_1) for the different carbons were eliminated, but assuming the nuclear Overhauser enhancement of all the carbons to be equal, showed that the actual structure contains one less carbon than 4. The ^{13}C NMR chemical shift data[8] are shown on the structure of 5. Structure 5 is also supported by its UV spectrum, which in methanol possesses absorptions at



5

231 (ε 23 000) and 272 nm (5200). This compares favorably with that of **3**, which has absorptions at 235 (ε 37 000), 277 (4500), and 365 nm[3] (47). This is in contrast to **6**, the analogy to **4**, which has λ_{max} at 317 nm (ε 30 000).



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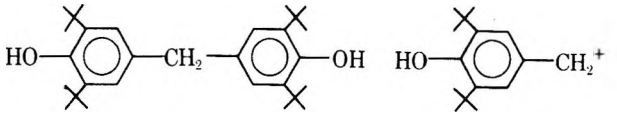
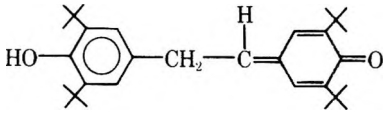
The mass spectrum of **5** did not reveal an M^+ peak but did give intense fragments at *m/e* 424 and 219, consistent with **7** and **8**, respectively. Indeed, a chloroform solution of **5** standing



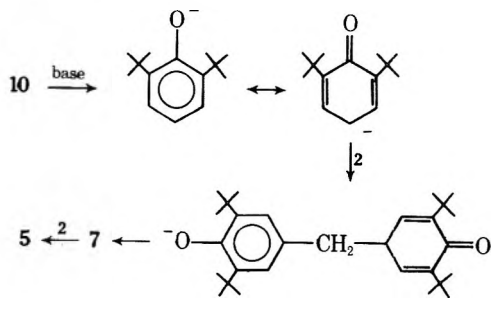
7 8

at room temperature for a day or two or refluxed for a few hours rapidly developed a yellow color. TLC of this solution indicated two primary products along with **5**. The major product was isolated in pure form by preparative TLC and was shown to compare exactly with authentic **7** by TLC, melting point, and IR. The second component, always contaminated by **5**, was orange. Its NMR[4a] and color were consistent with **9**. These components (**7** and **9**) also accompanied the formation of **5** in the initial synthesis, as determined by TLC.



9

The mechanism of formation of **5** from **1** and dimsyl anion requires that a one-carbon extrusion take place. Since this did not seem too likely,[9] we felt that we may be isolating a product which results from a reaction of **2** with an impurity, namely, 2,6-di-*tert*-butylphenol (**10**), which is present, as determined by TLC, in the 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol used to make **1**. A similar conclusion was drawn by Neureiter[3] in his isolation of **3**. Thus, the following mechanism[10] could account for the formation of **5**.



Further credence was lent to this proposed mechanism by carrying out the following experiments. When **1**, which was TLC free of **10** (by using pure 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol to form **1**), was reacted with the dimsyl anion, no **5** was observed. However, when pure **1** was converted to **2** using triethylamine[3] in benzene instead of the dimsyl anion and subsequently reacted with **7** (or **10**), **5** was produced in yields comparable to those from the Me_2SO reactions. Thus, the nature of the base is unimportant, while **7** appears to be a probable intermediate in the formation of **5**.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. All TLC analyses were performed on Analtech, Inc., precoated glass plates of silica gel using 7:3 hexane–benzene as the eluent and UV and visible light and iodine vapor for visualization. The preparative scale plates were 1000-μm thick silica gel on glass from Analtech. The elemental analysis was obtained on a CHN analyzer at the Avon Lake Technical Center of B. F. Goodrich Co. The ^1H NMR spectra were obtained on a Varian Model A-60 and the ^{13}C NMR spectrum on a Bruker Model HX-90E. The mass spectrum was obtained on a Perkin-Elmer Model 270.

3,5-Di-*tert*-butyl-4-hydroxybenzyl Chloride (1). Concentrated HCl (300 mL, 3.6 mol) was added to a slurry of unpurified 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol (236 g, 1.0 mol, Ethyl Corp.) in hexane and was stirred at ambient temperature overnight under nitrogen. The resulting two layers were separated and the hexane layer washed with water, dried ($MgSO_4$), and evaporated to afford 245.5 g (96.5%) of a yellow-orange liquid,[3] whose IR and NMR were consistent with the desired structure. When purified (recrystallization from hexane and then benzene) benzyl alcohol was used, **1** was pale yellow.

2,6-Di-*tert*-butyl-4,4-bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)2,5-cyclohexadienone (5). Sodium amide (1.0 g, 0.026 mol) was added to dry Me_2SO (15 mL) at 25 °C under nitrogen. The mixture was heated to 50 °C and kept there for 2 h. Upon cooling to 25 °C, **1** (6.52 g, 0.026 mol, prepared from unpurified benzyl alcohol) in Me_2SO (15 mL) was added dropwise over 2 h. The temperature rose to 30 °C. The resulting blue-green mixture was poured into acidic water to give a yellow precipitate, which was removed by vacuum filtration and dried in a vacuum desiccator. This solid (6.16 g) was slurred in boiling methanol (40–50 mL), cooled, filtered, and washed to afford a faintly yellow solid. This material was boiled in methanol (400 mL) and filtered hot to remove an insoluble white solid,[11] mp 286–287 °C. The mother liquor was concentrated to crystallize 0.8 g of **5**, mp 152–154 °C, which was shown to be TLC pure. A second crop can also be taken. Anal. Calcd for $C_{44}H_{66}O_3$: C, 82.17; H, 10.37. Found: C, 82.90; H, 10.62.

Acknowledgment. We would like to thank Tim Pratt and Charles Jacobs for assisting with some of the reactions, R. Whitehead for the UV work, K. Welch for the mass spectral work, and F. Baron for the analytical data. Discussions with Professor Paul D. Bartlett and comments by referees were also very valuable.

Registry No.—**1**, 955-01-1; **5**, 62078-82-4; 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol, 88-26-6.

References and Notes

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(2) J. C. Westfahl, *Rubber Chem. Technol.*, **46**, 1134 (1973).
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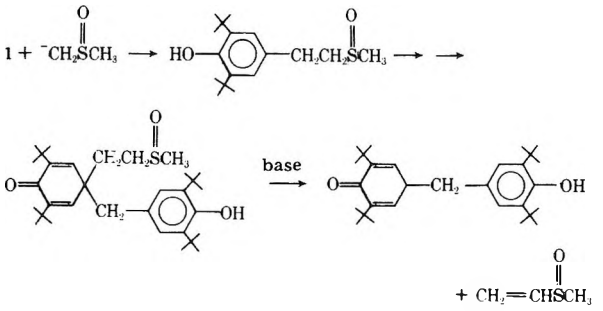
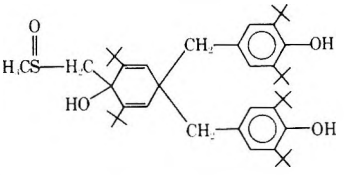
(5) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy", Academic Press, New York, N.Y., 1963.
(6) By comparison, **3** in deuteriochloroform possessed chemical shifts of 1.31 for the quinoid *tert*-butyl, 1.40 for the aromatic *tert*-butyl, 5.1 for the hindered phenolic hydroxyl, 6.43 for the quinoid ring hydrogens, and 6.97 for the aromatic ring hydrogens (downfield from internal Me_4Si).[3]
(7) The FFT spectrum was obtained on a 16% solution in deuteriochloroform by making 54 scans using a 300-s interval between scans, with a pulse width of 11.5 μs (90°) and a 6000 Hz sweep width.
(8) The assignments of chemical shifts to the various carbon atoms were made based upon the peak heights and are downfield from the ^{13}C signal of Me_4Si.
(9) A mechanism can be devised wherein a one-carbon extrusion could be accomplished by the intimate participation of the dimsyl anion in the mechanism, e.g.



Attempts to trap methyl vinyl sulfoxide using anthracene, a Michael receptor, failed.

(10) We thank referee 1 for his fruitful comments and suggestions concerning the mechanism.

(11) This compound could not be unequivocally identified. Owing to its very low solubility, a satisfactory NMR spectrum could not be obtained, although it appeared to possess two different *tert*-butyl groups and a methyl group. The infrared spectrum (KBr) showed absorptions at 3618 and 3400 cm^{-1}, indicating both hindered and bound hydroxyl groups; a single peak at 1638 cm^{-1}, unlike the doublet characteristic of cyclohexadienones,[3] suggesting a nonconjugated double bond; and an absorption at 1020 cm^{-1} possibly due to a sulfoxide absorption. The mass spectrum gave an apparent parent ion at *m/e* 728 ± 4. A spray reagent used to detect sulfoxides on TLC plates[12] gave a positive test. Based upon these data, a possible structure would be an adduct between the dimsyl anion and **5**, e.g.



(12) J. S. Grossert and R. F. Langler, *J. Chromatogr.*, **97**, 83 (1974).

A Dramatic Solvent Effect in the Diels–Alder Reactions of Ortho Benzoquinones

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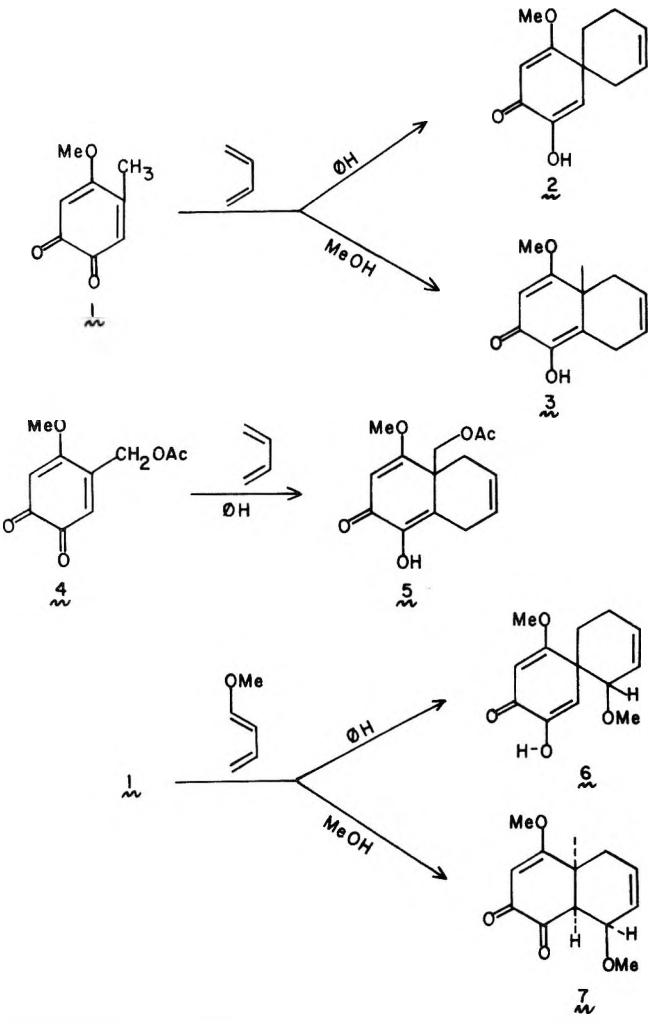
Received December 16, 1976

Conventional wisdom has it that solvent effects are of relatively nominal importance in determining the course of Diels–Alder reactions.[1] This might be expected in the light of the concerted nature perceived for the [2 + 4] cycloaddition process.[2]

Recently we have investigated the efficacy of 5-substituted 4-methoxy-1,2-benzoquinones as dienophiles.[3,4] Compound **1** reacts with 1,3-butadiene in benzene quite slowly. Upon heating at 105 °C (sealed tube) for 5 h, a 60% yield of "abnormal" adduct **2** was obtained.[3] Under these conditions we did not isolate any of the expected "normal" product **3**, though the absence of an authentic sample precluded a definitive statement as to whether small amounts of **3** might have been produced. Curiously, this "abnormal" process, involving enolization of the 5-alkyl group followed by cycloaddition to the tautomeric quinone methide,[5] is quite structure dependent since, under the same conditions, ortho quinone **4** gives only the expected product **5**.[4] In studying Diels–Alder reactions of compound **4**, we found that cycloaddition occurred more rapidly and efficiently when the reactions were conducted in methanol. Accordingly, it was of interest to examine the cycloaddition of **1** with 1,3-butadiene in this solvent.

Reaction of **1** with 1,3-butadiene in methanol at 100 °C (sealed tube) for 20 h gave, upon rapid chromatography on Florisil, a 63% yield of a crystalline 1:1 adduct, mp 103.5–104 °C, whose spectral properties clearly define it to be the "expected" product, **3**.[6] Examination of the NMR spectrum of the crude reaction mixture indicated the presence of ca. 12% of abnormal adduct **2**.[7] Thus a pronounced solvent effect is observed in promoting the course of the two modes of Diels–Alder reaction of **1** with 1,3-butadiene.[8]



A similar trend was observed in studying the cycloaddition of **1** with *trans*-1-methoxybutadiene. In benzene, upon heating under reflux for 6 h, a 37% yield of spiro adduct **6**, mp 110–111 °C, is obtained.[9] Since the compound is rather unstable to chromatography, a clearer definition of the competing processes was provided by examination of the NMR spectrum of the crude reaction mixture. This indicated a 5:1 ratio of **6**:**7** (vide infra). Conversely, when the reaction was conducted in methanol under reflux, a 67% yield of normal adduct **7**, mp 118.5–119.5 °C, was obtained after chromatography on Florisil. NMR analysis prior to chromatography indicated the ratio of **6**:**7** to be ca. 1:10.[7]

We have studied the effect of mixed solvents on the course of these cycloadditions. Using a 1:1 molar mixture of methanol–benzene (100 °C, sealed tube) reaction of **1** with butadiene gave essentially the same product distribution (**7** ≫ **6**) as with pure methanol. However, reaction of **1** with 1-methoxybutadiene in 1:1 molar methanol–benzene gave ca. a 1:1 mixture of **7**:**6**.

Clearly, these data do not allow for a precise definition of the role of solvents in determining the course of Diels–Alder products. However, they suggest that solvent manipulation may be of more useful consequence in producing desired results than has been hitherto supposed.

Experimental Section[10]

Diels–Alder Reaction of Quinone (1) with 1,3-Butadiene in Absolute Methanol. Formation of *dl*-1-Hydroxy-4-methoxy-

4a-methyl-4a,5-dihydronaphthalen-2(8*H*)-one (3). A solution of 0.250 g (1.65 mmol) of quinone 1 in 5 mL of absolute methanol and 3.5 mL of 1,3-butadiene was heated in a sealed glass tube at 100 °C for 20 h. The color changed from red-orange to light yellow during this time. Evaporation of the volatiles left a residue which was *rapidly* chromatographed on 30 g of Florisil. Elution with 3:1 hexane–ethyl acetate afforded 0.214 g (63%) of adduct **3**. Washing with pentane gave analytically pure material: mp 103.5–104 °C; λ_{max} ($CHCl_3$) 2.86, 6.20 μ; δ ($CDCl_3$, 250 MHz) 1.38 (s, 3), 2.11 (d, J = 17.5 Hz, 1), 2.56 (dd, J = 17.5, 4 Hz, 1), 2.86 (d, J = 20 Hz, 1), 3.45 (d, J = 20 Hz, 1), 3.78 (s, 3), 5.66 (s, 1), 5.67–5.75 (m, 2), 6.70 (s, 1 exchanges with D_2O).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.62; H, 6.74.

Diels–Alder Reaction of Quinone (1) with 1-Methoxy-1, 3-butadiene in Absolute Methanol. Preparation of *dl*-4aα-Methyl-8aα-4,8β-dimethoxy-1,2,4a,5,8,8a-hexahydronaphthalene-1,2-dione (7). To a solution of 0.200 g (1.32 mmol) of quinone 1 in 5 mL of absolute methanol was added 0.331 g (3.95 mmol] of 1-methoxy-1,3-butadiene (Aldrich). The orange solution was heated under reflux under a nitrogen atmosphere for 6 h. During this time the color became yellow. The solution was cooled and the volatiles removed in vacuo to afford a brown solid which upon trituration with pentane containing a small amount of ether gave 0.206 g (67%) of adduct (7), as an off-white crystalline solid: mp 118.5–119.5 °C; λ_{max} ($CHCl_3$) 5.80, 6.06, 6.23 μ; δ ($CDCl_3$, 250 MHz) 1.34 (s, 3), 1.71 (d, J = 15 Hz, 1), 2.85 (d,d J = 15, 6 Hz, 1), 3.09 (d, J = 9 Hz, 1), 3.23 (s, 3), 3.81 (s, 3), 4.00 (d, J = 9 Hz, 1), 5.78 (s, 1), 5.80–5.99 (m, 2).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.07; H, 6.78.

Diels–Alder Reaction of Quinone (1) with 1-Methoxy-1,3-butadiene in Benzene. Formation of Spiro Adduct (6). To a solution of 0.150 g (0.99 mmol) of quinone (1) in 6 mL of benzene was added 0.250 g (2.96 mmol) of 1-methoxy-1,3-butadiene. The solution was heated under reflux for 6 h. The reaction mixture was cooled and the volatiles evaporated in vacuo to give an oil. This was *rapidly* chromatographed on 20 g of Florisil. Elution with 3:1 hexane–ethyl acetate afforded 0.087 g (37%) of spiro adduct (**6**): mp 110–111 °C; λ_{max} ($CHCl_3$) 6.11, 6.38 μ; δ ($CDCl_3$, 60 MHz) 1.8–3.0 (m, 5), 3.4 (s, 3), 3.9 (s, 3), 5.1 (m, 1) 5.6 (s, 1), 5.9–6.1 (m, 2), 6.8 (q. 1).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.96; H, 6.81.

Diels–Alder Reaction of Quinone (1) with 1,3-Butadiene in 1:1 Molar Ratio Benzene–Absolute Methanol. A solution of 0.100 g (0.66 mmol) of quinone (1), 2 mL of 1,3-butadiene, and 2 mL of a 1:1 molar ratio solution of benzene–absolute methanol was heated at 100 °C in a sealed glass tube for 20 h. The color changed from red-orange to a light yellow during this time. Evaporation of the volatiles gave an oil which was *rapidly* chromatographed on 12 g of Florisil. Elution with 3:1 hexane–ethyl acetate afforded 0.075 g (56%) of adduct **3**.

Diels–Alder Reaction of Quinone (1) with 1-Methoxy-1,3-butadiene in 1:1 Molar Ratio Benzene–Absolute Methanol. To a solution of 0.100 g (0.66 mmol) of quinone (1) in 2 mL of 1:1 molar ratio solution of benzene–methanol was added 0.175 g (3.16 equiv, 2.08 mmol) of 1-methoxy-1,3-butadiene. The solution was heated under reflux under N_2 for 6 h. The volatiles were removed completely in vacuo to give an oil which could not be crystallized. The crude NMR spectra of this material showed it to be a mixture of adduct 7 and spiro adduct 6 in a ratio of approximately 1:1.

Acknowledgments. These studies were supported by PHS Grant CA-12107-10-12 and by a grant from the Merck Corp. NMR spectra were obtained on facilities supported by PHS Grant RR-00292-08. The assistance of Mr. Vance Bell and Mr. Glen Herman in obtaining mass spectra is gratefully acknowledged.

Registry No.—1, 13523-09-6; 3, 62006-21-7; 6, 62006-22-8; 7, 62006-23-9; 1,3-butadiene, 106-99-0; methanol, 67-56-1; 1-methoxy-1,3-butadiene, 3036-66-6; benzene, 71-43-2.

References and Notes

(1) For the effect of solvent polarity on endo–exo ratios in Diels–Alder reactions see J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962); K. Nakagawa, Y. Ishii, and M. Ogawa, *Chem. Lett.*, 511 (1976).
(2) See S. Seltzer, *Adv. Alicyclic Chem.* 2, 1 (1960).
(3) S. Mazza, S. Danishefsky, and P. M. McCurry, *J. Org. Chem.*, **39**, 3610 (1974).
(4) S. Danishefsky, P. F. Schuda, S. Mazza, and K. Kato, *J. Org. Chem.*, **41**, 3468 (1976).
(5) Cf. inter alia (a) L. F. Fieser and C. K. Bradsher, *J. Am. Chem. Soc.*, **61**, 417 (1939); (b) L. F. Fieser and M. Fieser, *ibid.*, **61**, 596 (1939); (c) W. Brown, J. W. A. Findlay, and A. B. Turner, *Chem. Commun.*, 10 (1968); (d) S. M. Ali and A. B. Turner, *J. Chem. Soc., Perkin Trans. 1*, 2225 (1974).
(6) As previously observed[4] the normal adducts of orthoquinones with 1,3-butadiene exist as the diosphenols while those derived from *trans*-1-methoxy-1,3-butadiene exist in the α-diketone form.
(7) Unfortunately, in our hands, these products are unstable to column or gas chromatography. Only the major components are isolated after substantial loss by rapid chromatography on Florisil. Product ratios are thus approximate and are based on integration of the angular methyl signal of the normal adducts relative to the methoxy signals of both compounds.
(8) For a report indicating that Diels–Alder cycloaddition to quinones (though not acid catalyzed) occurs faster in ethanol than in benzene see A. Wasserman, *J. Chem. Soc.*, 828 (1935).
(9) The stereochemistry of the secondary methoxyl group is unassigned. Apparently only a single isomer is produced in the "normal" mode.
(10) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded in chloroform solution using sodium chloride optics on either a Perkin-Elmer 137 infrared spectrophotometer or a Perkin-Elmer 247 infrared spectrophotometer. The polystyrene absorption at 6.238 μ was used as a reference. Only selected high intensity absorptions are reported. The NMR spectra were measured in $CDCl_3$ with tetramethylsilane as an internal reference. Chemical shifts are reported in parts per million (δ) relative to Me_4Si. Elemental analyses were conducted by Galbraith Laboratories, Inc., Knoxville, Tenn.

Studies on *N*-Alkyl-2(1*H*)-pyridothione. 1. A New Synthetic Method for Thiols

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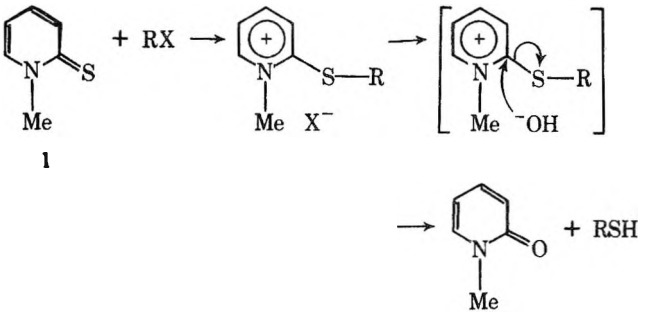
Received November 29, 1976

Widely used laboratory methods for the preparation of thiols are the reaction of alkyl halides with sodium hydrosulfide[1] or thiourea with subsequent alkaline hydrolysis,[2] and the direct alkylation of free sulfur with aryllithium[3] or Grignard reagents.[4] Although the thiourea method has been generally employed in preparative scale, α-mercaptocarbonyl compounds cannot be obtained because of thiazole formation.[5]

In this laboratory, the chemistry of *N*-methyl-2-alkylthiopyridinium salts has been investigated as an extension of studies on *N*-(ω-haloalkyl)pyridinium salts.[6] It was found in preliminary experiments that *N*-methyl-2(1*H*)-pyridothione



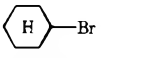
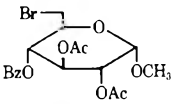
1

(1) reacted readily with alkyl halides to give the corresponding 2-alkylthiopyridinium salts, which were very labile under alkaline conditions.

We now wish to describe briefly a new preparative method for various kinds of thiol by alkaline hydrolysis of these salts, which are activated intermediates similar to *S*-thiouronium salts.[2] Primary and secondary halide, α-halo ketone, α- and β-halocarboxylic ester, and halo sugar were employed as alkyl halide for quaternization.

A series of the key intermediates, *N*-methyl-2-alkylthiopyridinium salts, was synthesized in refluxing ethanol in yields of 81–84% (see Table I). A little higher temperature (in

Table I. Reaction of 1 with Alkyl Halides and Hydrolysis of the Salts

Run	RX		Solvent	Time, h	Yield, %, of the salt		Yield, %, of thiol[b]	
1	$PhCH_2Br$	2a	CH_3CN	0.5	2b	83	2c	90
2	$PhCH_2CH_2Br$	3a	EtOH	4	3b	84	3c	82
3		4a	*n*-PrOH	16	4b	*a*	4c	70
4	$ClCH_2COPh$	5a	EtOH	4	5b	81	5c	72[c]
5	$ClCH_2COOEt$	6a	EtOH	4	6b	83	6c	65[d]
6		7a	*n*-PrOH	8	7b	*a*	7c	71[c]
7	$BrCH_2CH_2COOCH_2CH_2Ph$	8a	EtOH	4	8b	*a*	8c	0[e]

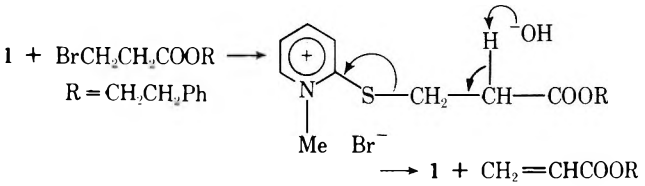
[a] Too hygroscopic to isolate. [b] Calculated from disulfide. [c] Isolated as thiol.[9] [d] Obtained after reesterification. [e] β-Elimination product only was isolated.

1-propanol) was more effective in the case of more hindered cyclohexyl bromide (**4a**) and methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-acetyl-α-D-glucopyranoside[7] (**7a**) prepared by NBS reaction.[8]

Hydrolytic cleavage of the C–S bond of the salts proceeded smoothly (within 30 min) in aqueous sodium hydroxide at room temperature. Acidification with hydrochloric acid gave the corresponding thiols, which in runs 1–3 and 5 were isolated as the odorless disulfides with iodine treatment. These reactions were performed without isolation of the quaternary salts. Although, at the hydrolysis step, blocking groups acetyl, benzoyl, and phenethyl were not affected in runs 6 and 7, the ethyl acetate derivative (**6b**) was saponified under the same conditions to give α-mercaptoacetic acid which was reesterified for isolation (run 5). The structure of the syrupy methyl 4-*O*-benzoyl-2,3-di-*O*-acetyl-6-thio-α-D-glucopyranoside (**7c**) was determined by microanalysis and ^1H NMR data in which SH appears at 1.20 ppm as a triplet.

It is particularly noteworthy that this method is nicely applicable to preparation of α-mercaptocarbonyl compounds (**5c, 6c**) and thio sugar **7c** with yields of 72, 65, and 71%, respectively.

However, when this method was applied to phenethyl β-bromopropionate (run 7), the intermediary salt (**8a**) underwent β-elimination under the hydrolysis conditions to give phenethyl acrylate in 68% yield with recovery of **1**.



Experimental Section[10]

Preparation of the Quaternary Salts. A mixture of *N*-methyl-2(1*H*)-pyridothione (1, 1.25 g, 0.01 mol) and a series of alkyl halides (0.01 mol) was refluxed in the solvent for a suitable time (see Table I). After removal of solvent, the crude solid was recrystallized from the solvent described below.

2b (CH_3CN), mp 183–184 °C.

Anal. Calcd for $C_{13}H_{14}NSBr$: C, 52.72; H, 4.76; N 4.73; S, 10.80. Found: C, 52.47; H, 4.68; N, 4.56; S, 10.54.

3b (*i*-PrOH), mp 148–150 °C.

Anal. Calcd for $C_{14}H_{16}NSBr$: C, 54.20; H, 5.20; N, 4.52; S, 10.32. Found: C, 54.56; H, 5.20; N, 4.58; S, 10.23.

5b (*i*-PrOH) did not show a clear melting point.

Anal. Calcd for $C_{14}H_{14}OSCl$: C, 60.11; H, 5.05; N, 5.01; S, 11.44. Found: C, 59.98; H, 5.01; N, 4.94; S, 11.21.

6b (*i*-PrOH) did not show a clear melting point.

Anal. Calcd for $C_{10}H_{14}O_2NSCl$: C, 48.49; H, 5.70; N, 5.66; S, 12.92. Found: C, 48.24; H, 5.45; N, 5.53; S, 12.78.

Other salts were too hygroscopic to isolate.

General Procedure for Thiols. The above crude solid was dissolved in water (10 mL) and then treated with 1 N sodium hydroxide (15 mL) for 30 min at room temperature. Thiol generated by acidification with 1 N hydrochloric acid (10 mL) was extracted with chloroform. The extract contained practically pure thiol.

α-Mercaptoacetophenone 5c (1.1 g, 72%): bp 95 °C (0.7 mm) [lit.[9] bp 87–90 °C (0.5 mm)]; ^1H NMR δ 3.90 (2 H, d, J = 8.0 Hz, CH_2S) and 2.10 (1 H, t, J = 8.0 Hz, SH).

Methyl 4-*O*-Benzoyl-2,3-di-*O*-acetyl-6-thio-α-D-glucopyranoside (7c). The syrup obtained by removal of the chloroform extract was chromatographed to give syrup **7c** (2.8 g, 71%): $[\alpha]^{22}_D$ +175° (*c* 2.2, ethanol); ^1H NMR δ 1.20 (1 H, t, J = 8.0 Hz, SH).

Anal. Calcd for $C_{18}H_{22}O_8S$: C, 54.27; H, 5.33; S, 8.04. Found: C, 54.43; H, 5.72; S, 7.88.

Isolation as Disulfides. Phenylmethanethiol (2c), 2-Phenylethanethiol (3c), and Cyclohexanethiol (4c). The chloroform solution was treated with iodine (1.5 g)–1 N sodium hydroxide (15 mL) and then washed with aqueous sodium hyposulfide to remove excess iodine. After evaporation, the residue was purified by column chromatography (2.5 × 10 cm). The disulfide of **2c** (1.1 g, 90%) was crystallized from ethanol (5 mL): mp 70–71 °C (lit.[11] mp 72 °C); ^1H NMR δ 3.63 (4 H, s, CH_2).

Disulfide of **3c** (1.1 g, 82%): bp 180 °C (0.7 mm) [lit.[12] bp 172–175 °C (0.8 mm)]; ^1H NMR δ 3.43 (8 H, s, CH_2CH_2).

Disulfide of **4c** (0.81 g, 72%): bp 125 °C (0.2 mm) [lit.[13] bp 130–131 °C (0.35 mm)]; ^1H NMR δ 2.67 (2 H, m, SCH).

Ethyl α-Mercaptoacetate (6c). After iodine oxidation, the product was esterified in refluxing ethanol containing a catalytic amount of concentrated sulfuric acid for 2 h. To the mixture was added barium carbonate and then the mixture was filtered. After evaporation, the liquid was distilled to give **6c** (0.78 g, 65%): bp 165 °C (12 mm) [lit.[14] bp 164 °C (14 mm)]; δ 3.63 (4 H, s, CH_2).

Registry No.—**1**, 2044-27-1; **2a**, 100-39-0; **2b**, 62058-65-5; **2c** disulfide, 150-60-7; **3a**, 103-63-9; **3b**, 62058-66-6; **3c** disulfide, 27846-22-6; **4a**, 108-85-0; **4c** disulfide, 2550-40-5; **5a**, 532-27-4; **5b**, 62058-67-7; **5c**, 2462-02-4; **6a**, 105-39-5; **6b**, 62058-68-8; **6c**, 623-51-8; **7a**, 56543-19-2; **7c**, 62058,69-9; **8a**, 62058-70-2.

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T-60 spectrometer using tetramethylsilane as internal standard in chloroform-d_1. Satisfactory analytical data (±0.3%) were obtained on all products. Column chromatography was performed on silica gel (Wako C300, Japan) using chloroform for elution.

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Chemisorbed Chromyl Chloride as a Selective Oxidant

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Selective oxidation is one of the most important of all chemical transformation. Many oxidants, however, remain too vigorous for such application. In this regard, one of the distinct advantages which heterogeneous reactions offer is the ability to isolate and moderate reactive species by chemisorption. Such procedures frequently have the additional virtue that intermediate products which under homogeneous conditions would prove difficult or impossible to isolate, for a variety of reasons become readily isolable under heterogeneous conditions. We have explored the possibility of moderating the reactivity of several strong oxidants by employing them as chemisorbed reagents on a high-surface, inert support. Here we report the results of one such investigation: specifically, the utility of chromyl chloride adsorbed on silica–alumina as a convenient, efficient, economical reagent for the oxidation of alcohols under neutral, nonaqueous conditions.

$$RCH_2OH \xrightarrow[CH_2Cl_2,\ 25\ °C]{CrO_2Cl_2/SiO_2-Al_2O_3} RCHO$$

$$RR'CHOH \xrightarrow[CH_2Cl_2,\ 25\ °C]{CrO_2Cl_2/SiO_2-Al_2O_3} RR'CO$$

This reaction seems to be applicable to the oxidation of primary and secondary alcohols to the respective aldehyde and ketone. A preliminary examination of the functional group compatibility of this reagent indicates that halocarbons, esters, lactones, nitriles, and ethers appear inert. Olefins, on the other hand, undergo oxidative cleavage. Thus, the same reagent will, for example, convert stilbene to benzaldehyde in 71% yield.[2]

Chromyl chloride is a vigorous oxidant whose action on organic substrates generally produces complex mixtures of products.[3] Recently, Sharpless and co-workers have demonstrated that a substantial moderation of this reactivity toward certain substrates (specifically olefins) can be achieved if these reactions are carried out at low temperatures.[4a] Further moderation can be achieved by employing a reagent derived by admixing chromyl chloride with *tert*-butyl alcohol and pyridine in methylene chloride at low temperatures.[4b] The resulting reagent is useful for the homogeneous oxidation of alcohols to aldehydes and ketones.

It is clear from the results in Table I that the chromyl chloride chemisorbed on silica–alumina is a great deal more selective than the homogeneous reagent. It is not apparent, however, whether this enhanced selectivity is a result of the inherently reduced reactivity of the chemisorbed species relative to that of chromyl chloride, or to the ability of the rigid support to immobilize a highly reactive species [e.g., Cr(IV)] so as to prevent its further possible reactions,[13a] reactions which could ultimately lead to a complex mixture of reaction products such as observed under homogeneous conditions.

Several investigators have recently employed the concept of utilizing reagents adsorbed on inert inorganic supports for organic synthesis.[5-7] Of these, three in particular bear brief comparison.[8] Lalancette and co-workers[9] have reported that primary but not secondary alcohols are oxidized to the corresponding aldehydes by a reagent purported to be CrO_3–graphite.[10] Complementing this activity are the results of Posner and co-workers,[6] who found that secondary but not primary alcohols are effectively oxidized by trichloroacetaldehyde when carried out over highly activated alumina. In contrast, the reactivity of chemisorbed chromyl chloride compares to that of the more standard reagents for alcohol oxidation[13] with the distinct advantages of preparative and manipulative convenience, similar to those recently reported

Table I. Reaction of Alcohols with Chromyl Chloride Adsorbed on Silica–Alumina[a]

Substrate	Registry no.	Product (%)[b]	Registry no.	Reaction time, h
1-Octanol	111-87-5	1-Octanal (94)	124-13-0	5
2-Octanol	123-96-6	2-Octanone (94)	111-13-7	24
2,2-Dimethylpropanol	75-84-3	2,2-Dimethylpropanal (78)	630-19-3	24
4-*tert*-Butylcyclohexanol	98-52-2	4-*tert*-Butylcyclohexanone (89)	98-53-3	6
exo-2-Norbornanol	497-37-0	2-Norbornanone (87)	497-38-1	24
1-Phenylethanol	60-12-8	Acetophenone (100)	98-86-2	5
Methyl mandelate	771-90-4	Methyl (2-keto-2-phenyl)acetate (77)	15206-55-0	
		Benzaldehyde (14)	100-52-7	3
Benzoin	119-53-9	Benzil (89)[c]	134-81-6	
		Benzaldehyde (6)		24
3-β-Cholestanol	17608-41-2	Cholestan-3-one (89)[c]	15600-08-5	5
Benzyl alcohol	100-51-6	Benzaldehyde (94)		5
4-Nitrobenzyl alcohol	619-73-8	4-Nitrobenzaldehyde (87) (83)[c]	555-16-8	5
4-Cyanobenzyl alcohol	874-89-5	4-Cyanobenzaldehyde (85)	105-07-7	5
4-Methylbenzyl alcohol	589-18-4	4-Methylbenzaldehyde (100)	104-87-0	4
2-Chlorocyclohexanol	1561-86-0	2-Chlorocyclohexanone (87)	822-87-7	24
2-Bromocyclohexanol	24796-87-0	2-Bromocyclohexanone (95)	822-85-5	24
2-Bromo-1-indanol	5400-80-6	2-Bromo-1-indanone (77)	1775-27-5	12

[a] Reactions carried out at 25 °C in methylene chloride solvent. Substrate to oxidant ratio: 0.10 mol to ~180 g of CrO_2Cl_2–SiO_2–Al_2O_3 reagent (2.92% Cr by weight[15]). [b] Yields, unless otherwise indicated, were determined by GLC or HPLC. Products were identified by comparison of their IR and mass spectra with those of authentic samples as well as GLC retention times and melting points where applicable. [c] Value based on isolated yield.

by Cainelli and co-workers for the oxidation of alcohols by chromic acid on anion exchange resins.[14]

Experimental Section

In a typical procedure, a solution of CrO_2Cl_2 (10.0 g) in methylene chloride (100 mL) is added with stirring to a slurry of SiO_2–Al_2O_3 (90.0 g, Grace Davison No. 135) in methylene chloride (150 mL). After stirring for an additional 5 min, the yellow-orange solid was collected by suction filtration on a fritted-glass funnel and subsequently dried under reduced pressure. The resulting solid can be used immediately or stored indefinitely if reasonable precautions against moisture are observed.

The following description represents a typical oxidation procedure. Two grams of the above reagent (1.10 mmol of Cr as determined by elemental analysis[15]) are placed in a flask along with 20 mL of methylene chloride and a Teflon-coated stirrer bar. A solution of 1-octanol (0.143 g, 1.10 mmol) in methylene chloride (5 mL) is added and the flask equipped with a drying tube. The resulting mixture is stirred for 5 h before adding 0.5 mL of methanol and filtering. The residual solids are rinsed with two 10-mL portions of methylene chloride and the combined clear, colorless filtrates analyzed directly by GLC. The yield of 1-octanal is 94%; none of the corresponding carboxylic acid is observed. A summary of the results obtained with other representative substrates is presented in Table I.

Registry No.—Chromyl chloride, 14977-61-8.

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Dynamic Carbon-13 Nuclear Magnetic Resonance Spectra of Benzobullvalene and *o*-Toluobullvalene

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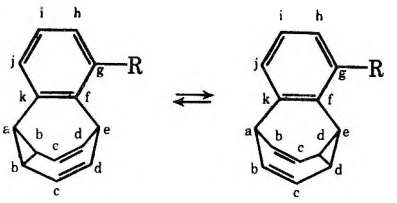
The factors which control the rate of the Cope rearrangement in bullvalene and related compounds are a topic of considerable interest.[1] The elegant work of Oth[2] and Günther[3] has shown that variable temperature ^{13}C NMR is an ideal tool for such investigations. The synthesis and dynamic ^{13}C NMR study of benzobullvalene (**1**, R = H) and *o*-toluobullvalene (**1**, R = Me) is now reported.

The synthesis of these compounds was based on Doering's



1 **2**

rational scheme for the preparation of bullvalene[4] employing the benzyne adduct of tropone[5] as a starting material. Eisenstadt[6] has recently published an analogous procedure. The low- and high-temperature ^{13}C NMR chemical shifts and their assignments are given in Table I. Peaks were assigned on the basis of intensity, chemical shift, multiplicity in off-resonance proton decoupled spectra, and by following their pairwise coalescence as temperature was increased. The assignment of carbons a and e in *o*-toluobullvalene is critical for the assignment of the major isomer for this nondegenerate case. In benzobullvalene, the cyclopropane carbon, 1a or 2e, is upfield of the methine carbon, 1e or 2a, based on the known assignment of bullvalene.[2,3] The introduction of the methyl group in o-toluobullvalene results in an upfield shift of 5.9 ppm in the high field peak of minor isomer as the only significant shift change. Based on the well-established,[7] γ-upfield shift of methyl groups, the major isomer is assigned structure **2**, R = Me. Based on peak intensities in the low temperature spectrum, the equilibrium constant was found to be 1.6 ± 0.3 at −59 °C. Based on the population averaged chemical shifts at 143 °C, an equilibrium constant of 1.1 ± 0.3 is obtained. The preference for the methyl group on the same side of the molecule as the cyclopropane is consistent with the data recently reported for the methyl group in 9-ethylidenebarbaralene.[8] The reason for this preference remains obscure.

The dynamic parameters for the Cope rearrangement in benzobullvalene were determined by variable temperature carbon-13 NMR. A program[9] employing an equal population two site exchange process was used to calculate the theoretical line shapes. The large spread of chemical shift differences between exchanging carbons permitted observation of line broadening phenomena from −50 to 120 °C. The activation parameters are shown in Table II together with those reported for bullvalene. It is perhaps worth noting that the factor of 2 rate increase (0 °C) induced by replacing a double bond in bullvalene with a benzo group is the smallest structurally induced perturbation on the rate of the degenerate Cope reaction in bridged homotropilidenes.

Our plans to examine a range of substituted benzobullvalenes were thwarted by the observation that the reaction of tropone with 3-chloro- and 3-methoxybenzyne (generated from the 6-substituted anthranilic acids) gave substituted cycloheptatrienylbenzofuran derivatives.

Experimental Section[10]

Proton NMR spectra were recorded on Varian A-60 and XL-100-15 spectrometers in $CDCl_3$. Chemical shifts are reported in δ units from internal Me_4Si. IR spectra were recorded in KBr disks on Perkin-Elmer 257 and 727 spectrometers and mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed by the Purdue Microanalytical Service. Melting points are uncorrected.

Tropone,[11] 6,7-benzobicyclo[3.2.2]nonatrien-2-one,[12] and 6,7-benzobicyclo[3.2.2]nonatrien-2-ol[13] were prepared by previously published methods. Details of an improved procedure for the preparation of benzobullvalene are given in the microfilm edition. The product had mp 109–110 °C (lit.[6,14] 89, 110–111 °C). Spectral details for the o-toluobullvalene intermediates may also be found in the microfilm edition.

Methyl-6,7-benzobicyclo[3.2.2]nona-3,6,8-trien-2-one (I). In a 600-mL beaker equipped with a stirring bar and thermometer 3-methylanthranilic acid (32.0 g, 0.212 mol) was dissolved in dry THF (250 mL). After cooling in an ice bath Cl_3CCO_2H (0.3 g) dissolved in

Table I. Carbon-13 Chemical Shifts of Benzobullvalenes[a,b]

	Benzobullvalene		o-Toluobullvalene		
Carbon	−59 °C	143 °C	(1) −60 °C	(2) −60 °C	140 °C
a	25.0	33.2	25.6	39.6	33.9
b	20.3	77.5	20.2	127.0	78.3
c	126.1	126.1	126.3	126.3	126.5
d	127.2	77.5	126.9	20.4	75.1
e	39.1	33.2	32.1	19.1	26.5
f	(136.7)	137.8			
g	127.0	129.3			
h	126.4[c]	126.4	125.3	126.3	125.6
i	126.0[c]	126.4	129.0	129.3	129.0
j	131.0	129.3	130.8	125.5	128.0
k	(136.7)	137.8			
Me			21.1	21.3	20.2

[a] Chemical shifts are reported relative to internal Me_4Si. At low temperatures, shifts were determined directly, at high temperature shifts were measured relative to solvent and corrected to Me_4Si using the room temperature shift between Me_4Si and solvent. [b] Chemical shifts for bullvalene:[3] a, 20.5; c, 127.2; d, 128.1; e, 30.0. [c] The assignment of pairs of peaks may be reversed.

Table II. Activation Parameters for Cope Rearrangement

Compd	E_A, kcal/mol	A × 10^{13} s^{-1}	k (0 °C), s^{-1}	Ref
Benzobull-valene	11.8	0.37	1350	This work
Bullvalene	13.18	2.37	671	a
	13.9	10	670	b
	11.5	0.13	790	b
	12.8	0.78	416	c

[a] Reference 3. [b] Reference 2. [c] A. Allerhand and H. S. Gutowsky, *J. Am. Chem. Soc.*, **87**, 4092 (1965).

THF (10 mL) was added, followed by the slow addition of isoamyl nitrite (45 mL, 39.2 g, 0.335 mol) over a 5-min period. After warming to 18–25 °C for 1 h, the red precipitate was cooled, collected on a plastic funnel with greased filter paper, washed with excess cold THF, and transferred with a minimum of dry THF to a dry three-neck 500-mL flask equipped with a condenser and N_2 inlet tube. Tropone (20.0 g, 0.189 mol) was added and the reaction flask was immersed in a 35–37 °C oil bath. The reaction should be carefully watched, since the decomposition of the diazonium salt can become very violent with a small increase in temperature. After 8 h the reaction was cooled, concentrated on the rotary evaporator, and filtered over alumina (200 mL) in a 350-mL coarse fritted-disk funnel with ether (1 L). The filtrate was concentrated to 400 mL and dried over $MgSO_4$. Filtration followed by rotary evaporation yielded approximately 35 mL of a black liquid which was vacuum distilled (Hg diffusion pump) to recover unreacted tropone (9.01 g, 45.5%) at 55–58 °C, and the desired ketones I (12.06 g, 32.6%, 59.3% conversion) at 110–114 °C. I slowly crystallized upon refrigeration or the addition of a trace of ether. The solid was partially dissolved in hot pentane and filtered to yield the pure isomer Ia. The recrystallized solid was a mixture of both Ia and Ib: mp 60–65 and 90–95 °C for the mixture, 118–120 °C for Ia; NMR Ia, δ 2.42 (s, 3 H, CH_3), 4.29 (br dd, J = 8.5, 8,0, 1.5, 1 Hz, H-5), 4.96 (d, t, J = 7.5, 1.5, 1.5 Hz, H-1), 5.28 (dq (br ddd), J = 11, 1.5, 1 Hz, H-3), 6.63 (t, d, J = 7.5, 7.5, 7.5 Hz, H-9), 7.00 (ddd, J = 8, 7.5, 1.5 Hz, H-8), 7.10 (br s, 3 H, aromatic), 7.32 (dd, J = 11, 8.5 Hz, H-4); NMR Ib, δ 2.39 (s, 3 H, CH_3), 4.50–4.73 (m, 2 H, H-1 and H-5), 5.26 (br dd, J = 11, 1.5, 1 Hz, H-3), 6.66 (ddd, J = 8, 6.5, 1.5 Hz, H-9), 6.95 (ddd, J = 8, 6.5, 1.5 Hz, H-9), 7.05–7.19 (m, 3 H, aromatic), 7.35 (dd, J = 11, 8.5 Hz, H-4).

Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.65; H, 6.27.

Methylbenzobicyclo[3.2.2]nona-3,6,8-trien-2-ol (II). In a dried 500-mL flask purged with N_2, ketone Ia (1.00 g, 5.1 mmol) was dissolved in ether (300 mL) and cooled in a dry ice–acetone bath. $LiAlH_4$ (2.1 equiv, 0.101 g, 2.68 mmol) was added over a 15-min period with stirring. After 1.5 h an aliquot was filtered and examined by thin layer chromatography using 50% ether–pentane as the eluent. The chromatogram showed two spots which had smaller R_f values than the starting ketone. After 2–2.5 h the reduction was complete and quenched with a 20% aqueous sodium–potassium tartrate solution (15 mL), warmed to room temperature, and diluted with H_2O (100 mL). The phases were separated and the aqueous layer was extracted with more ether (three 50-mL portions). The ether extracts were dried over $MgSO_4$, filtered, and rotary evaporated to give the crude alcohol (1.03 g). Recrystallization from hexane yielded 0.93 g (92%) of IIa. If the mixture of ketones Ia and Ib were reduced, recrystallization recovered 75% of II as a solid, while the remaining 20% was an amorphous oil: mp 106–107 °C (endo isomer IIa only); NMR δ 1.65 (br s, 1 H), 2.45 (s, 3 H), 3.76 (br t, J = 7 Hz, 1 H), 4.14–4.45 (m, 2 H), 5.06 (d, t, J = 10, 3 Hz, 1 H), 6.24–6.64 (m, 2 H), 6.87–7.20 (m, 4 H).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.41; H, 7.12. Found: C, 84.79; H, 7.37.

Methylbenzobarbaralone (IV). (a) Rearrangement of II to III. Methylbenzo[3.2.2]nonatrienol (II) (0.500 g, 2.52 mmol) was dissolved in 33% dioxane–H_2O (150 mL) in a 500-mL flask. $HClO_4$ (70%, 15 mL) was added and stirred for 44 h. An aliquot was quenched in solid Na_2CO_3 and ether and examined by thin layer chromatography using 50% pentane–ether as the eluent. Once the major isomer of II had disappeared, an additional portion of 70% $HClO_4$ (15 mL) was added. After 48 h the reaction was carefully neutralized with small portions of solid Na_2CO_3, diluted with H_2O (100 mL), and extracted with ether (five 50-mL portions). The ether extracts are dried over $MgSO_4$, filtered, and rotary evaporated to give approximately 0.7 g of crude III.

(b) Oxidation of III to IV. Crude alcohol III was stirred with activated molecular sieves in dry CH_2Cl_2 under N_2 for several hours. The CrO_3 (6 equiv, 2.36 g, 23.6 mmol) dried under vacuum over P_2O_5 was added to a stirred solution of dry pyridine (12 equiv, 3.8 mL) and dry CH_2Cl_2 (100 mL) in a flame-dried, three-neck, 300-mL flask purged with N_2. After 15 min alcohol III was added to the homogeneous burgundy colored solution. (If a black insoluble solid was present the oxidizing agent was wet and should be discarded.) After 15 min 2-propanol (15 mL) was added and stirred for 5 min more. The reaction was transferred with ether (100 mL) to a separatory funnel and washed with 5% NaOH (three 100-mL portions) and 5% HCl (three 100-mL portions). If the organic phase was still highly colored, more washings were done with 5% NaOH and 5% HCl. The reaction mixture was finally washed with saturated $NaHCO_3$ (one 100-mL portion) and saturated NaCl (one 100-mL portion) and dried over $MgSO_4$. Filtration followed by rotary evaporation yields 0.373 g (75.4%) of crude ketone IV. Recrystallization from pentane or hexane yielded 59% of a mixture of the isomeric methylbenzobarbaralone (IV) (isomer a, 57%; isomer b, 43%): mp 109–110 °C (mixture of isomers); NMR IVa, δ 2.22–2.88 (m, 2 H, H-1 and H-2), 2.29 (s, 3 H, CH_3), 3.34 (t, J = 8 Hz, 1 H, H-8), 3.98 (br dd, J = 6.5, 2.5 Hz, 1 H, H-5), 5.63–6.09 (m, 2 H, H-3 and H-4), 6.82–7.15 (m, 3 H); NMR IVb, δ 2.22–2.88 (m, 2 H, H-1 and H-2), 2.41 (s, 3 H, CH_3), 3.34 (dd, J = 8, 7 Hz, 1 H, H-8), 3.69 (br dd, J = 6.5, 2.5 Hz, 1 H, H-5), 5.63 (m, 2 H, H-3 and H-4), 6.82–7.15 (m, 3 H).

Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.44; H, 6.44.

Methylbenzobullvalone (V). Methylbenzobarbaralone (IV) 1.81 g, 9.23 mmol) was dissolved in dry ether (200 mL) in a dry 1-L filtering flask immersed in an ice bath with an addition funnel, stirring bar,

and purged under nitrogen. BF_3·OEt_2 (1 equiv, 1.14 mL, 92 mmol) was added and stirred for 15 min. Previously distilled CH_2N_2 (12.75 equiv, 210 mL each of 0.31 and 0.25 M dried over KOH for 1 h) was added over a 1.5-h period to the reaction mixture. After the addition the reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL), filtered, washed with ether (100 mL), and diluted with H_2O (100 mL). The phases were separated and the aqueous layer extracted with more ether (two 25-mL portions). The combined ether extracts were dried over $MgSO_4$. Filtration followed by rotary evaporation gave an oily product which was chromatographed over silica gel (75 g, 80% CH_2Cl_2–hexane) to yield 0.97 g (50.4%) of V and 0.30 g (16.6%) of recovered IV: NMR V, δ 1.8–2.9 (m, 3 H), 2.36 and 2.44 (s, 3 H), 2.29 (m, 2 H), 3.74 and 4.12 (d, J = 9 Hz, 1 H), 5.77 (m, 1 H), 6.13 (m, 1 H), 6.8–7.3 (m, 3 H).

Methylbenzobullvalone Tosylhydrazone (VI). In a dry 50-mL flask purged with N_2, methylbenzobullvalone (V) (0.80 g, 3.8 mmol) and tosylhydrazine (0.70 g, 3.7 mmol) were stirred in dry ether (25 mL). After 57 h the product was filtered and washed with Et_2O (10 mL) to yield 0.428 g. Additional stirring of the filtrate for 36 h gave 10% more product. The total yield of crude VI was 0.478 g (34%), which was 90% one isomer VIa. The ether filtrates were concentrated on the rotary evaporator to give an additional 0.69 g of a puffy yellow solid. NMR indicated that 75% was probably VI. Estimated yield of VI was roughly 70%: mp, turns brown at 137 °C, 142–144 °C dec.

Methylbenzobullvalene (1, R = Me). Freshly distilled isopropylamine (3 equiv, 0.6 mL, 4.2 mmol) was dissolved in ether (100 mL) in a dry three-neck 300-mL flask equipped with a stirring bar and purged under N_2. After cooling the reaction in a dry ice-2-propanol bath, 3 equiv of n-BuLi (2.4 mL of 2.4 M in hexane) was added, and the mixture was warmed to 0 °C. Upon cooling the reaction flask to −78 °C, solid VI (0.217 g, 1.04 mmol) was added and the reaction was slowly warmed to room temperature. After several hours (3–8 h) the reaction was quenched with cold water (50 mL) and separated. The aqueous phase was extracted with ether (three 15-mL portions). The combined ether extracts were washed with 5% HCl (25 mL), saturated $NaHCO_3$ (25 mL), and saturated NaCl (25 mL), and dried over $MgSO_4$. Filtration followed by rotary evaporation gave a white solid: NMR δ 2.26 (s, 3 H); 2.82 (t, J = 9.5 Hz, 1 H), 2.17 (t, J = 9.5 Hz, 1 H), 3.5–4.6 (v br s, 4 H), 5.78 (complex t, 2 H), 6.75–7.20 (m, 3 H); IR (CCl_4) 685 (w), 700 (w), 730 (s), 750 (br s), 800 (s), 810 (sh), 815 (m), 875 (w), 915 (w), 975 (w), 1035 (w), 1095 (w), 1260 (w), 1375 (m), 1410 (w), 1450 (m), 1570 (s), 1580 (s), 1590 (w), 1650 (m), 2870 (w), 2970 (br m), 3030 (s), 3070 (sh) cm^{-1}; MS 195 (7.1), 194 (43.4), 193 (30.7), 192 (7.1), 191 (7.1), 189 (56.7), 180 (15.6), 179 (100), 178 (67.9), 177 (7.1), 176 (5.2), 166 (3.8), 165 (12.7), 153 (3.8), 152 (10.4), 151 (2.8), 142 (3.3), 141 (3.8), 139 (3.8), 129 (3.3), 128 (13.7), 127 (3.8), 115 (6.1), 96 (3.8), 89 (7.6), 77 (2.8), 76 (3.8), 63 (4.3), 51 (3.8), 39 (4.7).

Anal. Calcd for $C_{15}H_{14}$: C, 92.73; H, 7.26. Found: C, 92.44; H, 7.51.

Variable Temperature Carbon-13 NMR Spectra. Proton square wave decoupled[15] carbon-13 spectra were recorded on a modified Varian XL-100-15 spectrometer operating in the Fourier transform mode. The 25.16-MHz excitation frequency was supplied by a Hewlett-Packard Model 8660A frequency synthesizer. Data were collected and calculated on a Nicolet 1080-20 computer. Field-frequency lock was provided by a sample of acetone-d_6 contained in the annulus of a 12-mm tube. The sample itself was placed in a 10-mm tube inside the 12-mm tube. Data points (8K) were collected with a 5-KHz window resulting in 4K real data points after transformation. The excitation pulse length varied from 70 μs (pulse angle 52°) at low temperature to 30 μs (pulse angle 23°) at high temperature. The pulse repetition rate was 1.1 s, and a receiver recovery delay of 200 μs was employed. A minimum of 8192 scans was accumulated in each case. Chemical shifts were calculated from internal tetramethylsilane using the computer calculated frequency separation between peak maxima.

Temperature control was provided by a flow of precooled nitrogen gas using the Varian V4341 temperature controller. Temperature was measured with a Wilmad 5-mm low temperature thermometer and/or a chromel–alumel thermocouple. The temperature sensors were placed at the level of the observation coil immersed in a 12-mm tube containing $CHCl_2CHCl_2$ filled to the same level as the sample. Calibration studies both inside and outside the spectrometer showed that a substantial stem correction (over 10° at low temperature) was required for the thermometer, which varied with the ambient temperature. The thermocouple was used for all reported temperature measurements. Temperatures were recorded before and after data accumulation and were held constant within ±0.5 °C. The absolute temperature is presumed to be accurate to ±1 °C. The samples were prepared by dissolving 0.35 mg of benzobullvalene (0.121 mg of *o*-toluobullvalene) in 2.5 mL of $CHCl_2CHCl_2$ together with 2–3 drops of tetramethylsilane. No corrections for the temperature dependence of chemical shifts were applied in the calculations.

Registry No.—Ia, 61990-59-8; Ib, 61990-60-1; II, 61990-61-2; III, 61990-64-5; IVa, 61990-62-3; IVb, 61990-63-4; V, 61990-91-8; VIa, 61990-65-6; VIb, 61990-66-7; VIIa, 61990-67-8; VIIb, 62015-28-5; VIII, 34886-96-9; IX, 61990-68-9; X, 61990-69-0; benzobullvalene, 50653-71-9; methylbenzobullvalene, 61990-70-3; 3-methylanthranilic acid, 4389-45-1; tropone, 539-80-0; bullvalene, 1005-51-2.

Supplementary Material Available. An expanded Experimental Section, Tables III–V (11 pages). Ordering information is given on any current masthead page.

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Preparation of Uracil

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Over the last seven decades, uracil, a molecule of interest to organic and biochemists alike, and its derivatives have been prepared by a variety of reactions. Methods of synthetic utility as well as chemical curiosity include synthesis from 2-thiouracil and chloroacetic acid followed by hydrolysis,[1] malic acid and urea in oleum,[2] maleic or fumaric acid and urea in PPA,[3] cyclization of substituted ureiodopropionic acid to dihydrouracil followed by bromination–dehydrobromination,[4] treatment of β-alkoxy acrylamides with ammonia or amines followed by dilute alkali,[5] and palladium salt catalyzed oxidative cyclization of acryloylurea.[6]

This report describes the preparation of uracil by condensing urea and propiolic acid[7] under acid catalysis in refluxing benzene. Uracil-forming reactions run in acidic solvents present formidable problems on plant scale; in this case, the use of organic solvents provides an acceptable alternate. Compared to commercial uracil processes,[1,2] the reaction is

Table I. Uracil and Derivatives

Urea, mol	Acid,[a] mol	Solvent, mL, temp, h	HMDS (mL), h reflux	Product, % yield[b]
Urea, 0.071	P, 0.071	C_6H_6, 120, reflux, 18	40, 5	III, 45–65
Urea, 0.071	P, 0.071	DMF, 60, 80, 18	40, 5	III, 8
Urea, 0.071	P, 0.071	H_2O, 60, 80, 18		III, trace
Methylurea, 0.071	P, 0.071	C_6H_6, 120, reflux, 18	40, 18	V, 20 VI, 7
Thiourea, 0.071	P, 0.071	C_6H_6, 120, reflux, 48	40, 18	No 2-thiouracil
Urea, 0.061	T, 0.060	C_6H_6, 120, reflux, 96	50, 18	IV, 33

[a] P = propiolic acid, T = tetrolic acid. [b] GLC yields of the trimethylsilyl derivatives III, uracil; IV, 6-methyluracil; V, 3-methyluracil; VI, 1-methyluracil.

simple to perform, potentially inexpensive,[8] and offers minimal chemical disposal problems.

Results

The reactants were stirred in refluxing benzene containing several drops of concentrated sulfuric acid[9] for 18 h. Uracil can be isolated by filtration and repeated recrystallization; however, it was more convenient to convert uracil to its bis(trimethylsilyl) derivative[10] which was isolated by distillation. Yields of uracil as high as 65% (based on propiolic acid) have been detected by GLC, but the range of 45–55% was more common. Propiolic acid was completely consumed after the 18-h reflux period. During silylation unreacted urea was quantitatively converted to its easily isolable bis(trimethylsilyl) derivative.[11] Thus, interrupting the reaction by silylation after 3, 7, and 18 h showed 30, 52, and 79% consumption of urea, respectively. At these intervals the product ratio essentially was unchanged; attempts at intermediate isolation or detection of intermediate buildup were unsuccessful.

The reaction was extended to the synthesis of uracil derivatives by appropriate substitution of reactants (see Table I). Reaction between thiourea and propiolic acid afforded no 2-thiouracil probably owing to ynylation at sulfur.[12] Compounds prepared were characterized by comparison of their physical and spectral properties with those of authentic samples.

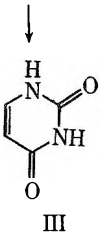
Discussion

In this uracil-forming reaction, the failure to detect or isolate intermediates is consistent with a two-step reaction where the second step is considerably faster than the first. A reasonable sequence follows.

$H_2NCONH_2 + HC{\equiv}CCO_2H$

$\longrightarrow$ $[H_2NCONHCH{=}CHCO_2H$ or $HC{\equiv}CCONHCONH_2]$

I II



III

Based on literature references[5,13,14] on related reactions the intervention of I[15] is preferred over II.

In an attempt to qualitatively determine which functional group (triple bond or acid) is the first to react, model reactions were investigated. Reaction between urea and model acids (e.g., p-$NO_2C_6H_4CO_2H$) or acetylenes (e.g., $C_8F_{17}C{\equiv}CH$) under simulated uracil reaction conditions gave >95% recovery of starting materials. In retrospect, this is reconcilable; reactions involving urea performed in nonpolar aprotic solvents are rare[16] presumably owing to the heterogeneity of the system. The success of the uracil forming reaction then suggests an intimacy between the reacting partners. Thus, admixing urea and propiolic acid in warm benzene followed by cooling quantitatively deposits an isolable 1:1 crystalline adduct. In the uracil forming reaction, benzene probably serves not as a solvent but rather as a medium for water removal and heat transfer.

Experimental Section

Materials. Urea (USP crystals) was supplied by Mallinckrodt; propiolic acid and substituted ureas were purchased from Aldrich. Commercial grade hexamethyldisilazane (HMDS), PCR, Inc., was used throughout. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer while a Hewlett-Packard 5712 instrument using a 6 ft × 0.125 in. 10% UCL-45:8% OV-7 (50:50 mix) on Gas Chrom 2 (80–100 mesh) column at 170 °C was used to obtain GLC data.

Uracil from Urea and Propiolic Acid. Urea (4.3 g, 0.071 mol) and anhydrous benzene (120 mL) were stirred together at 25 °C when propiolic acid (5.0 g, 0.071 mol) was introduced rapidly. Solids underwent a change in crystal size shortly after the acid was added. Three drops of concentrated sulfuric acid were added and the solution was heated to reflux. After ca. 6 h, water began to separate (Dean-Stark trap) and was removed as formed. After 18 h of reflux, the reaction mixture was allowed to cool to 25 °C. At this time ca. 0.6–0.8 mL of water had been removed; the solid product (ca. 8–9 g) was insoluble in C_6H_6. TLC of the solids (dissolved in water, eluted with a 70:40:10 by volume mixture of ethyl acetate–acetone–water and visualized by UV) showed uracil as the major component accompanied by two slower and one faster moving minor components. The benzene was decanted and 40 mL of HMDS added. The resulting mixture was refluxed for 5 h (ammonia evolved), cooled, and pressure filtered (coarse frit) with care taken to avoid atmospheric moisture. The crystalline solid was washed with HMDS (10 mL) and dried under vacuum affording 3.4 g of bis(trimethylsilyl)urea (79% consumption of urea), mp 218–220 °C (lit.[11] 222–224 °C). At this point the filtrate containing bis(trimethylsilyl)uracil could either be mixed with a known quantity of n-amylbenzene (internal standard) and analyzed by GLC (for yields, see Table I) or distilled. On distillation the fraction of bp 76–81 °C (2 mm) [lit.[10] bp 123 °C (18 mm)] was >97% bis(trimethylsilyl)uracil. TLC of the silylated uracil derivative was identical with that of uracil; evidently, hydrolysis occurs during analysis. This silyl derivative was easily converted to uracil in quantitative yield by treatment with aqueous acetone at 25 °C.

The same procedure was used to prepare the substituted uracil derivatives; for details see Table I.

Complex Isolation. Urea (2.6 g, 0.043 mol) and propiolic acid (3.0 g, 0.043 mol) were placed in a flask with benzene (16 mL). The mixture was heated with stirring to 64 °C over a 25-min period, then cooled to 40 °C and pressure filtered. The resulting white solid was dried at 1 mm for 3 h and weighed 5.35 g, mp 60–63 °C. Infrared (KBr) showed bands at 2.95, 4.72, 6, 6.2, 6.95, 7.35, 7.85, 11.1, 11.6, 12.9, 13.2, and 14.25 μ.

Anal. Calcd for $C_4H_6N_2O_3$: C, 36.9; H, 4.6; N, 21.5. Found: C, 36.7; H, 4.7; N, 21.7.

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Registry No.—I, 62076-97-5; III, 66-22-8; IV, 626-48-2; V, 608-34,4; VI, 615-77-0; urea, 57-13-6; methylurea, 598-50-5; thiourea, 62-56-6; propiolic acid, 471-25-0; tetrolic acid, 590-93-2.

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Synthesis of Hexahydroquino[8,7-*h*]quinolines. Cis and Trans Isomers of 3,9-Dimethyl-4b,5,6,10b,11,12-hexahydroquino[8,7-*h*]quinoline

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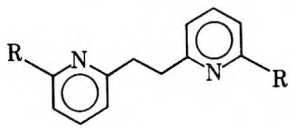
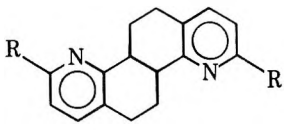
Preliminary findings suggestive of the biological importance of some 1,2-di(2-pyridyl)ethane derivatives (I) prompted a research program aimed at the synthesis of some steroidal



I



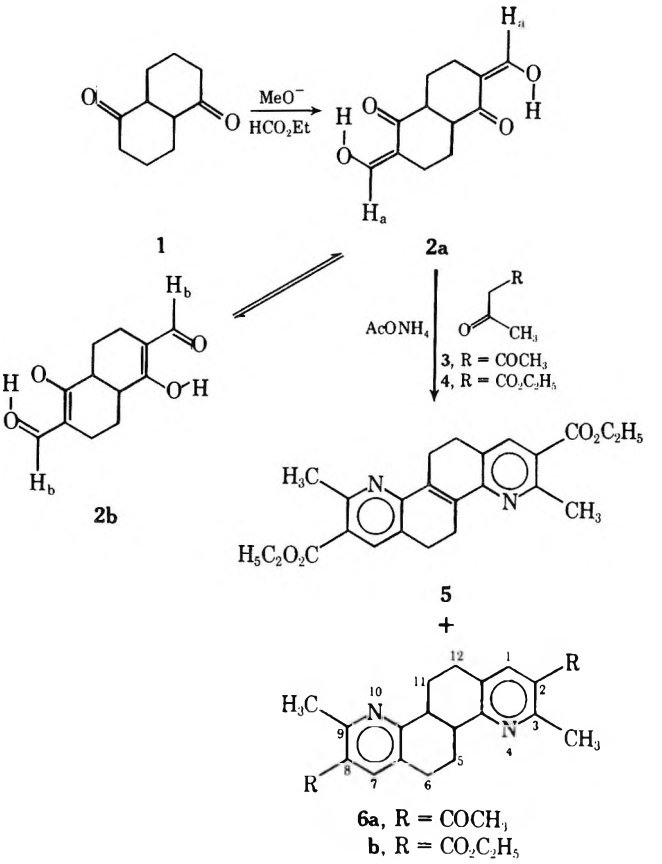
II

analogues which could be regarded as their rigid counterparts (II). The synthetic sequence leading to these type of medicinally interesting compounds started with pure *trans*-decalin-1,5-dione (**1**)[1] (Scheme I). Treatment of **1** with ethyl formate in pyridine utilizing sodium methoxide as catalyst afforded compound **2** in good yields. NMR spectral data of **2** seem to indicate that the compound exists as a mixture of rapidly equilibrating tautomers with an average signal for the H_a and H_b protons at δ 9.00. According to the formula proposed by Garbisch[2] for this type of equilibrium the mixture is 92% in favor of tautomer **2b**. In addition, a singlet at δ 14.5, accounting for two protons, underwent easy exchange with D_2O.

Heating **2** with either acetylacetone (**3**) or ethyl acetoacetate (**4**), without solvent and in the presence of ammonium acetate, afforded **6a** and **6b**, respectively, in fair yields. Along with **6b**, it was possible to isolate after chromatography a fluorescent material for which all available data indicated to have structure **5**. Structures of these compounds are in agreement with the appearance of singlets between δ 7.72 and 8.20, in the NMR spectra, which correspond to γ protons of a pyridine nucleus. This synthetic procedure is similar to the one employed by Breitmaier et al.[3] for the synthesis of cycloalkeno(*b*)pyridines from the corresponding α-(aminomethylene)cycloalkanones with either **3** or **4** in the presence of catalytic amounts of ammonium acetate.

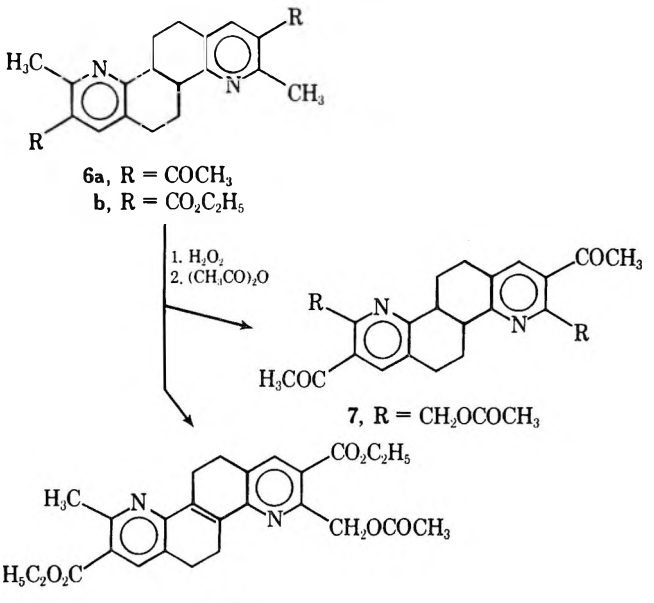
An objective was to functionalize both α-methyl groups of the pyridine rings and later to eliminate the carbomethoxy group of **6b**. The functionalization step was successful when

Scheme I



6a, R = $COCH_3$
b, R = $CO_2C_2H_5$

Scheme II



8

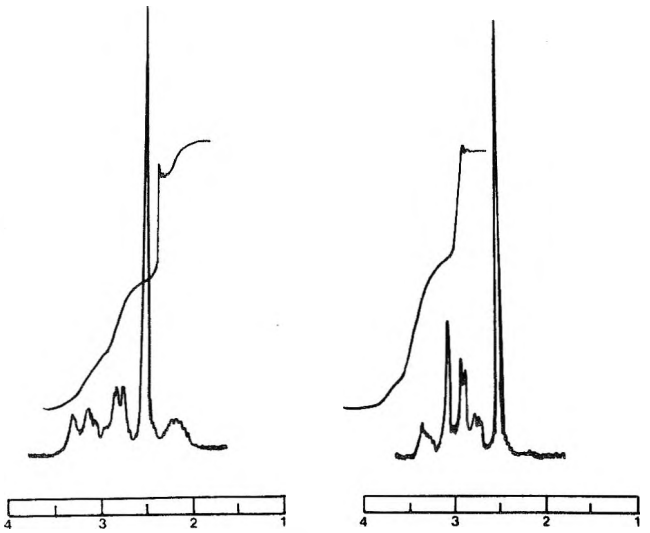
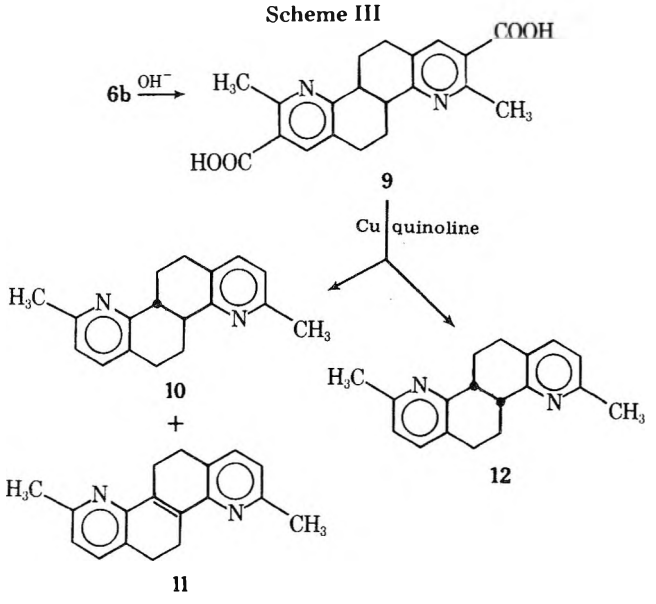


Figure 1. NMR spectra of cis and trans isomers **12** and **10**.

tried with **6a**, since its di-*N*-oxide when refluxed in acetic anhydride[4] rearranged in the expected manner to the desired diester **7**. However, in the case of **6b**, which was to be decarboxylated at a later stage, rearrangement of its di-*N*-oxide occurred in a different manner, affording compound **8** (Scheme II). A rearrangement of this type has been described in the literature for 1,2-di(6-methyl-2-pyridyl)ethane di-*N*-oxide.[4] Compound **8** was characterized by its NMR spectrum, which indicated that one α-methyl group had remained intact. The presence of a highly conjugated system was evidenced by the UV spectrum of **8**, which showed an intense absorption band at 364 nm similar to that of compound **5**. In addition, the compound in solution presented an intense fluorescence when observed under UV light. At the present time, we do not have a satisfactory explanation for the differences observed in the rearrangement of the di-*N*-oxides of **6a** and **6b**. In both cases, however, the yields are low and a great deal of tar is formed.

An alternative approach, which consisted of carrying out the decarboxylative step first, was attempted despite the possibility that a similar process that led to compound **8** would take place again at the functionalization step. Compound **6b** was hydrolyzed to the corresponding diacid (**9**) and, after several attempts to decarboxylate it, success was achieved by refluxing the compound in the presence of powdered copper in freshly distilled quinoline (Scheme III).

Scheme III



After workup, the material isolated showed a characteristic NMR AB pattern in the aromatic region, which suggested that decarboxylation had taken place. However, when the product was chromatographed on TLC it appeared to be a mixture of two components with two distinct R_f values. In addition, the spot with the larger R_f was highly fluorescent when observed under UV light, whereas the one with the smaller R_f was not. When the sample of crude decarboxylated product was column chromatographed, 0.5 g (15% yield) of the component with the larger R_f (first eluted) and 1.8 g (55% yield) of the component with the smaller R_f were separated. The first component, however, was found to be contaminated by the material responsible for the fluorescence. Several recrystallizations from ethyl acetate afforded a crystalline material, mp 215 °C, which was free from any fluorescence. The structure of the fluorescent contaminant was postulated to be the unsaturated compound **11** in view of the molecular ion peak at *m/e* 262 observed in the mass spectrum and the remarkable similitarity of its UV spectrum with that of compounds **5** and **8**. Both the purified material, mp 215 °C, and the last compound isolated from the column, mp 108 °C, showed similar IR, UV, and MS with characteristic molecular ion peaks at *m/e* 264. The NMR spectra, however, almost identical in the aromatic region, demonstrated substantial differences in the aliphatic region (Figure 1). Aside from the chemical shift of the singlet corresponding to both α-methyl groups at δ 2.5, only the compound with the smaller R_f value (mp 108 °C) presented broad resonance lines upfield relative to 2.5. All the evidence suggested the presence of cis and trans isomers of the decarboxylated product (**10** and **12**), but NMR data was not considered reliable enough to assign the corresponding structures.

Crystals of the higher melting isomer)mp 215 °C) obtained in lower yields and consequently thought to be from the cis isomer were found to be suitable for x-ray analysis. X-ray measurements[5] uniquely indicated space group $P2_{1/a}$, with a = 7.37 (1), b = 12.77 (1), c = 7.66 (1) Å, β = 100.5 (1)°. The observed density corresponds to two molecules in the unit cell and since this space group requires four asymmetric units, the compound must possess a center of symmetry. Since the cis structure does not have a center of symmetry, the higher melting isomer has to have the trans configuration.

In view of the fact that the trans isomer was obtained in lower yields it means that somewhere along the synthetic sequence from *trans*-**1** to the final decarboxylated mixture, the preferred stereochemistry was inverted to the most stable cis isomer. NMR spectral comparison between compound **2** and both *cis*- and *trans*-decalin-1,5-dione clearly established that compound **2** has the trans configuration. Furthermore, compound **2** was also obtained starting from pure *cis*-decalin-1,5-dione. In the following step, however, the stereochemistry of the isolated diester **6b** (85% yield) is likely to have been inverted to the cis configuration in view of the similarity observed for portions of the NMR spectra of both cis isomer **12** and diester **6b**, in the region corresponding to the decalin backbone protons. Diester **6b** was isolated chromatographically pure, and since reesterification of diacid **9**, obtained from the hydrolysis of pure **6b**, afforded a single product identical in all respect to its precursor, it means diacid **9** also has the cis configuration. After decarboxylation, the major product retained the preferred cis configuration and some smaller amount inverted to the trans configuration possibly by a mechanism involving removal of one of the acidic bridgehead protons during quinoline reflux.[6]

Scale models confirm that the cis configuration appears to be less strained and more flexible than the trans configuration for these type of compounds. In addition, as inferred from Figure 2, it is likely the NMR signals observed upfield from δ 2.5 for the cis isomer might correspond to those decalin

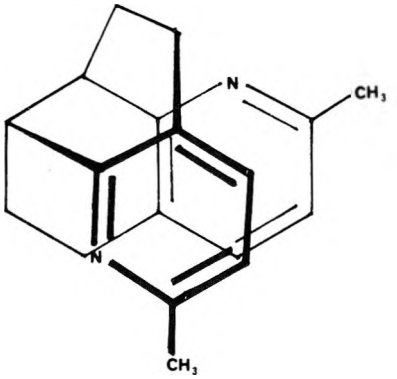


Figure 2. Puckered conformation of the cis isomer (**12**).

backbone protons situated above the shielding cone of the aromatic pyridines, a situation that is never encountered in the more rigid trans configuration.

Finally, when the functionalization step in the cis isomer (**12**) was carried out through its corresponding di-*N*-oxide, the reaction underwent extensive decomposition and no pure product could be isolated.

Experimental Section

General. All chemical reagents are commercially available. They were purchased either from E. Merck or Aldrich Chemical Co. Melting points were determined by means of an Electrothermal capillary melting point apparatus, and they are uncorrected. A Perkin-Elmer Model 727 infrared spectrophotometer was employed for IR spectra, using either Nujol mulls or chloroform solutions. A Varian Associates Model EM-360 analytical NMR spectrometer was used for NMR spectra of deuteriochloroform solutions with internal tetramethylsilane (δ 0.00 ppm) at ambient temperatures. Ultraviolet spectra were recorded on a Beckman Model 25 spectrophotometer, utilizing 1-cm path cells. Mass spectra were obtained in a Hitachi Perkin-Elmer RMU-6H instrument at 70 eV. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

***trans*-Decalin-1,5-dione (1).** This compound was prepared according to the procedure of Johnson et al., mp 162–164 °C [lit.[1] mp 164–166 °C].

***trans*-2,6-Bis(hydroxymethylene)decalin-1,5-dione (2).** A mixture of 1.66 g (10 mmol) of **1**, 2.16 g (40 mmol) of $NaOCH_3$, 9.2 mL (130 mmol) of ethyl formate, and 70 mL of dry pyridine was stirred under nitrogen at room temperature for 21 h. After the mixture was adjusted to a pH between 5 and 6 with the aid of 51 mL of AcOH and 471 mL of water, it was extracted with benzene several times. The benzene layers were thoroughly washed with water and then were extracted with 2% KOH solution. The basic extracts were washed with ether and then after reacidification with AcOH they were thoroughly extracted again with benzene. The benzene extracts were dried (Na_2SO_4) and then were reduced to dryness to give 2 g (90%) of crude **2**. Recrystallization from acetone afforded **2** as a fine yellow powder, mp 155–157 °C: IR (Nujol) 1640 and 1570 cm^{-1}; NMR ($CDCl_3$) δ 2.3 (br m, 10), 9.00 (s, 2), and 14.50 (s, 2); mass spectrum *m/e* 222 (M^+·).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.69; H, 6.38.

***cis*-Diethyl 3,9-Dimethyl-4b,5,6,10b,11,12-hexahydroquino[8,7-*h*]quinoline-2,8-dicarboxylate (6b).** A mixture of 2 g (9 mmol) of **2** and 3.10 g of ethyl acetoacetate (**4**) was heated for 18 h at 125 °C in the presence of 2.78 g of ammonium acetate. The solid formed was taken up in $CHCl_3$ and extracted with 25% HCl. The acid extracts were washed with ether and, after basification with 25% NaOH, the yellow precipitate formed was extracted with $CHCl_3$, dried (Na_2SO_4), and reduced to dryness to give 3.12 g (85%) of crude product. After column chromatography by means of SiO_2 and chloroform, and following recrystallization from ethyl acetate, 1.28 g (35%) of pure **6b** was obtained as colorless crystals, mp 201–202 °C: IR ($CHCl_3$) 1720 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (t, 6), 2.25 (br m, 4), 2.70 (s, 6), 3.10 (br m, 6), 4.40 (q, 4), and 7.97 (s, 2); mass spectrum *m/e* 408 (M^+·).

Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.75; H, 6.88; N, 6.90.

Diethyl 3,9-Dimethyl-5,6,11,12-tetrahydroquino[8,7-*h*]quinoline-2,8-dicarboxylate (5). From the chromatography column of the previous reaction, a yellow powder contained in the first fractions was isolated. Recrystallization from acetone afforded 0.05 g (1.4%) of **5** as yellow crystals, mp 229–229.5 °C: IR (Nujol) 1720 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (t, 6), 2.90 (s, 6), 3.2 (s, 8), 4.50 (q, 4), and 8.20 (s, 2); mass spectrum *m/e* 406 (M^+·).

Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.86; H, 6.50; N, 6.81.

***cis*-2,8-Diacetyl-3,9-dimethyl-4b,5,6,10b,11,12-hexahydroquino[8,7-*h*]quinoline (6a).** This compound, obtained under the same experimental conditions as for **6b**, afforded after recrystallization from CH_3CN pure **6a**, mp 251–253 °C: IR ($CHCl_3$) 1690 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (br m, 4), 2.65 (s, 6), 2.75 (s, 6), 3.00 (br m, 6), and 7.72 (s, 2); mass spectrum *m/e* 348 (M^+·).

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.01; H, 6.86; N, 8.19.

***cis*-2,8-Diacetyl-3,9-bis(acetoxymethyl)-4b,5,6,10b,11,12-hexahydroquino[8,7-*h*]quinoline (7).** After isolation of 1.53 g (4 mmol) of the crude *N*-oxide of **6a**, which was prepared according to general literature procedures,[4] it was heated at 100 °C for 6 h with 8 mL of acetic anhydride. The mixture was cooled and the solid which formed was filtered and washed with water. The solid was recrystallized from CH_3CN to afford 0.45 g (37%) of pure **7**, mp 239–240 °C: IR (Nujol) 1740, 1680, 1600, and 1240 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (br m, 4), 2.25 (s, 6), 2.60 (s, 6), 3.00 (br m, 6), 5.50 (s, 4), and 7.70 (s, 2); mass spectrum *m/e* 464 (M^+·).

Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.22; H, 6.08; N, 6.03. Found: C, 67.03; H, 5.98; N, 6.05.

Diethyl 3-Acetoxymethyl-9-methyl-5,6,11,12-tetrahydroquino[8,7-*h*]quinoline-2,8-dicarboxylate (8). A similar procedure as for **7** was followed starting with 2.2 g (5.4 mmol) of **6b**. The corresponding di-*N*-oxide rearranged in acetic anhydride and, after reduction to dryness, the semisolid residue obtained was treated with charcoal in bng acetone. Following filtration, cooling gave a yellow powder. It was collected and chromatographed by use of SiO_2 and benzene–ethyl acetate (2:1). The first fraction collected was recrystallized from ethyl acetate to afford 0.4 g (16%) of **8** as fine yellow crystals, mp 154–156 °G IR (Nujol) 1750, 1720, 1600, and 1260 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (t, 6), 2.20 (s, 3), 2.80 (s, 3), 3.00 (br s, 8), 4.4 (q, 4), 5.65 (s, 2), 8.00 (s, 1), and 8.10 (s, 1); mass spectrum *m/e* 464 (M^+·).

Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.22; H, 6.08; N, 6.03. Found: C, 67.09; H, 6.02; N, 5.92.

Hydrolysis and Decarboxylation of 6b. A mixture of 5.1 g (12.5 mmol) of **6b**, 110 mL of ethanol, 110 mL of water, and 1.46 g of KOH was refluxed for 2 h. Once the alcohol was removed by distillation, the aqueous solution was treated with 10% HCl until a pH of 3 was reached. After cooling overnight in the refrigerator a fine solid was formed which was filtered and dried, affording 4.3 g of the crude diacid (**9**). A mixture of 2.33 g of the diacid, 9.8 g of powdered copper, and 400 mL of freshly distilled quinoline was refluxed for 4 h, whereupon a vigorous evolution of CO_2 took place. After distilling off the quinoline, the residue was taken up in $CHCl_3$, filtered, and reduced to dryness. The remaining dark semisolid (still contaminated with some quinoline) was chromatographed by means of 200 g of SiO_2 with ethyl acetate as eluent. The first product collected was the trans isomer (**10**), which afforded 0.5 g (15%) of a material still contaminated by a fluorescent compound. Several recrystallizations from ethyl acetate afforded a crystalline material free from any fluorescence, mp 215–217 °C: IR (Nujol) 1600 and 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.5 (s, 6), 2.95 (m, 10), 6.90 (d, 2, J = 4 Hz), and 7.32 (d, 2, J = 4 Hz); mass spectrum *m/e* (rel intensity) 264 (100) (parent), 263 (88), 249 (16), 158 (20), 146 (12), 144 (22), 133 (12), 132 (28), and 131 (28).

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.77; 7.63; N, 10.60. Found: C, 81.63 H, 7.56; N, 10.42.

After collecting some quinoline as a second fraction, the cis isomer (**12**) began to elute from the column, affording 1.8 g (55%) of pure product which was recrystallized as white needles from ethyl acetate, mp 106–108 °C: IR (Nujol) 1600 and 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (br m, 2), 2.50 (s, 6), 3.15 (br m, 8), 6.95 (d, 2, J = 4 Hz), and 7.40 (d, 2, J = 4 Hz); mass spectrum *m/e* (rel intensity) 264 (100) (parent), 263 (60), 249 (16), 158 (8), 146 (62), 144 (38), 133 (24), 132 (34), and 131 (34).

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.60. Found: C, 81.60; H, 7.81; N, 10.42.

Acknowledgment. The authors wish to thank Dr. Víctor M. Márquez, Sr., for his encouragement during this study and Dr. Tatsuhiko Nakano and Professor Joseph H. Burchalter for their very helpful discussions throughout the course of this work.

Registry No.—**1**, 42245-85-2; **2a**, 62016-00-6; **2b**, 62016-12-0; **3**, 123-54-6; **4**, 141-97-9; **5**, 62016-01-7; **6a**, 62016-02-8; **6a** di-*N*-oxide, 62016-03-9; **6b**, 62016-04-0; **6b** di-*N*-oxide, 62016-05-1; **7**, 62016-06-2; **8**, 62016-07-3; **9**, 62016-08-4; **10**, 62016-09-5; **11**, 62016-10-8; **12**, 62016-11-9.

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Friedel–Crafts Type Preparation of Triphenylphosphine[1a]

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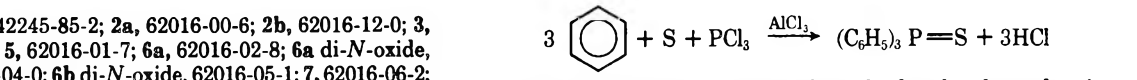
Triarylphosphines, of which triphenylphosphine is the most widely employed member, are generally prepared through organometallic precursors, such as the reaction of phenylmagnesium halides or phenyllithium with phosphorus trihalides.[2]

We now wish to describe a convenient, simple Friedel–Crafts type preparation of triphenylphosphine. The reaction of phosphorus trichloride with benzene under Friedel–Crafts conditions has been widely studied, but only phenyldichlorophosphine and diphenylchlorophosphine have been obtained as products, and under no conditions could the reaction be directed to yield triphenylphosphine (probably owing to an unfavorable disproportionation equilibrium).[3] Phosphorus oxychloride also fails to give triphenylphosphine oxide. Phosphorus sulfochloride ($PSCl_3$), on the other hand, yields triphenylphosphine sulfide upon reaction with benzene and excess aluminum chloride.[4] As triphenylphosphine sulfide offers the possibility of being desulfurized (reduced) to give triphenylphosphine this reaction path offered a good possibility to the simplified Friedel–Crafts type preparation of triphenylphosphine without recourse to organometallic reagents.

We have now found a greatly simplified method to prepare triphenylphosphine sulfide in 71% yield directly from benzene by reacting it with sulfur, phosphorus trichloride, and aluminum chloride. Various methods can be applied for the desulfurization of triphenylphosphine sulfide.[5-7]



We have found the preferred method to be the reduction with sodium naphthanide,[7] giving 89% yield, although desulfurization with iron filings (80%) is also convenient. The reaction with Raney nickel,[6] however, gave considerably lower (15%) yields.

Experimental Section

Preparation of Triphenylphosphine. Into a 500-mL round-bottom flask fitted with a reflux condenser and drying tube under nitrogen purge were added $AlCl_3$ (64 g, 0.48 mol), PCl_3 (16.55 g, 0.12 mol), S (3.85 g, 0.12 mol), and excess benzene (150 mL), to serve both as a reactant and solvent. The solution was stirred magnetically while being heated to reflux for a period of 8 h. Thereafter, to the cooled solution 125 mL of ice water was added. The organic layers were separated and the water layer extracted three times with benzene. The combined benzene solution was dried over Na_2SO_4, and after evaporating solvent left a yellow solid. Recrystallization from acetone–water yielded 25 g (71%) of pure triphenylphosphine sulfide, $Ph_3P{=}S$, mp 158–160 °C. Desulfurization of triphenylphosphine sulfide can be carried out by method A or B.

A. With Sodium Naphthanide.[7] To a 50-mL flask fitted with a reflux condenser and nitrogen purge were charged 25 mL of THF, 6.1 g of naphthalene (0.05 mol), and 1.1 g of Na (0.05 mol). To the deep green solution was added slowly with stirring 4.6 g of triphenylphosphine (0.02 mol). After the addition was complete, the solution was refluxed for 4 h. The cooled solution was quenched with water. Steam distillation followed by extraction with ether and recrystallization from ethanol gave 3.69 (89%) of pure triphenylphosphine, mp 79–81 °C.

B. With Iron Filings.[4] To a 250-mL round-bottom flask fitted with reflux condenser and thermometer and under nitrogen purge were added 25 g of triphenylphosphine sulfide (0.1 mol) and 0.1 g of Fe filings (0.15 mol). The reaction mixture was heated to 370 °C for 2 h. After cooling the crude product was dissolved in ethanol and filtered, and after evaporation of solvent recrystallized from fresh ethanol to give 18.0 g (8) of triphenylphosphine, mp 79–81 °C.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—Triphenylphosphine, 603-35-0; benzene, 71-43-2; PCl_3, 7719-12-2; triphenylphosphine sulfide, 3878-45-3; sulfur, 7704-34-9.

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Unusual Photocyclization of a Naphthalene–Diphenylethylene Bichromophore. 1,2-Hydrogen Migration in a 1,4 Diradical

Summary: The naphthalene–diphenylethylene bichromophore **1** undergoes photochemical cyclization to cyclopropane derivative **8** by a process which appears to involve an unusual hydrogen migration in a 1,4 diradical.

Sir: Apart from cis–trans isomerization, the most prevalent intramolecular photochemical reaction of the β-alkylstyrenes and -1,1-diphenylethylenes which we have examined is cyclopropane formation via the 1,2-migration of a γ substituent to the β carbon;[1,2] in certain β-alkyldiphenylethylene cases a rare 1,2-vinyl hydrogen shift predominates.[3] We now report results of an investigation of the photochemistry of the bichromophoric molecule 4-methyl-4-(1-naphthyl)-1,1-diphenylpentene (**1**). The principal locus of electronic excitation in the lowest excited singlet state of **1** should be the naphthalene portion of the molecule. By contrast, in the other compounds investigated[1,3] the excitation energy was concentrated in the aryl olefin grouping. We find that (1) this change is accompanied by a marked change in photochemical behavior from that of the previous systems studied,[1-3] and (2) the reaction of **1** appears to involve an unusual conversion of a 1,4 diradical to a cyclopropylmethyl derivative via hydrogen migration.

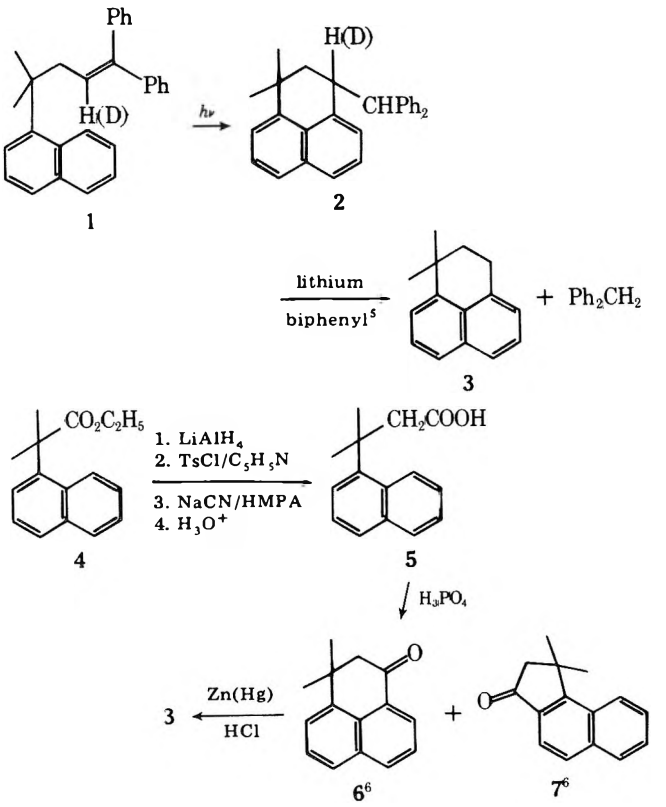
Irradiation[4] for 2 h of a solution of 0.520 g of **1** in 110 mL of cyclohexane resulted in the complete disappearance of **1** and the formation of one major product isolated in 60% yield. (See paragraph at end of paper regarding supplementary material.) The NMR spectrum of this product suggested either the 1,8-cyclized compound **2** or the analogous product in which cyclization had occurred at the 2 position of the naphthalene ring instead. That **2** was indeed the correct structure of the photoproduct was determined as outlined in Scheme I.

To aid in mechanistic studies **1d** containing >95% deuterium at C-2 was prepared and irradiated. NMR analysis of the resulting **2d** revealed that no migration of the deuterium had occurred in the transformation **1** → **2** (Scheme I). Thus, in contrast to the photochemistry of the 4-phenyl analogue of **1**,[3b] irradiation of **1** does not result in migration of a vinyl hydrogen. Benzophenone-sensitized irradiation of **1** gave no discernible product formation.

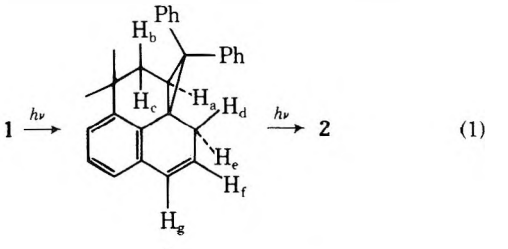
Though **2** was the only product isolated from **1** in our initial photolyses, analyses of reaction solutions obtained after photolysis of **1** for very brief periods revealed the transient appearance and disappearance of another compound. This thermally labile compound never comprised more than ~10% of the reaction mixture, a result of its efficient further photochemical transformation to **2**. However, by careful chromatography of product mixtures resulting from short periods of irradiation of several samples of **1** we were able to isolate sufficient quantities of pure intermediate, mp 138.8–139.5 °C, to permit characterization.

The UV spectrum of the intermediate showed a broad, unstructured long wavelength absorption band having λ_{max} at ~270 nm (ε 5550) on the edge of a stronger band having λ_{max} at 239 nm. The transformation of the naphthalene chromophore of **1** to a 1,2-dihydronaphthalene structure was thereby indicated.[7] The mass spectrum (80 eV) showed a parent ion at *m/e* 362 (rel intensity 6) and a base peak at *m/e* 169 ($M - Ph_2CCHCH_2$). These data, together with the fact that irradiation of the intermediate provided **2** in ~80% yield, suggested the compound to be either cyclopropane **8** or cyclobutane **9**. The formation of cyclobutane adducts through both inter-[7a,8] and intramolecular[7b] photochemical reactions of naphthalene derivatives with olefins has been noted frequently in the recent literature.

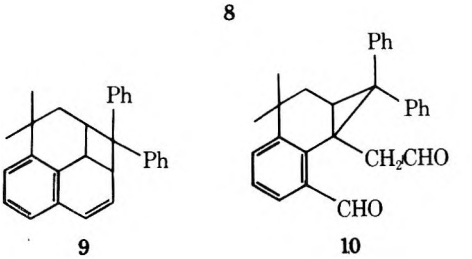
Scheme I

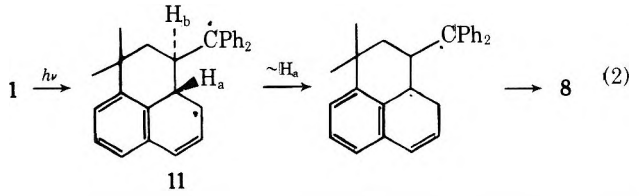


However, 270-MHz NMR analysis revealed the transient compound to have the more unusual structure **8**. The NMR spectrum showed δ 1.03 (s, 3, CH_3), 1.20 (s, 3, CH_3), three 1 H dd's at 2.33 (J = 4.3, 10.3 Hz), 1.78 (J = 4.3, 13.0 Hz), and 2.09 (J = 10.3, 13.0 Hz) assigned to H_{a-c},[9] a 1 H dd at 1.61 (J = 17.3, 5.9 Hz) and a 1 H d (each peak of which is a poorly defined apparent triplet) at 2.58 (J = 17.3 Hz) arising from H_d and H_e,[9] 5.97 (m, 1, H_f), 6.73 (dd, 1, H_g, J = 10.0, 2.5 Hz), and



(1)





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6.80–7.43 (m, 13, arom) ppm. Particularly noteworthy points about this spectrum are (a) H_{a-c} are coupled to each other but show no observable coupling to any other hydrogens, and (b) the large coupling constant (17.3 Hz) between H_d and H_e indicates that they are geminal.[10]

Chemical evidence that the product isolated does have structure 8 was provided by its ozonolysis to a dialdehyde (10), the NMR spectrum of which showed two distinctive aldehyde signals: a singlet at δ 10.67 and a doublet of doublets (J = 2.2, 2.5 Hz) at 9.15. (We did not isolate 10 in pure form; the NMR spectrum was taken of the crude ozonolysis reaction product.) The dialdehyde that would be obtained from 9 would not show this splitting pattern for the aldehyde hydrogens. Structure 8 is the one compatible with all our evidence.

The most likely pathway for the formation of 8 from 1 involves initial bonding between C-8 of the naphthalene ring and C-2 of the double bond to form 1,4 diradical 11 followed by hydrogen migration and ring closure (eq 2).[11] We note, though, that such a mechanism ascribes exceedingly novel behavior to 11, for the normal modes of reaction of 1,4 diradicals are either fragmentation to olefins or cyclization to cyclobutanes.[12,13] However, inspection of molecular models helps to elucidate why such an unusual reaction course is followed in the present case. Thus, the sterically most favorable mode of initial vinyl–naphthyl bonding is that which results in diradical 11 having H_a and H_b trans to each other. Closure of 11 to a cyclobutane would involve considerable strain; the p orbitals which must join to form the four-membered ring cannot become optimally aligned for bonding. Likewise, fragmentation of 11 to 1 is hindered by poor overlap between the newly formed bond and the p orbital on C-7 of the naphthalene ring; cleavage to starting olefin therefore does not totally dominate the chemistry of 11.[14] On the other hand, in 11 the bond to H_a on the naphthalene C-8 is nearly parallel to the adjacent p orbital on C-7, an arrangement optimal for migration of this hydrogen. Thus with the normal fragmentation and cyclization processes hindered, an unusual hydrogen migration prevails.

The migration of hydrogen to an adjacent radical center such as that postulated in eq 2 has not been observed to occur in monoradicals.[15,16] In the present case, however, we are dealing with a diradical, and the following points should be noted. (1) The conversion of 11 to 8 may be a concerted process—the homologue of the commonly observed conversion of a 1,3 diradical to an olefin.[17] Simultaneous carbon–carbon bond formation would lower the normally high barrier to migration. (2) The ^1S state of a diradical species such as 11 has considerable zwitterionic character.[18] It is possible that a polarization[19] of 11 in its ^1S state considerably enhances hydrogen migration relative to a similar migration in a monoradical.

The high yield, facile conversion of cyclopropane 8 to 2 is not unusual. Analogous reactions have been found by Griffin and others to occur with good efficiency upon irradiation of numerous 2-alkylarylcyclopropanes.[2b,20]

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Supplementary Material Available. The experimental details of this work (13 pages). Ordering information is given on any current masthead.

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(14) Diradical 11 may well undergo reversion to 1; such a process would not be detected. However, the transformation of 1 to 8 is qualitatively an efficient one. This efficiency is indicative of some difficulty in the cleavage process.
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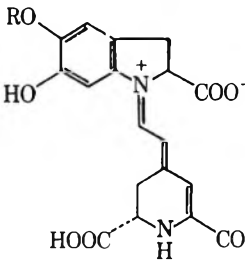
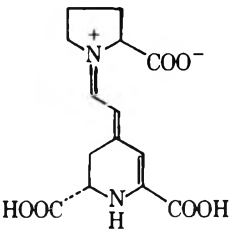
A Synthesis of Betalamic Acid

Summary: *N*-Benzylnorteloidinone (6) available by Robinson–Schöpf synthesis was converted to the ortho ester 7 with methyl orthoformate; catalytic debenzylation followed by addition of allylmagnesium bromide gave 9 which was transformed to the *O*-benzoylhydroxylamine 10 with benzoyl peroxide; acetylation and deprotection gave diol 12, which on two consecutive oxidations furnished the aldehyde 14; betalamic acid dimethyl ester was obtained from 14 by oxidation with lead tetracetate in methanol; and the latter was converted to betanidin trimethyl ester following a known procedure.

Sir: Betalains are water-soluble red-violet and yellow pigments, occurring naturally in plants belonging to the order *Centrospermae.*[1] Extensive work on their structures culminated in 1965 when Dreiding and coworkers[2] proposed expression 1 for betanin, the red pigment of the beet (*Beta vulgaris*). Shortly thereafter indicaxanthin was isolated from the cactus *Opuntia ficus indica Mill.* and shown to have structure 3.[3] The long suspected relationship between the red betacyanins and the yellow betaxanthins was confirmed by chemical interconversion of betanidin (2) and indicaxanthin (3).[4] Betalamic acid (4), the precursor of the 1,7-diazaheptamethinium unit in these coloring matters was subsequently



1, R = β-D-glucose
2, R = H



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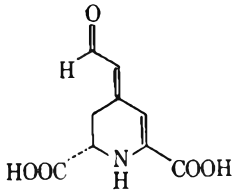

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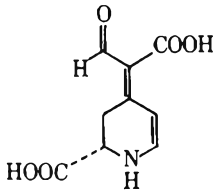

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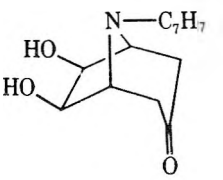
detected as such in nature[5] while muscaflavin (5) and muscaaurin were isolated from the fungus *Amanita muscaria.*[6] The former is an isomer of betalamic acid (4) and the latter a new betaxanthin containing ibotenic acid.[6]

Betalamic acid (4) and betanidin (2) were found to be sensitive to oxidation and easily afford pyridines. Consequently it was decided to synthesize betalamic acid (4) on a structural framework that did not allow such unwanted aromatizations until the final product had been reached.[7]

N-Benzylnorteloidinone (6), mp 84–85 °C,[8] obtained in 40–50% yield by Robinson–Schöpf synthesis[9] was converted to a 10:1 mixture (major epimer mp 101 °C) of ortho esters 7 by heating the diol with excess methyl orthoformate in methylene chloride–trifluoroacetic acid for 2 h at reflux (98% yield). The secondary amine 8, mp 106–108 °C, available by hydrogenolysis of 7 in methanol–trifluoroacetic acid over a palladium-on-carbon catalyst (97%) was combined with allylmagnesium bromide in ether–tetrahydrofuran at 0 °C to yield 72% carbinol 9, mp 137 °C.[10] Condensation with dibenzoyl peroxide[11] in DMF containing suspended potassium carbonate (10–30 h, 25 °C) afforded the *O*-benzoylhydroxylamine 10, mp 109 °C (80–100%). The carbinol 10 was acetylated with acetic anhydride in the presence of 4-dimethylaminopyridine[12] (8 days' reflux in ether) and the product was submitted to aqueous oxalic acid (30 min, 25 °C). Monoformate 11, mp 159–160 °C, obtained in 93% yield was saponified to the diol 12, mp 171–175 °C[13] (86%), by exposure to aqueous sodium bicarbonate (25 °C, 7 days). Oxidation to the orange diketone 13 [mp 146 °C; visible max ($CHCl_3$) 496 nm (ε 45); IR ($CHCl_3$) 1790, 1777, 1745 cm^{-1}] was accomplished in 76% yield with *N*-chlorosuccinimide–dimethyl sulfide[14] at −30 °C in toluene followed by treatment with triethylamine. Ozonolysis of 13 in ethyl acetate–methanol at −78 °C and reduction with dimethyl sulfide[15] gave the orange aldehyde 14 [mp 134 °C dec; visible max ($CHCl_3$) 497 nm (ε 25); IR 1785, 1775, 1750



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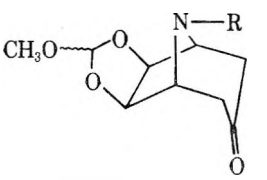
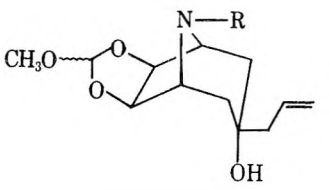
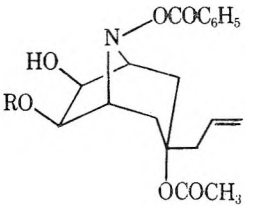


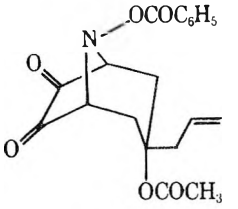
7, R = C_7H_7
8, R = H



9, R = H
10, R = $OCOC_6H_5$



11, R = HCO
12, R = H



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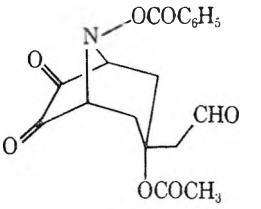

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cm^{-1} (80%)]. In a further oxidation this nonenolizable diketone 14 was cleaved with lead tetraacetate[16] in benzene–methanol 1:1 (0 °C, 45 min) and the product purified by column chromatography over silica gel. The resulting racemic betalamic acid dimethyl ester was characterized as the stable semicarbazone[20] (34%) [mp 183–188 °C (lit.[17] mp 204–205 °C for optically active material prepared from natural betalamic acid); UV max (95% C_2H_5OH) 375, 265 nm (ε 33 700, 10 500)] whose NMR spectrum in $(CD_3)_2SO$ was identical with that published in ref 17. Condensation of betalamic acid dimethyl ester semicarbazone with L-cyclodopa methyl ester in methanolic hydrochloric acid is known to afford betanidin (2) trimethyl ester hydrochloride.[7] We have verified this observation by condensing the synthetic semicarbazone in water at pH 4.5 with racemic *O,O*-diacetylcyclodopa methyl ester hydrochloride.[18] The resulting violet-red solution exhibited visible max 550 nm typical for betanidin.

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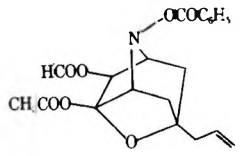

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(19) NIH Predoctoral Trainee, 1975–present (Grant 1 T32 CA 09112).
(20) **Note Added in Proof.** The identity of betalamic acid dimethyl ester semicarbazone has been confirmed by comparison with a sample kindly provided by Professor A. S. Dreiding.

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MEM Chloride ®

For the protection of alcohols

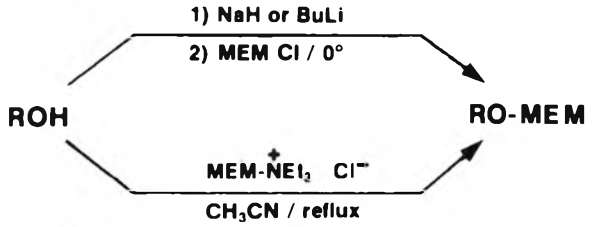
The recent introduction[1] of **β-methoxyethoxymethyl (MEM) ethers** as protected derivatives of

$$CH_3OCH_2CH_2OCH_2 = MEM$$

primary, secondary, and tertiary alcohols provides a valuable addition to the organic chemist's armamentarium of protective methods. Because of the ease of formation and specificity of cleavage conditions, the **MEM group** serves as a valuable addition to the more traditional hydroxyl protecting groups[2] such as tetrahydropyranyl and benzyl. The achiral **MEM group** does not introduce a new center of asymmetry when used for the protection of chiral alcohols.

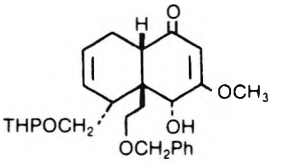
MEM ethers are stable to strong bases, organometallic reagents, oxidizing agents and mild acids.

The formation of **MEM ethers** can be effected either under aprotic basic conditions by reaction of the sodium or lithium salt of the alcohol with **MEM chloride** in THF or dimethoxyethane, or under aprotic neutral conditions by reaction of the alcohol with **MEM-triethylammonium chloride** in acetonitrile. Although the ammonium salt is hygroscopic, it can be prepared readily from **MEM chloride** and triethylamine.

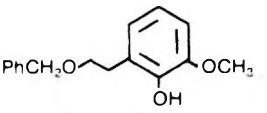


MEM ethers can also be prepared from the alcohol and **MEM chloride** in the presence of diisopropylethylamine in CH_2Cl_2. Yields of the **MEM derivatives** by these methods are excellent, usually exceeding 90%.

MEM ethers are cleaved by either anhydrous $ZnBr_2$ or $TiCl_4$ in CH_2Cl_2 solution at room temperature. Other Lewis acids such as $ZnCl_2$, ZnI_2, $SnBr_4$, $SnCl_4$, $ZrCl_4$, $MgCl_2$ and $MgBr_2$ can be used to effect **MEM ether** cleavage, but these are less effective. Examples of some alcohols which have been converted to **MEM ethers** and selectively cleaved include **1** and **2**.



1



2

The specificity of the cleavage conditions is hypothesized to be due to the formation of a cyclic complex with the Lewis acid ($ZnBr_2$, $TiCl_4$) which facilitates the cleavage of the **MEM ether**. Thus, the cleavage of methoxymethyl ethers is markedly slower than that of the corresponding **MEM derivative** under the same conditions. On the other hand, THP, *t*-butyldimethylsilyl and other silyl protecting groups are selectively cleaved in the presence of **MEM ethers** by the use of catalytic amounts of *p*-toluenesulfonic acid in methanol at room temperature for 3 hours. Acetyl, benzoyl, benzyl, allyl, methylthiomethyl, 2,2,2-trichloroethyl and 2-chloroethyl derivatives can all be selectively cleaved in the presence of **MEM ethers**.

Aldrich is pleased to offer **MEM chloride** in kilogram units.

References:

1) E.J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).
2) C.B. Reese in "Protective Groups in Organic Chemistry," J.F.W. McOmie, Ed., Plenum Press, London, 1973, Chapter 3.

19,354-2 MEM chloride 25g $15.00
100g $40.00; 1kg $240.00

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