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THE JOURNAL OF Organic Chemistry

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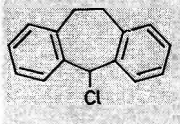

Reagent for the introduction of the 5-dibenzosuberyl moiety, a new protecting group for amines, amino acids, alcohols, thiols and carboxylic acids; stable to HCl but easily removed by formic acid or TFA: J. Pless, Helv. Chim. Acta **1976,** *59,* 499

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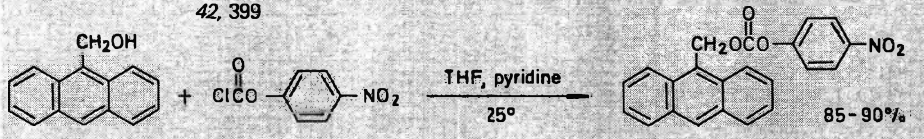

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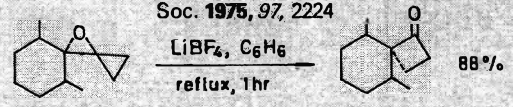
Superior catalyst for rearrangements of oxaspiropentanes: B.M. Trost et al., J. Am. Chem. Soc. **1975,** *97,* 2224



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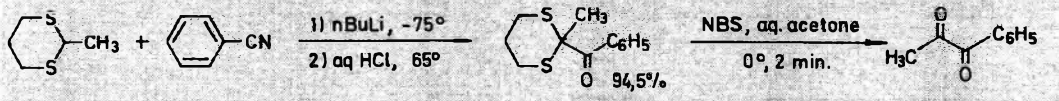

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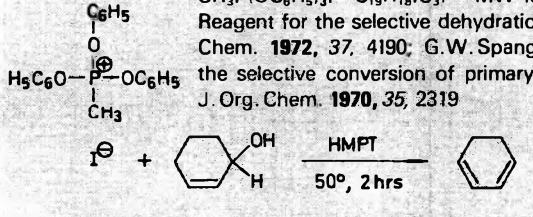

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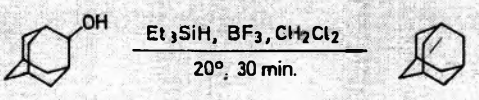

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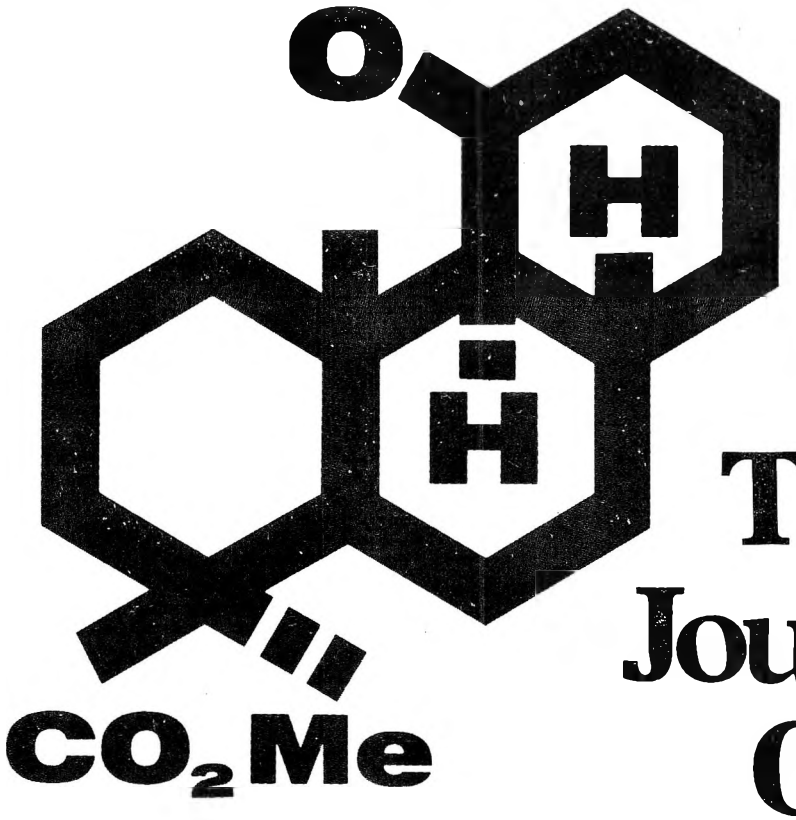

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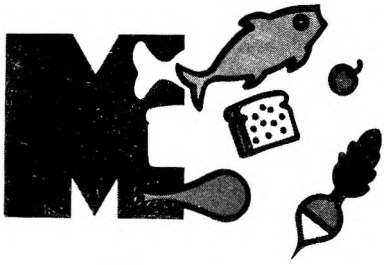

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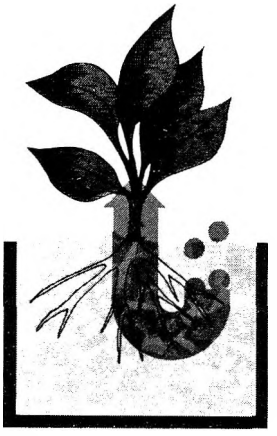

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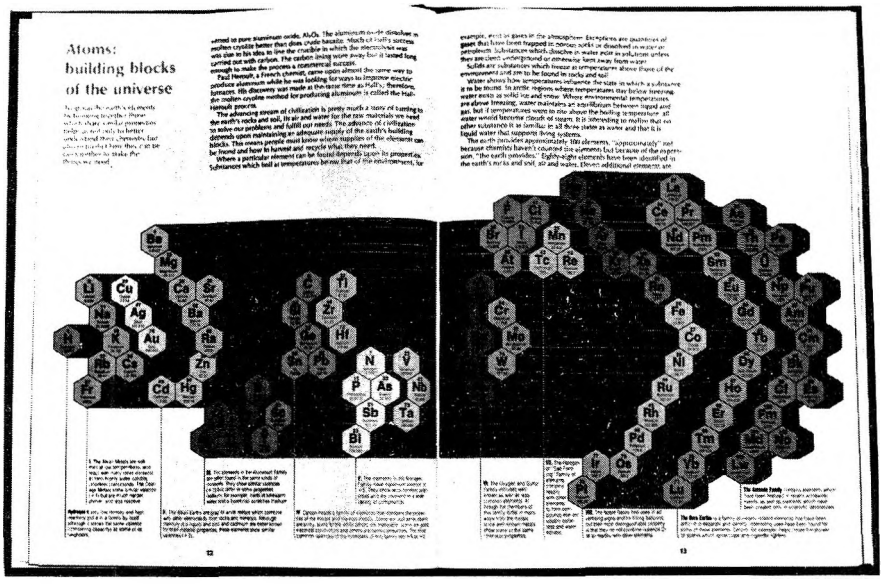

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MARCH 3, 1978

Relative Rate Constants for Hydrogen Atom Abstraction by the Cyclohexanethiyl and Benzenethiyl Radicals

William A. Pryor,* Gabriel Gojon,[1] and Daniel F. Church

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

Received June 28, 1977

Relative values of the rate constants k (eq 1) for hydrogen atom abstraction from a number of organic substrates by cyclohexanethiyl and benzenethiyl radicals at 80 °C are reported. Good correlations with both σ and σ^+ constants were found for ring-substituted ethylbenzene and cumene derivatives, and some limited data for toluenes also are reported. Two new methods were developed to obtain these data; the key feature of both is that tritium-labeled thiol (RSH*) is used as a solvent. In this environment, reversal of the hydrogen abstraction reaction (eq 2) leads to labeling of the hydrogen donor (QH), and k is related to the radioactivity incorporated into the recovered QH*. Isotope effects are involved in the calculations, but they can be evaluated independently. Thiyl radicals are found to be extremely selective, more so than even bromine atoms or CCl_3· radicals. Surprisingly, both cyclohexanethiyl and benzenethiyl radicals, and also bromine atoms, show remarkably similar polar effects; this is not what would be expected on the basis of heats of reaction or electron affinities. It is suggested that this similarity might be attributable to the similar polarizabilities of bromine atoms and thiyl radicals.

Thiyl radicals are important species in organic free-radical chemistry[2-4] and in biology,[5] and their reactions are the subject of several critical reviews. Hydrogen abstraction by thiyl radicals from organic substrates is amply documented,[2a,c,d,4,5] and work by Walling and Rabinowitz[6] and by Kooyman[7] provided important qualitative and semiquantitative information. However, no quantitative data on hydrogen abstraction by thiyl radicals (eq 1) have been published.

$$\mathrm{RS\cdot} + \mathrm{QH} \xrightarrow{k} \mathrm{RSH} + \mathrm{Q\cdot} \qquad (1)$$

In a preliminary communication,[8] we reported a method for the quantitative study of eq 1 and preliminary results for the cyclohexanethiyl radical. We here present further data on the cyclohexanethiyl radical and also data on the benzenethiyl radical.

Because there were no data in the literature against which to test our method, we developed two independent techniques[8] for the determination of relative values of k. The key feature of both techniques is the use of tritium-labeled thiol (RSH*) as a solvent. In this environment, Q· radicals generated in eq 1 abstract hydrogen from labeled solvent RSH*, resulting in the substrate becoming tritium labeled (eq 2). The

$$\mathrm{Q\cdot} + \mathrm{RSH^*} \rightarrow \mathrm{QH^*} + \mathrm{RS\cdot} \qquad (2)$$

level of radioactivity in the recovered QH* is related to the specific rate constant for eq 1. Tritium isotope effects are involved in the calculation, but they can be evaluated independently.[9] Therefore, the very reversibility of eq 1, which hindered previous studies,[2a] is utilized in our kinetic technique.

Experimental Section

Materials. Purification and preparation of the materials and equipment are described in detail elsewhere.[10]

Product Studies. Products from the reaction of cyclohexanethiol with cumene were determined by GLC analysis. Low injection temperatures were necessary to prevent further reaction. The results of these experiments are shown in Table I and are discussed further in the Appendix.

Kinetic Methods. Two kinetic methods were used and it will be convenient to describe them here.

A. Competitive Method. Reaction mixtures were typically ~0.25 M in each QH and ~0.01 M in 2,2′-azobis(isobutyronitrile) (AIBN), and the specific activity of the thiol was 10^{11}–10^{12} disintegrations per minute per mole (dpm/mol). Preweighed quantities of two hydrogen donors (QH's) and AIBN were placed in a volumetric flask and dissolved in labeled thiol; aliquots of the solution were transferred to Pyrex glass ampules, which were then degassed and sealed under vacuum. The samples were allowed to react for 5 h at 80.0 ± 0.1 °C. Sample workup involved some or all of the following steps (the intervening water washings are omitted): dilution with petroleum ether or diethyl ether; extraction with 20% sodium hydroxide; addition of 10% silver nitrate and centrifugation; extraction with saturated mercuric nitrate in dilute nitric acid; drying and quick treatment with active Raney nickel. Most of the solvent was evaporated at reduced pressure, and the donors usually were separated by GLC and subsequently radioassayed.

B. Standard Reaction Method. Reaction mixtures were initially ~0.25 M in triphenyl phosphite (TPP), ~0.25 M in QH, and ~0.01 M in AIBN. Reaction times were variable (10–70 min at 80.0 ± 0.1 °C); the ampules were thermally quenched and were opened just prior to determination of cyclohexane content by GLC. Sample preparation and workup were accomplished by the procedures outlined in connection with the competitive method; the recovered donor (QH) was separated from the remaining solvent and trace impurities by GLC, and then the donor was radioassayed.

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Table I. Product Studies [a] of Reaction Mixtures Compounded with AIBN and Cumene in Cyclohexanethiol Solvent

Run	1	2	3	4	5
Reaction time,[b] h	5.0	5.0	9.62	9.62	9.62
$[Cumene]_i$	0	0.50	0	0.50	2.5
$[C_6H_{11}SH]_i$	8.2	7.7	8.2	7.7	5.7
$[AIBN]_i \times 10^3$	6.90	7.19	19.4	18.5	17.6
$[Isobutyronitrile]_f \times 10^3$	5.8	8.25	18.3	18.8	18.0
	(44.6)[c]	(60.8)[c]	(47.4)[c]	(51)[c]	(51.4)[c]
$[Dicyclohexyl\ disulfide]_f \times 10^3$	3.7	4.1	10.2	9.7	5.55
$[A_2] \times 10^3$ [d]	1.65	2.23	4.7	4.4	4.3
	(25.3)[c]	(32.9)[c]	(24.4)[c]	(23.9)[c]	(24.6)[c]
$[Bicumene]_f \times 10^3$		0		0	~1.3
[Sulfide 2] $\times 10^3$ [d]		0		0	~4.6
[Sulfide 1][d]		Trace[e]		Trace[e]	Trace[e]
Recovery of $C_6H_{11}S\cdot$ radicals, %[f]	127	100	112	103	101
Recovery of A· radicals, %	70	85	72	75	76

[a] Reaction temperature was 80 °C. Brackets denote concentrations in moles per liter. Subscripts i and f indicate initial and final concentrations, respectively. [b] After 5 h, 93.8% of the AIBN has reacted; after 9.62 h, 99.6% has reacted. [c] Conversion (%), based on AIBN decomposed. [d] Tetramethylsuccinodinitrile is A_2; cyclohexyl 2-(phenylpropyl) sulfide is sulfide **2**; cyclohexyl 1-methyl-1-phenyethyl sulfide is sulfide **1** (R =cyclohexyl). [e] See ref 10. [f] Assuming that the numbers of thiyl radicals and isobutyronitrile molecules formed are the same.

Tritium Activity Determination. Two different radioassay procedures were utilized: proportional gas-flow and liquid scintillation counting. Gas-flow counting was accomplished by means of a Model 4498 gas radiochromatography system from Nuclear Chicago coupled to a Varian Aerograph Model 200 gas chromatograph fitted with thermal conductivity detector and recorder. Alternatively, sample components were individually trapped by delivery of the effluent gases (as a stream of fine bubbles) into a low-potassium vial containing 15.0 mL of a toluene-based solution of liquid scintillation fluors, and each trapped component's specific activity was measured using a Packard Tri-Carb liquid scintillation spectrometer (Model 3365). Counting efficiency was determined by automatic external standardization. The component's gross activity was corrected by subtracting from it both background activity and the activity contributed by traces of radiochemical impurities that might have been collected along with the component. The latter correction was usually small, amounting to 1–5% of the gross activity; it was obtained from the net disintegration rates of the two fractions that were collected just before and after the component's peak and from the collection times of all three fractions. This "radiochemical background" per minute of collection time was taken to be the average of the net disintegration rates per minute of collection time for the leading and trailing fractions. Since values obtained by using different chromatographic columns and/or flow-counting methods agreed well with activities corrected for "radiochemical background", we feel that the correction is sufficiently accurate.

Liquid scintillation counting of thiols proved to present special problems; however, the thiols could be counted successfully if oxygen was excluded from the vial and Packard's "Permafluor" was used in toluene solution.[11a]

Measurement of Isotope Effects. Isotope effects for both thiyl radicals were measured using ethylbenzene and ethylbenzene-d_{10}. For the cyclohexanethiyl radical, ethylbenzene was compared with cumene, ethylbenzene-d_{10} with *p*-nitrocumene, and cumene with *p*-nitrocumene. For the benzenethiyl radical, ethylbenzene-d_{10} was compared with *p*-ethylnitrobenzene. Thus, in all cases, three ratios of rate constants were measured: QH vs. Q′H, QD vs. Q″H, and Q′H vs. Q″H. This experimental design allows both ethylbenzene and ethylbenzene-d_{10} to be compared with a substrate of roughly comparable reactivity and from which each could be easily separated by GLC.

Results

Derivation of Kinetic Expressions. We used two methods for determining the relative reactivities of hydrogen donors toward thiyl radicals. The first involves direct competition of two donors with thiyl radicals generated by the thermal decomposition of AIBN in tritiated thiol solvent. This scheme is shown in eq 3–7, where QH and Q°H are the two hydrogen

$$AIBN \rightarrow 2A\cdot \xrightarrow{RSH} 2RS\cdot \quad (3)$$

$$RS\cdot + QH \xrightarrow{k} RSH + Q\cdot \quad (4)$$

$$Q\cdot + RSH(RST) \xrightarrow{k_H(k_T)} QH(QT) + RS\cdot \quad (5)$$

$$RS\cdot + Q^\circ H \xrightarrow{k^\circ} RSH + Q^\circ\cdot \quad (6)$$

$$Q^\circ\cdot + RSH(RST) \xrightarrow{k^\circ_H(k^\circ_T)} Q^\circ H(Q^\circ T) + RS\cdot \quad (7)$$

donors, and the Q· and Q°· radicals become labeled as they abstract hydrogen (tritium) from the thiol solvent. If a steady state in these substrate radicals is assumed, kinetic analysis yields eq 8. Since [RST]/[RSH] is much less than unity, and

$$\frac{k}{k^\circ} = \left[\frac{k_H/k_T + [RST]/[RSH]}{k^\circ_H/k^\circ_T + [RST]/[RSH]}\right]\left[\frac{d[QT]/[QH]}{d[Q^\circ T]/[Q^\circ H]}\right] \quad (8)$$

since both k_H/k_T and k°_H/k°_T are primary kinetic isotope effects and are greater than unity, eq 8 can be simplified to give eq 9. At low conversions, the concentrations of QH and

$$\frac{k}{k^\circ} = \left[\frac{k_H/k_T}{k^\circ_H/k^\circ_T}\right]\left[\frac{d[QT]/[QH]}{d[Q^\circ T]/[Q^\circ H]}\right] \quad (9)$$

Q°H remain essentially unchanged, and d[QT] and d[Q°T] may be approximated by the final concentrations of these species. Thus, eq 9 reduces to eq 10. Finally, since [QT]/[QH]

$$\frac{k}{k^\circ} = \left[\frac{k_H/k_T}{k^\circ_H/k^\circ_T}\right]\left[\frac{[QT]/[QH]}{[Q^\circ T]/[Q^\circ H]}\right] \quad (10)$$

is proportional to the specific activity of QH (A_{QH}), we obtain eq 11, in which the relative rate constant for eq 4 is expressed

$$\frac{k}{k^\circ} = \left[\frac{k_H/k_T}{k^\circ_H/k^\circ_T}\right]\left[\frac{A_{QH}}{A_{Q^\circ H}}\right] \quad (11)$$

as a function of kinetic isotope effects for hydrogen abstraction from labeled solvent by substrate radicals and the specific activity ratio of the two substrates after reaction.

The second method is similar, except that only one hydrogen donor is involved, and the desulfuration of thiyl radicals by triphenyl phosphite (TPP)[12] is the standard reaction. This sequence is shown in eq 12 and 13. Kinetic analysis of the

$$RS\cdot + (PhO)_3P \xrightarrow{k_P} R\cdot + (PhO)_3P{=}S \quad (12)$$

$$R\cdot + RSH(RST) \xrightarrow{k'_H(k'_T)} RH(RT) + RS\cdot \quad (13)$$

system comprised of eq 3–5, 12, and 13 yields eq 14. Since $[RST]/[RSH] \ll 1$, $k'_T/k'_H < 1$, and $k_H/k_T > 1$, and at low

Table II. Relative Rate Constants[a] for Hydrogen Abstraction by Thiyl Radicals at 80 °C (per Reactive Hydrogen)

Hydrogen donor	Registry no.	A_{QH}/A_{EtPh} Cyclohexanethiyl[b]	A_{QH}/A_{EtPh} Benzenethiyl[c]	n[d]	Isotope correction factor[e]	Rel k values (eq 1) Cyclohexanethiyl[f]	Rel k values (eq 1) Benzenethiyl
n-Dodecane	112-40-3	0.03		20	0.59	0.002	
Thioanisole	100-68-5	<0.063		3	1.00[g]	<0.042	
Anisole	100-66-3	0.0075		3	1.00[g]	0.005	
Ethyl N,N-dimethylaminoacetate	33229-89-9	0.02		2	1.00[g]	0.02	
2,3,4-Trimethylpentane	565-75-3	0.0435		3	0.83	0.024	
Neopentylbenzene	1007-26-7	0.0143		2	1.00	0.014	
Toluene	108-88-3	0.045		3	0.93	0.028	
m-Xylene	108-38-3	0.129[h]		6	0.93	0.040	
Mesitylene	108-67-8	0.256		9	0.93	0.053	
p-Xylene	106-42-3	0.198		6	0.93	0.061	
Ethylbenzene-d_{10}	25837-05-2	0.120	0.133	2	1.00	0.120	0.133
p-Nitroethylbenzene	100-12-9	0.371	0.396	2	1.00	0.371	0.396
p-Bromoethylbenzene	1585-07-5	0.73	0.76	2	1.00	0.73	0.76
Ethylbenzene	100-41-4	(1.00)	(1.00)	2	(1.00)	(1.00)	(1.00)
m-Ethylanisole	10568-38-4	1.10		2	1.00	1.10	
m-Ethyltoluene	620-14-4	1.25[i]		2	1.00	1.25	
p-Ethyltoluene	622-96-8	1.60[i]	1.87[i]	2	1.00	1.60	1.87
p-Ethylanisole	1515-95-3	3.01	3.53	2	1.00	3.01	3.53
Diphenylmethane	101-81-5	1.47	2.79	2	1.08	1.59	3.01
p-Nitrocumene	1817-47-6	1.19		1	1.00	2.38	
Cumene	98-82-8	3.15	4.01	1	1.00	6.30	8.02
p-Cymene	99-87-6	5.08[h]		1	1.00	10.2	
p-Methoxycumene	4132-48-3	6.91		1	1.00	13.8	
Triphenylmethane	519-73-3	8.0		1	1.11	17.8[j]	
Benzyl methyl ether	538-86-3	24.5		2	1.11	27.2	
1,2,3,4-Tetrahydronaphthalene	119-64-2		17.1	2[k]	1.00		17.1
9,10-Dihydroanthracene	613-31-0	180		2[k]	1.11	200[j]	

[a] Relative to ethylbenzene (k = 1.00). Reproducibility of these data is ±5% except for the deuterated compounds for which it is ±10%. [b] Most of these data were obtained only by the competitive method. Registry no.: 40210-86-4. [c] Determined by the competitive method only. Registry no.: 4985-62-0. [d] Number of equivalent reactive hydrogens assumed. [e] The isotope correction factor equals $(k_H/k_T)_{QH}/(k_H/k_T)_{EtPh}$; see text. [f] Multiplying these values by 1×10^6 gives approximate absolute rate constants in units of M^{-1} s^{-1}; see text. [g] Assumed to be unity; no data available. [h] Determined by both methods. [i] These are the measured ratios. It is assumed that only secondary benzylic hydrogens are abstracted. [j] Perhaps low by a factor of 2; see discussion in text. [k] See ref 23b,c.

conversions d[QT] = [QT] and d[RH] = [RH], eq 14 can be reduced and rearranged to yield eq 15, where again the A values are specific activities.

$$\frac{d[QT]}{d[RH]} = \left[\frac{k[QH]}{k_P[TPP]}\right]\left[\frac{1 + (k'_T/k'_H)([RST]/[RSH])}{1 + (k_H/k_T)([RSH]/[RST])}\right] \quad (14)$$

$$A_{QH}[TPP] = (k/k_P)(k_T/k_H)A_{RSH}[RH] \quad (15)$$

A plot of A_{QH} [TPP] vs. [RH] should be linear and have a slope M that is proportional to the rate constant for hydrogen abstraction from QH by thiyl radicals. If this is done for two different QH's, eq 16a and 16b are obtained; these can be combined to yield eq 17. The relative reactivities obtained from eq 17 can be directly compared with those obtained using the first method, eq 11.

$$M_{QH} = (k/k_P)(k_T/k_H)(A_{RSH}) \quad (16a)$$

$$M_{Q°H} = (k°/k_P)(k°_T/k°_H)(A°_{RSH}) \quad (16b)$$

$$\frac{k}{k°} = \left[\frac{M_{QH}}{M_{Q°H}}\right]\left[\frac{A_{RSH}}{A°_{RSH}}\right]\left[\frac{k_H/k_T}{k°_H/k°_T}\right] \quad (17)$$

A number of control experiments were performed to test the validity of these kinetic schemes and to probe for possible failures. These experiments are discussed in the Appendix.

Relative Reactivities of Hydrocarbons toward Thiyl Radicals. Equation 11 allows the calculation of relative values of k from the ratio of specific activities of the recovered QH's and an isotope effect correction term. The values of $A_{QH}/A_{Q°H}$, where Q°H is ethylbenzene, for both cyclohexanethiyl and benzenethiyl radicals are given in the third and fourth columns of Table II, respectively. These data are on a per molecule basis. The isotope effects for hydrogen abstraction from *tert*-butyl mercaptan by a number of carbon-centered radicals have been measured;[9a,11] these values are shown in Table III. If it is assumed that these values are not substantially affected by the nature of the thiol,[9a] but only by the structure of the carbon-centered radical (primary, secondary, benzylic, etc.), then these isotope effects can be used to estimate the isotope effect correction factors $(k_H/k_T)/(k°_H/k°_T)$ required in eq 11. These estimated correction factors are listed in the sixth column of Table II. Relative values of k can then be derived by multiplying the measured activity ratios by the isotope correction factors. These relative k values, on a per hydrogen basis, are tabulated for the cyclohexanethiyl and benzenethiyl radicals in the last two columns of Table II.

Absolute Rate Constants. Absolute rate constants can be obtained for reaction 1, where RS· is the cyclohexanethiyl radical and QH is ethylbenzene, using eq 16b. For this treatment, it must be assumed that k_P has the same value[12] (1.2×10^7 M^{-1} s^{-1} at 70 °C) for both the cyclohexanethiyl radical and the n-butanethiyl radical reacting with TPP. The other numerical values required are $M_{Q°H} = 7.7 \times 10^9$ dpm/mol, $(A_{RSH})_{Q°H} = 8.0 \times 10^{11}$ dpm/mol, and the primary tritium isotope effect, $k°_H/k°_T$, for hydrogen abstraction from cyclohexanethiol by 1-phenethyl radicals.[10] Assuming the value of this isotope effect is 10 (see the previous section), the absolute rate constant (per molecule) for the reaction of the cyclohexanethiyl radical with ethylbenzene is approximately 1×10^6 M^{-1} s^{-1}. Using this value, all the relative k values for the cyclohexanethiyl radical in Table II can be put on an absolute basis by multiplying by 1×10^6.

Isotope Effects for Hydrogen Abstraction by Thiyl Radicals. Using ethylbenzene-d_{10}, the deuterium kinetic isotope effects for hydrogen abstraction by the two thiyl

Table III. Kinetic Isotope Effects on Hydrogen Atom Abstraction from *tert*-Butyl Mercaptan by Carbon Radicals in Solution [a]

Radical	k_H/k_T (80 °C)
3-Heptyl	5.89
Triethylmethyl	8.33
Benzyl	9.28
Diphenylmethyl	~10.8
Triphenylmethyl	11.1

[a] Taken from K. G. Kneipp, Dissertation, Louisiana State University, Baton Rouge, La., 1971. Also see ref 9a.

Table IV. Relative Rate Constants for Hydrogen Abstraction from Aralkyl Hydrocarbons by Various Radicals (per Hydrogen Atom)

Radical	Substrate			Rxn temp, °C
	Toluene	Ethylbenzene	Cumene	
Ph·	0.22	1	2.1	60[a]
CH_3·	0.22	1	3.1	65, 110[b]
Br·	0.04	1	2.3	77[c]
Cl_3C·	0.02	1	5.2	40[d]
$C_6H_{11}S$·	0.03	1	6.3	80[e]
PhS·	*f*	1	8.0	80[e]

[a] R. F. Bridger and G. A. Russell, *J. Am. Chem. Soc.*, 85, 3754 (1963). [b] W. A. Pryor, D. L. Fuller, and J. P. Stanley, *ibid.*, 94, 1632 (1972). [c] S. S. Friedrich, E. C. Friedrich, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, 34, 900 (1969). [d] G. A. Russell and C. DeBoer, *J. Am. Chem. Soc.*, 85, 3136 (1963). [e] This work. [f] The PhS· radical is not sufficiently reactive toward toluene to allow accurate determination of this value.

radicals were determined. The k_H/k_D values are 8 for both the cyclohexanethiyl and the benzenethiyl radicals. These values are probably accurate to 10%. With perdeuterated ethylbenzene as the substrate, the α- and β-deuterium atoms give rise to secondary kinetic isotope effects. However, these effects will not be of sufficient magnitude to make a significant contribution to our reported primary isotope effects.[11d]

Discussion

Table II gives relative k values (eq 1) for 26 hydrogen donors. It is satisfying that the qualitative results reported by Walling[6] and by Kooyman[6] are in reasonably good agreement with our data. Most of our results were obtained by the competitive method (eq 3–7) because it can be applied to both alkanethiyl and arenethiyl radicals and is less time consuming than the phosphite ester procedure.

Selectivity of Thiyl Radicals. The relative rate constants for the cyclohexanethiyl radical vary by 10^5 as the nature of the donor is varied. Thiyl radicals, therefore, are extremely selective in hydrogen atom abstraction reactions. For comparison purposes, Table IV gives the relative rate constants for hydrogen abstraction from toluene, ethylbenzene, and cumene by six radicals. These data show the considerable selectivity of thiyl radicals relative to other radicals that have been studied. Toward aralkyl hydrocarbons, both thiyl radicals are even more selective than are bromine atoms.[13-15] Cyclohexanethiyl is roughly as selective as the trichloromethyl radical.[16,17] The data suggest that the benzenethiyl radical is the most selective of the group.

Diphenylmethane is somewhat more reactive than ethylbenzene toward both thiyl radicals (see Table II), whereas the opposite is true for bromine atoms.[14] Russell has pointed out that, of all the common radicals and atoms, only the chlorine and bromine atoms give a reaction series in which diphenylmethane is less reactive than ethylbenzene.[18] This peculiarity

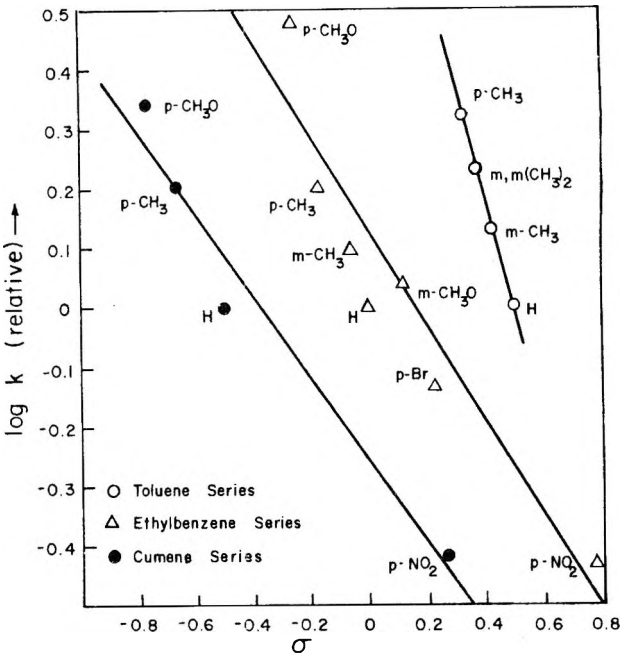

Figure 1. Hammett correlations for benzylic hydrogen abstraction by the cyclohexanethiyl radical. The σ scale has been adjusted by −0.5 for the cumene series and +0.5 for the toluene series to allow all three lines to be shown on the same plot.

of the halogen atoms can be rationalized as due to their tendency to attack sites of high electron density. The high electron affinities of the chlorine and bromine atoms (3.61 and 3.36 eV, respectively[19]) render them strongly electrophilic, and the electron-withdrawing inductive effect of a phenyl substituent deactivates benzylic hydrogens toward highly electrophilic reagents. Thiyl radicals, which are characterized by lower electron affinities than the halogens,[20] seem to follow a reactivity pattern similar to that of other nonhalogen radicals.

The benzylic hydrogens in neopentylbenzene are less reactive than are those in ethylbenzene toward both bromine atoms and cyclohexanethiyl radicals; this probably reflects the similar steric requirements[21] of Br· and $C_6H_{11}S$· radicals.

Most stable free radicals readily abstract hydrogen from thiols;[2f,9a,22] however, triphenylmethyl radicals seem to be able to persist for relatively long time periods in the presence of thiols. Lewis[9c] reports that the reaction of triphenylmethyl dimer with excess benzenethiol in toluene solution yields phenyltrityl sulfide and triphenylmethane in equimolar amounts; diphenyl disulfide could not be detected. Thus, trityl radicals probably participate in termination reactions in our system, and this violates one of the assumptions involved in the derivation of eq 11 and 17. Therefore, our measured values of k could be up to 50% smaller for triphenylmethane than the true value; i.e., only half the trityl radicals may react with thiol and become labeled.

The high reactivity of the secondary benzylic hydrogens in 9,10-dihydroanthracene and tetralin can be compared with the lower k values for ethylbenzene or diphenylmethane, which also possess secondary benzylic hydrogens. This is quite general; peroxy, trichloromethyl, methyl, phenyl, *tert*-butoxy, chlorine, and bromine radicals behave similarly.[23]

Hammett Equation Correlations. The relative k values (Table II) for hydrogen abstraction from ring-substituted toluenes, ethylbenzenes, and cumenes by the cyclohexanethiyl radical and from ethylbenzenes by benzenethiyl radicals were correlated with both σ and σ^+ substituent parameters. (See Figures 1–3.) The results of these correlations are listed in

Table V. ρ Values for Hydrogen Abstraction by Cyclohexanethiyl and Benzenethiyl Radicals at 80 °C

Abstracting radical	Substrate	Solvent	No. of data points	Substituent[a] constants	ρ[b]	C.L.[c]	Correlation coeff
Cyclohexanethiyl	Toluenes	Cyclohexanethiol	4	σ	−1.96	0.26	0.999
Cyclohexanethiyl	Toluenes	Cyclohexanethiol	4	σ^+	−1.00	1.21	0.900
Cyclohexanethiyl	Ethylbenzenes	Cyclohexanethiol	7	σ	−0.76	0.13	0.943
Cyclohexanethiyl	Ethylbenzenes	Cyclohexanethiol	7	σ^+	−0.59	0.07	0.990
Cyclohexanethiyl	Cumenes	Cyclohexanethiol	4	σ	−0.69	0.41	0.980
Cyclohexanethiyl	Cumenes	Cyclohexanethiol	4	σ^+	−0.50	0.14	0.991
Benzenethiyl	Ethylbenzenes	Benzenethiol	5	σ	−0.82	0.59	0.934
Benzenethiyl	Ethylbenzenes	Benzenethiol	5	σ^+	−0.62	0.12	0.990

[a] The substituent constants were taken from R. D. Gilliam, "Introduction to Physical Organic Chemistry", Addison-Wesley, Reading, Mass., 1970. [b] Determined by the standard linear regression techniques. [c] Confidence limit given by (standard deviation of the slope)(t-test value at the 95% confidence level). See G. W. Snedecor, "Statistical Methods", 4th ed, Iowa State College Press, Ames, Iowa, 1946, pp 153 and 549; W. H. Davis, Jr., and W. A. Pryor, *J. Chem. Educ.*, **53**, 285 (1976).

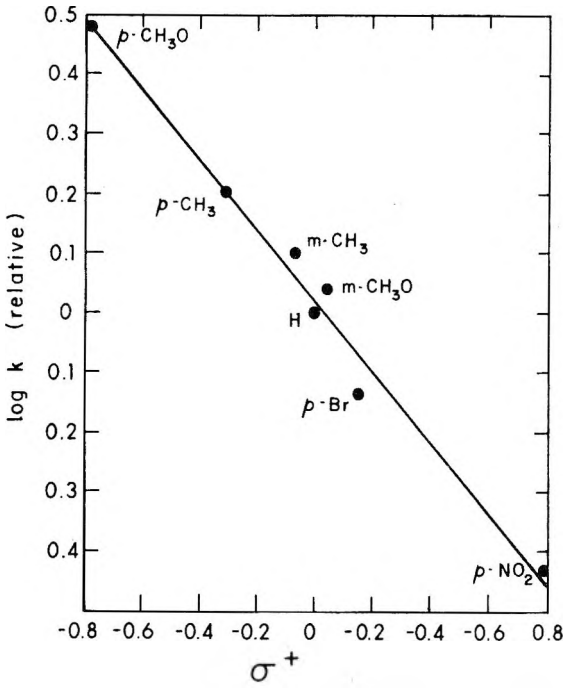

Figure 2. Hammett–Brown correlation for hydrogen abstraction from ethylbenzenes by the cyclohexanethiyl radical.

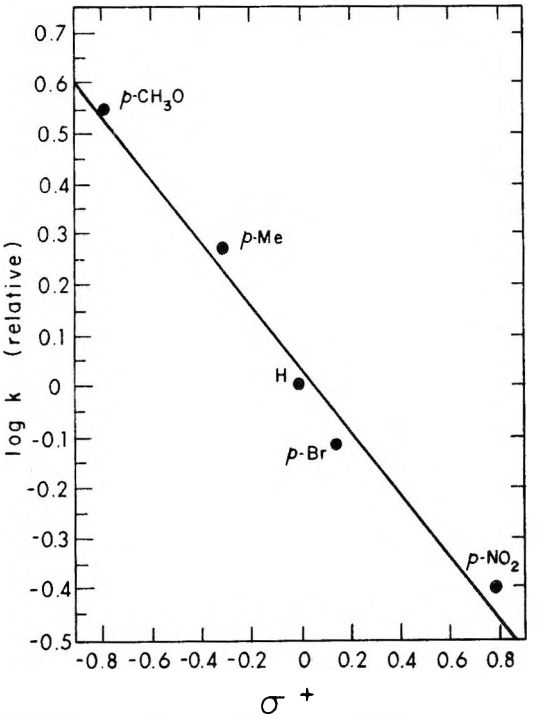

Figure 3. Hammett–Brown correlation for hydrogen abstraction from ethylbenzenes by the benzenethiyl radical.

Table V. The σ^+ parameters give a better correlation of the data in all cases except for hydrogen abstraction from toluenes by the cyclohexanethiyl radical. There, σ parameters give a markedly better fit; however, only four points could be determined in this series because of the low reactivity of the toluenes, and it is doubtful if the distinction between σ and σ^+ is statistically significant. As expected, these ρ values imply electrophilic character for both thiyl radicals.[24] The absolute values of ρ decrease as the hydrogen atom donor changes from toluene to ethylbenzene to cumene for abstraction by the cyclohexanethiyl radical. This is a trend also observed for bromine atoms.[25]

Similarity of ρ Values for Hydrogen Abstraction by the Two Thiyl Radicals. It is remarkable that the ρ values for hydrogen abstraction from ethylbenzene by the two thiyl radicals are, within experimental error, the same (see Table VI). The benzenethiyl radical has a substantially greater electron affinity than does the cyclohexanethiyl radical. Thus, according to the usual polar effects arguments,[4b,14,26] the transition state for hydrogen abstraction by the benzenethiyl radical should contain a larger contribution from the charge-separated form **2**. This should, in turn, lead to a more negative ρ.[26-28] Furthermore, abstraction by the benzenethiyl radical is 10 kcal/mol less exothermic than is abstraction by cyclohexanethiyl radical, and this also would lead one to expect a more negative ρ for the former reaction.[28,29]

$$\underset{\mathbf{1}}{\mathrm{ArCH_2\,\dot{H}\,X}} \leftrightarrow \underset{\mathbf{2}}{\mathrm{Ar\overset{+}{C}H_2\,\dot{H}\,\overset{-}{X}}} \leftrightarrow \underset{\mathbf{3}}{\mathrm{Ar\overset{-}{C}H_2\,\dot{H}\,\overset{+}{X}}}$$

The results, however, show that the ρ values are the same, in spite of the differences in the electron affinities and heats of reaction of the two thiyl radicals. These are three possibilities that can account for this unexpected result.

(1) The experimentally determined ρ values may be in error. This does not seem likely. Both ρ values were determined by identical experimental procedures, and, as described in the Appendix, control experiments demonstrate the trustworthiness of the method.

(2) Another possibility is that both the electron affinities of the two thiyl radicals and the bond dissociation energies of the corresponding thiols are actually more nearly the same than the literature indicates. This is a rather stringent requirement, since if *either* the electron affinities or the BDE values are different, then a more negative ρ value for hydrogen abstraction by benzenethiyl radical would be expected.[26-28]

However, it is not likely that either the electron affinities

Table VI. Thermochemical, Polar, and Kinetic Data on Three Radicals

	Radical, X·		
	$C_6H_{11}S$·	PhS·	Br·
X· + $ArCH_3$, ρ	−1.9[a]		−1.8[b]
X· + ArC_2H_5, ρ^+	−0.6[a]	−0.6[a]	−0.68[b,c]
Electron affinity, eV	1.5[d]	2.5[e]	3.36[f]
BDE (X–H), kcal/mol	92	82	87
ΔH, X· + $ArCH_3$, kcal/mol	−7	3	−2
ΔH, X· + ArC_2H_5, kcal/mol	−10	0	−5
k_H/k_D using EtPh-d_{10}	8	8	
k_H/k_D using MePh-d_1			4.6[g]
Polarizability[h]	8.1	8.4	8.6

[a] This work. [b] W. A. Pryor, T. H. Lin, J. P. Stanley, and R. W. Henderson, *J. Am. Chem. Soc.*, **95**, 6993 (1973); the value is extremely solvent dependent. [c] Recalculation of data of R. L. Huang and K. H. Lee, *J. Chem. Soc. C*, 935 (1966). [d] *n*-BuS·, ref 20b. [e] Upper limit, ref 20c. [f] Reference 19. [g] Value found in the solution phase by K. R. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.*, **80**, 3033 (1958). Tanner et al.[11b] suggest that this solution phase value may be low due to cage return. However, this value is comparable to the other solution phase values shown. [h] Reference 35.

or the BDE values are the same for both cyclohexanethiyl and benzenethiyl radicals. First, while the electron affinities are reported to differ by 1 eV or less, it is doubtful that they are identical.[20] Second, the BDE values of cyclohexanethiol and benzenethiol would not be expected to be identical. When we first discussed these data,[30] the BDE values for RS–H and PhS–H were reported to be 88 and 75 kcal/mol. At that time we proposed that[30] the similar selectivities we observed for the RS· and PhS· radicals ". . . suggests that the BDE's of the S–H bonds in cyclohexanethiol and benzenethiol do not differ by as much as is generally believed". Recently, Benson[31] has calculated these BDE to be 92 and 82 kcal/mol, respectively. Evidence can be cited which suggests that the actual BDE values for RSH and PhSH may be even more similar than Benson's new values indicate;[32-34] however, it is unlikely that they are sufficiently similar to rationalize the identical ρ values observed for the two thiyl radicals.

(3) The final possibility, and the one we favor, is that some as yet unidentified factor makes a significant contribution to the magnitude of ρ. Table VI includes data for not only the two thiyl radicals but also for bromine atoms. The ρ values for hydrogen abstraction from ethylbenzene by all three of these radicals are, essentially, the same. However, the electron affinities vary from 1.5 to 3.4 eV, while the heats of reaction range over 10 kcal/mol. Clearly, electron affinity and BDE arguments cannot be used here to rationalize the observed ρ values. However, it is interesting to note that there is one property of the attacking radical which is the same in all three cases. That property is the *polarizability* of that atom to which the bond with hydrogen will be formed.[35] Just as it is an important factor contributing to a species' nucleophilicity,[36] polarizability may also be significant in determining the electrophilicity of a radical in hydrogen abstractions.

Note Added in Proof: In an article just published, R. H. Krech and D. L. McFadden (*J. Am. Chem. Soc.*, **99**, 8402 (1977)) show that the activation energies for hydrogen abstraction reactions in a homologous series of exothermic reactions are proportional to the inverse of the polarizabilities of the hydrogen donor and the attacking atom. In this connection, it also is interesting that the absolute rate constant for the reaction of *tert*-butoxy radicals with cumene is reported to be 9×10^5 M^{-1} s^{-1} at 25 °C by R. D. Small, Jr., and J. C. Scaiano (private communication; submitted for publication in *J. Am. Chem. Soc.*). This value is quite similar to the rate constant for the reation of $C_6H_{11}S$· with cumene at 80 °C, approximatly 6×10^6 M^{-1} s^{-1} given in Table II and the discussion here. The heats of these two reactions are −25 and −13 kcal/mol, respectively.

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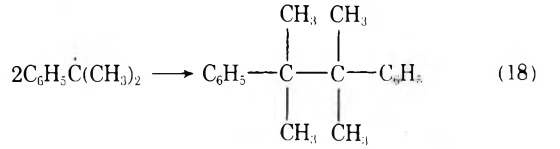
Appendix

Effect of Isolation Procedure on QH Activity. A sample of tritium-labeled triphenylmethane (6.8×10^8 dpm/mol, recovered from kinetic runs) was subjected to the normal workup procedure; no decrease in the activity was observed. Therefore, exchange between the benzylic hydrogens in the substrate and those of water (or other molecules) upon workup can be excluded, even for the more reactive substrates studied. Quantitative collection (trapping) was demonstrated for every liquid substrate studied by control experiments.[10] The assumptions that [RSH] ≫ [RST], low conversions, and the low extent of labeling of QH were met. (About one thiol molecule in 10^5 contained tritium.)

Most of the critical assumptions made in deriving eq 11 and 17 amount to the neglect of specific reactions. Such "wrong" reactions were ruled out on the basis of control experiments that are discussed in the paragraphs below.

Controls on Q· + X·, Reactions 18–21. If a Q· radical participates in termination reactions instead of reverting to (labeled) donor, the abstraction reaction that led to the Q· radical would not be detected, and the activity level in the recovered QH would be spuriously low. Cumene was chosen as a model substrate to study possible Q· termination reactions.

Participation of cumyl radicals in termination reactions[6] (eq 18–21) was ruled out by detailed product studies in cyclohexanethiol solvent (Table I) using GLC of reaction mixtures similar to those in the competitive method (eq 3–7) but containing cumene (0.25–0.5 M) as the only hydrogen donor. (In eq 18–21, A· is a 2-cyano-2-propyl radical and X· is any radical in the system.) Equation 22 depicts the most probable



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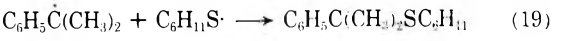

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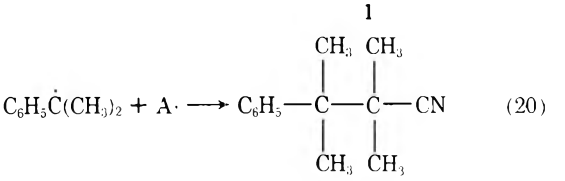

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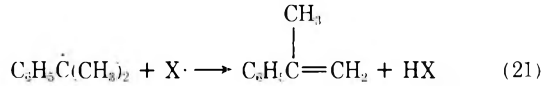

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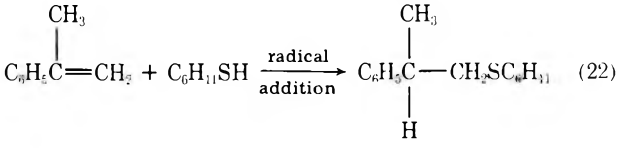

(22)

fate[6] of the α-methylstyrene formed in reaction 21. The amounts of bicumyl and of sulfides **4** and **5** produced in these control reaction mixtures could account for less than 1% of the cumyl radicals generated. Table I shows that the yield of AH (isobutyronitrile) (for 0.5 M cumeme) is roughly twice that of dicyclohexyl disulfide, indicating that dimerization of the thiyl radicals (eq 23) is the most important termination reaction occurring in free solution in systems containing up to 0.5 M cumene.

$$2C_6H_{11}S\cdot \rightarrow C_6H_{11}S\text{–}SC_6H_{11} \qquad (23)$$

As cumene concentration increases, the observed trends in the yields of bicumyl and **5** are consistent with expectations based on our kinetic analysis; specifically, a proportionality between the steady-state concentration of Q· and the concentration of QH is predicted.[10] Thus, neither bicumyl nor sulfide **5** is found in reaction mixtures up to 0.5 M in cumene (runs 1–4, Table I), but they both form in substantial amounts when 2.5 M cumene is used (run 5). Therefore, as QH and Q· concentrations increase, there is an enhancement in the rates of termination reactions in which Q· participates and in the yields of the corresponding termination products. At the highest cumene concentration (run 5) the ratio of molar yields of disulfide to isobutyronitrile (AH) falls to 0.31, a value which is consistent with the observation of termination reactions other than disulfide formation. Since 19 out of 25 substrates investigated are less reactive than cumene, they are expected to give rise to lower steady-state concentrations of Q· and less termination involving Q· radicals.

Controls on Q°· + QH, Reaction 24. It is possible that radicals other than RS· might abstract hydrogen from QH. In competitive runs (eq 3–7), for instance, reaction 24 could take place. Reaction 24 is likely to introduce complications by quenching the radicals (Q°·) from the less reactive donor, without labeling them, and simultaneously generating Q· radicals which become labeled and counted, leading to spuriously high $A_{QH}/A_{Q°H}$ ratios.

$$Q°\cdot + QH \xrightarrow{k_{24}} Q°H + Q\cdot \qquad (24)$$

The self-consistency of relative rates obtained within the framework of the competitive method, eq 3–7, can be tested in the following manner. The relative reactivities of substrates A and B are determined by a direct competition, and the results are compared with the outcome of a calculation based on the results of two actual competitions, one between A and C (a third substrate) and another between B and C (eq 25). Equation 25 can be justified only if rate constant ratios are proportional to the ratio of the rate constants if reaction 24 is included in the kinetic scheme. The excellent agreement observed between directly and indirectly obtained rate constant ratios[10] suggests that reaction 24 must not occur.

$$\frac{(k)_A}{(k)_B} = \frac{(k)_A}{(k)_C}\frac{(k)_C}{(k)_B} \qquad (25)$$

We also studied the effect of variations in the experimental parameters on the measured relative reactivities. The competition between ethylbenzene and cumene toward the cyclohexanethiyl radical was chosen as a model; reaction times were varied 4.3-fold, extents of reaction by 2.4-fold, concentration of combined donors sevenfold, and ratio of concentrations of donors 20-fold. None of these variations affected the measured relative reactivities.[10] Use of *tert*-butyl cyclohexaneperoxycarboxylate in place of AIBN also failed to affect the relative k_H values.[10] The rate of reaction 24 is modified by the above variations, but the activity ratios and, consequently, the ratio of rate constants for cumene and ethylbenzene remain constant, suggesting that reaction 24 is not kinetically significant.

Controls on C_6H_{11}· + QH, Reaction 26. The "reference reaction" in the second method is desulfuration of cyclohexanethiyl radicals by TPP, eq 12;[12] this yields cyclohexyl radicals that might abstract hydrogen from the donor (QH) present in the sample (eq 26). Occurrence of reaction 26 would lead to spuriously high reactivities. As stated above, use of *tert*-butyl cyclohexaneperoxycarboxylate instead of AIBN as the initiator did not affect the measured relative reactivities; this perester yields *tert*-butoxy and cyclohexyl radicals, and if either of these radicals attacked the substrates in kinetically significant amounts, the values of k_H would have been affected. The linearity observed in plots[10] of A_{QH} [TPP] vs. [C_6H_{12}] also argues against the occurrence of reaction 26. In addition, inclusion of reaction 26 in the kinetic scheme would not allow elimination of the terms involving concentrations of reactive intermediates, and the final equation would no longer lead to linear plots. Finally, the excellent agreement of the results obtained by both kinetic methods[8] suggests that reaction 26 does not interfere when the second method is used.

$$C_6H_{11}\cdot + QH \rightarrow C_6H_{12} + Q\cdot \qquad (26)$$

Controls on A· + QH, Reaction 27. If 2-cyano-2-propyl radicals (A·) from AIBN abstract hydrogen from the substrate(s), the observed selectivities would be characteristic of A· radicals and not of RS· radicals. However, since the same reactivity ratios were obtained when either *tert*-butyl peroxycyclohexanecarboxylate or AIBN initiation was used, such ratios reflect abstraction by some radical other than A·.

$$A\cdot + QH \rightarrow AH + Q\cdot \qquad (27)$$

Controls on Miscellaneous Reactions. It is conceivable that the nucleus of the aromatic substrates might become labeled. However, oxidative degradation of labeled ethylbenzene (recovered from kinetic runs) yields benzoic acid without residual activity. It is also possible to envision labeling and/or cyclohexane formation taking place via ionic or other unidentified pathways. The absence of labeling and cyclohexane in reaction samples from kinetic runs in which no initiator had been used excludes these complications.

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Stable Free Radicals. 7. 1-Alkyl-4-carbomethoxypyridinyls

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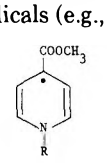
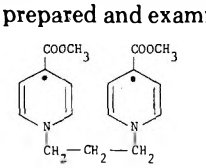
The synthesis of the 1-*tert*-butyl-4-carbomethoxypyridinyl radical is described and its properties are compared with the corresponding 1-methyl, 1-ethyl, and 1-isopropyl radicals. Although the *tert*-butyl radical appears to be the most stable in pure form and less susceptible to π-mer formation, its chemical reactivity toward bromochloromethane is very similar to that of the other 1-alkyl radicals. The nature of the products of reaction of 1-isopropyl-4-carbomethoxypyridinyl with bromochloromethane has been elucidated.

Stable pyridinyl radicals[2,4] (1) were first isolated in 1963[5] and have since proven useful for mechanistic studies.[6,7] Pyridinyl diradicals (e.g., 2) were also prepared and examined.[8,9]



1

R = CH_3, CH_3CH_2, $(CH_3)_2CH$, $(CH_3)_3C$



2

The formation of π-mers from pyridinyl monoradicals (intermolecular)[10] and from diradicals[9,11] (intramolecular) made necessary an understanding of the effect of *N*-alkyl substitution on the properties of pyridinyl monoradicals. Our more recent discovery of pyridinyl radical complexation with bis(pyridinium) ions[12] accentuated the need. Although the 1-ethyl radical has been described previously,[13] only few data have been noted for the 1-methyl and 1-isopropyl radicals.[10] We have now been able to complete the series with the 1-*tert*-butyl radical and shall describe in this article the preparation and certain properties of the simplest 1-alkyl-4-carbomethoxypyridinyl radicals (1).

Results

Synthesis of Salts. Methyl isonicotinate readily reacts with methyl, ethyl, and isopropyl iodides to form the desired salts

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Table I. Visible Absorption Maxima for 1-Alkyl-4-carbomethoxypyridinyls in Acetonitrile and 2-Methyltetrahydrofuran

Radical	Registry no.	Solvent, λ_{max} (nm) CH_3CN	2-MF[a]
CH_3	64754-20-7	635	647.5
CH_3CH_2	39327-12-3	632.5	642.5
$(CH_3)_2CH$	64754-19-4	630	637.5
$(CH_3)_3C$	64754-21-8	618	627.5

[a] 2-Methyltetrahydrofuran

(eq 1). *tert*-Butyl iodide could not be induced to react in this way, nor did the usual Zincke reaction via the inaccessible 1-(2,4-dinitrophenyl)-4-carbomethoxypyridinium chloride succeed. An important improvement introduced by Verhoeven[14] permitted us to prepare the *p*-toluenesulfonate salt, and from that the 1-*tert*-butyl-4-carbomethoxypyridinium iodide could be prepared (eq 2). The *tert*-butyl salt was not especially unstable, had a yellow color, and exhibited charge-transfer bands at slightly longer wavelengths than the 1-ethyl salt.

$$RI + \underset{\text{methyl isonicotinate}}{NC_5H_4COOCH_3} \rightarrow \underset{3}{RNC_5H_4COOCH_3{}^+I^-} \quad (1)$$

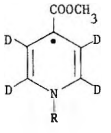
$$R = CH_3, CH_3CH_2, (CH_3)_2CH$$

$$1\text{-}[2,4\text{-}(NO_2)_2C_6H_3]NC_5H_4COOCH_3{}^+ OTs^- + t\text{-}BuNH_2 \xrightarrow{NaI} 3 \quad (2)$$

$$R = (CH_3)_3C$$

Methyl isonicotinate-d_4 (88 ± 2% deuterated by NMR) was prepared from 4-picoline-d_4 through oxidation with hot aqueous $KMnO_4$. The deuterated picoline was prepared through Pd-C catalyzed exchange at 240 °C on 4-picoline using D_2 and D_2O.[15,16] 1-Methyl-4-carbomethoxypyridinium-d_4 and -d_7 iodides were prepared through reaction of the ester with CH_3I and CD_3I, respectively.

Preparation of Radicals. All four 1-alkyl-4-carbomethoxypyridinyls and the deuterated radicals **4a** and **4b** were



4a R = CH_3; **4b** R = CD_3

prepared through sodium amalgam reduction of the corresponding salt in acetonitrile under oxygen-free conditions (eq 3) (1-ethyl and 1-isopropyl radicals[17]). Reduction of the 1-methyl salt was carried out between −30 and −40 °C; the more reactive 1-methyl radical still contained other light-absorbing impurities even after two distillations. Successive extractions (benzene, isopentane) were utilized for the 1-*tert*-butyl radical to avoid a volatile impurity (probably *tert*-butyl iodide).

$$\underset{3}{RPy^+I^-} \xrightarrow[CH_3CN]{3\%\ Na(Hg)} \underset{1}{RPy\cdot} \quad (3)$$

Physical Properties of Radicals: (a) Volatility and Appearance. Distillation of the radicals suggests the following order of volatility: isopropyl > ethyl > *tert*-butyl ≃ methyl. The isopropyl radical forms long blue needles at room temperature (mp ~50 °C) and small blue needles mp >25 °C of the *tert*-butyl radical can be obtained on crystallization from isopentane. Both ethyl[13] and methyl radicals are deep emerald-green liquids at room temperature, but both yield sapphire-blue solids at low temperatures.

(b) Visible Absorption Spectra. The maximum of the weak absorption band of the spectra of 1-alkyl-4-carbomethoxypyridinyls shifts to shorter wavelengths as the branching of the 1-alkyl group increases, the effect being slightly more evident in a less polar solvent (Table I). [In the UV, the 392-nm peak for the 1-*tert*-butyl radical was about 15% more intense (ϵ_{max} 5450) than that for the 1-ethyl radical (ϵ_{max} 4700).] The absorption coefficient for the visible band increased substantially (up to twofold) for the ethyl and isopropyl radicals, modestly for the methyl radical (due to accompanying decomposition), and not at all for the *tert*-butyl radical at room temperature in concentrated solutions (2 M for all radicals except *tert*-butyl, for which 0.2 M was the concentration used).

A dilute solution of *tert*-butyl radical (1.5×10^{-3} M) in MTHF showed no increase in light absorption between 500 and 1000 nm on cooling to −118 °C, but a more concentrated solution (0.05 M) exhibited a weak absorption at 650 ± 10 nm at the low temperature. *tert*-Butyl π-mer, observed at low temperatures, has λ_{max} 660 (ϵ >100).[18a]

(c) Photoelectron Spectrum. Ionization Potential. Using a moderately concentrated solution of 1-ethyl-4-carbomethoxypyridinyl radical sent by air from Tel-Aviv to Sussex, Murrell and Suffolk[18b] reported an adiabatic ionization potential of 6.8 eV and a vertical ionization potential of 7.2 eV for the radical.

(d) EPR Data. EPR spectra for the 1-alkyl-4-carbomethoxypyridinyls in 2-methyltetrahydrofuran (MTHF) are illustrated in Figure 1: 1-methyl (36.8 G), 1-ethyl (27.4 G), isopropyl (20.8 G), *tert*-butyl (20.8 G). Hyperfine splitting constants, $a_N \simeq 6.3$–7.0 G and 2,6 $a_H \simeq 3.4$ G, accounted for the main features of the spectra with complexities introduced by two different orientations of the carbomethoxy group.

Cooling concentrated (0.05 M) MTHF solutions of 1-methyl, 1-ethyl, or 1-isopropyl radicals to 77 K caused a substantial loss in signal strength, as expected for the formation of diamagnetic dimers.[10] In each case, a triplet signal (ca. 0.1–0.2% of radical in this form) was noted with a full-field separation of 83 G for the 1-ethyl case. A half-field signal comparable in strength to that of the full field was observed. The results for the 1-ethyl radical have been confirmed by Ikegami, Watanabe, and Seto,[19] who also noted a concentration dependence for the signal.

A solution of the 1-*tert*-butyl radical (0.05 M in MTHF) exhibited a substantial decrease in signal strength (67%) on cooling from 25 °C to 187 K.

Further cooling to 103 K led to an increased signal strength (two times that at 19 °C) with no sign of triplet signal.

Chemical Properties of Radicals. (a) Thermal Stability. Obvious differences in the stability of the pure radicals appeared during their preparation, with the methyl radical clearly susceptible to decomposition as seen through the loss of volatile material. Using a very short-path-length cell (0.005 cm) it was possible to follow the loss of visible absorption for 2 M acetonitrile solutions of the radicals. Decomposition did not follow simple kinetic laws (first or second order). No decomposition was observed for the *tert*-butyl radical. Approximate half-lives for the decomposition reaction of each radical can be stated: methyl (1 h), ethyl (13 h), isopropyl (≫100 h), *tert*-butyl (≫140 h), all values applying to 2 M solution. In the course of other experiments, we have heated 10^{-3} M solutions of the 1-ethyl radical in acetonitrile for several days at 71 °C with only a 3–4% decrease in optical density in the visible region.

(b) Reaction with Bromochloromethane: Kinetics. The rate of reaction of the alkylpyridinyls with bromochloromethane was followed at 25 °C in acetonitrile solution using the 620–640-nm visible absorption band of the radicals. The reaction has been shown to proceed according to the atom-

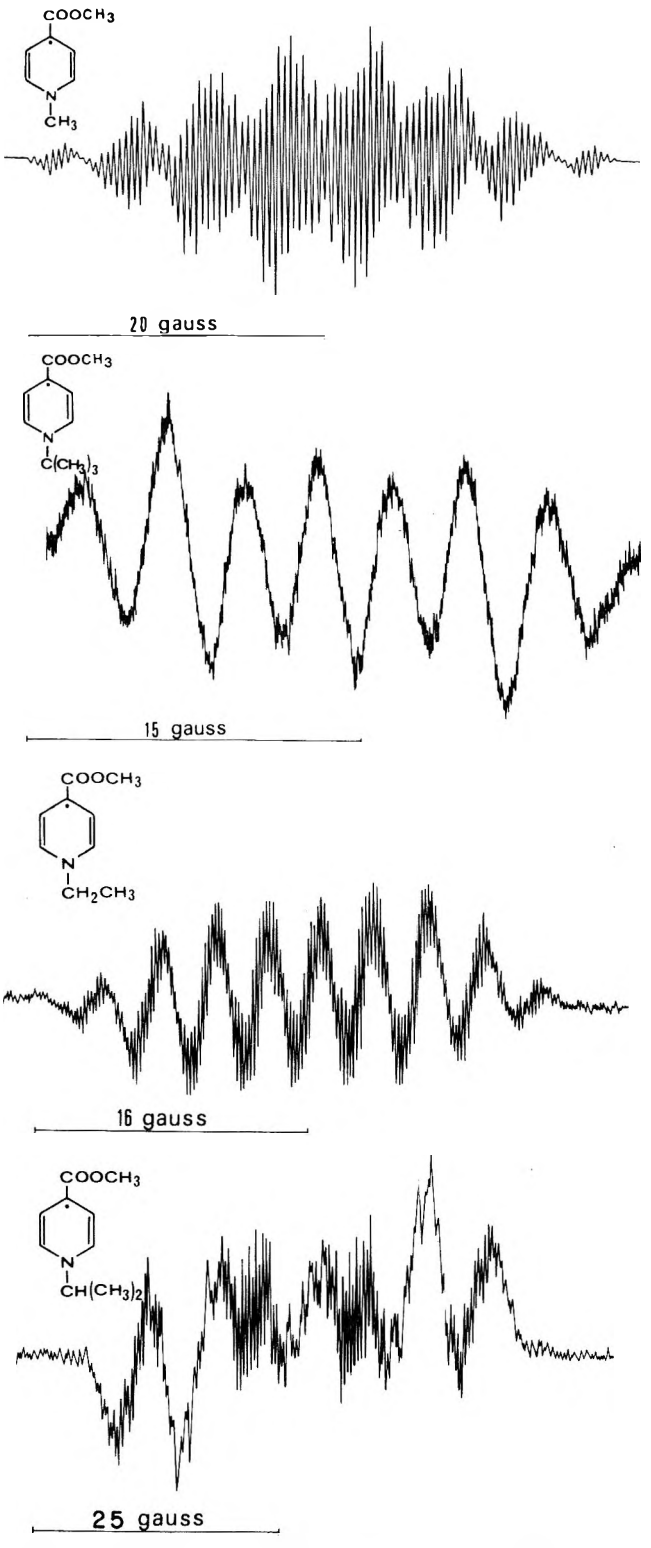


Figure 1. EPR spectra of 1-alkyl-4-carbomethoxypyridinyls in 2-methyltetrahydrofuran.

transfer pathway outlined in eq 4–6.[6,20] The kinetic constants are summarized in Table II.

$$RPy\cdot + BrCH_2Cl \rightarrow RPyBr + \cdot CH_2Cl \quad (4)$$

$$RPy\cdot + \cdot CH_2Cl \rightarrow RPyCH_2Cl \quad (5)$$

$$RPybr \rightarrow RPy^+Br^- \quad (6)$$

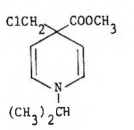
(c) Reaction with Bromochloromethane: Products. The reaction of a large quantity of 1-isopropyl-4-carbomethoxypyridinyl with bromochloromethane in acetonitrile was carried out for the purpose of determining the products of the reaction. The 1-isopropyl-4-carbomethoxypyridinium bromide salt (see eq 6) was isolated in over 35% yield and identified by UV, IR, and NMR spectra. We have shown elsewhere that eq 4 is required by the solvent effect data, there being almost no effect of solvent polarity on the rate of the closely related reaction of the 1-ethyl radical with dibromomethane.[6] In other words, the unstable bromodihydropyridine is an intermediate in the reaction, although not detected directly in this case. It is worth noting that 1-methyl-3,5-dicyano-4-iodo-1,4-dihydropyridine dissociates with difficulty even in aqueous solution.[21]

Table II. Rates of Reaction of Alkylpyridinyls with Bromochloromethane in Acetonitrile at 25 °C

1-Alkyl group	$[BrCH_2Cl]$, M	$k_{obsd} \times 10^4$, s^{-1}	$k_2 \times 10^5$,[a] M^{-1}, s^{-1}
Me	1.10	1.05	4.79
	1.13	1.17	5.21
	1.15	1.20	5.21
			(av 5.07)
Et	0.859	0.861	5.02
	1.45	1.46	5.05
	1.54	1.40	4.54
			(av 4.87)
i-Pr	1.10	1.42	6.45
	1.14	1.37	6.01
	1.36	1.62	5.97
			(av 6.14)
t-Bu	1.66	2.29	6.90
	2.42	3.93	8.12
			(av 7.51)

[a] The rate constant, k_2, was corrected by dividing by the number of pyridinyl radicals consumed (two) for every molecule of reacting halocarbon.

The other product was identified as a mixture of dihydropyridines **4** and **5**. These compounds were sensitive to oxygen and were thermally unstable,[22] making detailed characterization very difficult. Similar compounds have been shown to rearrange by Eisner and co-workers.[23] Identification was aided greatly by the presence of the isopropyl group, since two sets of characteristic doublets appeared in the NMR spectrum of the mixture at δ 1.25 and 1.30. The roughly equal peak heights indicated that 1-isopropyl-4-carbomethoxy-4-chloromethyl-1,4-dihydropyridine (**4**) and 1-isopropyl-2-chloromethyl-4-carbomethoxy-1,2-dihydropyridine (**5**) were formed



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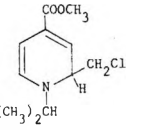

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in roughly equal amounts. Strong peaks centered at δ 3.7 and 3.8 indicated the methyl groups of the ester and small peaks at δ 4.5 and 6.1 were those expected for dihydropyridines.[22]

Discussion

The survey we have carried out on some of the physical and chemical properties of the 1-alkyl-4-carbomethoxypyridinyls has revealed that several are dependent upon the nature (and size) of the 1-alkyl group.

EPR Spectra. The width of the EPR spectrum for a 1-alkyl-4-carbomethoxypyridinyl is very much dependent upon the number of hydrogens on the α-carbon of the alkyl group. The spectral widths for the spectra shown in Figure 1 are:

Table III. Coupling Constants for Deuteropyridinyl Radicals

Solvent	a_N (4b), G	$a_{H(CH_3)}$ (4a), G	Spectral width (4a),[a] G
Water–acetonitrile (1:9)	6.35 ± 0.05	5.50 ± 0.08	29.19 ± 0.03
Methanol–acetonitrile (1:9)	6.36 ± 0.02	5.45 ± 0.04	29.07 ± 0.02
Acetonitrile	6.37 ± 0.07	5.87 ± 0.08	30.34 ± 0.02
Benzene	6.50 ± 0.04	5.94 ± 0.06	30.81 ± 0.02

[a] Total width (i.e., total splitting) of the spectrum in gauss was measured between points of zero slope on the first derivative spectrum.

(1-alkyl group) CH_3, 36.8 G; CH_3CH_2, 27.4 G; *i*-Pr, 20.8 G; and *t*-Bu, 20.8 G. In addition, as illustrated in Figure 2, the spectral width for the CH_3-d_4 radical is 29.2 G and that for CD_3-d_4 is 12.7 G. The nitrogen splitting appears to increase slightly from the 1-CH_3 (6.26 G)[10] to the 1-$(CH_3)_3C$ (≃7.0 G). Solvent polarity (*Z* value range[24,25] ~20) change has only a minor effect on the nitrogen splitting constant and a slightly larger effect on the α-hydrogen splitting of the 1-alkyl group (Table III).

The most important conclusion to be derived from these results is that the 1-alkyl-4-carbomethoxypyridinyl radical is not very polar, since a much larger change in splitting constants or spectral width would have been expected for a radical in which charge separation was important.[26] The conclusion is in agreement with a previous opinion based on (a) solubility of the radicals in very nonpolar solvents, like hexane, and (b) kinetic results for atom-transfer reactions in solvents of different polarity.[6,7]

Dimerization (π-merization). Three properties reflect the changes due to dimerization of pyridinyl radicals (eq 7). These are (a) the loss of EPR signal strength, (b) the growth of a visible absorption band, and (c) loss of volatility.

$$\underset{\text{singlet}}{\text{Py}\cdot + \text{Py}\cdot \rightleftharpoons (\text{Py}\cdot)_2} \rightleftharpoons \underset{\text{triplet}}{(\text{Py}\cdot)_2} \qquad (7)$$

The methyl, ethyl, and isopropyl radicals all show very large losses in EPR signal strength on cooling to 77 K in MTHF. The changes parallel the appearance of a strong visible absorption close to the location of the weak visible absorption of the monoradical. The *tert*-butyl derivative also shows a decrease in EPR signal strength down to 195 K. Preponderant π-mer formation for 1-methyl-, 1-ethyl-, and 1-isopropyl-4-carbomethoxypyridinyls in MTHF at low temperature gives way to modest π-mer formation for the 1-*tert*-butyl radical.

The relative volatility observed for the radicals is suggestive of an order of association, combined with an effect of molecular weight: isopropyl > ethyl > *tert*-butyl ≃ methyl.

The triplet dimer in equilibrium with the singlet dimer occurs for the 1-methyl, 1-ethyl, and 1-isopropyl radicals but apparently not for the 1-*tert*-butyl radical (eq. 7). Ikegami and co-workers have reported the production of isomeric triplet dimers on irradiation, and have proposed some difference in structure on the basis of zero-field splitting parameters.[19,27]

Stability. The survival of pyridinyl radicals is a practical fact of great utility in the study of the chemical and physical properties of pyridinyl radical and diradicals.[4] Our studies show that very high concentrations of free radical (2 M) favor decomposition. Dilute solutions in acetonitrile are very stable. At present, there is no evidence for dimerization to a compound with a localized covalent bond and no information on the products of decomposition of the free radicals in nonaqueous solvents.

Reactivity toward Halocarbons. There is essentially no effect of the 1-alkyl group on the rate of bromine atom transfer from bromochloromethane to pyridinyl radical. The products of the reaction with the 1-isopropylpyridinyl radical and bromochloromethane show that the sum of reactivities of the 2 and 6 positions are about equal to that of the 4 position, approximately what might have been expected on the basis of the spin densities estimated for these positions on the basis of EPR spectra.[4]

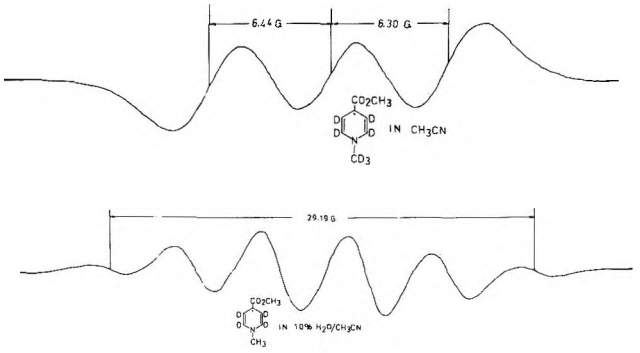

Figure 2. EPR spectra of (a) 1-trideuteriomethyl-4-carbomethoxypyridinyl-d_4 and (b) 1-methyl-4-carbomethoxypyridinyl-d_4 in 2-methyltetrahydrofuran. The splitting constant for the nitrogen is derived from the spectrum as shown in a.

Experimental Section

Solvents. Acetonitrile (spectroquality, Matheson, Coleman and Bell, E. Merck, Darmstadt) was degassed and stored over previously gassed (24 h, 1×10^5 Torr, 450 °C) molecular sieves (4A) (Linde Co.). Degassed solvent was distilled onto a mixture of magnesium turnings and 1,1′-trimethylenebis(4-carbomethoxypyridinium) diiodide (the magnesium complex of the bis(pyridinyl) diradical thus generated is highly reactive toward oxygen and possible other impurities[11]) before distillation into the desired apparatus or storage tube. This method gives routinely pure CH_3CN (no radical-reactive impurities). It has been used for small quantities of CD_3CN and appears to be the best purification method for CH_3CN for vacuum line use. 2-Methyltetrahydrofuran (MTHF) (Eastman Organic, Fluka) was refluxed over sodium for 10 days and then distilled. The material was degassed, distilled onto sodium and anthracene and, when needed, into a reaction apparatus.

Spectroscopic Measurements. UV–Vis. Cary Model 14 or 17 spectrophotometers were used.

Salts. 1-Methyl-4-carbomethoxypyridinium iodide, two crystallizations from methanol, mp 189–190 °C (dec) (in bath 184 °C), lit.[24] 190–191 °C (dec) (in bath 184 °C). 1-Ethyl-4-carbomethoxypyridinium iodide: mp 110–111 °C (lit.[24] 111–112 °C). 1-Isopropyl-4-carbomethoxypyridinium iodide. Isopropyl iodide (44 g, 0.26 mol) and methyl isonicotinate (4-carbomethoxypyridine) (30 g, 0.22 mol) were refluxed for 27 days in a mixture of acetone (25 cm^3)–ethyl ether (200 cm^3), yielding the yellow salt (1.7 g, 2.4% yield) in pure form, mp 134–136 °C. Anal. Calcd for $C_{10}H_{14}NO_2I$: C, 39,10; H, 4.60; N, 4.56; I, 41.32. Found: C, 39.40; H, 4.58; N, 4.43; I, 41.53. Less pure material, mp 129–134 °C, formed in 25% acetone–ether but could not be further purified. Pure reactants warmed to 35–40 °C gave salt, mp 130–132 °C.

1-*tert*-Butyl-4-carbomethoxypyridinium iodide–1-(2,4-dinitrophenyl)-4-carbomethoxypyridinium *p*-toluenesulfonate[14] (3.8 g, 8.0 mmol) in methanol (50 cm^3) was added dropwise to a solution of *tert*-butylamine (730 mg, 10.0 mmol) in methanol (10 cm^3). After addition, stirring 2 h, and removal of most of the solvent, the mixture was poured into ether (500 cm^3) and the precipitate was filtered off and dried. The 1-*tert*-butyl-4-carbomethoxypyridinium *p*-toluenesulfonate (1.6 g, 4.4 mmol) was dissolved in acetone (300 cm^3) and mixed with sodium iodide (0.75 g, 5.0 mmol) in acetone (100 cm^3). Sodium *p*-toluenesulfonate was filtered off, the solvent was removed,

and the residue was crystallized from isopropyl alcohol–acetone to give yellow crystals of iodide salt: mp 175–180 °C. yellow-red, 185–190 °C (dec); equiv wt calcd 321; found 315.5. NMR (D_2O) δ 1.8 (s, 9 H) (*t*-Bu), 4.0 (s, 3 H) (ester CH_3), 8.72 (d, 2 H) (3,5-H on ring), 9.55 (d, 2 H) (2,6-H on ring). Charge-transfer bands: (CH_2Cl_2) concn λ_{max} (ϵ_{max}) 8×10^{-4}, 441.7 (980); 14×10^{-4}, 441.2 (1000); 23×10^{-4}, 440.0 (1070); 52×10^{-4}, 438.0 (1090) (*i*-PrOH) 15×10^{-4}, 382.0 (322). These charge-transfer bands occur at slightly lower energies than those for 1-ethyl-4-carbomethoxypyridinium iodide:[24] (CH_2Cl_2) 20×10^{-4}, 438.1 (1150); (*i*-PrOH) 26×10^{-4}, 374.7 (532).

Pyridinyl Radicals. Sodium amalgam reduction according to the procedure of Kosower and Waits[17] was suitable for the preparation of all four 1-alkyl-4-carbomethoxypyridinyl radicals. However, the reactivity of the methyl radical was such that the reduction had to be carried out between −30 and −40 °C. All of the radicals could be distilled as noted in the text. However, the *tert*-butyl radical was contaminated with a volatile substance with absorption at 260 nm, thought to be *tert*-butyl iodide (volatility, light absorption). The *tert*-butyl radical was therefore extracted from the reduction mixture (30 min, 0 °C) with benzene, the benzene was removed after filtration, the radical was extracted with isopentane, the solution was filtered, the isopentane was removed, and acetonitrile was introduced. No volatile impurity was seen in the extraction procedure. All operations were carried out in all-glass apparatuses with complete exclusion of oxygen. Final solutions were normally stored at −10 °C in a number of tubes carrying breakseals for further investigations.

Kinetics Studies. (a) Reaction with Bromochloromethane. Solutions containing approximately 5×10^{-3} M radical in acetonitrile were mixed with sufficient bromochloromethane to produce a ~1 M solution of halocarbon. The decrease in the visible absorption peak was followed at 25 °C. At the end of the kinetic run, the halocarbon concentration was determined by GLC. Data fitted first-order kinetics to more than 60% reaction. Results are recorded in Table II.

(b) Thermal Stability. Large amounts of radical were prepared and transferred in acetonitrile as solutions approximately 0.15 M in radical, since all of the radicals were moderately stable at this concentration. The solutions were concentrated to approximately 2 M and transferred to an apparatus carrying a specially made quartz cell with 0.005-cm path length and openings at both top and bottom. The course of decomposition was followed at the maximum in the visible. Deviations from Beer's law were readily noted, the absorption being about twice as great as expected at the high concentration at 25 °C. The change in optical densities did not fit either first- or second-order kinetics, but approximate times for the half-decomposition of each radical could be obtained as follows: 1-methyl-4-carbomethoxypyridinyl (~1 h), 1-ethyl radical (~13 h), 1-isopropyl radical (≫100 h), 1-*tert*-butyl radical (≫150 h). At 75 °C, the isopropyl radical increased in absoprtion at 630 nm ($t_{1/2}$ 5–6 h) and then decreased after 30 h. A new absorption band at 480 nm increased with a $t_{1/2}$ of about 20 h.

Product Studies. Reaction of 1-isopropyl-4-carbomethoxypyridinyl with bromochloromethane. An acetonitrile solution of isopropyl radical (100 cm^3, 0.0376 M) was mixed with bromochloromethane (15 cm^3) (Kodak, degassed on line). Color change showed that the reaction was complete within 4.5 h. The solvent was removed and the residue was extracted twice with cyclohexane (30 cm^3)–benzene (10 cm^3). A brown solid residue, mp 60–98 °C, was shown to be somewhat impure 1-isopropyl-4-carbomethoxypyridinium bromide (0.310 g, 34.9%); NMR (D_2O) δ 1.69 (6 H, d) ($(CH_3)_2CH$), 4.00 (3 H, s) (CH_3O), 5.20 (1 H, heptet) (CHN), 8.52 (2 H, d) (3,5-H), 9.15 (2 H, d) (2,6-H); UV λ_{max} 220, 274 nm; IR almost identical to that for iodide salt. Solvent of extract was removed and oxygen-free acetone-d_6 was used to dissolve the residue, ~0.35 g (81% yield for chloromethyldihydropyridine): NMR two almost equal sets of doublets, centered at λ 1.25 and 1.30, represented the isopropyl groups of two isomeric products (δ 3.70 and 3.80), the methyl groups of the CH_3OOC– groups of two isomeric products, and (δ 4.5 and 6.1) unresolved peaks expected for a mixture of two dihydropyridines. The NMR had to be taken soon after the separation procedure described above because of the thermal instability of the products; their reactivity toward oxygen also made the experiment troublesome to execute.

EPR Studies. Solutions of radicals in MTHF were adjusted to approximately 0.05 M using the visible absorption band. Concentrations are thus approximate due to (10–20%?) dimerization, with a consequent increase in visible absorption. These solutions were used for evaluation of triplet dimer content. There were no obvious differences in triplet dimer signal strength between rapidly cooled and annealed samples. Solutions of ca. 10^{-4} M were used for high-resolution EPR spectra. The *tert*-butyl radical exhibited the same EPR spectrum at 10^{-3} M and 8.4×10^{-5} M at 25 °C.

Hydrogen Abstraction. Attempts to demonstrate hydrogen abstraction by 1-isopropyl-4-carbomethoxypyridinyl radical (ca. 0.01 M) in acetonitrile were carried out for a number of good hydrogen donors. 9,10-Dihydroanthracene (0.125 M): 11.5% decrease in the visible absorption in 96 h at 25 °C; 5% decrease after 6 h at 60 °C. 1-Benzyl-3-carbamido-1,4-dihydropyridine (0.125 M): 13% decrease, 25 °C, 96 h; 6% decrease, 60 °C, 6 h. Cumene (0.125 M): 17 h, 25 °C, no change; 6% decrease, 5.5 h, 60 °C. 1-Dodecanethiol (0.1 M): slow reaction, 25 °C, approximate $k = 3.3 \times 10^{-6}$ s^{-1}.

Acknowledgment. The Israel Academy of Sciences and the National Institutes of Health are thanked for financial support.

Registry No.— **4**, 64714-75-6; **4a**, 64754-22-9; **4b**, 64754-23-0; **5**, 64714-76-7; 1-isopropyl-4-carbomethoxypyridinium iodide, 15012-99-4; isopropyl iodide, 75-30-9; methyl isonicotinate, 2459-09-8; 1-*tert*-butyl-4-carbomethoxyridinium iodide, 64714-71-2; 1-(2,4-dinitrophenyl)-4-carbomethoxypyridinium *p*-toluenesulfonate, 53365-04-1; *tert*-butylamine, 75-64-9; 1-*tert*-butyl-4-carbomethoxypyridinium *p*-toluenesulfonate, 64714-73-4; bromochloromethane, 74-9705; 1-isopropyl-4-carbomethoxypyridinium bromide, 64714-74-5.

References and Notes

(1) (a) Tel-Aviv University. (b) State University of New York, at Stony Brook.
(2) The conditions and time scale of the experiment define the experimenter's view of the stability of the radical. For a radical to be "stable" under a particular set of conditions means that the radical "persists" long enough to be manipulated and measured. We reserve the term "stable" for radicals which can be isolated in reasonably pure form. In the case of 1-alkyl-4-carbomethoxypyridinyls, stability can be considerable in the absence of oxygen, a finding confirmed for differently substituted pyridinyl radicals by M. Itoh and S. Nagakura, *Bull Chem. Soc. Jpn.*, **39**, 369 (1966), A. R. Katritsky and F. Soti, *J. Chem. Soc., Perkin Trans. 1*, 1427 (1974), and Y. Ikegami, personal communication.
For a different emphasis of meaning, the reader might consult D. Griller and K. U. Ingold, *Acc. Chem. Res.*, **9**, 13 (1976), but should he wish to make a choice between the two terms, he might do well to consider the first definition of the word persist (ref 3) "to be obstinately repetitious, insistent or tenacious in some activity".
(3) The American Heritage Dictionary of the English Language, W. Morris, Ed., American Heritage-Houghton Mifflin, Boston, 1969, p 978.
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Comparisons of the Inden-1-yl, Fluoren-9-yl, and Cycloprop[2,3]inden-1-yl Cations

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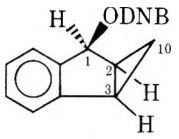
The first-order rate constants for hydrolysis of the inden-1-yl and fluoren-9-yl 3,5-dinitrobenzoates in 80% aqueous acetone at 80 °C have been indirectly determined. By comparison with kinetic data for hydrolysis of suitable model compounds under similar conditions, these can be estimated to be approximately 10^{11}- and 10^{8}-fold, respectively, retarded in rate by the presence of destabilizing antiaromatic effects in their rate-determining activated complexes for ionization. Comparisons with the much smaller corresponding antihomoaromatic rate retardations of about 10^{3}-fold for hydrolyses of the cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates under the same reaction conditions have also been made. A possible explanation for the differing magnitudes of the rate-retarding effects is offered.

Introduction

We recently reported[1] a detailed investigation of the rates and products of hydrolysis of the *endo*- and *exo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates (**1** and **2**, respectively) in 80% aqueous acetone. Kinetic comparisons with model compounds clearly showed the presence of moderate rate-retarding antihomoaromatic effects in the reactions of these systems. Also, from the effects on rate of introducing methyl substituents at C-3 and C-10, it could be concluded that delocalization of positive charge to C-3 in the activated complexes for ionization of both **1** and **2** is prohibited. However, considerable positive charge is delocalized to C-10 in these species.



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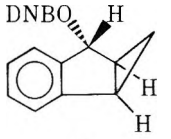

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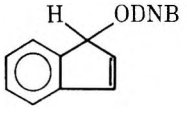
In connection with the above study and with the interesting question of the comparative behaviors of cyclopropane rings, carbon–carbon double bonds, and benzene rings in delocalization of positive charge, we became interested in obtaining quantitative information in the indene system concerning the relative effectiveness of cyclopropane rings in transmitting rate-retarding antihomoaromatic effects vs. carbon–carbon double bonds and benzene rings in transmitting rate-retarding antiaromatic effects. Thus, we wished to determine the rates of hydrolysis of the inden-1-yl and fluoren-9-yl 3,5-dinitrobenzoates (**3** and **4**, respectively) in 80% aqueous acetone for comparison with the rates of hydrolysis of suitable model systems in which antiaromatic interactions are precluded, and with the rate data obtained earlier[1] with the cycloprop[2,3]-inden-1-yl 3,5-dinitrobenzoates **1** and **2**. The results of these studies are described below.



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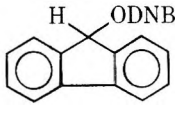

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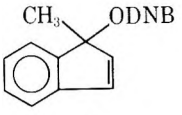
Results and Discussion

Initial solvolytic studies in 80% aqueous acetone at 100 °C with both the inden-1-yl and fluoren-9-yl 3,5-dinitrobenzoates (**3** and **4**, respectively) revealed very slow rates of acid production which were almost identical for both compounds (k_1 = ~10^{-7} s^{-1} at 100 °C). Also, the acid production continued well beyond the expected theoretical infinities. These results suggest that the primary source of acid was not from hydrolysis of the esters, but from a different process such as slow oxidation of the solvent.[2] Thus, the maximum rate constants for hydrolysis of both **3** and **4** in 80% aqueous acetone at 100 °C must be 10^{-7} s^{-1}, but the actual values may be several powers of ten smaller. Isolation of unreacted **3** showed that its apparent low solvolytic reactivity was not the result of a 1,3-proton shift[3] to give the isomeric vinylic inden-3-yl ester.

Because of the problems described above, an indirect approach was required to obtain estimates of the desired rates of hydrolysis of **3** and **4** in 80% aqueous acetone via first-order nucleophilic substitution mechanisms. Thus, studies of the rates of hydrolysis of the 1-methylinden-1-yl (**5**) and 9-methylfluoren-9-yl (**6**) 3,5-dinitrobenzoates and of the model compounds **7** and **8** were carried out in 80% aqueous acetone. The tertiary derivatives **5** and **6** are considerably more reactive than the corresponding secondary esters **3** and **4** and are also able to react only via an ionization mechanism. Then, to enable prediction of the expected α-CH_3/H rate ratios for the inden-1-yl and fluoren-9-yl systems in 80% aqueous acetone, the rates of solvolysis of **3** and **5** and of the model compound **7** in the strongly ionizing but poorly nucleophilic[4] 2,2,2-trifluoroethanol solvent were determined. The results of these studies are summarized in Tables I and II.



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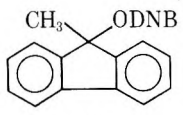

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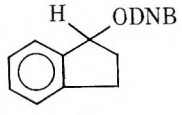

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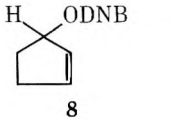

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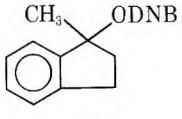

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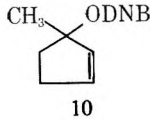

10

For the purpose of the rate comparisons, solvolytic data for **4**, **6**, and **9** in 2,2,2-trifluoroethanol and for **9** and **10** in 80% aqueous acetone would ideally also have been desirable. However, we were unable to carry out a kinetic study with the fluorenyl derivatives **4** and **6** in 2,2,2-trifluoroethanol owing to their low solubilities. Also, we were unsuccessful in attempts to prepare **9** owing to its high reactivity. Several attempts to prepare **9** from the corresponding tertiary alcohol resulted only in isolation of 3-methylindene. It is presumed that **10** should be even more reactive than **9**.

Included among the attempts to prepare **9** were low-temperature reactions of 1-methylindan-1-ol with 3,5-dinitrobenzoyl chloride in pyridine followed by low temperature

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Table I. Rates of Hydrolysis of Some 3,5-Dinitrobenzoates in 80% Aqueous Acetone

Compd	Registry no.	Concn, 10^3 M	Temp, °C	$10^5 k_1$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
3	53820-88-5	7.7	100.0	<0.01		
4	64666-55-3	1.2	100.0	<0.01		
5	64666-56-4	4.8	100.0	10.5 ± 0.4		
		6.1	80.0	1.31 ± 0.05	26.6 ± 1.0	−5.9 ± 2.9
6	64666-57-5	7.9	80.0	105 ± 1		
		9.2	60.0	13.5 ± 0.2	23.3 ± 0.2	−11.2 ± 0.6
7	61463-15-8	7.8	100.0	30.6 ± 0.4		
		11.5	80.0	4.53 ± 0.04	24.3 ± 0.4	−9.9 ± 1.1
8	64666-40-6	10.6	80.0	116 ± 5		
		12.1	60.0	13.7 ± 0.7	24.3 ± 1.1	−8.2 ± 3.4

Table II. Rates of Solvolysis of Some 3,5-Dinitrobenzoates in 2,2,2-Trifluoroethanol

Compd	Concn, 10^3 M	Temp, °C	$10^5 k_1$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
3	4.1	125.0	0.110 ± 0.005		
	5.4	100.0	0.0104 ± 0.0003	27.1 ± 0.9	−14.1 ± 2.6
		80.0	(0.00124)		
5		80.0	(91.2)		
	4.5	60.0	11.3 ± 0.1		
	4.9	39.9	1.07 ± 0.4	23.7 ± 1.3	−5.9 ± 4.2
7		80.0	(343)		
	5.4	60.0	49.6 ± 1.1		
	6.9	39.9	5.59 ± 0.28	21.9 ± 0.7	−8.4 ± 2.3

aqueous as well as nonaqueous workups. Also, reactions of the tertiary alcohol were carried out with sodium hydride or with methyllithium in ether followed by addition of 3,5-dinitrobenzoyl chloride at −20 °C. In the latter case, a white solid presumed to be **9** was obtained on evaporation of the ether solvent at lower than 0 °C. However, on warming to room temperature, this liquified to a mixture shown by NMR examination to consist of 3-methylindene and 3,5-dinitrobenzoic acid.

To obtain information regarding just how reactive is the tertiary 1-methylindan-1-yl system as compared to the secondary indan-1-yl system, we carried out a brief NMR study of the reactions of the alcohols corresponding to **7** and **9** in dry acetic acid at 40 °C. It was found that the 1-methylindan-1-ol reacted to give 3-methylindene 1000 times faster than indan-1-ol reacted to give indan-1-yl acetate. No evidence could be found for even transient formation of 1-methylindan-1-yl acetate from the 1-methylindan-1-ol. The 1000-fold rate difference would not appear alone to suffice to explain our inability to isolate **9**. Thus, other factors such as the pronounced tendency of the 1-methylindan-1-yl system to undergo elimination may also be responsible.

In considering the data in Table II for the reactions run in the 2,2,2-trifluoroethanol solvent, it is seen that inden-1-yl 3,5-dinitrobenzoate (**3**) is approximately 10^5 less reactive than 1-methylinden-1-yl 3,5-dinitrobenzoate (**5**). This 10^5 α-CH_3/H rate ratio in the inden-1-yl system is in the same range as that expected[5] for limiting solvolyses of simple alkyl systems in which no charge delocalization is possible. However, it differs significantly from the smaller values of about 10^2–10^3 commonly observed[5] for systems in which benzylic-type charge delocalization is possible.

Using the approximately 10^5 rate ratios between **3** and **5** or **7** in 2,2,2-trifluoroethanol reported in Table II, one can then estimate for 80% aqueous acetone, where **5** and **7** also exhibit similar relative reactivities, that the first-order rate constant for ionization of inden-1-yl 3,5-dinitrobenzoate (**3**) should be approximately 1×10^{-10} s^{-1} at 80 °C. Furthermore, assuming a similar 10^5 α-CH_3/H rate ratio for the fluoren-9-yl system, a first-order rate constant for the ionization of **4** in 80% aqueous acetone at 80 °C of approximately 1×10^{-9} s^{-1} can be obtained. This estimated value for **4** appears quite reasonable and also in accord with literature kinetic data for other fluoren-9-yl derivatives which have appeared earlier. Thus, both Ledwith and Morris,[6] in their studies of the relative rates of hydrolysis of the fluoren-9-yl and benzhydryl *p*-toluenesulfonates in 90% aqueous tetrahydrofuran at 25 and 0 °C, and Lovins, Andrews, and Keefer,[7] in their studies of the relative rates of reaction of the corresponding bromides in 80% aqueous ethanol at about 70 °C, found fluoren-9-yl to benzhydryl rate ratios of about 10^{-3}. From Goering and Hopf's data[8] for the hydrolysis of benzhydryl *p*-nitrobenzoate in 90% aqueous acetone, one can estimate that in 80% aqueous acetone at 80 °C k_1 for the 3,5-dinitrobenzoate should be approximately 1×10^{-6} s^{-1}. Thus, using this value and a 10^{-3} fluoren-9-yl to benzhydryl rate ratio, k_1 for hydrolysis of fluoren-9-yl 3,5-dinitrobenzoate in 80% aqueous acetone at 80 °C can be estimated to be about 1×10^{-9} s^{-1}.

Finally, using the above derived rate constants for **3** and **4** and other data reported in Table I or from the literature, the relative rates of reaction summarized in Table III can be obtained. Based on the information in Table III, simple additive substituent effects in the cyclopentyl system point to the inden-1-yl (**3**), fluoren-9-yl (**4**), and cycloprop[2,3]inden-1-yl (**1** and **2**) 3,5-dinitrobenzoates being about 10^{12}, 10^9, and 10^4, respectively, less reactive than would be expected in the absence of antiaromatic or antihomoaromatic effects. However, it should be noted that these rate-retardation factors based on simple additive substituent effects are likely to be somewhat high. Our earlier work[1] on the cycloprop[2,3]inden-1-yl systems **1** and **2** involving a more detailed study of cumulative conjugating substituent effects showed that a realistic antihomoaromatic rate-retardation factor for this system is about 10^3. Thus, one can conclude that antiaromatic destabilizing effects in the activated complexes for the ionization of **3** and **4** actually produce rate retardations of approximately 10^{11} and 10^8, respectively.

The observation that the rate-retarding antiaromatic effects

Table III. Estimated Relative Rates for Limiting S_N1 Hydrolyses of Some 3,5-Dinitrobenzoates in 80% Aqueous Acetone at 80 °C

System	k_1, s^{-1}	k_{rel}
Inden-1-yl (3)	1×10^{-10}	1
Fluoren-9-yl (4)	1×10^{-9}	10
Cycloprop[2,3]inden-1-yl (1 or 2)	3×10^{-5} [a]	10^5
Indan-1-yl (7)	5×10^{-5}	10^5
Cyclopenten-3-yl (8)	1×10^{-3}	10^7
Bicyclo[3.1.0]hexan-2-yl (11)	2×10^{-6} [b]	10^4
Cyclopentyl (12)	1×10^{-10} [c]	(1)

[a] Estimated from the data of E. C. Friedrich and D. B. Taggart, *J. Org. Chem.*, **42**, 1437 (1977). [b] Estimated from the data of E. C. Friedrich and M. A. Saleh, *J. Am. Chem. Soc.*, **95**, 2617 (1973). [c] Estimated from the data of H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 5008 (1964); and K. B. Wiberg and W.-F. Chen, *J. Am. Chem. Soc.*, **96**, 3900 (1974).

upon the reactions of **3** and **4** are of considerably greater magnitude than are the rate-retarding antihomoaromatic effects upon the reactions of **1** and **2** requires some comment. This may be due in part to a carbon–carbon π bond in a benzocyclopenten-3-yl or cyclopenten-3-yl type cation being better for charge delocalization due to stereoelectronic reasons than is a cyclopropane ring in a bicyclo[3.1.0]hexan-2-yl type cation. Thus, it is seen from the results in Table III that **7** and **8** are 10^1 and 10^3 more reactive than **11**. However, the major reason is most likely related to the observation[1] that in the cycloprop[2,3]inden-1-yl system a stabilizing interaction involving delocalization of charge to the C-10 cyclopropyl methylene is present which can at least partially counteract any destabilizing antihomoaromatic interactions. Such a type of counteracting stabilization is not available to the antiaromatic inden-1-yl and fluoren-9-yl systems.

Experimental Section

General. Melting and boiling points are uncorrected. Infrared spectra were run on a Perkin-Elmer 237B grating infrared spectrophotometer either as mineral oil mulls or in potassium bromide pellets. NMR spectra were run on a Varian Associates A-60A instrument, and chemical shifts are reported in ppm (δ) downfield from a Me_4Si internal standard. Mass spectra were run by Mr. John Voth or Mr. Paulus Bruins of the University of California, Davis, on a CEC Model 21-104 single-focusing instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Inden-1-yl 3,5-Dinitrobenzoate. This dinitrobenzoate was prepared employing a slight modification of our earlier reported[3] procedure. After cooling the pyridine solvent to −25 °C, 1.7 g (0.013 mol) of inden-1-ol[3] was added followed by the addition in portions of 3.5 g (0.015 mol) of 3,5-dinitrobenzoyl chloride. The reaction mixture was maintained at −20 to −25 °C for 2 h and then poured into 160 mL of ice-cold 1 M hydrochloric acid. The precipitate collected was recrystallized from 150 mL of 1:1 chloroform–petroleum ether (30–60 °C) to yield 3.35 g of crude inden-1-yl 3,5-dinitrobenzoate, mp 136–145 °C. Further recrystallization of 2.3 g of this material from acetone yielded 1.7 g (61%) of pure inden-1-yl 3,5-dinitrobenzoate: mp 145.5–146.5 °C [lit.[3] mp 142–145 °C]; NMR ($CDCl_3$) 6.5 (m, 2 H, CHODNB and CHCHODNB), 6.9 (dd, J = 2 and 6 Hz, 1 H, CH-arom), 7.3 (m, 4 H, arom), and 9.2 ppm (s, 3 H, arom).

Fluoren-9-ol. This material was prepared by lithium aluminum hydride reduction of 15 g (0.083 mol) of fluoren-9-one in ether. Workup and recrystallization from 1:1 ether–petroleum ether (30–60 °C) afforded 7.9 g (52%) of fluoren-9-ol: mp 154.5–156.5 °C [lit.[9] mp 154–155 °C]; NMR ($CDCl_3$) (external Me_4Si) δ 2.2 (s, 1 H, OH), 5.7 (s, 1 H, CHOH), and 7.7 ppm (m, 8 H, arom).

Fluoren-9-yl 3,5-Dinitrobenzoate. In the usual manner, 1.8 g (0.010 mol) of fluoren-9-ol in pyridine at 0 °C was treated with 3.0 g (0.0130 mol) of 3,5-dinitrobenzoyl chloride. After workup, recrystallization from 1:1 hexane–chloroform afforded 2.4 g (63%) of fluoren-9-yl 3,5-dinitrobenzoate: mp 215.5–217.5 °C; NMR ($CDCl_3$) δ 7.2 (s, 1 H, CHODNB), 7.6 (m, 8 H, arom), and 9.3 ppm (s, 3 H, arom).

Anal. Calcd for $C_{20}H_{12}N_2O_6$: C, 63.83; H, 3.21; N, 7.44. Found: C, 63.77; H, 3.16; N, 7.35.

1-Methylinden-1-ol. Initially, phenyllithium was prepared by the slow addition of an ethereal solution of 25.2 g (0.16 mol) of bromobenzene to 2.2 g (0.32 mol) of small pieces of lithium wire in ether and under a nitrogen atmosphere. This mixture was stirred at room temperature for 12 h, then 17.6 g (0.14 mol) of 1-methylindene[3] in ether was added, and the solution was cooled to −78 °C. Oxygen was bubbled into the resulting solution of methylindenyllithium at a rate of 40 L/h for 1 h. After neutralization by dropwise addition of 80 mL of 1 N hydrochloric acid, 40 g of potassium iodide in 100 mL of 1:1 water–acetic acid was added. The solution was stirred briefly and then transferred to a separatory funnel. Extraction with ether was followed by washing the combined ethereal solution with saturated sodium bicarbonate solution and saturated sodium chloride solution and then drying over anhydrous magnesium sulfate. The solid remaining, after removal of the ether, was recrystallized from 3:1 chloroform–pentane to yield 7.9 g (40%) of 1-methylinden-1-ol: mp 96–98 °C; NMR (CCl_4) δ 1.5 (s, 3 H, CH_3), 1.8 (s, 1 H, OH), 6.2 (d, J = 6 Hz, 1 H, CHC(OH)-CH_3), 6.5 (d, J = 6 Hz, 1 H, CH-arom), and 7.1 ppm (m, 4 H, arom); IR (mineral oil) 3225 (OH), 3145 (OH), and 1100 cm^{-1} (CO); mass spectrum (70 eV) *m/e* (rel intensity) 147 (9), 146 (77), 145 (30), 132 (10), 131 (100), 128 (17), 127 (11), 115 (13), 103 (21), 102 (11), 77 (15).

1-Methylinden-1-yl 3,5-Dinitrobenzoate. Following the usual procedure, 1.06 g (0.0073 mol) of 1-methylinden-1-ol in pyridine at 0 °C was treated with 2.0 g (0.0088 mol) of 3,5-dinitrobenzoyl chloride. Workup was followed by unsuccessful attempts at recrystallization of the resulting gummy solid from ether, ether–pentane, or ether–mixed hexanes. However, removal of all the solvents and drying of the resulting yellow powder under vacuum at room temperature for 24 h provided 1.31 g (55%) of 1-methylinden-1-yl 3,5-dinitrobenzoate: mp 71–73 °C; NMR ($CDCl_3$) δ 1.9 (s, 3 H, CH_3), 6.7 (q, 2 H, CH=CH), 7.3 (m, 4 H, arom), and 9.1 ppm (m, 3 H, arom).

Anal. Calcd for $C_{17}H_{12}N_2O_6$: C, 60.00; H, 3.55. Found: C, 60.15; H, 3.60.

9-Methylfluoren-9-ol. Methylmagnesium bromide was prepared under nitrogen from 1.1 g (0.045 mol) of magnesium turnings in anhydrous ether by adding 6.6 g (0.046 mol) of methyl iodide in ether. After stirring at room temperature for 1 h, 5.5 g (0.031 mol) of fluoren-9-one was added and the resulting mixture was stirred at reflux for 1 h. Neutralization with ice-cold 2 M sulfuric acid was followed by ether extraction. The ethereal solution was washed with saturated sodium bicarbonate and dried over anhydrous magnesium sulfate. Concentration of the ether solution to 100 mL followed by cooling to −25 °C provided 5.0 g (83%) of white plates of 9-methylfluoren-9-ol: mp 173–174 °C [lit.[10] mp 174–175 °C].

9-Methylfluoren-9-yl 3,5-Dinitrobenzoate. In portions, 2.3 g (0.010 mol) of 3,5-dinitrobenzoyl chloride was added to 1.45 g (0.074 mol) of 9-methylfluoren-9-ol in pyridine at 0 °C. Workup followed by recrystallization from 60 mL of ether afforded 2.4 g (83%) of 9-methylfluoren-9-yl 3,5-dinitrobenzoate: mp 107–110 °C dec; NMR ($CDCl_3$) δ 2.0 (s, 3 H, CH_3), 7.4 (m, 8 H, arom), and 9.0 ppm (m, 3 H, arom).

Anal. Calcd for $C_{21}H_{14}N_2O_6$: C, 64.62; H, 3.62. Found: C, 64.49; H, 3.58.

Indan-1-yl 3,5-Dinitrobenzoate. This material was prepared as described[1] by us in an earlier paper.

1-Methylindan-1-ol. The reaction of 2.47 g (0.020 mol) of indan-1-one with methyllithium in ether followed by workup and recrystallization from *n*-pentane produced 1.70 g (52%) of 1-methylindan-1-ol: mp 55–56 °C [lit.[11] mp 56–57 °C]; NMR (CCl_4) δ 1.3 (s, 3 H, CH_3), 2.0 (m, 2 H, $CH_2C(OH)CH_3$), 2.7 (m, 2 H, CH_2-arom), 3.2 (br s, 1 H, OH) and 7.0 ppm (m, 4 H, arom).

Cyclopenten-3-yl 3,5-Dinitrobenzoate. In the usual manner, 2.5 g (0.030 mol) of cyclopenten-3-ol[12] in pyridine was treated with 8.3 g (0.036 mol) of 3,5-dinitrobenzoyl chloride. Workup and recrystallization from chloroform–*n*-pentane produced 4.7 g (57%) of slightly impure product, mp 118–121 °C. A second recrystallization of a portion of this material yielded small white crystals of pure cyclopenten-3-yl 3,5-dinitrobenzoate: mp 122–123 °C; NMR ($CDCl_3$) δ 2.5 (m, 4 H, CH_2CH_2), 6.0 (m, 2 H, CH=CH), 6.2 (m, 1 H, CHODNB), and 9.1 ppm (s, 3 H, arom).

Anal. Calcd for $C_{12}H_{10}N_2O_6$: C, 51.81; H, 3.62. Found: C, 51.72; H, 3.56.

Kinetics in 80% Aqueous Acetone. The equipment, solvents, procedure used for measuring reactions rates, and treatment of the data were as described earlier.[1] All runs were carried out in duplicate.

2,2,2-Trifluoroethanol. This solvent was dried over anhydrous sodium carbonate and redistilled from powdered 4A Linde molecular sieves through a 50-cm Widmer column.

Kinetics in 2,2,2-Trifluoroethanol. Kinetic studies in 2,2,2-trifluoroethanol were almost identical to those in 80% aqueous acetone. As an example, 0.0709 g (2.16×10^{-4} mol) of indan-1-yl 3,5-dinitrobenzoate was dissolved in 27 mL of anhydrous 2,2,2-trifluoroethanol, and five equivalent portions were sealed in ampules. The ampules were placed in an oil bath at 39.9 °C and removed at convenient intervals. After cooling in ice water followed by equilibration to room temperature, a 5-mL aliquot was taken with a calibrated automatic pipet. This sample was added to 30 mL of ice-cold 5:1 acetone–water and titrated to a bromothymol blue end point using 0.0107 N sodium methoxide in methanol.

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Registry No.—Inden-1-ol, 61463-21-6; 3,5-dinitrobenzoyl chloride, 99-33-2; fluoren-9-one, 486-25-9; fluoren-9-ol, 1689-64-1; 1-methylindene, 767-59-9; methylindenyllithium, 55563-47-8; 1-methylinden-1-ol, 64666-41-7; 9-methylfluoren-9-ol, 6311-22-4; indan-1-one, 83-33-0; 1-methylindan-1-ol, 64666-42-8; cyclopenten-3-ol, 3212-60-0; inden-1-yl cation, 42949-14-4; fluoren-9-yl cation, 19873-39-3; cycloprop[2,3]inden-1-yl cation, 56377-03-8.

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Persistent Cyclic Diacylhydrazyl Radicals from Urazoles and Pyrazolidine-3,5-diones

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Lead dioxide oxidation of 1,4-disubstituted urazoles **4** or 1,4,4-trisubstituted pyrazolidine-3,5-diones **6** affords the corresponding cyclic diacylhydrazyl radicals. A number of these radicals are quite persistent. For example, 1-α-cumyl- and 1-*tert*-butylurazole radicals **4g**•–**4k**• and 1-phenylpyrazolidinedione radicals **6e**• and **6f**• are in mobile equilibrium with and can be isolated as their tetrazane dimers. As solid dimers, these radicals are indefinitely persistent. Solution lifetimes of pyrazolidinedione radicals **6g**• and **6h**•, 1-phenylurazole radicals **4d**• and **4f**•, and 1-α-cumylurazole radical **4i**• are less than 1 week, whereas solution lifetimes of 1-α-cumylurazole radicals **4g**• and **4h**• and 1-*tert*-butylurazole radicals **4j**• and **4k**• are extremely long and comparable to that of DPPH. The extent of dimerization of several of the radicals has been measured in carbon tetrachloride, benzene, and acetonitrile and shows that 1-α-cumyl- and 1-*tert*-butylurazole radicals are more polar than their tetrazane dimers and that 1-phenylpyrazolidinedione radicals are more than 90% dimerized at concentrations greater than 5×10^{-2} M. Infrared carbonyl stretching frequencies of isolable radicals and their solid tetrazane dimers are compared with those of the corresponding urazole and pyrazolidinedione precursors. These data are also used to exclude the possible existence of dimeric structures in which the carbonyl oxygen is involved in the dimeric linkage. Visible spectral data are reported for highly colored urazole and pyrazolidinedione radicals. EPR spectra of these cyclic diacylhydrazyl radicals are indicative of π radicals and show delocalization of unpaired spin density over the entire heterocycle for the urazole radicals. For the pyrazolidinedione radicals delocalization is restricted primarily to the nitrogens. Additional hyperfine splitting occurs when a phenyl group is bonded to N-1 (but not N-4) in urazole radicals. No splitting is observed for the aromatic ring of a cumyl group bonded to N-1. Persistence of 1-α-cumyl- and 1-*tert*-butylurazole radicals is described as a consequence of steric crowding of the site formally bearing the unpaired electron, substitution by other groups or atoms for hydrogen at sites where disrpoportionation could occur, and delocalization of unpaired spin density. The imide nitrogen of the urazoles reduces the ability of the carbonyl groups to delocalize hydrazyl nitrogen lone pairs. This effect increases delocalization of unpaired spin density in and persistence of 1-α-cumyl- and 1-*tert*-butylurazole radicals relative to α-cumylpyrazolidinedione radicals which lack an imide nitrogen.

Although organic free radicals are typically transient and unisolable, there are notable exceptions. Arylhydrazyl radicals, including the exceptionally persistent[3] diphenylpicrylhydrazyl (DPPH), are among the most extensively studied free radicals known.[4] Recently, interest has been focused on hydrazyl radicals which lack directly bonded aromatic groups,[5–15] and one of these non-arylhydrazyl radicals has been isolated as its dimeric tetrazane.[1] Although cyclic diacylhydrazines have long been known,[16,17] their potential as precursors of hydrazyl radicals has remained unexploited until now. We herein report studies of cyclic diacylhydrazyl radicals derived from urazoles and pyrazolidinediones.

Results

Preparation of Urazoles and Pyrazolidine-3,5-diones. 1,4-Disubstituted urazoles (1,2,4-triazolidine-3,5-diones) were prepared *via* a modified Zinner and Deucker[16] procedure (Scheme I). Treatment of carbazates **2**, formed by the reaction of hydrazines **1** and ethyl chloroformate, with substituted isocyanates furnishes semicarbazides **3**. Cyclization of **3** with potassium hydroxide provides the desired urazoles **4** in good yields. Pyrazolidine-3,5-diones **6** were prepared by sodium ethoxide induced reaction of hydrazines **1** with disubstituted malonates **5** according to the method of Conrad and Zart[17]

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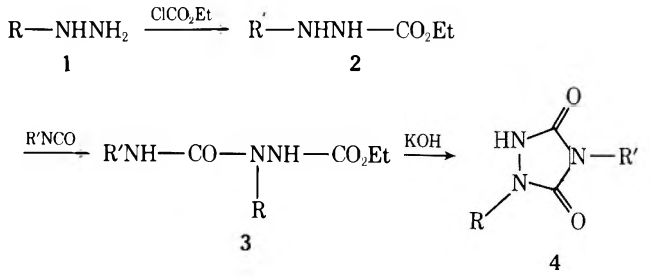
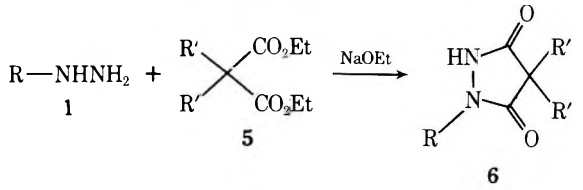
Scheme I



a: R = Ph
b: R = $PhCMe_2$
c: R = *t*-Bu
d: R = R′ = Ph
e: R = Ph, R′ = Me
f: R = Ph, R′ = *t*-Bu
g: R = $PhCMe_2$, R′ = Ph
h: R = $PhCMe_2$, R′ = Me
i: R = $PhCMe_2$, R′ = *t*-Bu
j: R = *t*-Bu, R′ = Ph
k: R = *t*-Bu, R′ = Me
l: R = C_6H_{11}, R′ = Me

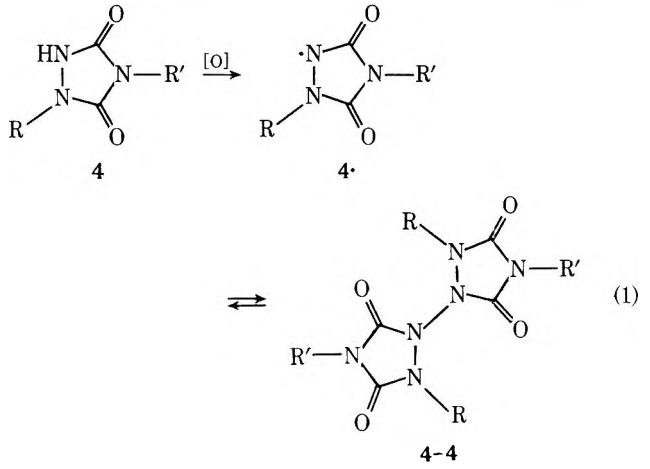
Scheme II



a: R = Ph
b: R = $PhCMe_2$
c: R′ = Et
d: R′ = Me
e: R = Ph, R′ = Et
f: R = Ph, R′ = Me
g: R = $PhCMe_3$, R′ = Et
h: R = $PhCMe_2$, R′ = Me

(Scheme II).

Urazole Radicals. When treated with a variety of oxidizing agents (*tert*-butyl hypochlorite, *N*-bromosuccinimide, lead dioxide) solutions of urazoles **4** provide highly colored paramagnetic solutions of urazole radicals **4·** (eq 1). Though af-



(1)

fording radicals in only mediocre yields, reactions utilizing lead dioxide are particularly clean. Hence, this reagent is preferred for preparative purposes and is especially useful for preparing solutions of transient radicals. 1-α-Cumyl- and 1-*tert*-butylurazoles **4g–k** provide highly colored solutions of radicals **4g–k·**, from which crystalline tetrazane dimers **4-4** can be isolated. Radicals **4g–k·** can be stored indefinitely in the form of these tetrazane dimers. In solution, a mobile equilibrium exists between radical and dimer. In benzene, the lifetimes of urazole radicals **4g·**, **4h·**, **4j·**, and **4k·** appear to be comparable to that of DPPH. However, α-cumyl-*tert*-butylurazole radical **4i·** is less persistent, decomposing within 3 days.

In contrast to the persistence of 1-α-cumyl- and 1-*tert*-butylurazole radicals, 1-phenyl- and 1-cyclohexylurazole radicals **4d–f·** and **4l·**, respectively, are transient. Benzene

Table I. Visible Absorption Maxima for Urazole and Pyrazolidinedione Radicals in Benzene Solution

Radical	Registry no.	λ_{max}, nm	ϵ^a	Concn, M[b]
4d·	64739-49-7	500, 570[c]		
4e·	64739-50-0	331,[c] 337		
		437, 561		
4f·	64739-51-1	330,[c] 338		
		435, 550		
4g·	64739-52-2	316	2400	3.10×10^{-4}
		480	260	2.58×10^{-2}
4h·	52809-14-0	300	2900	3.04×10^{-4}
		380	1200	6.07×10^{-4}
4i·	64754-32-1	297	2500	3.02×10^{-4}
		370[c]	980	3.02×10^{-4}
		410[c]	600	3.02×10^{-4}
4j·	64739-53-3	313	2800	3.10×10^{-4}
		440	270	3.10×10^{-3}
4k·	64739-54-4	303	3100	3.14×10^{-4}
		413	590	1.57×10^{-3}
4l·	64739-55-5	415,[c] 507		
		521, 537		
		547,[c] 506		
6e·	64739-56-6	355	43	1.89×10^{-2}
		487	15	5.05×10^{-2}
6f·	64739-57-7	370[c]	76	5.06×10^{-3}
		480	16	5.06×10^{-2}
6g·	64739-58-8	646		

[a] Extinction coefficients are concentration dependent. [b] Concentration of radical assuming no dimerization. [c] Shoulder.

solutions of urazole radicals **4d·** and **4l·** decompose within 12 hr, **4e·** within 24 hr, and **4f·** within *ca.* 3 days. Upon decomposition, colored radicals **4d–f·** and **4l·** provide colorless (yellow for **4l·**), uncharacterized precipitates that are difficulty soluble even in polar solvents such as acetone or DMSO. Attempts to chromatographically purify or isolate radicals **4d–f·** and **4l·** have resulted in their decomposition.

Solutions of α-cumyl radicals **4h·** and **4i·**, *tert*-butyl radical **4k·**, and cyclohexyl radical **4l·** are orange colored because of broad absorption bands centered near 300 nm and extending out to 600–650 nm. Superimposed on these bands are smaller absorption maxima, the data for which are summarized in Table I. Replacement of the alkyl group on N-4 with an aromatic group as in 4-phenyl radicals **4g·** and **4j·** causes the radical to take on a reddish color that results from an increased absorption in the 450–630 nm region. Replacement of the alkyl group on N-1 with phenyl affords radicals that are purple-brown or purple-gray in color. Purple-brown 1-phenylurazole radicals **4e·** and **4f·** have visible absorption maxima at *ca.* 337 nm which tail into other absorption peaks and on past 700 nm. Diphenylurazole radical **4d·** has an absorption maximum at 500 nm superimposed on the tail of a UV peak which also continues on past 700 nm.

Observing that the color of solutions of either 1-α-cumyl- or 1-*tert*-butylurazole radicals reversibly fades upon cooling and noting that these radicals fail to obey Beer's Law, it was inferred that the radicals are in equilibrium with the dimeric

Table II. Equilibrium Constants for the Association of Urazole Radicals in Solution at 25 °C

Urazole Radical	$K_{Assoc.}$ CCl_4	C_6H_6	CH_3CN
4g·	6.0 ± 0.8	1.8 ± 0.7	0.16 ± 0.01
4h·	12 ± 2	4.5 ± 0.4	0.58 ± 0.30
4i·	6.1 ± 2.1	1.4 ± 0.2	0.36 ± 0.10
4j·	1.5 ± 0.4	0.66 ± 0.06	0.33 ± 0.22
4k·	5.6 ± 1.2	3.2 ± 1.1	1.6 ± 0.6

Table III. Infrared Carbonyl Stretching Frequencies of Urazoles, Urazole Radicals, Pyrazolidinediones, and Pyrazolidinedione Radicals[a]

Dione ($CHCl_3$)	Registry no.	$\nu_{C=O}$ (cm^{-1})	Radical ($CHCl_3$)	$\nu_{C=O}$ (cm^{-1})	Tetrazane (KBr)	Registry no.	$\nu_{C=O}$ (cm^{-1})	Dione (KBr)	$\nu_{C=O}$ (cm^{-1})
4g	64739-59-9	1775 (m) 1712 (s)	**4g·**	1761 (m) 1743 (m), 1705 (s)	**4g–4g**	64739-35-1	1792 (m), 1744 (s), 1706 (m)	**4g**	1773 (m) 1697 (s)
4h	52809-13-9	1770 (m) 1710 (s)	**4h·**	1806 (w), 1777 (m) 1739 (m), 1707 (s)	**4h–4h**	52809-05-9	1805 (m), 1792 (m) 1732 (s), 1706 (m)	**4h**	1763 (m) 1693 (s)
4i	64739-60-2	1762 (m) 1702 (s)	**4i·**	1763 (m) 1728 (m), 1693 (s)	**4i–4i**	64739-36-2	1800 (w), 1785 (w) 1734 (s), 1696 (s)	**4i**	1764 (m) 1692 (s)
4j	64739-61-3	1770 (m) 1691 (s)	**4j·**	1764 (m) 1701 (s)	**4j–4j**	64739-37-3	1808 (m), 1792 (m) 1742 (s), 1709 (m)	**4j**	1769 (m) 1704 (s)
4k	64739-62-4	1760 (m) 1689 (s)	**4k·**	1766 (m), 1740 (m), 1706 (s)	**4k–4k**	64739-38-4	1807 (m), 1793 (m) 1732 (s), 1708[b] (m)	**4k**	1760 (m) 1702 (s)
6e	1732-61-2	1742 (m) 1694 (s)	**6e–6e**	1790 (m), 1763 (m), 1729 (s)	**6e–6e**	64739-39-5	1800 (m), 1773 (m), 1732 (s)	**6e**	1746 (s) 1678 (s)
6f	57186-07-9	1760 (m) 1742 (m), 1695 (s)	**6f–6f**	1790 (m) 1777 (m), 1732 (s)	**6f–6f**	64739-40-8	1798 (m), 1776 (m), 1731 (s)	**6f**	1748 (s) 1685 (s)
6g	64739-63-5	1740 (m) 1691 (s)	**6g·**	1756 (m) 1693 (s)					

[a] w = weak, m = medium, s = strong. [b] Shoulder.

Table IV. Hyperfine Splitting for Urazole and Pyrazolidinedione Radicals at 25 °C[a,b]

Radical	$a_{N\text{-}2(1)}$(G)	$a_{N\text{-}1(2)}$(G)	$a_{N\text{-}2(1)}/a_{N\text{-}1(2)}$	$a_{N\text{-}4}$(G)	a_H(G)
4d·	7.7[c]	5.7[c]	0.74	1.45	1.35 (3H), 0.60 (2H)
4e·	7.7[c]	5.7[c]	0.74	1.45	1.35 (3H), 0.60 (5H)
4f·	7.7[c]	5.7[c]	0.74	1.40	1.40 (3H), 0.60 (2H)
4g·[e]	7.75	6.30	0.81	1.50	
4h·	7.70	6.25	0.81	1.47	0.56 (3H)
4i·[e]	7.70	6.25	0.81	1.45	
4j·	7.50	6.05	0.81	1.45	
4k·	7.55	6.15	0.81	1.50	0.65 (3H), 0.13[d] (9H)
6e·	7.75	5.60	0.72		1.40 (3H), 0.60 (2H)
6f·	7.85	5.60	0.71		1.40 (3H), 0.60 (2H) 0.15[d]
6g·	8.05	6.35	0.79		
6h·	8.10	6.40	0.78		

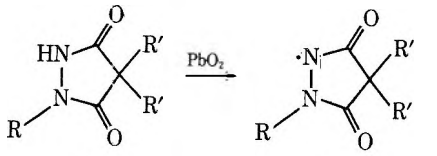
[a] 0.05 G, unless otherwise stated. [b] In benzene solution, unless otherwise stated. [c] ±0.10 G. [d] ±0.02 G. [e] In carbon disulfide solution.

tetrazanes. Equilibrium constants for the association of these radicals (Table II) were determined by vapor pressure osmometry for carbon tetrachloride, benzene, and acetonitrile solution. Though these data are not of high precision, it is evident that the tendency of the radicals to associate decreases as solvent polarity increases.

Urazoles **4g–k**, whether as solids or in solution, have two infrared carbonyl absorptions, 1775–1760 (m) and 1715–1690 (s) cm^{-1}. In the solid state, the corresponding tetrazane dimers exhibit four absorption peaks, 1810–1800 (m), 1795–1785 (m), 1745–1730 (s), and 1710–1695 (m–s) cm^{-1}. In solution, the urazole radicals have three carbonyl absorptions, 1780–1760 (m), 1745–1725 (m–s), and 1710–1695 (s) cm^{-1}. Detailed infrared carbonyl data for diacylhydrazines, radicals, and dimers appear in Table III.

In urazole radicals, the hyperfine splitting constants (hfsc) for each of the three types of nitrogen are relatively insensitive to structural variation (Table IV). The EPR spectra of 4-phenylurazole radicals **4d·** and **4g·** are virtually identical to those of 4-*tert*-butyl analogs **4f·** and **4i·**, indicating that unpaired spin density is not appreciably delocalized into the N-4 phenyl since splitting by the aromatic hydrogens is too small to be observed.[18] Urazole radicals **4g·**, **48·**, and **4j·** have almost identical EPR spectra and clearly show the unequal splitting of the three urazole nitrogens. *tert*-Butylmethylurazole radical **4k·** gives rise to an EPR spectrum similar to that of α-cumylmethyl radical **4h·**[1] but has an additional hfsc due to the coupling of the *tert*-butyl hydrogens. The EPR spectra of 1-phenylurazole radicals **4d·** and **4f·** are almost identical and show that the splitting caused by the N-1 phenyl arises from the unequal coupling of the two equivalent *meta* hydrogens and the three equivalent *ortho* and *para* hydrogens. The EPR spectrum of phenylmethyl radical **4e·** is similar to those for other 1-phenylurazole radicals, but has an additional splitting arising from the N-4 methyl group. Cyclohexylurazole radical **4l·**, the only radical studied in which a carbon α to the hydrazyl nitrogens bears a hydrogen, gives rise to a complex EPR spectrum that has frustrated interpretation.

Pyrazolidine-3,5-dione Radicals. Solutions of colorless pyrazolidinediones **6** afford highly colored solutions of pyrazolidinedione radicals **6·** (eq 2) when treated with lead dioxide. Solutions of α-cumylpyrazolidinedione radicals **6g·** and **6h·** are emerald green whereas the related phenyl radicals **6e·** and **6f·** are brownish-red. Solutions containing dimethyl radical **6h·** become colorless within 2 hr. Diethyl radical **6g·**, however, can be chromatographically purified, but decomposed to uncharacterized yellow gum when attempts were made to isolate it or its dimer. A green solution of unchromatographed **6g·** decomposes over a period of several days at 25 °C. Evaporation of solutions of chromatographically purified 1-phen-



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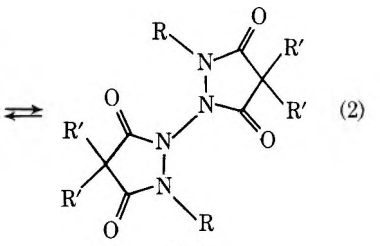


6-6 (2)

ylpyrazolidinedione radicals **6e·** and **6f·** provide the dimers **6–6** as tan solids that appear to be indefinitely stable. However, in benzene solution, these radicals decompose within 2 weeks at 25 °C to give orange-red diamagnetic solutions.

The visible spectrum of α-cumylpyrazolidinedione radical **6g·** (Table I) has a tail from the UV region extending into the visible, a minimum at 529 nm, and a maximum at 646 nm that continues on past 700 nm. Diethylphenyl radical **6e·** also has a visible tail of a UV absorption and several discrete visible absorption maxima. Although basically similar to that of **6e·**, the visible spectrum of dimethyl radical **6f·** has a shoulder rather than a discrete maximum in the 370 nm region.

The color of solutions of 1-phenylpyrazolidinedione radicals **6e·** and **6f·** also fades reversibly upon cooling, but to a smaller degree than for 1-α-cumyl- or 1-*tert*-butylurazole radicals. Vapor pressure osmometric studies indicate that at concentrations greater than 5×10^{-2} *M* in either carbon tetrachloride, benzene, or acetonitrile, radicals **6e·** and **6f·** are greater than 90% dimerized. Similarly, the green color of 1-α-cumylpyrazolidinedione radicals **6g·** and **6h·** fades reversibly upon cooling. By analogy with urazole radicals, the presence of an equilibrium between **6g·** and **6h·** and their tetrazane dimers is inferred. The inability to isolate **6g·** or **6h·** prevented the determination of their association constants by vapor pressure osmometry.

As solids, pyrazolidinediones have two strong infrared carbonyl absorptions at 1750–1745 and 1685–1675 cm^{-1} (Table III); in chloroform solution there are typically two absorptions, 1745–1740 (m) and 1695–1690 (s) cm^{-1}. In solution, the tetrazane dimers of 1-phenylpyrazolidinedione radicals exhibit three carbonyl absorptions 1790 (m), 1771–1763 (m), and 1729 (s) cm^{-1}. α-Cumyl radical **6g·**, however, exhibits only two carbonyl absorptions. As solids, the carbonyl absorption of tetrazane dimers **6e–6e** and **6f–6f** occur at 1800–1795 (m), 1780–1770 (m), and 1735–1730 (s) cm^{-1}.

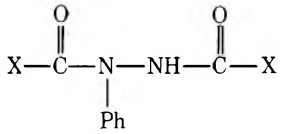
The EPR spectra of 1-α-cumylpyrazolidinedione radicals **6g·** and **6h·** are virtually identical and have nine lines owing to unequal splitting by the hydrazyl nitrogens (Table IV). Phenyldiethyl radical **6e·** gives rise to an EPR spectrum that shows coupling of the hydrazyl nitrogens and the aromatic hydrogens. Phenyldimethyl radical **6f·** has the same basic EPR spectrum as **6e·** but contains an additional hyperfine splitting of *ca.* 0.15 G.

Discussion

1-α-Cumyl- and 1-*tert*-butylurazole radicals are unique as they are the first hydrazyl radicals to be isolated in which the hydrazyl nitrogens lack a directly bonded aromatic group. Both urazole and pyrazolidinedione radicals are true hydrazyl radicals as evidenced by the magnitude of the hyperfine splitting constants.[19]

Three conditions are generally considered prerequisite for persistence of hydrazyl radicals: (a) steric congestion of the site formally bearing the unpaired electron, (b) substitution of hydrogen by other groups or atoms at sites where disproportionation may occur, and (c) delocalization of unpaired electron spin density.[4,20,21] All of these conditions are fulfilled in the 1-α-cumyl- and 1-*tert*-butylurazole radicals. The steric bulk necessary to retard reactions at the divalent nitrogen is provided by the α-cumyl and *tert*-butyl groups. The nearly identical behavior and properties (similarity of visible spectra, EPR spectra, IR spectra, association constants, and persistence) of the radicals bearing these substituents indicate that the aromatic ring of the cumyl group is not involved in delocalization of unpaired spin density. Such delocalization, however, does occur in hydrazyl radicals bearing directly bonded aromatic groups. Like DPPH, 1-α-cumyl- or 1-*tert*-butylurazole radicals do not react with molecular oxygen but are capable of reacting with compounds having abstractable hydrogen atoms. Neither 1-α-cumyl- nor 1-*tert*-butylurazole radicals have hydrogens on carbons α to the hydrazyl nitrogens and hence do not undergo disproportonation. 1-Cyclohexylurazole radical **4l·**, however, has an α hydrogen and is observed to rapidly decompose.

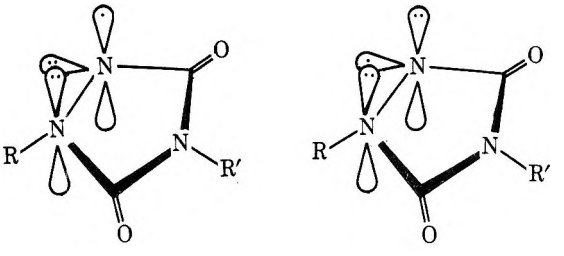
The EPR spectra of urazole radicals show that the unpaired electron is delocalized over the entire heterocycle. When treated with lead dioxide, solutions of acyclic diacylhydrazines **7** and **8** give rise to weak EPR spectra that exhibit strong coupling of the unpaired electron to only one nitrogen (Table IV), a characteristic of hydrazoxyl radicals.[9,22] The contrasting behavior of cyclic and acyclic diacylhydrazines presumably results from conformational preferences. At 44 °C, the 60 MHz NMR spectra of **7** and **8** each exhibit two equally intense peaks



7: X = OEt
8: X = NHMe

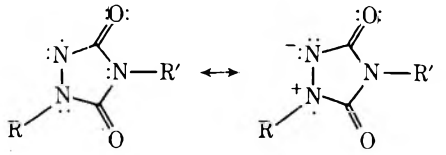
for the α-cumyl methyls, indicative of restricted N-N rotation[23–26] and an orthogonal relationship between the two acyl groups. The rotational barrier for **7** is calculated[26,27] from the coalesence temperature of these diastereotopic signals (T_c = 85–90 °C, $\Delta\nu$ = 9 Hz) to be *ca.* 19 kcal/mole. This orthogonal geometry prevents overlapping of the p orbitals of the adjacent nitrogens. In the cyclic urazoles and pyrazolidinediones, the two acyl groups are forced into a coplanar relationship that, consequently, allows efficient overlap of the hydrazyl nitrogen p orbitals. Thus, delocalization of the unpaired electron over the two hydrazyl nitrogens is facilitated in the urazole and pyrazolidinedione radicals (because of the parallel orbital alignment) relative to the acyclic diacylhydrazines.

EPR spectra indicate that urazole radicals are ground state π radicals **9** (σ lone pair) rather than Σ radicals **10** (π lone pair).



9 **10**

Although resonance structure **11** is used to represent urazole radicals, the a_{N-1}/a_{N-2} ratios for urazole radicals (0.74–0.81) and pyrazolidinedione radicals (0.71–0.79) are similar to that of DPPH (0.83)[28] and indicates significant unpaired spin



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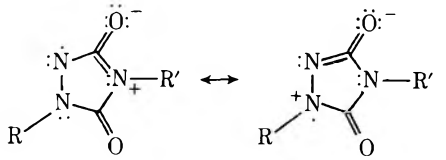
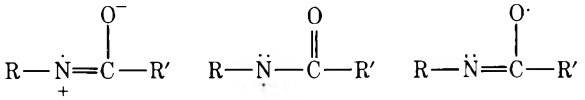


13 14

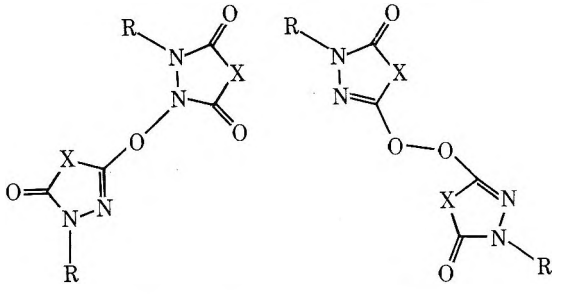
density on the trivalent nitrogen as represented by canonical form **12**. Charge separation thus induced can be further delocalized as in **14**.[39] The nearly equal $a_{CH_3}/a_{N\text{-}4}$ values of 4-methylurazole radicals **4e**• (0.41), **4h**• (0.38), and the phthalimide radical anion (0.35)[30] suggest a similar geometry about the imide nitrogen in these systems. The importance of this imide nitrogen toward the persistence of 1-α-cumyl and 1-*tert*-butylurazole radicals is strongly suggested by the lesser persistence of the α-cumylpyrazolidinedione radicals. Simple amido radicals **16** have been observed by EPR spectroscopy but are transient.[31] The preferred delocalization of a lone pair of electrons (**15**) over the delocalization of the unpaired electron[32] (**17**) has the effect of localizing unpaired electron spin



15 16 17

density on the amide nitrogen and renders the radical more reactive. Delocalization of the imide nitrogen lone pair onto the carbonyl oxygen (shown in **13**) reduces the ability of this carbonyl group to delocalize the lone pair of electrons on the divalent nitrogen. Similar reasoning leads to the expectation that α-cumylpyrazolidinedione radicals should be less persistent than the analogous urazole radicals. This proves to be the case.

The well known[4] reversible dimerization of hydrazyl radicals to tetrazanes was first observed by Goldschmidt[33] and later studied by Wilmarth and Schwartz[34] for 1,1-diaryl-2-acylhydrazyl radicals. In the case of urazole and pyrazolidinedione radicals, three different dimeric linkages are conceivable: N–N (*e.g.*, **4–4** or **6–6**), O–N (**18**), or 0–0 (**19**). Strucutres such as **18** and **19** that include carbonyl oxygen in the linkage are ruled out on the basis of infrared spectral data. Dimers **18** and **19** would be expected to have strong absorp-



18 19

tions at *ca.* 1605 and *ca.* 1513 cm^{-1}, characteristic of the O–C=N functionality in these structures.[35] No such absorptions are noted in the infrared spectra of the dimers.[36]

The decreasing tendency for urazole radicals to associate in solution as solvent polarity increases demonstrates greater polarity for the radicals than for the dimers as might be expected on the basis of dipolar canonical structures such as **12–14**.

Experimental Section

General. Melting points were taken in open Pyrex capillary tubes using a Büchi "Schmelzpunktbestimmungs Apparat" and are uncorrected. Infrared spectra were taken on a Beckman IR-12 grating spectrophotometer. Visible spectra were recorded with a Cary 14 spectrophotometer. NMR spectra were obtained with Varian A-60A or HA-100 spectrometers. Chemical shifts, δ, are expressed in ppm relative to internal tetramethylsilane. EPR spectra were recorded with a Varian E-9 X-Band spectrometer. Mass spectra were obtained with Varian MAT CH-5 or 731 mass spectrometers. Mass spectral data processing equipment employed was provided by NIH Grants CA 11388 and GM 16864 from the National Cancer Institute and the National Institute of General Medical Sciences, respectively. Elemental analyses were performed by the Microanalytical Laboratory of the School of Chemical Sciences, University of Illinois. Vapor pressure osmometry data were obtained with a Mechrolab 301A vapor pressure osometer operating at 25.0 ± 0.2 °C.

All hydrazines, isocyanates, and chloroformates were distilled prior to use. Other commercially available reagents and reagent grade solvents were used without further purification, unless otherwise stated. Column chromatography was carried out on Brinkmann 0.05–0.2 mm silica gel. Analytical thin layer chromatography (tlc) was performed on Merck 0.25 mm precoated fluorescent silica gel plates.

EPR Samples. Solutions of transient radicals were prepared by stirring a solution of the urazole or pyrazolidinedione with lead dioxide and anhydrous sodium sulfate. After 30 sec–5 min, these mixtures were filtered, the filtrates placed in 4 mm o.d. quartz tubes, and the samples stored at −196 °C. Solutions of persistent radicals were prepared as described above or by dissolving the appropriate amount of the isolated tetrazane dimer in the desired solvent. All samples were vacuum degassed by at least 3 freeze-pump-thaw cycles and sealed while frozen under high vacuum. Samples of transient radicals were stored at −196 °C when not being observed.

Syntheses. The preparation of a typical urazole is outlined below. Experimental procedures for the preparation of the remaining urazoles are provided in the supplementary material.

Ethyl 3-α-Cumylcarbazate (2b). To a mechanically stirred solution of α-cumylhydrazine[37] (**1b**, 30.05 g, 0.20 mol) and triethylamine (20.24 g, 0.20 mol) in anhydrous ether (400 ml), which was cooled to below 0 °C in an ice-acetone bath, was added a solution of ethyl chloroformate (21.60 g, 0.20 mol) in anhydrous ether (200 ml) at a rate that maintained the temp below 5 °C. After the addition was completed, the resulting mixture was allowed to warm to room temperature, and filtered. Removal of the solvent from the filtrate at reduced pressure and vacuum distillation afforded 40.16 g (0.181 mol, 90%) of carbazate **2b** as a viscous, yellow oil: bp 120 °C (0.05 Torr); IR ($CHCl_3$) 3435, 3375, and 3325 (NH), 3015, 2990, and 2945 (CH), 1724 (C=O), 1532, 1497, 1471, 1446, 1383 (CMe_w), 1368 (CMe_2), 1256 (C–CO), 1177, 1154, 1048, and 707 cm^{-1}; NMR ($CDCl_3$) 1.18 (t, 3, J = 7 Hz, OCH_2CH_3), 1.43 (s, 6, $C(CH_3)_2$), 4.05 (s, 1, CNHN), and 4.08 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 6.05 (s, 1, CONHN), and 7.1–7.6 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 222 (weak, M^+), 120 (11), 119 (100), 104 (14), 91 (53), 79 (11), 77 (10), 41 (19), and 29 (10).

Anal. Calcd for $(C_{12}H_{18}N_2O_2)$ C, H, N.

1-Carbethoxy-2-α-cumyl-4-methylsemicarbazide (3h). A solution of α-cumyl carbazate **2b** (91.36 g, 0.41 mol) and methyl isocyanate (33.5 g, 0.587 mol) in benzene (600 ml) was heated at reflux for 4 hr. Removal of the solvent under reduced pressure followed by vacuum drying of the resultant viscous, slightly yellow liquid afforded a foam-like solid. Washing of the solid with benzene (3X) and vacuum drying furnished 94.09 g (0.337 mol, 82%) of semicarbazide **3h** as a white solid: mp 144–145.5 °C; IR ($CHCl_3$) 3485, 3445, 3380, and 3265 (NH), 3015, 3995, and 2950 (CH), 1750 (carbamate C=O), 1679 (urea C=O), 1522, 1496, 1387 (CMe_2), 1240 (C–O), 1060, and 707 cm^{-1}; NMR ($CDCl_3$) 1.25 (t, 3, J = 7 Hz, OCH_2CH_3), 1.60 (s, 6, $C(CH_3)_2$), 2.52 (d, 3, J = 5 Hz, $NHCH_3$), 4.18 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.92 (q, 1, $CONHCH_3$), 7.0–7.7 (m, 5, C_6H_5), and 8.47 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 279 (weak, M^+), 161 (14), 120 (11), 119 (100), 104 (27), 41 (14), and 28 (10).

Anal. Calcd for $(C_{14}H_{21}N_3O_3)$ C, H, N.

1-α-Cumyl-4-methylurazole (4h). A solution of semicarbazide **3h** (96.90 g, 0.347 mol) in aq 25% potassium hydroxide (200 ml) was heated on a steam bath for 2 hr. After diluting with water (200 ml) and

cooling to 0 °C, the solution was acidified with concentrated hydrochloric acid causing a solid to form. Filtration, washing the isolated solid with water until the washings were neutral, and recrystallization from ethanol afforded 72.27 g (0.310 mol, 89%) of urazole **4h**: mp 129.5–130.5 °C [EtOH; lit.[38] mp 126.5–127 °C (sublimation)]; IR ($CHCl_3$) 3365 (NH), 3015 and 2985 (CH), 1770 and 1710 (C=O), 1477, 1390 (CMe_2), and 1371 (CMe_2) cm^{-1}; IR (KBr) 3265 (NH), 2995 and 2940 (CH), 1763 and 1693 (C=O), 1482, 1452, 1383 (CMe_2), 1366 (CMe_2), 1232, 770, and 702 cm^{-1}; NMR ($CDCl_3$) 1.80 (s, 6, $C(CH_3)_2$), 2.95 (s, 3, NCH_3), 7.3–7.5 (m, 5, C_6H_5), and 8.82 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 233 (weak, M^+), 120 (11), 119 (100), 91 (38), 79 (6), 77 (7), and 41 (8).

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.73; H, 6.44; N, 18.13.

1-α-Cumyl-4-phenylurazole (4g). Mp 159.5–161 °C; IR ($CHCl_3$) 3370 (NH), 3025 and 2990 (CH), 1775 and 1712 (C=O), 1507, 1430, 1390 (CMe_2), and 1370 (CMe_2) cm^{-1}; IR (KBr) 3170 (NH), 3070, 2995, and 2980 (CH), 1773 and 1697 (C=O), 1495, 1427, 1383 (CMe_2), 1364 (CMe_2), 866, 775, and 700 cm^{-1}; NMR ($CDCl_3$) 1.82 (s, 6, $C(CH_3)_2$), 7.1–7.5 (m, 10, C_6H_5), and 8.38 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 295 (weak, M^+), 120 (11), 119 (100), 91 (32), 77 (7), and 41 (12).

Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.26; H, 5.86; N, 14.22.

1-α-Cumyl-4-*tert*-butylurazole (4i). Mp 149.5–150.5 °C; IR ($CHCl_3$) 3365 (NH), 3020, 2990, and 2940 (CH), 1762 and 1702 (C=O), 1400, and 1373 cm^{-1}; IR (KBr) 3430, 3180 (NH), 3070, 3040, 3010, 2985, and 2950 (CH), 1764 and 1692 (C=O), 1467, 1412, 1385, 1378, 1370, 1270, 1177, 778, 768, and 702 cm^{-1}; NMR ($CDCl_3$) 1.53 (s, 9, $C(CH_3)_3$), 1.75 (s, 6, $C(CH_3)_2$), 7.1–7.5 (m, 5, C_6H_5), and 8.42 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 275 (weak, M^+), 120 (10), 119 (100), 91 (37), 79 (5), 77 (6), 57 (9), 41 (20), 29 (5), and 29 (5).

Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.45; H, 7.69; N, 15.26. Found: C, 65.30; H, 7.61; N, 15.57.

1-*tert*-Butyl-4-phenylurazole (4j). Mp 150–153.5 °C (EtOAc); IR ($CHCl_3$) 3370 and 3180 (NH), 3030 and 2980 (CH), 1770 and 1691 (C=O), 1498, 1425, 1393 (CMe_3), and 1364 (CMe_3) cm^{-1}; IR (KBr) 3450 and 3180 (NH), 3075 and 2980 (CH), 1769 and 1704 (C=O), 1506, 1433, 1396 (CMe_3), 1369 (CMe_3), 1213, 774, and 716 cm^{-1}; NMR ($CDCl_3$) 1.46 (s, 9, $C(CH_3)_3$), 7.3–7.6 (m, 5, C_6H_5), and 9.37 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 233 (8, M^+), 178 (10), 177 (95), 120 (12), 119 (13), 93 (6), 91 (7), 77 (6), 64 (5), 58 (5), 57 (100), 56 (7), 41 (32), 39 (6), and 29 (27).

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 62.05; H, 6.58; N, 18.25.

1-*tert*-Butyl-4-methylurazole (4k). Mp 129–130.5 °C (EtOAc); IR ($CHCl_3$) 3380 and 3180 (NH), 3030 and 2985 (CH), 1760 and 1689 (C=O), 1480, 1399 (CMe_3)$_3$ and 1368 (CMe_3) cm^{-1}; IR (KBr) 3450 and 3175 (NH), 2980 (CH), 1760 and 1702 (C=O), 1483, 1396 (CMe_3), 1370 (CMe_3), and 1221 cm^{-1}; NMR ($CDCl_3$) 1.46 (s, 9, $C(CH_3)_3$), 3.02 (s, 3, NCH_3), and 9.24 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 171 (7, M^+), 116 (7), 115 (87), 58 (15), 57 (100), 56 (10), 42 (5), 41 (35), 29 (24), and 28 (5).

Anal. Calcd for $C_7H_{13}N_3O_2$: C, 49.11; H, 7.65; N, 24.54. Found: C, 49.51; H, 7.60; N, 24.80.

1-Phenyl-4,4-diethylpyrazolidine-3,5-dione (6e). Treatment of a solution of diethyl diethylmalonate (**5c**, 21.63 g, 0.100 mol) and phenylhydrazine (**1a**, 11.00 g, 0.102 mol) in absolute ethanol (50 ml) with sodium ethoxide (0.110 mol) according to the method of Conrad and Zart[15a] afforded, after work-up and recrystallization (EtOAc), 7.64 g (33 mmol, 33%) of a colorless solid: mp 110.5–112 °C [lit.[17a] mp 114–115 °C (EtOH)]; IR ($CHCl_3$) 3360 and 3155 (NH), 3015, 2975, 2940, and 2885 (CH), 1742 and 1694 (C=O), 1597, 1498, 1460, and 1308 cm^{-1}; IR (KBr) 3440 and 3135 (NH), 2965, 2930, and 2875 (CH), 1746, and 1678 (C=O), 1502, 1447, 1308, 752, and 723 cm^{-1}; NMR ($CDCl_3$) 0.90 (t, 6, J = 7 Hz, CH_2CH_3), 1.83 (q, 4, J = 7 Hz, CCH_2CH_3), 7.1–7.7 (m, 5, C_6H_5), and 10.13 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 233 (14, m + 1), 232 (90, M^+), 204 (23), 189 (18), 108 (10), 98 (67), 97 (100), 91 (10), 83 (64), 77 (36), 69 (33), 55 (36), 51 (13), 43 (10), 41 (30), 39 (12), 29 (28), 28 (15), and 27 (11).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.22; H, 7.09; N, 12.12.

1-Phenyl-4,4-dimethylpyrazolidine-3,5-dione (6f). Treatment of a solution of phenylhydrazine (**1a**, 11.00 g, 0.102 mol) and diethyl dimethylmalonate (**5d**, 18.82 g, 0.100 mol) in absolute ethanol (50 ml) with sodium ethoxide (0.117 mol) according to the method of Conrad and Zart[17a] afforded, after work-up and recrystallization (EtOAc), 14.14 g (69 mmol, 69%) of a colorless solid: mp 180–182 °C; IR ($CHCl_3$) 3355 and 3150 (NH), 3020, 2980, 2935, and 2875 (CH), 1760, 1742, and 1695 (C=O), 1595, 1498, 1391, 1247, 1230, and 1199 cm^{-1}; IR (KBr) 3440 and 3135 (NH), 2985, 2975, 2940, and 2880 (CH), 1748 and 1685 (C=O), 1597, 1501, 1440, 1389, 1346, 1336, 1300, 760, and 745 cm^{-1}; NMR ($CDCl_3$) 1.40 (s, 6, $C(CH_3)_2$), 7.1–7.7 (m, 5, C_6H_5), and 10.27 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 205 (14, m + 1), 204 (100, M^+), 148 (19), 107 (23), 105 (14), 91 (10), 77 (41), 70 (74), 69 (22), 51 (16), 43 (19), 42 (31), 41 (26), and 39 (12)

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.81; H, 5.89; N, 13.99.

1-α-Cumyl-4,4-diethylpyrazolidine-3,5-dione (6g). Treatment of a solution of α-cumylhydrazine[37] (**1b**, 6.00 g, 40 mmol) and diethyl diethylamalonate (**5c**, 9.00 g, 41.7 mmol) in absolute ethanol (30 ml) with sodium ethoxide (48 mmol) according to the method of Conrad and Zart[17a] afforded, after work-up and recrystallization (EtOAc), 3.09 g (11.3 mmol, 28%) of a colorless solid: mp 117.5–118.5 °C; IR ($CHCl_3$) 3370 (NH), 3020, 2975, 2940, and 2885 (CH), 1740 and 1691 (C=O), 1459, 1449, 1443, 1390 (CMe_2), 1369 (CMe_2), 1305, 1188, 1174, and 704 cm^{-1}; NMR ($CDCl_3$) 0.76 (t, 6, J = 7.5 Hz, CH_2CH_3), 1.68 (q, 4, J = 7.5 Hz, CCH_2CH_3), 1.87 (s, 6, $C(CH_3)_2$), 7.1–7.4 (m, 5, C_6H_5), and 8.62 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 274 (1, M^+), 120 (10), 119 (100), 118 (4), 91 (25), 79 (4), and 41 (10).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.23; H, 8.04; N, 10.15.

1-α-Cumyl-4,4-dimethylpyrazolidine-3,5-dione (6h). Treatment of a solution of diethyl dimethylmalonate (**5d**, 7.60 g, 40.3 mmol) and α-cumylhydrazine[37] (**1b**, 6.00 g, 40.0 mmol) in absolute ethanol (30 ml) with sodium ethoxide (48 mmol) according to the method of Conrad and Zart[17a] afforded, after work-up and recrystallization (EtOAc), 3.29 g (13.4 mmol, 33%) of a colorless solid: mp 145–146.5 °C; IR (KBr) 3435 and 3235 (NH), 2995, 2980, 2935, and 2875 (CH), 1740 and 1682 (C=O), 1467, 1447, 1419, 1392 (CMe_2), 1368 (CMe_2), 1360 (CMe_2), 1344, 775, 766, 706, and 700 cm^{-1}; NMR ($CDCl_3$) 1.20 (s, 6, $(CO)_2C(CH_3)_2$), 1.84 (s, 6, $PhC(CH_3)_2$), 7.1–7.4 (m, 5, C_6H_5), and 8.92 (s, 1, CONH); mass spectrum (70 eV) *m/e* (rel intensity) 246 (weak, M^+), 120 (10), 119 (100), 118 (4), 91 (31), 79 (5), 77 (4), and 41 (12).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.42; H, 7.23; N, 11.43.

1-α-Cumyl-4-phenylurazole Radical (4g·). A solution of urazole **4g** (1.48 g, 5.01 mmol) in benzene (75 ml) was stirred with lead dioxide (2.39 g) and anhydrous sodium sulfate (2.14 g) for 2.5 hr at room temperature. Filtration and concentration of the filtrate afforded a brown oil, which was chromatographed on silica gel with chloroform. Collection of the mobile colored band, and evaporation at reduced pressure afforded, after vacuum drying, 0.69 g (2.34 mmol, 47%) of an off-white solid: mp 113.5–115.5 °C; IR ($CHCl_3$) 3075, 3045, 3000, and 2955 (CH), 1761, 1743, and 1705 (C=O), 1505, 1399, 1372 (CMe_2), and 1127 cm^{-1}; IR (KBr) 3070, 2990, and 2940 (CH), 1792, 1744, and 1706 (C=O), 1500, 1402, 1372 (CMe_2), 1240, 1187, 1147, 769, 731, 714, 701, and 689 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 294 (weak, M^+), 120 (10), 119 (100), 118 (8), 91 (30), and 41 (11).

Anal. Calcd for $C_{17}H_{16}N_3O_2$: C, 69.37; H, 5.48; N, 14.28; mol wt, 294.1242. Found: C, 68.86; H, 5.60; N, 14.00; mol wt, 294.1239 (mass spectrum).

1-α-Cumyl-4-methylurazole Radical (4h·). A solution of urazole **4h** (1.17 g, 5.0 mmol) in benzene (25 ml) was treated with lead dioxide (2.39 g, 10 mmol) and anhydrous sodium sulfate (2.14 g) as described for radical **4g·**. After chromatographic purification (SiO_2/$CHCl_3$), 0.70 g (3.05 mmol, 61%) of a beige solid was obtained: mp 108–109 °C; IR ($CHCl_3$) 3040, 3000, and 2960 (CH), 1806, 1777, 1739, and 1707 (C=O), 1452, 1396, 1373 (CMe_2), and 706 cm^{-1}; IR (KBr) 3015, 3995, 2975, and 2950 (CH), 1805, 1792, 1732, and 1706 (C=O), 1465, 1455, 1395, 1379 (CMe_2), 1140, 781, 775, 739, and 709 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 232 (5, M^+), 120 (11), 119 (100), 118 (9), 117 (7), 103 (9), 91 (41), 79 (7), 77 (8), 51 (5), and 41 (13).

Anal. Calcd for $C_{12}H_{14}N_3O_2$: C, 62.06; H, 6.08; N, 18.09; mol wt, 232.1086. Found: C, 62.04; H, 5.98; N, 18.01; mol wt, 232.1080 (mass spec).

1-α-Cumyl-4-*tert*-butylurazole Radical (4i·). Treatment of a solution of urazole **4i** (1.38 g, 5.01 mmol) in benzene (75 ml) with lead dioxide (2.39 g, 10 mmol) and anhydrous sodium sulfate (2.14 g) as described for radical **4g·** afforded, after chromatographic purification (SiO_2/$CHCl_3$), 1.07 g (3.90 mmol, 78%) of a beige solid: mp 83.5–85.5 °C; IR ($CHCl_3$) 2990 and 2945 (CH), 1763, 1728, and 1693 (C=O), 1393, 1360, and 703 cm^{-1}; IR (KBr) 2985 and 2940 (CH), 1800, 1785, 1734, and 1696 (C=O), 1371, 1267, 1151, 769, 750, and 705 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 274 (weak, M^+), 217 (6), 120 (10), 119 (100), 118 (7), 91 (22), 57 (9), and 41 (13).

Anal. Calcd for $C_{15}H_{20}N_3O_2$: C, 65.67; H, 7.35; N, 15.32; mol wt,

274.1555. Found: C, 65.65; H, 7.46; N, 15.03; mol wt, 274.1557 (mass spectrum).

1-*tert*-Butyl-4-phenylurazole Radical (4j·). Treatment of a solution of urazole **4j** (1.16 g, 4.97 mmol) in benzene (75 ml) with lead dioxide (2.39 g, 10.0 mmol) and anhydrous sodium sulfate as described for radical **4g·** afforded, after chromatographic purification (SiO_2/$CHCl_3$), 0.58 g (2.50 mmol, 50%) of a light wine red solid: mp 74.5–76.5 °C; IR ($CHCl_3$) 2995 and 2945 (CH), 1764 and 1701 (C=O), 1504, 1403, and 1373 (CMe_3) cm^{-1}; IR (KBr) 3015, 2995, and 2950 (CH), 1808, 1792, 1742, and 1709 (C=O), 1509, 1498, 1421, 1403, 1371 (CMe_3), 1207, 1191, 752, 746, 735, and 717 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 232 (4, M^+), 177 (7), 120 (5), 119 (28), 91 (4), 58 (5), 57 (100), 41 (9), and 29 (5).

Anal. Calcd for $C_{12}H_{14}N_3O_2$: C, 62.06; H, 6.08; N, 18.09; mol wt, 232.1086. Found: C, 62.03; H, 6.21; N, 17.85: mol wt, 232.1087 (mass spectrum).

1-*tert*-Butyl-4-methylurazole Radical (4k·). A solution of urazole **4k** (0.86 g, 5.02 mmol) in benzene (75 ml) was treated with lead dioxide (2.39 g, 10.0 mmol) and anhydrous sodium sulfate (2.14 g) as described for radical **4g·**. After chromatographic purification (SiO_2/$CHCl_3$), 0.23 g (1.35 mmol, 27%) of a beige solid was obtained: mp 94–96 °C; IR ($CHCl_3$) 3025, 2980, and 2930 (CH), 1766, 1740, and 1706 (C=O), 1455, 1399 (CMe_3), 1375 (CMe_3), 1271, 1139, and 1004 cm^{-1}; IR (KBr) 2965 and 2940 (CH), 1807, 1793, and 1732 (C=O), 1463, 1398 (CMe_3), 1371 (CMe_3), 1289, 1266, and 1118 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 170 (3, M^+), 116 (10), 115 (34), 98 (10), 58 (8), 57 (100), 56 (14), 42 (8), 41 (36), 39 (6), and 29 (18).

Anal. Calcd for $C_7H_{12}N_3O_2$: C, 49.40; H, 7.11; N, 24.69; mol wt, 170.0930. Found: C, 49.57; H, 7.28; N, 24,48; mol wt, 170.0933 (mass spectrum).

1-Phenyl-4,4-diethylpyrazolidine-3,5-dione Radical (6e·). Treatment of a solution of pyrazolidinedione **6e** (1.16 g, 4.99 mmol) with lead dioxide (2.39 g, 10 mmol) and anhydrous sodium sulfate (2.14 g) as described for radical **4g·** afforded, after chromatographic purification (SiO_2/$CHCl_3$), 0.44 g (2.17 mmol, 44%) of a brown solid: mp 106–108 °C; IR ($CHCl_3$) 3040, 2995, 2945, and 2880 (CH), 1799, 1777, and 1732 (C=O), 1499, 1390, 1336, and 1308 cm^{-1}; IR (KBr) 3070, 2990, 2945, and 2880 (CH), 1798, 1776, and 1731 (C=O), 1498, 1392, 1346, 1313, 1296, 779, 752, 724, and 695 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 205 (10, m + 2), 204 (76, m + 1), 203 (15, M^+), 154 (21), 148 (15), 112 (12), 107 (19), 105 (15), 91 (13), 85 (52), 83 (80), 78 (80), 77 (86), 74 (10), 71 (11), 70 (100), 69 (21), 64 (11), 57 (11), 52 (19), 51 (40), 50 (21), 48 (12), 47 (26), 44 (15), 43 (38), 42 (48), 41 (48), 39 (38), 36 (12), and 35 (10).

Anal. Calcd for $C_{11}H_{11}N_2O_2$: C, 65.01; H, 5.46; N, 13.78; mol wt, 203.0820. Found: C, 65.08; H, 5.54; N, 13.68; mol wt, 203.0823 (mass spectrum).

1-α-Cumyl-4,4-diethylpyrazolidine-3,5-dione Radical (6g·). A solution of pyrazolidinedione **6g** in chloroform was stirred with lead dioxide and anhydrous sodium sulfate for 20 min. The product was purified by applying the reaction mixture to a short column of silica gel and eluting with chloroform. Collection of the mobile green band and concentration at reduced pressure with a bath temperature below 25 °C afforded an emerald green solution of radical **6g·**: IR ($CHCl_3$) 3000, 2980, 2950, 2890 (CH), 1756, 1793 (C=O), 1463, 1258, 1125, and 706 cm^{-1}.

***tert*-Butylhydrazine (1c).**[39,40] To an etheral solution of *tert*-butylmagnesium chloride prepared from magnesium (31 g, 1.28 mol) and *tert*-butyl chloride (118 g, 1.27 mol) in anhydrous ether (650 ml) was added a solution of diphenyldiazomethane[41] (166 g, 0.855 mol) in anhydrous ether (350 ml). After standing overnight, the reaction mixture was worked-up with saturated ammonium chloride. Recrystallization from ethanol afforded 172.56 g (0.684 mol, 80%) of benzophenone *tert*-butylhydrazone: mp 76–78 °C (lit.[39] mp 73.5–75 °C).

To a slurry of benzophenone *tert*-butylhydrazone (165 g, 0.654 mol) in ethanol (350 ml) was added concentrated hydrochloric acid (235 ml), causing all of the solid to dissolve. While being stirred at room temperature for 2 days, this solution became cloudy. After stirring for an additional day, a solid had formed. This mixture was separated by filtration and the solid (mp 45 °C) was shown to be benzophenone (mp 48 °C). Concentration of the filtrate to about 1/2 of the original volume under reduced pressure caused more solid to precipitate from solution. This solid was also separated by filtration and shown to be benzophenone. The filtrate was extracted with ether (3X). Removal of the liquid from the aqueous phase under reduced pressure afforded an off-white solid, which was dried *in vacuo*. Absolute ethanol was added to the solid, the mixture thoroughly mixed, and the ethanol removed under reduced pressure. This process was repreated a second time. Finally, the solid was thoroughly washed with benzene. After filtration, 48.15 g (0.386 mol, 59%) of *tert*-butylhydrazine hydrochloride was obtained. A small sample was recrystallized from ethanol: mp 190–192 °C (lit.[39] mp 189 °C).

tert-Butylhydrazine was obtained by distilling the hydrochloride from 25% sodium hydroxide. The distillate was dried with sodium hydroxide and then distilled from barium oxide.

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Registry No.—**1a**, 100-63-0; **1b**, 3178-39-0; **1c**, 32064-67-8; **2a**, 6233-02-9; **2b**, 52809-11-7; **2c**, 64739-41-9; **3d**, 64739-42-0; **3e**, 64739-43-1; **3f**, 64739-44-2; **3g**, 64739-45-3; **3h**, 52809-12-8; **3i**, 64739-46-4; **3j**, 64739-47-5; **3k**, 64739-48-6; **4d**, 34874-03-8; **4e**, 4500-23-3; **4f**, 64728-39-8; **4l**, 64728-40-1; **5c**, 77-25-8; **5d**, 1619-62-1; **6h**, 64728-41-2; , **6h·**, 64728-44-5; **7**, 64728-42-3; **8**, 64728-43-4; ethyl chloroformate, 541-41-3; ethyl isocyanate, 624-83-9; phenyl isocyanate, 03-71-9; *tert*-butyl isocyanate, 609-86-5.

Supplementary Material Available: EPR spectra of radicals **4e·**, **4f·**, **4i·**, **4k·**, **4l·**, **6e·**, **6f·**, **6g·**, and spectral data (NMR, infrared, mass spectra), elemental analyses, and procedures for preparation of carbazates **2c**, semicarbazides **3d–g**, **3i–k**, urazoles **4d–g**, **4k–l**, and hydrazines **7** and **8** (17 pages). Ordering information is given on any current masthead page.

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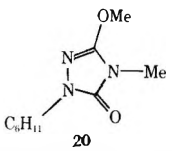

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Ionization and Fragmentation of Tri-*tert*-butylcarbinol. Evidence for a Transient *tert*-Butyl Carbanion in Me_2SO?

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The title compound undergoes immediate fragmentation to di-*tert*-butyl ketone and isobutane when treated with the potassium salt of dimethyl sulfoxide in that solvent at 25 °C. The reaction is highly exothermic, the heat evolved corresponding closely to Schleyer's estimate of the strain energy. Tri-*tert*-butylcarbinol is unassociated in carbon tetrachloride under conditions where neopentyl alcohol and di-*tert*-butylcarbinol show strong intermolecular hydrogen bonding. The latter two alcohols are recovered quantitatively under the conditions where the title compound is cleaved completely. The evidence can be interpreted in terms of mechanisms which involve a *tert*-butyl radical or a *tert*-butyl carbanion. The latter seems much more likely.

In the course of a systematic investigation[1-5] of Brønsted acidity in dimethyl sulfoxide (Me_2SO), we observed a steady decrease in enthalpy of deprotonation (ΔH_D) for aliphatic alcohols as bulky groups were substituted on the α carbon. However, when the limiting member of the series, tri-*tert*-butylcarbinol, was deprotonated a highly exothermic release of heat was observed which far exceeded that expected from the trend of the less crowded members. An excellent correlation had been found previously between the pK_a's of Brønsted acids in Me_2SO and their heats of deprotonation, ΔH_D.[4] On that basis, the ΔH_D of −23.2 kcal/mol for tri-*tert*-butylcarbinol suggests that its pK_a in Me_2SO should be about 22.5, or roughly equivalent to that of phenol. However, it was found that the alcohol did not dissolve in a dilute aqueous solution of sodium hydroxide. Examination of its acidity by Professor Bordwell's group at Northwestern University (using a Steiner-type indicator titration in Me_2SO) showed that the alcohol was not nearly as acidic as the heat of deprotonation suggested.

It was noted that easy fragmentation of the alcohol occurred in the pulsed ion cyclotron resonance spectrometer and that steric hindrance seemed to reduce the rate of the gas-phase proton transfer. Fragmentation in solution was also suggested by spectral evidence. A ^1H NMR spectrum of the deprotonation product showed a sharp singlet at 0.98 ppm, corresponding almost exactly to that of the starting alcohol. However, an infrared spectrum of the product solution showed a strong band in the carbonyl region at 1680 cm^{-1} suggesting the formation of di-*tert*-butyl ketone through a fragmentation reaction similar to those reported by Cram,[6] Zook,[7] and Lomas[8] in which either a *tert*-butyl carbanion or radical was ejected. Preliminary evidence supporting this possibility came when gas evolution was observed concurrently with deprotonation. Clearly, a careful recovery experiment was called for. The details of this investigation and strong evidence in favor of a facile base-catalyzed elimination of a *tert*-butyl carbanion will be described below.

Experimental Section

Synthesis. Tri-*tert*-butylcarbinol was prepared following the procedure of Bartlett and Lefferts.[9] In our hands yields were low (ca. 40%) with some improvement to 60% by addition of tetramethylethylenediamine to activate the reaction of *tert*-butyllithium (Ventron). The product was freed of residual di-*tert*-butyl ketone by steam distillation then recrystallized repeatedly from an ethanol–ice water mixture and vacuum sublimed until it was homogeneous to gas chromatography on a 9-ft column of SF-96 on Chromosorb W. A constant, but not very sharp, melting point between 116 and 117 °C (lit.[9] 117.5 °C) was achieved. The ^1H NMR spectrum in $CHCl_3$ at 250 MHz showed a single absorption at 0.98 ppm integrating for 27 protons and a small spike at 1.08 ppm, integrating for one proton, which disappeared in the presence of added D_2O.

Di-*tert*-butylcarbinol was prepared by reduction of di-*tert*-butyl ketone in ether with $LiAlH_4$. After solvent stripping, a white crystalline solid was left. The crystals were air dried and then dried over phosphorus pentoxide under vacuum. After several vacuum sublimations, the crystals gave a mp of 49–50 °C (lit.[10] 50 °C). Analysis by GLC on a 9-ft column of SF-96 on Chromosorb W revealed only one peak. The ^1H NMR spectrum in $CHCl_3$ at 250 MHz showed a peak at 0.98 ppm integrating for 18 protons, a peak at 2.52 ppm for one

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proton, and a single proton peak at 1.61 ppm which disappeared in the presence of D_2O.

For comparison, di-*tert*-butyl ketone (Chemical Samples Co.) showed a single absorption at 0.98 ppm. Except for peak heights at equivalent concentrations, this spectrum was identical with that of tri-*tert*-butylcarbinol whose hydroxyl proton has been exchanged with D_2O.

Neopentyl alcohol (Aldrich Chemical Co.) was recrystallized from petroleum ether and vacuum sublimed to a constant melting point, 54.6–55.6 °C (lit.[11] 53 °C). ^1H NMR spectra in $CDCl_3$ at 60 MHz showed peaks at 0.98, 3.2, and 3.9 ppm integrating respectively for nine, two, and one protons, the latter absorption being removable upon treatment with D_2O.

Spectra. The pulsed ion cyclotron resonance (ICR) spectrometer designed and constructed at the University of California, Irvine, was utilized for the determination of the gas-phase acidities of neopentyl alcohol, di-*tert*-butylcarbinol, and tri-*tert*-butylcarbinol.[2] The instrument is essentially a mass spectrometer which is capable of trapping gaseous ions efficiently for times up to several seconds.[12] The relative acidity of the Brønsted acids AH and BH can be determined by measuring equilibrium constants for reactions such as

$$AH + B^- \rightarrow BH + A^-$$

The pulsed ICR spectrometer can measure the equilibrium abundance of the two anions A^- and B^-, and an ionization gauge calibrated by a capacitance manometer was used to measure the partial pressures of AH and BH in the system. Experiments were performed at very low pressures in the range from 10^{-6} to 10^{-4} Torr. Under these conditions the anions A^- and B^- exist as free gaseous ions. Both positive ion and negative ion mass spectra can be obtained by this technique. Positive ion spectra were taken at short delay times for each of the alcohols, and in all cases the positive ion ICR spectra were found to resemble closely the conventional electron impact mass spectra. This serves as a check for the purity of the samples as admitted into the spectrometer. Negative ions were generated by dissociative electron capture on methyl nitrite or Me_2SO

$$CH_3ONO + e^- \rightarrow CH_3O^- + NO$$

$$(CH_3)_2S{=}O + e^- \rightarrow CH_3S\overset{\overset{O}{\|}}{C}H_2^- + H$$

Since the strongest base of the alkoxide series in the gas phase is CH_3O^- it was most generally useful as a deprotonating reagent for the other aliphatic alcohols.

Proton magnetic resonance spectra were recorded on either a Varian A-60D, a Hitachi-Perkin Elmer R-20, or the HF-250 MHz instrument at Mellon Institute. Reproductions of the spectra of the three alcohols discussed here, before and after recovery experiments, are presented in ref 13. Chemical shifts are referred to an external tetramethylsilane standard. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer or a Beckman IR4 spectrometer. Mass spectra were recorded on an Associated Electrical Industries MS-9 spectrometer.

Recovery Experiments. Upon finding that tri-*tert*-butylcarbinol underwent a rapid exothermic reaction in $K^+Me_2SYL^-$ solutions, careful quantitative recovery experiments were initiated with di-*tert*-butylcarbinol and neopentyl alcohol as controls. The $K^+Me_2SYL^-$ base concentrations were usually 0.1 M; however, the base concentration was varied from 0.05 to 1.0 M for tri-*tert*-butylcarbinol with the same results. The apparatus and procedure followed were essentially the same for all three recovery experiments except that the tri-*tert*-butylcarbinol experiment was repeated on a vacuum line. A 150-mL round-bottom flask equipped with a gas inlet tube, O-ring-adapted joint, and a ground glass joint was connected to a mineral oil bubbler and purged continuously with argon. Forty milliliters of pure Me_2SO were measured from the storage bottle. A 20-mL hypodermic syringe was used to withdraw 10 mL of the 1.0 M $K^+Me_2SYL^-$ stock solution for delivery into the flask. Purified carbinol was added to a solids addition bulb which was fitted onto the ground glass joint. A balloon was stretched over the mouth of the O-ring joint and was bound tightly. The basic solution was stirred continuously with a magnetic spin bar. The flask and balloon were filled several times with argon, which was expelled through the bubbler. The solids addition bulb was rotated slowly so that alcohol addition was complete after 20 to 25 min. Neither the solution nor balloon showed any evidence of gas evolution in the case of neopentyl or di-*tert*-butylcarbinol.

Addition of tri-*tert*-butylcarbinol, however, caused a gas to be evolved which was captured in the balloon. After quenching the solution with ice, neutralizing with 0.1 N HCl, extracting with ether, and drying the ethereal solution over potassium carbonate, GLC analysis revealed that no tri-*tert*-butylcarbinol was recovered and that a new compound had been formed. Infrared analysis identified this product as di-*tert*-butyl ketone. Analysis on a 10-ft column of 3% SE-30 and on a 10-ft column of 3% OV-17 positively confirmed this identification by spiking with authentic material. No trace of di-*tert*-butylcarbinol was seen on the GLC recording and this was confirmed by spiking with a bona fide sample. In contrast, complete recovery of pure neopentyl alcohol and di-*tert*-butylcarbinol was achieved through the same work-up from treatment of these compounds with $K^+Me_2SYL^-$.

In a replica experiment the same reaction vessel was assembled and connected to the vacuum line via the O-ring joint. The system was evacuated several times and then isolated from the pump. The solid alcohol was added slowly and the gas was collected in a gas buret. When all the sample was dissolved and gas evolution was complete, a liquid nitrogen cold trap was used to condense the gas in a storage flask fitted with a vacuum stopcock. The line was reopened to the pump to remove all noncondensable impurities. The storage flask and the reaction flask were closed and removed from the vacuum line. This sample of gas was identified positively as isobutane by comparison with a sample from Union Carbide. A separate experiment performed with $K^+Me_2SYL^-$-d_5 in Me_2SO-d_6 (99.5%, Norrell Chemical Co.) gave identical results except for a parent peak at *m/e* 59 and several fragmentation patterns shifted by one mass unit.

Mass spectra were run at 15, 20, 75 eV for the collected gas and at 20 and 70 eV for authentic samples of isobutane and isobutene under the same conditions. These experiments showed clearly that the product gas was isobutane which did not contain a detectable amount of the olefin.

Results

Gas-Phase Reactions. Reaction of CH_3O^- with ethanol, 2-propanol, *tert*-butyl alcohol, neopentanol, and di-*tert*-butylcarbinol in the pulsed ICR spectrometer gave exclusively the corresponding M-1 alkoxide ions. However, tri-*tert*-butylcarbinol under the same conditions fragmented to give negative ions at *m/e* 199, 141, and 127 with relative abundances 9, 100, and 14%, respectively. Even when a weaker base such as $CH_3SOCH_2^-$ was used, fragmentation to give the same peaks was still observed. The small peak at *m/e* 199 is probably the conjugate base of tri-*tert*-butylcarbinol. We can only speculate on the structures of the two ions of lower mass.

Association Studies. The unusually crowded structure of tri-*tert*-butylcarbinol implies that its alkoxide ion would receive less stabilization by solvation or ion pairing than would those from less hindered alcohols. It should also be less associated through hydrogen bonding than other alcohols. An IR concentration study of the hydroxyl band (~2.72 μm) shows it to be unusually sharp. It does not broaden or shift when the concentration is varied from 2.5 to 10% carbinol in carbon tetrachloride. In sharp contrast, neopentyl alcohol exhibits two bands in the O–H stretching region due to a hydrogen-bonded and a nonhydrogen-bonded stretching frequency. The nonhydrogen-bonded stretching frequency is superimposable upon the hydroxyl band of tri-*tert*-butylcarbinol.

Although tri-*tert*-butylcarbinol does not self-associate, it can act as a hydrogen-bond donor to the solvent. In Me_2SO, the hydroxyl stretching frequency is lowered and the band is broadened.

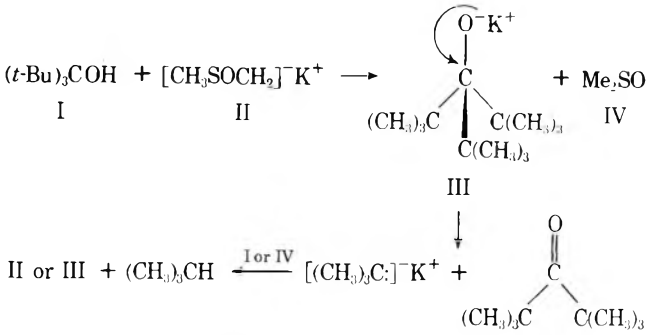
In further contrast to neopentyl and other alcohols studied, a thermometric titration of tri-*tert*-butylcarbinol into carbon tetrachloride shows no detectable heat of dilution.

Discussion

The evidence presented in the foregoing sections may be summarized as follows: (a) In the gas phase, tri-*tert*-butylcarbinol is the most acidic of the aliphatic alcohols we have studied. Its behavior follows the systematic trend established by its less branched homologues. However, it is kinetically unstable and shows a strong tendency to fragment. (b) Reaction of tri-*tert*-butylcarbinol with dimsylate anion in Me_2SO is anomalously exothermic. This is not due to its abnormally high acidity, as shown by its failure to dissolve in aqueous

sodium hydroxide and its failure to titrate with $K^+Me_2SYL^-$ in Me_2SO in the predicted pK_a range. (c) Recovery experiments, which retrieved neopentyl alcohol and di-*tert*-butylcarbinol quantitatively after deprotonation in Me_2SO, show that tri-*tert*-butylcarbinol is converted completely and instantly to di-*tert*-butyl ketone and isobutane.

We propose that this reaction occurs through the expulsion of a *tert*-butyl carbanion in accordance with the following mechanistic scheme:



This mechanism is entirely analogous to the retro-Grignard addition proposed by Zook[7] for the cleavage of di-*tert*-butylneopentylcarbinol with sodium hydride in ether. Cram[6] likewise observed cleavage of some heavily substituted tertiary alcohols in the course of his classic investigations of electrophilic aliphatic substitution. The striking feature in the present case is the instantaneous expulsion of a completely aliphatic moiety under relatively moderate conditions in strongly basic solution. Zook's cleavage required reaction times of 1 to 6 h at 200 to 400 °C. Cram's leaving groups carried resonance stabilizing aromatic or cyano groups.

Schleyer[14] has calculated the strain energy for tri-*tert*-butylmethane as 40.4 kcal/mol and that for 1,1-di-*tert*-butylethane is 15.0 kcal/mol. The heat of reaction of tri-*tert*-butylcarbinol with $K^+Me_2SYL^-$, −23.2 kcal/mol, is close to the difference (−25 kcal/mol) in strain energy for these compounds and is probably the driving force for the reaction.

We can produce no iron-clad evidence against a radical cleavage pathway[8,15] through *tert*-butyl radical or di-*tert*-butylketyl. Tri-*tert*-butylmethyl radical and di-*tert*-butylmethyl radical are remarkably stable because of steric hindrance against dimerization.[16] One might reasonably presume that di-*tert*-butylketyl would also be fairly long lived for the same reason. However, the lack of coupling products[6] in our product mixture and the initiation of the reaction by strong base make a radical pathway seem much less likely than the carbanion mechanism.[17] In view of the high rate of the reaction and the high melting point of Me_2SO, CIDNP or ESR experiments to test for *tert*-butyl radicals at low temperatures would be difficult, but not impossible.[18,19]

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Registry No.—Tri-*tert*-butylcarbinol, 41902-42-5; di-*tert*-butylcarbinol, 14609-79-1; neopentyl alcohol, 75-84-3; dimethyl sulfoxide, 67-68-5.

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Periselectivity in the [4 + 2] and [6 + 4] Cycloadditions of Diphenylnitrilimine to Tropone

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The cycloaddition of diphenylnitrilimine, generated from the dehydrochlorination of α-chlorobenzylidenephenylhydrazine, to tropone gives a [6 + 4] adduct in 4% yield, a 2:1 adduct (4%) of unknown structure, and three partially aromatized [4 + 2] adducts in 54, 5, and 5% yield. Attempted photochemical decarbonylation of the [6 + 4] adduct gave only a mixture of rearranged products, while pyrolysis of the [6 + 4] adduct resulted in a [1,5]sigmatropic shift and formation of one of the partially aromatic [4 + 2] adducts. The periselectivity observed here is similar to that of nitrile oxide, but differs substantially from that observed with other dipoles and with dienes. Electronic origins of these differences are discussed.

Introduction

In 1970, we reported the first examples of [6 + 4] cycloadditions of 1,3-dipoles across the termini of trienes.[2,3] The [6 + 4] cycloaddition of diphenylnitrilimine to tropone[2] and the [6 + 4] cycloaddition of diazomethane to dimethylfulvene[3] were prototypes of a general method for the synthesis of new heterocyclic systems. However, in the interim, remarkably few

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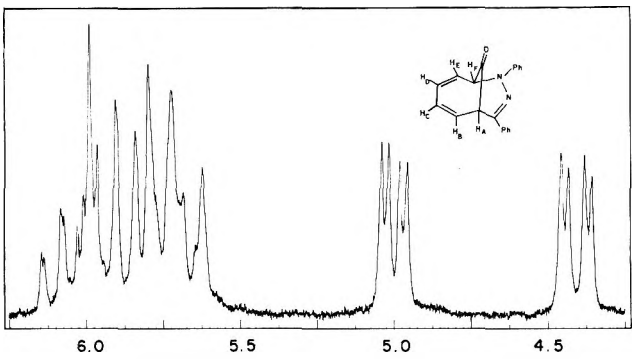


Figure 1. 100-MHz NMR spectrum of [6 + 4] adduct **1** (the aromatic region of the spectrum is not shown).

1,3-dipolar cycloadditions of this type have been discovered. The [6 + 4] cycloadditions of mesito- and benzonitrile oxide to tropone compete poorly with [4 + 2] cycloadditions.[4] The [6 + 4] dimerization of a cyclic azomethine ylide and its [6 + 4] cycloaddition to fulvenes have also been reported,[5] and we have found that diazomethane adds in a [6 + 4] fashion to 6-phenylfulvene.[6] We predicted in 1973 that nitrile ylides, a class of electron-rich 1,3-dipoles, would add in a [6 + 4] fashion to fulvenes,[7] and Padwa has recently confirmed this experimentally.[8] The formal [6 + 4] cycloaddition of cycloheptatriene to "S_3" is another possible example,[9] and the electron-rich 6-dimethylaminofulvene adds in a [6 + 4] fashion to nitrile oxides.[10]

Thus, the [6 + 4] cycloadditions of diphenylnitrilimine and two aryl nitrile oxides, which compete poorly with [4 + 2] additions, are the only documented cases of 1,3-dipolar cycloadditions across the 2,7 positions of tropone. These results stand in marked contrast to the results of diene cycloadditions to tropone, where cyclopentadiene and cyclohexadiene,[11a] isobenzofulvenes,[11b] perhaps dimethyl-, methyl-, and phenylfulvenes,[11c,12] several acyclic dienes,[11d] cyclopentadienones,[11e] and a benzopyrone[11f] all react preferentially in the [6 + 4] fashion, tropone behaving as a 6π addend.

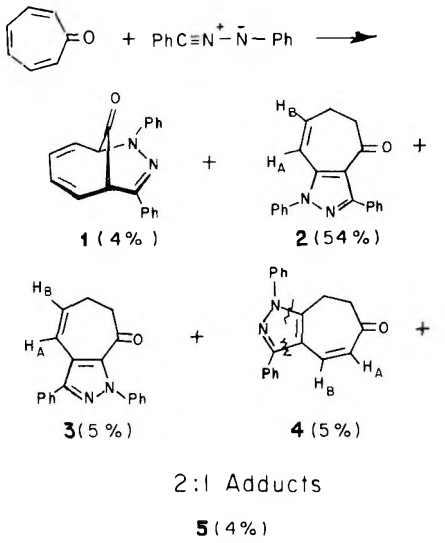
Because of our interest in the development of understanding of periselectivity in cycloadditions,[12] and in order to obtain quantities of the [6 + 4] diphenylnitrilimine–tropone adduct to attempt transformations to other novel heterocyclic systems, we have reinvestigated the reaction of diphenylnitrilimine to tropone. We report here full details of the reaction reported in the earlier communication,[2] structures of three additional minor products formed in this reaction, and results of investigations of the thermal and photochemical behavior of the [6 + 4] adduct. After submission of this work, Gandolfi and co-workers published a parallel study in which the structure of the major adduct **2** (see below) was proven,[13] and was found to have a different regiochemistry from that assigned in our earlier communication.[2]

Cycloaddition Products

The reaction of tropone with diphenylnitrilimine, generated in situ from α-chlorobenzylidenephenylhydrazine and triethylamine in benzene at room temperature, produced a mixture of adducts (Scheme I). The major adduct, **2**, precipitates from the reaction mixture, and careful column chromatography of the remaining solution gave five reaction products (**1**–**5**). The first four of these proved to be 1:1 adducts, while the last was a 2:1 adduct of diphenylnitrilimine and tropone. The structures of the major adduct, **2**, and the [6 + 4] adduct, **1**, were reported earlier,[2] but the work of Gandolfi et al. indicates that our assignment of structure to **2** was incorrect.

The structure of the [6 + 4] adduct **1**, mp 112–113 °C, formed in 4% yield, is clearly revealed from the NMR spectrum, shown in Figure 1, and the infrared spectrum. The bridging carbonyl is revealed by the stretching absorption at 5.79 μm, while the 100-MHz NMR spectrum, shown in Figure 1, is only compatible with the addition of the 1,3-dipole across the 2 and 7 positions of tropone. Thus, the two bridgehead protons (H_A and H_F) each appear as a sharp doublets of doublets. The doubly allylic bridgehead proton (H_A) (δ 4.52) has vicinal (J_{AB}) and "*W* (through carbonyl)"[14] (J_{AF}) couplings of 7.7 and 2.5 Hz, respectively, while the other bridgehead proton (H_F) is shifted downfield to δ 5.02 by the nitrogen and has vicinal (J_{EF}) and "*W*" (J_{AF}) couplings of 6.0 and 2.5 Hz. The olefinic protons appear as a complex multiplet between 5.5 and 6.4 ppm, which is the ABMN part of an ABMNXY system. Vicinal olefinic couplings (J_{BC} and J_{DE}) of approximately 11 Hz, and J_{CD} of approximately 6.5 Hz, along with smaller long-range couplings could be discerned from the spectrum.

Scheme I



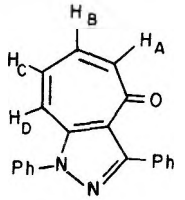
Compound **5**, mp 216–217 °C, proved to be an inseparable mixture of 2:1 adducts **5a** and **5b**. The IR spectrum of this mixture revealed a bridging carbonyl stretching at 5.74 μm while the NMR spectrum indicated that **5** consisted of two closely related adducts, **5a** and **5b**, present in a 2:1 ratio. The major isomer, **5a**, gave a broadened AB resonance (δ_A 3.82, δ_B 4.54, J_{AB} = 0.1 Hz), while **5b** gave a similar pattern in the vinylic region, but with the chemical shifts more nearly identical (δ_A 4.06, δ_B 4.44, J_{AB} = 9.0 Hz). None of the remaining resonances are in the olefinic region of the spectrum. Reactions of the adducts, **1** or **4**, gave 2:1 adducts which were different from **5**. We cannot propose a structure of **5** consistent with all of the data.

The major adduct, **2**, mp 188–189 °C, could be isolated in a total yield of 54% by combining the material which precipitated from the reaction mixture with that obtained by chromatography. The strong carbonyl stretch at 6.07 μm was indicative of an α,β-unsaturated ketone moiety, while the multiplets at 2.3–3.0 (4 H) and 6.2-6.5 ppm (2 H) were indicative of the absence of protons on the unsaturated carbons α and β to the carbonyl. On this basis, the major isomer must have either the structure **2** or **3**. We earlier assigned to the major isomer structure **3**[2] on the basis of similar regioselectivity in other nitrile imine cycloadditions to α,β-unsaturated carbonyl compounds.[15]

The 100-MHz NMR spectrum has an AA'BB' multiplet between 2.5 and 2.8 ppm and an ABX_2 pattern centered at 6.4 ppm. In a further attempt to simplify the NMR spectrum of **2**, deuterium exchange with NaOEt in EtOD was attempted. However, under conditions required for exchange, all of the protons other than the phenyl protons were replaced by

deuterium. Although this is compatible with the structure of **2** shown, it was of no aid in distinguishing **2** from **3.**

Adduct **2** could be dehydrogenated with chloranil in refluxing *n*-amyl alcohol. The resulting pyrazolotropone (**6**) had



6

tropone-like carbonyl absorptions at 6.05 and 6.2 μm and the NMR spectrum gave a complex multiplet between 6.5 and 7.2 ppm. Aromatic character is reflected in the closeness of these resonances and their downfield shifts with respect to resonances in α,β-unsaturated ketones.

The compound to which we assign structure **3,** mp 152 °C, was obtained in 5% yield. The IR spectrum of this compound has a carbonyl stretch at 5.99 μm, indicative of an α,β-unsaturated ketone structure, and an upfield multiplet in the NMR at 2.3–2.9 ppm very similar in appearance to that of **2.** However, the olefinic protons form a resolved AB pattern, with one proton (H_B) appearing at δ 6.18 as a doublet of triplets (J_{AB} = 11.0 Hz, J_{BC} = 6.0 Hz) and the second (H_B) appearing as a broadened doublet at δ 6.68 (J_{AB} = 11.0 Hz, $J_{AC} \leq 0.5$ Hz). The main NMR spectral difference between **2** and **3** is the downfield shift of one of the olefinic resonances in **3** as compared to **2.**

The structural assignments shown in Scheme I, rather than the opposite, have been shown to be correct by the work of Gandolfi et al., who prepared the dihydro analogue of **3** by independent synthesis, and degraded **3** to a compound of unequivocal structure.[13]

Both **2** and **3** must arise from the initial [4 + 2] cycloaddition of the 1,3-dipole to the 2,3-double bond of tropone, followed by a hydrogen shift, probably base catalyzed, since triethylamine was present in the reaction mixture. Hydrogen shifts ultimately result in the formation of the aromatized pyrazole rings.

Finally, adduct **4,** mp 134 °C, formed in 5% yield, was clearly an α,β-unsaturated ketone with protons on the α and β carbons. The carbonyl stretch at 6.05 μm and the AB pattern (δ_A 6.10, δ_B 7.00, J_{AB} = 12.0 Hz) in the NMR spectrum are fully in accord with expectation for structure **4,** although no evidence for the orientation of the diphenylnitrilimine moiety relative to the cycloheptadiene moiety has been obtained. The protons on saturated carbons appear as a narrow multiplet between 2.6 and 3.3 ppm. Compound **4** arises from 1,3-dipolar cycloaddition to the γ,δ double bond of tropone, with subsequent isomerization to only one of the two possible aromatized products.

Thermal and Attempted Photochemical Transformations of [6 + 4] Adduct 1. One feature of **1** which prompted this study was the possibility that photochemical or thermal extrusion of CO would provide an additional entry into nine-membered 10π-electron heterocyclic systems,[16] as shown on the left of Scheme II. However, photolysis of **1** under various conditions (see Experimental Section) produced a complex mixture of compounds with a prominent broad carbonyl stretching region in the IR at 5.99 μm. Although interesting transformations of the type observed in [6 + 4] adducts of tropone with dienes[17] are no doubt occurring, the lack of evidence for decarbonylation has discouraged us from further investigations of the photolysis of **1.**

However, heating **1** at 150 °C in Me_2SO solution caused formation of the previously elucidated adduct **3** in 50% yield.

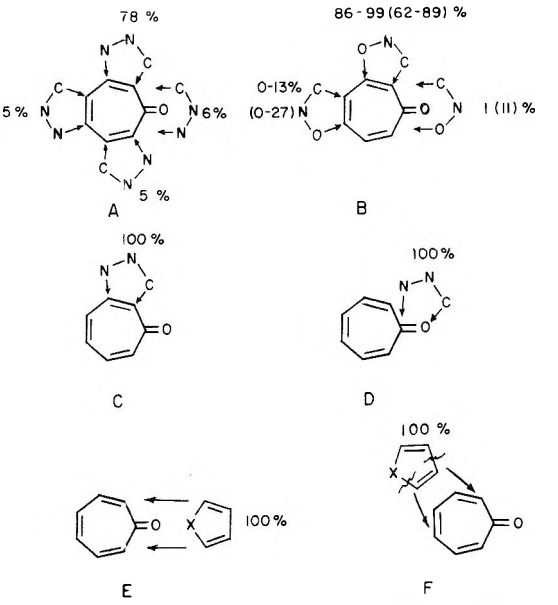


Figure 2. Summary of regio- and periselectivity observed in cycloadditions of 1,3-dipoles and dienes to tropone: A, diphenylnitrilimine (this work and ref 13); B, mesitonitrile oxide (benzonitrile oxide) (ref 4); C, diazomethane (ref 9) and dimethyldiazomethane (ref 20); D, *N*-phenylsydnone (ref 21); E, cyclopentadienones (ref 11e), cyclopentadiene and cyclohexadiene (ref 11a), isobenzofulvenes (ref 11b); benzopyrone, (ref 11d); F, 5-substituted cyclopentadienes (ref 22), cycloheptatriene (ref 23), fulvenes (ref 11c, 12).

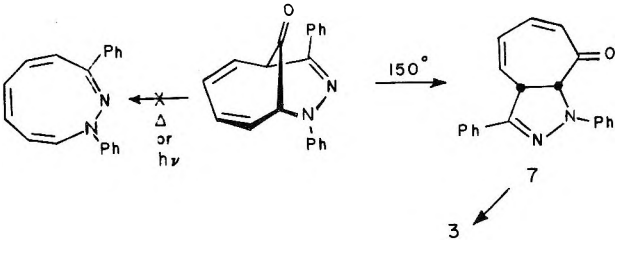
This transformation can be envisioned as a [1,5] sigmatropic shift to form **7,** followed by subsequent [1,5] sigmatropic (or base-catalyzed] hydrogen shifts to form the aromatized product **3.**

In the [6 + 4] adduct **1,** two different [1,5] sigmatropic shifts could occur, one involving cleavage of a double allylic CN bond and the other of a CC bond which is allylic at one terminus and vinylic on the second. The first migration would lead to formation of the compound we have called **3,** while the second cleavage would ultimately give **2.** The surprising migration of the vinyl group, rather than the allylic nitrogen terminus, has some analogy in the rearrangements of spirononatriene, where the vinyl carbon, rather than allylic carbon, migrates preferentially.[18]

Discussion

In Figure 2, we have summarized the regio- and periselectivity results found in this work, with percentages normalized to 100%. The figure also summarizes the results of other 1,3-dipolar and diene cycloadditons to tropone. The periselective [4 + 2] cycloadditions of 1,3-dipoles (A–D) to tropone are puzzling, since unhindered dienes generally undergo periselective [6 + 4] cycloadditions (E) to tropone. This is all the more remarkable since both electron-rich (butadiene, isoprene, cyclopentadiene, cyclohexadiene, isobenzofulvenes, and perhaps fulvenes) and electron-deficient (cyclopentadienones, benzopyrone) dienes undergo [6 + 4] cycloadditions (E) to tropone, while electron-rich (diazoalkanes)[19,20] (C) and

Scheme II



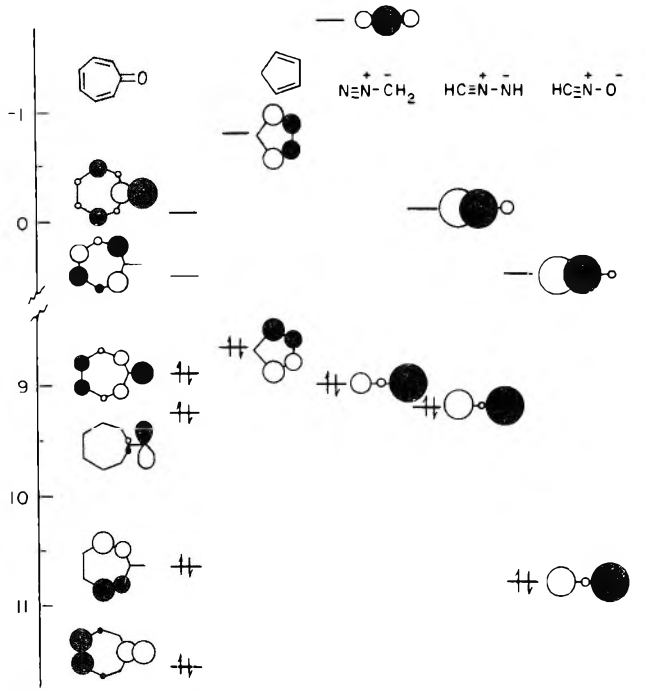


Figure 3. The π molecular orbitals of tropone (STO-3G), cyclopentadiene, and several 1,3-dipoles.[27] Filled and vacant MO energies are negatives of ionization potentials (from PES)[26] and negatives of estimated electron affinities, respectively.

electron-deficient (nitrile oxide, nitrile imine, and sydnone)[21] (A, B, D) dipoles prefer [4 + 2] cycloadditions.

In order to attempt a rationale of this divergent behavior of dienes and 1,3-dipoles, 4π-electron systems which are otherwise similar in their cycloaddition behavior, we turn to the molecular orbitals of tropone, which are shown in Figure 3. The MO's shown are calculated by an ab initio method[24] using the STO-3G basis set.[25] The orbital coefficients are those obtained from the calculations, while the occupied orbital energies are negatives of photoelectron ionization potentials[26] and the vacant orbital energies are negatives of estimates of electron affinities.

This figure also includes the frontier orbitals of cyclopentadiene, which adds in a [6 + 4] fashion to tropone, diazomethane, the parent nitrilimine, and fulminic acid, three 1,3-dipoles whose frontier orbital energies have been measured or closely estimated.[27]

The reactivity of tropone toward electrophilic species should be dominated by the HOMO, a π orbital, which is 1.75 eV higher in energy than the second highest π orbital. Particularly "hard" electrophiles may also react at the relatively negative oxygen. In reactions with dienes, the tropone HOMO should favor [6 + 4] cycloaddition or cycloaddition to the 4,5 double bond. The third occupied orbital will, however, lead to stabilization of cycloaddition to the 2,3 double bond.

The LUMO of tropone is a normal, somewhat polarized, triene orbital. It also would appear to favor [6 + 4] cycloaddition or [4 + 2] addition to the 4,5 double bond. The presence of the relatively low-lying SLUMO complicates this picture, since reaction at C-3 is favored here. However, the propensity for cyclopentadienes and other simple dienes to add in a [6 + 4] fashion to tropone can be used as empirical evidence in favor of the importance of the HOMO and LUMO in determining the periselectivity of reactions of dienes.

Returning to the problem at hand, the orbital diagram makes even more apparent the difficulty of explaining the lack of substantial amounts of [6 + 4] adducts in reactions of 1,3-dipoles with tropone. Diazomethane, which has an IP similar to cyclopentadiene, and fulminic acid, which has a similar electron affinity, both avoid the [6 + 4] route, as does nitrile imine, which is only slightly more electrophilic than cyclopentadiene.

There also do not seem to be large differences in geometrical factors between dienes and 1,3-dipoles. Thus, the distance between termini is 2.44 Å in diazomethane, while the 1,4-distance is 2.24 Å in cyclopentadiene. Both should be easily able to span the 2,7 distance of tropone (2.55 Å).

The only compelling difference between dienes and 1,3-dipoles which might explain the failure of the latter to undergo [6 + 4] cycloaddition is the relatively large positive charge on the central atom of 1,3-dipoles (0.10–0.47), which must come in close proximity to the partially postively charged carbon of tropone (charge = +0.16) in the transition state of a concerted [6 + 4] 1,3-dipolar cycloaddition. However, for a charge of +0.16 on the carbonyl carbon, +0.5 on the central nitrogen of the 1,3-dipoles, and an assumed separation of 2.2 Å in the transition state, the Coulombic repulsion amounts to only 0.5 kcal/mol, and this seems insufficient to account for the exclusive [6 + 4] cycloaddition in the absence of this interaction and only small amounts of [6 + 4] adduct in the presence of this interaction. An effect worth at least several kilocalories per mole is required to explain the difference between 1,3-dipoles and carbocyclic dienes.

Turning to the various [4 + 2] routes observed, we note first that the preferential addition of the nitrilimine to the 2,3 double bond of tropone can be rationalized by frontier orbital predictions. For both nitrile oxides and imines, the interaction of the LUMO of these species with the HOMO of tropone determines the preferred regioselectivity. With the highly nucleophilic diazomethane, maximum transition-state stabilization occurs when the more nucleophilic carbon terminus (site of highest HOMO coefficient) becomes united with the C-2 of tropone, which has a larger LUMO coefficient than C-3.

We are continuing to explore the origins of periselectivity in this and related cycloadditions by both experimental and theoretical techniques.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by Mr. Ralph Seab at L.S.U.

Reaction of Tropone with Diphenylnitrilimine. Tropone (10 g) and α-chlorobenzylidenephenylhydrazine (4.6 g) were dissolved in benzene (60 mL), and triethylamine (6 mL) in benzene (25 mL) was added over a period of 6 h with stirring under nitrogen. The mixture was left at room temperature for 12 h. The precipitated Et_3N·HCl was filtered off and the benzene solution was washed thoroughly with water. Concentration of the solution and cooling afforded crystals (3.2 g), mp 180–185 °C. Recrystallization from methanol furnished pure material (2.8 g) **2**, mp 188–189 °C. The residual gummy material was chromatographed on alumina (50 g). Elution with 1:3–2:3 benzene/petroleum ether gave a fraction which consisted of three components on TLC. These components were separated on thick-layer plates. Two elutions with 8:2 benzene/cyclohexane gave three fractions.

Fraction I consisted of 250 mg of **1**, mp 112–113 °C (from methanol). Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37; N, 9.32. Found: C, 79.73; H, 5.41; N, 9.35.

Fraction II consisted of 250 mg of **5**, mp 216–217 °C (from methanol). Anal. Calcd for $C_{33}H_{26}N_4O$: C, 80.14; H, 5.30; N, 11.33. Found: C, 79.86; H, 5.52; N, 11.00.

Fraction III consisted of 300 mg of **3**, mp 152 °C (from methanol). Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37; N, 9.32. Found: C, 80.18; H, 5.36; N, 9.32.

Further elution of the alumina column using benzene and then 1:1 benzene/chloroform gave a fraction consisting of two components on TLC. These were separated by preparative TLC using 5:1 cyclohexane/ethyl acetate to give two fractions.

Fraction I′ consisted of 300 mg of **4**, mp 134 °C (from methanol). Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37: N, 9.32. Found: C, 79.70; H, 5.39; N, 9.27.

Fraction II′ consisted of **2**, mp 188–189 °C (from methanol). This material was identical with the crystalline material 2 initially ob-

tained. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37; N, 9.32. Found: C, 79.76; H, 5.23; N, 9.19.

Chloranil Treatment of Adduct 2. A solution of **2** (100 mg) in *n*-amyl alcohol (5 mL) was refluxed under nitrogen for 3 h with chloranil (500 mg). Excess *n*-amyl alcohol was distilled off under vacuum and the residue was taken up in chloroform and shaken with 4% NaOH solution to remove chloranil. Removal of the solvent in vacuo left a solid residue which was purified by eluting through a column of alumina (6 g) with 1:1 benzene/chloroform. Recrystallization from methanol afforded 50 mg of **6**, mp 175 °C. Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.40; H, 4.76; N, 9.28.

Deuteration Studies on 2. (a) A solution of **2** (100 mg) in tetrahydrofuran (3 mL) was stirred under nitrogen for 20 h with a solution of sodium (~10 mg) in D_2O (2 mL). The reaction mixture was extracted with methylene chloride. The NMR spectrum was identical with that of the undeuterated material.

(b) To a solution of Na (~10 mg) in EtOD (4 mL), **2** (100 mg) was added. The mixture was kept at 60 °C for 20 min under nitrogen and then D_2O (1 mL) was added. The reaction mixture was extracted with methylene chloride. The NMR spectrum of this material indicated exchange of all the protons except the phenyl protons.

Thermal Rearrangement of the [6 + 4] Adduct 1. A solution of **1** (100 mg) in Me_2SO (1 mL) was heated gradually to 150 °C and kept at that temperature for 1 h under N_2. The reaction mixture was diluted with water and extracted with methylene chloride. Removal of the solvent in vacuo gave a solid residue which was purified by filtration through a column of alumina with benzene eluent. Crystallization from methanol afforded 50 mg of a material, mp 150 °C, which was identical with the [4 + 2] adduct **3** already obtained.

Photolysis of the [6 + 4] Adduct 1. (a) A solution of **1** (100 mg) in benzene (350 mL) was irradiated with a Rayonet 3500 Å lamp in a Pyrex vessel under nitrogen. Even after 16 h of irradiation, the reaction mixture showed considerable starting material remaining (from NMR), besides a few spots having lower R_f than the original compound on TLC.

(b) A solution of the compound (100 mg) in benzene (350 mL) was irradiated with a Rayonet 3000 Å lamp in a quartz vessel under nitrogen. After 12 h of irradiation, the starting material was not visible by TLC. At least four spots were detectable by TLC having lower R_f values than the starting material. The infrared spectrum of this mixture indicated the presence of several α,β-unsaturated ketones.

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Registry No.—**1**, 32499-79-9; **2**, 63788-67-0; **3**, 31108-24-4; **4**, 64666-44-0; **6**, 63788-69-2; tropone, 539-80-0; α-chlorobenzylidenephenylhydrazine, 15424-14-3; diphenylnitrilimine, 15409-32-2.

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Possible Role of Charge-Transfer Complexes in Cationic Polar Cycloaddition

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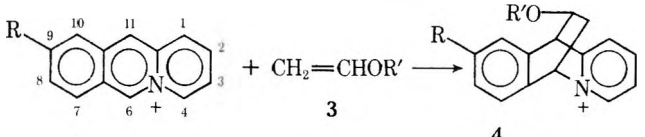
The log of the relative rate constants (k/k_0) for the cycloaddition of ethyl vinyl ether for a series of 9-substituted acridizinium perchlorates gave a significant correlation when plotted against the Hammett σ_p. The values for ρ were higher than those found earlier using styrene or acrylonitrile with the same substrate, but significantly lower than would be expected for a two-step reaction. The reaction in which para-substituted phenoxyethylenes are added to the acridizinium ion was studied in the same way, and a significant correlation between log k/k_0 and the σ_n of van Bekkum, Verkade, and Wepster was found. The activation parameters for the forward and retro reactions were determined for the cycloaddition of 2,3-dimethylisoquinolinium iodide with ethyl vinyl ether and found to be within the ranges established for the classical Diels–Alder reaction. A significant correlation has been found between the log of the relative rates of cycloaddition of para-substituted styrenes and published values for ^{13}C chemical shift of the β carbon of the styrenes. Spectroscopic evidence indicates that the acridizinium ion forms charge-transfer complexes with donor molecules, and analysis of the second-order rate constant for the cycloaddition of *N*-vinylcarbazole with the acridizinium ion shows that there is a decrease in the apparent rate constant with increased concentration of *N*-vinylcarbazole. These data can be interpreted as evidence for the presence of a charge-transfer complex in the reaction mixture. It appears likely that cationic polar cycloaddition proceeds via charge-transfer complexes.

Cationic polar cycloaddition[1,2] is characterized by being nearly always 100% regioselective and, where easily polarized unsymmetrical alkenes are involved, strongly stereoselective. Both of these selectivity effects appear to arise from the uneven distribution of the positive charge in the cation. One of the cycloaddition termini furnished by the cation is always the most positively polarized carbon in the molecule, while the other is more electron-rich and has no positive charge in any of the canonical forms contributing to the resonance hybrid.

A useful model for predicting the regiochemistry of polar cycloaddition requires the initial attack by the more negatively polarizable end of the alkene upon the most positive carbon atom of the cation. There is no difficulty in using this model to rationalize the regiochemistry of 19 of the 20 unsymmetrical addends which had been allowed to react with the acridizinium ion (**2**) at the time that the subject was last reviewed.[2]



1
2, R = H

3

4
5, R = H

That the 20th addend, acrylonitrile, adds with the β-carbon atom attacking the most positive carbon (position 6) of the acridizinium ion[3] was at first interpreted as indicating that polar influences are unimportant;[3] it was later rationalized by the suggestion[4] that *polarizability* and not ground-state polarization must be the determining factor in the regiochemistry of adduction. This opinion gains support from the frontier orbital calculations[5] which show that when acrylonitrile acts as a donor in cycloaddition the largest highest occupied molecular orbital (HOMO) coefficient is indeed that of the β-carbon atom of the double bond.

Since vinyl ethers have been shown to add to 2,3-dimethylisoquinolinium salts[6,7] and to the acridizinium ion[6] in a manner that is completely both regioselective and stereoselective (cf. **5**), it was felt important to learn more about the kinetics of this type of polar cycloaddition. With acridizinium derivatives significant correlations of the log of the relative rate of addition with the Hammett substituent constant, σ_p, were shown earlier for the addition of 9-substituted acridizinium perchlorate (**1**) to styrene[9] at 65 °C and to acrylonitrile[4] at 130 °C. In Table I are recorded the results of a similar study carried out at 0 °C using ethyl vinyl ether (**3**, R′ = Et) as the substrate. From the table it can be seen that the rate of reaction increases (over 100-fold) with the increase in the electron-withdrawing power of the 9 substituent on the acridizinium nucleus.

A Hammett plot (Figure 1) of the rate data was made using primary para substituent constants, where available, as well as the recommended statistical treatment.[12] Once again, a significant correlation (r = 0.995) was obtained. The electrophilicity of the acridizinium ion is clearly important whether the olefinic addend be a strong or weak nucleophile. A satisfactory correlation could not be obtained when Hammett σ_m constants were used.

In Table II can be seen a comparison of the reaction constants (ρ) obtained in studies of the rate of cycloaddition of various addends with 9-substituted acridizium derivatives; in each case ρ is based on primary σ constants, where available. As would be expected from its greater potential as an electron donor, ethyl vinyl ether gives a higher value of ρ than did the addends studied previously with the acridizinium ion, but the range of ρ values observed for the three vinyl addends is small considering the great change in polarity of the vinyl substituents. Significantly the value of ρ for ethyl vinyl ether is much smaller than the value of ρ (7.1) which has been reported[13] for the addition of vinyl ethers to tetracyanoethylene, a reaction believed to involve two steps.

Another method for studying polar influences on the cycloaddition of vinyl ethers is to use 4-substituted phenoxyethylenes (**3**, R′ = aryl). In Table III will be seen the results obtained when cycloaddition of phenoxyethylene with acridizinium perchlorate (**2**) was carried out at 65 °C in dimethyl sulfoxide.

Since the vinyl group is separated from the substituted phenyl ring by an oxygen atom, it would be predicted that the effect of the substituent would be inductive in nature. A satisfactory correlation of the reaction rates (r = 0.985) was made by a plot of log k/k_0 vs. the van Bekkum, Verkade, and Wepster[11] σ_n (Figure 2). The NMR spectra of the adducts examined did not permit us to determine whether the cycloaddition occurs stereoselectively as it has been shown[7] to do with alkyl vinyl ethers.

From activation parameters of some examples of the clas-

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Table I. Rates of Addition of Ethyl Vinyl Ether[a] to 9-Substituted Acridizinium Perchlorates (1) at 0 °C

9-Substituent, R	Registry no.	$k \times 10^3$, min^{-1}	σ_p[b]	Trials
Me	27705-56-2	0.71 ± 0.02	−0.170 ± 0.02[b]	3
H	18507-95-4	1.95 ± 0.07	0.000	3
F	1695-36-9	3.0 ± 0.2	0.062 ± 0.02[b]	3
Cl	1695-37-0	6.0 ± 0.1	0.227 ± 0.02[c]	3
COOMe	27705-64-2	12.8 ± 0.4	0.463 ± 0.02[d]	2
NO_2	27755-38-0	79.7 ± 3.9	0.778 ± 0.02[c]	2

[a] Registry no.: ethyl vinyl ether, 109-92-2. [b] Hammett para substituent constant. [c] Reference 10. [d] Reference 11.

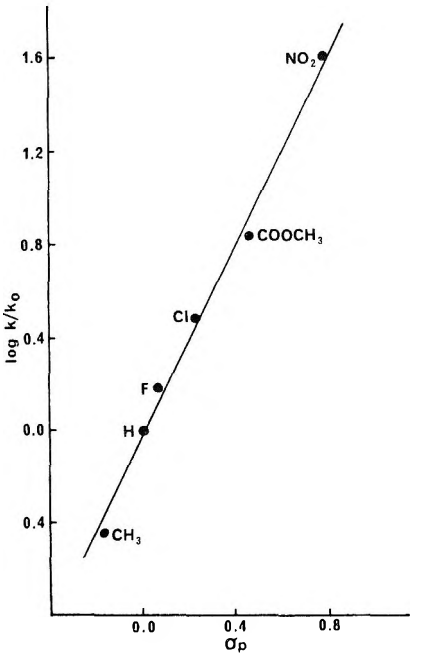


Figure 1. Plot of log k/k_0 for the cycloaddition of 9-substituted acridizinium perchlorates with ethyl vinyl ether vs. σ_p.

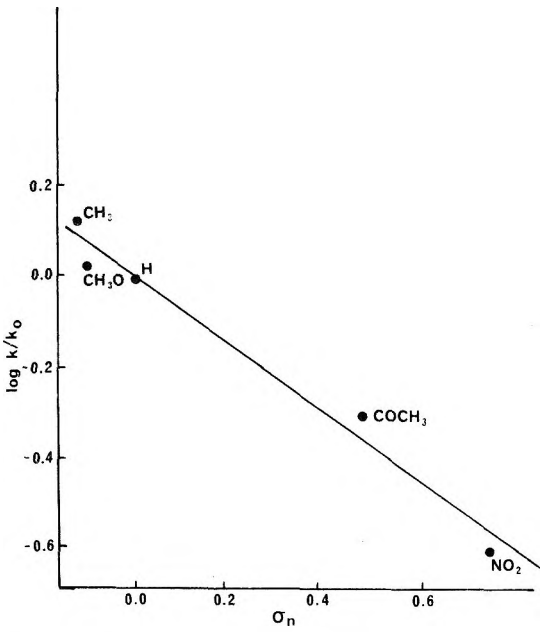
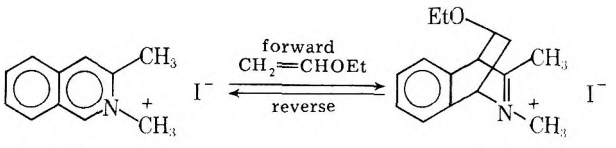


Figure 2. Hammett plot for the cycloaddition of acridizinium ion with aryl vinyl ethers at 65 °C using the σ_n of van Bekkum et al.

sical Diels–Alder reaction, it has been shown[14,15] that the geometry of the transition state for that reaction must be very similar to that of the adduct, and the generally accepted belief that the transition state is cyclic rather than linear is supported in at least one instance[15,16] by calculation of the entropies of activation for both possibilities.

Since the addition of ethyl vinyl ether to the 2,3-dimethylisoquinolinium ion (**6**) is easily reversible, the system



6 **7**

promises to be useful for comparison of the activation parameters for the reverse and forward reaction for polar cycloaddition.

The forward reaction was carried out at 0 and 25 °C using pseudo-first-order conditions. The enthalpy of activation, $\Delta H^{\ddagger}_f$, for the forward reaction was found to be 14.6 kcal/mol, slightly higher than that for the average Diels–Alder reaction,[15] while the entropy of activation, $\Delta S^{\ddagger}_f = -32.2$ eu,[17] lies within the range reported for the classical Diels–Alder (forward) reaction[15] and suggests a highly ordered transition state.

The reverse reaction can be monitored at 62.5 and 104 °C, and the kinetics observed are first order. The enthalpy of activity of the reverse reaction, $\Delta H^{\ddagger}_r$ was 26.2 kcal/mol, or 11.6 kcal/mol higher than $\Delta H^{\ddagger}_f$, but still within the range of reported Diels–Alder reverse enthalpies.[15] The negative entropy of activation, $\Delta S^{\ddagger}_r = -2.4$ eu, was quite similar to that expected for a classical retro-Diels–Alder reaction.[15] Thus, the total picture shows a highly ordered transition state which must be very close in structure to the adduct. This similarity in reaction parameters to the classical Diels–Alder reaction suggests that in polar cycloaddition there is also a cyclic rather than a linear transition state, although the possibility of a two-stage reaction is not ruled out.

Table II. Hammett Reaction Constants (ρ) Obtained by Cycloaddition of Alkenes with 9-Substituted Acridizinium Ions

Alkene	Temp, °C	ρ	r	Ref
Acrylonitrile	130	1.13 ± 0.21	0.95	4
Styrene	65	1.69 ± 0.07	0.994	9
Ethyl vinyl ether	0	2.06 ± 0.11	0.995	

Table III. Rate Data for the Cycloaddition of Acridizinium Perchlorate by Phenoxyethylenes at 65 °C

Para substituent	Registry no.	σ_n[a]	$k \times 10^3$, min^{-1}
CH_3	1005-62-5	−0.14	8.47
OCH_3	4024-19-5	−0.11	6.67
H	766-94-9	0.0	6.41
$COCH_3$	1849-92-9	0.5	3.19
NO_2	940-14-7	0.77	1.55

[a] Reference 11.

The Mechanism of Cationic Polar Cycloaddition

A mechanism for cationic polar cycloaddition must account for each of the following observations. (1) Cationic polar cycloadditions are usually 100% regioselective,[2] and where readily polarizible electron-rich alkenes are involved, very stereoselective.[6-8] The regiochemistry observed is consistent with the attack of a cation on the more negatively polarized carbon of the olefinic bond, while the 100% stereoselectivity observed with the very polar alkenes is that which would be expected if there were an electrostatic repulsion between the quaternary nitrogen atom of the alkenophile and the center of positive charge in the polarized alkene. (2) In the acridizinium ion, position 6 plays a unique role in the rate-determining process. In the cycloaddition of styrene with the acridizinium cation having a methyl group at position 6, the negative entropy of activation is much larger than for one having a methyl group at position 11, the other terminus for cycloaddition.[18] There is a significant correlation (Table III) between the log of the relative rate (k/k_0) of cycloaddition and the Hammett para substituent constant (σ_p) (but not for σ_m) for the 9-substituted acridizinium system (**1**).[4,9] For 9-substituted acridizinium cations there is also a significant correlation between the relative rate of cycloaddition and the NMR chemical shift of the proton at position 6.[19] (3) In the cycloaddition of the acridizinium ion with para-substituted styrenes it is evident that the β carbon of the vinyl group plays a unique role in the rate-controlling process. The ^{13}C NMR chemical shifts of the β carbon of the vinyl group of the para-substituted styrenes give a significant correlation with the logarithm of that relative rate of cycloaddition, while the chemical shifts of the α carbon of the vinyl group do not (see Experimental Section). (4) Activation parameters for polar cycloaddition of 2,3-dimethylisoquinolinium ion and for the retro reaction are consistent with the parameters observed for cycloadditon and retro reaction in the classical Diels–Alder reaction. (5) There is no evidence that a carbonium ion exists as an intermediate in cationic polar cycloaddition. It is now clear that earlier claims from this laboratory[20] that the very slow addition of diethyl maleate to the acridizinium ion in the presence of sodium acetate to give a mixture of cis and trans addition products are erroneous and a consequence of undetected fumarate in the (excess) maleate used. While the study of the geometrical isomer of a more reactive 1,2-disubstituted ethylene should be carried out, it seems unlikely that any lack of stereospecificity will be observed. Neither external nor internal carbonium ion traps have provided evidence for the existence of carbonium ion intermediates in cationic polar cycloaddition. With the acridizinium ion, norbornadiene gives a 90% yield of simple 1,4-addition products[21] without any evidence of the presence of nortricyclene derivatives. As pointed out earlier, this must either indicate the lack of a carbonium ion intermediate or (as now seems much less likely) one which exists for an extremely short lifetime. Since some type of sterochemical sorting-out process must be involved in a cycloaddition which (in some cases) is 100% stereoselective, a carbonium ion, in particular one that is unusually short-lived, would seem an inadequate intermediate.

In summary, the mechanism for cationic polar cycloaddition must rationalize the obvious regiochemical and stereochemical resemblance to the attack of a cation on a polarized alkene with the absence of any evidence for an intermediate carbonium ion and with the existence of reaction parameters which suggest a concerted cycloaddition reaction. The most plausible explanation, and one put forward earlier[22] in a more tentative manner, is that charge-transfer complexes exist as intermediates or as stages along the reaction pathway in cationic polar cycloaddition.

Aromatic quaternary salts are known[23,24] to play an acceptor role in charge-transfer complex formation with electron-rich donors. For example, the 2-methylisoquinolinium ion has been reported to form such complexes with iodide ion,[25] dimethylaniline,[26] polycyclic hydrocarbons,[27] or isoquinoline.[28] Indeed the phenomenon is so general that it would be difficult to doubt that π complexes exist between alkenes and the cations (e.g., **2** and **6**) which undergo polar cycloaddition with them. The question on which there is no consensus is whether the observed complexes are relevant to the mechanism of polar cycloaddition.

Considering the mechanism of the classical Diels–Alder reaction, Woodward[29] quite early arrived at the conclusion that the initial interaction leading to cycloaddition involved charge-transfer complexes. The explanation was accepted by Kloetzl[30] in a review of the cycloaddition reactions of maleic anhydride. More recent reviewers of both the Diels–Alder reaction[31] and of charge-transfer complexes[32] give serious consideration to the possible role of such complexes in cycloaddition. Konovalov[33] et al. have shown that there is a linear relationship between the rates of reaction of a series of *N*-arylmaleimides and their abilities to form charge-transfer complexes with *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine, and Tyutyulkov and Markov,[34] from LCAO–MO calculations, have shown that a π complex is formed between maleic anhydride and various condensed aromatic hydrocarbons and that a correlation exists between the delocalization energy of the π complex and the corresponding values for Brown's para-delocalization energy, which is in turn a useful measure of Diels–Alder reactivity.[35]

One of the most important recent theoretical developments in connection with cycloaddition has been the application of the frontier orbital approach.[36-39] This method has been used successfully to account for reaction rates and regioselectivity by considering the interaction of the highest occupied molecular orbital (HOMO) of the donor and the lowest unoccupied molecular orbital (LUMO) of the acceptor. It is pertinent that consideration of the same type of HOMO–LUMO interaction has been used successfully in explaining the formation of charge-transfer complexes.[40] In a recent rationalization of cycloaddition behavior by use of Hückel frontier orbitals, Mok and Nye[41] have taken as a premise that charge-transfer complexation occurs along the reaction coordinate for cycloaddition.

In cationic polar cycloaddition the observations made to date can be explained in terms of isomeric transition states which are either charge-transfer complexes or closely related to such ion structure. The differences in the energies of activation for reaction via the several regioisomeric and stereoisomeric transition states must, in most cases, arise from differences in the polar influences lying along the reaction pathway. These polar influences include the initial frontier orbital interaction.

Like the isoquinolinium ion (**6**), the acridizinium ion (**2**) appears to form weak charge-transfer complexes. When 1,2-dimethoxybenzene (veratrole) was added to acridizinium perchlorate in dimethyl sulfoxide solution there was a marked intensification of the usual yellow color and the visible absorption spectrum of the mixture was not that which results from the addition of the spectra of pure samples of the two solutes. There was a slight (4%) decrease in the absorption at 399 nm, but a more dramatic change occurred in the longer wavelength range. Whereas the uncomplexed acridizinium ion gave no perceptible absorption beyond 435 nm, at the same concentration the acridizinium ion to which 1,2-dimethoxybenzene had been added continued to absorb to about 470 nm. It was noted also that the addition of dimethoxybenzene completely quenched the fluorescence of the acridizinium ion, as does the addition of electron-rich olefins.

Like the Diels–Alder reaction in which only certain of the

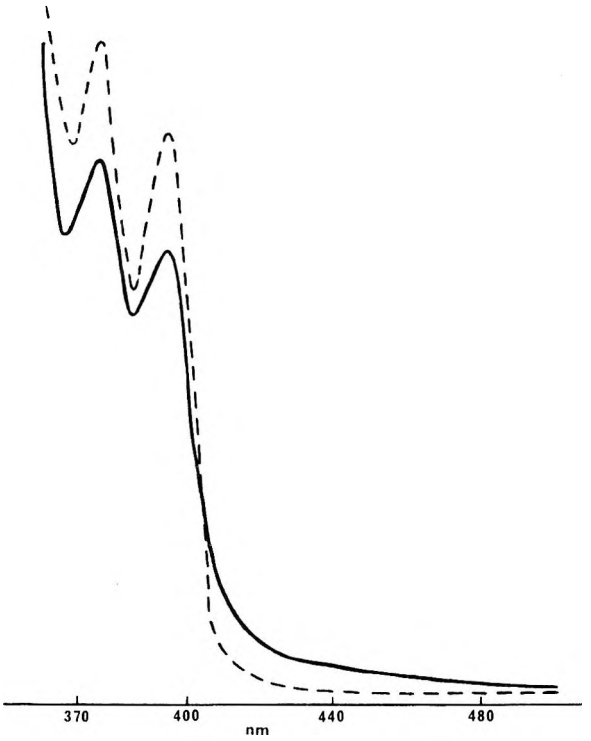


Figure 3. (A) The sum of the absorptions of individual acetonitrile solutions, one 5×10^{-4} M in acridizinium tetrafluoroborate and the other 0.2 M in *N*-vinylcarbazole (- -). (B) Absorption of a combined solution of 5×10^{-4} M in acridizinium tetrafluoroborate and 0.2 M in *N*-vinylcarbazole (–).

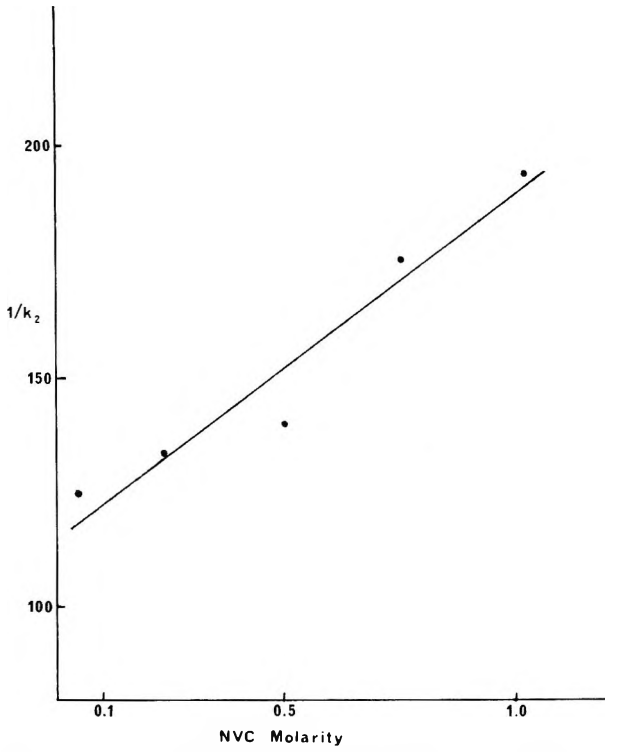
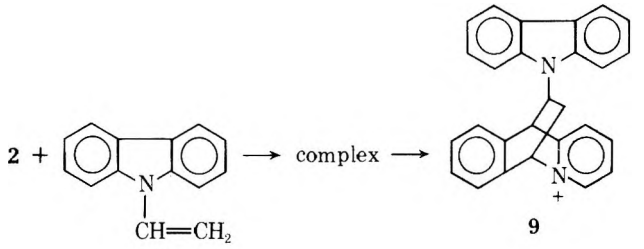


Figure 4. Second-order rate constants, k (mol^{-1} L s^{-1}), for the reaction of NVC (*N*-vinylcarbazole) with a 0.005 M solution of acridizinium tetrafluoroborate.

donor–acceptor combinations give perceptible transient color changes, only two of the more reactive alkenes studied produced similar transient color changes with the acridizinium ion. The two alkenes which showed color with the acridizinium ion were 1-morpholino-1-phenylethylene and *N*-vinylcarbazole (**8**). The latter alkene (**8**) underwent cycloaddition to form **9** slowly enough to permit a convenient quantitative spec-



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troscopic study of complex formation. Figure 3 shows the sum of the individual absorptions for a 5×10^{-4} M acetonitrile solution of acridizinium tetrafluoroborate and of a 0.2 M solution of *N*-vinylcarbazole as curve A. Curve B is for a mixture in which the two components are present at the same concentrations. Whereas the sum of the individual spectra (curve A) showed no perceptible absorption beyond 435 nm, the vinylcarbazole–acridizinium mixture (curve B) continued to absorb beyond 480 nm, a characteristic evidence[42] of charge-transfer interaction. This tailing of the spectrum arises from a lowering of the energy[43] of the π^* orbital (lowest unoccupied molecular orbital) in the acridizinium ion. Since this is the orbital of the acridizinium ion most closely involved in cycloaddition reactions,[44] the change is in accord with predictions based on frontier orbital theory.[36b,38b,45] Frontier orbital theory may also explain[46] the quenching of fluorescence observed when acridizinium ion is treated with vinylcarbazole or other electron-rich molecules.

As a possible test for complex formation during cycloaddition, Andrews and Keefer[47] determined whether the pseudo-first-order rate constants obtained when an excess of maleic anhydride (or chloromaleic anhydride) reacted with 9,10-dimethylanthracene increased directly with an increasing concentration of the anhydride and whether the apparent second-order rate constant remained constant under these conditions. The failure of the reaction to meet these tests was offered as evidence that a considerable quantity of the hydrocarbon was complexed.

A parallel behavior has been observed for the cycloaddition of the acridizinium ion in the presence of excess *N*-vinylcarbazole in the concentration range found to give pseudo-first-order kinetics. A plot (Figure 4) of the apparent second-order rate constant vs. olefin concentration shows the expected decline in the rate constant with increased concentration of the olefin ($r = 0.97$). Following the treatment of Andrews and Keefer,[47] an equilibrium constant, $K = 0.65$ mol^{-1} L, was obtained for the complexation reaction.

A possible alternative explanation for the observed change in rate constant might be that polar cycloadditions may be highly susceptible to slight changes in the polarity of the solvent, such as those produced when the concentration of the alkene is changed. While the effect of solvent polarity on the rate of cycloaddition of the acridizinium ion with *N*-vinylcarbazole has not been studied, it is known that for the addition of styrene to the same substrate the ratio of the rate of addition in ethyl acetate to that in dimethyl sulfoxide is only 1.3, indicating that great changes in solvent polarity have but little effect on the rate of polar cycloaddition. There is certainly no evidence for the existence of the extremely large effects of solvent polarity which would be needed as an alternate explanation for the apparent change in the second-order rate constant shown in Figure 4.

While the demonstration that a charge-transfer complex exists when a very reactive alkene adds to the acridizinium ion, it does not prove that the complex is an intermediate rather than an irrelevant side reaction[48] of the cycloaddition. In view

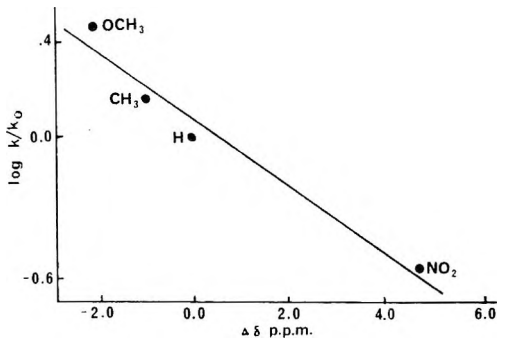
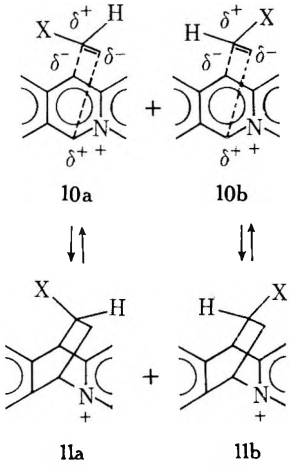


Figure 5. Plot of log k/k_0 vs. the reported[55] ^{13}C NMR chemical shift values for the β carbon of para-substituted styrenes.

of the successful application of frontier orbital calculations to both charge-transfer complex formation[49] and to cycloaddition,[34-37] it would seem remarkable if for a single cation there were two distinct types of frontier electron interaction, one leading only to complex formation and the other exclusively to cycloaddition. Since a charge-transfer complex can form without the creation of a true σ bond, no carbonium ion need be formed. The orientation of this molecular complex (**10a** or **10b**) must determine both the regiochemistry and stereochemistry of the adducts (**11a** or **11b**). If X represents



a group which can easily release electrons, the center of positive charge of the alkene moiety of the complex (**10**) would lie further along the C–X bond than if the group were less polarizable. In a complex in which such a polarization of the C–X band had occurred, coulombic repulsion would make geometrical isomer **10a** of lower energy than **10b**, in which the centers of positive charge lie closer together. The differences in energy between **10a** and **10b** would not be large even for highly polarized X groups, and it is not remarkable that when X is less highly polarizable, addition occurs with only moderate stereoselectivity.

Arguments offered for the existence of charge-transfer complexes in the the classical Diels–Alder reaction[41] where both donor and acceptor molecules are uncharged become even more cogent in the case of cationic polar cycloaddition in which the acceptor is actually a cation. Certainly the proposal of a π complex preceding σ-bond formation is consistent with currently accepted[50] mechanisms for the addition of other cationic reagents to alkenes and affords the best explanation of how a cation can participate in essentially a two-stage reaction without the creation of an intermediate carbonium ion.

Experimental Section

Melting points were taken in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were determined with a Varian A-60 or T-60 instrument or a Joelco MH 100 spectrometer using tetramethylsilane as an internal standard. A Beckman Model DB-G spectrometer was used to measure the rates of addition or cycloreversion.

Rates of Cycloaddition of Ethyl Vinyl Ether to 9-Substituted Acridizinium Perchlorates (1). The 9-substituted acridizinium derivatives were prepared as previously described.[9] All solvents were freshly distilled before use. A small quantity of hydroquinone was added to the stock solutions of ethyl vinyl ether to retard polymerization.

To 1 mL (0.05 mmol) of a 0.05 M solution of the substituted acridizinium perchlorate in acetonitrile at 0 °C was added 1 mL (0.5 mmol) of 0.5 M ethyl vinyl ether in acetonitrile at 0 °C. The mixture was maintained at 0 ± 0.2 °C by use of an ice bath (Dewar flask). The progress of the reaction was followed by observing the disappearance of the absorption (A) at the long wavelength maximum in the visible spectrum. Samples were prepared by a 100 μL/50 mL dilution with 95% ethanol. The rate for each trial was obtained by a nonweighted least-squares fit of $-\log A$ vs. time. The reported rate (Table I) is an average of 2–3 trials.

Phenoxyethylenes (3). All of the phenoxyethylenes used in our study are known compounds prepared by the action of potassium *tert*-butoxide on the appropriate 2-bromoethyl phenyl ether essentially following the directions given by Dombroski[51] for the preparation of 4-nitrophenoxyethylene.

The method of purification and observed physical constants of the vinyl ethers follow.

Phenyl: by repeated distillation, bp 30 °C (0.4 mm) [lit.[52] bp 54 °C (17 mm)]; IR (neat) 6.04, 6.24, 6.68, 7.18, 7.60, 8.04 (brd), 8.60 (brd), 9.24 (s), 10.40 (brd), 11.64, 12.44, 13.24, 14.44 μm.

***p*-Nitrophenyl:** by chromatography on silica gel using 30–60 °C petroleum ether followed by benzene as eluents and sublimation followed by recrystallization, nearly colorless, mp 56–58 °C (lit.[51] 55–56 °C); NMR ($CDCl_3$) δ 4.8 (complex, 2, vinyl), 6.61 (q, 1, vinyl), 7–9.1 (complex, 4, aromatic).

***p*-Tolyl:** by distillation, bp 44–46 °C (0.6 mm) [lit.[52] 72.5 °C (17 mm)], followed by chromatography on silica gel; NMR ($CDCl_3$) δ 2.27 (s, 3, Me), 4.5 (complex, 2, vinyl), 6.6 (q, 1, vinyl), 7.0 (q, 4, aromatic).

***p*-Methoxyphenyl:** by distillation, bp 53–54 °C (0.8 mm) [lit.[52] 91.0–91.5 °C (12 mm)], and further purified by column chromatography on silica gel; NMR ($CDCl_3$) δ 3.76 (s, 3, Me), 4.50 (complex q, 2, vinyl), 6.61 (q, 1, vinyl), 6.95 (d, 4, aromatic).

***p*-Acetylphenyl:** by distillation, bp 81–85 °C (0.4 mm) [lit.[53] bp 128.5 °C (13 mm)], and chromatography on silica gel; NMR ($CDCl_3$) δ 2.52 (s, 3, Me), 4.78 (complex q, 2, vinyl), 6.75 (q, 1, vinyl), 7.1–8.02 (complex, 4, aromatic).

Rates of Cycloaddition of Phenoxyethylenes to the Acridizinium Ion (2 → 5) at 65 °C. The rate studies were carried out in dimethyl sulfoxide solution as described earlier for the cycloaddition of styrene,[9] a ratio of 10 mol of phenoxyethylene to 1 mol of acridizinium being used to assure pseudo-first-order kinetics. Each rate was measured in triplicate and was reproducible within approximately 5%. With *p*-nitrophenoxyethylene a small correction factor was needed to compensate for absorption by the olefin at 397 nm. Correlation coefficients for plots of ln $1/A$ vs. time were in all cases greater than 0.99. The data are recorded in Table III.

Adducts (5, R′ = Aryl) Obtained by Reaction of Acridizinium Perchlorate (2) with Aryl Vinyl Ethers. (A) With *p*-Methoxyphenyl (3, R′ = *p*-$CH_3OC_6H_4$): A mixture containing 0.5 g of acridizinium perchlorate[54] and 0.3 g of *p*-methoxyphenyl vinyl ether in 50 mL of acetonitrile was refluxed for 18 h. The solvent was removed under vacuum, and the residue was triturated with ether. A portion of the resulting solid was reserved for NMR analysis and a portion recrystallized from ethanol, mp 218–219 °C; NMR (crude product in $CDCl_3$) δ 1.78 (s, 3), 5.05 (brd s, 1), 5.57 (d, 1), 6.6–8.6 (complex, 14), 9.30 (d, 1).

Anal. Calcd for $C_{22}H_{20}NClO_6$: C, 61.47; H, 4.69; N, 3.26. Found: C, 61.43; H, 4.72; N, 3.03.

(B) With *p*-Nitrophenyl (3, R′ = *p*-$NO_2C_6H_4$): The acridizinium adduct (**5**, R′ = *p*-$NO_2C_6H_4$) was prepared similarly, mp 218.5–220 °C.

Anal. Calcd for $C_{21}H_{17}N_2ClO_7$: C, 56.70; H, 3.85; N, 6.30. Found: C, 56.51; H, 3.71; N, 6.22.

Activation Parameters for the Cycloaddition of 2,3-Dimethylisoquinolinium Iodide (6) with Ethyl Vinyl Ether. The rate constants for the cycloaddition were determined at 0 °C as described earlier[19] and in essentially the same way at 25 °C. The enthalpy of activation was calculated from plots of ln k/T vs. $1/T$. The $\Delta G^{\ddagger}_f$ and $\Delta S^{\ddagger}_f$ were calculated by means of eq 1 and 2. The observed

rate constants were $0.062 \pm 0.002 \times 10^3$ min^{-1} at 0 °C and $0.61 \pm 0.006 \times 10^3$ min^{-1} at 25 °C.

$$k = \frac{KT}{h} e^{-\Delta G^{\ddagger}/RT} \quad (1)$$

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \quad (2)$$

Activation Parameters for the Cycloreversion of the 2,3-Dimethylisoquinolinium Iodide–Ethyl Vinyl Ether Adduct (7). In a three-neck round-bottom flask equipped with a nitrogen inlet tube, stopper, condenser, and a magnetic stirring bar was placed 50 mL of dimethylformamide, and the gas inlet tube was adjusted so that nitrogen bubbled slowly through the liquid. The flask was heated in a silicone oil bath at 62.5 ± 0.5 °C (or 104 ± 0.5 °C). When the flask and its contents had reached bath temperature, 89.0 mg (0.250 mmol) of the cycloadduct was added, and the mixture was stirred vigorously with nitrogen bubbling slowly through the solution. The progress of the decomposition was followed by observing the increase of the long wavelength absorption in the UV spectrum of the 2,3-dimethylisoquinolinium ion. Samples slightly larger than 100 μL were withdrawn and cooled in ice. Exactly 100 μL of the cold solution was diluted to 10 mL with 95% ethanol for the UV analysis. The rates were obtained by plotting −log (cycloadduct) vs. time. The rate constants ($k \times 10^3$ min^{-1}) were found to be 1.08 at 62.5 °C and 93.8 at 104 °C.

Correlation of Log of Relative Rate (k/k_0) for Cycloaddition of Para-Substituted Styrenes with Published Data for the ^{13}C Chemical Shifts. The availability[55] of C_α and C_β ^{13}C chemical shifts for several para-substituted styrenes made it possible to determine whether these parameters were related to the relative rate of cycloaddition[56] of these styrenes with acridizinium perchlorate. The rate constants ($\times 10^{-2}$ min^{-1}) observed at 100 °C for the reaction of the para-substituted styrenes with acridizinium perchlorate were as follows: MeO, 15.0 ± 0.7; Me, 7.4 ± 0.4; H, 5.1 ± 0.3; NO_2, 1.5 ± 0.1. A plot of log k/k_0 vs. the reported ^{13}C chemical shifts of the β carbon of the styrene side chain is shown in Figure 5. The correlation constant (r = 0.985) shows an acceptable[12] correlation ($r \geqq 0.95$). The slope of the line is 0.14 ± 0.02 Hz^{-1}. A similar plot of log k/k_0 vs. the ^{13}C chemical shift of the α carbon of the styrene side chain has a slope of 0.35 ± 0.38 Hz^{-1} and an unacceptable correlation constant of 0.61.

Investigation of Charge-Transfer Interaction. The acetonitrile used as solvent was shown to be transparent in the spectral range studied. Separate stock solutions of acridizinium tetrafluoroborate, 1×10^{-3} M, and thrice recrystallized *N*-vinylcarbazole, 0.4 M, were prepared. Individual spectra were made after dilution of the proper stock solution with an equal volume of solvent, while the solution of the complex was made by addition of equal volumes of the two stock solutions. The spectra are shown in Figure 3.

The rate studies were again carried out essentially as described earlier[9] using a constant acridizinium tetrafluoroborate concentration of 0.005 M in dimethyl sulfoxide solution and various concentrations of thrice recrystallized *N*-vinylcarbazole. The reaction was monitored by dilution of 100-μL aliquots to 5 mL with methanol and measuring the absorption at 395 nm using 1-cm quartz cells. Pseudo-first-order kinetics were observed at all of the *N*-vinylcarbazole concentrations studied. A plot of the change in second-order rate constant with change in *N*-vinylcarbazole concentration is shown in Figure 4. The treatment of Andrews and Keefer[47] was followed in the calculation of the equilibrium constant.

Effect of Solvent Polarity on the Rate of Cycloaddition of Styrene with Acridizinium Hexafluorophosphate. Stock solutions, each 1.0×10^{-4} M in the acridizinium salt, were prepared using ethyl acetate or dimethyl sulfoxide as the solvent. To 150 mL (1.5×10^{-5} mol) of the acridizinium salt solution was added 4.3 mL (3.75×10^{-2} mol) of styrene, and the mixture was heated in a thermostat at 66 °C. Samples were withdrawn periodically, cooled rapidly, and transferred directly to a spectrophotometer cell. Calculations made in the usual way gave pseudo-first-order rate constants k(ethyl acetate) = 9.1×10^{-3} min^{-1} and k(dimethyl sulfoxide) = 6.8×10^{-3} min^{-1}.

Registry No.—*N*-Vinylcarbazole, 1484-13-5; **5** (R′ = *p*-$MeOC_6H_4$), 64740-21-2; **5** (R′ = *p*-$NO_2C_6H_4$), 64682-17-3; **6**, 32431-36-0; **7**, 64682-18-4; *p*-methoxystyrene, 637-69-4; *p*-methylstyrene, 622-97-9; styrene, 100-42-5; *p*-nitrostyrene, 100-13-0.

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Pyridopyrimidines. 9. An Unusual Rearrangement in the 8-Substituted Pyrido[2,3-*d*]pyrimidine Series. Application of the Selective Nuclear Overhauser Effect to Unambiguous Proton Chemical Shift Assignment

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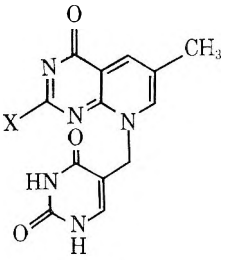
The synthesis of a series of 8-substituted pyrido[2,3-*d*]pyrimidines, the prototype of which was 5-(6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine-8-yl)methyluracil (**6**), is reported. A facile rearrangement of the uracil-methyl moiety from N-8 to N-3 of the pyridopyrimidine was observed. The sites of alkylation on the various pyridopyrimidines were established in part by ^{1}H NMR. Unequivocal assignment of the various proton signals was made by the first application of a new ^{13}C NMR technique, selective nuclear Overhauser effect (SNOE), to so complex a system of spins. The mechanism of the rearrangement was determined to be inter- rather than intramolecular by crossover experiments in which the rearrangement of an 8-substituted pyridopyrimidine in the presence of a different pyridopyrimidine gave a mixture of both 3-substituted pyridopyrimidines. Further details of the mechanism are discussed.

As a part of a program directed toward the synthesis of "transition state" inhibitors of thymidylate synthetase, the synthesis of some model 5-(pyrido[2,3-*d*]pyrimidin-8-yl)-methyluracil derivatives was undertaken. These models (**1**)



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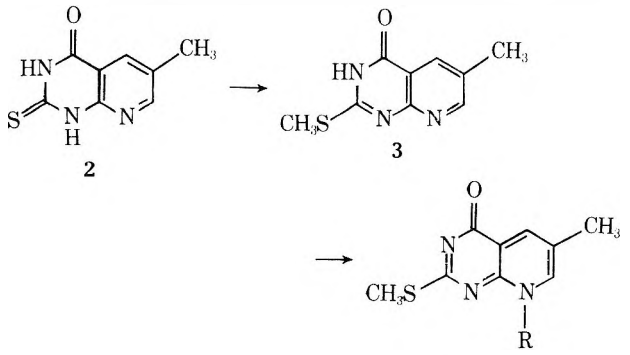
contain certain structural elements which have been implicated[2,3] in the one-carbon transfer from a reduced folate to 2′-deoxyuridylic acid in the synthesis of thymidylic acid.

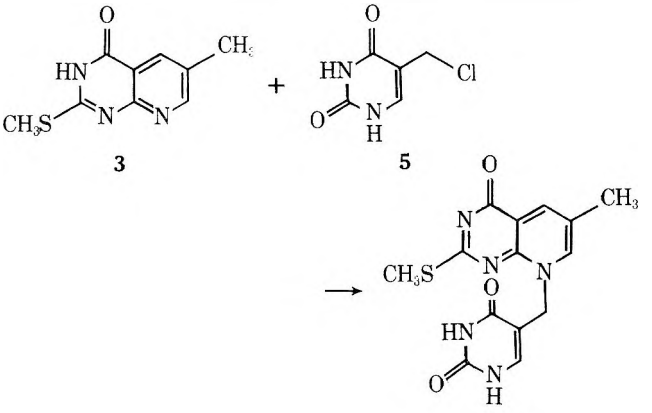
It was established from previous studies that the site most readily alkylated in pyrido[2,3-*d*]pyrimidines containing an aromatic pyridine ring in neutral aprotic solvent was N-8.[4] Alkylation of 6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]-pyrimidine (**3**) (prepared by methylation of the corresponding 2-thione derivative **2**[5]) with alkyl halide (e.g., methyl iodide, 1-bromo-3-methyl-2-butene) in anhydrous dimethylformamide gave the 8-alkylpyrido[2,3-*d*]pyrimidine derivatives **4a** and **4b**. A large bathochromic shift (about 50 nm) in the UV



2 **3**

4a, R = CH_3
b, R = $(CH_3)_2C{=}CHCH_2$-

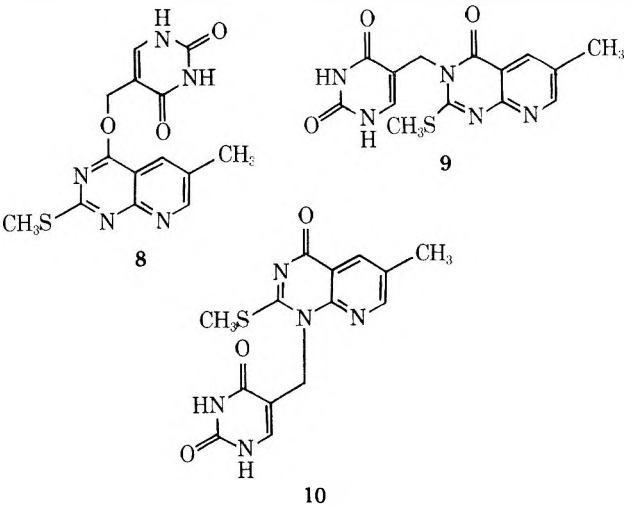
maxima of neutral and anionic species, the similarity (342 nm for **3** and 345 nm for **4**) in acidic solution, and a downfield shift of 0.30 ppm of the pyridine γ proton in the ^{1}H NMR spectrum (vide infra) confirmed the site of alkylation.[4] In a similar reaction, carried out under identical conditions, alkylation of **3** with 5-chloromethyluracil (**5**)[6] gave 5-(6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidin-8-yl)methyluracil (**6**). The



3 **5** **6**

site of alkylation was confirmed by the similarity of the UV spectrum and the proton chemical shifts with those of **4**.

An attempted crystallization of **6** from dimethylformamide–water gave a colorless compound whose UV spectrum was completely different from that of **6**. Elemental analysis indicated that the new compound was a structural isomer of **6**. ^{1}H NMR spectral data revealed that the aromatization of the pyridine moiety had occurred, as shown by the similarity of α- and γ-pyridine proton chemical shifts with those of **3**. The above facts suggested that a rearrangement occurred during crystallization. Three possible structures (**8**–**10**) can be written



8 **9** **10**

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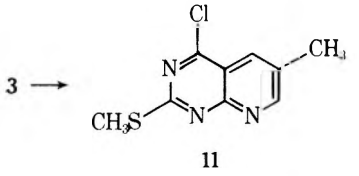
for the new compound. Structure **8** was eliminated from consideration by comparison of the UV spectrum of the product with that of 4-methoxy-2-methylmercapto-6-methylpyrido[2,3-*d*]pyrimidine (**12**), prepared from **3** by



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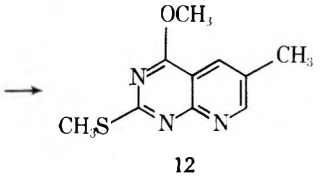

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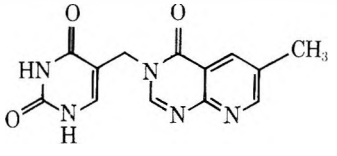
treatment with phosphorus oxychloride followed by a nucleophilic displacement of the 4-chlorine in **11** by methoxide. Though these spectra eliminated structure **8**, it was not possible to differentiate between structures **9** and **10** on the basis of UV spectral evidence.

Raney nickel dethiation of the rearrangement product **8** (or **10**) gave a new compound **13**, with a molecular ion at *m/e* 285. The absence of the 2-CH_3S group was evident in the ^1H NMR spectrum by the disappearance of $-SCH_3$ at δ 2.66 and the appearance of a singlet at δ 8.55. The UV spectrum of this compound (at pH 1, 7, and 11) closely resembled that of 3-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**14**), the structure of which had been established by an unambiguous synthetic procedure.[4] On the basis of these data the structure of **13** was



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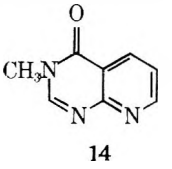

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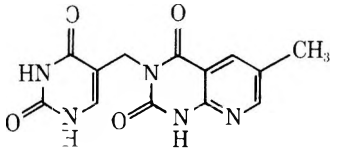
established to be 5-(6-methyl-4-oxopyrido[2,3-*d*]pyrimidin-8-yl)methyluracil. Therefore the structure of the rearrangement product should be **9** rather than **10**.

To confirm the structure **9** the compound was hydrolyzed in 18% HCl to **15**. The UV spectrum closely resembled that of **16**[4] in acidic, neutral, and basic solutions.



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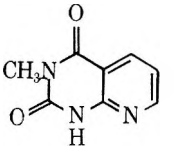

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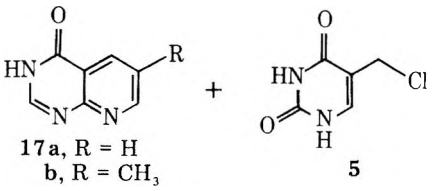
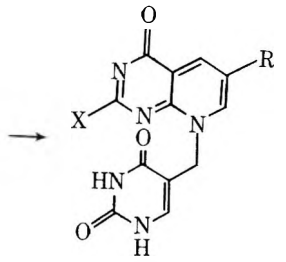
Alkylation of 4-oxopyrido[2,3-*d*]pyrimidine (**17a**) and its 6-methyl derivative **17b** with 5-chloromethyluracil (**5**) gave the 5-(4-oxopyrido[2,3-*d*]pyrimidin-8-yl)methyluracils (**18**).

These compounds also underwent rearrangement to give **19** and **13**; the latter was identical with the one (**13**) obtained by Raney nickel dethiation of **9**. The above rearrangements were readily carried out by refluxing the compounds in dimethylacetamide for 5–10 min, or in the case of **18**, simply by dissolution in Me_2SO. It is noteworthy that the presence of a methylthio group at C-2 of the pyridopyrimidine in **6** afforded some stabilization; it was necessary to heat Me_2SO solutions of **6** for several minutes at ~50 °C to effect complete rearrangement.

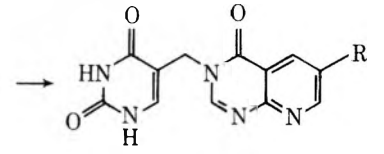
In order to assess the importance of an ionizable proton on the uracil moiety in promoting the rearrangement, a 1,3-



17a, R = H
b, R = CH_3 **5**

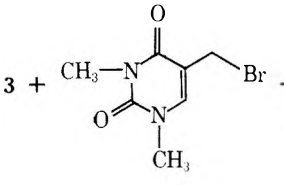


18a, R = H
b, R = CH_3



19, R = H
13, R = CH_3

dimethyluracil derivative was prepared. The alkylating agent selected was 5-bromomethyl-1,3-dimethyluracil (**21**). Methylation of 5-benzyloxymethyluracil[7] gave the 1,3-dimethyl derivative, which was converted to 5-bromomethyl-1,3-dimethyluracil (**21**) by treatment with HBr in dioxane. The reaction of **3** with the 5-bromomethylpyrimidine **21** gave the expected 1,3-dimethyl-5-(6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidin-8-yl)methyluracil (**22**). Both **22** and the



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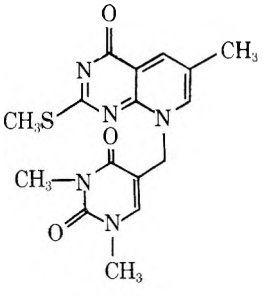


22

8-(3-methyl-2-butenyl) derivative **4b** were stable in DMF at reflux (2 days) and could be recrystallized from ethanol.

Nuclear Magnetic Resonance Studies

Proton magnetic resonance spectra have been used in the assignment of the site of alkylation of the pyrido[2,3-*d*]pyrimidine nucleus in the following manner. Alkylation at the pyridine nitrogen of an aromatic pyridine,[8] pyrido[2,3-*d*]-pyrimidine,[4] or other fused-ring system containing a pyridine ring[9] leads to downfield shifts of the pyridine γ proton and either upfield or downfield shifts, generally of smaller magnitude, of the α proton (the "α effect"[10]). Alkylation of a lactam system (for example N-1 or N-3 of **17**), on the other hand, leads to a pronounced downfield shift of an adjacent proton signal with almost no effect on other proton chemical shifts.[4,11] This technique was used in an earlier study in his series to assign the site of methylation and ribosylation of 4-oxo- and 2,4-dioxopyrido[2,3-*d*]pyrimidines.[4] It is obvious that the success of the technique relies on accurate assignments of the pyridine α and γ signals (pyrido[2,3-*d*]pyrimidine H-7 and H-5, respectively). In the previous study,[4] the more downfield of the two proton signals was assigned to H-7 in accord with numerous studies on pyridines and fused pyridines.[12] The

Table I. ^{1}H NMR Chemical Shifts for a Series of Pyrido[2,3-*d*]pyrimidines

Compd	Registry no.	Chemical shift, δ[a]					
		H-2	H-5	H-6	H-7	$-CH_2-$	H-6′ [b]
3	64600-46-0		8.23		8.73		
4b	64600-47-1		8.53		8.68		
6	64600-48-2		8.53		8.67	5.26	7.70
9	64600-49-3		8.28		8.78	4.92	7.12
13	64600-50-6	8.55	8.27		8.80	4.78	7.62
15[c]	64600-51-7		8.57		8.97	5.15	7.97
17a	24410-19-3	8.40	8.53	7.57	8.98		
17b	64600-52-8	8.20	8.25		8.73		
18a[c]	64600-53-9	8.70	9.30	8.03	9.50	5.90	8.33
18b[c]	64600-54-0	8.80	9.37		9.53	5.98	8.50
19	64600-55-1	8.63	8.50	7.53	8.93	4.79	7.63
22	64600-56-2		8.55		8.72	5.40	8.07
23	21038-66-4		8.23	7.22	8.57		
24	49738-87-6		8.07		8.45		

[a] Unless otherwise noted, ^{1}H NMR spectra were recorded at 60 MHz in Me_2SO-d_6 with DSS (sodium 2,2-dimethyl-2-dimethyl-2-silapentanesulfonate) as internal reference. [b] H-6′ refers to the proton at position 6 of the uracil moiety. [c] Trifluoroacetic acid with internal Me_4Si; rapid rearrangement occurred in Me_2So-d_6.

Table II. ^{13}C NMR Chemical Shifts[a] and ^{13}C–Proton Coupling Constants[b] for a Series of Pyrido[2,3-*d*]pyrimidines at 89 °C

Compd	C-2	C-4	C-4a	C-5	C-6	C-7	C-8a
17a	149.4 (204.9, z)	162.5 (6.5, 4.0)	118.9 (7.2)	136.4 (165.5, 6.3, 2.3)	123.2 (166.7, 6.8, 1.6)	156.4 (179.8, 7.9, 3.8)	159.5 (12.0, 6.0)
23	151.2 (z)	163.1 (4.3)	111.0 (7.5, 1.3)	137.2 (166.3, 6.6, 2.2)	119.7 (168.1, 7.5, 1.3)	155.3 (180.6, 5.8, 3.7)	153.4 (9.9, 6.0)
24	151.1 (z)	163.2 (3.8)	110.4 (z)	136.8 (164.5, m)	129.0 (z)	155.7 (178.0, m)	151.4 (o)
3	160.5 (o)	162.8 (3.9)	115.4 (z)	135.7 (164.1, m)	131.7 (o)	156.9 (177.2, m)	159.6 (10.8, 6.0)

[a] Referenced to internal dioxane at 67.4 ppm with an accuracy of ±0.2 ppm. The chemical shift of the 6-methyl carbon in **22** and **3** is 18.0 and 18.3 ppm, respectively. The $-S^{13}CH_3$ chemical shift in **3** is 13.6 ppm. [b] ^{13}C–^{1}H coupling constants (listed in parentheses) are in units of hertz with an accuracy of ±0.5 Hz. The following abbreviations are used: (m) complicated multiplet from long-range coupling to methyl and other ring protons; (o) long-range couplings not analyzable due to overlapping structure; (z) no long-range couplings to within experimental error.

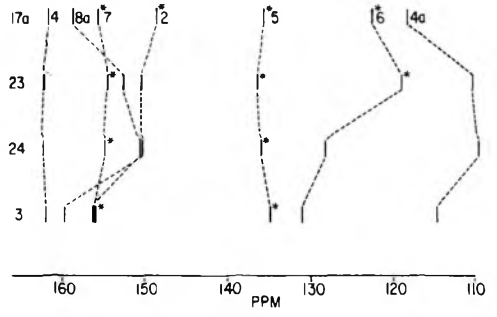
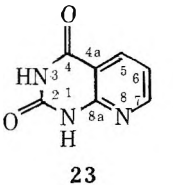


Figure 1. ^{13}C NMR chemical shift correlation diagram. Methine carbon resonances are indicated by asterisks. Chemical shifts are referenced to Me_4Si.

greater downfield shift of the higher field (H-5) proton signal upon alkylation was used to assign the site as N-8.

Subsequently a study on the synthesis, ^{1}H NMR, and ^{13}C NMR of a series of closely related pyrido[2,3-*d*]pyrimidines appeared in which these proton chemical shift assignments were reversed[5] without, however, reference to the earlier publication.[4] This report[5] clearly necessitated a reexamination of the original assignments and a reevaluation of the ^{1}H NMR technique described above for the assignment of the site of alkylation. In order to resolve these questions,[13] the following set of pyridopyrimidines was selected for further study: 4-oxo- (**17a**),[14] 2,4-dioxo- (**23**), 2,4-dioxo-6-methyl- (**24**),[5,15] and 6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine (**3**).



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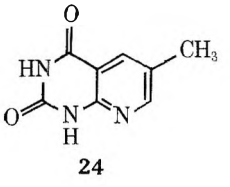

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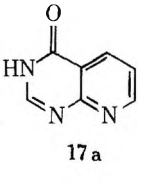


17a

A detailed analysis of the ^{1}H NMR and ^{13}C NMR spectra of compounds **23, 24, 3,** and **17a** was undertaken. The proton spectra (Table I) were unambiguous except for the assignment of H-7 and H-5; the assignments for the other nonexchangeable protons for **17a, 23,** and **24** were reported earlier.[4,5] It remained then to remove the ambiguity in the assignment of H-5 and H-7. The procedure to be followed was to obtain accurate ^{13}C NMR assignments for the compounds under study, then to observe the effect of selective saturation[16] of the ^{13}C satellites in the ^{1}H NMR spectrum on the ^{13}C NMR signals.

The ^{13}C NMR data are presented in Table II, and the correlation diagram for the ^{13}C chemical shifts is shown as Figure 1. The chemical shift assignments were based on the following analysis of spectroscopic data. The fully proton-coupled spectrum of each compound was compared with the proton-decoupled spectrum. Carbon resonances associated with di-

rectly bonded protons were immediately identified by the large (164–205 Hz) splitting patterns. These methine ^{13}C chemical shifts are indicated by an asterisk in Figure 1, and the values of $^{1}J_{^{13}C-^{1}H}$ are listed in parentheses in Table II. The long-range $J_{^{13}C-^{1}H}$ values are also listed, although they were not identified by selective proton-decoupling experiments. Because of the limited digital resolution of the spectrometer and because only simple first-order analysis was applied to interpret the coupled spectra, couplings <1.5 Hz were not reported and the estimated error limits were correspondingly large. However, the effects of long-range coupling, both resolved and unresolved, were used to assign resonances to specific carbons. For example, the two high-field methyl resonances of **3** were differentiated by the sharpness of the 1:3:3:1 quartet centered at 13.6 ppm, which contrasted with the diffuse 1:3:3:1 quartet at 18.0 ppm. Since the methyl group at C-6 can exhibit long-range coupling to H-5 and H-7, while $-S^{13}CH_3$ has no near protons that are not in rapid exchange, the assignment is unquestionably correct, but qualitative with respect to long-range coupling constants.

The methine ^{13}C resonances were assigned by considering both the chemical shifts and the magnitude of $^{1}J_{^{13}C-^{1}H}$. It has been shown[17,18] that the carbon α to the nitrogen atom in pyridine-like aromatic systems resonates at lower field than either the β or γ carbons and that $^{1}J_{^{13}C_{\alpha}-^{1}H}$ is approximately 15 Hz larger than $^{1}J_{^{13}C_{\beta}-^{1}H}$ and $^{1}J_{^{13}C_{\gamma}-^{1}H}$.[17] This empirical rule identified C-7 in all four compounds studied here. C-2 in **17a** was identified by the unique magnitude of $^{1}J_{^{13}C-^{1}H}$ and the *absence* of long-range couplings. C-6 was identified in **24** and **3** by the characteristic 9–10 ppm downfield shift of one of the two remaining (C-5 and C-6) methine resonances in **23** when the proton was replaced by a methyl group.[19] By elimination, the remaining ^{13}C absorption with a proton directly bonded must have been C-5; in addition, this absorption frequency was relatively constant over this closely related series. Thus, from low to high field, these carbon resonances occurred in the order C-7, C-5, and C-6. It should be noted that the long-range coupling patterns are in total qualitative agreement with these conclusions.

The quaternary carbon assignments are included for completeness; they were based on long-range coupling patterns and conclusions drawn from the chemical shift correlation diagram. C-4a was the highest field quaternary ring carbon resonance, and was thus easily identified in **23** and **17a.** In **24** and **3** the quaternary resonances at 129.0 and 131.7 ppm were previously assigned to C-6 on the basis of the methyl substituent effect;[19] thus, by the process of elimination, the upfield resonances were C-4a. The long-range splitting patterns were entirely consistent if it were assumed that $^{2}J_{^{13}C-^{1}H}$ to H-5 was 1.3 Hz or less and $^{3}J_{^{13}C-^{1}H}$ to H-6 in **23** and **17a** was about 7.4 Hz. The furthest downfield resonance for each compound was assigned as C-4; this assignment gave a consistent $^{3}J_{^{13}C-^{1}H}$ of about 4 Hz with H-5, as well as an additional three-bond coupling constant of 6.5 Hz with H-2 in **71a.** The chemical shifts of C-4 are remarkably constant over this series of compounds. C-2 was identified by its very sharp resonances in **23, 24,** and **17a,** indicating the absence of any nearby nonexchanging protons that could provide fine structure or broadening. In **3** C-2 was assigned by the process of elimination, since it was overlapped with the fine structure of C-7. The long-range couplings of C-8a were used for conclusive identification in **23, 17a,** and **3.** In **17a** the doublet of doublets was quite broad, indicating a third unresolved $^{3}J_{^{13}C-^{1}H}$. In **24** all other resonances were identified, so C-8a was assigned by default to 151.4 ppm. The assigned order of carbon signals, from low to high field, for **24** was established as C-4, C-7, C-8a, C-2, C-5, C-6, C-4a, C-methyl. This may be contrasted with the earlier reported order[5] of C-4, C-5, C-2 = C-8a, C-7, C-4a, C-6, C-methyl. Thus, by utilizing the coupled and decoupled

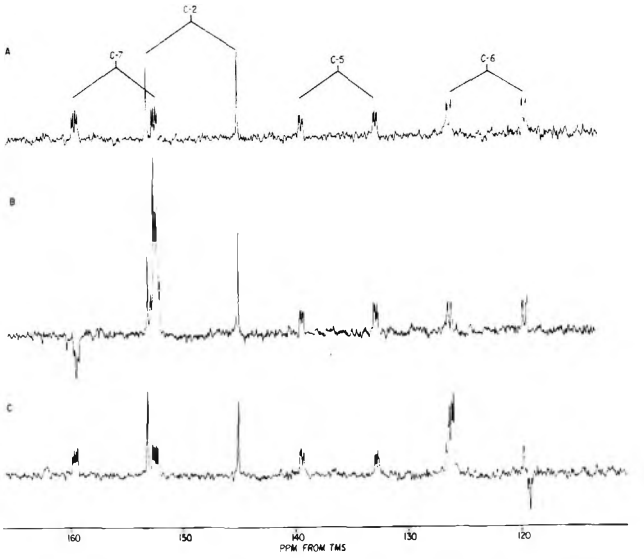


Figure 2. The proton-coupled ^{13}C NMR spectrum of 4-oxopyrido[2,3-*d*]pyrimidine (**17a**). Transients (20 000) of 2 s each and a 90° flip angle were accumulated, weighted, and Fourier transformed to give the above spectra. The quaternary carbons are saturated under these conditions, and hence not visible. (A) Proton decoupler *off* at all times, giving a reference intensity pattern. (B) Same as A except proton decoupler *on* continuously at approximately −18 dBm at 90 Hz downfield from 8.98 ppm. (C) Same as B except decoupler frequency at 83 Hz upfield from 7.57 ppm. Very small decoupling effects in B and C are evident, since it was necessary to saturate a spectral region of about 15 Hz to effect the SNOE.

^{13}C NMR spectra in conjunction with two highly reliable empirical rules, the ^{13}C NMR spectra were completely assigned with high confidence in their accuracy.

Once the carbon assignments were firmly established, it became possible to make unequivocal assignments of the H-5 and H-7 proton signals for each of these compounds. The method used was the recently described[16] selective nuclear Overhauser effect (SNOE); this represents the first practical application of this useful technique for unambiguous proton signal assignments in complex organic molecules.

The $^{13}C-^{1}H$ one-bond coupling constants were readily available from the fully coupled ^{13}C NMR spectrum. Thus, even though the ^{13}C satellite signals were not detectable in proton spectra under the present conditions of measurement, their absolute positions were known with certainty. The SNOE technque involves moderate power rf irradiation of a narrow spectral band corresponding to a single ^{13}C satellite in the proton spectrum while observing the effect on the ^{13}C NMR spectrum. As may be seen in Figure 2, irradiation of the lowest field ^{13}C satellite proton signal of **17a** (90 Hz downfield from 8.98 ppm) caused a dramatic intensity alteration in the multiplet at lowest field of the four protonated carbon signals, leaving the others essentially unchanged. Since that carbon signal was unequivocally identified as that of C-7, the lowest field proton signal must be attributable to H-7. Similarly, irradiation of the high-field satellite (83 Hz upfield from 7.57 ppm) caused a major alteration in the intensity of the high-field ^{13}C NMR multiplet with only minor effects on the rest of the spectrum. This finding is compatible only with the order (from low to high field) of H-7 > H-5 > H-6 and provides the first unequivocal evidence for that assignment. The SNOE technique was similarly applied to the satellites of H-5 in **17a** and of H-7 and H-5 in **3:** the resulting proton assignments are shown in Table I.

With the proton assignments firmly established, it was possible to reexamine the technique described above for establishing the site of N-alkylation. All the ^{1}H NMR data hitherto reported for *N*-alkylpyrido[2,3-*d*]pyrimidines were,

when correct[4,13b,20] rather than erroneous[5,21] assignments of chemical structure were made, completely consistent with the described technique; i.e., the largest deshielding effect resulting from N-8 alkylation was experienced by the H-5 (pyridine γ) proton, and alkylation of a lactam nitrogen resulted in marked deshielding of an adjacent carbon-bound proton with little effect on other protons in the molecule. The first of these approaches may be illustrated by comparing the data (Table I) for 6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine (**3**) with its 9-(3-methyl-2-butenyl) (**4b**), 8-(uracil-5-methyl) (**6**), and 3-(uracil-5-methyl) (**9**) derivatives. The relevant protons in this case are H-5 (γ) and H-7 (α). In the spectra of both **4b** and **6**, as predicted, the H-5 signal appeared 0.30 ppm downfield from those of starting **3**, while the H-7 protons were shielded by about 0.05 ppm. In the spectrum of the 3-substituted derivative **9**, the chemical shifts closely resembled those of the parent heterocycle. The effect upon a neighboring proton of alkylation at lactam nitrogen is illustrated by comparing the spectral data for **13** and **17**; H-2 was deshielded by 0.35 ppm, whereas the signals for H-5 and H-7 were virtually unaffected.

To summarize, rigorous assignments of the proton chemical shifts for H-5, H-6, and H-7 in the pyridine ring of the pyrido[2,3-*d*]pyrimidine ring system have been carried out by means of the new technique of selective saturation of ^{13}C satellites. These assignments, in turn, confirmed the validity of the proton chemical shift approach to the determination of the site of alkylation in this ring system.

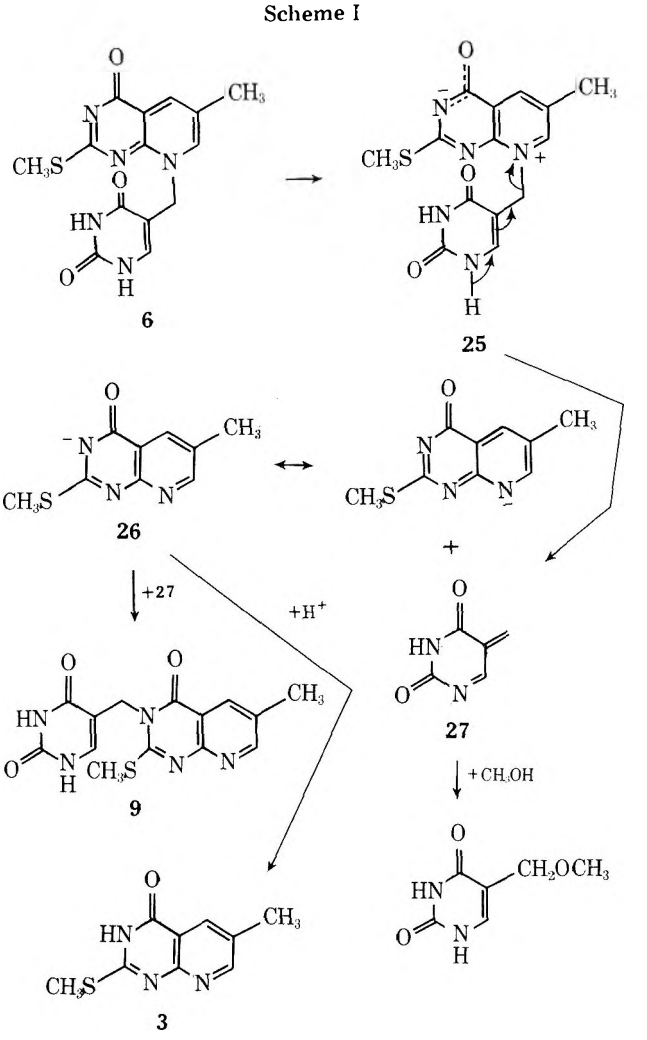
Mechanism

Careful examination of the reaction mixture in the rearrangement of **6** to **9** revealed the presence of a small amount of 6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine. This suggested that the reaction might be intermolecular rather than intramolecular in nature. Confirmation of this hypothesis was provided by three experiments. First a solution of **6** in methanol was heated for a short while at reflux; the only products were 5-methoxymethyluracil[22] and **3**. Second, **6** was rearranged in the presence of 6-methyl-4-oxopyrido[2,3-*d*]-pyrimidine (**17b**). Complete reaction gave rise to 5-(6-methyl-4-oxopyrido[2,3-*d*]pyrimidin-3-yl)methyluracil (**13**) and its 2-methylthio derivative **9** in a 2:1 ratio. Third, the reverse experiment (transalkylation of **3** by **18b**) also gave **13** and **9**; in this case a 4:1 ratio was observed.

A mechanism which is fully consistent with the above observations is presented in Scheme I. The intense fluorescence exhibited by **6** is indicative of substantial zwitterionic character as shown in resonance structure **25**. The pyridopyrimidinyl moiety in such a molecule must be a good leaving group. It would be expected from Santi's excellent study on the methanolysis of 5-(*p*-nitrophenoxy)methyluracil[23] that loss of the proton at the pyrimidine N-1 would greatly facilitate cleavage of the C–N bond between the heterocycles; as noted above, even slightly basic conditions result in extremely rapid rearrangement. Such cleavage would lead to the neutral, electrophilic, highly reactive species **27**[23] and the anion of the pyridopyrimidine **26**. Protonation of the anion and nucleophilic attack of methanol on the exocyclic methylene group of **27** led to the products observed in methanol (vide supra).

The transalkylation reactions between **17b** and **6** and between **3** and **18b** provided unequivocal evidence for the intermolecularity of the rearrangement. Two routes by which a uracilmethyl moiety might be transferred from N-8 of one derivative to N-3 of another required consideration. The first was a rapid acid–base equilibration between, for example, anion **26** and neutral pyridopyrimidine **17b**. The resulting mixture of anions could then undergo attack on N-3 of either

Scheme I



molecule by reactive intermediate **27**. The alternative route would be alkylation at N-8 of **17b** by **6** (or **3** by **18b**) followed by rearrangement of each 8-alkyl derivative as shown in Scheme I. Either of these pathways could account for the observed differences in product ratios; such factors as rate of dissociation of **6** or **17b** to anion and **27**, rate and site of alkylation, rate of proton transfer from neutral species to anions, and steric effects of the methylthio group vs. the proton at C-2 would make a detailed kinetic analysis a formidable problem indeed. However, the differing stabilities toward rearrangement of **6** and **18b** permitted a choice to be made between the two routes by means of a simple ^1H NMR experiment.

A solution of 6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]-pyrimidine (**3**) in Me_2SO-d_6 was treated with 5-(6-methyl-4-oxopyrido[2,3-*d*]pyrimidin-8-yl)methyluracil (**18b**). The ^1H NMR spectrum was recorded immediately after mixing and at 5-min intervals for about 0.5 h. The initial spectrum contained three peaks in the δ 4.5–5.5 region characteristic of the methylene groups. The peak locations and their assignments (made by comparison with the pure compounds **6, 9, 18b,** and **13**) were at δ 5.45 (**18b**), 5.33 (**6**), and 4.77 (**13**). No signal attributable to **9** was observed. During the subsequent 0.5 h the signal arising from **18b** gradually disappeared, whereas those attributable to **6** and **13** increased in intensity. Finally, the solution was briefly heated to ~50 °C. The methylene resonance of **6** disappeared and the only remaining signals, at δ 4.75 and 4.88, were those of the two rearranged products **13** and **9** in a ratio of 2.3:1. This experiment provided unequivocal evidence that the second of the two routes described above was operative; namely, that N-8 alkylation is prerequisite to formation of the rearranged product.

Experimental Section

^{1}H NMR spectra were obtained on a JEOL-60H or Varian-EM-360 spectrometer. All spectra were taken at ambient temperature using 5-mm tubes. UV spectra were run on a Cary-15 spectrophotometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Analyses were performed by Het-Chem-Co, Harrisonville, Mo.

^{13}C NMR data were determined on an XL-100-15 spectrometer operating in the Fourier transform mode. Chemical shifts were measured over 5000-Hz spectral width with an 8K data table (1.25 Hz/real point); coupled spectra were obtained over narrower spectral widths to increase digital resolution. The proton spin decoupler was gated *off* during data acquisition and *on* during the pulse delay to enhance the intensity of the coupled spectra. Also, 48 dB/octave audio low-pass filtering prevented aliasing of interfering signals into the coupled spectral region of interest.

All spectra were taken at 89 °C in 12-mm o.d. tubes. The concentrations varied greatly according to solubilities in Me_2SO-d_6. No special precautions were taken to dry the solvent or compounds, hence exchangeable protons did not exhibit couplings in the ^{13}C NMR spectra.

6-Methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine (3). To a solution of 10.2 g (52.8 mmol) of 6-methyl-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine[5] in 110 mL of 1 N sodium hydroxide was added 5 mL (6.66 g, 52.8 mmol) of dimethyl sulfate. The solution was stirred at room temperature for 6 h. The precipitated solid was filtered and air dried. The solid was dissolved in water and made slightly acidic (pH 5–6) with 6 N acetic acid. The precipitate was filtered and dried. The original filtrate was acidified with 6 N acetic acid (pH 5–6). The precipitated solid was filtered and dried.

The combined solids were crystallized from dimethylformamide to give 7.1 g (52%) of **3**. An analytical sample was prepared by crystallization from methanol: mp 255–257 °C; MS *m/e* 207 (M^+), 192 ($M - 15$); UV λ_{max} (ϵ_{max}) (pH 1) 276 (17 900), 290 (15 600), 342 (14 850); (pH 7) 259 (15 500), 274 (16 700), 312.5 (70); (pH 14) 256 (25 950), 275 (11 650), 328 nm (7600). Anal ($C_9H_9N_3OS$·0.5H_2O): C, H, N.

6-Methyl-4-oxopyrido[2,3-*d*]pyrimidine (17b). To a refluxing solution of 4.32 g (20 mmol) of **3** in 100 mL of dimethylformamide was added 15 g (wet weight) of Raney Ni and the suspension was refluxed for 10 h. The mixture was filtered through Celite and the filtrate was evaporated in vacuo. The solid was crystallized from water to give 2.2 g (65%) of **17b**: mp >270 °C; MS *m/e* 161 (M^+); UV λ_{max} (ϵ_{max}) (pH 1) 266 (5800), 320 (9400); (pH 7) 261 (7500), 305 (18 200), 316 (6170); (pH 11) 275 (5000), 318 nm (8200). Anal. ($C_8H_7N_3O$·0.5H_2O): C, H, N.

6,8-Dimethyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine (4a). To a suspension of 1.08 g (5 mmol) of **3** in 20 mL of anhydrous dimethylformamide was added 1 mL of methyl iodide. A clear solution was obtained. The solution was stirred at room temperature for 6 h. The precipitated solid was filtered and dried. The solid was dissolved in water then made alkaline with dilute ammonium hydroxide. The precipitated solid was filtered and dried. Crystallization from dimethylformamide gave 0.8 g (70%) of **4a**: mp 270 °C; MS *m/e* 221 (M^+), 206 ($M - CH_3$); UV λ_{max} (ϵ_{max}) (pH 1) 278 (15 650), 298 (14 100), 345 (15 200); (pH 7) 274 (25 500), 376 (12 850); (pH 11) 274 (25 500), 378 nm (12 850). Anal. ($C_{10}H_{11}N_3OS$·0.5H_2O): C, H, N.

6-Methyl-2-methylthio-8-(3-methyl-2-butenyl)-4-oxopyrido[2,3-*d*]pyrimidine (4b). To a suspension of 0.43 g (2 mmol) of **3** in 8 mL of anhydrous dimethylformamide was added 0.3 g (2 mmol) of 1-bromo-3-methyl-2-butene. After 8 h of stirring at room temperature, the precipitated solid was filtered, dried, and dissolved in water. The solution was made alkaline with 5% bicarbonate solution. The bright yellow solid was filtered, dried, and crystallized from ethanol to give 0.36 g (67%) of 4b: mp 223–224 °C; MS *m/e* 275 (M^+); UV λ_{max} (ϵ_{max}) (pH 1) 276 (14 550), 284 (1900), 294 (13 250), 347 (1550); (pH 7) 276 (24 000), 368 (12 650); (pH 11) 276 (24 000), 368 nm (12 650). Anal. ($C_{14}H_{17}N_3OS$·0.5H_2O): C, H, N.

5-(6-Methyl-2-methylthio-4-oxopyrido[2,3-d]pyrimidin-8-yl)methyluracil (6). To a suspension of 2.16 g (10 mmol) of **3** in 50 mL of anhydrous dimethylformamide, 1.61 g (10 mmol) of 5-chloromethyluracil[6] (**5**) was added and the mixture was stirred at room temperature. A clear solution was obtained. After stirring for 6 h at room temperature, the precipitated solid was filtered, dissolved in water, and made alkaline with 5% bicarbonate solution. The bright yellow solid was filtered, washed and a small quantity of ethanol, and dried over P_2O_5 at 20 mm to give 2.54 g (71%) of **6**: mp >300 °C; MS (CI) *m/e* 332 (MH^+); UV λ_{max} (ϵ_{max}) (pH 1) 269 (19 300), 295 (13 000), 351 (1850); (pH 7) 274 (26 700), 371 (13 150); (pH 11) 275 (30 700), 370 nm (13 350). Anal. ($C_{14}H_{13}N_5O_3S$·1.5H_2O): C, H, N.

5-(4-Oxopyrido[2,3-*d*]pyrimidin-8-yl)methyluracil (18a). To a suspension of 1.47 g (10 mmol) of **17a**[14] in 50 mL of anhydrous dimethylformamide was added 1.61 g (10 mmol) of 5-chloromethyluracil (**5**) and the reaction was carried out exactly as described above for **6**. The yield of **18a** was 1.87 g (69%): mp >300 °C; MS *m/e* 271 (M^+); UV λ_{max} (ϵ_{max}) (pH 1) 261 (10 250), 327 (10 700); (pH 7) 246 (13 950), 261 (8800), 361 (9200); (pH 11) 284 (9950), 359 nm (10 000). Anal. ($C_{12}H_9N_5O_3$): C, H, N.

5-(6-Methyl-4-oxopyrido[2,3-*d*]pyrimidin-8-yl)methyluracil (18b). To a suspension of 0.85 g (5 mmol) of **17b** in 15 mL of anhydrous dimethyl sulfoxide (distilled from calcium hydride) was added 0.81 g (5 mmol) of 5-chloromethyluracil (**5**) and the mixture was stirred for 8 h at room temperature. The yellow solution was poured with stirring into 100 mL of methylene chloride and the precipitate was filtered. The highly hygroscopic solid was quickly dissolved in water. The solution was made alkaline with 5% bicarbonate solution. The precipitated solid was filtered, washed with water and a small amount of ethanol, and dried over P_2O_5 at 20 mm to give 0.84 g (57%) of **18b**: mp >300 °C; MS (CI) *m/e* 286 (MH^+); UV λ_{max} (ϵ_{max}) (pH 1) 263 (1800), 331 (9700); (pH 7) 251 (13 200), 263 (10 300), 365 (7250); (pH 11) 245 (10 300), 284 (1200), 364 nm (8700). Anal. ($C_{13}H_{11}N_5O_3$·0.5H_2O): C, H, N.

5-(6-Methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidin-3-yl)methyluracil (9). A suspension of 3.59 g (10 mmol) of **6** in 40 mL of dimethylacetamide was refluxed for 5 min. Charcoal was added to the hot solution and was filtered through Celite. The filtrate was cooled to room temperature and water was added to the cloud point. After standing for 2 h at room temperature the solid was filtered, washed with water, and dried to give 2.62 g (77%) of **9**. An analytical sample was prepared by crystallization from methanol: mp 258–259 °C; MS *m/e* 331; UV λ_{max} (ϵ_{max}) (pH 1) 266 (19 750), 285 (16 500), 295 (1850), 345 (13 100); (pH 7) 276 (21 550), 320 (6350); (pH 11) 283 (22 650), 321.5 nm (6050). Anal. ($C_{14}H_{13}N_5O_3S$·0.5H_2O): C, H, N.

5-(6-Methyl-4-oxopyrido]2,3-*d*]pyrimidin-3-yl)methyluracil (13). Method A. A suspension of 0.59 g (2 mmol) of **18b** in 8 mL of dimethylacetamide was heated to reflux for 5 min. A white solid precipitated even before complete dissolution of **18b** occurred. The mixture was refluxed for 2–3 min more and allowed to cool to room temperature. The precipitated solid was filtered, dried, and crystallized from dimethylformamide to give 0.40 g (71%) of **13**: mp >270 °C; MS *m/e* 285 (M^+); UV λ_{max} (ϵ_{max}) (pH 1) 264 (12 000), 327 (8600); (pH 7) 265 (15 150), 306 (5850), 317 (4200); (pH 11) 275 (13 100), 287.5 (12 800), 317 nm (4450). Anal. ($C_{13}H_{11}N_5O_3$): C, H, N.

Method B. A solution of 0.68 g (2 mmol) of **9** in 25 mL of dimethylformamide was stirred at 80 °C for 4 h with 4 g (wet weight) of Raney Ni. The solution was filtered hot through Celite and washed with hot dimethylformamide. The combined filtrate was evaporated to a small volume and cooled to give 0.17 g (31%) of **13**, mp >270 °C. This compound is identical with the one (TLC with $CHCl_3$/MeOH 85:15, CH_3CH/H_2O 80:20, MS, and ^{1}H NMR) prepared from **18b**.

5-(4-Oxopyrido[2,3-*d*]pyrimidin-3-y)methyluracil (19). A suspension of 1.35 g (5 mmol) of **18a** in 20 mL of dimethylacetamide was refluxed for 5 min. A white solid precipitated even before complete dissolution of **19** occurred. Refluxing was continued for 2–3 min more and cooled to room temperature. The precipitated solid was filtered, dried, and crystallized from dimethylformamide to give 1.06 g (76%) of **19**: mp >300 °C; MS *m/e* 271; UV λ_{max} (ϵ_{max}) (pH 1) 264 (11 550), 318 (7700); (pH 7) 264 (1150), 299 (5900), 310 (4300); (pH 11) 288 (13 400), 275 (12 250), 310 nm (5100). Anal. ($C_{12}H_9N_5O_3$): C, H, N.

5-(2,4-Dioxo-6-methyl-4-oxopyrido[2,3-*d*]pyrimidin-3-yl)-methyluracil (15). A solution of 0.68 g (2 mmol) of **9** in 20 mL of 18% HCl was refluxed for 8 h. The solution was evaporated to dryness. The white solid was repeatedly evaporated with water to remove traces of acid. The residue was recrystallized from dimethylformamide to give 0.68 g (63%) of **15**: mp >300 °C; MS *m/e* 301 (M^+); UV λ_{max} (ϵ_{max}) (pH 1) 247 (11 800), 262.5 (8000), 315 (6550); (pH 7) 247 (11 650), 262.5 (8000), 315 (6150); (pH 11) 271 (1400), 345 nm (4400). Anal. ($C_{13}H_{11}N_5O_4$·0.5H_2O): C, H, N.

Methanolysis of 5-(6-methyl-2-methylthio-4-oxopyridopyrimidin-8-yl)methyluracil (6). A suspension of 0.17 g (0.5 mmol) of **6** in 20 mL of methanol was refluxed for 6 h. Thin layer chromatography ($CHCl_3$/MeOH 90:10) indicated the presence of two compounds. The mixture was separated on a silica gel column using $CHCl_3$/MeOH (90:10) mixture as the eluent to give 80 mg of 6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine (3) and 65 mg of 5-methoxymethyluracil.[22] The above compounds were identified by comparing their ^{1}H NMR, MS, and TLC with those of the authentic material.

Transalkylation of 6-Methyl-4-oxopyrido[2,3-*d*]pyrimidine

17b with 5-(6-Methyl-2-methylthiopyrido[2,3-*d*]pyrimidin-8-yl)methyluracil (6). A mixture of 73.5 mg (0.5 mmol) of **17b** and 170 mg of **6** were heated in 3 mL of dimethylacetamide. A clear solution was obtained. The solution was boiled for 2–3 min. The solid obtained on cooling (70 mg) was filtered and dried. The compound **13** was identical with the one obtained by the rearrangement of **18b** in dimethylacetamide and Raney Ni dethiation of **9** (based on TLC, ^{1}H NMR, and MS). The filtrate was found to contain a small amount of **13** along with 6-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**17b**), 6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine (**3**), and 5-(6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidin-3-yl)methyluracil (**9**) based on thin layer chromatography ($CHCl_3$/MeOH 90:10).

The above experiment was repeated and the solvent was removed under vacuum. A ^{1}H NMR analysis of the mixture showed that the ratio of **13** to **9** was 2:1 (based on the ratio of 5-CH_2 protons).

In a similar experiment, when the transalkylation of **3** with **18a** was carried out, the ratio of **13** to **9** was found to be 4:1.

5-Benzyloxymethyl-1,3-dimethyluracil (20). To a solution of 2.32 g (10 mmol) of 5-benzyloxymethyluracil[7] in 20 mL of anhydrous dimethylformamide was added 0.88 g of sodium hydride (55% dispersion in oil). After the hydrogen evolution ceased, 1.5 mL of methyl iodide was added. After stirring for 5–6 h at room temperature, the solution was carefully poured into 50 mL of water and extracted with petroleum ether. The aqueous layer was evaporated to dryness in vacuo. Trituration of the residue with water gave a solid which was filtered, dried, and crystallized from petroleum ether (30–60 °C) to give 1.58 g (61%) of **20**: mp 88–89 °C; ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 3, NCH_3), 3.36 (s, 3, NCH_3), 4.3 (d, J = 2 Hz, 2, CH_2), 4.6 (s, 2, CH_2), 7.21 (d, J = 2 Hz, 1, H-6), 7.33 (s, 5, C_6H_5); MS *m/e* 169 ($M^+ - C_6H_5 - CH_2$). Anal. ($C_{14}H_{16}N_2O_3$): C, H, N.

5-Bromomethyl-1,3-dimethyluracil (21). To 0.78 g (3 mmol) of **20**, 6 mL of 9% HBr in anhydrous dioxane was added. A clear solution was obtained. After 4 h of stirring, the mixture was evaporated to dryness. The residue was triturated with anhydrous ether. The precipitated solid was filtered, washed with a small quantity of ether, and air dried. Crystallization from petroleum ether (30–60 °C) gave 0.54 g (78%) of **21**: mp 165–166 °C; ^{1}H NMR ($CDCl_3$) δ 3.4 (s, 3, NCH_3), 3.46 (s, 3, NCH_3), 4.33 (s, 2, CH_2), 7.47 (s, 1, H-6); MS (CI) *m/e* 233 (MH^+). Anal. ($C_7H_9N_2O_2Br$): C, H, N.

1,3-Dimethyl-5-(6-methyl-2-methylthio-4-oxopyrido[2,3-*d*]-pyrimidin-8-yl)methyluracil (22). To a suspension of 0.43 g (2 mmol) of **3** in 5 mL of anhydrous dimethylformamide was added 0.47 g (2 mmol) of 5-bromomethyl-1,3-dimethyluracil (**21**). A clear solution was obtained in a few mintues. A white solid precipitated after 1 h. The mixture was stirred for 4 h more, filtered, and air dried. The solid was dissolved in water. The solution was made alkaline with 5% bicarbonate solution. The precipitated solid was filtered, washed with water, and dried. Crystallization from ethanol gave bright yellow crystals: mp 246–247.5 °C; MS *m/e* 259 (M^+); UV λ_{max} (ϵ_{max}) (pH 1) 266 (8450), 271 (22 250), 290 (13 300), 350 (15 350); (pH 7) 266 (8450), 274 (29 000), 366 (12 900); (pH 11) 266 (7900), 274 (29 800), 366 (13 400). Anal. ($C_{16}H_{17}N_5O_3S \cdot 0.5H_2O$): C, H, N.

4-Chloro-2-methylthio-6-methylpyrido[2,3-*d*]pyrimidine (11). A suspension of 2-methylthio-6-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**3**) (2.16 g, 10 mmol) was refluxed with 25 mL of phosphorus oxychloride for 12 h. The dark brown solution was evaporated under reduced pressure to a small volume. The residue was treated with crushed ice and extracted with methylene chloride. The combined extracts were washed with ice cold water and the organic layer was dried over Na_2SO_4. Evaporation of the solvent gave a brown solid. The solid was refluxed with 600 mL of petroleum ether (30–60 °C), the insoluble portion was removed by filtration, and the filtrate was concentrated to about 100 mL and cooled to give 0.84 g (37%) of **11**: mp 126–127 °C; ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3, CH_3), 2.73 (s, 3, SCH_3), 8.23 (m, 1, H-5), 9.23 (d, 1, H-7); MS (CI) *m/e* 226 (MH^+); UV λ_{max} (ϵ_{max}) (pH 1) 246 (16 250), 275 (19 400), 375 (8000); (pH 7) 243 (22 300), 271 (20 250), 354 (6350); (pH 11) 235 (15 350), 267 (20 400), 345.5 (8700). Anal. ($C_9H_8N_3ClS$): C, H, N.

4-Methoxy-6-methyl-2-methylthiopyrido[2,3-*d*]pyrimidine (12). To a solution of 70 mg (3 mmol) of Na dissolved in 10 mL of methanol was added 670 mg (3 mmol) of **11** and the solution was stirred at room temperature for 4 h. The solution was evaporated in vacuo and the residue was triturated with water. The precipitated solid was filtered and air dried. The solid was crystallized from petroleum ether (30–60 °C) to give 0.46 g (67%) of **12**: ^{1}H NMR (Me_2SO-d_6) δ 2.5 (s, 3, CH_3), 2.68 (s, 3, SCH_3), 4.1 (s, 3, OCH_3), 8.15 (m, 1, H-5), 8.88 (d, 1, H-7); MS (CI) *m/e* 222 (MH^+); UV λ_{max} (ϵ_{max}) (pH 1) 259 (21 350), 355 (11 650); (pH 7) 241.5 (17 000), 266 (18 200), 329.5 (7500); (pH 11) 241.5 (16 500), 266 (18 000), 329.3 nm (7500). Anal. ($C_{10}H_{11}N_3OS \cdot 0.5H_2O$): C, H, N.

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Registry No.—**2**, 49738-95-6; **4a**, 64600-57-3; **5**, 3590-48-5; **11**, 64600-58-4; **2**, 64600-59-5; **20**, 64600-60-8; **21**, 64600-61-9; 1-bromo-3-methyl-2-butene, 870-63-3; 5-benzyloxymethyluracil, 7295-02-5.

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Fluorination with Xenon Difluoride. 16. Fluorination of Some Benzocyclenes[1]

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The fluorination of indan with xenon difluoride in the presence of hydrogen fluoride occurred only at the β position, while further fluorination resulted in 5,6-difluoroindan. The fluorination of tetralin and o-xylene occurred both at α and β positions, with β attack predominating over α attack.

The influence of the attached alicyclic ring on the chemistry of benzocyclenes has received considerable attention from three main points of view. The first is the almost outdated hypothesis of bond fixation of the Kekule benzene structures, suggested by Mills and Nixon[2,3] in order to explain the influence of an alicyclic ring condensed with the benzene nucleus on the direction of electrophilic substitution, as in 5-hydroxyindane and 6-hydroxy-1,2,3,4-tetrahydronaphthalene. The second is the influence of strained energy in the ground state, arising from fusion of the alicyclic ring as evidenced by heat of combustion and hydrogenation.[4] The question of the Baker–Nathan effect (hyperconjugation)[5] of the alicyclic ring, in which the conformation of the ring may be quite significant, is the third main point of view.

In our continuing interest in acid-catalyzed liquid-phase fluorination with xenon difluoride,[6] we found it interesting to study the reaction with some benzocyclenes. We now report the reaction of xenon difluoride with indane, tetralin, and o-xylene.

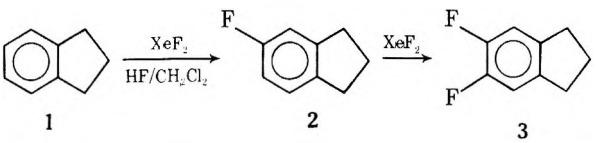
Results and Discussion

Most of the work on tetralin and indan has been directed toward supporting or disproving the possibility first postulated in 1930 by Mills and Nixon[2] of bond fixation of these compounds. Further examination of molecular models of the hydrocarbons orthoxylene, indane, and tetralin shows that the methylene groups adjacent to the aromatic ring in indane offer less steric hindrance in the α position than do the methyl or methylene groups in o-xylene and tetralin. Experimental evidence supports this conclusion.[7] However, bromination of the above mentioned systems hardly supported such an explanation and for this reason it has been suggested[8] that the transition state for α and β substitution must be taken into account.

We now report the reaction of xenon difluoride with some benzocyclenes. In a typical experiment we dissolved 1 mmol of compound in methylene chloride; anhydrous hydrogen fluoride (1 mmol) was introduced into the reaction mixture and under stirring at room temperature pure xenon difluoride (1 mmol) was added. The colorless solution turned dark blue and xenon gas was quickly evolved. After 10–30 min, when gas evolution had ceased, the crude reaction mixture was isolated by the usual work-up procedure, analyzed by NMR, and separated by preparative GLC or TLC. The crude reaction mixture formed by fluorination of indane (1) shows in its ^{19}F NMR a multiplet signal at δ −115.5 ppm, while the reaction mixture formed by further fluorination shows in its ^{19}F NMR a triplet signal at δ −139.5 ppm. Comparison of the NMR data of the products formed by fluorination to those of similar compounds[9] enabled us to establish that primary attack of the fluorine atom proceeds only at the β position and that further fluorination occurs again at the β position, thus forming 5,6-difluoroindane (3) (Scheme I).

Fluorination of o-xylene (4) resulted in a crude reaction mixture which shows in its ^{19}F NMR two signals at δ −122.25 ppm and at δ −123 ppm, in relative yields of 20 and 80%, respectively. Comparison with the literature data showed that β attack occurred predominantly (Scheme II).

Scheme I



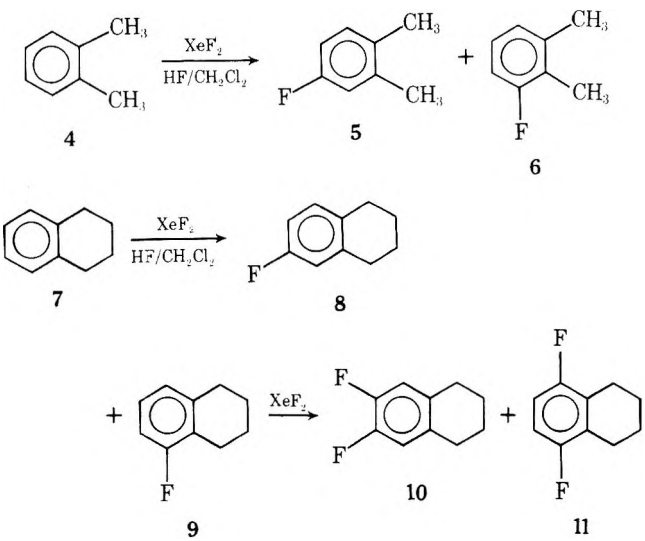
1 2 3

Fluorination of tetralin (7) also resulted in the formation of two products with relative yields of 30% (9) and 70% (8). We were unable to separate the isomers. However, further fluorination of the above-mentioned mixture yielded two products, which were separated by preparative GLC. The major product formed (10) shows in its ^{19}F NMR spectrum a triplet signal very similar to that displayed by 5,6-difluoroindane at δ −127 ppm and the minor product (11) shows in ^{19}F NMR a broad singlet signal at δ −101.25 ppm. On the basis of the above-mentioned data and their comparison to the NMR data of similar compounds, the major product could be established as 6,7-difluorotetralin (10) and the minor product as 5,8-difluorotetralin (11). In this case β attack was also favored.

The observed results of the fluorination of benzocyclane are parallel to those observed by bromination[8] of the same systems. However, we observed a higher degree of regioselectivity (Scheme IV).

The mechanism of the fluorination with xenon difluoride must involve catalysis by hydrogen fluoride since the reaction proved to be very slow without it. It may be expected that in the presence of hydrogen fluoride xenon difluoride behaves as an electrophile. Previously this has been suggested by Filler et al.[10] for the fluorination of some aromatic compounds. In the next step a π complex is probably formed between this electrophilic species and indane (or benzocyclane) (Scheme

Scheme II



4 5 6 7 8 9 10 11

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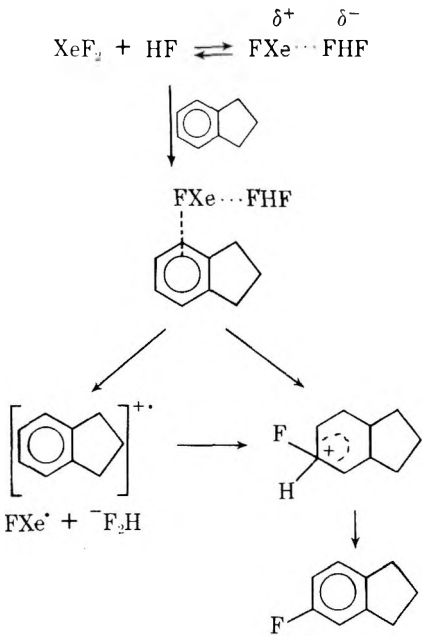
Scheme III



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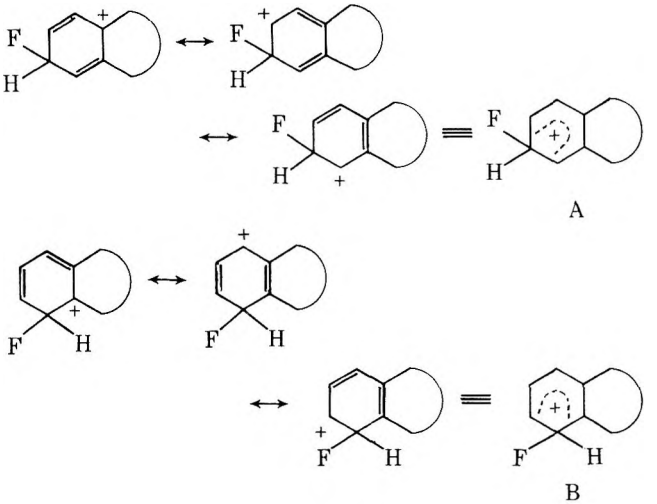
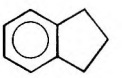
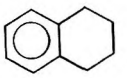
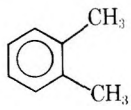
III) which could be transformed by heterolytic Xe–F bond cleavage into β-fluorocarbonium ion intermediates (in the case of o-xylene and tetralin also β-fluorocarbonium ion intermediates are formed), resulting, after the elimination of the proton, in β-substituted products. Furthermore, another possibility is the formation of the ion radical which has already been observed in the fluorination of some aromatic compounds[12] transforming in the next step by XeF· or XeF_2 into a β-fluorocarbonium ion. The high regioselectivity of the fluorination of indane strongly supports an ionic intermediate. The important difference between the two sets of resonant forms (Scheme IV) is reflected in the fact that in α substitution the bond common to the two rings has effectively two-thirds of the double bond character, while in β substitution it has one-third of the double bond character. Differences in the stabilization of fluorocarbonium ions A and B formed after β or α attack are probably greater than those in the case of bromination,[8] which is then reflected in the higher regioselectivity. This means that β attack is more predominant in the case of fluorination than in the case of bromination, as is shown in Scheme IV.

Scheme IV



	β attack, %	
	Br_2/AcOH	XeF_2/HF, CH_2Cl_2
	78 ± 3	100
	56 ± 2	70
	71 ± 3	80

Experimental Section

IR spectra were recorded by using a Perkin-Elmer 257 spectrometer and ^1H and ^{19}F NMR spectra by a JEOL JNM-PS-100 from CCl_4 solution with Me_4Si or CCl_3F as internal reference. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas–liquid partition chromatography was carried out on a Varian Aerograph, Model 1800, and TLC on Merck PSC-Fertigplatten silica gel F-254 (activated for 3 h at 120 °C before use).

Materials. Orthoxylene, indane, and tetralin are commercially available and were distilled before use. Hydrogen fluoride of Fluka Purum quality was used without further purification. Methylene chloride was purified[11] and stored over molecular sieves. Xenon difluoride was prepared by a photosynthetic method[12] and its purity was better than 99.5%.

5-Fluoroindane (2). To a solution of 1 mmol of **1** in methylene chloride (6 mL) was added 1 mmol of xenon difluoride at 25 °C and under stirring 1 mmol of HF was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was slowly evolved. After 10 min gas evolution had ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 mL), washed with 10 mL of 5% $NaHCO_3$ and water, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. The crude product (82%) was purified by preparative GLC (DDP, Varaport 30 70/80, 10%, T = 120 °C) and 60% of colorless liquid product (**2**) resulted: mass spectrum, Calcd for C_9H_9F m/e 136.0688, Found m/e 136.0686; m/e 136 (M^+, 98), 135 (100), 134 (13), 133 (46), 119 (40), 118 (16), 117 (40), 115 (31), 109 (41); F NMR δ −115.5 ppm (m); H NMR δ 2 (m, 2 H), 2.9 (m, 4 H), 7 ppm (m, 3 H).

5,6-Difluoroindane (3). To a solution of 1 mmol of **2** in methylene chloride (6 mL) was added 1 mmol of xenon difluoride at 25 °C and under stirring 1 mmol of HF was introduced into the reaction mixture. After 10 min gas evolution had ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 mL), washed with 10 mL of 5% $NaHCO_3$, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the crude product (80%) was purified by preparative GLC (DDP, Varaport 30 70/80, 10%, T = 120 °C), and 62% of colorless liquid product resulted: mass spectrum, Calcd for $C_9H_8F_2$ m/e 154.0594, Found m/e 154.0593; m/e 154 (M^+, 100%), 153 (90), 151 (34), 136 (70), 135 (96), 134 (23), 133 (49), 127 (28), 109 (19), 103 (47); F NMR δ −139.5 ppm (t, J = 10 Hz); H NMR δ 2 (m, 2 H), 2.7 (m, 4 H), 7 ppm (m, 2 H).

4-Fluoro-1,2-dimethylbenzene (5) and 3-Fluoro-1,2-dimethylbenzene (6). The fluorination, work-up procedure, and GLC purification were essentially the same as described for **2** or **3**. **5** was isolated as a colorless liquid product in 55% yield and **6** was isolated as a colorless liquid product in 12% yield. Both products have very similar mass spectra and their NMR data are in agreement with the literature ones[11]: F NMR for product **5**, δ F −123 ppm (m); H NMR for **5**, δ 6.8 (m, 3 H), 2.18 (s, 3 H), 2.185 ppm (s, 3 H); H NMR for **5**, F NMR for product **6**, δ −122.25 ppm (m); H NMR for **6**, δ 6.8 (m, 3 H), 2.18 (s, 3 H), 2.185 ppm (s, 3 H).

5-Fluorotetralin (9) and 6-Fluorotetralin (8). The fluorination and work-up procedure were essentially the same as for **2** and **3**. We were unable to separate the two isomers, although we have tried many different stationary phases. The crude reaction mixture showed in its ^{19}F NMR spectrum two signals: F NMR δ −120.75 ppm (30%) (**9**), −121.8 ppm (70%) (**8**); mass spectrum, Calcd for $C_{10}H_{11}F$ m/e 150.0845, Found m/e 150.0855; m/e 151 (M^+, 22.4), 150 (91), 149 (43), 146 (20), 135 (33), 133 (30), 123 (27), 122 (100), 109 (80), 96 (18).

Further fluorination of the crude reaction mixture under the conditions mentioned above resulted in the formation of two products, which could be separated by preparative GLC (DDP, Varaport 30 70/80, 10%, T = 120 °C). 6,7-Difluorotetralin (**10**) and 5,8-difluorotetralin (**11**), both colorless liquid products, were isolated in 50 and 13% yield respectively. Product **10**: F NMR δ −127 ppm (t, J = 10 Hz); H NMR δ 1.8 (m, 4 H), 2.75 (m, 4 H), 6.75 ppm (t, 2 H); mass spectrum,

Calcd for $C_{10}H_{10}F_2$ *m/e* 168.0745, Found *m/e* 168.0745; *m/e* 168 (M^+, 24), 151 (16), 150 (86), 149 (25), 140 (42), 135 (14), 133 (14), 127 (22), 122 (100), 109 (90). Product 11: F NMR δ −101.25 ppm (broad singlet); H NMR δ 1.75 (m, 4 H), 2.25 (m, 4 H), 6.3 ppm (broad singlet, 2 H); mass spectrum, Calcd for $C_{10}H_{10}F_2$ *m/e* 168.0745, Found *m/e* 168.0750; *m/e* 168 (M^+, 53), 151 (19), 150 (87), 149 (26), 140 (72), 135 (20), 133 (21), 127 (28), 122 (100), 109 (84).

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Registry No.—**1**, 496-11-7; **2**, 37530-82-8; **3**, 64683-00-7; **4**, 95-47-6; **5**, 452-64-2; **6**, 443-82-3; **7**, 119-64-2; **8**, 2840-40-6; **9**, 700-45-8; **10**, 64683-01-8; **11**, 64683-02-9; XeF_2, 13709-36-9.

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Products and Kinetics of Decarboxylation of Activated and Unactivated Aromatic Cuprous Carboxylates in Pyridine and in Quinoline[1a]

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Aromatic cuprous carboxylates can be prepared in a state suitable for kinetic and product studies of their decarboxylations in quinoline and pyridine by reducing the cupric salt with copper in the decarboxylation solvent. The results were indistinguishable from those obtained from the same salts prepared by treatment of the acids with cuprous *tert*-butoxide, a more tedious procedure. The major neutral product, besides carbon dioxide, for the decarboxylation of $ArCO_2Cu$ is ArH except in the case of cuprous *o*-nitrobenzoate in which it is Ar_2. The hydrogen which replaces the carboxyl group appears to be derived largely from the solvent and is released during the substitution of aryl groups into solvent molecules and the coupling of solvent molecules. In quinoline, the latter type of product consists mainly of biquinolyls and some oxybiquinolyls. Since approximately the same composition of solvent-derived products is obtained from the decarboxylations of all of the aromatic salts and by heating pentafluorophenylcopper in quinoline, it is believed that arylcopper and quinolylcopper intermediates are involved; this is the first evidence for such intermediates in the case of nonactivated cuprous carboxylates. Such intermediates, the clean first-order kinetics, evidence against a radical process, and the similarity with respect to substituent, solvent, and ligand effects between this reaction and the Ullmann biaryl coupling as well as copper-induced exchange processes lead to a new mechanistic suggestion which involves an oxidative addition of the carboxyl C–C bond to the copper(I) followed by loss of carbon dioxide. An efficient method of preparation of 2-deuterioquinoline is presented, as is a nearly complete analysis of the 250-MHz spectrum of 2,2′-difluorobenzophenone.

Introduction

The decarboxylation of aromatic carboxylic acids by heating them in quinoline solution in the presence of copper metal or copper salts (the copper–quinoline decarboxylation) has been widely used[2] since its discovery in 1930 by Shepard, Winslow, and Johnson.[3] Previous work in this laboratory indicates that cuprous and cupric salts decarboxylate at approximately the same rate, but that the latter are converted to the former under the reaction conditions.[4,5] For preparative purposes, the reaction is most easily performed by heating the acid in quinoline under an inert atmosphere in the presence of cuprous oxide.[4,6]

The work of Nilsson and co-workers provided early evidence that in the decarboxylations of o-nitrobenzoic, 2-furoic, 2-thenoic, and 3,4,5-trichloro-2-thenoic acids or their copper(I) salts arylcopper intermediates are involved.[6,7] The intermediates are capable of condensing with aryl iodides present in the quinoline to form mixed biaryls. Furthermore, the first of these yielded some 2,2′-dinitrobiphenyl, a product expected from self-coupling of *o*-nitrophenylcopper. In the case of the chlorinated thenoic acid, the quenching with hydrochloric acid of samples withdrawn during the course of the reaction revealed a protonatable intermediate.[8]

This conclusion was confirmed by an experiment reported by Cairncross, Roland, Henderson, and Sheppard, who were able to isolate the relatively stable pentafluorophenylcopper from the low temperature decarboxylation of cuprous pentafluorobenzoate.[9] However, these workers provided evidence that *o*-nitrophenylcopper does not accumulate in the quinoline during the decarboxylation of cuprous *o*-nitrobenzoate, although its presence was demonstrated by the Nilsson method of trapping the intermediate with aryl iodide and by its self-coupling to form biaryl.

Our own work[4] and that of Cairncross et al.[9] demonstrated that the rate of reaction is greater the better the ability of the

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solvent or additive to complex cuprous ion; it was found,[4] for example, that 2,2′-bipyridyl and 1,10-phenanthroline are rather good catalysts. Furthermore, the cupric salts of the saturated acids, adamantane-1-carboxylic acid and dodecanoic acid, failed to decarboxylate under conditions that caused rapid decarboxylation of a number of cupric salts of aromatic acids;[4,10] Cairncross et al.[9] took advantage of such relative reactivities to selectively monodecarboxylate a dicarboxylic acid possessing both aromatic and unconjugated carboxyl groups. It has been pointed out[4] that a radical intermediate is unlikely in view of the very predominant retention of configuration which occurs in the decarboxylation of geometrically isomeric α,β-unsaturated carboxylic acids[11] and the corresponding copper(I) and copper(II) carboxylates.[4]

An investigation of the kinetics of decarboxylation of several copper(I) and copper(II) carboxylates in quinoline revealed that the reactions are first order in the salts and, as stated above, that the rate constants are essentially the same for copper(I) and copper(II) salts.[4] The rate of decarboxylation of excess carboxylic acid in the presence of varying amounts of cuprous oxide was directly proportional to both the concentration of the acid and the quantity of cuprous oxide added. Furthermore, the cuprous and cupric carboxylates can behave as catalysts for the decarboxylation of excess acid.[4]

Chodowska-Palicka and Nilsson[12] have studied the kinetics of decarboxylation of the very activated (toward decarboxylation) salt copper(I) *o*-nitrobenzoate and the moderately active copper(I) *p*-nitrobenzoate in quinoline. In the former case, although good first-order rate constants were observed in individual runs, the rate constants varied in unexpected ways with changes in initial concentration of the salts. Thus, increasing the concentration of pure cuprous salt caused a *decrease* in the rate constant. On the other hand, when free carboxylic acid was present, an increase in the concentration of cuprous salt resulted in a large increase in the rate constant. Finally, apparent catalysis by copper metal was noted.

All of the previous evidence for organocopper intermediates in copper–quinoline decarboxylations have involved "activated" acids such as *o*-nitro-, *p*-nitro-, or pentafluorobenzoic acids. Indeed, all product studies of the decarboxylation of pure cuprous carboxylates have involved such activated compounds. Other product studies have involved the presence of contaminants which are generated during the in situ preparation of the cuprous salt; for example, water is formed by the reaction of cuprous oxide with carboxylic acids and oxidized quinolines are formed[4,5] when cupric carboxylates are reduced to the cuprous salts.[5] Our earlier kinetic studies[4] suffer from the same shortcoming; those of Nilsson[12] involve only activated cuprous carboxylates and the effects of concentration appear to negate the conclusion that the decarboxylation is first order in cuprous carboxylate. In the present paper, we report product and kinetic studies of the decarboxylation of a variety of pure cuprous carboxylates in pyridine and quinoline; a number of new types of products are reported and our kinetic results for cuprous *o*-nitrobenzoate are shown not to be in agreement with published conclusions. We also comment on the ease of various preparative methods for cuprous carboxylates and the suitability of these methods for product and kinetic studies.

Results

Acquisition of Kinetic Data. The decarboxylations were generally performed by heating the reactants in the dry solvent under nitrogen ebullition. The carbon dioxide evolution was monitored by passing the effluent gas stream through a drying tube and then through tubes filled with Ascarite, which absorbed the carbon dioxide. Two Ascarite tubes were used so that one could be weighed while the other continued to absorb carbon dioxide. The increase in weight of the Ascarite tubes was determined as a function of time and was a direct measure of the amount of carbon dioxide produced for a given time interval. The computations required for the analysis of the data were carried out on a PDP-10 time-sharing computer equipped with a Calcomp plotter. The mass data were transformed, appropriate to first-order kinetics, to $\log A/(A - X)$, where A is the ultimate mass of carbon dioxide released during complete reaction and X is the amount at a given time, and plotted vs. time. A straight line was fitted to the middle third of the ordered data. Using the parameters of this preliminary fit, 95% confidence limits were computed for all other points. All observed pairs of data which lay within these limits were used in fitting a new straight line to the data. This process of fitting and testing was continued so long as data pairs were included or discarded from the data set. The unrepresentative points which were eliminated constituted less than 5% of the data and they occurred almost exclusively in the early parts of the runs when the carbon dioxide had not yet completely displaced the nitrogen in the apparatus. Once self-consistency was obtained, the retained points and the kinetic parameters were plotted on a labeled graph. In all instances in which the kinetic data were acceptable, the correlation coefficient for the straight line was at least 0.99.

Preparation of Cuprous Carboxylates and the Kinetics of Their Decarboxylation. At the time that this research was begun, two methods appeared appropriate for the preparation of aromatic cuprous carboxylates. The first (method A), which was used previously[14] in this laboratory, involves heating the carboxylic acid and cuprous oxide in xylene with continuous removal of the water by azeotropic distillation; this method was found not to be general, failing for quinaldic, o-fluorobenzoic, and *o*-chlorobenzoic acids, and was thus used in only one experiment which was designed to compare the product mixtures obtained upon decarboxylation of cuprous benzoate prepared by different methods. The second, which was advocated recently,[9] involves the reaction between *m*-(trifluoromethyl)phenylcopper and the carboxylic acid; this method has the disadvantage for kinetic work that the arylcopper slowly undergoes self-coupling at room temperature and is therefore contaminated with varying amounts of biaryl and copper metal, a fact which makes it difficult to determine the stoichiometric quantities and which may lead to contamination of the salt with the metal.

An alternative general method, which does not have this disadvantage, was therefore developed. It consisted of the reaction of pure, freshly sublimed, cuprous *tert*-butoxide[15] with the carboxylic acid; this procedure is designated method B. Cuprous benzoate, prepared in this way, had the same color and infrared spectrum as that prepared by the azeotropic distillation method and the products of its decarboxylation were the same (see below). Cuprous *o*-nitrobenzoate, which was prepared by method B, gave excellent first-order kinetics upon decarboxylation in pyridine and in quinoline. More significantly, the rate constants in both solvents were identical within experimental error with those exhibited by the same salts prepared by the redox method (D) described below (Table I). The rate constants for the decomposition of this salt prepared by methods B and D at various concentrations and in the presence of various additives are recorded in Table I. Several other cuprous carboxylates prepared by the cuprous *tert*-butoxide method also gave good first-order kinetics upon decarboxylation (Table II).

However, the satisfactory results obtained by the use of method B came at a great expense in time; the cuprous *tert*-butoxide is very sensitive to air and moisture and must be handled in an efficiently operating glove box. For this reason, two in situ methods for the preparation of cuprous carboxylates were examined. The first (method C), which had been employed earlier for the production in high yield of 2,2′-di-

Table I. Rates of Decarboxylation of Cuprous *o*-Nitrobenzoate in Pyridine and Quinoline

Concn, M	Prep[a]	Solvent[b]	Temp, °C	Additive (concn, M)	$k \times 10^4$, s^{-1}
0.60	B	Q	122		1.97 ± 0.05
0.75	D	Q	122		2.00 ± 0.08
0.22	C	Q	137		2.2 ± 0.2[c]
0.65	B	P	116		3.07 ± 0.05
0.18	D	P	116		3.03 ± 0.03
0.37	D	P	116		3.1
0.75	D	P	116		3.13 ± 0.03
0.75	D	P	116	bis(cyclohexene)copper(I) triflate (0.16)	3.16
0.75	D	P	116	cuprous iodide (0.75)	3.2
0.75	D	P	116	benzoic acid (0.35)	3.5

[a] Method of preparation: B, acid + cuprous *tert*-butoxide; C, in situ preparation from anhydride + cuprous oxide; D, in situ preparation from cupric salt + copper metal. [b] P = pyridine; Q = quinoline. [c] Rate-determining step is not decarboxylation; see text.

Table II. Rate Constants for the Decarboxylation of Cuprous Salts in Quinoline[a]

Registry no.	Cuprous salt[b]	Prep[c]	Temp, °C	$k \times 10^4$, s^{-1}
35425-38-8	*p*-Nitrobenzoate	D[d]	197	14.9 ± 0.4
64508-51-6	3-Methyl-4-nitrobenzoate	D[d]	197	8.5 ± 0.2
64508-52-7	Picolinate	D[d]	233	2.76
64508-53-8	Quinaldate	D[d]	197	3.02 ± 0.11
14604-51-4	Benzoate	D[d]	197	0.45 ± 0.01
	Benzoate[e]	D[d]	197	0.42
	Benzoate	D[d]	200	0.88 ± 0.03
	Benzoate	D[d]	203	0.99 ± 0.04
	Benzoate	D[f]	216	1.84 ± 0.04
64508-54-9	*o*-Methylbenzoate	D[d]	197	1.76 ± 0.08
	o-Methylbenzoate	D[c]	200	3.2 ± 0.10
	o-Methylbenzoate	D[f]	200	3.2 ± 0.1
64508-55-0	1-Naphthoate	D[d]	197	2.71 ± 0.11
64508-56-1	2-*tert*-Butylbenzoate	D[d]	197	2.05
64508-57-2	2,6-Dimethylbenzoate	D[d]	197	0.97 ± 0.2
446-25-3	*o*-Fluorobenzoate	D[d]	178	0.73 ± 0.01
	o-Fluorobenzoate[g]	D[d]	178	0.76
	o-Fluorobenzoate	D[d]	192	2.7 ± 0.05
	o-Fluorobenzoate	D[d]	197	3.7 ± 0.1
	o-Fluorobenzoate[h]	D[d]	197	3.7
	o-Fluorobenzoate	D[d]	200	4.01 ± 0.07
27269-44-9	*o*-Nitrobenzoate	B	122	1.97 ± 0.05
64508-58-3	3-Methyl-2-nitrobenzoate	B	122	0.201 ± 0.003
27269-45-0	6-Chloro-2-nitrobenzoate	B	122	5.78
64508-59-4	6-Methyl-2-nitrobenzoate	B	157	2.15

[a] The yields of carbon dioxide were generally over 90%, but never below 85%. [b] Concentrations range from 0.59 to 0.75 M except for next to last entry (0.32 M) and last entry (1.5 M). [c] Method of preparation; see footnotes to Table I. [d] The copper–cupric salt mixture was heated at 130 °C for 30 min prior to raising the temperature to that indicated. [e] Fivefold excess of copper metal. [f] The reactants were added to quinoline at the temperature indicated. [g] Tetrakisacetonitrilecopper(I) perchlorate (0.36 M) present. [h] Cuprous iodide present.

nitrobiphenyl from cuprous *o*-nitrobenzoate.[4] involves the treatment of the carboxylic anhydride with cuprous oxide in the heterocyclic solvent which is to be used for the decarboxylation; however, it was found that in the case of o-nitrobenzoic anhydride a significantly higher temperature was required in order to attain the same rate of carbon dioxide evolution as that exhibited by the preformed cuprous carboxylate (Table I), indicating that cleavage of the anhydride rather than decarboxylation was rate determining and therefore method C was used only for product studies for which it proved quite convenient (see below).

The second in situ method (D) consisted of reduction of the cupric carboxylate with copper metal in quinoline solution.[16a] An electron spin resonance spectrum of a quinoline solution of cupric o-nitrobenzoate containing suspended copper, recorded at room temperature under nitrogen, exhibited a broad asymmetric signal typical of the cupric ion. After the solution had been heated at 55 °C for 3 min, the signal intensity decreased to <0.1% of the original value, indicating that the copper(II) had been reduced to the diamagnetic copper(I). The physical appearance of the solution obtained by heating the cupric *o*-nitrobenzoate and copper metal in quinoline under nitrogen was the same as that of a solution of cuprous o-nitrobenzoate and quinoline obtained by method B; i.e., the solution was homogeneous and red-orange in color. When the experiment was repeated in the absence of copper metal the solution remained dark blue and the asymmetric cupric signal at 55 °C was not diminished after 30 min of heating. It should be noted that this redox reaction proceeds rapidly at a temperature far below that at which decarboxylation occurs at a measurable rate; furthermore, the decarboxylation of cuprous *o*-nitrobenzoate occurs at the lowest temperature of all of the salts studied. It may be seen (Table I) that the copper–cupric couple method (D), which generates the cuprous salt in situ, produces the same rate constants as those obtained from the cuprous salt which is preformed by the cuprous *tert*-butoxide method (B) in the case of cuprous *o*-nitrobenzoate.[16b] Furthermore, as indicated below, the products are the same as

Table III. Product Yields in Decarboxylation of Cuprous Carboxylates in Quinoline

Cuprous salt (method)[a]	Concn, M	Temp, °C	% CO_2	% ArH	% Ar_2	% Ar_2CO	% $QAr^{b,c}$	% $QCOAr^{b,d}$	% $(Q_2 + Q_2O)^e$
Benzoate (C)	2.5	220[f]	67.2 ± 0.4[g]	63.6 ± 1.4[g]	*h*	*i*	*h*	>6	–[j,k]
Benzoate (C)[l]	2.5	220[f]	67.5	51.5[m]	–	–	–	–	–
Benzoate (A)	2.5	220[n]	76.1	*o*	*i*	*o*	*o*	*o*	–
Benzoate (B)	0.75	220[n]	65.8	53.8	–	–	–	–	–
Benzoate (D)	0.75	200	85	*o*	*o*	*o*	*n*	*o*	17
o-Nitrobenzoate (D)	0.75	122	91	23	62	*h*	7.3	*h*	0.4
p-Nitrobenzoate (D)	1.00	197	93	74	*h*	*h*	14	*h*	51
p-Nitrobenzoate (C)	2.5	200	91	*p*	*h*	*h*	*p*	*h*	–
o-Fluorobenzoate (D)	0.75	197	96	*p*	10	*p*	–	–	–
o-Fluorobenzoate (C)	2.5	195	66	*p*	*p*	>13	*p*	*q*	*p*
3-Methyl-2-nitrobenzoate (C)	0.59	122	87	74	14	*h*	*p*	*h*	–
1-Naphthoate (D)	0.75	197	93	71	*h*	–	–	–	*p*
o-Methoxybenzoate (C)	2.5	215	58[q,r]	*p*	*h*	*p*	*h*	*p*	–

[a] Method of preparation; see text. [b] See ref 19 for yield basis. [c] Isomeric arylquinoline mixture. [d] Acylquinoline. In the benzoate case, it is 2-benzoylquinoline; in other cases, the structure was not determined. In some cases more than one isomer was detected. [e] Yield based on eq 5. [f] Anhydride and Cu_2O added at temperature of decarboxylation. [g] Average of three runs. [h] None detected. [i] Trace product. [j] Dash indicates that presence was not determined. [k] *N*-(2-Quinolyl)-2-quinolone detected as minor product. [l] Conducted in 2-deuterioquinoline (81% monodeuterated). [m] 13% monodeuterated. [n] Reactants mixed at 25 °C. [o] Semiquantitative analysis only; the order of yields was the same as that for the first run. [p] Present, but yield not determined. [q] Present as minor product. [r] Reaction might not have been brought to completion.

those obtained via methods A–C. Therefore, this method has been used for most of the kinetic runs and for much of the product study.

All of the decarboxylations studied generated excellent first-order kinetics and the rate constants were unaffected by the presence of cuprous ion, supplied as bis(cyclohexene)-copper(I) triflate,[17] cuprous iodide, or tetrakisacetonitrile-copper(I) perchlorate,[18] or of benzoic acid (Tables I and II). In the case of cuprous *o*-nitrobenzoate, the first-order kinetics are verified by the insensitivity of the rate constants to concentration (Table I); this result appears to conflict with those of an earlier study.[12]

Products. The products were of two types: those derived only from the cuprous carboxylate and those derived from the solvent (the latter type was investigated only for the cases in which quinoline was the solvent). The most prominent members of the former category were carbon dioxide, a major product in all cases, and arene (the product of replacement of the cuprocarboxyl group with a hydrogen atom), which was always a major product even when no obvious "active proton" source was present. In most of the cases in which the arene yield was determined, it was over 50% (Table III); only in the case of cuprous o-nitrobenzoate was the yield (18–23%) of arene less and in that case another aryl-containing product, 2,2′-dinitrobiphenyl (biaryl), was formed in 63% yield. The only other salts which produced biaryl in noticeable yield were cuprous 3-methyl-2-nitrobenzoate and *o*-fluorobenzoate, in which cases the yields were 14 and 10%, respectively.

The only other type of product in this category which was formed in significant yield was diaryl ketone. A 13% yield of 2,2′-difluorobenzophenone was isolated from the decarboxylation product of cuprous *o*-fluorobenzoate generated from the reaction of the anhydride and cuprous oxide; a major factor in the structural proof of this ketone is its 250-MHz NMR spectrum, which is analyzed in the Appendix. The corresponding ketones also appeared (by gas chromatography) to be products of comparable significance in the decarboxylation of cuprous *o*-nitrobenzoate, pentafluorobenzoate, and *o*-methoxybenzoate. The decarboxylations of cuprous benzoate, generated by all four methods, produced trace amounts of benzophenone and the decarboxylation of cuprous *p*-methoxybenzoate produced trace amounts of the corresponding ketone. That of *p*-nitrobenzoate yielded no detectable quantity of the ketone.

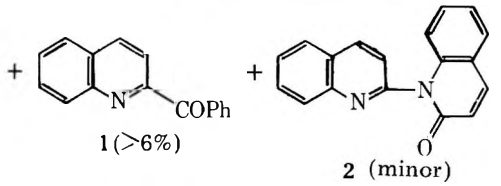
The products containing the quinoline nucleus were of two general types, those containing an aryl nucleus as well, such as aryl- and acylquinolines, and those containing only the quinoline nucleus, such as biquinolyls (Q_2) and compounds containing an oxygen in addition to two quinolyl groups (oxybiquinolyls, Q_2O). The decarboxylation of cuprous benzoate, prepared by any of the four methods, yielded 2-benzoylquinoline (**1**). This product was isolated in 6% yield[19] from the reaction of benzoic anhydride with cuprous oxide (method C), but some was undoubtedly lost during the extensive purification procedure; the same product was isolated by preparative high-pressure liquid chromatography from the decarboxylation of cuprous benzoate prepared by the redox method (D). It is worthwhile to note that considering the 67% yield of carbon dioxide formed in the decarboxylation leading to the 6% of **1**, a maximum yield[19] of 33% of the latter is possible.

The gas chromatograms of most of the product mixtures (but not of that from cuprous benzoate) exhibited at least two peaks, the combined gas chromatographic mass spectrum of which indicated that they are probably arylquinolines. Some gas chromatographic yields are given in Table III. Only in the case of cuprous *p*-nitrobenzoate could the yield (14%)[19] of arylquinolines be considered substantial.

All of the product mixtures exhibited a number of gas chromatographic peaks, the mass spectra of which suggest that they are biquinolyls and monooxygenated biquinolyls. None of the biquinolyls is 2,2′-biquinoline, a sample of which was in hand. Two of the biquinolyls were isolated in small amounts by HPLC of the products of decarboxylation of cuprous *p*-nitrobenzoate and are labeled biquinolyls 1 and 2 (Q_2-1, and Q_2-2). The first of these (Q_2-1) was also isolated from the cuprous benzoate decarboxylation. Their melting points and mass spectra are described in the Experimental Section. The oxygenated biquinolyls are apparently not phenols, since extracting the mixture with strong aqueous base did not change the appearance of the gas chromatogram. A very minor product of this kind, formed in the cuprous benzoate experiment, was shown to be *N*-2-quinolyl-2-quinolone (**2**) by comparison of its retention time and mass spectrum with those of an authentic sample. The predominant oxybiquinoline isomer, labeled Q_2O-1 in Table IV (see paragraph at end of paper about supplementary material), is presumably

Scheme I

$$PhCO_2Cu + C_9H_7N \xrightarrow{\Delta} CO_2 + PhH + Ph_2CO$$
67% 64% tr



1 (>6%) 2 (minor)

$$+ [(C_9H_6N)_2 + (C_9H_6N)_2O] \quad (1)$$
17%

$$o\text{-}FC_6H_4CO_2Cu + C_9H_7N \xrightarrow{\Delta} CO_2 + PhF + (FC_6H_4)_2CO$$
96% major >13%

$$+ (FC_6H_4)_2 + C_9H_6NCOC_6H_4F + [(C_9H_6N)_2 + (C_9H_6N)_2O] \quad (2)$$
10% minor

$$o\text{-}NO_2C_6H_4CO_2Cu + C_9H_7N \xrightarrow{\Delta} CO_2 + PhNO_2$$
91% 23%

$$+ (o\text{-}NO_2C_6H_4)_2 + C_9H_6NC_6H_4NO_2 + [(C_9H_6N)_2$$
62% 0.8%

$$+ (C_9H_6N)_2O] \quad (3)$$
0.4%

$$p\text{-}NO_2C_6H_4CO_2Cu + C_9H_7N \xrightarrow{\Delta} CO_2 + PhNO_2$$
93% 74%

$$+ C_9H_6NC_6H_4NO_2 + [(C_9H_6N)_2 + (C_9H_6N)_2O] \quad (4)$$
14% 51%

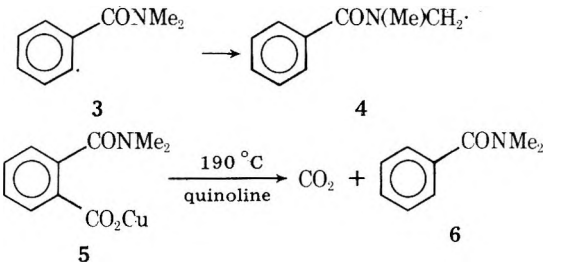
either another *N*-quinolylquinolone or a diquinolyl ether. Another compound with a somewhat longer retention time than Q_2O-1 did not elute from the gas chromatograph attached to the mass spectrometer and its constitution is unknown; however, judging from its retention time, this material, labeled "unknown" in Table IV, probably contains two quinolyl groups. Finally, a very small quantity of 2-quinolinol was identified and isolated from the cuprous benzoate decarboxylation.

A significant finding is that the relative gas chromatographic peak heights of compounds Q_2-1, Q_2-2, Q_2O-1, and the unknown were remarkably similar in all of the decarboxylation products in which they were measured (Table IV). Furthermore, these same four compounds were observed in approximately the same relative yields when pentafluorophenylcopper was submitted to the reaction conditions (Table IV).

Equations 1–4 (Scheme I), in which information from more than one method is combined, provide a concise overall picture of the types and quantities of products which are formed in some representative examples.

The cuprous salts (formed by the redox method D) of the saturated acids 1-adamantanecarboxylic and dodecanoic acid were found to decarboxylate extremely slowly in quinoline; only about 6% of carbon dioxide was evolved in 3 h at 205 °C. Adamantane was the main neutral product in the former case; in addition, adamantylquinolines were produced and the pattern of biquinolyls and oxybiquinolines was the same as that from the decarboxylations of the aromatic carboxylates. However, in the case of cuprous decanoate, the neutral layer contained about 12 compounds and, although traces of nonylquinolines were formed, the traces of biquinolyls and oxybiquinolines differed gas chromatographically from those obtained from the aromatic carboxylates.

It has previously been shown that the o-*N*,*N*-dimethylbenzamido radical (**3**) undergoes an extremely rapid 1,5-hydrogen atom transfer to yield **4**.[20,21] In order to probe the possibility that aryl radicals are intermediates in the copper–quinoline decarboxylation, cuprous *N*,*N*-dimethylphthalamate (**5**) was decarboxylated at 190 °C in quinoline; a quantitative yield of carbon dioxide was produced and the only neutral organic product was *N*,*N*-dimethylbenzamide (**6**).



The modes of formation of 2,2′-dinitrobiphenyl and especially of nitrobenzene, the major organic products from the decarboxylation of cuprous *o*-nitrobenzoate, were investigated next. Table V (see paragraph at end of paper about supplementary material) indicates how the yields of these two products vary with concentration and additives. There is a tendency for the yield of biaryl to increase at the expense of that of nitrobenzene as the concentration of reactants increases and as the concentration of external cuprous salts increase. Although the presence of benzoic acid does not change the rate constant for decarboxylation (Table I), the presence of 0.2 M benzoic acid causes a very marked increase in the ratio of nitrobenzene to biaryl produced; carboxy-labeled deuteriobenzoic acid has the same effect but leads to nitrobenzene which is 52% monodeuterated. It thus appears that an intermediate or product is becoming protonated; this is consistent with the earlier finding[4] that the presence of water increases the yield of nitrobenzene relative to that of biaryl. If an arylcopper intermediate has a choice of protonation or self-coupling, then the presence of cupric salts could affect the ratio of arene to biaryl produced, since cupric salts have been shown[22] to increase the rate of self-coupling of arylcopper(I) compounds; however, the presence of 0.75 M cupric chloride during the decarboxylation of cuprous *o*-fluorobenzoate, *p*-nitrobenzoate, and 1-naphthoate (all 0.75 M in quinoline solution at 200 °C) did not change the distribution of organic products.

In order to explore the possibility that the species which becomes protonated accumulates in the reaction mixture, samples were withdrawn at 5-min intervals (starting 25 min after the required temperature was reached) and quenched with DCl, and the deuterium incorporation into the nitrobenzene and the ratio of gas chromatographic peak heights of nitrobenzene to those of 2,2-dinitrobiphenyl were determined. The values of the latter at increasing times were found to be as follows: 24, 2.0, 1.5, 1.2, 1.3, 1.1, 1.1, 1.2, 1.3, 1.2; no deuterium was found in the nitrobenzene. In another experiment in which HCl was used for the quench and the first sample withdrawn 5 min earlier, the peak height ratios were 128, 21, 12, 1.3, 1.2, 1.8, 1.4, 0.9, 0.9, 0.9, 1.0.

These experiments imply that the species which is being protonated, presumably an arylcopper, is an intermediate which does not accumulate in the reaction mixture. This is consistent with the finding of Cairncross et al.[9] that a putative arylcopper intermediate could be trapped with iodobenzoate if the latter were present during the decarboxylation of cuprous *o*-nitrobenzoate in quinoline but not if it were added after gas evolution had ceased.

The quenching experiments also provide a clue as to the origin of at least some of the protons which replace the carboxylate groups. It appears that a small quantity of a proton source is present, probably as a contaminant, in the solvent and that the intermediate is easily protonated as long as the proton source lasts. When pyridine which was 1.25 M in D_2O

was used as the medium, the nitrobenzene (80% yield) formed by decarboxylation was 94% monodeuterated. However, moisture in the solvent could only account for 0.7% of the 18% of nitrobenzene ordinarily produced, since a Karl Fischer titration of the purified quinoline which was used as solvent was found to be 2.5×10^{-3} M in water. Another possible source of protons is the water of hydration of the cupric *o*-nitrobenzoate. When the latter was shaken in D_2O, placed for 12 h in a vacuum desiccator which was evacuated by a mechanical pump, and then decarboxylated, the arene (48% yield) produced by its decarboxylation was found to be deuterated to the extent of 54%. However, cupric *o*-nitrobenzoate which had been heated in an oven for 12 h at ~110 °C prior to being placed in a vacuum desiccator (the usual procedure used in this work) was subjected to elemental analysis and found to be anhydrous within the usual limits of error. The major source of "active protons" in the solution may be water contaminating the copper powder; an analysis performed after the completion of most of the work reported here indicated that this metal contained 0.8% water, enough to account for about 26% of the nitrobenzene produced.

The remainder of the protons appear to be slowly generated during the reaction and it is reasonable to suppose that these protons are released during the various coupling reactions of the quinoline. This supposition was verified by conducting the decarboxylation of cuprous *o*-nitrobenzoate (prepared by method B) in a 1.25 M solution in 2-deuterioquinoline (97 ± 0.7% enriched);[23] 7% of the nitrobenzene formed (20% yield) was monodeuterated. When cuprous benzoate was decarboxylated in 2-deuterioquinoline (81% monodeuterated) a substantial decrease in benzene formation was observed (Table III), probably indicating an isotope effect, and the benzene was 13% monodeuterated. In view of the types of compounds containing quinolyl groups identified in the product mixtures, it is clear that protons are also released from positions other than the 2 position of quinoline and the solvent must thus be considered as a major source of hydrogen.

Two experiments were performed in order to determine if the ketones produced in the decarboxylations could result from attack of an anhydride on an arylcopper. In the first, *m*-(trifluoromethyl)phenylcopper[24] was treated with benzoic anhydride in ether at room temperature; combined GC–MS analysis indicated the presence of 3-(trifluoromethyl)benzophenone, in addition to 3-trifluoromethylphenyl benzoate, ethyl benzoate, and 3,3′-bis(trifluoromethyl)biphenyl, the normal product of self-coupling of the arylcopper.[24,25] In the second experiment, *o*-nitrobenzoic anhydride was heated in quinoline at 140 °C in the presence of an equivalent quantity of cuprous oxide and benzoic anhydride, since the former anhydride readily undergoes decarboxylation under these conditions and the latter decarboxylates slowly even at 200 °C; analysis of the neutral layer by GC–MS indicated the presence of 2-nitrobenzophenone, presumably formed by benzoylation of a reaction intermediate, in addition to nitrobenzene and 2,2′-dinitrobiphenyl.

Discussion

Preparative Methods for Cuprous Carboxylates. An apparently general, albeit tedious, method (B) for preparing cuprous carboxylates is the exchange reaction between carboxylic acids and freshly sublimed cuprous *tert*-butoxide. An in situ method, C, which consists of generation of the cuprous salt by heating the anhydride with cuprous oxide in the quinoline solvent, is satisfactory for product studies but not for studies of the kinetics of decarboxylation. The preferred method, D, appropriate for both types of studies, is the reduction by copper powder of the corresponding cupric salt in quinoline or pyridine.

The Question of an Aryl Radical Intermediate. The argument of Cohen and Schambach[4] against a radical intermediate on the basis of the high stereoselectivity in geometrically isomeric vinyl systems is supported by the production of only *N,N*-dimethylbenzamide (**6**) from the decarboxylation of the cuprous salt (**5**) of *N,N*-dimethylphthalamic acid, since the formation of the aryl radical **3** would be expected to yield products derived from the radical **4**; the 1,5-hydrogen shift which converts **3** to **4** is detectable even in the presence of a large concentration of cupric chloride,[20,21] which is capable of transferring a chlorine atom to an organic radical at a rate approaching that of a diffusion-controlled process.[26] Thus radical **3** could only be involved if some unknown reaction which yields **6** from the aryl radical is faster than this exceedingly rapid hydrogen transfer.

The Question of an Arylcopper Intermediate. Prior to the initiation of the present work, the evidence for an organocopper intermediate in the copper–quinoline decarboxylation consisted of trapping of the intermediate by aryl iodides and by protons, self-coupling to form biaryls, and, in one case, isolation of an aryl copper. However, all of these demonstrations have occurred with arenecarboxylates which are activated toward decarboxylation, usually by the presence of strong electron-withdrawing groups. No self-coupling was observed in the present work except with *o*-fluoro and o-nitro substituents. Attempted trapping of an intermediate with aryl iodides in the case of nonactivated cuprous carboxylates would be impractical, since cuprous carboxylates themselves react rapidly with aryl iodides to form aryl carboxylates at the temperatures required for decarboxylation.[14]

However, an important indication that organocoppers may also be present in the decarboxylations of nonactivated cuprous carboxylates is that four biquinolyl and oxybiquinolyl products were formed in similar proportions in the decarboxylations of all of the aromatic cuprous carboxylates in quinoline but not when cuprous decanoate, which hardly decarboxylates under the usual conditions, was heated in quinoline solution. The same four products were formed in similar proportions during the decarboxylation of cuprous pentafluorobenzoate, a reaction which has been shown to produce an isolable organocopper, and, most importantly, during the heating of an authentic sample of pentafluorophenylcopper in quinoline at the temperature at which the majority of the decarboxylations were performed (Table IV). It is thus likely that an organocopper is somehow involved in the production of these four compounds. It may be that organocoppers formed in the decarboxylation of unactivated acids metalate the quinoline to produce quinolylcoppers faster than they self-couple and the quinolylcoppers may then couple or undergo further reaction; a mechanism for quinoline metalation is suggested below.

The identification of ketone products in which an acyl group has replaced the carboxyl group can be readily explained on the basis of acylation of an arylcopper by an anhydride. 2-Nitrobenzophenone was formed when benzoic anhydride was present during the decarboxylation of cuprous *o*-nitrobenzoate in quinoline. Furthermore, *m*-(trifluoromethyl)phenylcopper was successfully benzoylated with the same anhydride.

However, the absence of self-coupling in a number of cases must cause some reservations about the possibility of organocoppers as major intermediates. It has been shown by Lewin and Cohen[8] that the copper-induced coupling of *p*-iodotoluene in quinoline produces an intermediate, thought to be an organocopper, which is capable of self-coupling or protonation by an acid. In the present work, the decarboxylation of cuprous *p*-toluate gave no bitolyl; this was true even when Ullmann reaction conditions were simulated by adding copper metal and cuprous iodide to the reaction mixture. Nevertheless, this evidence against organocopper intermediates in

nonactivated cases should not be considered definitive, since the behavior of the organocopper intermediate in these reactions may be decisively controlled by the oxidation state of the metal and the nature of the ligands as the intermediate is produced.[27]

Source of Protons. The major product formed in the decarboxylation of most of the cuprous carboxylates is one in which the carboxyl group has been replaced by a proton. As indicated above, a portion of the protons which replace the carboxyl group is probably derived from traces of water in the reagents, particularly the copper metal. Much of the remainder presumably must be derived from the hydrogen atoms of the quinoline. This is indicated by the experiments in which 2-deuterioquinoline was used as solvent. The yield of benzene from cuprous benzoate was significantly decreased (Table III), presumably due to an isotope effect, and the benzene formed was partially monodeuterated; similarly, the nitrobenzene from cuprous *o*-nitrobenzoate was partially monodeuterated. Since all of the substitution is not at the 2 position in the quinoline-containing products, it is clear that protons from unlabeled positions of the 2-deuterioquinoline must also be released. Assuming that all of the protons released from the quinoline (QH) are utilized in the replacement of carboxyl groups, the stoichiometry indicated in the equations

$$2ArCO_2Cu + QH \rightarrow ArH + QCOAr + CO_2 + Cu_2O \quad (5)$$

$$2ArCO_2Cu + QH \rightarrow ArH + QAr + 2CO_2 + 2Cu \quad (6)$$

$$2ArCO_2Cu + 2QH \rightarrow 2ArH + Q_2 + 2CO_2 + 2Cu \quad (7)$$

$$4ArCO_2Cu + 2QH \rightarrow 2ArH + Q_2O + (ArCO)_2O + 2CO_2 + 4Cu \quad (8)$$

appears likely for the production of acyl- and arylquinolines (QCOAr and QAr), biquinolyls (Q_2), and oxybiquinolyls (Q_2O), respectively. In the case of the last equation, the anhydride could react with Cu_2O from eq 5 to regenerate cuprous carboxylate, it could react with traces of water to yield carboxylic acid and thence arene and CO_2, or it could be used to acylate a quinolylcopper (see below).[31]

The reaction of an arylcopper(I) compound with quinoline has also been noted recently by Lewin.[32] She has found that 1-naphthylcopper reacts at 160 °C with quinoline to give ~50% naphthalene, 1,1′-binaphthyl, two isomers of 1-naphthylquinoline, and small quantities of biquinolyls. Essentially the same results were obtained when 1-iodonaphthalene was heated in quinoline with copper under the same conditions.

$$ArCu + QH \rightarrow QAr + QQ + ArH$$

It is thus clear that arylcopper(I) compounds can react with quinoline. At the present state of knowledge of transition metal organometallics, reasonable mechanisms can be put forth for the results reported here.

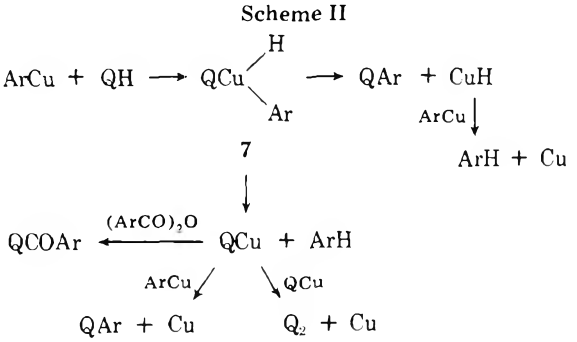
Oxidative addition of aromatic CH bonds to transition metals in low oxidation states is a recognized process.[33] Such an oxidative addition of a CH bond of quinoline to the copper of an arylcopper(I) reactant or intermediate would lead to the organocopper(III) 7 (Scheme II).[28] This key intermediate could undergo reductive elimination in either of two directions. One of these leads to an arylquinoline and cuprous hydride; the latter would be capable of reacting with an arylcopper to yield arene and copper metal.[34] The other direction leads to an arene and a quinolylcopper; the latter could become acylated, as demonstrated in the Results section, by a molecule of anhydride (formed by eq 8 or by the reverse of the reaction of cuprous oxide with anhydride to produce cuprous carboxylate by method C), it could couple with arylcopper to yield an arylquinoline, or it could couple with another quinolylcopper to produce a biquinolyl.

Table VI. Relationship of Yields of Arenes and Quinoline-Containing Products[a]

Cuprous salt	% yield of arene	% yield of (QAr + QCOAr + Q_2 + Q_2O)
o-Nitrobenzoate	23	7.7
Benzoate	54–64	23
p-Nitrobenzoate	74	65

[a] Data from Table III.

Scheme II



An apparently analogous replacement of a copper(I) attached to an sp^2 carbon atom by hydrogen (presumably derived from solvent) was observed by van Koten and Noltes[35] when the organocopper compound was heated in quinoline to 200 °C. Another analogy, possibly occurring by the same type of mechanism, is the exchange of the proton at the 2 position of acrylonitrile for a deuteron when the former is treated with a copper(I)–isonitrile complex and Me_3COD.[36]

If, indeed, some of the arene is produced by adventitious proton sources present in the reactants and the remainder by the hydrogens released from the quinoline, the yields of quinoline-containing products should be a sensitive function of the yield of arene. This, in fact, appears to be true for the three cases in which the yields of the basic products were determined (Table VI).

Kinetic Order. The kinetics are clearly first order in the cuprous carboxylate in all cases. In the case of cuprous *o*-nitrobenzoate, this order is confirmed by the invariance of the rate with concentration over the limited range studied (Table I)[37] and its insensitivity to the presence of soluble cuprous salts. Since the cuprous carboxylate consists of two parts, a cation and an anion, the first-order kinetics could be indicative that: (1) the cuprous carboxylate behaves as a single unit; (2) the reaction is first order in carboxylate and zero order in cuprous ion; or (3) the reaction is first order in cuprous ion and zero order in the carboxylate ion. The second possibility may be excluded by a study involving cupric o-nitrobenzoate, which was shown to decarboxylate 100 times slower than the cuprous salt; cuprous ion is thus required for the decarboxylation.[38] The third possibility is excluded by the results presented in Tables I and II; added cuprous salts are shown not to influence the rate of decarboxylation of the cuprous carboxylate. It therefore appears that the cuprous carboxylate is acting as a unit and the reaction is first order in this unit. This behavior by the cuprous carboxylate could be explained as the result of ion pairing, which would certainly be expected in a solvent of such low polarity.

Substituent Effects. The relative rates for the decarboxylation of substituted cuprous benzoates in quinoline at 197 °C are (Table II): *p*-nitro, 33; 3-methyl-4-nitro, 20; *o*-fluoro, 8.8; *o*-*tert*-butyl, 4.9; *o*-methyl, 4.2; 2,6-dimethyl, 2.3; unsubstituted, 1.0. Only the o-nitro group has a very substantial effect, allowing a comparable rate at 122 °C. When the 2-nitro group is twisted out of the plane of the ring by an *o*-methyl

group (cuprous 3-methyl-2-nitrobenzoate), the rate decreases by a factor of 10. When a methyl group is placed ortho to the carboxylate function in cuprous *o*-nitrobenzoate, a large decrease in rate is also noted.

The *p*-nitro substituent moderately accelerates the reaction (Table II). Twisting the nitro group out of the plane of the ring, as in the case of cuprous 3-methyl-4-nitrobenzoate, decreases the influence of this group. The *o*-fluoro substituent also mildly accelerates the reaction. *o*-*tert*-Butyl and o-methyl groups weakly accelerate the reaction. The substitution of a second *o*-methyl group decreases the rate slightly. An *o*-methyl group introduced in addition to an *o*-nitro group already present greatly slows the rate of the reaction (Table II). The nitrogen of the pyridine ring in the 2 position is very much less effective than an *o*-nitro substituent at facilitating the decarboxylation.

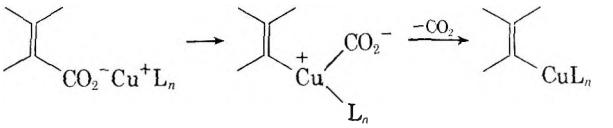
Solvent Effects. This study represents the first reported instance in which pyridine was used as the solvent for the decarboxylation reaction of cuprous salts. From the work of Cohen and Schambach[4] and of Cairncross, Roland, Henderson, and Sheppard[9] it is seen that the rate of the decarboxylation is enhanced by the presence of complexing agents for cuprous ions, and the better the complexing ability of the agent the more effective it is in promoting the reaction. The rate enhancement by 2,2′-bipyridyl was reported to be greater than that by 2,2′-biquinoline.[4] This same sort of relationship seems to hold in the present study. The rate constant found for the decarboxylation of cuprous *o*-nitrobenzoate in quinoline at 122 °C is 1.96×10^{-4} s^{-1}, while that for the decarboxylation of the same salt in pyridine at 116 °C is $(3.13 \pm 0.03) \times 10^{-4}$ s^{-1}. The faster rate in pyridine may be due to less steric hindrance to complexation of the cuprous ion by the smaller pyridine molecule.

Thermodynamic Parameters. Decarboxylations of two of the salts in quinoline at several temperatures (Table II) has allowed the computation[39] of the following thermodynamic quantities of activation: cuprous benzoate, $\Delta H^{\ddagger} = 33$ kcal/mol and $\Delta S^{\ddagger} = -7.3$ cal/deg-mol; cuprous *o*-fluorobenzoate, $\Delta H^{\ddagger} = 39$ kcal/mol and $\Delta S^{\ddagger} +9.9$ cal/deg-mol.

The Role of Copper in the Loss of Carbon Dioxide. Cohen and Schambach[4] have proposed that the copper(I) ion, with its heterocyclic ligands, forms a τ complex with the aromatic ring of the carboxylate anion. Loss of carbon dioxide from the complex yields a σ carbanion stabilized by the π-complexed metal ion. This species then collapses to an arylcopper(I) compound. The present results are consistent with this mechanism in that one cuprous ion and one carboxylate are involved, electron withdrawing groups increase the rate, and ortho substituents, which are expected to cause steric strain which is relieved in the transition state for loss of carbon dioxide, generally increase the rate. The attenuation of this rate increase with the introduction of a second ortho substituent could be due to steric hindrance to π-complex formation which could occur near the vacant ortho site when a single ortho substituent is present. The ortho nitro group, in addition to having steric bulk and being electron withdrawing, may complex with the copper(I) during the π complexation of the latter.

However, the kinetic results reported here suggest a close mechanistic relationship between the cuprous carboxylate decarboxylation, the Ullmann biaryl coupling,[40-42] and the exchange reaction of aryl and vinyl halides with the anions of copper(I) salts.[20,41,43-49] In all three types of reaction, substituent effects on the rate are extremely modest, nearly all substituents increase the rate, and nitro groups are activating in both ortho and para positions but the ortho effect is far more pronounced. Extensive kinetic studies on the exchange reaction have established that it is first order in copper(I); whereas such studies are precluded in the usual heterogeneous biaryl coupling, the recently discovered homogeneous Ullmann biaryl coupling (which under some conditions is accompanied by an exchange process) was also found to be first order in copper(I).[30] In all three cases, a reaction intermediate, presumed to be an organocopper, can be protonated in the presence of acids.[4,7,8,14,20,30,50,51] In all three reactions, vinyl derivatives react with high degrees of retention of configuration,[4,11b,50,54] a fact which is believed to support a nonradical process; other evidence against a radical mechanism in these reactions is also found in the present results and in ref 20, 30 and 53.

In view of these similarities, it is tempting to suggest a similar mode of participation by copper(I) in these processes. An oxidative addition of the aryl or vinyl halide to the copper(I) appears to be indicated in the Ullmann biaryl reaction[30] and in the exchange reactions.[20,52] Application to the decarboxylation reaction would involve insertion of the copper(I), with associated ligands, into the carbon–carbon bond of the carboxylate (possibly after forming a π complex with the aromatic ring) to form a copper(III) intermediate which would be capable of rapid conversion to a copper(I) compound by loss of carbon dioxide.



The suggested process is analogous to the oxidative addition of aromatic CH groups to various transition metals.[33] In view of the fact that CH and CCO_2^- often behave analogously (one has been termed a carboxylogue of the other[55]), it does not seem unreasonable to suggest such a mechanism.

The small substituent effects are well accounted for by such a mechanism, since a substantial charge never gets dispersed into the ring. On the other hand, the carbon atom bearing the carboxylate group decreases its oxidation number during the substitution by the metal and this accounts for the accelerating effect of electron-withdrawing groups; rather similar substituent effects have been noted in the oxidative addition of aromatic CH groups to transition metal complexes.[33,56] The role of the *o*-nitro group in coordinating with the metal during the process is also understandable.

Conclusions

Cuprous carboxylates for decarboxylation studies can be prepared generally by treatment of carboxylic acids with sublimed cuprous *tert*-butoxide or more readily by reduction of a cupric carboxylate with copper metal in the pyridine or quinoline that is to be used as a solvent.

The coupling to a biaryl found with cuprous *o*-nitrobenzoate is not a general reaction. Unactivated cuprous carboxylates decompose in quinoline to form arene and a variety of other products, most of them derived from the solvent; the protons that replace the carboxyl group appear to be derived largely from the solvent. The pattern of products containing two quinoline nuclei is the same for all of the aromatic decarboxylations studied and for the products of reaction of an authentic arylcopper with quinoline, and this is the main evidence for an arylcopper intermediate in the case of unactivated carboxylates. The rich variety of products formed in most cases makes it unlikely that the decarboxylation of pure cuprous carboxylates in heterocyclic solvents will be a generally useful synthetic procedure.

The kinetics and especially the substituent effects are consistent either with a mechanism in which a cuprous ion, π complexed to the aromatic ring, stabilizes the developing negative charge as the carbon dioxide is lost or one in which the carboxyl carbon–carbon bond oxidatively adds to the metal ion (which may be similarly π-complexed), followed by

loss of the carbon dioxide ligand from the resulting copper(III) species.

Experimental Section

Melting points (mp) are corrected. Infrared (IR) spectra were recorded on a Beckman IR-8 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra at 60 MHz were taken on Varian A-60D and T-60 spectrometers and those at 250 MHz were taken on a custom built spectrometer utilizing a supercooled solanoid; chemical shift data are reported in units of δ (ppm) relative to internal tetramethylsilane. Mass spectra (MS) were recorded at an ionizing voltage of 70 eV, unless otherwise specified, on an LKB-9000 combined gas chromatograph–mass spectrometer; the *m/e* values are followed in parentheses by the intensity as a percentage of the base peak and the assignment, if known. The combined GLC–mass spectra of all arenes and of the arylquinolines of unknown isomeric structure are recorded in the supplementary material (see paragraph at the end of the paper). High-resolution mass spectra were taken on an AEI MS-9 spectrometer. Gas-liquid chromatographic (GLC) analyses were performed on a Hewlett-Packard 5750 gas chromatograph equipped with a Disc integrator or a Hewlett-Packard electronic integrator. Yields were calculated from peak areas using internal standard techniques. High-pressure liquid chromatography was performed on a DuPont 600 instrument.

Decarboxylation Procedure. Most of the kinetic runs were replicated at least three times; the error limits given in the tables are average deviations for the three or more runs. The reproducibility was always excellent and in a few cases only one decarboxylation was performed; no error limits are listed for those cases.

A. Apparatus. The glassware was dried in an oven at 110 °C for 24 h, assembled while hot, and purged with nitrogen for 30 min. A three-neck (four-neck, when samples were to be withdrawn) round-bottom flask fitted with a condenser, thermometer, and gas inlet tube and containing a magnetic stirring bar was used. During reaction, the evolved carbon dioxide was swept with a stream of nitrogen through the condenser and a cold trap cooled by a mixture of dry ice and isopropyl alcohol and finally through two Ascarite tubes which absorbed the carbon dioxide. The reaction temperature was maintained either by an electric mantle or a sand bath (Tecam, Techne, L and D., Duxford, England) controlled within ±0.5 °C by a Thermowatch (I^2R, model L-6, Cheltenham, Pa.).

B. Method B. The cuprous salt, prepared (see below) by metalation of the appropriate acid with cuprous *tert*-butoxide, was charged into the flask which was contained in a dry and oxygen-free atmosphere in a glove box. After the apparatus had been removed from the glovebox, the freshly distilled solvent was injected through a serum cap into the flask. A thermometer was substituted for the serum cap, the system was purged with nitrogen until the Ascarite tubes reached a constant weight, the flask was heated to the desired temperature, and the weighings commenced; the experiment was terminated when carbon dioxide evolution ceased.

C. Method C. A mixture of the solvent and cuprous oxide under a nitrogen purge was heated at the reaction temperature until the weights of the Ascarite tubes had stabilized, the anhydride was quickly added, and the tube weighings were started.

D. Method D. A mixture of the cupric salt (prepared as described below), an equivalent quantity of copper powder, and the solvent was heated to 70 °C for 30 min in the case of cupric salts containing *o*-nitro groups and to 130 °C in the case of other cupric salts. The Ascarite tubes were weighed, the flask was heated to the decarboxylation temperature, and the weighings were started.

E. Analysis of Products. (1) General Procedure. In most cases the qualitative and/or quantitative analyses of a reaction mixture or sample were performed using gas-liquid chromatography (GLC). The columns used are indicated in each case and the nitrogen flow rate was 60 mL/min; the initial column temperature was 80 °C with a programmed rise of 8 or 10°/min to 300 °C, where the temperature was maintained for 10 min. Combined GLC–mass spectrometric analyses were conducted on columns of 1.5% SE-30, 3% OV-17, or 2.0% Dexsil; the column temperature was slowly increased from 80 °C to the column limit and maintained at that temperature.

In order to prepare the product mixtures for qualitative and semiquantitative analysis approximately half of the mixture was dissolved in ether, and this solution was extracted with 1 N hydrochloric acid, washed with water, dried over anhydrous magnesium sulfate, and concentrated to provide the neutral fraction; the acid extract was neutralized with sodium bicarbonate, made slightly basic with concentrated ammonium hydroxide, extracted with ether, and dried over anhydrous magnesium sulfate to give the basic fraction. When the neutral fraction was to be analyzed quantitatively, the internal standard, *n*-octadecane, was added to the entire reaction mixture, which was then treated in the manner described above. When the basic fraction was to be analyzed quantitatively, the quinoline solvent was first removed by vacuum distillation and the internal standard, durene, was then added.

(2) Cuprous *o*-Nitrobenzoate (Methods B, C, and D, Pyridine and Quinoline). Regardless of the method of preparation, the neutral fraction, analyzed on a 3% OV-17 column, contained the following products [compound, retention time, mass spectrum *m/e* (rel intensity, assignment)]: nitrobenzene, 5.9 min; 2,2′-dinitrobiphenyl, 22 min, 199 (14.6), 198 (100, P − NO_2), 168 (16, P − NO_2 − NO), 140 (11), 139 (41), 116 (10), 115 (27), 63 (14) (no parent peak was evident even at 12.5 eV). The mass spectra were similar to those of authentic samples and the identities were further confirmed by coinjection on both the OV-17 and 1% OV-1 columns. Further confirmation was obtained when 2,2′-dinitrobiphenyl was isolated in 69% yield by distillation from a pyridine run; its melting point, 127.5–128.0 °C, was identical with that of the authentic sample (Aldrich).

The basic fractions from pyridine runs contained only traces of material, the mass spectra of which indicated that they may be 2-nitrodiphenylamine and an isomer of o-nitrophenylpyridine. The basic fractions from the quinoline runs analyzed by GLC–MS as follows: isomer of *o*-nitrophenylquinoline, 18 min; isomer of *o*-nitrophenylquinoline, 20.2 min; isomer of *o*-nitrophenylquinoline, 20.4 min; isomer of biquinoline, hereafter referred to as biquinolyl 1 (Q_2-1), 22 min, 257 (19.2, P + 1), 256 (96, P), 255 (100, P − H), 254 (13.3), 229 (5.5), 228 (8.2), 227 (8.2), 200 (4.5), 201 (4.5), 128 (12.6, quinolyl$^+$), 127 (4.5), 101 (10, quinolyl$^+$ − HCN); isomer of diquinolyl ether, hereafter referred to as oxybiquinolyl 1 (Q_2O-1), 22.5 min, 273 (6.8, P + 1), 272 (24.6, P), 271 (100, P − H), 243 (11), 231 (6), 136 (9), 128 (13, quinolyl$^+$), 101 (12, quinolyl$^+$ − HCN), 77 (6). The coinjection of 2,2′-biquinoline and the reaction mixture containing biquinolyl isomer 1 on 3% OV-17 indicated that the biquinolyl isomer 1 is not 2,2′-biquinoline. The coinjection of the reaction mixture and 2,2′-diquinolyl ether[57a] produced an increase in the peak height of the diquinolyl ether isomer 1 relative to the other peaks, and peaks foreign to the reaction mixture did not appear; unfortunately, this is not an unambiguous identification, since a second column satisfactory for coinjection could not be found and the melting point of this material (see below) involves an ambiguity.

(3) Cuprous 3-Methyl-2-nitrobenzoate (C, Quinoline). The neutral fraction on 3% OV-17 indicated the presence of: *o*-nitrotoluene, 6.2 min; 3,3′-dimethyl-2,2′-dinitrobiphenyl, 2.3 min, 228 (2.3), 227 (17.9), 226 (100, P − NO_2), 208 (12), 207 (21), 198 (14), 196 (20, P − NO_2 − NO), 195 (22), 183 (12), 180 (11), 170 (11), 165 (18), 115 (24), 104 (11), 91 (11), 89 (15), 77 (32), 75 (18), 74 (11), 65 (22) (no parent peak was present at 20 eV). The identity of *o*-nitrotoluene was confirmed by coinjection with an authentic sample. An authentic sample of the biaryl was not available; however, the fact that the retention time is slightly greater than that of 2,2′-dinitrobiphenyl and the similarity of the fragmentation patterns of the two compounds add credence to its identification.

The following compounds were identified by GLC–MS in the basic fraction: isomer of 3-methyl-2-nitrophenylquinoline, 12.2 min; isomer of 3-methyl-2-nitrophenylquinoline, 16.5 min; isomer of 3-methyl-2-nitrophenylquinoline, 17.4 min.

(4) Cuprous *p*-Nitrobenzoate (D, Quinoline). Nitrobenzene, identified by its retention time and mass spectrum, was the only neutral product. The GLC–MS analysis of the basic fraction revealed the presence of: 2-quinolinol, 16 min, identified by comparison with an authentic sample (Eastman) with respect to melting point, GLC, and MS behavior; isomer of *p*-nitrophenylquinoline, 19 min; isomer of *p*-nitrophenylquinoline, 19.5 min; isomer of *p*-nitrophenylquinoline, 20.7 min; biquinolyl 1, 22.2 min; oxybiquinolyl 1, 22.5 min; unknown (hereafter known as biquinolyl 2, Q_2-2), 23.4 min, 257 (20, P + 1), 256 (100, P), 255 (47), 154 (16), 128 (28, quinolyl$^+$), 97 (9), 85 (10), 82 (10), 71 (15), 69 (12). Biquinolyl 1 and oxybiquinolyl 1 were identified by comparison of their MS with those of the corresponding products from decarboxylation of cuprous o-nitrobenzoate and by coinjection of the products from the two reactions.

Three solid compounds were isolated from the basic fraction (after evaporation of the quinoline) by preparative high-pressure liquid chromatography on a Porasil A column (2 ft × 0.35 in.) using a solvent initially composed of 2% isopropyl alcohol, 3% ethyl acetate, and 95% hexane; the eluting power was increased by the addition of methylene chloride or ethyl acetate via a step gradient method and the pressure was increased stepwise during the course of the separation. The first of these was 2-quinolinol: mp 199.5–200.0 °C (lit.[57b] mp 199–200 °C); its GC and MS properties were identical with those of an authentic

sample. The second compound, eluted in a trace quantity as a tan solid, mp 97.5–98.5 °C, was identified as biquinolyl 2 on the basis of its mass spectrum and coinjection behavior. A third compound was a white solid, mp 123–124 °C, which was identified as biquinolyl 1 on the basis its GC and MS behavior.

(5) Cuprous Benzoate (D, Quinoline). The total product was submitted to GC–MS and, after evaporation of the quinoline, to the high-pressure liquid chromatography procedure described immediately above. The following compounds were isolated: benzophenone, a white solid, mp 49.0–49.5 °C, identical with an authentic sample; 2-benzoylquinoline, a yellow solid, mp 110.5–111.0 °C (lit.[58] mp 110.0–111.0 °C), whose MS and GC (coinjection) behavior was identical with that of an authentic sample prepared by the Friedel–Crafts acylation of benzene[58] with quinaldyl chloride,[59] MS 234 (12.5, P + 1), 233 (73, P), 232 (47), 206 (16), 205 (100, P − CO), 204 (86), 128 (15, quinolyl$^+$), 105 (80, $C_6H_5CO^+$), 101 (13), 77 (83, $C_6H_5^+$); biquinolyl 1, isolated as a white solid, mp 123.0–123.5 °C;[60] oxybiquinolyl 1, mp 176.0–176.5 °C.[63] In addition to these compounds, the following were identified by GC–MS: phenylquinoline isomer; biquinolyl 2; *N*-2-quinolyl-2-quinolone (**2**), 272 (47, P), 271 (100, P − H), 243 (14), 128 (10, quinolyl$^+$), 101 (10). The MS and GC coinjection behavior of the latter was identical with that of an authentic sample.[57a]

(6) Cuprous o-Fluorobenzoate. 2,2′-Difluorobenzophenone was isolated in 13% yield as a pale yellow liquid from the neutral fraction of the reaction of the anhydride with cuprous oxide in quinoline (method C) by chromatography on neutral alumina: IR (neat) 3106 (w, CH stretch), 1684 (m) and 1661 (s, carbonyl doublet), 1618 (s), 1580 (m), 1481 (s), 1453 (s), 1305 (s), 1287 (m), 1247 (m), 1224 (s, CF stretch[65a]), 931 (s), 754 (s, br) cm^{-1} (only the carbonyl doublet is recorded in a literature spectrum[66]); MS 218 (25, P), 123 (100, $C_6H_4FCO^+$), 95 (36, $C_6H_4F^+$), 75 (16); high-resolution MS calcd for $C_{13}H_8F_2O$, 218.0543; found, 218.0544.

A complete analysis of the ^{1}H NMR spectrum is in the appendix.

2,2′-Difluorobiphenyl was isolated by sublimation in 7% yield from the neutral fraction of the decarboxylation mixture of the salt prepared by method D. The white solid had mp 120.0–120.5 °C, whereas a sample from Pierce Chemical Co. had mp 119.5–120.5 °C. The two samples were shown to be identical by coinjection on two columns: MS 191 (13.5, P + 1), 190 (100, P), 189 (19), 188 (18), 170 (10, P − H − F), 74 (30), 59 (50). The gas chromatograms of the products from both decarboxylations showed fluorobenzene as a major product (identified by coinjections on Porapak Q and on 10% Carbowax). The basic fraction was very minor and by GC–MS it showed the presence of three isomers of o-fluorophenylquinoline as well as biquinolyl 1.

(7) Cuprous 1-Naphthoate (D, Quinoline). Naphthalene was isolated by sublimation from the neutral layer and identified by melting point, coinjection on two columns with an authentic sample, and its mass spectrum. By GC–MS, the basic layer contained Q_2-1, Q_2-2, Q_2O, and the unknown.

(8) Cuprous 3-Methyl-4-nitrobenzoate (D, Quinoline). The neutral fraction contained *o*-nitrotoluene and the basic fraction contained the same compounds as that from decarboxylation of cuprous benzoate.

(9) Cuprous 6-Methyl-2-nitrobenzoate (B, Quinoline). The neutral layer contained only *m*-nitrotoluene and the basic layer closely resembled that from the decarboxylation of cuprous benzoate.

(10) Cuprous o-Methylbenzoate (D, Quinoline). The neutral layer contained toluene and no more than 1% of 2,2′-dimethylbiphenyl. The composition of the basic layer closely resembled that from the decarboxylation of cuprous *p*-nitrobenzoate.

(11) Cuprous Pentafluorobenzoate (D, Quinoline). The neutral layer contained decafluorobiphenyl: 335 (12.7, P + 1), 334 (100, P), 333 (12), 315 (11, P − F), 294 (23), 272 (12), 265 (28), 259 (11), 198 (13), 197 (69), 167 (14, $C_6F_5^+$), 135 (52), 117 (14). The basic layer contained two isomers of pentafluorophenylquinoline as well as the usual four components containing two quinoline nuclei each; the latter four compounds were identified by coinjection with the basic product of decarboxylation of cuprous *p*-nitrobenzoate.

(12) Cuprous 2,6-Dimethylbenzoate (D, Quinoline). The major product in the neutral layer was *m*-xylene. The basic layer contained the usual four products containing two quinoline moieties each.

(13) Cuprous o-*tert*-Butylbenzoate (D, Quinoline). Only the neutral layer was analyzed by GLC. It contained *tert*-butylbenzene as indicated by coinjection on two columns. In addition, a 45% yield of *tert*-butylbenzene was recovered from the cold trap through which the nitrogen was swept.

(14) Cuprous α-Picolinate (D, Quinoline). Analysis of the product by GLC–MS indicated the presence of pyridine, three isomers of pyridylquinoline, and the four isomers containing two quinoline nuclei each.

(15) Cuprous Quinaldate (D, Quinoline). The quinoline could not be detected since it was the solvent. The usual other four components were also present.

(16) Cuprous *N,N*-Dimethylphthalamate (D, Quinoline). The neutral layer contained only *N,N*-dimethylbenzamide. The basic layer was not analyzed.

(17) Cuprous 1-Adamantanecarboxylate (D, Quinoline). The main component of the neutral layer coinjected with a sample of authentic adamantane: MS 137 (11, P + 1), 136 (100, P), 135 (27), 121 (10), 117 (10), 85 (18), 84 (22), 71 (13), 70 (29), 69 (35), 68 (7), 67 (10). The basic layer contained three compounds with the expected mass spectra of adamantylquinoline isomers in addition to the usual four compounds containing two quinoline nuclei each.

(18) Cuprous Decanoate (D, Quinoline). The neutral layer contained about 12 components in comparable quantities. The basic layer contained three compounds which had the molecular weight (272) of oxybiquinolyls, one of the molecular weight (256) of a biquinolyl, and a compound of apparent molecular weight 275.

(19) Decarboxylation of Cupric o-Nitrobenzoate in Refluxing Pyridine. At the end of a 2-h period, the salt was 5% decarboxylated. After 96 h, the yield of CO_2 was 80 ± 3%.

Reaction of Pentafluorophenylcopper and Quinoline. Approximately 0.2 mmol of pentafluorophenylcopper (Pierce) was heated in quinoline (10 mL) under nitrogen at the temperature which was maintained during the majority of the decarboxylation reactions (197 °C). The basic layer from this reaction was coinjected with the basic layer from the decarboxylation of cuprous pentafluorobenzoate. This indicated that, except for two minor components in the cuprous pentafluorobenzoate product, the basic layers of the two reaction mixtures contained the same compounds. The comparison of the mass spectra of compounds in the basic layer also indicated that at least two of the biquinoline isomers were the same in both reactions. However, it appears that there is somewhat less arylated quinoline product formed in the reaction of pentafluorophenylcopper.

Preparation of Anhydrides. All of the anhydrides with the exception of o-fluorobenzoic anhydride were prepared as follows. A benzene solution of the acid and a slight excess of thionyl chloride were heated at reflux for 4 h. The cooled solution was added to a benzene solution containing 1 equiv of the acid and 2 equiv of pyridine. After the solution had been stirred for 10 min, it was washed consecutively with aqueous sodium bicarbonate and with water and evaporated. The anhydrides were recrystallized from benzene–hexane.

***o*-Fluorobenzoic Anhydride.** The acid was dehydrated in 57% yield with acetic anhydride.[67] Recrystallization from benzene–hexane provided white crystals: mp 58.0–59.0 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (t of d, 2 H, $J_{6,F} = J_{5,6} = 8$ Hz, $J_{4,6} = 2$ Hz, H-6) and 7.85–6.93 (m, 6 H, aromatic); IR (Nujol) 1783 (s) and 1706 (s, carbonyl), 1616 (m), 1587 (m), 1488 (m), 1305 (m), 1279 (m), 1220 (s, br, carbon fluorine[65a]), 1168 (m), 1157 (m), 1110 (m, br), 1060 (m), 984 (m, br), 773 (m), 760 (s, br), 740 (s), 680 (m, br) cm^{-1}; MS 262 (8, P), 123 (100, $C_6H_4FCO^+$), 95 (24, $C_6H_4F^+$), 75 (13); 15-eV mass spectrum 262 (23, P), 234 (13), 218 (12), 123 (100); high-resolution MS calcd for $C_{14}H_8F_2O_3$, 262.0441; found, 262.0433.

Cuprous *tert*-Butoxide.[15] In a glovebox under an atmosphere of nitrogen which had been deoxygenated by means of hot copper turnings, freshly prepared CuCl[68] was added to a flask containing tetrahydrofuran which had been distilled under nitrogen from $LiAlH_4$. An equivalent amount of the lithium *tert*-butoxide (prepared according to the procedure of Kamienski and Lewis,[69] except that a lithium dispersion in mineral oil was used instead of lithium rod) was slowly added to the stirred solution. After the solution had been subjected to intimate mixing, the tetrahydrofuran was carefully removed by evaporation under reduced pressure. The removal of 20 mL of tetrahydrofuran required approximately 12 h of pumping at 0.5 Torr. The dark yellow crude cuprous *tert*-butoxide was packed in a sublimator which was then removed from the glovebox. The cuprous *tert*-butoxide was sublimed at a pressure of 0.1 Torr and a temperature of 170 °C. The sublimator was thoroughly dried, returned to the drybox, and opened.

Preparation of Cuprous Carboxylates from Cuprous *tert*-Butoxide. In a glovebox under a purified nitrogen atmosphere, the sublimed cuprous *tert*-butoxide (20 mmol) was added to a solution of the acid (20 mmol) in toluene (40 mL). The mixture was stirred for 5 min and filtered. The recovered finely divided solid was washed with hot toluene in order to dissolve traces of cupric salts, dried, and placed into the reaction vessel used for the decarboxylation.

Preparation of Cupric Salts. One method consisted of adding a slight excess of aqueous cupric sulfate solution to a solution of the

sodium salt of the acid at 0 °C stirring for 12 h at 25 °C, filtering, and washing the precipitated salt with cold water. A second method consisted of heating a solution of the acid in toluene or xylene at reflux for 24 h with a suspension of the stoichiometric amount of cupric carbonate with removal of the generated water by azeotropic distillation, then removing most of the solvent by distillation, and filtering the salt in a glovebox. Salt prepared by either procedure was dried in an oven at 110 °C for 24 h and stored in a vacuum desiccator for at least 12 h.

2-Deuterioquinoline. A mixture of quinaldic acid and a tenfold excess of D_2O was heated under nitrogen until the acid dissolved. The water was removed utilizing a rotary evaporator and the solid was placed in a vacuum desiccator which was evacuated by an oil pump for a period of 12 h. The above procedure was repeated twice. The solid was then distilled under nitrogen using a short-path condenser to obtain a 95% yield of (97.0 ± 0.7%) monodeuteriated quinoline. The resonance due to the 2 proton in the NMR spectrum of quinoline virtually disappeared in the labeled sample.

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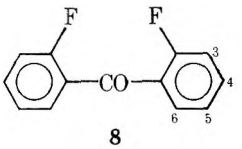
Appendix A—250-MHz ^{1}H NMR Spectrum of 2,2′-Difluorobenzophenone (8)

Secure assignments could be made for all chemical shifts and coupling constants except $J_{F,4}$, which could be estimated: ($CDCl_3$) δ 7.698 (t of d, 2 H, $J_{5,6} = J_{F,6} = 7.66$ Hz, $J_{4,6} = 1.67$ Hz, H-6), 7.515 (m, 2 H, width 26 Hz, H-4), 7.231 (t of d, 2 H, $J_{4,5} = J_{5,6} = 7.66$ Hz, $J_{3,5} = 1.00$ Hz, H-5), and 7.087 (d of d, 2 H, $J_{F,3} = 10.00$ Hz, $J_{3,4} = 8.33$ Hz, $J_{3,5} \simeq 1$ Hz, H-3).



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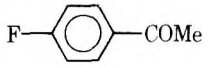

9

Several points are noteworthy. The width of the multiplet at δ 7.515 is 26 Hz and was calculated to be 25 Hz, assuming that the coupling constant between the fluorine and the 4 hydrogen is equal to that between the fluorine and 6 hydrogen ($J_{F,6} = 7.66$ Hz). The proton absorbing at highest field (δ 7.087) is the 3 proton, which is ortho to a fluorine atom and meta to the carbonyl group. An analogous situation[65b] occurs in *p*-fluoroacetophenone (**9**). The proton ortho to the fluorine but meta to the carbonyl absorbs at δ 7.05 like the 3 proton in **8**, and its signal is split about equally ($J \simeq 8$ Hz) by the fluorine and the adjacent proton. The proton–fluorine coupling constants as well as the proton–proton coupling constants are consistent with those found in a series of substituted fluorobenzenes.[70]

Furthermore, the ^{1}H NMR spectrum of 2-fluorobenzoic acid, determined in the present study, exhibits a low-field peak for the 6 proton: NMR ($CDCl_3$) δ 12.53 (br s, 1 H, OH), 8.07 (t of d, 1 H, $J_{F,6} = J_{5,6} = 7$ Hz, $J_{4,6} = 2$ Hz, H-6), and 7.84–6.91 (complex, 2 H, aromatic). The 6 proton of o-fluorobenzoic anhydride exhibits the same low-field proton signal: NMR ($CDCl_3$) δ 8.07 (t of d, 2 H, $J_{F,6} = J_{5,6} = 8$ Hz, $J_{4,6} = 2$ Hz, H-6), and 7.85–6.93 (complex, 6 H, aromatic).

Appendix B—Calculation of Proton Balance

Presumably, the hydrogen replacing the carboxylate group is supplied, at least in part, from that released in the formation of biquinolyls, oxybiquinolyls, and arylquinolines; in this way we can account for the increase in arene which accompanies an increase in quinoline-containing products (Table VI). In the decarboxylation of cuprous *p*-nitrobenzoate in which 13.9 mmol (93%) of carbon dioxide was released, it can be determined from the yields of quinoline-containing products that their formation would liberate 9.8 mg-atoms of hydrogen, which is 88% of the 11.2 mg-atoms required for the replacement of the carboxylate group by hydrogen during the production of the 11.2 mmol (74%) of nitrobenzene which was formed.

Registry No.—Cuprous *o*-methoxybenzoate, 64508-60-7; pyridine, 110-86-1; quinoline, 91-22-5; *o*-nitrobenzoic acid, 552-16-9; cuprous *tert*-butoxide, 35342-67-7; cuprous oxide, 1317-39-1; o-nitrobenzoic acid anhydride, 49619-45-6; cupric *o*-nitrobenzoate, 5819-30-7; nitrobenzene, 98-95-3; 2,2′-dinitrobiphenyl, 2436-96-6; 3-methyl-2-nitrobenzoic acid anhydride, 64508-61-8; 3,3′-dimethyl-2,2′-dinitrobiphenyl, 64508-62-9; *o*-nitrotoluene, 88-72-2; cupric *p*-nitrobenzoate, 5819-29-4; 2-quinolinol, 59-31-4; cupric benzoate, 533-01-7; benzophenone, 119-61-9; 2-benzoylquinoline, 16576-25-3; quinaldyl chloride, 50342-01-3; *N*-(2-quinolyl)-2-quinolone, 10168-37-3; *o*-fluorobenzoic acid anhydride, 64508-63-0; cupric o-fluorobenzoate, 50671-56-2; 2,2′-difluorobenzophenone, 342-23-4; 2,2′-difluorobiphenyl, 388-82-9; cupric 1-naphthoate, 14041-38-4; naphthalene, 91-20-3; cupric 3-methyl-4-nitrobenzoate, 64508-41-4; 6-methyl-2-nitrobenzoic acid, 13506-76-8; *m*-nitrotoluene, 99-08-1; cupric *o*-methylbenzoate, 5819-24-9; 2,2′-dimethylbiphenyl, 605-39-0; cuprous pentafluorobenzoate, 27269-46-1; cupric pentafluorobenzoate, 46251-93-8; decafluorobiphenyl, 434-90-2; cupric 2,6-dimethylbenzoate, 64508-42-5; *m*-xylene, 108-38-3; cupric o-*tert*-butylbenzoate, 64508-43-6; *tert*-butylbenzene, 98-06-6; cupric α-picolinate, 6955-25-5; cupric quinaldate, 64508-44-7; cupric *N,N*-dimethylphthalamate, 64508-45-8; cuprous *N,N*-dimethylphthalamate, 64508-46-9; *N,N*-dimethylbenzamide, 611-74-5; cuprous 1-adamantanecarboxylate, 64508-47-0; cupric 1-adamantanecarboxylate, 64508-48-1; adamantane, 281-23-2; cupric decanoate, 28567-33-1; cuprous decanoate, 64508-49-2; pentafluorophenylcopper, 18206-43-4; 3-methyl-2-nitrobenzoic acid, 5437-38-7; o-fluorobenzoic acid, 445-29-4; CuCl, 7758-89-6; lithium *tert*-butoxide, 1907-33-1; *p*-fluoroacetophenone, 403-42-9; 6-chloro-2-nitrobenzoic acid, 5344-49-0; benzoic anhydride, 93-97-0; benzoic acid, 65-85-0; *p*-nitrobenzoic anhydride, 902-47-6; *o*-methoxybenzoic anhydride, 64508-50-5.

Supplementary Material Available: relative peak heights of the biquinolyls and oxybiquinolyls produced by interaction with the quinoline solvent (Table IV), yields of nitrobenzene and 2,2′-dinitrobiphenyl in the decarboxylation of cuprous o-nitrobenzoate under various conditions (Table V), and complete mass spectrometric data, obtained by combined GLC–MS, for all arenes and arylquinolines presented in the order in which they are described in the Experimental Section (4 pages). Ordering information is given on any current masthead page.

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$$2ArCO_2Cu + C_9H_7N \rightarrow C_9H_6NCOAr + ArH + Cu_2O + CO_2$$
$$2ArCO_2Cu + C_9H_7N \rightarrow C_9H_6NAr + ArH + 2Cu + 2CO_2$$

However, if these equations are used in yield calculations, confusion may arise in the calculation of material balances of aryl groups.

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(28) (a) For discussions of the formation of copper(III) compounds by oxidative additions to arylcopper(I) compounds and extensive references, see ref 20 and 30; (b) a similar oxidative addition of C–H to copper(I) has been suggested to account for the hydrogen removal from ether solvents by arylcopper intermediates.[25]

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Stereochemical Studies on 3,4-Benzobicyclo[4.1.0]hept-3-en-2-ol Systems and Solvolytic Studies on Its *p*-Nitrobenzoates

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Synthesis, geometrical assignment, and solvolysis of 1,6-substituted 3,4-benzobicyclo[4.1.0]hept-3-en-2-yl *p*-nitrobenzoates (**1a–c**) are described. In the stereochemical study of the parent alcohols (**8a–c**), a new comparative method has been proposed together with the previous result for **8d**. The method involves the comparison of relative molar lanthanide-induced shift (RLIS[5]) for certain protons in each alcohol. Anti geometry of the hydroxyl relative to the cyclopropane methylene group was assigned for all the substrates. This method will be promising in application to the other systems in which the framework is similar to each other. The kinetic result was also compatible with the product distribution, in which homoallylic tertiary and syn-secondary alcohols dominated because of the presence of both an aromatic ring and a cyclopropyl group adjacent to the reaction center. The reaction intermediate may be a homonaphthalenium ion.

There is abundant evidence for a stabilization effect of the cyclopropyl group in electron-deficient species.[1] Since a phenyl group shows the similar effect, the difference of the origin between both groups has been the subject of recent investigations.[2] For instance, Traylor et al. suggested that there might be vertical stabilization for the transition state in the solvolyses of some strained substrates,[2a,b] or Olah, Brown, and other investigators discussed the difference of their ability in rate acceleration of solvolysis in these two kinds of groups.[2e,g,h] The authors have been investigating the solvolysis of the unique cyclopropylphenylmethyl system (**1a–d**), in which both groups could competitively exert influence upon the rate as well as upon products. In one example of this system (**1d**),[3] it was suggested that σ participation rather than π conjugation might contribute to the rate acceleration, and that the intermediate of solvolysis might be a nonclassical homonaphthalenium cation in which a positive charge would be delocalized not only in the benzene ring but also in the cyclopropane ring.

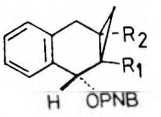
During our solvolytic study of all of the *anti*-3,4-benzobicyclo[4.1.0]hept-3-en-2-yl *p*-nitrobenzoates (**1a–d**), the authors have encountered the serious difficulty of assigning syn/anti geometry between a hydroxyl group and the methylene of a cyclopropane ring in the parent alcohols. In this paper, we wish to report a useful expedient for the purpose of dividing each alcohol into two series of geometric isomers from comparison of the lanthanide-induced shifts in the NMR spectrum and also to discuss the solvolytic reactivity of these esters (**1a–d**), in which the substituent at the C_1 or C_6 position is hydrogen, methyl, or trimethylene group.

Results and Discussion

Synthesis. Each *p*-nitrobenzoate was prepared by the sequence outlined in Scheme I. The *p*-nitrobenzoate **1a** was obtained by esterification of **8a**, which was synthesized by Julia et al.,[4] and the synthesis of **1d** was previously reported.[3] Here, we report the preparation of **1b** and **1c** in detail.

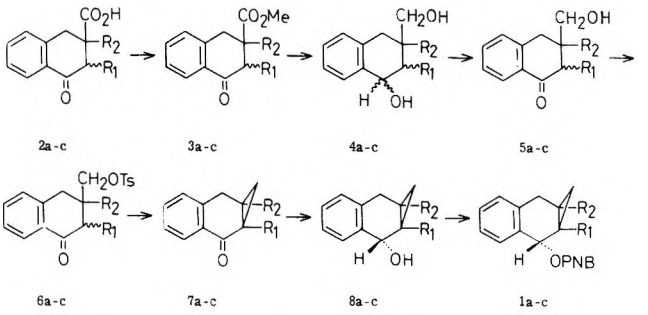
The keto acid **2b** was obtained by the earlier method.[5] In the course of preparation of **2b**, treatment of unsaturated cyano ester **9** with potassium cyanide gave potassium salt **10**

Chart I

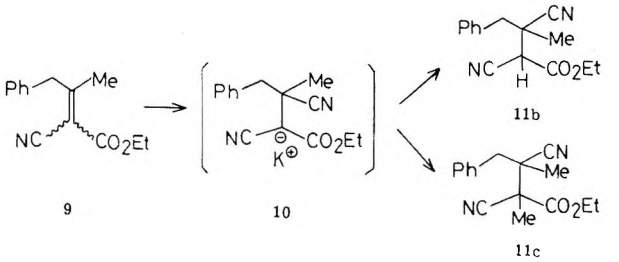


	R_1	R_2
1a	H	H
1b	H	Me
1c	Me	Me
1d	$-(CH_2)_3-$	

Scheme I



Scheme II

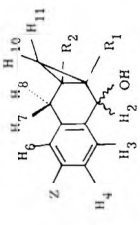


(Scheme II), which was quenched by hydrochloric acid to afford monomethyldicyano ester **11b**. Using methyl iodide in place of hydrochloric acid gave rise to dimethyldicyano ester **11c** in 73–76% yield without isolation of **11b** as an intermediate. So **11c** could be obtained directly from **9**.

Intramolecular cyclization of **11c** by means of sulfuric acid in aqueous acetic acid directly gave rise to the keto acid **2c** in moderate yield (30%). Esterification with diazomethane converted **2b** and **2c** almost quantitatively into the esters **3b** and **3c**, which were reduced by lithium aluminum hydride to give a mixture of geometric isomers of diol **4b** and **4c**. Oxidation of **4b** and **4c** with active manganese dioxide gave the keto alcohols **5b** and **5c**. Their tosylates (**6b,c**) were prepared in the general method, then the sulfonic acid was eliminated by potassium hydroxide in aqueous dioxane, giving the ketones **7b** and **7c**. Spectroscopic analysis supported the assigned structure of these cyclopropyl phenyl ketones (**7b,c**) as shown in Table V.[19] Reduction of **7a–c** with lithium aluminum hydride in ether gave the alcohols **8a–c** in 84–96% yield. Although there are two geometric isomers, syn and anti, in these alcohols, only one of the isomers was obtained in each case, judging from spectroscopic analysis. The assignment of signals in the NMR spectra is tabulated along with those of **8d** and **8e** in Table I. The *p*-nitrobenzoates **1a–c** were then prepared from these alcohols by the ordinary method.[3]

0022-3263/78/1943-0849$01.00/0

Table I. Chemical Shifts (δ), $(\Delta Eu)_i$ Values, and Relative Lanthanide-Induced Shifts (RLIS[i]) for 3,4-Benzobicyclo[4.1.0]hept-3-en-2-ol Systems



Registry no.	Compd		H_2	H_3	H_4	Z	H_6	H_7	H_8	H_{10}	H_{11}	OH[m]	R_1	R_2	r^n
64414-40-0	8a	δ	5.06[a]	7.7-7.5[b]		7.3-7.0[b]		3.00[c]	3.00[c]	0.63-0.17[b]		1.87[d]	1.8-1.3[b]		
		$-(\Delta Eu)_i$	23.50	17.30		2.75		4.53		9.43	6.41	85.70	12.79	4.05	
		RLIS[i]	1.00	0.74		0.12		0.19		0.40	0.27	3.65	0.54	0.17	0.993
64414-41-1	8b	δ	5.02[e]	7.7-7.5[b]		7.3-7.0[b]		2.87[d]	2.87[d]		0.43-0.16[b]	1.83[d]	1.5-1.3[b]	1.28[d]	
		$-(\Delta Eu)_i$	22.69	15.90		2.62		3.76		9.94	5.86	79.58	11.85	2.22	
		RLIS[i]	1.00	0.70		0.12		0.17		0.44	0.26	3.51	0.52	0.12	0.996
64414-42-2	8c	δ	4.73[d]	7.7-7.6[b]		7.3-7.1[b]		2.88[d]	2.88[d]	−0.07[f]	0.27[f]	1.7[d]	1.40[d]	1.30[d]	
		$-(\Delta Eu)_i$	23.46	15.44		2.18		4.43		10.80	7.30	87.62	8.99	3.22	
		RLIS[i]	1.00	0.66		0.09		0.19		0.46	0.31	3.73	0.38	0.14	0.999
58717 76 3	8d	δ l	4.83[d]	7.7-7.4[b]		7.3-6.9[b]		2.79[g]	3.15[g]	0.36[d]	0.36[d]	2.5-1.3		2.5-1.3[b]	
		$-(\Delta Eu)_i$	23.86	16.06		2.48		4.55	4.58	11.48	7.50	91.20			
		RLIS[i]	1.00	0.67		0.10		0.19	0.19	0.48	0.31	3.82			
60425-21-0	8e	δ l	4.83[d]	7.56[h]	7.03[i]	2.30[d]	6.90[c]	2.82[g]	3.16[g]	0.36[d]	0.36[d]	2.4-1.2	2.4-1.2[b]		
		$-(\Delta Eu)_i$	36.26	24.76	2.88	2.25	4.00	6.50	6.63	16.51	11.00	108.04			
		RLIS[i]	1.00	0.86	0.08	0.06	0.11	0.18	0.18	0.46	0.30	2.98			0.999
64474-23-3	12a	δ	5.03[a]			7.2-7.1[b]		2.90[j]	3.33[k]	0.03-0.2[b]	0.67-0.3[b]	2.15[b]	1.6-1.2[b]		
		$-(\Delta Eu)_i$	33.06	11.31		4.78		8.48	14.14	9.57	6.57	110.49	20.88	8.70	
		RLIS[i]	1.00	0.34		0.14		0.27	0.43	0.29	0.20	3.34	0.63	0.26	0.864

[a] Doublet, J = 3 Hz. [b] Multiplet. [c] Doublet, J = 5 Hz. [d] Singlet. [e] Doublet, J = 4 Hz. [f] AB quartet, J = 5 Hz. [g] AB quartet, J = 16 Hz. [h] Doublet, J = 9 Hz. [i] Double doublet, J = 9, 2 Hz. [j] Double AB quartet, J = 16, 1 Hz. [k] Double AB quartet, J = 16, 3 Hz. [l] Reference 3. [m] The hydroxyl protons were not included in the correlation, since they are known to correlate poorly because of their closeness to the europium ion. [n] Correlation coefficients in the relationship between RLIS[i] and $RLIS^i_{8d}$.

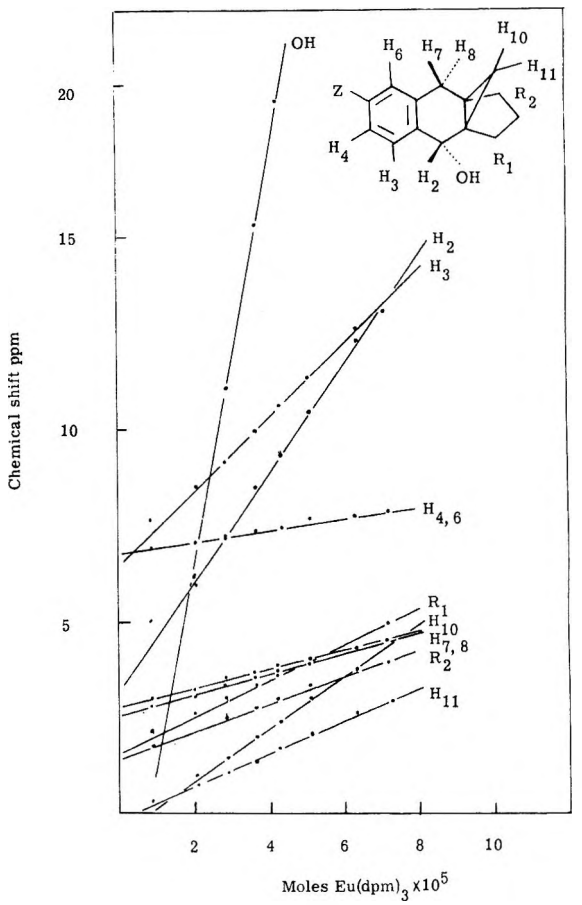
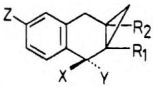


Figure 1. Variation in the chemical shift for the different protons of 3,4-benzotricyclo[4.3.1.0[1,6]]dec-3-en-2-ol (**8d**) (0.168 mmol in 0.4 mL of $CDCl_3$) with increasing concentration of $Eu(dpm)_3$.

Geometric Assignment of 8a–e. The geometric assignment of syn/anti (or cis/trans) cyclopropane stereochemistry on each alcohol was an important problem in the consideration of the solvolytic reactivity among these esters (**1a–d**). There are many recent applications that the lanthanide-induced chemical shifts observed in rigid oxygenated bicyclic molecules were interpreted by the McConnell–Robertson version of the pseudocontact interaction and then related to the stereochemistry of these molecules.[6,7] We have attempted to apply the somewhat different procedure to our alcohols **8a–d** and



	R_1	R_2	X	Y	Z
8a	H	H	H	OH	H
8b	H	Me	H	OH	H
8c	Me	Me	H	OH	H
8d	-$(CH_2)_3$-		H	OH	H
8e	-$(CH_2)_3$-		H	OH	Me
12a	H	H	OH	H	H
12d	-$(CH_2)_3$-		OH	H	H

its related alcohol **8e**[3a] in which the conformations might not be completely rigid, but be rather *flexible*. According to the generalized method, the dependence of the chemical shifts of all the protons in each alcohol (**8a, 8b, 8c, 8d,** or **8e**) was first studied in NMR measurement by dissolving successively a weighed amount of tris(dipivaloylmethanato)europium, $Eu(dpm)_3$, into a deuteriochloroform solution of the alcohol. For one instance, the result for **8d** is shown in Figure 1. The shift tendency of the corresponding protons in all the other alcohols (**8a–c** and **8e**) was found to be quite similar to this figure. The similarity of these figures suggests that corresponding protons in this series of alcohols are located in sim-

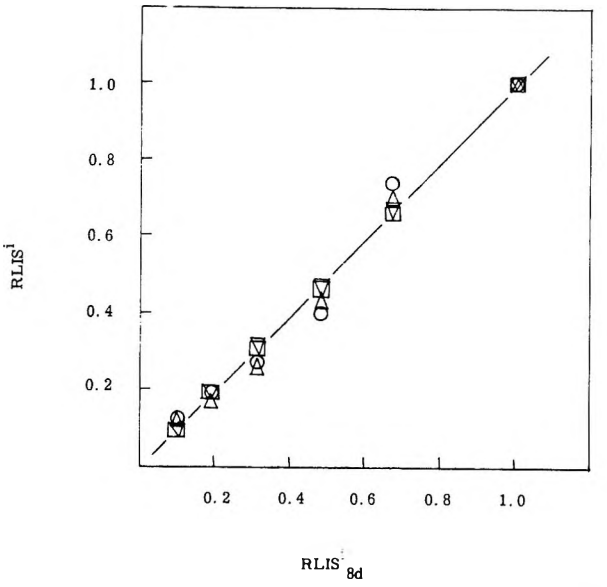


Figure 2. Relationship between relative induced shifts (RLIS^i) for **8a** (○), **8b** (△), **8c** (▽), and **8e** (□) and the standard value (RLIS$^i_{8d}$) for **8d.**

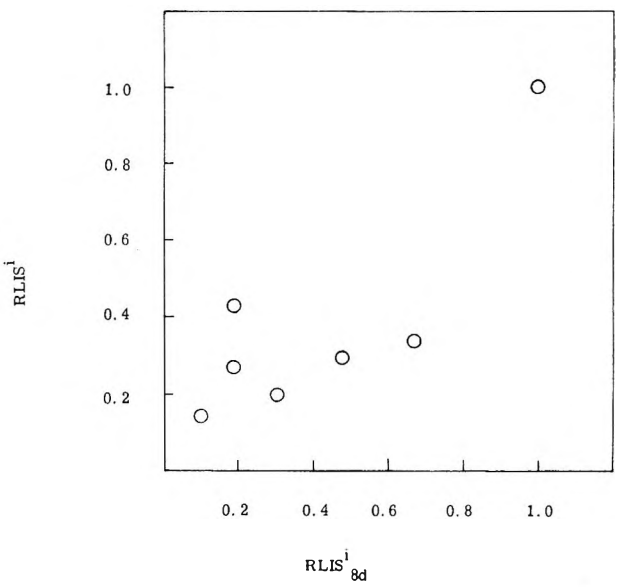


Figure 3. Relationship between relative induced shifts (RLIS^i) for **12a** (○) and the standard value (RLIS$^i_{8d}$) for **8d.**

ilar circumstances with regard to the shift reagents, especially to its metal. The definition of the similarity, however, is ambiguous.

In general, the molar induced shift, $(\Delta Eu)_i$, is defined as the difference between the chemical shift of a given proton, H_i, measured without the reagent and the shift with the equimolar reagent.[8] Also, excellent fits have been reported in various rigid systems for the proportionality of $(\Delta Eu)_i$ with $(3\cos^2\theta_i - 1)/r_i^3$, where r_i is the distance between the metal and the proton (H_i) and θ_i is the angle between the r_i vector and the magnetic axis of the complex.[7,9] Recently, Sullivan suggested that extreme caution should be paid in assigning configurations to nonrigid molecules based on the correlation of observed lanthanide-induced shifts in NMR spectra with those obtained by the McConnel-Robertson equation.[10] Since $(\Delta Eu)_i$ may be sensitive to the experimental conditions and to the character of a given molecule, the suggestion is worthy of attention. Instead of indirect comparison of such figures as Figure 1 obtained for each compound, the following relative ratio, RLIS^i, may serve as a more useful measure to compare molecular structure for one alcohol with that for another, even if these conformations might be considerably *flexible.*

$$\text{RLIS}^i = (\Delta Eu)_i/(\Delta Eu)_2$$

Here, the alcohol **8d** was selected as the reference compound which was investigated in detail in our laboratory.[3] Thus, RLIS$^i_{8d}$ was calculated for each proton of **8d,** using the α proton, H_2, as the standard, which showed the biggest shift with the exception of the hydroxylic proton. The relative induced shift, RLIS^i, was also obtained in the same way for each proton in the other secondary alcohols, **8a, 8b, 8c,** and **8e,** based upon the α proton in each compound. Then the relative induced shifts, RLIS$^i_{8a-c,e}$, of protons H_{3-8} and $H_{10,11}$, in **8a–c** and **8e** were plotted against RLIS$^i_{8d}$ of the corresponding protons in **8d.** As shown in Figure 2, a good linearity is clearly observed. This does mean that relative magnetic environments for each proton bearing on the basic carbon skeleton in one of the series of alcohols (**8a–e**) are quite similar to each other, without any assumption for the coordinated position of the shift reagent. Consequently, it may be deduced that the geometrical structure of these alcohols should be same as far as the syn or anti problem is concerned. Since R_1 and R_2 in the above general formulas provide a variety of groups, such as H, Me, or $-(CH_2)_3-$, the RLIS^i values for these protons were not treated in the first step of this treatment. The plots of H_{10} and H_{11} (methylene protons of the cyclopropane ring) in **8a** and **8b** are slightly deviated from the good linear line obtained by the above treatment. This minute difference might arise from the fact that the relative situation of these protons with H_2 in **8a** and **8b** would be somewhat dissimilar to the situation in the other alcohols, **8c–e.** Presumably the carbon skeleton of both **8a** and **8b** may be more easily modified by coordination of the shift reagent owing to less substitution of alkyl groups at C_1 and C_6. In other words, conformation of coordinating alcohols might be insignificantly different from each other.

Although we could not isolate a sufficient amount of both epimers in all the alcohol pairs in the present experiment, only **12a,** which is the epimer of **8a,** was obtained in a satisfactory degree of purity from the solvolysis of **1a.** The values of RLIS^i for the corresponding protons of this epimer were also plotted against RLIS$^i_{8d}$ as indicated in Figure 3. In this case the plots are markedly scattered and no linear relationship is observed contrary to the above. Since **12a** was characterized as an isomer of **8a** from the other experimental evidence, the geometrical series of this compound may be different from that of **8d.**

From these results it may be suggested that the relative relationship of RLIS^i is expected to be proportional among these geometrically analogous series of alcohols, even though the definite conformation is not clear or considerably *flexible.* The structural assignment by this relationship is based on the assumption that, in the same syn or anti isomeric series of alcohols (**8a–e**), both the distance, r_i, and the angle, θ_i, might be comparably varied with each proton relative to H_2 in these bicyclic alcohols. In the different epimeric series of alcohols, such relationship might be lost, since the relative situation for each proton should be dissimilar to the above. These are criteria of the present proposal to assign these 3,4-benzobicyclo[4.1.0]hept-3-en-2-ol derivatives to which series of geometric isomers.

The next step is determination of syn or anti geometry for one of the compounds **8a–e.** In order to distinguish the geometry for bicyclic secondary α-cyclopropylcarbinol, some of the following experimental values can be compared: chemical shifts of α-carbinyl proton,[11] coupling constants between α and its adjacent proton,[12] or relative reactivity of its esters in

Table II. Chemical Shift of α Proton and Spin–Spin Coupling Constant between α Proton and Its Adjacent Proton for 3,4-Benzobicyclo[4.1.0]hept-3-en-2-ol Systems

Compd	δ_a[a]	Compd	Registry no.	δ_s[a]	$\Delta\delta$[b]
8a	5.06 (J = 3 Hz)	12a		5.05 (J = 3 Hz)	−0.01
8b	5.02 (J = 4 Hz)	12b	64474-64-2	5.00 (J = 3 Hz)[c]	−0.02
8c	4.63				
8d	4.83[d]	12d	58692-29-8	5.04[d]	0.21[d]

[a] Chemical shifts for α proton are listed in δ (ppm) relative to tetramethylsilane. [b] $\Delta\delta = \delta_s - \delta_a$. [c] This value was observed in a mixture of isomeric alcohols. [d] Reference 3.

solvolysis.[13] In the present case, no decision could be made for the geometry of **8a, 8b, 8c, 12a,** and **12b** from both $\Delta\delta$ and J in Table II. As clearly shown in the previous paper, **8d** has been assigned as the anti epimer from the fact that the α proton of **8d** exhibits its signal at higher field than that of **12d** and that its p-nitrobenzoate (**1d**) solvolyzes slower than the epimeric isomer.[3a] Combining this assignment with the above linear correlation, the series of alcohols **8a–e** could be ascribed to the anti isomers. This may be one of the beneficial points in the present treatment of RLIS[i], when other procedures could not be employed for determining geometric relation. This method will be promising in application to the other systems.

Kinetic Studies. The rates of solvolysis of p-nitrobenzoates **1a–c** in 80% aqueous acetone were determined by titration of p-nitrobenzoic acid. The titration was carried out by employing an automatic titration instrument after quenching by anhydrous acetone in an ice bath. The results and the related values are summarized in Table III.

All four p-nitrobenzoates **1a–d** belong to the same anti series of the bicyclo[4.1.0]hept-3-en-2-yl alcohol, so that direct comparison can be made in these solvolyses. As shown from the substituent effect on the benzene ring of **1d,** its absolute value ($\rho = -2.11$) was exceptionally small among many secondary benzylic systems.[3b] The result, together with the other evidence, could be interpreted in terms of σ participation of the 1-bicyclo[3.1.0]hexyl group in **1d** rather than π conjugation.[3] Similar interpretation may be adapted to solvolysis of the other three esters (**1a–c**).

There are small differences in rate among these four esters, **1d** ≳ **1c** > **1b** > **1a.** The following discussion can be taken into account for the explanation. Owing to the steric repulsion of the nonbonded methyl groups, the ground state of **1c** might be destabilized compared with the other esters. Such destabilization decreases in the case of **1b,** resulting in slower rate. Along with a lesser degree of such repulsion, the above σ participation should be reduced especially in **1a,** since the methyl group is lacking at the 1 position of the bicyclo[4.1.0]-heptyl framework where a positive charge develops in the transition state. As a result, the above order or reactivity was observed in the present experiment.

The effect of substitution in the cyclopropyl ring on the rate of solvolysis of cyclopropylmethyl 3,5-dinitrobenzoates was investigated by Schleyer et al. They showed that the introduction of a methyl group at the C_2 position or a trimethylene group between the C_1 and C_2 position results in 10 or 300 times accelerative effect, respectively, in solvolysis.[14] As compared with these primary esters, the magnitude of the rate effects in the 3,4-benzobicyclo[4.1.0]hept-3-en-2-yl system was smaller (three or ten times, respectively). This result indicated that the extent of charge distribution to the cyclopropyl ring at the transition state must be small due to the secondary system, in which the positive charge is also spread in the aromatic ring. However, it is interesting to note that the alkyl substituent effect of the present system (**1a,b,d**) runs well parallel with the effect of Schleyer's system, although the degree decreased one tenth because of partial charge delocalization stated above.

Products Studies. It was confirmed that **8a–c,** the parent alcohols, are stable under the solvolytic conditions if 2,6-lutidine is present. The study on the kinetic solvolysis products of **1a–c** was carried out in 80% aqueous acetone in the presence of 2,6-lutidine. After about 10 half-lives, the products were extracted by usual workup process and analyzed by using NMR spectroscopy. Solvolyses of **1a** and **1c** gave rise to an almost pure sample, secondary alcohol **12a** and tertiary alcohol **13c,** respectively, but solvolysis of **1b** produced a mixture of the secondary and the tertiary alcohols (**12b** and **13b**). The pure sample of **13b** was obtained by acid-catalyzed isomerization of **8b.** These alcohols were assigned by comparison of the NMR spectrum with that of the authentic samples, except **12b.**[15] The product distributions were determined from the ratio of integral intensity for the characteristic signals (α or vinylic protons) in the NMR spectra. The results are summarized in Table IV. The primary alcohols **14a–c** could not be detected in any case.

The product distributions in solvolysis may depend upon a number of effects, for instance the charge density and the

Table III. Rates of Solvolysis of p-Nitrobenzoates (1a, 1b, 1c, and 1d) in 80% Aqueous Acetone

Registry no.	Compd	Temp, °C[a]	10^5k, s^{-1} [b]	$\Delta H^{\ddagger}$, kcal/mol[c]	$\Delta S^{\ddagger}$, eu[c]	k_{rel}
64414-43-3	**1a**	55.0	28.6 ± 1.5			
		45.0	8.91 ± 0.27			
		35.0	2.53 ± 0.09			
		25.0	0.667[e]	23.9	−2.0	1.0
64414-44-4	**1b**	45.0	22.6 ± 0.8			
		35.0	7.38 ± 0.27			
		25.0	2.16 ± 0.12	21.1	−9.1	3.2
64414-45-5	**1c**	45.0	89.6 ± 5.0			
		35.0	27.0 ± 1.5			
		25.0	6.96 ± 0.12	22.7	−1.4	10.4
58717-77-4	**1d**	40.0	48.6 ± 0.3[d]			
		30.0	15.1 ± 0.4[d]			
		25.0	8.60 ± 0.5[d,f]	20.6[d]	−8.0[d]	12.9

[a] ±0.03 °C. [b] Kinetic plots were linear to 75% conversion (2 half-lives). [c] Calculated from $\Delta H^{\ddagger} = R(T_1T_2/T_2 - T_1) \ln (T_1k_2/T_2k_1)$, $\Delta S^{\ddagger} = R \ln (k_1h/kT_1) \Delta H^{\ddagger}/T_1$: T_1, absolute temperature; h, Planck's constant; k, Boltzmann's constant. [d] Reference 3. [e] Calculated from $\Delta H^{\ddagger}$. [f] The rate, which was measured by using an automatic titrating apparatus, was $k = (8.81 \pm 0.11) \times 10^{-5}$ s^{-1} at 25.0 °C.

Table IV. Product Distributions of Solvolysis of 1a-d in the Presence of 2,6-Lutidine

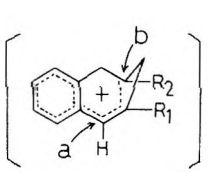
p-Nitrobenzoate 1a-d	Product, %[a] 8a-d	12a-d	13a-d	14a-d
1a (R_1 = H; R_2 = H)	0	~100	0	0
1b (R_1 = H; R_2 = Me)	0	42	58	0
1c (R_1 = Me; R_2 = Me)	0	0	~100	0
1d[b] (R_1, R_2 = $-(CH_2)_3-$)	13	42	45	0

[a] The product distribution was determined by the NMR spectrum and its integral intensity for the α hydrogen of 8a-d and 12a-d or vinyl hydrogen of 13a-d. [b] Reference 3.

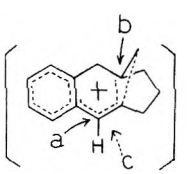
circumstances of the carbon atoms attacked nucleophilically by solvent. The *anti*-3,4-benzobicyclo[4.1.0]heptenyl system (**1d**) was solvolyzed not to afford stereoelectronically favorable primary alcohols **14d** (backside participation of the σ bond in the cyclopropane ring), but to produce secondary (**8d** and **12d**) and tertiary alcohols (**13d**). Solvolysis of **1a** and **1b** predominantly gave rise to *syn*-alcohols **12a** and **12b** in contrast with the products obtained from **1d**.

These results might be explained on the basis of the formation of a considerably stable (long lifetime) intermediate in which the positive charge would be highly delocalized not only on the aromatic part but also on the cyclopropane ring, as in the homonaphthalenium cation (**15a-c**). In aqueous media, this intermediate carbocation (**15a-c**) might undergo discharge of water from sides a and b in the formula (**15a-c**) to be converted into the final products.

In the bicyclo[3.1.0]hex-2-yl or bicyclo[4.1.0]hept-2-yl systems in the absence of an aromatic ring adjacent to the reaction center, each solvolysis of these *p*-nitrobenzoates gave rise to a mixture of syn and anti isomer along with the other alcohol.[16] These results indicate that there should be little difference, both electrical and steric, between exo and endo attack of a nucleophile to the cationic intermediate. Since the solvolysis products of **1a** and **1b** contained secondary cyclopropylphenylmethyl alcohol with only syn-type geometry, it is evident that the intermediate may be described as a homonaphthalenium ion in which nucleophilic attack from the exo side (c) is severely hindered by the highly delocalized electrons. However in **1d**, the positive charge might be further delocalized into the primary carbon (C_7) in the intermediate ion **15d** because of the scissors effect by the trimethylene group or the lower stability of bridgehead cation. Furthermore, **15d** would make it possible for the solvent to attack from the side c in the formula to afford the anti secondary alcohol **8d**.[3] The kinetic result was also compatible with the product distribution.



15a-c



15d

Experimental Section

All the melting points are uncorrected. Infrared spectra were recorded with a Hitachi 215 grating IR spectrophotometer. NMR measurements were carried out on a Varian T-60 instrument using tetramethylsilane as an internal reference.

3,4-Benzobicyclo[4.1.0]hept-3-en-2-one (**7a**) was prepared by the modified method of the literature.[4] The details of the synthesis of the 3,4-benzotricyclo[4.3.1.$0^{2,6}$]hept-3-en-2-yl series (**1d, 8d, 8e**) were previously reported.[3] The synthesis of the 6-methyl- and 1,6-dimethyl-3,4-benzobicyclo[4.1.0]hept-3-en-2-yl series is reported in detail in this paper.

2-Benzyl-2-methylsuccinic Acid. To the solution of 27.5 g (0.12 mol) of ethyl 1-methyl-2-phenylethylidenecyanoacetate (**9**)[17] in 60 mL of methanol was added an aqueous solution (35 mL) of potassium cyanide (9.0 g, 0.14 mol) with stirring and cooling by water for several minutes; then the mixture was acidified with diluted hydrochloric acid. The dicyano ester **11b** was obtained by ether extraction. Without further purification a mixture of **11b**, concentrated hydrochloric acid (300 mL), and glacial acetic acid (150 mL) was heated under reflux with vigorous stirring for 20 h. The crude 2-benzyl-2-methylsuccinic acid separated as crystals when the reaction mixture was cooled. The pure sample (15.0 g) was recrystallized from ethanol, mp 143–145 °C (lit. 144 °C),[18] in 57% yield.

3-Carboxy-3-methyl-1-tetralone (2b). A solution of 14.0 g (0.063 mol) of the above dicarboxylic acid dissolved in 140 mL of concentrated sulfuric acid was stirred for 1 day at room temperature. After being poured onto 1.4 kg of crushed ice, the crude keto acid **2b** was obtained by filtration. The product was recrystallized from ethanol to give a pure sample: mp 166–169 °C (lit. 168–170 °C);[5] 10.5 g (82% yield); IR (Nujol) 1720 (CO_2H), 1665 (CO), 1185, 900, 755 cm^{-1}.

Ethyl 2,3-Dicyano-2,3-dimethyl-4-phenylbutyrate (11c). To the solution of **9** (25.6 g, 0.11 mol) in 80 mL of 95% ethanol was added an aqueous solution (39 mL) of potassium cyanide (12.8 g, 0.2 mol) with stirring. After several minutes the solution of methyl iodide (31.2 g, 0.22 mol) in 60 mL of 95% ethanol was added to the above mixture and the stirring was continued for 16 h at room temperature. The distillation of extract gave 22.8 g of dicyano ester **11c** in 76% yield, bp 180–182 °C (3 mm), and then the oil was gradually solidified at room temperature: mp 61–74 °C; IR (Nujol) 2240 (CN), 1745 (CO_2Et) cm^{-1}; NMR ($CDCl_3$) δ 7.36 (s, 5 H, aromatic), 4.35 (q, J = 7.5 Hz, 2 H, methylene), 3.15 and 2.81 (ABq, J = 13.5 Hz, 2 H, benzyl), 1.92 (s, 3 H, methyl), 1.40 (s, 3 H, methyl), 1.35 (t, J = 7.5 Hz, 3 H, methyl).

3-Carboxy-2,3-dimethyl-1-tetralone (2c). A mixture of **11c** (10 g, 0.037 mol), concentrated sulfuric acid (50 g), glacial acetic acid (20 g), and water (9 mL) was heated at 90 °C for 3 h and at 110 °C for 17 h. After the reaction mixture was poured onto crushed ice, 2.3 g of a mixture of geometric isomers (**2c**) was obtained by ordinary workup process in 30% yield. Recrystallization from benzene gave rise to a pure sample: mp 141–143 °C (main product); IR (Nujol) 1700 (CO_2H), 1690 (CO) cm^{-1}; NMR ($CDCl_3$) δ 10.68 (s, 1 H, carboxylic), 7.1–7.7 (m, 3 H, aromatic), 7.9–8.2 (m, 1 H, aromatic), 2.96 and 3.52 (ABq, J = 16.5 Hz, 2 H, benzyl), 3.10 (q, J = 7.5 Hz, methine), 1.20 (d, J = 7.5 Hz, 3 H, methyl), 1.19 (s, 3 H, methyl).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.16; H, 6.36.

1-Hydroxy-3-hydroxymethyl-3-methyltetraline (4b). The keto ester **3b** (mp 62–63 °C from benzene) was prepared from 13.7 g (0.067 mol) of **2b** and diazomethane in ether in good yield. Spectral data for **3b:** IR (Nujol) 1725 (CO_2Me), 1680 (CO), 1215, 1110, 770 cm^{-1}; NMR ($CDCl_3$) δ 8.2–7.2 (m, 4 H, aromatic), 3.65 (s, 3 H, methyl), 2.93 and 3.33 (ABq, J = 11 Hz, 2 H, methylene), 2.60 and 3.10 (ABq, J = 17 Hz, 2 H, benzyl), 1.40 (s, 3 H, methyl).

Reduction of 6.5 g (0.03 mol) of **3b** with 3.9 g of $LiAlH_4$ in 100 mL of dry ether was carried out by the ordinary method. Recrystallization from chloroform gave a colorless solid, mp 132–133 °C, **4b** (2.5 g, 43%) and oily residue (2.8 g, 46%) which seemed to be an epimeric mixture of **4b** judging from spectral data. Spectral data for **4b:** IR (Nujol) 3220 (OH), 1045, 1020, 745 cm^{-1}; NMR (C_5H_5N) δ 5.33 (d d, J = 6, 10 Hz, 1 H, α hydrogen), 3.70 (s, 3 H, methyl), 2.93 and 2.63 (ABq, J = 16 Hz, 2 H, benzyl), 2.77 (d, ABq, J = 13, 6 Hz, 1 H, methylene), 1.87 (d, ABq, J = 13, 10 Hz, 1 H, methylene), 1.60 (s, 3 H, methyl) and other signals for aromatic and hydroxy hydrogens: mass m/e 192 ($C_{12}H_{16}O_2$).

1-Hydroxy-2,3-dimethyl-3-hydroxymethyltetraline (4c). The keto ester **3c** was prepared from 9.0 g (0.041 mol) of **2c** and diazomethane in ether in 98% yield. Spectral data for **3c:** IR (neat) 1730 (CO_2Me), 1690 (CO), 1600, 1220, 1100, 740 cm^{-1}; NMR ($CDCl_3$) δ 8.1–7.9 (m, 1 H, aromatic), 7.5–7.1 (m, 3 H, aromatic), 3.68 (s, 3 H, methyl), 3.47 and 2.93 (ABq, J = 16.5 Hz, 2 H, benzyl), 2.7 (q, J = 7.5 Hz, methine), 1.20 (s, 3 H, methyl), 1.17 (d, J = 7.5 Hz, 3 H, methyl).

Reduction of **3c** (5.9 g, 0.07 mol) with $LiAlH_4$ (4.0 g) yielded **4c** (1.4 g, 25% yield) and an oily product (3.3 g, 59% yield) which seemed to be a mixture of **4c** and its epimeric isomer. The crude **4c** purified by

recrystallization from chloroform: mp 149–151 °C; IR (Nujol) 3300 (OH), 1030, 1010, 740 cm^{-1}; NMR (C_5H_5N) δ 5.31 (d, J = 6 Hz, 1 H, α hydrogen), 3.70 (s, 2 H, oxymethyl), 2.89 and 2.75 (ABq, J = 16.5 Hz, 2 H, benzyl), 2.50 (m, 1 H, methine), 1.28 (s, 3 H, methyl), 1.27 (d, J = 7 Hz, 3 H, methyl) and other signals; mass spectrum m/e 206 ($C_{13}H_{18}O_2$).

6-Methyl-3,4-benzobicyclo[4.1.0]hept-3-en-2-one (7b). A suspension of 4.03 g (0.021 mol) of solid diol **4b** and 12 g of active MnO_2 in 450 mL of dry benzene was stirred at room temperature for 30 h. The product **5b** (3.72 g) was obtained by filtration of the reagent and evaporation of the solvent. Spectral data for crude **5b:** IR (neat) 3450 (OH), 1680 (CO), 1600, 1290, 1040, 760 cm^{-1}; NMR ($CDCl_3$) δ 8.2–7.1 (m, 4 H, aromatic), 3.48 (s, 2 H, oxymethyl), 3.13 and 2.77 (ABq, J = 17 Hz, 2 H, benzyl), 2.46 and 2.69 (ABq, J = 17 Hz, 2 H, methylene), 2.03 (br s, 1 H, hydroxyl), 1.03 (s, 3 H, methyl).

The pyridine solution (80 mL) of the crude keto alcohol **5b** (4.0 g) was added into the same solution (30 mL) of p-toluenesulfonyl chloride (12.0 g) under cooling in an ice–water bath. The mixture was then stirred at room temperature for 24 h. Ordinary extraction gave crude tosylate 6b (7.2 g): IR (Nujol) 1685 (CO), 1600, 1350 (SO_2), 1170 (SO_2), 980, 960 cm^{-1}; NMR ($CDCl_3$) δ 8.2–7.7 (m, 1 H, aromatic), 7.5–7.2 (m, 3 H, aromatic), 7.77 and 7.30 (ABq, J = 8 Hz, 4 H, aromatic), 3.83 (s, 2 H, oxymethyl), 3.10 and 2.70 (ABq, J = 16 Hz, 2 H, benzyl), 2.63 and 2.30 (ABq, J = 16 Hz, 2 H, methylene), 2.47 (s, 3 H, methyl), 1.03 (s, 3 H, methyl).

The above tosylate (**6b**) solution dissolved in dioxane (200 mL) was added to methanolic potassium hydroxide (10 g of KOH in 100 mL of MeOH) solution. The mixture was stirred at room temperature for 5 h and ordinary workup gave rise to a colorless oil (**7b,** 2.4 g) in 66% yield from **4c.** Mass spectrum for **7b:** m/e 172 ($C_{12}H_{12}O$), 157 ($M^+ - 15$), 129 ($M^+ - 43$). NMR and IR data are shown in Table V.[19]

1,6-Dimethyl-3,4-benzobicyclo[4.1.0]hept-3-en-2-one (7c). By a method similar to that used in the preparation of **7b, 7c** (oil, 417 mg) was obtained from **4c** (1.43 g). Spectral data for keto alcohol **5c:** IR (neat) 3450 (OH), 1675 (CO), 1030, 740 cm^{-1}; NMR ($CDCl_3$) δ 8.1–7.9 (1 H, m, aromatic), 7.7–7.1 (m, 3 H, aromatic), 3.61 and 3.43 (ABq, J = 10.5 Hz, 2 H, oxymethyl), 3.31 and 2.71 (ABq, J = 16 Hz, 2 H, benzyl), 2.81 (q, J = 7 Hz, 1 H, methine), 2.1 (br s, 1 H, hydroxyl), 1.20 (d, J = 7 Hz, 3 H, methyl), 0.83 (s, 3 H, methyl). Spectral data for tosylate **6c:** mp 129–131 °C; IR (Nujol) 1675 (CO), 1350 (SO_2), 1165 (SO_2), 960, 840 cm^{-1}; NMR ($CDCl_3$) δ 8.2–7.8 (m, 1 H, aromatic), 7.5–7.1 (m, 3 H, aromatic), 7.87 and 7.37 (ABq, J = 8 Hz, 4 H, aromatic), 3.43 and 3.61 (ABq, J = 10.5 Hz, 2 H, oxymethyl), 3.31 and 2.71 (ABq, J = 15.8 Hz, 2 H, benzyl), 2.45 (s, 3 H, methyl), 2.81 (q, J = 7.0 Hz, 1 H, methine), 1.20 (d, J = 7.0 Hz, 3 H, methyl), 0.83 (s, 3 H, methyl). Mass spectrum for **7c:** m/e 186 ($C_{13}H_{14}O$), 171 ($M^+ - 15$), 143 ($M^+ - 43$). NMR and IR data are shown in Table V.[19]

Reduction of the 3,4-Benzobicyclo[4.1.0]hept-3-en-2-one derivatives (7a). 3,4-Benzobicyclo[4.1.0]hept-3-en-2-ol (8a). To a stirred suspension of 420 mg (11 mmol) of $LiAlH_4$ in 30 mL of dry ether was added a solution of 338 mg (2.1 mmol) of **7a**[4] in 40 mL of ether. The mixture was stirred for 1 h at 0 °C and for 20 h at room temperature before the excess hydride was carefully decomposed with 0.5 mL of water. The ether layer was decanted and the precipitate was washed several times with ether. The combined organic layer was dried over anhydrous K_2CO_3. The solvent was removed under reduced pressure to yield 305 mg of a colorless solid. Recrystallization from n-pentane gave a pure product (**8a;** 284 mg, 84%): mp 81.5–82 °C (lit.[4] mp 85–86 °C); IR (Nujol) 3300 (OH), 1030, 730 cm^{-1}; NMR data are compiled in Table I.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.22; H, 7.49.

6-Methyl-3,4-benzobicyclo[4.1.0]hept-3-en-2-ol (8b). Reduction of **7b** (475 mg) with $LiAlH_4$ (550 mg) yielded **8b** (90%), which was recrystallized from n-pentane to give a pure sample: mp 88–90 °C; IR (Nujol) 3350 (OH), 1020, 740 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.43; H, 8.07.

3,4-Benzo-1,6-dimethylbicyclo[4.1.0]hept-3-en-2-ol (8c). Reduction of **7c** (205 mg, 1.1 mmol) with $LiAlH_4$ (210 mg) yielded **8c** (mp 94–95 °C from n-pentane, 133 mg, 65%): IR (Nujol) 3350 (OH), 1030, 740 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.57; H, 8.48.

Europium Shift Reagents Studies. A sample of 30–60 mg of the alcohol (**8a–e** and **12a**) was dissolved in 0.4–0.6 mL of deuteriochloroform and the spectrum was recorded at 1500-Hz sweep width. A weighed sample of commercially available $Eu(dpm)_3$ (from the Wako Co.) was successively dissolved in a deuteriochloroform solution of the alcohol and then the NMR spectrum was measured immediately. Shifts were plotted against the molarity of $Eu(dpm)_3$ (see Figure 1 for the plots in the case of **8d** as one example). The calculation of each $(\Delta Eu)_i$ value,[8] which is defined as the difference between the chemical shift of a given proton, H_i, measured without the reagent and the shifts with the equimolar reagent, was carried out for definite protons and the relative induced shifts, $RLIS^i = (\Delta Eu)_i/(\Delta Eu)_2$, were thus obtained. These values were shown in Table I.

3,4-Benzobicyclo[4.1.0]hept-3-en-2-yl p-Nitrobenzoate (1a). The p-nitrobenzoate **1a** was prepared by allowing 367 mg (2.3 mmol) of **8a** to react with 630 mg (3.4 mmol) of p-nitrobenzoyl chloride in 10 mL of dry pyridine at 5 °C for 1 day. The product was extracted with ether and the organic layer was washed with water, 1 M hydrochloric acid, 5% aqueous sodium hydrogen carbonate, and water. The ether layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. A light yellow solid was recrystallized from n-hexane to give **1a** (150 mg, 50%): mp 110–111 °C. NMR and IR data of **1a–c** are summarized in Table V.[19]

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.70; H, 4.99; N, 4.07.

3,4-Benzo-6-methylbicyclo[4.1.0]hept-3-en-2-yl p-Nitrobenzoate (1b) and 3,4-Benzo-1,6-dimethylbicyclo[4.1.0]hept-3-en-2-yl p-Nitrobenzoate (1c). By a method similar to that used in the preparation of **1a, 1b** (mp 106.5–107.5 °C, 67%) and **1c** (mp 109.5–110 °C, 72%) were obtained.

Anal. Calcd for $C_{19}H_{17}O_4N$ (**1b**): C, 70.57; H, 5.30; N, 4.33. Found: C, 70.28; H, 5.30; N, 4.41.

Anal. Calcd for $C_{20}H_{19}O_4N$ (**1c**): C, 71.20; H, 5.68; N, 4.15. Found: C, 70.90; H, 5.76; N, 4.16.

General Kinetic Procedures. For each run approximately 100 mg of p-nitrobenzoate was weighed into a 100-mL volumetric flask and dissolved in 80% aqueous acetone; the 80% aqueous acetone mixture was prepared by mixing 80 mL of dry acetone with 20 mL of distilled water. Rates at 25.0 ± 0.03 °C were measured by quenching 5.00-mL aliquots in 25 mL of dry acetone and immediately titrating with a standard aqueous sodium hydroxide (0.01 M) using an automatic titrating apparatus (Hitachi-Horiba automatic titrator using glass electrode). Rates at the other temperatures (35.0, 45.0, 55.0 °C in accuracy, ±0.03 °C) were measured by means of ampules. In each case, 100 mL of ~0.003 M 80% aqueous acetone solution of the p-nitrobenzoate was prepared, and 11-mL portions were sealed into ampules. A set of ampules was immersed in a water bath at the appropriate temperature. After allowing 5–10 min for temperature equilibration, the zero point was taken. The ampules were removed from the bath and immersed into ice–water to stop the solvolyses. After cooling to 0 °C, a 5.00-mL portion of the solution was removed and titrated with aqueous sodium hydroxide in the same method as described above. Kinetic plots were linear to 75% conversion and reported values are the average of two separate runs (Table III). In all cases infinite titers were measured after ~10 half-lives and 95–105% of theoretical p-nitrobenzoic acid was removed.

Treatment of 8a–c with p-Nitrobenzoic Acid. A solution of 200 mg (1.15 mmol) of **8b** and 196 mg (1.15 mmol) of p-nitrobenzoic acid dissolved in 100 mL of 80% aqueous acetone was warmed at 45 °C for 2 days. Into the solution was added 190 mg (2.2 mmol) of $NaHCO_3$ and most of the acetone was removed under reduced pressure followed by extraction with ether, washing the ether layer with water, and drying it over anhydrous K_2CO_3. The solvent was removed at reduced pressure to give 165 mg (82%) of a yellow oil. Spectral data showed that the oil was 1-methyl-3,4-benzohepta-3,5-dien-1-ol (**13b**). Spectral data for **13b:** IR (CCl_4) 3450 (OH), 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.12 (s, 4 H, aromatic), 6.51 (d, J = 11 Hz, 1 H, vinyl), 5.86 (dt, J = 11 and 5.5 Hz, 1 H, vinyl), 2.79 (s, 2 H, benzyl), 2.32 (d, J = 5.5 Hz, 2 H, methylene), 2.22 (s, 1 H, hydroxyl), 1.27 (s, 3 H, methyl); mass m/e 174 ($C_{12}H_{14}O$), 131 ($M^+ - 43$).

By the method similar to that used in the reaction of **8b,** 1,6-dimethyl-3,4-benzohept-3,5-dien-1-ol (**13c,** an oily product, 35 mg) was obtained from **8c** (40 mg). Spectral data for **13c:** IR (CCl_4) 3400 (OH), 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 4H, aromatic), 6.47 (br s, 1H, vinyl), 2.79 (s, 2H, benzyl), 2.15 (s, 2H, methylene), 2.04 (s, 3H, methyl), 1.70 (s, 1H, hydroxyl), 1.37 (s, 3 H, methyl); mass m/e 188 ($C_{13}H_{16}O$), 145 ($M^+ - 43$).

Under the same conditions, **8a** was not isomerized appreciably after 1 month.

Preparative Solvolysis of 1a–c. A solution of 87 mg (0.28 mmol) of **1a** and 0.15 mL (~1.4 mmol) of 2,6-lutidine in 100 mL of 80% aqueous acetone was heated at 35 °C for 80 h (~10 half-lives). The solution was concentrated under reduced pressure, 200 mL of water was added, and the resulting suspension was extracted with ether. The combined ether extracts were washed with water and dried over anhydrous K_2CO_3. Removing the solvent under reduced pressure gave

39 mg (85%) of a light yellow oil. It was found from its NMR spectrum that the oily residue consisted almost entirely of one component, the epimer of **8a**, *syn*-3,4-benzobicyclo[4.1.0]hept-3-en-2-ol (**12a**): IR (neat) 3350 (OH), 1030, 980, 740 cm^{-1}; NMR is shown in Table I.

The other esters (**1b** and **1c**) were solvolyzed by the method similar to that used in solvolysis of **1a** and the product distribution was determined by the NMR spectrum and its integral intensity for α hydrogen or vinyl hydrogen. The results was shown in Table IV. The NMR spectrum of the epimer of **8b** was assumed from that of products **12b** and **13b**. NMR spectrum for **12b** ($CDCl_3$): δ 7.12 (s, 4 H, aromatic), 5.00 (d, J = 3 Hz, 1 H, α hydrogen), 3.20 and 2.88 (ABq, J = 16 Hz, 2 H, benzyl), 1.30 (s, 3 H, methyl), 1.48–0 (m, 3 H, cyclopropyl), and the other signals.

A mixture containing 100 mg of **8b** (0.58 mmol), 300 mg (2.9 mmol) of 2,6-lutidine, and 100 mg (0.6 mmol) of *p*-nitrobenzoic acid in 100 mL of 80% aqueous acetone was heated at 45 °C for 1 day. After usual workup, 93 mg of colorless solid was obtained. A comparison of the NMR spectrum before and after heating showed that **8b** was stable to the reaction conditions. Similar treatment of **8a** and **8c** gave the same results.

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Registry No.—*cis*-**2b**, 64425-83-8; *trans*-**2b**, 64414-48-8; **2c**, 64425-29-2; **3b**, 64414-49-9; **3c**, 64414-50-2; *cis*-**4b**, 64414-51-3; *trans*-**4b**, 64414-52-4; **4c**, 64414-53-5; **5b**, 64414-54-6; **5c**, 64414-55-7; **6b**, 64414-56-8; **6c**, 64414-36-4; **7a**, 27346-16-3; **7b**, 64414-46-6; **7c**, 64414-47-7; **9**, 7148-59-6; **11b**, 29840-37-7; **11c**, 64414-37-5; **13b**, 64414-38-6; **13c**, 64414-39-7; 2-benzyl-2-methylsuccinic acid, 32980-47-5; *p*-toluenesulfonyl chloride, 98-59-9; *p*-nitrobenzoyl chloride, 122-04-3; *p*-nitrobenzoic acid, 62-23-7; 2,6-lutidine, 108-48-5.

Supplementary Material Available: infrared and proton NMR data for **1a–c** and **7a–c** (Table V) (4 pages). Ordering information is given on any current masthead page.

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A Carbon-13 Nuclear Magnetic Resonance Investigation of Substituted 4-X-2,6-Dinitroanisoles and Related Meisenheimer 1,1-Complexes

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Carbon-13 NMR chemical shifts for various substituted 4-X-2,6-dinitroanisoles **1** (X = SO_2CF_3, NO_2, CN, SO_2CH_3, COC_6H_5, CF_3, Cl, H) and related *gem*-dimethoxyl adducts **2** (X = SO_2CF_3, NO_2, CN, SO_2CH_3, COC_6H_5, CF_3) are reported. In the case of anisoles **1** the deviations from additivity of substituent effects observed for $C_{2,6}$ and C_1 together with the absence of a deshielding of C_4 indicate an inhibition of resonance of the *o*-nitro groups. Good linear correlations with the Swain and Lupton reactivity parameters are observed for δ_{C_1}, $^1J_{^{13}C_7H}$, $^1J_{C_3H_3}$ in these tetrasubstituted benzenes. ^{13}C chemical shifts measured for adducts **2** reveal an increase in the negative charge located at $C_{2,6}$ and C_4, but a decrease at $C_{3,5}$, in agreement with SCFMO calculations. However, no relation exists between these shifts and the known thermodynamic stability of adducts **2**.

The reaction of methoxide ions with substituted 4-X-2,6-dinitroanisoles **1** usually gives the *gem*-dimethoxyl 1,1-complexes **2** as the stable products.[2] From thermodynamic and kinetic studies on the one hand[2-6] and crystallographic and ^1H NMR studies on the other hand,[2-7,11] it appears that the electron-withdrawing ability of the ring substituents and the release of steric compression which exists between the methoxyl group and the adjacent nitro groups in the parent ethers **1** are two major factors responsible for the stability of complexes **2**. Since they are known to depend on steric and charge distribution effects, ^{13}C chemical shifts could be reasonably expected to yield further information on both of these

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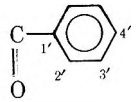
Table I. ^{13}C Chemical Shifts of 4-X-2,6-Dinitroanisoles 1 in Me_2SO-d_6 with Me_4Si as Internal Standard

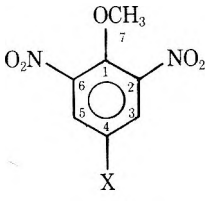
X	Registry no.	δ_{C_1}	δ_{C_2}	δ_{C_3}	δ_{C_4}	δ_{C_7}	δ_X	$^1J_{C_7H}$	$^1J_{C_3H_3}$	$^3J_{C_3H_5}$	$^2J_{C_4H_3}$	Other coupling const
H	3535-67-9	146.2_5	144.5_6	129.6_5	125.0_5	64.3_5						
Cl	6302-58-5	145.1_6	144.9_1	129.3_2	128.2_4	64.5_2		148.9	176	6.0_5	5.1_5	
CF_3	317-70-4	149.2_3	144.8_1	126.8_6	124.6_0	64.5_9	122.1_2	149.7	173.8			$^1J_{CXF} = 272.8$ $^2J_{C_4F} = 35.4$ $^3J_{C_3F} = 3.6$
CN	19018-96-3	149.7_3	144.3_9	133.6_1	107.0_3	64.5_6	115.3_7	149.7	177	7.4	1.9_5	$^3J_{CXH_3} = 5.4$
SO_2CH_3	39880-50-7	150.1_0	144.1_8	128.4_9	135.8_8	64.5_8	43.0_2	149.9	175.5	6.9_5		
$CO—C_6H_5$	39880-47-2	149.0_4	144.0_4	130.1_1	132.4_6	64.4_8	*a*	149.6	172.2	7.6_5	1.2	$^2J_{C_2H_3} = 2.5_5$
NO_2	606-35-9	150.8_3	143.8_7	124.6_0	141.4_4	64.8_0		150.1	177.9	5.5		
SO_2CF_3	19822-29-8	153.1_1	144.9_3	131.5_6	124.0_6	64.8_1	119.1_9	150.5	177.8			$^1J_{CXF} = 325.6$

[a] X = 

$\delta_{C_1'} = 135.1_9$, $\delta_{C_2'} = 129.8_9$, $\delta_{C_3'} = 128.8_1$, $\delta_{C_4'} = 133.6_4$, $\delta_{CO} = 191.2_8$.

factors. Following a previous ^1H NMR study[11], we have therefore performed a ^{13}C NMR spectroscopic study of anisoles 1 and 1,1-complexes 2.

During the course of our work, Olah and Mayr published a paper in which they reported a similar investigation of isomeric 2-X-4,6-dinitroanisoles 3 and corresponding 1,1-complexes 4.[12] The constancy of the steric strain in our anisoles 1 allows, however, a more precise structural analysis.



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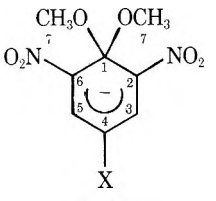

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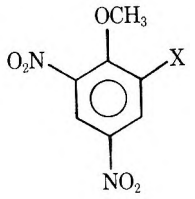

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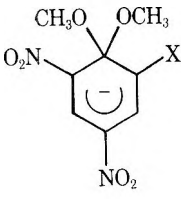

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Results

Because of the symmetrical structures of anisoles 1 and complexes 2, ^{13}C NMR spectra showed four signals for the ring carbons and one signal for the methoxyl carbon(s). Other absorptions were observed for carbons belonging to the X substituent. Assignments were deduced from proton-coupled spectra and intensity arguments.

Substituted Anisoles 1. The high-field absorption ($\simeq$64.5 ppm) which gave a quartet in the proton-coupled spectra ($^1J_{C_7H} \simeq 150$ Hz) was unambiguously assigned to the methoxyl C_7 carbon. C_1, whose resonance was observed at low field (145–153 ppm), appeared as a poorly resolved multiplet in the proton-coupled spectra. This unresolved fine structure suggests that C_1 is spin coupled through three bonds to the three protons of the OCH_3 group and the two protons H_3 and H_5.

The shielding of carbons $C_{2,6}$ was expected to be only slightly affected by the X substituent which is located in a meta position. Their resonance appeared in a narrow range around 144 ppm. Furthermore, these carbons have neither $^1J_{CH}$ nor $^3J_{CH}$ but only $^2J_{CH}$ and $^4J_{CH}$ coupling constants which are known to be small. In the proton coupled spectra, they gave a broad signal, which is probably due to the effect of the adjacent ^{14}N nucleus.

In the proton-decoupled spectra, the signal belonging to carbons $C_{3,5}$ was very intense because of the nuclear Overhauser effect. This signal became a double doublet in the proton-coupled spectra due to the $^1J_{CH}$ and $^3J_{CH}$ coupling constants. For X = CF_3, the $C_{3,5}$ resonance was a quartet showing a $^3J_{CF}$ coupling constant ($^3J_{C_3F} = 3.6$ Hz).

As expected, C_4 which is directly attached to the X substituent had the most affected shielding; its shift covers a wide range (107–141 ppm). When X = CF_3, this signal was a quartet ($^2J_{C_4F} = 35.4$ Hz). In the proton-coupled spectra, the C_4 resonance was the X part of an A_2X system and gave a triplet ($^2J_{C_4H} = 1$–5 Hz).

Finally, these assignments were confirmed by the use of additivity of substituent effects when these effects were known (vide infra). The results are summarized in Table I.

Anionic Complexes 2. The intense signal at ca. 52 ppm was assigned to the methoxyl carbons C_7; this assignment was confirmed by selective irradiation of the corresponding methoxyl protons.

The resonance of the sp^3 carbon C_1 was observed around 102–104 ppm. In the proton-coupled spectra, it was a poorly resolved multiplet (compare C_1 in the parent anisoles). The low-field absorptions (126–136 ppm) were assigned to $C_{2,6}$ and $C_{3,5}$ respectively as follows. In the proton-coupled spectra, each of these carbons appears as the X part of an ABX system where $\nu_A - \nu_B$ is very small since it corresponds to a ^{13}C isotope effect.[13,23] In the case of $C_{3,5}$ the magnitudes of J_{AX} and J_{BX} are quite different, since these coupling constants are $^1J_{CH}$ and $^3J_{CH}$, respectively, and these carbons gave a double doublet. On the other hand, in the case of $C_{2,6}$, both J_{AX} and J_{BX} are small (as expected for $^2J_{CH}$ and $^4J_{CH}$ coupling constants), and the resonance of these carbons was a 1:1:1 triplet; the separation of the outer lines gave the sum $|^2J_{CH} + {}^4J_{CH}|$. Proton-coupled spectra also allowed an unambiguous assignment of the C_4 resonance, which appeared as the X part of an A_2X system and gave a 1:2:1 triplet.

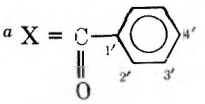
When X = SO_2CF_3, a quartet was observed for the carbon resonance of the trifluoromethyl group ($^1J_{CF} = 326.2$) and a small coupling through three bonds ($^3J_{C_4F} = 2$ Hz) was resolved in the C_4 signal. C–F coupling constants through one, two, and three bonds were also observed for X = CF_3. The results are summarized in Table II.

Discussion

Substituted Anisoles. (1) Additivity of Substituent Effects. Conformational Features. The ^{13}C chemical shifts

Table II. ^{13}C Chemical Shifts of 1,1-Dimethoxy-2,6-dinitro-4-X-cyclohexadienate Anions 2 in Me_2SO-d_6 with Me_4Si as Internal Standard

X	Registry no.	δ_{C_1}	δ_{C_2}	δ_{C_3}	δ_{C_4}	δ_{C_7}	δ_X	$^1J_{C_7H}$	$^1J_{C_3H_3}$	$^3J_{C_3H_5}$	$^4J_{C_2H_5}$	$\Sigma\lvert J_{C_2H_3}$ +	Other coupling const
CF_3	28933-97-3	104.5_0	126.3_3	131.6_6	94.3_7	51.9_5	125.4_1	142.5					$^1J_{CF} = 268.0$ $^2J_{C_4F} = 34.6$ $^3J_{C_3F} = 3.1$
CN	25549-13-7	102.7_4	127.8_7	136.3_7	73.6_8	51.9_3	120.9_1	142.6	163	7.2	5.7		$^3J_{C_XH_3} = 4.7$
SO_2CH_3	40203-26-7	103.0_5	126.7_9	132.6_9	103.7_9	51.9_0	44.6_1	142.3	162.7	6.5	5.6		
$CO-C_6H_5$	40203-23-4	102.6_6	128.4_4	135.7_1	104.2_1	51.8_8	*a*	142.5	159.4	7.3	5.5		
NO_2	12128-30-2	102.0_5	128.6_4	128.9_0	117.4_1	52.1_1	—	143.5	165.5	5.2	6.3		$^2J_{C_4H_3} = 3.7$
SO_2CF_3	35298-04-5	102.1_1	128.9_2	133.0_5	87.8_0	52.1_9	120.3_1	143.2	164.5	6.4	6.2		$^1J_{CF} = 326.2$ $^3J_{C_4F} \simeq {}^2J_{C_4H_3} \simeq 2$

[a] X = 

$\delta_{CO} = 189.6_5$, $\delta_{C_1'} = 139.5_9$, $\delta_{C_2'} = 128.0_6$, $\delta_{C_3'} = 128.0_6$, $\delta_{C_4'} = 130.1_6$.

Table III. Observed and Predicted Aryl Carbon Shieldings Relative to Benzene for 4-X-2,6-Dinitroanisoles 1

	$\Delta\delta_{exptl}$				$\Delta\delta_{calcd}$[a]				$\Delta\delta_{calcd} - \Delta\delta_{exptl}$			
X	C_1	C_2	C_3	C_4	C_1	C_2	C_3	C_4	C_1	C_2	C_3	C_4
H	17.7_5	16.0_6	1.1_5	-3.4_5	21.8	6.5	2.0	−5.9	4.0_5	-9.5_6	0.8_5	-2.4_5
Cl	16.6_6	16.4_1	0.8_2	-0.2_6	19.9	7.8	2.4	0.3	3.2_4	-8.6_1	1.5_8	0.5_6
CF_3 (c)	20.7_3	16.3_1	-1.6_4	-3.9_0	25.0	6.8	−0.2	−14.9	4.2_7	-9.5_1	1.4_4	−11.0
(d)					25.0	6.8	−1.0	−3.1	4.2_7	-9.5_1	0.6_4	0.8_0
CN	21.2_3	15.8_9	5.1_1	-21.4_7	25.7	7.1	5.6	−21.3	4.4_7	-8.7_9	0.4_9	0.1_7
SO_2CH_3	21.6_0	15.6_8	-0.0_1	7.3_8	26.6	7.1	0.5	6.4	5.0	-8.5_8	0.5_1	-0.9_8
COC_6H_5	20.5_4	15.5_4	1.6_1	3.9_6	25.4	6.3	3.7	3.5	4.8_6	-9.2_4	2.0_9	-0.4_6
NO_2	22.3_3	15.3_7	−3.9	12.9_4	27.6	7.4	−2.8	14.1	5.2_7	-7.9_7	1.1	1.1_6

	$\Delta\delta'_{calcd}$[b]				$\Delta\delta'_{calcd} - \Delta\delta_{exptl}$			
X	C_1	C_2	C_3	C_4	C_1	C_2	C_3	C_4
H								
Cl	15.8_5	17.3_6	1.5_5	2.7_5	-0.8_1	0.9_5	0.7_3	3.0_1
CF_3 (c)	20.9_5	16.3_6	-1.0_5	-12.4_5	0.2_2	0.0_5	0.5_9	-8.5_6
(d)	20.9_5	16.3_6	-1.8_5	-0.6_5	0.2_2	0.0_5	-0.2_1	3.2_5
CN	21.6_5	16.6_6	4.7_5	-18.8_5	0.4_2	0.7_7	-0.3_6	2.6_2
SO_2CH_3	22.5_5	16.1_2	-0.3_5	8.8_5	0.9_5	0.4_4	-0.3_4	1.4_7
COC_6H_5	21.3_5	15.8_6	2.8_5	5.9_5	0.8_1	0.3_2	1.2_4	1.9_9
NO_2	23.5_5	16.9_6	-3.6_5	16.5_5	1.2_2	1.5_9	0.2_5	3.6_1

[a] $\Delta\delta$ values calculated from benzene. [b] $\Delta\delta'$ values calculated from 2,6-dinitroanisole. [c] Values with increments from ref 15 and 16. [d] Values with increments determined in this work.

of polysubstituted aromatics can be calculated by using the additivity of substituent effects.[14] Provided that the substituents are not ortho to each other, good additivity relationships are usually found, with differences between observed and calculated shifts less than ±2 ppm. In ortho-substituted derivatives, the additivity relation breaks down and ^{13}C shieldings have been shown to reflect the degree of steric hindrance to electronic interactions.[15]

Table III compares the calculated ($\Delta\delta_{calcd}$) and observed ($\Delta\delta_{exptl}$) shifts relative to that of benzene (128.5 ppm). Although substituent effects of monosubstituted benzenes were measured in CCl_4[16,17] or $CDCl_3$[18] and our values in Me_2SO-d_6, the agreement is quite good for C_3 and C_4; the discrepancy observed for C_4 in the case of the trifluoromethyl derivative will be discussed later. In contrast, strong deviations occur for C_1 and C_2. In every case, C_1 is more shielded than expected from the calculations ($\Delta\delta_{calcd} - \Delta\delta_{exptl} \simeq +4$ ppm) whereas an opposite trend is observed for C_2 ($\Delta\delta_{calcd} - \Delta\delta_{exptl} = -9$ ppm). These deviations reflect the existence of a severe steric compression in ortho dinitroanisoles 1, which results in the steric inhibition of resonance of the *o*-nitro groups and not in that of the methoxyl group as was recently concluded by Olah and Mayr.[12]

Indeed, a distorted coplanarity of the methoxyl group should result in an attenuation of the conjugative electron release by oxygen and therefore in a deshielding of C_4. Such an effect is, in fact, observed in 2,6-dialkylanisoles[15] where the methoxyl group is known to lie out of the aromatic plane. In contrast, this effect is absent in 2-nitroanisole,[15] 2-X-4,6-dinitroanisoles,[12] and in the 4-X-2,6-dinitroanisoles examined here. We therefore conclude from ^{13}C chemical shifts that the methoxyl groups in anisoles 1 and 3 lie in the aromatic plane, while the adjacent nitro groups are twisted out of this plane. This conclusion is in full agreement with that obtained from ^1H NMR studies[11,19] as well as from x-ray data[7] on 2,4,6-trinitrophenetole; in the solid state, dihedral angles of 32 and 61° have been observed between the ring and the nitro groups ortho to the ethoxyl group.

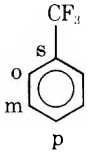
As the X substituent is attached to C_4, it should be emphasized that the geometry of C_1 in all the anisoles 1 must be

independent of X. Hence, it was of interest to check further substituent effects by taking into account the distorted geometry of the o-nitro groups. Assuming additivity effects from the 4-X substituent, we have recalculated ^{13}C chemical shifts by using the experimental ^{13}C shifts of 2,6-dinitroanisole 1 (X = H) as the reference compound. As can be seen in Table III, excellent agreement is now obtained between the $\Delta\delta'_{calcd}$ and the $\Delta\delta_{exptl}$ values for C_1, $C_{2,6}$, and $C_{3,5}$ ($\Delta\delta'_{calcd} - \Delta\delta_{exptl} < 1.6$ ppm). However, C_4 is more shielded than expected from these calculations and the difference $\Delta\delta'_{calcd} - \Delta\delta_{exptl}$ varies from 2 to 3.6 ppm. Thus, the additivity of substituent effects holds for C_1 and C_2 and C_3 in these tetrasubstituted benzenes when the twisting of the o-nitro groups is taken into account but it fails for C_4 which is directly bonded to the X substituent. Similar nonadditive ^{13}C substituent effects have been recently observed in para-disubstituted benzenes.[20]

(2) The Abnormal Behavior of the Trifluoromethyl Derivative. The large deviation observed for C_4 in the trifluoromethyl derivative 1 (X = CF_3) suggested a possible error in the reported ^{13}C chemical shift of trifluoromethylbenzene (**5**).[16,17] A reexamination of the ^{13}C spectrum of **5**, using experimental conditions similar to those previously described,[16] gave the following substituent shifts (relative to internal C_6H_6) and ^{13}C–F coupling constants.

C_s, +2.8 C_o, −3 C_m, +0.3 C_p, +3.2 (in ppm)
$^2J_{CF} = 32.4$ $^3J_{CF} = 3.7$ $^4J_{CF} < 0.4$ $^5J_{CF} = 0.9$ (in Hz)

Comparing with reported data shows that the value for C_s (−9 ppm[16,17]) has to be significantly changed. Indeed, our revised value gives a calculated shift for C_4 which is consistent with experiment (see Table III).



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(3) Correlation of Substituent Effects with Substituent Parameters. Recent articles have shown that substituent effects can be, in some cases, related to substituent constants by means of a two-parameter equation involving either the Taft or Hammett constants[21-23] or the Swain and Lupton reactivity parameters F and R.[24-27] Thus, in monosubstituted benzenes, good correlations have been obtained between the ^{13}C shifts of the para carbon and the σ_I, σ_R constants[22] as well as between some $J_{^{13}CH}$ coupling constants and the σ_I, σ_p constants.[23] Similarly, chemical shifts and coupling constants in some substituted heteroaromatic compounds have been found to correlate with F and R.[24,25]

Since the anisoles 1 are tetrasubstituted compounds, it was of a special interest to look for the existence of such correlations between their ^{13}C shifts or $J_{^{13}CH}$ coupling constants and, for instance, the F and R parameters of the X substituent. The regression equations $z_k = i_k + f_kF + r_kR$ where z_k is the NMR parameter and f_k and r_k are the regression constants were calculated by a linear least-squares multiple correlation computer program. All substituents were included in the data, except X = SO_2CF_3, for which the F and R parameters are so far not known.[26,27] Good correlations (c, correlation coefficient; σ, standard deviation) were obtained for δ_{C_1}, $^1J_{^{13}C_7H}$, and $^1J_{C_3H_3}$. The equations are:

$$\delta_{C_1} = (145.88 \pm 0.41) + (2.15 \pm 0.83)F + (11.92 \pm 1.50)R$$
$$c = 0.982, \quad \sigma = 0.475$$

$$^1J_{^{13}C_7H} = (148.74 \pm 0.17) + (0.84 \pm 0.22)F + (2.06 \pm 0.21)R$$
$$c = 0.985, \quad \sigma = 0.109$$

$$^1J_{C_3H_3} = (169.08 \pm 1.36) + (8.94 \pm 1.70)F - (4.87 \pm 2.64)R$$
$$c = 0.952, \quad \sigma = 0.835$$

As expected, the chemical shift of C_1 depends on both inductive and mesomeric effects of the X substituent. The positive signs found for the regression constants indicate that electron-withdrawing groups (−I, −M) give downfield shifts while the two contributions are of opposite signs for the (−I, +M) substituents. In this latter case, upfield shifts can then be observed, which is the case for X = Cl.

The correlation obtained for the $^1J_{^{13}C_7H}$ coupling constant of the methoxyl group indicates that this coupling is weakly affected by inductive and mesomeric effects and it increases when X is electron withdrawing (−I, −M). The regression constants f and r have opposite signs in the equation for $^1J_{C_3H_3}$. However, the inductive contribution fF is greater than the mesomeric one rR, so that both (−I, −M) and (−I, +M) substituents tend to increase $^1J_{C_3H_3}$. Although a comparison with monosubstituted benzenes is difficult (the corresponding $J_{^{13}CH}$ values were correlated with the σ_p, σ_I constants), both results suggest that the coupling constants $^1J_{CH}$ in substituted aromatic compounds are dependent on both inductive and mesomeric effects of the substituents.[23]

The lack of correlation between chemical shifts of C_2, C_3, and C_4 with F and R is in accord with a recent study of Smith and Proulx.[28] These authors have succeeded in correlating ^{13}C, ^1H, and ^{19}F chemical shifts in aromatic and olefinic systems with substituent effects by using a three-parameter equation of the type:

$$\delta = aF + bR + cQ + d$$

where F and R are the Swain and Lupton parameters and Q is the semiempirical parameter initially proposed by Schaefer et al. to rationalize the ortho effect.[29] The equations obtained for ^{13}C shifts in aromatic systems show that the absolute value of the cQ contribution decreases with increasing the number of bonds between the X substituent and the considered carbon. As a consequence, this factor becomes negligible only for the para carbon, i.e., C_1 in the anisoles 1.

Anionic Complexes 2. As can be seen in Table II, the ^{13}C shifts in anionic σ complexes 2 are not significantly affected by the X substituent, with the exception of C_4 which is directly bonded to X. On the other hand, the number of complexes is too limited for testing the existence of possible correlations with the F and R parameters.

Going from anisoles 1 to complexes 2 results in a strong upfield shift of both C_1 and the methoxyl carbon. This is consistent with the change in the hydridization of C_1. Moreover, in agreement with SCFMO calculations[30,31] which predict an increase in the negative charge located at the 2, 4, and 6 positions and a decrease at the 3 and 5 positions, we observed that resonances of $C_{2,6}$ and C_4 move to high field whereas those of $C_{3,5}$ move slightly to low-field.

According to Olah and Mayr,[12] the charge effects would be essentially responsible for the changes in sp^2 carbon shifts between anisoles 1 and complexes 2. In such an hypothesis, a decrease in the $\Sigma\Delta\delta$ sum of the changes in the ^{13}C shifts of sp^2 carbons should reflect an increase in the electron density of the olefinic carbons in 2 and therefore a parallel decrease in the fraction of the negative charge absorbed by the two nitro groups and the X substituent. As seen in Table IV, the $\Sigma\Delta\delta$ values are decreasing according to the sequence NO_2, COC_6H_5, CF_3, SO_2CH_3, CN, and SO_2CF_3 indicating that the negative charge would be delocalized to the greatest extent in the trinitro compound and to the least extent in the trifluoromethylsulfonyl complex.

Such a result is unexpected and difficult to assess for the following reasons. As previously mentioned, the stability of *gem*-dimethoxyl complexes is mainly dependent on the release

Table IV. Comparison of the Thermodynamic Stability of Adducts 2 with the Differences between Their ^{13}C NMR Shifts and Those of the Parent Anisoles 1

X	$\Delta\delta_{C_2}$	$\Delta\delta_{C_3}$	$\Delta\delta_{C_4}$	$\Sigma\Delta\delta^a$	$K_b{}^b$
CF_3	-18.4_8	$+4.8_0$	-30.2_3	-57.5_9	5
COC_6H_5	-15.6_0	$+5.6_0$	-28.2_5	-48.2_5	45[c]
SO_2CH_3	-17.3_9	$+4.2_0$	-32.0_9	-58.4_7	101
CN	-16.5_2	$+2.7_6$	-33.3_5	-60.8_7	168
NO_2	-15.2_3	$+4.3_0$	-24.0_3	-45.8_9	19500
SO_2CF_3	-16.0_1	$+1.4_9$	-36.2_6	-65.3_0	1.2×10^6

[a] $\Sigma\Delta\delta = 2(\Delta\delta_{C_2} + \Delta\delta_{C_3}) + \Delta\delta_{C_4}$. [b] Values at 20 °C, ref 5. [c] F. Terrier, unpublished results.

of steric compression which exists in the parent anisoles and the electron-withdrawing character of the ring substituents. Since the former factor is constant in our series, it would be reasonable that the stability order found experimentally for complexes **2** be parallel to the above $\Sigma\Delta\delta$ sequence. That this conclusion is contradicted by the results is obvious from Table IV where we list the values measured for the equilibrium constants for formation of complexes **2** in methanol. In contrast, the observed stability sequence $SO_2CF_3 > NO_2 > CN \simeq SO_2CH_3 > COC_6H_5 > CF_3$ is entirely consistent with the known electronic effects of the substituents. We therefore conclude that ^{13}C NMR chemical shifts are not simply related to the electron-withdrawing effect of the ring substituents and that due care must be taken in their analysis. A similar situation was, indeed, recently observed by Larsen and Bouis in the case of some benzoyl cations.[32]

Experimental Section

^{13}C NMR spectra were recorded at 25.17 MHz on a Varian XL-100-12 W.G. spectrometer in the Fourier transform mode. The instrument was equipped with a 620 L-100-16 K on-line computer. All spectra were run in dimethyl sulfoxide-d_6 ($c \simeq 0.8$ M) using the solvent ^2H signal for internal field-frequency lock. The temperature of the probe was 31 ± 2 °C.

^{13}C chemical shifts were measured relative to internal Me_4Si using standard conditions of ^1H noise decoupling and spectral width of 5000 Hz (digital resolution: 1.25 Hz/point). C–H and C–F coupling constants were measured using 2500 or 1000 Hz spectral widths (digital resolution: 0.68 or 0.25 Hz/point). Proton coupled ^{13}C spectra were obtained with gated proton decoupling (gated off during the data acquisition time but on during the pulse delay) to retain the nuclear Overhauser signal enhancement[33].

Various substituted 4-X-2,6-dinitroanisoles and related 1,1-complexes were prepared as previously described.[11]

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Carcinogen Chemistry. 2.[1] Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study of the Ambident Carbocationic Nature of Iminium Ions and Its Relevance to the Aminoalkylating Ability of Related Chemical Carcinogens

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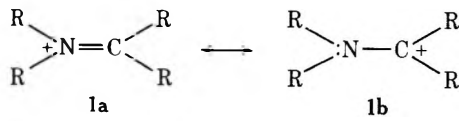
^1H and ^{13}C NMR spectroscopic investigation of aliphatic and aromatic iminium ions was carried out for their structural study and to determine the extent of the contribution of their carbenium ion character based on a comparison of the iminium ions with isoelectronic model compounds. CNDO/2 calculations of simple aliphatic iminium ions were also performed and related to the ^1H and ^{13}C NMR chemical shifts. *N*- and *C*-methyl substituents were found to polarize the charge density of the π bond, resulting in shielding and deshielding effects, respectively.

In our preceding paper we reported the in vitro formation of *N*-methylmethyleniminium in the acid cleavage reaction of *N,N*-dimethylnitrosamine and raised the possible role of iminium ions as aminoalkylating agents responsible for the carcinogenic alkylating ability of nitrosamines.[1] The ^1H NMR spectroscopic study of some protonated imines has been also reported in our previous studies.[2] The results indicated that protonated imines are predominantly iminium ions **1a** with limited contribution from the aminocarbenium ion structures, **1b**. Since ^{13}C NMR spectroscopy has proved to be most useful in studying the structure of carbocationic systems, it was expected to give a better indication of the relative importance of the contribution of **1a** to **1b**.



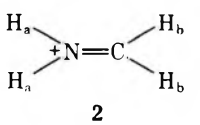
1a **1b**

We have consequently carried out a ^{13}C NMR spectroscopic study of a series of aliphatic and aromatic iminium ions, prepared by known procedures.[3-5] Since it was considered that nucleophilic anions, such as chloride and iodide, would exchange with the iminium centers, the less nucleophilic tetrafluoroborate salts were prepared and used in our study. CNDO/2 calculations of the simple aliphatic iminium ions were also performed, and the results were correlated with the ^1H and ^{13}C NMR data.

Results

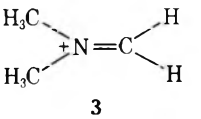
The NMR spectroscopic data of alkyliminium ions are summarized in Table I and those of aryliminium in Table II. For a comparison the ^{13}C NMR data of the parent arylimines are listed in Table III.

Methyleniminium Ion. The ^1H NMR spectrum of **2** at 60 MHz shows a complex pattern. A simpler first-order ^1H NMR spectrum is observed at 100 MHz in SO_2 solution at −60 °C. The triplet of doublets of doublets at δ_{1H} (Me_4Si) 10.67 is assigned to the H_a protons on the basis of their J_{N-H} coupling. The J_{N-H} coupling constant of 67.0 Hz is consistent with a sp^2 hybridized nitrogen.[6] The H_b absorption appears as a doublet of doublets at δ_{1H} (Me_4Si) 8.54 with trans and cis coupling constants of 18 and 14 Hz, respectively. The proton-decoupled ^{13}C NMR spectrum of **2** consists of a triplet at δ_{13C} (Me_4Si) 176.1 with J_{N-C} coupling of 0.4 Hz.



2

***N,N*-Dimethylmethyleniminium Ion.** The ^1H NMR spectrum of ion **3** in SO_2 at −60 °C shows a broad pentet at δ_{1H} (Me_4Si) 3.63 for the methyl groups and a slightly broadened peak at δ_{1H} (Me_4Si) 7.70 for the methylene protons. The multiplicities can be attributed to the trans and cis coupling of the *N*-methyl groups' protons to the methylene protons. The proton-decoupled ^{13}C NMR spectrum of **3** consists of two triplets at δ_{13C} (Me_4Si) 49.1 and 167.9 with C–N coupling constants of 0.2 and 0.5 Hz, respectively. These two signals correspond to the *N*-methyl and the methylene carbon absorptions, respectively.



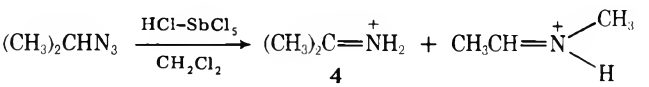
3

It has been previously found that methyl azide with HCl–$SbCl_5$ gives methyleniminium hexachloroantimonate.[2]

$$CH_3N_3 + HCl\text{–}SbCl_5 \rightarrow CH_2{=}N^+H_2SbCl_6^- + N_2$$

In continuation of our studies, ethyl and isopropyl azide were used in attempted preparation of the corresponding iminium salts, but the acid rearrangement of these alkyl azides resulted in mixtures of different iminium salts, due to competitive methyl and hydrogen migrations. The rearrangement products and their relative amounts (determined by peak integration of the iminium ions) are listed in Table IV.

The reaction of isopropyl azide with HCl–$SbCl_5$ in methylene chloride is typical of the acid-catalyzed rearrangement reactions studied. By ^1H NMR spectroscopy of the resulting products, we were able to identify the 2-propylideniminium (**4**) and the *N*-methylethylideniminium (**5**) ions. When the ^{13}C NMR spectrum of this solution was obtained, the high-intensity peaks corresponding to the major product, 2-propylideniminium ion, were easily identified relative to the six lower intensity peaks of the minor products. These latter signals were assigned to the cis and trans isomers of the *N*-methylethylideniminium ions.



4 **5**

The *N*-methyl group of the *N*-methylmethyleniminium ion absorbs at δ_{13C} 42.2. This absorption was used as a model for the trans isomer of the *N*-methylethylideniminium ion **6**. There are two *N*-methyl absorptions, one at δ_{13C} (Me_4Si) 40.4 and the other at δ_{13C} (Me_4Si) 33.9. These are assigned to the

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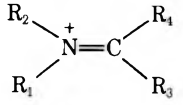
Table I. ^1H and ^{13}C NMR Spectroscopic Data[a] of Aliphatic Iminium Salts



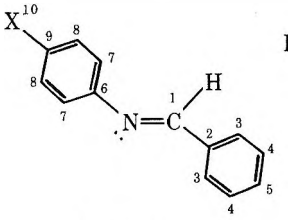
Compd	Registry no.	R_1	R_2	R_3	R_4	^1H NMR (Me_4Si)[b] R_1	R_2	R_3	R_4	$J_{1,2}$	$J_{1,4}$	$J_{1,3}$	J_{NH}	^{13}C NMR (Me_4Si) R_1	R_2	R_3	R_4	$\overset{+}{N}$=C
3	811-63-2	CH_3	CH_3	H	H[c]		3.63 brp		7.70 brm					49.1	49.1			167.9
5	64611-34-3	CH_3	H	H	CH_3[e]	4.00	dt	11.00 brt	8.19 qdd	8.45 tq	5.5	13.0	7.8	66.0	42.2			170.8
2	64611-39-8	H	H	H	H[d]		10.67 tdd		8.54 tdd					67.0				176.1
7	64611-41-2	CH_3	H	CH_3	H[d]	3.80	d		8.5	2.8					33.9		16.9		183.6
6	64611-42-3	CH_3	H	H	CH_3[d]	3.80	d		8.5	2.8					40.4			21.2	183.8
9	56995-77-8	H	H	H	CH_3[d]		9.90 brt		8.80 brm	2.77 brm				69.0				22.3	189.5
10	64611-43-4	CH_3	CH_3	CH_3	CH_3[c]		3.50 sp		2.37 sp			1.0			44.5	44.5	24.5	24.5	189.5
11	64611-35-4	CH_3	H	CH_3	CH_3[e]	3.63	d	9.60 m	2.80 s	2.70 s	6.0				34.2		20.0	27.1	195.5
12	56995-78-9	H	H	CH_3	CH_3[d]		9.40 brt		2.53 brs					64.0			25.3	25.3	201.6

[a] All chemical shifts from external Me_4Si are obtained on a Varian A-56-60 spectrometer for ^1H NMR and an XL-100 spectrometer for ^{13}C NMR. [b] ^1H NMR spectra from the HA-100. [c] In SO_2 solution at −60 °C with BF_4^- as the anion. [d] In SO_2 solution at −60 °C with $SbCl_6^-$ as the anion. [e] In magic acid solution.

Table II. Carbon-13 NMR Data for the Protonated Aromatic Imines

Compd	Registry no.	X	Rxn mixture	1	2	3	4	5	6	7	8	9	10	J_{C_1-H}, Hz
13	19696-25-4	H	HSO_3F/SO_2ClF	165.6 d	126.0 s		130.0 d	140.2 d	135.4 s	120.6 d	132.8 d	132.2 d		
			BF_4^-/SO_2	165.6 d	126.0 s	130.4 d	130.0 d	139.6 d	136.0 s	121.3 d	133.2 d	129.6 d		
14	64611-44-5	CH_3	Magic acid/SO_2	163.9 d	125.9 s	131.7 d	130.9 d	140.0 d	133.0 s	120.7 d	132.7 d	143.7 s	20.5 q	178.9
			BF_4^-/SO_2	163.9 d	126.2 s	131.4 d	130.6 d	139.2 d	133.5 s	121.0 d	133.2 d	142.9 s	20.6 q	
15	64611-45-6	OCH_3	Cl^-/SO_2	161.9 d	126.0 s	132.4 d	130.7 d	138.9 d	128.8 s	122.5 d	115.7 d	160.9 s	55.1 q	
			Magic acid/SO_2	168.5 d	125.5 s	133.8 d	131.1 d	141.5 d	136.5 s	124.1 d	121.1 d	152.4 s	74.1 q	181.4
16	17321-91-4	Cl	Magic acid/SO_2	165.9 d	125.8 s	131.0 d	131.0 d	140.7 d	134.1 s	122.3 d	133.8 d	137.5 s		
17	64611-46-7	NO_2	HSO_3F/SO_2ClF	171.2 d	125.6 s	131.7 d	131.7 d	144.3 d	142.3 s	124.0 d	131.7	147.3 s		180.5
18	19696-24-3	H	HSO_3F/SO_2ClF	172.7 d	125.7 s	131.7 d	130.6 d	139.2 d	39.5 q					179.1
19	64611-47-8	OCH_3	Magic acid/SO_2	171.2 d	126.9 s	134.9 d	119.2 d	156.6 s	40.5 q	72.7 q				180.0
			BF_4^-/SO_2	169.8 d	118.7 s	134.8 d	115.9 d	167.0 s	39.2 d	55.8 q				

Table III. Carbon-13 NMR Spectroscopic Data of Some Imines



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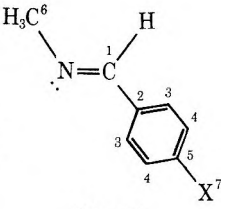


24, 25

Compd	Registry no.	X[a,b]	1	2	3	4	5	6	7	8	9	10
20	1613-90-7	CH_3O	159.3 d	137.6 s	129.8 d	129.7 d	132.1 d	146.0 s	115.5 d	123.3 d	159.4 s	56.5 q
21	1613-92-9	CH_3	159.9 d	137.4 s	129.5 d	129.5 d	131.9 d	150.3 s	121.8 d	130.7 d	136.5 s,	21.8 q
8	1750-36-3	H	161.4 d	137.4 s	130.2 d	129.8 d	132.4 d	153.2 s	122.0 d	129.8 d	127.0 d	
22	1613-89-4	Cl	161.4 d	137.0 s	130.2 d	129.9 d	132.6 d	151.4 s	123.3 d	129.8 d	132.6 s	
23	785-81-9	NO_2	163.8 d	136.5 s	130.4 d	130.1 d	133.5 s	159.0 s	122.4 d	126.1 d	146.5 s	
24	25521-74-8	H	162.2 d	137.3 s	129.0 d	128.6 d	130.8 d	48.2 q				
25	60682-83-9	MeO	161.7 d	130.1 s	130.1 d	114.4 d	162.1 s	48.1 q	55.3 q			

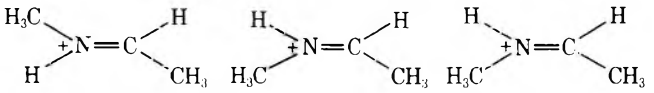
[a] All shifts are reported from Me_4Si. [b] In $CDCl_3$ as solvent.

Table IV. Products of the Acid Rearrangement of the Alkyl Azides with HCl–$SbCl_5$ in Methylene Chloride Solution

RN_3	% yield (rel)	Product ions[a]
R = CH_3–	100.0	Methyleniminium (2)
R = Et–	86.6	Acetaldiminium (9)
	13.4	*N*-Methylethyleniminium (5)
R = *i*-Pr–	68.5	2-Propylideniminium (11)
	31.5	*cis*- and *trans*-*N*-methyliminium (7 and 6)

[a] As hexachloroantimonate salts.

trans and cis isomers, respectively. Two *C*-methyl absorptions at δ_{13C} (Me_4Si) 21.2 and 16.9 are assigned to the trans and cis isomers, respectively, on the basis that the *cis*-*N*-methyl and -*C*-methyl of **7** are more shielded due to a γ-substituent effect.[7] The *C*-methyl shift of **7** is approximately 5.5 ppm more



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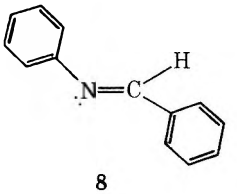
shielded from the *C*-methyl of the ethylideniminium ion used as a model. The iminium carbons were found at δ_{13C} (Me_4Si) 183.8 and 183.6, but no assignment to the cis and trans isomers can be made for these shifts, presently.

The ^{13}C NMR chemical shift assignments of the *N*-phenyl- and *C*-phenylimines were based on NMR measurements, including proton-decoupled, off-resonance, and fully decoupled experiments and their comparison with model compounds. Since the assignments of the carbons of the phenyl group for the *N*-methylbenzaldiminium ion **18** are unambiguous, they were used as models for identifying the ^{13}C NMR absorptions of the *C*-phenyl group of *N*-phenylbenzaldimine (**8**). The *N*-phenyl carbons were assigned by an off-resonance experiment, by peak intensities, and by comparison with ^{13}C NMR spectrum of aniline. The para-substituted *N*-phenyl carbons of **8** were assigned on the basis of simple additivity relationships using the ^{13}C shifts of monosubstituted benzenes (Table III).[8]

The ^{13}C NMR chemical shifts of the protonated aromatic imines **13–19** were assinged in a similar manner. The addivity relationships used to determine the ^{13}C chemical shifts of the *N*-phenyl group of of the protonated imines **13–17** do not fit as closely in this case as found for the parent imines themselves. Specifically, the "magic acid" solutions of N-protonated *p*-methoxy-, *p*-chloro-, and *p*-nitrophenylbenzaldimines **15–17** deviate the most. This could be due to a second protonation on the N-donor function. However, the iminium carbons in the aryl-substituted ions show characteristic chemical shifts in the range of δ_{13C} (Me_4Si) 163.–171.0 (Table II).



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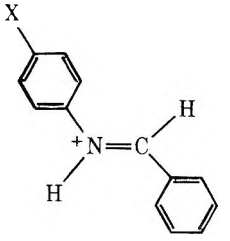
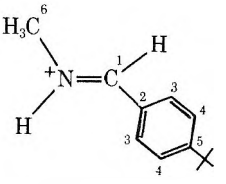


13, X = H
14, X = CH_3
15, X = OCH_3
16, X = Cl
17, X = NO_2

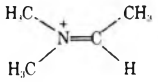


18, X = H
19, X = OCH_3

Charge densities were estimated from CNDO/2 calculations. The geometries of the molecules used were based on standard bond lengths and angles.[9] The 2p (π) and total charge densities for the aliphatic iminium ions are summarized in Table V.

In our previous ^1H NMR study of iminium ions, it was concluded that the iminium resonance forms **1a** are predominant over the aminocarbenium forms **1b**.[1] The basis for this conclusion was the observation that protonated 2-propylidenemethylamine showed two different *C*-methyl groups which by far were not as deshielded as those in a typical carbenium ion, such as the *tert*-butyl cation.[10] From the 17-Hz trans J_{HC-NH} coupling constant of the *N*-methylbenzaldiminium ion, it was concluded that geometry has more effect than charge on the ^1H chemical shifts of iminium ions. This evidence suggests a predominance of resonance structures **1a** over **1b**. However, the carbon shift of the iminium carbon should give a more direct indication of the importance of forms **1a** and **1b** rather than the adjacent proton shift.

Table V. Calculated Charge Densities at Nitrogen and Carbon in Iminium Ions

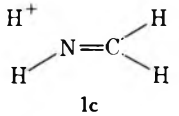
Compd	Registry no.	$2p_z$ (π)[a] N	$2p_z$ (π)[a] C	Total charge N	Total charge C
2	28963-72-6	−0.4581	0.4581	−0.050	0.297
9	52900-33-1	−0.5708	0.4657	−0.109	0.332
12	62399-23-9	−0.6440	0.4634	−0.150	0.349
5	54533-35-6	−0.3672	0.3591	0.032	0.236
7	64611-36-5	−0.4902	0.3957	−0.034	0.287
6	64611-37-6	−0.4902	0.3974	−0.036	0.287
11	19696-23-2	−0.5740	0.4130	−0.082	0.316
3	28149-27-1	−0.2850	0.2590	0.098	0.180
	52594-29-3	−0.4137	0.3293	0.031	0.243
10	44364-22-9	−0.5062	0.3611	−0.020	0.282

[a] Charge represented in electrons.

Discussion

In the present work, a study of the carbenium ion character of the methyleniminium ion was carried out in relation to substituent on nitrogen and carbon. The ^{13}C NMR chemical shifts were compared with respect to inductive and polarization effects of the double bond by changing methyl substituents. This method was used in a study of trigonal carbons with methyl substituents by Olah and Forsyth.[11]

It was instructive to compare the ^1H and ^{13}C NMR data with the charge density calculations of the parent methyleniminium ion **2** by CNDO/2. The total charge density calculations show a charge on nitrogen of −0.05 and on carbon of 0.297. The hydrogens bonded to nitrogen are significantly positive relative to the hydrogens of the methylene and one can infer the importance of a nonbonded proton and the methylenimine structure **1c**.[12] However, the methylene moiety



1c

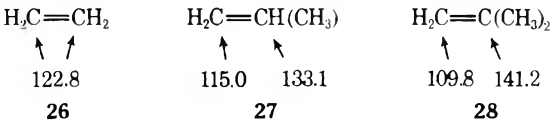
is still more positively charged than that of the ammonium group.

The ^1H NMR chemical shifts of the hydrogens of ammonium and the methylene group, respectively, found at δ 10.67 and 8.54,[13,14] are deshielded from those of the isoelectronic ethylene of δ 5.3. The deshieldings demonstrate the positive character of the methyleniminium ion, in accord with the CNDO/2 calculations, which also indicate more positive character of the ammonium hydrogens relative to methylene hydrogens. The ^{13}C NMR chemical shift of the methyleniminium ion of $\delta_{^{13}C}$ 176.1 is deshielded from that of the isoelectronic ethylene of $\delta_{^{13}C}$ 122.0 and shows a more positively charged methylene carbon for the methyleniminium ion than that of ethylene.[15]

The ^1H and ^{13}C NMR data correlate qualitatively well with the CNDO/2 calculations of the methyleniminium ion. In the simple resonance argument, they represent the importance of **1b** and **1c** over **1a**. The deshielding of 54.1 ppm from the ethylene to methleniminium carbon shows a strong contribution of the aminocarbenium form. However, the comparison of the ^{13}C NMR shifts of protonated formaldehyde or a carbenium ion indicates a much lesser contribution of carbenium character for the methyleniminium ion.

In the simple methyleniminium ion studied, CNDO/2 charge density calculations for the 2p (π) orbitals of nitrogen and carbon showed a strongly polarized double bond, with electron donation to the nitrogen. However, in the σ framework the inductive effect is in the opposite direction. With *N*-methyl substitution, there is a decrease in the polarization of the π bond, with carbon becoming more negative and nitrogen positive. This increase in electron density at carbon with *N*-methyl substitution coincides with the shielding of the iminium carbon.

The shieldings of the β carbon are not unusual. Although the magnitude of the shieldings are different for the ^{13}C chemical shifts for the methylene groups of the isoelectronic alkenes (**26**–**28**) and iminium ions, the direction of the

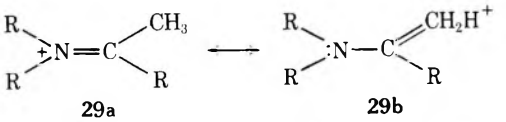


26 **27** **28**

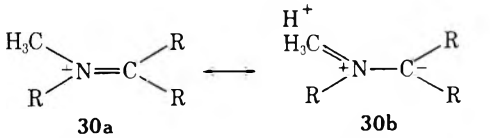
chemical shift differences indicates that π polarization is the predominant effect.

The CNDO/2 calculations for *C*-methyl substitution show an increase in electron density at the 2p (π) orbital on nitrogen. However, the π-electron density on the iminium carbon shows no change. The decrease of the σ-electron density on the iminium carbon is much too small to account for the deshieldings in the ^{13}C NMR spectra. Since hyperconjugative electron donation of the *C*-methyl group should be important to the iminium center in this electron-deficient cation,[16] the polarization of the iminium double bond will increase as reflected in the 2p (π) electron density on nitrogen. Thus, on *C*-methyl substitution the iminium carbon receives electron density from the methyl group and donates to the nitrogen through the π system. In the CNDO/2 calculations for the iminium carbon, this balances out to almost no change in the 2p (π) charge density.

The results can be rationalized using simple resonance arguments. Since a *C*-methyl group can stabilize the iminium ion **29a** by hyperconjugation (**29b**), a polarization of the iminium double bond through the π system will increase the importance of structure **1b** to **1a**. However, on *N*-methyl substitution hyperconjugative stabilization is much less likely (**30b**) and inductive stabilization (**30a**) delocalizes electron



29a **29b**

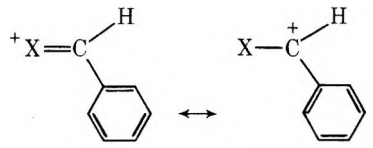


30a **30b**

density into nitrogen. This causes a reverse polarization of the iminium bond, increasing the importance of **1a** and **1b**.

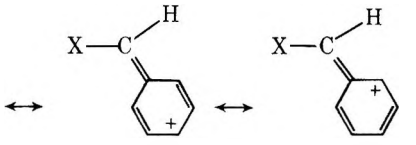
It has been generally recognized that delocalization of charge to a phenyl ring is related to the amount of charge

Scheme I



31a, X = CH_3
32a, X = Cl
33a, X = OH
18a, X = $NHCH_3$
34a, X = CH_2

18b, 31-34b



18c, 31-34c 18d, 31-34d

compd	registry no.	carbon-13 shifts C+	ortho	para
31	25414-93-1	230.7	155.1	161.6
32	56683-65-9	210.7	153.5	163.2
33	3441-73-4	204.7	146.1	148.9
18	63933-59-5	172.7	131.7	139.2
34	34504-74-0	135.8	126.7	128.2[a]

[a] See ref 23.

density on the carbenium center. From ^{13}C NMR chemical shift data and CNDO/2 calculations, it has been shown that the carbenium center and the ortho and para carbons of the phenyl substituent are of particular importance. Thus, the effects of *C*-phenyl and *N*-phenyl substitution on imines were investigated by ^{13}C NMR spectroscopy. A comparison of the ^{13}C NMR chemical shifts of the isoelectronic phenylcarbenium ions with substituents such as CH_3, Cl, OH, and CH_2^- (**31–34**) with the protonated imines should give an indication of the importance of the aminocarbenium structure **1a.**

From CNDO/2 calculations for **31–33**[17] the electron density of the cations was correlated with the ^{13}C chemical shifts. Since the delocalization patterns are similar to those obtained from resonance structures, the latter will be used for simplicity. The ^{13}C NMR chemical shift of the carbenium center and the ortho and para carbons for **31–34** and **18** are listed in Scheme I. A comparison of these ^{13}C shifts will demonstrate the means of stabilization in the *C*-phenyl-substituted iminium ions. Since the phenyl group is common among **31–34** and **18,** the resonance delocalization of the phenyl ring will be relative to the stabilization provided by the other groups. With a strongly stabilizing group, delocalization into the phenyl ring will become less important and vice versa. For example, in the case of the phenylmethylcarbenium ion **31,** there is no interaction with a nonbonded pair of electrons from the methyl group. Consequently, in ion **31,** the charge is delocalized primarily into the phenyl ring by resonance stabilization as shown by the deshielding of the ^{13}C NMR shift of the carbenium center and those of the ortho and para carbons of the phenyl ring. However, stabilization by a nonbonded pair of electrons as in styrene (**34**) results in very little delocalization of electron density into the phenyl ring.

These two systems (**31** and **34**) represent the extremes in stabilization. In **31,** where there is no stabilization by a nonbonded pair of electrons, maximum electron delocalization into the ring results in the deshielding of the ^{13}C chemical shifts of the ortho and para carbons. Thus, structures **31b–d** are important compared to **31a.** However, in **34,** where the nonbonded pair fully contributes, the resonance structure **34a** is the most important one.

In the *C*-phenyl-substituted iminium ion, there is a balance between stabilization by resonance and a nonbonded pair of electrons. Although the ^{13}C NMR chemical shift data demonstrate the importance of **18a,** the deshieldings of the carbenium center and the ortho and para carbons of the phenyl ring do show the ambident carbenium ion nature of the iminium ion. This is also supported by ^{13}C NMR data of the parent imine **24.** It should be noted again that charge delocalization is relative to the charge density on the carbenium center.

Conclusions

It is apparent from the present ^{13}C NMR spectroscopic study and related CNDO/2 calculations that the iminium structures **1a** predominate over the aminocarbenium ion forms **1b,** when comparing iminium ions to carbenium ions and protonated ketones. This is due to the ability of the nonbonded electron pair of the nitrogen atoms to stabilize the adjacent positive charge. The various C substituents slightly change the importance of **1a** relative to **1b,** but **1a** still remains the most important. The aminocarbenium forms are, however, significant and cannot be neglected as indicated by the deshielding of iminium carbon as compared to the parent imine. The present study thus clearly establishes the ambident carbocationic nature of iminium ions. Iminium ions therefore should be able to act as electrophilic aminoalkylating agents through involvement of their aminocarbenium ion character. As nitrosamines were shown to readily form in vitro iminium ions under acid-catalyzed conditions and, therefore, probably also under in vivo conditions, we are extending our studies to the alkylation of suitable nucleophiles, including nucleic acid bases. with iminium ions and nitrosamines, respectively.

Experimental Section

Aliphatic iminium salts were prepared by reported methods.[3-5] Methyleniminium hexachloroantimonate was prepared from methyl azide,[18] hydrochloric acid, and antimony pentachloride in methylene chloride.[3] Ethylideniminium and 2-propylideniminium hexachloroantimonate were prepared from ethyl azide[19] and isopropyl azide, respectively, using the above method. A small amount of the *N*-methylmethyleniminium ion (14%) was found in the ethyl azide rearrangement product. Similarly, *cis*- and *trans*-*N*-methylethylideniminium hexachloroantimonates (31.5%) were identified in the 2-propylideniminium salt.

***N*-Methylmethyleniminium Ion.** This ion was prepared by heating *N*-nitrosodimethylamine (~200 mg) in fluorosulfonic acid (2 mL) for 2 days at 130 °C. The ion was identified by both its ^1H and ^{13}C NMR spectra.

***N*-Methyl-2-propylideniminium Ion.** This ion was prepared by dissolving the imine[2] (~200 mg) in SO_2 (1 mL) cooled in a dry ice–acetone bath. This solution was added with good stirring to a solution of "magic acid" (1 mL) and SO_2 (1 mL) and cooled in a dry ice bath.

***N,N*-Dimethylmethyleniminium Tetrafluoroborate.** *N,N*-Dimethylmethyleniminium iodide was previously prepared[4] from the thermoylsis of iodomethyltrimethylammonium iodide. Since it is thought that the iodide is a too reactive nucelophile, we exchanged iodide for tetrafluoroborate by dissolving the iodide salt in sulfur dioxide and adding an excess of silver tetrafluoroborate. The solution was filtered through a glass wool filter and analyzed by ^1H NMR and ^{13}C NMR.

***N,N*-Dimethyl-2-propylideniminium tetrafluoroborate** was prepared using dimethylammonium tetrafluoroborate and acetone by Leornard's method.[5]

All aromatic imines have been previously prepared from the corresponding amines and aldehydes.[20,21] The iminium salts of these imines were prepared by passing anhydrous hydrochloric acid into an etheral solution of the imine. This method was found to be generally useful. Salts such as the hydrochloride of 2-propylidene-*N*-isopropylimine were isolated as crystalline salts.

Preparation of Isopropyl Azide.[22] Isopropyl bromide (40.0 g, 0.34 mol) was refluxed overnight in 200 mL of dimethylformamide containing 50 mL of water and sodium azide (25.0 g, 0.39 mol). The product was distilled out of the reaction mixture, dried with sodium sulfate, and upon redistillation gave 21.0 g (90%) of isopropyl azide.

NMR Spectroscopic Studies. All ^1H and ^{13}C NMR spectra were obtained on Varian A-56-60, HA-100, and XL-100 instruments equipped with a variable temperature unit. All chemical shifts are reported from external Me_4Si.

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Registry No.—5·$SbCl_6^-$, 64611-38-7; 11·$SbCl_6^-$, 56995-78-9; **26**, 74-85-1; **27**, 115-07-1; **28**, 115-11-7.

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Oxyfunctionalization of Hydrocarbons. 8.[1] Electrophilic Hydroxylation of Benzene, Alkylbenzenes, and Halobenzenes with Hydrogen Peroxide in Superacids

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The hydroxylation of benzene, alkylbenzenes, and halobenzenes with hydrogen peroxide was carried out in high yields in superacidic media at low temperature. Phenols formed are protonated by the superacid and thus are deactivated against further electrophilic attack or secondary oxidation.

Introduction

Although there have been reports of the direct, one-step hydroxylation of aromatic compounds with peracids in the presence of acid catalysts, monohydroxylated products, i.e., phenols, have generally been obtained in only low yield.[2] While moderate to good yields of phenols, based on the amount of hydrogen peroxide used, were reported for the $AlCl_3$-catalyzed reaction of simple aromatics with hydrogen peroxide, a tenfold excess of the aromatics was used over hydrogen peroxide.[2k] The conversion of the aromatics thus was low, probably due to the fact that introduction of an OH group into the aromatic ring markedly increases its reactivity and thus tends to promote further reactions.[3]

It is well recognized that phenols are completely protonated in superacidic solutions.[4] This raised the possibility that protonation of phenols, once formed in these media, might cause their deactivation to further electrophilic attack. We wish to report the results of the electrophilic hydroxylation of aromatics with hydrogen peroxide in superacidic media, which allow the clean, high-yield preparation of monohydroxylated products.

Results and Discussion

Solutions of aromatics were reacted with 98% hydrogen peroxide in FSO_3H–SO_2ClF and FSO_3H–SbF_5 (1:1)–SO_2ClF solution at −78 °C, respectively. Formed protonated phenols were analyzed by ^1H NMR spectroscopy.[4] Results are summarized in Table I.

Data indicate that protonation of the starting aromatics, which are benzene, ethylbenzene, toluene, *p*-xylene, in increasing order, themselves decrease the yields of hydroxylation in magic acid (FSO_3H–SbF_5 (1:1)–SO_2ClF) solution. In the weaker acid system, FSO_3H–SO_2ClF, the protonation of aromatic hydrocarbons is reversible; thus, no such deactivation is apparent. No hydroxylation of phenol and anisole was observed with hydrogen peroxide in superacids, as was also the case with nitrobenzene and benzonitrile. The formally strongly electron-donating –OH and OCH_3 groups protonate in the reaction medium, preventing further reaction. Yields (based on the aromatics used) are high, because the phenols produced are protonated and thus deactivated toward further electrophilic attack.

A more comprehensive study of the hydroxylation of halo- and alkylbenzenes is summarized in Table II, showing isomer distributions and yields obtained. Data, in this case, were obtained by quenching the solutions and analyzing acidic products by gas–liquid chromatography. All aromatics, including polymethylbenzenes, show predominant ortho–para orientation. Hydroxylation of *m*-xylene, for example, did not yield 3,5-dimethylphenol. It should be noticed, however, that in several cases the position of the methyl group of phenols produced differs from that of the starting hydrocarbons. This is the case for 2,6-dimethylphenol obtained from *o*-xylene, 2,4-dimethylphenol from *p*-xylene, 2,3,6-trimethylphenol from 1,2,3-trimethylbenzene, and 2,4,6-trimethylphenol from 1,2,4-trimethylbenzene. The amount of these products cannot

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Table I. Hydroxylation of Aromatics with Hydrogen Peroxide in Superacids at −78 °C

Acid	Substituted arene	% yield[a] of phenols H	CH_3	C_2H_5	p-$(CH_3)_2$	$(CH_2)_3CO_2H$	F	Cl	Br
FSO_3H–SO_2ClF		60	>90	>90	80	>90			Polymer
FSO_3H–SbF_5 (1:1)–SO_2ClF		80	30	60	No		>90	>90	>90

[a] Based on direct ^1H NMR analysis of the reaction mixtures.

Table II. Yields and Isomer Distributions of the Hydroxylation of Aromatics[a]

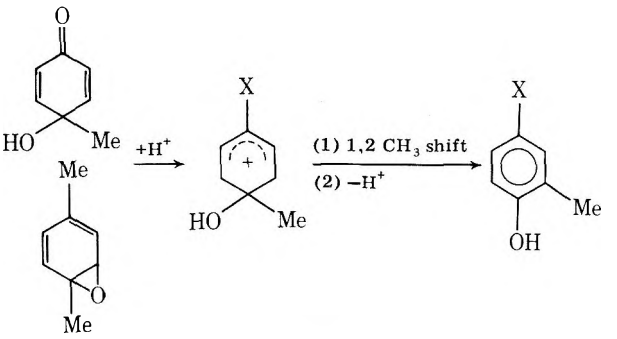
Starting aromatic	Registry no.	% isomer distribution[b]			% yield[c]
Benzene	71-43-2				67
Fluorobenzene	462-06-6	24 (2)	3 (3)	73 (4)	82
Chlorobenzene	108-90-7	28 (2)	7 (3)	65 (4)	53
Toluene	108-88-3	71 (2)	6 (3)	23 (4)	67
Ethylbenzene	100-41-4	68 (2)	6 (3)	26 (4)	70
sec-Butylbenzene	135-98-8	49 (2)	11 (3)	40 (4)	55
Isobutylbenzene	538-68-2	65 (2)	7 (3)	28 (4)	83
n-Amylbenzene	538-68-1	64 (2)	7 (3)	29 (4)	67
o-Xylene	95-47-6	12 (2,6)	59 (2,3)	29 (3,4)	63
m-Xylene	108-38-3	16 (2,6)	2 (2,5)	82 (2,4) 1 (2,3)	73
p-Xylene	106-42-3	64 (2,5)	36 (2,4)		65
1,2,3-Trimethylbenzene	526-73-8	3 (2,3,6)	91 (2,3,4)	6 (3,4,5)	43
1,2,4-Trimethylbenzene	95-63-6	9 (2,4,6)	30 (2,3,6)	61 (2,3,5 + 3,4,6)	57
1,3,5-Trimethylbenzene	108-67-8	100 (2,4,6)			57

[a] In FSO_3H–SO_2ClF solution at dry-ice temperature. [b] Based on chromatographic analysis of quenched phenolic products. Parentheses show position of substituent(s). [c] Based on aromatics used.

Table III. Hydroxylation of Ethylbenzene in Various Acidic Media

Acid system	Reaction temp, °C	% yield[a]	% isomer distribution ortho	meta	para
FSO_3H–SO_2ClF	−78	70	68	7	26
HF–BF_3	−78	79	69	9	21
CF_3SO_3H–SO_2ClF	~−50	80	65	9	26
HF	~20	41	55	13	32
CF_3CO_2H	~20	17			
CH_3CO_2H	~20	1			

[a] See Table II, footnote *c*.



X = OH or Me

be accounted for by possible impurities in the starting hydrocarbons. Further, in a control experiment, starting hydrocarbons at the low reaction temperature did not tend to isomerize. *p*-Xylene did not show isomerization under the reaction condition employed. Thus, it is reasonable to suggest that in the hydroxyarenium ion intermediates of the reactions 1,2-methyl shifts can take place prior to deprotonation.

Kaubisch et al.[5] have reported that *p*-xylene 1,2-oxide is converted to 2,4-dimethylphenol in 87% yield under neutral conditions and o-xylene 1,6-oxide produced 2,6-dimethylphenol in 37% yield in the presence of CF_3CO_2H. It also has been reported that 4-hydroxy-4-methylcyclohexadienone yielded 2-methylhydroquinone under acid conditions.[6] These examples tie in well with the suggested mechanism for our present observations.

To gain further information on the hydroxylation reaction of aromatics, ethylbenzene was hydroxylated in various acidic media (Table III).

In HF–BF_3 solution, the yield of ethylphenols was similarly high as in FSO_3H–SO_2ClF and CF_3SO_3H–SO_2ClF solutions and the isomer distributions in these solvents, and even in the weaker HF system, were almost identical. This indicates that the active hydroxylating species is not a persulfuric acid but protonated hydrogen peroxide.

In preparative experiments hydroxyaromatic products were separated from quenched reaction mixtures by distillation. Results are shown in Table IV. Phenolic products were obtained in good yields except in the case of the benzene–FSO_3H system which solidified at the reaction temperature, did not dissolve, was difficult to mix with hydrogen peroxide, and

Table IV. Preparative Hydroxylation of Aromatics[a]

Starting aromatics (g, mol)	H_2O_2, mol	Acid (4–2 mL of SO_2ClF)	Phenolic products g (mol)	Isolated yield, %
Benzene (1, 0.013)	0.015	FSO_3H	0.19 (0.0020)	16
Benzene (1, 0.013)	0.015	FSO_3H–SbF_5 (1:1)	0.66 (0.0070)	54
Isobutylbenzene (1.11, 0.0083)	0.010	FSO_3H	0.63 (0.0042)	50
1,3,5-Trimethylbenzene (0.99, 0.0082)	0.010	FSO_3H	0.54 (0.0040)	48

[a] All experiments were carried out at −78 °C.

tended to heat up suddenly by heat of reaction. On the other hand, in FSO_3H–SbF_5 (1:1)–SO_2ClF solution benzene dissolved readily, was easily mixed with hydrogen peroxide, and gave phenol in 54% isolated yield.

Experimental Section

Hydroxylation of Aromatic Compounds. To a vigorously stirred solution of the corresponding aromatics in the appropriate superacidic solvent (FSO_3H–SO_2ClF, FSO_3H–SbF_5–SO_2ClF, CF_3SO_3H–SO_2ClF, HF–BF_3, or HF), a solution of 98% hydrogen peroxide (FMC Corp.) in the same solvent was added dropwise at the specified temperature (generally −78 °C), kept constant by external cooling. Some of the aromatics did not completely dissolve into acidic solvents and these reactions were carried out in the well-stirred heterogeneous systems. As the reactions proceeded, however, the media became homogeneous because formed product phenols are soluble in the acidic solvents. An aliquot of the resulting solution was analyzed by ^1H NMR at the same low temperature. After 30-min reaction time, the solution was quenched by dropwise addition to ice-cold aqueous sodium chloride solution. The mixture was extracted with ether. The ether extracts washed with 10% sodium bicarbonate solution to remove acid and phenols were then extracted by 10% sodium hydroxide or Claisen's alkali solution. The dried ether layer was rotary evaporated to remove the solvent, and residual products were analyzed by IR, GLC, and NMR, usually showing only unreacted aromatics. After acidification of the phenol extracts and ether extraction, the solvent was distilled and the products were analyzed either by GLC, after methylation by dimethyl sulfate in aqueous alkali solution, or after trimethyl silylation in the case of cresols [using a Perkin-Elmer Model 900 gas chromatograph equipped with 0.010 in. i.d. × 150 ft. stainless-steel capillary column, coated with MBMA (*m*-bis(*m*-phenoxy)benzene + apiezon L) and operated at a column temperature of 140 or 160 °C with 20 psi of He pressure]. Alternatively, products were isolated by vacuum distillation. The generally used quantities in analytical runs were 0.0027 mol of aromatics, 0.0030 mol of hydrogen peroxide, 2 mL of acid, and 1 mL of solvent. In preparative runs, 0.013 mol of aromatics was reacted with 0.015 mol of hydrogen peroxide. Acidic solvents used were FSO_3H–SO_2ClF or SO_2 at −78 °C, FSO_3H–SbF_5 (1:1)–SO_2ClF at −78 °C, HF–BF_3 at −78 °C, CF_3SO_3H–SO_2ClF at ca. −50 °C (its melting point), HF at −78 °C, CF_3CO_2H and CH_3CO_2H at room temperature.

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Registry No.—H_2O_2, 7722-84-1.

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Stereochemistry of the Reductive Debromination of (*R*)-*meso*- and (*S*)-*meso*-3-Methyl-2,4-dibromopentane

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The reductive 1,3-dehalogenations of the stereoisomeric 3-methyl-2,4-dibromopentanes with zinc, chromous sulfate, or sodium have been shown to proceed by an inversion process at one carbon atom and by a nonstereospecific process at the other. (*R*)-*meso*-3-Methyl-2,4-dibromopentane gave only the trans isomer of 1,2,3-trimethylcyclopropane, while the (*S*)-*meso*-dibromide gave mixtures of the *cis*- and *trans*-cyclopropanes.

The reductive 1,3-dehalogenation synthesis of cyclopropanes was first reported by Gustavson[1,2] and Freund.[3] The method has been extensively used preparatively,[4] but mechanistic studies have been few. The present study provides a partial remedy for that deficiency by an investigation of the stereochemistry of the process with three different reducing agents.

Some stereochemical information was in the literature prior to the publication of the present work.[5-9] Most notable is the report of Fry and Britton[5] on reductions of stereoisomeric 2,4-dibromopentanes. They found that the meso and *dl* forms gave roughly the same mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes upon electrochemical reduction in Me_2SO and that the 2*S*,4*S* isomer of the dibromide gave a mixture of the *cis*-cyclopropane and the (1*R*,2*R*)-cyclopropane with high optical purity. The results require a stepwise mechanism with loss of stereochemistry at one carbon and essentially complete inversion at the other. A similar result was obtained with sodium naphthalenide as reducing agent, but larger experimental errors made the conclusions less definitive.

A contrasting result was obtained by Trost[7] on the reactions of *meso*- and *dl*-2,4-dibromopentane with *n*-butyllithium in THF at low temperatures. The reactions were stereoselective, with the meso compound forming primarily *cis*-1,2-dimethylcyclopropane and the *dl* compound forming primarily the *trans*-cyclopropane. Since the experiment was not done with an optically active 2,4-dibromopentane, it cannot be determined if one of the carbons undergoes stereospecific inversion or retention in this experiment, nor can it be determined whether the predominant overall stereochemistry is double inversion or double retention. Several mechanistic possibilities must therefore be considered.

An interesting stereoselectivity has been observed in the reductive debromination of *meso*- and *dl*-bis(α-bromobenzyl)

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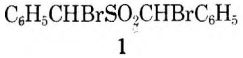
Table I. Product Yields and Composition[a] from the 1,3 Eliminations of (*R*)-*meso*-3-Methyl-2,4-dibromopentane

Product	Percent composition of products[b] Zn/PrOH-H_2O/ 0 °C	Cr^{2+}/ Me_2SO-H_2O/ RT[c]	Na/dioxane/ reflux
	95.7	87.6	55.5
	<0.8		<0.7
	3.5	12.4	27.7
			9.0
			7.1
Total yield[d]	60	26	42

[a] Uncorrected relative percent as determined by integration of the appropriate peak areas from vapor-phase chromatographic (VPC) analysis of the products. [b] Column headings list the reagent, solvent, and temperature used to effect 1,3 elimination. Results are the average of two independent runs. [c] RT = room temperature. [d] Percent yield based on dibromide assuming a product molecular weight of 84 g/mol, determined by VPC from the addition of an internal standard.

sulfone (**1**)[8] and a stereochemical dependence of the competition between debromination and reduction to a monobromide in the 2,8-dibromo-3,6-dibenzobicyclo[3.3.0]octadienes (**2**).[9] These rather special structural situations do not appear



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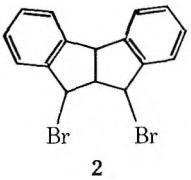

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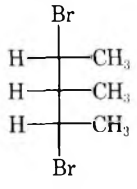
to provide unambiguous indications of the inherent stereochemical preferences or requirements of the simple reductive 1,3 elimination.

The substrates selected for the present investigation were (*R*)-*meso*- and (*S*)-*meso*-3-methyl-2,4-dibromopentane (**3** and **4**, respectively). These provide the same kind of stereochemical information as optically active 2,4-dibromopentane, but do so without the need for optical resolutions and without the potential errors in measurement of optical yield. The experimental analysis is basically just the determination of the cis/trans ratio in the product, 1,2,3-trimethylcyclopropane. Compounds **3** and **4** had been previously characterized in this laboratory[10] but had not been isolated as pure isomers. Dibromide **3** would give cis product from a double retention



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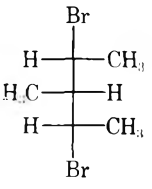

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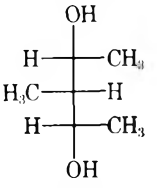
pathway and trans from double inversion or retention–inversion. Dibromide **4** would give cis product from double inversion and trans from double retention or retention–inversion. The reader will readily see that the *dl* isomer of **3** and **4** would not yield additional stereochemical information. It has therefore not been used in pure form as a substrate in this investigation.

Compounds **3** and **4** were prepared from the (*S*)-*meso*- and (*R*)-*meso*-diols **5** and **6**. Each of these was already available as a mixture with the *dl* isomer.[10] Separation of the high-boiling, viscous diols by fractional distillation was not convenient with the available equipment, so the mixtures were converted to the 1,3-dioxane derivatives with formaldehyde and then fractionated. The dioxanes were then individually converted to the diols by acid-catalyzed methanolysis.[11]

The conversions of **5** to **3** and **6** to **4** were done with triphenylphosphine dibromide in benzene. Under these condi-



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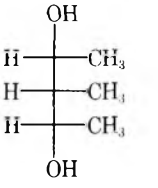

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tions, **5** [(*S*)-*meso*] gave a product which was 86% **3** [(*R*)-*meso*] and 14% *dl*. If tetra-*n*-butylammonium bromide was included in the reaction mixture to favor S_N2 over S_N1 processes, a 17% yield of **3** contaminated with only about 2–4% of the *dl* isomer was obtained.

The reaction of **6** [(*R*)-*meso*] with triphenylphosphine dibromide and tetra-*n*-butylammonium bromide gave only a 4% yield of **4** [(*S*)-*meso*], the main isolated product being allylic bromide **7**. A small sample of the product was purified to show that no (*R*)-*meso*- or *dl*-dibromide was present, but subsequent experiments were done on a mixture of **4** and **7**. It was established that **7** does not give any reduction products which interfere in the analysis of the *cis*- and *trans*-1,2,3-trimethylcyclopropanes.

$CH_3CH{=}C(CH_3)CHBrCH_3$

7

Stereochemical Results. The reaction conditions for three different reducing agents were worked out on a mixture of stereoisomers of 2,4-dibromo-3-methylpentane (to conserve the pure meso isomers). Subsequent reactions with the separated meso forms gave the results summarized in Tables I and II.

The fact that no *cis*-1,2,3-trimethylcyclopropane, within the limits of detection, was obtained from any of the reducing agents and the (*R*)-*meso*-dibromide means that there was at least one inversion at carbon in every ring closure. The fact that both *cis*- and *trans*-cyclopropanes were obtained from the (*S*)-*meso*-dibromide means that the remaining carbon center underwent either inversion (to give cis) or retention (to give trans). Under the conditions in Table II, zinc in aqueous *n*-propyl alcohol at 0 °C favored double inversion over retention–inversion, while sodium in refluxing dioxane showed the opposite preference.

The loss of stereochemistry at one carbon suggests that under all three reducing conditions there is formed an intermediate radical, carbanion, or organometallic species, which does not preserve the original configuration, followed by an internal concerted homolytic or nucleophilic displacement of the second bromine with the expected clean inversion. Concerted 1,3 eliminations, which would presumably be stereospecific at both carbons, are thus not likely in the present systems.[12] The results are similar to those in the aforementioned electrochemical reductions by Fry but somewhat in contrast with the *n*-butyllithium reductions by Trost.

Experimental Section[13]

Infrared (IR) spectra were recorded on a Perkin-Elmer 137 Infracord using sodium chloride plates. Nuclear magnetic resonance

(NMR) spectra were recorded on Varian T-60, A-60A, EM-390, HA-100, or HR-220 instruments. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Jeol FX-60 Fourier transform spectrometer. Chemical shifts are expressed in parts per million relative to tetramethylsilane, which is used as an internal standard and assigned the value $\delta = 0$ ppm. Vapor-phase chromatography (VPC) was done on an F and M Model 300 for analytical separations, and preparative scale separations were made on a Varian Aerograph Model 700. Both instruments were equipped with differential thermal conductivity detectors. Helium was used as the carrier gas, and separations were effected with the following columns: (A) 12 ft × 0.25 in. 10% FFAP on 60–80 AW/DMCS Chromosorb G, (B) 6 ft × 0.25 in. 10% FFAP on 60–80 Chromosorb P, (C) 10 ft × 0.25 in. 15% Carbowax 20M on 60–80 Chromosorb G, (D) 12 ft × 0.25 in. 20% dioctylphthalate on 60–80 Chromosorb P, (E) 5 ft × 0.25 in. 5% 1,2,3-tris(2-cyanoethoxy)propane on 60–80 AW/DMCS Chromosorb G, (F) 20 ft × 0.25 in. 10% Apiezon L on 60–80 AW/DMCS Chromosorb P, (G) 13 ft × 3/8 in. 20% FFAP on 60–80 Chromosorb P, (H) 12 ft × 3/8 in. 20% Carbowax 20M on Anakrom ABS. All columns were made of coiled copper tubing. The compositions of any mixtures are reported, based on the integrated area under the appropriate chart peak, and are uncorrected for differences in thermal conductivity.

Melting points were determined on a Büchi "Schmeltzpunktbestimmungsapparat" and were uncorrected.

Materials. "Commercial" 3-methyl-2,4-pentanediol refers to that purchased from Baker Chemical Co. Otherwise, this compound was prepared by standard procedures.[4] Ether was distilled from sodium hydride under nitrogen prior to use, benzene was distilled from calcium hydride under nitrogen, tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl, and dioxane was purified by refluxing with aqueous hydrochloric acid, followed by treatment with potassium hydroxide and distillation from sodium benzophenone ketyl under nitrogen. All other chemicals and solvents were reagent grade and were used without further purification. Ground glass joints were lubricated with Dow Corning high-vacuum silicone lubricant.

Mixed Isomers of 2,4-Dibromo-3-methylpentane. A stirred solution of 43.2 g (0.4 mol) of sodium bromide in 840 mL of DMF under nitrogen was heated to 55–60 °C. Then 85.2 g (0.2 mol) of 3-methyl-2,4-pentanediol ditosylate[10] (from commercial diol) was added to the solution and the resulting mixture stirred for 160 h at 55 °C. The reaction mixture was poured into 2100 mL of water and extracted with 4 × 100 mL portions of ether. The organic extract was washed with water to remove residual DMF and then dried over anhydrous potassium carbonate. The solvent was removed, and vacuum distillation of the crude product gave 15.1 g (31%) of 3-methyl-2,4-dibromopentane, bp 67–70 °C (4.5 mm) [lit.[10] bp 71 °C (4.6 mm)]. The product was identified by IR and NMR as well as VPC analysis on column B at 130 °C, which gave only one peak with a retention time of 11 min, characteristic of the dibromide.

(*Z*)-3-Methyl-3-penten-2-ol was prepared by the method of House and Ro[14] but was shown by its NMR spectrum to be contaminated with about 12% of the *E* isomer[14] (signal at δ 4.07). Fractional distillation failed to separate the alcohols, so the mixture was converted to the acetates for fractionation.

A solution of 374 mL (2.0 M, 0.774 mol) of *n*-butyllithium in hexane was stirred and cooled to 0 °C under a nitrogen atmosphere. A mixture of the (*Z*)- and (*E*)-3-methyl-3-penten-2-ols, 75.7 g (0.757 mol), was added slowly over a 3-h period while the temperature was maintained below 5 °C. Then 54.8 mL (0.77 mol) of acetyl chloride was added slowly, and after the addition was complete, the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was then poured into 400 mL of ice–water and the small amount of solid formed was removed by filtration. The aqueous phase was extracted with hexane and the combined hexane extracts were dried over anhydrous magnesium sulfate. The solvent was removed and the crude product was purified by vacuum distillation: bp 86–89 °C (85 mm) [lit.[15] bp 49–50 °C (14 mm)]; 73.88 g (69%). VPC on column C at 125 °C indicated a mixture of 77.4% (*Z*)-3-methyl-3-penten-2-ol acetate, 12.3% (*E*)-acetate, and 10.3% unreacted alcohol, identified by coinjection with authentic samples. Separation of the mixture was effected by fractional distillation (113 mm) through a 4-ft column packed with glass helices and equipped with a heated jacket. The first fractions of the distillate were mixtures of the (*Z*)-acetate and unreacted alcohol, which were easily separated by chromatography on silica gel eluted with 10% ether in hexane. The next fraction of the distillate was found to be pure (*Z*)-3-methyl-3-penten-2-ol acetate identified by VPC, NMR, and IR: NMR δ 1.23 (d, J = 6.7 Hz, 3 H), 1.64, (m, 6 H), 1.95 (s, 3 H), 5.22 (m, 1 H), 5.67 (q, J = 6.7 Hz, 1 H), in agreement with that of an authentic sample. The later fractions of the distillation were identified as mixtures of the (*Z*)- and (*E*)-acetates which could be further separated by preparative VPC on column H at 150 °C; the first compound eluted was the (*Z*)-acetate, followed by the *E* isomer.

A solution of 35.98 g (0.253 mol) of (*Z*)-3-methyl-3-penten-2-ol acetate in 360 mL of dry ether was added to a suspension of 6.72 g (0.177 mol) of lithium aluminum hydride in 225 mL of ether at a rate to maintain reflux. The mixture was refluxed for an additional 1.5 h and then 7 mL of water was added dropwise, followed by 7 mL of 15% sodium hydroxide and an additional 58 mL of water. The reaction mixture was filtered to remove solid hydroxides and the solid was washed with ether. The ether solution was concentrated to 200 mL and washed with water and brine. The aqueous washings were extracted twice with ether and the combined ether solutions were dried over anhydrous magnesium sulfate. The ether was evaporated and the crude product, 22.0 g (87%), was vacuum distilled to give 21.0 g (83%) of (*Z*)-3-methyl-3-penten-2-ol: bp 87–88 °C (90 mm) (lit.[14] bp 140–141 °C); NMR δ 1.16 (d, J = 6.5 Hz, 3 H), 1.61 (m, 6 H), 3.40 (variable, s, 1 H), 4.74 (q, J = 6.5 Hz, 1 H), 5.20 (m, 1 H). No *E* alcohol could be detected in the NMR spectrum.

(*S*)-*meso*-4,5,6-Trimethyl-1,3-dioxane was prepared as a mixture with the *dl* isomer, as previously described.[10] The mixture was separated by fractional distillation through a 4-ft column packed with glass helices and equipped with a heated jacket; the *S*-meso isomer with bp 82.5–83.5 °C (96 mm) and estimated by VPC to be >99.5% pure was obtained, followed by the *dl* isomer at bp 93–94 °C (94 mm). The isomers were also readily separated on preparative VPC (column G). The NMR spectrum of the *S*-meso in CCl_4 showed δ 0.75 (d, J = 6.0 Hz, 3 H), 1.16 (d, J = 6.0 Hz, 7 H, obscures 1 H multiplet), 3.18 (d of q, J = 9.0 Hz, J' = 6.0 Hz, 2 H), 4.72 (AB quartet, J = 6.0 Hz, 2 H).

(*R*)-*meso*-4,5,6-Trimethyl-1,3-dioxane was prepared as a mixture with the *dl* isomer[10] and subjected to fractional distillation as for the *S*-meso form above, but because the original mixture contained only about 18% of the *R*-meso (from VPC analysis on column A), it was not possible to obtain the pure *R*-meso with the available equipment. An enriched fraction, bp 84–99 °C (123 mm), containing 41% *R*-meso was obtained as a forerun. This mixture was separated by preparative VPC on column G at 140 °C. The NMR spectrum of *R*-meso showed δ 0.91 (d, J = 6.6 Hz, 3 H), 1.14 (d, J = 6.6 Hz, 7 H, hides 1 H multiplet), 3.67 (q of d, J = 6.6 Hz, J' = 2.4 Hz, 2 H), 4.73 (AB quartet, J = 6.0 Hz, 2 H).

(*S*)-*meso*-3-Methyl-2,4-pentanediol (5). A solution of 27.83 g (0.21 mol) of (*S*)-*meso*-4,5,6-trimethyl-1,3-dioxane and 20 g (0.1 mol) of *p*-toluenesulfonic acid in 135 mL of methanol was heated to 88–90

Table II. Product Yields and Composition[a] from the 1,3 Eliminations of (*S*)-*meso*-3-Methyl-2,4-dibromopentane[b]

Product	Percent composition of products[c] Zn/PrOH-H_2O/ 0 °C	Cr^{2+}/ Me_2SO-H_2O/ RT[d]	Na/dioxane/ reflux
	25.0	17.4	29.9
	56.3	18.2	19.2
	18.7	24.0	11.8
			18.7
		40.4	20.4
Total yield[e]	38	12	38

[a] Uncorrected relative percent as determined by integration of the appropriate peak areas from vapor-phase chromatographic (VPC) analysis of the products. [b] Mixture of 57% (*S*)-*meso*-3-methyl-2,4-dibromopentane and 43% 3-methyl-4-bromo-2-pentene by NMR. [c] Column headings list reagent, solvent, and temperature used to effect 1,3 elimination. [d] RT = room temperature. [e] Percent yield based on dibromide, assuming a product molecular weight of 84 g/mol, determined by VPC from addition of an internal standard.

°C for 216 h, after which time the theoretical amount of dimethoxymethane had distilled. The mixture was cooled and neutralized with 7.75 g (0.1 mol) of diethylamine and the methanol was then removed by evaporation. Then 120 mL of water was added to the crude product and the aqueous solution was continuously extracted with ether for 144 h, after which time the extract was dried over anhydrous magnesium sulfate and the solvent removed. Vacuum distillation of the crude product gave 19.5 g (79%) of (*S*)-*meso*-3-methyl-2,4-pentanediol: bp 91–93 °C (2.4 mm); NMR δ 0.74 (d, *J* = 7.0 Hz, 3 H), 1.13 (d, *J* = 6.5 Hz, 6 H), 1.38 (q of d, *J* = 7.0 Hz, *J'* = 2 Hz, 1 H), 3.63 (quintet, *J* = 6.5 Hz, 2 H), 5.14 (variable, s, 2 H) [lit.[11] NMR δ 0.73 (d, *J* = 6.5 Hz, 3 H), 1.12 (d, *J* = 6.5 Hz, 6 H), 1.35 (m, 1 H), 3.71 (m, 2 H)].

(*R*)-*meso*-3-Methyl-2,4-pentanediol (6). By the same procedure used for the preparation **5**, 4.89 g (37.56 mmol) of (*R*)-*meso*-4,5,6-trimethyl-1,3-dioxane and 3.51 g of *p*-toluenesulfonic acid in 24 mL of methanol for 120 h yielded 3.63 g (82%) of crude oil (solvent removed but product not distilled). The NMR spectrum indicated that the oil was sufficiently pure 6 to use without further purification: NMR δ 0.83 (d, *J* = 6 Hz, 3 H), 1.08 (d, *J* = 6 Hz, 7 H, hides 1 H multiplet), 3.82 (m, 2 H), 4.21 (variable, s, 2 H) [lit.[11] NMR δ 0.88 (d, *J* = 6.5 Hz, 3 H), 1.16 (d, *J* = 6.5 Hz, 7 H, hides 1 H multiplet), 4.03 (m, 2 H)].

(*R*)-*meso*-3-Methyl-2,4-dibromopentane (3). A solution of 36.46 g (0.139 mmol) of triphenylphosphine in 270 mL of dry benzene was stirred under nitrogen at 4 °C while a solution of 22.2 g (0.139 mol) of bromine in 10 mL of benzene was added slowly, followed by 13.54 g (0.042 mol) of tetra-*n*-butylammonium bromide in 125 mL of benzene. Then 8.2 g (0.069 mol) of (*S*)-*meso*-3-methyl-2,4-pentanediol in 85 mL of benzene was added rapidly. The mixture was heated to 60 °C for 40 min with a moderate flow of nitrogen through the solution. The reaction mixture was then cooled to 8 °C and filtered to remove triphenylphosphine oxide. The benzene was evaporated, the orange residue was extracted six times with low petroleum ether, and the extracts were washed with sodium bicarbonate and water and then dried over anhydrous magnesium sulfate. The solvent was removed and the crude product was purified by vacuum distillation [bp 69 °C (4.2 mm), 2.82 g (17%)], identified as (*R*)-*meso*-3-methyl-2,4-dibromopentane: NMR δ 1.22 (d, *J* = 6 Hz, 3 H), 1.74 (d, *J* = 6.5 Hz, 7 H, hides 1 H multiplet), 4.16 (q of d, *J* = 6.5 Hz, *J'* = 6.0 Hz, 2 H) [lit.[10] NMR δ 1.21 (d, *J* = 7 Hz, 3 H), 1.75 (d, *J* = 7 Hz, 6 H), 1.9 (m, 1 H), 4.19 (quintet, *J* = 6 Hz, 2 H)]. The NMR showed that contamination by the (*S*)-*meso*- or *dl*-dibromide could amount to no more than ~3%. The ^{13}C NMR spectrum contained the expected four resonances which were assigned by the aid of the partially coupled spectrum and in analogy to the ^{13}C NMR of *meso*-2,4-dichloropentane:[16] ^{13}C NMR δ 14.17 (q, C-6), 24.45 (q, C-1 and C-5), 48.77 (d, C-3), 54.33 (d, C-2 and C-4).

(*S*)-*meso*-3-Methyl-2,4-dibromopentane (4). A 3.6-g (30.46 mmol) sample of (*R*)-*meso*-3-methyl-2,4-pentanediol was allowed to react with triphenylphosphine dibromide (61.0 mmol) in the presence of tetra-*n*-butylammonium bromide (18.46 mmol), under identical conditions as employed for the reaction of the (*S*)-*meso*-diol above. A yield of crude product (2.19 g) was obtained and subjected to short-path vacuum distillation. The first fraction, bp <50 °C (4.5 mm), 0.85 g, was shown to be 3-methyl-4-bromo-2-pentene by comparison of its NMR spectrum with that of an authentic sample.[10] Fraction two, bp >50 °C (4.5 mm), 0.5 g, was shown by NMR to consist of ~57% (*S*)-*meso*-3-methyl-2,4-dibromopentane and ~43% 3-methyl-4-bromo-2-pentene. A small sample of the (*S*)-*meso*-dibromide was purified by preparative VPC on column E at 110 °C. The NMR spectrum showed that it was pure (*S*)-*meso*-3-methyl-2,4-dibromopentane and was contaminated by the (*R*)-*meso*- and *dl*-bromides to no more than a few percent: NMR δ 1.13 (d, *J* = 7.0 Hz, 3 H), 1.63 (d, *J* = 7.0 Hz, 6 H), 2.24 (m, 1 H), 4.28 (quintet, *J* = 7.0 Hz, 2 H) [lit.[10] NMR δ 1.15 (d, *J* = 6.5 Hz, 3 H), 1.67 (d, *J* = 7.5 Hz, 6 H), 2.27 (m, 1 H), 4.35 (quintet, *J* = 6.5 Hz, 2 H)].

Reaction of 3-Methyl-2,4-dibromopentane with Zinc. A 50-mL round-bottom flask was equipped with a mechanical stirrer, a nitrogen inlet, and an outlet attached to a collection apparatus, which consisted of two cold traps connected in series and cooled to −78 °C. The flask was charged with 0.9 g (13.77 mg-atoms) of zinc dust in 4 mL of a 3:1 1-propanol–water mixture and stirred at 0 °C. Then 1.12 g (4.59 mmol) of (*R*)-*meso*-3-methyl-2,4-dibromopentane was added and the reaction allowed to warm to room temperature over an 18–20-h period. The flask was then warmed to 50 °C and purged with nitrogen for 5–10 min, after which time the product that collected in the cold traps was dried over anhydrous magnesium sulfate. The product was analyzed by VPC on column D at 110 °C after the addition of *n*-pentane as an internal standard. The products were separated by preparative VPC on column D and identified from their IR and NMR spectra.[10,17] The results are shown in Table I.

An alternative procedure was used for the (*S*)-*meso*-dibromide because of the limited amount available. A breakseal tube was charged on one side with 0.08 g (1.22 mg-atoms) of zinc dust in 0.3 mL of a 3:1 1-propanol–water mixture and a small magnetic stirring bar and sealed under vacuum. The other side of the tube was charged with 0.13 g of a mixture of 57% (*S*)-*meso*-3-methyl-2,4-dibromopentane and 43% 3-methyl-4-bromo-2-pentene in 0.1 mL of the same solvent mixture and sealed under vacuum. The seal was broken and the reactants were allowed to mix. The tube was placed in an ice bath and the mixture was agitated by means of the small magnetic stirring bar. After 16 h, the tube was cooled to −78 °C and opened. The contents were distilled trap to trap at 1.0 mm in order to remove inorganic salts. A known amount of *n*-pentane was added to the product mixture as an internal standard and the mixture was analyzed by VPC on column D at 110 °C. The results are shown in Table II.

One set of control experiments showed that mixtures of *cis*- and *trans*-1,2,3-trimethylcyclopropane present in reactions of zinc with ethylene dibromide in 3:1 1-propanol–water at 0–50 °C did not change in composition beyond experimental error (1%).

A control reaction in which 0.1 g (0.61 mmol) of 3-methyl-4-bromo-2-pentene was allowed to react with 0.08 g (1.22 mg-atoms) of zinc in the small-scale manner described above showed that the only product was 3-methyl-2-pentene, as determined by VPC.

Reaction of 3-Methyl-2,4-dibromopentane with Chromous Sulfate. A 100-mL round-bottom flask was fitted with a magnetic stirrer and an adaptor, which was equipped with a stopcock below a rubber septum cap. In the flask, 20 mL of Me_2SO was degassed with nitrogen for 45 min. Then 23 mL (0.51 N, 11.73 mmol) of chromous sulfate[18] was introduced through the septum and stopcock via syringe. Then a degassed solution of 0.7123 g (2.92 mmol) of (*R*)-*meso*-3-methyl-2,4-dibromopentane in 2 mL of Me_2SO was added via syringe. The stopcock was closed and the reaction mixture was stirred for 22 h at room temperature. The septum cap was removed and the flask connected to two cold traps in series, the first cooled to −8 °C and the second to −78 °C. The flask was cooled to 0 °C and the pressure in the system was reduced to ~40 mm. The reaction flask was then allowed to warm to room temperature over a 45-min period, and the product which collected in the cold traps was washed with water and dried over anhydrous magnesium sulfate. Cyclohexane was added as an internal standard and the mixture analyzed by VPC on column F at 110 °C. The products were identified by VPC and NMR as *trans*-1,2,3-trimethylcyclopropane, *cis*-1,2,3-trimethylcyclopropane, and 3-methyl-2-pentene in the ratios shown in Table I.

A small-scale procedure was used for the (*S*)-*meso*-dibromide. A breakseal tube was evacuated on one side and flushed with nitrogen four times, and then 1.81 mL (0.94 N, 1.69 mmol) of chromous sulfate was injected into the tube under nitrogen. The tube was then sealed under vacuum. The other side of the tube was charged with 0.13 g of 57% (*S*)-*meso*-3-methyl-2,4-dibromopentane and 43% 3-methyl-4-bromo-2-pentene in 2 mL of Me_2SO and evacuated and flushed with nitrogen four times. This side was then sealed under vacuum. The seal was broken and the reactants were mixed. The initially pale blue solution of chromous sulfate turned to a light green upon mixing with the dibromide. The reaction was agitated by means of the small magnetic stirring bar at room temperature for 24 h. The tube was then cooled to −78 °C and opened. The contents were placed in a small flask with 1 mL of toluene, and the mixture was stirred for 20 min. The toluene extract was washed three times with water, dried over anhydrous magnesium sulfate, and analyzed by VPC on column F at 85 °C after the addition of a known amount of cyclohexane as an internal standard. The products were *trans*-1,2,3-trimethylcyclopropane, *cis*-1,2,3-trimethylcyclopropane, 3-methyl-2-pentene, and 3-methyl-1,3-pentadiene in the ratios shown in Table II. The diene was probably formed from the 3-methyl-4-bromo-2-pentene present initially and was identified as 3-methyl-1,3-pentadiene by coinjection with an authentic sample on VPC and by comparison of its NMR and IR spectra to those of authentic samples.[10]

Two control reactions were run to show that the composition of a mixture of the two cyclopropanes did not change (beyond experimental error) in solution with a reacting system of chromous sulfate and ethylene dibromide at room temperature for 24 h.

Reaction of 3-Methyl-2,4-dibromopentane with Sodium. A 50-mL round-bottom flask was equipped with a magnetic stirrer, nitrogen inlet, and reflux condenser connected to two cold traps in series, cooled to −78 °C. Freshly cut sodium, 0.7 g (30.4 mg-atoms), in 10 mL of dry dioxane was placed in the flask and the mixture was stirred and heated to reflux. Then a solution of 0.91 g (3.7 mmol) of (*R*)-*meso*-3-methyl-2,4-dibromopentane in 5 mL of dioxane was

added and the reaction mixture was refluxed for 20 h. The system was purged with nitrogen for 1 h and the product which collected in the cold traps was analyzed by VPC on column F at 90 °C after the addition of a known amount of *n*-pentane as an internal standard. For two independent reactions, the overall yields of hydrocarbons averaged 42% and had the composition shown in Table I. The products were identified by VPC by peak enhancement upon coinjection of authentic samples and by separation via preparative VPC. The first eluted was *trans*-1,2,3-trimethylcyclopropane, identified by comparison of the NMR and IR spectra to those of authentic samples.[10] The second eluted was 3-methylpentane, identified by comparison of its IR and NMR spectra to those of an authentic sample.[17] The next compound eluted was identified as 3-methyl-2-pentene by comparison of its NMR to that of an authentic sample.[17] The fourth compound eluted was *cis*-1,2,3-trimethylcyclopropane, also identified by comparison of its NMR and IR spectra to those of authentic samples.[10] The last compound was identified as 3-methyl-1,3-pentadiene: NMR δ 1.68 (m, 6 H), 4.95 (m, 2 H), 5.55 (m, 1 H), 6.4 (m, 1 H) [lit.[10] NMR δ 1.7 (m, 6 H), 5.0 (m, 2 H), 5.5 (m, 1 H), 6.4 (m, 1 H)].

A small-scale procedure was used for the (S)-*meso*-dibromide. A dry combustion tube was charged with 0.08 g (3.5 mg-atoms) of freshly cut sodium in 0.6 mL of dry dioxane and cooled to −78 °C. To the cooled mixture, 0.13 g of a mixture of 57% (*S*)-*meso*-methyl-2,4-dibromopentane and 43% 3-methyl-4-bromo-2-pentene in 0.3 mL of dry dioxane was added. The tube was sealed under a vacuum and then heated at 125 °C in an oil bath for 17 h. The tube was cooled to −78 °C and opened. The contents were distilled trap to trap at 1.0 mm to remove inorganic salts, and a known amount of *n*-pentane was added as an internal standard. The mixture was analyzed by VPC on column F at 85 °C. The products were identified as above and were as shown in Table II.

Two control reactions were run under the conditions of the larger scale procedure to show that the composition of a mixture of the two cyclopropanes did not change (beyond experimental error) in the reaction mixture of sodium with ethylene dibromide in dioxane.

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Registry No.—**3**, 40814-61-7; **4**, 40814-60-6; **5**, 25618-03-5; **6**, 30781-40-9; (*E*)-3-methyl-3-penten-2-ol, 24652-51-5; acetyl chloride, 75-36-5; (*E*)-3-methyl-3-penten-2-ol acetate, 64683-04-1; (*Z*)-3-methyl-3-penten-2-ol acetate, 64683-05-2; (*Z*)-3-methyl-3-penten-2-ol, 64683-06-3; (*S*)-*meso*-4,5,6-trimethyl-1,3-dioxane, 28163-74-8; *dl*-4,5,6-trimethyl-1,3-dioxane, 40902-89-4; (*R*)-*meso*-4,5,6-trimethyl-1,3-dioxane, 26561-69-3.

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Competing Nucleophilic Processes in Haloalkynes. Carbanionic Attacks

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Carbanions (R_3C^-) derived from triphenylmethane and benzhydryl cyanide displace chloride ion from phenylchloroacetylene in KOH–glycol dimethyl ether (glyme) to give $PhC{\equiv}CCR_3$. Similarly, benzhydryl cyanide anion in glyme reacts with mercuric bis(chloroacetylide) to give the substitution product $Hg(C{\equiv}CPh_2CN)_2$. In other cases, the "first" substitution products often react further: those of benzyl and benzhydryl cyanides are converted to dimers; cyclopentadiene and methylcyclopentadiene in KOH–dimethyl sulfoxide lead ultimately to phenylethynyl- and 1,1′-phenylethynylferrocenes; from fluorene and ethyl malonate in glyme or Me_2SO β,β adducts, e.g., β,β-difluorenylstyrene, are produced; with benzyl cyanide in Me_2SO a 1:2 adduct forms. As nucleophiles, the anions derived from diphenylmethane and dimethyl sulfoxide anions differ in that they abstract chlorine from phenylchloroacetylene—diphenyldiacetylene is the only isolated product. Given a carbanionic nucleophile and an activated haloalkyne, conditions which favor substitution and minimize addition and halogen abstraction are a relatively low p*K* of the parent carbon acid and an aprotic medium, e.g., glyme.

Based on success with several nucleophilic substitutions at an acetylenic carbon,[1] our plan was to develop syntheses according to eq 1. As written in ionic form, process 1 has little, perhaps no precedent; most organometallics (R_3CM), whether predominantly ionic or covalent, are largely aggregated in most organic solvents.

$$PhC{\equiv}CCl + R_3C^- \rightarrow PhC{\equiv}CCR_3 + Cl^- \qquad (1)$$

In this paper, examples of eq 1 are described. Since diversions to other products were typical, we became equally concerned with the competing processes involving carbanionic attacks on a haloalkyne. As a result, limitations in and conditions for the use of process 1 in syntheses can now be appreciated.

Now couplings between sp carbon and other carbon reagents, e.g., organometallics of Li, Na, Mg, Zn, Sn, Pb, have *sometimes* given the product of eq 1.[2] These syntheses, as well as ours with organosodiums to be described below, are probable examples of the use of aggregated nucleophiles. From a synthetic viewpoint, however, "organocopper reagents constitute a breakthrough in the synthesis of [these] carbon–carbon bonds"[2a] and obviously should be considered for any route to $R'C{\equiv}CCR_3$.

Three broad categories for nucleophilic substitution at an acetylenic carbon have emerged.[1] Ionic attacks on triphilic haloalkyne are delineated in Scheme I. Clearly, the intermediates **2**–**4** may be intercepted, e.g., by proton donors (HA), and the expected product never obtained. The second group of mechanisms involves aggregates, that is, polymeric species,

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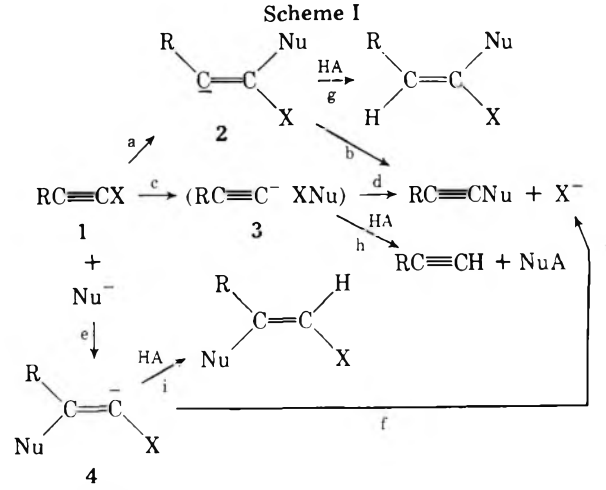
Scheme I



e.g., RLi, ArCu, RMgX, etc. The earliest example may be the coupling,[3]

$$ClC{\equiv}CCl + NaC(C_2H_5)(COOC_2H_5)_2 \rightarrow ClC{\equiv}CC(C_2H_5)(COOC_2H_5)_2 \quad (2)$$

which was followed by a few scattered examples involving several organometallics.[1,2] The third group of mechanisms involves radicals, anions, and/or redox processes at some stage, e.g., eq 3.[4]

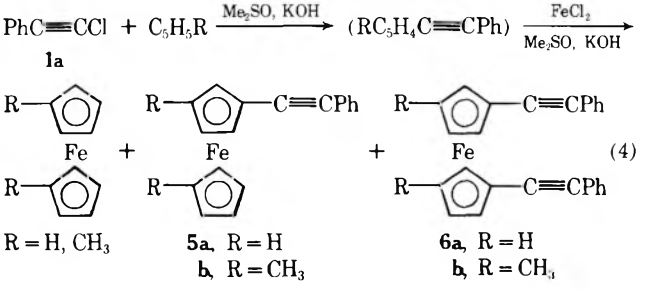
$$PhC{\equiv}CH + R_2NH \xrightarrow[C_6H_6,O_2,\ 0\ °C]{Cu(OAc)_2 \cdot H_2O} PhC{\equiv}CNR_2 + (PhC{\equiv}C)_2 \quad (3)$$

Just as ionic intermediates can be diverted in Scheme I, it should be equally possible to find analogous competing steps in the aggregate and radical mechanisms. These ideas will be useful in rationalizing the paths to some of the products we found.

Results

Since the pK's of the carbon acid are important indicators of how easy it was to form the carbanion, these are included in the text. Typically, we began with powdered potassium hydroxide in dry dimethyl sulfoxide (Me_2SO) as a medium for our reactions (p$K \simeq 33$).[5] This is easy to prepare;[5] it is strongly basic and ion association in it is minimal.[6a,7] Unfortunately, this system is not inert; it can deliver protons, and we did in fact obtain addition reactions in some cases as in steps g, h, i of Scheme I. Moreover, Me_2SO may be capable of reducing positive halogen and would probably trap XNu in Scheme I. For these reasons we also used glycol dimethyl ether (glyme) as an alternate solvent and generated the carbanions in other ways. With the exception of a few test cases, there was no attempt to optimize the yields by exploring a wide variety of reaction conditions. On the other hand a careful analysis of what came out of a given set of reaction conditions was made.

Two cyclopentadienes (pK = 18)[6c] and phenylchloroacetylene (**1a**) reacted according to eq 1. The products or their anions were trapped with ferrous chloride and we had a new synthesis of ethynylferrocenes in hand (eq 4). Several variations of the solvent, e.g., glyme or tetrahydrofuran (THF) in the cyclopentadiene reaction, gave lower yields of **5a** and **6a** and are not recommended.



It is of interest that the ethynylcyclopentadienes ($XC_5H_4C{\equiv}CR$) are virtually unknown. Recently, the simplest member was prepared by pyrolysis, detected spectroscopically, trapped chemically in solution, but has not been isolated.[8] In the case of cyclopentadiene, we detected a new triple bond absorption in the IR spectrum ($\nu_{C\equiv C}$ 2180 cm^{-1}) of the reaction solution. This disappeared during workup. Attempts to intercept $C_5H_5C{\equiv}CPh$ by maleic anhydride in cycloaddition or by R_2NH in addition across the triple bond[8] or to trap $PhC{\equiv}CC_5H_4^-$ and other carbanions with carbon dioxide were unsuccessful.

Triphenylmethane (pK = 31)[6a] and Me_2SO–KOH gave the product (**7**) expected from eq 1 and a small amount of adduct (**8**). On the other hand both fluorene (pK = 22.6)[6a] and ethyl malonate (p$K(H_2O)$ = 13)[7] yielded adducts **9, 10.**[9]

$$\mathbf{1a} + R_3CH \xrightarrow[Me_2SO]{KOH} PhC{\equiv}CCPh_3 + PhCH{=}CR_2 \quad (5)$$

7 **8**, R = Ph_3C; **9**, R = 9-fluorenyl; **10**, R = $HC(COOC_2H_5)_2$

When sodium fluorenide and ethyl sodiomalonate reacted with **1a** in glyme, the same adducts (**9, 10**) were obtained. Whatever the details of the mechanism leading to **8–10**, the availability of protons is essential; these may derive from the Me_2SO, the carbon acid moiety (as reagent, intermediate, or product), and possibly from workup.

With benzyl cyanide (pK = 22)[6b] in Me_2SO, the major product is still another type of adduct (**11**). It appears that substitution proceeds according to eq 1 and the ethynyl product may isomerize to the allene (eq 6). Either of these may

$$\mathbf{1a} + PhCH_2CN \xrightarrow[Me_2SO]{KOH} (PhC{\equiv}CCHCNPh) \overset{?}{\rightleftharpoons} (PhHC{=}C{=}CCNPh) \rightarrow Ph(NC)C{=}C(CH(CN)Ph)(CH_2Ph)$$

11

$$+ [PhHCCC(CN)Ph]_2 \quad (6)$$

12

react further with $PhCHCN^-$; allowing for proton shifts but ignoring geometrical isomerism, six products may be formed. A referee has suggested that the 1:2 adduct has the structure given for **11**, since its magnetically nonequivalent benzylic protons could give rise to the ^1H NMR shifts that we observed. As for the dimer **12**, it is probably a 1,2-dimethylenecyclobutane formed by typical allene dimerization[10] of 1-cyano-1,3-diphenylallene. This allene appears to be unknown.

In passing, it should be mentioned that the transformations of eq 6 do *not* involve positive halogen transfers (see step c, Scheme I) or redox steps, since these would probably have led to phenylacetylene, 1,2-dicyanostilbene, or perhaps diphenylsuccinonitrile.[11]

The course of the benzhydryl cyanide (pK = 17.5)[6b] reaction is highly medium dependent. In glyme, the anion of this

$$Ph_2CHCN + \mathbf{1a} \xrightarrow[glyme]{Na} PhC{\equiv}CC(Ph)_2CN + Ph_2CH_2 \quad (7)$$

13

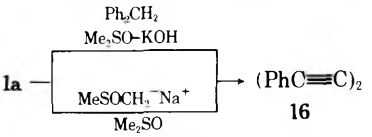
Me_2SO, KOH → $(Ph_2CCHPh)_2$ (**15**)

Al_2O_3 → $PhC{\equiv}CC(Ph)_2CONH_2$ (**14**)

carbon acid leads to the expected substitution product (**13**). In the course of purifying **13** by chromatography on alumina, we also obtained an hydrolysis product (**14**). Unexpectedly, some diphenylmethane (~15%) is formed, presumably by anionic removal of CN; this is a reaction which has been noted for analogous systems which yield a stable carbanion.[12]

In Me_2SO–KOH, the products are numerous and again different. The dimer (**15**) indicated in eq 7 is not one of the known 1,2-dimethylenecyclobutanes one would expect from triphenylallene.[10a] This point was checked by correspondence with Professor E. Dehmlow and by comparison with an authentic isomer which he sent us. Compound **15** does not appear to be a hydrorubrene (5,6,11,12-tetraphenyltetrahydronaphthacene)[13] nor is it 3-(1′,3′-diphenyl-2′-indenyl)-1,3,3-triphenylprop-1-ene obtained by the action of acid on 1,3,3-triphenylpropynol.[14] The assignment of structure to this "allene dimer" requires further study. What is again interesting is that the CN group seems to have been lost, probably during later stages of the reaction; anions or perhaps radical anions may be involved here. As far as we can tell, the chemistry that we find differs from what has been found for cations or anions derived from $Ph_2CCCHPh$.[10a,b,13] Halogen abstraction (step c, Scheme I), however, appears to be absent, since phenylacetylene and tetraphenylsuccinonitrile were absent.[11]

The anions of two carbon acids, namely, diphenylmethane (pK = 29),[6a] and Me_2SO (pK = 35),[6a] converted **1a** to diphenyldiacetylene. We are inclined to believe that the diacetylene is formed in a coupling reaction after halogen abstraction from **1a** and/or electron transfer (eq 8).



(8)

As our final example we used a "protected" chloroacetylene (chloroacetylene is oxygen sensitive and dangerous).

$$Hg(C{\equiv}CCl)_2 + Ph_2CCN^-Na^+ \xrightarrow[\textbf{1b}]{(MeOCH_2)_2} \underset{\textbf{17}}{(Ph_2C(CN)C{\equiv}C)_2Hg} \quad (9)$$

Mercuric chloroacetylide (**1b**) may be regarded as a potential synthon for the ethynyl moiety, since mercury (II) may be readily exchanged for protons. Besides "holding" chloroethynyl, mercury may also activate the triple bond to nucleophilic attack. Overall, this would amount to a method for the introduction of ethynyl.

Summary

We assume that the reactions in Me_2SO–KOH are essentially those of ions while those of $R_3C^-Na^+$ in glyme are those of aggregates. Much of Scheme I appears to be represented by anions from our group of carbon acids. Proton availability and mobility in the medium leads to further transformations in the "first" products, e.g., to diadducts, dimers, etc. Roughly speaking, the success of process 1 as a synthesis appears to decline as the pK increases. Thus, anions of relatively weak acids appear to favor halogen abstraction rather than attack at the terminal carbon. Although the Me_2SO–KOH medium works well for relatively strong carbon acids, the less convenient route of generating $R_3C^-Na^+$ and treating it with a haloalkyne in glyme probably has wider applicability for process 1.

Experimental Section

Infrared spectra were recorded on Perkin-Elmer 237 and Beckman IR-8 spectrophotometers. Proton magnetic resonance spectra were obtained on a Varian T-60 spectrometer and are relative to internal tetramethysilane. Mass spectra were obtained on a Varian-MAT CH7 instrument operating at 50 eV. Ultraviolet spectra were obtained on a Cary 15 spectrometer. Melting points were taken in glass capillary tubes on a Mel-Temp heated block and are uncorrected. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

Standard Procedures. The usual conditions for reactions in Me_2SO–KOH were adapted from Jolly.[5] A 200-mL three-necked flask was fitted with a nitrogen inlet and a condenser topped by a drying tube of $CaCl_2$ leading to a gas bubbler containing mineral oil. Potassium hydroxide (>85%, reagent grade), which was pulverized in a dry bag, and dried Me_2SO (40–50 mL for up to 0.03 mol scale reaction) were added. For each 0.01 mol of carbon acid 4 g of KOH were used. The mixture was stirred under nitrogen for times which depended roughly on the pK of the carbon acid. A solution of **1a** in Me_2SO (20–30 mL for up to 0.03 mol scale reaction) was added dropwise over a period of 0.5–1 h while the solution was cooled in an ice bath. The mixture was stirred and checked occasionally for changes in its IR spectrum. After the reaction was complete, the mixture was stirred up with dry ice powder and water, often for many hours. This mixture was extracted with $CHCl_3$; the extract was washed free of Me_2SO and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (CC) on alumina or silica gel, or on both (Al_2O_3, SiO_2); the usual order of eluting solvents was hexane, benzene, chlorinated solvents, etc.

Phenylethynylferrocene (5a) and 1,1′-Di(phenylethynyl)ferrocene (6a). Cyclopentadiene monomer (3.3 mL, 0.04 mol) in Me_2SO (50 mL)–KOH (15 g) was stirred for 1 h; **1a** (0.04 mol, 4 mL) in Me_2SO (30 mL) was added dropwise in 15 min and the temperature rose to ca. 50–60 °C. After 30 min, $FeCl_2{\cdot}4H_2O$ (8 g) in Me_2SO (100 mL) was added dropwise over a period of 30 min and the mixture was stirred ca. 24 h at ~25 °C. The reaction flask was cooled in an ice bath, 50 mL of water was added, and the mixture was stirred for ca. 12 h. Hydrochloric acid (1 M) was used to neutralize the reaction mixture and the organic products were extracted and separated (CC, Al_2O_3, SiO_2). The first eluate (hexane) yielded ferrocene: 0.85 g (23%); mp 172 °C. The second eluate in benzene yielded **5a** (1.2 g, 21%): mp 121–123 °C (lit.[16] 121–123 °C); IR (KBr) 2210 (cm^{-1}); NMR ($CDCl_3$) δ 4.46 (s, 7 H), 4.73 (t, 2 H), 7.25–7.93 (5 H); MS m/e 285 (parent). The next eluates of benzene/chloroform (1:1) yielded a red-orange solid **6a** which was recrystallized from benzene (0.8 g, 10%): mp 170–171 °C (lit.[16] 174–175.5 °C); NMR ($CDCl_3$) δ 4.55 (t, 4 H, J = 2 Hz), 4.76 (t, 4 H, J = 2 Hz), 7.63 (m, 10 H); MS m/e 385 (parent). The final eluted material could not be identified.

1,1′-Dimethyl-3-phenylethynylferrocene (5b) and 1,1′-Dimethyl-3,3′-di(phenylethynyl)ferrocene (6b). Freshly prepared methylcyclopentadiene (3.2 g, 0.04 mol) in Me_2SO (50 mL)–KOH (15 g) was stirred for 1 h; **1a** (4 mL, 0.04 mol) in Me_2SO (10 mL) was added dropwise over a period of 30 min while the mixture was cooled in an ice slush. After being stirred for 1 h at ~25 °C an IR check showed that $\nu_{C\equiv C}$ of the starting material was absent. Then a solution of $FeCl_2{\cdot}4H_2O$ (8 g, 0.08 mol) in Me_2SO (75 mL) was added dropwise (30 min). After 12 h, the mixture was poured onto dry ice. The brown solid which formed was filtered off. The filtrate was extracted with chloroform; after workup this yielded a red oil (8.19 g) which was purified (CC, Al_2O_3). The first eluate (hexane) yielded 1,1′-dimethylferrocene (0.6 g, 14%): mp 38 °C (lit.[17] 38 °C); NMR (CCl_4) δ 2.1 (s, 6 H), 4.15 (s, 8 H).

The eluate in CCl_4 yielded **5b** as an orange-red oil (3.45 g, 55%): bp >210 °C dec; $n^{25}D$ 1.5950; IR (neat) 3080, 2950, 2920, 2202, 1600, 1500, 1030, 804, 750 cm^{-1}; NMR (CCl_4) δ 2.06 (s, 3 H), 2.2 (s, 3 H), 4.01–4.4 (m, 7 H) 7.1–7.6 (m, 5 H); MS m/e 314 (parent). Anal. Calcd for $C_{20}H_{18}Fe$: C, 76.45; H, 5.77. Found: C, 76.55; H, 5.91.

The eluates in $CHCl_3$ yielded **6b** as a red oil (1.05 g, 12.6%): bp >230 °C dec; $n^{25}D$ 1.5875; IR (neat) 3080, 3055, 2920, 2200, 1600, 1495, 1440, 1025, 780, 750, 682 cm^{-1}; NMR (CCl_4) δ 2.08 (s, 6 H), 4.1–4.28 (m, 6 H), 7.08–7.6 (m, 10 H). Anal. Calcd for $C_{28}H_{22}Fe$: C, 81.17; H, 5.35. Found: C, 80.93; H, 4.96.

Final eluates in $CHCl_3$–CH_3OH yielded a dark solid (0.5 g, mp >300 °C).

Tetraphenylpropyne (7) and 1,3,3,3-Tetraphenyl-3-triphenylmethylpropene (8). Triphenylmethane (4.9 g, 0.02 mol) in Me_2SO (50 mL)–KOH (8 g) was stirred for 3 days; **1a** (2.72 g, 0.02 mol) in Me_2SO (20 mL) was added dropwise over a period of 1 h. After being stirred for 1 h, the mixture was poured onto dry ice in water (50 mL). The organic solids were taken up in benzene and separated (CC, Al_2O_3, SiO_2). The hexane eluate yielded triphenylmethane (4 g, 82%). The second eluate (C_6H_6) yielded **7** (0.77 g, 12%), from petroleum ether: mp 139 °C (lit.[18] 139 °C); IR (KBr) 1600, 750, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.4–7.7; MS m/e 344 (parent). The third eluate ($CHCl_3$)

yielded 8 (0.24 g, 2%): mp 214–216 °C, from benzene; IR (KBr) 1600, 755, 703 cm^{-1}; NMR ($CDCl_3$) δ 7.0 (s, 1 H), 7.0 ~7.3 (35 H); MS *m/e* 588 (parent). Anal. Calcd for $C_{40}H_{36}$: C, 93.84; H, 6.16. Found: C, 93.77; H, 6.45.

β,β-Di(9-fluorenyl)styrene (9). Fluorene (5 g, 0.03 mol) in Me_2SO (40 mL)–KOH (12 g) was stirred overnight and cooled to 5–10 °C; **1a** (4.2 g, 0.03 mol) in Me_2SO (30 mL) was added dropwise over a period of 1 h, while the flask was kept at ca. 10 °C. After 3 h the mixture was poured onto a slurry of dry ice in acetone (150 mL). Organic materials were eventually extracted and separated (CC, Al_2O_3, SiO_2). The first eluate in petroleum ether yielded a white solid (0.27 g) of mp 55–56 °C which was not identified; the last eluate contained amorphous solids (0.82 g). The benzene eluate yielded **9** as a white solid (48%): mp 232–233 °C; IR (KBr) 1590 cm^{-1}; NMR ($CDCl_3$) δ 3.7 (s, 2 H), 6.7 (s, 1 H), 7.2–8.4 (m, 21 H); MS *m/e* 432 (parent). Anal. Calcd for $C_{34}H_{24}$: C, 94.41; H, 5.59. Found: C, 93.97; H, 5.83.

A run with sodium fluorenide (0.01 mol) in glyme yielded fluorene (0.3 g, 18%) and **9** (1.55 g, 32%).

Diethyl 2,4-Carbethoxy-3-benzylideneglutarate (10). Ethyl malonate (3.2 g, 0.02 mol) in Me_2SO–KOH was stirred for 18 h; **1a** (1.7 mL, 0.02 mol) was added (30 min). After 12 h at 25 °C, the mixture was treated with dry ice–water (12 h), worked up, and purified (CC, SiO_2). The first eluate in *n*-hexane contained both starting materials (ca. 5%). The second eluate in carbon tetrachloride yielded **10**, a liquid (2.3 g, 27%): bp 245–247 °C; IR (neat) 3470 (b, w), 2975, 1720–1770 (b), 1600, 1480, 895, 770, 750 cm^{-1}; NMR (CCl_4) δ 1.25 (t, 6 H, J = 7 Hz), 1.27 (t, 6 H, J = 7 Hz), 4.13 (d + d, 4 H, J = 7 Hz); 4.16 (d + d, 4 H, J = 7 Hz), 4.45 (s, 1 H), 4.60 (s, 1 H), 7.0 (s, 1 H), 7.3 (s, 5 H); MS *m/e* 420 (parent). Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.85; H, 6.71. Found: C, 63.15; H, 6.89.

A reaction of ethyl sodiomalonate with phenylchloroacetylene in glyme yielded 14% of **10**.

Reaction of Benzyl Cyanide with 1a. Benzyl cyanide (0.23 g, 0.02 mol) in Me_2SO (50 mL)–KOH (8 g) was stirred for 3 h; **1a** (1.7 mL, 0.02 mol) in Me_2SO (20 mL) was added dropwise in 30 min while the reactants were cooled in ice slush. After 12 h at ~25 °C, the mixture was treated with dry ice and water (50 mL) and stirred for 5 h. The mixture was worked up and purified (CC, Al_2O_3). The eluate in benzene yielded **11** (1.8 g, 25%) as white crystals: mp 128–129 °C; IR (KBr) 2223, 2200, 1600, 1480, 1450, 780, 740, 680 cm^{-1}; NMR ($CDCl_3$) δ 3.6 (d, 1 H, J = 15 Hz), 4.06 (d, 1 H, J = 15 Hz), 5.11 (s, 1 H), 7.21 (s, 10 H), 7.46 (s, 5 H); MS *m/e* 334 (parent). A tentative structure for **11** has been given in eq 6. The ^1H NMR data are consistent with the presence of three nonaromatic, nonolefinic protons. The chemical shifts and the coupling pattern are in accord with two magnetically nonequivalent benzylic protons[19a,b] and an isolated proton on a substituted sp^3 carbon.[19c] Anal. Calcd for $C_{24}H_{18}N_2$: C, 86.20 H, 5.40. Found: C, 86.29; H, 5.44.

The second eluate in CCl_4 yielded **12** as white crystals (0.6 g, 7%): mp 162–163 °C; IR (KBr) 2240, 1590, 1480, 1444, 755, 690 cm^{-1}; NMR ($CDCl_3$) δ 6.33 (s, 1 H), 6.9–7.83 (m, ~21 H); MS *m/e* 434 (parent). This compound is presumed to be dimer of 1-cyano-1,3-diphenylallene. Anal. Calcd for $C_{32}H_{22}N_2$: C, 88.45; H, 5.10. Found: C, 88.46; H, 5.24.

When the synthesis was repeated with α-cyanobenzylsodium (0.01 mol) in glyme, 23% of **1a** was recovered and 13% of **11** was isolated.

3-Cyano-1,3,3-triphenylpropyne (13) and 3-Carboxyamide-1,3,3-triphenylpropyne (14). Diphenylacetonitrile (1.93 g, 0.01 mol) with sodium (0.25 g, 0.01 mol) in glyme (30 mL) were stirred under nitrogen and heated to reflux temperature for 12 h; **1a** (0.87 mL, 0.01 mol) in glyme (20 mL) was added dropwise (30 min) while the reaction mixture was cooled in ice slush. The mixture was left at ~25 °C for 36 h and treated with dry ice–water. Workup and purification (CC, Al_2O_3, SiO_2) yielded a colorless liquid (0.5 g) in the first eluate (CCl_4) whose IR and NMR spectra were those of diphenylmethane. The second eluate (CCl_4) yielded **13** as a yellow oil (1.8 g, 61%): bp >300 °C; IR (neat) 2220, 2215, 1600, 1495, 1450, 750, 685 cm^{-1}; NMR (CCl_4) δ 7.03–7.7 (m); MS *m/e* 293 (parent). Anal. Calcd for $C_{22}H_{15}N$ (**13**): C, 90.07; H, 5.15. Found: C, 90.32; H, 5.24. The third eluate ($CHCl_3$) yielded **14** (0.7 g, 23%), a white solid apparently produced by hydrolysis on Al_2O_3: mp 173–174 °C; IR (KBr) 3450, 3140, 1693, 1600, 1490, 1455, 755, 687 cm^{-1}; NMR ($CDCl_3$) δ 6.4–6.8 (s, b, 2 H), 7.1–7.6 (m, 15 H); MS *m/e* 311 (parent). Anal. Calcd for $C_{22}H_{17}NO$ (**14**); C, 84.86; H, 5.50. Found: C, 84.86; H, 5.54.

Products of the Reactions of Diphenylacetonitrile Anion with 1a in Me_2SO. After diphenylacetonitrile (1.93 g, 0.01 mol) in Me_2SO–KOH was stirred for 1 h, **1a** (0.87 mL) in Me_2SO (20 mL) was added (30 min) and the mixture was left at ~25 °C for 12 h. Workup and purification (CC, Al_2O_3, SiO_2) yielded **15**, a white solid, as the main product in the first eluate (benzene): mp 158–159 °C; IR (KBr) 1600, 1490, 1440, 1070, 1030, 765, 700 cm^{-1}; NMR ($CDCl_3$) δ 3.65 (s, 1 H), 6.86 (s, 10 H), 7.16 (s, 5 H); MS *m/e* 537 ± 1 (parent 536); UV (EtOH) λ (log ε) 301 (4.02), 2.64 (3.94) nm. The composition of **15** is that of a dimer of triphenylpropyne. Anal. Calcd for $C_{42}H_{32}$: C, 93.99; H, 6.01. Found: C, 94.12; H, 6.13. The second eluate (benzene) yielded pale yellow crystals: mp 147–148 °C; IR (KBr) 1620, 1600, 1490, 1445, 1230, 770, 735, 700 cm^{-1}; NMR (CCl_4) δ 7.1–7.8 (m); MS *m/e* 550 ± 1. The elemental analysis but not the molecular weight is analogous to that of **15**: Anal. Found: C, 94.12; H, 6.13. The third eluate ($CHCl_3$) yielded white crystals: mp 152 °C; IR (KBr) 3380, 3180, 1655, 1500, 1400, 1260, 740, 700 cm^{-1}; NMR ($CDCl_3$) 5.18 (s, 1 H), 7.6 (s, 15 H); MS *m/e* 549 ± 1. Anal. Found: C, 78.41; H, 6.16. When **15** was heated for 10 min at 170 °C, a white solid was produced, which had: mp 243–244 °C; NMR ($CDCl_3$) δ 2.83 (d, 1 H, J = 15 Hz), 3.61 (d, 1 H, J = 15 Hz), 4.07 (s, 2 H), 6.9–7.3, 7.35 (m, broad).

Reaction of Diphenylmethyl or Dimethylsulfinyl Anions with 1a. Diphenylmethane (5.04 g, 0.03 mol) was stirred with Me_2SO (50 mL)–KOH (12 g) for 3 days, then **1a** (4.2 g, 0.03 mol) was added dropwise over a period of 1 h. After 6 h the mixture was poured onto a slurry of dry ice in water (50 mL). Workup of the mixture followed (CC, Al_2O_3, SiO_2) and yielded diphenylmethane in the first eluate and oils later. The second eluate yielded diphenyldiacetylene (**16**) (26%), mp 81 °C, spectroscopically identical to an authentic sample.

Sodium hydride (2.16 g, 0.03 mol) was stirred in Me_2SO (30 mL) at ~75 °C for 2 h after the evoluation of hydrogen had ceased. The solution was cooled to ca. 10–15 °C and **1a** (2.6 mL) in Me_2SO (20 mL) was added dropwise (30 min). After 1 h at ~25 °C and 12 h at ~45 °C the mixture was poured into ice slush yielding an oily product which was purified (CC, SiO_2). The first eluate in *n*-hexane yielded **16** (1 g, 33%), mp 81–82 °C.

Bis(3-cyano-3,3-diphenylprop-1-ynyl)mercury (17). Diphenylacetonitrile (1.93 g, 0.01 mol), sodium (0.25 g, 0.01 mol), and glyme (50 mL) were stirred under nitrogen at reflux temperature for 12 h. The mixture was cooled to ca. −40 °C and mercury bis(chloroacetylide)[20] (3.2 g) was added to it over a period of 0.5 h. The reaction mixture was left for 1 day at ~25 °C and 1 day at ~55 °C and then poured into ice water. The white solid (3.8 g) was taken up in chloroform and further purified (CC, SiO_2) and recrystallized from chloroform. It had: mp 262–264.5 °C; IR (KBr) 2120 (w), 1595, 1485, 1450, 760, 745, 695 cm^{-1}; NMR ($CDCl_3$) δ 7.16–7.66. Anal. Calcd for $C_{32}H_{20}N_2Hg$: C, 60.11; H, 3.18. Found: C, 60.1; H, 3.23.

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Registry No.—**1a**, 1483-82-5; **5a**, 1292-14-4; **5b**, 64784-62-9; **6a**, 12100-65-1; **6b**, 64784-63-0; **7**, 20143-13-9; **8**, 64771-52-4; **9**, 64771-53-5; **10**, 64771-54-6; **11**, 64771-55-7; **12**, 64771-69-3; **13**, 64771-56-8; **14**, 64771-57-9; **15**, 64771-70-6; **16**, 25213-31-4; **17**, 64771-58-0; $FeCl_2$, 7758-94-3; cyclopentadiene, 542-92-7; ferrocene, 102-54-5; methylcyclopentadiene, 96-39-9; 1,1′-dimethylferrocene, 1291-47-0; triphenylmethane, 519-73-3; fluorene, 86-73-7; ethyl malonate, 105-53-3; ethyl sodiomalonate, 43167-10-8; benzyl cyanide, 140-29-4; α-cyanobenzylsodium, 26388-11-4; diphenylacetonitrile, 86-29-3; mercury bis(chloroacetylide), 64771-59-1.

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α,α′-Dibromocycloalkanols and 3-Bromocycloalkene Oxides

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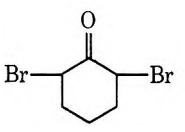
Stereoselective syntheses of the isomeric 2,6-dibromocyclohexanols and 3-bromocyclohexene oxides, as well as the related cyclooctane and cyclododecane derivatives, are reported.

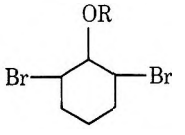
A forthcoming publication will describe our studies on the action of zinc on α,α′-dibromocycloalkanols and 3-bromocycloalkene oxides. Herein we consider the procedures by which these compounds were prepared and the evidence upon which their stereochemical assignments rest.

Results and Discussion

Dibromocyclohexanols. Bromination of cyclohexanone in acetic acid afforded *cis*-2,6-dibromocyclohexanone (**1**).[2,3] Reduction of **1** with sodium borohydride in ethanol[4] gave *cis,cis*-dibromocyclohexanol (**2**) and only a small amount of the *trans,trans*-dibromohydrin **3**. The overlapping signals for the CHBr and CHOH protons in **2** were unsuitable for structural assignments; however, the acetate derivative **2a** showed



1



2, R = H
2a, R = Ac

a triplet at 5.59 ppm (J = 2 Hz) and a multiplet at 4.09 ppm ($W_{1/2}$ = 28 Hz) which suggests the presence of an equatorial HCOAc proton and axial CHBr protons.

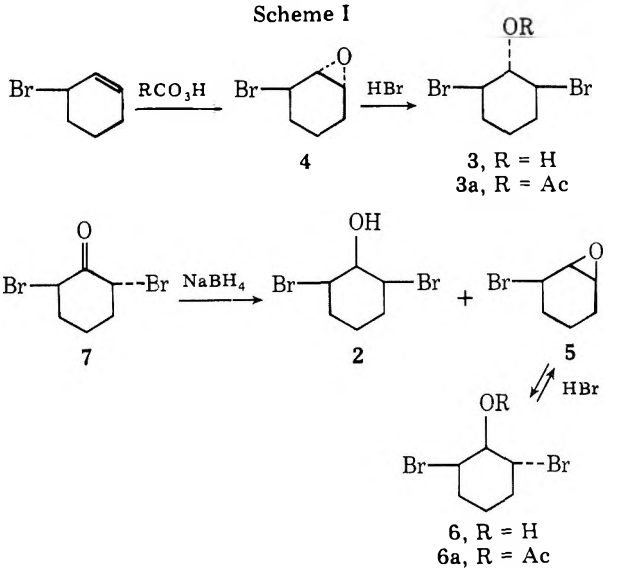
trans,trans-2,6-Dibromocyclohexanol (**3**) was obtained by the sequence shown in Scheme I. Epoxidation of 3-bromocyclohexene with *m*-chloroperbenzoic acid afforded *trans*-3-bromocyclohexene oxide (**4**).[5] The stereochemistry of **4** was assigned on the basis of the expected approach of the epoxidizing agent from the less-hindered side of the carbon–carbon double bond,[7] i.e., anti to the bromine atom. This assignment was confirmed by conversion of **4** to **3** using fuming hydrobromic acid. Dibromohydrin **3**, in turn, gave *cis*-2,6-dibromocyclohexanone (**1**) on oxidation using the Jones procedure.

The large coupling constant (J = 10.5 Hz) for the HCOAc proton in acetate **3a** placed it in an axial position. The HCBr protons must also be axial, as indicated by a complex multiplet at 3.90 ppm with $W_{1/2}$ = 31 Hz.

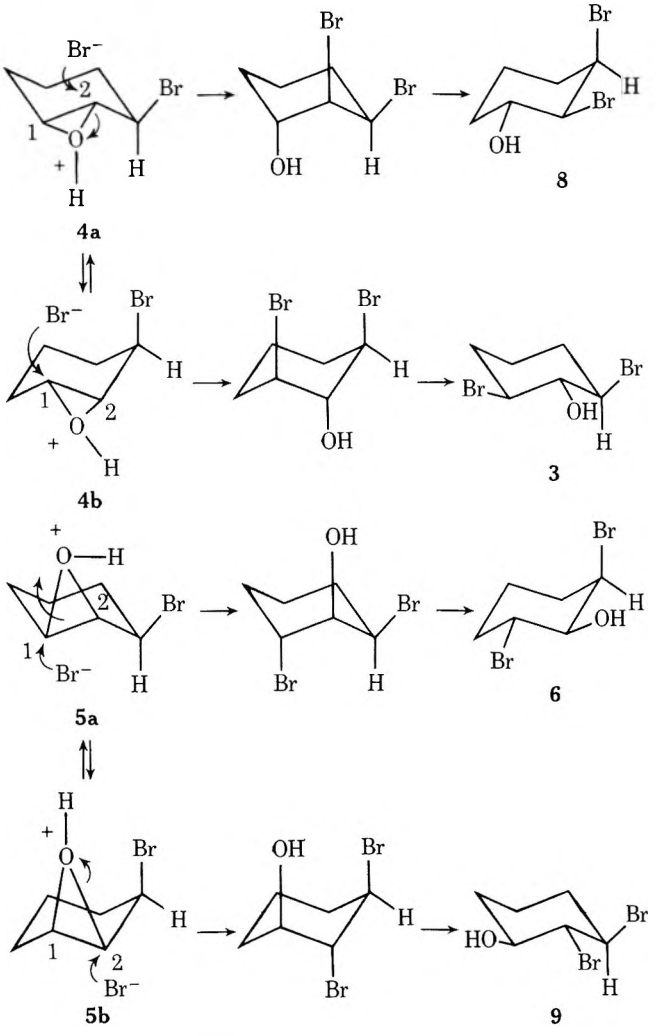
Although the successful reduction of substituted *trans*-2,6-dibromocyclohexanones to *cis,trans*-2,6-dibromocyclohexanols with potassium borohydride has been reported,[4] the use of sodium borohydride in the reduction of *trans*-2,6-dibromocyclohexanone (**7**) led to a mixture of *cis,cis*-dibromohydrin **2** and *cis*-3-bromocyclohexane oxide (**5**). A similar epimerization of an α-bromo ketone during sodium borohydride reduction has been noted by other investigators[8] and we have observed the same behavior in the sodium borohydride reduction of the 2,8-dibromocyclooctanones. Apparently epimerization competes with reduction when the carbonyl group is slowly reduced.

Reduction of *trans*-2,6-dibromocyclohexanone (**7**) with lithium aluminum hydride[8,9] gave a mixture of *cis,trans*-2,6-dibromocyclohexanol (**6**) and *cis*-3-bromocyclohexene oxide (**5**) as indicated by TLC and infrared examination of the crude product. Epoxide **5** was easily obtained in pure form by column chromatography, conditions under which the *cis,trans*-dibromohydrin **6** is converted into epoxide **5**. Epoxide **5** was cleanly transformed into *cis,trans*-**6** by treatment with hydrobromic acid.

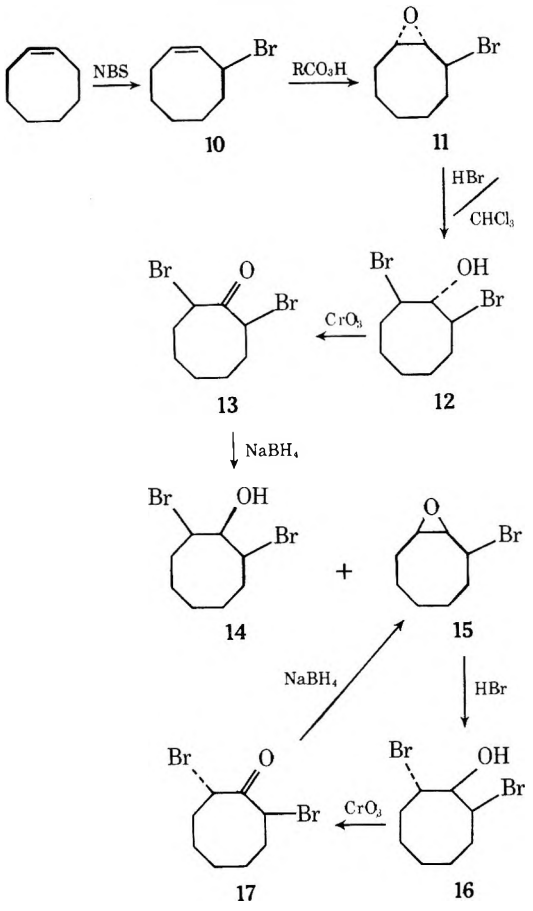
Scheme I



Scheme II



Scheme III



cis,trans-2,6-Dibromocyclohexanol (**6**) showed three downfield multiplets, the most informative being a doublet of doublets assigned to the HCO proton which displayed $J_{1,2}$ = 8 Hz and $J_{1,6}$ = 3 Hz, requiring this proton to be axial, the C-6 proton to be equatorial, and the C-2 proton to be axial in accord with the assigned structure.

If it is assumed that acid-promoted ring opening of cyclohexene oxides proceed in a *trans*-diaxial manner, then a priori, the *trans*-oxide **4** might give dibromohydrins **3** or **8** and the *cis*-oxide **5** might afford the dibromohydrins **6** or **9**, depending upon the direction of the opening of the epoxide ring (Scheme II).

In actual fact, *trans*-bromo epoxide **4** yields dibromohydrin **3** and *cis*-bromo epoxide **5** yields dibromohydrin **6**. In each case the ring opening occurs with high stereoselectivity;[6] consequently, the transition state energies of ring opening leading to dibromohydrins **8** and **9** must be higher in energy than those leading to **3** and **6**.

It is known that bond breaking in acid-catalyzed oxide ring openings is far advanced in the transition state;[10] consequently, the stability of the intermediate carbonium ion would be expected to be reflected in the transition state energy. As the carbon–oxygen bond at C-2 begins to break in conformer **4a** or **5b**, the incipient positive charge at C-2 is destabilized by the inductive effect of the adjacent bromine atom. This would raise the transition state energy of the ring opening at C-2.

On the other hand, potential 1,3-diaxial interactions in transition **4b** leading ultimately to dibromohydrin **3** would be expected to deter ring cleavage at C-1. Evidently the inductive effect of the electronegative bromine atom is the controlling factor in the ring opening. Bannard has come to a similar conclusion regarding the acid-promoted ring openings of *cis*- and *trans*-3-methoxycyclohexene oxides,[11] while Needler[12] has observed the formation of *trans,trans*-2-chlorocyclohexanol derivatives in the ring opening of *trans*-3-chlorocyclohexene oxide.

2,8-Dibromocyclooctanols. The three 2,8-dibromocyclooctanols were obtained, as outlined in Scheme III, using reactions which parallel those employed in the six-membered series.

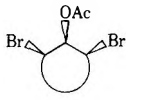
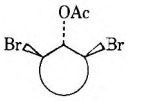
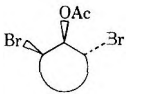
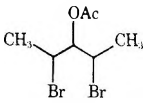
Epoxidation of 3-bromocyclooctene (**10**) gave *trans*-3-bromocyclooctene oxide (**11**), which was converted to *trans,trans*-2,8-dibromocyclooctanol (**12**) by treatment with hydrobromic acid. Oxidation of **12** using the Jones procedure afforded *cis*-2,8-dibromocyclooctanone (**13**).

Sodium borohydride reduction of *cis*-2,8-dibromocyclooctanone (**13**) afforded a mixture of *cis*-3-bromocyclooctene oxide (**15**) and *cis,cis*-2,8-dibromocyclooctanol (**14**) in a ratio of 3:1. Sodium borohydride reduction of *trans*-dibromide **17** gave the *cis*-bromo epoxide **15** and a small amount of *cis,cis*-dibromohydrin **14**. It is apparent that epimerization of the dibromocyclooctanones competes with the slow reduction of the carbonyl group and that reduction of *trans*-dibromide **17** leads to epoxide **15**, whereas reduction of the *cis*-dibromide **13** affords the *cis,cis*-dibromohydrin **14**.

The last stereoisomer in this series, *cis,trans*-2,8-dibromocyclooctanol (**16**), was obtained by treating a solution of *cis*-bromo epoxide **15** in chloroform with hydrobromic acid.

The structures assigned compounds **11**–**17** are based on their method of preparation, analysis of NMR spectra, and further chemical transformations. The *cis,cis*-dibromohydrin **14** was the only isomer which could be chromatographed on acid-washed alumina. Chromatography of *trans,trans*-**12** and *cis,trans*-**16** cleanly gave *trans*-bromo epoxide **11** and *cis*-bromo epoxide **15**, respectively.

Table I. NMR Spectra of 6-, 8-, and 12-Membered Ring Dibromo Acetates and 2,4-Dibromo-3-pentyl Acetate

	Compd	−CHBr	−CHOAc
	C_6	4.09	5.59 (t, J = 2 Hz)
	C_8	4.41 (m)	5.85 (t, J = 2 Hz)
	C_{12}	4.23 ("q")	5.55 (t, J = 5 Hz)
	C_6	3.90 (m)	5.33 (t, J = 10.5 Hz)
	C_8	4.25 (m)	5.43 (t, J = 9.5 Hz)
	C_{12}	4.26 ("q")	5.27 (t, J = 5 Hz)
	C_6	4.70 (m) 4.32 (m)	4.88 (d of d, J = 3, 8 Hz
	C_8	4.37 (m)	5.22 (d of d, J = 9.5, 2 Hz)
	C_{12}	4.25 (m)	5.62 (d of d, J = 10.3, 1.8 Hz)
 *dl*		4.31 (m)	5.02 (t, J = 5.5 Hz)

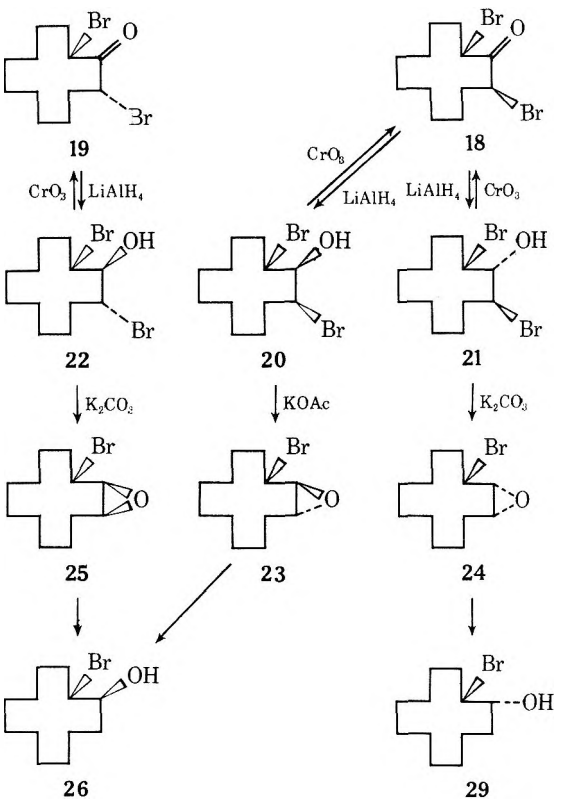
The cyclooctane ring is known to adopt a number of low energy conformations[13] in which C-1, C-2, C-3, C-7, and C-8 atoms take up positions resembling the chair conformation of a cyclohexane ring. Examination of Table I demonstrates a close parallel between the multiplicities and spin coupling constants of the HCBr and HCO protons in the related six- and eight-membered ring isomers, adding additional support for the geometric assignments made in the cyclooctane series.

Dibromocyclododecanols. The dibromohydrins in the 12-membered ring series were prepared by a modification of Garbisch's procedure.[14] Bromination of cyclododecanone in ether afforded a 7:3 mixture of *cis*- and *trans*-2,12-dibromocyclododecanones from which the pure *cis*-**18** and *trans*-**19** could be obtained by fractional crystallization. Lithium aluminum hydride reduction of *cis*-**18** gave *cis,cis*-2,12-dibromocyclododecanol (**20**) and *trans,trans*-2,12-dibromocyclododecanol (**21**),[15] which were separated by chromatography (Scheme IV). Reduction of *trans*-dibromocyclododecanone **19** afforded a single alcohol, *cis,trans*-2,12-dibromocyclododecanol (**22**), confirming the trans relationship of the two bromine atoms in the parent ketone. Jones oxidation of each dibromohydrin gave only the original parent dibromo ketone, demonstrating the absence of epimerization during hydride reduction.

cis,cis-Dibromohydrin **20** was readily converted to *cis*-3-bromo-*trans*-1,2-epoxycyclododecane (**23**) by treatment with potassium acetate in acetone. These conditions had no effect on *trans,trans*-dibromohydrin **21** or *cis,trans*-dibromohydrin **22** and the more basic potassium carbonate in aqueous methanol was required to produce *trans*-3-bromo-*cis*-1,2-epoxycyclododecane (**24**) and *cis*-3-bromo-*cis*-1,2-epoxycyclododecane (**25**), respectively. Only one of the two possible epoxides was formed from *cis,trans*-dibromohydrin **22** and the structure **24** was assigned on the basis of evidence to be discussed later. A mixture of epoxides **23**, **24**, and **25** was obtained on epoxidation of 3-bromocyclododecene; once again we failed to observe the formation of the fourth bromo epoxide.

Chemical transformations were required to differentiate between *cis,cis*-dibromohydrin **20** and *trans,trans*-dibromohydrin **21**, since NMR spectral data, unlike the situation in the six- and eight-membered rings, gave no clue to their identity (See Table I). The cis,cis configuration was assigned to **20** on the basis of its reduction with lithium aluminum hydride to *cis*-2-bromocyclododecanol (**26**), which was also

Scheme IV

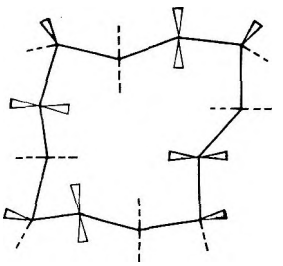


prepared from *trans*-cyclodecene oxide (**27**) and hydrobromic acid. Additional support for the cis,cis configuration was provided by the formation of *cis*-bromohydrin **26** on lithium aluminum hydride reduction of *cis*-bromo *trans*-epoxide **23**.

Lithium aluminum hydride reduction of *trans,trans*-dibromohydrin **21** gave a mixture of starting dibromohydrin **21**, cyclododecanol (**28**), and 7% of *trans*-2-bromocyclododecanol (**29**). Apparently, the reduction of **29** to cyclododecanol (**28**) occurs faster than the initial reduction of dibromohydrin **21**. Lithium aluminum hydride reduction of *trans*-bromo *cis*-epoxide **24** afforded *trans*-bromohydrin **29** in 75% yield.

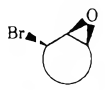
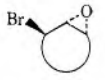
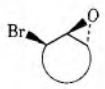
Finally, lithium aluminum hydride reduction of the epoxide derived from *cis,trans*-dibromohydrin **22** gave, in addition to recovered epoxide and 2-cyclodecenol, a low yield of *cis*-2-bromocyclododecanol (**26**), which suggests the epoxide has the constitution represented by structure **25**.

Evidence has accumulated indicating the cyclododecane ring assumes a square conformation[16] of D_{4h} symmetry in which each side is composed of a butane segment with the corner atoms common to two segments. This arrangement permits a completely staggered conformation for each carbon atom.



The coupling constants observed for *cis*-2-bromocyclododecanol (**26**) and its acetate derivative (J = 2.0 and 1.6 Hz) and *trans*-2-bromocyclododecanol (**29**) (J = 7.0 and 7.3 Hz) suggest that the cyclododecane ring adopts a square shape with the large groups pointing outward and at least one of the

Table II. NMR Spectra of 3-Bromocycloakene Oxides

	CHBr	CH—CH
	C_6 4.43 (d of t) C_8 4.59 (m) C_{12} 3.63 (m)	3.38 (d) 3.20 (m) 3.06 (m) and 2.92 (m)
	C_6 4.52 (m) C_8 3.81 (m) C_{12} 3.92 (m)	3.28 (m) 3.07 and 2.91 (br d's) 3.21 (m) and 3.07 (m)
	C_{12} 4.64 (m)	3.10 (d of t) 2.72 (t)

groups attached to a corner carbon. In this conformation the trans isomer has a large dihedral angle (~170°) between vicinal hydrogens and should give rise to a large coupling constant, whereas the dihedral angle in the cis isomer is close to 60° and it would be expected to show a small coupling constant in accord with the experimental observations. Arranging the large groups along the "side" of the square would predict just the opposite dihedral angles for the cis and trans isomers and would require the cis isomer to have a large group facing into the ring.

In the case of the dibromohydrins or their acetate derivatives it seems reasonable to assume the most stable conformation of the cyclododecane ring would involve a "square" with the large groups pointing away from the ring. Two interconvertible conformations can be envisioned, a symmetric one where the acetate group occupies a corner and is flanked by bromine atoms, and an unsymmetric conformation in which a bromine atom is at a corner and the acetate and second bromine atom are at side positions. The symmetric conformation correctly predicts the relative HCOAc chemical shift and the unequal HCBr–CHOAc coupling constants (J_{AX} = 10.3 and J_{BX} = 1.8 Hz) displayed by the acetate derivative of *cis,trans*-2,12-dibromocyclododecanol (**22**).

The acetate derivatives derived from the *cis,cis*- and *trans,trans*-dibromohydrins both exhibit vicinal coupling constants equal to 5 Hz, which is almost identical with that displayed by the open-chain analogue *dl*-2,4-dibromo-3-pentyl acetate (**31**). Neither the symmetric nor unsymmetric conformation described above predicts this value and suggests that even with three large groups, *cis,cis*-**20** and *trans,trans*-**21** are sufficiently mobile to attain an average conformation comparable with that of an open-chain analogue.

Finally, mention is made of the upfield chemical shift for the –CHBr proton in bromo expoxides **24** and **25** and *trans*-3-bromocyclooctene oxide (**11**) (see Table II) which demands conformations for these compounds where the CHBr proton lies above and in the shielding cone of the epoxide ring.[17] Examination of the cyclododecane square model suggests that if one of the oxygen atoms of a *cis*-epoxide is located at a "corner", the CHBr proton will extend over the epoxide ring and result in an upfield shift, whereas, with a *trans*-epoxide ring the CHBr proton is directed away from the epoxide ring and would be expected to exhibit a normal chemical shift. Examination of molecular models of *cis*- and *trans*-bromocyclooctene oxides **11** and **15** likewise illustrate that the CHBr proton can only be positioned over the epoxide ring in the trans isomer **11**.

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were measured with a Perkin-Elmer Infracord Model 137-B. NMR spectra were recorded with Varian Associates A-60A and Perkin-Elmer R-32 instruments and are reported in parts per million from tetramethylsilane as an internal standard. Mass spectra were determined on a Hitachi RMU-6D instrument by the Purdue University Spectral Service. Microanalyses were performed by Dr. C. S. Yeh and associates.

***cis,cis*-2,6-Dibromocyclohexanol (2).** To 3.5 g of *cis*-2,6-dibromocyclohexanone (**1**)[2] in 30 mL of absolute ethanol at 5 °C was added dropwise a solution of 800 mg of sodium borohydride in 80 mL of ethanol. The mixture was allowed to stir for 5 h at 5 °C and 30 h at ambient temperature. The mixture was diluted with water, neutralized to pH 7 with 5% hydrochloric acid, and extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated to leave a light green oil which solidified on cooling. Recrystallization from hexane gave 1.56 g (45%) of **2**: mp 60–62 °C; IR (CCl_4) 2.69 μm; NMR (CCl_4) 1.0–2.3 (m, 6, $-CH_2-$), 2.5 (d, 1, J = 3 Hz, –CHO**H**), and 3.9 ppm (m, 3, –CHO and CHBr).

Anal. Calcd for $C_6H_{10}Br_2O$: C, 27.91; H, 3.87; Br, 62.01. Found: C, 28.16; H, 4.02; Br, 61.85.

***cis,cis*-2,6-Dibromocyclohexyl Acetate (2a).** A mixture of 150 mg of **2**, 500 mg of powdered magnesium, and 5 mL of acetyl chloride was stirred for 38 h at ambient temperature. The solution was decanted and the solids washed thoroughly with ether. Water was added slowly to the combined supernatant and ether washings. The ether solution was then washed with 5% sodium bicarbonate solution, dried, and concentrated to afford 140 mg of solid which was recrystallized from hexane and showed: mp 76–78 °C; IR ($CHCl_3$) 5.79 μm; NMR ($CDCl_3$) 1.6–2.1 (m, 6, $-CH_2-$), 2.13 (s, 3, CH_3CO_2-), 4.09 (m, 2, $W_{1/2}$ = 23 Hz, –CHBr), and 5.59 ppm (t, 1, J = 2 Hz, –CHOAc); mass spectrum (70 eV) *m/e* 256[18] (P – 42), 238 (P – 60), 219 (P – Br), and 159 (P – 60 – Br).

Anal. Calcd for $C_8H_{12}Br_2O_2$: C, 32.00; H, 4.00; Br, 53.33. Found: C, 32.21; H, 3.85; Br, 53.35.

***trans*-3-Bromocyclohexene Oxide (4).** To 8.35 g (0.052 mol) of 3-bromocyclohexene[19] in 40 mL of chloroform at ice-bath temperature was added over a 15-min period a solution of 15.0 g of 85% *m*-chloroperbenzoic acid in 200 mL of chloroform. The mixture was stirred at ambient temperature for 30 h, filtered, washed with 10% sodium sulfite solution and 5% sodium bicarbonate solution, dried, concentrated, and distilled under diminished pressure to give 5.09 g of oxide **4**: bp 64–68 °C (4 mm); $n^{20}D$ 1.5151–1.5158; IR (CCl_4) 8.00, 8.48, 9.89, and 10.31 μm; NMR (CCl_4) 1.1–2.2 (m, 6, $-CH_2-$), 3.28 (m, 2, c-CHCHO), and 4.52 ppm (m, 1, –CHBr).

Anal. Calcd for C_6H_9BrO: C, 40.68; H, 5.08; Br, 45.20. Found: C, 40.65; H, 4.98; Br, 45.40.

***trans,trans*-2,6-Dibromocyclohexanol (3).** A mixture of 734 mg of oxide **4** in 10 mL of chloroform and 10 mL of fuming hydrobromic acid was stirred vigorously for 70 min. The layers were separated and the aqueous phase was washed with chloroform. The combined chloroform layers were washed with 10% aqueous sodium carbonate, dried, and concentrated to furnish 783 mg of white solid. The analytical sample of **3** was obtained by recrystallization from hexane: mp 93–95 °C; IR ($CHCl_3$) 2.74 μm; NMR ($CDCl_3$) 1.1–2.6 (m, 6, $-CH_2-$), 3.0 (s, 1, –OH), and 3.88 ppm (m, 3, –CHO, –CHBr); mass spectrum *m/e* 256 (P), 238 (P – 18), 177 (P – Br), 159 (P – 18 – Br).

Anal. Calcd for $C_6H_{10}Br_2O$: C, 27.91; H, 3.87; Br, 62.01. Found: C, 27.85; H, 3.85; Br, 62.18.

A solution of 102 mg of **3** in 4 mL of acetone at 40 °C was treated with 3.1 mL of Jones reagent. The usual workup after 30 min gave 73 mg of solid whose IR spectrum indicated the presence of some unreacted alcohol. This material was again treated with Jones reagent and workup gave 50 mg of solid. Recrystallization from hexane gave a solid, mp 106–108 °C, whose infrared spectrum was identical with that of an authentic sample of *cis*-2,6-dibromocyclohexanone (**1**).

***trans,trans*-2,6-Dibromocyclohexyl Acetate (3a).** Using the procedure described earlier, 183 mg of **3** afforded 176 mg of **3a**. The analytical sample was prepared by crystallization from hexane: mp 113–115 °C; IR ($CHCl_3$) 5.81 μm; NMR ($CDCl_3$) 1.4–2.7 (m, 6, $-CH_2-$), 2.19 (s, 3, CH_3CO_2-), 3.90 (m, 2, $W_{1/2}$ = 31 Hz, –CHBr) and 5.33 ppm (t, 1, J = 10.5 Hz, –CHOAc); mass spectrum *m/e* 256 (P – 42), 238 (P – 60), 219 (P – Br), 159 (P – 60 – Br).

Anal. Calcd for $C_8H_{12}Br_2O_2$: C, 32.00; H, 4.00; Br, 53.33. Found: C, 32.16; H, 4.04; Br, 53.23.

***cis,trans*-2,6-Dibromocyclohexanol (6).** To 1.69 g (6.6 mmol) of *trans*-2,6-dibromocyclohexanone (**7**)[2,3] in 50 mL of ether was added 85 mg (2.24 mmol) of lithium aluminum hydride. The reaction mixture was stirred for 20 min and then worked up to afford 955 mg of colorless oil. The analytical sample was obtained by evaporative distillation [55 °C (0.05 mm)]: IR 2.86 μm; NMR ($CDCl_3$) 1.5–2.6 (m, 6, $-CH_2-$), 3.05 (s, 1, –OH), 3.72 (d of d, 1, $J_{1,2}$ = 8, $J_{1,6}$ = 3 Hz, HCO), 4.35 (m, 1, –CHBr), and 4.75 ppm (m, 1, –CHBr); mass spectrum *m/e* 260 (P) and 179 (P – Br).

Anal. Calcd for $C_6H_{10}Br_2O$: C, 27.91; H, 3.91. Found: C, 27.90; H, 4.11.

Oxidation of **6** employing the Jones procedure afforded a solid, mp 33–35 °C, whose IR and NMR were identical with those of authentic *trans*-2,6-dibromocyclohexanone (**7**).

The acetate derivative of **6** could not be induced to crystallize: NMR (CCl_4) 1.6–2.5 (m, 6, $-CH_2$), 2.10 (s, 3, CH_3CO_2), 4.32 (m, 1, $W_{1/2}$ = 27 Hz, –CHBr), 4.70 (m, 1, $W_{1/2}$ = 15 Hz, –CHBr), and 4.88 ppm (d of d, 1, J = 8, 3 Hz, –CHOAc); mass spectrum m/e 256 (P − 42), 238 (P − 60), 219 (P − Br), and 159 (P − 60 − Br).

***cis*-3-Bromocyclohexene Oxide (5).** A 0.415 g sample of *cis,trans*-2,6-dibromocyclohexanol (**6**) was placed on 18 g of acid-washed alumina and was eluted with 5–10% ether in pentane to give 0.25 g (87%) of *cis*-bromo epoxide **5**. The analytical sample of **5** was prepared by evaporative distillation [51–55 °C (0.17 mm)]: IR 10.63 and 12.58 μm; NMR 1.0–2.18 (m, 6, $-CH_2-$), 3.38 (m, 2, c-CHCHO), and 4.43 ppm (d of t, 1, –CHBr); mass spectrum (70 eV) m/e (rel intensity) 177 (0.68), 175 (0.57), 97 (100), 79 (27), 67 (29), 43 (23), 39 (57).

Anal. Calcd for C_6H_9BrO: C, 40.71; H, 5.12. Found: C, 40.71; H, 5.26.

A mixture of 0.50 g of epoxide **5** in 10 mL of $CHCl_3$ and 10 mL of 47% hydrobromic acid was stirred for 70 min. The usual workup left 0.55 g of an oil whose infrared spectrum was identical with that of *cis,trans*-**6** and whose NMR spectrum only displayed signals shown by alcohol **6**.

Sodium Borohydride Reduction of *trans*-2,6-Dibromocyclohexanone (7). To 1.6 g of *trans*-2,6-dibromocyclohexanone (**7**) in 50 mL of absolute ethanol at 0 °C was added a solution of 236 mg of sodium borohydride in 40 mL of absolute ethanol. The mixture was stirred for 5 h and worked up to leave 1.02 g of yellow oil. Thin layer chromatography indicated the presence of a mixture of *cis,cis*-2,6-dibromocyclohexanol (**2**) and *cis*-3-bromocyclohexene oxide (**5**).

This mixture was treated in chloroform with fuming hydrobromic acid and after workup and chromatography on silica gel gave 310 mg of a mixture which was free of a small amount of carbonyl impurity present in the crude product.

A small portion (40 mg) of the chromatographed product was treated with acetyl chloride and magnesium to afford a mixture of acetates **2a** and **6a**, which were identified by TLC comparison with authentic samples. Integration of the triplet at 5.69 ppm and doublet of doublets at 5.00 ppm suggested **2a** and **6a** were present in a ratio of 3:5.

***trans*-3-Bromocyclooctene Oxide (11).** To a solution of 25.6 g (0.135 mol) of 3-bromocyclooctene[20] in 50 mL of chloroform at 5 °C was added dropwise a solution of 29.3 g (0.156 mol) of 85% *m*-chloroperbenzoic acid in 300 mL of chloroform. After stirring at room temperature for 18 h, workup and distillation gave 22.3 g (80%) of epoxide **11**: bp 64–68 °C (0.2 mm); $n^{23}D$ 1.5224; NMR (CCl_4) 1.8–2.1 (m, 10, $-CH_2-$), 2.91 (br d, 1, c-CCHO), 3.07 (br d, 1, c-CHCO), and 3.81 ppm (m, 1, $W_{1/2}$ = 25 Hz, –CHBr); mass spectrum m/e 159 (P − 45) and 125 (P − Br).

Anal. Calcd for $C_8H_{13}OBr$: C, 46.82; H, 6.34; Br, 39.02. Found: C, 46.70; H, 6.20; Br, 39.22.

***trans,trans*-2,3-Dibromocyclooctanol (12).** A mixture of 15 mL of fuming hydrobromic acid and a solution of 2.43 g of epoxide **11** in 30 mL of chloroform was stirred vigorously at ambient temperature for 12 h. The usual workup gave 2.75 g of oil which gradually solidified. Two recrystallizations from hexane afforded 637 mg of pure **12**: mp 62–64 °C; IR (CCl_4) 2.73 μm; NMR (CCl_4) 1.72 (m, 6, $-CH_2-$), 2.35 (m, 4, $-CH_2CBr$), 3.03 (s, 1, –OH), and 4.28 ppm (m, 3, –CHOH, –CHBr).

Anal. Calcd for $C_8H_{14}OBr_2$: C, 33.57; H, 4.89; Br, 55.94. Found: C, 33.34; H, 4.97; Br, 55.88.

***trans,trans*-2,8-Dibromocyclooctyl acetate** was prepared from **12** by stirring with magnesium and acetyl chloride and was purified by recrystallization from hexane: mp 82–83 °C; NMR (CCl_4) 2.08 (s, 3, CH_3CO_2-), 1.78 (m, 6, $-CH_2-$), 2.3 (m, 4), 4.25 (m, 2, $W_{1/2}$ = 25 Hz, –CHBr), and 5.43 ppm (t, 1, J = 9.5 Hz, –CHOAc).

Anal. Calcd for $C_{10}H_{16}Br_2O_2$: C, 36.59; H, 4.88; Br, 48.76. Found: C, 36.81; H, 4.92; Br, 48.77.

***cis*-2,8-Dibromocyclooctanone (13).** To a solution of 362 mg of *trans,trans*-2,8-dibromocyclooctanol (**12**) in 25 mL of pure acetone at 10 °C was slowly added a solution containing 309 mg of chromium trioxide and 0.30 mL of concentrated sulfuric acid in 2 mL of water. The usual workup of the reaction mixture gave 283 mg of **13**. The analytical sample of **13** was prepared by recrystallization from hexane and showed: mp 93.5–95.5 °C; IR (CCl_4) 5.72 μm; NMR ($CDCl_3$) 1.0–2.71 (m, 10, $-CH_2-$) and 4.91 ppm (d of d, 2, $W_{1/2}$ = 13.5 Hz, –CHBr).

Anal. Calcd for $C_8H_{12}Br_2O$: C, 33.80; H, 4.22; Br, 56.34. Found: C, 33.54; H, 4.37; Br, 56.24.

Sodium Borohydride Reduction of *cis*-2,8-Dibromocyclooctanone (13). A solution of 2.3 g (8.1 mmol) of *cis*-2,8-dibromocyclooctanone (**13**) and 0.31 g (8.1 mmol) of sodium borohydride in 50 mL of absolute ethanol was stirred at ambient temperature for 86 h. The mixture was worked up to give 1.7 g of an oil which was chromatographed on 110 g of Florisil using 2% ether–hexane as an eluant. The first component to be eluted, 790 mg, was *cis,cis*-2,8-dibromocyclooctanol (**14**): mp 54–54.2 °C; IR (CCl_4) 2.72 μm; NMR (CCl_4) 1.2–2.8 (m, 10), 2.68 (d, 1, J = 4 Hz, –OH), 4.38 (m, 2, $W_{1/2}$ = 21 Hz, –CHBr), and 4.69 ppm (m, 1, –CHO). The 2.68-ppm doublet disappeared when trifluoroacetic acid was added and the signal at 4.69 ppm collapsed to a triplet, J = 2 Hz.

Anal. Calcd for $C_8H_{14}Br_2O$: C, 33.57; H, 4.89; Br, 55.94. Found: C, 33.76; H, 4.79; Br, 55.74.

The later chromatographic fractions containing **14** (140 mg) were contaminated with *cis*-3-bromocyclooctene oxide (**15**). Evaporative distillation of these fractions gave 60 mg of **14** and 80 mg of **15**.

The last chromatographic fractions gave **15**. A pure sample of epoxide **15** was obtained by evaporative distillation; NMR (CCl_4) 1.2–2.5 (m, 10), 3.20 (m, c-CHCHO), and 4.59 ppm (m, 1, $W_{1/2}$ = 22 Hz, –CHBr).

Anal. Calcd for $C_8H_{13}BrO$: C, 46.82; H, 6.34; Br, 39.02. Found: C, 46.61; H, 6.28; Br, 39.19.

Sodium Borohydride Reduction of *trans*-2,8-Dibromocyclooctanone (17). A solution of 730 mg (19.2 mmol) of sodium borohydride in 90 mL of absolute ethanol was slowly added to a solution of 3.4 g (11.9 mmol) of *trans*-2,8-dibromocyclooctanone (**17**)[21] (mp 75.5–77.5 °C) in 100 mL of absolute ethanol and the mixture was stirred at ambient temperature for 18 h. The usual workup gave 1.4 g of oil which was chromatographed on 80 g of Florisil using 1% ether–hexane as an eluant to furnish 919 mg of *cis*-3-bromocyclooctene oxide (**15**). The first fractions of **15** were contaminated with *cis,cis*-2,8-dibromooctanol (**14**). The epoxide **15** was separated by evaporative distillation at 50 °C and 5 mm. The residue from distillation (57 mg) was recrystallized from hexane, mp 55–56 °C, and showed an IR spectrum identical with that of cis,cis alcohol **14**.

***cis,trans*-2,8-Dibromocyclooctanol (16).** A solution of 853 mg of *cis*-3-bromocyclooctene oxide (**15**) in 10 mL of chloroform was stirred vigorously at ambient temperature with 2 mL of fuming hydrobromic acid. The organic layer was separated and washed with 5% sodium bicarbonate solution, dried, and concentrated to yield 1.01 g of oil. Column chromatography using 80 g of Florisil and 10–50% benzene–hexane as eluant gave 800 mg of cis,trans alcohol **16**. A pure sample of **16** was obtained by evaporative distillation at 80 °C and 0.2 mm: IR 2.73 μm; NMR (CCl_4) 1.4–2.5 (m, 10, $-CH_2-$), 2.79 (s, 1, –OH), 4.0–4.8 (m, 3, –CHO and –CHBr); mass spectrum m/e 288 (P), and 270 (P − 18).

The use of Florisil as the support for the chromatographic purification was necessitated by the fact that silica gel and basic alumina appeared to react with the alcohols, while acid-washed alumina converted cis,trans alcohol **16** and trans,trans alcohol **12** into bromo epoxides **15** and **11**, respectively. Thus 395 mg of crude *cis,trans*-dibromo alcohol **16** on chromatography using acid-washed alumina gave 280 mg of bromo epoxide **15** as the only recoverable product. Similarly, chromatography of 228 mg of *trans,trans*-dibromo alcohol **12** on acid-washed alumina and elution with 60% hexane–ether gave 156 mg of bromo epoxide **11**. *cis cis*-Dibromo alcohol **14** was recovered unchanged from chromatography under these conditions.

***cis,trans*-2,8-Dibromocyclooctyl Acetate (16a).** Acetylation of **16** using magnesium and acetyl chloride gave oily acetate **16a**: NMR 1.6–2.0 (m, 6, $-CH_2-$), 2.09 (s, 3, CH_3CO-), 2.0–2.7 (m, 4, $-CH_2CBr$) 4.37 (m, 2, $W_{1/2}$ = 25 Hz, –CHBr), 5.22 (d of d, 1, J = 9.5, 2 Hz, –CHOAc).

Epimerization of *trans*-2,8-Dibromocyclooctanone (17). To 70 mL of absolute ethanol was added 23 mg of sodium and 2.09 g of *trans*-2,8-dibromocyclooctanone (**17**). Aliquots (5 mL) were removed at various time intervals and were diluted with water and extracted with ether. The organic phase was separated, dried, and evaporated and the resulting solid analyzed by NMR. The *trans*-dibromide showed an apparent triplet centered at 4.63 ppm, whereas the *cis*-dibromide (**13**) displayed a quartet centered at 4.92 ppm. In 1 h the *trans/cis* ratio was 5.6:1. After 13 h it reached 4.3:1 and did not change afterwards (82 h).

***cis,trans*-2,12-Dibromocyclododecanol (22).** To an ethereal solution of 5.01 g (0.0147 mol) of *trans*-2,12-dibromocyclododecanone (**19**),[14] mp 44–45 °C, was added 0.579 g (0.0152 mol) of lithium aluminum hydride and the mixture was stirred for 3 h at ambient temperature. Workup led to the isolation of 4.28 g of oil which crystallized

on standing. Recrystallization from ether afforded 3.28 g (65%) of *cis,trans*-**22**: mp 73–75 °C (lit.[14] 76 °C); NMR ($CDCl_3$) 1.35 and 1.94 (s and m, 18), 2.87 (s, 1, –OH), 4.15 (m, 2, $W_{1/2}$ = 11 Hz), and 4.42 ppm (m, 1, $W_{1/2}$ = 18 Hz); IR ($CHCl_3$) 2.78 μm.

Oxidation of **22** according to the Jones procedure occurred rapidly and afforded 67% of a solid whose melting point and NMR spectrum were identical with that of *trans*-2,12-dibromocyclododecanone (**19**).

cis,trans-2,12-Dibromocyclododecyl acetate (**22a**) was prepared in 85% yield by acetylation of **22** with acetyl chloride in the presence of magnesium powder and showed: mp 90–95 °C; IR ($CHCl_3$) 5.70 μm; NMR ($CDCl_3$) 1.38 and 1.96 (s and m, 18), 2.17 (s, 3, CH_3CO_2–), 4.25 (m, 2, –CHBr) and 5.62 (d or d, 1, J = 10.3, 1.8 Hz, –CHOAc).

***cis,cis*- and *trans,trans*-2,12-Dibromocyclododecanol (20 and 21).** To an ether solution of 8.25 g (0.243 mol) of *cis*-2,12-dibromocyclododecanone (**18**),[14] mp 123–125 °C, was slowly added 0.7 g (0.0184 mol) of lithium aluminum hydride. The mixture was stirred at ambient temperature for 8 h and worked up to give 7.20 g of oil. Chromatography of 4.371 g of the oil on 100 g of silica gel using 5% ether–pentane as an eluant yielded 2.16 g of pure *cis,cis*-**20** followed by 1.23 g of pure *trans,trans*-**21**.

cis,cis-2,12-Dibromocyclododecanol (**20**) showed: mp 37–38 °C (lit.[14] mp 40 °C); IR ($CDCl_3$) 2.76 μm; NMR ($CDCl_3$) 1.38 and 2.05 (s and m, 18), 2.82 (m, 1, –OH), and 4.32 ppm (m, 3, CHBr and –CHO–).

trans,trans-2,12-Dibromocyclododecanol (**21**) proved to be an oil and could not be induced to crystallize:[15] IR ($CHCl_3$) 2.81 μm; NMR ($CDCl_3$) 1.4 and 2.0 (s and m, 18), 2.60 (s, 1, –OH), 3.78 ("t", 1, J = 5 Hz, –CHO–), and 4.32 ppm ("q", 2, J = 5 Hz, –CHBr).

Oxidation of **20** and **21** using the Jones procedure afforded *cis*-2,12-dibromocyclododecanone (**18**) in yields of 65 and 80%, respectively.

cis,cis-2,12-Dibromocyclododecyl acetate (**20a**) was obtained in 90% yield from the reaction of **20** with acetyl chloride and magnesium powder and exhibited: IR 5.68 μm; NMR ($CDCl_3$) 1.32 and 1.90 (s and m, 18), 2.10 (s, 3, CH_3CO_2–), 4.23 ("q", 2, –CHBr), and 5.55 ppm (t, 1, J = 5 Hz, –CHOAc).

trans,trans-2,12-Dibromocyclododecyl acetate (**21a**) was prepared in 93% yield by the same procedure and showed: IR 5.70 μm; NMR ($CDCl_3$) 1.32 and 1.90 (s and m, 18), 2.09 (s, 3, CH_3CO_2–), 4.26 ("q", 2, –CHBr), and 5.27 ppm (t, 1, J = 5 Hz, –CHOAc).

***cis*-3-Bromo-*cis*-1,2-epoxycyclodecane (25).** To a solution of 2.36 g (6.91 mmol) of *cis,trans*-**22** in 50 mL of methanol was added 2.0 g (14.5 mmol) of potassium carbonate in 10 mL of methanol and 1 mL of water. The mixture was stirred for 2.5 h, concentrated to 20 mL in vacuo, diluted with water, and extracted with ether. The ether was dried ($MgSO_4$) and evaporated to afford 1.395 g (77%) of *cis*-bromo *cis*-epoxide **25**. An analytical sample of **25** was obtained by evaporative distillation: NMR ($CDCl_3$) 1.38 and 2.01 (s and m, 18), 2.92 (m, 1, c-CHCO), 3.06 (m, 1, c-CHCO), and 3.63 ppm (m, 1, –CHBr); mass spectrum m/e 181 (38%) (P – Br).

Anal. Calcd for $C_{12}H_{21}BrO$: C, 55.18; H, 8.10. Found: C, 55.47; H, 8.38.

When a chloroform solution of *cis*-bromo *cis*-epoxide **25** was kept with 47% hydrobromic acid for 4 days there was obtained a 93% yield of an oil whose NMR spectrum was identical with that of *cis,trans*-2,12-dibromocyclododecanol (**22**).

***cis*-3-Bromo-*trans*-1,2-epoxycyclododecane (23).** A solution of 2.15 g (6.29 mmol) of *cis,cis*-2,12-dibromocyclododecanol (**20**) and 4.90 g (0.05 mol) of potassium acetate in 100 mL of acetone was kept at ambient temperature for 72 h. Workup afforded 1.12 g of an oil. The analytical sample of bromo epoxide **23** was obtained by evaporative distillation [40 °C (0.05 mm)]: NMR ($CDCl_3$) 1.4 and 2.10 (s and m, 18), 2.72 (t, 1, J = 2 Hz, c-CHCO), 3.10 (d of t, 1, J = 2, 10 Hz, c-CHCO), and 4.64 ppm (m, 1, –CHBr); mass spectrum m/e 181 (48%) (P – Br).

Anal. Calcd for $C_{12}H_{21}BrO$: C, 55.18; H, 8.10. Found: C, 55.00; H, 8.03.

When a chloroform solution of 0.375 g of *cis*-bromo *trans*-epoxide **23** was stirred with 20 mL of 47% hydrobromic acid for 24 h at ambient temperature there was obtained 0.297 g of oil whose NMR spectrum indicated the presence of 70% of *cis,cis*-2,12-dibromocyclododecanol (**20**) and 30% of an unidentified olefinic material.

***trans*-3-Bromo-*cis*-1,2-epoxycyclododecane (24).** To a solution of 0.726 g (2.12 mmol) of *trans,trans*-2,12-dibromocyclododecanol (**21**) in 50 mL of methanol was added 1.0 g (7.24 mmol) of potassium carbonate in 10 mL of methanol and 1 mL of water. The mixture was stirred overnight at ambient temperature and worked up to give an oil which solidified on standing. Recrystallization from pentane at −78 °C gave 0.371 g of pure bromo epoxide **24**: mp 47–49 °C; NMR ($CDCl_3$) 1.4 and 2.05 (s and m, 18), 3.07 and 3.21 (m, 2, c-CHCO), and 3.92 ppm (m, 1, –CHBr); mass spectrum m/e 181 (31%) (P – Br).

Anal. Calcd for $C_{12}H_{21}BrO$: C, 55.18; H, 8.10. Found: C, 55.09; H, 8.05.

A chloroform solution containing 0.5 g of *trans*-bromo *cis*-epoxide **24** was stirred with 15 mL of 47% hydrobromic to give 0.4 g (61%) of an oil whose NMR spectrum was identical with that of *trans,trans*-2,12-dibromocyclododecanol (**21**).

Lithium Aluminum Hydride Reduction of Dibromohydrins and Bromo Epoxides. A. *cis,cis*-2,12-Dibromocyclododecanol (20). A mixture of 0.384 g (1.12 mmol) of **20** and 0.0906 g (2.38 mmol) of lithium aluminum hydride in 15 mL of ether was refluxed for 20 h. Water was added slowly until the precipitate coagulated. The ether was decanted, dried ($MgSO_4$), and evaporated to leave an oil which was chromatographed on silica gel. Elution with 10% ether–pentane afforded unreacted **20** and 0.0862 g (39%) of solid whose melting point and NMR were identical with that of *cis*-2-bromocyclododecanol (**26**).

B. *trans,trans*-2,12-Dibromocyclododecanol (21). Heating a mixture of 0.85 g (2.48 mmol) of **21** with 0.19 g (5.02 mmol) of lithium aluminum hydride in 15 mL of ether as described above gave, after chromatography on silica gel using 10% ether–pentane as an eluant, dibromohydrin **21**, cyclododecanol, *trans*-bromo *cis*-epoxide **24**, and 0.047 g (7%) of *trans*-2-bromocyclododecanol (**29**).

C. *cis*-3-Bromo-*trans*-1,2-epoxycyclododecane (23). To a solution of 3.72 g (14.21 mmol) of epoxide **23** in 100 mL of ether was added 1.33 g (34.6 mmol) of lithium aluminum hydride and the mixture was stirred at ambient temperature for 24 h and then refluxed for 12 h. The mixture was poured into water, the layers were separated, and the aqueous phase was extracted with ether. The ether was dried ($MgSO_4$) and evaporated to leave 2.09 g of oil. Chromatography of 0.314 g of this oil on silica gel using 13% ether–pentane as eluant gave 0.033 g of epoxide **23**, 0.078 g (30%) of *cis*-2-bromocyclododecanol (**26**), and 0.137 g of a mixture of cyclododecanol and 2-cyclododecenol.

D. *trans*-3-Bromo-*cis*-1,2-epoxycyclododecane (24). A solution of 0.498 g (1.9 mmol) of *trans*-bromo *cis*-epoxide **24** in 18 mL of anhydrous THF was mixed with 9.33 mL of 0.3 M (2.8 mmol) lithium aluminum hydride in THF and the solution was kept at ambient temperature for 24 h. The solution was poured into water and extracted with ether. The ether was dried and evaporated to give 0.381 g (76%) of solid whose NMR was identical with that of *trans*-2-bromocyclododecanol (*29*).

E. *cis*-3-Bromo-*cis*-1,2-epoxycyclododecane (25). Treatment of 0.61 g (2.34 mmol) of epoxide **25** with 10.5 mL of 0.27 M (2.79 mmol) lithium aluminum hydride in THF as described above afforded a mixture whose NMR spectrum indicated the presence of epoxide **25**, 2-cyclododecenol, and *cis*-2-bromocyclododecanol (**26**) (~10%).

***cis*-2-Bromocyclododecanol (26).** Epoxidation of pure *trans*-cyclododecene[22] with *m*-chloroperbenzoic acid gave *trans*-cyclododecene oxide (**27**): NMR ($CDCl_3$) 1.1–2.4 (m, 20), 2.61 (m, 1, c-CHCO), and 2.76 ppm (m, 1, c-CHCO). Treatment of 2.63 g of *trans*-cyclododecene oxide (**27**) in chloroform with 3.0 mL of 47% hydrobromic acid afforded 3.27 g of *cis*-2-bromocyclododecanol (**26**): mp 62–63 °C (lit.[23] mp 64–65 °C); NMR ($CDCl_3$) 1.3–2.3 (m, 21, $-CH_2-$ and –OH), 3.88 (m, 1, –CHO–) and 4.35 ppm (m, 1, –CHBr).

cis-2-Bromocyclododecyl acetate (**26a**) was prepared in 90% yield by acetylation of **26** with acetyl chloride and magnesium powder and showed: IR 5.73 and 8.10 μm; NMR ($CDCl_3$) 1.35 and 2.0 (s and m, 20), 2.08 (s, 3, CH_3CO_2–), 4.26 (m, 1, –CHBr), and 5.18 ppm (m, 1, –CHOAc).

***trans*-2-Bromocyclododecanol (29).** Epoxidation of pure *cis*-cyclododecene[21] afforded *cis*-cyclododecene oxide (**30**): NMR 1.2–2.0 (m, 20), 2.78 (m, 1, c-CHCO) and 2.92 ppm (m, 1, c-CHCO). A solution of 1.60 g of epoxide **30** in chloroform was stirred overnight at ambient temperature with 1.5 mL of 47% hydrobromic acid to give 2.02 g of *trans*-2-bromocyclododecanol (**29**): mp 66–67 °C; NMR ($CDCl_3$) 1.3–2.1 (m, 20), 2.2 (s, 1, –OH), 3.78 (m, 1, c-CHCO), and 4.32 ppm (m, 1, –CHBr).

trans-2-Bromocyclododecyl acetate was obtained in 81% yield by acetylation of **29** with acetyl chloride in the presence of magnesium powder and showed: IR 5.72 and 8.1 μm; NMR 1.35 and 1.95 (s and m, 20), 2.06 (s, 3, CH_3CO_2–), 4.25 (m, 1, –CHBr), and 5.20 ppm (m, 1, –CHOAc).

Registry No.—**1**, 16080-75-4; **2**, 64714-59-6; **2a**, 64714-60-9; **3**, 56391-36-7; **3a**, 64714-61-0; **4**, 56421-06-8; **5**, 56421-05-7; **6**, 56391-35-6; **6** acetate, 64714-62-1; **7**, 16080-74-3; **10**, 7422-06-2; **11**, 64714-63-2; **12**, 64714-64-3; **12** acetate, 64714-65-4; **13**, 64714-66-5; **14**, 64714-67-6; **14** acetate, 64714-68-7; **15**, 64753-29-3; **16**, 64714-69-8; **16** acetate.

64714-70-1; **17**, 16110-80-8; **18**, 19914-84-2; **19**, 19914-85-3; **20**, 64753-30-6; **20a**, 64753-31-7; **21**, 64753-32-8; **21a**, 64753-33-9; **22**, 64714-55-2; **22a**, 64714-56-3; **23**, 64714-57-4; **24**, 64753-27-1; **25**, 64753-28-2; **26**, 61153-78-4; **26a**, 61177-56-8; **29**, 61247-14-1; **32** acetate, 61153-80-8; **30**, 1502-29-0; **31**, 64714-58-5; acetyl chloride, 75-36-5; 3-bromocyclohexene, 1521-51-3.

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Reaction of Lithium *N,N*-Dialkylamide Enolates with Trialkylchlorosilanes

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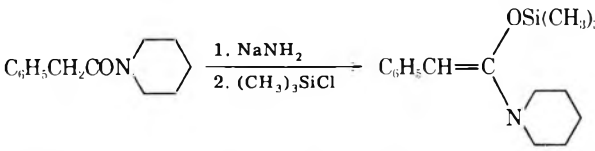
Lithium *N,N*-dialkylamide enolates were reacted in THF solution with trialkylchlorosilanes to give both C-silylated and O-silylated products. Acetamide enolates give predominantly C-silylation, while more highly substituted amide enolates give predominantly O-silylation with trimethylchlorosilane. *tert*-Butyldimethylchlorosilane gives increased amounts of O-silylation. Both C-silylated and O-silylated products hydrolyze with aqueous acid to the starting amide. O-Silylated compounds isomerize to C-silylated products on heating.

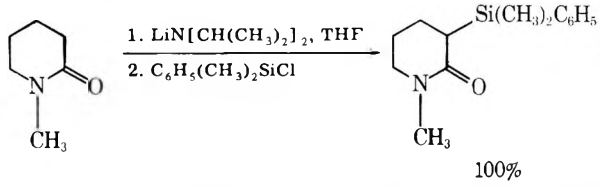
The reactions of ketone and ester enolates with trialkylhalosilanes have been studied extensively. Ketone enolates silylate exclusively at oxygen to form trialkylsilyl enol ethers.[1] Ester enolates, on the other hand, silylate at either oxygen (O-silylation) or at carbon (C-silylation) depending on the structure of the ester.[2]

In contrast, only fragmentary reports on the reaction of amide enolates with silylating reagents have appeared. Klebe reported that the sodium enolate of 1-phenylacetylpiperidide reacts with trimethylchlorosilane to give the O-silylated product, α-(1-piperidino)-β-phenyl-*O*-trimethylsilylvinyl ether, in unspecified yield (eq 1).[3] On the other hand, Trost



(1)

found that the lithium enolate of 1-methyl-2-piperidone reacts with dimethylphenylchlorosilane to give exclusively C-silylation (eq 2).[4] Most recently, Hudrlik reported that the lithium enolate of *N,N*-dimethylacetamide gave a 78% yield of the C-silylation product (eq 3), while the enolate of *N*-acetylaziridine gave a 33% yield of the O-silylation product (eq 4).[5]



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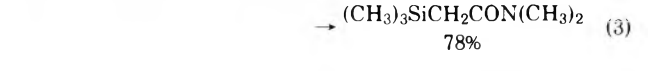

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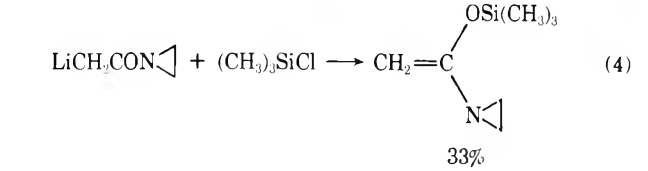

(4)

We recently reported that lithium *N,N*-dialkylamide enolates have appreciably greater stability than lithium ester enolates.[6] Considering the growing synthetic importance of the silyl derivatives of ester enolates,[7] we have undertaken a study of the reaction of *N,N*-dialkylamide enolates with trialkylhalosilanes. We report here the results of that study, together with information on the hydrolytic and thermal behavior of the products.

Results and Discussion

Silylation of Lithium Amide Enolates. Solutions of lithio *N,N*-dialkylamides were prepared by addition of the appropriate amide to tetrahydrofuran (THF) solutions of lithium diisopropylamide at 0 °C (eq 5).[6] The solutions were treated with a slight excess of silylating reagent (either trimethylchlorosilane or *tert*-butyldimethylchlorosilane) and then allowed to stir at room temperature for 30 min. The resultant

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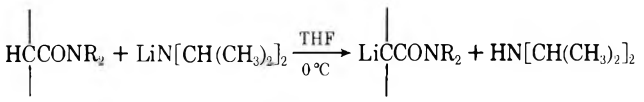

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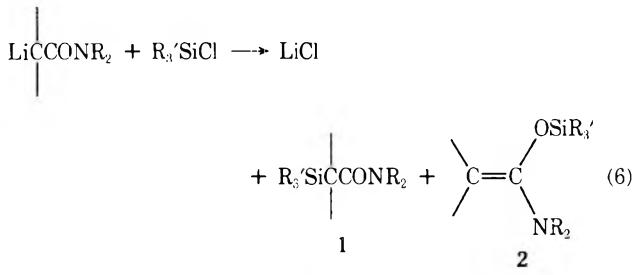
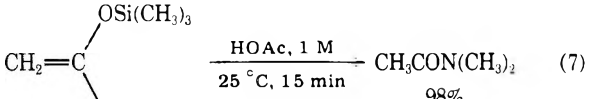
mixtures of C-silylated (**1**) and O-silylated (**2**) products (eq 6) were analyzed by GLC with the results shown in Table I.



(6)

The enolate of *N,N*-dimethylacetamide is silylated by trimethylchlorosilane almost exclusively at carbon (entry 1, Table I). Alkyl substitution at the α carbon, however, strongly favors O-silylation, presumably for steric reasons (entries 2, 3, and 6). On the other hand, substitution of bulkier groups at the nitrogen of the amide leads to slightly greater amounts of C-silylated products (entry 1 vs. entry 4 and entry 2 vs. entry 5). These results are similar to those reported for the effect of alkyl substitution on the reaction of lithium ester enolates with silylating reagents.[2b] Finally, the bulkier silylating reagent, *tert*-butyldimethylchlorosilane, tends to give increased amounts of O-silylated products (entry 7 vs. entry 1 and entry 9 vs. entry 2), especially in the presence of hexamethylphosphoric triamide (entry 8).

The identity of silylation products was based primarily on the observed ^{1}H NMR coupling patterns; however, the chemical shifts of α protons are also diagnostic. Thus, the chemical shift of α protons for **1** is similar to that of the starting amides (δ 2.0–2.5), while the chemical shift of vinyl protons for the corresponding **2** is always at lower field (δ 2.7–3.5). In addition, the O-silylated products were more readily hydrolyzed by dilute acid. For example, the *O*-trimethylsilyl derivative of *N,N*-dimethylacetamide (**3**) is hydrolyzed quantitatively by stirring a THF solution with 1 M acetic acid at room temperature (eq 7). Under similar conditions, the *C*-trimethylsilyl derivative **4** is stable to 2 M acetic acid but is hydrolyzed rapidly with 1 M hydrochloric acid



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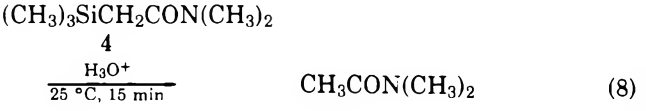
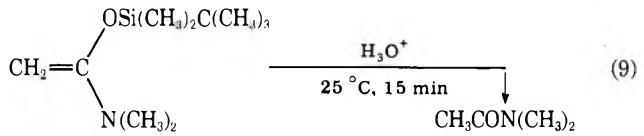


(8)

2 M HOAc, trace (99% recovered **4**)
1 M HCl, 83% (5 min); 100% (15 min)

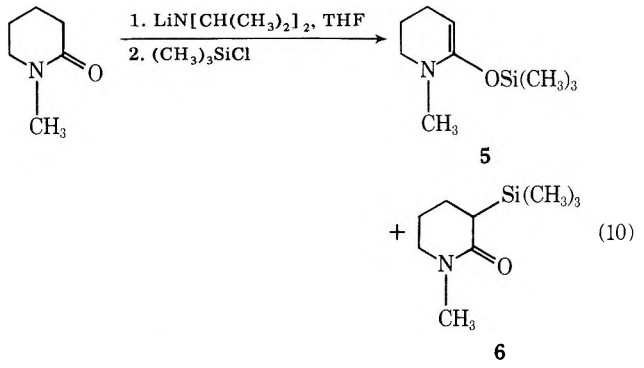
As expected, the *tert*-butyldimethylsilyl derivatives are more resistant to hydrolysis than the corresponding trimethylsilyl derivatives (eq 9), and this fact may be of use in synthetic applications. The rapid hydrolysis of the O-silylated amides is similar to the behavior reported for the O-silylated derivatives of ester enolates.[2b] However, the C-silylated derivatives of ester enolates appear to be more stable to acid-catalyzed hydrolysis. For example, ethyl 2-trimethylsilylacetate is unchanged after stirring a THF solution with 2 M hydrochloric acid for 15 min at 25 °C.[2b]



(9)

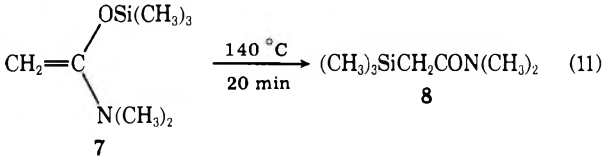
1 M HOAc, trace
1 M HCl, 100% (5 min)

Isomerization of O-Silylated and C-Silylated Products. The product ratios shown in Table I did not change when reaction mixtures were allowed to stir for up to 12 h at room temperature prior to quenching. With one exception, there was no evidence for isomerization on GLC, as indicated by close agreement of product ratios determined by both GLC and by ^{1}H NMR. Again, with one exception, the major component of each reaction could be isolated by vacuum distillation, and samples so obtained remained pure on storage for periods of several months. The exceptional compound was the O-silylated derivative of *N*-methylpiperidone (**5**). GLC analyses of reaction mixtures containing **5** showed up to 70% of the C-silylated derivative **6**, while ^{1}H NMR analysis indicated only 10% of **6** (eq 10). Furthermore, vacuum distillation



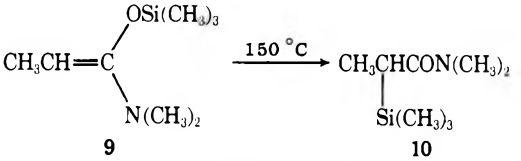
(10)

of the reaction mixtures gave only low yields of **5** (20–30%), together with 40–50% yields of **6**. Although samples of **5** obtained in this way were stable on storage at room temperature, as judged by ^{1}H NMR analysis, injection onto the GLC again showed **6** as the major component. Consequently, it appears that **5** thermally isomerizes to the more stable **6**. A similar isomerization was previously observed by Lutsenko[8] who reported that the *O*-silyl derivative of *N,N*-dimethylacetamide (**7**) is quantitatively isomerized to the *C*-silyl derivative **8** in 20 min at 140 °C (eq 11).



(11)

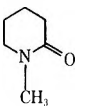
We examined the isomerization of the *O*-silyl derivative of *N,N*-dimethylpropanoamide (**9**) to the C-silylated derivative **10**. A pure sample of **9** was heated under an argon atmosphere to 150 °C, and samples were removed periodically and analyzed by GLC and ^{1}H NMR for **9** and **10**. Heating for periods



0 min, 100% **9**, 0% **10**
1 h, 68% **9**, 32% **10**
8 h, 50% **9**, 50% **10**
48 h, 18% **9**, 82% **10**

longer than 48 h gave a slightly greater ratio of **10** to **9** but the total recovery decreased and several higher boiling compo-

Table I. Reaction of Lithio *N,N*-Dialkylacetamides with Silyl Halides



Entry	Amide	Silyl halide[a]	Yields, %[b] *C*-Silyl	*O*-Silyl
1	$CH_3CON(CH_3)_2$	TMCS	93	7
2	$CH_3CH_2CON(CH_3)_2$	TMCS	10	90
3	$CH_3CH_2CH_2CON(CH_3)_2$	TMCS	<1	99
4	$CH_3CON(CH_2CH_3)_2$	TMCS	95	5
5	$CH_3CH_2CON[CH(CH_3)_2]_2$	TMCS	40	60
6		TMCS	10	90
7	$CH_3CON(CH_3)_2$	TBCS	65	35
8	$CH_3CON(CH_3)_2$	TBCS, HMPA[c]	35	75
9	$CH_3CH_2CON(CH_3)_2$	TBCS	<1	99

[a] TMCS is trimethylchlorosilane; TBCS is *tert*-butyldimethylchlorosilane. [b] Yields are relative yields obtained by GLC; absolute yields were in the range 90–100%. [c] Reaction run in the presence of hexamethylphosphoric triamide.

Scheme I

$$(CH_3)_3SiCH_2CON(CH_3)_2 \rightarrow (CH_3)_3SiN(CH_3)_2 + CH_2{=}C{=}O$$

$$CH_2C{=}O + 7 \text{ or } 8 \rightarrow 11$$

nents appeared. Although these components were not identified, we did observe that heating solutions of 4 to 150 °C for 60 min gave a single high-boiling product, identified as *N,N*-dimethyl-3-trimethylsiloxy-3-propenoamide (11).

$$\underset{4}{(CH_3)_3SiCH_2CON(CH_3)_2} \xrightarrow[1\text{ h}]{150\ ^\circ C} \underset{11}{CH_2{=}C(OSi(CH_3)_3)CH_2CON(CH_3)_2} \quad (11)$$

11 was previously observed as a product of the reaction of ketene with the *O*-silyl derivative of *N,N*-dimethylacetamide 7.[8] A likely pathway for the formation of 11 is thus as shown in Scheme I.[9]

It appears likely that *C*-silyl derivatives of amides are generally more stable than the *O*-silyl derivatives. Presumably, this is a result of a greater resonance interaction of the nitrogen atom with the amide carbonyl in the *C*-silyl derivative. In accord with this, it is noted that the *C*-silyl derivatives show separate ^1H NMR signals for the two alkyl groups attached to nitrogen, indicative of restricted rotation around the N–CO bond while the *O*-silyl derivatives invariably show identical chemical shifts for the alkyl groups attached to nitrogen.

Experimental Section

^1H NMR spectra were recorded on a Varian T-60 with Me_4Si as the internal standard. Infrared spectra were recorded in CCl_4 solution using a Perkin-Elmer 237B grating spectrometer. GLC analyses were obtained with a Varian 920 using 6 ft × 0.25 in. stainless steel columns packed with 3% Carbowax 20M on non-acid-washed Chromosorb G support. The same column was used for preparative GLC. *n*-Butyllithium (Aldrich) was titrated before use by the procedure of Watson and Eastham.[10] Diisopropylamine was distilled from CaH_2 and stored under argon. THF was distilled from the sodium ketyl of benzophenone just prior to use.

Silylation of *N,N*-Dialkylamides with Trimethylchlorosilane. Procedures for GLC Analysis. The following procedure, illustrated for *N,N*-dimethylacetamide, is representative of procedures used to obtain the results in Table I. A 50-mL round-bottomed flask equipped with a magnetic stirring bar, septum inlet, and mercury bubbler was flushed with argon and charged with 10 mL of pentane and 6.30 mL (10 mmol) of *n*-butyllithium in hexane. The flask was immersed in an ice–water bath and 1.4 mL (10 mmol) of diisopropylamine was injected. The cooling bath was removed and the reaction mixture was stirred for 5 min at room temperature. Volatile material was removed under vacuum and the white residue of lithium diisopropylamide was dissolved in 20 mL of THF. The flask was then immersed in an ice–water bath and 0.95 mL (10 mmol) of *N,N*-dimethylacetamide was added dropwise. After 15 min, the resultant clear solution of lithio *N,N*-dimethylacetamide was treated with 1.40 mL (11 mmol) of trimethylchlorosilane, added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 20 min. Pentane (20 mL) was then added to precipitate LiCl, and the filtered solution was analyzed directly by GLC using internal standard to establish the presence of 8.9 mmol (89%) of *N,N*-dimethyltrimethylsilylacetamide (4) and 0.67 mmol (6.7%) of 1-trimethylsiloxy-1-dimethylaminoethene (3). A similar procedure was used with other amides to obtain the results presented in Table I.

Silylation of *N,N*-Dialkylamides with *tert*-Butyldimethylchlorosilane. Procedure for GLC Analysis. A procedure identical with that described above was used except that 1.65 g (11 mmol) of *tert*-butyldimethylchlorosilane[11] was substituted for the trimethylchlorosilane, and the reaction mixtures were stirred at room temperature for 10 h prior to addition of pentane and GLC analysis. Reactions using HMPA as solvent additive (1.7 mL, 10 mmol, added just prior to silyl halide) were appreciably faster but were analyzed after 2 h at room temperature.

Silylation of *N,N*-Dialkylamides. Preparative Scale. Reactions were run as described above except that a 50-mmol scale of *N,N*-dialkylamide was used. Minor components comprising less than 10% of the product yield were generally isolated by preparative GLC. C-Silylated products were isolated by addition of 10 mL of 1 M acetic acid (a minimal amount is necessary because many of the low molecular weight products are extremely soluble in water) to the reaction mixture. The separated organic layer was dried over anhydrous K_2CO_3 and subjected to vacuum distillation. O-Silylated products, because of their ease of hydrolysis, were generally obtained by direct vacuum distillation of unquenched reaction mixtures. Using this procedure, the following compounds were obtained (all new products gave satisfactory C and H elemental analysis).

***N,N*-Dimethyl-2-trimethylsilylacetamide:** isolated yield, 80%; bp (0.2 Torr) 47–49 °C; ^1H NMR (CCl_4, internal Me_4Si) δ 2.87 (s, 3 H), 2.73 (s, 3 H), 1.30 (s, 2 H), 0.07 (s, 9 H).

1-Trimethylsiloxy-1-dimethylaminoethene: isolated by preparative GLC; ^1H NMR (CCl_4, internal Me_4Si) δ 2.89 (d, 1 H, J = 2 Hz), 2.86 (d, 1 H, J = 2 Hz), 2.47 (s, 6 H), 0.15 (s, 9 H).

1-Trimethylsiloxy-1-dimethylaminopropene: isolated yield, 82%; bp (0.2 Torr) 55–58 °C; ^1H NMR (CCl_4, internal Me_4Si) δ 3.5 (q, 1 H, J = 6 Hz), 2.4 (s, 6 H), 1.5 (d, 3 H, J = 6 Hz), 0.25 (s, 9 H).

***N,N*-Dimethyl-2-trimethylsilylpropanoamide:** isolated by preparative GLC; ^1H NMR (CCl_4, internal Me_4Si) δ 3.1 (s, 3 H), 2.9 (s, 3 H), 2.4 (q, 1 H, J = 6 Hz), 1.6 (d, 3 H, J = 6 Hz), 0.10 (s, 9 H).

1-Trimethylsiloxy-1-dimethylamino-1-butene: isolated yield, 85%; bp (0.1 Torr) 50–52 °C; ^1H NMR (CCl_4, internal Me_4Si) δ 3.57 (t, 1 H), 2.5 (s, 6 H), 1.42 (m, 2 H), 1.01 (t, 3 H), 0.27 (s, 9 H).

***N,N*-Diethyl-2-trimethylsilylpropanoamide:** isolated yield, 80%; bp (0.1 Torr) 50–52 °C; ^1H NMR (CCl_4, internal Me_4Si) δ 3.20 (q, 4 H), 1.8 (s, 2 H), 1.2 (m, 6 H), 0.05 (s, 9 H).

***N,N*-Diisopropyl-2-trimethylsilylpropanoamide:** isolated yield, 34%; bp (0.05 Torr) 60–61 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 3.4 (m, 2 H), 2.4 (q, 1 H, J = 5 Hz), 1.6 (d, 3 H, J = 5 Hz), 1.4 (m, 12 H), 0.10 (s, 9 H).

1-Trimethylsiloxy-1-diisopropylaminopropene: isolated by preparative GLC; ^{1}H NMR (CCl_4, internal Me_4Si) δ 3.4 (q, 1 H, J = 6 Hz), 2.6 (m, 2 H), 1.5 (d, 3 H), 1.4 (m, 12 H), 0.23 (s, 9 H).

O-Silylated derivative of 1-methyl-2-piperidine (5): isolated yield, 25%; bp (3 Torr) 80–85 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 3.9 (t, 1 H, J = 4 Hz), 3.0 (m, 2 H), 2.7 (s, 3 H), 2.0 (m, 4 H), 0.14 (s, 9 H).

C-Silylated derivative of 1-methyl-2-piperidone (6): isolated yield, 40%; bp (4 Torr) 98–100 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 3.4 (m, 2 H), 3.1 (s, 3 H), 2.5 (m, 1 H), 2.0 (m, 4 H), 0.08 (s, 9 H).

1-*tert*-Butyldimethylsiloxy-1-dimethylaminoethene: isolated by preparative GLC; ^{1}H NMR (CCl_4, internal Me_4Si) δ 2.77 (m, 2 H), 2.43 (s, 6 H), 0.87 (s, 9 H), 0.13 (s, 6 H); IR (CCl_4) 1640 cm^{-1} (C=C).

***N,N*-Dimethyl-2-*tert*-butyldimethylsilylacetamide:** isolated yield (THF solvent), 60%; bp (0.6 Torr) 88–90 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 2.93 (s, 3 H), 2.83 (s, 3 H), 1.83 (s, 2 H), 0.93 (s, 9 H), 0.07 (s, 6 H); IR (CCl_4) 1630 cm^{-1} (C=O).

1-*tert*-Butyldimethylsiloxy-1-dimethylaminopropene: isolated yield, 90%; bp (0.6 Torr) 58 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 3.50 (q, 1 H), 2.37 (s, 6 H), 1.43 (d, 3 H), 0.97 (s, 9 H), 0.13 (s, 6 H); IR (CCl_4) 1665 cm^{-1} (C=C).

Hydrolysis of Silylated Derivatives of Amides. *N,N*-Dimethyltrimethylsilylacetamide (**4**), 10 mmol, was dissolved in 10 mL of THF in a round-bottom flask under a nitrogen atmosphere. Acetic acid (5 mL, 2 M) was injected and the solution was stirred for 15 min in a 25 °C water bath. At the end of this time, the solution was saturated with anhydrous K_2CO_3 and analyzed by GLC. The recovery of **4** was 99% (9.9 mmol). A similar experiment using 5 mL of 2 M hydrochloric acid in place of acetic acid gave a 17% yield of **4** (1.7 mmol), together with a 83% yield of *N,N*-dimethylacetamide (8.3 mmol) after 5 min of stirring and a 100% yield (10 mmol) of *N,N*-dimethylacetamide after 15 min. Similar procedures were used with other silylated derivatives.

Thermolysis of 4. A 50-mL round-bottom flask equipped with septum inlet and reflux condenser was flushed with nitrogen and 5.4 mL (15 mmol) of **4** was injected. The compound was heated to 160 °C for 1 h. At the end of this time, GLC analysis showed traces of **4** (<1 mmol), together with a component of longer retention time. Vacuum distillation gave 1.0 g (5 mmol) of **11**: bp (0.1 Torr) 60–65 °C; ^{1}H NMR spectrum (CCl_4, internal Me_4Si) δ 4.1 (m, 2 H), 3.0 (s, 2 H), 2.9 (s, 3 H), 2.8 (s, 3 H), 0.21 (s, 9 H).

Acknowledgment. We thank the National Science Foundation for partial support of this work.

Registry No.—**3**, 23138-90-1; **4**, 23184-28-3; **5**, 64728-08-1; **6**, 64728-09-2; 1-trimethylsiloxy-1-dimethylaminopropene, 64728-10-5; *N,N*-dimethyl-2-trimethylsilylpropanoamide, 64728-11-6; 1-trimethylsilyloxy-1-dimethylamino-1-butene, 64728-12-7; *N,N*-diethyl-2-trimethylsilylpropanoamide, 64728-13-8; *N,N*-diisopropyl-2-trimethylsilylpropanoamide, 64728-14-9; 1-trimethylsiloxy-1-diisopropylaminopropene, 64728-15-0; 1-*tert*-butyldimethylsiloxy-1-dimethylaminoethene, 64728-16-1; *N,N*-dimethyl-2-*tert*-butyldimethylsilylacetamide, 64728-17-2; 1-*tert*-butyldimethylsiloxy-1-dimethylaminopropene, 64728-18-3; *N,N*-dimethylacetamide, 127-19-5; lithio *N,N*-dimethylacetamide, 55259-70-6; *N,N*-dimethylpropanoamide, 758-96-3; lithio *N,N*-dimethylpropanoamide, 58079-54-2; *N,N*-dimethylbutyramide, 760-79-2; lithio *N,N*-dimethylbutyramide, 55259-71-7; *N,N*-diethylacetamide, 685-91-6; lithio *N,N*-diethylacetamide, 62702-96-9; *N,N*-diisopropylpropanoamide, 1113-75-3; lithio *N,N*-diisopropylpropanoamide, 64728-06-9; *N*-methyl-2-piperidone, 931-20-4; lithio *N*-methyl-2-piperidone, 64728-05-8; TMCS, 75-77-4; TBCS, 18162-48-6; lithium diisopropylamide, 4111-54-0.

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Mass Spectral Fragmentation of Substituted Pentaphenylcyclopentadienols

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The mass spectral decomposition pathway for a series of pentaphenylcyclopentadienols substituted in the para position of the 1- or 3- and 4-phenyl rings has been observed to consist of a continuum of two superimposed pathways with the choice of the major decomposition mode being determined by the electron-donating or -withdrawing ability of the substituents. Attempts to establish a linear-free-energy relationship for the mass spectral decomposition of the 1-para-substituted phenylcarbinols were unsuccessful, whereas similar attempts with the 3- and 4-para-substituted phenylcarbinols were successful.

The mass spectral fragmentations of tetracyclone, tetraarylquinones, and tetraphenylthiophene dioxides have been extensively studied by Bursey et al.[1-5] who has also published extensively on the use of fluorine as a "dead label" in the decomposition of pentaphenylcyclopentadienols.[1,3,5] The most interesting aspect of their work is the mass spectral production and decomposition of the parent and fluorosubstituted tetraphenyltetrahedrane radical cations from the decomposition of 1,2,3,4,5-pentaphenylcyclopentadien-2,4-ol-1 (**1**, R = H) and its *p*-fluoro derivatives.[5]

Since a large number of mono- and disubstituted pentaphenylcyclopentadienols have been prepared in our laboratories for a kinetic study of the electronic effects involved in a [1,5]-sigmatropic phenyl shift in such systems,[6-8] it became of interest to study the mass spectral fragmentations[9] of the complete family of 1-(para-substituted phenyl)-2,3,4,5-te-

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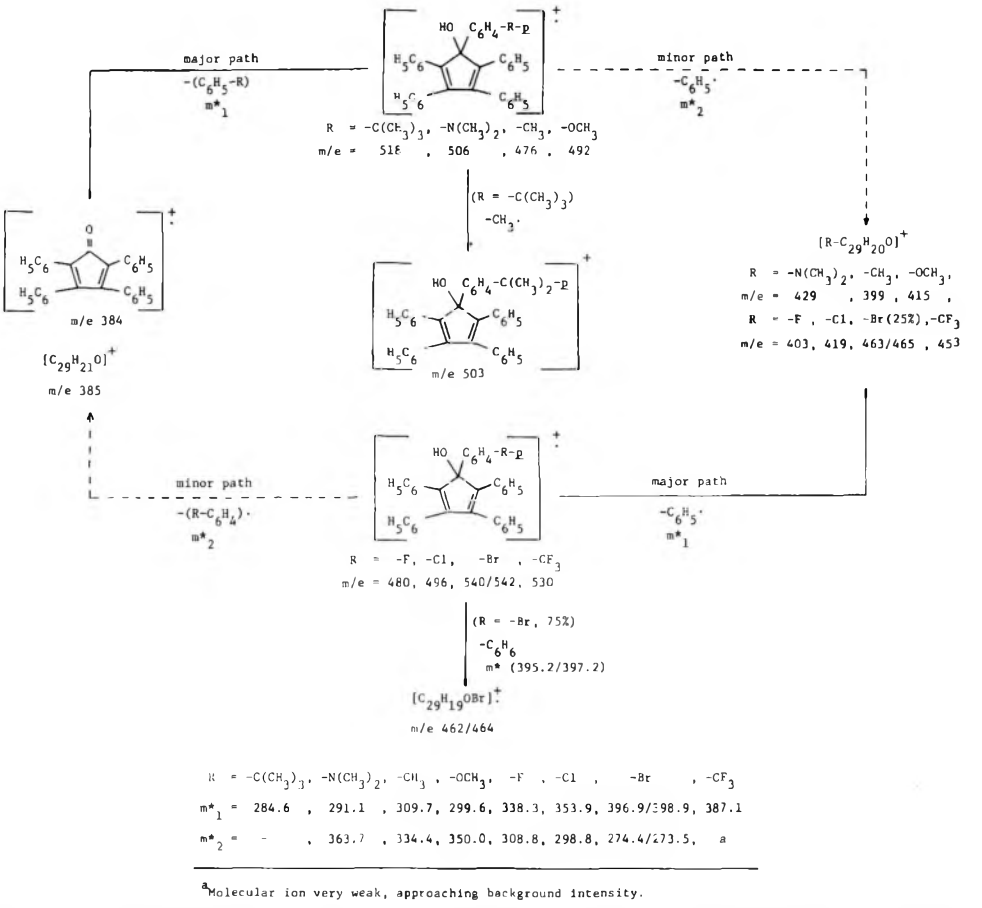
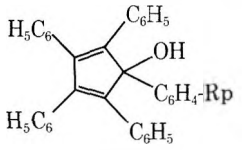
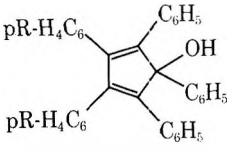


Figure 1. Mass spectral decomposition pathways of 1-(para-substituted phenyl)-2,3,4,5-tetraphenylcyclopentadien-2,4-ols-1.

traphenylcyclopentadien-2,4-ols-1 (**1**), and bis[3- and 4-(para-substituted phenyl)]-2,5-diphenylcyclopentadien-2,4-ols-1 (**2**) shown below. Of the substituted carbinols shown



1, R = $C(CH_3)_3$, $N(CH_3)_2$, OCH_3, CH_3, H, F, Cl, Br, CF_3



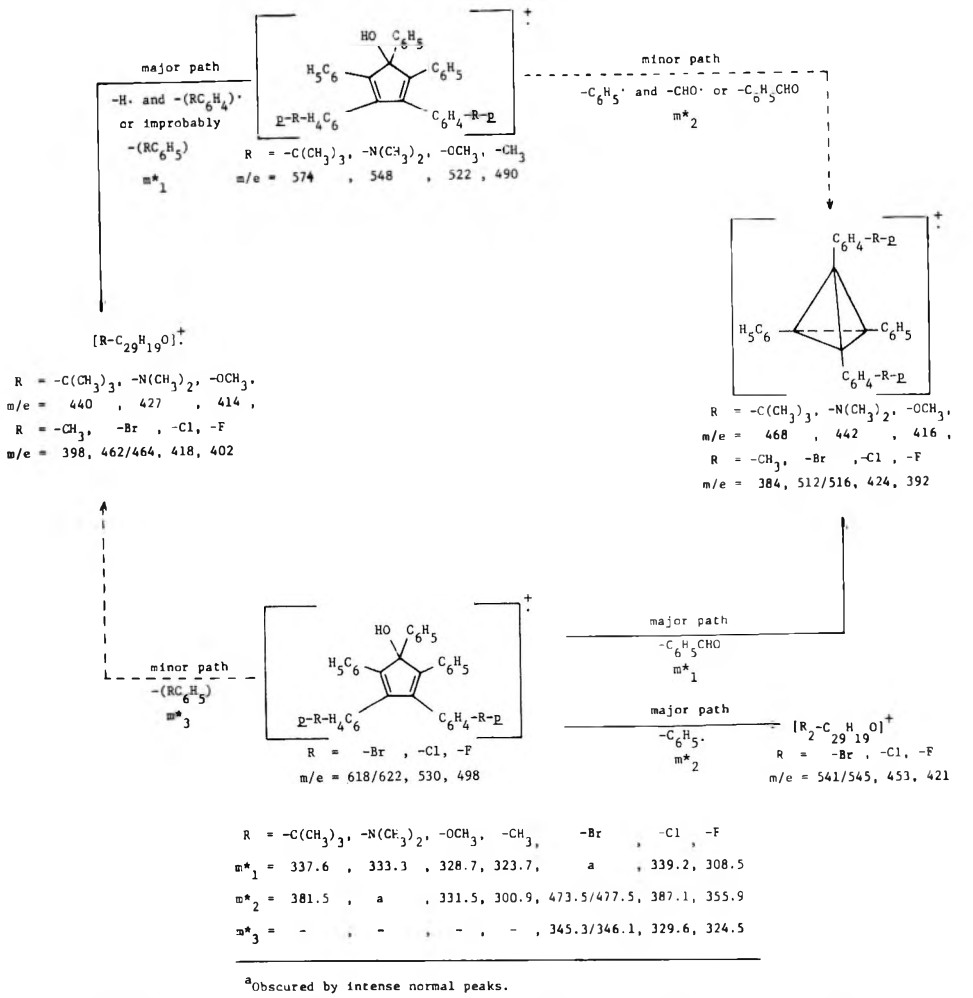
2, R = $C(CH_3)_3$, $N(CH_3)_2$, OCH_3, CH_3, F, Cl, Br

only two have been studied previously by Bursey et al.,[5] **1**, R = H and F, and in our hands both showed similar initial decomposition patterns as previously reported.[5]

The substituent effect we have observed for the initial decomposition of carbinols **1** causes a continuum of two superimposed decomposition paths. At one extreme of the continuum is the decomposition pathway observed for **1** (R = $C(CH_3)_3$). By critical investigation of the peak intensities and prominent metastable ion peaks it was established that the initial breakdown for this carbinol consisted of loss of CH_3·, or the loss of $C_6H_5C(CH_3)_3$ (metastable ion at 284.6) (Figure 1).

Investigation of carbinols **1** (R = $N(CH_3)_2$, OCH_3, or CH_3) was expected to show a similar decomposition pathway, consisting of the loss of C_6H_5R. This was indeed observed as the major decomposition pathway; however, a minor decomposition pathway consisting of the loss of C_6H_5· was also observed (Figure 1). This minor decomposition pathway is observed to become the major decomposition pathway as the substituents are changed from strongly electron donating to weakly electron donating to weakly electron withdrawing to strongly electron withdrawing. Thus, observation of the mass spectral decomposition of carbinols **1** (R = F, Cl, or CF_3) shows the major decomposition pathway to consist of loss of C_6H_5·. With the aid of metastable ions it can be seen that with these substituents the minor pathway appears to be decomposition in the "normal" manner, i.e., loss of RC_6H_4· (Figure 1). In the case of carbinol **1** (R = Br) however, although the minor decomposition pathway is exactly as described above, and approximately 25% of the parent molecular ion decomposes via the major pathway already discussed for the other electron-withdrawing substituents, the majority (~75%) of the parent ion decomposes via a different major decomposition pathway consisting of the loss of C_6H_6·. To establish if this new major decomposition pathway was unique for carbinol **1** (R = Br) alone, the *p*-iodo analogue (**1**, R = I) was investigated and, although it is not illustrated on Figure 1, this carbinol also decomposed via the two major pathways reported for carbinol **1** (R = Br) but in a 10 to 90% ratio, respectively. Possibly the differences in electronegativity between F, Cl, Br, and I can account for this difference in the ratio of the initial major decomposition pathways.

Observation of the mass spectral decomposition of carbinols **2** again shows that the substituents do play a significant role in the choice of which route in the decomposition continuum the molecule will follow. With electron-donating substituents, the major decomposition pathway is observed to be loss of one *p*-RC_6H_4 group, most likely via a stepwise loss of H· and RC_6H_4· instead of a concerted loss of *p*-RC_6H_5 (Figure 2).



[a] Obscured by intense normal peaks.

Figure 2. Mass spectral decomposition pathways of bis[3- and 4-(para-substituted phenyl)]-2,5-diphenylcyclopentadien-2,4-ols-1.

The minor decomposition pathway observed for these compounds (**2**, R = $C(CH_3)_3$, $N(CH_3)_2$, OCH_3, and CH_3) again consisted of loss of the units C_6H_5· and CHO· sequentially or loss of the entire C_6H_5CHO unit, to produce the monosubstituted tetraphenyltetrahedrane cation radical.

Also represented in Figure 2 are the major and minor decomposition pathways for the carbinols **2** (R = Br, Cl, and F) containing electron-withdrawing substituents. It can be seen that in these cases the major and minor decomposition pathways observed for carbinols **2** containing electron-donating substituents have now become reversed. It is also interesting to note that in varying degrees and with all substituents, loss of one of the monosubstituted phenyl units is observed even though this unit is structurally removed from the carbinol center in the molecule.

Although Bursey et al.[5] have described the major decomposition pattern of the *p*-fluoro-substituted carbinols they studied as a "stepwise loss of the elements aryl and CHO·" and we have observed this stepwise loss with the para-halo carbinols **2**, it does not appear that this sequence represents the major decomposition pathway for either the fluoro-, bromo-, or chloro-substituted carbinols **2** (R = F, Br, or Cl) because of the greater intensities observed for both the ions corresponding to P-C_6H_4X and the metastable ions at 324.5, 345.7, or 329.6, respectively, which are consistent with the loss of C_6H_4X from the parent ions **2** (R = F, Br, or Cl). It also appears that this loss of C_6H_4F from the parent ion of **2** (R = F) may have occurred in the *p*-fluoro-substituted carbinol studied by Bursey et al.[5] and may be the reason that they were unable to unequivocally establish T_d symmetry for the di(*p*-fluoro)-substituted tetraphenyltetrahedrane radical cation they observed.

In view of the results obtained with both classes of carbinols **1** and **2**, it appears that in every case the major fragmentation pathway involves the loss of the most electron-donating aromatic group, either as Ar·, or as Ar· and H·, or possibly as ArH. Thus, given a choice between the loss of RC_6H_4 (R = $C(CH_3)_3$, $N(CH_3)_2$, OCH_3, or CH_3) or C_6H_5·, carbinols **1** and **2** fragment by loss of RC_6H_4 (Figures 1 and 2), but given a choice between the loss of RC_6H_4 (R = F, Cl, Br, or CF_3) or C_6H_5·, the same carbinols fragment by loss of C_6H_5· preferentially (Figures 1 and 2).

In addition to the partial hydrogen and phenyl scrambling observed to occur in the respective molecular ions of all of the mono- and disubstituted carbinols **1** and **2** studied before fragmentation, it was observed that the intensity ratios of the normal peaks for these carbinols were independent of both the ionization voltage used (down to values very near the appearance potentials) and the temperature of the probe (80–240 °C). The most startling observation about the mass spectral fragmentation of these carbinols was made with the aid of high-resolution mass spectrometry[10] which shows that oxygen is lost $(M - 16)^{+}$· to the extent of 10–15% from the parent ions of all the carbinols studied.

Although attempts to establish a free-energy relationship[11–14] and a Hammett plot for the carbinols **1** proved unsuccessful using any of the common fragmentation routes in the initial portion of the decomposition of these alcohols, attempts to establish such a relationship with the carbinols **2** was successful. Thus, using the relationship shown below, a

Chart I

R	Mp (°C) and lit. ref or Anal.
H	175–176[18]
$C(CH_3)_3$	103–104; Calcd for $C_{39}H_{34}O$: C, 90.31; H, 6.61. Found: C, 90.13; H, 6.72
$N(CH_3)_2$	229–230 (lit.[19] 248–249)
OCH_3	201–202 (lit.[20,21] 203)
CH_3	192–192.5 (lit.[22] 188–189, 199–200)
F	183.5–184.5 (lit.[5] 180–182)
Cl	211–212; Calcd for $C_{35}H_{25}OCl$: C, 84.58; H, 5.07; Cl, 7.13. Found. C, 84.64; H, 5.01; Cl, 7.10
Br	217–219; Calcd for $C_{35}H_{25}OBr$: C, 77.64; H, 4.65; Br, 14.75. Found: C, 77.62; H, 4.57; Br, 14.73
CF_3	210–211; Calcd for $C_{36}H_{25}OF_3$: C, 81.49; H, 4.75; F, 10.74. Found: C, 81.40; H, 4.77; F, 10.69

Chart II

R	b	Mp (°C) and lit. ref or Anal. for carbinols 2
$C(CH_3)_3$	a	218–219; Calcd for $C_{43}H_{42}O$: C, 89.85; H, 7.36. Found: C, 89.56; H, 7.22
$N(CH_3)_2$	17, 18, 23	225–226 (lit. 270–271,[17] 252,[19] 225–226[23])
OCH_3	24, 25, 26	195–196; Calcd for $C_{37}H_{30}O_3$: C, 85.03; H, 5.79. Found: C, 84.82; H, 5.98
CH_3	24, 25, 26	207–208; Calcd for $C_{37}H_{30}O$: C, 90.58; H, 6.16. Found: C, 90.27; H, 6.32
F	1	163–164; Calcd for $C_{35}H_{24}OF_2$: C, 84.32; H, 4.85; F, 7.62. Found: C, 84.19; H, 5.12; F, 7.55
Cl	26, 27	159–160; Calcd for $C_{35}H_{24}OCl_2$: C, 79.10; H, 4.55; Cl, 13.34. Found: C, 79.08; H, 4.58; Cl, 13.35
Br	16, 24, 25	190–191 (lit.[16] 195)

[a] New compound, preparation of benzil, cyclone, and carbinol given below. [b] Reference to substituted cyclone starting material.

plot of log Z/Z_0 vs. σ_p[15] for the carbinols **2** afforded a straight-line relationship with ρ calculated to be -2.84 using a linear least-squares program (Figure 3).

$$Z = \frac{[(p\text{-}RC_6H_4)(C_6H_5)_3C_5O]^{+\cdot}}{[(p\text{-}RC_6H_4)_2(C_6H_5)_3C_5OH]^{+\cdot}}$$

The negative ρ obtained indicates that the mass spectral decomposition of these carbinols is assisted by electron donation at the reaction site, or at the 3 and 4 position of the cyclopentadiene ring. Also, as the substituent R becomes less electron donating this decomposition pathway decreases in importance. This approach holds for the carbinols **2** where R = $N(CH_3)_2$, OCH_3, Br, Cl and F but not where R = $C(CH_3)_3$ or CH_3, since with these substituents there is considerable loss of CH_3. However, if a plot of log Z/Z_0 vs. σ_p is made for carbinol **2** when R = CH_3 and where Z_0 is the parent molecular ion minus a CH_3 (m/e 475), and Z equals the parent minus $C_6H_5CH_3$, a point on the existing straight line is obtained. Application of this approach to carbinol **2** where R = $C(CH_3)_3$ and where Z_0 = [P − CH_3] and Z = [P − [$C_6H_5C(CH_3)_3$]] affords similar results.

Experimental Section

General. Mass spectra for all compounds were obtained on both an Hitachi Perkin-Elmer RMU-7 double focusing mass spectrometer and a modified Varian MAT 112 double focusing mass spectrometer connected to a SpectroSystem 101 MS Varian Mat (620/1-100) computer system equipped with a Tektronix storage oscilloscope to provide hard copies of spectra. With both instruments the carbinols were introduced into the ionization chamber maintained at 175 °C using a direct inlet probe and spectra were recorded at 75 eV, with an ionizing current of 80 μA. Low-voltage spectra on both instruments were recorded with a filment current of 2.0 and 2.4 μA. With the Hitachi Perkin-Elmer RMU-7 double focusing mass spectrometer, mass assignments were based upon high boiling perfluorokerosene as an internal standard.

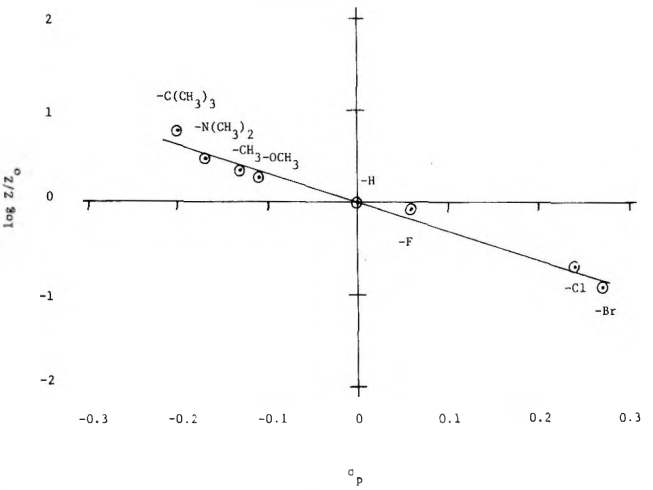


Figure 3. Hammett plot of log Z/Z_0 vs. σ_p for carbinols **2**.

Preparation of Carbinols 1. These carbinols were prepared in the normal manner[16,17] by Grignard addition of the appropriately para-substituted phenylmagnesium bromide to tetracyclone (Chart I).

Preparation of Carbinols 2. These carbinols were prepared by Grignard addition of phenylmagnesium bromide to the appropriate 3- and 4-(para-substituted phenyl)-2,5-diphenylcyclopentadien-2,4-ones-1. Listed in Chart II are the literature reference to the appropriately substituted tetracyclones as well as the melting points and analyses for the new carbinols.

4,4′-Di(*tert*-butyl)benzil. *p*-(*tert*-Butyl)bromobenzene (K & K, Labs) was converted to *p*-(*tert*-butyl)benzaldehyde according to the literature procedure.[28] Treatment of 243 g (1.5 mol) of *p*-(*tert*-butyl)benzaldehyde dissolved in 300 mL of 95% ethanol with 30 g (0.46 mol) of potassium cyanide dissolved in 150 mL of water all contained in a 1-L three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser produced a red oil after 3.5 h of refluxing. Cooling with stirring overnight afforded 74.2 g (0.23 mol, 30%) of the corresponding benzoin which was oxidized as obtained without further purification using the Weiss and Appel[29] procedure to give 64.0 g (0.20 mol, 88%) of 4,4′-di(*tert*-butyl)benzil, mp 104–104.5 °C (lit.[30] 104–104.5 °C).

3,4-Bis[*p*-(*tert*-butyl)phenyl]-2,5-diphenylcyclopentadien-2,4-one-1. This compound was prepared by Fieser's method[31] from 4,4′-di(*tert*-butyl)benzil and 1,3-diphenylpropanone in 90% yield, mp 251–252 °C. Anal. Calcd for $C_{37}H_{36}O$: C, 89.52; H, 7.29. Found: C, 89.72; H, 7.37.

3,4-Bis[*p*-(*tert*-butyl)phenyl]-1,2,5-triphenylcyclopentadien-2,4-ol-1. Into a 500 mL, three-necked, round-bottomed flask equipped with a magnetic stirrer and a reflux condenser is placed 9.9 g (0.02 mol) of the above cyclone dissolved in 100 mL of anhydrous benzene. To this solution is added dropwise an ether solution of phenylmagnesium bromide prepared from 1.96 g (0.08 g-atom) of magnesium, 13 4 g (0.08 mol) of bromobenzene, and 50 mL of anhydrous ether. After the addition is completed and the reaction subsides, the resulting mixture is refluxed for 2 h, cooled in an ice bath, and hydrolyzed with 100 mL of 10% ammonium chloride solution and the organic layer was separated, washed twice with water, and dried over anhydrous magnesium sulfate. The organic solution is filtered and concentrated to about 30 mL and 200 mL of petroleum ether (bp 30–60 °C) was added to afford the crude alcohol. Recrystallization from benzene–ethanol (95%) afforded 11.4 g (0.0198 mol, 99%) of carbinol.

Acknowledgment. The authors wish to extend their sincere appreciation to Professor Burnaby Munson and Mr. Charles W. Polley for performing the high-resolution mass spectrometry and to Professor David G. I. Kingston for his comments during the reading of this manuscript.

Registry No.—**1** (R = $C(CH_3)_3$), 64706-17-8; **1** (R = $N(CH_3)_2$), 752-09-0; **1** (R = OCH_3), 64706-18-9; **1** (R = CH_3), 64706-19-0; **1** (R

= F), 24523-58-8; 1 (R = Cl), 15946-43-7; 1 (R = Br), 19057-23-9; 1 (R = CF_3), 64706-20-3; 2 (R = $C(CH_3)_3$), 64706-21-4; 2 (R = $N(CH_3)_2$), 916-86-9; 2 (R = OCH_3), 64706-22-5; 2 (R = CH_3), 19059-95-1; 2 (R = F), 64706-23-6; 2 (R = Cl), 22926-90-5; 2 (R = Br), 56549-00-9; 2 (R = H), 2137-74-8; phenyl bromide, 108-86-1; 3,4-bis[*p*-(*tert*-butyl)-phenyl]-2,5-diphenylcyclopentadien-2,4-one-1, 64706-24-7; 3,4-bis[*p*-(dimethylamino)phenyl]-2,5-diphenylcyclopentadien-2,4-one-1, 751-71-3; 3,4-bis[*p*-(dimethoxy)phenyl]-2,5-diphenylcyclopentadien-2,4-one-1, 668-29-1; 3,4-bis[*p*-methylphenyl]2,5-diphenylcyclopentadien-2,4-one-1, 38305-61-2; 3,4-bis[*p*-fluorophenyl]-2,5-diphenylcyclopentadien-2,4-one-1, 56805-29-9; 3,4-bis[*p*-chlorophenyl]-2,5-diphenylcyclopentadien-2,4-one-1, 38268-08-5; 3,4-bis[*p*-bromophenyl]-2,5-diphenylcyclopentadien-2,4-one-1, 38268-11-0; 2,3,4,5-tetraphenylcyclopentadien-2,4-one-1, 479-33-4.

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(9) Although only the initial mass spectral fragmentations are reported and discussed in this paper, the complete fragmentation pattern for all compounds has been determined and interpreted and is available upon request.
(10) We thank Professor Burnaby Munson and Mr. Charles Polley for performing these experiments for us.
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Synthesis and Absolute Configuration of (−)-D_{2d}-Bisnoradamantan-2-one (Tricyclo[3.3.0.0^{3,7}]octan-2-one)[1]

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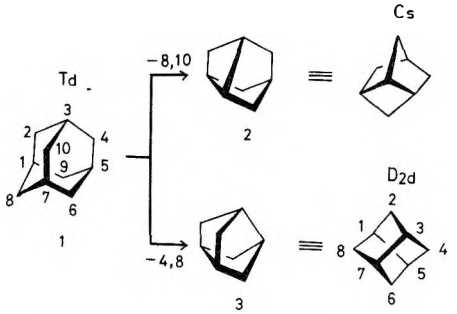
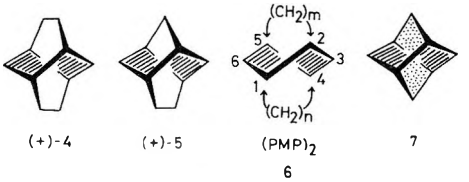
(−)-Tricyclo[3.3.0.0^{3,7}]octane-2-carboxylic acid (**23**) was converted into (−)-D_{2d}-bisnoradamantan-2-one (**9**), whose circular dichroism spectrum indicated the 1*R*,3*R*,5*R*,7*R* absolute configuration.

Although the high symmetry (T_d) inherent to the adamantane molecule (**1**) requires stereochemical equivalence among all of the six methylene groups, sets of two methylene groups can be classified into two different categories: the sets made of two methylene groups not situated on the same C_2 axis (e.g., 8–10) and the sets made of two methylene groups situated on the same C_2 axis (e.g., 4–8). Simultaneous removal of the two methylene groups (e.g., 8–10) belonging to the former category gives tricyclo[3.2.1.0^{3,6}]octane (**2**)[2] with C_s



symmetry. On the other hand, simultaneous removal of the two methylene groups (e.g., 4–8) classified in the latter category will afford tricyclo[3.3.0.0^{3,7}]octane (**3**),[3] which belongs to the D_{2d} point group and which, for convenience, shall be referred to as D_{2d}-bisnoradamantane in this paper.

In D_{2d}-bisnoradamantane (**3**), one can discern a D_2 twist-boat cyclohexane moiety which is specified by hatching. We have been interested in syntheses and chiroptical properties of high-symmetry chiral (gyrochiral[4]) cage-shaped molecules, and preparations of (+)-twistane (**4**)[5] having D_2 symmetry



and (+)-twist-brendane (**5**)[6] having C_2 symmetry, both with known absolute configurations, that have been reported from our laboratory.

In these molecules, the $(PMP)_2$ chiral twist-boat conformation of the cyclohexane ring is frozen by means of two short bridges, $(CH_2)_m$ and $(CH_2)_n$, spanning over the C-1 and C-4 as well as C-2 and C-5 carbon atoms as shown in structure **6**. D_{2d}-Bisnoradamantane corresponds to **6** with $m = n = 1$, and the molecular model (**7**) of this compound shows that the molecule consists of two enantiomeric D_2 twist-boat cyclohexane species (the hatched and the dotted ones indicated in formula **7**) fused together as shown in **7**. This molecular geometry results in two sets of homotopic methylene groups

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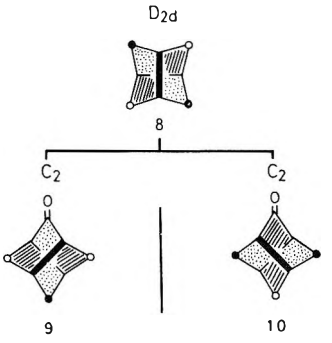
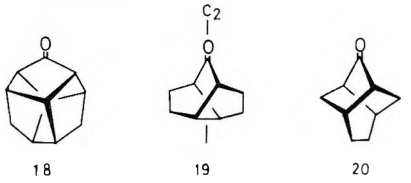
which are illustrated with the closed and the open circles in structure **8**.



Since reflection through the planes of symmetry interchanges these sets of methylene groups (○ ⇌ ●), they are in turn enantiotopic. This symmetric D_{2d}-bisnoradamantane (**8**) can be desymmetrized by converting one of the enantiotopic methylene groups into a carbonyl group, and the chiralities of resulting D_{2d}-bisnoradamantan-2-one molecules **9** and **10** are determined by the choice of the methylene group to be converted into the carbonyl group. In a preceding paper,[7] we reported preparations of optically active D_{2d}-bisnoradamantan-2-one derivatives **16** and **17** (Scheme I) with known absolute configurations from (−)-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene (**11**)[8] via the oxetanes **14** and **15**, but our efforts to convert **16** and **17** into D_{2d}-bisnoradamantan-2-one **9** with known absolute configuration have failed.

Our current research on the microbial stereo-differentiating reduction of cage-shaped ketones whose C_2 axes coincide with their carbonyl axes has indicated that *Curvularia lunata* preferentially reduces the enantiomers **18**, **19**, and **20**, all with



the carbonyl group flaked by the homotopic carbon atoms with *R* configuration,[9] and the obvious extention of this study required the preparation of D_{2d}-bisnoradamantan-2-one **9** in optical active form as well as the information about its absolute configuration.

Besides its simple beauty of symmetry, D_{2d}-bisnoradamantan-2-one (**9**) ($C_8H_{10}O$) is conspicuous for being one of the simplest gyrochiral cage-shaped molecules. We report in the present paper the first successful synthesis of optically active **9** as well as its absolute configuration.

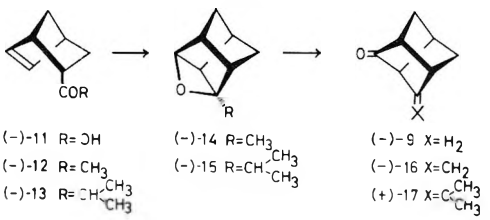
Results and Discussion

Fruitless attempts to convert (−)-**16** and (+)-**17**, both with known absolute configurations, to optically active D_{2d}-bisnoradamantan-2-one (**9**) prompted us to abandon this strategy, and our next efforts were directed toward (1) a new route to optically active **9**, (2) preparation of optically active D_{2d}-bisnoradamantan-2-one derivative **30** from an intermediate with known absolute configuration, and (3) elucidation of the absolute configuration of optically active **9** by comparing its circular dichroism (CD) spectrum with that of **30**.

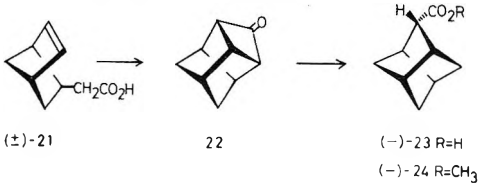
Synthesis of (−)-D_{2d}-Bisnoradamantan-2-one (9). Alkaline ring fission of the tetracyclic ketone **22**, prepared from (±)-*endo*-carboxylic acid **21** following Sauers' procedure,[3e] furnished (±)-tricyclo[3.3.0.$0^{3,7}$]octane-2-carboxylic acid (**23**), whose optical resolution was accomplished using (+)-2-(1-aminoethyl)naphthalene as the resolving agent.

Although recrystallization of the salt from acetone appeared

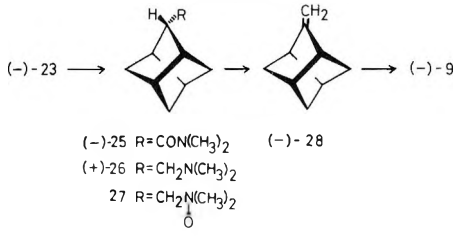
Scheme I



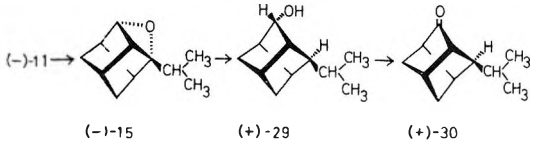
Scheme II



Scheme III



Scheme IV



to result in fairly good resolution, as evidenced by the similar optical rotations of the isolated acids, $[\alpha]_D$ −22.5° and +22.1°, an optical purity measurement with the tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(facam)$_3$][10] chiral NMR shift reagent indicated 70% optical purity for the (+)-methyl ester (**24**), $[\alpha]_D$ +14.5°, prepared from the (+)-acid (**23**), $[\alpha]_D$ +22.1°. The (−)-acid (**23**), $[\alpha]_D$ −22.5°, was converted into the (−)-dimethylamide (**25**, Scheme III), $[\alpha]_D$ −3.2°, whose $LiAlH_4$ reduction afforded the (+)-dimethylamine (**26**), $[\alpha]_D$ +5.7°. Oxidation with 30% hydrogen peroxide followed by pyrolysis[11] of the resulting amine oxide (**27**) at 160 °C yielded an oily product (59%), $[\alpha]_D$ −32.1°, whose NMR spectrum exhibited a sharp singlet of olefinic protons centered at δ 4.09, indicating C_2 symmetrical structure **28** for this olefin. Ozonization of (−)-**28** in methylene chloride at −78 °C[12] and reductive cleavage of the ozonide with zinc and acetic acid completed the synthesis of (−)-D_{2d}-bisnoradamantan-2-one (**9**): mp 103–105 °C; $[\alpha]_D$ −55.9°. Because of its extreme volatility, elemental analysis could not be performed, but the identity of (−)-**9** was established by comparison of its NMR and mass spectrum and VPC and TLC results with a racemic specimen prepared by Sauers' procedure.[3f]

Synthesis of (+)-4-Isopropyltricyclo[3.3.0.$0^{3,7}$]octan-2-one (30). Elucidation of the absolute configuration of (−)-**9** by means of CD spectral analysis required an optically active D_{2d}-bisnoradamantan-2-one derivative as a reference substance, and Scheme IV illustrates the preparation of the (+)-(4*S*)-isopropyl derivative (**30**) from (−)-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene (**11**)[8] with known absolute configuration.

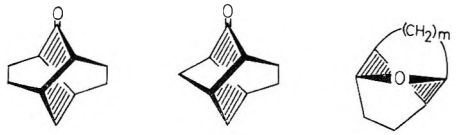
Preparation of (−)-isopropyl ketone **13** from the (−)-*endo*-carboxylic acid **11** and its subsequent Paterno-Buchi

Table I. CD Spectra of (−)-Bisnoradamantan-2-one (9) and (+)-4-Isopropylbisnoradamantan-2-one (30) (in Isooctane)

(−)-9		(+)-30	
[θ], deg cm²/dmol	λmax, nm	[θ], deg cm²/dmol	λmax, nm
−9.71 × 10³ sh	281.6	−2.48 × 10³	299.5
−1.05 × 10⁴	286.3	−2.43 × 10³ sh	304.0
−9.91 × 10³ sh	290.4		
−7.77 × 10³ sh	296.2		

photocyclization to (−)-isopropyl oxetane **15** were reported in our preceding paper.[7] Heating (−)-**15**, $[\alpha]_D$ −5.8°, with $LiAlH_4$ in *N*-methylmorpholine[3f] gave a (+)-alcohol (59%), $[\alpha]_D$ +2.8°, to which the stereochemistry (**29**) was assigned from the analogy to the methyl derivative.[13] Jones oxidation converted (+)-**29** to the requisite ketone **30**, and the configurational relations outlined in Schemes I and IV are indicative of its 1*R*,3*R*,4*S*,5*R*,7*R* absolute configuration.

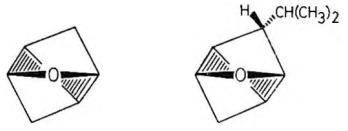
Absolute Configurations and Chiroptical Properties. Table I lists CD spectral data of (+)-(1*R*,3*R*,4*S*,5*R*,7*R*)-4-isopropyltricyclo[3.3.0.0^{3,7}]octan-2-one (**30**) and (−)-D_{2d}-bisnoradamantan-2-one (**9**), and a comparison of their Cotton effects indicates the 1*R*,3*R*,5*R*,7*R* absolute configuration for (−)-**9**. Circular dichroism spectra of various tricyclic ketones (e.g., (−)-**31**[5a] and (−)-**32**[6a]), prepared from intermediates of



(−)-31 (−)-32 33

known absolute configurations, indicate that the sign of the CD curve due to the n → π* transition around 300 nm can be predicted by applying the octant rule to the "outer ring"[14] in the projection formula **33** which holds the carbonyl group at the "point of twist."[15]

Applying this generalization to the projection formula **34**



34 35

of (−)-**9** with a negative Cotton effect (Table I), we again obtain the 1*R*,3*R*,5*R*,7*R* absolute configuration for this ketone. It appears pertinent to point out here that, although our assignment of the 4*S* configuration to (+)-isopropyl derivative **30** was made by mere analogy, this does not affect the sign of the Cotton effect, as can be seen from the projection formula **35**.

Experimental Section

Infrared spectral data were obtained with a Hitachi EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a JNM-MH-100 spectrometer. Ultraviolet spectra were recorded on a Beckman DB spectrometer. Optical rotations were measured with a JASCO-DIP-SL automatic polarimeter. Circular dichroism data were measured on a JASCO J-40 spectropolarimeter. Elemental analyses were determined on a Yanagimoto CHN-Corder type II. All melting points and boiling points are uncorrected.

(±)-Tricyclo[3.3.0.0^{3,7}]octane-2-carboxylic acid (23) was prepared as described by Sauers and Kelly,[3e] mp 99–100.5 °C (lit.[3e] mp 99–100.5 °C).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.85; H, 8.01.

Optical Resolution of Tricyclo[3.3.0.0^{3,7}]octane-2-carboxylic Acid (23). To a solution of (±)-**23** (34.9 g, 0.230 mol) in acetone (1.9 L) was added a solution of (+)-2-(1-aminoethyl)naphthalene (39.2 g, 0.230 mol) in acetone (300 mL) with stirring. The mixture was heated under reflux for 5 h, and 1 L of acetone was then distilled away. The salt solution was allowed to stand overnight at room temperature, and the deposited solid was collected by filtration (the filtrate was reserved for isolation of (+)-**23**) to give 57.2 g of dextrorotatory salt, $[\alpha]^{16}_D$ +12.4° (c 0.305, $CHCl_3$). Several fractional recrystallizations of the (+)-salt from acetone afforded 24.5 g of salt with $[\alpha]^{14}_D$ +5.3° (c 0.311, $CHCl_3$), mp 181–183 °C.

Anal. Calcd for $C_{21}H_{25}O_2N$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.69; H, 7.74; N, 4.19.

To this dextrorotatory salt (13.5 g, 0.0420 mol) was added 5% NaOH aqueous solution (160 mL), and the mixture was stirred for 3 h at room temperature. The reaction mixture was extracted with ether to remove the amine and then made acidic with HCl. The acidic solution was extracted with ether, and the extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 6.22 g of a white solid, $[\alpha]^{15}_D$ −16.2° (c 0.576, $CHCl_3$), which was recrystallized from *n*-hexane to yield 3.30 g of (−)-**23**: $[\alpha]^{15}_D$ −22.5° (c 0.800, $CHCl_3$); mp 85–86 °C (in a sealed tube).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.81; H, 7.95.

The filtrate that separated from the salt of (−)-**23** was concentrated to give a crystalline material which was recrystallized from acetone to afford 5.8 g of the dextrorotatory salt, $[\alpha]^{18}_D$ +24.8° (c 0.320, $CHCl_3$). This salt (5.50 g) was treated with 5% NaOH aqueous solution (70 mL), and the same workup described for (−)-**23** gave 2.30 g of (+)-**23**, $[\alpha]^{18}_D$ +19.1° (c 0.305, $CHCl_3$). Several recrystallizations of the (+)-carboxylic acid from *n*-hexane afforded 850 mg of (+)-**23**: $[\alpha]^{18}_D$ +22.1° (c 0.581, $CHCl_3$); mp 80–84 °C.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.81; H, 7.96.

(+)-Methyl Tricyclo[3.3.0.0^{3,7}]octane-2-carboxylate (24). To a solution of (+)-**23** (600 mg, 3.94 mmol), $[\alpha]^{18}_D$ +22.1°, in ether (20 mL) was added an excess of diazomethane in ether with ice cooling, and the mixture was stirred for 2 h at room temperature. After decomposition of excess diazomethane with acetic acid, the solution was washed successively with a saturated $NaHCO_3$ solution and water and dried over $MgSO_4$. Evaporation of the solvent gave 0.63 g of an oily product, which was distilled to yield 490 mg of (+)-**24** (75% yield): bp 83–84 °C (4 mm); $[\alpha]^{17}_D$ +14.5° (c 1.05, $CHCl_3$); IR (neat film) 1735, 1443, 1365, 1043 cm^{-1}; NMR (CCl_4) δ 1.39 (br s, 6 H), 2.42 (br s, 4 H), 2.55 (br s, 1 H), 3.55 (s, 3 H); NMR (CCl_4; Eu(facam)$_3$/(+)-**24** = 0.188 molar ratio) δ 5.92 and 6.01 (anisochronous CO_2CH_3 signals).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.34. Found: C, 71.91; H, 8.38.

(−)-*N,N*-Dimethyltricyclo[3.3.0.0^{3,7}]octane-2-carboxamide (25). To a solution of (−)-**23** (5.50 g, 0.0362 mol) in dry benzene (55 mL) was slowly added thionyl chloride (7.50 g, 0.0630 mol) with ice cooling. After stirring for 3 days at room temperature, the reaction mixture was concentrated under reduced pressure to give 7.45 g of acid chloride, which was used without further purification. A solution of the acid chloride (7.45 g) in dry benzene (35 mL) was added dropwise to a solution of dimethylamine (8.5 mL) in dry benzene (30 mL) with ice cooling. After stirring for 9 h at room temperature, the reaction mixture was poured into ice water and made acidic with HCl. The mixture was extracted with ether, and the extract was washed with saturated $NaHCO_3$ solution and water and dried over $MgSO_4$. Removal of the solvent gave 5.61 g of **25** as a white solid (87% yield): $[\alpha]^{18}_D$ −3.2° (c 0.702, $CHCl_3$); mp 82–84 °C (in a sealed tube); IR (KBr) 1625, 1419, 1398, 1169, 1155 cm^{-1}.

Anal. Calcd for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.85; H, 9.50; N, 7.78.

(+)-2-*N,N*-Dimethylaminomethyltricyclo[3.3.0.0^{3,7}]octane (26). To a suspension of $LiAlH_4$ (1.20 g, 0.0316 mol) in dry ether (40 mL) was added dropwise a solution of (−)-amide **25** (5.60 g, 0.0313 mol) in dry ether (70 mL), and the mixture was refluxed gently for 20 h. Excessive reducing agent and the reaction complex were decomposed by successive addition of 3 mL of water and a solution of NaOH (67 g) in water (170 mL) to the chilled reaction mixture. Distillation of the reaction mixture gave about 250 mL of the distillate containing the resulting amine (**26**), which was extracted with ether. The ethereal extract was washed successively with saturated $NaHCO_3$ solution and water and dried over NaOH. Evaporation of the solvent gave an oily product, which was distilled to yield 4.50 g of **26** (87% yield): bp 102–103 °C (20 mm); $[\alpha]^{18}_D$ +5.7° (c 1.38, $CHCl_3$); IR (neat film) 2980, 2870, 2850, 2830, 2795, 2705, 1460, 1295, 1046, 1027, 850 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.48. Found: C, 79.70; H, 11.74; N, 8.40.

(−)-2-Methylenetricyclo[3.3.0.0^{3,7}]octane (28). After a 30% hydrogen peroxide solution (3.1 g) was slowly added to a solution of (+)-**26** (4.40 g, 0.0267 mol) in methanol (7 mL) chilled in an ice–salt bath, the mixture was gradually warmed to room temperature with stirring. After stirring for 24 h, the mixture was chilled in an ice–salt bath. Additional 30% hydrogen peroxide (3.1 g) was added to the reaction mixture which was further stirred for 30 h at room temperature. The remaining hydrogen peroxide was destroyed by stirring with 5% Pd-on-carbon (20 mg) for 24 h; the catalyst was removed by filtration, and the filtrate was condensed to give amine oxide **27** as a waxy product. The amine oxide (**27**) was heated at 20 mm in a small distilling flask connected to a trap which was cooled in a dry ice–acetone bath. Decomposition of the amine oxide began at 160 °C and was complete after 1 h. The distillate was dissolved in 200 mL of ether, and the ethereal solution was washed successively with 10% HCl, saturated $NaHCO_3$ solution, and water and dried over $MgSO_4$. Evaporation of the solvent gave an oily product, which was distilled to yield 1.90 g of **28** (59% yield based on **26**): bp 92–93 °C (120 mm); $[\alpha]^{18}_D$ −32.1° (*c* 1.68, EtOH); NMR (CCl_4) δ 1.42 (s, 6 H), 2.38 (m, 4 H), 4.09 (s, 2 H); IR (neat film) 3060, 1683, 860 cm^{-1}; CD (*c* 1.88 × 10^{-4}, isooctane) $[\theta]$ −6.96 × 10^4 (192 nm).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.87; H, 10.11.

(−)-Tricyclo[3.3.0.0^{3,7}]octan-2-one (9). A stream of oxygen containing about 7% ozone was passed into a chilled solution (−78 °C) of (−)-**28** (520 mg, 4.33 mmol) in methylene chloride (20 mL) until an intense blue color persisted. The solution was allowed to warm to room temperature, and excess ozone was purged by passing a stream of nitrogen through the solution. The reaction mixture was poured into a mixture of zinc powder (1.2 g), acetic acid (1 mL), and water (100 mL) and stirred for 6 h at room temperature. The organic layer was separated, washed with saturated $NaHCO_3$ solution and water, and dried over $MgSO_4$. The solvent was carefully evaporated through a short distillation column to give a solid, which was chromatographed on neutral alumina (Woelm, activity II). Fractions eluted with pentane gave 174 mg of **9** (33% yield), which was further purified by sublimation at 65 °C in a nitrogen atmosphere to give a pure sample: mp 103–105 °C (in a sealed tube) (lit.[3f] racemate, mp 106–110 °C); $[\alpha]^{13}_D$ −55.9° (*c* 0.347, EtOH); IR (KBr) 1770 cm^{-1}; CD (*c* 1.17 × 10^{-2}, isooctane) $[\theta]$ 0 (237 nm), −9.71 × 10^3 sh (281.6), −1.05 × 10^4 (286.3), −9.91 × 10^3 sh (290.4), −7.77 × 10^3 sh (296.2), 0 (320.5); UV max (isooctane) 282 nm (ϵ 25.3); NMR (CCl_4) δ 1.62 (brd s, 6 H), 2.20 (m, 2 H), 2.57 (m, 2 H); mass spectrum *m/e* 122 (M^+).

Because of its high volatility, elemental analysis could not be performed.

(+)-4-Isopropyltricyclo[3.3.0.0^{3,7}]octan-2-ol (29). To a refluxing slurry of $LiAlH_4$ (1.52 g, 0.0400 mol) in *N*-methylmorpholine (50 mL) a solution of (−)-oxetane (**15**),[7] $[\alpha]^{20}_D$ −5.78° (820 mg, 5.00 mmol), in *N*-methylmorpholine (15 mL) was added over 1 h, and refluxing with stirring was continued for 5 days. The excess hydride was decomposed by dropwise addition of methanol, and the reaction mixture was poured into dilute HCl. The resulting mixture was extracted with ether, and the extract was washed with saturated $NaHCO_3$ solution and water and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel. Earlier fractions eluted with pentane gave 80 mg of the starting material, and later fractions eluted with ether–pentane (1:1 volume) afforded 0.88 g of **29**, which was distilled to yield 492 mg of **29** (59% yield): bp 119–122 °C (25 mm); $[\alpha]^{20}_D$ +2.3° (c 0.568, EtOH); IR (neat film) 3450, 1065 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.29; H, 10.80.

(+)-4-Isopropyltricyclo[3.3.0.0^{3,7}]octan-2-one (30). To a solution of (+)-**29** (300 mg, 1.81 mmol) in acetone (5 mL) was added an excess of Jones reagent[16] at 0–5 °C, and the mixture was stirred for 3 h at this temperature. The reaction mixture was diluted with water and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and water and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel, and fractions eluted with pentane–ether (4:1 volume) gave 0.11 g of an oily product, which was distilled to afford 90 mg of **30** (30% yield): bp 125 °C [bath temperature (20 mm)]; $[\alpha]^{23}_D$ +18.2° (*c* 0.665, EtOH); IR (neat film) 1760 cm^{-1}; CD (*c* 2.10 × 10^{-2}, isooctane) $[\theta]$ 0 (250 nm), −2.48 × 10^3 (299.5), −2.43 × 10^3 sh (304), 0 (327).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.18; H, 9.77.

Registry No.—(−)-**9**, 61826-77-5; (−)-**15**, 58001-98-2; (±)-**23**, 61775-75-5; (+)-**23** (+)-2-(1-aminoethyl), naphthalene salt, 64783-62-6; (+)-**23**, 64753-43-1; (−)-**23** (+)-2-(1-aminoethyl)naphthalene salt, 64753-44-2; (−)-**23**, 61826-78-6; (−)-**23** acid chloride, 64715-14-6; (+)-**24**, 64715-15-7; (−)-**25**, 61775-76-6; (+)-**26**, 61775-77-7; **27**, 61775-79-9; (−)-**28**, 61775-80-2; (+)-**29**, 61775-78-8; (+)-**30**, 61775-81-3; (+)-2-(1-aminoethyl)naphthalene, 3906-16-9; thionyl chloride, 7719-09-7; dimethylamine, 124-40-3.

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Asymmetric Synthesis of (+)- or (−)-2-Methyloctanal via the Metalloenamines of Chiral Alkoxy Amines

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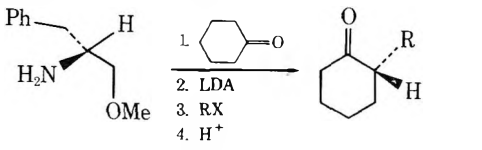
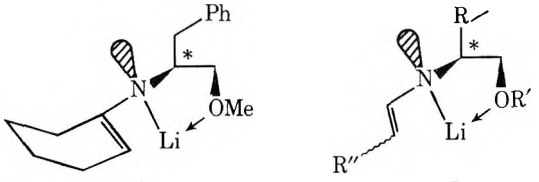
An asymmetric synthesis of the title aldehyde (1) was investigated using chiral amines derived from (*S*)- or (*R*)-phenylalanine, (*S*)-leucine, (*S*)-valine, and (*R*)-phenylglycine (2). These amino acids were transformed into their chiral amino alcohols (3) via reduction and then alkylated with various alkyl, alkoxyalkyl, and dimethylaminoalkyl halides. The alkoxy amines (4) were treated with propionaldehyde or octanal to afford the chiral aldimines 5 and 6, respectively. Metalation of these aldimines followed by alkylation with *n*-hexyl iodide or methyl iodide gave, after hydrolysis, either optical antipode of 2-methyloctanal in enantiomeric excess as high as 58%. A study was made of the various parameters affecting this process, which included changing alkoxy (R′) and substituent R in the amino component 4.

In recent years the desire for efficient asymmetric syntheses has resulted in a number of investigations which have lent some credence to the notion that modern synthetic methodology may have reached the level of sophistication to properly meet this challenge. A number of excellent reviews on this subject have appeared since 1971 and the progress toward efficient asymmetric synthesis becomes more evident as the reader proceeds from the reviews of Morrison and Mosher (1971),[3] to Scott and Valentine (1974),[4] to Kagan and Fiaud (1977).[5]

In 1976, this laboratory reported an asymmetric synthesis of 2-alkylcyclohexanones[6] using a chiral amine (eq 1), furnishing the products in 82–100% ee. The key feature in this process, which was deemed responsible for the high degree of asymmetric induction, was a suitably situated methoxy group which imparted rigidity to the chiral lithiated enamine (A).



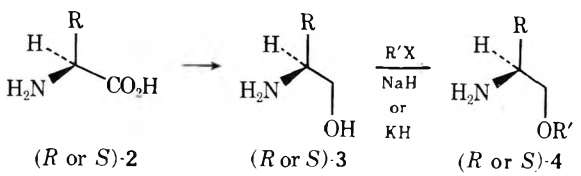
(1)



R″ = Me or *n*-Hex

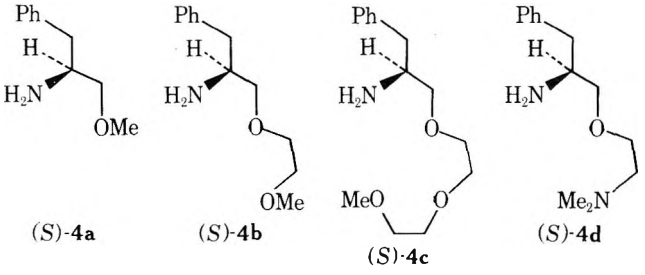
Additional studies by other laboratories[7,8] have since been reported and support the necessity of the alkoxyl group in metalloenamines during the crucial alkylating step.

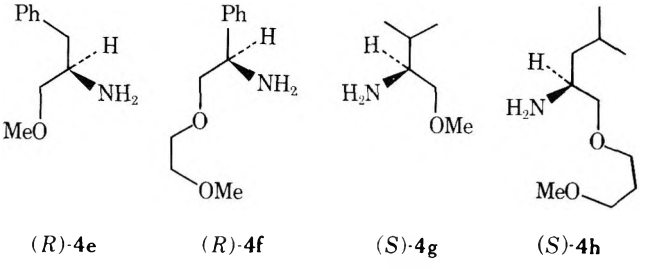
We now describe the results of a study designed to extend this concept to the alkylation of aldehydes via the chiral lithio enamines B. A detailed study was carried out varying R, R′, base, and solvent and this system proved to be more complex and less efficient for arriving at a chiral aldehyde, e.g., 2-methyloctanal (1). The chiral amines 4 were all prepared (Experimental Section) from (*S*)- or (*R*)-acids 2 using hydride

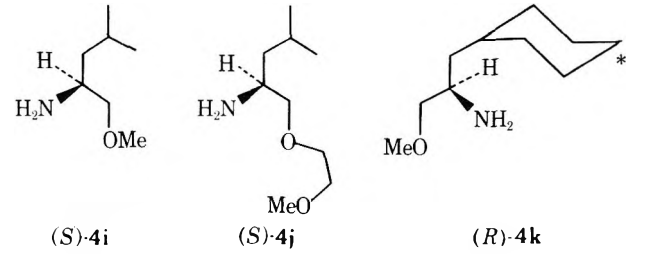


(*R* or *S*)-2 (*R* or *S*)-3 (*R* or *S*)-4

reagents, followed by alkylation of 3 with various alkyl halides. In all cases, the reduction of 2 to 3 proceeded with little or no racemization, as indicated by ^{19}F NMR data of diasteriomeric amides (Mosher amides)[9] and comparison with literature $[\alpha]_D$ values.[10] In order to assess the role of the alkyl and alkoxyl groups in 4 the series 4a–k were prepared and subjected to the synthesis of the known (*R*)- or (*S*)-2-methyloctanal (1) via the aldimines 5 and 6.







The aldimines 5 and 6 were all prepared by treating equimolar quantities of amine and aldehyde in benzene with sodium sulfate. The sensitive aldimines were isolated in 95–100% yield and, although unstable as neat liquids, could be stored as 0.4 M solutions in THF at −30 °C. The purity of the aldimines were 95 ± 5% as determined by NMR and aliquots of their THF solutions were utilized in this study. Physical data for these aldimines are given in the Experimental Section. The aldimines were assumed to be in the *E* configuration based upon the report by Hine[11] and ^{13}C NMR studies which showed only a single resonance for the amino carbon (160–167 ppm). A mixture of (*E*,*Z*)-aldimines would be expected to exhibit different chemical shifts.

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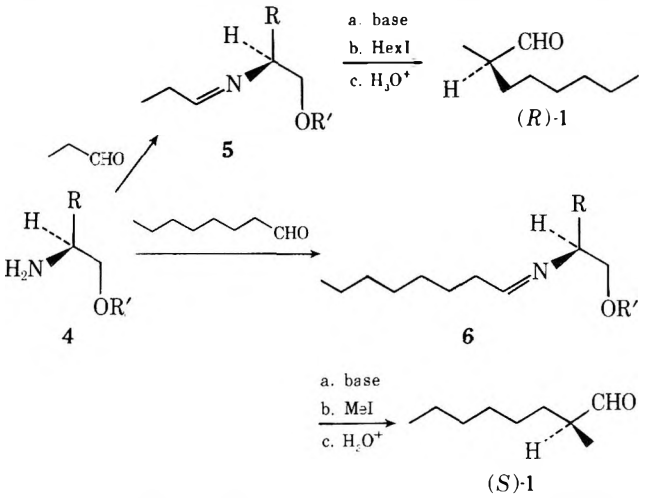
Table I. Asymmetric Synthesis of (*R*)- and (*S*)-2-Methyloctanal

		A. From Propylaldimine[a]				B. From *n*-Octylaldimine[a]			
Entry	Configuration of R	% yield[b]	$[\alpha]_D$[c] (neat)	%ee	Configuration	% yield[b]	$[\alpha]_D$[c] (neat)	%ee	Configuration
1	(*S*)-*i*-Pr (**5g**)	76	−7.73	26	*R*	67	+6.40	21	*S*
2	(*S*)-*i*-Bu (**5i**)	62	−8.64	29	*R*	72	+10.11	34	*S*
3	(*R*)-$C_6H_{11}CH_2$ (**5k**)	34	+5.06	17	*S*	62	−7.39	25	*R*
4	(*R*)-Phenyl (**5e**)	67	+11.0	37	*S*	59	−7.95	33	*R*
5	(*S*)-Benzyl (**5a**)	36	−12.55	42[d,e]	*R*	46	+14.05	47[d,e]	*S*

[a] All metalations performed at −23 °C in THF and all alkylations performed at −78 °C. [b] Distilled yields of pure aldehyde except for entry 5; see footnote *e*. [c] Based on $[\alpha]^{25}_D$ +29.9° (neat, *l* = 1) for pure (*S*)-(+)-2-methyloctanal. [d] Botteghi and C. Salamon, *Tetrahedron Lett.*, 4287 (1974). [d] Oxidized to 2-methyloctanoic acid to confirm %ee. [e] Extrapolated from ~70:30 mixture containing either *n*-hexyl iodide or octanal, see Experimental Section.

Metalation of chiral methoxyaldimines **5** and **6** with lithium diisopropylamide (LDA), followed by alkylation with *n*-hexyl



iodide or methyl iodide, respectively, gave, after hydrolysis (sodium acetate–acetic acid), (*R*)- or (*S*)-2-methyloctanal (**1**) in enantiomeric excess (ee) ranging from 17 to 47% (Table I).

The chemical yields of distilled products ranged from 34 to 76% based upon the starting aldimines. Thus, varying the nature of the R substituent in **4** from isoalkyl to benzyl to phenyl has a relatively small effect upon the %ee of the 2-methyloctanal.

It is of interest to note from Table I that the propyl aldimines derived from (*S*)-methoxyamines gave the aldehyde enriched in the *R* enantiomer, while those derived from the (*R*)-methoxyamine gave the aldehyde enriched in the *S* enantiomer. Furthermore, reversing the order of alkylating agent and aldimine gave the reverse enantiomers. Although the highest degree of asymmetric induction was observed for the benzylaldimines (entry 5, Table I), this was also accompanied by the lowest chemical yield due to 20–25% incomplete metalation. A variety of experiments (excess base, longer metalation time, variable temperatures of metalation) failed to increase the efficiency of metalation.

The moderate level of asymmetric synthesis for 2-methyloctanal may be due to several factors, the most important of which is the *E*/*Z* ratio of metalloenamines **7** and **8**. By considering the geometry of the *E*,*Z* isomers, it is possible to conceive of two conformers for each (**7A**, **7B** and **8A**, **8B**). The additional conformers, in which the alkenyl and R groups are

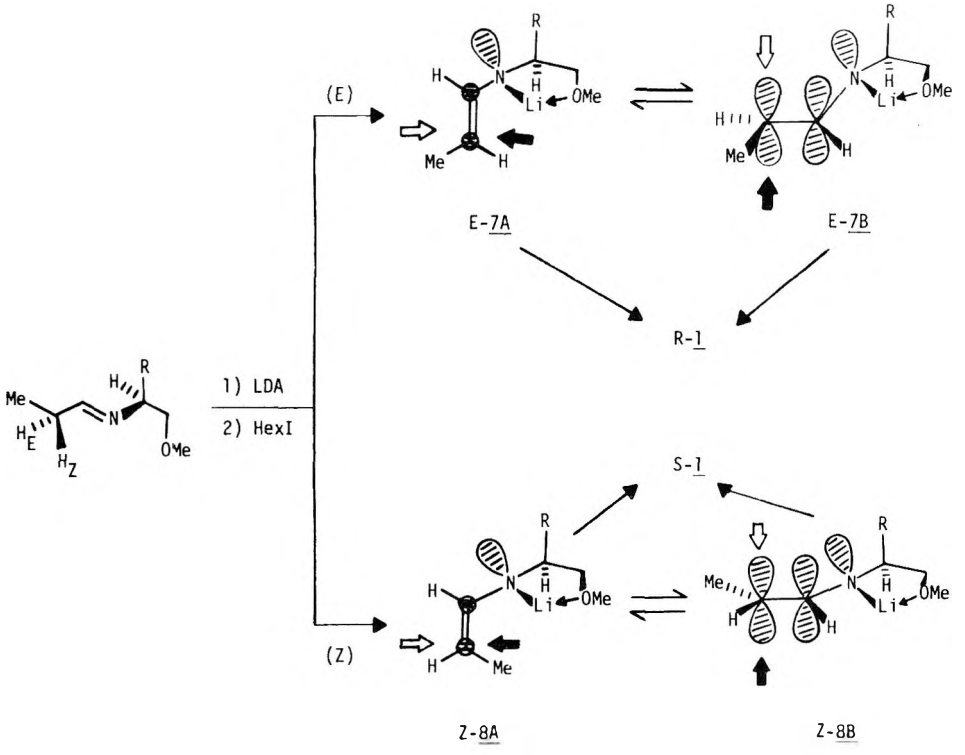
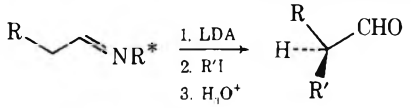


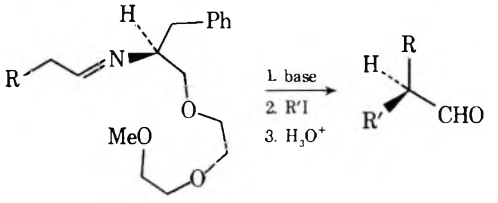
Table II. Alkoxy Effects in Chiral Aldimines[a]



Alkoxyamines	Aldimine R	R'I	% yield[b]	$[\alpha]_D$[c]	%ee	Configuration
(*S*)-**4j**	Me	*n*-Hex	74	−12.6	42	R
(*S*)-**4j**	Hex	Me	73	+11.2	37	S
(*S*)-**4h**	Me	*n*-Hex	53	−6.12	20	R
(*R*)-**4f**	Me	*n*-Hex	70	+15.5	52	S
(*R*)-**4f**	*n*-Hex	Me	57	−10.3	31	R
(*S*)-**4b**	Me	*n*-Hex	70	−11.4[d,i]	39	R
(*S*)-**4c**	*n*-Hex	Me	48	+14.5[e,i]	48	S
(*S*)-**4c**	Me	*n*-Hex	60	−15.2[f,i]	51	R
(*S*)-**4d**	*n*-Hex	Me[h]	75	+16.3[g,i]	54	S

[a] All metalations performed at −23 °C in THF and all alkylations performed at −78 °C. [b] Distilled yields. [c] Rotations are as neat liquids unless stated otherwise. [d] *c* 8.6; $CHCl_3$. [e] *c* 8.8; $CHCl_3$. [f] *c* 11.4; $CHCl_3$. [g] *c* 9.1; $CHCl_3$. [h] Lithium 2,2,6,6-tetramethylpiperidide used as the base. [i] Extrapolated from mixtures (~75:25) of aldehyde and *n*-hexyl iodide or octanal (see Experimental Section).

Table III. Effect of Base on Asymmetric Synthesis of 2-Methyloctanal

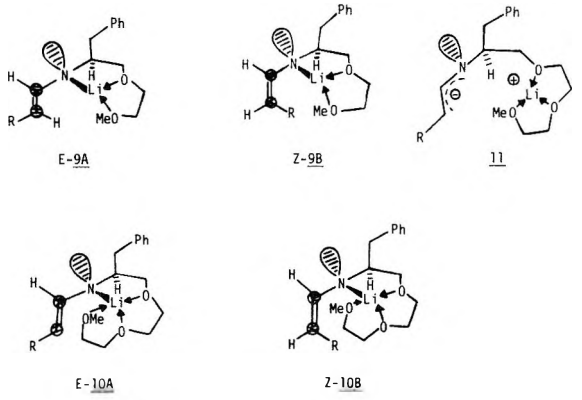


R	R'I	Base[a]	% yield[c]	$[\alpha]^{25}_D$ (*c*, $CHCl_3$)[d]	% ee (configuration)
Me	*n*-Hex	$KNEt_2$	13	−1.15 (12.7)	3.8 (*R*)
Me	*n*-Hex	$LiN(i\text{-}Pr)_2$	70	−11.4 (8.6)	39 (*R*)
n-Hex	Me	$(Me_3)_2SiN$-Li	9	+11.5 (3.4)	39 (*S*)
n-Hex	Me	LiTMP[b]	70	+17.3 (6.8)	58 (*S*)

[a] Metalations performed in THF at −23 °C (2–4 h) and alkyl iodide added at −78 °C (2–4 h). [b] LiTMP = lithium 2,2,6,6-tetramethylpiperidide. [c] All reagents added in equivalent amounts. [d] Extrapolated from mixtures (~75:25) of aldehydes and *n*-hexyl iodide or octanal (see Experimental Section).

cis (by inversion through the nitrogen lone pair), would exhibit severe 1,2-nonbonded interactions and are omitted from this argument. The black and white arrows for **7A** and **8A** indicate the possible approaches (above and below plane of paper, respectively) of hexyl iodide to the metalloenamines. For the *E* isomer (**7A, 7B**) approach via the black arrows would lead to the (*R*)-aldehyde which is observed in enantiomeric excess in all cases where the aldimine possesses the *S* configuration. Conformation **7A** would lead to the transition state where the N–Li orbital is parallel to the π orbital of the alkene, whereas **7B** is leading to the transition state involving developing overlap of the nonbonded pair on nitrogen with the π orbitals.[7] Which of these two alignments are in play is not known at this time. Entry of the alkyl halide from the opposite side (white arrows) is seemingly less attractive (space filling CPK models), but if it does occur, it would give the opposite antipode of 2-methyloctanal. Consideration of the *Z* isomers (**8A, 8B**), in two similar conformations leading to the transition state, would require approach of the hexyl iodide from the direction indicated by the black arrows and would lead to the (*S*)-aldehyde. The approach from the directions of the white arrow (again, less accessible) would furnish the enantiomeric aldehyde. If it is assumed that the metalation of **5** gives a mixture of *E* and *Z* metalloenamines[12] **7A** and **8A**, respectively, with *E* isomer predominating, then entry of the alkyl halide would follow the course depicted by the black arrows (more accessible entry route) and the %ee of the aldehyde would merely reflect the *E*/*Z* ratio of **7A** to **8A**. However, it would be expected to find different *E*/*Z* ratios of **7** and **8** with increasing size of the alkyl group on the alkene moiety and this simply was not the case as seen from addition of methyl iodide to the octenylaldimine **6**. Thus, there must be some approach of the alkyl halide from the side indicated by the white arrows. It is important to note that the %ee of the aldehyde generally increased when the substituent R on **7** or **8** was larger, supporting the assumption that topside (or inside) attack on **7** (**A, B**) and **8** (**A, B**) (white arrows) was becoming increasingly difficult.

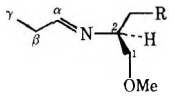
To gain further insight into those critical factors responsible for a high level of asymmetric induction, the nature of the alkoxy group was varied. Thus, aldimines derived from alkoxy amines **4** (**b, c, d, f, h,** and **j**) were prepared and subjected to the metalation–alkylation sequence leading to (*R*)- or (*S*)-2-methyloctanal. The results are summarized in Table II. The %ee of the product using polyoxy or aminooxy ligands was generally increased over the methoxyamines (**4a, 4e, 4g, 4i**), but only to the extent of 10–20%. This increase in asymmetric induction may be attributed to the increase in the *E* metalloenamine **9A** over the *Z* isomer (**9B**) or the *E* isomer **10A** over (*Z*)-**10B**. Models indicate that there is considerably more crowding in **9B** and **10B** due to the presence of a second or third ligand in the lithioenamine. However, the effect of these additional ligands was disappointingly small and it is also possible that the ligands are functioning as a "crown" which weakens the N–Li band resulting in a delocalized azaallyl anion **11**. This would cause a loss in rigidity and open up the lithio enamine to alkylation from several modes of approach. All that may be said of the results to data is that increasing the number of ligands to the lithium may result in the creation of opposing effects: (1) increasing *E*/*Z* ratio of **9** and **10**, which



is a favorable effect; and (2) furnishing a less rigid delocalized species **11**, which would be unfavorable. It is, nevertheless, important to state that the configuration of 2-methyloctanal obtained in ~50% ee is that derived from frontside (perpendicular to the page) entry of the alkyl halide to (*E*)-**9A** or (*E*)-**10A** (or its conformer analogous to **7B** and **8B**).

Finally, a study to determine whether the size or nature of the base was critical to this process was undertaken. If the *E*/*Z* ratio of the lithioenamine was determined by removal of the *pro-R* or *pro-S* proton in **12**, then the *E*/*Z* ratio for **13** would be kinetically controlled. No evidence in support of equilibrating lithioenamines **13** has been found, since the %ee of the

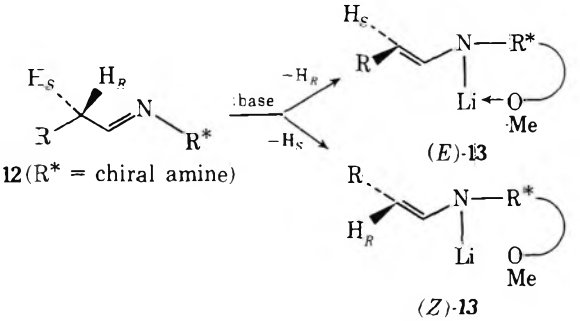
Table IV. ^{13}C NMR Chemical Shifts of Aldimines[a]



R	Carbon α	β	γ	1	2	3	OMe	Other
Phenyl	166.9	28.9	10.3	76.1	72.0	39.2	59.0	ipso 139.0 ortho 129.9 meta 128.2 para 126.2
Isopropyl	166.0	29.1	10.5	76.9	68.3	41.4	58.9	H–C 24.3 $(CH_3)_2$ 23.7; 21.5
	160.3	32.5	10.7					56.5, 29.7

[a] All chemical shifts reported in parts per million relative to internal Me_4Si. Spectra were obtained on samples 1–3 M in $CDCl_3$ with 5% added Me_4Si. Assignments were confirmed by coupled spectra.

2-methyloctanal was unchanged by varing the temperature (−78 to 0 °C) or aging **13** (2–24 h) prior to the alkylation step.



The results of deprotonation using various bases are presented in Table III. The addition of alkyl- or aryllithium reagents such as *n*-BuLi, *sec*-BuLi, *t*-BuLi, and PhLi to the C=N bond precluded their use in this study. Therefore, only bulky nonnucleophilic bases could be employed. The highest %ee achieved in this study was derived from the use of the lithium 2,2,6,6-tetramethylpiperidide (LiTMP), which also produced the chiral aldehyde in 70% chemical yield. The use of potassium diethylamide gave the lowest enantiomeric purity of the aldehyde as well as a poor chemical yield. The low %ee observed for the aldehyde may be attributed to the poor chelating ability of potassium ion in the metalloenamine **10**. With respect to solvent effects in this reaction, THF was consistently the superior medium, while ether, dimethoxyethane, and hexane–ether and hexane–THF solvents gave poor chemical yield (12–30%) and poor enantiomeric purity of aldehyde (12–30%). Addition of DMF or HMPA to reaction mixtures did little to affect the asymmetric induction, presumably because of the strong intramolecular chelation of the alkoxy groups on the chiral amine. This lack of effect using HMPA was also observed by Enders using chiral methoxy derivatives of (*S*)-proline.[8]

In summary, an asymmetric synthesis of 2-methyloctanal was achieved in 58% ee (Table III). The factors controlling this process have been examined and complete understanding of the reaction is still incomplete. Undoubtedly, direct observation of the lithioenamines by NMR techniques would be desirable as well as a more accurate description of the transition state involved. These are the goals now being pursued as well as the synthesis of different chiral aldehydes and ketones.

Experimental Section[13]

(*S*)-(−)-Phenylalininol (3, R = $PhCH_2$) was prepared according to the method of Yamada:[14] mp 88–90 °C, $[\alpha]^{25}_D$ −25.4° (*c* 1.22, EtOH). Alternatively, **3** (R = $PhCH_2$) was prepared by the procedure of *Brown*[15] *(B_2H_6) and that of Lane*[16] *and all three methods gave* similar results. The latter method,[16] in our hands, proved to be the most convenient.

The enantiomeric purity was confirmed as >95% by preparing the Mosher amides as follows: A solution of 0.5 mmol of (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride ($[\alpha]^{24}_D$ −127° (5.41, CCl_4))[9] was added with stirring to an ice-cold solution of 0.5 mmol of (−)-phenylalininol containing 1.0 mmol of triethylamine. After several minutes, a solid appeared and the mixture was allowed to warm to ambient temperature and stirred overnight. After filtration to remove the solid, the filtrate was concentrated in vacuo to furnish the theoretical amount of amide as colorless solid: NMR ($CDCl_3$) δ 7.63–6.97 (m, 12), 4.55 (m, 1, NH), 3.91–2.99 (m, 6), 2.99 (d, 2). The ^{19}F NMR spectrum at 56.5 MHz using trifluoroacetic acid as an external standard showed only a single ^{19}F peak at 278 Hz.[17]

***(S)*-(+)-Valinol (3, R = *i*-Pr)** *was purchased from Aldrich,* $[\alpha]^{25}_D$ 18.5° (*c* 7.83, EtOH); however, the literature value[18] is $[\alpha]^{25}_D$ +15.6° (EtOH). The Mosher amide prepared as above showed on ^{19}F NMR analysis a single peak at 280 Hz, indicating that the compound is at least >95% enantiomerically pure and that the rotational data is sensitive to some trace impurities.[10]

(*S*)-(+)-Leucinol (3, R = *i*-Bu) was purchased from Aldrich and had $[\alpha]^{25}_D$ +4.89° (neat). Leucinol was also prepared by the three methods described earlier[14–16] and gave widely varying $[\alpha]_D$ values between 1.2 and 4.9° (neat); $[\alpha]_D$ reported[19] was 1.57° (neat). The Mosher amides for (*S*)-(+)-leucinol have been prepared and all methods of its formation[14–16] gave material of >95% ee by ^{19}F NMR measurements.[10] To prepare (*S*)-(+)-leucinol of constant rotation from all three reduction methods, the hydrochloride salts were prepared. A solution of 100 mL of absolute ethanol containing 2.36 g of *(S)*-(+)-leucinol *[Aldrich* $[\alpha]^{25}_D$ *+4.84° (neat, l = 1.0)] was treated* with dry hydrogen chloride. The solvent was evaporated and the residue was recrystallized (ether–ethanol) twice to give a colorless solid: mp 124–126 °C (sealed capillary) with a crystal change at 95–98 °C; $[\alpha]^{20}_D$ +11.4°, $[\alpha]^{20}_{365}$ +31.8 (*c* 4.3, ethanol). The hydrochloride was neutralized in 3 N sodium hydroxide, extracted with ether, dried (Na_2SO_4), and distilled, bp 95 °C (9 mm), to a colorless oil: $[\alpha]^{20}_D$ +1.21° (neat, *l* = 1).

(*R*)-(−)-Phenylglycinol (3, R = Ph) was purchased from Aldrich: mp 75–78 °C; $[\alpha]^{20}_D$ −27.1° (*c* 5.36, MeOH): (lit.[20] $[\alpha]^{20}_D$ −25.8° (*c* 6.60, MeOH). The Mosher amide was prepared as above and ^{19}F NMR (acetone-d_6) showed a single peak at 680 Hz (trifluoroacetic acid used as external standard at 94.1 MHz).

(*S*)-(−)-2-Amino-1-methoxy-3-phenylpropane (4a). A solution of 18.4 g (0.122 mol) of (*S*)-(−)-phenylalininol in 250 mL of anhydrous tetrahydrofuran was added *dropwise to a stirred suspension of* 5.23 g (0.130 mol) of potassium hydride (pentane washed) in 100 mL of tetrahydrofuran at 25 °C under nitrogen. The resulting pale yellow gelatinous mixture was allowed to stand overnight and then a solution of 17.0 g (0.119 mol) of methyl iodide in 150 mL of THF was added dropwise over 2 h. Mixing was accomplished by external shaking, since the gelatinous mixture would not stir with magnetic stirring bars. The reaction components were allowed to mix an additional 3 h and then poured into 1 L of cold saturated brine, extracted with ether (3×), dried with Na_2SO_4, and concentrated to give 24.9 g of crude product. Distillation gave 17.1 g, bp 55–59 °C (0.1 mm), of a clear oil which on standing became cloudy and rapidly produced a white precipitate

which was found to be the carbonate. It was subsequently found that conversion of the freshly distilled methoxyamine to its hydrochloride salt was a more convenient way to store the compound. Thus the methoxyamine (17.0 g), immediately after distillation, was dissolved in 700 mL of absolute ethanol and dry HCl bubbled in for 10 min. The resulting solution was concentrated, in vacuo, to furnish 20.5 g of a colorless solid which was recrystallized from ethanol–ether (13:1): mp 151–152 °C; $[\alpha]^{25}_{578}$ +19.7° (c 2.5, EtOH), $[\alpha]^{25}_{407}$ +41.8°; IR (KBr) 3600–2300, 1265, 1203, 1125, 1071, 1052, 953, 790, 698 cm^{-1}; NMR (D_2O) δ 7.37 (br s, 5), 3.59 (m, 1), 3.54 (s, 2), 3,34 (s, 3), 2.90 (d, 2).

Anal. Calcd for $C_{10}H_{16}NOCl$: C, 59.55; H, 8.00. Found: C, 59.73; H, 7.98.

To release the free methoxyamine, it was dissolved in 5% potassium carbonate solution and extracted with ether, dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation at 52 °C (0.1 mm) gave **4a** as a clear oil: $[\alpha]^{23}_{478}$ −14.7° (c 6, benzene), $[\alpha]^{23}_{407}$ −46.2; IR (neat) 3439, 3012, 1355, 1192, 1119, 1110, 913, 743, 699 cm^{-1}; NMR ($CDCl_3$) δ 7.24 (s, 5), 3.35 (br s, 6), 2.68 (m, 2), 1.75 (br s, 2). The latter signal disappeared on shaking with D_2O. Analysis of the free methoxyamine was not performed due to its facile reaction with atmospheric carbon dioxide.

(*S*)-(−)-2-Amino-1-(2-methoxyethoxy)-3-phenylpropane (4b). A solution of 3.0 g (20 mmol) of (*S*)-(−)-phenylalininol in 7 mL of dry THF and 1.5 mL of acetonitrile was added to 0.6 g of NaH (hexane washed) and the mixture was heated to reflux for 6 h. The mixture was then treated with 2.8 g (30 mmol) of 1-chloro-2-methoxyethane[21] and heated at reflux for 120 h. After cooling, 50 mL of ether was added and then treated with 50 mL of water. The aqueous layer was extracted (2×) with 50 mL of ether and all the ethereal solutions were combined. The ether solution was washed (2×) with 50 mL of brine, dried (K_2CO_3), and concentrated. The residue was distilled to give 2.6 g (64%) of a colorless oil: bp 92–94 °C (0.03 mm); $[\alpha]^{25}_{D}$ −9.4°, $[\alpha]^{25}_{365}$ −29.90° (*c* 11.8, benzene); NMR ($CDCl_3$) δ 7.20 (m, 5), 3.73–2.00 (m, 9), 3.33 (s, 3), 1.80 (br s, 2); IR (neat) 3370, 3300, 1600, 1195, 1110, 1025 cm^{-1}. The product was >99% pure by VPC (UCW-98, 200 °C). This procedure also gave **4b** on 20-g scale.

Anal. Calcd for $C_{12}H_{19}O_2N$: C, 68.87; H, 9.15. Found: C, 68.98; H, 8.78.

(*S*)-(−)-2-Amino-1-(2-methoxyethoxyethoxy)-3-phenylpropane (4c) was prepared in an identical procedure as that described for **4b**: yield 13.2 g (62%); bp 142–145 °C (0.05 mm); $[\alpha]^{25}_{D}$ −3.5°, $[\alpha]^{25}_{365}$ −14.9° (*c* 10.7, benzene); IR (neat) 3370, 3300, 1195, 1110 cm^{-1}; NMR ($CDCl_3$) δ 7.16 (m, 5), 3.66–2.13 (m, 13), 3.30 (s, 3), 1.53 (br s, 2). The product was >98.5% pure by VPC (UCW-98, 250 °C).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 65.94; H, 8.55.

(*S*)-(−)-2-Amino-1-(2-dimethylaminoethoxy)-3-phenylpropane (4d) was prepared by Mr. Donald R. Williams of this group and kindly provided for this study: bp 98–104 °C (0.05 mm); $[\alpha]^{25}_{D}$ −3.17° (*c* 2.33, benzene). Details of this preparation will be reported in the future.

(*R*)-(−)-1-Amino-1-phenyl-2-methoxyethane (4e)[22] was prepared according to the procedure for **4a** using potassium hydride–methyl iodide on a 10.0-g scale from (*R*)-(−)-phenylglycinol (Aldrich): yield 6.8 g (62%) of a clear oil; bp 47–50 °C (0.02 mm); $[\alpha]^{23}_{D}$ −51.4° (c 7.08, benzene), $[\alpha]_{365}$ −136°. As in the case of **4a**, the compound became cloudy after 1 h due to reaction with atmospheric carbon dioxide. It was characterized through its hydrochloride salt: mp 150–151 °C (ethyl acetate); $[\alpha]^{23}_{D}$ −28.7° (c 2.5, EtOH); IR (KBr) 3200–2400, 1590, 1500, 1450, 1385, 1200, 1090, 1030, 960, 915, 760, 700 cm^{-1}; NMR (D_2O, external Me_4Si) δ 7.45 (s, 5), 3.65 (s, 3), 4.60 (t, 1), 3.80 (d, 2), 3.40 (s, 3).

Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.50. Found: C, 57.52; H, 7.35.

(*R*)-(−)-1-Amino-1-phenyl-2-(2-methoxyethoxy)ethane (4f). A solution of 20 g of (*R*)-(−)-phenylglycinol (Aldrich) in 50 mL of dry THF and 11.0 mL of acetonitrile was added to 4.40 g of sodium hydride (hexane washed) and stirred at 25 °C for 1 h, then heated to reflux for 1 h. A solution of 34.2 g of 2-chloroethyl methyl ether in 25 mL of THF was added and the mixture heated for 70 h with occasional external shaking. The mixture was poured into 100 mL of water and extracted (3×) with 100-mL portions of dichloromethane. The organic extracts were washed three times with 50-mL portions of brine, dried (K_2CO_3), concentrated, and distilled to give 19.2 g (67%) of a colorless oil: bp 83–85 °C (0.05 mm); $[\alpha]^{25}_{D}$ −42.0°, $[\alpha]^{25}_{365}$ −116.3° (*c* 10.1, benzene); IR (neat) 3380, 3350, 1610, 1360, 1200, 1100, 860, 760, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (m, 5), 4.22 (d of d, 1, J = 3.7 and 8.5 Hz), 3.58 (m, 6), 3.35 (s, 3), 1.89 (br s, 2).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.43; H, 8.58.

(*S*)-(+)-1-Methoxy-2-amino-3-methylbutane (4g) was prepared as described previously for **4a** using 3.7 g of sodium hydride, 15.0 g of L-valinol (Aldrich), and 20.6 g of methyl iodide in THF. The crude product (12.8 g) was distilled, bp 57 °C (34 mm), affording 9.3 g of **4g** as a clear liquid containing a small amount of *N*-methyl by-product (NMR and VPC). Further purification was accomplished via the hydrochloride prepared by passing dry HCl into **4g** in absolute ethanol. Crystallization gave 12 g of a yellow solid which was recrystallized (ethanol–ether) furnishing 8.7 g (51%) of a colorless solid: mp 166–167 °C; $[\alpha]^{25}_{D}$ +11.8°, $[\alpha]^{25}_{407}$ +26.7 (c 2.7, EtOH); IR (KBr) 3500–2500, 1585, 1468, 1395, 1380, 1203, 1105, 948 cm^{-1}; NMR (D_2O) δ 4.71 (br s, 3), 3.68 (m, 3), 3.43 (s, 3), 2.01 (m, 1), 1.03 and 0.99 (d, 6, J = 8.4 Hz).

Anal. Calcd for $C_6H_{16}NOCl$: C, 46.91; H, 10.49. Found: C, 47.00; H, 10.29.

The free amine **4g** was liberated with 10% sodium hydroxide solution followed by extraction with ether. Distillation gave 5.21 g (31% from L-valinol) as a clear liquid: bp 56 °C (31 mm); $[\alpha]^{25}_{D}$ +23.7°, $[\alpha]^{25}_{407}$ +50.0 (c 6.2, benzene). Analysis was not performed on free methoxyamine due to its facile reaction with atmospheric carbon dioxide.

(*S*)-(−)-1-Methoxy-2-amino-4-methylpentane (4i) was prepared from (*S*)-leucinol using NaH–methyl iodide in THF as described for **4a**. The hydrochloride was obtained in 35% yield as hygroscopic colorless crystals: mp 135–137 °C (chloroform–ether); $[\alpha]^{25}_{D}$ +15.3°, $[\alpha]^{25}_{407}$ +33.8° (c 4.0, EtOH).

Anal. Calcd for $C_7H_{18}NOCl$: C, 50.12; H, 10.84. Found: C, 50.08; H, 11.02.

The free amine **4i** was obtained by treatment of the hydrochloride with 10% potassium carbonate solution and ether extraction. The ethereal residue was distilled to furnish **4i** as a clear liquid: bp 72–73 °C (35 mm); $[\alpha]^{25}_{D}$ −3.35°, $[\alpha]^{25}_{407}$ −6.33 (c 6.7, benzene); IR (neat) 3360, 2945, 1585, 1469, 1385, 1365, 1199, 1167, 1112, 979, 875, 834 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (s, 3), 3.05 (m, 3), 1.71 (m, 1), 1.44 (br s, 2), 1.18 (t, 2), 0.91 and 0.89 (d, 6); the peak at δ 1.44 disappeared on addition of D_2O.

Anal. Calcd for $C_7H_{17}NO$: C, 64.05; H, 13.08. Found: C, 63.85; H, 13.12.

(*S*)-(+)-1-(3-Methoxypropoxy)-2-amino-4-methylpentane (4h). A mixture of 15.0 g of (*S*)-(+)-leucinol and 20.0 g of phthalic anhydride was heated for 1 h at 140 °C and cooled before adding 200 mL of ether. The ether solution was washed successively with 10% potassium carbonate, water, 10% hydrochloric acid, water, and saturated salt solution. After drying (Na_2SO_4) and concentration, the crude phthalimide (27.8 g) was obtained (88%) as a viscous oil. Without further purification, a solution of 86 mmol of the phthalimide in 75 mL of THF was added to 104 mmol of sodium hydride and allowed to stir overnight. Allyl bromide (124 mmol) in 25 mL of THF was added and after 2 h, 200 mL of ether was added followed by 200 mL of water. The layers were separated and the organic phase was washed (brine) and dried (Na_2SO_4) to afford 20.6 g (83%) of the crude allyl ether. Without further purification, the allyl ether (20.0 g, 70 mmol) was dissolved in 80 mL of glyme and treated dropwise with 24 mL (24 mmol) of borane–THF (1 M solution) at room temperature. After stirring for 1 h, 8.5 mL of 3 N sodium hydroxide was carefully added followed by 8.5 mL of 30% hydrogen peroxide and the temperature kept below 40 °C by an external bath. Ether (100 mL) was added after 1 h and the layers separated. The aqueous layer was extracted with ether and the combined ether layers were washed with brine, dried (Na_2SO_4), and concentrated to give 18.0 g (82%) of the alcohol. The crude product, as in the previous step, showed NMR and IR data consistent with structure. The crude phthalimido alcohol (59 mmol) was dissolved in 25 mL of THF and treated with 73 mmol of NaH and stirred for 15 h. A solution of 90 mmol of methyl iodide in 15 mL of THF was added and stirred for 24 h at room temperature. The usual workup (water, ether extraction, brine wash, drying concentration) gave 14.6 g (78%) of the methoxy ether, which was treated directly with 1.6 g of hydrazine in 75 mL of ethanol and heated to reflux for 2 h. The solid mass was removed by filtration and washed twice with cold ethanol. After concentration of the ethanol solutions, the residue was taken up in ether, filtered to remove solid material, and concentrated again to leave an oil, which was distilled, bp 77–82 °C (0.5 mm), to give 3.10 g of clear, colorless oil: $[\alpha]^{25}_{D}$ +1.96°, $[\alpha]^{25}_{365}$ +8.24° (c 5.93, benzene); IR (neat) 3370, 2925, 1470, 1388, 1360, 1193, 1109, 835 cm^{-1}; NMR ($CDCl_3$) δ 3.56 (m, 2), 3.32 (m, 6), 3.10 (d, 1), 1.82 (pentet, 2, J = 6.5 Hz), 1.25 (m, 3), 0.97 and 0.90 (d, 6, J = 6.1 Hz). VPC (UCW-98) indicated **4h** was >95% pure.

Anal. Calcd for $C_{10}H_{23}NO_2$: C, 63.43; H, 12.27. Found: C, 63.16; H, 11.99.

(*S*)-(+)-1-(2-Methoxyethoxy)-2-amino-4-methylpentane (4j).

A solution of 23.2 g (0.195 mol) of (*S*)-leucinol in 50 mL of THF and 12 mL of acetonitrile was treated with 5.6 g (0.23 mol) of NaH and stirred for 2 h at 55 °C. A solution of 19.0 g of 2-chloroethyl methyl ether (0.2 mol) in 25 mL of THF was added and the mixture heated to reflux for 90 h. After quenching in 100 mL of water and extracting with ether, the ethereal extracts were washed with brine, dried, and concentrated. The residual oil was distilled, bp 92–94 °C (10 mm), to obtain a clear colorless oil: $[\alpha]^{25}_{D}$ +4.41°, $[\alpha]^{25}_{407}$ +12.07° (c 5.6, benzene); IR (neat) 3300, 2950, 1589, 1466, 1384, 1200, 1090, 881 cm^{-1}; NMR ($CDCl_3$) δ 3.85–2.95 (m, 10), 2.20–1.36 (m, 4), 1.20 (t, 2, J = 7 Hz), 0.96 and 0.94 (d, 6).

Anal. Calcd for $C_9H_{21}NO_2$: C, 61.66; H, 12.10. Found: C, 61.94; H, 12.26.

(*R*)-(+)-1-Methoxy-2-amino-3-cyclohexylpropane (4k). A solution of (*R*)-**4a** ($[\alpha]^{25}_{578}$ −19.5°) was hydrogenated with 15% by weight of 5% $RhAl_2O_3$ in ethanol at 45 psi. Workup gave **4k:** bp 90–91 °C (2 mm); $[\alpha]^{25}_{D}$ + 5.74°, $[\alpha]^{25}_{407}$ +13.2° (c 5.5, benzene); IR (neat) 3360, 2890, 1580, 1443, 1363, 1187, 1101, 843, 820 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (s, 3), 3.18 (m, 3), 1.73 (m, 6), 1.27(m, 9).

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36. Found: C, 70.41; H, 12.25.

Formation of Aldimines 5 and 6. General Procedure. To a stirred solution (0 °C) of 10 mmol of the alkoxyamine dissolved in 30 mL of benzene (previously washed with concentrated sulfuric acid and distilled) was added 10 mmol of the pure aldehyde (propanal or octanal). An immediate cloudiness usually resulted on addition of the aldehyde. The mixture was allowed to warm to room temperature and ~15 g of anhydrous sodium sulfate added. After stirring the mixture an additional 30–40 min, it was filtered and the sodium sulfate washed thoroughly with dry ether. The solvent was removed by evaporation first with aspirator pressure and then with the vacuum pump (0.5 mm) to generally furnish 9.5–10 mmol of the aldimine as a colorless oil. Spectral data were immediately taken: IR (neat) 1662–1690 cm^{-1} (C=N); NMR ($CDCl_3$) δ 7.5–7.8 (t, 1, J = 4.9–5.1 Hz, –HC=N–). The aldimines were dissolved in THF (0.4 M) and stored at −20 to −30 °C. Attempts to store the aldimines as neat liquids resulted in deteriorations. As solutions, the aldimines were conveniently transferred via syringe to reaction vessels.

The aldimines were shown to be a single isomer by ^{13}C NMR of several representative examples (Table IV). *N-tert*-Butylpropylaldimine is included for reference.

(*R*)- or (*S*)-2-Methyloctanal (1). General Procedure. All the experiments described in Tables I–III were performed following the general procedure described below. All were conducted at approximately 0.25 M concentration (final concentration in THF only) and generally on aldimine solutions which had been stored in the freezer (−25 °C). Metalations and alkylations were monitored by withdrawing a 0.5-mL aliquot and quenching with methyl iodide and water, respectively. Determination of reaction course was made by NMR analysis. All the bases employed (Table III) were prepared in situ by addition of *n*-butyllithium or potassium hydride to an equimolar quantity of amine at 0 °C in THF. Stirring was continued for 30–60 min at 0 °C (or room temperature in the case of potassium diethylamide). Where appropriate (KH), the stoichiometric quantity of hydrogen was collected.

To a stirred solution of 11 mmol of base (−23 °C dry ice–CCl_4, under nitrogen atmosphere) in 10 mL of THF was added over 5 min 10 mmol of the aldimine (**5** or **6**) dissolved in 25 mL of THF. The resulting solution (generally yellow, but in some cases colorless) was stirred at −23 °C for 30 min and then cooled to −78 °C (dry ice–isopropyl alcohol). The halide (methyl or hexyl iodide, 10–12 mmol) dissolved in 5 mL of THF was then added and the reaction mixture stirred for 2–7 h at −78 °C and complete conversion was determined by removing aliquots. After warming to room temperature and addition of 50 mL of ether, the cloudy mixture was poured into 100 mL of water and the phases were separated. The aqueous phase was extracted with ether and the combined organic phases were washed with brine, dried (K_2CO_3 or Na_2SO_4), and concentrated. The crude alkylated aldimines were hydrolyzed by dissolving in 30 mL of pentane and shaking for 5 min in a separatory funnel with an aqueous acetic acid–sodium acetate solution (prepared from 37.5 mL of acetic acid, 37.5 mL of water, and 16.2 g of sodium acetate). The layers are separated and the aqueous acid layer is extracted once with 30 mL of fresh pentane. *Both layers are kept*, since the chiral alkoxy amine may be recovered from the aqueous phase. The combined pentane layers were washed successively with water, 10% sodium bicarbonate, and water and dried over sodium sulfate. Evaporation of the filtered pentane gave the crude aldehyde as a pale yellow liquid. Bulb-to-bulb distillation at 90 °C (4 mm) furnished a clear, colorless product which was free of impurities by VPC, NMR, and IR analysis. For the aldimine derived from alkoxyphenylalininols (**4a–d**) incomplete metalation always produced *n*-hexyl iodide or octanal from aldimines **5** and **6**, respectively. Thus, 2-methyloctanal could not be purified by distillation and VPC indicated only 70–75% product. The $[\alpha]_D$ for 2-methyloctanal (entry 5, Table I; last four entries in Table II, all entries in Table III) was therefore extrapolated from known prepared mixtures with octanal or hexyl iodide. That this extrapolation was valid was proven by starting with pure 2-methyloctanal (collected from VPC instrument), $[\alpha]^{25}_{D}$ −8.90°, and preparing (wt/wt) solutions of 12.7, 25.7, 44.6% *n*-hexyl iodide. Plotting weight percent vs. $[\alpha]_D$ gave a straight line. A similar check was made using octanal–2-methyloctanal solutions of 55.4, 74.3, 87.3% and the plot weight percent vs. $[\alpha]_D$ was again linear.

Recovery of Chiral Alkoxy Amines 4. The hydrolysis solution (NaOAc–HOAc) from above was neutralized with solid potassium hydroxide and extracted with ether (3×). The ethereal extracts were washed with brine, dried (K_2CO_3), and concentrated to yield the crude chiral amine in 80–88% yield. Distillation afforded the pure amine in 70–75% recovery and examination of the $[\alpha]_D$ values indicated, in every case, that no racemization had occurred.

(*R*)- or (*S*)-2-Methyloctanoic Acid. Further confirmation of the validity of the extrapolated rotation data in Table I (entry 5) was obtained by oxidizing 2-methyloctanal, $[\alpha]^{25}_{D}$ −12.55° and $[\alpha]^{25}_{D}$ +14.05°, with silver oxide according to the method of Shamma.[23] A solution of 1.49 g of (*R*)-(−)-2-methyloctanal (containing 30% *n*-hexyl iodide) in 40 mL of absolute ethanol was added to 5.0 g of silver nitrate in 5 mL of water. A solution of 2.8 g of KOH dissolved in 50 mL of water was added and a black precipitate formed immediately. The mixture was stirred for 1 h and filtered. The silver residue was washed with water and the combined filtrates were extracted with ether. The ether was discarded. Acidification of the filtrate (concentrated HCl) and several extractions with ether followed. The ethereal solution was washed with water, brine, and water, dried ($MgSO_4$), and concentrated. Distillation (bulb-to-bulb) of the residue gave the product: bp 95 °C (5 mm); 575 mg; $[\alpha]^{25}_{D}$ −6.94°; $[\alpha]^{25}_{407}$ −16.40° (neat, l = 1); d^{25} = 0.905; $[M]^{25}_{D}$ −11.0°. The literature[24] reports $[M]^{25}_{D}$ +26.0° for (*S*)-(+)-2-methyloctanoic acid. Thus, the ee for the acid derived from the aldehyde was 42%.

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Registry No.—(*S*)-**1**, 55352-42-6; (*R*)-**1**, 49642-49-1; (*S*)-**3** (R = $PhCH_2$), 3182-95-4; (*S*)-3 (R = $PhCH_2$) Mosher amide, 64715-79-3; (*S*)-**3** (R = *i*-Pr), 2026-48-4; (*S*)-**3** (R = *i*-Bu), 7533-40-6; (*S*)-**3** (R = *i*-Bu) HCl, 17016-87-4; (*R*)-**3** (R = Ph), 56613-80-0; **4a**, 64715-80-6; **4a** HCl, 64715-81-7; **4b**, 64715-82-8; **4c**, 64715-83-9; **4d**, 64715-84-0; **4e**, 64715-85-1; **4e** HCl, 64715-86-2; **4f**, 64715-87-3; **4g**, 64715-88-4; **4g** HCl, 64715-89-5; **4h**, 64715-90-8; **4i**, 64715-91-9; **4i** HCl, 64715-92-0; **4j**, 64715-93-1; **4k**, 64715-57-7; **5a**, 64715-58-8; **5b**, 64715-59-9; **5c**, 64715-60-2; **5e**, 64715-61-3; **5f**, 64715-62-4; **5g**, 64715-63-5; **5h**, 64715-64-6; **5i**, 64740-18-7; **5j**, 64715-65-7; **5k**, 64715-66-8; **6a**, 64715-67-9; **6c**, 64715-68-0; **6d**, 64715-69-1; **6e**, 64715-70-4; **6f**, 64715-71-5; **6g**, 64715-72-6; **6i**, 64715-73-7; **6j**, 64715-74-8; **6k**, 64715-75-9; (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride, 39637-99-5; methyl iodide, 74-88-4; 1-chloro-2-methoxyethane, 627-42-9; phthalic anhydride, 85-44-9; (*S*)-(+)-leucinol phthalimide derivative, 64715-76-0; allyl bromide, 106-95-6; (*S*)-(+)-leucinol phthalimide derivative, allyl ether, 64715-77-1; (*S*)-(+)-leucinol phthalimide derivative, 3-hydroxypropyl ether, 64715-78-2; propanal, 123-38-6; octanal, 124-13-0; *N-tert*-butylpropylaldimine, 7020-81-7; hexyl iodide, 638-45-9; (*S*)-(+)-2-methyloctanoic acid, 61866-40-8.

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Stereochemical Aspects of Substitution Reactions of Stannyl and Germyl Anionoids with Cyclohexyl Derivatives

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The reactions of trimethyltinlithium (in THF) and trimethylgermaniumlithium (in HMPA) with some 4-alkylcyclohexyl bromides and tosylates have been conducted, and product stereochemistry has been established by ^{1}H and ^{13}C NMR spectroscopy. With the cis bromides both the stannyl and the germyl anionoids yield mixtures of *cis*- and *trans*-4-alkylcyclohexylstannanes and -germanes, respectively, whereas the stannyl anionoid reacts cleanly with inversion with *trans*-4-methylcyclohexyl tosylate. Both anionoids react in a straightforward way with cyclohexene oxide to yield the corresponding *trans*-2-hydroxycyclohexyl metalloids. Certain of our results contrast with some of those in a previous report. Variable-temperature ^{13}C NMR examination of *cis*-4-methylcyclohexyltrimethylgermane, and other considerations, yield a $-\Delta G°_{203}$[Ge(CH$_3$)$_3$] of 2.1 ± 0.2 kcal/mol (*A* value), somewhat greater than the *A* value for CH$_3$ (1.74 kcal/mol).

Introduction

The reactions of organic halides with alkali metal derivatives of organometal anions have been extensively utilized for the formation of carbon–metal bonds as illustrated below:

$$R'_xM^-M_1^+ + RX \rightarrow R'_xMR + M_1X \ldots\ldots \quad (1)$$

This general area has been reviewed.[1]

This approach to carbon–metal bond formation has been particularly useful in group 4B chemistry, and many tetraorganostannanes have been synthesised in this manner.

$$R_3SnM + R'X \rightarrow R_3SnR' + MX \ldots\ldots \quad (2)$$

(R_3Sn = $(CH_3)_3Sn$, $(C_6H_5)_3Sn$; M = Na, K, Li)

Derivatives of silicon, germanium, and lead have also been obtained in the same general way.[1]

Stereochemical studies of the reaction (eq 2) have been reported and inversion of configuration at carbon was the general result, in keeping with the suspicion that the reaction was S_N2 in character.[2] Other transformations, however, indicated that other mechanisms must also be possible.[1d,3,4]

Recently, there has been great interest in the fine details of these anionoid substitutions, particularly for the systems in eq 2. In particular, Koermer, Hall, and Traylor[5] reported that whereas the 4-*tert*-butylcyclohexyl Grignard reagent on reaction with trimethyltin chloride provided overwhelmingly trans product, reaction of *cis*-4-*tert*-butylcyclohexyl bromide with $(CH_3)_3SnLi$ (in THF) yielded *cis*-4-*tert*-butylcyclohexyltrimethylstannane. The latter compound also resulted from the displacement of tosylate in the *trans*-4-*tert*-butylcyclohexyl derivative by $(CH_3)_3SnLi$ (in THF). These sequences seemed very attractive as they could provide geometric isomers of cyclohexyltin systems of high isomeric purity for other studies. Kuivila and co-workers[6] have also been conducting systematic studies of the reactions of stannyl anionoids under various conditions and have established that the stereochemistry of the reaction with certain bromonorbornenes (eq 2) is profoundly dependent upon the solvent and alkali metal counterion in $(CH_3)_3SnM$.

For some time we have been pursuing spectroscopic and conformational studies[7,8] of cyclohexyl derivatives of group 4B and have required 4-alkylcyclohexyl derivatives of tin and germanium of established stereochemistry. We have utilized reactions of $(CH_3)_3SnLi$ (in THF) and $(CH_3)_3GeLi$ (in HMPA) with cyclohexyl bromides and tosylates, as well as the Grignard route. In this report, we wish to present our conclusions concerning the stereochemistry of certain of these displacements (formally on carbon).

Results and Discussion

(A) Organotin Systems. The stereochemistry of the displacement of bromide and tosylate by $(CH_3)_3SnLi$ in the following cases (eq 3 and 4) has been examined.

In addition to tetraorganostannane product significant amounts of alkylcyclohexene (elimination) and hexamethyldistannane were also formed in these reactions.[5,6]

^{1}H NMR spectroscopy has been widely employed to determine the stereochemistry of substituted cyclohexyl sys-

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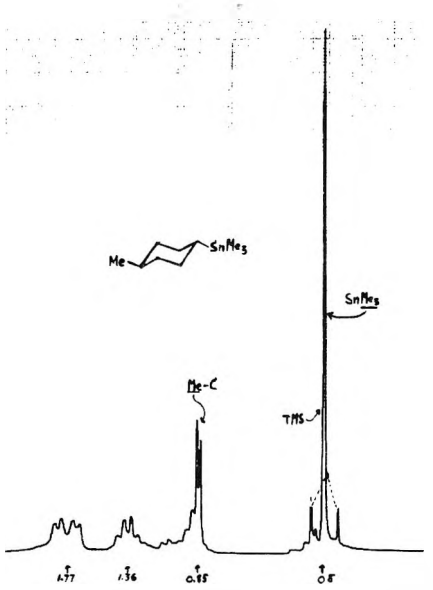
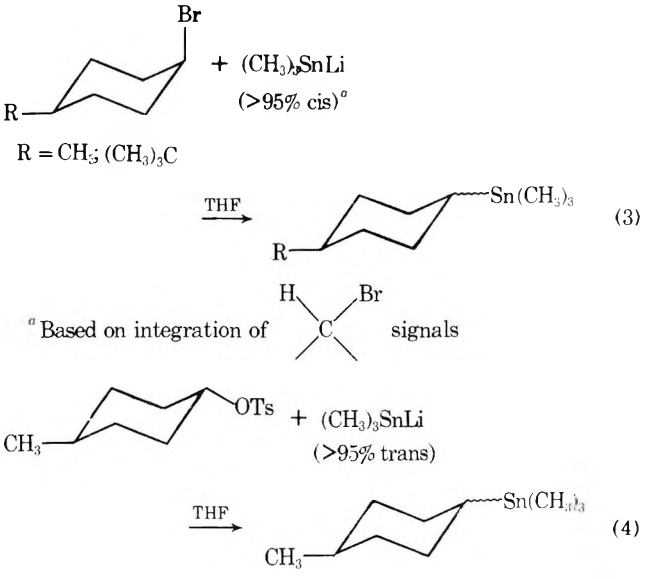


Figure 1. The 270-MHz ^1H NMR spectrum of *trans*-4-methylcyclohexyltrimethylstannane, showing the CH_3Sn resonance to the high field of Me_4Si. (Chemical shifts quoted in the text have been obtained from 100-MHz spectra.) This compound was obtained from the Grignard reaction of 4-methylcyclohexyl bromide with trimethyltin chloride.



tems, particularly when an electronegative group significantly deshields the methine proton from the general cyclohexyl absorption, so that ^1H–^1H coupling constants can be measured.[9] In the tin compounds, there were good reasons for anticipating that the methine proton (>C(H)Sn) would not be strongly deshielded and the ^1H NMR approach would be of rather limited use.[10] We did, nevertheless, expect some differences in the general spectral shape of *cis*- and *trans*-4-alkylcyclohexyltin isomers.[9] Studies of the ^{13}C NMR spectra of cyclohexyl and related organostannanes have provided a bank of data of $^{117,119}Sn$–^{13}C coupling constants and chemical shifts, which would constitute the basis of a definitive approach to isomer determination (vide infra).[5a,11,12] In addition, it would be advantageous to obtain, in essentially pure form, one of the possible isomers. Fortunately there were reports which indicated that *trans*-4-methylcyclohexyltrimethylstannane was accessible.

Jensen and Nakamaye[13] reported that reaction of 4-methylcyclohexyl Grignard yielded predominantly (>80%) trans mercurial, and this has been confirmed by ^1H and ^{13}C NMR spectroscopy.[14] We anticipated that use of $(CH_3)_3SnCl$ as an electrophile would not seriously alter this stereochemical pattern. The Grignard reagent from >95% *cis*-4-methylcyclohexyl bromide on reaction with $(CH_3)_3SnCl$ yielded a 4-methylcyclohexyltrimethylstannane which exhibited a single $(CH_3)_3Sn$ ^1H resonance (Figure 1) at δ −0.045 ($J_{^{119}Sn-^1H}$ = 52 Hz), and a doublet (δ 0.84, $J \simeq 7$ Hz) for CH_3C. The proton-decoupled PFT ^{13}C spectrum (Figure 2) confirmed the presence of one isomer (six signals excluding ^{119}Sn satellites) with δ CH_3Sn at −12.00 ppm and CCH_3 at +23.26 ppm. These chemical shifts agree nicely with those for equatorial $Sn(CH_3)_3$[7] and CCH_3[15] in cyclohexyl systems. The ring carbon chemical shifts were in good agreement with those calculated (on the basis of additivity) from equatorial $Sn(CH_3)_3$ and CH_3 induced shifts.[16] The value of the vicinal ^{13}C–^{119}Sn coupling constant (^3J) was 67.5 Hz, absolutely consistent[11] with a dihedral angle of 180° as present in the trans isomer. There is therefore no doubt that this stannane is the *trans*-4-methylcyclohexyl derivative.

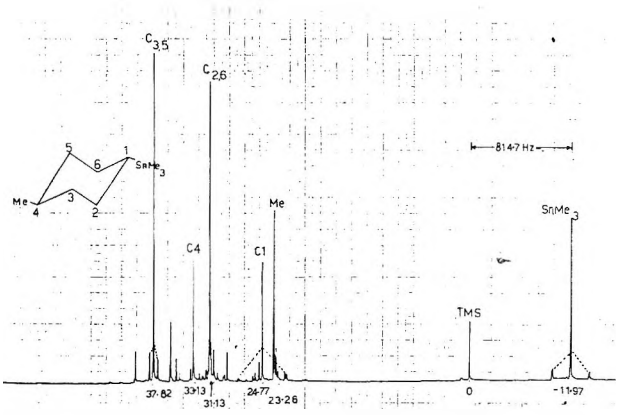


Figure 2. The proton-decoupled PFT 67.89-MHz ^{13}C spectrum of *trans*-4-methylcyclohexyltrimethylstannane obtained by the Grignard route. Assignments are indicated, and the lone $Sn(CH_3)_3$ signal indicates high isomeric purity. The vicinal ^{119}Sn–^{13}C coupling (about $C_{3,5}$) is consistent with the trans description. (A number of low-intensity signals may be associated with bicyclohexyl formation.)

Reaction of *trans*-4-Methylcyclohexyl Tosylate with $(CH_3)_3SnLi$. *trans*-4-Methylcyclohexyl tosylate (>95% trans) was prepared and reacted with $(CH_3)_3SnLi$, and on workup and distillation yielded an essentially pure isomer of 4-methylcyclohexyltrimethylstannane, as judged by the lone $(CH_3)_3Sn$ signal at δ 0.05 ($J_{^{119}Sn-^1H} \sim 52$ Hz) in the ^1H spectrum (Figure 3), with the CCH_3 doublet ($J \sim 7$ Hz) at δ +0.90. The distinct differences between the above $Sn(CH_3)_3$ and CCH_3 chemical shifts, and those for the trans isomer discussed previously, indicated possession of the pure *cis*-4-methylcyclohexyl derivative. The ^{13}C spectrum (Figure 4) confirmed the presence of one isomer, as a total of six signals (neglecting $^{117,119}Sn$ satellites) was observed, and the chemical shift pattern was different from that for the trans compound but completely consistent with that anticipated for the cis isomer.

Before discussing these ^{13}C parameters it is important to remember that while the *trans*-4-methylcyclohexyl derivative could be discussed in terms of a homogeneous (e,e) conformation the cis isomer must be treated as a two-component mobile (e,a) system, with comparable populations of A and B as shown in eq 5.

Employing the conformational free energies (A values) for CH_3 (1.74 kcal/mol)[15] and $Sn(CH_3)_3$ (1.06 kcal/mol),[7] it is possible to calculate that at ~300 K, [A]/[B] ~ 3:1. This deduction for the cis isomer allows a calculated "average" vicinal ^{119}Sn–^{13}C coupling constant of ~24 Hz, utilizing the Karplus-type dependence previously established[11] for this cou-

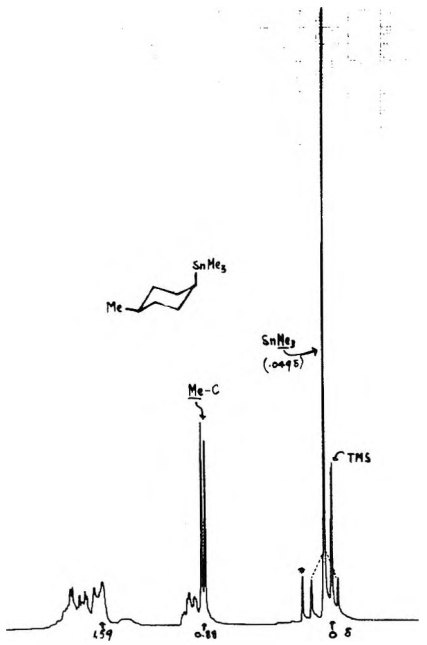
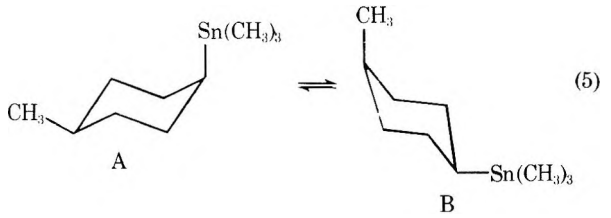


Figure 3. The 270-MHz ^1H NMR spectrum of *cis*-4-methylcyclohexyltrimethylstannane showing the CH_3Sn resonance to the low field of Me_4Si. The general cyclohexyl absorption is dissimilar to that of the trans isomer (Figure 1). This compound was obtained from the reaction of *trans*-4-methylcyclohexyl tosylate with $(CH_3)_3SnLi$. (Chemical shifts quoted in the text were measured from 100-MHz spectra.)



(5)

pling [~10 Hz for $\theta = 60°$ in A; ~67 Hz for $\theta = 180°$ in B]. The observed $^3J_{vic}$ of 23.1 Hz is in satisfying agreement with this analysis. The other ^{13}C parameters also must be analyzed on this basis, and the observed shift of −9.85 ppm for $Sn(CH_3)_3$ is appropriate for this ~3:1 mixture of A and B, given that $\delta_{Sn(CH_3)}$(equatorial) ~−12.00 ppm and $\delta_{Sn(CH_3)_3}$(axial) is ~−9.20 ppm[7] (i.e., ¼[(3 × 9.20) + 12.00]). Similarly, the observed chemical shift for CCH_3 of 22.00 ppm is in close agreement with the computed value of 21.96 ppm based on the established shifts for axial (17.43 ppm) and equatorial (23.47 ppm) methyl groups in methylcyclohexane.[15] Comparison of predicted and observed chemical shifts for ring carbons in A ⇌ B strictly is not possible, as only the γ carbon shifts, where strong compressional effects operate, are available for the axial forms of methylcyclohexane[16] and cyclohexyltrimethylstannane.[7] Even in their absence, however, the above correspondences of calculated and observed ^{13}C NMR properties leave no doubt that reaction of the *trans*-4-methylcyclohexyl tosylate yields only the *cis*-tin compound (along with some olefin and hexamethylditin).[5]

It is instructive also to compare the ^1H NMR spectra of the *trans*- and *cis*-4-methylcyclohexyltrimethylstannanes. In the cis isomer, both the CH_3Sn and CH_3C resonances (+0.05 and +0.90 ppm, respectively) are downfield from the corresponding resonances (−0.045 and 0.84 ppm, respectively) in the trans compound. These differences are expected, as the axial CH_3 group in methylcyclohexane is known to resonate at lower field than the equatorial.[17] It is very reasonable that an axial $Sn(CH_3)_3$ will behave similarly, as "steric deshielding" would be operative for both axial CH_3 and $Sn(CH_3)_3$ groups.

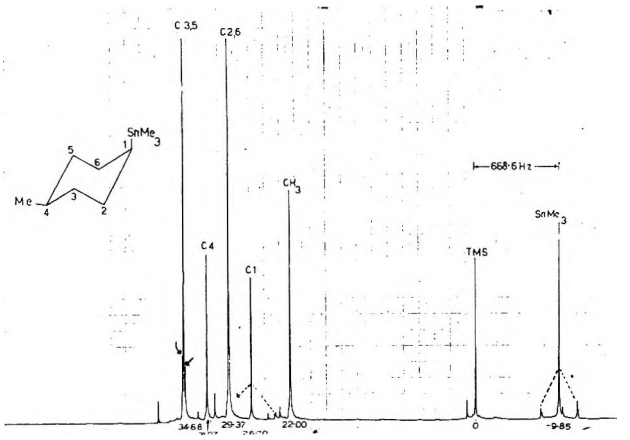


Figure 4. The proton-decoupled PFT 67.89-MHz ^{13}C spectrum of *cis*-4-methylcyclohexyltrimethylstannane. The chemical shifts and the magnitude of the vicinal ^{119}Sn–^{13}C coupling constant confirm the cis structure.

Another anticipated difference in the ^1H spectra of the isomers concerns the position and multiplicity of the methine proton $>C(H)SnMe_3$.[9]

In the trans isomer, this proton (axial) should be at higher field (by ~0.5 ppm) and appear as a broadened triplet (two trans diaxial couplings), whereas this proton in the cis isomer (now predominantly an equatorial proton) should be narrower and to lower field.[9] In the ^1H spectrum of the trans isomer, a broadened triplet ($J \sim 12$ Hz) at δ 1.24 is superimposed on the general absorption, whereas in the cis isomer this absorption is absent, and there has been a shift of intensity to lower field in the δ 1.5–1.9 region. In the low-temperature (−80 °C) 270-MHz ^1H spectrum of cyclohexyltrimethylstannane two components of what appears to be a triplet ($J \sim 11$–12 Hz) at δ 1.28 are clearly visible and are tentatively assigned to the methine proton in this compound.[36] Differences of this type should be visible also in the spectra of the pure *cis*- and *trans*-4-*tert*-butyl derivatives, and we were surprised at the report that these isomers (other than for the $Sn(CH_3)_3$ resonances) provided "identical" spectra.[5,18]

The above data demonstrate that reaction of *trans*-4-methylcyclohexyl tosylate with $(CH_3)_3SnLi$ proceeds with inversion at carbon to yield the *cis*-tin compound. The same conclusion has been reached for the *tert*-butylcyclohexyl system by Koermer, Hall, and Traylor.[5] With the availability of the spectroscopic data for the authentic cis and trans isomers above, we are now in a position to assign the isomers formed from the 4-alkyl cyclohexyl bromides.

***cis*-4-Methylcyclohexyl Bromide with Trimethyltinlithium.** The reaction of predominantly (>95%) *cis*-4-methylcyclohexyl bromide with $(CH_3)_3SnLi$ yielded an oil, the analysis of which corresponds to 4-methylcyclohexyltrimethylstannane. The 100-MHz ^1H NMR spectrum exhibited two $(CH_3)_3Sn$ signals at −0.04 and +0.05 ppm in the ratio of ~2:1, such resonance positions corresponding nicely with those for trans and cis isomers, respectively (vid supra) (see Figure 5). The CCH_3 doublets half overlapped as expected ("three" lines instead of four), and other features were consistent with a cis,trans mixture. The PFT ^{13}C spectrum (Figure 6) establishes the presence of both isomers, with resonances present essentially identical in position with those alluded to above for the authentic trans and cis isomers. The isomer ratio is trans/cis ~2.3:1, based on the $(CH_3)_3Sn$ signal intensities.

***cis*-4-*tert*-Butylcyclohexyl Bromide with Trimethyltinlithium.** This reaction (employing >95% *cis*-bromide) yielded the expected tetraorganostannane which was clearly an isomeric mixture. A duality of $(CH_3)_3Sn$ signals (~2:1) appeared in the ^1H (Figure 7) (+0.07 and −0.03 ppm)

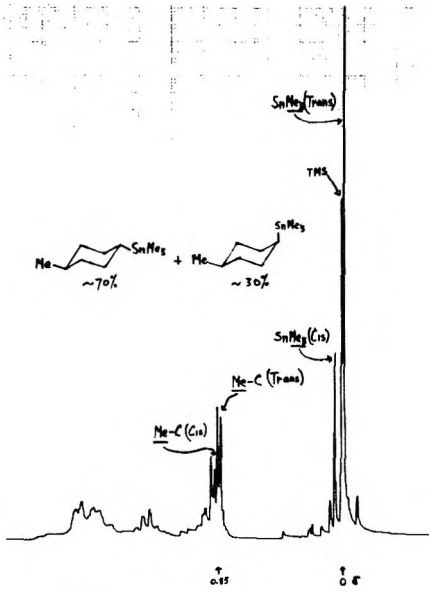


Figure 5. The 270-MHz ^1H spectrum of the isomeric mixture of stannanes obtained from (>93%) *cis*-4-methylcyclohexyl bromide and $(CH_3)_3SnLi$. Comparison with the ^1H spectra of the authentic cis and trans isomers confirms the predominance of the trans isomer.

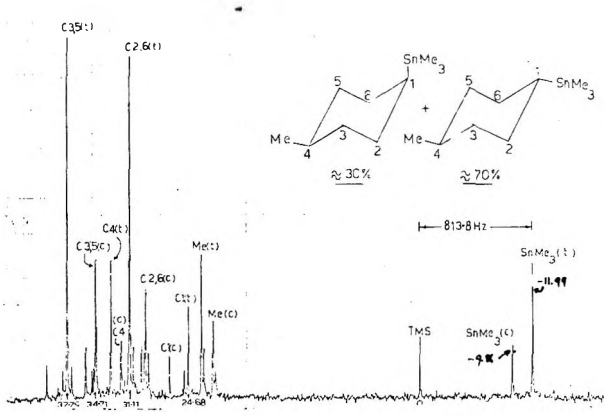


Figure 6. The proton-decoupled PFT 67.89-MHz ^{13}C spectrum of the stannane mixture obtained from (>95%) *cis*-4-methylcyclohexyl bromide and $(CH_3)_3SnLi$. The trans isomer clearly predominates, as deduced from the ^1H spectrum (Figure 5).

and ^{13}C (Figure 8) (−9.41 and −12.04 ppm) NMR spectra (with the higher field signals more intense) with the $C(CH_3)_3$ resonance at +0.85 ppm (^1H). We did conduct a reaction between *trans*-4-*tert*-butylcyclohexyl tosylate and $(CH_3)_3SnLi$ and obtained an impure product whose ^1H spectrum nevertheless was appropriate for a 4-*tert*-butylcyclohexyltrimethylstannane and was isomerically homogeneous. The $Sn(CH_3)_3$ resonance at +0.07 ppm characterized an axial $Sn(CH_3)_3$ group, assuming an inversion mechanism established in the case of the 4-CH_3 counterpart. There was no "broad triplet" absorption in the δ ~1.2 region, previously ascribed to an axial methine proton >C(^1H)$SnMe_3$.

Consideration of the above data establishes the predominance of the trans isomer. In particular, −12.04 ppm in the ^{13}C spectrum agrees very well with shifts established for equatorial $Sn(CH_3)_3$.[7] Note that the shift of −9.41 ppm for $Sn(CH_3)_3$ in the cis isomer is somewhat to lower field than the corresponding signal (at −9.85 ppm) for *cis*-4-methylcyclohexyltrimethylstannane. This is because the 4-*tert*-butyl group is more effective than a 4-CH_3 group in controlling the position of the (a,e) conformational equilibrium in the *cis*-4-alkylcyclohexyltin compounds, and the shift of −9.41 ppm agrees

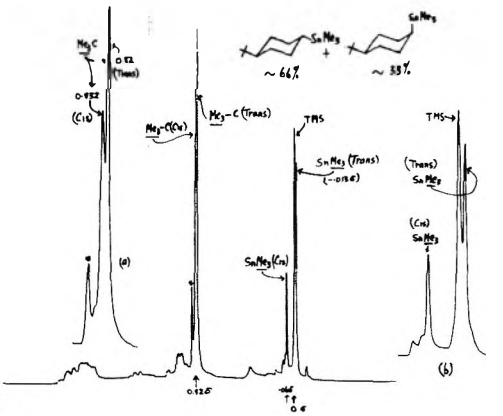


Figure 7. The 270-MHz ^1H NMR spectrum of the stannane mixture obtained from (>95%) *cis*-4-*tert*-butylcyclohexyl bromide and $(CH_3)_3SnLi$. Chemical shift considerations strongly suggest the predominance of the trans isomer.

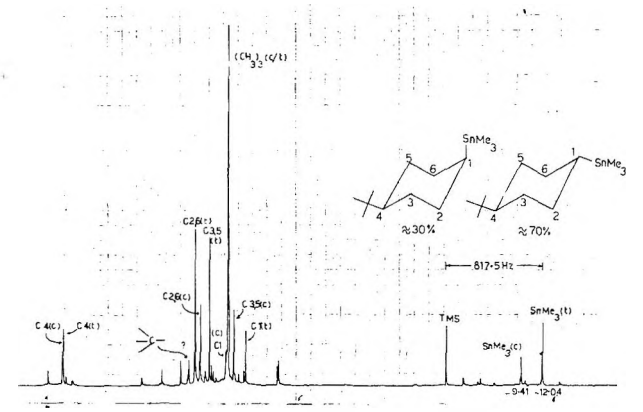
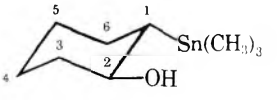


Figure 8. The proton-decoupled PFT 67.89-MHz ^{13}C spectrum of the stannane mixture obtained from (>95%) *cis*-4-*tert*-butylcyclohexyl bromide and $(CH_3)_3SnLi$. Consideration of $Sn(CH_3)_3$ resonances and vicinal ^{119}Sn–^{13}C couplings confirm the predominance of the trans isomer.

reasonably well with that for axial $Sn(CH_3)_3$ in cyclohexyltrimethylstannane (−9.27 ppm).[7] Further compelling evidence that the trans isomer predominates follows from the values of vicinal (^3J) ^{119}Sn–^{13}C couplings. A value of 67.1 Hz is associated with the more intense carbon resonance vicinal to tin and corresponds to a trans (θ = 180°) arrangement. The other vicinal coupling (12 Hz) agrees well with a predicted value[11] of ~10 Hz for θ = 60°, as present in the cis isomer. It is also interesting to note that in the ^1H spectrum of this product mixture there is significant absorption in the δ 1.2 region, as expected for an axial methine proton, >C(^1H)-$SnMe_3$, in the trans isomer.

These results on the 4-*tert*-butyl system contrast markedly with those of Traylor et al.[5] who reported formation of exclusively cis isomer.[18]

Cyclohexene Oxide with Trimethyltinlithium. Cyclohexene oxide reacted smoothly and a hydroxycyclohexyltrimethylstannane was obtained and shown to be isomerically pure by its ^1H and (particularly) its ^{13}C spectrum, the latter



exhibiting the anticipated seven signals (excluding $^{117,119}Sn$ satellites). In the ^1H spectrum, the methine proton >C(H)OH at δ 3.54 was quite broad ($W_{1/2}$ ~ 24 Hz), indicating two adjacent trans diaxial protons. Thus, the trans diequatorial structure is implicated and supported by the ^{13}C spectrum,

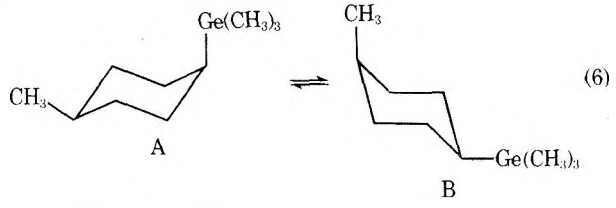
particularly the values of the two different vicinal $^{119}Sn-^{11}C$ couplings of 52 and 50 Hz. The calculated chemical shifts, based on the known substitutent effects of equatorial $Sn(CH_3)_3$[7] and OH[19] in cyclohexanes agree quite well with those observed. The largest discrepancies occur for C_1 and C_3. The vicinal couplings are slightly smaller than in alkyl-substituted cyclohexylstannanes, but the effect of oxygen functionality on vicinal $M^{13}C$ couplings has been noted before in organomercury systems.[14]

Thus the above reaction proceeds with inversion at carbon to yield *trans*-2-hydroxycyclohexyltrimethylstannane. Recently Fish and Broline reported the same stereochemical outcome for the reaction of triphenyltinsodium with cyclohexene oxide.[20]

(B) Organogermanium Systems. In view of the results obtained with $(CH_3)_3SnLi$, we decided to examine similar reactions with $(CH_3)_3GeLi$, now routinely prepared from $(CH_3)_3GeBr$ using hexamethylphosphoric triamide as solvent.[21] Our feeling was that electron-transfer and/or -displacement reactions at bromine in the 4-alkylcyclohexyl bromides may be more important with this reagent,[22] leading to a greater degree of overall retention at carbon.

***cis*-4-Methylcyclohexyl Bromide with $(CH_3)_3GeLi$.** In the ^1H NMR spectrum of the product 4-methylcyclohexyltrimethylgermane, $(CH_3)_3Ge$ resonances at δ 0.035 and 0.08 are observed, with the lower field resonance more intense (~2.5:1). As explained previously for the tin systems, this lower field resonance is more likely to be $Ge(CH_3)_3$ in the cis isomer, as this group will, to a significant degree, be axial, depending on the equilibrium constant for (a,e) interconversion. This constant in turn is dependent on the *A* values of the CH_3 and $Ge(CH_3)_3$ groups. Two overlapping CCH_3 doublets are discernible in the ^1H spectrum, at 0.86 and 0.94 ppm, with the lower field one more intense, again consistent with a predominance of cis isomer. In the ^{13}C spectrum, $(CH_3)_3Ge$ signals at −4.48 and −3.18 ppm are recorded, again with the lower field resonance more intense. Reasonable extrapolation from the NMR data for the analogous isomeric tin compounds indicates the predominant formation of *cis*-4-methylcyclohexyltrimethylgermane. In addition, cyclohexyltrimethylgermane itself[8a] (from cyclohexyl bromide and $(CH_3)_3GeLi$) shows ^1H and ^{13}C shifts (for $Ge(CH_3)_2$) at δ 0.05 and −4.49, respectively, and $Ge(CH_3)_3$ is certain to prefer strongly an equatorial orientation (vide infra). These conclusions were confirmed in the following way.

We reasoned that the *A* value for $Ge(CH_3)_3$ would be greater than that for $Sn(CH_3)_3$ (1.06 ± 0.14 kcal/mole)[7] and in all probability be quite comparable with that for CH_3 (1.74 kcal/mole).[15] Hence the following equilibrium (eq 6) would



(6)

obtain with $K \sim 1$ at low temperatures. Therefore, if the −3.18-ppm carbon signal ($Ge(CH_3)_3$) at ambient temperature were ascribable to the above mobile cis system, the signal should collapse with reducing temperature and, at the slow interconversion limit, be replaced by two signals, one for axial $Ge(CH_3)_3$ (A) and another for equatorial $Ge(CH_3)_3$ (B). However, the −4.48-ppm signal, alleged above to represent $Ge(CH_3)_3$ in the *trans*-4-methyl isomer, should be essentially nondependent on temperature. On cooling from 302 K through 253 K, the 3.18-ppm signal broadens and at 203 K has disappeared to be replaced by new signals at ~−1.2 ppm and another more intense signal, unfortunately but not unexpectedly, overlapping with the signal ascribed to $Ge(CH_3)_3$ in the trans compound. In addition the CH_3C signal at 19.75 ppm (302 K) resolves into signals at 17.45 (axial CH_3C in B)[15] and 23.17 ppm (equatorial CH_3 in A) at 203 K, with the former representing B clearly more intense. K_{203} [B]/[A] is calculated to be ~3. This temperature dependence and chemical shift correlations establish the dominant isomer to be cis.

Concordant data is obtained from the 4-*tert*-butylcyclohexyl system described below.

***cis*-4-*tert*-Butylcyclohexyl Bromide with $(CH_3)_3GeLi$.** 4-*tert*-Butylcyclohexyltrimethylgermane was isolated from this reaction and exhibited $(CH_3)_3Ge$ ^1H resonances at δ 0.05 and 0.16 and ^{13}C signals for $(CH_3)_3Ge$ at −1.17 and −4.49 ppm, with the lower field resonance in each case more intense (~2.5:1). Note the remarkably good agreement between the shift of −1.17 ppm for axial $Ge(CH_3)_3$ here and that for the axial $Ge(CH_3)_3$ in the "frozen" (a,e) form of the *cis*-4-methylcyclohexyl derivative. This is because in the *cis*-4-*tert*-butyl derivative the *tert*-butyl group will greatly favor the equatorial orientation, necessitating an axial $Ge(CH_3)_3$. Also noteworthy is the correspondence between the equatorial $Ge(CH_3)_3$ shift in the *trans*-4-methyl (−4.48 ppm), *trans*-4-*tert*-butyl (−4.49 ppm), and cyclohexyltrimethylgermane itself (−4.49 ppm).

We did attempt to synthesize pure *trans*-4-methylcyclohexyltrimethylgermane via the Grignard route which provided access to the tin compound, but the reaction yielded virtually none of the desired compound. Additionally, we reacted *trans*-4-methylcyclohexyl tosylate with $(CH_3)_3GeLi$, hoping to produce the cis isomer. None of the desired compound was isolated.

In any event, the ^1H and ^{13}C NMR data establish the formation of isomeric mixtures in these $(CH_3)_3GeLi$ reactions with *cis*-4-alkylcyclohexyl bromides, with the cis isomers predominating.

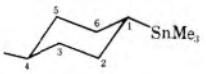
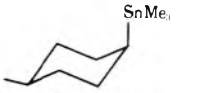
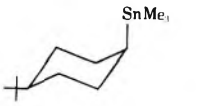
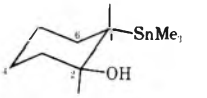
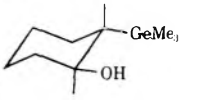
Reaction of Cyclohexene Oxide with $(CH_3)_3GeLi$. This reaction proceeded smoothly and in high yield to provide a colorless oil which solidified at room temperature. The microanalysis and ^1H and ^{13}C spectra establish its constitution as *trans*-2-hydroxycyclohexyltrimethylgermane. The methine proton (>C(**H**)OH) with $W_{1/2} \sim 24$ Hz for its ^1H signal (δ 3.4) requires two trans diaxial vicinal couplings. In a related compound, the methine proton (>C(**H**)OH) in *cis*-2-hydroxycyclohexyltrimethylsilane[23] (δ 4.15) has $W_{1/2} \sim 11$ Hz, consistent with an equatorial orientation. The PFT ^{13}C spectrum established the presence of one isomer (total of seven signals; also one $(CH_3)_3Ge$ signal in the ^1H spectrum) and the observed shifts agreed nicely with those calculated for the trans isomer, assuming additive substituent effects on the ^{13}C shifts by OH and $Ge(CH_3)_3$ groups, both equatorial.[16,19] As in the case of $(CH_3)_3SnLi$, epoxide ring opening proceeds with anti stereochemistry. A full listing of ^{13}C NMR parameters is in Table I.

Substitution Mechanisms. $(CH_3)_3SnLi$ Reactions. The formation of pure *cis*-4-methylcyclohexyltrimethylstannane from *trans*-4-methylcyclohexyl tosylate and *trans*-2-hydroxycyclohexyltrimethylstannane from cyclohexene oxide require inversion of configuration at carbon. There seems no justification in postulating other than an S_N2 mechanism for these transformations, which is consistent with the displacement of "hard" oxy-type leaving groups. Traylor et al.[5] reported inversion of configuration for $(CH_3)_3Sn$ displacement on *trans*-4-*tert*-butylcyclohexyl tosylate.

The nonstereospecific nature of the reactions with *cis*-4-methyl- and *cis*-4-*tert*-butylcyclohexyl bromides requires other mechanistic considerations, but it is possible or even probable that the trans (inverted) product also results from simple S_N2 displacements. Kinetic evidence supporting an S_N2 description is not available for any of these systems.

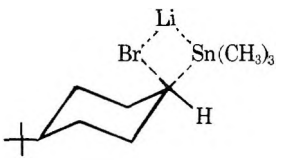
There are a number of possible mechanisms that could

Table I. Carbon-13 NMR Chemical Shifts[a] of Cyclohexyl Compounds

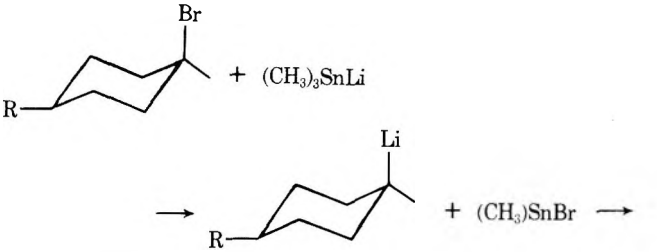
Registry no.	Compd	Carbon 1	2	3	4	5	6	$M(CH_3)_3$	CH_3	CH_3C
64871-26-7		24.77 (~390)	31.13 (nr)	37.82 (67.5)	33.13	37.82 (67.5)	31.13 (nr)	−11.97 (305; 289)	23.26	
	Calcd	24.45	30.87	37.88	32.53	37.88	30.87			
64871-27-8		26.70 (403.2; 384.7)	29.37 (nr)	34.68 (23.1)	31.97	34.68 (23.1)	29.37 (nr)	−9.85 (~292)	22.00	
64871-28-9		25.26	31.72	29.91 (67.1)	48.53	29.91 (67.1)	31.72	−12.04	27.46	32.49?
	Calcd	24.26	31.67	30.18	48.83	30.18	31.67			
38630-14-7		27.80	31.06	26.78 (12.0)	48.57	26.78 (12.0)	31.06	−9.41	27.53	nl
	Calcd			26.33		26.33				
		35.39 (~300)	74.34 (nr)	38.30 (52)	25.14	27.40 (50)	29.24 (nr)	−10.57		
64871-29-0	Calcd (trans)	32.65	74.07	36.88	25.83	27.38	29.77			
64871-30-3	Calcd (cis, axial OH)	30.25	68.67	34.5	20.13	28.28	24.07			
58992-27-1		27.90	28.74	28.31	27.06	28.31	28.74	−4.48		
64871-31-4		27.03	28.85	36.94	32.28	36.94	28.85	−4.49	23.18	
	Calcd	27.6	28.74	37.3	32.66	37.3	28.74			
64871-32-5		27.35	24.71	33.43	29.56	33.43	24.71	−3.24	19.59	
64871-33-6		27.22?	28.9	28.9	48.08	28.9	28.9	−4.49	27.5	32.61
	Calcd	27.51	28.83	28.75	48.07	28.75	28.83		27.5	32.26
64871-34-7		27.5	27.5?	25.39	48.36	25.39	27.5?	−1.17	27.5	33.42
		36.72	73.51	37.97	25.15	27.37	26.8	−2.74		
64871-08-5	Calcd (trans)	35.8	71.94	36.21	25.96	~28.00	27.64			
64871-10-9	Calcd (cis, axial OH)	33.4	66.54	33.81	20.26	27.6	21.94			

[a] Referenced to internal Me_4Si for $CDCl_3$ solvent. Low-temperature spectra for CD_2Cl_2 solvent. Numbers in parentheses refer to ^{13}C-^{119}Sn coupling constants. Calculated chemical shifts assume additivity of substituent effects on chemical shifts. [b] In the spectrum of the *cis*- and *trans*-4-*tert*-butylcyclohexyltrimethylgermanes there is considerable signal overlap at 27.5 and 28.9 ppm, and some assignments are therefore uncertain.

explain the retention (i.e., cis) product. The simplest would be a four-center process, but this cannot operate exclusively, as other products, e.g., hexamethylditin, cycloalkene, and almost certainly bicyclohexyls, need to be explained. The cycloalkene may arise mainly from β elimination, and decomposition of the resulting $(CH_3)_3SnH$ would yield hexamethylditin.



A strong possibility as a first step is a displacement formally on bromine to yield (via bromo–lithium exchange) a 4-alkylcyclohexyllithium and $(CH_3)_3SnBr$.[5,6] (Subsequent reaction of $(CH_3)_3SnBr$ and $(CH_3)_3SnLi$ would produce hexamethylditin.) The above reaction is indicated to yield *cis*-4-alkylcyclohexyllithium, which seems very plausible when mechanisms for this bromo–lithium exchange are considered. Rapid capture by $(CH_3)_3SnBr$ would then yield the tetraorganostannane, and Traylor[5] considered this sequence would produce pure *cis*-tin compound. However, the stereochemistry of electrophilic substitution at the carbon–lithium bond is by no means settled, and variable results have been reported.



Glaze[24] has reported that deuteriolysis of 4-*tert*-butylcyclohexyllithium proceeds with predominant retention at carbon, whereas bromination (with molecular bromine in pentane) yields predominantly inverted product, with temperature effects on the cis/trans ratio being unexplained.[25] Radicals may be implicated in these reactions. More polar brominating agents, e.g., pyridine-Br_2, were reported to proceed with predominant retention.[26] Most pertinent perhaps was the finding[26] that trimethylsilyl chloride reacted with 4-*tert*-butylcyclohexyllithium with predominant retention, and a similar outcome is reasonable for $(CH_3)_3SnBr$. A further aspect concerns the configurational stability of the C–Li bond in an ether solvent (THF) at 25–30 °C. There is evidence that ethers promote C–Li bond dissociation so that carbanion-triggered inversion may occur and hence lead to some trans product.[27] Bicyclohexyl formation might be explained in part by coupling of the cyclohexyllithium with unreacted cyclohexyl bromide.

Electron transfer from $(CH_3)_3SnLi$ to bromine must also be considered and would proceed as shown in eq 7. Tetraorganostannane, alkylbicyclohexyls, and hexamethylditin would be anticipated products, and almost certainly some *trans*-4-alkylcyclohexyltrimethylstannane would result, when the component radical stabilities are considered. At the moment, we have no evidence that this explanation is superior to one involving a combination of S_N2 at carbon (to yield the trans compound) and the two-step halogen–lithium‖ coupling reaction to yield the cis compound. Also no evidence is available to indicate stereochemistry at the tin center during these reactions. Very recently[28] ESR studies of certain metalate ion reactions with alkyl halides were reported,and in the case of $(CH_3)_3SnLi$ and cyclopropylcarbinyl halides it was concluded that a free-radical pathway was operative to extents regulated by the halide, solvent, etc.

$(CH_3)_3GeLi$ Reactions. The $(CH_3)_3GeLi$ reactions differ in that cis product clearly predominates (~2.5:1) for 4-CH_3 and 4-*tert*-butyl systems. Previously Bulten and Noltes[29] had investigated the reactions of $(CH_3)_3GeLi$ (in HMPA) with a variety of substrates, but no mechanistic conclusions could be drawn. Subsequently Eaborn, Hill, and Simpson[30] investigated reactions of optically active ethyl(1-naphthyl)phenylgermyllithium (R'_3Ge^*Li) with alkyl halides (RX) to yield optically active (R'_3GeR) compounds. Processes proceeding with both predominant retention (e.g., CH_3Br, $PhCH_2Cl$, $CH_2{=}CHCH_2Cl$) and inversion (e.g., CH_3I, $CH_2{=}CHCH_2I$, $PhCH_2I$) at germanium were identified. Suggestions were that the retention process involved direct coupling between R'_3Ge^*Li and RX in a four-center process, whereas the inversion process resulted from halogen–lithium exchange to give R'_3GeX and RLi (four-center retention) followed by coupling between R'_3GeX and RLi with inversion at germanium. Clearly a mechanistic duality was demonstrated for these reactions.

In the cases reported herein, it is clear that the mechanisms outlined for the $(CH_3)_3Sn$ reactions may also be operative to varying degrees. The most appealing suggestions are that the ~30% *trans*-4-alkylcyclohexyltrimethylgermane results from straightforward S_N2 displacement, while the cis compound is the result of halogen–lithium exchange (retention) followed by capture (with retention) of the cyclohexyllithium by $(CH_3)_3GeBr$. Eaborn's results indicate that alkyl bromides (e.g., isopropyl) react with predominant retention at germanium, a result consistent with an S_N2 description, although stereochemistry at carbon was not established. We would anticipate that electron-transfer mechanisms would be more important for R_3GeLi than R_3SnLi, but definite evidence along these lines is still being sought. Ring opening of cyclohexene oxide by $(CH_3)_3GeLi$ almost certainly requires the S_N2 description.

It is worthwhile emphasizing that bridgehead chlorides are unreactive toward $(CH_3)_3SnLi$, whereas bridgehead bromides are reactive[5,18] and provide a straightforward route to bridgehead tin derivatives. In view of this reactivity of bridgehead bromides which must proceed with retention, the variable stereochemistry in certain 7-norbornyl systems,[6] and the mixed stereochemistry for simple cyclic bromides reported here, it is clear that both stereochemical outcomes are possible and regulated by factors as yet incompletely defined.

The Conformational Preference of the Trimethylgermyl Group $(CH_3)_3Ge$. Previously we determined conformational free-energy differences for $Sn(CH_3)_3$ and $Pb(CH_3)_3$ in cyclohexane by direct observation.[7] Data accumulated in this work allow an indirect, but nevertheless useful, estimate of $\Delta G°(Ge(CH_3)_3)$. We have already discussed the variable-temperature ^{13}C spectra of *cis*-4-methylcyclohexyltrimethylgermane, and deduced that $K([B]/[A]) \sim 3$. Using the recently determined[15] $-\Delta G°(CH_3)$ of 1.74 kcal/mol, a $-\Delta G°_{203}[Ge(CH_3)_3]$ of 2.1–2.2 kcal/mol can be calculated. This assumes additivity of conformational energies. Alternatively, we can employ the chemical shift of CCH_3 in the mobile cis form (at 302 K) (19.75 ppm) in conjunction with those for equatorial CCH_3 (23.47 ppm) and axial CCH_3 (17.43 ppm)[15] to calculate another value of [B]/[A]. This procedure leads to $-\Delta G°[Ge(CH_3)_3]$ of 2.0 kcal/mol. The same method applied to $Ge(CH_3)_3$ chemical shifts gives a virtually identical result. That these "additivity" procedures are reasonable follows from calculations on the closely related cyclohexyltin systems. The directly determined $-\Delta G°_{204}[Sn(CH_3)_3]$ is 1.06 ± 0.14 kcal/mol,[7] whereas a value of 1.03 kcal/mol is obtained by utilizing the chemical shifts of either CCH_3 or $Sn(CH_3)_3$ in the mobile *cis*-4-methylcyclohexyltrimethylstannane, together with the appropriate reference values for equatorial and axial groups. There is no doubt the *A* value ($A = -\Delta G° = RT \ln K$) for $Ge(CH_3)_3$ is greater than that for CH_3, and the $Ge(CH_3)_3$ (~2.0 kcal/mol), $Sn(CH_3)_3$ (~1.1 kcal/mol), and $Pb(CH_3)_3$ (~0.7 kcal/mol) sequence reflects increasing C–M bond lengths, which apparently in part offset increasing atom size.

Experimental Section

Compounds. ***cis*-4-Methylcyclohexyl bromide** was prepared from commercial (predominantly trans ~65–70%) 4-methylcyclohexanol by reaction with triphenylphosphine dibromide in dry acetonitrile: yields were of the order of 55–60%; bp 75–78 °C (18 mm) [lit. 64–65 °C at (14 mm)];[32] the ^1H NMR spectrum showed the bromide to be >95% cis, H_{eq} at δ 4.45 (narrow m) and H_{ax} (~5%) at 3.9 (br).

***cis*-4-*tert*-Butylcyclohexyl bromide** was obtained in the same way from the alcohol (~80% trans): bp 38–40 °C (0.3 mm); mp 20–23 °C [lit. bp 70 °C (2 mm); mp 23–25 °C];[31] ^1H NMR H_{eq} at δ 4.7, $(CH_3)_3C$ at 0.9.

***trans*-4-Methylcyclohexyl tosylate** was prepared from trans alcohol, obtained by the method of Stork and White:[32] bp 101–102 °C (56 mm) [lit. 100.5–101 °C (56 mm)].[32] This alcohol showed >C(H)OH (axial) at 3.5 ppm (>95%) and >C(H)OH (equatorial) at 3.9 ppm. The tosylate was prepared in the standard way from tosyl chloride in pyridine: mp 70.5–71 °C (lit. 70.8–71.8 °C);[33] ^1H NMR H_{ax} at 4.3 ppm (br m).

Cyclohexene oxide was prepared, via the bromohydrin, in the manner outlined by Read and Hurst:[33] bp 66 °C (60 mm) [lit. 129–130 °C (760 mm)]; ^1H NMR δ 1.4 (4 H), 1.9 (4 H), 3.15 (2 H). Another identical sample was obtained by treating cyclohexene with *m*-chloroperbenzoic acid in the usual way.

***trans*-4-Methylcyclohexyltrimethylstannane** was obtained from the reaction of the Grignard reagent (prepared from (>95% *cis*-4-methylcyclohexyl bromide in the normal way) with $(CH_3)_3SnCl$. Standard workup and distillation yielded a clear oil with bp 68–72 °C (3–5 mm). VPC analysis indicated slight contamination with another component, suspected to be bis(4-methylcyclohexyl).

Anal. Calcd for $C_{10}H_{22}Sn$: C, 46.00; H, 8.4. Found: C, 48.1; H, 8.7. Although the carbon analysis is slightly high, the ^1H and ^{13}C NMR confirm the consitution. The yield of distilled material was about 30%.

Preparation of Trimethyltinlithium. This reagent was prepared basically in the manner described by Tamborski and co-workers.[34] Lithium metal (3.36 g, 0.48 mol) was cut into small pieces which were then protected and flattened with a hammer. The flattened Li pieces (now about the size of a cent) were then cut into smaller pieces (~2-mm wide) and placed in the reaction vessel containing anhydrous THF. The vessel (250-mL round-bottom flask) was fitted with a condenser, drying tube, N_2 inlet, and pressure equalizing dropping funnel. $(CH_3)_3SnCl$ (9.58 g, 0.048 mol) was dissolved in dry THF (~30 mL) and placed in the dropping funnel. The reaction vessel was cooled (0 to ~−5 °C) and blanketed with N_2, and the Li/THF was stirred vigorously. The $(CH_3)_3SnCl$ solution was added dropwise, and a color change to dark olive green usually appeared after about 15 min. Stirring was continued for about 2 h. The unreacted Li metal was removed by filtering the solution (under N_2 pressure) through a fitted bent side arm into an attached 250-mL three-neck round-bottom flask. The $(CH_3)_3SnLi$ solution is then available for reaction.

***cis*-4-Methylcyclohexyltrimethylstannane.** *trans*-4-Methylcyclohexyl tosylate (11.5 g, 0.043 mol) in dry THF (~30 mL) was added dropwise to the preformed $(CH_3)_3SnLi$ solution cooled to 0 °C under N_2. Reaction proceeded for a total of 5 h, and then the system was quenched with 20% NH_4Cl solution (~20 mL). The ethereal layer was separated and the aqueous layer extracted with ether. The combined organic layers were dried ($MgSO_4$) and ether was removed under reduced pressure. A ^1H NMR spectrum of the crude product was obtained, and $(CH_3)_3Sn$ resonances were observed for the desired product, as well as for hexamethyldistannane, which occurs to lower field and has two sets of $^{117,119}Sn$ satellites. Distillation yielded an oil: bp 95–100 °C (20 mm).

Anal. Calcd for $C_{10}H_{22}Sn$: C, 46.00; H, 8.4. Found: C, 44.17, H, 8.46. The ^1H and ^{13}C NMR spectra establish its constitution. (The yield was 40%.) Significant amounts of alkene and hexamethylditin were identified by ^1H NMR analysis.

***cis*- and *trans*-4-Methylcyclohexyltrimethylstannane.** The *cis*-4-methylcyclohexyl bromide (~10 g, 0.057 mol) was added to $(CH_3)_3SnLi$ in THF (~0.058 mol) and allowed to react for about 3 h. Workup in the standard way provided a crude oil which was found to have a trans/cis ratio of ~2:1, which was unchanged by our distillation procedure. The purified stannane had bp 57–59 °C (3 mm) (yield ~35%).

Anal. Calcd for $C_{10}H_{22}Sn$: C, 46.00; H, 8.44. Found: C, 46.06; H, 8.63. Concordant ^1H and ^{13}C spectra were obtained and described in the text. Hexamethylditin and probably bicyclohexyls were also found.

***cis*- and *trans*-4-*tert*-Butylcyclohexyltrimethylstannane** were prepared as described above for the 4-CH_3 isomer, and the crude oil obtained was examined by ^1H NMR to determine the cis/trans ratio. Substantial amounts of hexamethylditin were found and slightly contaminated the desired product on distillation, which had no effect on the cis/trans ratio. The yield was again poor (30–35%): bp 104–108 °C (4 mm).

Anal. Calcd for $C_{13}H_{28}Sn$: C, 51.48; H, 9.24. Found: C, 50.92; H, 9.24.

***trans*-2-Hydroxycyclohexyltrimethylstannane.** Cyclohexene oxide (4.5 g, 0.046 mol) was reacted with $(CH_3)_3SnLi$ (0.046 mol) in the manner described for the bromides, and the product was obtained in quite pure form in good yield (80%): bp 90 °C (3–4 mm); ^1H NMR δ 0.06 (9 H, $(CH_3)_3Sn$, $J \sim 52$ Hz), 1.0–2.2 (10 H, ring protons including –OH), 3.54 (m, 1 H, >C(**H**)OH).

Anal. Calcd for $C_9H_{20}SnO$: C, 41.11; H, 7.61. Found: C, 40.33; H, 7.81.

Preparation of Trimethylgermyllithium. The procedure described by Bulten and Noltes[21] was followed in essentially all details, and the filtered solution reacted with the bromides as described above.

Cyclohexyltrimethylgermane was prepared from the bromide and had boiling point [75 °C (20 mm)] and NMR spectra in agreement with those obtained previously.[8a]

***cis*- and *trans*-4-Methylcyclohexyltrimethylgermane.** *cis*-4-Methylcyclohexyl bromide (>95% cis) reacted with $(CH_3)_3GeLi$ in the normal way and distillation provided three fractions, which almost certainly contained some 4-cyclohexyl material as judged by ^1H NMR integration and VPC analysis (T = 70 °C, Hipase 3600 column). Fraction 3 [bp 78 °C (19 mm)] contained ~10% dicyclohexyls and 90% of the desired product as a mixture of isomers.

Anal. Calcd for $C_{10}H_{22}Ge$: C, 55.91; H, 10.25. Found: C, 56.7; H, 10.5. This corresponds to 95% germanium compound and 5% of 4,4′-dimethylbicyclohexane.

The mass spectrum exhibited peaks characteristic of the five germanium isotopes, and the cracking pattern observed was consistent with that anticipated for an unsymmetrical A_3GeB type.[35] A molecular ion m/e 216 for ^{74}Ge (36.47%) was observed, with correct isotopic intensities.

***cis*- and *trans*-4-*tert*-Butylcyclohexyltrimethylgermane** was obtained from the reaction of $(CH_3)_3GeLi$ with *cis*-4-*tert*-butylcyclohexyl bromide. The crude product was distilled to give three fractions, the first of which was mainly unreacted *cis*-bromide. Fractions 2 and 3, which were white solids at room temperature, contained no unreacted *cis*-bromide as revealed by the ^1H NMR spectrum. The germane product exhibited two $Ge(CH_3)_3$ peaks at δ 0.05 and 0.16 with the latter more intense [bp 90 °C (5 mm)].

Anal. Calcd for $C_{13}H_{28}Ge$: C, 60.79; H, 10.91. Found: C, 60.8; H, 11.22.

The mass spectrum exhibited a molecular ion at m/e 257 with the correct isotopic intensities. Other germanium-containing ions at m/e 242 (loss of CH_3), 200 (loss of *tert*-butyl), and 118 [$(CH_3)_3Ge$] were observed.

2-Hydroxycyclohexyltrimethylgermane. This product was obtained in satisfactory yield (~60%) as an oil which distilled [bp 96 °C (9 mm)] as a clear oil, but which soon solidified at room temperature (16 °C). The ^1H NMR spectrum exhibited one $(CH_3)_3Ge$ signal at δ 0.12, while >C(**H**)OH resonated at δ 3.4 as a broad band with the ring protons spread from δ 1 to 2; ν_{OH} observed at 3350 cm^{-1}. The mass spectrum did not contain a molecular ion at m/e 217, but a high intensity peak at m/e 199, corresponding to loss of H_2O.

Anal. Calcd for $C_9H_{20}OGe$: C, 49.8; H, 9.2. Found: C, 48.3; H, 9.36.

Solvents. Tetrahydrofuran was dried by distillation from a mixture of lithium aluminium hydride and calcium hydride and stored over 4A molecular sieves.

Hexamethylphosphoric triamide was treated with calcium hydride until bubbling activity stopped. The partly dried solvent was then stirred with sodium until the characteristic blue color persisted. When needed the HMPA was freshly distilled: bp 80–81 °C (3 mm).

NMR Spectra. ^1H NMR spectra were obtained for solutions in either $CDCl_3$ or CCl_4 and referenced to internal Me_4Si on Varian T-60 or Jeol MH100 spectrometers. Some ^1H spectra were obtained at 270 MHz at the National NMR Center in Canberra. ^{13}C spectra were obtained at either 22.625 or 67.89 MHz on Bruker spectrometers for $CDCl_3$ solutions referred to internal Me_4Si. Variable-temperature spectra were obtained for CD_2Cl_2 solutions.

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Registry No.—*cis*-4-Methylcyclohexyl bromide, 28046-90-4; *trans*-methylcyclohexanol, 28046-91-5; triphenylphosphine dibromide, 1034-39-5; *cis*-4-*tert*-butylcyclohexyl bromide, 5009-36-9; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; *trans*-4-methylcyclohexyl tosylate, 7453-05-6; tosyl chloride, 98-59-9; cyclohexene oxide, 286-20-4; $(CH_3)_3SnCl$, 1066-45-1; $(CH_3)_3SnLi$, 17946-71-3; Li, 7439-93-2; $(CH_3)_3GeLi$, 18489-76-4.

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Use of the Thallium Trinitrate Catalyzed Rearrangement of Ketones in the Synthesis of an Acidic Morphinan Derivative

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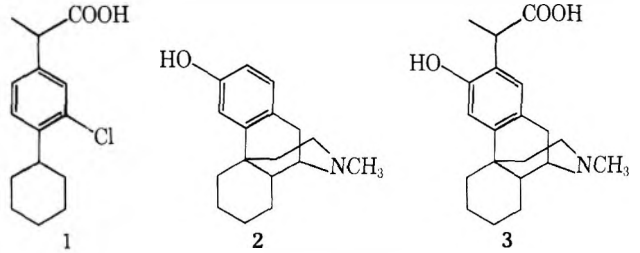
The introduction of the α-methylacetic acid side chain on D,L-*N*-methyl-3-hydroxymorphinan was carried out in an unsuccessful attempt to combine analgesic activity with the antiinflammatory activity associated with 2-arylpropionic acid derivatives. Using D,L-*N*-allyl-3-hydroxymorphinan as starting material, the key steps in the reaction sequence are the thallium trinitrate rearrangement of D,L-2-acetyl-3-methoxy-*N*-carboethoxymorphinan followed by the careful monomethylation of the acetic acid side chain of the rearrangement product using methyl iodide and lithium diisopropylamide. The Taylor–McKillop rearrangement is demonstrated to be useful in complex systems such as the morphinan.

In an attempt to combine both central analgesic and antiinflammatory activity in a single molecule we have developed a synthetic route to **3**, a molecule possessing both the structural features of the antiinflammatory phenylpropionic acids (**1**)[1] and the morphinan analgesics such as levorphanol (**2**).[2]



1 2 3

Results and Discussion

The synthetic plan envisaged introduction of the 2-propionic acid side chain on a suitable morphinan intermediate employing acylation, followed by rearrangement to the acid using the recently developed thallium trinitrate procedure of McKillop and Taylor.[3] Because there was insufficient information available on whether this reaction would proceed well with a propiophenone or with a free phenolic hydroxyl present, some initial model experiments were carried out. Direct rearrangement of propiophenone to methyl α-methylphenylacetate under the conditions of McKillop and Taylor gives poor yields.[3] Thallium trinitrate adsorbed on an insoluble inorganic support such as Florisil[4] or K-10[5] has been utilized to carry out this direct transformation. In our hands TTN adsorbed on Florisil led to none of the desired product and propiophenone was recovered quantitatively. The activity of this reagent was confirmed by reaction with acetophenone, which gave methyl phenylacetate in high yields. Therefore, instead of trying to sort out the reasons for such behavior with adsorbed thallium trinitrate, it proved more efficient to rely on direct methylation of the acetic acid side chain.

An attempted thallium-catalyzed rearrangement of *o*-hydroxyacetophenone (**5a**) at room temperature for 24 h gave no reaction, while the corresponding methyl ether (**5b**) was converted smoothly to the phenylacetate derivative **6b** in 15 min. Thus blocking of phenolic *o*-hydroxy groups is a requirement in the thallium trinitrate reaction.

As this rearrangement has been reported to proceed with difficulty with basic molecules[6] (presumably due to complex formation with the basic center), application of the thallium reaction to the morphinan system would be expected to require prior conversion of the amine to an acyl or carbamate derivative.

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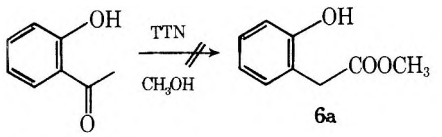
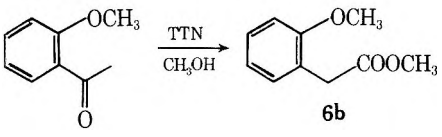


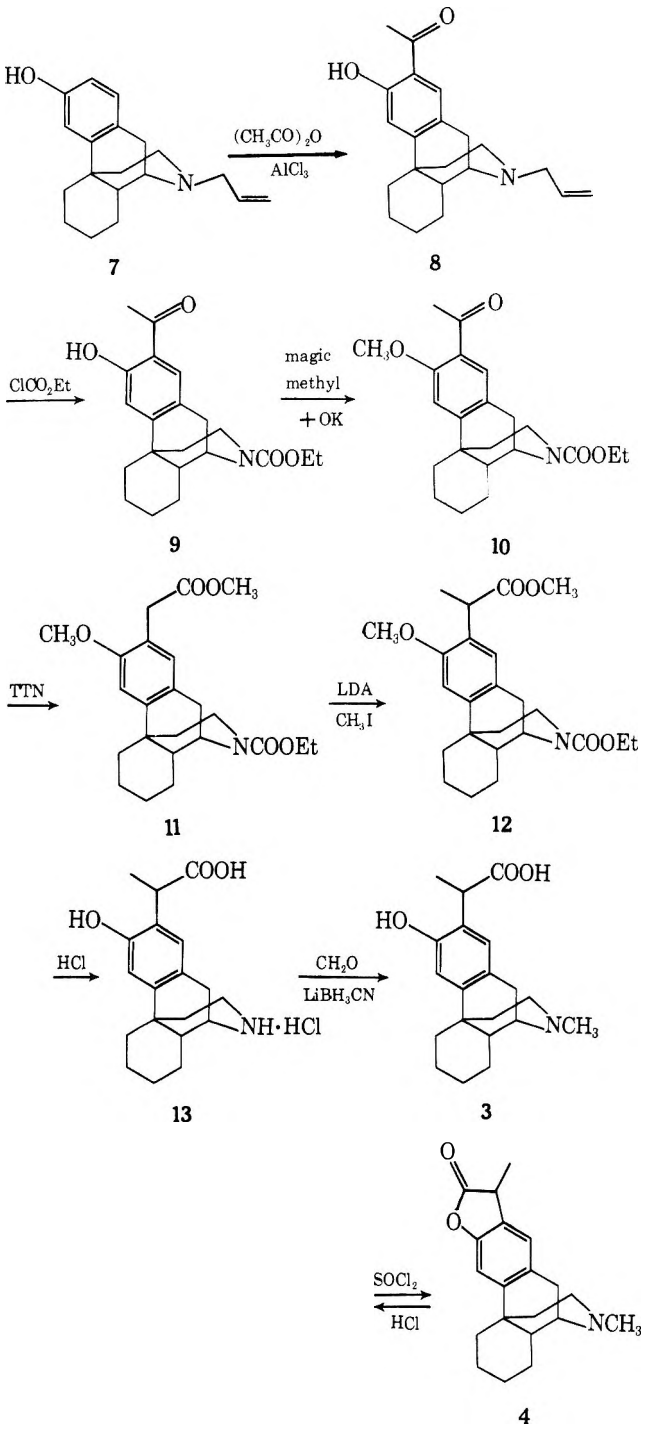
5a 6a



5b 6b

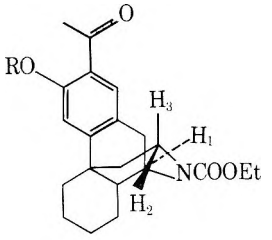
The plan of synthesis of **3** is outlined in Scheme I. D,L-3-Hydroxy-*N*-allylmorphinan (**7**) required as starting material was prepared according to the general procedure of Schnider and co-workers.[7]

Scheme I



Acetylation of **7** to give **8** employing acetic anhydride and aluminum chloride at 140 °C in nitrobenzene took place in 30 min exclusively at the 2 position. The position of acetylation was easily established from the two aromatic singlets at δ 7.03 and 7.67, demonstrating the para relationship of the two protons. The vigorous conditions required for acetylation were presumably a consequence of the presence of the basic nitrogen.[8]

Compound **8** was converted to **9** by reaction with ethyl chloroformate in refluxing benzene. The 220-MHz proton NMR spectrum of **9** indicated restricted rotation of the carboethoxy group as evidenced by the two broad singlets at δ 4.30 and 4.44 for equatorial H_1. The proton H_2, also deshielded as a consequence of lying in the carbonyl plane,[9] is seen as a pair of doublets centered at δ 3.88. The axial proton H_3 on the carbon α to the nitrogen showed an absorption of about δ 2.57 as several lines partially hidden by the acetyl group. Shielding was due to the proton being axial and over the π system of the benzene ring.[10]



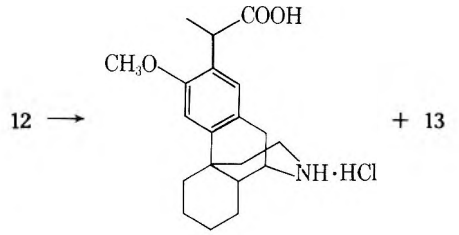
9

The potassium salt of **9**, generated by treatment with potassium *tert*-butoxide in glyme, was easily and quantitatively methylated with magic methyl (methyl fluorosulfonate)[11] at room temperature within 5 min to give **10**. Again with **10**, the 220-MHz NMR spectrum showed evidence of restricted rotation of the carbamate group as the equatorial α protons lying in the plane of the carbonyl are at δ 4.35 and 3.84 as broad signals. This indicates that the ambient temperature is essentially the coalescence temperature.

Thallium trinitrate rearrangement occurred smoothly on this ketone with the transformation **10** to **11** completed within 30 min at room temperature. The structure of **11** was proven by analysis, mass spectrometry, and NMR, which showed the expected methylene singlet at δ 3.40. Restricted rotation was again observed with two broad and poorly resolved absorptions at δ 4.38 and 4.23 for the proton H_1 and δ 3.90 and 3.81 for proton H_2.

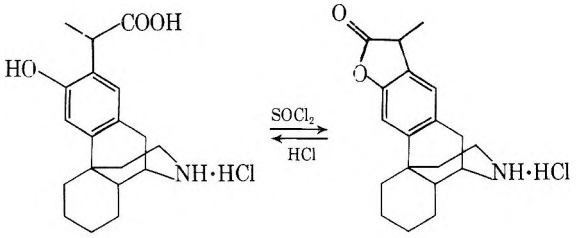
The C-alkylation of **11** was carried out using lithium diisopropylamide in tetrahydrofuran at −70 °C according to the procedure of Rathke,[12] in which the anion is quenched with excess methyl iodide. With careful precautions to exclude moisture, it was possible to obtain **12** with <1% of either starting material **9** or dialkylated ester. It was essential that the reaction be monitored by mass spectrometry in order to determine the exact quantity of base to be used.

The complete hydrolysis of **12** to **13** in acid proved to be a very slow reaction. The ester functionality disappeared first, followed by much slower hydrolysis of the carbamate function. After 3 days of refluxing **12** in equal volumes of concentrated hydrochloric acid and acetic acid, it was possible to detect and isolate the corresponding methoxy derivative **14**. After 144 h of reflux, the removal of the methoxyl group was completed. The resulting solution contained a mixture of the hydroxy acid **13** and its corresponding lactone **15**, easily detected by its infrared carbonyl at 1820 cm^{-1}. Treatment with chloroform afforded a clean separation of the lactone **15** from the hydroxy acid **13**. Heating the lactone in dilute hydrochloric acid solution and repeating the chloroform treatment eventually afforded a high yield of the hydrochloride salt of **13**. Further



14

examination of this equilibrium demonstrated that heating with thionyl chloride afforded a clean conversion of **13** to **15**.



13 15

The N-methylation of **13** to **3** was accomplished with the conditions of Borsch and collaborators[13] using formaldehyde and sodium cyanoborohydride in acetonitrile. Again, there was an equilibrium between the acid form **3** and the lactone **4**.

Biological testing on both **3** and **4** revealed neither analgesic nor antiinflammatory activity.

Experimental Section

Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer. A Varian EM-360 instrument was used to record NMR spectra in deuteriochloroform using tetramethylsilane as an internal standard. Elemental analyses were carried out by Dr. C. Daessle, Organic Microanalyses. The low-resolution mass spectral analyses were performed by Morgan-Schaffer Corp. and the high-resolution mass spectral analyses were performed on an AEI MS 902 mass spectrometer. The 220-MHz NMR spectra were carried out by the Canadian 220-MHz NMR Centre.

All reactions as well as column chromatography were followed by TLC using precoated 0.25-mm silica gel plates (Eastman Kodak) with visualization of spot either by UV or by exposure to iodine vapors.

Methyl Phenylacetate. To acetophenone (120 mg, 1 mmol) in carbon tetrachloride (5 mL) was added 1.5 g of thallium trinitrate adsorbed on Florisil prepared by adding 4.5 g of thallium trinitrate dissolved in 5 mL of methanol and 5 mL of methyl orthoformate to 10 g of Florisil and evaporating under vacuum to constant weight. The mixture was stirred at room temperature for 20 h. The spent reagent was removed by filtration, the filtrate was washed with water, dried, and evaporated under vacuum to an oil, identical with authentic methyl phenylacetate by Ir.[14]

Under identical conditions, propiophenone (135 mg, 1 mmol) was recovered intact after 20 h of reaction.

Methyl *o*-Methoxyphenylacetate (6b). o-Methoxyacetophenone (150 mg, 1 mmol) was added to 2.5 mL of methanol and 0.5 mL of 70% perchloric acid. It was cooled to 0 °C with an ice bath and thallium trinitrate (500 mL, 1.13 mmol) was added. It was stirred and when it reached room temperature, the reaction mixture was poured onto water and extracted with methylene chloride, washed with water, and dried over sodium sulfate. The residue was distilled under vacuum to yield 102 mg (60%) of methyl o-methoxyphenylacetate: bp 120 °C (20 mm); IR: 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.61 (2 H, s, CH_2), 3.66 (3 H, s, CH_3), 3.81 (3 H, s, CH_3), 7.00 (4 H, m, aromatic).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.71. Found: C, 66.20; H, 6.50.

The use of identical conditions on *o*-hydroxyacetophenone left it unchanged after 24 h at room temperature.

D,L-*N*-Allyl-3-hydroxymorphinan (7). D,L-*N*-Allyl-3-hydroxymorphinan (**7**) was prepared essentially by the method of Schnider and Hellerbach with an overall yield of 21% from cyclohexenylacetonitrile: mp 184–186 °C (lit.[7] 177–179.5 °C).

D,L-*N*-Allyl-2-acetyl-3-hydroxymorphinan (8). D,L-*N*-Allyl-3-hydroxymorphinan (6.7 g, 23.7 mmol), aluminium chloride (31 g, 0.23 mol), and acetic anhydride (7.5 mL) in 120 mL of nitrobenzene were heated under nitrogen for 30 min. Water was added and the nitrobenzene was removed by steam distillation. The aqueous solution was made basic with ammonium hydroxide and extracted three times with ethyl acetate. The extract was washed with water and dried (Na_2SO_4). Evaporation under vacuum left D,L-*N*-allyl-2-acetyl-3-hydroxymorphinan as a yellow oil (5.7 g, 74%): homogeneous by TLC, R_f 0.5 (ethyl acetate); IR 1655 (C=O), 1630 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 2.67 (3 H, s, CH_3), 7.03 (1 H, s, H_4), 7.67 (1 H, s, H_1); MS M^+ 325; hydrochloride salt mp 280–283 °C dec.

Anal. Calcd for $C_{21}H_{27}NO_2$·HCl: C, 69.69; H, 7.80; N, 3.87; Cl, 9.80. Found: C, 70.11; H, 8.00; N, 3.75; Cl, 9.80.

D,L-*N*-Carboethoxy-2-acetyl-3-hydroxymorphinan (9). D,L-*N*-Allyl-2-acetyl-3-hydroxymorphinan (6.7 g, 20.6 mmol) in 65 mL of benzene was treated with 65 mL of freshly distilled ethyl chloroformate. Reflux was maintained for 13 h after which the volatiles were removed under vacuum. The solid residue was dissolved in 300 mL of methylene chloride; the solution was washed with dilute hydrochloric acid and with water, dried (Na_2SO_4), and concentrated under vacuum. The residual oil was triturated in ether. The solid *N*-carboethoxy-2-acetyl-3-hydroxymorphinan (5.4 g, 74%) was filtered and air dried: mp 176–178.5 °C; it was homogeneous by TLC, R_f 0.8 (2% methanol in chloroform); IR 1710 and 1665 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz, CH_3), 2.60 (3 H, s, CH_3CO), 4.13 (2 H, q, J = 7 Hz, CH_2), 6.90 (1 H, s, H_4), 7.43 (1 H, s, H_1); MS M^+ 357.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 69.95; H, 7.56; N, 4.02.

D,L-*N*-Carboethoxy-2-acetyl-3-methoxymorphinan (10). To D,L-*N*-carboethoxy-2-acetyl-3-hydroxymorphinan (1.79 g, 5.0 mmol) in 50 mL of dimethoxyethane was added potassium *tert*-butoxide (0.85 g, 7.5 mmol) and then methyl fluorosulfonate (0.57 g, 5 mmol). Stirring was maintained for 15 min at room temperature. The reaction was quenched with water and then extracted with ether. The ether extract was washed with water and dried (Na_2SO_4). Evaporation yielded D,L-*N*-carboethoxy-2-acetyl-3-methoxymorphinan as an oil that crystallized on standing (1.8 g, 98%): mp 100–100.5 °C; it was homogeneous by TLC, R_f 0.6 (chloroform–petroleum ether, 1:1 v/v); IR 1715 and 1685 cm^{-1} (C=O); NMR ($CDCl_3$); δ 1.25 (3 H, t, J = 7 Hz, CH_2), 2.63 (3 H, s, CH_3CO), 3.90 (3 H, s, CH_3), 4.20 (2 H, q, J = 7 Hz, CH_2), 6.90 (1 H, s, H_4), 7.52 (1 H, s, H_1); MS M^+ 371.

Anal. Calcd for $C_{22}H_2NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.74; H, 8.05; N, 3.65.

D,L-*N*-Carboethoxy-2-carbomethoxymethyl-3-methoxymorphinan (11). D,L-*N*-Carboethoxy-2-acetyl-3-methoxymorphinan (2.9 g, 7.9 mmol) was dissolved in 50 mL of methanol. The solution was cooled and 9.2 mL of 70% perchloric acid was added slowly. Thallium trinitrate hydrate (7.0 g, 15.9 mmol) was then added. Within 5 min, a precipitate of thallous nitrate appeared. The suspension was stirred at room temperature for 45 min and then poured onto water. Following extraction with chloroform, drying over sodium sulfate, and evaporation, D,L-*N*-carboethoxy-2-carbomethoxymethyl-3-methoxymorphinan was obtained as an oil that crystallized on standing: mp 94.5–95 °C; homogeneous by TLC, R_f 0.8 in chloroform–petroleum ether, 1:1 v/v; IR 1755 and 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz, CH_3), 3.63 (2 H, s, CH_2), 3.75 (3 H, s, CH_3OCO), 3.85 (3 H, s, CH_3O), 6.85 (1 H, s, H_4), 7.00 (1 H, s, H_1).

Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.86; H, 8.22; N, 3.70.

D,L-*N*-Carboethoxy-2-(1-carbomethoxyethyl)-3-methoxymorphinan (12). D,L-*N*-Carboethoxy-2-carbomethoxymethyl)-3-methoxymorphinan (7.8 g, 19.4 mmol) in 40 mL of anhydrous tetrahydrofuran was added slowly to a solution of lithium diisopropylamide (2.08 g, 19.4 mmol) in 35 mL of tetrahydrofuran maintained at −75 °C. The mixture was stirred for 10 min then quenched by the addition of 20 mL of methyl iodide. The reaction was stirred for 20 minutes while the temperature was allowed to increase to room temperature. Water was added and the resulting mixture extracted twice with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated to yield 8.04 g (100%) of D,L-*N*-carboethoxy-2-(carbomethoxyethyl)-3-methoxymorphinan as an oil which solidified to an amorphous solid, homogeneous by TLC; R_f 0.5 in methylene chloride. Mass analysis revealed the product to be a mixture with the relative heights of apparent ions being 1.3% for starting material, 98.2% for monomethyl substituted, and 0.5% for dimethyl substituted: IR 1760 and 1705 cm^{-1} (C=O); NMR δ 1.27 (3 H, t, J = 7 Hz, CH_3), 1.43 (3 H, d, J = 7 Hz, CH_3), 3.67 (3 H, s, CH_3OCO), 3.80 (3 H, s, CH_3O), 4.13 (2 H, q, J = 7 Hz, CH_2), 6.77 (1 H, s, H_4), 6.93 (1 H, s, H_1).

Anal. Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.55; H, 7.77; N, 3.27.

D,L-2-(1-Carboxyethyl)-3-hydroxymorphinan Hydrochloride (13). D,L-*N*-Carboethoxy-2-carbomethoxyethyl-3-methoxymorphinan (4.1 g, 9.9 mmol) in 100 mL of acetic acid and 100 mL of concentrated hydrochloric acid was refluxed for a period of 6 days under a nitrogen atmosphere. The reaction mixture was evaporated and the residue treated with 60 mL of chloroform. The solid that crystallized was filtered, washed with chloroform, and air dried. The filtrate was evaporate to dryness and the residue heated with 20 mL of 1 N hydrochloric acid on a steam bath for 30 min. Following evaporation to dryness and repeat treatment a second crop of crystals was obtained. The two crops were combined to yield 2.5 g (74%) of D,L-2-(1-carboxyethyl)-3-hydroxymorphinan hydrochloride: mp 216–225 °C dec; IR 1730 cm^{-1} (C=O); NMR (D_2O) δ 1.45 (3 H, d, J = 7 Hz, CH_3), 6.97 (1 H, s, H_4), 7.15 (1 H, s, H_1); MS M^+ 315.

Anal. Calcd for $C_{19}H_{25}NO_3$·HCl: C, 64.85; H, 7.45; N, 3.98; Cl, 10.08. Found: C, 64.65; H, 7.34; N, 3.74; Cl, 10.04.

D,L-*N*-Methyl-2-(1-carboxyethyl)-3-hydroxymorphinan (3). To D,L-2-(1-carboxyethyl)-3-hydroxymorphinan hydrochloride (2.5 g, 7.1 mmol) suspended in 25 mL of acetonitrile was added 3.0 mL of 36% aqueous formaldehyde. After stirring 5 min, addition of sodium cyanoborohydride (2.0 g, 32 mmol) was made. Complete solution occurred, but within 5 min, an oily black material was observed. Stirring was continued for 45 min while acetic acid was added to maintain a pH of 6–7. The reaction mixture was taken to dryness and the black residue suspended in 100 mL of chloroform. The mixture was treated with 5 mL of thionyl chloride under reflux for 30 min and then filtered. The residue was washed well with chloroform and the filtrate was evaporated to yield 2.2 g (84%) of the lactone of D,L-*N*-methyl-2-(1-carboxyethyl)-3-hydroxymorphinan hydrochloride. This solid was suspended in 50 mL of 1 N hydrochloric acid and refluxed for 1 h. The solution was passed through a column of Dowex 50, H^+ charged. Elution with ammonium hydroxide (1.5 N) yielded 1.2 g of D,L-*N*-methyl-2-(1-carboxyethyl)-3-hydroxymorphinan: mp 237–239 °C; homogeneous by TLC, R_f 0.8 in methanol–chloroform–concentrated ammonia, 4:8:0.5 v/v/v; IR 1570 cm^{-1} (C=O); NMR (D_2O) δ 1.35 (3 H, d, J = 7 Hz, CH_3), 2.90 (3 H, s, CH_3N), 6.97 (1 H, s, H_4), 7.17 (1 H, s, H_1); MS $M^+ - H_2O$ 311; no M^+ detected.

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.71; H, 8.65; N, 4.40.

Lactone of D,L-*N*-Methyl-2-(1-carboxyethyl)-3-hydroxymorphinan Oxalate Salt (4). Crude lactone of D,L-*N*-methyl-2-carboxyethyl-3-hydroxymorphinan hydrochloride (1.0 g, 3.04 mmol) suspended in ether was carefully neutralized with dilute ammonium hydroxide. The ether layer was washed with water, dried over sodium sulfate, and concentrated to yield 0.64 g of the free lactone as an oil. This was dissolved in 25 mL of isopropyl alcohol and a solution of oxalic acid in isopropyl alcohol (180 mg, 2 mmol in 1 mL) was added. The oxalate salt which slowly crystallized overnight was filtered to yield 520 mg of salt; mp 162 °C dec; IR 1810 cm^{-1} (C=O); NMR ($CDCl_3$) (on free base) δ 1.57 (3 H, d, J = 7 Hz, CH_3), 2.43 (3 H, s, CH_3N), 7.00 (1 H, s, H_4), 7.27 (1 H, s, H_1); MS M^+ 311.

Anal. Calcd for $C_{20}H_{25}NO_2·C_2H_2O_4$: C, 65.10; H, 6.50; N, 3.61. Found: C, 64.89; H, 6.84; N, 3.89.

Acknowledgments. The authors would like to extend their appreciation to Mr. R. E. Rhodes for recording the high resolution mass spectra and to Mr. J. Scheigetz for preparing the *N*-allyl-3-hydroxymorphinan. The authors express their thanks to Drs. Alan W. Douglas and E. W. Tristram for helpful comments and suggestions on this manuscript. The authors wish also to thank Dr. K. T. Liu, Princeton University, for a helpful discussion on the preparation and use of TTN adsorbed on Florisil.

Registry No.—**3**, 64739-24-8; **4**, 64739-25-9; 4 HCl, 64739-26-0; **4** oxalate, 64739-27-1; **6b**, 27798-60-3; **7**, 64783-66-0; **8**, 64739-28-2; 8 HCl, 64739-29-3; **9**, 64739-30-6; **10**, 64739-31-7; **11**, 64739-32-8; **12**, 64739-33-9; **13**, 64739-34-0; methyl phenylacetate, 101-41-7; acetophenone, 98-86-2; methyl orthoformate, 149-73-5; *o*-methoxyacetophenone, 579-74-8; methanol, 67-56-1; acetic anhydride, 108-24-7; ethyl chloroformate, 541-41-3; methyl fluorosulfonate, 421-20-5; methyl iodide, 74-88-4; formaldehyde, 50-00-0; TTN, 13746-98-0.

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Reactivity of Cyclic Five- and Six-Membered Aryl α-Disulfones toward Nucleophiles

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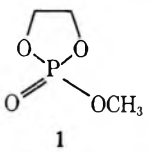
The rates of reaction of a cyclic five-membered aryl α-disulfone, naphtho[1,8-*cd*]-1,2-dithiole 1,1,2,2-tetroxide (**7**), and a six-membered compound, dibenzo[*ce*]-1,2-dithiin 1,1,2,2-tetroxide (**8**), with a variety of nucleophiles have been measured under the same conditions for which data are available on the rates of reaction of the nucleophiles with phenyl α-disulfone. In marked contrast to the behavior of the corresponding sultone, 1-naphthol-8-sulfonic acid sultone (**5**), which hydrolyzes 10^7 times faster than its open-chain analogue, α-disulfone **7** does not hydrolyze, or undergo any other nucleophilic substitution reactions, significantly faster than either phenyl α-disulfone or **8**. Measurement of the heat of alkaline hydrolysis of **7** suggests that this may be due to the fact that, in contrast to the situation with sultone **5**, there is no significant strain associated with the five-membered ring in **7**. Although **7** reacts with many nucleophiles (OH^-, HO_2^-, CN^-, NH_2NH_2) at about the same rate as does phenyl α-disulfone, it reacts with cyclic secondary and tertiary amines from 200 to 800 times slower than does the open-chain α-disulfone. This is believed to be due to a steric effect in which in **7** an ortho position in the naphthalene ring interferes with the approach of more bulky nucleophiles to the sulfonyl group. With phenyl α-disulfone such interference can be avoided by appropriate rotation of a phenyl group.

Certain cyclic five-membered sulfates and sultones undergo hydrolysis from 10^5 to 10^7 times faster than their acyclic analogues.[2] The situation is reminiscent of the phenomena observed in the hydrolysis of cyclic five-membered phosphates and phostonates.[3] Thus, just as methyl ethylene phosphate, **1**, hydrolyzes about 10^6 faster than trimethyl phosphate, **2**,



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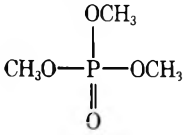

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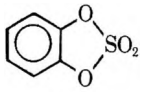

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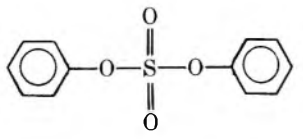

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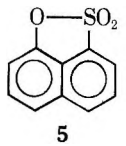
so catechol sulfate, **3**, hydrolyzes 2×10^7 faster than diphenyl sulfate, **4**.

In the case of the phosphorus derivatives, Westheimer[3] has made a convincing case that the rate acceleration is due to a relief of strain in the five-membered ring that occurs on going from the starting ester to a trigonal-bipyramidal intermediate in which the ring spans an apical and radial position. Data on the heat of hydrolysis[4] and x-ray studies of their structure[5] suggest that a comparable amount of ring strain is present in cyclic five-membered sulfates and sultones. The natural inference is that the large rate accelerations observed for the five-membered sulfates and sultones also have their origin in the relief of strain that occurs on going from the starting ester to a trigonal-bipyramidal intermediate (or transition state) in which the five-membered ring spans an apical and a radial position.

One of the five-membered cyclic sultones that undergoes hydrolysis much faster than an open-chain sultone is 1-naphthol-8-sulfonic acid sultone (**5**). Kaiser, Kudo, and Zaborsky[2c] showed that **5** hydrolyzes in alkaline solution 2.5×10^7 times faster than diphenyl sulfate (**4**) and 5×10^5 times faster than phenyl α-toluenesulfonate (**6**). From ^{18}O-labeling experiments on closely related substrates,[6] hydrolysis of **5** is known to take place via S–O bond cleavage, so that the large rate enhancement observed for this compound is definitely associated with an enhanced rate of substitution at the sulfonyl sulfur.



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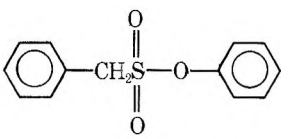

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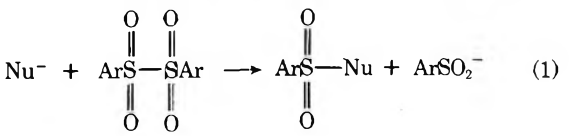
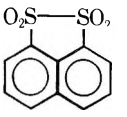
In recent years we have studied extensively[7] nucleophilic substitution reactions of aryl α-disulfones. These can be represented generally as shown in eq 1 and are obviously re-



(1)

actions that, like the hydrolysis of **5**, involve nucleophilic substitution at the sulfonyl sulfur.

We were interested in whether or not hydrolysis and other nucleophilic substitution reactions of naphtho[1,8-*cd*]-1,2-dithiole 1,1,2,2-tetroxide (**7**), the cyclic five-membered α-



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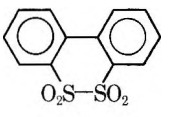

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disulfone analogous to **5**, would show the same sort of very large rate accelerations relative to phenyl α-disulfone, $PhSO_2SO_2Ph$ (**9**), as one observes for sultone **5** relative to open-chain aryl sulfonates.

While examining the rates of reaction of **7** with various nucleophiles we have also looked at the rates of reaction of the cyclic six-membered α-disulfone dibenzo[*ce*]-1,2-dithiin 1,1,2,2-tetroxide (**8**) with many of the same nucleophiles. In the case of sulfates and sultones, cyclic six-membered compounds, in marked contrast to the behavior of five-membered ones, do *not* hydrolyze at appreciably faster rates than their acyclic analogues.

Results

The synthesis of α-disulfones **7** and **8** is outlined in an accompanying paper.[8] The kinetics of their reactions with nucleophiles at 25 °C in 60% dioxane as solvent were followed spectrophotometrically (either conventional or stopped-flow)

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Table I. Kinetics of the Reaction of Anionic Nucleophiles with 7 and 8 in 60% Dioxane at 25 °C

α-Disulfone, concentration (M)	Nucleophile	[Nu⁻], M	[NuH], M	k_1, s⁻¹	$k_{Nu} = k_1/[Nu^-]$, M⁻¹ s⁻¹
7, 2.2×10^{-4}	OH^-	0.10		19.7	2.0×10^2
		0.08		15.9	2.0×10^2
		0.06		11.7	2.0×10^2
		0.04		8.0	2.0×10^2
		0.02		3.8	1.9×10^2
1.0×10^{-4}	CN^-	*a*	*a*	*a*	8.0
2.7×10^{-4}	HO_2^-	0.002	0.0165	12.7	6.4×10^3
8, 1.1×10^{-4}	OH^-	0.04		9.4	2.4×10^2
		0.02		4.7	2.4×10^2
1.4×10^{-4}	CN^-	*a*	*a*	*a*	3.5
1.3×10^{-4}	HO_2^-	0.004	0.016	59.8	1.5×10^4
		0.002	0.018	28.1	1.4×10^4
	OCl^-	0.002		2.87	1.4×10^3
		0.001		1.36	1.4×10^3

[a] For data for individual runs see Table III of ref 8.

Table II. Kinetics of the Reaction of Various Nitrogen Bases with 7, 8, and Phenyl α-Disulfone in 60% Dioxane at 25 °C

α-Disulfone, concentration (M)	Nucleophile	[Nu], M	[NuH⁺], M	$k_1 \times 10^2$, s⁻¹	$k_{Nu} = k_1/[Nu]$, M⁻¹ s⁻¹
7, 1.0×10^{-4}	Piperidine	0.016	0.016	0.77	0.48
		0.008	0.008	0.39	0.49
	Piperazine	0.016	0.016	0.38	0.24
		0.008	0.008	0.167	0.21
	Morpholine	0.08	0.08	0.194	0.024
			0.04	0.205	0.026
		0.04	0.04	0.109	0.026
		0.02	0.02	0.046	0.023
			0.01	0.047	0.024
	Quinuclidine	0.10	0.10	1.27	0.127
	3-Quinuclidinol	0.08	0.08	0.234	0.029
		0.04	0.04	0.112	0.028
	Triethylenediamine (Dabco)	0.08	0.08	0.109	0.0136
		0.04	0.04	0.055	0.0137
		0.08	0.08	0.068 (D_2O)	0.0084
		0.04	0.04	0.034 (D_2O)	0.0084
	NH_2NH_2	0.0106	0.010	2.66	2.52
		0.00422	0.0040	1.07	2.53
8, 1.1×10^{-4}	Morpholine	0.04	0.04	5.3	1.33
		0.02	0.02	2.6	1.30
1.0×10^{-4}	Triethylenediamine (Dabco)	0.08	0.08	0.52	0.066
		0.04	0.04	0.25	0.063
9, 4.2×10^{-5}	Quinuclidine	0.0040	0.0043	39.0	98
		0.0020	0.0022	18.6	93
	3-Quinuclidinol	0.0025	0.0025	6.05 ± 0.01	24.4
	Triethylenediamine (Dabco)	0.010	0.010	11.5	11.5
		0.0050	0.0050	16.13	12.3

under conditions where the nucleophile was always present in large stoichiometric excess over the α-disulfone so that the disappearance of the α-disulfone followed first-order kinetics. The reactions involving 8 were followed at its long wavelength absorption maximum, 313 nm. In the case of 7, however, reaction with nucleophiles is not generally accompanied by much change in the absorbance at the long wavelength absorption maximum of 7 (302 nm), and so wavelengths in the region 320–335 nm were used.

The reactions of 7 and 8 investigated consisted of the following: (a) reaction with a group of nitrogen bases; (b) reaction with a group of common anionic nucleophiles; (c) the spontaneous hydrolysis of 7. The reactions involving the nitrogen bases were all studied in buffers (usually 1:1) of the nitrogen base and its conjugate acid. Some of the reactions involving the anionic nucleophiles were also studied in buffers of the nucleophile, Nu^-, and its conjugate acid, NuH. Certain of the nitrogen bases examined, namely, quinuclidine and related cyclic tertiary amines, were ones for which kinetic data had not been previously obtained for phenyl α-disulfone. For this reason the reactivity of these particular tertiary amines toward $PhSO_2SO_2Ph$ was also determined, along with their reactivity toward 7, in the present work.

The data for the runs involving the anionic nucleophiles and 7 and 8 are summarized in Table I, while the results for the nitrogen-base nucleophiles and the different α-disulfones are given in Table II. The data for the spontaneous hydrolysis of 7 are given in Table III. In each case, k_1 is the experimental first-order rate constant for the disappearance of the α-disulfone under the reaction conditions in question.

That all of the reactions in Tables I and II are first order in nucleophile is shown by the fact that for any given α-disulfone–nucleophile system k_1/[nucleophile] is independent of nucleophile concentration. Second-order rate constants, $k_{Nu} = k_1$/[nucleophile], for each system studied are also tabulated in Tables I and II.

Table III. Kinetics of the Spontaneous Hydrolysis of Naphtho[1,8-*cd*]-1,2-dithiole 1,1,2,2-Tetroxide (7) in 60% Dioxane[a]

Temp, °C	$k_1 \times 10^4$, s^{-1} [b]	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu
94.0	2.31 ± 0.01		
90.0	1.81 ± 0.01		
80.0	1.01 ± 0.03	14.6	−37.8
69.5	0.62 ± 0.06		
59.7	0.29 ± 0.01		

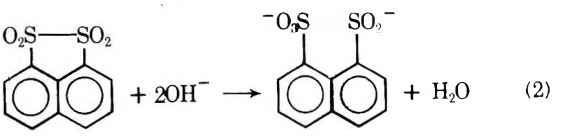
[a] All runs were in the presence of 0.01 M $HClO_4$. Other experiments showed that perchloric acid concentrations up to 0.1 M had no effect on the rate. [b] All results are the average of several runs.

Discussion

Table IV gives the rate constants for the reaction of the various nucleophiles with both the five-membered (7) and the six-membered (8) cyclic α-disulfones. For each case it also indicates the reactivity of the cyclic α-disulfone compared to that of phenyl α-disulfone, i.e., $k_7/k_{(PhSO_2)_2}$ or $k_8/k_{(PhSO_2)_2}$.

From inspection of the table it is at once apparent that *in no case* does the cyclic five-membered α-disulfone react much faster than phenyl α-disulfone. The dramatic rate accelerations observed by Kaiser and co-workers[2c] with the analogous cyclic sultone **5** are simply not seen with **7**. Only in one case, that of reaction with cyanide ion, does the cyclic five-membered α-disulfone react more than 10 times faster than the open-chain compound, and even there the size of $k_7/k_{(PhSO_2)_2}$, 18, is many orders of magnitude smaller than the 10^5–10^7 rate accelerations characteristic of cyclic five-membered sulfates and sultones.

We noted earlier that the large rate accelerations observed[2] with **5** and with cyclic five-membered sulfates are believed to be due to the existence of significant strain in the cyclic substrates, which is relieved on going to a trigonal-bipyramidal intermediate or transition state. The lack of any rate acceleration for cyclic α-disulfone **7** would thus seem to suggest that either there is no significant strain associated with the α-disulfone ring in **7** or else that going from reactant to transition state (or intermediate) in the α-disulfone reactions for some reason does not lead to relief of strain in the way that it does for the substitution reactions of cyclic sulfates and sultones. We have measured the $\Delta H°$ (−54.2 kcal/mol) associated with the alkaline hydrolysis of **7** (eq 2) and find it to be slightly over 3 kcal/mol *smaller* than $\Delta H°$ (−57.3 kcal/mol) for the alkaline hydrolysis of phenyl α-disulfone:[9] $PhSO_2SO_2Ph + 2OH^- \rightarrow PhSO_2^- + PhSO_3^- + H_2O$. Unfortunately, since we do not



(2)

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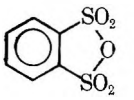
know to what extent reaction product **10** is destabilized thermochemically due to interference between the sulfonate and sulfinate groups in the 1 and 8 positions,[10] we cannot say definitely that the smaller heat of alkaline hydrolysis of **7** compared to phenyl α-disulfone proves that there is little or no strain in the α-disulfone ring of **7**. However, given this caveat, the results do seem to suggest that the lack of rate acceleration for the cyclic five-membered α-disulfone is because there is not the strain associated with the five-membered ring in **7** that one finds in the corresponding sultone **5**.

α-Disulfone **7** is not the only cyclic five-membered sulfonyl derivative that does not show a marked rate acceleration compared to its acyclic analogue. Thus, Laird and Spence[12] have found that the solvolysis rates of the two cyclic sulfonic anhydrides **11** and **12** are not greatly different from their open-chain analogues.



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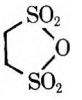

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Although no nucleophiles studied react with **7** much faster than they do with $PhSO_2SO_2Ph$, the cyclic secondary and tertiary amines in Table IV all react much slower (factor of 200 to 800). One should note, however, that this very marked reduction in rate is not seen with all nitrogen bases; the reactivity of hydrazine toward **7** is only a modest factor of six smaller than its reactivity toward phenyl α-disulfone, rather than the much larger factor of 200–800 observed with the cyclic amines.

Ritchie and co-workers[13] have examined the reactivity of a wide range of nucleophiles toward a pair of carbonium ions that differ significantly in the degree of steric hindrance they present to the approach of a nucleophile to their electrophilic center. Their results indicate that the reactivity of cyanide ion, hydrogen peroxide anion, and hydrazine (which they term "unhindered nucleophiles") is not affected by the increased steric hindrance at the reaction center of the more hindered carbonium ion; on the other hand, the relative reactivity of morpholine, piperidine, and piperazine is very significantly reduced.

Given Ritchie's findings,[13] we believe that a steric effect is almost certainly the correct explanation for the low reactivity

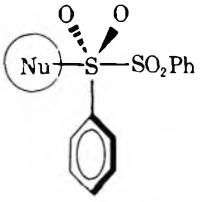
Table IV. Reactivity of Cyclic Five- and Six-Membered Aryl α-Disulfones toward Nucleophiles[a]

Nucleophile	Registry no.	5-Membered		6-Membered	
		k_7,[b] $M^{-1} s^{-1}$	$k_7/k_{(PhSO_2)_2}$	k_8,[c] $M^{-1} s^{-1}$	$k_8/k_{(PhSO_2)_2}$
OH^-	14280-30-9	200	2.6	240	3.2
HO_2^-	14691-59-9	6.4×10^3	1.1	1.5×10^4	2.8
CN^-	57-12-5	8.0	18	3.5	7.8
OCl^-	14380-61-1			1.4×10^3	1.8
Spontaneous hydrolysis (80 °C)		1.0×10^{-4}	1.0		
Piperidine	110-89-4	0.49	0.0041		
Piperazine	110-85-0	0.23	0.0048		
Morpholine	110-91-8	0.025	0.0021	1.3	0.11
NH_2NH_2	302-01-2	2.5	0.16		
Quinuclidine	100-76-5	0.13	0.0013		
3-Quinuclidinol	1619-34-7	0.029	0.0012		
Triethylenediamine (Dabco)	280-57-9	0.014	0.0011	0.065	0.0055

[a] All data are for 60% dioxane as solvent at 25 °C, except the spontaneous hydrolysis of **7** where data are at 80 °C. [b] Registry no.: **7**, 62609-77-2. [c] Registry no.: **8**, 64728-07-0.

of the cyclic secondary and tertiary amines toward **7** as compared to their reactivity toward $PhSO_2SO_2Ph$. Such an explanation is, of course, consistent with the fact that the reactivity toward **7** of unhindered nucleophiles like NH_2NH_2, CN^-, and HO_2^- is not greatly different than their reactivity toward the open-chain α-disulfone.

The substitution reactions of the α-disulfones presumably go through an intermediate (or transition state) in which the reacting nucleophile and the departing sulfinate ion occupy the apical positions of a trigonal bipyramid. In the case of the open-chain α-disulfones it is possible to rotate the phenyl group attached to the sulfonyl group undergoing substitution in such a way that it will present a minimum of hindrance to an incoming nucleophile (see structure **13**). On the other hand,



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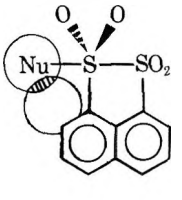

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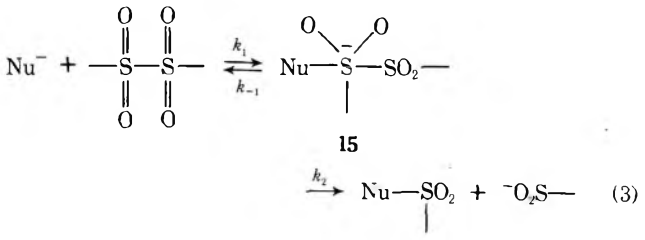
the structure of **7** is such that the ortho position to the point of attachment of the sulfonyl group will inevitably interfere (see structure **14**) with the approach of any nucleophile that has significant steric requirements.

Let us now discuss briefly an alternative explanation for the low reactivity of **7** toward cyclic secondary and tertiary amines which was carefully considered but rejected as being inconsistent with certain aspects of the experimental results. Assume that the substitutions involving α-disulfones take place by a mechanism where an intermediate (**15**) is present on the reaction coordinate and which can be formulated generally as shown in eq 3. In analogous substitutions of carboxylic acid derivatives, Gravitz and Jencks[14] have shown that k_{-1} for amines ($Nu^- = \gg N:$) is 10^5 times larger than k_{-1} for oxyanions ($Nu^- = -O^-$) of equivalent basicity. If one were to assume that k_2 for cyclic α-disulfone **7** was much smaller than k_2 for phenyl α-disulfone, then one could conceivably have the following situation: with $PhSO_2SO_2Ph$ as the substrate k_2 for **15** would be larger than k_{-1} for all nucleophiles in Table IV, and for the open-chain α-disulfone k_1 (the attack of the nucleophile on the α-disulfone) would be rate-determining; on the other hand, with cyclic α-disulfone **7**, although one would still have $k_2 > k_{-1}$ for nucleophiles like OH^-, HO_2^-, and CN^-, with the amines, where k_{-1} was much larger, one could have the opposite situation where $k_2 \ll k_{-1}$, and the measured rate constant, which would now be given by $k_1(k_2/k_{-1})$, could be much smaller than that found for phenyl α-disulfone, even though k_1 had essentially the same value as for the open-chain compound.



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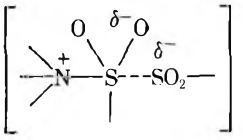
$$\xrightarrow{k_2} Nu{-}SO_2{-} + {}^-O_2S{-} \qquad (3)$$

Such an explanation is at variance with several aspects of the experimental results, however. First, if in the reactions of the amines k_1 were rate determining for their reactions with phenyl α-disulfone while k_2 were rate determining for their reactions with **7**, one would expect that β_{nuc} (from a plot of log k_{amine} vs. pK_a of amine H^+) should be much larger for the reactions involving **7** and the amines than for those involving phenyl α-disulfone; β_{nuc} is, of course, proportional to the amount of positive charge on the nitrogen atom in the rate-determining transition state and should therefore be much larger for a case where step k_2 is rate determining and the transition state is given by **16** than in a case where step k_1 is rate determining and the transition state resembles **17**.[15] The



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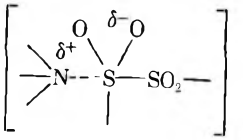

17

actual β_{nuc} values for the different α-disulfone–amine reactions are as follows: $PhSO_2SO_2Ph$ with cyclic secondary amines, 0.39, with cyclic tertiary amines, 0.51; **7** with cyclic secondary amines, 0.50, with cyclic tertiary amines, 0.53. Clearly one does not see the large increase in β_{nuc} for the reactions of **7** that would be required by the proposed explanation. The fact that hydrazine reacts almost as rapidly with **7** as it does with phenyl α-disulfone, even though the cyclic secondary and tertiary amines do not, is also not in accord with an explanation based on the mechanism in eq 3 and a change in the rate-determining step for the reaction of amines with **7**, since such an explanation would predict the hydrazine–**7** reaction should be as markedly retarded as those of the other amines in Table IV. For these reasons we consider that this explanation can be rejected in favor of the one involving steric retardation of the reaction of cyclic amines with **7** outlined earlier.

The reaction of the cyclic tertiary amines with phenyl α-disulfone definitely involves nucleophilic attack by the amine and not general base catalysis by the amine of the attack of water on the α-disulfone. The clear evidence for this is the fact that the rate constant for the reaction of 3-quinuclidinol with $PhSO_2SO_2Ph$ is approximately 10^3 times larger than that for triethylamine,[16] even though the latter tertiary amine is about a factor of 10 stronger base. One might wonder, however, in view of the markedly lower rates of reaction of the cyclic tertiary amines with **7**, whether these reactions still involve nucleophilic attack or whether, alternatively, one now has general base catalysis by the amine. Two considerations lead us to believe that nucleophilic attack is still involved, despite the low rates. First, the β value associated with the reaction of the cyclic tertiary amines with **7** is the same within experimental error as the β value associated with their reaction with phenyl α-disulfone, where we know that nucleophilic attack by the amine is involved. Second, we have measured the solvent isotope effect associated with the reaction of Dabco with **7**, and the value we find, $k_{H_2O}/k_{D_2O} = 1.6$, is below the range of 1.9–4.4, typical of reactions where amines act as general base catalysts.[17] Earlier work[16b,18] has found solvent isotope effects of about 1.4 for reactions in 60% dioxane involving sulfur substrates in which tertiary amines act as nucleophilic catalysts.

Experimental Section

Preparation and Purification of Materials. The preparation of naphtho[1,8-*cd*]-1,2-dithiole 1,1,2,2-tetroxide (**7**) and dibenzo[*ce*]-1,2-dithiin 1,1,2,2-tetroxide (**8**) is described in an accompanying paper.[8] Triethylenediamine (Aldrich) was purified by recrystallization from benzene–hexane. Dioxane was purified by the procedure of Hess and Frahm[19] and was then stored frozen at −20 °C to prevent formation of peroxides prior to use. Piperidine, morpholine, piperazine, and phenyl α-disulfone were purified as outlined by Kice and Legan.[7a] For all the other reagents the highest purity commercially available material was used without further purification.

Procedure for Kinetic Runs. Depending on the rapidity of the particular reaction, either conventional or stopped-flow spectrophotometry was used to follow the kinetics. For the runs in Tables I and II the general procedures used were those already outlined in

detail by Kice and Legan[7a] for following the kinetics of the reactions of nucleophiles with phenyl α-disulfone. Reactions of 8 were followed at 313 nm, while those of 7 were followed at whatever wavelength in the 320–335-nm range had been shown by preliminary experiments to lead to the largest change in absorbance. The reactions of phenyl α-disulfone with the cyclic tertiary amines were followed at 255 nm in the case of both Dabco and quinuclidine and at 245 nm in the case of 3-quinuclidinol. The spontaneous hydrolysis of 7 at elevated temperatures was followed using the same type of procedure employed[7c] to follow the spontaneous hydrolysis of phenyl α-disulfone.

Thermochemistry of the Alkaline Hydrolysis of 7. The experimental procedures used for the calorimetric measurements on the heat of alkaline hydrolysis of 7 were the same as those previously described[9] for studying the heat of alkaline hydrolysis of phenyl α-disulfone.

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Registry No.—**9,** 10409-06-0.

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Reaction of Cyanide and Sulfite Ions with Oxidized Derivatives of Dibenzo[*ce*]-1,2-dithiin and Naphtho[1,8-*cd*]-1,2-dithiole

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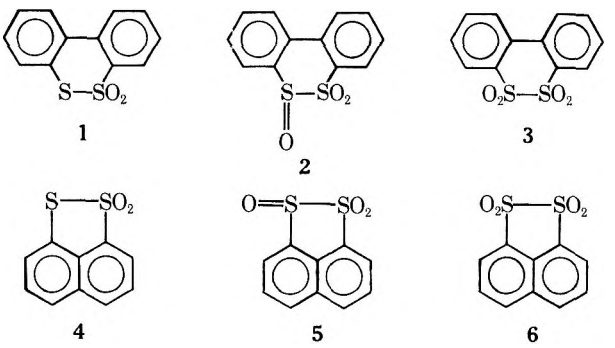
The cyclic thiolsulfonates dibenzo[*ce*]-1,2-dithiin 1,1-dioxide (**1**) and naphtho[1,8-*cd*]-1,2-dithiole 1,1-dioxide (**4**) react rapidly in aqueous dioxane with excess cyanide or sulfite to undergo opening of the thiolsulfonate ring with formation (from reaction with CN^-) of thiocyanates (**8** and **10**, respectively) and (from sulfite) Bunte salts (**7** and **9**). Acidification of the final reaction solutions with carboxylic acid buffers of appropriate pH leads to rapid reversal of the ring-opening reactions and quantitative regeneration of **1** or **4** (Schemes I–IV). Surprisingly, in the regeneration of the cyclic thiolsulfonates from the thiocyanates or Bunte salts the CN group in each thiocyanate is displaced by $-SO_2^-$ about 30 times faster than the $-SO_3^-$ group in the analogous Bunte salt, thereby showing that in certain circumstances thiocyanates can be better sulfenylating agents than the analogous Bunte salt. Kinetic and equilibrium measurements on the various reactions show that the equilibrium constants for opening of the six-membered thiolsulfonate ring in **1** are about 20 times larger than those for opening the five-membered thiolsulfonate ring in **4**, even though the *rates* of ring opening for **4** are faster in each case by a factor of about 10. While the analogous cyclic α-disulfones **3** and **6** react with sulfite and cyanide to undergo opening of the α-disulfone ring, acidification of the final reaction solution does not lead to regeneration of the α-disulfone. Reasons for this difference in behavior from that found with thiolsulfonates **1** and **4** are presented. Cyclic sulfinyl sulfone **2**, dibenzo[ce]-1,2-dithiin 1,1,2-trioxide, reacts rapidly and quantitatively with sulfite ion to give a Bunte salt *S*-oxide (**16**). In acetate or chloroacetate buffers **16** decomposes to regenerate **2**, which then undergoes rapid hydrolysis to diphenyl-2,2′-disulfinate (**17**). In more acid buffers **16** undergoes an extremely rapid acid-catalyzed decomposition that leads to cyclic thiolsulfonate **1** via the mechanism shown in Scheme V.

As part of a general study of the reaction of nucleophiles toward oxidized derivatives of dibenzo[*ce*]-1,2-dithiin (compounds **1–3**) and naphtho[1,8-*cd*]-1,2-dithiole (compounds **4–6**) we have examined the reaction of cyanide ion and sulfite ion with the majority of these substrates. We find that the reaction of these two nucleophiles with the various substrates exhibits interesting, informative, and, in some cases, rather unexpected variations in behavior with both substrate and nucleophile. For example, with certain of the substrates, *but not with others,* opening of the ring by cleavage of the sulfur–sulfur bond through nucleophilic attack of sulfite or cyanide on one of the sulfurs can be readily and quantitatively



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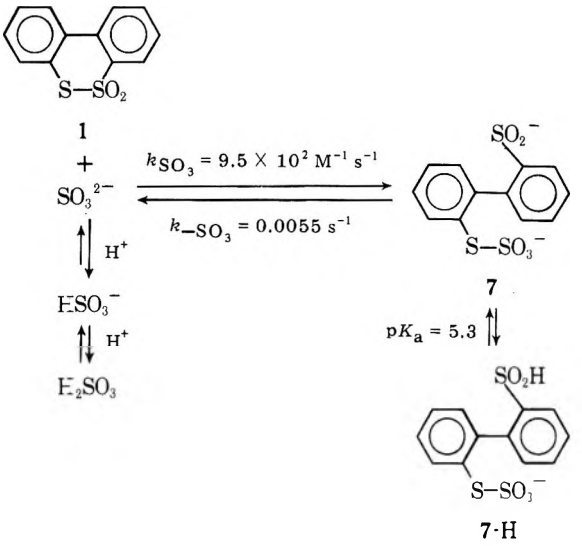
Scheme I. Reaction of Sulfite with Dibenzo[*ce*]-1,2-dithiin 1,1-Dioxide in 60% Dioxane at 25 °C



$K_{eq} = (k_{SO_3}/k_{-SO_3}) = 1.7 \times 10^5\ M^{-1}$

reversed by an appropriate change in the pH of the reaction solution. Surprisingly, in re-forming thiolsulfonates **1** or **4** from the ring-opened structures we find that CN^- is displaced considerably more rapidly from an –SCN group by $-SO_2^-$ than is SO_3^{2-} from $-SSO_3^-$.

Our observations on these and other aspects of the reaction of cyanide and sulfite with **1**–**6** form the subject of this paper.

Results and Discussion

Reaction of Sulfite and Cyanide with Dibenzo[*ce*]-1,2-dithiin 1,1-Dioxide (1). At 25 °C in 60% dioxane as solvent dibenzo[*ce*]-1,2-dithiin 1,1-dioxide (**1**) reacts rapidly with excess sulfite ion to cleave the sulfur–sulfur bond in **1** and form Bunte salt **7** (Scheme I). The reaction can be followed by monitoring the disappearance of the absorption maximum due to **1** at 296 nm by stopped-flow spectrophotometry. As can be seen from Table I, the experimental first-order rate constant for the disappearance of **1** is proportional to sulfite concentration. From $k_1/[SO_3^{2-}]$ the second-order rate constant for the reaction of SO_3^{2-} with **1** (k_{SO_3} in Scheme I) is found to be $9.5 \times 10^2\ M^{-1}\ s^{-1}$.

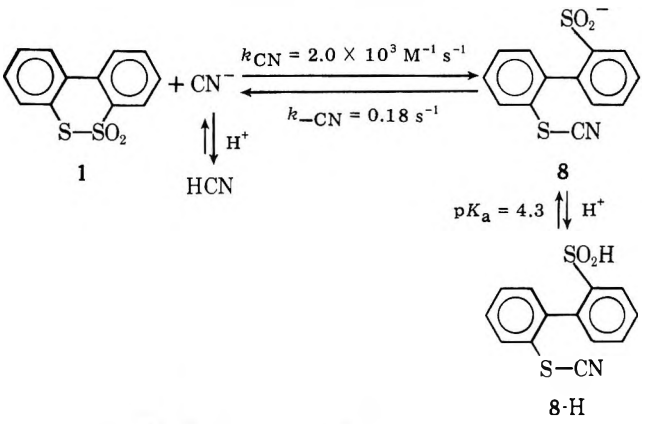
Thiolsulfonate **1** also reacts rapidly with excess cyanide (1:1 CN^-/HCN buffer) to undergo ring opening to thiocyanate **8** (Scheme II). The kinetic data for the reaction, which can be followed in the same way as the **1**–sulfite reaction, are also listed in Table I, and from $k_1/[CN^-]$ the second-order rate constant for the reaction of cyanide with **1** (k_{CN} in Scheme II) is $2.0 \times 10^3\ M^{-1}\ s^{-1}$.

If either Bunte salt **7** (Scheme I) or thiocyanate **8** (Scheme II) is treated with a buffer of sufficient acidity to completely protonate SO_3^{2-} to HSO_3^- or CN^- to HCN, but not one so acid as to protonate too extensively the $-SO_2^-$ group of either **7** or **8**, then both Bunte salt **7** and thiocyanate **8** revert back readily and quantitatively to **1** (reactions k_{-SO_3} of Scheme I

Table I. Kinetics of the Reaction of Excess Sulfite or Cyanide with Dibenzo[ce]-1,2-dithiin Dioxide in 60% Dioxane at 25 °C

$10^4[1]_0$, M	$10^3[SO_3^{2-}]$, M	$[CN^-]$ = [HCN], M	k_1, s^{-1}	$k_1/[SO_3^{2-}]$, $M^{-1}\ s^{-1}$	$k_1/[CN^-]$, $M^{-1}\ s^{-1}$
1.0	4.0		3.7	9.3×10^2	
	8.0		7.7	9.6×10^2	
		0.02	39.4		2.0×10^3
		0.01	20.1		2.0×10^3

Scheme II. Reaction of Cyanide with Dibenzo[*ce*]-1,2-dithiin 1,1-Dioxide in 60% Dioxane at 25 °C



$K_{eq} = (k_{CN}/k_{-CN}) = 1.1 \times 10^4\ M^{-1}$

and k_{-CN} of Scheme II) via displacement of, respectively, the $-SO_3^-$ group of the Bunte salt and the CN group of the thiocyanate, by the sulfinate ion function present in either **7** or **8**. The kinetic behavior of the reversion of **7** or **8** to **1** is outlined in the following paragraphs.

Thiolsulfonate **1** (10^{-4} M) was treated with excess cyanide ($[CN^-] = 5 \times 10^{-4}$ M), and after the reaction of **1** with CN^- to give **8** was complete, as evidenced by no further decrease in the absorbance at 296 nm, the solution was acidified by the injection of a small amount of a concentrated solution of chloroacetic acid/sodium chloroacetate buffer sufficient to give a final chloroacetic concentration in the range 0.01–0.02 M and a chloroacetate concentration of 0.01 M. The increase in the absorbance of the solution at 296 nm was then followed, and after a few minutes not only had the absorbance at 296 nm returned to the value expected for a 10^{-4} M solution of **1** but also the complete spectrum was identical with that of thiolsulfonate **1**. A plot of log $(A^{296}_\infty - A^{296})$ vs. time for each run showed excellent linearity; the slopes of these plots gave k_{-1} (the experimental first-order rate constant for the reversion of **8** to **1**).

In 60% dioxane a 1:1 $ClCH_2COO^-/ClCH_2COOH$ buffer has pH 5.48.[1] Unpublished work in this laboratory[2] indicates the pK_a for benzenesulfinic acid in 60% dioxane is between 4.2 and 4.3. The observed k_{-1}'s for the reversion of **8** to **1** as a function of buffer pH are [(pH of buffer), k_{-1}] (5.48) 0.17 and (5.18) 0.155 $s.^{-1}$ An experiment in which the solution was acidified with 0.1 M $HClO_4$, rather than a chloroacetate buffer, showed that regeneration of **1** from the thiocyanate, while eventually complete, was orders of magnitude slower than in the chloroacetate buffer. This shows that the $-SO_2H$ group in **8**-H is very unreactive relative to the $-SO_2^-$ group in **8** insofar as performing the displacement of the CN group from the thiocyanate function. The actual value of k_{-CN} in Scheme II is therefore related to the measured k_{-1}'s by eq 1, where K_a is

$$k_{-CN} = k_{-1}\left[\frac{K_a}{K_a + a_{H^+}}\right] \quad (1)$$

the acid dissociation constant for **8**-H in 60% dioxane. Assuming that the pK_a for **8**-H is essentially the same as that[2] for $PhSO_2H$ (4.3) gives a calculated k_{-CN} which is independent of pH and has a value of $0.18\ s^{-1}$. From this value and that for k_{CN} determined earlier, $K_{eq} = (k_{CN}/k_{-CN})$ is equal to $1.1 \times 10^4\ M^{-1}$.

To check on the correctness of this value of K_{eq} we also carried out an experiment in which small increments of cyanide (as a 1:1 CN^-/HCN buffer) were added to a 10^{-4} M solution of **1** in 60% dioxane and the final equilibrium absorbance at 296 nm after the addition of each increment was measured. From these data, the absorbance at 296 nm in the

Table II. Kinetics of the Reaction of Excess Sulfite or Cyanide with Naphtho[1,8-*cd*]-1,2-dithiole 1,1-Dioxide in 60% Dioxane at 25 °C

$10^4[4]_0$, M	$10^3[SO_3^{2-}]$, M	$[CN^-] = [HCN]$, M	k_{exptl}, s^{-1}
2.0	2.0		24
	4.0		51
0.5		0.0025	76[a]

[a] Average of several runs; rates reproducible to ±3%.

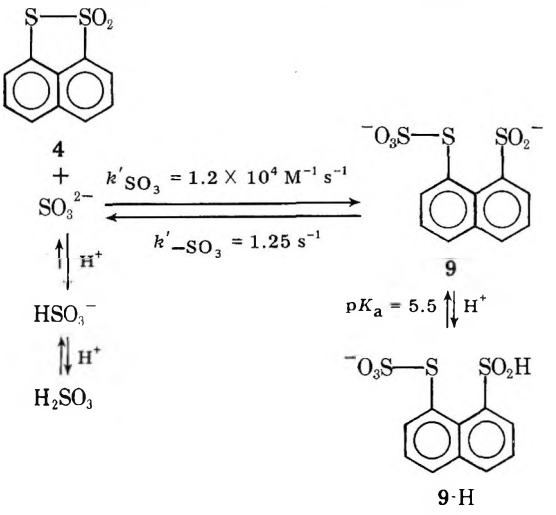
absence of added cyanide and the absorbance at this wavelength when sufficient excess CN^- has been added to convert **1** completely to **8**, one can calculate values of K_{eq}. We obtained $1.05 \pm 0.08 \times 10^4$ M^{-1}, in excellent agreement with the value estimated from the rates of the forward and reverse reactions.

The reversion of Bunte salt **7** to **1** was studied kinetically in the same way as the reversion of **8** to **1**, i.e., after the reaction of **1** (10^{-4} M) with 5×10^{-4} M sodium sulfite, the solution was acidified by addition of a small amount of concentrated chloroacetate buffer and the increase in optical density at 296 nm was followed. Regeneration of **1** from **7** was quantitative and followed excellent first-order kinetics. The observed k_{-1}'s for the reversion of **7** to **1** as a function of buffer pH were [(pH of buffer), k_{-1}] (5.78) 0.00426, (5.48) 0.00324, and (5.17) 0.00234 s^{-1}. One sees that there is much more dependence of k_{-1} on the buffer pH than in the experiments with **8**. Apparently the $-SSO_3^-$ group exerts a very significant acid-weakening effect on the $-SO_2H$ group in **7**-H such that its pK_a is about 1.0-pK_a unit larger than that of **8**-H, and therefore a considerable fraction of **7** is protonated to **7**-H in the more acidic of the chloroacetate buffers. Using a value of 5.3 for the pK_a of **7**-H and the measured k_{-1}'s, the relation $k_{-SO_3} = k_{-1}(K_a/K_a + a_{H^+})$ gives a value for k_{-SO_3} which is independent of pH and equal to $5.5 \pm 0.1 \times 10^{-3}$ s^{-1}. From this and k_{SO_3}, $K_{eq} = (k_{SO_3}/k_{-SO_3})$ for the $SO_3^{2-} + 1 \rightleftarrows 7$ equilibrium is 1.7×10^5 M^{-1}.

The fact that k_{-CN} for **8** (intramolecular displacement of CN^- from $-SCN$ by $-SO_2^-$) is about 30 times *faster* than k_{-SO_3} for **7** (intramolecular displacement of SO_3^{2-} from $-SSO_3^-$ by $-SO_2^-$) is surprising, interesting, and unexpected since the impression gained from the literature[3,4] is that Bunte salts are generally considered to be more reactive sulfenylating agents than thiocyanates. To make sure that the greater ease of displacement of CN^- from $-SCN$ in **8** as compared to SO_3^{2-} from $-SSO_3^-$ in **7** was not due to some peculiarity unique to the dibenzo[*ce*]-1,2-dithiin system, we therefore felt it was important to investigate the rates of the forward and reverse reactions associated with the analogous equilibria involving sulfite and cyanide and the cyclic 5-membered thiolsulfonate, naphtho[1,8-*cd*]-1,2-dithiole 1,1-dioxide (**4**). Such studies would have the additional bonus of indicating to what extent the equilibrium constants for ring opening were influenced by the change from **1** to **4**. Based on the behavior[13] of the equilibria involving the hydrolysis of the two cyclic sulfinyl sulfones **2** and **5** to their respective disulfinic acids, the change from **1** to **4** might be expected to lead to a sizeable decrease in K_{eq} for ring opening.

Reaction of Sulfite and Cyanide with Naphtho[1,8-*cd*]-1,2-dithiole 1,1-Dioxide (4). The reaction of **4** with either excess sulfite or excess cyanide (1:1 CN^-/HCN buffer) can be followed by stopped-flow spectrophotometry at 304 nm. The experimental first-order rate constants for the various runs are given in Table II. Because, as will become evident shortly, the rates of reverse reactions (k'_{-SO_3} in Scheme III and k'_{-CN} in Scheme IV) are much faster relative to the rates of the forward reactions than in the case of **1**, it turns out that

Scheme III. Reaction of Sulfite with Naphtho[1,8-*cd*]-1,2-dithiole 1,1-Dioxide in 60% Dioxane at 25 °C



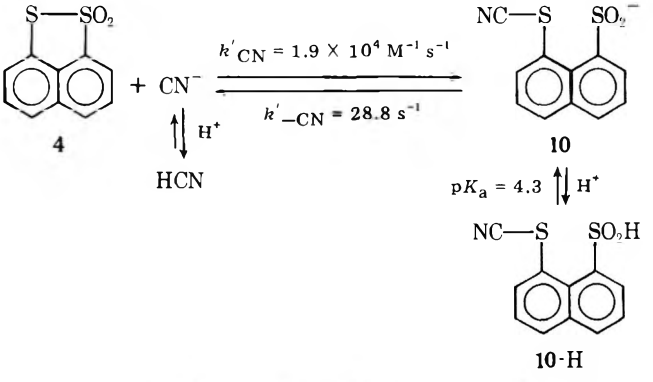
$K'_{eq} = (k'_{SO_3}/k'_{-SO_3}) = 9 \times 10^3$ M^{-1}

under the conditions in Table II, particularly for cyanide, the reactions do not go entirely to completion, and so k_{exptl} for each run is actually equal to $(k'_{Nu}[Nu^-] + k'_{-Nu})$ rather than to just $k'_{Nu}[Nu^-]$.[5] We will therefore defer calculation of k'_{SO_3} and k'_{CN} for **4** until after we have outlined the determination of k'_{-SO_3} and k'_{-CN} from the experiments outlined in the next several paragraphs.

To determine the rate (k'_{-CN}) at which thiocyanate **10** (Scheme IV) reverts to **4** a solution prepared from **4** (2×10^{-4} M) and a 1:1 CN^-/HCN buffer containing $[CN^-] = 0.002$ M was placed in one of the reservoir syringes of a stopped-flow spectrophotometer and a chloroacetate buffer of appropriate pH was placed in the other syringe. The two solutions were then mixed, and the increase in the absorbance of the solution at 304 nm as **4** was regenerated from **10** was monitored. Good first-order kinetics were observed, and the experimental first-order rate constants were [(pH of buffer), k_{-1}] (5.48) 27.1 and (5.18) 25.4 s^{-1}. These measured k_{-1} values and an assumed pK_a for **10**-H of 4.3 (the same value as used for **8**-H) give a value of k'_{-CN} which is independent of pH and equal to 28.8 ± 0.1 s^{-1}. The value of k'_{CN} for the reaction of CN^- with **4** can then be calculated from this value of k'_{-CN} and k_{exptl} for cyanide in Table II: $k'_{CN} = (k_{exptl} - k'_{-CN})/[CN^-] = 1.9 \times 10^4$ M^{-1} s^{-1}. From the values of k'_{CN} and k'_{-CN}, K_{eq} for the **4** + CN^- $\rightleftarrows$ **10** equilibrium is equal to 6.6×10^2 M^{-1}.

Rate constant k'_{-SO_3} for reversion of Bunte salt **9** (Scheme III) to **4** was determined from similar experiments in which a solution prepared from 2×10^{-4} M **4** plus 4×10^{-3} M sodium sulfite was mixed with chloroacetate buffers of varying pH in

Scheme IV. Reaction of Cyanide with Naphtho[1,8-*cd*]-1,2-dithiole 1,1-Dioxide in 60% Dioxane at 25 °C



$K'_{eq} = (k'_{CN}/k'_{-CN}) = 6.6 \times 10^2$ M^{-1}

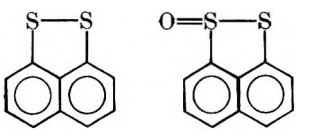
a stopped-flow spectrophotometer, and the regeneration of **4** from **9** followed. The experimental first-order rate constants were [(pH of buffer), k_{-1}] (5.78) 0.85, (5.48) 0.62, and (5.17) 0.39 s^{-1}. The sizeable decline in k_{-1} with decreasing pH shows, as was true earlier for Bunte salt **7**, that a considerable fraction of **9** is protonated to **9**-H in the more acidic chloroacetate buffers. If one assumes that the pK_a of the $-SO_2H$ group in **9**-H is 5.5 (or 0.2-pK_a unit larger than that for **7**-H), then k'_{-SO_3} as calculated from $k_{-1}(K_a/K_a + a_{H^+})$ is independent of pH and has a value of 1.25 ± 0.02 s^{-1}. Using this value of k'_{-SO_3} and the values of k_{exptl} for the reaction of sulfite with **4** in Table II, $k'_{SO_3} = (k_{exptl} - k'_{-SO_3})/[SO_3^{2-}] = 1.18 \pm 0.04 \times 10^4$ M^{-1} s^{-1}. This gives $K_{eq} = (k'_{SO_3}/k'_{-SO_3}) = 9 \times 10^3$ M^{-1} for the **4** + SO_3^{2-} ⇄ **9** equilibrium.

Comparison of the rate and equilibrium constants for the equilibria involving **4** (Schemes III and IV) with those for the equilibria involving **1** (Schemes I and II) reveals the following points of significance. First, as we had suspected might be the case, the equilibrium constants (K'_{eq}) for opening of the thiolsulfonate ring in **4** are about 20 times smaller in each instance than the equilibrium constants for the analogous ring-opening reactions involving **1**. Notice that this occurs even though the rate constants for the opening of the thiolsulfonate ring in **4** (k'_{SO_3} and k'_{CN}) are about 10 times faster for each nucleophile than for their analogous reaction (k_{SO_3} or k_{CN}) with **1**. The reason that both equilibrium constants for **4** are smaller than the analogous K_{eq}'s for **1** is that re-formation of the thiolsulfonate ring from **9** and **10** (k'_{-SO_3} and k'_{-CN}, respectively) is in each instance about 200 times faster than the corresponding reaction of **7** (k_{-SO_3}) or **8** (k_{-CN}). That both (k'_{-SO_3}/k_{-SO_3}) and (k'_{-CN}/k_{-CN}) should be of this large magnitude is not surprising. To go from **7** or **8** to the transition-state geometry necessary for the displacement reactions leading to **1** undoubtedly involves a significantly larger loss of rotational freedom (and therefore less favorable $\Delta G^{\ddagger}$) than to go from **9** or **10** to the transition-state geometry for the reactions leading to **4**.

The second point of particular significance is that, just as was true for **7** and **8**, we also find here that k'_{-CN} for **10** is about 25 times larger than k'_{-SO_3} for **9**. In other words, in this system, just as in the one derived from **1**, one again finds that $-SO_2^-$ can displace CN^- from –SCN considerably more readily than it can displace SO_3^{2-} from $-SSO_3^-$. These results clearly demonstrate that a thiocyanate group can be more reactive as a sulfenylating agent than a Bunte salt under appropriate reaction conditions, a fact that does not seem to have been recognized previously. Notice that the present reaction conditions are such that, as soon as either SO_3^{2-} or CN^- is displaced, it is removed from further participation by protonation to either nonnucleophilic (HCN, H_2SO_3) or weakly nucleophilic (HSO_3^-) species.

At the same time one should recognize that the intramolecular character of the displacements involving $-SO_2^-$ and –SCN in **8** and **10** makes these reactions many orders of magnitude faster than, for example, the corresponding intermolecular displacement by $PhSO_2^-$ on PhSCN, i.e., $PhSO_2^-$ + PhSCN → $PhSO_2SPh$ + CN^-. Thus we found that, although some thiolsulfonate was formed on heating a solution containing 0.1 M $PhSO_2Na$ and 0.1 M PhSCN in a (1:1) chloroacetate buffer in 60% dioxane at 60 °C for 90 h, the yield was much too low to make the process of any synthetic value, and about 60% of the phenyl thiocyanate was recovered unreacted.

One other point regarding the reaction of cyanide with **4** is worth discussion. According to Tamagaki, Hirota, and Oae,[7] thiolsulfonate **4** when treated with 2 mol of cyanide in methanol at room temperature for 2 days gives the corresponding cyclic disulfide, naphtho[1,8-*cd*]-1,2-dithiole (**11**), in 72% yield, plus an undetermined amount of sodium cyanate. To determine to what extent and how rapidly thiocyanate **10**, proposed by Oae and co-workers[7] as the initial intermediate in their reaction, goes to disulfide **11** under our reaction conditions, 60% dioxane and a 1:1 CN^-/HCN buffer, we treated **4** (10^{-4} M) with a large excess of cyanide ([CN^-] = [HCN] = 0.016 M) and observed the ultraviolet spectrum of the solution over a period of 1 week at room temperature. While we did see the gradual appearance of measurable absorption at 368 nm, where disulfide **11** has a strong maximum (ε 13 200), its rate of appearance was very slow, and even after 7 days the amount of **11** formed corresponded to only about 25% of the amount of **4** originally present. To measure the amount of **10** remaining at that point, the reaction solution was acidified by the addition of excess chloroacetate buffer. Although some **4** was thereby regenerated, the amount was small enough to show that most of the thiocyanate had indeed reacted further by the end of 7 days, even though only about 25% had been transformed to disulfide. The spectrum suggested that a considerable amount of thiolsulfinate **12** was present after acidification of the reaction solution.



11 **12**

It is clear that under our reaction conditions the transformation of **10** to **11** is much slower than reported by Oae.[7] This may have its origin in the fact that our reaction medium is a 1:1 CN^-/HCN buffer rather than the considerably more basic solution of sodium cyanide in methanol used by Oae and coworkers. We hope to explore the slow transformation of **10** to **11** more carefully in the future. In any event, one should, of course, realize that it is *orders of magnitude* slower than the very rapid forward and reverse steps of the **4** + CN^- ⇄ **10** equilibrium that have been the principal object of our attention in the present work.

Tamagaki, Hirota, and Oae[7] also suggested that the rate constant for opening of the thiolsulfonate ring in **4** by cyanide (k'_{CN}) was probably much slower than the rate of reaction of cyanide with phenyl benzenethiolsulfonate (eq 2). The rate constant for eq 2 has been measured by Kice, Rogers, and Warheit[8] at 25 °C in 60% dioxane, and one sees that it is actually about two times *slower* than k'_{CN} for **4** and *not* many times faster as suggested by Oae.[7]

$$CN^- + PhS\text{–}SO_2Ph \xrightarrow{k_2 = 7.8 \times 10^3\ M^{-1}\ s^{-1}} PhSCN + PhSO_2^- \quad (2)$$

Reaction of Sulfite and Cyanide with Dibenzo[*ce*]-1,2-dithiin 1,1,2,2-Tetraoxide (3) and Naphtho[1,8-*cd*]-1,2-dithiole 1,1,2,2-Tetraoxide (6). Having found that the opening of the thiolsulfonate ring in either **1** or **4** by either sulfite or cyanide ion can be readily and quantitatively reversed by acidifying the reaction solution with a buffer of appropriate pH, we were naturally curious as to whether or not similar reversal of the opening of the ring would be possible with more highly oxidized derivatives of dibenzo[*ce*]-1,2-dithiin and naphtho[1,8-*cd*]-1,2-dithiole.

Cyclic α-disulfones **3** and **6** react quite readily with excess cyanide, and the course of the reactions can be conveniently followed spectrophotometrically. The reaction of **3** with excess sulfite can be followed similarly. The disappearance of the α-disulfones in all cases follows good first-order kinetics. Both the experimental first-order rate constants, k_1, and the second-order rate constants, as calculated from either $k_1/[CN^-]$ or $k_1/[SO_3^{2-}]$, are tabulated in Table III. The second-order rate constants are not too greatly different from those found for the reaction of phenyl α-disulfone, $PhSO_2SO_2Ph$, with the

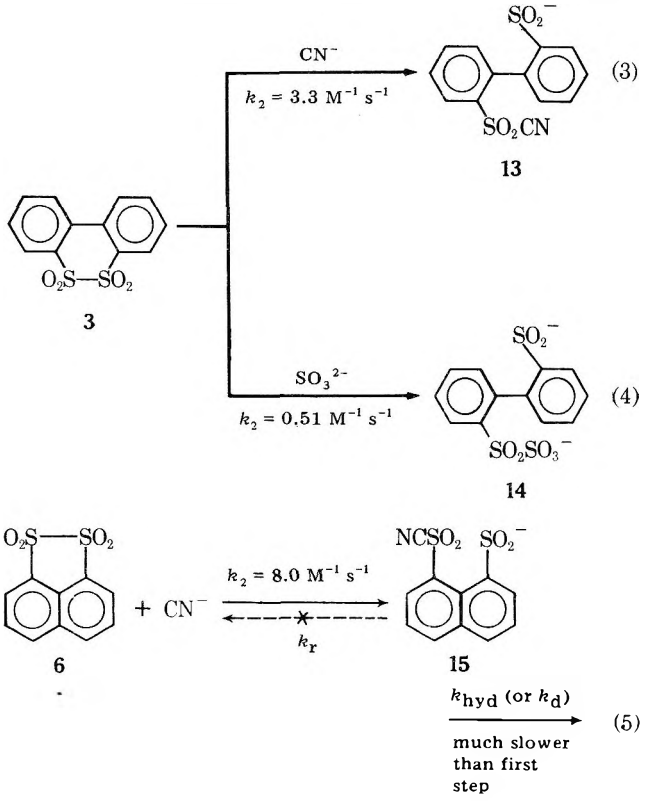
Table III. Kinetics of the Reaction of Excess Cyanide or Sulfite with Cyclic α-Disulfones 3 and 6 in 60% Dioxane at 25 °C

α-Disulfone, concentration (M)	$[CN^-]$ = [HCN], M	$[SO_3^{2-}]$, M	$k_1 \times 10^2$, s^{-1}	$k_1/[CN^-]$, $M^{-1}\,s^{-1}$	$k_1/[SO_3^{2-}]$, $M^{-1}\,s^{-1}$
3, 1.4×10^{-4}	0.04		14.0	3.5	
	0.02		6.8	3.4	
1.0×10^{-4}	0.001		0.31	3.1	
6, 1.0×10^{-4}	0.008		6.24	7.8	
	0.004		3.24	8.1	
3, 1.0×10^{-4}		0.01	0.51		0.51
		0.005	0.25		0.50

same nucleophiles under the same conditions (CN^-,[9a] 0.45 $M^{-1}\,s^{-1}$; SO_3^{2-},[9b] 1.0 $M^{-1}\,s^{-1}$).

In marked contrast to the type of behavior observed with the systems derived from thiolsulfonates **1** and **4**, acidification with a chloroacetate buffer of the final reaction solution from the reaction of either **3** or **6** with cyanide or sulfite does *not* lead to any regeneration of **3** or **6**.

The failure to re-form any α-disulfone on acidification of the reaction solutions could be due to either of two causes. The first possibility is that the intermediates (**13**, **14**, and **15**) formed on the reaction of the cyclic α-disulfones with cyanide (eq 3 and 5) or sulfite (eq 4) are all quite unstable and break



down or hydrolyze so rapidly that there is effectively none of the intermediate left by the time the initial reaction between the α-disulfone and the nucleophile is complete and the solution is acidified with the chloroacetate buffer. The alternative is that the intermediate is sufficiently stable to still be present in significant concentration when the solution is acidified but that the conversion of the intermediate back to the cyclic α-disulfone (step k_r in eq 5, for example) simply has too slow a rate to be able to compete with even a relatively slow decomposition (or hydrolysis) of the intermediate. In the case of the reactions involving **3**, the spectral behavior of the reaction solutions does not provide any clue as to which explanation is right, but in the case of the reaction of cyanide with

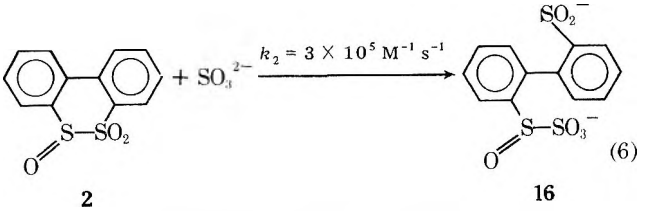
Table IV. Kinetics of the Reaction of Excess Sulfite Ion with Dibenzo[ce]-1,2-dithiin 1,1,2-Trioxide in 60% Dioxane at 25 °C

$10^4[2]_0$, M	$10^3[SO_3^{2-}]$, M	k_1, s^{-1}	$k_1/[SO_3^{2-}]$, $M^{-1}\,s^{-1}$
0.75	0.75	2.4×10^2	3×10^5
	1.5	4.8×10^2	3×10^5

α-disulfone **6** (eq 5) it is possible to state unequivocally that it is the second alternative which is the correct one.

The initial reaction of **6** with cyanide to yield intermediate **15** is accompanied by a decrease in absorbance at 322 nm. This is then followed by a kinetically *much slower* second process that leads to a further significant decrease in the absorbance of the solution at 322 nm and which is associated with the decomposition (or hydrolysis) of **15**. In this case, then, the sequence of spectral changes definitely shows that the rate of disappearance of the intermediate is much slower than its rate of formation. The intermediate (**15**) is therefore present at a concentration comparable to the initial concentration of **6** when the reaction solution is acidified with the chloroacetate buffer. If upon acidification **15** were to revert to **6** at an appreciable rate (step k_r in eq 5), one would see an increase in the absorbance of the solution at 322 nm. However, what is actually observed is only the slow further decline in absorbance associated with the hydrolysis (or decomposition) of **15**. The first-order rate constant for the disappearance of **15** in the chloroacetate buffer is $\sim 5 \times 10^{-4}\,s^{-1}$. Since k_r for **15** must be considerably slower than this, it cannot have a value larger than $\sim 5 \times 10^{-5}\,s^{-1}$ and, for the reasons outlined in a footnote,[10] is actually probably much smaller than this. Based on the behavior of **8** vs. **10**, one would expect k_r for **13** to be considerably slower than that for **15**. For this reason it seems reasonable to believe that in that system cyclization of **13** to **3** would have too slow a rate to be able to compete with other routes for the disappearance of **13** in the chloroacetate buffer.

Reaction of Sulfite Ion with Dibenzo[*ce*]-1,2-dithiin 1,1,2-Trioxide (2).[12] Cyclic sulfinyl sulfone **2** reacts extremely rapidly with sulfite ion in 60% dioxane. The reaction is accompanied by the disappearance of the maximum at 310 nm associated with **2** and the appearance of a new maximum at 280 nm (ε 6400) associated with the reaction product. Isolation of the reaction product and examination of its infrared spectrum show unequivocally that the product possesses a Bunte salt *S*-oxide functional group, $-S(O)SO_3^-$, and has structure **16** (eq 6). The kinetics of the reaction of **2** with excess sulfite are summarized in Table IV.



2 16

Upon acidification, solutions of Bunte salt *S*-oxide **16** exhibit behavior which varies in a striking manner with pH, as regards both the rate of disappearance of **16** and the reaction products. The rate and product data for the disappearance of **16** are given in Table V. Note that in each case where the rate has been determined in a buffer there is no dependence of rate on total buffer concentration. This shows that catalysis of the decomposition of **16** by either carboxylate ions or carboxylic acids is not a factor under our reaction conditions.

Examination of Table V reveals the following points: (1) although the rate of disappearance of **16** changes only very little on going from 1:1 acetate buffers (pH 7.44) to 1:1 chlo-

Table V. Kinetics of the Disappearance of Bunte Salt *S*-Oxide 16 in 60% Dioxane at 25 °C as a Function of pH

$10^4[16]_0$, M	Reaction conditions	pH	[RCOOH] = [RCOO⁻], M	$k_1 \times 10$, s^{-1} [a]	Major product
1.0	1:1 AcO⁻/AcOH buffer	7.44	0.02	0.0022	17
			0.01	0.0024	
			0.005	0.0022	
	1:1 chloroacetate buffer	5.48	0.02	0.004	17 [b]
			0.01	0.003	
	1:1 dichloroacetate buffer	4.0	0.005	0.38	1
			0.0025	0.37	
	1:1 trifluoroacetate buffer	2.8	0.006	3.3	1
	0.01 M $HClO_4$	2.0		12	1

[a] In cases where the major reaction product is 1, rates were followed by measuring the increase in absorbance at 296 nm (λ_{max} for 1). In other cases, rates were followed by measuring the decrease in absorbance at 280 nm (λ_{max} for 16). [b] Final spectrum suggests some 1 is also formed.

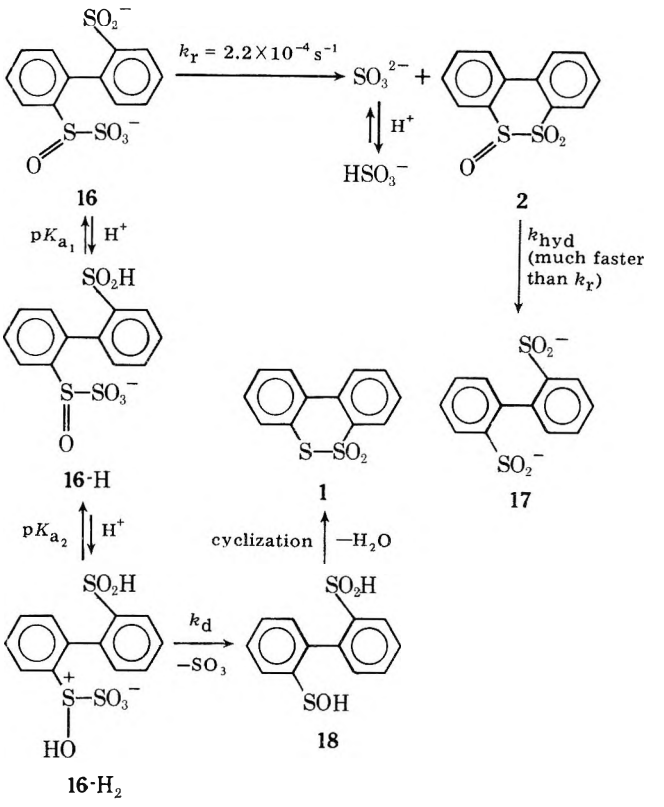
roacetate buffers (pH 5.48), it increases dramatically with further decreases in pH; (2) in those acid solutions in which it decomposes rapidly 16 yields cyclic thiolsulfonate 1 as the only important organic product; (3) on the other hand, in the acetate buffers no significant amount of 1 is formed, and from the spectrum of the solution at the end of the reaction (and the change that occurs if it is then acidified with perchloric acid) it appears that the major organic product is diphenyl-2,2′-disulfinate (17);[13] (4) in the chloroacetate buffer 17 is also an important product, but the final spectrum of the solution suggests that some 1 is formed too.

Before presenting the mechanistic scheme that will satisfactorily accommodate all of these various observations, it is important to mention that in separate experiments we found that cyclic sulfinyl sulfone 2 is hydrolyzed to 17 in a 1:1 acetate buffer ([AcO^-] = 0.005 M) about 100 times faster (0.02 s^{-1}) than the rate of disappearance of 16 in the same medium.

Scheme V outlines what we believe are the mechanisms for the decomposition of Bunte salt *S*-oxide 16 under the different reaction conditions. Let us first consider the slow decomposition that occurs in the acetate buffers. We believe that this has as its rate-determining step the relatively slow reversion ($k_r = 2.2 \times 10^{-4}$ s^{-1}) of 16 to sulfite ion and cyclic sulfinyl sulfone 2. Since the hydrolysis of 2 to 17 in these buffers is much faster than k_r, the presence of 2 as an intermediate is not detectable spectrophotometrically. Sulfite ion is, of course, protonated to bisulfite as soon as it is formed, and this, plus the rather rapid rate of hydrolysis of 2 under these conditions, keeps the reverse of step k_r from becoming of any kinetic importance, even in the final stages of the reaction.[14] Earlier studies,[15,16] which have shown that aromatic sulfinates will react with reactive sulfinyl derivatives to form sulfinyl sulfones under conditions where they do not react with the analogous sulfonyl derivatives to give an α-disulfone, are consistent with the idea that 16 should be able to revert to 2 at a reasonable rate (just as 7 reverts to 1) even though the equivalent intermediate 14 from the reaction of α-disulfone 3 with sulfite does not revert to 3 on acidification with a carboxylate buffer of appropriate pH.

Taking k_1 for the disappearance of 16 in a 1:1 acetate buffer as equal to k_r, one obtains a value of K_{eq} for the 2 + SO_3^{2-} ⇄ 16 equilibrium of 1.4×10^9 M^{-1}, i.e., $K_{eq} = [k_2 \text{ (for eq 6)}/k_r]$. This is 10^4 times larger than the equilibrium constant for the 1 + SO_3^{2-} ⇄ 7 equilibrium. On a free energy basis this means that the opening of the sulfinyl sulfone ring in 2 by sulfite ion

Scheme V. Mechanism of Decomposition of Bunte Salt *S*-Oxide 16 in 60% Dioxane



is 5.5 kcal/mol more favorable than the opening of the analogous thiolsulfonate ring in 1 by the same reagent.

Based on the behavior of the 1 + SO_3^{2-} ⇄ 7 equilibrium, one would expect that the rate of reversion of 16 to 2 plus sulfite ion would be independent of pH in carboxylic acid buffers until one reaches buffers of sufficient acidity to begin protonating 16 to its conjugate acid 16-H. At that point the rate would begin to decrease with decreasing pH because the $-SO_2H$ group in 16-H should be quite unreactive relative to the $-SO_2^-$ group in 16 insofar as performing the displacement of SO_3^{2-} from the Bunte salt *S*-oxide function.

Examination of Table V shows that, although the rate of disappearance of 16 is effectively independent of pH as the pH of the buffer is changed from 7.44 to 5.48, further decreases in pH lead *not* to a decrease but rather to a dramatic increase in rate. Clearly, then, a completely different mechanism for the disappearance of 16 becomes important as the acidity of the reaction medium is increased sufficiently, and this new mechanism leads to 1, rather than 17, as the organic product.

Given the pK_a of Bunte salt 7, it seems reasonable to believe that the pK_a of the sulfinate group in 16 should be no less than about 5.0. Protonation of 16 to 16-H should therefore be virtually complete at pH 4.0. The fact that the rate of disappearance of the Bunte salt *S*-oxide continues to increase markedly as the pH is lowered beyond this point shows that the rapid decomposition to 1 in acid solutions involves the addition of *more than just one proton* to 16.

A straightforward and reasonable mechanism of this type for the acid-catalyzed decomposition of 16 is shown in Scheme V. It involves (a) the reversible protonation of the sulfinyl group in 16-H to give 16-H_2, (b) decomposition of 16-H_2 by loss of sulfur trioxide to afford 18, and (c) cyclization of this mixed sulfenic–sulfinic acid to give thiolsulfonate 1. Formation of a thiolsulfonate by the reaction of an aromatic sulfenic acid with a sulfinic acid has been observed before.[2,17] The intramolecular nature of this reaction in the case of the con-

version of 18 to 1 should allow it to occur particularly readily.

The pK_a of 16-H_2, although unknown, is presumably less than 0. Given that, and assuming k_d to be rate determining, the mechanism for the acid-catalyzed decomposition of 16 shown in Scheme V predicts that the acid-catalyzed rate constant, k_{H^+}, under our reaction conditions will be given by eq 7. The mechanism therefore predicts that until $a_{H^+} > K_{a_1}$

$$k_{H^+} = \left[\frac{k_d}{K_{a_2}}\right]\left[\frac{a_{H^+}{}^2}{K_{a_1} + a_{H^+}}\right] \quad (7)$$

the reaction should exhibit a greater than first-power dependence on a_{H^+}. That this is indeed the case is suggested by the fact that changing from a chloroacetate buffer of pH 5.48 to a dichloroacetate buffer of pH 4.00, an increase of a factor of 30 in a_{H^+}, leads to a greater than 100-fold increase in k_{H^+} (remember that the main contributor to the rate of decomposition of 16 in the chloroacetate buffer is still the reaction that leads to 17 rather than the acid-catalyzed decomposition to 1).

Once $a_{H^+} \gg K_{a_1}$ the mechanism predicts that k_{H^+} should increase linearly with a_{H^+}. Inspection of the data for the pH range 2.0–4.0 in Table V shows that the actual increase in k_{H^+} is somewhat smaller than predicted from eq 7 and that the effect becomes more pronounced the lower the pH. We believe this is due to the fact that at higher acidities the cyclization of 18 to 1 becomes slower than k_{H^+}, with the result that the measured rate of formation of 1 becomes slower than predicted from eq 7.[18]

The mechanism in Scheme V for the acid-catalyzed decomposition of the Bunte salt *S*-oxide has considerable analogy to the mechanism[19] of the acid-catalyzed decomposition of an ordinary Bunte salt (eq 8). In eq 8 zwitterion 19, rather 16-H_2, undergoes loss of sulfur trioxide. When one compares the rates of the two acid-catalyzed decompositions under a given set of reaction conditions (0.01 M $HClO_4$ in 60% dioxane at 25 °C), one finds that the rate of decomposition of Bunte salt *S*-oxide 16 is a staggering 3×10^8 times *faster* than the rate of decomposition of the Bunte salt $PhSSO_3^-$. The Bunte salt *S*-oxide is thus over 10^8 times *less stable* in acid solution than an analogous Bunte salt. Presumably one of the major factors responsible for this is the much greater basicity of the sulfinyl group in the *S*-oxide as compared to the sulfide sulfur in the Bunte salt, i.e., K_{a_2} in Scheme V $\ll K'_a$ in eq 8;

$$C_6H_5\text{—}S\text{—}SO_3^- + H^+ \underset{}{\overset{K'_a}{\rightleftharpoons}} \underset{\displaystyle H}{C_6H_5\text{—}\overset{+}{S}\text{—}SO_3^-} \quad \textbf{19}$$

$$\xrightarrow{k'_d} C_6H_5\text{—}SH + SO_3 \quad (8)$$

sulfinyl groups are known generally to be much more basic than equivalently substituted sulfide functionalities.[20]

We had also hoped to be able to study the reaction of cyanide ion with 2. However, experimental difficulties, which are outlined in detail in the Experimental Section, precluded our obtaining any informative or meaningful data on this particular system (and also the reaction of 5 with CN^-), other than apparently to provide some indication of the rate of hydrolysis of the sulfinyl cyanide function, -S(O)CN, produced on opening of the sulfinyl sulfone ring by cyanide ion.

Experimental Section

Synthesis of Cyclic Thiolsulfonates, Sulfinyl Sulfones, and α-Disulfones. Dibenzo[*ce*]-1,2-dithiin 1,1-dioxide (1) and 1,1,2-trioxide (2) were prepared as described in a previous paper,[13] as was also naphtho[1,8-*cd*]-1,2-dithiole 1,1,2-trioxide (5). Naphtho[1,8-*cd*]-1,2-dithiole 1,1-dioxide (4) was prepared following the procedure of Zweig and Hoffman.[22]

Dibenzo[*ce*]-1,2-dithiin 1,1,2,2-Tetroxide (3). Thiolsulfonate 1 (1.0 g, 4.0 mmol) was dissolved in 25 mL of chloroform, a solution of 1.8 g (8.9 mmol) of 85% *m*-chloroperbenzoic acid in 3.0 mL of the same solvent was added to it at room temperature, and the solution was stirred for 4 days. The white precipitate of 3 was removed by filtration. The filtrate was then extracted three times with 5% sodium bicarbonate to remove *m*-chlorobenzoic acid. It was then washed with water and dried over anhydrous magnesium sulfate. Concentration of the chloroform solution led to the precipitation of additional crops of 3. The combined crops of 3 were recrystallized from chloroform/hexane to afford pure 3, mp 244–245 °C dec, in 73% yield (0.83 g); IR (KBr) SO_2 absorptions at 1343 s, 1329 s, 1167 s, 1147 cm^{-1} ms; UV (60% dioxane) λ_{max} 313 nm (ϵ 6450).

Anal. Calcd for $C_{12}H_8S_2O_4$: C, 51.42; H, 2.88; S, 22.87. Found: C, 51.30; H, 2.99; S, 22.87.

Naphtho[1,8-*cd*]-1,2-dithiole 1,1,2,2-Tetroxide (6). A solution of 0.284 g of 4 in 10 mL of chloroform was mixed with a solution of 0.53 g of 85% *m*-chloroperbenzoic acid in 10 mL of the same solvent, and the mixture was stirred for 1 day at room temperature. The chloroform solution was then extracted three times with 5% sodium bicarbonate, washed once with water, and dried over $MgSO_4$, most of the chloroform removed under reduced pressure, and hexane added to precipitate α-disulfone 6. The precipitate was recrystallized from chloroform/hexane, giving 0.15 g (46%) of pure 6. The compound has no melting point but decomposes slowly on heating above 200 °C; IR (KBr) SO_2 absorptions at 1350, 1180, 1120 cm^{-1}; UV (60% dioxane) λ_{max} 302 nm (ϵ 6500).[23]

Anal. Calcd for $C_{10}H_6S_2O_4$: C, 47.23; H, 2.38. Found: C, 46.91; H, 2.65.

Purification of Reagents. Reagent grade sodium sulfite, potassium cyanide, acetic acid, chloroacetic acid, dichloroacetic acid, trifluoroacetic acid, and sodium acetate were used without further purification. 1,4-Dioxane was purified by the procedure of Hess and Frahm,[25] and the freshly distilled dioxane was then frozen and stored at −20 °C to prevent the formation of peroxides prior to use. Doubly distilled water was used in all kinetic runs.

Procedure for Kinetic Runs. Reaction of Excess Sulfite or Cyanide with Substrates. In the runs using cyanide, 1:1 CN^-/HCN buffers were prepared by adding 1 mol of perchloric acid (as a dilute standardized solution in aqueous dioxane) to an aqueous dioxane solution containing 2 mol of cyanide. The resulting concentrated stock 1:1 buffer solution was then diluted further to achieve the cyanide concentration desired for a particular run.

The reactions of 1 and 4 were followed by stopped-flow spectrophotometry by mixing an equal volume of a 60% dioxane solution of either 1 or 4 with a solution of either sodium sulfite or 1:1 CN^-/HCN buffer in the same solvent. The reactions of 1 were followed at 296 nm and those with 4 at 304 nm.

Because of the rapid hydrolysis of 2 in aqueous dioxane, the stopped-flow procedure for following its reaction with sulfite involved mixing an equal volume of a solution of 2 in anhydrous dioxane with one of a solution of sodium sulfite in 20% dioxane. This procedure has been shown by Kice and Mullan[26] to be valid for following the kinetics of rapid nucleophilic substitution reactions of sulfinyl sulfones. The reaction was followed at 310 nm.

The much slower reactions of α-disulfones 3 and 6 were followed by conventional spectrophotometry. A known volume (3.6 mL) of either a solution of sodium sulfite or a 1:1 CN^-/HCN buffer in 60% dioxane was placed in a spectrophotometer cell in the thermostatted cell compartment of a Cary Model 17 spectrophotometer, and, once thermal equilibration was achieved, the reaction was initiated by injecting 36 μL of a 10^{-2} M solution of either 3 or 6 in anhydrous dioxane into the other solution with immediate mixing. The reactions involving 3 were followed at 313 nm and those involving 6 at 322 nm.

Regeneration of 1 from 7 and 8. Solutions of 7 (or 8) were prepared by reacting 1 (10^{-4} M) with either 5×10^{-4} M CN^- (1:1 CN^-/HCN buffer) or 5×10^{-4} M sodium sulfite in 60% dioxane. To 3.6 mL of these solutions in a thermostatted spectrophotometer cell was then added 36 μL of a concentrated chloroacetic acid/sodium chloroacetate buffer (these buffers contained 1 M sodium chloroacetate and either 0.5, 1.0, or 2.0 M chloroacetic acid), and the increase in the absorbance of the solution with time at 296 nm was then followed. The final absorbance at 296 nm corresponded in each case to the complete regeneration of 1, and the final complete spectrum in the ultraviolet region corresponded to that expected for a 10^{-4} M solution of 1.

Regeneration of 4 from 9 and 10. To study the regeneration of 4 from 9 a solution of 9 was prepared by dissolving 1.1 mg of 4 and 12.6 mg of sodium sulfite in 25 mL of 60% dioxane. This solution was

placed in one of the reservoir syringes of a stopped-flow spectrophotometer, while chloroacetate buffers of varying pH were placed in the other reservoir syringe. Upon mixing of the two solutions the change in the optical density of the solution with time at 304 nm was followed.

The procedure for following the regeneration of **4** from **10** was similar except that in this case a solution of an equilibrium mixture of **4** and **10** was prepared by dissolving 2.2 mg of **4** in 50 mL of a 1:1 CN^-/HCN buffer in 60% dioxane having $[CN^-] = 0.002$ M. This was then placed in one of the reservoir syringes of the stopped-flow spectrophotometer and mixed with different chloroacetate buffers.

Slow Further Reaction of 10 to Give 11. To 3.6 mL of a 60% dioxane solution containing $[CN^-] = [HCN] = 0.016$ M was added 36 μL of a 10^{-2} M solution of **4** in pure dioxane, and the absorbance of the solution at 368 nm (λ_{max} for **11**) was monitored periodically during the course of a week. At the end of that time the absorbance at 368 nm corresponded to only 0.27 of that expected for complete conversion of **10** to disulfide **11**. The solution was then treated with sufficient concentrated chloroacetic acid buffer to convert all of the cyanide ion to HCN (and allow any **10** still present to revert to **4**), and the complete spectrum of the solution was examined. While there was evidence for the regeneration of some **4**, the amount was modest; comparison with known spectra of **4**, **11**, and **12** suggested that a considerable amount of thiolsulfinate **12** was present.

Failure to Regenerate 3 or 6 on Acidification of Final Reaction Solutions from Reaction of 3 or 6 with Sulfite and Cyanide. The final reaction solutions from the reaction of **3** (10^{-4} M) with either 1×10^{-3} M cyanide ion in a 1:1 CN^-/HCN buffer or 5×10^{-3} M sulfite ion were acidified by the addition of 36 μL of a chloroacetate buffer containing 1 M $ClCH_2COO^-$ and 2 M $ClCH_2COOH$. The absorbance of the solution in the region around 313 nm, where **3** has its absorbance maximum, was then monitored with time. There was *no* increase in optical density at 313 nm; regeneration of **3** under these conditions therefore does not occur.

α-Disulfone **6** (10^{-4} M) was reacted at 25 °C with a 1:1 CN^-/HCN buffer containing $[CN^-] = 0.004$ M, and as soon as the rather rapid reaction was complete (t = 3.5 min for 10 half-lives) the 3.6 mL of reaction solution was acidified by the addition of 36 μL of 1:1 chloroacetate buffer, 1.0 M in chloroacetic acid. Acidification led to no increase with time in the optical density at 322 nm, as would have occurred if **6** had been regenerated. Instead, there was a slow further decrease in the absorbance at 322 nm ($k_1 = 5 \times 10^{-4}$ s^{-1}), presumably due to the slow hydrolysis (or decomposition) of the intermediate (**15**) that had been formed in the initial rapid reaction.

Preparation of Bunte Salt *S*-Oxide 16. A solution of 6.3 mg (0.05 mmol) of sodium sulfite in 1 mL of water was added quickly at room temperature with good stirring to a solution of 13.2 mg (0.05 mmol) of **2** in 1 mL of anhydrous dioxane. As soon as the addition was complete the clear solution was frozen, and the solvents were removed by lyophilization. The white crystalline residue of **16** so obtained was used without further purification. In the 900–1300-cm^{-1} region the infrared spectrum of **16** (KBr) showed a strong peak centered at 1220 cm^{-1}, a peak of moderate intensity at 1115 cm^{-1}, and a strong, broad band consisting of a series of overlapping absorptions between 940–1070 cm^{-1}. The ultraviolet spectrum (60% dioxane) had a λ_{max} at 280 nm (ϵ 6400). When heated slowly in a sealed capillary tube **16** began to decompose slowly above 40 °C with substantial contraction of the sample in volume and apparent evolution of a gas. The decomposition was rapid at 70 °C. Exposure of this gas to a solution of barium chloride caused the solution to become turbid, suggesting the gas is probably sulfur trioxide. The solid remaining after the decomposition of **16** did not melt below 300 °C.

Kinetics and Products of the Decomposition of Bunte Salt *S*-Oxide 16. A 1.2×10^{-4} M solution of **16** in 60% dioxane was prepared, and 3.6 mL of the solution was placed in a thermostatted, 1-cm spectrophotometer cell in the Cary 17. A 36-μL amount of 1 M $HClO_4$ solution was then added to this solution. One observed the immediate disappearance of the 280-nm peak associated with **16** and the appearance of the spectrum characteristic of cyclic thiolsulfonate **1** with peaks at 296 and 262 nm. Based on the optical density at 296 nm and the initial concentration of **16**, the yield of **1** under these conditions is essentially quantitative.

In a second similar experiment 3.6 mL of the 1.2×10^{-4} M solution of **16** was treated with 72 μL of a 1:1 acetate/acetic acid buffer ($[AcO^-] = [AcOH] = 1$ M). The disappearance of the peak for **16** at 280 nm was now relatively slow and could be followed by conventional spectrophotometry. A scan of the spectrum of the final solution at the end of the reaction showed no evidence of a peak at 296 nm. The ultraviolet spectrum of the final solution was very similar to that for disulfinate **17**. The final reaction solution was then acidified with sufficient concentrated perchloric acid to neutralize the buffer and give $[H^+] = 10^{-2}$ M, and the spectrum was then rescanned. The change in the spectrum was essentially the same as that observed[13] when a solution of **17** is acidified. Of particular importance, there was a small decrease in absorbance at 296 nm. Were **16** decomposing in the acetate buffer to yield some other species than **17** that was capable of yielding **1** readily upon acidification to pH 2, acidification of the final reaction solution would have led to the appearance of the 296-nm peak associated with **1**. One should also note that other work in this laboratory[2] has indicated that the reaction of a sulfenic acid with a sulfinic acid to give a thiolsulfonate will take place sufficiently readily in 60% dioxane in a 1:1 acetate buffer, so that if decomposition of **16** in that buffer led to **18** (presumably as its monoanion, given the pK_a's of the $-SO_2H$ and more weakly acidic $-SOH$ groups) it would go over to **1** in the buffer.

Additional kinetic experiments on the decomposition of **16** were carried out by adding varying amounts of the concentrated acetate buffer to 3.6 mL of the solution of **16** and following the change in absorbance with time at 280 nm.

In 1:1 chloroacetate buffers, the kinetics were followed in the same way as in acetate buffers. The behavior of **16** was slightly different than in acetate buffers in that the final reaction solution had a slight absorption peak at 296 nm, indicating some **1** had been formed. However, the fact that upon acidification with excess perchloric acid the absorbance of the final reaction solution again decreased at 296 nm shows that **17** is still the more important product.

In 1:1 dichloroacetate buffers the rate, although fast, was still slow enough to be followed by conventional spectrophotometry. However, since under these conditions, as in more acid solutions, the essentially exclusive organic product is **1**, the kinetics were studied by following the increase in optical density at 296 nm rather than the change at 280 nm.

The rate of decomposition of **16** in either 10^{-2} M $HClO_4$ or a 1:1 trifluoroacetate buffer was too fast to be followed by conventional spectrophotometry. Rates in these media were therefore measured by stopped-flow spectrophotometry by mixing a solution of **16** with the acidic solution and then following the change in absorbance at 296 nm.

Reaction of Cyanide Ion with Cyclic Sulfinyl Sulfones 2 and 5. When a solution of **2** (2×10^{-4} M) in pure dioxane was mixed in the stopped-flow spectrophotometer with an equal volume of a series of CN^-/HCN buffers in 20% dioxane, $[CN^-] = 0.002$–0.008 M, and the change in the absorbance with time at 310 nm (λ_{max} for **2**) was monitored, the following results were obtained. For $[CN^-] \geq 0.002$ M after mixing, plots of log $(A - A_\infty)$ vs. time were nicely linear, but the experimental first-order rate constant ($k_1 = 6.6$ s^{-1} for 1:1 CN^-/HCN buffer) was independent of $[CN^-]$. For $[CN^-] = 0.001$ M, plots of log $(A - A_\infty)$ vs. time showed some curvature; the initial slopes were about 75% those for the higher cyanide concentrations, while the slopes of the final portions of each run were about half those for the higher cyanide concentrations. Although independent of cyanide concentration, the rates for $[CN^-] \geq 0.002$ M were dependent on the CN^-/HCN buffer ratio, being approximately twice as large in a series of 2:1 CN^-/HCN buffers as they were in the series of 1:1 CN^-/HCN buffers. Obviously, what is being measured is not the rate of reaction of CN^- with **2** since this would show a first-order dependence on $[CN^-]$ throughout. On the other hand, the dependence of the rate on buffer ratio indicates that the process being measured is one whose rate depends on the concentration of $[OH^-]$. Since cyanide ion is reactive enough compared to hydroxide ion toward acyclic aromatic sulfinyl sulfones so that reaction with cyanide is the only process of kinetic importance in CN^-/HCN buffers,[26] it is hard to believe that what we are following here is the alkaline hydrolysis of **2** itself. Therefore we are inclined to believe that the explanation for the peculiar kinetic behavior observed with **2** and CN^- is that the opening of the sulfinyl sulfone ring in **2** by cyanide is more rapid at $[CN^-] \geq 0.002$ M than the process we are following but does not lead to much of a change in absorbance at 310 nm. Hydrolysis of the intermediate resulting from this reaction, presumably a sulfinyl cyanide, $-S(O)CN$, does involve a sizeable decrease in absorbance at 310 nm, and it is this process that is what one follows via stopped-flow studies. The rate of hydrolysis of the sulfinyl cyanide might be expected to depend on $[OH^-]$ but be independent of $[CN^-]$. Due to the rate of spontaneous hydrolysis of sulfinyl sulfones, all kinetic studies using stopped-flow spectrophotometry with these substrates in 60% dioxane have to be done by mixing a solution of the sulfinyl sulfone in anhydrous dioxane with a 20% dioxane solution of the nucleophilic reactant,[26] with a resultant period immediately after mixing where *small* changes in absorbance cannot be measured reliably. Because of this, it is not possible in the present system to ascertain whether or not there is a

small, rapid initial absorbance change with the rate proportional to [CN^-] preceding the process associated with the large absorbance change which is easy to measure. We tried to see if the situation could be improved by using a different wavelength to follow the reaction but without success.

In the case of the reaction of **5** with cyanide the situation is no better because here the total overall absorbance change associated with the transformation of **5** to the final reaction products is so small as to make any reliable kinetic studies impossible, given the special type of mixing that has to be employed in stopped-flow kinetic work with sulfinyl sulfones.

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Registry No.—**1**, 25331-82-2; **2**, 63059-28-9; **3**, 64728-07-0; **4**, 40227-43-8; **5**, 57821-65-5; **6**, 62609-77-2; **7**, 64754-26-3; **8**, 64754-27-4; **9**, 64754-28-5; **10**, 64754-29-6; **16**, 64754-25-2; sulfite, 14265-45-3; cyanide, 57-12-5.

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$$A \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} B$$

the experimental first-order rate constant is equal to $(k_1 + k_{-1})$.[6]
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(10) A value of 5×10^{-5} s^{-1} for k_r in eq 5 would mean that K_{eq} for the **6** + CN^- ⇄ **15** equilibrium was only 600 times larger than K_{eq} for the **4** + CN^- ⇄ **10** equilibrium. However, there are good reasons to believe it should actually be at least 100 times larger than this and that k_r for **15** is therefore in actuality much smaller than 5×10^{-5} s^{-1}. Specifically, other studies[11] have suggested that the equilibrium constant for a ring-opening reaction involving a cyclic α-disulfone will normally be much larger than for the same reaction and the analogous cyclic sulfinyl sulfone. Since results to be discussed in the next section indicate that K_{eq} for a reaction involving 2 is 5×10^4 times larger than K_{eq} for the same reaction involving **1**, one would certainly expect K_{eq} for the **6** + CN^- ⇄ **15** equilibrium to be at least 10^4 larger than K_{eq} for the **4** + CN^- ⇄ **10** equilibrium, and therefore that k_r for **15** must be much smaller than 5×10^{-5} s^{-1}.
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(13) M. M. Chau and J. L. Kice, *J. Org. Chem.*, **42**, 3265 (1977).
(14) Since no sulfite is present initially, the reverse of step k_r cannot be important at the start of the decomposition of **16**. Were it to become significant during the later stages of the reaction, one would see this manifested in a decline in the rate of disappearance of **16** and upward curvature in the first-order rate plots. This was not observed. For the reverse of step k_r to be kinetically important it would have to be faster than k_{hyd}. Three factors combine to prevent this from being the case in the present system, despite the large rate constant ($k_2 = 3 \times 10^5$ M^{-1} s^{-1}) for the reaction of **2** with SO_3^{2-}. These are the following: (a) even at the end of the reaction the total amount of sulfite plus bisulfite present is only 10^{-4} M, i.e., equal to the initial concentration of **16**; (b) the fraction of sulfite remaining unprotonated in the acetate buffers is very small; (c) the rate of hydrolysis of **2** in the acetate buffers is quite fast ($k_{hyd} \geq 0.02$ s^{-1}).
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Diaziridinones (2,3-Diazacyclopropanones). Structure (X Ray).[1a] Thermal Decomposition via a Nitrenoid Fragment[1b]

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The structure of a diazacyclopropanone, bis(*p*-bromo-α,α-dimethylbenzyl)diaziridinone (**3**), has been determined by x-ray analysis. The substituents attached to the nitrogen atoms are 56° above and below the plane defined by the ring atoms; the bond lengths in the ring are 1.60 (N–N) and 1.325 Å (N–CO). Thermal decomposition of the diaziridinone affords the following (in moles of product per mole of reactant): *p*-bromo-α,α-dimethylbenzyl isocyanate (**9**) (0.35), *p*-bromo-*N*-(1-methylethylidene)benzenamine (**10**) (0.24), *N*-(1-*p*-bromophenylethylidene)-methanamine (**11**) (<0.01), p-bromo-α-methylstyrene (**12**) (0.15), and p-bromocumene (**13**) (0.01). The major path of decomposition is fragmentation to the isocyanate **9** and a nitrenoid species which rearranges (aryl migration) to imine **10**.

Diaziridinones (2,3-diazacyclopropanones) pose several problems of interest in structure and reactivity.[2] NMR and IR data for *N,N'*-di-*tert*-alkyldiaziridinones are suggestive of the nonplanar trans structure **1**.[2a] Physical data and reactions of a bicyclic diaziridinone **2** are in accord with structure **2**, although the NMR shows a single methyl signal (and a single methylene signal) even down to −150 °C.[2c]

Here we report the structure of the diaziridinone **3**, determined by x-ray analysis, and a study of the thermal decomposition of this diaziridinone.

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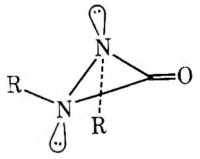
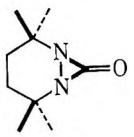


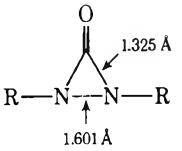
1



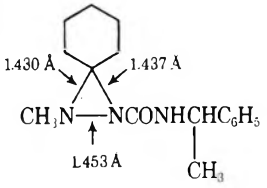
2

Structure of the Diaziridinone 3. The diaziridinone was prepared from the corresponding urea.[2a] The structure (Figure 1; see the Experimental Section for details on the x-ray analysis)[3] is seen to be the transoid arrangement of structure **1**. The substituent atoms, C-2 of Figure 1, are 56° above and below the plane defined by the ring atoms. Comparisons of the ring bond lengths of **3** with related small-ring systems **4**,[4a] **5**,[4b] **6**,[4c,d] **7**,[4e] and **8**[4b] are summarized in Chart I. The N–N bond length in the diaziridinone **3** (and in the thiadiaziridine 1,1-dioxide **6**)[4c,d] is considerably longer than the N–N bond in acyclic systems (e.g., the N–N bond length in F_2N–NF_2[5a] is 1.47 Å; in H_2N–NH_2,[5a] 1.45 Å; in OCH–NH–NH–CHO,[5b] 1.39 Å) or six-membered ring systems (the N–N bond length in 3,4-dimethyl-3,4-diazabicyclo[4.4.0]decane is 1.486 Å; in 2,3-dimethyl-2,3-diazatricyclo[8.4.0.0^{4,9}]tetradec-9-ene, 1.450 Å).[6a,b] The N–CO bond in **3**, 1.325 Å, is close to the value for N–CO, 1.33 Å,[5c] in typical planar amide systems and considerably shorter than the value for N–Csp^2 in 2,4,6-trimethylnitrobenzene, 1.48 Å,[6c] or the average value for N–Csp^3, 1.47 Å.[5c] However, the C=O bond length in **3** is 1.20 Å, the same (within experimental error) as the C=O length in the cyclopropanone **7**,[4e] 1.19 Å, and in the aziridinone **5**,[4b] 1.20 Å; these values are closer to those for typical ketone C=O lengths, 1.215 Å,[5d] than for amide C=O lengths, 1.235 Å.[5d] In summary, the diaziridinone N–N bond is unusually long and the N–CO bonds are unusually short. The geometry for **3** established in this study and the IR carbonyl absorptions of diaziridinones (1855–1880 cm^{-1} vs. 1837–1850 cm^{-1} for aziridinones and 1813–1840 cm^{-1} for cyclopropanones)[2] are not in accord with amide resonance stabilization in diaziridinones. The relative reactivity toward nucleophiles of diaziridinones and cyclopropanones[2b] remains something of a puzzle; the lower reactivity of diaziridinones may be associated, in part, with the larger internal carbonyl angle (see Chart I), with repulsion between a nitrogen lone pair and an attacking nucleophile, and with amide resonance (reduced, but presumably not absent, in **3**).

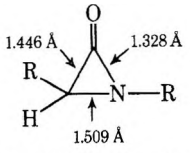
Chart I



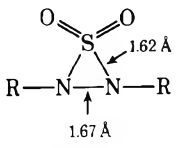
3,[a] ∠NCN = 74.6°



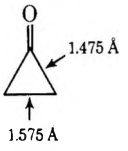
4, ∠NCN = 60.9°



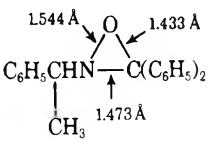
5,[b] ∠N-CO-N = 65.7°



6,[c] ∠NSN = 62°



7, ∠C-CO-C = 64.6°



8, NCO = 64.2°

[a] R = *p*-$BrC_6H_4C(CH_3)_2$-. [b] R = 1-Adamantyl. [c] R = $(CH_3)_3CCH_2C(CH_3)_2$-.

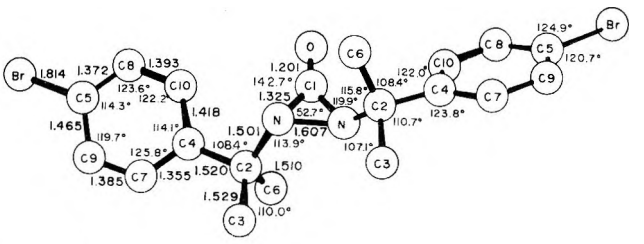
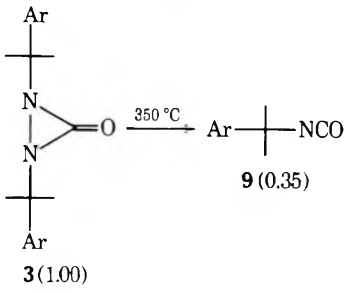
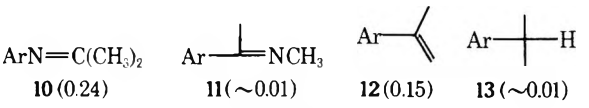


Figure 1.

Chart II



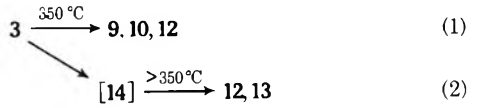
3 (1.00)



10 (0.24) **11** (~0.01) **12** (0.15) **13** (~0.01)

Ar = *p*-BrC_6H_4-

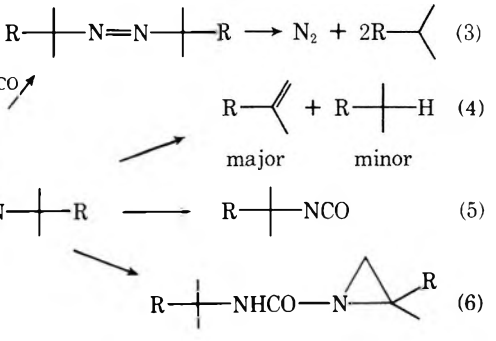
Thermal Decomposition of the Diaziridinone 3. At temperatures above 200 °C, compound **3** decomposes. Because of the sensitivity of some of the products to moisture, the study was carried out directly on GC columns, with decomposition in the injection port (glass liner). The results are summarized in Chart II. The values in parentheses are moles of product per mole of reactant. Yields of products **9**, **10**, and **12** account for 50% of the diaziridinone. Raising the injection port from 350 to 425 °C increased the amount of styrene **12** without decreasing **9** and **10** (Table I), implying a second path for formation of **12** (e.g., eq 2).



(1)

(2)

Previous studies on diaziridinones have provided evidence for several modes of decomposition (eq 3–6).[2,7]



(3)

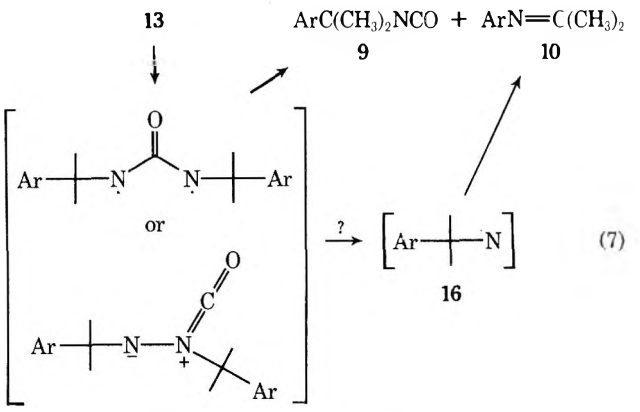
(4)

(5)

(6)

15

The principal contribution of the present thermal study is the evidence for involvement of a nitrenoid species, leading to the imine **10** (Chart II). The large amounts of isocyanate **9** and imine **10** are most simply ascribed to formation of both by a common path, e.g., eq 7. In a search for evidence on ni-



trene **16**, the corresponding azide, **17a**, was prepared. Decomposition of a series of azides of type **17** has been described,[8] affording mixtures of the two possible imines, **10** and **11** (eq 8). Compound **17a** was decomposed under the condi-

$$\underset{17}{Ar + N_3} \xrightarrow{\Delta} \underset{10}{ArN{=}C(CH_3)_2} + \underset{11}{ArC(CH_3){=}NCH_3} \quad (8)$$

• **17a**, Ar = p − BrC_6H_4

tions of decomposition of diaziridinone **3**. Both imines were obtained. In contrast to **3**, the ratio of **10**/**11** from **17a** was quite dependent on the GC column temperature. Alternate injection of **17a** and **3** on a Carbowax column at 225 °C afforded these results.

substrate $\xrightarrow[\Delta]{}$ **10**/**11**

azide **17a** ~2:1

diaziridinone **3** ~50:1

Clearly, under these conditions, decomposition of **17a** and **3** is not proceeding by a common intermediate.[9] Decomposition of **17** (Ar = C_6H_5) affords the two possible imines: from thermal decomposition, **10′**/**11′** = 2:1; from photochemical decomposition, **10′**/**11′** = 1:2.[8]

Also of interest is the possibility of conversion of **3** to p-bromocumyl radicals, N_2 and CO, either stepwise (eq 3) or synchronously. Di-*tert*-butyldiaziridinone undergoes some decarbonylation, affording di-*tert*-butyldiazene.[7] Decarbonylation of **3** would be followed instantly by decomposition of the resulting diazene (azo) compound and is the probable origin, via radical–radical disproportionation, of the small amount, 1%, of cumene **13** (and an equal amount of styrene **12**). Overall, styrene **12** is formed in large excess over the cumene **13** (see Chart II), suggestive of direct formation of most of **12** by the cyclic six-center decomposition of **3**. Some p-bromocumyl radicals may transfer a hydrogen atom to diaziridinone **3**, initiating a radical chain process known to convert diaziridinones to aziridine rearrangement products, **15**[2a] (eq 6), and to ureas. In all likelihood some **15** is produced from **3**, and the increase in styrene **12** at higher decomposition temperature (Table I) is ascribed to the breakdown of **15** (eq 2, **14** = **15**).

In summary, a primary mode of decomposition of the diaziridinone **3** is breaking of ring bonds and fragmentation to the isocyanate **9**. Aryl migration is the principal reaction path in the nitrenoid fragment, affording imine **10**.

Experimental Section

***p*-Bromo-α-methylstyrene:** mp 14–15 °C (lit.[10] 11 °C); NMR (CCl_4) 2.10 (s, 3 H), 5.0 (m, 1 H), 5.27 (s, 1 H), 7.23 (q, 4 H).

***N*-(*p*-Bromo-α,α-dimethylbenzyl)formamide** was prepared by a Ritter reaction.[11] To a cooled mixture of acetic acid (5 mL) and 96% sodium cyanide (6 g) at 0 °C was added a cooled solution of sulfuric acid (25 g) and glacial acetic acid (5 mL). The mixture was allowed to come to room temperature as p-bromo-α,α-dimethylbenzyl alcohol (10 g)[12] was added, maintaining the temperature between 25 and 30 °C. The reaction mixture was stirred for 12 h at room temperature, neutralized (aqueous K_2CO_3), and extracted with ether, and the ethereal layer was washed, dried, and evaporated. The product was recrystallized from pentane to give *N*-(p-bromo-α,α-dimethylbenzyl)formamide: 9.0 g (79%); mp 106–107 °C; NMR (CCl_4) 1.6 (s, 6 H), 7.0–7.5 (m, 4 H), 7.6–8.2 (1 H); IR 1690 cm^{-1}. Anal. Calcd for $C_{10}H_{12}NOBr$: C, 49.60; H, 4.96; N, 5.78; Br, 33.05. Found: C, 49.51; H, 4.97; N, 5.56; Br, 33.26.

***p*-Bromo-α,α-dimethylbenzylamine.** The formamide (12 g, 0.05 mol) was heated at relfux for 5 h in 120 mL of 20% sodium hydroxide solution and then steam distilled. The distillate was extracted several times with ether, and the ethereal portion was washed with water and dried over potassium carbonate. The ether was removed on a steam bath, and the crude product was distilled [142–144 °C (10 mm)], giving the amine as a colorless liquid: 8.55 g (81%); n^{25}_D 1.5547; NMR (CCl_4) 1.4 (s, 6 H), 7.5 (s, 4 H) [lit.[13] bp 122–124 °C (8 mm)]. Anal. Calcd for $C_9H_{12}NBr$: C, 50.45; H, 5.61; N, 6.54. Found: C, 50.57; H. 5.67; N, 6.40.

1,3-Bis(*p*-bromo-α,α-dimethylbenzyl)urea. The p-bromo-α,α-dimethylbenzylamine (1.55 g, 0.00724 mol) was heated with urea (0.403 g, 0.00672 mol) for 15 h at 140–150 °C. The product was recrystallized from acetone to give the dialkylurea as white needles: 0.92 g (56%); mp 236–237 °C; IR ($CHCl_3$) 1660 cm^{-1}; UV (in acetonitrile) 275 nm (ε 417), 267 (647), 260 (585). Anal. Calcd for $C_{19}H_{22}N_2OBr_2$: C, 50.20; H, 4.84; N, 6.17; Br, 35.20. Found: C, 50.34; H, 5.03; N, 6.23; Br, 34.78.

Bis(*p*-bromo-α,α-dimethylbenzyl)diaziridinone was prepared from the corresponding urea (mp 236–237 °C) by the method of Greene et al.[2a] (method B), using *tert*-butyl alcohol as solvent. The crude product, a yellow oily solid, was recrystallized from pentane, giving the diaziridinone as white plates: mp 76–77 °C; 63% yield; IR (CCl_4) intense doublet at 1885, 1850, sharp band at 1585 cm^{-1}; NMR (CCl_4) 1.47 (s, 12 H), 7.25 (q, 8 H, J = 9 Hz); UV (in acetonitrile) 274 nm (ε 383), 263 (689), 257 (746). Anal. Calcd for $C_{19}H_{20}N_2OBr_2$: C, 50.46; H, 4.45; N, 6.19; Br, 35.34. Found: C, 50.58; H, 4.47; N, 6.49; Br, 35.37.

***N*-(1-*p*-Bromophenylethylidene)methanamine (imine 11)** was prepared by the method of Kyba.[14] A mixture of p-bromoacetophenone, methylamine, and molecular sieves in ether was heated at 100 °C in an autoclave for 55 h. Distillation of the reaction mixture afforded the imine: mp 67–70 °C; IR ($CHCl_3$) 2960 (s), 1640 (s, sh), 1590 (s, sh), 1485 (s, sh), 1085 (s, sh), 1010 (s, sh); NMR ($CDCl_3$) 2.17 (s, 3 H), 3.30 (s, 3 H), 7.50 (q, 4 H, J = 9 Hz).

***p*-Bromo-*N*-(1-methylethylidene)benzenamine (imine 10)** was prepared in 43% yield: bp 57–58 °C (0.04–0.05 mmHg) [lit.[15] bp 98–102 °C (5 mmHg)]; IR ($CHCl_3$) 2960 (m), 1660 (s, sh), 1480 (s, sh), 1065 (m, sh), 1000 (m, sh), 840 (s); NMR ($CDCl_3$) 1.72 (s, 3 H), 2.10 (s, 3 H), 6.53 (d, 2 H), 7.35 (d, 2 H).

***p*-Bromo-α,α-dimethylbenzyl Isocyanate (9).** Phosgene gas was bubbled through 35 mL of toluene for 10 min and the solution brought to reflux. A solution of 2.14 g (0.01 mol) of the amine in 10 mL of toluene was added dropwise and with stirring to the refluxing toluene solution over a period of 1.5 h. A continuous stream of phosgene gas was maintained throughout the addition and 10 min thereafter. The reaction mixture was refluxed vigorously for 2 h. The toluene was removed by distillation and the residue was fractionally distilled, giving 1.65 g (69%) of the isocyanate: bp 144–164 °C (10 mmHg); IR ($CHCl_3$) 2970 (w), 2270 (s), 1100 (m, sh), 1010 (m, sh); NMR ($CDCl_3$) 1.67 (s, 6 H), 7.33 (q, 4 H, J = 9 Hz).

***p*-Bromocumene** was prepared by the method of Bruce and Todd[16] by the action of isopropyl chloride on a suspension of aluminum chloride in bromobenzene. A mixture of products was obtained from which a sample of the pure para isomer was isolated by gas chromatography on a 6-ft column of 15% SE-30 on Chromosorb W (80–100 mesh): IR (CCl_4) 2960 (s), 1490 (s), 1460 (s), 1400 (m, sh), 1080 (s), 1010 (s); NMR 1.20 (d, 6 H, J = 7 Hz), 2.80 (septet, 1 H, J = 7 Hz), 7.13 (q, 4 H, J = 9 Hz).

***p*-Bromo-α,α-dimethylbenzyl azide** was prepared by the method of Saunders and Caress[8] and purified by chromatography on alumina:

Table I. Decomposition of the Diaziridinone 3

Injection port temp, °C	Products (mol/mol of 3)			
	9	10	12	13
300	0.35	0.25	0.15	0.01
350	0.35	0.25	0.15	0.01
375	0.35	0.25	0.16	0.02
400	0.35	0.25	0.25	(0.08)
425	0.35	0.25	0.27	(0.15)

IR (CCl_4) 3320 (w, br), 2980 (m), 2450 (w, br), 2090 (s), 1490 (m), 1400 (m, sh), 1370 (m, sh), 1150 (m), 1100 (m, sh), 1010 (m, sh); NMR (neat) 1.47 (s, 6 H), 7.23 (q, 4 H, J = 9 Hz).

Thermal Decompositions. A. Diaziridinone. The diaziridinone (in concentrated cyclohexane solution) and the azide were decomposed by injection into a gas chromatograph with the injection port at 350 °C. Peaks were identified by collection and spectral comparison (IR and NMR) with authentic samples. The imines, styrene **12**, and the cumene were also checked by coinjection of authentic samples with the diaziridinone. Two 6 ft × 0.25 in. aluminum columns were used: one of 15% (w/w) silicone oil SE-30 and one of 15% (w/w) Carbowax 20M, both on a 80–100 mesh Chromosorb W diatomite support. Pyrex glass liners were used in the injection port. Yield and product ratio data were obtained using hydrocarbon standards (undecane, tridecane, and pentadecane). The order of elution and relative retention times on SE-30 were $C_{11}H_{24}$ (0.45), *p*-bromocumene (0.73), *p*-bromo-α-methylstyrene (0.87), $C_{13}H_{28}$ (1.00), unknown (E2) (1.1), *p*-bromo-*N*-(1-methylethylidene)benzenamine (imine **10**) (1.45), *p*-bromo-α,α-dimethylbenzyl isocyanate (1.98), and $C_{15}H_{32}$ (2.38). *N*-(1-*p*-Bromophenylethylidene)methanamine (imine **11**) has the same retention time as the isocyanate; collection of the isocyanate peak from decomposition of a sample of the diaziridinone and examination by IR and NMR showed no evidence for imine **11**. On the Carbowax column, the order of elution of the products is the same; the isocyanate, however, is not eluted. A peak of the same retention time as imine **11** is observed, corresponding to <0.5% yield. The results are summarized in Chart II and Table I.

B. Azide. Thermal decomposition of *p*-bromo-α,α-dimethylbenzyl azide and product analysis were carried out as described above. The major products are the styrene, imine **10**, and imine **11**. On the SE-30 column, imine **11** and the azide have the same retention time; on the Carbowax column, imine **10** and the azide have the same retention time. The ratio of imine **10** to imine **11** is dependent on column temperature, associated, in part, with some variability in the extent of decomposition of the azide. Analysis was best carried out on the Carbowax column with the injection port at 350 °C and the column at 225 °C.

Crystal data for 3: $C_{18}H_{20}Br_2N_2O$; mp 76–77 °C; orthorhombic; space group $p2_12_12$; a = 7.79 (4), b = 17.70 (7), c = 6.86 (2) Å. By assuming two molecules per unit cell (thus explicitly forcing the molecule, itself, to have a twofold rotation axis), a reasonable density of 1.586 g/cm^3 was calculated. Least-squares lattice constants were determined from 20 measurements of the copper $K\alpha_1 - K\alpha_2$ doublet at values of 2θ greater than 65° under fine conditions (1° takeoff angle and 0.05° slit). The measurements were taken on a G.E. XRD-5 diffractometer. Subsequently, three-dimensional intensity data were collected on a G.E. XRD-490 automated diffractometer system using the stationary-counter, stationary-crystal method. balanced Ni and Co Ross filters; and Cu Kα radiation. A total of 1130 reflections were measured to a 2θ limit of 140°. Of these, 717 reflections were considered statistically significant and only these reflections were used in the structure determination. The structure was solved by the standard heavy atom method and refined by block-diagonal least-squares techniques to a final $R = \Sigma||kF_o| - |F_c||/\Sigma|kF_o|$ of 0.06, and a weighted $R_2 = \Sigma[w||kF_o| - |F_c||^2/\Sigma w|kF_o|^2]^{1/2}$ of 0.069. The shift errors in the last cycle of refinements were all less than 0.002. The positions of the phenyl hydrogen atoms were calculated based upon a reasonable chemical model (CH = 1.0 Å; CHC = 120°) and then included in the final cycles of least-squares refinement as fixed contributors. A final difference Fourier map was essentially featureless, with only the ripples about the bromine heavy-atom positions exceeding 0.4 e/Å^3. (See paragraph regarding supplementary material.)

Acknowledgment. We wish to thank Professor Timberlake of the University of New Orleans for his interest and assistance in this work and to call attention to related work of his laboratory.[4c,17]

Registry No.—**3**, 64586-25-0; **9**, 64586-20-5; **10**, 40938-44-1; **11**, 64586-22-7; *p*-bromo-α-methylstyrene, 6888-79-5; *N*-(*p*-bromo-α,α-dimethylbenzyl)formamide, 64586-24-9; *p*-bromo-α,α-dimethylbenzyl alcohol, 2077-19-2; sodium cyanide, 143-33-9; *p*-bromo-α,α-dimethylbenzylamine, 17797-12-5; 1,3-bis(*p*-bromo-α,α-dimethylbenzyl)urea, 64586-23-8; urea, 57-13-6; *p*-bromoacetophenone, 99-90-1; methylamine, 74-89-5; phosgene, 75-44-5; *p*-bromocumene, 586-61-8; *p*-bromo-α,α-dimethylbenzyl azide, 64586-21-6.

Supplementary Material Available: A list of atomic coordinate positions and anisotropic thermal parameters for the nonhydrogens and the calculated positions for the hydrogen atoms (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Supported, in part, by the General Research Support Branch, Division of Research Resources; National Institutes of Health, Grant No. RR-506-01-72 (R.J.M.); and the Warner Lambert Pharmaceutical Company (L.M.T.). (b) Supported, in part, by U.S. Public Health Service Research Grant CA-16592 from the National Cancer Institute (F.D.G.).
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Chemistry of 1,3-Butadiene-2,3-dicarbonitrile. 1

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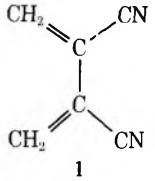
Hydrogenation of butadiene-1,2-dicarbonitrile (1) yielded *cis*- and *trans*-2-butene-2,3-dicarbonitrile, while bromine or chlorine gave 1,4-dihalo-2-butene-2,3-dicarbonitrile. Reaction of 1 with methanolic hydrogen halide gave 2,3-bis(halomethyl)succinimide. Secondary amines easily added to 1, resulting in formation of *cis*- and *trans*-1-amino-2-butene-2,3-dicarbonitriles, which underwent an amine-catalyzed tautomerization to 1-amino-1-butene-2,3-dicarbonitriles. Hydrolysis of the latter gave 2,3-dicyanobutyraldehyde. Also described are the preparation of 1-methoxy-2-butene-2,3-dicarbonitrile, 2,3-dicyano-1,4-butanedithiol diacetate, disodium 2,3-dicyano-1,4-butanedisulfonate, and 1-(*p*-toluenesulfonyl)-2-butene-2,3-dicarbonitrile by reaction of 1 with methanol, thiolacetic acid, sodium bisulfite, and *p*-toluenesulfinic acid, respectively. Hydration of 1 with sulfuric acid gave the diamide **23**, and conditions are described for the Ritter reaction of 1.

The reactions of 1,3-butadiene-2-carboxylic and -2,3-dicarboxylic acid derivatives have received little attention. Some work has been reported on the chemistry of the esters of the diacid[1] and with certain derivatives of the monoacid.[2] Convenient syntheses of dienes of these types, especially the diacid derivatives, have been developed recently,[3,4] and definitive chemistry of 1,3-butadiene-2,3-dicarbonitrile (1) is beginning to appear.[3]

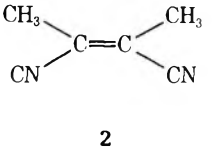
For some time we have been interested in the chemistry of **1**. Befitting such a multifunctional molecule, this diene possesses a diverse, often unique reactivity. This report will be concerned with solvolytic and conventional double-bond addition reactions that 1 undergoes, while its behavior as a strongly electron-deficient diene will be dealt with separately.

Results and Discussion

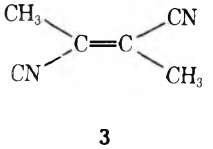
Hydrogenation. Catalytic reduction of 1 occurred under mild conditions to give *cis*- and *trans*-2-butene-2,3-dicarbonitrile (**2** and **3**, respectively) as the major products.[5] Al-



1



2



3

though these products have been described previously,[6] it is nevertheless appropriate to relate their spectral properties (Table I) to isomer structure, since such data were important in defining the structures of other products obtained in this study.

The absorption in the infrared region due to carbon–carbon double bond stretching (at ca. 1600 cm^{-1}) is normally substantial only with symmetrically substituted olefins. Since **3** is symmetric in so far as the dipole may be affected, while **2** is not, only the latter (i.e., symmetrically substituted maleonitriles vis a vis isomeric fumaronitriles) will exhibit a (relatively) significant absorption in this region.

From the NMR data in Table I, the salient observations are: (a) the resonances for the hydrogens in **3** are shifted downfield relative to those for **2**, because both cyano groups participate in deshielding the methyl groups to a larger extent in the former than in the latter; and (b) steric perturbations of the relatively bulky adjacent methyl groups in **2** shift this (methyl carbon) resonance upfield relative to that of **3**, as normally observed in systems such as this.[7]

Since the spectral data are thus in agreement with the structures of the known **2** and **3**, comparison of similar data from other cis,trans pairs prepared in this work permitted structural assignments to be made with a reasonable level of confidence. Accordingly, cis structures were assigned to those isomers having a relatively significant absorption at ca. 1600 cm^{-1} and exhibiting resonances from the hydrogens on the allylic carbons slightly upfield those of the trans isomers. (These criteria resulted in the cis structure being assigned the isomer having the lower up; this is normally expected.)

Halogenation and Hydrohalogenation. Under ultraviolet irradiation, diene **1** underwent ready addition of one molecule of bromine to give 1,4-dibromo-2-butene-2-3-dicarbonitrile (**4**). Even with excess bromine, **4** was the only observed product. Without light, the addition was very slow. The reaction was not affected by the addition of hydrogen bromide, lithium bromide, or aluminum chloride. Although thin-layer chromatography (TLC) indicated that two products were formed (closely related isomers, since the ^1H NMR spectrum of the mixture was a single peak), careful and repeated attempts to separate by HPLC were not successful. In an analogous manner, **1** underwent reaction with chlorine to give 1,4-dichloro-2-butene-2,3-dicarbonitrile (**5**). All attempts to add iodine to **1** failed.

The diene **1** was relatively inert to hydrogen chloride in an aprotic solvent, even under irradiation or in the presence of stannic chloride. However, in hot methanol addition of 2 mol of the acid occurred with concurrent reaction of the nitrile groups to yield, after hydrolysis, 20–25% of 2,3-bis(chloromethyl)succinimide (**7**) of undetermined stereochemistry. The dibromo analogue **6** was formed in low yield (at room temperature) in a similar manner. Ethanolic hydrogen chloride failed to react with **1** after several days at room temperature. In a further study of related systems, **4** failed to undergo solvolysis (at the nitrile group) with either hydrogen halide in methanol. Thus, recovery of **4** was nearly quantitative after treatment with methanolic hydrogen bromide at 50 °C.

The reactivity of **1** toward hydrogen halide only in the presence of methanol suggests that reaction at the nitrile group to yield a cyclic imido chloride or ester may precede or is at least involved in the addition to the double bond. Lending support to this is the observed lability (toward dimerization and polymerization) of the imide and anhydride of 1,3-butadiene-2,3-dicarboxylic acid,[8] suggesting a highly reactive system in structures such as these (and the proposed cyclic imide intermediate). The resistance of **4** toward solvolysis with methanolic hydrogen halide suggests further that the overall reaction (i.e., formation of **6** and **7**) may occur as a more-or-less concerted addition-solvolysis process, or at least a closely related sequential process. Otherwise, the exact process for the moment remains obscure.

Results of attempts to use the dibromo derivative **4** as a reactive intermediate were disappointing. While reaction with various nucleophilic reagents (e.g., cyanide, sulfide, thiourea, acetate, and amines) occurred, giving generally intensely

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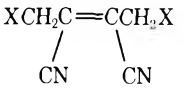
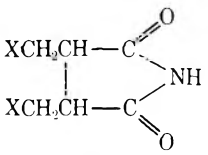
Table I. Properties of Products from Hydrogenation of Diene 1

	Product 2	Product 3
Yield, % (by VPC)	35	52
Mp.,[a] °C	40–46	81.5–82.5
IR absorption, cm^{-1}		
CN	2220	2220
C=C	1620	
^1H NMR ($CDCl_3$) δ (ppm)		
CH_3	2.07 (s)	2.27 (s)
^{13}C NMR ($CDCl_3$) δ (ppm)		
CH_3	17.46	20.16
C=C	124.80	124.92
CN	117.26	116.19

[a] Lit. mp for **2** 48 °C and for **3** 81 °C; see ref 6.



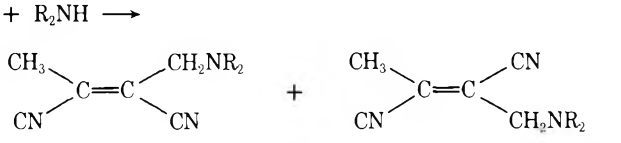
4, X = Br
5, X = Cl



6, X = Br
7, X = Cl

colored reaction solutions, discrete reaction products could not be isolated. For example, *tert*-butylamine in acetonitrile underwent a rapid and exothermic reaction with **4** to give *tert*-butylammonium bromide almost quantitatively; however, attempts to isolate anything from the tarry residual product by a variety of methods were fruitless.

Addition of Amines. Diene **1** has marginal stability in the presence of bases.[9] However, as the result of the polarization induced by the two strongly electronegative nitrile groups, it undergoes facile addition reactions with secondary amines. Thus, with piperidine in benzene at room temperature, a 72% yield of a 1:3 mixture of *cis*- and *trans*-1-(1-piperidino)-2-butene-2,3-dicarbonitrile (**8** and **9**, respectively) was isolated. Similarly, morpholine gave a 55% yield of *cis*- and *trans*-1-(1-morpholino)-2-butene-2,3-dicarbonitrile (**10** and **11**, respectively). Dimethylamine gave the analogous products **12** and **13**, although only the latter was characterized. Pyrrolidine



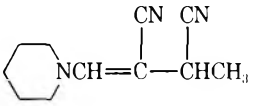
8, R = $(-CH_2-)_5$
10, R = $[-(CH_2)_2O(CH_2)_2-]$
12, R = CH_3

9, R = $(-CH_2-)_5$
11, R = $[-(CH_2)_2O(CH_2)_2-]$
13, R = CH_3

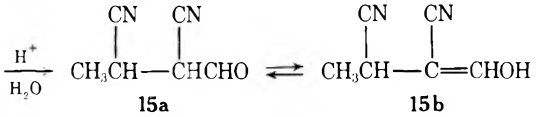
and di-*n*-octylamine underwent similar reaction with **1**, but the oily products appeared to be less stable and were not rigorously identified. Diphenylamine underwent reaction with **1** in hot acetic acid in the presence of copper or cupric acetate,[10] but a complex reaction mixture resisted separation and purification by a number of means.[11]

While both **8** and **9** were formed under mild conditions, **9** was thermally favored. Thus, reaction of **1** with piperidine at higher temperatures (e.g., in hot benzene) gave only **9** (by TLC and NMR), and mixtures of **8** and **9** yielded only **9** upon distillation. The trans isomer **9** was reasonably stable thermally. Although no similar study was made of the other amine derivatives, it is assumed that the trans adducts were similarly favored (and yield data supported this; see Experimental Section).

In addition to this thermal cis to trans isomerization, the mixed adducts **8** and **9** underwent a base-catalyzed tautomerization to the cyanoenamine **14**, 1-(1-piperidino)-1-butene-2,3-dicarbonitrile, by treatment with, e.g., hot piperidine. The same product **14** was obtained when the diene **1** was added directly to an excess of the hot amine. The structure of **14** was proven by both spectral and chemical means. It exhibited intense absorption in the infrared region at ca. 1640^{-1} cm, characteristic of a strongly polarized double bond, and a singlet resonance (^1H NMR) corresponding to one hydrogen in the olefinic region.[12] The product **14** underwent facile acid-catalyzed hydrolysis to give 2,3-dicyanobutyraldehyde (**15a**). From both IR and NMR data, this was found to be in



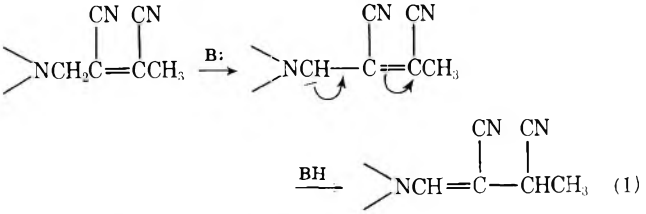
14



15a **15b**

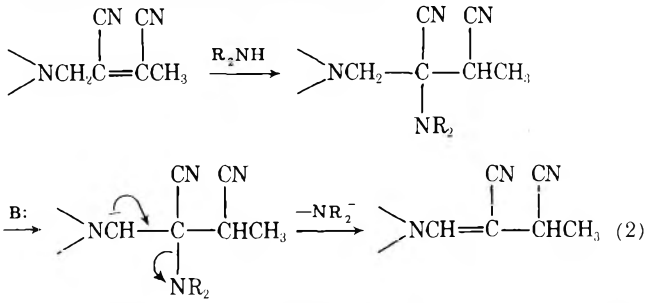
dynamic equilibrium with its enol **15b**, with the latter predominant (see Experimental Section).

The initial formation of the adducts **8** and **9** was very fast (by NMR monitoring; complete in a short time, even at 0 °C), while the tautomerization, a (1,3)-prototropic shift, was considerably slower. With catalytic amounts of piperidine (in hot toluene), the tautomerization was very slow, while in hot piperidine itself, the **9** → **14** process was complete in 20 min. Furthermore, there was no formation of **14** from **9** in hot triethylamine, which approximates piperidine in base strength. Assuming that there is no significant difference in the activity of these two amines due to steric differences, this latter finding precludes the formation of **14** by a simple proton removal and subsequent isomerization (eq 1). An alternative mechanism



(1)

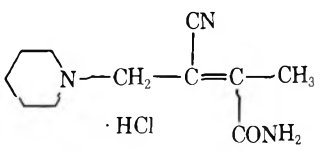
may be an addition–elimination process, in which another molecule of the secondary amine adds (at the carbon β to the amine) to the initial 1,4 adduct, as reported for the similar reaction of butadiene-2-carbonitrile,[2d] followed by proton abstraction and elimination (eq 2).[13]



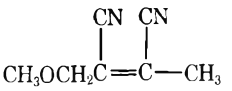
(2)

Isomerization of the mixed piperidine adducts **8** and **9** with di-*n*-propylamine resulted also in the formation of **14** (by VPC), in addition to a number of other products which were not readily separated or identified. Similarly, treatment of the mixed morpholine adducts **10** and **11** with hot piperidine gave (by TLC) a complex mixture of at least four products.[14] While these results suggested the complexity of the process, because discrete reaction products could not be isolated, no further light was shed on the tautomerization mechanism.

The adduct **9** underwent reaction with methanolic hydrogen chloride to give 77% of the hydrochloride of an apparently isomerically pure cyanoamide, tentatively assigned the structure **16**, 1-(1-piperidino)-2-cyano-2-butene-3-carboxamide hydrochloride.[15]



16

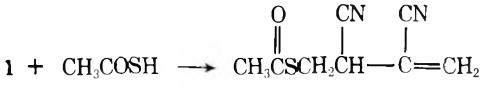


17

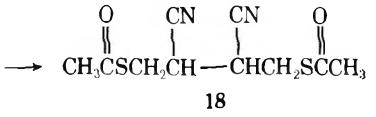
While secondary amines generally gave well-characterized addition products with **1**, reactions with primary amines were more complex. Thus, methylamine yielded viscous, variously colored (dark) products (by liquid chromatographic separation) of limited stability that gave spectral (IR) evidence for the presence of amine, nitrile, and enamine groups. With *tert*-butylamine, monitoring by ^1H NMR showed that adduction was complete in 10 min. Further reaction occurred, but discrete products could not be separated, although again spectral evidence suggested that cyanoenamines were formed.

Addition of Alcohol The reaction of **1** with methanol, in the presence of 1,8-bis(dimethylamino)naphthalene, a strongly basic but weakly nucleophilic amine catalyst, gave a modest yield of **17**, 1-methoxy-2-butene-2,3-dicarbonitrile, as a 1:3 mixture of cis,trans isomers. There was no reaction in the absence of catalyst. Under identical conditions, treatment with ethanol resulted in polymerization of **1**. Polymerization also occurred in methanol in the presence of the similar catalysts 2,2,6,6-tetramethylpiperidine and 1,5-diazabicyclo[4.3.0]non-5-ene, and no **17** could be isolated.

Reaction with Sulfur Nucleophiles The diene **1** underwent ready reaction with thiolacetic acid in THF; analysis (VPC) showed that reaction was complete in a few minutes, even at 0 °C, and that two major (volatile) products were formed. Interestingly, no reaction occurred in dichloromethane, suggesting that the process may be free radical and depends on a trace of peroxide present in the ether (THF) solvent for initiation. A small amount of a crystalline product was isolated that was apparently 2,3-dicyano-1,4-butanedithiol diacetate (**18**). Although the NMR spectrum of the major oily product indicated the presence of terminal methylene and acetyl groups, there were other resonances that could not be assigned to a simple structure such as the monoadduct 2,3-dicyano-3-butene-1-thiol acetate (**18a**) (see Experimental Section). This major product(s) thus remains unidentified. No attempt was made to add simple mercaptans to **1**.

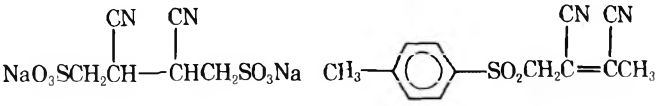


18a

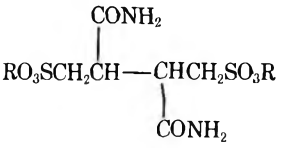


18

The diene **1** reacted exothermally with 2 equiv of sodium bisulfite to give a high yield of **19**, disodium 2,3-dicyano-1,4-butanedisulfonate. The reaction was much more complex when only 1 equiv of sodium bisulfite was used, giving discoloration and insoluble, apparently polymeric products. Sodium *p*-toluenesulfinate was sufficiently basic to polymerize diene **1** in aqueous solution. However, in acetic acid at ca. 70 °C, reaction occurred to give 96% of 1-(p-toluenesulfonyl)-2-butene-2,3-dicarbonitrile, **20**, as a 2:1 mixture of the cis,trans isomers.



19 **20**

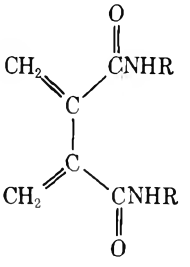


21, R = Na
22, R = CH_3

The salt **19** underwent a complex reaction with methanolic hydrogen chloride. Two products were isolated in low yield which were assigned the structures disodium 2,3-dicarbamoyl-1,4-butanedisulfonate (**21**) and the corresponding dimethyl ester **22**.[16] A sulfonic acid ion-exchange resin apparently converted **19** to the free acid, but no attempt was made to rigorously purify or characterize the waxy solid product.

Hydrolysis and Similar Reactions The best method found for the hydration of the cyano groups of **1** was by treatment of a sulfuric acid solution of **1** with ice. This afforded 1,3-butadiene-2,3-dicarboxamide (**23**) in ca. 50% yield. Although more severe treatment with sulfuric acid yielded a product that gave spectral evidence for the presence of acid groups, no rigorous attempt was made to prepare the diacid from **1**.

Interestingly, solutions of **1** in acetic acid or in formic acid failed to undergo any apparent reaction with sulfuric acid. However, in the presence of a suitable substrate, these conditions allowed a successful Ritter reaction to occur. Thus, in 97% formic acid the diene **1** gave *N,N'*-di-*tert*-butyl-1,3-butadiene-2,3-dicarboxamide, **24**, and *N,N'*-bis(2-methyl-2-butyl)-1,3-butadiene-2,3-dicarboxamide, **25**, with *tert*-butyl alcohol and 2-methyl-2-butene, respectively.



23, R = H
24, R = $C(CH_3)_3$
25, R = $C(CH_3)_2CH_2CH_3$

Conclusions

Although 1,3-butadiene-2,3-dicarbonitrile, **1**, is potentially a useful intermediate to numerous types of derivatives, its value is limited by its propensity to polymerize or otherwise form often intractable products under free-radical or basic conditions. Where these processes are rapid, e.g., addition of thiolacetic acid or secondary amines, monomeric products may often be isolated in good yield; this indicates perhaps that polymerization is a slower process than addition, at least under the described conditions.

In the studies that gave characterizable products, two types of additions were noted. Thus, hydrogen, halogen, arenesulfinic acid, and amines gave 1,4 addition products, while hydrogen halide, bisulfite, and apparently thiolacetic acid gave 1,2 addition products. Especially striking are the results with the grossly similar sodium bisulfite and arenesulfinic acid, yielding **19** and **20**, respectively. We have no explanation for this diverse behavior at present.

Experimental Section[17]

2-Butene-2,3-dicarbonitrile (2 and 3). About 20 mL of freshly distilled tetrahydrofuran (THF) was mixed with ca. 0.25 g of 10% palladium on charcoal in a Brown Hydrogenator. The catalyst was treated with hydrogen, and a solution of 1.0 g of 1 in 20 mL of THF containing 2 drops of glacial acetic acid was added. Hydrogen uptake was complete in about 1 h. Products were separated by liquid chromatography on silica gel, eluting with a mixture of cyclohexane and dichloromethane. Physical and spectral properties of the products are given in Table I.

1,4-Dibromo-2-butene-2,3-dicarbonitrile (4). A solution of 10.0 g (0.096 mol) of 1 in 100 mL of chloroform was stirred in a Pyrex flask under irradiation by a (external) UV light source while a solution of 17 g (0.106 mol) of bromine in 40 mL of chloroform was added dropwise over a 30-min period; the temperature was kept at 19–20 °C by cooling in a water bath. After another 90 min, the solvent was removed under aspirator pressure. The residue, an orange mixture of crystals in an oil, was dissolved in dichloromethane (Norit); chilling at −20 °C gave 21.1 g (83%) of yellow, crystalline **4**: mp 106–112 °C (from a mixture of dichloromethane and hexane); IR (KBr) 2270 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.43 (s, CH_2). Anal. Calcd for $C_6H_4Br_2N_2$: C, 27.30; H, 1.53; Br, 60.55; N, 10.61. Found: C, 27.28; H, 1.48; Br, 58.9; N, 10.69.

1,4-Dichloro-2-butene-2,3-dicarbonitrile (5). A solution of 4.6 g (0.044 mol) of 1 in 100 mL of chloroform, in a Pyrex flask, was stirred at 30–35 °C under irradiation from a (external) UV source while chloride was added through a gas dispersion tube. When an excess of chlorine was present (persistent yellow color; after ca. 3 h), the addition of the gas was terminated, and the reaction solution was allowed to stand overnight at room temperature. After removing a small amount of an insoluble material, hexane was added to the solution to the cloud point. Several crops of crystals were obtained by chilling to −20 °C and addition of more hexane to give a total of ca. 7.3 g (94%) of **5**; this solid discolored upon standing. Sublimation (high vacuum) gave a white, crystalline product, mp 102–103.5 °C, that retained its white color; IR (KBr) 2270 (CN) cm^{-1}; ^1H NMR ($CDCl_3$; run on the crude product) δ 4.45 (s, CH_2) and 3.0 (impurity). Anal. Calcd for $C_6H_4Cl_2N_2$: C, 41.18; H, 2.30; Cl, 40.51; N, 16.01. Found: C, 40.81; H, 2.54; Cl, 40.29; N, 15.43.

2,3-Bis(chloromethyl)succinimide (7). A solution of 9.0 g (0.086 mol) of 1 in 150 mL of methanol was stirred under nitrogen while a slow stream of anhydrous hydrogen chloride was added through a gas dispersion tube. No provision was made for cooling the reaction, and the gas was added for a total of 7–8 h (no attempt was made to meter the flow). The solvent was stripped under aspirator pressure. The residual paste was taken up in 100 mL of water. After allowing the mixture to stand overnight at room temperature, the product was extracted into methylene chloride. After drying (mole sieve), decolorizing (Norit A), and concentration, chilling the solution to −20 °C gave 3.77 g (23%) of **7**: mp 121–123 °C (from methylene chloride); IR (KBr) 3226 (NH), 1695 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.8 (broad s, 1, NH), 4.0 (CH_2 portion of an $A_2B_2X_2$ pattern, 4), 3.4 (CH portion of an $A_2B_2X_2$ pattern, 2). Anal. Calcd for $C_6H_7NO_2Cl$: C, 36.76; H, 3.60; Cl, 36.17; N, 7.15. Found: C, 36.93; H, 3.81; Cl, 36.9; N, 6.99.

2,3-Bis(bromomethyl)succinimide (6). A solution of 4.0 g (0.038 mol) of 1 in 100 mL of methanol was treated with gaseous hydrogen bromide in a manner similar to that described for the preparation of **7**. Addition required 2 h, and the temperature was kept at 20–27 °C. After concentrating the reaction solution to a volume of ca. 50 mL under aspirator pressure, 100 mL of water was added. A small amount (0.48 g, 4%) of (probably) 4-bromo-2-bromomethyl-3-cyanobutyramide was removed: IR (KBr) 3280 and 3180 (NH_2), 2270 (CN), 1665 and 1615 (amide) cm^{-1}. Anal. Calcd for $C_6H_8Br_2N_2O$: C, 25.38; H, 2.84; Br, 56.34; N, 9.86. Found: C, 27.7; H, 2.8; Br, 56.3; N, 9.9. After removal of this product, the yellow aqueous filtrate was extracted with dichloromethane. Evaporation of the extracts gave an oil. Addition of ether gave 0.62 g (6%) of **6**:[18] mp 129–130 °C; IR (KBr) 3225 and 3075 (NH_2), 1820, 1785, and 1710 (imide) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0 (broad s, 0.7, NH), 3.8 (m, 4, CH_2), 3.5 (m, 2.3, CH), 1.7 (impurity, 5% of H). Anal. Calcd for $C_6H_7Br_2NO_2$: Br, 56.08. Found: Br, 55.1.

1-Piperidino-2-butene-2,3-dicarbonitrile (8 and 9). A solution of 1.53 g (0.015 mol) of 1 in 50 mL of benzene was stirred under nitrogen while 1.25 g (0.015 mol) of freshly distilled piperidine was added over a 10–15-min period. The slightly exothermic reaction (temperature rose about 5 °C) was accompanied by a color change from yellow to gray-green; continued stirring at room temperature for an hour gave a further color change to purple, then red, and finally dark red. After allowing the mixture to stand overnight at room temperature, the black solution was filtered to remove 0.04 g of a polymeric product; about 0.6 g of mixed 8 and **9**, mp 58–65 °C, was recovered from the mother liquor. Chromatographic separation (on silica gel, eluting with a mixture of hexane and ether) gave, first, **9**: mp 67.0–68.5 °C; IR (KBr) 2245 (CN) and 1625 (weak, C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (m, 2, CH_2C=),[19] 2.4 (m, 4, ring CH_2N), 2.20 (m, 3, CH_3),[19] 1.5 (m, ring CH_2, 6). Anal. Calcd. for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.50; H, 8.18; N, 21.73. After elution of **9**, 8 was collected: mp 46–48 °C; IR (KBr) 2220 (CN) and 1625 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.20 (m, 2, CH_2C=),[19] 2.4 (m, 4, ring CH_2N), 2.10 (m, 3, CH_3),[19] 1.5 (m, 6, CH_2). In another run, 8 and **9** were obtained in ca. 18 and 54% yields, respectively.

1-(1-Morpholino)-2-butene-2,3-dicarbonitrile (10 and 11). A solution of 2.19 g (0.021 mol) of 1 in 80 mL of THF was stirred while 1.74 g (0.020 mol) of morpholine was added as described for the preparation of 8 and **9**. After 24 h at room temperature, the blue solution was treated with Norit. The resulting amber solution was stripped under aspirator pressure to give 3.6 g of a dark solid. Recrystallization from hexane gave a mixture of white, crystalline **10** and **11** in a total yield of 2.18 g (55%): mp 79–83 °C; IR (KBr) 2220 (CN) and 1650 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (m, 4, CH_2O), 3.4 (m, CH_2C=, 2),[19] 2.6 (m, ring CH_2N, 4), 2.35 (m, CH_3, 3)[19] with minor resonances at δ 3.25, 2.90, 2.18, and 1.7; mass spectrum *m/e* (rel intensity) 191 (18), 105 (47), 100 (85), 86 (86). Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.87; H, 6.76; N, 22.00. Found: C, 63.22; H, 6.74; N, 22.40. TLC analysis of the crystalline product showed two components, one greatly preponderant. Chromatography on silica gel (eluting with a mixture of cyclohexane and ether) of a 0.2-g sample gave 0.185 g of white, crystalline **11**, mp 84–85.5 °C, with ^1H NMR resonances identical to the major resonances described above for the mixture, and 0.019 g of **10** as a colorless oil; ^1H NMR ($CDCl_3$) δ 3.25 and 2.18 (for the "non-morpholine" portion of the spectrum).

1-(Dimethylamino)-2-butene-2,3-dicarbonitrile (12 and 13). A solution of 0.47 g (0.0045 mol) of 1 in 50 mL of THF was treated with 130 mL (0.0054 mol) of gaseous dimethylamine in the manner described for the preparation of 8 and **9**. The solvent was removed under aspirator pressure from the red-brown reaction solution after 3 h to give 0.64 g of a residual oil. High vacuum sublimation gave 0.34 g of a (wet) white solid mixed with 0.08 g of a yellow oil.[20a] The former, recrystallized from a mixture of methylene chloride and hexane, gave 0.17 g (25%) of (probably) **13**: mp 34.5–35.5 °C; IR (KBr) 2220 (CN), 1620 (weak, C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (s with a shoulder,[20b] 2, CH_2C=) and 2.33 (s, 9, CH_3C= and CH_3N); mass spectrum *m/e* (rel intensity) 149 (1.3), 58 (100). Anal. Calcd for $C_8H_{11}N_3$: C, 64.40; H, 7.43; N, 28.17. Found: C, 64.4; H, 7.4; N, 28.3.

1-(1-Piperidino)-1-butene-2,3-dicarbonitrile (14). Piperidine (17 g) was stirred at 80 °C while 2.0 g (0.019 mol) of 1 was added over a 2-min period. After an hour, the brown solution was evaporated in a stream of nitrogen. The residual oil was extracted with hexane, and the hexane solution was distilled to give 1.53 g (43%) of 14: bp 156 °C (0.9 mmHg); mp 70.8–71.5 °C (ether); IR (KBr) 2270 and 2175 (CN), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.55 (s, 1, HC=), 3.1–3.6 (m, 5, CH_2N and HCC=), 1.6 (m, 6, ring CH_2), 1.5 (d, 3, CH_3). Anal. Calcd for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20. Found: C, 70.01; H, 7.98; N, 21.81.

2,3-Dicyanobutyraldehyde (15a) and 2,3-Dicyano-1-buten-1-ol (15b). The cyanoenamine **14**, 0.22 g (0.0012 mol), was added to 5 mL of 7% hydrochloric acid. The solid dissolved in about an hour. The colorless solution was extracted with ether. After drying (calcium chloride), evaporation gave 0.08 g (ca. 50%) of **15** as a colorless oil: IR (neat) 3225 (OH), 2775 and 1665 (aldehyde), 2220 (and "shoulder" ca. 2280, CN) cm^{-1}; ^1H NMR (acetone-d_6) δ 7.5 (s superimposed on a broad resonance, 1.67, HC=O and HC(OH)=C), 4.0 and 3.7 (2 "quartets" in a 1.4:1 integral ratio, 1, HCCN),[21] 1.45 (d, 3, CH_3).

1-(1-Piperidino)-2-cyano-2-butene-3-carboxamide Hydrochloride (16). A solution of 2.0 g (0.011 mol) of **9** in 75 mL of methanol was stirred in an ice bath while gaseous hydrogen chloride was added; the temperature rose to 58 °C during the (2 h) addition. The volatiles were removed under aspirator pressure to give 2.8 g of a cream-colored solid. The latter was stirred for 30 min or so with water and then the water was removed in vacuo. The product was dissolved in a mixture of ethanol and isopropyl alcohol. Cooling to −20 °C and addition of ether gave 1.97 g (77%) of **16**: mp 165–166 °C dec; IR (KBr) 3330, 3125, 1695, and 1610 (amide), broad absorption at 1850–2350 (salt), 2220 (CN) cm^{-1}; ^1H NMR (D_2O) δ 3.95 (s, 2, NCH_2C=), 3.2 (m, 4, ring CH_2N), 2.2 (s, 3, CH_3), 1.6 (m, 6, ring CH_2). Anal. Calcd for $C_{11}H_{17}N_3O$·HCl: C, 54.21; H, 7.44; N, 17.24. Found: C, 54.41; H, 7.35; N, 16.91.

1-Methoxy-2-butene-2,3-dicarbonitrile (17). To a stirred refluxing solution of 0.1 g of 1,8-bis(dimethylamino)naphthalene in 50 mL of methanol and 20 mL of acetonitrile was added 2.0 g (0.019 mol)

of 1 in a mixture of 25 mL each of methanol and acetonitrile over a 50-min period. The dark-brown solution was stripped under aspirator pressure, and the residue was extracted twice each with hexane and with ether. Removal of the solvent from the combined extracts gave 0.9 g of a yellow oil, which, by VPC, showed two major and at least six minor components. The major (oily) products, amounting to 73 and 22%, respectively, of the product mixture, were separated by chromatography on silica gel (eluting with a mixture of hexane and ether) and shown to be *trans*- and *cis*-**17**, respectively. *cis*-**17**: IR (neat) 2220 (CN), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16 (s, 2, CH_2O), 3.34 (s, 3, CH_3O), and 2.14 (s, 3, CH_3C). *trans*-**17**: IR (KBr) (practically identical to that for *cis*-**17**); ^1H NMR ($CDCl_3$) δ 4.27 (s, 2, CH_2O), 3.42 (s, 3, CH_3O), and 2.30 (s, 3, CH_3C).

Addition of Thiolacetic Acid to 1. A solution of 0.99 g (0.0095 mol) of 1 in ca. 40 mL of THF was stirred in an ice bath while 1.59 g (0.021 mol) of thiolacetic acid was added rapidly. After a few minutes (VPC showed complete reaction of 1 in less than 5 min), distillation from a water bath at 30 °C through a short-path column under high vacuum removed the solvent and excess thiolacetic acid. The residue, 2.0 g of an orange, viscous oil, was purified by dry-column chromatography (on silica gel). From 0.76 g of the oil was obtained, as one fraction, 0.13 g of a crystalline solid mixed with an oil. Removal of the oil by washing with ether gave 0.016 g of 2,3-dicyano-1,4-butanedithiol diacetate (**18**): IR (KBr) 2270 (CN), 1695 (broad and strong, ester) cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_2O_2S_2$: C, 46.85; H, 4.72; N, 10.93. Found: C, 47.25; H, 4.93; N, 11.44. Another fraction from the separation was 0.22 g of a pale yellow oil (unstable on the VPC injection port): IR (neat) 3175 (HC=?), 2250 (CN), 1710 (ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.3 (s, 1.23, H_2C=), 3.8 (m, 1.46), 3.4 (s, 0.77), 3.3 (d, 0.69), and 2.4 (s, 3, CH_3C=O).

Disodium 2,3-Dicyano-1,4-butanedisulfonate (19). A solution of 8 g (0.077 mol) of sodium bisulfite in 50 mL of water was stirred at room temperature with a solution of 3.3 g (0.032 mol) of 1 in 200 mL of ether. The ether layer immediately became yellow but became colorless again in 90 min; VPC analysis showed that reaction of 1 was complete. The aqueous phase was separated, and the water was removed in vacuo with gentle heating. The residual solid, 12.2 g (quantitative yield), was the trihydrate of the salt **19**: mp 225 °C dec; IR (KBr) 2270 (CN); ^1H NMR (D_2O) δ 4.8 (s, 6, H_2O), 4.0 (m, 2, CH), and 3.6 (m, 4, CH_2). Anal. Calcd for $C_6H_6N_2Na_2O_8S_2 \cdot 3H_2O$: C, 19.68; H, 3.30; N, 7.65; S, 17.51. Found: C, 19.76; H, 2.98; N, 7.63; S, 18.1. Bis(*S*-benzylisothiuronium) salt of **19** (poor mp, dec): Anal. Calcd for $C_{22}H_{28}N_6O_6S_4$: C, 44.13; H, 4.38; N, 14.04; S, 21.42. Found: C, 44.10; H, 4.61; N, 13.62; S, 20.9.

1-(*p*-Toluenesulfonyl)-2-butene-2,3-dicarbonitrile (20). A solution of 2.0 g (0.019 mol) of 1 in 35 mL of glacial acetic was stirred at 60 °C while a solution of 7.1 g (0.04 mol) of sodium *p*-toluenesulfinate in 25 mL of acetic acid and 10 mL of water was added dropwise during 20–25 min. The reaction was exothermic (temperature rose to ca. 85 °C), and the solution was allowed to stand at room temperature overnight. Analysis (by TLC) showed no 1 was present, and two products were formed in a 2:1 ratio in a crude yield of 96%. These were separated by preparative TLC. *cis*-**20** (80% pure by NMR): mp 138–150 °C; IR (KBr) 2250 (CN) 1625 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (A_2B_2 pattern, 4, aromatic H), 4.10 (s, 2, CH_2), 2.48 (s, 3, aromatic CH_3), and 2.14 (s, 3, allylic CH_3). Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 59.32; H, 4.52; N, 10.42; S, 12.2. *trans*-**20** (90% pure by NMR): mp 135.5–139 °C; IR (KBr) 2245 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (A_2B_2 pattern, 4, aromatic H), 4.20 (s, 2, CH_2), 2.50 (s, 3, aromatic CH_3), and 2.32 (s, 3, allylic CH_3).

Reaction of 19 with Methanolic Hydrogen Chloride. A suspension of 4.0 g (0.011 mol) of **19** in 75 mL of methanol was stirred at 50 °C (cooling as required) while gaseous hydrogen chloride was introduced for 2 h. The volatiles were removed under aspirator pressure. Water (50 mL) was added to the residual paste, and the mixture was stirred for 45 min. The white opalescent suspension was treated with aqueous sodium hydroxide to pH 8. Dimethyl 2,3-dicarbamoyl-1,4-butanedisulfonate (**22**) was removed as an insoluble white solid, 0.28 g (8%): mp 185 °C with (acidic) gaseous dec; IR (KBr) 3450 and 3330 (NH_2), 1670 (C=O), 1350 and 1160 (sulfonate) cm^{-1}. Anal. Calcd for $C_8H_{16}N_2O_8S_2$: C, 28.91; H, 4.85; N, 8.43. Found: C, 28.10; H, 5.01; N, 8.46. After removal of **22**, the aqueous filtrate was diluted with ethanol and cooled to give 0.65 g (15%) of a hydrate of disodium 2,3-dicarbamoyl-1,4-butanedisulfonate (**21**): IR (KBr) 3450 and 3330 (NH_2), 1665 (carbonyl), 1330 and 1200 (latter very strong and broad, sulfonate) cm^{-1}. Anal. Calcd for $C_6H_{10}N_2Na_2O_8S_2 \cdot 2.5H_2O$: C, 18.32; H, 3.84; N, 7.12. Found: C, 18.78; H, 4.03; N, 7.19.

1,3-Butadiene-2,3-dicarboxamide (23). A solution of 5.0 g (0.048 mol) of 1 in methylene chloride was filtered to remove a trace of polymer. The solvent was evaporated, and the residual 1 was added to 20 mL of 96% sulfuric acid. Solution occurred rapidly with little, if any, exotherm. The water-white solution was allowed to stand overnight at room temperature, becoming slightly discolored. It was then poured over 100 g of crushed ice. The resulting solid was filtered and washed well with cold water then THF and ether to give 2.97–3.25 g (44–56%) of **23** (about 1.0 g of unreacted 1 was recovered from the wash solutions, resulting in 55–70% net yields). This product was sparingly soluble in boiling water and was recovered as small, off-white crystals: mp 300 °C dec (ammonia evolved); IR (KBr) 3330 and 3125 (NH_2), 1665 and 1610 ($CONH_2$), 950 (=CH_2) cm^{-1}; mass spectrum *m/e* (rel intensity) 140 (5.2), 123 (32), 80 (21), 52 (100). Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 50.94; H, 5.64; N, 19.61.

***N,N'*-Di-*tert*-butyl-1,3-butadiene-2,3-dicarboxamide (24).** A solution of 2.6 g (0.025 mol) of 1 and 10 mL of *tert*-butyl alcohol in 50 mL of 97% formic acid was stirred under reflux (55–60 °C) for 20 h. A small amount of insoluble polymer was removed, and the water-white solution was poured into 500 mL of ice–water. The mixture was extracted three times with ether. After drying (magnesium sulfate), removal of the ether gave a solid residue. This was triturated with hexane,[22] and the residual material was digested with ether, leaving 0.59 g of **24** as an insoluble material and another 0.36 g of **24** (15% total yield) was recovered from the ether: fine white plates, mp 174–176 °C (from THF and ether at −70 °C); IR (KBr) 3250 (NH), 3030 (H-C=), 1550, 1610, and 1640 (CONH), 925 (=CH_2, with overtone at 1850) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 and 5.55 (2 doublets, 4, =CH_2), 5.80 (s, 2, NH), 1.30 (s, 9, CH_3); ^{13}C NMR ($CDCl_3$) δ165.4 (C=O), 143.2 (—C=), 123.9 (CH_2=), 51.7 (CN), 28.6 (CH_3); mass spectrum *m/e* (rel intensity) 252 (2.2), 180 (13), 179 (10), 124 (100).

***N,N'*-Bis(2-methyl-2-butyl)-1,3-butadiene-2,3-dicarboxamide (25).** A solution of 2.0 g (0.019 mol) of 1 and 10 g of 2-methyl-2-butene in 50 mL of 97% formic acid was stirred under gentle reflux for 24 h. Treating the reaction solution as described for the preparation of **24** gave 3.0 g of a residual solid. This was recrystallized from a mixture of THF and hexane at −70 °C to give 0.50 g (a second crop of 0.25 g; total yield of 15%) of **25**: mp 142–143 °C (ether–THF at −70 °C); IR (KBr) 3225 (NH), 3125 (HC=), 1610 and 1560 (CONH), 925 (=CH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.09 and 5.51 (2 doublets, 4, =CH_2), 5.77 (s, 2, NH), 1.77 (q, 4, CH_2), 1.34 (s, 12, CH_3), and 0.83 (t, 6, CH_3). Anal. Calcd for $C_{16}H_{28}N_2O_2$: C, 68.52; H, 10.06; N, 9.99. Found: C, 68.06; H, 10.15; N, 10.10.

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Registry No.—**1**, 19652-57-4; **2**, 6613-46-3; **3**, 6613-47-4; **4**, 59967-74-7; **5**, 59967-75-8; **6**, 64754-45-6; **7**, 64754-44-5; **8**, 58390-02-6; **9**, 58390-03-7; **10**, 64754-46-7; **11**, 64754-47-8; **12**, 64754-48-9; **13**, 64754-49-0; **14**, 64754-50-3; **15b**, 64754-51-4; **16**, 64754-52-5; *cis*-**17**, 64754-53-6; *trans*-**17**, 64754-54-7; **18**, 64754-55-8; **19**, 64771-38-6; **19** bis(*S*-benzylisothiuronium) salt, 64754-57-0; *cis*-**20**, 64754-58-1; *trans*-**20**, 64754-40-1; **21**, 64754-41-2; **22**, 64754-42-3; **23**, 64754-43-4; **24**, 64754-33-2; **25**, 64761-50-8; 4-bromo-2-bromomethyl-3-cyanobutyramide, 64784-28-7; piperidine, 110-89-4; morpholine, 110-91-8; dimethylamine, 124-40-3; thiolacetic acid, 507-09-5; methanol, 67-56-1; sodium bisulfite, 7631-90-5; sodium p-toluenesulfinate, 824-79-3; *tert*-butyl alcohol, 75-65-0; 2-methyl-2-butene, 513-35-9; 2-cyano-3-(*tert*-butylcarbamoyl)-1,3-butadiene, 64754-34-3.

References and Notes

(1) W. L. Bailey, R. L. Hudson, and E. T. Yates, *J. Org. Chem.*, **28**, 828 (1963).
(2) (a) E. Müller, R. Mayer-Mader, and K. Dinges, 163rd National Meeting of the American Chemical Society, April 1972, Preprint of INDE-44; (b) C. S. Marvel and N. O. Buice, *J. Am. Chem. Soc.*, **71**, 37 (1949); (c) M. Tanaka, *Kogyo Kagaku Zasshi*, **60**, 1509 (1957); *Chem. Abstr.*, **53**, 18925 (1959); (d) M. Tanaka and M. Yublo, *ibid.*, **61**, 714 (1958); *Chem. Abstr.*, **55**, 10313 (1961).
(3) (a) D. Belluš, K. von Redow, H. Sauter, and C. D. Weis, *Helv. Chim. Acta*, **56**, 3004 (1973); (b) D. Belluš and C. D. Weis, *Tetrahedron Lett.*, 999 (1973).
(4) (a) R. L. Cobb and J. E. Mahan, *J. Org. Chem.*, **42**, 2829 (1977); (b) R. L. Cobb and J. E. Mahan, unpublished observations.
(5) Minor products (7 and 5% yields by VPC) containing nonconjugated nitrile groups and no unsaturation (by IR and NMR) were formed. For these mixed products: mp 44–45 °C; ^1H NMR ($CDCl_3$) δ 2.80 (m, 2) 1.53 (d, 6); ^{13}C NMR ($CDCl_3$) δ 29.8 (CH), 15.8 (CH_3). Although the expected by-products are the diastereomers of butane-2,3-dicarbonitrile [lit. mp 56–58 °C and 45–46 °C for *d,l* and meso isomers, respectively; see R. P. Linstead and M.

Whalley, *J. Chem. Soc.*, 3722 (1955)] the NMR spectra of such a mixture should be more complicated than that obtained.

(6) W. F. Beech and H. A. Piggott, *J. Chem. Soc.*, 423 (1955).

(7) Further corroboration of this assignment is the slight shift in the opposite direction observed for the nitrile carbons. Although not as well demonstrated, steric perturbations apparently shift sp carbon resonances in a direction opposite to that found for sp^3 carbons. See, e.g., G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 130.

(8) See ref 4a and references cited therein.

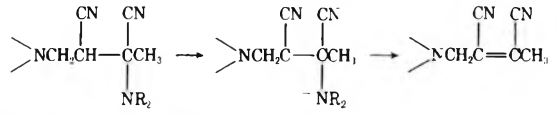
(9) It is appropriate to note that the diene **1** undergoes facile polymerization to give an intractable and often dark-colored product under such diverse conditions as solution in or contact with dimethylformamide, dimethyl sulfoxide, triphenylphosphine, some samples of ethanol, acetone, acetonitrile, amine vapors, aqueous alkali, and often with alkali-metal salts of weak acids.

(10) These conditions allow a "normal" addition of diphenylamine to acrylonitrile; see, e.g., R. C. Cookson and F. G. Mann, *J. Chem. Soc.*, 67 (1949), and J. T. Braunholtz and F. G. Mann, *ibid.*, 1817 (1953).

(11) By column chromatography, a small amount of an oily cyano (by IR) product was isolated which exhibited ^{1}H NMR resonances at δ 7.0–7.6 and 1.2–1.9 (a pair of doublets superimposed on a multiplet) in a proton ratio of 3–4:1. The resonances of the nonaromatic protons are too far upfield to correspond to any conceivable structure containing Ar_2NCH_2 and HCCN groups.

(12) While both *E* and *Z* isomers of **14** are possible, the single olefinic resonance suggests that only one is present. No attempt was made to determine this further.

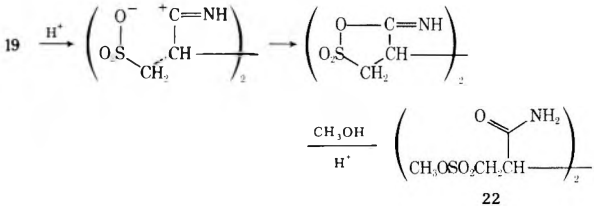
(13) Addition of the amine at the γ position (cf. eq 2), which may also occur, would not be observed, since proton abstraction and elimination would result in formation of the starting adduct



(14) Separation of these products by TLC was unsatisfactory. Analysis (by IR) of two isolated fractions showed strong cyanoenamine absorptions at ca. 2170 and 1640 cm^{-1}, but NMR studies of these same materials were equivocal. Crude product from a similar reaction of 10 and **11** with methylamine and with *tert*-butylamine also gave spectral evidence for the presence of a cyanoenamine.

(15) We are grateful to a referee for suggesting that amine participation would activate the γ nitrile to protonation and hydrolysis, yielding **16** rather than the alternative 1-(1-piperidino)-3-cyano-2-butene-2-carboxamide.

(16) Formation of a sulfonate ester by this means is unprecedented. If this structure is correct, a mechanism involving participation of the sulfonate and cyano groups may be visualized:



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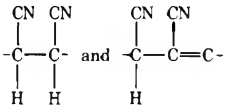
(17) Melting points (uncorrected) were recorded on a Mel-Temp apparatus; IR spectra were obtained on a Perkin-Elmer Model 137 Infracord; NMR spectra (vs. internal Me_4Si) were determined on Varian T60 and CFT20 instruments; mass spectra were recorded on a CEC 110B instrument (70 eV).

(18) There was insufficient material for a careful analysis. However, the data available give substantial confirmation of the structure.

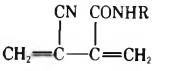
(19) The resonances for the methyl and allylic methylene hydrogens were complicated by long-range coupling effects.

(20) (a) Although not investigated, this oil may have been largely **12**. (b) The shoulder on this resonance may be due to the presence of **12** as an impurity.

(21) The broad resonance at δ 7.5 is due to active proton exchange, while the narrow singlet at δ 7.5 represents the aldehydic and enolic protons. The two "quartets" at δ 3.7 and 4.0 are due to the methine hydrogens of respectively, and the integral ratio (1:1.4) suggests that the latter (enol form) predominates in the equilibrium.



(22) Cooling the hexane extracts at −70 °C gave 0.44 g of a white crystalline solid which may have been the cyanoamide related to **24**



IR (KBr) 3225 (NH), 2275 (CN), 1640 and 1650 (CONH), 960, 925 (CH_2=) cm^{-1}.

Chemistry of 1,3-Butadiene-2,3-dicarbonitrile. 2. Reactions with Dienophiles

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Reaction of butadiene-2,3-dicarbonitrile (1) with diazomethane yielded the bipyrazoline **2**, which lost nitrogen thermally to give the bicyclopropane **3**. With ethyl diazoacetate, **1** gave the bipyrazoline **7**, but the major product was an intractable solid. **1** yielded the expected (4 + 2) cycloadducts with maleic anhydride, *N*-ethylmaleimide, methyl acrylate, acrylonitrile, 1-cyanovinyl acetate, ethyl vinyl ether, divinyl ether, 1-methoxycyclohexene, dimethylisobutenylamine, and 1-methoxycyclohexene. With furan, **1** gave both 1:1 benzofuran and 2:1 dibenzofuran types of adducts; with *N*-methylpyrrole, only the corresponding 2:1 type of adduct was isolated. With dimethyl acetylenedicarboxylate, **1** gave dimethyl 4,5-dicyanophthalate.

Because of its multifunctionality, the chemistry of 1,3-butadiene-2,3-dicarbonitrile (1) is rich and varied. It undergoes reactions characteristic of a conjugated diolefin,[1,2] an activated olefin,[3,4] and a nitrile.[3] As a strongly electron-deficient diene, **1** is an example of the less-studied class of dienes which exhibit an "inverse electron demand" in Diels–Alder reactions.[5] These are considered to undergo normal (2 + 4) cycloadditions only with electron-rich dienophiles, although other types of cycloadditions, e.g., (3 + 2), are not necessarily subject to these electronic restrictions. While some Diels–Alder reactions of **1** have been reported,[4] we wish to describe here the results of our study utilizing **1** as a diene in both (3 + 2) and (4 + 2) cycloaddition processes.

(3 + 2) Cycloadditions. The diene **1** underwent facile reaction with diazomethane to give 3,3′-bi(1-pyrazolinyl)-3,3′-dicarbonitrile (2) as a mixture of (probably) two (chiral) isomers. While there were subtle differences in the ^{1}H NMR spectra of these products (only one of which was isolated in

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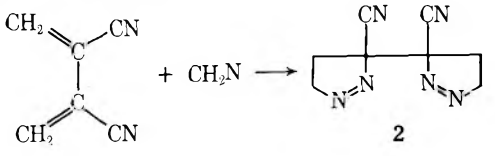
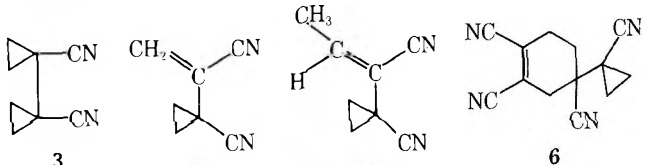
a pure form), no attempt was made to assign specific structures. This NMR evidence also ruled out the formation of the isomeric 4,4′-bipyrazoline.



1 2

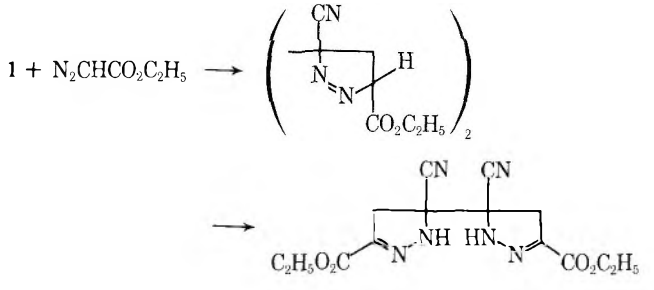
Upon heating to 100 °C, **2** underwent thermal extrusion of nitrogen to yield 1,1′-bicyclopropyl-1,1′-dicarbonitrile, **3**. Heating the crude diazomethane–diene **1** reaction product to 100 °C gave not only **3** but also 1-vinylcyclopropane-α,1-dicarbonitrile (**4**), 1-(1-propenyl)cyclopropane-α,1-dicarbonitrile (**5**), and 4-cyclopropylcyclohexene-α,1,2,4-tetracarbonitrile (**6**).[1,6] The methylated derivative **5**, the product of a



3 4 5 6

carbene insertion process, probably arose from **4** (or its pyrazoline precursor) and not by thermal rearrangement of **3** or by a secondary route during thermolysis of **2**, since decomposition of pure samples of **2** gave no spectral evidence for the presence of **5**.

Diene **1** underwent a similar reaction with ethyl diazoacetate to give a low yield of diethyl 5,5′-dicyano-5,5′-bi(2-pyrazolinyl-3-carboxylate) (**7**), the (conjugated) isomer of an

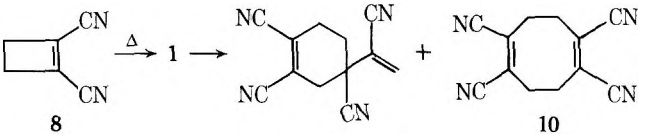


7

initially formed 1-pyrazoline.[7] The major product of this reaction was an almost intractable solid. Spectral data suggested the presence of NH, CN, C=N, and (ethyl) ester groups, but no reasonable single structure could be reconciled with all the data (see Experimental Section).

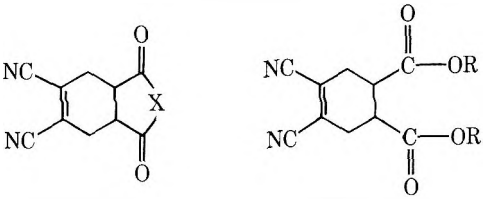
(4 + 2) Cycloadditions. An initial report of the failure of **1** to undergo reaction with maleic anhydride derivatives[9] was consistent with the classification of **1** as a diene with "inverse electron demand", as was a later account[4] of the types of dienophiles which do successfully add to **1** (simple olefins such as ethylene, cyclopentene, and norbornadiene; electron-rich dienophiles, such as indene, acenaphthalene, stilbene, vinylpyridine, and vinyl ethers; and *trans*-1,2-dichloroethylene). In the present work, we successfully prepared Diels–Alder adducts with these types of dienophiles and also with the electron-deficient acrylic and maleic acid derivatives. Indeed, only with strongly electronegative olefins, such as cyclobutene-1,2-dicarbonitrile (**8**), fumaronitrile, and tetracyanoethylene, and with simple olefins such as cyclohexene, vinylcyclohexene, and *cis,cis*-1,5-cyclooctadiene, were our efforts fruitless.

In some of the work with the less-reactive olefins, **8** was used as an in situ source of **1**.[10a] While little comparative study was made, with the few exceptions as noted, there was no difference in the reaction of the diene **1** itself and **8**. In the less-reactive systems, self-dimerization[1] of **1** to 4-vinylcyclohexene-α,1,2,4-tetracarbonitrile (**9**) and *cis,cis*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile (**10**) became a major competing process.



8 9 10

Heating a solid equimolar mixture of **1** with maleic anhydride gave a low yield of 4,5-dicyano-1,2,3,6-tetrahydrophthalic anhydride (**11**) in an exothermic process. Better yields were obtained using excess maleic anhydride, although isolation procedures resulted in hydrolysis of the initial anhydride **11** to the corresponding phthalic acid **12**. The best procedure that we found utilized the reaction of **8** with maleic anhydride in hot xylene, which gave **11** in a 50–60% yield; using no solvent gave inferior results. Interestingly, the reaction of **1** itself with maleic anhydride in hot benzene or toluene gave none of the desired Diels–Alder adduct.[10b] In a similar process, **1** with *N*-ethylmaleimide in hot THF gave a good yield of **13**, *N*-ethyl-4,5-dicyano-1,2,3,6-tetrahydrophthalimide; the product was contaminated with 15–20% of another material (not **9** or **10**) that could neither be readily removed nor (structurally) ascertained. The cyclobutene **8** with dimethyl maleate in hot xylene gave a mixture (ca. 1:1 by VPC) of (probably) dimethyl 4,5-dicyano-1,2,3,6-tetrahydrophthalate (**14**) and the dimer **9**; because separation could not be readily accomplished, confirmation of structure **14** was not attempted.

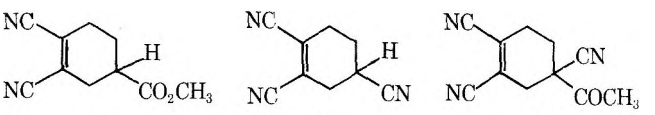


11, X = O
13, X = NC_2H_5

12, R = H
14, R = CH_3

In contrast to these successful cycloaddition processes, even under prolonged reaction conditions, fumaronitrile, cyclohexene-1,2-dicarbonitrile, and tetracyanoethylene were totally inert toward diene **1**.

Condensation of methyl acrylate, acrylonitrile, and 1-cyanovinyl acetate with either diene **1** or its precursor **8** gave the expected adducts methyl 3,4-dicyano-1,2,5,6-tetrahydrobenzoate (**15**), 3,4,5,6-tetrahydrobenzene-1,2,4-tricarbonitrile (**16**), and 1,3,4-tricyanocyclohex-3-en-1-yl acetate (**17**), respectively. The yields of **15** and **16** were nearly quantitative, while the major reaction of **1** in the presence of cyanovinyl acetate was formation of the dimers **9** and **10**, resulting in an estimated 25% yield of **17**. There was no evidence for the formation of cyclobutane derivatives from cyanovinyl acetate.[11]

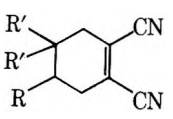


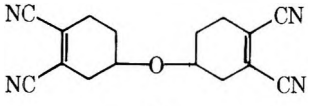
15 16 17

α-Chloroacrylonitrile proved to be essentially unreactive as a dienophile toward **1**, even under rigorous conditions (heating a large excess at 135 °C in cyclobutene **8**). After exhaustive work-up, the major products noted were the self-dimers **9** and **10** from diene **1**, and *cis*- and *trans*-1,2-dichlorocyclobutane-1,2-dicarbonitrile from chloroacrylonitrile;[12] there was evidence (spectral and VPC) that a small amount of the desired co-adduct may have been present in residual materials.

Styrene, with either **1** or **8**, gave a high yield of 4-phenyl-3,4,5,6-tetrahydrophthalonitrile, **18**. This existed in two crystalline modifications, a stable form, mp ca. 140 °C, and an unstable (to recrystallization) form, mp ca. 195 °C.

With vinyl ethers, cycloaddition occurred with **1** to give the expected adducts. Ethyl vinyl ether, divinyl ether, and 1-methoxycyclohexene gave 4-ethoxy-1-cyclohexene-1,2-dicarbonitrile (**19**), bis(3,4-dicyano-3-cyclohexen-1-yl) ether (**20**)





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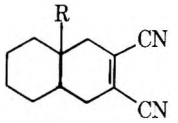
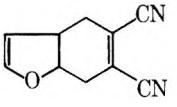
18, R = C_6H_5; R′ = H
19, R = C_2H_5O; R′ = H
25, R = $(CH_3)_2N$; R′ = CH_3



21, R = OCH_3
26, R = $N(CH_2)_2$

(as a mixture of two isomers), and 4a-methoxy-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2,3-dicarbonitrile (**21**), respectively. Interestingly, **21** was found only by utilizing **8** as an in situ source of **1** at a higher temperature than normally used (175 °C); reaction of this vinyl ether with **1** itself gave no cycloaddition, even at 135 °C.[10b] Methyl isopropenyl ether also failed to undergo reaction with **1**.

Furan, a vinyl ether as well as a diene, serves as a dienophile in its reactions with diene **1**.[4] The initial adduct, 7-oxabicyclo[4.3.0]nona-3,8-diene-3,4-dicarbonitrile (**22**), itself a vinyl ether, underwent further reaction with **1** to give 2-oxatricyclo[7.4.0.0^{3,8}]trideca-5,11-diene-5,6,11,12-tetracarbonitrile (**23**). The adduct **22** also underwent facile (2 + 2) cycloaddition with tetracyanoethylene (TCNE), giving 2-oxatricyclo[7.2.0.0^{3,8}]undec-5-ene-5,6,10,10,11,11-hexacarbonitrile (**24**). It was found also that diene **1** cycloadds to



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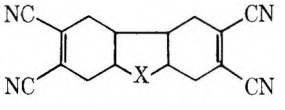
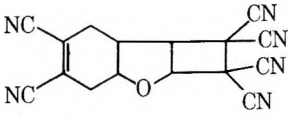


23, X = O
27, X = NCH_3



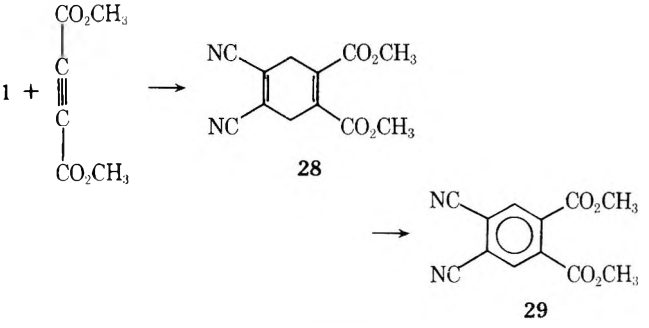
24

certain allylic ethers, e.g., those arising by reaction of furan as a diene with activated olefins.[13] On the other hand, 2,5-dimethoxy-2,5-dihydrofuran, another type of allylic ether, while apparently reacting with **1**, gave a complex mixture from which no discrete product could be isolated.

Enamines represent another class of electron-rich dienophiles that undergo cycloaddition with **1**. Dimethylisobutenylamine and 1-dimethylaminocyclohexene gave 4,4-dimethyl-5-dimethylamino-1-cyclohexene-1,2-dicarbonitrile (**25**) and 4a-dimethylamino-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2,3-dicarbonitrile (**26**), respectively. Formation of **25** was very rapid, being essentially complete upon mixing at room temperature (NMR monitoring); there was also no evidence for formation of a cyclobutane that would have arisen by a (2 + 2) cycloaddition.[14] This mode of addition has been noted in reactions of enamines with electron-deficient olefins such as acrylonitrile.[15] Thus, the diene **1** underwent reaction with this enamine strictly as a diene rather than as a substituted acrylonitrile. With either of these enamines, the reaction of **1** was characterized by the development of intensely (and variously) colored mixtures. Further, the yield of **26** was temperature dependent, as were the rate of the color change and the intensity and shade of the final reaction solution; the only by-product that could be isolated was a variously colored amorphous solid. Thus, at −20 °C the gray-green reaction solution deposited 46% of the amorphous product as a dark green-black solid, and yielded 13% of **26**. At room temperature, the colors were similar, but yields of the amorphous solid and **26** were 4 and 65%, respectively. At 50 °C, the reaction mixture was dark blue; only a trace of the amorphous solid could be isolated, but the yield of **26** was high (86%). The structure of the amorphous solid was not deduced. The intense colorations of the reaction mixture suggest the formation of a charge-transfer complex of the electron-rich enamine with the electron-deficient dinitrile **1**. In the absence of further information, it is futile at this time to speculate whether this complex is actually the intermediate to either the cycloadduct or the by-product.

Pyrrole, also an enamine, is a poor diene or dienophile vis-a-vis the analogous furan. In reaction with diene **1** (from **8** in situ), it gave only intractable material. With *N*-methylpyrrole, however, slow reaction occurred to give the nitrogen analogue of **23**, 2-aza-2-methyltricyclo[7.4.0.0^{3,8}]trideca-5,11-diene-5,6,11,12-tetracarbonitrile, **27**.

Dimethyl acetylenedicarboxylate underwent slow reaction with **1** to give dimethyl 4,5-dicyanophthalate (**29**), arising by aromatization of the initially formed cycloadduct **28**, as the



major product. A number of by-products were noted in the reaction mixture, but separation and purification problems precluded meaningful structural studies. Interestingly, diene **1** underwent cycloaddition with 1-penten-3-yne at the olefinic rather than the acetylenic bond; further details of this work will be reported separately.

Experimental Section[16]

3,3′-Bi(1-pyrazolinyl)-3,3′-dicarbonitrile (2). A filtered solution of 2.1 g (0.02 mol) of **1** in tetrahydrofuran (THF) was treated with ethereal diazomethane at room temperature until the yellow color persisted; some nitrogen was envolved during the reaction. The solution was concentrated in a stream of nitrogen to a volume of 10 mL; chilling of the solution at −70 °C gave 0.83 g (22%) of **2** as white crystals (from ether–pentane): mp 93 °C, with gentle effervescence; IR (KBr) 2250 (CN), 1565 (N=N) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 5.15 (t, 4, CH_2N=N), 2.40 (overlapping t, 4, CH_2); ^{13}C NMR (acetone-d_6) δ 119.4 (CN), 91.3 (quaternary C), 81.8 (CH_2N=N), 26.8 (CH_2).[17] After removal of this solid crop, ether was added to the mother liquor. Chilling at −70 °C gave another 0.29 g (8%) of the adduct **2**, mp 94 °C dec. The mother liquor was evaporated to dryness (keeping at room temperature), and the residue was taken up in ether. Addition of a little pentane and chilling at −70 °C gave white crystals, mp 67–68 °C. Recrystallization from ether gave a mixture of the adduct **2** and an isomer: mp 76–77 °C; IR (KBr) 2260 (CN), 1570 (N=N) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 5.06 and 5.15 (overlapping t, 4, CH_2 N=N), 2.2–2.8 (m, 4, CH_2); mass spectrum *m/e* (rel intensity) 132 ($M^+ - 2N_2$, 38), 131 (100), 117 (59), 105 (51), 104 (91), 66 (27).

A solution of 6.0 g (0.058 mol) of **1** in 50 mL of ether was treated in the same manner with a slight excess of ethereal diazomethane. After

2 weeks at room temperature, a small amount of insoluble polymer was removed and the solution was stripped in vacuo. Recrystallization of the residual oil from ether containing a little THF at −20 °C gave 1.88 g (17%) of white crystalline **2**, mp 98 °C dec. The filtrate was stripped in vacuo, and the residual oil was triturated three times with 150-mL portions of ether; concentration and chilling of the ether solution at −70 °C gave 0.14 g of a low-melting solid. The residue from the ether extraction was taken up in THF and added slowly to 100 mL of toluene at ca. 100 °C. Evolution of nitrogen was brisk. After an hour or so at 100 °C, the toluene was removed and the residual oil was digested twice with 150-mL portions of ether. Concentration of the ether solution gave 1.11 g (9%) of **6**[1] in two crops: mp 144–146 °C (from ether and THF). Removal of the ether from the filtrate gave 1–2 g of a residual oil, which was distilled under high vacuum through a short head. Analysis by VPC indicated the oily product was composed of (in the order of elution) 19, 58, and 20% of **4**, **5**, and **3**, respectively. These products were separated by preparative VPC. **3**: IR (neat) 2230 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (A_2B_2 pattern, CH_2);[13] mass spectrum *m/e* (rel intensity) 132 (21), 131 (100), 117 (55), 105 (48), 104 (99), 92 (26), 90 (28). **4** (a crystalline solid): IR (KBr) 2220 (CN), 1620 (C=C), 960 (=CH_2, with overtone at 1920) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.30 and 6.10 (s, 2, =CH_2), 1.4–1.75 (m, 4, CH_2); mass spectrum *m/e* (rel intensity) 118 (45), 117 (55), 91 (100), 78 (27). **5**: IR (neat) 2240 and 2220 (CN), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (q, 1, HC=), 2.05 (d, 3, CH_3), 1.50 (m, 4, CH_2); mass spectrum *m/e* (rel intensity) 132 (41), 131 (64), 117 (35), 105 (26), 104 (51), 92 (11), 90 (15).

A small sample of **2** (mp 93 °C dec) was added to toluene at 100 °C. Evolution of nitrogen was momentarily brisk. Removal of the toluene gave a pleasant-smelling oil; spectral details (IR and ^1H NMR) were practically identical with those of **3**.

Diethyl 5,5′-Dicyano-5,5′-bi(2-pyrazolinyl-3-carboxylate) (7). A solution of 5.2 g (0.05 mol) of **1** in 150 mL of THF was mixed with 11.4 g (0.10 mol) of ethyl diazoacetate in 50 mL of THF, giving an immediate white solid. After several days at room temperature, the insoluble solid (3.72 g) was removed and washed several times with acetone; this product could not be purified: IR (KBr) 3330 (NH), 2250 (CN), 1725 (C=O), 1615 (C=N, ?) cm^{-1}; ^1H NMR (acetone-d_6) δ 6.6 (broad s, 3, NH?), 4.2 (q, 2, ethyl CH_2), 2.4–3.4 (m, 24), 1.3 (t, 3, CH_3). Anal. Found: C, 65.38; H, 3.98; N, 25.77.[19] The THF mother liquor was concentrated to a volume of about 50 mL and chilled at −70 °C, giving another 1.27 g of gray product that was similar (spectrally) to the initial insoluble product. The THF mother liquor was stripped and the residue was taken up in ether, giving 1.82 g of an insoluble solid (evaporation of the ether gave ca. 4 g of unreacted ethyl diazoacetate). The solid was taken up in THF, removing 0.30 g of insoluble material. From the THF solution was isolated ca. 0.3 g of **7**: mp 223–225 °C (from a mixture of THF and ether); IR (KBr) 3335 (NH), 1710 (C=O), 1590 (C=N) cm^{-1}; ^1H NMR (perfluoroacetone deuterate) δ 4.95 (broad s, NH, 2), 4.43 (q, 4, ethyl CH_2), 3.55 (d, 4, ring CH_2), 1.39 (t, 6, CH_3); mass spectrum *m/e* (rel intensity) 278 (M^+ − 2HCN, 13), 277 (13), 232 (27), 231 (70), 203 (29).

Reaction of 1 with Maleic Anhydride. An intimate mixture of 0.60 g (0.006 mol) of polymer-free **1** and 0.58 (0.006 mol) g of maleic anhydride, under nitrogen, was heated gently in an open flame. When an exothermic reaction ensued, the flame was removed. The dark oily product was taken up in THF, removing 0.09 g of insoluble material. Cooling the THF gave 0.10 g (8%) of **4,5-dicyano-1,2,3,6-tetrahydrophthalic anhydride (11)** as off-white crystals: mp 181–184 °C dec (gaseous) (from a mixture of THF and ether); IR (KBr) 2210 (CN), 1850 and 1755 (anhydride C=O), 1600 (C=C) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.95 (m, 2, CH), 2.9–3.2 (m, 4, CH_2).

In another similar experiment, using 0.58 g (0.0056 mol) of **1** and 1.97 g (0.02 mol) of maleic anhydride, slow heating under nitrogen in an oil bath gave a moderately exothermic reaction at 80 °C as the melt became turbid; the temperature rose to about 120 °C (bath at 98 °C) over a 7-min interval and then began to drop. After another 15 min, the reaction mixture was added to 50 mL of water. The mixture was stirred vigorously at room temperature for an hour or so. Filtering gave 0.87 g (53%) of solid, mp 193 °C dec (gaseous). Recrystallization from acetone containing a little hexane gave 0.26 g of white crystalline **4,5-dicyano-1,2,3,6-tetrahydrophthalic acid (12)**: mp 205–207 °C dec (gaseous); IR (KBr) 3030–2630 (broad), 2250 (CN), 1725 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR (acetone-d_6) δ ca. 3.3 (m, 2, CH), ca. 3.0 (m, 4, CH_2). Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.6; H, 4.1; N, 12.4.

A mixture of 5.2 g (0.05 mol) of **8** and 4.9 g (0.05 mol) of maleic anhydride in 30 mL of xylene was heated under reflux for 3–4 h. As a crystalline solid gradually precipitated the mixture became quite dark. After cooling, the crude product (6.1 g, 60%) was recovered. This was recrystallized from a mixture of THF and ether to give 3.5 g of **11**, mp 200–202 °C.

***N*-Ethyl-4,5-dicyano-1,2,3,6-tetrahydrophthalimide (13).** A solution of 0.45 g (0.004 mol) of **1** and 0.50 g (0.004 mol) of *N*-ethylmaleimide in 20 mL of THF was heated under reflux overnight; VPC showed almost complete reaction. The solvent was removed and the residue was recrystallized from a mixture of THF and ether to give 0.48 g (50%) of **13** as fibrous, pearlescent crystals (VPC indicated about 80% purity): mp 95–96 °C; IR (KBr) 2220 (CN), 1785 and 1695 (imide C=O), 1615 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.50 (q superimposed on m, 5, CHCO and CH_2N), 2.95 (m, 4, ring CH_2), 1.80 (m, 1, ?), 1.08 (t, 3, CH_3); mass spectrum *m/e* (rel intensity) 229 (63), 214 (100), 202 (14), 200 (26), 187 (14), 185 (55), 130 (85), 103 (44). Anal.[20] Found: C, 64.8; H, 5.5; N, 16.3.

Methyl 3,4-Dicyano-1,2,5,6-tetrahydrobenzoate (15). A solution of 5.0 g (0.048 mol) of **1** and 0.25 g of hydroquinone in 25 mL of methyl acrylate was heated with (magnetic) stirring in a sealed glass bottle at ca. 100 °C for 4 days. After cooling and removing volatile material in vacuo, the residual solid (9.8 g) was recrystallized several times from mixtures of ether with THF or toluene to give **15** as small white crystals: mp 55–57 °C; IR (KBr) 2220 (CN), 1725 (C=O), 1615 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3, CH_3), 2.4–2.8 (m, 5, allylic CH_2, CH), 2.1 (m, 2, CH_2); mass spectrum *m/e* (rel intensity) 190 (16), 163 (15), 159 (13), 131 (70), 104 (100). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.22; H, 5.26; N, 14.77.

A mixture of 20 g (0.19 mol) of **8** and 0.25 g of hydroquinone in 100 mL of methyl acrylate was agitated in an autoclave at 130 °C for 24 h. The resulting solution was stripped in vacuo; the residue was recrystallized at −70 °C from 150 mL of ether containing a little hexane to give 32.3 g (91%) of **15**: mp 55–57 °C (another recrystallization from carbon tetrachloride gave off-white crystals, mp 57–58 °C).

3,4,5,6-Tetrahydrobenzene-1,2,4-tricarbonitrile (16). A solution of 5.0 g (0.048 mol) of **1** and 0.25 g of hydroquinone was treated with 50 mL of acrylonitrile in the manner described for the preparation of **15**. After removal of the excess acrylonitrile, the residual material was triturated eight times with 250-mL portions of ether. Concentration of the ether gave several crops of **16** as crystalline solid.

A solution of 20 g (0.19 mol) of **8** and 0.25 g of hydroquinone in 100 mL of acrylonitrile was heated as described for the preparation of **15**. After removal of excess acrylonitrile, the residual oil (29 g) was recrystallized at −70 °C from a mixture of ether and THF to give 24.4 g (82%) of **16** as cream-colored crystals: mp 62–64 °C (from toluene and ether); IR (KBr) 2250 and 2220 (CN), 1615 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7–3.2 (m, 1, HCCN), 2.4–2.8 (m, 4, allylic CH_2), 1.9–2.2 (m, 2, CH_2); mass spectrum *m/e* (rel intensity) 157 (43), 156 (31), 131 (26), 130 (89), 129 (35), 104 (100). Anal. Calcd for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 69.06; H, 4.54; N, 27.00.

1,3,4-Tricyanocyclohex-3-en-1-yl Acetate (17). A solution of 5.2 g (0.05 mol) of **1**, 6.0 g (0.054 mol) of 1-cyanovinyl acetate, and 0.25 g of hydroquinone in 100 mL of toluene was stirred under reflux for 40 h. Filtering the hot mixture gave 0.92 g (18%) of the dimer **10**,[1] mp 255–260 °C. Cooling the filtrate to −70 °C gave another 0.11 g (2%) of **10**. The mother liquor was stripped, and the residual, pale-yellow oil (9 g) was shaken with ether, causing precipitation of 2.89 g (56%) of the dimer **9**,[1] mp 123–125 °C. Concentration of the ether solution to a volume of 10 mL and chilling at −70 °C gave 0.10 g (4%) of unreacted **1**, mp 119–121 °C (by comparison spectrally with authentic **1**). The ether was removed from the filtrate, and the residue was heated at 100 °C under high vacuum. The residual oil (1.6 g) was recrystallized twice from ether to give a solid, mp 100–101 °C, that proved (by mass and NMR spectral data) to be a mixture of **9** and **17**.

A solution of 25 g (0.24 mol) of **8**, 25 g (0.23 mol) of 1-cyanovinyl acetate, and 0.5 g of hydroquinone in 100 mL of xylene was heated under reflux for 42 h. A dark-colored, intractable solid, 2.38 g, was removed, and the xylene solution was cooled in an ice bath to give 2.32 g (9%) of **10**, mp ca. 230 °C. Xylene was removed from the filtrate, and the residue was triturated four times with 200-mL portions of ether. The ether solution, upon concentration to a volume of 250 mL and cooling at 5 °C, gave 7.37 g of a mixture (by NMR) of **9** and **17**. Recrystallization three times from benzene gave **17** (another 1.5 g was recovered from the ether-insoluble material by recrystallization from THF): mp 123–125 °C; IR (KBr) 2250 (CN), 1770 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.33 (m, 2, allylic CH_2 β to nitrile), 2.3–2.9 (m, 4, other CH_2's), 2.16 (s, 3, CH_3); mass spectrum *m/e* (rel intensity) 157 (M^+ − $C_2H_2O_2$, 12), 153 (100), 128 (58), 104 (46), 60 (54).

4-Phenyl-3,4,5,6-tetrahydrophthalonitrile (18). A solution of 5.2 g (0.05 mol) of **1**, 10.4 g (0.10 mol) of styrene, 0.5 g of hydroquinone, and 25 mL of toluene was heated under reflux for 48 h. After removal

of 0.5 g of insoluble polymer, the toluene was removed from the solution, leaving 10 g of a residual solid. This was recrystallized from 200 mL of boiling methanol (removing 0.04 g of insoluble polystyrene) to give a total of 8.61 g (82%) of **18**, mp 193–195 °C; recrystallization twice from methanol (Norit) gave white crystalline **18**: mp 136–138 °C (see Discussion); IR (KBr) 2220 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1–7.4 (m, 5, aromatic CH), 2.4–2.9 (m, 5, CH and allylic CH_2), 1.8–2.1 (m, 2, CH_2); mass spectrum *m/e* (rel intensity) 208 (3.6), 104 (100). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.46. Found: C, 80.44; H, 5.69; N, 13.09.

A solution of 10.4 g (0.10 mol) of **8**, 40 g of styrene, 0.5 g of hydroquinone, and 35 mL of xylene was heated under reflux for 48 h. After cooling, 100 mL of ether was added. Chilling (−20 °C) gave a total of 15.6 g (75%) of **18**, mp 186–187 °C, which when recrystallized from methanol gave crystalline **18**, mp 136–137 °C (see Discussion).

4-Ethoxy-1-cyclohexene-1,2-dicarbonitrile (19). A solution of 0.76 g (0.007 mol) of **1**, 0.04 g of hydroquinone, 7.3 g of ethyl vinyl ether (freshly distilled), and 15 mL of THF was heated in a sealed tube at 80 °C for a few hours. After removal of a small amount of insoluble polymer, the solution was concentrated in a stream of nitrogen. Addition of hexane and cooling at −20 °C gave 1.20 g (93%) of **19**: mp 53–54 °C (from a mixture of ether and hexane); IR (KBr) 2175 (CN), 1615 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (m, 1, HCO), 3.50 (q, 2, CH_2O), 2.45 (m, 4, allylic CH_2), 1.87 (m, 2, CH_2), 1.17 (t, 3, CH_3); mass spectrum *m/e* (rel intensity) 176 (17), 131 (14), 105 (33), 104 (15), 72 (100). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.87; N, 15.90. Found: C, 68.1; H, 6.4; N, 16.1.

Bis(3,4-dicyano-3-cyclohexen-1-yl) Ether (20). A solution of 5.2 g (0.05 mol) of **1**, 2.0 g (0.028 mol) of divinyl ether, 0.25 g of hydroquinone, and 100 mL of benzene was heated at 100 °C with agitation in an autoclave for 44 h. After removal of insoluble polymer (0.10 g) the volatiles were removed in vacuo. The residual solid (7.5 g) was taken up in toluene containing a little ether. Cooling at −20 °C gave 3.08 g (22%) of **20**, mp 175–178 °C; recrystallization once from toluene containing a little acetone and once from THF (difficulty soluble) gave **20**: mp 187–190 °C; IR (KBr) 2220 (CN), 1615 (C=C) cm^{-1}; ^1H NMR (acetone-d_6) δ 4.15 (t, 2, HCO), 2.3–2.8 (m, 8, allylic CH_2), 1.8–2.1 (m, 4, CH_2); ^{13}C NMR (DMSO-d_6) δ 125.9 and 123.7 (C=C), 115.9 (CN), 66.5 (C–O), 33.2, 24.7, and 24.5 (CH_2, CH); mass spectrum (no volatility). Anal. Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.91; H, 4.80; N, 21.34. After removal of this product (3.08 g, above), a total of ca. 1.0 g of crystalline product was obtained from the toluene mother liquor in several crops. Multiple recrystallization from THF and mixtures of THF and ether gave another, much-more soluble isomer of **20**: mp 159–161 °C; IR, virtually identical to the other isomer; ^1H NMR (acetone-d_6) δ 4.15 (quintet, 2, HCO), 2.3–2.8 (m, 8, allylic CH_2), 1.7–2.0 (m, 4, CH_2).

4a-Methoxy-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2,3-dicarbonitrile (21). A solution of 5.2 g (0.05 mol) of **8** and 5.6 g (0.05 mol) of 1-methoxycyclohexene, in a pressure bottle, was heated at 170–175 °C for 12 h. After cooling, the reaction mixture was taken up in THF. After removal of a small amount of insoluble polymer, the solution was evaporated and the residue was taken up in 15 mL of ether. Cooling the solution at −70 °C gave 4.2 g (39%) of **21**, recrystallized twice from ether (Norit): mp 106–107 °C; IR (KBr) 2200 (CN), 1615 (C=C) 1075 (ether) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24 (s, 3, CH_3), 1.0–2.6 (m, 13, CH_2, CH); mass spectrum *m/e* 216 (M^+), 184, 173, 142, 112 (base peak). 104, 97. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.15; H, 7.45; N, 13.01. Found: C, 72.30; H, 7.92; N, 12.79.

Reaction of Diene 1 with Furan. A solution of 10.0 g (0.096 mol) of **1** and 0.5 g of hydroquinone in 150 mL of furan was agitated in an autoclave at 95 °C for 48 h. The resulting clear yellow solution, after removal of a little insoluble polymer, was stripped in vacuo. The residual solid (16.5 g), from ether, gave 14.8 g (90%) of **7-oxabicyclo[4.3.0]nona-3,8-diene-3,4-dicarbonitrile (22)**: mp 76–77 °C (from ether, Norit) (lit.[4] mp 74.5–75 °C); ^{13}C NMR (DMSO-d_6) δ 147 (=CH-O), 128.1 and 125.4 (=CCN), 115.9 (CN), 103.4 (—CH=), 77.9 (CHO), 39.7 (CHC), 32.1 and 31.1 (CH_2). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.37. Found: C, 69.31; H, 4.75; N, 16.19.

A solution of 5.2 g (0.05 mol) of **1**, 8.6 g (0.05 mol) of **22**, and 0.25 g of hydroquinone in 30 mL of xylene was stirred in a pressure bottle at 135 °C for 2 days. After removal of insoluble polymer (0.56 g, 11%), the volatiles were removed in vacuo. The residual solid (14.7 g) was taken up in THF, removing 0.20 g (4%) of insoluble **10**, mp 235–238 °C dec. The THF solution (ca. 75 mL) was treated with ether to the cloud point. Chilling at −70 °C gave a total of 5.13 g (37%) of **2-oxatricyclo[7.4.0.0^{3,8}]trideca-5,11-diene-5,6,11,12-tetracarbonitrile (23)** in 2 crops, mp ca. 175 °C. Multiple recrystallization from mixtures of THF with ether or acetone and finally from toluene (difficulty soluble) gave **23** as off-white leaves: mp 190–192 °C; IR (KBr) 2220 (CN), 1615 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.4 (m, 2, HCO), 2.6 (m, 8, allylic CH_2), 2.3 (m, 2, CH); ^{13}C NMR (DMSO-d_6) δ 124.5 and 126.2 (C=C), 115.9 (CN), 72.0 (CHO), 29.0 and 30.9 (CH_2) (CH resonance obscured by the solvent); ^{13}C NMR (hexafluoroacetone deuterate) δ 75.0 (CHO), 43.5 (CH), 31.1 and 32.3 (CH_2) (other resonances weak or obscured by the solvent).

Solutions of 0.86 g (0.005 mol) of **22** and 0.64 g (0.005 mol) of TCNE, each in 20 mL of THF, were mixed; the yellow TCNE color disappeared rapidly, as the resulting solution became a dull orange-brown. The solution was allowed to stand at room temperature for 2 weeks, as the color again became yellow. Upon partial evaporation of the solvent, white crystals appeared. Two crops (0.37 and 0.36 g, respectively, 50% yield) of adduct were collected and recrystallized from THF to give white, crystalline **2-oxatricyclo[7.2.0.0.^{3,8}]undeca-5-ene-5,6,10,10,11,11-hexacarbonitrile (24)**: mp 213–215 °C dec; IR (KBr) 2260 and 2235 (CN), 1630 (C=C), 1080 (ether) cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.35 (d, 1, $J \sim 6$ Hz, HCO adjacent to C_4 ring), 4.8–5.0 (m, 1, HCO adjacent to C_6 ring), 4.10 (d, 1, $J \sim 6$ Hz, HC adjacent to C_4 ring), ca. 3.5 (m, 1, HC adjacent to C_6 ring), ca. 3.0 and 2.5 (2m, 4, CH_2); mass spectrum (dec, giving a spectrum indicative of a mixture of furan, TCNE, and **1**).

4,4-Dimethyl-5-dimethylamino-1-cyclohexene-1,2-dicarbonitrile (25). A solution of 1.00 g (0.0096 mol) of **1** in 30 mL of THF, filtered to remove a trace of polymer, was mixed with 1.06 g (0.011 mol) of redistilled dimethylisobutenylamine. The resulting light yellow solution, stirred in a water bath under nitrogen at 50 °C, rapidly changed color to successively darker shades of green. After 90 min, the solution was concentrated. Addition of hexane and cooling at −20 °C gave 1.41 g (72%) of **25** in two crystalline crops; the product was purified by several recrystallizations from hexane (Norit): mp 101.5–102 °C; IR (KBr) 2250 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3–2.6 (m, 5, CH, CH_2), 2.30 (s, 6, CH_3N), 1.03 (s, 6, CH_3C); ^{13}C NMR ($CDCl_3$) δ 125.2 and 125.0 (C=C), ca. 112 (CN), 64.1 (CHN), 43.5 and 43.0 (CH_3N), 34.6 (quaternary C), 23.0 and 27.7 (CH_3C), 24.9 (CH_2); mass spectrum *m/e* (rel intensity) 203 (23), 188 (27), 160 (100). Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.94; H, 8.37; N, 20.69. Found: C, 71.0; H, 8.4; N, 20.6.

4a-Dimethylamino-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2,3-dicarbonitrile (26). A filtered solution of 0.57 g (0.0055 mol) of **1** in 50 mL of THF, in a bath at −50 °C, was stirred while a solution of 1.51 g (0.012 mol) of 1-dimethylaminocyclohexene in 10 mL of THF was added over a 5-min period. The intensely yellow solution, upon being allowed to warm slowly, became dark yellow at −30 °C, orange at −20 °C, amber at −10 °C, and then deep red. After 3 days at −20 °C, the dark gray-green solution was evaporated, and the residue was gently boiled in ether. An amorphous solid (0.84 g), which could not be purified, was removed; IR (KBr) 2170 and 2270 (broad, CN) cm^{-1}. The filtrate was mixed with hexane and chilled at −20 °C to give 0.24 g (13%) of a solid. Recrystallization from ether (Norit) gave white, crystalline **26**: mp 106.5–107.8 °C (the melt liberated dimethylamine above ca. 115 °C); IR (KBr) 2220 (CN), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2–2.6 (m, 4, allylic CH_2), 2.20 (s, 6, CH_3N), 1.2–2.0 (m, 9, CH_2, CH); ^{13}C NMR ($CDCl_3$) δ 125.2 and 123.0 (C=C), 116.0 (CN), 56.0 (CN), 34.6 (CH_3N), 34.3 and 32.5 (allylic CH_2), 29.9, 24.8, 24.4, and 22.3 (CH_2), 29.0 (CH); mass spectrum *m/e* 299 (M^+).

2-Aza-2-methyltricyclo[7.4.0.0^{3,8}]trideca-5,11-diene-5,6,11,12-tetracarbonitrile (27). A solution of 10.4 g (0.10 mol) of **8** and 7.2 g (0.089 mol) of *N*-methylpyrrole in 50 mL of benzene was stirred under reflux for 19 days. After removal of a small amount of insoluble material from the hot mixture, the solution was stripped finally under high vacuum to remove unreacted **8**. The residual oil was taken up in ether to give 1.70 g (total yield from several crops, 2.25 g) of **27** as off-white crystals: mp 194–195 °C dec (from acetonitrile); IR (KBr) 2220 (CN), 1630 and 1600 (C=C); ^1H NMR (acetonitrile-d_3) δ 3.0–3.2 (m, 2, HCN), 2.50 (m, 8, allylic CH_2), 2.33 (s, 3, CH_3), ca. 2.1 (m, 2, HCC); mass spectrum *m/e* (rel intensity) 289 (0.4), 27 (100).

Dimethyl 4,5-Dicyanophthalate (29). A filtered solution of 1.35 g (0.013 mol) of **1**, 5 mL of dimethyl acetylenedicarboxylate, and 0.05 g of hydroquinone in 50 mL of benzene was stirred under reflux for 3 weeks. Insoluble polymer (0.23 g, 17%) and benzene were removed from the mixture, leaving 7.3 g of an oil. This was taken up in ether and several crops of crystalline solid were obtained. Recrystallization from acetone at −70 °C gave white crystals of unknown structure (homogeneous by TLC): mp 203–204 °C; IR (KBr) 2220 (CN, w), 1760 and 1740 (CO, w and s), 1640 (C=C) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.7–3.9 (two pairs of doublets, $J \sim 5$ Hz, 5) 3.65 (s, 1), 3.47 (s, 1), 3.2–3.5 (m, 1), 2.78 (s, 1, reinforcing water impurity resonance, and thus may be exchangeable hydrogen impurity); mass spectrum *m/e* (rel intensity) 272 (0.9), 241 (1.8), 213 (11), 142 (6), 127 (5), 111 (15), 59 (83),

31 (100). After removal of this product, the ether mother liquor was chilled at −70 °C, giving 1.2 g of a yellow solid. This was dissolved in carbon tetrachloride, to remove a small amount of the insoluble dimer **9**. The solvent was removed, and the solid was purified further by HPLC (eluting with a mixture of 20% cyclohexane in chloroform), giving white, crystalline **29**: mp 135–137 °C (from ether and a little methylene chloride at −70 °C); IR (KBr) 2250 (CN), 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (s, 2, aromatic H), 4.00 (s, 6, CH_3); mass spectrum *m/e* (rel intensity) 244 (3.5), 213 (100).

Registry No.—**1**, 19652-57-4; **2** isomer 1, 64784-29-8; **2** isomer 2, 64784-30-1; **3**, 64760-88-9; **4**, 64760-90-3; **5**, 64760-91-4; **6**, 64760-89-0; **7**, 64760-92-5; **8**, 3716-97-0; **9**, 41793-19-5; **10**, 53399-95-4; **11**, 64760-93-6; **12**, 64760-95-8; **13**, 64760-94-7; **15**, 64760-97-0; **16**, 64760-98-1; **17**, 64760-99-2; **18**, 64761-00-8; **19**, 64760-80-1; **20** isomer 1, 64760-81-2; **20** isomer 2, 64760-96-9; **21**, 64760-82-3; **22**, 64760-83-4; **23**, 64760-84-5; **24**, 64760-86-7; **25**, 64760-85-6; **26**, 64760-87-8; **27**, 64760-79-8; **19**, 64754-35-4; diazomethane, 334-88-3; ethyl diazoacetate, 623-73-4; maleic anhydride, 108-31-6; *N*-ethylmaleimide, 128-53-0; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; 1-cyanovinyl acetate, 3061-65-2; styrene, 100-42-5; ethyl vinyl ether, 109-92-2; divinyl ether, 109-93-3; 1-methoxycyclohexene, 931-57-7; furan, 110-00-9; TCNE, 670-54-2; dimethylisobutenylamine, 6906-32-7; 1-dimethylaminocyclohexene, 13815-46-8; *N*-methylpyrrole, 96-54-8; dimethyl acetylenedicarboxylate, 762-42-5.

References and Notes

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(2) C. A. Uraneck, J. E. Burleigh, and R. L. Cobb, U.S. Patent 3 998 998 (1976).
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(4) D. Belluš, K. von Bredow, H. Sauter, and C. D. Weis, *Helv. Chim. Acta*, **56**, 3004 (1973).
(5) (a) D. Wollweber, "Diels-Alder Reaktionen", Georg Thieme Verlag, Stuttgart, 1972, p 66; (b) P. Beltrame in "Comprehensive Chemical Kinetics", Vol. 9, C. H. Bumford and C. F. H. Tipper, Ed., Elsevier Scientific Publishing Co., New York, N.Y., 1973, Chapter 2; (c) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, 16 (1967).
(6) The origin of **6** is obscure. It could have arisen from reaction of the dimer of **1** with diazomethane,[1] but this dimer was not normally present in the samples of **1** utilized in this study. Alternatively, reaction of **1** with **4** or its pyrazoline precursor is also a plausible route to **6**. No further study of these possibilities was made.
(7) Isomerization of initially-formed 1-pyrazolines was noted also with similar products from cyclobutene-1,2-dicarbonitrile[8] and *cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile.[1]
(8) R. L. Cobb and J. E. Mahan, *J. Org. Chem.*, **42**, 2597 (1977).
(9) D. Belluš and C. D. Weis, *Tetrahedron Lett.*, 999 (1973).
(10) (a) Diene **1**, the valence tautomer of **8**, is prepared conveniently by thermolysis of **8**[4] (see ref 1 for further comments on the conversion of **8** to **1** in hot solvents). (b) A study that would clarify the observed differences in the reactivity of **1** and **8** was not made. However, as a referee also noted, the rate of diene formation from **8** in hot xylene may be slow enough so that the amount of **1** produced at any one time is small relative to the concentration of the dienophile. Cycloaddition rather than polymerization is thus favored. No attempt to effect reactions of **1** itself with dienophiles above ca. 140 °C was made, since self-dimerization to **9** and **10** is a major process under these conditions. Optimum reaction conditions were not determined, and, except for the example noted (preparation of **21**), the reactions of **8** were also carried out at or below ca. 140 °C.
(11) Cyanovinyl acetate has been used as a probe in determining the dual reactivity occasionally observed in diene cycloadditions, i.e., (2 + 2) processes to cyclobutanes or (2 + 4) processes to cyclohexenes; see, e.g., J. C. Little, *J. Am. Chem. Soc.*, **87**, 4020 (1965), and P. D. Bartlett and K. E. Schueller, *ibid.*, **90**, 6077 (1968).
(12) The thermal dimerization of α-chloroacrylonitrile to 1,2-dichlorocyclobutane-1,2-dicarbonitrile has apparently not been previously observed.
(13) For example, the furan adduct of *cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile underwent reaction with TCNE.[1]
(14) A (2 + 2) cycloaddition from equimolar amounts of **1** and the enamine would give a product with NMR resonances at δ ca. 6–7. The resonance at δ ca. 6.4 for **1** completely disappeared, and this region became and remained essentially clear of even trace (at 70× amplification) resonances.
(15) (a) I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 2165 (1964); (b) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).
(16) Melting points, uncorrected, were obtained in a Mel-Temp apparatus; IR spectra were recorded on a Perkin-Elmer Model 137 Infracord; NMR spectra (vs. internal Me_4Si) were obtained on Varian T60, XL100, and CFT20 instruments; mass spectra were determined on a CEC 110B spectrometer (70 eV).
(17) Meaningful elemental analyses could not be obtained because of the slight instability of the product. However, spectral data adequately confirmed the structure.
(18) The complexity of the NMR spectrum suggests that this might be the meso product. Intuitively, a less complicated spectrum would be expected for the *d,l* isomer pair.
(19) Calcd. for $C_{18}H_{13}N_6O$: C, 65.64; H, 3.98; N, 25.52.
(20) Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. The impurity in this product was not either of the dimers **9** or **10** (by IR and VPC) and remains unknown.

Quinazolines and 1,4-Benzodiazepines. 84.[1] Synthesis and Reactions of Imidazo[1,5-*a*][1,4]benzodiazepines

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Condensation of 1,4-benzodiazepines having a *N*-nitrosomethylamino group in the 2 position with a primary nitroalkane led to the nitroalkylidene derivatives **3** and **4**. These nitro compounds were converted to imidazo[1,5-*a*][1,4]benzodiazepines by a sequence of steps involving catalytic reduction, condensation with triethyl orthoacetate, and oxidation with activated manganese dioxide. A variety of chemical transformations of the imidazobenzodiazepine **9** and the nitromethylene derivative **3** are described.

The synthesis of the pharmacologically active triazolo[4,3-*a*][1,4]benzodiazepines[2] revived interest in benzodiazepines with a heterocyclic ring fused to the 1,2 position and a review of such compounds has recently been published.[3] We report the synthesis and reactions of imidazo[1,5-*a*][1,4]benzodiazepines, compounds which differ in their ring fusion from their more easily accessible isomers described in the literature.[4]

The synthesis of the title compounds was facilitated by the discovery of the carbon–carbon bond forming reaction of the nitrosoamidines **2** with carbanions.[5] Thus, the condensation of the nitrosoamidine **2** (Scheme I), obtained by nitrosation of the corresponding amidines **1**, with the anion of a nitroalkane led to the 2-nitroalkylidene benzodiazepines **3a–c** and **4**. Other methods of preparing compounds **3** have subsequently been developed in our laboratories and were published recently.[6,7]

The stereochemistry assigned to the nitroalkylidenes is based on NMR data and in particular on the large chemical shift (δ 11–12 ppm) of the proton in the 1 position which may be due to intramolecular hydrogen bonding.

Catalytic hydrogenation of the nitro compounds **3b** or **3d** over Raney nickel afforded the 2-aminomethylbenzodiazepine **5**, characterized as a dimaleate salt. Heating the amine **5** with

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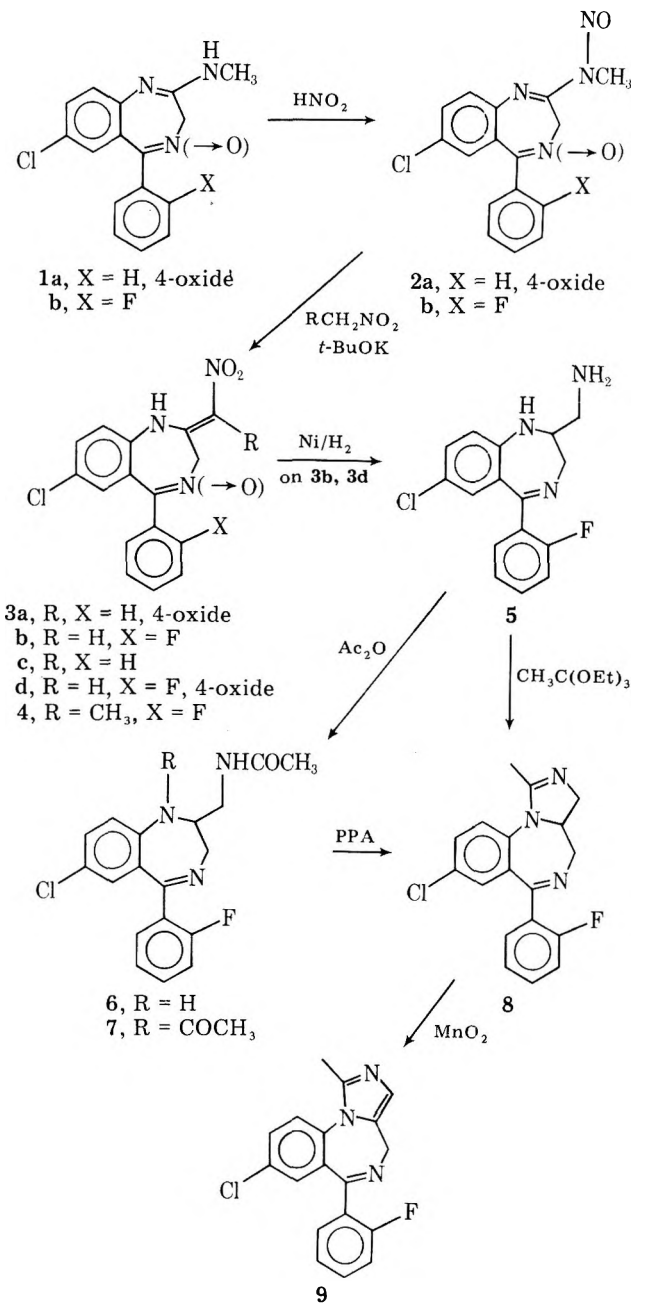
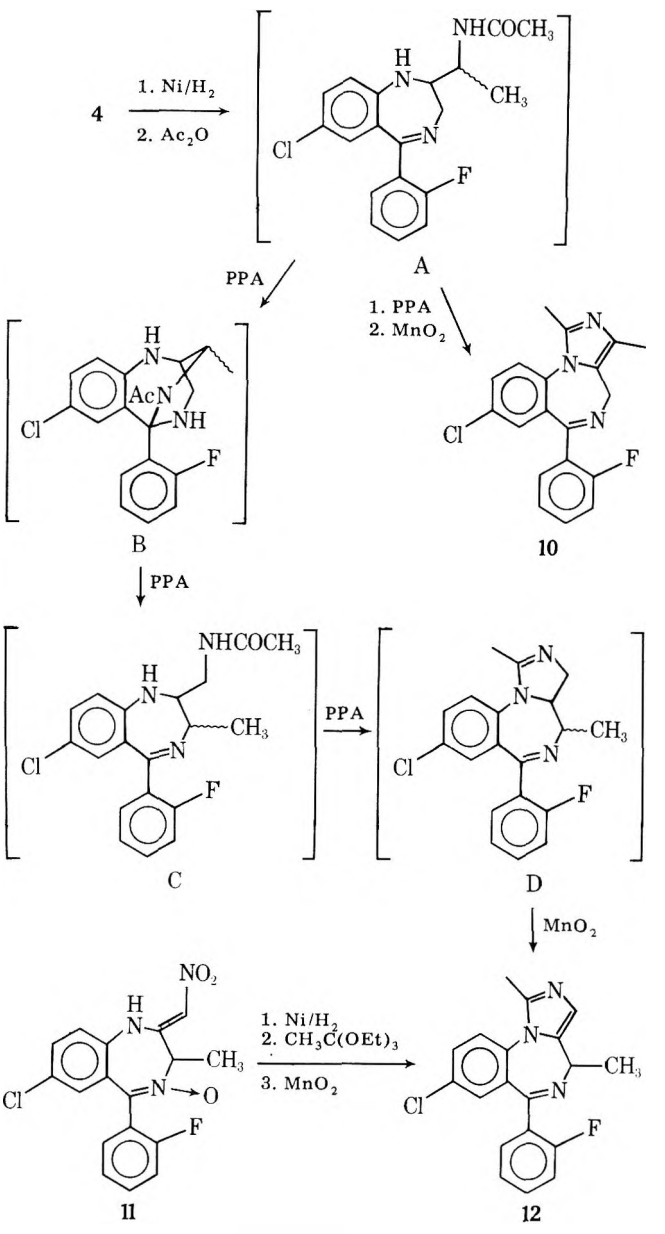
Scheme I



Scheme II



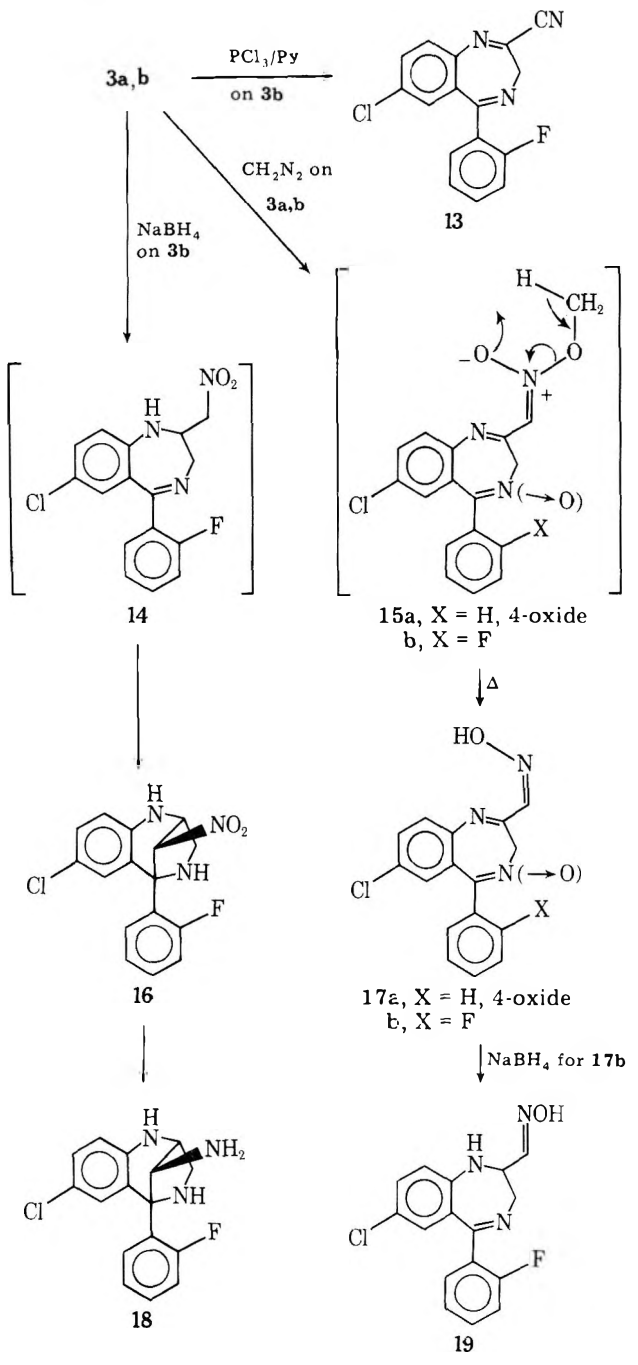
triethyl orthoacetate in boiling xylene gave the crystalline imidazoline **8** in good yield. The same imidazoline could also be obtained by cyclization of either the monoacetyl derivative **6** or the diacetate **7** by heating in polyphosphoric acid. The selective acetylation of the primary amino group of **5** was accomplished by reaction with acetic anhydride in methanol or in a two-phase system consisting of methylene chloride and aqueous sodium bicarbonate solution. The diacetate **7** was formed by acetylation of **5** with acetic anhydride in pyridine. The conversion of the imidazoline **8** to the desired imidazole **9** was carried out by oxidation with activated manganese dioxide.

When compound **4** was subjected to the same sequence of steps as described above for **3**, the expected imidazole **10** was obtained only as the minor product (Scheme II). The major product, separated by careful chromatography, was the 4-methylimidazobenzodiazepine **12**. The 4-methyl group of **12** appeared in the NMR spectrum as a doublet with $J = 6.5$ Hz at δ 1.85 ppm. The formation of **12** from **4** implies that the seven-membered ring was opened and reclosed with participation of the 2-aminoethyl moiety. Since no ring opening was observed during the acetylation step, the switch of the endocyclic and exocyclic amino groups must have occurred during the treatment of A with polyphosphoric acid, most likely by formation of the bridged intermediate B. N → N migration of the acetyl groups would then lead to C which undergoes cyclization to the imidazoline D.

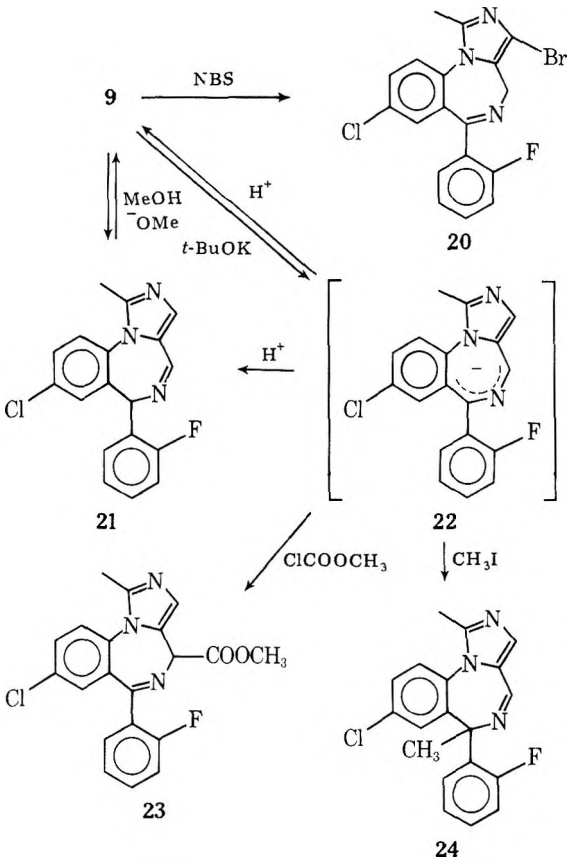
The 4-methylimidazobenzodiazepine **12** was better prepared by hydrogenation of the nitro compound **11**[6] followed by treatment with triethyl orthoacetate and oxidation with activated manganese dioxide. The two diastereoisomers formed by the reduction of **11** were not characterized but directly converted to a mixture of the corresponding imidazolines which again are not separated, since one asymmetric center was eliminated in the subsequent oxidation step. The racemate **12** was resolved into its optical antipodes using *O,O'*-dibenzoyl-*d*-tartaric acid. The levorotatory amorphous base gave a crystalline salt with *l*-tartaric acid with positive rotation, while the enantiomer formed a levorotatory salt with *d*-tartaric acid.

The borohydride in ethanol reduction of the exocyclic double bond in **3b** led to the bridged compound **16** (Scheme III), instead of the expected 2-nitromethyl derivative **14**. The structure of **16**, which was confirmed by single crystal x-ray analysis,[8] was originally derived from the analytical and

Scheme III



Scheme IV



spectroscopic data. The coupling between the protons at positions 2 and 10 (the bridging carbon atom) was found to be zero, corresponding to a dihedral angle of ~90°. This observation would agree with the assigned stereochemistry. An unusual long-range coupling of 2 Hz between the fluorine and C_{10} proton was observed and established by decoupling experiments. The transannular reaction of the nitromethyl intermediate **14** proceeded readily at room temperature and constitutes an exception to Baldwin's "Rules for Ring Closure",[9] since it involves a disfavored 5-endo trigonal cyclization. Catalytic reduction of the nitro group in **16** gave the corresponding amine **18**.

The nitrone function of **3a** was removed by treatment with phosphorus trichloride in methylene chloride without much affecting the nitromethylene moiety. However, a combination of phosphorus trichloride and pyridine converted the nitro compound **3b** in moderate yield to the 2-cyanobenzodiazepine **13**.[10] This reaction involved both a partial reduction of the nitro group and a dehydration.

Another partial reduction of the nitro group was observed on treatment with diazomethane. This reagent methylated the nitromethylene derivatives **3a,b** on the oxygen of the nitro group to form the thermally labile compounds **15a,b** (of which **15a** was characterized by NMR). Heating the crude methylation products in boiling toluene for 30 min afforded the highly crystalline oximes **17**. The formaldehyde eliminated during this thermolysis by the indicated cyclic mechanism was detected and identified as its 2,4-dinitrophenylhydrazone.

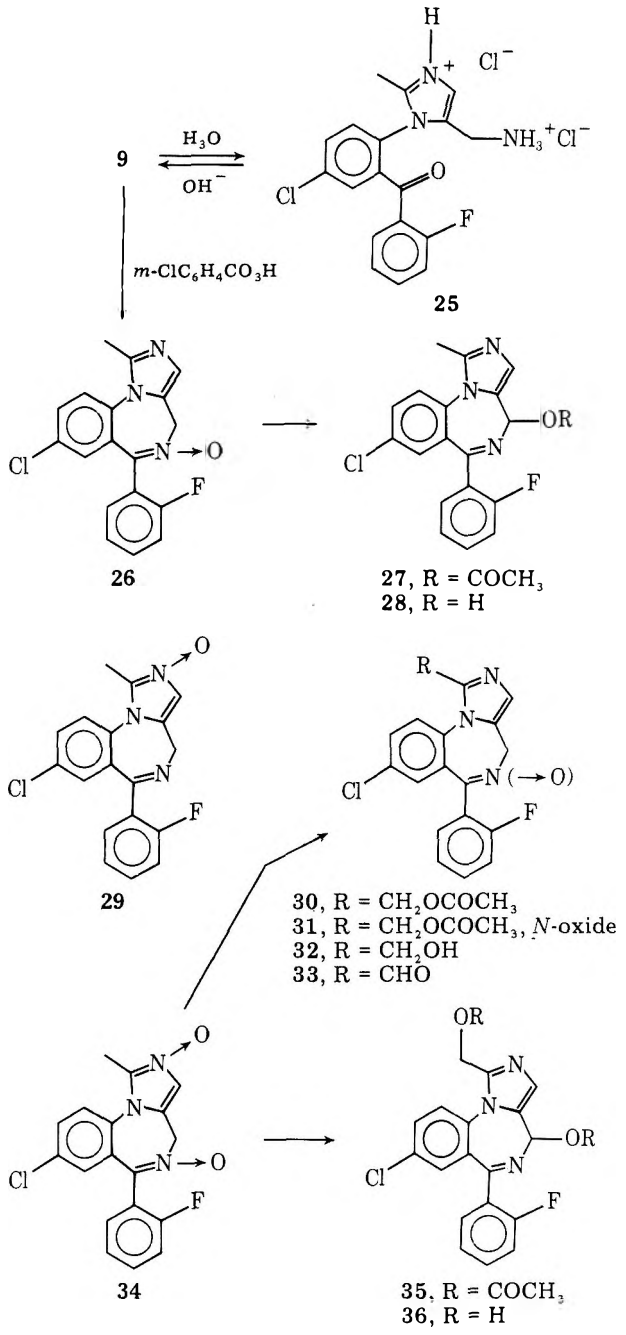
Sodium borohydride in ethanol selectively reduced the 1,2-imine moiety of **17b** and gave the 2-carboxaldoxime **19**.

The successful monoalkylation of the dianion of **3d** at low temperature to yield **11**[6] prompted us to investigate the alkylation of the imidazobenzodiazepine **9**. Methylation of this compound using potassium *tert*-butoxide and methyl iodide in dimethylformamide at −30 °C did not lead to **12** but only to the 6-methyl derivative **24** (Scheme IV). This shows that the ambident anion **22**, generated by abstraction of a proton from the 4 position, reacted with methyl iodide more readily at the 6 position. Protonation of the anion **22**, generated under the same conditions, was less selective and gave a mixture of the isomer **21** and starting material **9**. Equilibration of **21** in refluxing methanol containing methoxide resulted in almost complete conversion to **9**. According to an NMR spectroscopic estimate, the equilibrium mixture established under these conditions was composed of ~95% of **9** and 5% of **21**. Therefore it would appear that the isomer **21** is thermodynamically disfavored and that the formation of **24** and **21** by methylation or protonation of the anion **22** was due to kinetic control.

Reaction of the anion **22** with methyl chloroformate gave the 4-carboxylate **23**, although in low yield. Bromination of **9** with *N*-bromosuccinimide in acetic acid occurred predominantly on the imidazole ring and yielded the 3-bromo derivative **20**.

In acidic aqueous media, the imidazobenzodiazepine **9** exists in a pH-dependent equilibrium with the ring-opened structure **25** (Scheme V). The amount of ring-opened compound can be

Scheme V



determined spectroscopically or more accurately by reaction of the primary amino group of **25** with fluorescamine.[11] According to NMR, compound **9** was converted in over 90% to the open diprotonated species in a mixture of deuterium oxide–trifluoroacetic acid (1:1). The ring-opened compound **25** could be isolated as the crystalline dihydrochloride salt. The imidazole nitrogen in position 2 has a pK_a of 6.15 ± 0.1 and is much more basic than the imine nitrogen in position 5 which shows a pK_a of 1.7 ± 0.1. The open form **25** ring closes at neutral pH with a half-life of about 10 min.

The presence of two basic nitrogens complicated the oxidation of **9** with peracid. Thus, treatment of **9** with an excess of *m*-chloroperbenzoic acid led to a complex mixture containing the 5-oxide **26**, the 2-oxide **29**, and the 2,5-dioxide **34**. The 5-oxide **26** was the predominant product and was obtained by fractional crystallization. The much more polar and somewhat water-soluble 2-oxides, compounds **29** and **34**, were more difficult to isolate and had to be separated by chromatography.

The 5-oxide **26** underwent the usual Polonovsky reaction[12] and afforded the 4-acetoxy derivative **27** which was hydrolyzed to the corresponding alcohol **28**. We found that the 2-oxide function reacted preferentially under milder conditions with acetic anhydride, and thus we were able to convert the 2,5-dioxide **34** to the 1-acetoxymethyl 5-oxide **31**. Reduction of **31** with phosphorus trichloride gave compound **30**, which was also obtained by a Polonovsky rearrangement on compound **29**. For the preparation of **30**, it was therefore not necessary to separate the 2-oxide **29** from the 2,5-dioxide **34**. Hydrolysis of **30** gave the alcohol **32** which could be readily oxidized to the aldehyde **33** by the use of activated manganese dioxide. The di-*N*-oxide **34** was also subjected to a Polonovsky reaction and yielded the diacetate **35** and, after hydrolysis, the diol **36**.

Experimental Section

Melting points were determined in a capillary melting point apparatus. The UV spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. NMR spectra were recorded with a Varian T-60 or Varian HA-100 instrument using Me_4Si as an internal standard. IR spectra were determined on a Beckman IR-9 spectrometer. The mass spectra were determined on a CEC-21-100 B instrument at 70 eV. Silica gel from Merck (70–230 mesh) was used for chromatography and anhydrous sodium sulfate for drying purposes.

7-Chloro-5-(2-fluorophenyl)-2-methylamino-3*H*-1,4-benzodiazepine (1b). A solution of 200 g (0.695 mol) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one[13] in 2 L of tetrahydrofuran and 250 mL of benzene was saturated with methylamine with cooling in an ice bath. A solution of 190 g (1 mol) of titanium tetrachloride in 250 mL of benzene was added through a dropping funnel within 15 min. After addition, the mixture was stirred and refluxed for 3 h. Water, 600 mL, was added slowly to the cooled reaction mixture. The inorganic material was separated by filtration and washed well with tetrahydrofuran. The water layer was separated and the organic phase dried over sodium sulfate and evaporated. The crystalline residue was collected with ether to leave 205 g (98%) of product with mp 204–206 °C.

Anal. Calcd for $C_{16}H_{13}ClFN_3$: C, 63.69; H, 4.34; N, 13.93. Found: C, 63.57; H, 4.33; N, 14.00.

7-Chloro-5-(2-fluorophenyl)-2-(*N*-nitrosomethylamino)-3*H*-1,4-benzodiazepine (2b). Sodium nitrite, 34.5 g (0.5 mol), was added in three portions over a period of 30 min to a stirred solution of 120.6 g (0.4 mol) of **1b** in 500 mL of glacial acetic acid. The mixture was stirred for 3 h at room temperature and was then poured into water. The product was extracted with methylene chloride. The extracts were washed with water and saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated. Crystallization of the residue from ether yielded 79.4 g (60%) of product with mp 109–111 °C. For analysis, it was recrystallized from ether: mp 110–112 °C; UV λ_{max} 231 (ε 30 700), 300 (9200), infl 340 nm (5600); NMR ($CDCl_3$) δ 3.38 (s, 3, NCH_3), 4.95 (br s, 2, C_3-H), 6.8–7.8 ppm (m, 7, aromatic H).

Anal. Calcd for $C_{16}H_{12}ClFN_4O$: C, 58.10; H, 3.65; N, 16.94. Found: C, 58.07; H, 3.73; N, 17.00.

7-Chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-1,4-benzodiazepine 4-Oxide (3a). A solution of 33 g (0.1 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2a**)[14] in 100 mL of dimethylformamide was added to a mixture of 50 mL of nitromethane, 12.5 g (0.11 mol) of potassium *tert*-butoxide, and 100 mL of dimethylformamide. The reaction mixture was stirred under a stream of nitrogen for 1 h. After the addition of 10 mL of glacial acetic acid, the product was crystallized by the gradual addition of 250 mL of water. The precipitated yellow material was collected and washed with water, methanol, and ether to leave 23.5 g (71%) with mp 253–255 °C (dec). The analytical sample was recrystallized from methylene chloride and showed the same melting point: UV λ_{max} 235 (ε 26 600), 315 (18 200), 366 nm (19 400).

Anal. Calcd for $C_{16}H_{12}ClN_3O_3$: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.41; H, 3.63; N, 12.74.

7-Chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-1,4-benzodiazepine (3c). A mixture of 3.3 g (0.01 mol) of **3a**, 3.3 mL of phosphorus trichloride, and 300 mL of methylene chloride was stirred at room temperature for 4 h. The solution was washed with 10% aqueous sodium carbonate solution, dried over sodium sulfate, and

evaporated. The crude product was purified by chromatography over 100 g of silica gel using 10% (v/v) ethyl acetate in methylene chloride. The combined clean fractions were crystallized from methylene chloride/hexane to yield 1.8 g (57.5%) of light yellow crystals with mp 184–186 °C; UV λ_{max} 224 (ϵ 28 700), infl 260 (11 600), 364 nm (26 100); NMR ($CDCl_3$) δ 4.23 (s, 2, C_3-H), 6.68 (s, 1, $=CHNO_2$), 7.0–7.7 (m, 8, aromatic H), 11.3 ppm (br s, 1, NH).

Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.45; H, 3.80; N, 13.29.

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-2-nitromethylene-2*H*-1,4-benzodiazepine (3b). A solution of 33 g (0.1 mol) of **2b** in 100 mL of dry dimethylformamide was added to a mixture of 200 mL of dimethylformamide, 50 mL of nitromethane, and 14 g (0.125 mol) of potassium *tert*-butoxide which had been stirred under nitrogen for 15 min.

After stirring for 1 h at room temperature, the reaction mixture was acidified by addition of glacial acetic acid, diluted with water, and extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate, and evaporated. Crystallization of the residue from ether yielded 17.5 g (53%) of yellow crystals with mp 170–172 °C. The analytical sample was recrystallized from methylene chloride/ethanol: mp 174–176 °C; UV λ_{max} 223 (ϵ 28 000), 367 nm (25 100); NMR ($CDCl_3$) δ 4.33 (s, 2, C_3-H), 6.75 (s, 1, $=CHNO_2$), 6.8–7.8 (m, 7, aromatic H), 11.1 ppm (br s, 1, NH).

Anal. Calcd for $C_{16}H_{11}ClFN_3O_2$: C, 57.93; H, 3.34; N, 12.67. Found: C, 57.99; H, 3.53; N, 12.67.

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-2-(1-nitroethylene)-2*H*-1,4-benzodiazepine (4). A mixture of 11.2 g (0.1 mol) of potassium *tert*-butoxide, 50 mL of nitroethane, and 200 mL of dimethylformamide was stirred at room temperature for 15 min. A solution of 29 g (0.088 mol) of crude, oily **2b** in 100 mL of dimethylformamide was then added and stirring under nitrogen was continued for 5 h. The reaction mixture was neutralized by addition of glacial acetic acid and diluted with water. The product was extracted with ether. The extracts were washed with saturated aqueous sodium bicarbonate solution, dried, and evaporated. Crystallization from ether yielded 8.1 g (26.5%) of yellow crystals with mp 136–142 °C.

The analytical sample was recrystallized twice from methylene chloride/ethanol, mp 153–155 °C; UV λ_{max} 226 (ϵ 28 250), 390 nm (26 600); NMR ($CDCl_3$) δ 2.38 (s, 3, CH_3), 4.48 (br s, 2, C_3-H), 6.8–7.8 (m, 7, aromatic H), 12.4 (br s, 1, NH).

Anal. Calcd for $C_{17}H_{13}ClFN_3O_2$: C, 59.05; H, 3.79; N, 12.15. Found: C, 59.00; H, 3.79; N, 12.21.

2-Aminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine Dimaleate (5). A suspension of 17 g (0.05 mol) of **3d**[6] in 200 mL of tetrahydrofuran and 100 mL of methanol was hydrogenated in the presence of 17 g of Raney nickel at an initial pressure of 155 psi for 24 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in 50 mL of 2-propanol and warmed on the steam bath. A warm solution of 17 g of maleic acid in 50 mL of ethanol was added and the salt was allowed to crystallize by cooling in the ice bath. The yellow crystals were collected to yield 21.9 g (83%) with mp 196–198 °C.

The analytical sample was recrystallized from methanol/water/2-propanol.

Anal. Calcd for $C_{16}H_{15}ClFN_3(C_4H_4O_4)_2$: C, 53.79; H, 4.45; N, 7.84. Found: C, 53.70; H, 4.65; N, 7.80.

1-Acetyl-2-acetylaminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine (7). Compound **5**, 8.0 g (0.015 mol), was partitioned between methylene chloride and aqueous ammonia. The methylene chloride solution was washed with water, dried over sodium sulfate, and evaporated. The residue was dissolved in 50 mL of pyridine. After the addition of 10 mL of acetic anhydride, the mixture was heated on the steam bath for 4 h. The reagents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from methylene chloride/ether with seeding yielded 2.5 g (43%) of product with mp 213–215 °C. Seeds were obtained by chromatography over silica gel (40-fold amount) using 10% (v/v) ethanol in methylene chloride for elution. The analytical sample was recrystallized from ethyl acetate/hexane and had mp 215–217 °C; UV λ_{max} infl 225 (ϵ 25 800), infl 270 (4400), infl 285 nm (2500); IR ($CHCl_3$) 3350 (NH), 1665, 1535 cm^{-1} (–CON); NMR ($CDCl_3$) δ 1.88 (s, 3, $COCH_3$), 2.0 (s, 3, $COCH_3$), 2.7–3.8 (m, 3, $-CH_2NHCOCH_3$ and C_3-H), 4.1 (q, 1, J_{AB} = 11 Hz, J_{AX} = 4 Hz, C_3-H), 5.38 (m, 1, C_2-H), 6.66 (br s, 1, NH), 6.8–7.9 (m, 7, aromatic H).

Anal. Calcd for $C_{20}H_{19}ClFN_3O_2$: C, 61.94; H, 4.93; N, 10.83. Found: C, 62.25; H, 4.94; N, 10.71.

8-Chloro-3a,4-dihydro-6-(2-fluorophenyl)-1-methyl-3*H*-imidazo[1,5-*a*][1,4]benzodiazepine (8). (A) The dimaleate salt of **5**, 21.5 g (0.04 mol), was partitioned between 150 mL of methylene chloride and 100 mL of water containing 20 mL of concentrated aqueous ammonia. The organic phase was washed with water, separated, dried, and evaporated. The residue was dissolved in 100 mL of xylene and, following the addition of 22 mL (0.12 mol) of triethyl orthoacetate, the solution was heated to reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was crystallized from ether to yield 9 g (68%) of off-white crystals with mp 142–145 °C. The analytical sample was recrystallized from ethyl acetate: mp 144–146 °C; UV λ_{max} 213 (ϵ 37 000), infl 250 (11 500), sh 280 nm (3700); NMR ($CDCl_3$) δ 1.70 (s with fine structure, 3, CH_3), 3.46 (q, 1, J_{AB} = 12 Hz, J_{AX} = 4 Hz, C_4-H), 3.7–4.2 (m, 3, C_3-H, C_4-H), 4.7 (m, 1, C_{3a}-H), 6.8–7.8 ppm (m, 7, aromatic H).

(B) Acetic anhydride, 7 mL, was added to a solution of 6.06 g (0.02 mol) of **5** in 200 mL of methylene chloride. The solution was layered with 200 mL of saturated aqueous sodium bicarbonate and the mixture was stirred for 20 min. The organic layer was separated, washed with bicarbonate solution, dried, and evaporated to leave 6.1 g of resinous 2-acetaminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine (**6**). This material was heated with 40 g of polyphosphoric acid at 150 °C for 10 min. The initially orange color of the reaction mixture changed to a light yellow. The cooled reaction mixture was dissolved in water, made alkaline with ammonia and ice, and was extracted with methylene chloride. The extracts were dried and evaporated, and the residue was chromatographed over 120 g of silica gel using 20% (v/v) methanol in methylene chloride. Crystallization of the combined clean fractions from ether gave 3.5 g (53%) of crystalline **8** with mp 142–145 °C.

(C) A mixture of 0.5 g of (**7**) and 10 g of polyphosphoric acid was heated to 150–170 °C for 10 min. The cool reaction mixture was dissolved in ice water and the solution was made alkaline with ammonia. The precipitated base was extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed over 10 g of silica gel using 20% methanol in methylene chloride. The clean fractions were combined and evaporated. The residue was crystallized from ether to yield 0.1 g (23%) of product with mp 142–144 °C.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (9). A mixture of 13.1 g (0.04 mol) of **8**, 300 mL of toluene, and 65 g of activated manganese dioxide was heated to reflux with stirring for 40 min. The MnO_2 was filtered over Celite and was washed with tetrahydrofuran and methylene chloride. The filtrate was evaporated to leave 11.5 g of brown oil which was dissolved in 20 mL of hot ethanol and treated with a hot solution of 4.1 g (0.035 mol) of maleic acid in 15 mL of ethanol. After crystallization had started, 100 mL of ether was gradually added. The separated crystals were collected and washed with ether to yield 10.2 g (58%) of maleate with mp 114–117 °C (solvated).

This material was partitioned between methylene chloride and diluted aqueous ammonia. The organic phase was dried and evaporated. Crystallization from ether/methylene chloride/hexane yielded 6 g (46%) of colorless crystals with mp 158–160 °C; UV λ_{max} 220 (ϵ 30 000), infl ca. 240 nm (20 000); NMR ($CDCl_3$) δ 2.56 (s, 3, CH_3), 4.03 (d, 1) and 5.13 (d, 1) (AB system, J = 13 Hz, C_4-H), 6.8–7.8 ppm (m, 8, aromatic H and C_3-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3$: C, 66.36; H, 4.02; N, 12.90. Found: C, 66.35; H, 3.77; N, 12.78.

8-Chloro-1,3-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (10) and 8-Chloro-1,4-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine Dihydrochloride (12). Raney nickel, 5 teaspoonsful, was added to a solution of 17.3 g (0.05 mol) of **4** in 750 mL of tetrahydrofuran. The mixture was hydrogenated at atmospheric pressure for 4 h. The catalyst was removed by filtration over Celite and was washed well with methanol. The filtrate was evaporated to leave 14.1 g of crude 2-(1-aminoethyl)-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine as a reddish oil. This material was dissolved in 300 mL of methylene chloride. Following the addition of 14 mL of acetic anhydride, 300 mL of saturated aqueous sodium bicarbonate solution was added and the two-phase mixture was stirred at room temperature for 1 h. The methylene chloride layer was separated, washed with bicarbonate, dried, and evaporated. The residue, 13.5 g, of crude A was heated with 40 g of polyphosphoric acid for 10 min at 160–170 °C. The cool reaction mixture was diluted with water, made alkaline with ammonia, and extracted with methylene chloride. The extracts were washed with water, dried, and evaporated to leave 11 g of a brown residue which was chromatographed on 250 g of silica gel using 20% (v/v) methanol in methylene chloride. The thin-layer chromatographically homogeneous fractions were combined to yield 5.1 g of

resinous imidazoline which was subjected to the following oxidation.

A mixture of the above material, 20 g of activated manganese dioxide, and 300 mL of toluene was heated to reflux for 3 h using a Dean–Stark trap to remove the water. The manganese dioxide was separated by filtration over celite and was washed well with methylene chloride. The filtrate was evaporated and the residue, 4.2 g, was chromatographed with pressure over 150 g of silica gel H using 3% ethanol in methylene chloride. The first eluted major component was 8-chloro-1,4-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine (12): NMR ($CDCl_3$) δ 1.85 (d, 3, J = 6,5 Hz, $CHCH_3$), 3.04 (s, 3, CH_3), 4.18 (q, 1, J = 6.5 Hz, $-CHCH_3$), 6.7–7.8 ppm (m, 8, aromatic H).

It was converted to a crystalline dihydrochloride by treatment with ethanolic hydrogen chloride in ether: mp 247–250 °C (dec); yield 1.5 g (7.5% overall from nitromethylene derivative); UV sh 215 (ϵ 34 400), infl 250 (14 000), infl 280 nm (3050).

Anal. Calcd for $C_{19}H_{15}ClFN_3 \cdot 2HCl$: C, 55.29; H, 4.11; N, 10.18. Found: C, 55.11; H, 4.39; N, 9.90.

The more polar component could be crystallized from methylene chloride/ether/hexane to yield 0.3 g (1.8% based on the nitromethylene derivative) of 8-chloro-1,3-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo [1,5-*a*][1,4]benzodiazepine (**10**) with mp 178–180 °C: UV λ_{max} 218 (ϵ 32 000), infl 240 (19 200), infl 265 nm (8450); NMR ($CDCl_3$) δ 2.2 (s, 3, CH_3), 2.46 (s, 3, CH_3), 3.95 (d, 1) and 5.1 (d, 1) (AB system, J = 13 Hz, C_4-H), 5.7–7.8 ppm (m, 7, aromatic H).

Anal. Calcd for $C_{19}H_{15}ClFN_3$: C, 67.16; H, 4.45; N, 12.37. Found: C, 67.10; H, 4.38; N, 12.36.

8-Chloro-1,4-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine Dihydrochloride (12). A mixture of 216 g (0.6 mol) of 7-chloro-5-(2-fluorophenyl-1,3-dihydro-3-methyl-2-(nitromethylene)-2*H*-1,4-benzodiazepine 4-oxide (**11**),[6] 300 g of Raney nickel and 3 L of ethanol was hydrogenated for 16 h at an initial pressure of 480 psi. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in 400 mL of hot 2-propanol and treated with a hot solution of 140 g of maleic acid in 200 mL of ethanol. The crystals which separated upon cooling were collected and washed with ether to give 185 g (56%) of the dimaleate salt of 2-(1-aminoethyl)-7-chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine.

A portion of this salt, 100 g, was partitioned between aqueous ammonia and methylene chloride. The organic phase was dried and evaporated. The residue was dissolved in 500 mL of xylene and the solution was heated to reflux for 2 h after the addition of 100 mL of triethyl orthoacetate. The solvent was removed under reduced pressure to give 55 g of crude imidazoline which was dissolved in 600 mL of toluene and treated with 250 g of activated manganese dioxide. The mixture was stirred and heated to reflux with separation of water for 2 h. The MnO_2 was filtered off and washed well with methylene chloride and tetrahydrofuran. The filtrate was evaporated and the residue was dissolved in 60 mL of 2-propanol. The dihydrochloride was precipitated by the addition of ethanolic hydrogen chloride. The crystals were collected and washed with ether to yield 25 g (33%) of product with mp 245–248 °C.

Resolution of 12. A mixture of 17 g (0.05 mol) of racemic 8-chloro-1,4-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine, which had been liberated from its dihydrochloride by partitioning between methylene chloride and aqueous ammonia, 18.8 g (0.05 mol) of *O,O'*-dibenzoyl-*d*-tartaric acid hydrate, and 170 mL of ethanol was boiled until the solution was complete. For crystallization, the solution was allowed to sit overnight. The separated crystals were collected and washed with ethanol and ether to yield 8.4 g (47%) with mp 140–142 °C. Recrystallization from ethanol/ether yielded 4.4 g with mp 141–142 °C and $[\alpha]^{25}_D$ −43.39° (c 1% in methanol).

A solution of 1.6 g (0.0106 mol) of *l*-tartaric acid in 11 mL of ethanol was added to a solution of 3.5 g of the levorotatory base liberated from the above *O,O'*-dibenzoyl-*d*-tartrate, in 11 mL of ethanol. The crystals obtained were collected and washed with ethanol and ether to yield 2.8 g (55%) of product with mp 178–180 °C. Recrystallization from ethanol gave 2.1 g with mp 183–185 °C and $[\alpha]^{25}_D$ + 25.69° (c 1.012% in methanol). The amorphous base liberated from this salt showed a rotation of $[\alpha]^{25}_D$ −36.74° (c 0.939% in methylene chloride).

The mother liquor left after separation of the crystalline salt with *O,O'*-dibenzoyl-*d*-tartaric acid described above was evaporated and reconverted to the base by partitioning between aqueous ammonia and methylene chloride. The methylene chloride solution was dried over sodium sulfate and evaporated to yield 12 g of partly resolved base.

A solution of 9.7 g (0.029 mol) of this material in 15 mL of ethanol was treated with a solution of 4.4 g of *d*-tartaric acid in 14 mL of ethanol. The crystals which separated after several hours were collected to yield 3.2 g (23%) with mp 176–178 °C. Recrystallization from ethanol gave 2.1 g of product with mp 182–184 °C and $[\alpha]^{25}_D$ −24.96° (c 0.616% in methanol). The amorphous base liberated from this salt showed a rotation of $[\alpha]^{25}_D$ + 37.6° (c 1.0% in methylene chloride).

7-Chloro-2-cyano-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine (13). Phosphorus trichloride, 0.5 mL, was added to a solution of 1 g (0.0003 mol) of **3b** in 20 mL of methylene chloride and 20 mL of pyridine. The solvents were evaporated under reduced pressure after 4 h and the residue was taken up in methylene chloride. Some insoluble material was removed by filtration and the filtrate was evaporated and chromatographed over 20 g of silica gel using methylene chloride. The clean fractions were combined and evaporated, and the residue was crystallized from ether/hexane to yield 0.285 g (31.5%) with mp 106–110 °C; UV λ_{max} 215 (ϵ 28 500), sh 240 (20 200), sh 322 (3800), 338 nm (3820); NMR ($CDCl_3$) δ 4.18 (s, 2, C_3-H), 6.8–7.8 (m, 7, aromatic H).

Anal. Calcd for $C_{16}H_9ClFN_3$: C, 64.55; H, 3.05; N, 14.11. Found: C, 64.51; H, 2.96; N, 14.11.

7-Chloro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-10-nitro-2,5-methano-1*H*-1,4-benzodiazepine (16). A mixture of 20 g (0.06 mol) of **3b**, 200 mL of ethanol, 200 mL of methylene chloride, and 5 g (0.132 mol) of sodium borohydride was stirred at room temperature for 15 min. After dilution with water and methylene chloride, the organic layer was separated, dried, and evaporated. Crystallization of the residue from methylene chloride/ethyl acetate/hexane gave 17.7 g (88%) of light yellow crystals. The analytical sample was recrystallized from methylene chloride/ethyl acetate: mp 202–204 °C (dec); UV λ_{max} 258 (ϵ 12 200), 318 nm (2900); IR ($CHCl_3$) 3400 (NH), 1550 cm^{-1} (NO_2); NMR (Me_2SO-*d*) δ 3.24 (m, 1, C_3-H), 3.57 (m, 1, C_3-H), 3.98 (br t, J = 5 Hz, NH), 4.33 (t, 1, J = 4 Hz, C_2-H), 5.63 (d, 1, J = 2 Hz, C_{10}-H), 6.07 (d, 1, J = 2.5 Hz, C_6-H), 6.5–7.8 (m, 7, aromatic H and NH). Single crystal x-ray analysis[8] was performed on this compound.

Anal. Calcd for $C_{16}H_{13}ClFN_3O_2$: C, 57.58; H, 3.93; N, 12.59. Found: C, 57.59; H, 4.10; N, 12.55.

10-Amino-7-chloro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-2,5-methano-1*H*-1,4-benzodiazepine (18). A solution of 25 g (0.074 mol) of **16** in 500 mL of tetrahydrofuran and 250 mL of ethanol was hydrogenated at atmospheric pressure for 1 h in the presence of 2 teaspoonsful of Raney nickel. The catalyst was separated by filtration and the filtrate was evaporated under reduced pressure. Crystallization of the residue from ether yielded 16 g (70.5%) of colorless crystals with mp 138–140 °C. The analytical sample was recrystallized from ether/hexane: mp 142–145 °C; UV λ_{max} 262 (ϵ 9350), 267 (9380), 317 nm (2560).

Anal. Calcd for $C_{16}H_{15}ClFN_3$: C, 63.27; H, 4.98; N, 13.83. Found: C, 63.18; H, 5.08; N, 13.61.

7-Chloro-5-phenyl-3*H*-1,4-benzodiazepine-2-carboxaldoxime 4-Oxide (17a). A solution of 6.8 g (0.02 mol) of **3a** in 1600 mL of methylene chloride and 400 mL of methanol was treated with an excess of a solution of diazomethane in ether. After sitting at room temperature for 30 min, the excess diazomethane was destroyed by the addition of 10 mL of glacial acetic acid. The reaction mixture was washed with water and sodium bicarbonate solution, dried, and evaporated. The orange oil obtained consisted, according to the thin-layer chromatogram [5% (v/v) of methanol in chloroform], mainly of a product less polar than starting material. A sample of this material was purified by thick-layer chromatography and characterized by NMR: NMR (Me_2SO-*d*) δ 3.84 (s, 3, OCH_3), 5.03 (br s, 2, C_3-H), 6.8–7.8 (m, 9, aromatic H and $-CH{=}N$).

The crude product **15a** was heated to reflux for 30 min with 25 mL of toluene. The crystals which separated from the cooled reaction mixture were collected and washed with a small amount of ethanol and ether to leave 3.5 g (56%) of product which was recrystallized from ethanol. The analytical sample was recrystallized from methylene chloride/ether to give off-white crystals with mp 226–231 °C; UV λ_{max} 250 (ϵ 30 600), 291 (21 400), infl 350 nm (4200); NMR (Me_2SO-*d*) δ 4.86 (br s, 2, C_3-H), 6.96 (m, 1, C_6-H), 7.2–7.5 (m, 7, aromatic H), 8.02 (s, 1, $-CH{=}N$), 12.7 (br s, 1, OH).

Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.85; N, 13.39. Found: C, 61.24; H, 3.74; N, 13.35.

7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-carboxaldoxime (17b). Similarly, reaction of 0.33 g (0.001 mol) of **3b** with diazomethane followed by a 10-min reflux in xylene yielded 0.085 g (27%) of **17b**. The analytical sample was recrystallized from methylene chloride/methanol/ethyl acetate to give yellow crystals with mp 250–251 °C (dec); UV λ_{max} 232 (ϵ 31 500), infl 270 (16 000), 319 nm (5800); NMR (Me_2SO-*d*) δ 4.33 (br s, 2, C_3-H), 7–7.8 (m, 7, aromatic

H), 7.85 (s, 1, CH=N), 12.5 ppm (s, 1, OH).

Anal. Calcd for $C_{16}H_{11}ClFN_3O$: C, 60.87; H, 3.51; N, 13.31. Found: C, 60.70; H, 3.57; N, 13.12.

7-Chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine-2-carboxaldoxime (19). A mixture of 1.3 g (0.0038 mol) of **17b**, 50 mL of ethanol, 25 mL of methylene chloride, and 1 g (0.026 mol) of sodium borohydride was heated to reflux for 4 h. After standing overnight at room temperature, the reaction mixture was diluted with water. The organic layer was separated, dried, and evaporated. Crystallization from methylene chloride/ethyl acetate gave 0.4 g of yellowish crystals with mp 195–197 °C. An additional 0.3 g (total yield 58%) was obtained by chromatography of the mother liquor over 25 g of silica gel using 5% (v/v) ethanol in methylene chloride. For analysis, the product was recrystallized from methylene chloride/ethyl acetate, mp unchanged: UV λ_{max} 237 (ϵ 24 800), infl 270 (7800), 368 nm (3200); NMR (Me_2SO-d_6) δ 3.94 (d, 2, J = 4.5 Hz, C_3-H), 4.5 (m, 1, C_2-H), 6.5–7.6 (m, 9, aromatic H, NH, -CH=N), 10.85 ppm (s, 1, OH).

Anal. Calcd for $C_{16}H_{13}ClFN_3O$: C, 60.48; H, 4.12; N, 13.22. Found: C, 60.43; H, 4.27; N, 13.14.

3-Bromo-8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (20). A mixture of 10 g (0.03 mol) of **9**, 450 mL of chloroform, 30 mL of glacial acetic acid, and 13.7 g (0.077 mol) of *N*-bromosuccinimide was heated to reflux with stirring for 1.5 h. The cooled mixture was washed with saturated sodium bicarbonate solution and was dried and evaporated. The oily residue was chromatographed over 150 g of neutral aluminum oxide (Woelm). The impurities were eluted with methylene chloride and the product was eluted with ethyl acetate. Crystallization of the combined clean fractions from ether yielded 4.5 g (36.2%) of colorless crystals with mp 201–205 °C. For analysis, a sample was recrystallized from ether/hexane: mp 203–205 °C; UV sh 215 (ϵ 82 500), infl ~242 (44 500), infl 265 (20 700), infl 307 nm (2300); NMR ($CDCl_3$) δ 2.55 (s, 3, CH_3), 3.97 (d, 1) and 5.2 (d, 1) (AB system, J = 13 Hz, C_4-H), 6.8–7.8 (m, 7, aromatic H).

Anal. Calcd for $C_{18}H_{12}BrClFN_3$: C, 53.42; H, 2.99; N, 10.38. Found: C, 53.65; H, 2.95; N, 10.19.

8-Chloro-1,6-dimethyl-6-(2-fluorophenyl)-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine (24). A solution of 1.6 g (5 mmol) of **9** in 30 mL of dimethylformamide was cooled to −30 °C when 0.85 g (7.5 mmol) of potassium *tert*-butoxide was added. After stirring under nitrogen for 15 min at −30 to −10 °C, 0.5 mL (8 mmol) of methyl iodide was added. The mixture was stirred for 15 min without cooling and was then partitioned between aqueous bicarbonate and methylene chloride/toluene (1:3). The organic phase was dried and evaporated. Crystallization of the residue from ether yielded 0.9 g (54%) of product which was recrystallized twice from ethyl acetate/hexane for analysis: mp 165–167°; UV λ_{max} infl 228 (ϵ 16 600), 263 (8800), 270 (8500), infl 280 nm (7100); NMR ($CDCl_3$) δ 2.17 (s, 3, CH_3), 2.3 (s, 3, CH_3), 6.5–8.0 (m, 8, aromatic H, C_3-H), 8.47 (s, 1, C_4-H).

Anal. Calcd for $C_{19}H_{15}ClFN_3$: C, 67.16; H, 4.45; N, 12.37. Found: C, 67.41; H, 4.30; N, 12.42.

8-Chloro-6-(2-fluorophenyl)-1-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine (21). (A) Potassium *tert*-butoxide, 0.625 g (5.5 mmol), was added to a solution of 1.625 g (5 mmol) of **9** in 20 mL of dimethylformamide cooled to −30 °C. After stirring under nitrogen for 10 min at −30 °C, the dark mixture was acidified with 1 mL of glacial acetic acid and was then partitioned between aqueous bicarbonate and toluene/methylene chloride (3:1, v/v). The organic layer was separated, dried, and evaporated. the residue was chromatographed over 50 g of silica gel using 25% (v/v) methylene chloride in ethyl acetate. The less polar product was eluted first and was crystallized from ethyl acetate/hexane to yield 340 mg (21%) of product with mp 180–181 °C: UV λ_{max} infl 218 nm (ϵ 20 600), sh 265 (11 150), 255 (11 500), 267 (10 980), infl 288 (5600). NMR ($CDCl_3$) δ 2.7 (s, 3, CH_3), 5.61 (d, 1, J = 2 Hz, C_6-H), 6.77 (s, with fine structure, 1, C_3-H), 8.4 (d, 1, J = 2 Hz, C_4-H), 6.8–8.3 ppm (m, 7, aromatic H).

Anal. Calcd for $C_{18}H_{13}N_3ClF$: C, 66.37; H, 4.02; N, 12.90. Found: C, 66.56; H, 4.01; N, 12.85.

(B) Equilibration of 9 with Methoxide in Methanol. A mixture of 0.65 g (2 mmol) of **9**, 20 mL of methanol, and 0.1 g (0.9 mmol) of potassium *tert*-butoxide was heated to reflux for 16 h. After dilution with water, the mixture was extracted with methylene chloride. The extracts were dried and evaporated. A portion was azeotroped with carbon tetrachloride to determine the NMR spectrum which indicated 5 ± 1% of the isomer **21** having formed.

Equilibration of 21 to 9. (A) With *tert*-Butoxide in DMF. Potassium *tert*-butoxide, 0.125 g (1.1 mmol), was added to a solution of 0.325 g (1 mmol) of **21** in 20 mL of dimethylformamide cooled to −30 °C. After stirring at −30 to −20 °C for 15 min, the reaction mixture was acidified by the addition of 0.2 mL of glacial acetic acid and was partioned between aqueous sodium bicarbonate and methylene chloride/toluene (1:3). The organic phase was washed with water, dried, and evaporated. The residue was chromatographed over 20 g of silica gel using ethyl acetate for elution. After elution of 125 mg of starting material, 130 mg of **9** was collected and crystallized from ether/hexane, mp 156–158 °C.

(B) With Methoxide in Methanol. A solution of 0.325 g (1 mmol) of **21** in 10 mL of methanol was heated to reflux for 4 h after the addition of 50 mg (0.44 mmol) of potassium *tert*-butoxide. The reaction mixture was diluted with water and was extracted with methylene chloride. The extracts were dried and evaporated.

The residue was dissolved in a small amount of hot 2-propanol and combined with a hot solution of maleic acid in 2-propanol. The maleate salt of **9** was crystallized by the addition of ether to yield 380 mg (86%) of colorless crystals which, after drying at 90 °C under high vacuum, had mp 148–150 °C. Conversion to the base gave 220 mg (67.5%) of crystals with mp 156–158 °C.

Thin-layer chromatography showed the presence of a small amount of starting material.

Methyl 8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-4-carboxylate (23). Potassium *tert*-butoxide, 0.25 g (2.2 mmol), was added to a solution of 0.65 g (2 mmol) of **9** in 10 mL of dimethylformamide cooled to −30 °C. After stirring under nitrogen for 10 min, 0.2 mL of methyl chloroformate was added in one portion at −30 °C. When the reaction mixture had warmed to 0 °C it was partitioned between methylene chloride and saturated sodium bicarbonate solution. The methylene chloride layer was diluted with benzene, washed with bicarbonate solution and water, dried, and evaporated. The residue was chromatographed over 20 g of silica gel using ethyl acetate. Crystallization of the combined clean fractions of products from ether yielded 0.13 g (17%) of colorless crystals with mp 203–205 °C. The analytical sample was recrystallized from ethyl acetate/hexane: UV λ_{max} 220 (ϵ 32 000), infl 240 (21 200), infl 300 nm (1600); IR (KBr) 1750 cm^{-1} (COOMe); NMR ($CDCl_3$) δ 2.56 (s, 3, CH_3), 4.0 (s, 3, $COOCH_3$), 4.9 (s, 1, C_4-H), 6.8–8.0 (m, 8, aromatic H, C_3-H).

Anal. Calcd for $C_{20}H_{15}ClFN_3O_2$: C, 62.59; H, 3.94; N, 10.95. Found: C, 62.63; H, 3.92; N, 10.78.

5-Aminomethyl-1-[4-chloro-2-(2-fluorobenzoyl)phenyl]-2-methylimidazole Dihydrochloride (25). A solution of 25 g of **9** in 50 mL of water and 50 mL of concentrated hydrochloric acid was allowed to stand at room temperature for 3 h. Following the addition of 250 mL of 2-propanol, the mixture was evaporated partially under reduced pressure without heating. An additional 200 mL of 2-propanol was added and partial evaporation was resumed. The precipitated crystals were collected and washed well with 2-propanol and ether to yield 31.7 g (98%) of product with mp 302–307 °C (dec).

The analytical sample was recrystallized from methanol/2-propanol without heating: UV (0.1 N HCl) λ_{max} sh 215 (ϵ 26 700), 258 (12 000), infl 290 (4700); IR (KBr) 1650 cm^{-1} (CO).

Anal. Calcd for $C_{18}H_{15}ClFN_3O$·2HCl: C, 51.88; H, 4.11; N, 10.08. Found: C, 52.06; H, 4.13; N, 10.21.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 5-Oxide (26). A mixture of 9.75 g (0.03 mol) of **9**, 200 mL of methylene chloride, and 12 g (0.07 mol) of *m*-chloroperbenzoic acid was stirred for 1.5 h. The solution was then extracted with 3 × 150 mL of 1 N hydrochloric acid. The extracts were washed with ether, made alkaline with ammonia, and extracted with methylene chloride. The methylene chloride extracts were dried and evaporated, and the residue was crystallized from ethyl acetate to leave 4 g of product which was further purified by chromatography over 100 g of silica gel using 5% (v/v) ethanol in methylene chloride. The clean fractions were combined and evaporated. Crystallization of the residue from ethyl acetate/ether yielded 3.4 g (33%) of colorless crystals with mp 245–246 °C (dec): NMR (Me_2SO-d) δ 2.53 (s, 3, CH_3), 4.95 (d, 1) and 5.28 (d, 1) (AB system, J = 14 Hz, C_4-H), 6.8–8.0 (m, 8, aromatic H and C_3-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3O$: C, 63.26; H, 3.83; N, 12.30. Found: C, 63.35; H, 4.11; N, 12.22.

4-Acetoxy-8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (27). A solution of 4 g of **26** in 100 mL of acetic anhydride was heated on the steam bath for 24 h. The reagent was evaporated under reduced pressure, at the end azeotropically with xylene. The residue was chromatographed over 80 g of silica gel using 20% (v/v) methylene chloride in ethyl acetate. Crystallization of the clean fractions from methylene chloride/ether yielded 1.4 g of colorless crystals, mp 201–202 °C. A second crop (1.5 g) of contaminated product was recovered from other fractions to yield a total of 2.9 g (64.5%).

Anal. Calcd for $C_{20}H_{15}ClFN_3O_2$: C, 62.42; H, 4.19; N, 10.92. Found: C, 62.69; H, 3.96; N, 10.87.

8-Chloro-6-(2-fluorophenyl)-4-hydroxy-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (28). Compound **27**, 0.5 g (1.3 mmol), was added to 40 mL of methanol containing 4 mmol of sodium methoxide. After stirring under nitrogen for 0.5 h at room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in water and the solution was acidified with acetic acid. The precipitated crystals were collected and dissolved in methylene chloride. The solution was dried and evaporated, and the residue was crystallized from methylene chloride/ether to yield 0.4 g (90%) of colorless crystals with mp 185–186 °C: UV λ_{max} sh 220 (ϵ 34 800), infl 241 (21 200), infl 260 (10 600), infl 305 nm (1500); NMR (Me_2SO-*d*) δ 2.47 (s, 3, CH_3), 5.6 (br s, 1, C_4-H), 6.8–8.0 ppm (m, 9, aromatic H, C_3-H, OH).

Anal. Calcd for $C_{18}H_{13}ClFN_3O$: C, 63.26; H, 3.83; N, 12.29. Found: C, 63.04; H, 3.73; N, 12.01.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 2-Oxide (29) and 8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 2,5-Dioxide (34). A mixture of 9.75 g (0.03 mol) of **9**, 18 g (0.105 mol) of *m*-chloroperbenzoic acid, and 200 mL of methylene chloride was stirred at room temperature overnight. After dilution with 500 mL of ether, the reaction mixture was extracted two times with 100 mL of 2 N hydrochloric acid and two times with 100 mL of 1 N hydrochloric acid. The extracts were washed with ether, made alkaline with ammonia, and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from ethanol gave 2.2 g of the 5-oxide **26**. The mother liquor was saved for chromatography. The aqueous phase was evaporated under reduced pressure to dryness. The residue was washed out well with methylene chloride containing 20% (v/v) ethanol. The combined washings were evaporated to leave 1.5 g of oxide mixture which was chromatographed together with the material from the evaporated mother liquor above over 65 g of silica gel using first 20% (v/v) ethanol in methylene chloride to elute an additional 1.0 g of the 5-oxide **26** for a total of 3.2 g (31%). The solvent mixture methanol–methylene chloride (3:7) then eluted the 2-oxide **29** which was crystallized from ethyl acetate to give 0.26 g (2.5%) of crystals with mp 179–181 °C (dec), after recrystallization from ethyl acetate/methanol; UV λ_{max} 227 (ϵ 34 400), infl 245 (30 100), infl 270 (12 900), infl 315 nm (2750); NMR ($CDCl_3$) δ 2.67 (s, 3, CH_3), 4.05 (d, 1) and 5.1 (d, 1) (AB system, J = 13 Hz, C_4-H), 6.8–7.8 ppm (m, 8, aromatic H, C_3-H).

The 2,5-dioxide **34** was obtained from the later fractions and was crystallized from ethyl acetate to give 1.2 g (11%) of off-white crystals with mp 225–230 °C (dec). The analytical sample was recrystallized from methanol/ethyl acetate: UV λ_{max} 219 (ϵ 26 700), infl 241 (17 700), 267 (24 900), sh 308 nm (10 700); NMR (Me_2SO-*d*) δ 2.67 (s, 3, CH_3), 5.0 (s, 2, C_4-H), 6.8–7.8 ppm (m, 8, aromatic H and C_3-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3O_2$: C, 60.43; H, 3.55; N, 11.75. Found: C, 60.37; H, 3.61; N, 11.87.

1-Acetoxymethyl-8-chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 5-Oxide (31). A solution of 1 g (2.5 mmol) of **34** in 10 mL of acetic anhydride was heated on the steam bath for 15 min. The reagent was evaporated under reduced pressure and the residue was crystallized from ethyl acetate/ether to yield 0.9 g (80%) of crystals with mp 203–205 °C. For analysis it was recrystallized from ethyl acetate: UV λ_{max} 216 (ϵ 26 500), infl 230 (24 600), infl 257 (17 000), 297 nm (10 700); IR ($CHCl_3$) 1745 cm^{-1} (OCO); NMR ($CDCl_3$) δ 2.1 (s, 3, $COCH_3$), 5.08 (d, 1) and 5.61 (d, 1) (AB system, J = 13.5 Hz, $-CH_2O$), 5.13 (s, 2, C_4-H), 6.8–7.8 ppm (m, 8, aromatic H and C_3-H).

Anal. Calcd for $C_{20}H_{15}ClFN_3O_3$: C, 60.09; H, 3.78; N, 10.51. Found: C, 59.97; H, 3.71; N, 10.59.

1-Acetoxymethyl-8-chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (30). A mixture of 1 g (2.5 mmol) of **31**, 30 mL of methylene chloride, and 3 mL of phosphorus trichloride was allowed to sit at room temperature for 24 h. After evaporation under reduced pressure, the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ethyl acetate/hexane gave 0.75 g (78%) of colorless product with mp 151–152 °C. For analysis it was recrystallized from ethyl acetate/ether: UV λ_{max} 215 (ϵ 40 600), infl 241 (22 750), infl 305 nm (1300); IR ($CHCl_3$) 1745 cm^{-1} (OCO); NMR ($CDCl_3$) δ 2.08 (s, 3, $COCH_3$), 4.1 (d, 1) and 5.23 (d, 1) (AB system, J = 13 Hz, C_4-H), 5.03 (d, 1) and 5.65 (d, 1) (AB system, J = 13.5 Hz, $-CH_2O$), 6.8–7.8 ppm (m, 8, aromatic H, and C_3-H).

Anal. Calcd for $C_{20}H_{15}ClFN_3O_2$: C, 62.59; H, 3.94; N, 10.95. Found: C, 62.70; H, 3.83; N, 11.17.

8-Chloro-6-(2-fluorophenyl)-1-hydroxymethyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (32). Sodium methoxide, 0.3 g, was added to a solution of 1 g (2.6 mmol) of **30** in 20 mL of methanol. After standing for 10 min at room temperature, the separated crystals were collected, washed with aqueous methanol, methanol, and ether to yield 0.8 g (89%) of colorless product. The analytical sample was recrystallized from methylene chloride/ethanol: mp 258–260 °C; UV λ_{max} sh 215 (ϵ 33 100), infl 240 (25 000), infl 305 nm (1600); NMR (Me_2SO-*d*) δ 4.05 (d, 1) and 5.1 (d, 1) (AB system, J = 13 Hz, C_4-H), 4.33 (q, 1, J_{AB} = 13 Hz, J_{AX} = 6 Hz, $-CH_2O$), 4.76 (q, 1, J_{AB} = 13 Hz, J_{AX} = 5 Hz, $-CH_2O$), 5.66 (t, 1, J = 5.5 Hz, OH), 6.95 (s, 1, C_3-H), 7.0–7.8 (m, 6, aromatic H), 8.1 ppm (d, 1, J = 8 Hz, C_{10}-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3O$: C, 63.26; H, 3.83; N, 12.30. Found: C, 63.10; H, 3.70; N, 12.47.

8-Chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-1-carboxaldehyde (33). A mixture of 0.2 g (0.58 mmol) of **32**, 20 mL of methylene chloride, and 1 g of activated manganese dioxide was stirred at room temperature for 2 h. The manganese dioxide was removed by filtration over celite and the filtrate was evaporated. Crystallization of the residue from methylene chloride/ethyl acetate/hexane gave 90 mg (45%) of colorless crystals with mp 182–183 °C: UV λ_{max} infl 215 (ϵ 36 200), infl 250 (15 200), 294 nm (11 300); IR (KBr) 1690 cm^{-1} (CHO); NMR ($CDCl_3$) δ 4.0 (d, 1) and 5.21 (d, 1) (AB system, J = 13 Hz, C_4-H), 6.8–7.8 (m, 8, aromatic H, C_3-H), 9.9 ppm (s, 1, CHO).

Anal. Calcd for $C_{18}H_{11}ClFN_3O$: C, 63.63; H, 3.26; N, 12.37. Found: C, 63.69; H, 3.36; N, 12.57.

4-Acetoxy-1-acetoxymethyl-8-chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (35). A solution of 1.5 g (4.18 mmol) of **34** in 50 mL of acetic anhydride was heated to reflux for 1.5 h. The reagent was evaporated under reduced pressure, at the end azeotropically with toluene. The residue was filtered over a pad of silica gel using methylene chloride/ether. The filtrate was evaporated and crystallized from ethyl acetate/ether with seeding. Seeds were obtained by chromatography over a 40-fold amount of silica gel using benzene/ether, 1:1. The separated colorless crystals (0.65 g or 31.7%) were collected and recrystallized from ethyl acetate/hexane: mp 175–177 and 184–187 °C; NMR ($CDCl_3$) δ 2.05 (s, 3, $COCH_3$), 2.32 (s, 3, $COCH_3$), 4.96 (d, 1) and 5.56 (d, 1) (AB system, J = 13.5 Hz, $-CH_2O$), 6.66 (s, 1, C_4-H), 6.8–7.9 ppm (m, 8, aromatic H, and C_3-H).

Anal. Calcd for $C_{22}H_{17}ClFN_3O_4$: C, 59.80; H, 3.88; N, 9.51. Found: C, 59.82; H, 4.05; N, 9.40.

8-Chloro-6-(2-fluorophenyl)-4-hydroxy-1-hydroxymethyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (36). Sodium hydroxide, 10 mL, 1 N, was added to a solution of 0.65 g (1.47 mmol) of **35** in 30 mL of methanol. The mixture was heated on the steam bath for 15 min and was then partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from methylene chloride/ethanol yielded 0.39 g (74%) of colorless crystals. The analytical sample was recrystallized from tetrahydrofuran/ethanol: mp 238–240 °C; UV λ_{max} 216 (ϵ 36 600), sh 240 (23 500), sh 305 nm (1300); NMR (Me_2SO-*d*) δ 4.29 (q, 1, J_{AB} = 13 Hz, J_{AX} = 6 Hz, $-CH_2O$), 4.70 (q, 1, J_{AB} = 13 Hz, J_{AX} = 5.5 Hz, $-CH_2O$), 5.55 (d, 1, J = 6.5 Hz, C_4-H), 5.66 (t, 1, J = 5.5 Hz, $-CH_2OH$), 6.84 (d, 1, J = 6.5 Hz, $-OH$), 6.92 (s, 1, C_3-H), 7.0–7.8 (m, 6, aromatic H), 8.10 ppm (d, 1, J = 8 Hz, C_{10}-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3O_2$: C, 60.43; H, 3.66; N, 11.75. Found: C, 60.37; H, 3.85; N, 11.66.

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Registry No.—**1b**, 59467-61-7; **2a**, 51715-17-4; **2b**, 59467-62-8; **3a**, 59467-81-1; **3b**, 59467-63-9; **3c**, 59470-03-0; **3d**, 60656-76-0; **4**, 59467-87-7; **5**, 59467-64-0; **5** maleate, 59469-29-3; **6**, 59467-68-4; **7**, 59469-30-6; **8**, 59467-69-5; **9**, 59467-70-8; **9** maleate, 64740-70-1; **10**, 59467-90-2; **11**, 64740-71-2; (±)-**12**, 64740-72-3; (−)-**12**, 59468-15-4; (+)-**12**, 59468-18-7; (±)-12·2HCl, 64740-73-4; (−)-**12** *l*-tartrate, 63151-05-3; (−)-**12**, *O,O'*-dibenzoyl-*d*-tartrate, 64740-74-5; (+)-**12** *d*-tartrate, 63151-04-2; (+)-**12** *O,O'*-dibenzoyl-*d*-tartarate, 64740-75-6; **13**, 64740-58-5; **15a**, 64740-59-6; **16**, 64740-60-9; **17a**, 64740-61-0; **17b**, 64740-62-1; **18**, 64740-63-2; **19**, 64740-64-3; **20**, 59468-92-7; **21**,

59469-74-8; **23**, 64740-65-4; **24**, 64740-66-5; **25**, 59468-73-4; **26**, 59468-83-6; **27**, 59468-84-7; **28**, 5968-85-8; **29**, 59468-86-9; **30**, 59468-89-2; **31**, 59468-88-1; **32**, 59468-90-5; **33**, 59468-91-6; **34**, 59468-87-0; **35**, 64740-67-6; **36**, 64740-68-7; 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one, 2886-65-9; methylamine, 74-89-5; sodium nitrite, 7632-00-0; nitromethane, 75-52-5; nitroethane, 79-24-3; acetic anhydride, 108-24-7; triethylorthoacetate, 78-39-7; 2-(1-aminoethyl)-7-chloro-2,3-dihydra-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine, 59467-88-8; 2-(1-aminoethyl)-7-chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine dimalate, 64740-69-8; *O,O'*-dibenzoyl-*d*-tartaric acid, 2743-38-6; *l*-tartaric acid, 87-69-4; *d*-tartaric acid, 147-71-7; diazomethane, 334-88-3; *N*-bromosuccinimide, 128-08-5; methyl iodide, 74-88-4; methyl chloroformate, 79-22-1.

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Photochemistry of 2-Picolines in Alkaline Media. Intermediacy of Dewar Pyridines and Their Methides

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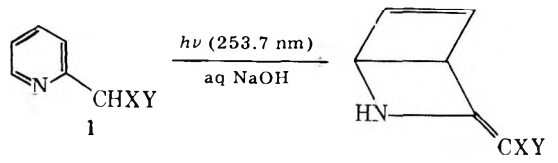
Photolysis of substituted 2-picoline (**1**) at 253.7 nm in aqueous alkali gives quantitatively 3-substituted methylene-2-azabicyclo[2.2.0]hex-5-ene (**2**). Hydration of **2** in the dark with neutral H_2O affords a product having absorption maxima (380 nm from **2a** and 383 nm from **2b**) which are the same as those of the product from direct photohydration of **1** in neutral aqueous solution. Independent irradiation of **2** with a high pressure Hg lamp in diethyl ether affords its isomer, ortho-substituted aniline (**3**). Thermolysis of **2** in refluxing *t*-BuOH gives **1** inefficiently, but not **3**. The results show that photoisomerization of **1** to **3** proceeds by means of a two-photon process via a Dewar pyridine analogue as its methide (**2**).

As reported in a preliminary communication,[1] the 2-picolines **1** can be photoisomerized to ortho-substituted anilines. A Dewar pyridine intermediate was postulated, but no decisive evidence for this was available. We have now isolated an intermediate (λ_{max} 284 nm from **1a** and 274 nm from **1b**) which collapses to the aniline on further irradiation at about 280 nm.

Irradiation of Substituted 2-Picolines (1) in Alkaline Media. Irradiation of alkyl 2-pyridylacetate (**1a**) (R = Me or Et) in aqueous NaOH[2] (pH 10–12) with 253.7-nm light afforded a single photoproduct (**2a**) with λ_{max} of 284 nm in a



(1)

1 **2**

a, X = H; Y = CO_2R (R = Me or Et)
b, X = H; Y = CN
c, X = Me; Y = CO_2Et

yield of 40% for R = Et. The 2-aza-3-alkoxycarbonylmethylenebicyclo[2.2.0]hex-5-ene structure (**2a**) is based on spectral evidence.

The molecular ion, 165, indicates that it is an isomer of **1a** (R = Et). The NMR spectrum shows five multiplets of equal area at δ 3.70, 3.92, 4.80, 6.37, and 6.43 which correspond to the protons at positions 7, 4, 1, 6, and 5, respectively.[4] It exhibits conjugated carbonyl at 1680 cm^{-1} in its infrared absorption region. Similarly, in the case of **2b**, the NMR spectra indicated the structure of **2b** (see Experimental Section). Moreover, a cyano group at 2180 cm^{-1} similarly indicates its conjugation with an enamine moiety.[5] 2-Alkoxycarbonyl- and 2-cyanoenamines are known to absorb at 270–290 nm with extinction coefficients in the magnitude of ~10 000[6,7] the order similar to 284 nm (ϵ 14 000) and 274 nm (ϵ 10 400) for **1a** (R = Me) and **1b**, respectively.

The NMR assignment for **2a** and **2b** was confirmed using **2c**, which was formed from **1c** and has a methyl at position 7. The NMR of **2c** indicates methyl protons at δ 1.64 with no signal of the lowest field at position 7. As reported with parent *cis*-β-aminoacrylonitriles, signals of the α proton and α methyl appear at δ 3.88 and 1.66, respectively,[7c] which are comparable with those of **2**.

On standing under air at room temperature, **2a** and **2b** were gradually converted into tarry materials which cannot be redissolved in diethyl ether, but **2a** and **2b** are stable in diethyl ether in the dark.

Dark Reaction of 3-Substituted Methylene-2-azabicyclo[2.2.0]hex-5-enes (2). On dissolution of **2a** (R = Me) in neutral water its UV peak migrates from 284 to 380 nm with an isosbestic point at 307 nm (Figure 1). Likewise, the peak of **2b** shifts to 383 nm with an isosbestic point at 295 nm on dissolution in water (Figure 1). A similar trend was also observed with hydration of **2c** (292 nm → 384 nm with an isosbestic point at 315 nm). Their first-order rate constants of decomposition at 15 °C are 1.7×10^{-2} min^{-1} for **2a** (R = Me), 0.98×10^{-2} min^{-1} for **2b**, and 0.73×10^{-2} min^{-1} for **2c**. Their

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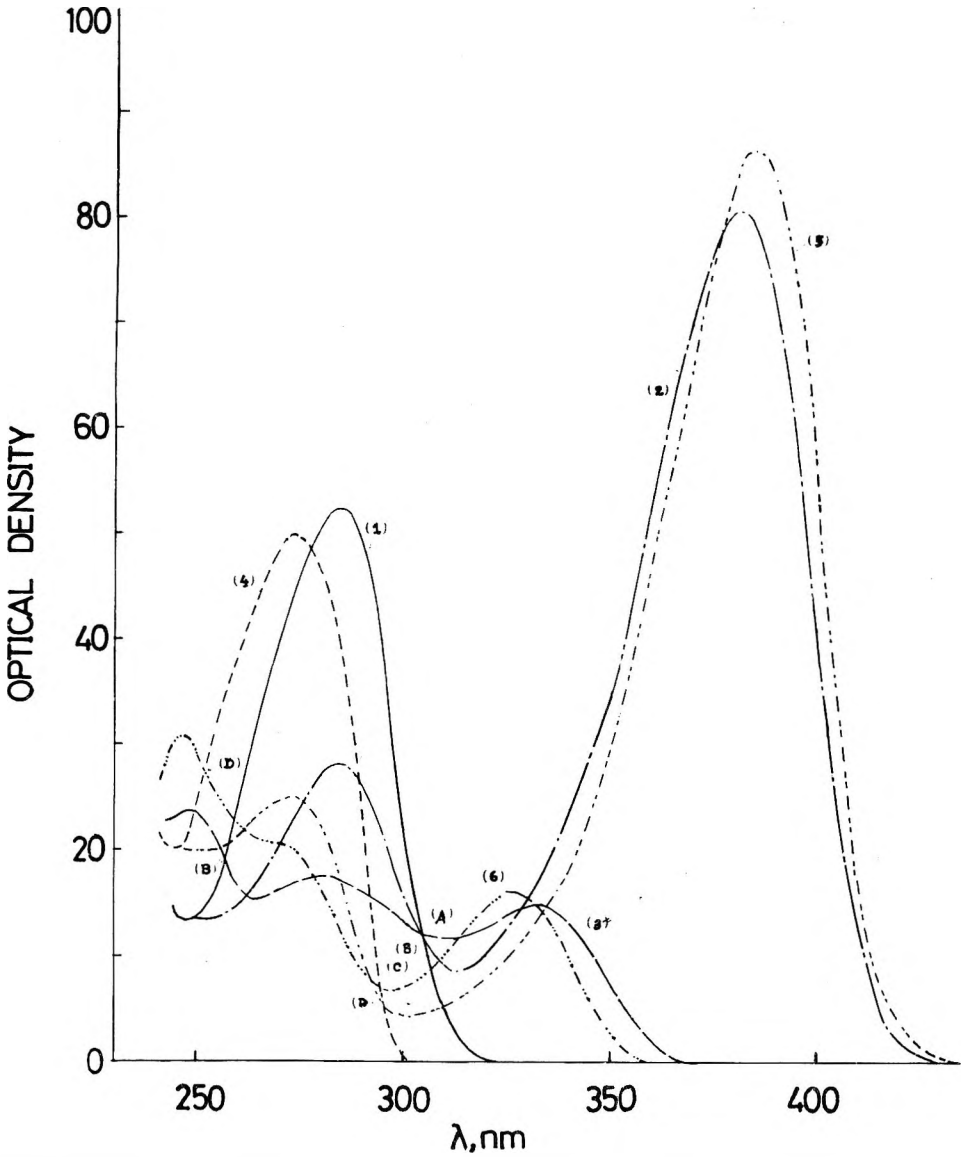


Figure 1. Ultraviolet absorption spectra of 2's: (1) (—) **2a**, 3.8×10^{-5} M in H_2O under air; (2) (– · –) after standing of **2a** in H_2O in the dark for 21 min at 15 °C; (3) (– –) after irradiation of **2a** for 35 min in diethyl ether; (4) (- - -) **2b**, 4.8×10^{-5} M in H_2O under air; (5) (– · · –) after standing of **2b** in H_2O in the dark for 24 min at 15 °C; (6) (– · · · –), after irradiation of **2b** for 40 min in diethyl ether. Isosbestic points (nm): (A) 307; (B) 258 and 304; (C) 295; (D) 254 and 295.

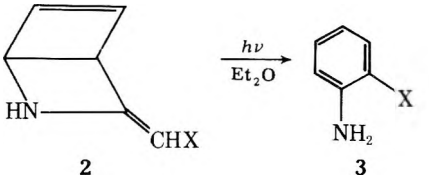
hydration was instantaneous upon acidification with 0.1 N HCl or 0.1 N acetic acid.

Independently, direct photohydration of **1** in aqueous solution gave products with peaks (380 nm from **1a** and 383 nm from **1b**) identical to those of the hydration products of **2** in the dark. Extraction of the hydrates from dilute aqueous solution was difficult, since they were very soluble in water. Our attempts to isolate them either as their hydrogenated products or as their bromine adducts failed.

Nevertheless, the presence of an aldehyde group in the hydration products is indicated by oxidation with Tollens reagent. Furthermore, the hydrates could be recyclized almost quantitatively (e.g., **1a** was obtained from the hydrate in a yield of 97% on standing in an aqueous solution for 4 days). These data show that the hydrates have open chain structures formed by the hydrolytic cleavage of the N–C bond. As is well known, pyridines are photohydrated via a Dewar pyridine to yield ω-aminopentadienals[3,8] having a characteristic UV peak at 370–390 nm which is in accord with our hydration products.

On the other hand, **2a** (R = Me) was gradually but not quantitatively restored to **1a** on refuxing in *tert*-butyl alcohol of **2a** for 46 h. The restoration of **2b** to **1b** was less quantitative despite almost complete decomposition of **2b** within 16 h to unknown products. Product **2c** is much more unstable than **2a** and **2b** and reverts to **1c** even in diethyl ether in a refrigerator; thus **2c** was not obtained free of **1c**.

Photochemical Reaction of 3-Substituted Methylene-2-azabicyclo[2.2.0]hex-5-enes (2). Irradiation of **2a** (R = Me) in diethyl ether with a high pressure Hg lamp gave **3a**, which showed a stoichiometric spectral change from 284



(2)

2 3

a, X = CO_2R (R = Me or Et)
b, X = CN

nm to 248 and 337 nm with isosbestic points at 258 and 304 nm (Figure 1). Analogous photolysis of **2b** results in the quantitative isomerization to anthranilonitrile (**3b**). However, photolysis of **2c** leads to no formation of any volatile materials.

Mechanism. The photoreaction of 1 to 3 proceeds by a two-photon process via a Dewar pyridine tautomer (2). The formation of 2 depends on the pH of the solution. The rate of formation of **2a** increases sharply at a pH of 7–11 and reaches a maximum at pH 11–12 at an equimolar mixture of **1a** and KOH. At higher pH, a gradual decrease of the formation rate of **2a** is observed, which may be caused, at least in part, by hydrolysis of the CO_2R group. The yield of **2a** was much less in acidic solution, where the hydrate is predominant. This fact reflects the subsequent hydration of **2a** once formed under these conditions. Therefore, the tautomers are stable only under the appropriate conditions (pH 11–12).

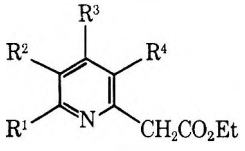
The photolysis of **1a** (R = Me) in diethyl ether at −20 to −30 °C exhibits an unaltered UV spectrum after being warmed up to room temperature, indicating quantitative reversion of **4a** to **1a**. However, the photolyzed mixture, on treatment with 1 N NaOH immediately after irradiation, contained **2a** (25%). Hence, the initial photoproduct would be a Dewar pyridine (4) which is then converted to 2 in alkaline solvent.

In imine–enamine equilibria of some vinyl amines, enamines are preferred to imines by changing solvent from nonpolar to polar.[9] Thus, the ratio of 2-phenylpropylidenemethylamine (imine) to the corresponding enamine varies from 72:28 in $CDCl_3$ to 32:68 in DMSO-d_6.[9b] Hence, **2** should be more stable than Dewar pyridines (4) in hydroxylic solvent.

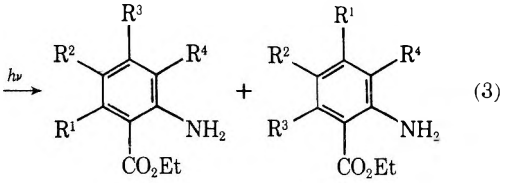
Nevertheless, addition of alkali to the system destabilizes 2 on UV irradiation. Decomposition of **2** occurred on UV irradiation at around 280 nm, irrespective of the presence and absence of alkali. In conclusion, the accumulation of **2** in alkali is attributable to the transparency of **2** toward 253.7-nm light, so that the tautomer **2** is unchanged, and at the same time alkali suppresses the further hydration of **2**.

The following reaction sequences (Scheme I) explain our observations for **1** → **3**.

Secondary transformation of **2** to **3** is a photochemically allowed [1,3] sigmatropic shift in a concerted manner, but the labeling studies in the pyridine ring by methyl (**6a–d**)[10] or



6



(3)

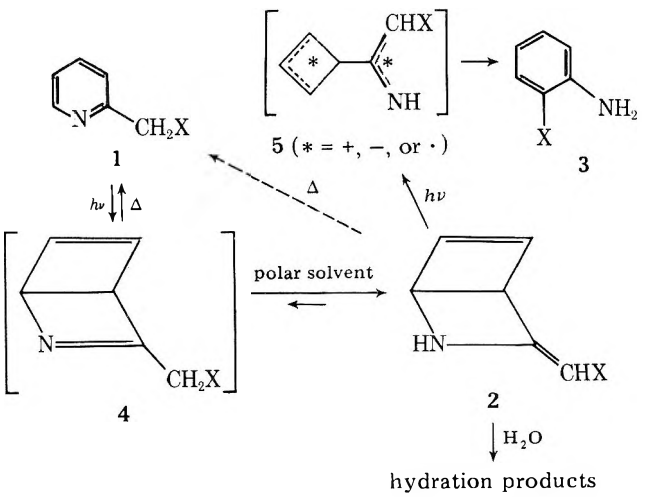
7 **8**

a, $R^1 = R^2 = R^3 = H$; $R^4 = Me$
b, $R^1 = R^2 = R^4 = H$; $R^3 = Me$
c, $R^1 = R^3 = R^4 = H$; $R^2 = Me$
d, $R^2 = R^3 = R^4 = H$; $R^1 = Me$
e, $R^2 = R^3 = R^4 = H$; $R^1 = D$

deuterium (**6e**)[11] indicated that significant scrambling of 4 and 6 substituents occurs in the product anthranilates (**7a–e, 8a–e**).

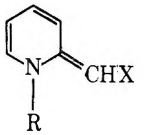
Among these 2-pyridylacetates (**6**), **6e** labeled with deuterium at R^1 is most suitable for following the skeletal reorganization because of the least substituent effect. Photolysis of **6e** gave equal amounts of **7e** and **8e**, which completely excludes the concerted mechanism. Hence, intervention of ring-cleaved intermediate **5** is more favorable.

Scheme I



(λ_{max} 284 nm for 2a; X = CO_2R, R = Me or Et)
(λ_{max} 274 nm for **2b**; X = CN)

Finally, it is of interest to note that 2 cannot be formed via 2-substituted methylene-1,2-dihydropyridine (**9a**, R = H), a tautomer of **1**, because the photolysis of *N*-methyl-2-



9a, R = H; X = CO_2Me or CN
b, R = Me; X = CO_2Et

ethoxycarbonylmethylene-1,2-dihydropyridine (**9b**) was found to give neither *N*-methylated **2a** nor ethyl *N*-methylanthranilate (i.e., *N*-methylated **3**).[12]

Experimental Section

The IR spectra were recorded by a Perkin-Elmer grating spectrophotometer, Model 337, the UV spectra by a Hitachi spectrophotometer, Model 124, the NMR spectra by a Hitachi NMR instrument, Model R-24B, and mass spectra either by a Shimadzu GC-MS Model 7000, or by a direct system technique using a Mattauchi-Herzog type (JMS-OSG) mass spectrometer. The irradiation light was obtained from either a Halos HIL 30-W low-pressure Hg lamp (253.7 nm) or a HIP 300-W high-pressure Hg lamp.

Materials. 2-Picolines (1) were prepared as described in the literature.[10] ω,ω′-Dicyano-2-picoline was prepared by the known procedure.[13]

Photolysis of Ethyl 2-Pyridylacetate (1) in Alkaline Media. A 25-mM aqueous NaOH solution (600 mL) of ethyl 2-pyridylacetate (**1a**) (0.243 g, 1.5 mmol) was irradiated at 253.7 nm for 4 h until the acetate (**1a**) was almost consumed. The reaction mixture was extracted into diethyl ether (20 mL × 3) and was condensed, after being dried on Na_2SO_4, to yield a pale-yellow oil (40% on the basis of starting **1a**). The isolated yield is lower compared to the spectroscopic one, presumably because of loss at the stage of extraction procedures. The oil was further purified by passing through a basic Al_2O_3 (Activity II–III, Merck) column using diethyl ether as an eluant (each fraction 5 mL). Fractions 9–11 were **2a** (R = Et), i.e., 2-aza-3-ethoxycarbonylmethylenebicyclo[2.2.0]hex-5-ene (90 mg). Its spectral characteristics were: mass spectrum *m/e* (rel intensity) 165 (M^+) (30), 119 (52), 105 (33), 99 (12), 94 (65), 93 (83), 92 (64), 80 (25), 79 (47), 77 (53), 67 (30), 66 (100), 65 (43), 58 (65), 54 (30), 53 (53), 52 (83), 51 (95), and 50 (17); IR ν_{max} (liquid film) 3350, 1680, 1290, and 1620 cm^{-1}; UV λ_{max} (MeOH) 284 nm (ϵ 14 000); NMR (δ in CCl_4) 6.43 (m, 1 H, H_5, $J_{4,5} \sim J_{5,6} \sim$ 2–3 Hz), 6.37 (m, 1 H, H_6, $J_{1,6} \sim$ 2–3 Hz), 4.80 (q, 1 H, $J_{1,4} \sim$ 2.5–3 Hz), 4.28 (q, 2 H, J = 7 Hz), 3.92 (m, 1 H, H_4), 3.70 (s, 1 H, H_7), 2.88 (bs, 1 H, NH), and 1.28 (t, 3 H, J = 7 Hz).

Photolysis of 2-Pyridylacetonitrile (1b) in Alkaline Media. A 25-mM aqueous NaOH solution (600 mL) of 2-pyridylacetonitrile (**1b**) (0.259 g, 2.2 mmol) was irradiated (Halos HIL 30-W) for 4 h. The mixture was contaminated by a small amount of anthranilonitrile (**2b**)

and **1b**, which were then eliminated by passing the mixture through an Al_2O_3 (Activity II–III) column using diethyl ether (each fraction 5 mL): fractions 3–5 (**3b**, trace), fraction 6 (**2b**, 122 mg, 47%), and fractions 7–14 (**1b** + **2b**). The structure of **2b** was characterized by the spectral data: mass spectrum *m/e* (rel intensity) 118 (M^+) (100), 91 (69), 78 (76), 67 (10), 66 (18), 65 (23), 64 (58), 63 (29), 53 (13), 52 (45), 51 (55), and 50 (34); IR ν_{max} (liquid film) 3350, 2180, 1270, and 1630 cm^{-1}; UV λ_{max} (MeOH) 274 nm (ϵ 10 400); NMR (δ in CCl_4) 6.45 (m, 1 H, H_5, $J_{4,5} \sim J_{5,6} \sim$ 2–3 Hz), 6.40 (m, 1 H, H_6, $J_{1,6} \sim$ 2 Hz), 4.72 (q, 1 H, H_1, $J_{1,4} \sim$ 3 Hz), 3.86 (m, 1 H, H_4), 3.86 (s, 1 H, H_7), and 2.52 (bs, 1 H, NH).

Photolysis of Ethyl 2-(2-Pyridyl)propionate (1c) in Alkaline Media. A 25-mM aqueous NaOH solution (600 mL) of ethyl 2-(2-pyridyl)propionate (**1c**) (0.4 g) was irradiated at 253.7 nm for 5 h. The reaction mixture was extracted into diethyl ether and was condensed, after being dried on Na_2SO_4, to yield an oil, which was passed through a basic Al_2O_3 (Activity II–III, Merck) column using diethyl ether as an eluant (each fraction 5 mL). Fractions 6–7 mainly involve **2c** (R = Et) (50 mg, 12.5%). Further purification was done with a column (Al_2O_3) in order to eliminate a small amount of **1c** from the contaminated **2c**: UV λ_{max} (MeOH) 292 nm; NMR (CCl_4) δ 6.53 (m, 1 H, H_5), 6.33 (m, 1 H, H_6), 4.64 (m, 1 H, H_1), 4.26 (m, 1 H, H_4), 4.00 (q, 2 H, CH_2), 1.64 (s, 3 H, Me), 1.20 (t, 3 H, Me), 2.2 (bs, 1 H, NH).

Hydration of Photoproducts (2). Addition of CO_2-free H_2O to **2** (ca. 10^{-4} M) at 15 °C causes the change from λ_{max} of **2** (284 nm for **2a**, 274 nm for **2b**, and 292 nm for **2c**) to λ_{max} of their hydration products (380, 383, and 384 nm, respectively). Their first-order rate constants of decomposition were measured by spectrophotometry to 1.7×10^{-2} min^{-1} for **2a** (R = Me), 0.98×10^{-2} min^{-1} for **2b**, and 0.73×10^{-2} min^{-1} for **2c**.

Thermolysis of Photoproducts (2). When a 8.1×10^{-5} M *t*-BuOH solution of **2a** was heated at 100 °C in an oil bath under air, the spectrum of **2a** was gradually restored to **1a**. On refluxing for 46 h, the starting **2a** disappeared and formation of **1a** was observed on the basis of UV and TLC (R_f 0.1 with benzene). But in the case of **2b**, restoration of **1b** was less quantitative, though its decomposition was almost complete within 16 h. The main product from **2b** was not identified.

Photolysis of Photoproducts (2). The photolysis of a 10^{-4} M diethyl ether solution of **2a** (R = Me) by a high-pressure Hg lamp (HIP 300-W) afforded methyl anthranilate (**3a**) quantitatively. Stoichiometric spectral change was observed from 284 nm to 248 and 337 nm with isosbestic points at 258 and 304 nm. Irradiation of **2b** in diethyl ether results in the formation of **3b** in view of spectrophotometry. The formation of **3** was further confirmed by TLC with benzene as an eluant (R_f 0.4 for **3a** and 0.45 for **3b**).

Preparative photolysis of **2a** (12.2 mg) in diethyl ether (100 mL) afforded only a single product (**3a**) (>90%).

Registry No.—**1a** (R = Me), 1658-42-0; **1a** (R = Et), 2739-98-2; **1b**, 2739-97-1; **1c**, 5552-85-2; **2a** (R = Et), 64741-21-5; **2a** (R = Et), 64741-24-8; **2b**, 64741-25-9; **2c**, 64741-26-0; **3a** (R = Et), 87-25-2; **3b**, 1885-29-6.

References and Notes

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(2) Photolysis of the acetate (**1a**) also results in the formation of a single photoproduct (**2a**) in the presence of a reducing agent, $NaBH_4$, where pyridine was transformed to 2-azabicyclo[2.2.0]hex-5-ene through hydrogenation of Dewar pyridine,[3] but there was no formation of the 1,2-dihydro analogue of **4**.
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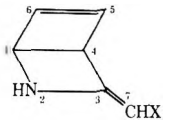
(4) The numbering system and coupling constants for the photoproduct (**2**) are as follows:



2

$J_{4,5} \sim J_{5,6} \sim J_{1,4} \sim J_{1,6} \sim$ 2–3 Hz

(5) The most significant feature in the IR spectra of the β-cyanovinylamine is the lowering of the C≡N band to 2200 cm^{-1} compared to the band with simple α,β-unsaturated nitrile (2230 cm^{-1}). This displacement is associated with a reduction in the triple bond character of the C≡N group and may be attributed to the contribution of the ionic resonance structure.[6] NCH=CHC≡N ⟷ $^+$N=CHCH=C=N$^-$.
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(11) K. Takagi and Y. Ogata, *J. Chem. Soc., Perkin Trans. 2*, in press.
(12) K. Takagi and Y. Ogata, *J. Chem. Soc., Perkin Trans. 2*, 1410 (1977).
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Chemistry of Heterocyclic Compounds. 27. An Improved Preparation of Pyridyldiphenylphosphines

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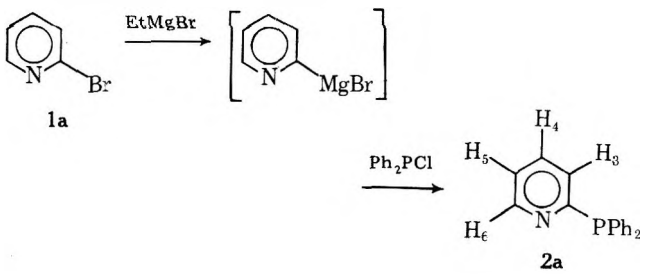
Presently, the preparation of pyridyldiphenylphosphine ligands is via the treatment of lithiopyridines with an appropriate halophosphine. In order to circumvent the major drawbacks of that procedure, i.e., low yields and the formation of unwanted pyridine side products, lithium diphenylphosphide has herein been shown to react smoothly with halopyridines to generate pyridyldiphenylphosphines. The general procedures for the synthesis of both the pyridylphosphines and the corresponding P→O have been described.

In 1948, Mann and Watson[1] reported a series of tertiary 2-pyridylamines, phosphines, and arsines synthesized during a chemotherapeutic investigation conducted toward the later half of World War II. In that classic work, the reaction of 2-pyridylmagnesium bromide[2,3a] on chlorodiphenylphosphine was used to prepare (20.4%) 2-pyridyldiphenylphosphine (**2a**). Similarly, other 2-pyridylphosphines (and arsines) were prepared via action of the same organometallic reagent on an appropriate chloride.[1] This basic procedure has been utilized by numerous researchers desirous of pyridylphosphines.[3]



1a **2a**

In 1955, it was reported that both 2-chloro- and 2-bromopyridine failed to react when subjected to either the Arbuzov or Michaelis–Becker reaction conditions.[4] Even though 2-halopyridines are relatively unreactive[5] toward nucleophilic

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Table I. Pyridylphosphines Prepared by Reaction of $LiPPh_2$ with Halopyridines[a]

Reactant	Registry no.	Phosphine	Registry no.	Reaction temp, °C	Yield,[b] %	Mp, °C (solv)[c]	Phosphine oxide	Registry no.	Yield,[b] %	Mp, °C (solv)
1a	109-04-6	**2a**	37943-90-1	65	55	83–84[d] (petroleum ether)	**3a**	64741-30-6	85	109–110 (C_6H_{12})
1b	109-09-1	**2a**		65	50	83–84 (petroleum ether)				
1d	626-61-9	**2b**	54750-98-0	25	*e*	64–66[f] (hexane)	**3b**	54750-99-1	42[g]	149–150[h] (EtOAc)
1e	626-05-1	**2c**	64741-27-1	25	*e*	124–125[i] (hexane)	**3c**	64741-31-7	32[g]	229–230 (acetone)
1f	17228-64-7	**6**	64741-28-2	65	36	192–193 (EtOAc)	**7**	64741-32-8	80	206–207 (EtOAc)
1g	49669-22-9	**8**	64741-29-3	65	21	198–199 ($CHCl_3$)	**9**	64741-33-9	89	>300 ($CHCl_3$)

[a] Satisfactory analytical data (±0.4% for C, H, and N) were obtained for all compounds listed. [b] Yields are of isolated products. [c] Recrystallization solvent. [d] Lit.[1] mp 84–85 °C (aqueous methanol). [e] Phosphine undergoes facile air oxidation; isolation can be accomplished with difficulty under anaerobic conditions. (Also see ref 11.) [f] Lit.[11] mp 66–69 °C (hexane under a nitrogen atmosphere). [g] Isolated yield without isolating the intermediary phosphine. [h] Lit.[11] mp 153–155 °C. [i] Prepared (92%) from **3c** by reduction according to the procedure of Cremer and Chorrat;[15] see Experimental Section.

substitution, the recent statement[6] that pyridyl halides do not react with phosphorus nucleophiles seemed to overstate the results which were based on limited available data.[4a] Interestingly, however, 2-chloroquinoline did react with sodium dibutylphosphite at 140 °C in xylene to afford the desired ester, which was smoothly hydrolyzed to 2-quinolylphosphonic acid in 28.5% yield.[4a] In view of our reported synthesis of macrocycles possessing a pyridine subunit[7] via direct nucleophilic substitution under similar reaction conditions to that of Burger et al.,[4a] we herein report the facile synthesis of pyridyldiphenylphosphines via direct nucleophilic substitution of a pyridyl halide by lithium diphenylphosphide.

Results and Discussion

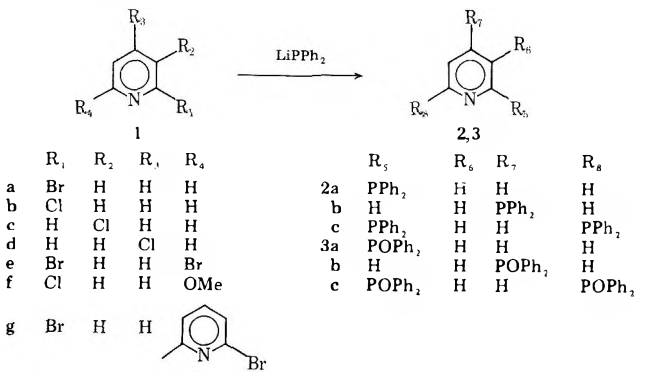
Lithium diphenylphosphide was conveniently prepared from chlorodiphenylphosphine and lithium metal in ethereal solvent.[8e] However, alternate procedures are available from either diphenylphosphine,[8a] prepared from chlorodiphenylphosphine upon treatment with lithium aluminum hydride,[9] with phenyllithium or triphenylphosphine,[8b,c] or diphenylphosphine[8d] with lithium in THF. The general ease of preparation, along with its enhanced nucleophilicity in substitution reactions, even of arylhalides,[8c] makes lithium diphenylphosphide an ideal reagent to attempt displacement of a pyridyl halide.

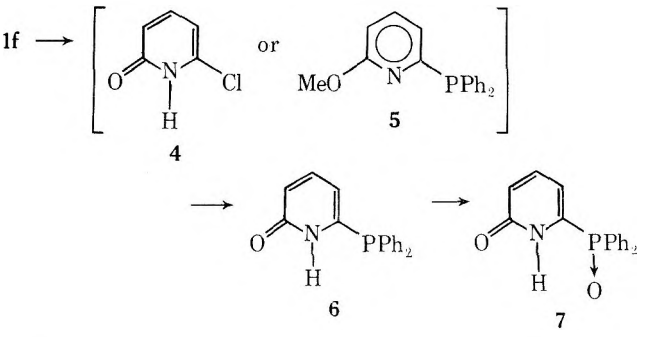
Table I summarizes the pyridylphosphines prepared by reaction of lithium diphenylphosphide with various halopyridines. No efforts were made to maximize the product yields. The reaction of lithium diphenylphosphide with 2-bromopyridine is presented in the Experimental Section as a typical procedure.[10] Although most pyridylphosphines can be isolated as the free phosphines, upon either prolonged exposure to air or mild oxidizing agents they were smoothly converted to the corresponding P oxides. Heteroaryl phosphines are normally difficult to isolate without minor oxide contaminants; e.g., phosphine **2b** can be isolated with difficulty under anaerobic conditions.[11] Phosphine oxides were easily prepared from the free phosphine via treatment with ethanolic hydrogen peroxide.[12] The degree of P oxide formation can be ascertained from the ^1H NMR spectral data in that the P→O causes a dramatic deshielding of the pyridyl hydrogens. The greatest effect of P→O formation is experienced by the 3-pyridyl hydrogen with a 0.8 to 0.9 ppm downfield shift, whereas, the other pyridyl hydrogens also show a measurable, but diminished, downfield shift. These observations are similar to those reported for tri-2-pyridylphosphine,[3c,e] its oxide,[3c,e] and selenide.[3e]

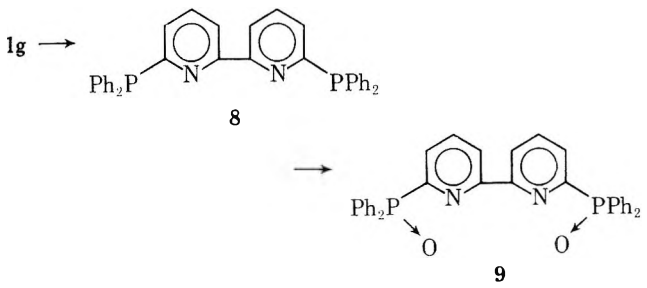
Reaction of 3-chloropyridine (**1c**) with lithium diphenylphosphide was attempted; however, only unreacted starting material was isolated. Although 3-halopyridine is generally resistant to nucleophilic substitution,[13] this result was unusual in light of the reactivity of this reagent toward simple aryl halides.[8c] Stronger phosphorus nucleophiles, e.g., $LiPEt_2$, or more rigorous conditions may be necessary to effect the displacement.

Treatment of **1f** with lithium diphenylphosphide afforded pyridone **6**. Two possible routes to **6** are possible: (1) displacement of the halide to afford **5** followed by demethylation or (2) demethylation to give **4**, which undergoes nucleophilic substitution. Similarly with nonheterocyclic ethers, Mann and Pragnell have reported the facile dealkylation of certain alkyl aryl ethers by diphenylphosphide ion.[14] Pyridone **6** was converted into the corresponding P oxide (**7**) by standard conditions.

6,6′-Dibromo-2,2′-bipyridyl (**1g**) was smoothly transformed into the bis(phosphine) **8**, subsequent oxidation with hydrogen peroxide generated the bis(phosphine oxide) **9** in 89% yield.







Conclusions

2- and 4-halopyridines react smoothly with lithium diphenylphosphide under mild conditions to generate the corresponding phosphines in greatly improved yields. The lithium phosphide reagent is much easier to prepare and handle than pyridyllithiums and is less subject to side reactions. Thus, this procedure offers a convenient route to novel, previously difficult to prepare, pyridylphosphine ligands.

Experimental Section

All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared spectra (IR) were recorded on a Beckmann IR-7 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian A-60-A spectrometer and are recorded in parts per million downfield from the internal standard of tetramethylsilane. All compounds were confirmed by mass spectral analysis obtained on a Hitachi Perkin-Elmer RMS-4 spectrometer by Mr. J. Murphy. Elemental analyses were performed by Mr. R. Seab in these laboratories.

Lithium Diphenylphosphide (50-mmol Solution). To a stirred mixture of lithium (700 mg, 100 mmol) in anhydrous tetrahydrofuran (50 mL) under nitrogen, a solution of freshly distilled chlorodiphenylphosphine (9 mL, 50 mmol) in dry THF (30 mL) was added dropwise over 1 h. After the addition was completed and appearance of a dark red coloration, the solution was refluxed for an additional 2 h prior to use.

General Reaction Procedure. 2-Pyridyldiphenylphosphine (2a). A stirred THF solution of lithium diphenylphosphide (50 mmol) was brought to reflux under nitrogen, then a solution of 2-bromopyridine (7.2 g, 45 mmol) in dry THF (25 mL) was added over a 30-min period, followed by an additional hour of reflux. After cooling to room temperature, the solution was concentrated in vacuo and aqueous hydrochloric acid (3 N, 50 mL) was added and then extracted with chloroform. The aqueous layer was neutralized with a dilute sodium carbonate solution. The resultant precipitate was dried and recrystallized from petroleum ether (bp 30–60 °C) to afford 2-pyridyldiphenylphosphine as colorless crystals: 6.5 g (55%); mp 83–84 °C (lit.[1] mp 84–85 °C); NMR ($CDCl_3$) δ 7.12 (m, 5-Pyr-H, 1 H), 7.32 (s, PPh_2), 7.25–7.6 (m, 3,4-Pyr-H), 8.71 (ddd, 6-Pyr-H, J = 6, 2, 1.5 Hz, 1 H); IR ($CHCl_3$) 2990, 1560, 1550, 1465, 1440, 1420, 1410, 1170, 1080, 980 cm^{-1}; mol wt (mass spectrum) m/e 263 (M^+).

2c: NMR ($CDCl_3$) δ 7.2–8.0 (m, all Pyr- and Ph-H); IR ($CHCl_3$) 2960, 1560. 1455, 1410, 1140, 1070, and 905 cm^{-1}.

6: NMR ($CDCl_3$) δ 6.09 (ddd, 5-PyrH, J = 7, 7, 1 Hz, 1 H), 6.45 (dd, 3-PyrH, J = 9, 1 Hz, 1 H), 7.1–7.8 (m, 4-PyrH and Ph-H, 12 H); IR ($CHCl_3$) 3380 (N–H), 2950, 1670 (amide), 1610, 1475, 1450, 1170, 1140, 1000, 975, 800 cm^{-1}; mol wt (mass spectra m/e 279 (M^+).

8: NMR ($CDCl_3$) δ 7.05–7.83 (m, 4,4′,5,5′-Pyr-H and Ph-H, 24 H), 8.25 (d, 3,3′-Pyr-H, J = 8 Hz, 2 H); IR ($CHCl_3$) 2995, 1550, 1530, 1465, 1405, 1170, 1140, 1080, 1065, 975 cm^{-1}; mol wt (mass spectra) m/e 524 (M^+).

General Procedure for the Preparation of Phosphine Oxides. 2-Pyridyldiphenylphosphine Oxide (3a). A mixture of **2a** (500 mg, 1.9 mmol), hydrogen peroxide (0.5 mL, 30%), and absolute ethanol (40 ml) was refluxed for 30 min. The solution was poured into water (ca. 100 mL) and extracted with chloroform. The organic extract was dried over magnesium sulfate, filtered, and concentrated to afford a white solid which was recrystallized from cyclohexane to give **3a**: 450 mg (85%); mp 109–110 °C; NMR ($CDCl_3$) δ 7.25–7.5 (m, 3,4,5-Ph-H, 5-Pyr-H, 7 H), 7.65–8.0 (m, 2,6-Ph-H, 4-Pyr-H, 5 H), 8.28 (ddd, 3-Pyr-H, J = 6,2,1.5 Hz, 1 H), 8.7 (ddd, 6-Pyr-H, J = 6,2,1.5 Hz, 1 H); IR ($CHCl_3$) 2970, 1585, 1560, 1480, 1420, 1300, 1160 (s, P→O), 1130, 1110, 985 cm^{-1}; mol wt (mass spectra) m/e 279 (M^+).

3b: NMR ($CDCl_3$) δ 7.28–7.93 (m, 3,5-Pyr-H and Ph-H, 12 H), 8.80 (ddd, 2,6-Pyr-H, J = 4.5, 4.5, 1.3 Hz, 2 H); IR ($CHCl_3$) 2995, 1575, 1480, 1435, 1400, 1315, 1220, 1175 (s, P→O), 1120, 975 cm^{-1}; mol wt (mass spectra) m/e 279 (M^+).

3c: NMR ($CDCl_3$) δ 7.00–8.45 (m, Pyr- and Ph-H); IR (KBr) 3000, 1575, 1495, 1445, 1200, 1160 (s, P→O), 1125, 1100, 1080, 990 cm^{-1}; mol wt (mass spectra) m/e 479 (M^+).

7: NMR ($CDCl_3$) δ 6.42 (dd, 5-Pyr-H, J = 7, 7 Hz, 1 H), 6.65 (d, 3-Pyr-H, J = 9 Hz, 1 H), 7.2–7.9 (m, 4-Pyr-H and Ph-H, 12 H), 8.2 (bs, NH, 1 H); IR ($CHCl_3$) 3350 (N–H), 2980, 2920, 1650 (amide), 1590, 1420, 1160 (s, P→O), 1120, 995, 890 cm^{-1}; mol wt (mass spectra) m/e 295 (M^+).

9: NMR ($CDCl_3$) δ 7.33–7.68 (m, 3,4,5-Ph-H, 12 H), 7.70–8.17 (m, 4,4′-Pyr-H and 2,6-Ph-H, 10 H), 8.20–8.48 (m, 3,3′,5,5′-Pyr-H, 4 H); IR ($CHCl_3$) 2970, 1570, 1550, 1420, 1370, 1170 (s, P→O), 1150, 1090, 1070, 990 cm^{-1}; mol wt (mass spectra) m/e 556 (M^+).

2,6-Bis(diphenylphosphino)pyridine (2c) was prepared (92%), according to the procedure of Cremer and Chorrat[15] by the reduction of **3c** with trichlorosilane in the presence of triethylamine: mp 124–125 °C (hexane); NMR ($CDCl_3$) δ 7.00 (m, 3,5-Pyr-H, 2 H), 7.08–7.48 (m, 4-Pyr-H, Ph-H, 21 H); IR ($CHCl_3$) 3000, 1565, 1490, 1430, 1375, 1180, 1100, 990 cm^{-1}. Anal. Calcd for $C_{29}H_{23}NP_2$: C, 77.84; H, 5.18; N, 3.13. Found: C, 77.77; H, 5.20; N, 3.00.

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Registry No.—$LiPPh_2$, 4551-02-0.

References and Notes

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Synthesis of Boron-Substituted Pyrimidines and Borazaroquinazolines[1]

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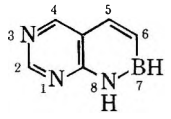
Two approaches to the synthesis of boron-substituted pyrimidines and borazaroquinazolines (1) have been explored First, (dibutoxyboryl)ethene and bromomalononitrile were converted to 1,1-dicyano-3-bromo-3-(dibutoxyboryl)propane (2), which was reduced with triphenyltin hydride to 1,1-dicyano-3-(dibutoxyboryl)propane (3), which condensed with thiourea to yield 2-mercapto-4,6-diamino-5-(2-dihydroxyborylethyl)pyrimidine (4a). However, conversion of 4a to a borazaroquinazoline was not attempted because the development of boron-substituted carbanion chemistry promised a more direct and efficient approach. This second method involved condensation of 4,6-dichloro-5-formylpyrimidine (5) with the carbanion from tetrakis(trimethylenedioxyboryl)methane to form 4,6-dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (6a), which on treatment with ammonia at 25 °C yielded 4-chloro-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (7a), which reacted with ammonia at 75 °C to form the 4-amino derivative 8. Improved yields were obtained in a similar sequence starting from tetrakis(ethylenedioxyboryl)methane. Characterization of the amino-substituted borazaroquinazolines was aided by ^{13}C NMR correlations.

Substitution of a boron atom for a carbon in a biochemically significant molecule might lead to antimetabolite activity. This hypothesis is reinforced by recent findings that phenylethaneboronic acid is a chymotrypsin inhibitor[2] and that a boron analogue of betaine shows some anticancer activity.[3] However, there are significant restrictions on the types of boron compounds that can be synthesized for such purposes. Instability toward hydrolysis is a problem with boron–nitrogen or boron–oxygen bonds, as well as with boron–carbon bonds activated by various neighboring functional groups. For example, purine analogues having boron in positions 2 or 8 (between nitrogen atoms) have been found to be unstable in hydroxylic media.[4,5] Boron-substituted pyrimidines made previously in this laboratory either deboronated easily or had the boron substituent in a position likely to interfere with rather than enhance any possible antimetabolite activity.[6] Butler and Soloway synthesized a boron analogue of dihydrouracil,[7] but they were unable to dehydrogenate it. Liao, Podrebarac, and Cheng made 5-dihydroxyboryluracil by a straightforward modernization of the classical boronic acid synthesis,[8] but this approach is not generally applicable to highly functionalized organoboron compounds.

7,8-Borazaroquinazoline (1) was chosen as the target ring system for synthesis for several reasons. Borazaro compounds



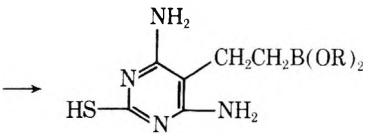
1

are generally stable, especially those having fused six-membered rings.[9] It appeared that there would be feasible synthetic routes to derivatives of 1. For analogy to the purines, it would be better to have a five-membered ring rather than the six-membered borazaro ring of 1, but it was hoped that biological activity might be found in spite of this weakness in design, and it was also hoped that knowledge of synthetic techniques and chemical properties gained in the synthesis of derivatives of 1 might eventually aid the synthesis of closer analogues to the purines.

Results and Discussion

The Bromomalononitrile–(Dibutoxyboryl)ethene Adduct. The first route attempted, with partial success, was based on the radical initiated addition of bromomalononitrile to (dibutoxyboryl)ethene (dibutyl vinylboronate), which

$$(NC)_2CHCH_2CHBrB(OC_4H_9)_2 \longrightarrow (NC)_2CHCH_2CH_2B(OC_4H_9)_2$$
2 3



4a, R = H
b, R = CH_3

yielded 85% of 1,1-dicyano-3-bromo-3-(dibutoxyboryl)propane (2).[10] Conversion of the malononitrile group of 2 to a pyrimidine required prior replacement of the reactive bromo function since under basic conditions 2 undergoes rapid ring closure to 1,1-dicyano-2-(dibutoxyboryl)cyclopropane.[10] Attempts to replace the bromide by solvolysis in neutral or acidic aqueous ethanol also yielded only the cyclopropane derivative.

Reduction of 2 with triphenyltin hydride, which proceeds under free-radical conditions,[11] gave fair yields of the desired product, 1,1-dicyano-3-(dibutoxyboryl)propane (3). There was a substantial amount of higher boiling byproduct, which had an elemental composition corresponding to the 1:2 telomer of malononitrile with (dibutoxyboryl)ethane, perhaps formed via radical carbon–carbon bond cleavage and addition reactions.

The reaction of 3 with thiourea in the presence of potassium *tert*-butoxide followed by hydrolysis readily yielded 2-mercapto-4,6-diamino-5-(2-dihydroxyborylethyl)pyrimidine (4a), which on crystallization from methanol was converted to the dimethoxyboryl derivative 4b.

Although cyclization and dehydrogenation of 4 should yield a derivative of 1, unsolved problems remain. The sulfhydryl group precludes catalytic dehydrogenation, and oxidative methods may cleave the carbon–boron bond. Attempted dehydrogenation of a dihydroborauracil derivative has failed.[7] Therefore, this route was abandoned when a more attractive alternative became apparent.

The Triborylmethide–Aldehyde Route. Tetrakis(organyldioxyboryl)methanes are easily converted to tris(organyldioxyboryl)methide ions, which condense efficiently with aldehydes.[12] This reaction is the basis for the successful route to a derivative of borazaroquinazoline (1). Lithium tris(trimethylenedioxyboryl)methide[13,14] and 4,6-dichloro-5-formylpyrimidine[15] gave mediocre yields of the expected product 4,6-dichloro-5-[2,2-bis(trimethylenedioxyboryl)-

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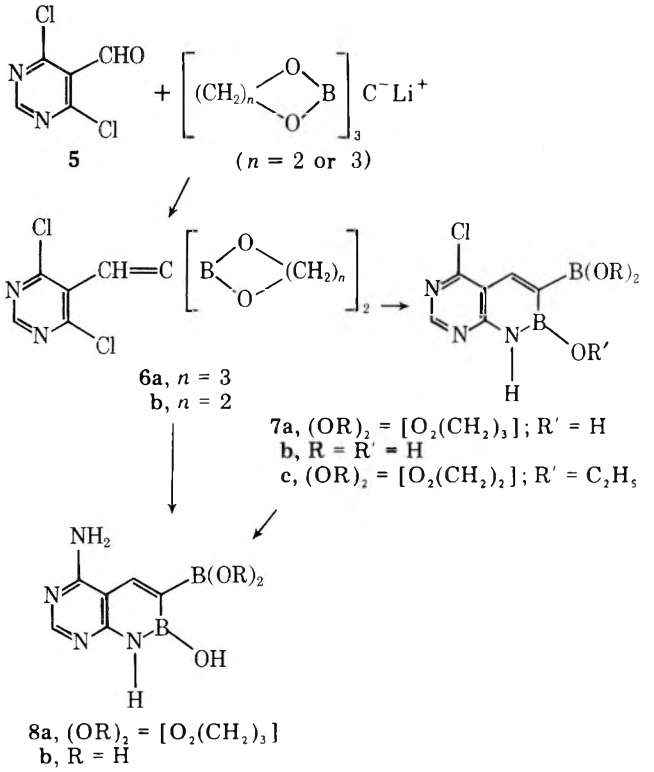
vinyl]pyrimidine (**6a**).

$$[(RO)_2B]_4C \xrightarrow{BuLi} [(RO)_2B]_3C^- \xrightarrow{R'CHO} R'CH{=}C[B(OR)_2]_2$$

The geminal boron functions in **6a** constitute an essential part of the synthetic strategy since subsequent ring closure requires the presence of a cis boron on the vinylic substituent and stereoselective synthesis of the cis isomer would be difficult.

Reaction of **6a** with liquid ammonia at 25 °C in a pressure vessel yielded 4-chloro-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (**7a**). The acquisition of the 7-hydroxyl group requires hydrolysis and implies that moisture was not fully excluded. Treatment of either **6a** or **7a** with liquid ammonia under autogenous pressure at 75 °C resulted in replacement of the second chlorine atom and formation of 4-amino-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (**8a**), which hydrolyzed to the 6-dihydroxyboryl derivative **8b** on aqueous workup. However, both **8a** and **8b** proved uncommonly difficult to purify and characterize, presumably because of interactions between the boron and amino functions, and the remainder of this work was devoted to proving these structures. Considerable improvement in the details of the synthesis resulted as a byproduct of this effort.



A significant improvement in yields resulted from the use of lithium tris(ethylenedioxyboryl)methide, $[(CH_2)_2O_2B]_3C^-Li^+$, in place of the trimethylene homologue, $[(CH_2)_3O_2B]_3C^-Li^+$, which had been used in previous work.[14] The insolubility of tetrakis(ethylenedioxyboryl)methane, $[(CH_2)_2O_2B]_4C$, in tetrahydrofuran (THF) had led to the belief that this compound could not be used for carbanion generation.[16] However, on reinvestigation the use of the ethylenedioxyboryl ester resulted in about the same yields of **6b** as had been obtained previously in the preparation of **6a**. Yields were significantly improved when special care was taken to ensure the purity of the tetrakis(ethylenedioxyboryl)methane and when dichloromethane was incorporated into the solvent mixture to increase the solubility, with about a 3:1 mixture of THF/dichloromethane providing excellent results. Preparations of **6a** had consistently given 30–35% yields, but the improved preparation of **6b** gave 77%, with much less formation of tarry byproducts.

Since previous work with lithium tris(trimethylenedioxyboryl)methide had generally given high yields of aldehyde condensation products,[14] the inefficient reaction of 4,6-dichloro-5-formylpyrimidine (**5**) may result from steric hindrance to attack at the aldehyde group, coupled with the availability of alternative reactive sites at the 4 and 6 positions of the pyrimidine. The ethylenedioxyboryl analogue should be less hindered at the carbanionic site.

The conversion of **6b** to **8b** in one step proceeded in about the same yield (80%) as conversion of **6a**. Conversion of **6a** to **7a** was only about 30%, but this is apparently an isolation problem dependent on the presence of sufficient fortuitous moisture to hydrolyze the BOR' group but not the $B(OR)_2$ to provide the particular species which happens to crystallize readily. From **6b**, two products, **7b** and **7c**, were isolated, one having exclusively hydroxy ligands on boron and the other having one ethylene glycol and one ethanol (recrystallization solvent) ligand, each in about 30% yield. However, since **7a** had already been fully characterized and **7** was not the major objective, no further attempts were made to simplify and improve this synthesis.

Characterization of 8. Although all of the precursors **6** and **7** readily gave good elemental analyses and had ^1H NMR spectra consistent with their assigned structures, neither **8a** nor **8b** yielded satisfactory analytical results at first, and the ^1H NMR spectra of these compounds, which have only two carbon-bound and therefore nonexchangeable protons on the borazaroquinazoline ring system, were not very informative even though the results were consistent with the assigned structures.

The problem with characterization of **8a** appeared to be an unusually tenacious retention of chloroform, the solvent which was used to crystallize this particular species. After normal drying procedures, samples of **8a** showed an extra ^1H NMR peak at δ 8.35 in perdeuteriodimethyl sulfoxide (Me_2SO-d_6), which was shown to correspond to chloroform in Me_2SO-d_6 by comparison with an authentic sample. Even after prolonged drying, the elemental analysis corresponded to retention of a small amount (~7 mol %) of chloroform even though it was not quite enough to detect using NMR.

The problems with the fully hydroxylated compound **8b** were more complicated. Recrystallized (microcrystalline) samples gave variable analytical results, generally low in nitrogen and high in boron. Two analytically pure samples were finally obtained after chromatography on cellulose with methanol/water as the eluting solvent. However, further structural confirmation was sought.

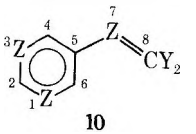
The ^1H NMR spectrum of **8b** showed the expected two singlets in the aromatic region. The low solubility of **8b** even in dimethyl sulfoxide made it difficult to get adequate NMR data, but in Me_2SO-d_6 it was possible to detect two broadened peaks attributed to NH in addition to the residual H_2O peak, which evidently included the B–OH and perhaps one NH absorption due to rapid exchange between these groups and water, or possibly due to water eliminated by condensation of B–OH to B–O–B or B–N linkages. The separate NH peaks were shown to undergo exchange broadening and shifting on addition of methanol.

The ^{11}B NMR spectrum of **8b** consisted of an exceedingly broad, ill-defined absorption and was of no use in characterization.

Ultraviolet spectra of **7b** and **8b** were consistent with the assigned structures.

Finally, in the hope of obtaining some additional data re-

Table I. 22.63-MHz ^{13}C NMR Spectra of Borylvinylpyrimidines and Related Compounds with Carbon Atoms Numbered as in Structure 10



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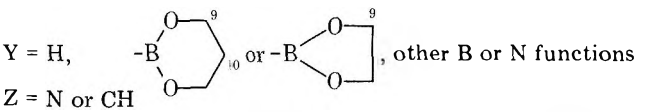
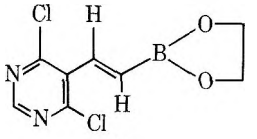


Compound	Registry no.	Solvent	δ (relative to Me_4Si) C_2	C_7	$C_{4,6}$, C_5	Other
9	64705-49-3	Me_2SO-d_6	156.6	139.4	159.5[a]	C_9, 65.7
6a	64705-50-6	Me_2SO-d_6	156.2[b]	142.6[c]	158.9[a]	C_9, 61.4, 61.6;[d] C_{10}, 26.5, 26.8[e]
		$CDCl_3$	154.3	142.6	158.5[a]	C_9, 60.8, 61.0; C_{10}, 25.8, 26.1
8a	64705-51-7	Me_2SO-d_6	157.4[f]	148.4	161.4	C_9, 61.4; C_{10}, 27.0
8b	64705-52-8	CD_3OD	158.3	148.0[g]	159.1[a]	
		Me_2SO-d_6	156.7[h]	148.2[g]	161.0[a,h]	Impurities, 98.5, 57.5[h]
Adenosine[i]		Me_2SO-d_6	152.7		C_4, 156.3; C_6, 149.2; C_5, 119.6; C_8, 140.5	
$C_6H_5CH{=}C[BO_2(CH_2)_3]_2$[j]		Me_2SO-d_6	128.0	149.1	$C_{1,3}$, $C_{4,6}$ 127.7, 128.5; C_5, 140.2;[a] C_9, 61.5; C_{10}, 26.8, 27.0	

[a] Weak. [b] From undecoupled spectrum, J_{CH} = 217 Hz. [c] J_{CH} = 168 Hz. [d] J_{CH} = 146 Hz; two peaks because of nonequivalent $BO_2(CH_2)_3$ groups. [e] J_{CH} = 141 Hz. [f] Paired with peak at δ 157.1. [g] 25–30 Hz wide at half height. [h] Spectrum very weak; additional peaks at δ 155.9, 160.5, 162.0, and in between, as if several related compounds are present. [i] Assigned in accord with ref 18 and 19. [j] For synthesis, see ref 14.

garding the more inaccessible parts of the structure of **8**, a series of ^{13}C NMR spectra were run on **6a**, **8a**, **8b**, and some related compounds. Fortunately, the ^{13}C NMR data proved consistent with the assigned structures (**8**), but unfortunately, only the two H-substituted carbons of the borazaroquinazoline ring could be detected unequivocally, with one additional ring carbon appearing as a weaker peak. The carbon bonded to two boron atoms was not detectable either in **8** or in model compounds. In an effort to obtain some clue as to where to look for



9

this elusive carbon absorption, 4,6-dichloro-5-[*trans*-2-(ethylenedioxyboryl)vinyl]pyrimidine (**9**) was synthesized from tris(ethylenedioxyboryl)methane[17] and 4,6-dichloro-5-formylpyrimidine (**5**), but in spite of the presence of the proton, the boron-bound carbon was not found. The ^{13}C NMR spectra are summarized in Table I.

It is apparent from Table I that the ^{13}C chemical shift pattern characteristic of the vinylpyrimidine group appears consistently throughout the series **6a**, **8a**, **8b**, and **9**, that the pyrimidine C_2 is not far from that in adenosine, and that the vinylic carbon β to boron (C_7 in **10**) has a similar chemical shift in both the pyrimidine series and in $C_6H_5CH{=}CH$-$[BO_2(CH_2)_3]_2$. The assignments are further confirmed by the CH coupling constants observed in an undecoupled spectrum of **6a**. The spectrum of **8b** in CD_3OD is consistent with the rest of the series, but the saturated solution was dilute and the spectrum was weak. Therefore, Me_2SO-d_6 was tried as solvent, but the spectrum was anomalously very weak and consisted of clusters of closely spaced peaks only partially distinguishable from background noise even with 56 000 scans. Evidently **8b** undergoes a variety of condensation reactions involving the NH and BOH groups in Me_2SO, resulting in the formation of a multiplicity of related species, probably oligomers. The molecular weight measured osmometrically in dimethylformamide was 220 (theory, 206), though this is not necessarily inconsistent with condensations which liberate water. The spectrum of **8a** showed a stronger than normal peak for C_4 (or C_5 or C_6) of structure **10**, as well as an anomalous double peak at δ 157.1–157.4 in the C_2 region, which might arise from the presence of two closely related species (e.g., BOH vs. BOB linkages) or detection of one of the normally missing carbon absorptions of the ring.

The failure to detect three out of four of the quaternary carbons in **6a**, **8a**, and **8b**, though frustrating for purposes of proof of structure, is not unprecedented.[20] If the relaxation time is longer than the pulse interval, the signal becomes saturated. With the very dilute solutions available for the compounds of primary interest, unduly long scan times would be required, and further attempts to detect the missing quaternary carbon signals were not undertaken.

It may be noted incidentally that the geometry of the borylvinyl group in **9** is trans, as shown by the ^1H NMR spectrum (J_{H-H} = 20 Hz) and expected on the basis of previous results.[14] Thus, **9** is not a suitable candidate for ring closure to borazaro compounds.

Compound **8b** was inactive in the standard P388 leukemia screen (Drug Development Branch, National Cancer Institute).

Experimental Section

Reactions were run under nitrogen or argon. Tetrahydrofuran (THF) and dichloromethane were dried over calcium hydride and distilled. Other reagent grade chemicals were used as supplied. The ^1H NMR spectra were obtained at 100 MHz with a JEOL JNM-MH-100 instrument or at 60 MHz with a Varian A-60 and are referred to internal tetramethylsilane (Me_4Si). ^{11}B NMR spectra were obtained at 32.1 MHz with the Varian HA-100 at the University of Idaho. ^{13}C NMR were obtained at 22.63 MHz with a Bruker WH-90 Fourier transform instrument and are referred to external Me_4Si. A Cary Model 15 ultraviolet spectrometer, a Beckman IR-5A infrared spectrometer, and a Varian M-66 mass spectrometer were used. Microanalyses were performed by Spang, Schwarzkopf, and Galbraith Laboratories. Melting points are uncorrected.

1,1-Dicyano-3-(dibutoxyboryl)propane (3). A mixture of 12.1 g of 1,1-dicyano-3-bromo-3-(dibutoxyboryl)propane (**2**),[10] 13.5 g of triphenyltin hydride,[11] and 0.1 g of azobis(isobutyronitrile) was heated at 70–80 °C for 2 h, and an additional 0.07 g of azobis(isobutyronitrile) was added, which led to the formation of a precipitate of triphenyltin bromide within a few seconds. The mixture was treated with 20 mL of water and filtered to remove the triphenyltin bromide (16 g, 97%).

The filtrate was extracted with ether, 20 mL of butanol was added, and the product was distilled, yield 3.14 g (34%), bp 94–103 °C (0.04 Torr). Anal. Calcd for $C_{13}H_{23}BN_2O_2$: C, 62.42; H, 9.27; B, 4.32; N, 11.20. Found: C, 62.24; H, 9.42; B, 4.10; N, 10.92.

A higher boiling byproduct, bp 110–160 °C (0.04 Torr), yield 3.0 g, was also obtained. This was redistilled, major portion bp 155–175 °C (0.04 Torr), and yielded an analysis not quite satisfactory for an adduct of 1 mol of malononitrile with 2 mol of dibutyl vinylborate. Anal. Calcd for $C_{23}H_{44}B_2N_2O_4$: C, 63.62; H, 10.21; B, 4.98; N, 6.45. Found: C, 62.73; H, 10.06; B, 5.51; N, 6.70.

2-Mercapto-4,6-diamino-5-(2-dihydroxyborylethyl)pyrimidine (4a). A solution of potassium *tert*-butoxide was prepared from 0.4 g of potassium metal and 30 mL of *tert*-butyl alcohol. A 0.53-g amount of thiourea and 1.5 g of 1,1-dicyano-3-(dibutoxyboryl)propane (3) were added, and the mixture was refluxed 17 h. The mixture was cooled, neutralized with acetic acid to pH 5, treated with 40 mL of water, and extracted with three 50-mL portions of ether. On standing 2 days at 5 °C, 0.52 g of product crystallized from the aqueous phase, and an additional 0.23 g was obtained by concentrating the mother liquor, total yield 60%; a sample did not melt but appeared to decompose at 270–325 °C. The analytical sample was recrystallized from water; IR (KBr) (Beckman IR 8) 3330 s, 3205 s, 2940 sh, 1620 s, 1550 s, 1515 s, 1475 m, 1408 m, 1380 s, 1357 sh, 1277 m, 1230 m, 1200 m, 1168 m, 1124 m, 1030 w, 968 w, 746 brd w cm^{-1}. Anal. Calcd for $C_6H_{11}BN_4O_2S + H_2O$: C, 31.05; H, 5.65; B, 4.66; N, 24.14; S, 13.82. Found: C, 31.32; H, 5.52; B, 4.52; N, 23.96; S, 14.09.

2-Mercapto-4,6-diamino-5-(2-dimethoxyborylethyl)pyrimidine (4b). When 200 mg of the dihydroxyboryl compound **4a** was dissolved in 1 mL of absolute methanol, the dimethoxy compound **4b** precipitated after a few seconds, yield 100–150 mg; 60-MHz ^1H NMR (Me_2SO-d_6) δ 3.17 (s, 6, OCH_3) and a series of broad, ill-defined peaks at δ 7.03 (s, 1, NH), 6.7 (s, 1 NH), 6.4 (s, 2, NH_2), 4.9 (~70 Hz wide, ~4, H_2O?), 2.3 (m?, 4?, CCH_2), 0.8 (~60 Hz wide, 4?, CH_2B). The integral values are probably grossly in error, and the spectrum is otherwise consistent with the assigned structure: IR (KBr) 3300 s, 3185 s, 2878 m, 1607 s, 1542 s, 1508 m, 1372 m, 1312 w, 1287 w, 1214 m, 1124 w, 1088 vw, 1047 w, 1002 w, 960 vw, 885 m, 850 vw, 797 w, 736 w, 697 vw, 671 vw cm^{-1}. Anal. Calcd for $C_8H_{15}BN_4O_2S$: C, 39.69; H, 6.25; B, 4.47; N, 23.14; S, 13.24. Found: C, 39.48; H, 6.49; B, 4.65; N, 22.98; S, 13.25.

4,6-Dichloro-5-formylpyrimidine (5) was prepared by the literature method[15] and later was purchased on special order from Aldrich. In order to obtain good yields (up to 55%), it appeared to be essential to extract the aldehyde product promptly with ether during hydrolysis of the crude reaction mixture with ice and water. The exothermic hydrolysis was controlled by the addition of ice.

4,6-Dichloro-5-[2,2-bis(ethylenedioxyboryl)vinyl]pyrimidine (6b). A slurry of 25.4 g (0.09 mol) of tetrakis(ethylenedioxyboryl)-methane[16] in 180 mL of dichloromethane and 600 mL of THF was cooled at −78 °C, and 36 mL of 2.4 M butyllithium in hexane was added dropwise with vigorous stirring for 30 min. The mixture was stirred for 2 h at −78 °C, and then a solution of 4,6-dichloro-5-formylpyrimidine (5) in 50 mL of THF was added. Stirring was continued while the mixture warmed to room temperature and the solids dissolved. After stirring overnight, the solution was concentrated and the residue was treated with a mixture of 250 mL of toluene and 250 mL of chloroform. The insoluble material was filtered and discarded, and the filtrate was concentrated under vacuum to crystallize the product, yield 21 g (77%), recrystallized from chloroform/toluene or chromatographed on cellulose with 1:1 chloroform/toluene as eluting solvent, mp 118–121 °C: 100-MHz ^1H NMR ($CDCl_3$) δ 8.68 (s, 1, NCHN), 7.80 (brd s, 1, CH=CB_2), 4.40 (s, 4, OCH_2CH_2O), 4.16 (s, 4, OCH_2CH_2O); ^{11}B NMR ($CDCl_3$) broad peak (~600 Hz) 15.6 ppm downfield from $B(OCH_3)_3$; IR (KBr) 2976 m, 2907 m, 1592 s, 1534 m, 1504 s, 1481 s, 1404 s, 1355 s, 1307 s, 1264 s, 1245 s, 1227 s, 1209 s, 1159 m, 1126 m, 1041 s, 1004 s, 985 m, 954 m, 941 m, 909 s, 840 s, 808 s, 792 s, 776 s, 740 s, 703 m, 692 s, 668 m, 649 m cm^{-1}. Anal. Calcd for $C_{10}H_{10}B_2Cl_2N_2O_4$: C, 38.16; H, 3.20; B, 6.87; Cl, 22.53; N, 8.90. Found: C, 38.00; H, 3.14; B, 6.82; Cl, 22.65; N, 8.86.

4,6-Dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (6a). The method was essentially the same as that used for the preparation of **6b**. The carbanion was prepared from 9.5 g (0.03 mol) of tetrakis(trimethylenedioxyboryl)methane in 150 mL of THF with 0.03 mol of butyllithium at −78 °C,[14] warmed to 0 °C, and cooled again to −78 °C before adding the 4,6-dichloro-5-formylpyrimidine (5). The yield was 3.1 g (33%), mp 156–157 °C: 100-MHz ^1H NMR ($CDCl_3$) δ 8.64 (s, 1, NCHN), 7.39 (brd s, 1, CH=CB_2), 4.10 (t, 4, OCH_2CH_2), 3.85 (t, 4, OCH_2CH_2), 1.93 (m, 4, $CH_2CH_2CH_2$); IR (KBr) 2967 m, 2899 m, 1600 s, 1531 m, 1508 s, 1481 s, 1418 s, 1376 s, 1339 s, 1311 s, 1274 s, 1250 s, 1212 s, 1140 m, 1111 s, 1004 m, 925 m, 904 m, 889 m, 856 m, 850 sh, 791 s, 769 m, 732 m, 714 s, 684 m, 669 s cm^{-1}. Anal. Calcd for $C_{12}H_{14}B_2Cl_2N_2O_4$: C, 42.05; H, 4.12; B, 6.31; N, 8.17. Found: C, 42.28; H, 4.05; B, 6.17; N, 7.90.

4,6-Dichloro-5-[2-(ethylenedioxyboryl)vinyl]pyrimidine (9). The procedure was essentially the same as that used for the preparation of **6a**. The carbanion was generated from 4.53 g (0.02 mol) of tris(ethylenedioxyboryl)methane[17] in 140 mL of THF at −78 °C. The yield was 0.85 g (17%), mp 81–88 °C: 100-MHz ^1H NMR ($CDCl_3$) δ 8.68 (s, 1, NCHN), 7.36 (d, J = 20 Hz, 1, CH=CHB), 6.46 (d, J = 20 Hz, 1, CH=CHB), 4.36 (s, 4, OCH_2CH_2O); IR (KBr) 3067 w, 2994 m, 2915 m, 1938 w, 1610 s, 1504 s, 1389 s, 1350 brd, 1311 s, 1236 s, 1221 s, 1175 s, 1122 m, 1019 s, 999 s, 985 sh, 949 s, 863 s, 847 m, 836 sh, 788 s, 706 w, 675 w, 651 w, 631 s cm^{-1}. Anal. Calcd for $C_8H_7BCl_2N_2O_2$: C, 39.24; H, 2.88; B, 4.41; Cl, 28.96; N, 11.44. Found: C, 39.31; H, 3.00; B, 4.24; Cl, 29.04; N, 11.38.

4-Chloro-6-dihydroxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (7b) and 4-Chloro-6-ethylenedioxyboryl-7-ethoxy-7,8-dihydro-7,8-borazaroquinazoline (7c). Liquid ammonia (22 mL) was distilled from sodium into a chilled (−78 °C) stainless steel bomb containing 4.3 g of 4,6-dichloro-5-[2,2-bis(ethylenedioxyboryl)vinyl]pyrimidine (**6b**) and a magnetic stirrer. The vessel was sealed (with care taken to prevent the entry of moisture), and the contents were stirred for 24 h at 20–25 °C (10 atm). The ammonia was vented, and the residue was treated with 100 mL of chloroform. The insoluble material, which was the hydroxy compound **7b**, was filtered, dissolved in 160 mL of 95% ethanol, and concentrated to crystallize the product, yield 1.0 g (33%). The analytical sample was recrystallized from 95% ethanol and finally from aqueous 33% ethanol in order to obtain material free from ethoxy groups (by NMR analysis), mp 217 °C dec; 100-MHz ^1H NMR (Me_2SO-d_6) δ 9.57 (brd s, 1, NH), 8.56 (s, 1, CH), 8.25 (brd s, 2, $B(OH)_2$), 7.79 (brd s, 1, BOH); UV (0.1 N HCl) 217 nm (ϵ 3.45 × 10^4), 302 (1.41 × 10^4); UV (H_2O) 216 nm (ϵ 3.31 × 10^4), 302 (1.205 × 10^4); UV (0.1 N NaOH) 3.17 nm (ϵ 1.60 × 10^4); IR (KBr) 3356 sh, 3175 s, 1592 s, 1563 s, 1471 m, 1377 s, 1337 s, 1297 m, 1261 s, 1149 m, 1130 sh, 1085 sh, 961 w, 925 w, 842 m, 795 m, 718 s cm^{-1}. Anal. Calcd for $C_6H_6B_2ClN_3O_3$: C, 32.00; H, 2.69; B, 9.60; Cl, 15.74; N, 18.66. Found: C, 31.88; H, 2.82; B, 9.59; Cl, 15.60; N, 18.48.

The chloroform solution from the foregoing preparation contained the ethylenedioxyboryl compound **7c**. After concentration under vacuum, the residue was dissolved in absolute ethanol and concentrated to crystallize the product, 1.2 g (35%); 100-MHz ^1H NMR ($CDCl_3$) δ 8.86 (s, 1, NCHN), 8.67 (s, 1, CH=C), 7.85 (brd s, 1, NH), 4.41 (s, impurity), 4.33 (s, 4, OCH_2CH_2O), 4.07 (q, <2, OCH_2CH_3), 3.73 (q?, impurity), 1.31 (t, ~3, CH_2CH_3); IR (KBr) 3378 s, 3195 s, 3115 sh, 2967 s, 1597 s, 1565 s, 1471 s, 1368 s, 1340 s, 1287 s, 1261 s, 1185 w, 1157 w, 1104 w, 1046 s, 990 m, 912 m, 862 m, 836 m, 795 m, 717 s, 706 s, 668 m, 640 s cm^{-1}. Anal. Calcd for $C_{10}H_{12}B_2ClN_3O_3$: C, 43.16; H, 3.98; B, 7.77; Cl, 12.74; N, 15.10. Found: C, 42.30; H, 4.08; B, 8.14; Cl, 13.07; N, 15.37.

4-Chloro-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (7a). 4,6-Dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (**6a**) was used in place of the ethylenedioxyboryl analogue **6b** in the procedure described for the preparation of **7b** and **7c**. In this case, the chloroform-insoluble material was not examined, but the filtrate was concentrated and the residue recrystallized from absolute ethanol, yielding 36% of **7a**; 100-MHz ^1H NMR ($CDCl_3$) δ 8.60 (s, 2, NCHN and CH=CB_2), 7.60 (brd s, 1, NH), 6.36 (s, 1, BOH), 4.18 (t, 4, OCH_2CH_2), 2.10 (m, 2, $CH_2CH_2CH_2$); ^1H NMR (Me_2SO-d_6) δ 9.80 (brd s, 1, NH), 8.64 (s, 1, NCHN), 8.40 (s, 1, CH=CB_2), 7.06 (s, 1, BOH), 4.15 (t, 4, OCH_2CH_2), 2.00 (m, 2, $CH_2CH_2CH_2$); IR (KBr) 3521 s, 3185 s, 3115 s, 2976 s, 2890 s, 1597 s, 1567 sh, 1548 sh, 1479 s, 1447 m, 1420 m, 1368 s, 1330 s, 1289 s, 1261 s, 1135 m, 1104 s, 1066 s, 1046 s, 997 w, 958 w, 892 m, 847 s, 822 m, 796 m, 727 s, 714 s, 682 w, 663 m, 643 s cm^{-1}; mass spectrum, *m/e* 267 (29), 266 (38), 265 (59, P), 264 (21), 211 (21), 210 (21), 209 (21), 208 (25), 196 (21), 195 (38), 183 (17), 182 (29), 181 (29), 167 (17), 166 (25), 155 (22), 128 (21), 127 (48), 126 (25), 103 (15), 120 (38), 101 (100). Anal. Calcd for $C_9H_{10}B_2ClN_3O_3$: C, 40.75; H, 3.80; B, 8.15; Cl, 13.36; N, 15.84. Found: C, 40.95; H, 3.85; B, 8.45; Cl, 13.18; N, 15.60.

4-Amino-6-dihydroxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (8b). Anhydrous ammonia (22 mL) was distilled from sodium into a chilled (−78 °C) stainless steel bomb containing 4.0 g of 4,6-dichloro-5-[2,2-bis(ethylenedioxyboryl)vinyl]pyrimidine (**6b**) and a magnetic stirrer. The lower half of the vessel was heated in an oil bath at 75 °C and stirred for 2 days (~30 atm). The vessel was cooled to 25 °C and vented. The residue was dissolved in 600 mL of methanol and filtered, and the filtrate was treated with 20 mL of water and concentrated under vacuum to precipitate the microcrystalline product, yield 2.1 g (80%). This material was chromatographed on cellulose with 4:1 methanol/water and then found to give only one spot

with TLC on silica gel with dimethylformamide (R_f 0.9) or aqueous 80% methanol (R_f 0.8). Attempted recrystallization usually resulted in partial decomposition, as shown by TLC. The analytical sample was dried for 9 h at 0.1 Torr at 100 °C. The compound darkened above 240 °C but did not melt up to 400 °C; 100-MHz ^{1}H NMR (Me_2SO-d_6) δ 8.55 (s, 1, NCHN), 8.10 (s, 1, CH=CB_2), 7.64 (broadened s, 1, NH), 7.18 (broadened s, 1, NH), 3.42 (s, ~10, NH, BOH, and H_2O from solvent); on addition of methanol dropwise, the δ 7.64 peak broadened, shifted downfield, and disappeared, and the δ 7.18 peak broadened somewhat without shifting; ^{1}H NMR (CD_3OD) δ 8.31 (brd s, CH=CB_2), 8.20 (s, NCHN); IR (KBr) 3205 brd s, 1656 sh, 1587 s, 1477 s, 1456 s, 1395 sh, 1339 s, 1270 brd s, tapering off with some irregularities to 950, 909 m, 803 m, 722 s, 691 m cm^{-1}; UV (H_2O) 203 nm (ϵ 19 550), 233 (16 870), 284 (8850), 302 (10 700); UV (0.1 N HCl) 225 nm (ϵ 17 150), 283 (12 650), 300 (10 460); UV (0.1 N NaOH) 228 nm (ϵ 19 400), 288 (10 610). Anal. Calcd for $C_6H_8B_2N_4O_3$: C, 35.03; H, 3.92; B, 10.51; N, 27.22; mol wt 206. Found: C, 35.24, 35.08; H, 3.74, 3.92; B, 10.44; N, 27.15, 27.08; mol wt (dimethylformamide) 220, (methanol) 235.

4-Amino-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (8a). 4,6-Dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (**6a**) was used in place of the ethylenedioxyboryl analogue **6b** in the procedure described for the preparation of **8b** Instead of methanol, the product was dissolved in 500 mL of chloroform, concentrated under vacuum to crystallize it, yield 70%, and recrystallized from chloroform and finally from toluene/absolute ethanol. The compound tenaciously retained 1 mol of chloroform, as shown by the persistent ^{1}H NMR peak at δ 8.35. After prolonged drying (56 °C, 30 h, 0.1 Torr) the NMR evidence of chloroform disappeared, but the analysis suggested the persistence of 7 mol % $CHCl_3$. The product did not melt at up to 300 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.92 (brd s, 1, NH), 8.44 (s, 1, NCHN), 8.05 (s, 1, CH=CB_2), 7.21 (brd s, 2, NH_2), 6.41 (s, 1, BOH), 4.07 (t, 4, OCH_2CH_2), 1.97 (m, 2, $CH_2CH_2CH_2$); IR (KBr) 3497 s, 3279 s, 3096 s, 2959 s, 1587 s, 1475 s, 1464 s, 1441 s, 1323 s, 1285 s, 1152 s, 1099 s, 1066 s, 961 m, 903 s, 838 m, 803 m, 745 s, 719 s, 692 s, 657 sh, 638 s cm^{-1}. Anal. Calcd for $C_9H_{12}B_2N_4O_3$ + 0.07 $CHCl_3$: C, 42.82; H, 4.78; B, 8.50; Cl, 3.02; N, 22.02 (calcd for $C_9H_{12}B_2N_4O_3$: C, 43.97; H, 4.92; B, 8.80; N, 22.79). Found: C, 42.44; H, 4.82; B, 8.47; Cl, 3.02; N, 21.91.

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Registry No.—**2,** 5271-82-9; **3,** 64728-21-8; **4a,** 64705-53-9; **4b,** 64728-22-9; **5,** 5305-40-8; **6b,** 64705-54-0; **7a,** 64705-55-1; **7b,** 64705-56-2; **7c,** 64705-57-3; thiourea, 62-56-6; tetrakis(ethylenedioxyboryl)methane, 50485-33-1; tetrakis(trimethylenedioxyboryl)methane, 42495-90-9; tris(ethylenedioxyboryl)methane, 59278-44-3.

References and Notes

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Reaction of Tertiary Glycidamides with Boron Trifluoride Etherate. Evaluation of the Potential for Rearrangement with Amide Group Migration[1]

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The reaction of a series of tertiary glycidamides with boron trifluoride etherate in benzene, methylene chloride, or chloroform was studied. The major process observed with (*E*)- and (*Z*)-*N,N*-diphenyl-3-phenylglycidamides (**1a,b**) as well as (*E*)- and (*Z*)-*N,N*-diphenyl-3-methyl-3-phenylglycidamides (**1c,d**) was stereospecific intramolecular Friedel–Crafts cyclization to give the corresponding 1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinones (**2**). A similar reaction was observed in the rearrangement of (*E*)-*N*-phenyl-*N*-methyl-2-methyl-3-phenylglycidamide (**1g**), although condensation with benzene solvent was also found in this case. The reaction of *N,N*-dialkyl-3-methyl-3-phenylglycidamides (**1e,f**) with boron trifluoride etherate led to formation of the corresponding *N,N*-dialkyl-2-hydroxy-3-phenyl-3-butenamides (**5d,f**). Finally (*E*)- and (*Z*)-*N,N*-dimethyl-2-methyl-3-phenylglycidamides (**1h,i**) gave fluorohydrin (**7a**) along with its BF_2 derivative (**7b**). Under more severe conditions **1i** was converted to *N,N*-dimethyl-2-phenylacetoacetamide (**9**), the product anticipated from amide group migration, along with *N,N*-dimethyl-3-phenyl-3-methylpyruvamide (**8**), formed by α-methyl migration.

Since House's[2] discovery of ketone migration in the boron trifluoride induced rearrangement of α,β-epoxy ketones, attention has been given to studies of rearrangement of various other α,β-epoxy carbonyl systems, including glycidic esters,[3] glycidic thiol esters,[4] and α,β-epoxy diazo ketones.[5] The reaction is of some mechanistic interest[2-4,6] in that it involves migration of an electron-deficient carbonyl carbon to a positive migration terminus. Recent work suggests that the

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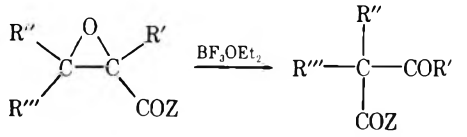
BF_3-induced rearrangement of glycidic esters is a concerted process proceeding with inversion of configuration at the migration terminus.[4c,6a]



Z = Ar, OR, SR, CHN_2

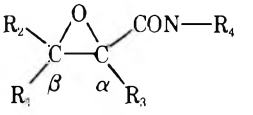
A study of the boron trifluoride induced rearrangement of glycidamides has not been reported, although examples of the reaction of glycidamides with aluminum chloride,[7] hydrochloric acid,[8,9] and sulfuric acid[9] are known. Thus *N*-methyl-*N*-phenyl-3,3-dimethylglycidamide is converted to 3-hydroxy-1,4,4-trimethyl-2(1*H*)-quinolinone in the presence of aluminum chloride.[7] Blicke and Faust[8] found that the 3,3-diphenylglycidamide is isomerized to diphenylpyruvamide when heated with HCl. Tung and Speziale[9] observed stereospecific conversion of (*E*)- and (*Z*)-*N*,*N*-diethyl-3-phenylglycidamides to the corresponding erythro and threo vicinal diols or chlorohydrins using aqueous sulfuric acid and hydrochloric acid in benzene or methanol solvents. In these cases the amide carbonyl function was not found to migrate. Indeed only one example of amide migration is known. This was observed in the base-induced benzilic acid rearrangement of α,β-diketo amides to α-hydroxymalonamides.[10]

We have thus undertaken a study of the boron trifluoride induced rearrangement of tertiary glycidamides with a view to evaluating the potential for amide migration in this system as well as to explore the synthetic utility of the process. At the outset it was recognized that the amide function is relatively basic and would thus compete effectively with the epoxide oxygen for the Lewis acid catalyst. Thus initially we examined the reaction of boron trifluoride etherate with relatively nonbasic amides, including *N*-phenyl- and *N*,*N*-diphenylglycidamides. α-Methyl- as well as β-methyl-substituted glycidamides were also studied in view of the observation by Kagan[3] that, whereas ethyl 3-phenylglycidate did not undergo rearrangement with ester migration, ethyl 2-methyl-3-phenylglycidate as well as ethyl 3-methyl-3-phenylglycidate did give ester migration products in high yield. In general we found a wide variety of products, including fluorohydrins, 2-hydroxy-3-butenamides and their BF_2 complexes, and both intra- and intermolecular Friedel–Crafts condensation products. In one instance a β-keto amide was obtained as a result of migration of the amide function. However, it appears that rearrangement with amide migration is not a pathway of major importance in the reaction of tertiary glycidamides with boron trifluoride etherate.

Results and Discussion

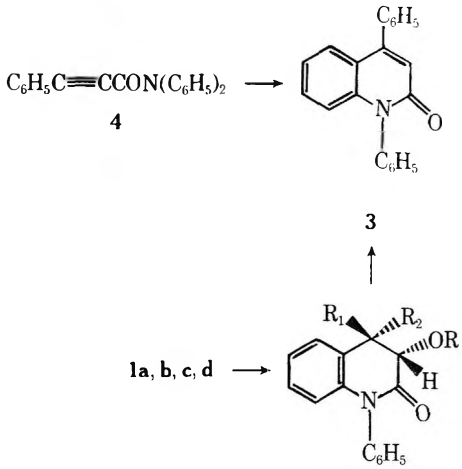
The required glycidamides were prepared by Darzens condensation of α-chloro tertiary amides with aldehydes and ketones using potassium *tert*-butoxide as the base.[9a,11] (*E*)-*N*,*N*-Diphenyl-3-phenylglycidamide (**1a**) was also obtained by *m*-chloroperbenzoic acid[12] epoxidation of (*E*)-*N*,*N*-diphenylcinnamamide.

The major process observed in the rearrangement of *N*,*N*-diphenyl tertiary glycidamides was intramolecular Friedel–Crafts cyclization, resulting in stereospecific formation of 3-hydroxy-4-phenyl-2(1*H*)-quinolinones. Of interest in this connection is the fact that formation of comparable intramolecular cyclization products was not found in the BF_3-induced rearrangement of *S*-phenyl thiolglycidates[4] or related phenyl oxygen glycidate esters,[3b] and such cyclization is probably not an important mode of reaction in these cases. Treatment of (*E*)-*N*,*N*-diphenyl-3-phenylglycidamide (**1a**)



1a, R_1, R_4, R_5 = C_6H_5; R_2, R_3 = H
b, R_2, R_4, R_5 = C_6H_5; R_1, R_3 = H
c, R_1, R_4, R_5 = C_6H_5; R_2 = CH_3; R_3 = H
d, R_2, R_4, R_5 = C_6H_5; R_1 = CH_3; R_3 = H
e, R_1 = C_6H_5; R_2 = CH_3; R_3 = H; R_4, R_5 = CH_2CH_3
f, R_1 = C_6H_5; R_2, R_4, R_5 = CH_3; R_3 = H
g, R_1, R_4 = C_6H_5; R_3, R_5 = CH_3; R_2 = H
h, R_1 = C_6H_5; R_3, R_4, R_5 = CH_3; R_2 = H
i, R_2 = C_6H_5; R_3, R_4, R_5 = CH_3; R_1 = H

with boron trifluoride etherate in refluxing benzene led to (*E*)-1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinone (**2a**) in 87%



2a, R, R_2 = H; R_1 = C_6H_5
b, R = $COCH_3$; R_1 = C_6H_5; R_2 = H
c, R = tosyl; R_1 = C_6H_5; R_2 = H
d, R, R_1 = H; R_2 = C_6H_5
e, R = tosyl; R_1 = H; R_2 = C_6H_5
f, R = H; R_1 = C_6H_5; R_2 = CH_3
g, R = $COCH_3$; R_1 = C_6H_5; R_2 = CH_3
h, R = H; R_1 = CH_3; R_2 = C_6H_5
i, R = $COCH_3$; R_1 = CH_3; R_2 = C_6H_5

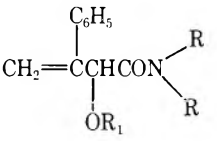
yield. Quinolinone **2a** was also obtained in high yield when the reaction was carried out in methylene chloride at room temperature for 30 min. The quinolinone assignment for **2a** was based on conversion to the corresponding fully aromatic quinolone **3** by pyrolysis of acetate **2b** or alternatively by heating tosylate **2c** with sodium hydroxide or sodium acetate in ethanol. The structure of **3** was established by independent synthesis involving treatment of *N*,*N*-diphenyl-3-phenylpropiolamide with boron trifluoride etherate in benzene.[13] The *E* configuration of **2a** was inferred from the fact that relatively low temperatures (250 °C) were sufficient in the acetate pyrolysis of **2b**. Furthermore, comparatively severe conditions were needed in the base-induced elimination of tosylate **2c** to give quinolone **3**. It was necessary to use excess sodium acetate in refluxing ethanol for 48 h to accomplish complete conversion of **2c** to **3**.

Using the same reaction conditions employed with (*E*)-glycidamide **1a** in benzene solvent, the *Z* isomer, **1b**, was converted to (*Z*)-1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinone (**2d**) in 75% yield. Assignment of the *Z* configuration to **2d** is supported by the observation that the tosylate derivative **2e** underwent facile elimination to quinolone **3** by treatment with sodium acetate in refluxing ethanol. The (*Z*)-tosylate **2e** was completely converted to quinolone **3** within 1 h. Under the same conditions less than 20% of (*E*)-tosylate **2c** was converted to quinolone **3**. Vicinal coupling constants for **2a** (14 Hz), **2b** (13 Hz), and **2d** (7 Hz) are in agreement with the stereochemical assignments. The closeness found for the values

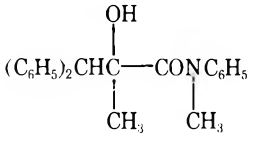
of **2c** (7 Hz) and **2e** (6 Hz) have precedent in earlier work on *E* and *Z* isomers of 3-methylamino-4-phenyl-2(1*H*)-quinolinone.[15]

NMR analysis of the crude reaction mixture obtained from the BF_3-induced rearrangement of (*Z*)-glycidamide **1b** did not indicate the presence of any (*E*)-quinolinone **2a.** Similarly, (*Z*)-quinolinone **2d** was not found in the rearrangement of (*E*)-glycidamide **1a.** Thus the formation of these quinolinones appears to be highly stereospecific. The generation of (*E*)-quinolinone **2a** from (*E*)-glycidamide **1a** and (*Z*)-quinolinone **2d** from (*Z*)-glycidamide **1b** suggests that the epoxide ring is opened with inversion of configuration at the β position.

The boron trifluoride induced rearrangement of (*E*)- and (*Z*)-*N,N*-diphenyl-3-methyl-3-phenylglycidamides (**1c,d**) proved to be somewhat less stereospecific. Both quinolinone isomers were isolated from the rearrangement of each of these glycidamides. However, one isomer, **2f,** which is presumably (*E*)-1,4-diphenyl-3-hydroxy-4-methyl-2(1*H*)-quinolinone, was the major product obtained from (*E*)-glycidamide **1c.** The (*Z*)-glycidamide **1d** gave predominantly the other isomer, presumably (*Z*)-quinolinone **2h.** The stereochemical assignments for **2f** and **2h** have not been rigorously established. In both rearrangements a lesser amount of *N,N*-diphenyl-2-hydroxy-3-phenyl-3-butenamide (**5a**) was also formed.



5a, R = C_6H_5; R_1 = H
b, R = C_6H_5; R_1 = $COCH_3$
c, R = C_2H_5; R_1 = BF_2
d, R = C_2H_5; R_1 = H
e, R = C_2H_5; R_1 = $COCH_3$
f, R = CH_3; R_1 = H



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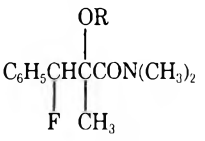
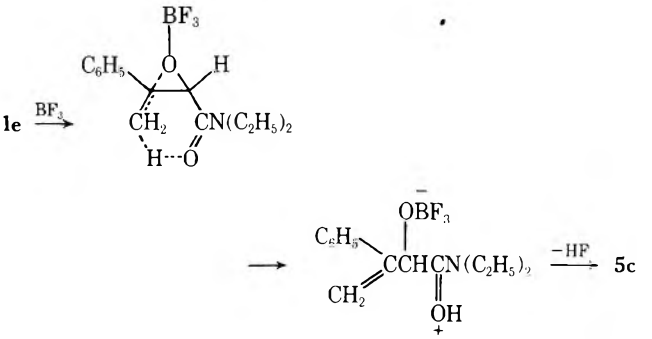


7a, R = H
b, R = BF_2
c, R = $COCH_3$

Analysis of the NMR spectrum of the crude reaction mixture from rearrangement of *E* isomer **1c** indicated an approximate ratio of 6:2.5:1.5 for compounds **2f, 2h,** and **5a,** respectively, while a ratio of 1:8:1 was found in the rearrangement of *Z* isomer **1d.**

Butenamide formation was also observed in the rearrangement of *N,N*-diethyl-3-methyl-3-phenylglycidamide (**1e**) in either benzene or methylene chloride solvent. When the reaction was carried out in benzene the BF_2 derivative **5c** was the major product isolated in 77% yield. **5c** was converted to the corresponding alcohol **5d** using sodium hydroxide in ethanol. Alcohol **5d** was obtained directly when the rearrangement was carried out in methylene chloride. Similarly, *N,N*-dimethyl-3-methyl-3-phenylglycidamide (**1f**) led primarily to hydroxybutenamide **5f** using boron trifluoride etherate in methylene chloride solvent. A rearrangement process of this type has been noted earlier in the reaction of BF_3 with 3-methyl-3-phenylglycidic esters,[3] although products arising from ester or alkyl group migration predominated in most of these cases. In contrast, this type of process was not observed for the BF_3-induced rearrangement of *S*-phenyl 3-methyl-3-phenylthiolglycidate[4] or in the corresponding β-methyl-β-phenyl α,β-epoxy ketone system.[2] In the amide case butenamide formation appears to be the major rearrangement process for *N,N*-dialkyl-3-methyl-3-phenylglycidamides. In the formation of butenamide **5c** the relatively basic *N,N*-dialkylamide function could assist in removal of a proton from the β-methyl group in formation of the product double bond (Scheme I). It is not clear in this case whether or not a carbonium ion intermediate is involved in the mechanism.

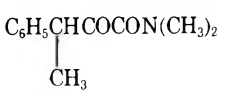
Scheme I



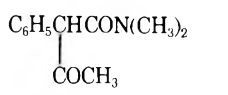
We have also examined the reaction of *N*-methyl-*N*-phenylglycidamide **1g** with boron trifluoride etherate in benzene solvent. As with the other BF_3-induced quinoline syntheses reported here, this reaction was also stereospecific. The presence of only one quinolinone isomer was indicated in the NMR spectrum of the crude reaction mixture. This compound is believed to be (*E*)-3,4-dihydro-1,3-dimethyl-3-hydroxy-4-phenyl-2(1*H*)-quinolinone. Also in the rearrangement of **1g,** a Friedel–Crafts reaction with benzene solvent was observed, resulting in formation of *N*-methyl-*N*-phenyl-3,3-diphenyl-2-hydroxy-2-methylpropionamide (**6**). A similar Friedel–Crafts reaction with solvent has been noted previously in the boron trifluoride induced rearrangement of ethyl 2-methyl-3-phenylglycidate in toluene solvent.[3b]

The rearrangement of (*Z*)-*N,N*-dimethyl-2-methyl-3-phenylglycidamide (**1i**) in methylene chloride led to formation of fluorohydrin (**7a**) along with its BF_2 derivative (**7b**). It is interesting that under the same conditions the *E* isomer **1h** gave rise to the same fluorohydrin diastereomer. A related result has been noted earlier by Tung and Speziale[9b] in the HCl-induced rearrangement of (*E*)- and (*Z*)-*N,N*-diethyl-3-phenylglycidamides in benzene solvent, leading in either case to the threo isomer of *N,N*-diethyl-3-chloro-3-phenyl-2-hydroxypropionamide. These workers suggest that neighboring group participation involving the amide function plays a role in the conversion of the *trans*-glycidamide to the *threo*-chlorohydrin, involving overall retention of configuration at the β position. It is likely that a similar neighboring group effect is involved in the BF_3-induced conversion of **1h** or **1i** to **7a.**

When under more severe conditions (*Z*)-glycidamide **1i** was warmed for 3.5 h in refluxing methylene chloride in the presence of excess boron trifluoride etherate, there was obtained a mixture of *erythro*- and *threo*-fluorohydrin stereoisomers **7a** along with smaller amounts of *N,N*-dimethyl-3-phenyl-3-methylpyruvamide (**8**) and *N,N*-dimethyl-2-phenylacetoacetamide (**9**). Formation of this same mixture



8



9

of **8** and **9** along with the two fluorohydrin diastereomers was found when **7a** was warmed in refluxing methylene chloride for 3 h in the presence of excess boron trifluoride etherate. However, neither fluorohydrin diastereomer was found after **1i** was allowed to reflux for 6 h in chloroform in the presence of excess boron trifluoride etherate. Under these conditions pyruvamide **8** was isolated in 19% yield along with a smaller amount (~5%) of **9.** When **1i** was allowed to reflux for 6 h in chloroform in the presence of only 1 equiv of boron trifluoride

etherate there was obtained 15% pyruvamide **8**, 27% acetoacetamide **9**, and 10% of the mixture of fluorohydrin diastereomers. Acetoacetamide **9** is the product expected from amide migration. The structure of **9** was established by conversion to 3-methyl-4-phenyl-3-pyrazolin-5-one using hydrazine hydrate in ethanol.

These results suggest that glycidamide **1i** is initially converted to fluorohydrin **7a** or its BF_2 derivative **7b**. Under more severe conditions the fluorohydrin undergoes rearrangement with either methyl or amide migration. A parallel for this is seen in the rearrangement of (*E*)-benzalacetophenone oxide with excess boron trifluoride etherate to give a mixture of *threo*-3-fluoro-2-hydroxy-1,3-diphenyl-1-propanone and α-formyldeoxybenzoin.[16] In the presence of excess boron trifluoride etherate the fluorohydrin is converted directly to α-formyldeoxybenzoin, the rearrangement product formed as a result of benzoyl migration. Kinetic examination[2e] of this process did not permit a distinction between direct conversion of the epoxy ketone to the rearrangement product as opposed to involvement of the fluorohydrin as an obligatory intermediate in the rearrangement.

In the rearrangement of **1i** in refluxing chloroform the percent of amide migration relative to α-methyl migration increases as the concentration of BF_3 is lowered. This result may be explained if we assume that coordination of BF_3 with the amide carbonyl group would lower its migratory aptitude. With excess BF_3 present it is conceivable that the amide function could be complexed with 1 molecule of BF_3 at the same time a second BF_3 molecule is involved in generating an electron-deficient site at the β position. This would give methyl migration an advantage, thus increasing the relative amount of the pyruvamide product when higher concentrations of catalyst are employed.

In summary, amide migration does not appear to be as general a phenomena as ketone, ester, or thiol ester migration, at least in the BF_3-induced rearrangement of α,β-epoxy carbonyl systems. For example, *N*-arylglycidamides tend to undergo intramolecular Friedel–Crafts cyclization in contrast to *S*-aryl thiol esters[4] or *O*-aryl oxygen esters,[3b] which give carbonyl or hydrogen migration products. β-Methylglycidamides give butenamides rather than products resulting from carbonyl migration, while glycidic esters[3] give both types of products and α,β-epoxy ketones[2] as well as glycidic thiol esters[4] give primarily the carbonyl migration product. With respect to a glycidamide system such as **1i** where butenamide formation or intramolecular Friedel–Crafts cyclization is not possible, the amide shift does occur but only after initial conversion to the fluorohydrin adduct. Relatively severe conditions are then required before this fluorohydrin will give rearrangement with amide migration. One explanation for this apparent reluctance of the amide group to migrate lies in its high relative basicity. This property may lead to serious competing reactions, including strong coordination of the amide function with the Lewis acid catalyst or amide carbonyl association with the electron-deficient β position to give a 2-amino-2-oxetanyl cation intermediate. It is of interest that, when these side reactions are reduced by the use of only 1 equiv of catalyst, the relative importance of amide migration increases to the point where the migratory aptitude of the amide function is greater than that of the α-methyl group.

In any case, the reaction of BF_3 with tertiary glycidamides appears to have considerable synthetic utility. The process offers an efficient stereospecific method for the preparation of 3-hydroxy-4-phenyl-2(1*H*)-quinolinones from the corresponding *N*-phenyl tertiary glycidamides. *N,N*-Dialkyl-3-phenyl-3-methylglycidamides are converted in high yield to the corresponding 2-hydroxy-3-butenamides, and fluorohydrins may be obtained stereospecifically in high yield from *N,N*-dialkyl-2-methyl-3-phenylglycidamides.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrometer. The ultraviolet spectra were recorded on a Cary Model 14 spectrometer. Nuclear magnetic resonance spectra were recorded on the Varian A-60A spectrometer using tetramethylsilane as an internal standard. Benzene was dried over sodium metal, and ether was dried over $LiAlH_4$. Both were distilled prior to use. The *tert*-butyl alcohol was dried over CaH_2 and distilled prior to use. Methylene chloride and chloroform were dried over phosphorus pentoxide and distilled prior to use. The petroleum ether had a boiling point range of 60–110 °C. The silica gel used for column chromatography was Baker reagent grade (60–200 mesh). Silica gel GF-254 (Merck) was used for the preparative thin-layer chromatography. Melting points and boiling points are uncorrected. Elemental analyses were performed by M. H. W. Laboratories, Garden City, Mich.

(*E*)-*N,N*-Diethyl-3-methyl-3-phenylglycidamide (1e) was prepared according to the method of Speziale and Frazier:[11] mp 94–95 °C (lit.[11] mp 94–95 °C); NMR ($CDCl_3$) δ 0.62 (t, 3 H, *J* = 7.5 Hz), 1.09 (t, 3 H, *J* = 7.5 Hz), 1.78 (s, 3 H), 2.70–3.50 (m, 4 H), 3.65 (s, 1 H), 7.05–7.50 (m, 5 H); IR (KBr) 1665 cm^{-1}.

The following glycidamides were prepared in a similar fashion: **(*E*)- and (*Z*)-*N,N*-diphenyl-3-phenylglycidamides (1a,b)** were obtained in the reaction of *N,N*-diphenyl-2-chloroacetamide[17] with benzaldehyde. The NMR spectrum of the crude reaction mixture indicated the presence of approximately 70% of the *E* isomer and 30% *Z*. Treatment of the mixture with 1:1 ether and hexane led to formation of crystals of **1a**, which were purified by fractional crystallization from ethanol. This afforded pure **1a** in 59% yield: mp 111–112 °C; NMR ($CDCl_3$) δ 3.39 (d, 1 H, *J* = 1.5 Hz), 4.27 (d, 1 H, *J* = 1.5 Hz), 7.32 (s) and 7.36 (s) (15 H); IR (KBr) 1675 cm^{-1}; UV λ_{max} (EtOH) 233 nm (ε 14 400). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.51; N, 4.44. Found: C, 80.12; H, 5.59; N, 4.49.

The hexane–ether mother liquors obtained from the isolation of **1a** were concentrated to give a yellow oil which was dried under reduced pressure for 3 days. The resulting solid was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in benzene. The purified material was recrystallized from benzene–hexane to give the pure *Z* isomer **1b** in 25% yield: mp 112–114 °C; NMR ($CDCl_3$) δ 3.75 and 3.85 (AB quartet, 2 H, *J* = 4.5 Hz), 6.88–7.50 (m, 15 H); IR (KBr) 1675 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.51; N, 4.44. Found: C, 80.13; H, 5.64; N, 4.31.

(*E*)- and (*Z*)-*N,N*-diphenyl-3-methyl-3-phenylglycidamide (1c,d) were obtained in about equal amounts in the Darzens condensation of acetophenone with *N,N*-diphenyl-2-chloroacetamide. The mixture was separated by fractional crystallization from ethanol and water. For the *E* isomer **1c**: mp 143–144 °C; NMR ($CDCl_3$) δ 1.80 (s, 3 H), 3.24 (s, 1 H), 7.25 (singlet superimposed on a multiplet between δ 6.90 and 7.40, 15 H); IR (KBr) 1680 cm^{-1}; UV λ_{max} (EtOH) 238 nm (ε 16 300). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.98; H, 5.96; N, 4.09.

For the *Z* isomer **1d**: mp 120–121 °C; NMR ($CDCl_3$) δ 1.40 (s, 3 H), 3.65 (s, 1 H), 6.70–7.60 (m, 15 H); IR (KBr) 1680 cm^{-1}; UV λ_{max} (EtOH) 233 nm (ε 12 300). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.42; H, 5.72; N, 4.12.

(*E*)-*N*-Methyl-*N*-phenyl-2-methyl-3-phenylglycidamide (1g) was obtained from benzaldehyde and *N*-methyl-*N*-phenyl-2-chloropropionamide in 68% yield: mp 149–151 °C; NMR ($CDCl_3$) δ 1.15 (s, 3 H), 3.38 (s, 3 H), 4.10 (s, 1 H), 6.85–7.50 (m, 10 H); IR (KBr) 1650 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.19; H, 6.26; N, 5.18.

N-Methyl-*N*-phenyl-2-chloropropionamide was prepared from *N*-methylaniline and 2-chloropropionyl chloride (Aldrich Chemical Co.) in ether in the presence of pyridine: mp 49–51 °C (ethanol); NMR (CCl_4) δ 1.50 (d, 1 H, *J* = 6.5 Hz), 3.25 (s, 3 H), 4.25 (q, 1 H, *J* = 6.5 Hz), 7.38 (s, 5 H). Anal. Calcd for $C_{10}H_{12}NOCl$: C, 60.76; H, 6.12; N, 7.09; Cl, 17.94. Found: C, 60.69; H, 5.99; N, 7.03; Cl, 18.17.

(*E*)-*N,N*-Dimethyl-3-methyl-3-phenylglycidamide (1f) was obtained from acetophenone and *N,N*-dimethyl-2-chloroacetamide[18] in 60% yield: mp 57–58 °C; NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.66 (s, 3 H), 2.97 (s, 3 H), 3.71 (s, 1 H), 7.17–7.53 (m, 5 H); IR (KBr) 1650 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.07; H, 7.35; N, 6.83. Found: C, 70.07; H, 7.35; N, 6.75.

(*E*)- and (*Z*)-*N,N*-dimethyl-2-methyl-3-phenylglycidamides (1h,i) were obtained from benzaldehyde and *N,N*-dimethyl-2-chloropropionamide[19] in 49% yield (60% *E* and 40% *Z*). The two isomers were separated by preparative thin-layer chromatography on silica gel using 3:1 benzene–ethyl acetate as eluent. The *Z* isomer **1i** was recrystallized from benzene–hexane: mp 98–100 °C; NMR ($CDCl_3$) δ 1.69 (s, 3 H), 2.70 (s, 3 H), 2.85 (s, 3 H), 3.93 (s, 1 H), 7.26 (s, 5 H); IR

(KBr) 1645 cm^{-1}. Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.31; H, 7.45; N, 6.45.

The *E* isomer **1h** was obtained as an oil: NMR ($CDCl_3$) δ 1.30 (s, 3 H), 2.98 (s, 3 H), 3.17 (s, 3 H), 4.17 (s, 1 H), 7.36 (s, 5 H); IR (film) 1650 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.97; H, 7.35; N, 6.54.

Epoxidation of (*E*)-*N,N*-Diphenylcinnamamide. The following procedure was also used in the preparation of **1a:** 85% *m*-chloroperbenzoic acid (1.31 g, 6.5 mmol) in methylene chloride (30 mL) was added to (*E*)-*N,N*-diphenylcinnamamide[20] (5.0 mmol, 1.50 g) in methylene chloride (30 mL). The reaction was allowed to reflux for 56 h before workup by extraction with saturated sodium sulfite followed by repeated extractions with 5% sodium bicarbonate. Evaporation of the methylene chloride gave a residue which was subjected to column chromatography on silica gel eluting with benzene and chloroform, affording **1a** as a solid. Recrystallization from ethanol gave pure **1a**, mp 110–111 °C. The NMR spectrum of this material was identical with that of **1a** obtained in the Darzens condensation described above. The mixture melting point with the Darzens material was not depressed.

Reaction of 1a with Boron Trifluoride Etherate. An excess of boron trifluoride etherate (15 mL, 0.12 mol) was added to a solution of **1a** (1.40 g, 4.4 mmol) in anhydrous benzene (50 mL) under nitrogen, and the mixture was refluxed for 8 h. After cooling to room temperature the benzene solution was washed with 5% NaCl. The benzene layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give the quinolinone product **2a** (1.21 g, 3.8 mmol, 87%), mp 225–228 °C. An analytical sample was obtained by recrystallization from 1:1 chloroform–petroleum ether: mp 230–231 °C; NMR ($CDCl_3$) δ 3.91 (d, 1 H, J = 1.5 Hz, exchangable with D_2O), 4.36 (d, 1 H, J = 14 Hz), 4.81 (doublet of doublets, 1 H, J = 14, 1.5 Hz), 6.50–7.85 (m, 14 H); IR (KBr) 3450, 1670 cm^{-1}; λ_{max} (EtOH) 252 nm (ϵ 10 000). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.51; N, 4.44. Found: C, 80.07; H, 5.44; N, 4.44.

Acetate 2b was obtained by treating **2a** (0.12 g, 0.38 mmol) with acetic anhydride (3 mL) and pyridine (3 mL). The mixture was kept overnight at room temperature. The excess pyridine and acetic anhydride were evaporated under reduced pressure, and water (2 mL) was added to the residual oil. This resulted in the formation of a white solid (0.102 g, 75%), mp 151–153 °C. Recrystallization from ethanol gave an analytical sample: mp 156–157 °C; NMR ($CDCl_3$) δ 1.92 (s, 3 H), 4.59 (d, 1 H, J = 13 Hz), 5.93 (d, 1 H, J = 13 Hz), 6.30–7.60 (m, 14 H); IR (KBr) 1700, 1750 cm^{-1}. Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.37; H, 5.32; N, 3.93. Found: C, 77.60; H, 5.47; N, 3.85.

Tosylate 2c was prepared in the following manner. A solution of *p*-toluenesulfonyl chloride (1.81 g) in anhydrous benzene (20 mL) was added to a solution of **2a** (3.00 g) in benzene (120 mL). In a separate flask sodium hydride (2.28 g of a 57% dispersion in mineral oil) was washed with hexane (2 × 25 mL) and benzene (20 mL) was added. This NaH–benzene suspension was then added to the mixture of **2a** and *p*-toluenesulfonyl chloride. After stirring for 80 min at room temperature, the mixture was filtered through a scintered glass funnel and the benzene layer was concentrated to give a solid (4.02 g, 90%), mp 186–189 °C. This was recrystallized from ethanol to give an analytical sample: mp 190–192 °C; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 4.54 (d, 1 H, J = 7 Hz), 5.33 (d, 1 H, J = 7 Hz), 6.20–6.50 (m, 1 H), 6.80–7.70 (m, 17 H); IR (KBr) 1705 cm^{-1}. Anal. Calcd for $C_{28}H_{23}NO_4S$: C, 71.62; H, 4.90; N, 2.98; S, 6.82. Found: C, 71.74; H, 4.95; N, 2.78; S, 6.60.

Conversion of Acetate 2b to 1,2-Dihydro-1,4-diphenyl-2-quinolone (3). 2b (1.20 g, 3.8 mmol) was placed in a short-path distillation flask and heated under nitrogen for 4 h at 240 °C. A liquid distilled out of the flask, leaving a residue that solidified on cooling. The resulting solid was washed with a 1:1 mixture of ether and petroleum ether (50 mL) to give impure crystals, mp 110–120 °C. Recrystallization from ether gave pure **3** (0.752 g, 2.5 mmol, 67%): mp 150–152 °C; NMR ($CDCl_3$) δ 6.85–7.70 (m, 13 H), 6.60–6.80 (m, 2 H); IR (KBr) 1655 cm^{-1}; UV λ_{max} (EtOH) 225 nm (ϵ 62 000), 280 (20 000), 330 (11 900). Anal. Calcd for $C_{21}H_{15}NO$: C, 84.84; H, 5.05; N, 4.71. Found: C, 84.89; H, 5.10; N, 4.84. This material was found to be identical (mixture melting point and IR spectra) with authentic **3** prepared as described below.

Conversion of Tosylate 2c to Quinolone 3. 2c (0.500 g, 1.1 mmol) in absolute ethanol (100 mL) was treated with a solution of sodium acetate (4.49 g, 54 mmol) in absolute ethanol (70 mL). This was refluxed for 48 h. The ethanol was evaporated under reduced pressure, and the residue was treated with water (25 mL) and benzene (50 mL). The benzene layer was separated, and the aqueous solution was extracted again with benzene (2 × 50 mL). The combined benzene extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give an oil. Addition of ether resulted in formation of a solid (0.320 g). Recrystallization from a 1:1 mixture of ether and petroleum ether gave pure **3**: mp 150–152 °C; NMR ($CDCl_3$) δ 6.85–7.70 (m, 13 H), 6.60–6.80 (m, 2 H); IR (KBr) 1655 cm^{-1}; UV λ_{max} (EtOH) 225 nm (ϵ 64 000), 280 (21 600), 330 (13 500). The mixture melting point with authentic **3**, prepared as described below, was not depressed. The IR spectra of both samples were identical.

***N,N*-Diphenyl-3-phenylpropiolamide (4) and Its Conversion to Quinolone 3.** To a mixture of *N,N*-diphenylamine (1.35 g, 8.0 mmol) and pyridine (0.63 g, 8.0 mmol) in anhydrous ether (70 mL) was added dropwise at 0 °C under nitrogen atmosphere phenylpropiolyl chloride[21] (1.29 g, 7.9 mmol) in ether (10 mL) over a period of 1.5 h. The reaction was maintained at 0 °C for an additional 2 h, followed by 1 h at room temperature. Water (10 mL) and ether (50 mL) were added. The ether layer was separated, and the aqueous layer was extracted again with ether (50 mL). The combined ether layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow solid (2.20 g, 93%), mp 136–138 °C. Recrystallization from ether and petroleum ether gave an analytical sample of **4** as colorless prisms: mp 141–142 °C; NMR ($CDCl_3$) δ 7.20 (s) and 7.35 (s) superimposed on a multiplet between δ 7.00 and 7.55; IR (KBr) 2220, 1640 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO$: C, 84.84; H, 5.05; N, 4.71. Found: C, 84.72; H, 5.25; N, 4.46.

An excess of boron trifluoride etherate (10 mL, 0.80 mmol) was added to a solution of **4** (0.500 g, 1.7 mmol) in anhydrous benzene (50 mL) under a nitrogen atmosphere, and the solution was refluxed for 36 h. It was then washed with a 5% NaCl solution, and the benzene layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel, eluting with petroleum ether followed by a mixture of petroleum ether and ether (1:1), to obtain the product. This was recrystallized from ether to give pure **3** (0.260 g, 52%), mp 150–152 °C.

Rearrangement of 1b. The same procedure used with **1a** was followed. NMR analysis of the crude reaction mixture indicated the presence of only the *Z* isomer of 1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinone (**2d**). Recrystallization from benzene–hexane gave pure (*Z*)-quinolinone (75%): mp 134–136 °C; NMR ($CDCl_3$) δ 3.68 (s, 1 H), 4.50 (d, 1 H, J = 7 Hz), 4.82 (d, 1 H, J = 7 Hz), 6.50–7.70, (m, 14 H); IR (KBr) 3450, 1680 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.51; N, 4.44. Found: C, 79.73; H, 5.54; N, 4.19.

Tosylate 2e was prepared using the same procedure described earlier for the preparation of tosylate **2c.** The product was purified by preparative thin-layer chromatography on silica gel, eluting with absolute ethanol in benzene. An analytical sample was obtained by recrystallization from benzene: mp 171–172 °C; NMR ($CDCl_3$) δ 2.38 (s, 3 H), 4.66 (d, 1 H, J = 6 Hz), 5.68 (d, 1 H, J = 6 Hz), 6.35–6.65 (m, 1 H), 6.90–7.55 (m, 15 H), 7.84 (d, 2 H, J = 9 Hz); IR (KBr) 1700 cm^{-1}. Anal. Calcd for $C_{28}H_{23}NO_4S$: C, 71.62; H, 4.90; N, 2.98; S, 6.82. Found: C, 71.88; H, 5.08; N, 2.80; S, 6.68.

Conversion of Tosylate 2e to Quinolone 3. Tosylate **2e** (50 mg) was dissolved in benzene (0.5 mL), and 4 mL of a solution of sodium acetate (4.1 g) in 95% ethanol (100 mL) was added. The mixture was allowed to reflux for 1 h, at which point TLC analysis indicated complete conversion to quinolone **3.** Workup in the usual way followed by recrystallization from ether and hexane gave pure **3**, mp 151–153 °C. The mixture melting point with authentic **3** was not depressed. The IR spectrum was identical with that of authentic **3.**

Using the same reaction conditions the conversion of tosylate **2c** to **3** was less than 20% complete after refluxing for a period of 1 h.

Rearrangement of 1c. The procedure used with **1a** was followed with the exception that the reaction was complete within 4 h at reflux in benzene. NMR analysis of the crude reaction mixture indicated that it contained **2f, 2h,** and **5a** in a ratio of 6:2.5:1.5. The crude oil was treated with ether to give a solid which was recrystallized from ethanol to give pure **2f** (50%): mp 179–180 °C; NMR ($CDCl_3$) δ 1.70 (s, 3 H), 3.75 (d, 1 H, J = 2 Hz, exchangeable with D_2O), 4.87 (d, 1 H, J = 2 Hz), 6.70–7.80 (m, 14 H); IR (KBr) 3450, 1675 cm^{-1}; UV λ_{max} (EtOH) 258 nm (ϵ 16 000). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.20; H, 6.08; N, 4.22.

A second compound, **5a,** was isolated as a solid from the mother liquors obtained from recrystallization of **2f.** This material was recrystallized from ethanol to give pure **5a** (10%): mp 155–156 °C; NMR ($CDCl_3$) δ 4.10 (broad s, 1 H), 5.05 (s, 1 H), 5.15 (s, 1 H), 5.25 (s, 1 H), 7.10–7.30 (m, 15 H); IR (KBr) 3440, 1660, 920 cm^{-1}; UV λ_{max} (EtOH) 238 nm (ϵ 10 100). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.47; H, 5.59; N, 4.24.

2h was isolated by subjecting some of the material obtained from the crude reaction mixture to preparative thin-layer chromatography on silica gel, eluting with 2% ethanol in benzene (**2h** ran just below the other quinolinone **2f**). The **2h** isolated in this way was identical with the major product obtained in the reaction of **1d** with boron trifluoride

etherate as described below.

Acetate 2g: mp 190–191 °C; NMR ($CDCl_3$) δ 1.81 (s, 3 H), 1.88 (s, 3 H), 6.17 (s, 1 H), 6.35–7.60 (m, 14 H); IR (KBr) 1750, 1700 cm^{-1}; UV λ_{max} (EtOH) 255 nm (ε 13 000). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.69; N, 3.77. Found: C, 77.39; H, 5.49; N, 3.57.

Acetate 5b: mp 116–117 °C; NMR ($CDCl_3$) δ 2.08 (s, 3 H), 5.51 and 5.55 (s, 2 H), 6.01 (s, 1 H), 7.00–7.25 (m, 15 H); IR (KBr) 1740, 1685, 930 cm^{-1}; UV λ_{max} (EtOH) 238 nm (ε 22 000). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.69; N, 3.77. Found: C, 77.61; H, 5.96; N, 3.57.

Rearrangement of 1d. This was carried out employing the same procedure used with **1c**. NMR analysis of the crude reaction mixture indicated the presence of **2f, 2h,** and **5a** in a ratio of 1:8:1. The major product, **2h,** was obtained by column chromatography on silica gel, eluting initially with benzene followed by 0.5% ethanol in benzene. Recrystallization from hexane and benzene gave an analytical sample: mp 150–151 °C; NMR ($CDCl_3$) δ 2.02 (s, 3 H), 3.98 (d, 1 H, J = 3.5 Hz, exchangeable with D_2O), 4.52 (d, 1 H, J = 3.5 Hz), 6.50–7.65 (m, 14 H); IR (KBr) 3470, 1685 cm^{-1}; UV λ_{max} (EtOH) 246 nm (ε 10 000). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.50; H, 5.79; N, 4.22.

Acetate 2i: mp 146–147 °C; NMR ($CDCl_3$) δ 1.87 (s, 3 H), 2.35 (s, 3 H), 5.77 (s, 1 H), 6.45–7.65 (m, 14 H); IR (KBr) 1755, 1710 cm^{-1}; UV λ_{max} 246 nm (ε 10 000). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.85; H, 5.78; N, 3.81.

Rearrangement of 1e. The same conditions were followed that were employed with **1a** with the exception that the reaction was refluxed for 5 h in benzene. Using the same workup procedure, crude **5c** was obtained in 77% yield, mp 120–122 °C. Recrystallization from ether and petroleum ether gave an analytical sample: mp 122–124 °C; NMR ($CDCl_3$) δ 0.85–1.30 (overlapping triplets, 6 H), 3.90 (m, 4 H), 5.30–5.65 (m, 3 H), 7.15–7.65 (m, 5 H); IR (KBr) 1665, 895 cm^{-1}; UV λ_{max} (EtOH) 240 nm (ε 11 200). Anal. Calcd for $C_{14}H_{18}NO_2BF_2$: C, 59.81; H, 6.40; N, 4.98; B, 3.85; F, 13.4. Found: C, 59.86; H, 6.54; N, 5.06; B, 3.8; F, 12.8.

The hydrolysis of **5c** (1.00 g, 3.5 mmol) was carried out in 95% ethanol (80 mL) using NaOH (0.30 g, 7.5 mmol). After standing overnight at room temperature, the base was neutralized with 10% HCl and the ethanol was removed under reduced pressure. The residue was treated with water and extracted with ether, and the combined ether extracts were dried (Na_2SO_4) and concentrated to give an oil (0.830 g) which was distilled under reduced pressure [bath temperature, 175 °C (0.25 mm)]. **5d** was obtained as a colorless oil that solidified in the receiver, mp 31–32 °C. Recrystallization from ether gave an analytical sample: mp 31–32 °C; NMR ($CDCl_3$) δ 1.03 (t, 6 H, J = 7.0 Hz), 2.80–3.70 (m, 4 H), 4.32 (d, 1 H, J = 6.0 Hz), 4.85 (d, 1 H, J = 6.0 Hz), 5.15 (s, 1 H), 5.34 (s, 1 H), 7.00–7.60 (m, 5 H); IR (KBr) 3400, 1640, 915 cm^{-1}; UV λ_{max} (EtOH) 236 nm (ε 10 700). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.00. Found: C, 72.27; H, 7.94; N, 5.87.

Acetate 5e: $n^{25}D$ 1.5233; NMR ($CDCl_3$) δ 0.90–1.30 (m, 6 H), 2.15 (s, 3 H), 3.95–3.75 (m, 4 H), 5.48 (s, 1 H), 5.63 (s, 1 H), 6.12 (s, 1 H), 7.20–7.50 (m, 5 H); IR (film) 1740, 1660, 915 cm^{-1}; UV λ_{max} (EtOH) 235 nm (ε 10 000). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.81; H, 7.63; N, 5.09. Found: C, 69.69; H, 7.87; N, 4.87.

Rearrangement of 1f. The glycidamide **1f** (0.50 g, 2.4 mmol) was suspended in anhydrous methylene chloride (25 mL) at room temperature, and boron trifluoride etherate (0.35 mL, 2.8 mmol) was added with stirring over a period of 1 min. The reaction was stirred for 1 h at room temperature before it was poured into a mixture of ether (100 mL) and water (100 mL). The layers were separated, and the water was reextracted with ether (100 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil (0.45 g). Examination of the NMR spectrum of this material indicated that it was essentially pure butenamide **5f**. An analytical sample was obtained by column chromatography on silica gel, eluting with 20% ethyl acetate in benzene, followed by short-path distillation under reduced pressure to give **5f** as a colorless oil: $n^{23}D$ 1.5417; NMR ($CDCl_3$) δ 2.78 (s, 3 H), 2.95 (s, 3 H), 4.41 (broad s, 1 H), 5.03 (broad s, 1 H), 5.20 (s, 1 H), 5.42 (s, 1 H), 7.15–7.65 (m, 5 H); IR (film) 3400, 1660, 1640, 910 cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.13; H, 7.56; N, 6.90.

Rearrangement of 1g was carried out in benzene solvent using the conditions described for **1c**. Analysis of the NMR spectrum of the crude reaction mixture indicated the presence of 1,3-dimethyl-4-phenyl-3-hydroxy-2(1*H*)-quinolinone and **6** in a ratio of 3:1. A small amount of unidentified material (~2%) was also obtained. The latter had low solubility in chloroform and melted with decomposition at 240–245 °C. The mixture was separated by column chromatography on silica gel, eluting with 1% ethanol in benzene. **6** was eluted first from the column. It was recrystallized from ethanol and hexane: mp 135–136 °C; NMR ($CDCl_3$) δ 1.24 (s, 3 H), 3.16 (s, 3 H), 3.80 (broad s, 1 H), 4.15 (s, 1 H), 6.75–7.50 (m, 15 H); IR (KBr) 3360, 1610 (broad) cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.89; H, 6.80; N, 3.88.

Further elution of the silica gel column gave the quinolinone, which was also recrystallized from ethanol and hexane: mp 159–160 °C; NMR ($CDCl_3$) δ 1.41 (s, 3 H), 3.47 (s, 3 H), 3.60 (s, 1 H, exchangeable with D_2O), 4.11 (s, 1 H), 6.85–7.45 (m, 9 H); IR (KBr) 3420, 1670 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.31; H, 6.45; N, 5.32.

Rearrangement of 1i and 1h. (*Z*)-Glycidamide **1i** (1.00 g, 4.86 mmol) was suspended in anhydrous methylene chloride (45 mL) under a nitrogen atmosphere, and boron trifluoride etherate (1.4 mL) was added with stirring over a period of 1 min. The reaction was allowed to stir at room temperature for 1.5 h before quenching by pouring into a mixture of water (200 mL) and ether (200 mL). The organic layer was separated, and the water layer was reextracted with ether (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a solid which by NMR analysis proved to be a mixture of fluorohydrin **7a** along with its BF_2 derivative **7b**. An identical result was obtained in the rearrangement of (*E*)-glycidamide **1h** carried out in a separate experiment using the same reaction conditions. This solid was washed with chloroform, and the remaining residue (0.50 g) was crystallized from acetone to give pure **7b:** mp 139–141 °C; NMR ($[CD_3]_2CO$) δ 1.55 (d, 3 H, J = 2 Hz), 3.35 (s, 3 H), 3.67 (s, 3 H), 5.95 (d, 1 H, J = 45 Hz), 7.30–7.80 (m, 5 H); IR (KBr) 1680 cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_2NF_3B$: C, 52.78; H, 5.54; N, 5.13. Found: C, 52.37; H, 5.78; N, 4.92.

The chloroform washings were combined and evaporated to give a residue (0.40 g) which was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in benzene, followed by crystallization from benzene–hexane to give **7a:** mp 87–89 °C; NMR ($CDCl_3$) δ 1.45 (d, 3 H, J = 2 Hz), 3.12 (s, 6 H), 4.50 (s, 1 H), 5.70 (d, 1 H, J = 45 Hz), 7.30 (s, 5 H); IR (KBr) 3410, 1620 cm^{-1}. Anal. Calcd for $C_{12}H_{16}NO_2F$: C, 64.00; H, 7.11; N, 6.22; F, 8.44. Found: C, 63.99; H, 7.23; N, 6.03; F, 8.22.

Acetate 7c was prepared by dissolving fluorohydrin **7a** (0.10 g) in acetyl chloride (3 mL) followed by stirring for 1.5 h at room temperature. The reaction was poured into ether (50 mL) and water (100 mL), and the water layer was separated and extracted with ether (50 mL). The combined ether layers were dried (Na_2SO_4) and concentrated to give a yellow oil (92 mg), which after standing at 5 °C for 4 days solidified. Crystallization from hexane gave an analytical sample: mp 61–63 °C; NMR ($CDCl_3$) δ 1.52 (d, 3 H, J = 1 Hz), 2.10 (s, 3 H), 3.03 (s, 6 H), 5.63 (d, 1 H, J = 45 Hz), 7.37 (s, 5 H); IR (KBr) 1745, 1640 cm^{-1}. Anal. Calcd for $C_{14}H_{18}NO_3F$: C, 62.92; H, 6.74; N, 5.24. Found: C, 62.68; H, 6.68; N, 5.43.

In a separate experiment boron trifluoride etherate (0.50 mL, 4 mmol) was added to **1i** (205 mg, 1.0 mmol) in anhydrous methylene chloride (10 mL), and the solution was allowed to reflux for 3.5 h before quenching by adding water (5 mL). This was refluxed an additional 15 min. The water layer was separated and extracted with methylene chloride (2 × 20 mL). The combined methylene chloride layers were dried (Na_2SO_4) and concentrated to give a mixture that was separated by preparative thin-layer chromatography, eluting with 5% ethanol in benzene. The products were extracted from the silica gel using 5% ethanol in chloroform. The first major band (R_f 0.7) proved to be *N,N*-dimethyl-3-phenyl-3-methylpyruvamide (**8**, 20 mg). An analytical sample was obtained by short-path distillation under reduced pressure: mp 36–38 °C; NMR ($CDCl_3$) δ 1.50 (d, 3 H, J = 7 Hz), 2.53 (s, 3 H), 2.80 (s, 3 H), 4.52 (q, 1 H, J = 7 Hz), 7.27 (s, 5 H); IR (film) 1710, 1645 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.48; H, 7.39; N, 6.82.

The next major band (R_f 0.5) was a 6:4 mixture of fluorohydrin **7a** and its diastereomer. The NMR spectrum in $CDCl_3$ suggested the following data for this diastereomer: δ 1.62 (d, 3 H, J = 1.5 Hz), 3.01 (s, 6 H), 4.0 (s, 1 H), 5.65 (d, 1 H, J = 45 Hz), 7.33 (s, 5 H).

In a third experiment boron trifluoride etherate (0.50 mL, 4 mmol) was added to **1i** (205 mg, 1.0 mmol) in anhydrous chloroform (10 mL), and the solution was allowed to reflux for 6 h. Water (5 mL) was added and refluxing was continued for 15 min. Workup in the usual way, including silica gel preparative thin-layer chromatography, eluting with 5% ethanol in benzene, gave in the first band pyruvamide **8** (40 mg, 19%) followed by a smaller band consisting primarily of *N,N*-dimethyl-2-phenylacetoacetamide (**9**, ~5%). This was converted to 3-methyl-4-phenyl-3-pyrazolin-5-one (mp 208–210 °C) using hydrazine hydrate in ethanol. The mixture melting point with an authentic sample[4a] was not depressed.

In a fourth experiment boron trifluoride etherate (0.25 mL, 2 mmol)

was added to **1i** (410 mg, 2.0 mmol) in $CHCl_3$ (5 mL), and the solution was allowed to reflux for 6 h. Workup in the usual way followed by preparative thin-layer chromatography gave pyruvamide **8** (15%) in the first band followed by the mixture of fluorohydrin diastereomers (10%) and finally acetoacetamide **9** (28%): NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.88 (s, 3 H), 2.97 (s, 3 H), 4.84 (s, 1 H), 7.30 (broad s, 5 H).

3-Methyl-4-phenyl-3-pyrazolin-5-one was prepared in the usual way.[4a,b] Preparative TLC, eluting with ethyl acetate, and finally recrystallization from ethanol–water gave the pure pyrazolone, mp 210–211 °C. The mixture melting point with authentic pyrazolone[4a] was not depressed, and the IR spectrum was identical with that of the authentic material.

Rearrangement of 7a. Boron trifluoride etherate (0.25 mL) was added to **7a** (113 mg) in anhydrous methylene chloride (5 mL), and the solution was allowed to reflux for 3 h before quenching with water (5 mL). This was then refluxed for 15 min and worked up in the usual way. Purification by preparative TLC followed by NMR analysis of the separated products indicated the presence of pyruvamide **8** (10% yield), acetoacetamide **9** (4%), and a 55:45 mixture (35%) of fluorohydrin **7a** together with its diastereomer.

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Registry No.—**1a**, 64754-77-4; **1b**, 64754-78-5; **1c**, 64754-79-6; **1d**, 64754-80-9; **1e**, 64754-81-0; **1f**, 64754-82-1; **1g**, 64754-83-2; **1h**, 64754-84-3; **1i**, 64754-85-4; **2a**, 64754-86-5; **2b**, 64754-87-6; **2c**, 64754-88-7; **2d**, 64761-01-9; **2e**, 64761-02-0; **2f**, 64761-03-1; **2g**, 64761-04-2; **2h**, 64761-05-3; **2i**, 64761-96-4; **3**, 32870-22-7; **4**, 64761-0705; **5a**, 64761-08-6; **5b**, 64761-09-7; **5c**, 64761-10-0; **5d**, 64761-11-1; **5e**, 64761-12-2; **5f**, 64754-59-2; **6**, 64754-60-5; **7a**, 64754-62-7; **7a** isomer, 64754-61-6; **7b**, 64754-64-8; **7c**, 64771-36-4; **8**, 64754-64-9; **9**, 64771-37-5; *N,N*-diphenyl-2-chloroacetamide, 5428-43-3; benzaldehyde, 100-52-7; acetophenone, 98-86-2; *N*-methyl-*N*-phenyl-2-chloropropionamide, 64754-68-3; *N,N*-dimethyl-2-chloroacetamide, 2675-89-0; *N,N*-dimethyl-2-chloropropionamide, 10397-68-9; (*E*)-*N,N*-diphenylcinnamamide, 64754-65-0; boron trifluoride etherate, 109-63-7; p-toluenesulfonyl chloride, 98-59-9; *N,N*-diphenylamine, 122-39-4; phenylpropiolyl chloride, 7299-58-3; (*E*)-3,4-dihydro-1,3-dimethyl-3-hydroxy-4-phenyl-2(1*H*)-quinolinone, 64754-66-1; 3-methyl-4-phenyl-3-pyrazolin-5-one, 64754-67-2; *n*-methylaniline, 100-61-8; 2-chloropropionyl chloride, 7623-09-8; hydrazine, 302-01-2.

References and Notes

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New Synthesis of a 9-Substituted Adenine

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A new sequence of reactions, utilizing as the key intermediate 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine, has been employed to allow the preparation of a 9-substituted adenine from 4,5,6-triaminopyrimidine. Specifically, 9-(2-chloro-6-fluorobenzyl)adenine was readily prepared, uncontaminated with other positional isomers in a series of mild transformations. The method holds promise as a route to a wide variety of specifically substituted adenine derivatives.

The biological activity of adenine nucleosides and nucleotides[1,2] has prompted vigorous chemical activity directed toward the synthesis of specifically substituted adenine derivatives.[3,4] Specifically, adenine derivatives substituted at position 9 have received considerable attention.[5–8] We describe in this paper a new approach to the synthesis of 9-substituted adenine derivatives which allows the unambiguous introduction of the 9 substituent through a sequence of mild, efficient reactions.

Taylor et al.[8] have reported that 9-substituted adenines (**2**) may be prepared via reductive cleavage and subsequent cyclization of 7-amidofurazano[3,4-*d*]pyrimidines (**1**). Although a wide variety of adenine derivatives was prepared, the authors were unable to effect the conversion of 5-unsubstituted 7-amidofurazano[3,4-*d*]pyrimidines (**1**, R = H) to 2-unsubstituted adenines (**2**, R = H) due to the hydrolytic instability of the former compounds. We wish to report that the highly active coccidiostat 9-(2-chloro-6-fluorobenzyl)adenine[9] (**9**), a derivative possessing a hydrogen in the 2 position, may be readily prepared without isomer contamination (see Scheme I).

Treatment of 4,5,6-triaminopyrimidine (**3**) with thionyl chloride afforded 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (**4**)[10] in 79% yield. Nucleophilic displacement of the 7-amino group[11] of **4** was effected by reaction at 100 °C with 2-chloro-6-fluorobenzylamine (**5**) to provide **6** in 93% yield. Alternatively, **6** could be prepared from **4** in 25% yield by treatment of **4** with ammonia and 2-chloro-6-fluorobenzyl

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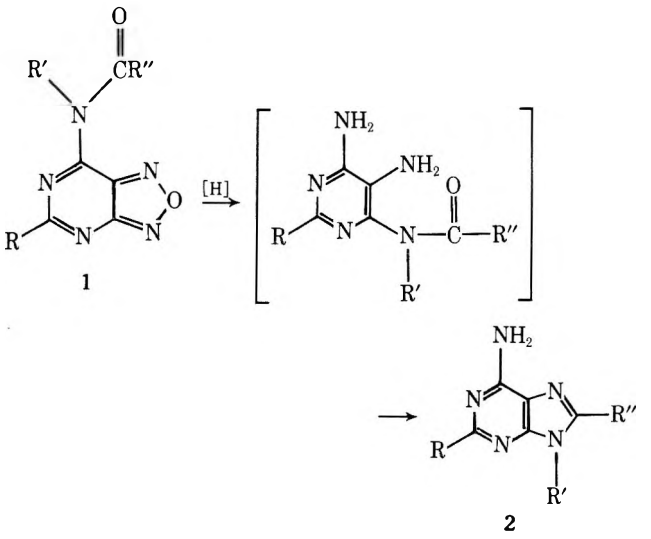
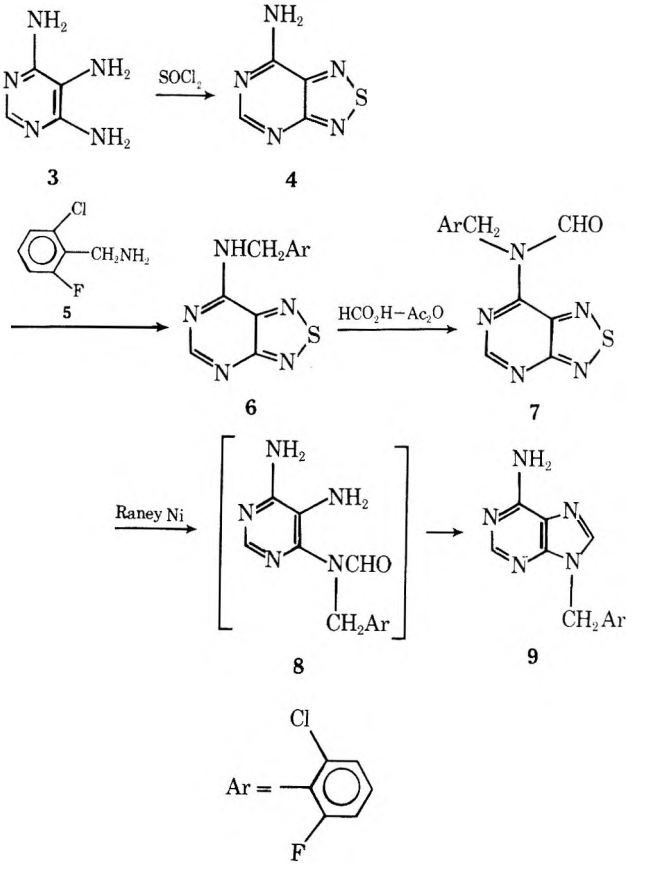


chloride in a sealed vessel at 110 °C. Formylation of **6** was carried out at room temperature with formic acetic anhydride yielding **7** as a stable solid in 91% yield. At this point some difficulty was encountered in the reductive cyclization as some of the better known methods, i.e., zinc–acetic acid, zinc–acetic acid–ethanol, and iron–acetic acid, failed to produce any **9**. However, treatment of **7** in ethanol–water with Raney nickel at room temperature resulted in smooth desulfurization and formation of **9** in 40% yield.[12]

The present method thus constitutes a new, mild route to 9-alkylated adenines which are unsubstituted in the 2 position.

Scheme I



Experimental Section

NMR spectra were recorded on a Varian A-60A spectrometer with tetramethylsilane as internal standard.

7-Amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine[10] (4). A flask was charged with 19.78 g (0.15 mol) of **3** and 163.0 g (137 mol) of thionyl chloride, and the mixture was stirred at reflux for 18 h. The dark orange reaction mixture was then taken to dryness on the rotary evaporator and to the residue were added 500 mL of water and 40 mL of methanol. The pH of the resulting solution was adjusted to 7.5–8.0 with saturated sodium bicarbonate solution and this solution was heated to reflux. The hot mixture was filtered and the filtrate was cooled to 0–5 °C in an ice bath. The solid was collected and washed with 2 × 50 mL of ice water and then 2 × 50 mL of ether. The resulting tan product was dried under vacuum at 70 °C overnight to afford 18.2 g (79%) of **4**: mp 247–249 °C (lit.[10] mp 248 °C); TLC on silica gel (8:1 chloroform–methanol) showed one spot at R_f 0.4.

2-Chloro-6-fluorobenzylamine (5).[13] An autoclave was charged with 89.0 g (0.5 mol) of 2-chloro-6-fluorobenzyl chloride, 170.0 g (10 mol) of ammonia, and 50 mL of benzene. The reaction vessel was sealed and the contents heated at 10 °C for 15 h. The excess ammonia was then carefully evaporated off (nitrogen stream) from the cooled contents of the autoclave. The residue was then washed with water, and the dried ($MgSO_4$) organic phase was fractionated to afford 72.4 g (90%) of **5** as a clear liquid: bp 99–100 °C (20 mm) [lit.[12] bp 94–96 °C (18 mm)]; NMR ($CDCl_3$) δ 1.46 (s, 2 H), 3.88 (d, 2 H), 7.00 (m, 3 H).

7-(2-Chloro-6-fluorobenzyl)amino[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine (6). A flask was charged with 1.54 g (0.01 mol) of **4** and 4.0 g (0.025 mol) of **5**. This suspension was stirred and heated at 105 °C for 18 h. Then, 10 mL of water and 20 mL of hexane were added in one portion, and the resulting solid was collected. The cake was washed with hexane and then dried at 50 °C under vacuum to afford 2.86 g (97%) of the desired product: mp 224–226 °C; TLC on silica gel (8:1 chloroform–methanol) shows a single fluorescent blue spot at R_f 0.8; NMR (Me_2SO-d_6) δ 4.92 (2 H, s), 7.21 (br s, 3 H), 8.44 (s, 1 H), 9.45 (s, 1 H). Anal. Calcd for $C_{11}H_7ClFN_5S$: C, 44.68; H, 2.38; N, 23.68. Found: C, 44.36; H, 2.38; N, 24.24.

Pyrimidine **6** was also prepared from **4** via the following route. An autoclave was charged with 1.54 g (0.01 mol) of **4**, 5.1 g (0.3 mol) of ammonia, and 4.48 g (0.025 mol) of 1-chloro-6-fluorobenzyl chloride. The vessel was then sealed and the contents heated at 110 °C for 15 h. After cooling and evaporation of the excess ammonia, the resulting solid was collected and washed successively with water and hexane to afford a 25% yield of **6**.

7-(*N*-Formyl-*N*-2-chloro-6-fluorobenzyl)amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (7). Formic acetic anhydride was prepared by stirring for 1 h at 0–5 °C a solution of 18.4 g (0.4 mol) of 98% formic acid and 40.8 g (0.4 mol) of acetic anhydride. Then, 40 mL of this solution was added to 2.0 g (0.0067 mol) of **6** and the solution stirred overnight. At this time any insoluble material was filtered off and the filtrate stripped in vacuo at 50 °C. The solid residue was washed with ether and then recrystallized from methanol to afford 2.0 g (91%) of the desired compound: mp 133–135 °C; TLC on silica gel (16:1 chloroform–methanol) showed one spot with R_f 0.8; IR ($CHCl_3$) 1730, 1540, 1120, 940 cm^{-1}; NMR (Me_2SO-d_6) δ 5.55 (s, 2 H), 7.30 (br s, 3 H), 9.11 (s, 1 H), 10.33 (s, 1 H).

9-(2-Chloro-6-fluorobenzyl)adenine (9). A flask was charged with 0.5 g (0.0016 mol) of **7**, 15 mL of ethanol, 15 mL of water, and 7.0 g of Raney nickel. This dark suspension was stirred at room temperature for 2 h, at which time TLC analysis showed that all of **7** had been consumed. The reaction mixture was filtered through Celite and the cake was washed with 200 mL of boiling methanol. The clear filtrate was stripped to afford a white solid which was recrystalized from methanol–water to afford 0.18 g (40%) of the desired adenine derivative: mp 245–246 °C; TLC on silica gel (16:1 chloroform–methanol) gave one spot with R_f 0.4; NMR (acetic acid-d_4) δ 5.70 (2 H, d), 7.35 (3 H, m), 8.15 (1 H, s), 8.43 (1 H, s). Anal. Calcd for $C_{12}H_9ClFN_5$: C, 51.90; H, 3.27; N, 25.22; Cl, 12.77. Found: C, 51.77: H, 3.30; N, 25.43; Cl, 12.49.

Registry No.—**3**, 118-70-7; **4**, 2829-57-4; **5**, 15205-15-9; **6**, 64825-52-1; **7**, 64825-53-2; **9**, 55779-18-5; thionyl chloride, 7719-09-7; 2-chloro-6-fluorobenzyl chloride, 55117-15-2; formic acetic anhydride, 2258-42-6; formic acid, 64-18-6; acetic anhydride, 108-24-7.

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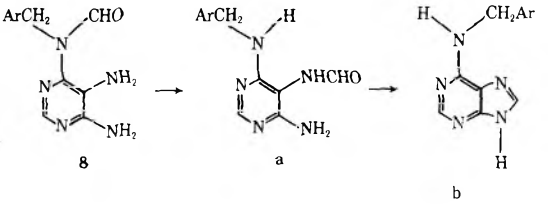

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9-(6-Deoxyhexofuranosyl)adenine Nucleosides. Further Studies on the Acetolysis of Hexofuranosides

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Methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside was treated with a 10:1 mixture of acetic acid–acetic anhydride containing 5% sulfuric acid. The crude product was coupled with 6-benzamidochloromercuripurine by the titanium tetrachloride method. Removal of blocking groups and chromatography afforded a mixture of nucleosides which were separated by rechromatographing the mixture on an anion-exchange resin. 9-(6-Deoxy-α-L-talofuranosyl)adenine and 9-(6-deoxy-β-L-galactofuranosyl)adenine were obtained in similar amounts. In a like manner, methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside was subjected to the same reaction sequence. In this case too, a mixture of nucleosides was obtained. Separation of the desired 9-(6-deoxy-α-D-altrofuranosyl)adenine was achieved by selective destruction of the allo nucleoside. This was accomplished by short-term oxidation with periodate, reduction of the aldehyde groups with borohydride, and chromatography on an anion-exchange resin. Unlike previous experiments in which only C-2′, C-3′ trans nucleosides were obtained, the sugar derivatives in the present experiments did not undergo complete epimerization at C-2.

In a previous article,[2] reasons for the preparation of nucleosides derived from 6-deoxyhexofuranoses were mentioned and, over the past few years, papers concerned with this subject matter have appeared from this laboratory.[3-5]

A key reaction in some of the synthetic schemes has been acetolysis of appropriately blocked glycosides. During the reaction, acid-labile groups such as anomeric methoxyls and isopropylidene groups are exchanged for acetyl or acetoxyl groups.[6] However, when the acetolysis reaction is performed with a furanose sugar derivative containing three contiguous hydroxyl groups linked to the ring, epimerization at C-2 often occurs if the hydroxyls at C-2 and C-3 are in a cis relationship.[7-9] The best reaction conditions appeared to be a 10:1 acetic acid–acetic anhydride mixture containing 3–5% sulfuric acid.[5,7-9] The reaction has also been scaled up into a useful synthetic tool for the preparation of novel carbohydrates and nucleosides.[2,5,10-12] In the latter case, a number of hexofuranosyl nucleosides with a trans relationship at the C-2′,C-3′ hydroxyl groups have been prepared from hexofuranosides that originally had these hydroxyls in a cis orientation.[5,11,12] In each case, the only major nucleoside product obtained was the one having the C-2′,C-3′ trans arrangement. It was also necessary that C-5 of the sugar be blocked with a benzoyl group rather than an acetate so that acetate exchange and ring rearrangement to the pyranose form did not occur; otherwise, epimerization was incomplete and a substantial amount of the hexopyranosyl nucleoside of the starting sugar was obtained.[5,10-12] The preparation of some new 9-(6-deoxyhexofuranosyl)adenine nucleosides and some interesting developments with the acetolysis reaction are the subject of this article.

The sugar derivatives needed for the preparation of the nucleosides reported herein were obtained starting from 6-deoxy-L-mannose (L-rhamnose). The synthetic pathway is illustrated in Scheme I for purposes of clarity and was based upon literature methods.[13-15]

Acetolysis of methyl 5-*O*-benzoyl-2,3-*O*-isopropylidene-α-L-talofuranoside (**6**) gave a syrup (**7**) which was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method.[16] The blocking groups were removed with sodium methoxide in boiling methanol. Chromatography on an anion-exchange column using Dekker's technique[17] of elution with aqueous methanol gave a product which was shown to be a mixture of at least two nucleosides from the value of the optical rotation and from the rate of consumption of periodate. In the latter case, there was a very rapid initial uptake of periodate corresponding to 50–60% of the total material and then a slow uptake over several days until completion of the oxidation. The mixture was rechromatographed with a more dilute aqueous methanol solution. Two nucleosides separated, both of which were crystallized. The first nucleoside to come off the column was 9-(6-deoxy-α-L-talofuranosyl)adenine (**8**). It had previously been prepared from **6** but had not been obtained in crystalline form.[15] More recently, it was obtained by the reaction of 2′,3′-*O*-isopropylideneadenosine-5′-aldehyde with methylmagnesium iodide and crystallized from ethanol as an hemialcoholate.[18] In the present work, **8** was obtained in an anhydrous, unsolvated form having a melting point considerably higher than that of the hemialcoholate. The optical rotation, rate of periodate consumption, and substrate activity with adenosine deaminase (adenosine aminohydrolase EC 3.5.4.4) verified the identity of **8**.

The second nucleoside eluted from the column was 9-(6-

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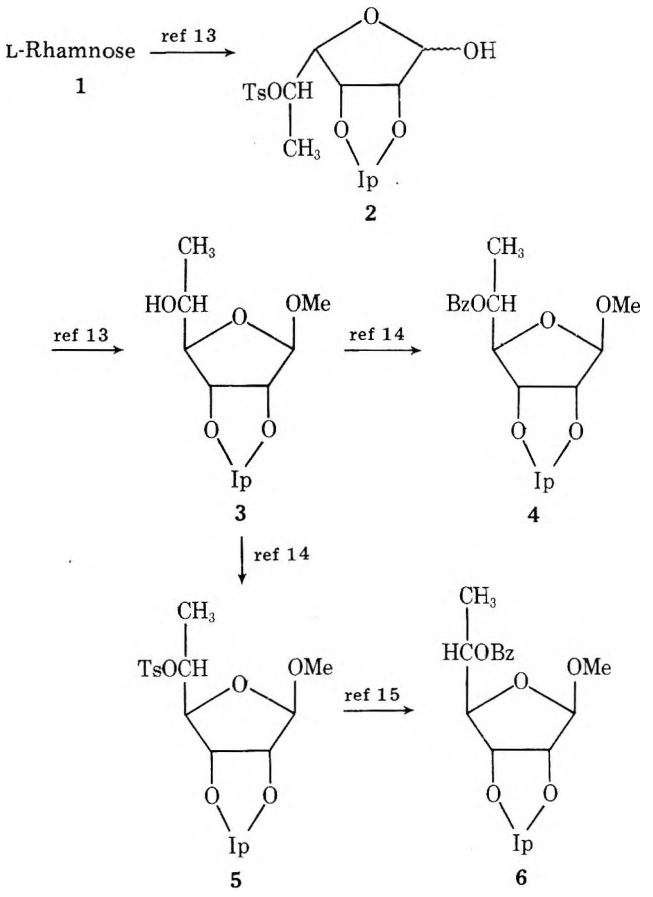
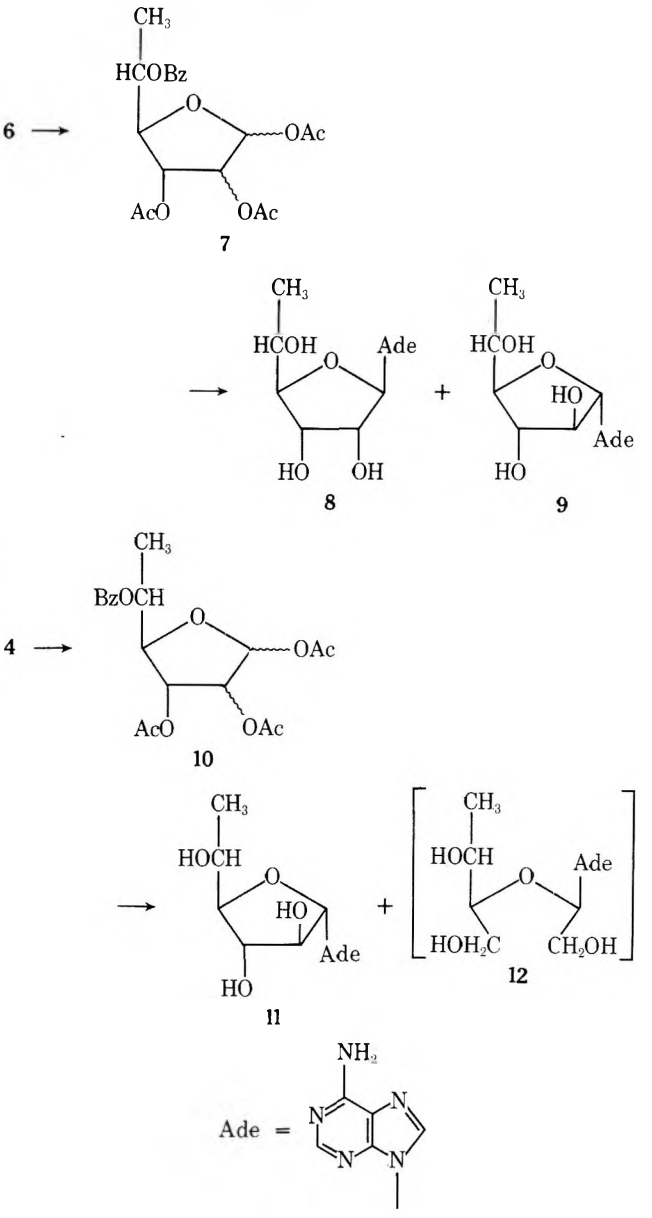
Scheme I



Scheme II



deoxy-β-L-galactofuranosyl)adenine (**9**, 9-β-L-fucofuranosyladenine), which crystallized from water.

Acetolysis of **4** afforded a syrupy product (**10**) which was condensed with 6-benzamidochloromercuripurine in the same manner as in the preparation of nucleosides 8 and **9**. After removal of blocking groups and chromatography on an anion-exchange resin, a crystalline mixture of at least two nucleosides was obtained, as indicated by the wide range of melting and the consumption of periodate. In this case, 35–40% of the total periodate consumed was taken up rapidly, indicating that approximately this much of the mixture was 9-(6-deoxy-β-D-allofuranosyl)adenine. Further attempts to separate these two nucleosides, the second of which was the desired 9-(6-deoxy-α-D-altrofuranosyl)adenine (**11**), failed to resolve them. Since 9-(6-deoxy-β-D-allofuranosyl)adenine can be better prepared from **4** using a route not involving acetolysis,[14] it appeared to be advantageous to use periodate oxidation over a short time to oxidize it selectively, reduce it to the dialcohol, and utilize the anion-exchange column again to isolate the desired nucleoside. It was expected that without the ring hydroxyls the dialcohol would pass through the column well ahead of the nucleoside.[17] In fact, this is what happened. After periodate oxidation, the aldehyde groups were reduced with sodium borohydride, the sodium ions were removed with a cation-exchange resin in the acid form, and the boric acid produced was evaporated as methyl borate. Column chromatography first gave a peak containing the dialcohol **12**, which appeared to be one of a mixture of components, as indicated by the NMR spectrum and the value of the optical rotation. Further purification and characterization of this material was not pursued. The desired product, 9-(6-deoxy-α-D-altrofuranosyl)adenine (**11**), was eluted with 60% aqueous methanol and was obtained in crystalline form from acetone.

The UV spectra of **9** and **11** showed that they were *N*-9 substituted nucleosides. The elemental analysis of **11** suggested that it had 0.5 mol of acetone as solvate of crystallization. This was verified by the infrared spectrum which had a carbonyl peak at 1715 cm^{-1} and the NMR spectrum which had the acetone methyl at δ 1.87 and integrated for exactly 0.5 mol of acetone methyl proton per mole of nucleoside. Periodate uptake experiments showed that each nucleoside had the furanose ring form. Rearrangement to a pyranose ring would have resulted in the consumption of 2 mol of periodate and not 1 mol. The rate of consumption was indicative of the relative configuration of the hydroxyl groups at C-2′ and C-3′. Whereas the talo nucleoside 8 completely consumed nearly 1 mol of periodate almost instantly, **9** and **11** each required several days to consume the same amount. It is known from previous experience that it is C-2 of the sugar that epimerizes[2-12] and this is verified again in this work, since the data of the physical properties of the new nucleosides **9** and **11** do not conform to that of 9-(6-deoxy-α-L-idofuranosyl)adenine[2] or 9-(6-deoxy-β-D-glucofuranosyl)adenine,[19] respectively, the nucleosides expected if C-3 would have inverted instead of C-2.

Unfortunately, the NMR spectra of **9** and **11** did not give conclusive information regarding the nature of the anomeric configurations. The anomeric proton of **9** was partially ob-

Table I. Optical Rotations of Nucleosides and Their Alcohols

9-(6′-Deoxyhexofuranosyl)-adenine	$[\alpha]_D$ of nucleoside, deg	Registry no.	$[\alpha]_D$ of nucleoside alcohol deg[a]
α-L-talo (**8**)	−39.7	35868-16-7	+72
β-L-galacto (**9**)	+73.2	64811-72-9	−48
α-D-altro (**11**)	+52.9	64811-73-0	−62

[a] Based upon the calculated dry weight of the alcohol product.

scured by other protons, and the anomeric proton of **11** was a doublet with a coupling constant too large to assign a configuration.[20] It was expected that the nucleosides would have the adenine ring in a configuration trans to the hydroxyl at C-2′.[21] Comparison of the optical rotations of the new nucleosides with the optical rotations of other hexofuranosyl nucleosides[2] appeared to confirm the configurational assignments. The anomeric configuration of **8**, although not demonstrated in the original work,[15] was clearly demonstrated by its preparation from 9-β-D-ribofuranosyladenine (adenosine).[18] Moreover, **8** was a substrate for adenosine deaminase, but **9** and **11** were not. Adenosine deaminase only catalyzes the rapid deamination of adenine nucleosides having a β-D or α-L configuration if other structural requirements[2,22] for substrate activity are fulfilled. Since **9** and **11** have structural features which otherwise would allow them to act as substrates, the fact that they do not can be construed as evidence for the assigned anomeric configurations.

Another argument in support of the assigned anomeric configurations is based upon an observation made in a previous paper.[2] It had been noticed[2] that alcohols derived from nucleosides that have been oxidized with periodate and the aldehyde groups reduced acquire an optical rotation of fairly large value and sign opposite to that of the original nucleoside. The number of asymmetric carbon atoms in the alcohol does not appear to matter. Nucleosides having a β-D or α-L configuration yield alcohols which have a positive optical rotation, and nucleosides having an α-D or β-L configuration yield alcohols which have a negative optical rotation. Table I reports the optical rotations of nucleosides **8**, **9** and **11** and the alcohols derived from them. These data also support the assignments of anomeric configuration of the nucleosides.

The results obtained from the acetolysis reaction were somewhat disappointing for preparative purposes. Only a minor portion of the hexofuranosides appear to have epimerized at C-2 and as a result the main products still possessed the cis configuration. Previously, I had reported epimerizations of hexofuranosides which were virtually complete. This was particularly the case when the hydroxyl at C-5 was blocked with a benzoyl group, a group that is not displaced and does not migrate under acetolysis conditions. In the earliest experiments from this laboratory,[4,5] the acetyl group at C-5 appeared to allow rearrangement of the furanose ring to a pyranose ring which prevented a significant portion of the sugar from undergoing epimerization. Proof of this was obtained in the form of the pyranosyl nucleoside of the original sugar. Since pyranosyl nucleosides were not obtained in the present case, there is no reason to believe that this is happening here in spite of the benzoyl group. However, comparison of the structures of the hexofuranosides used in the present work to the ones used previously do reveal a fundamental difference. The cis hydroxyl groups at C-2 and C-3 in the previous work were located on the same side of the furanose ring as the C-4 tail containing C-5 and C-6. In the present work, these two hydroxyl groups were on the opposite side of the ring from the C-4 tail. Therefore, one could easily suspect that the benzoyl group is simply sterically hindering the formation of the proposed[7,8] orthoester ion intermediate. The recent transformation of methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside into 9-(5-deoxy-α-D-arabinofuranosyl)adenine[23] by the same route would tend to support this view; no D-ribonucleoside was obtained. The problem is that recent unpublished experiments of this laboratory reveal that 5,6-unsaturated hexofuranosides, such as methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside, also do not afford good yields of C-2 epimerized products after acetolysis and formation of the nucleosides. Apparently, the success or failure of this reaction with hexofuranosides is greatly determined by thermodynamic factors.

Experimental Section[24]

9-(6-Deoxy-α-L-talofuranosyl)adenine (8) and 9-(6-Deoxy-β-L-galactofuranosyl)adenine (9). Methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside[15] (2.64 g) was acetolyzed for 5 days at room temperature in a mixture containing 5 mL of acetic anhydride, 50 mL of acetic acid, and 2.6 mL of concentrated sulfuric acid. The mixture was poured into 200 mL of ice, stirred until the ice melted, and extracted with chloroform (3 × 40 mL). The extracts were combined, washed with water (2 × 125 mL), saturated sodium bicarbonate (2 × 125 mL), and water (150 mL), and dried. Evaporation of the chloroform and three coevaporations with benzene gave a colorless syrup weighing 1.89 g.

The syrup was dissolved in 160 mL of 1,2-dichloroethane and placed in a three-neck flask fitted with a take-off adapter, a condenser, and a drying tube. 6-Benzamidochloromercuripurine (2.70 g) and Celite-545 (2.70 g) were added, and 25 mL of solvent was distilled. A solution containing 0.75 mL of titanium tetrachloride in 25 mL of fresh 1,2-dichloroethane was then added, and the stirred mixture was heated under reflux for 21 h. The mixture was cooled to room temperature, and 100 mL of saturated sodium bicarbonate was added, stirred for 1.5 h, and filtered by suction. The filter cake was washed with 200 mL of hot 1,2-dichloroethane, the organic layer was separated, and the solvent was evaporated. The residue was dissolved in 100 mL of chloroform, washed with 30% potassium iodide solution (2 × 100 mL) and water (150 mL), and dried. Evaporation of the chloroform gave a yellow foam weighing 2.57 g. This was dissolved in 70 mL of methanol and treated with 7 mL of 1 N methanolic sodium methoxide solution. The solution was refluxed for 1.5 h, cooled to room temperature, and neutralized with Amberlite CG-120 (H^+) ion-exchange resin. The resin was filtered off, the methanol was evaporated, and the residue was coevaporated several times with water to get rid of methyl benzoate. The dark product was dissolved in water and added to the top of a column (15 × 1.8 cm) of Bio-Rad AG 1-X2 (OH^-, 200–400 mesh) ion-exchange resin that had been packed in water. The column was eluted with 30% aqueous methanol and the major UV-absorbing peak was evaporated to a foam and then rechromatographed on a larger column (33 × 2 cm). The column was eluted with water and 14-mL fractions were collected. The solvent was changed to 10% methanol at tube 71 and 12-mL fractions were collected. Fractions 121–228 were pooled and evaporated to a white foam which was dried by coevaporation with ethanol. Crystallization was effected from ethanol upon standing in an open flask. This product was identified as 9-(6-deoxy-α-L-talofuranosyl)adenine (**8**) and weighed 213 mg. A second crop of crystals weighing 35 mg was also obtained. The crystals were dried over phosphorus pentoxide for 24 h under high vacuum at 100 °C, mp 206–209 °C, softening at 201 °C with the formation of tiny droplets: $[\alpha]^{25}_D$ −39.7° (*c* 0.897, water) (lit.[18] $[\alpha]_D$ −39 ± 2°).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.41 N, 24.80. Found: C, 46.76; H, 5.46; N, 24.98.

Fractions 238–430, the other major peak, were combined and evaporated. 9-(6-Deoxy-β-L-galactofuranosyl)adenine (**9**) was crystallized from water in two crops to give 223 mg, mp 240–242 °C, with tiny droplets forming shortly before melting: $[\alpha]^{25}_D$ +73.2° (*c* 0.877, water); UV λ_{max} (H_2O) 259 nm (ε 14 980); NMR (Me_2SO-d_6) δ 8.17, 8.03 (both s, 1 proton each, H-8, H-2), ~5.80 (H-1′ overlapping with 2′,3′-OH), 1.06 (d, 3, CH_3).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.41; N, 24.90. Found: C, 46.96; H, 5.30; N, 24.89.

9-(6-Deoxy-α-D-altrofuranosyl)adenine (11). Methyl 2,3-*O*-isopropylidene-5-*O*-benzoyl-6-deoxy-β-D-allofuranoside[14] (4.44 g) was acetolyzed for 7 days in a mixture containing 80 mL of acetic acid,

8 mL of acetic anhydride, and 4.4 mL of concentrated sulfuric acid. The contents were poured into 300 mL of ice and stirred until the ice melted. The mixture was extracted with chloroform (3 × 50 mL), and the extracts were combined, washed with water (2 × 150 mL), saturated sodium bicarbonate (2 × 150 mL), and water (150 mL) and dried. Evaporation of the chloroform and several coevaporations with benzene gave a clear, colorless syrup weighing 2.8 g.

The syrup was reacted with 4.0 g of 6-benzamidochloromercuripurine in 230 mL of 1,2-dichloroethane containing 4 g of Celite-545 and 1.1 mL of titanium tetrachloride as described above for the preparation of **8** and **9**. A yellow foam weighing 3.86 g was obtained which was dissolved in 75 mL of methanol and treated under reflux with 8 mL of 1 N methanolic sodium methoxide. The reaction proceeded for 1.5 h and was neutralized and methyl benzoate removed as described above. The dark residue was dissolved in water and chromatographed on a column (31 × 2 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) resin. The column was eluted with water (1 L), 10% aqueous methanol (2 L), and 20% aqueous methanol (4 L). The major UV-absorbing peak came off in the latter solvent system. The solvents were evaporated and a little color was removed with Darco G-60 charcoal. After evaporation, a solid residue remained which was crystallized from acetone in several crops to afford 1.243 g. The wide melting range above 108 °C and the $[\alpha]_D$ −13° indicated that this was a mixture. A periodate uptake experiment revealed that at least 35–40% of this material had a cis relationship between C-2′ and C-3′. The solid (1.187 g) was dissolved in 50 mL of water, chilled to 15 °C, and treated with 1.0 g of sodium periodate. The reaction was kept at room temperature for 45 min, 0.3 g of ethylene glycol was added in 3 mL of water, and after another 15 min the mixture was poured into 350 mL of vigorously stirred ethanol. Fifteen minutes later the salt was removed by filtration and washed with two 20-mL portions of ethanol. The solvents were evaporated (30 °C), and the remaining syrup was dissolved in 65 mL of water and treated with a solution containing 0.9 g of sodium borohydride in 10 mL of water. The reaction proceeded for 2 h, the excess borohydride was decomposed and the pH adjusted to neutrality with Bio-Rad AG50W-X8 (H^+) ion-exchange resin. The mixture was filtered through a pad of Celite, the water was evaporated, and the residue was coevaporated three times with methanol to remove boric acid as methyl borate. The residue was dissolved in water and chromatographed on the anion-exchange resin used previously (32 × 2 cm column) and 15-mL fractions were collected using the following solvent systems: water (1L), 10% aqueous methanol (1L), 20% aqueous methanol (2L), and finally 60% aqueous methanol. The major UV-absorbing peaks were in tubes 23–77 and 279–316, the latter being eluted with the last solvent used. The material in tubes 23–77 precipitated from ethanol to afford 511 mg containing the alcohol **12**, but judged to be a mixture of components based upon the optical rotation, $[\alpha]^{25}_D$ −7° (c 1.12, water), and NMR spectrum. No further work was done on this sample.

Fractions 279–316 were combined, the solvents were evaporated, and the residue was crystallized from acetone (scratching). Two more recrystallizations from acetone gave 141 mg of pure 9-(6-deoxy-α-D-altrofuranosyl)adenine (**11**) containing 0.5 mol of acetone of crystallization, mp 112–115 °C, to a very, viscous syrup: $[\alpha]^{25}_D$ +52.9° (c 0.77, water); UV λ_{max} (H_2O) 260 nm (ε 13 480); IR 1715 cm^{-1} (C=O, acetone); NMR (Me_2SO-d_6)δ 8.17, 8.03 (both s, 1 proton each, H-8, H-2), 5.82 (d, 1, J = 4 Hz, H-1′), 1.87 (s, 3, acetone CH_3), 1.10 (d, 3, C-6′ CH_3).

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot 0.5CH_3C(=O)CH_3$: C, 48.38; H, 5.84; N, 22.57. Found: C, 48.41; H, 5.95; N, 21.89.

Periodate Uptake. The procedure of Rammler and Rabinowitz[25] in which the disappearance of periodate is measured at 300 nm was used to determine periodate consumption. Nucleoside **8** consumed 0.85 molar equiv in less than 5 min, whereas nucleoside **9** required 65.5 h to consume 0.90 molar equiv. Nucleoside **11** consumed 0.91 molar equiv of periodate in 72 h.

Polarimetric Studies. Details of the procedure to oxidize and reduce small samples of the nucleosides appear in a previous article.[2] The results are shown in Table I.

Deamination with Adenosine Deaminase. Deamination was followed at 265 nm at 25 °C in 0.05 M phosphate buffer (pH 7.6).[26] The concentration of nucleosides was approximately 5×10^{-5} M, and 3 mL of this solution was placed in a cuvette and 0.1 mL of enzyme (Sigma Chemical Co.) containing 2.1 units was added. Nucleoside **8** underwent complete deamination in about 3 min; nucleosides **9** and **11** were not substrates even with enzyme levels as high as 53 units per cuvette.

Registry No.—**4**, 29325-26-6; **6**, 28538-27-4; **7** isomer I, 64761-44-0; **7** isomer II, 64761-45-1; **10** isomer I, 64761-46-2; **10** isomer II, 64761-47-3; 6-benzamidochloromercuripurine, 17187-65-4.

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Total Synthesis of 2-Azaestratrienes[1]

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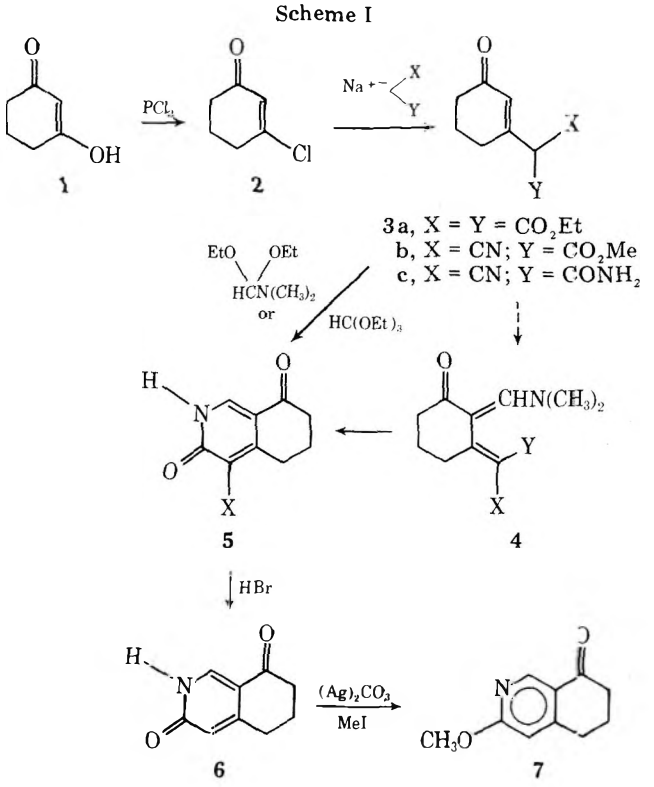
The total synthesis of (±)-2-azaestradiol 3-methyl ether (15) as well as its 11β-methyl homologue 28 is described. This work necessitated the development of a synthesis of 6-methoxy-7-aza-1-tetralone (7), a heretofore unknown compound. In the course of the preparation of this tetralone, a novel α-pyridone synthesis was developed. The chemical reduction of the 8,9 double bond in each series was accompanied by destruction of the methoxypyridine A ring. Rearomatization of the dihydropyridines 14 and 27 with DDQ regenerated the methoxypyridine nucleus and gave the desired products. A by-product of the DDQ reaction in the 11β-methyl series was identified as (±)-9ξ-hydroxy-2-azaestradiol 3-methyl ether (29).

Our study of the effect of a heteroatom at the 2 position of the steroid nucleus had disclosed unique biological properties of the 2-azaestradiol 3-methyl ether series.[2] The engthy reaction sequence necessary for the preparation of these compounds from naturally occurring steroid starting material prompted an investigation of the total synthesis of this series.[3] Moreover, the development of a total synthetic pathway would provide a means of preparing the 11β-methyl homologues of the parent compounds. These 11-methylated derivatives of the estradiol 3-methyl ether series were shown to possess enhanced biological properties,[4] and it was of interest to determine whether enhancement of the biological properties of the 2-azaestradiol 3-methyl ether series would also result.

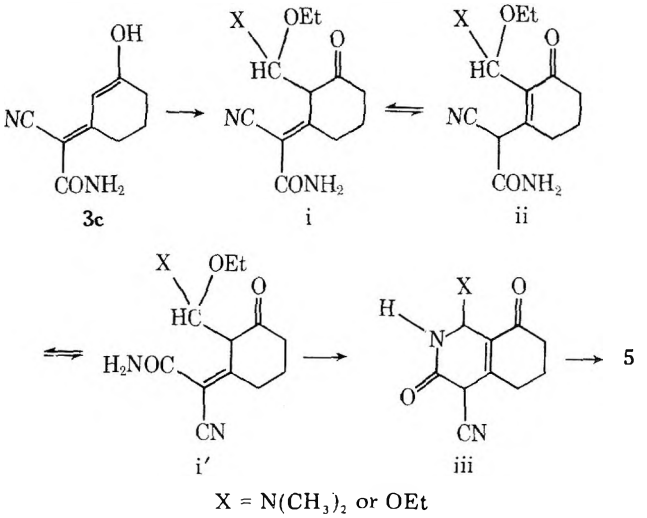
The classic approach to the total synthesis of estrone derivatives appeared appropriate for these compounds and a modified Torgov[5] sequence was pursued. This made the 7-aza analogue of 6-methoxy-1-tetralone, an heretofore unknown compound, the key intermediate in the proposed synthesis. Our initial attempts at the preparation of this compound (Scheme I) were to contact 3-chlorocyclohex-2-en-1-one (2)[6] with the sodium salts of various malonate derivatives. The resultant products (3) were then condensed with the ethyl ketal of dimethylformamide in order to obtain the dimethylaminomethylene derivatives 4. These in turn were expected to provide the bicyclic α-pyridone 5 after transamination of the dimethylamino functionality of 4 with ammonia and subsequent cyclization. This route proved to be unfruitful with 3a and 3b due to the refractory nature of these substances to form dimethylaminomethylene derivatives. In each of these cases the enol ether derivative of the starting material was the observed (by NMR spectroscopy) but uncharacterized product.[7] However, when the 3-cyanoacetamido adduct 3c was condensed with dimethylformamide diethyl acetal in dimethylformamide at room temperature, the bicyclic α-pyridone 5 (X = CN) was produced rather auspiciously in a single step in high yield.[8]

It was later determined that this transformation could also be realized using the somewhat less reactive but considerably less expensive triethyl orthoformate. Thus, by heating 3c in dimethylformamide with an excess of this reagent at steam bath temperatures, a yield comparable to that obtained with the ketal reagent (ca. 85%) was obtained. We envision the mechanism of this heterocycle synthesis as proceeding via attack of these reagents, at the carbon atom α to the carbonyl to form i which would be in equilibrium with i′ and ii. This latter form would allow free rotation of the side chain and maximize cyclization to iii, which upon further elimination affords 5.

Scheme I



1 2 3a b c 4 5 6 7



X = $N(CH_3)_2$ or OEt

To complete our synthesis of the desired tetralone, the nitrile was removed by treatment of 5 with concentrated aqueous hydrobromic acid, which gave 2,3,5,6,7,8-hexahydro-3,8-dioxoisoquinoline (6) in 85% yield. This novel approach to α-pyridones has been studied in greater detail and will be reported on more fully in a later manuscript. Alkylation of the silver salt of 6 with methyl iodide in benzene[9] yielded the desired 6-methoxy-7-aza-1-tetralone (7) in yields up to 70% and provided 7 in about 30% yield from 1.

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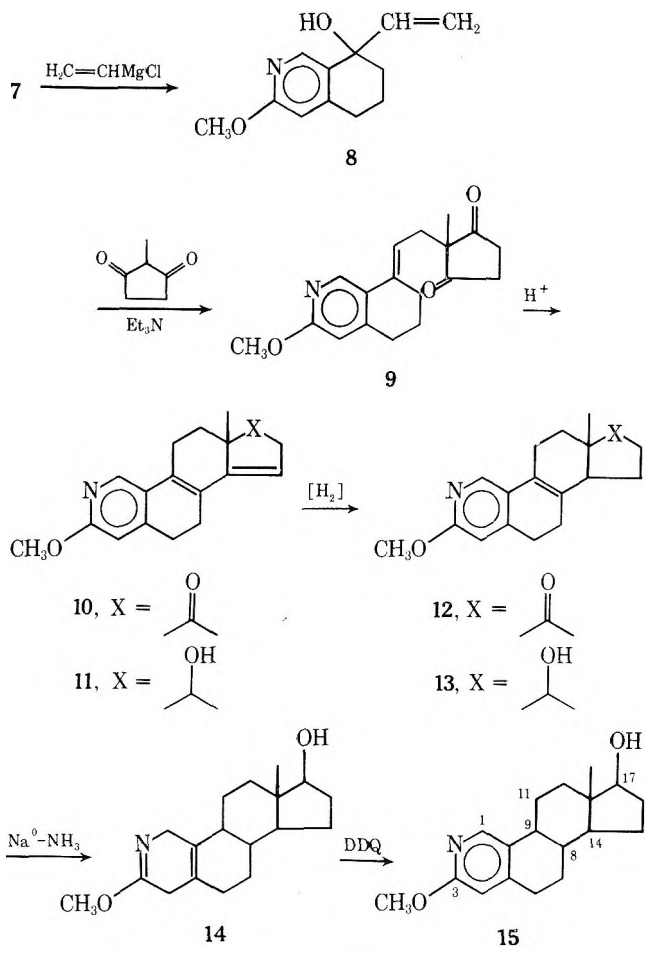
Scheme II



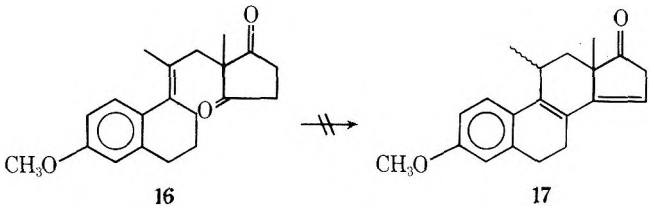
The construction of the steroid ring system is shown in Scheme II. Treatment of **7** with excess vinylmagnesium chloride in xylene gave the vinylcarbinol **8**, which was not characterized but rather condensed with 2-methylcyclopenta-1,3-dione in refluxing xylene to afford **9** in 44% yield from **7**. Cyclization of **9** was sluggish, paralleling the reactivity of the 4-azaestratrienes and the 4,6-diaza steroids reported by Huisman et al.[10] and Bonet et al.,[11] respectively. In each case these molecules become refractory to the acid-catalyzed isomerization of the 9,11 double bond to the 8,9 position, which is necessary for cyclization,[12] due to the presence of a protonated nitrogen in the molecule. However, we found that by refluxing **9** in xylene–dioxane with 2–3 equiv of tosyl acid the tetracyclic product **10** could be obtained in moderate yield.

Reduction of the ketone **10** with sodium borohydride in methanol gave (±)-3-methoxy-2-azaestra-1,3,5(10),8,14-pentaen-17-ol (**11**). This compound underwent catalytic hydrogenation over palladium on calcium carbonate to afford the desired 14α product **13** in 90% yield. The assignment of the stereochemistry at the 14-carbon atom is based on the fact that this compound was the preponderant product of the hydrogenation and the position of the 18-CH_3 resonance of this isomer is upfield (ca. 0.20 ppm) from the 18-CH_3 resonance of the minor isomer.[13,14]

We had also hydrogenated **10** to provide **12** which upon sodium borohydride reduction also gave **13.** However, the 14α/14β isomer ratio which was determined by NMR spectroscopy from the relative intensities of the 18-CH_3 resonances of the two compounds was greater when hydrogenation was carried out on the alcohol **11** rather than the ketone **10** (9:1 vs. 8:2, respectively). This result parallels that previously observed in these laboratories on work done in the carbocyclic series as well as that of Huisman et al. on 6-thia steroids.[15]

The critical step in the total synthesis of the estradiol 3-methyl ether analogue was trans reduction of the 8,9 double bond. Earlier reports by Huisman[14] had indicated that the aromatic nucleus did not survive chemical reduction in the 4-azaestratriene series. Indeed, we also observed this phenomenon when **13** was treated with sodium in liquid ammonia at −70 °C. However, inspection of the NMR spectrum of the product mixture of this reaction indicated that, along with a small amount of the desired 2-azaestratriene, was the preponderant component of the reaction which possessed no aromatic or vinyl protons. The presence of considerable resonance in the allylic proton region (at ~3.7 ppm) suggested that the $\Delta^{2,5(10)}$-diene **14** was the probable product. Treatment of this mixture then with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided the desired 2-azaestradiol 3-methyl ether (**15**) now as the preponderant product. This compound proved to be spectroscopically identical with that prepared from natural steroidal starting material.[2]

Our attention then turned to the preparation of the 11β-methyl analogues of this series. The Torgov approach to these compounds in the carbocyclic series was not particularly successful, because the diketone **16** resisted isomerization of its double bond to the 8,9 position[16] which is necessary for cyclization to **17**.[12] We thus pursued the approach previously

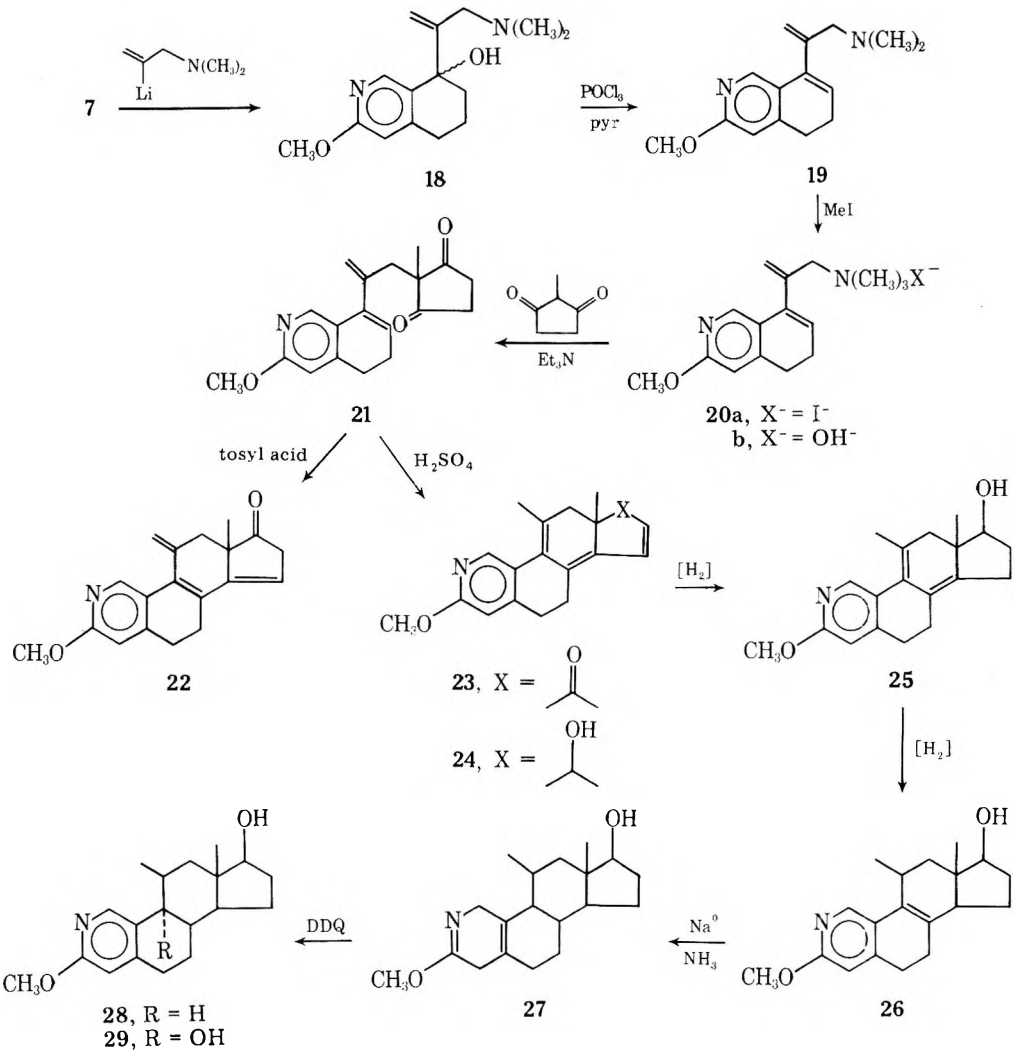


developed in these laboratories for the synthesis of 11-methylated estratrienes, utilizing 2-bromo-3-dimethylamino-1-propene.[17] We found this reagent readily undergoes halogen–metal exchange in the presence of *n*-butyllithium at −25 to −40 °C.[18] This method had several advantages over use of the Grignard reagent of this halide[19] due to the ease of preparation and cleaner resultant product. Thus, treatment of **7** with this lithium reagent (Scheme III) provided the dimethylaminocarbinol **18** in good yield, which was dehydrated to the corresponding diene **19** using phosphorus oxychloride–pyridine. The crude product **19** was then quaternized with methyl iodide to form the ammonium salt **20a.**

As pointed out in the earlier work from these laboratories,[17] C-alkylation of the allylic carbon atom attached to the nitrogen atom with 2-methylcyclopenta-1,3-dione was optimized when the iodide anion was converted to the hydroxide by treatment of the iodide with aqueous silver oxide. We have also found this to be true in our series. Direct alkylation of **20a** with the dione led to low yields of **21** whereas the quaternary ammonium hydroxide **20b** provided the desired adduct **21** in good yield.

Attempts to cyclize the diketone **21** to the tetracyclic product **22** under those conditions utilized in the previous series provided a reaction product comprised of a mixture of components whose characterization was not pursued. The exocyclic triene **22** is apparently unstable to these reaction conditions, and alternate methods for this transformation were investigated. It was found that by using concentrated sulfuric acid at room temperature, **21** is smoothly cyclized with subsequent isomerization of the double bonds into conjugation with the 17-ketone to afford 3-methoxy-11-methyl-2-azaestra-1,3,5(10),9 (11),8 (14),15-hexaen-17-one (**23**) in yields up to 90%.[20] In contrast to the 11-methylene isomer of the carbocyclic series,[17] this tetracyclic hexaene is quite stable at room temperature, apparently due to the conjugation of the double bonds with the carbonyl.

Scheme III



(3)

The 17-ketone was reduced to the corresponding 17-alcohol **24** with diisobutylaluminum hydride. Stepwise catalytic hydrogenation of **24** over palladium on carbon first provided the pentaene **25** and then the tetraene **26**. The initial reduction step procedes via a 1,2 process across the 15,16 double bond, whereas the latter step via a 1,4 addition across the 8(14),9(11) double bonds affording the resultant 3-methoxy-11β-methyl-2-azaestra-1,3,5(10),8-tetraen-17-ol (**26**) with both hydrogen atoms on the same side of the molecule. The 11β-methyl stereochemistry of this product was based on precedent established in previous work in the carbocyclic series where hydrogenation was shown to produce the 11β-methyl isomer.[21]

11β-Methyl-2-azaestradiol 3-methyl ether (**28**) was produced as in the previous series. Reduction of **26** with sodium in liquid ammonia at −70 °C provided a mixture of components, with a structure devoid of aromaticity in preponderance. Subsequent treatment with DDQ gave the desired aromatic product **28** as well as a small amount of polar contaminant (by thin-layer chromatography). Isolation of this latter material by column chromatography afforded a substance whose mass spectrum [M^+ 317 (3.5%), $M^+ - H_2O$ 299 (100%)] and elemental analysis indicated a molecule which differed from **28** by an additional oxygen atom (hydroxyl group). The absence of a downfield proton accompanying this additional hydroxyl group in the NMR spectrum of **29** indicated that it occupied a tertiary position. This would be consistent with its origin, which probably occurred during DDQ treatment. It seems plausible that **28** reacted with the excess DDQ present to generate a benzilic, tertiary carbonium ion which was hydrated during the course of the reaction due to the presence of moisture. This type of product has also been observed in the treatment of 11-oxoestrones with DDQ in a recent study by Turner and co-workers.[22]

The assignment of the configuration of this hydroxyl group has not been unequivocally established. A comparison of the NMR spectra of **28** and **29** reveals only slight variations in the chemical shifts of most resonances with the exception of the 1 proton (7.95 and 8.25 ppm, respectively). The Dreiding model of each isomer fails to reveal an obvious reason for the difference in the chemical shift of this proton on the basis of an interspatial interaction with the hydroxyl group. Furthermore, the 100-MHz proton NMR spectra containing europium shift reagent or the ^{13}C NMR spectrum of this compound failed to provide conclusive evidence for the assignment of its structure.[23] On a mechanistic basis, we favor the structure containing the 9α-hydroxyl group. Hydration of the 9-carbonium ion is sterically hindered on the β face of the molecule by the presence of the two axial methyl groups which would appear to effectively prevent β entry of the water molecule.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken on Varian A-60A, T-60, or 100XL-15 spectrometers using Me_4Si as an internal standard. UV spectra were obtained in MeOH on a Beckman DK-2A. Infrared spectra were obtained on a Beckman IR-12 spectrophotometer. The spectra were run by the group of Mr. A. J. Damascus and the microanalyses were performed by the group of Mr. E. Zielinski. Hydrogenations were carried out by Mr. M. Scaros and

associates. Mass spectra were recorded by Dr. J. Hribar and associates using an AEI MS-30. TLC's were run on 7.6-cm microscope slides covered with 0.25-mm thickness of Woelm F silica with a magnesium silicate binder. Visualization of spots was by phosphomolybdic acid (5% by weight in ethanol) followed by heat.

3-Chlorocyclohex-2-en-1-one (2). To 400 g (3.57 mol) of dihydroresorcinol in 2 L of chloroform was added 161.2 g (1.13 mol) of phosphorus trichloride, and the reaction mixture was refluxed under an atmosphere of nitrogen for 3 h. After cooling, the solution was poured into 1 L of an ice–water mixture, and the two layers were separated. The aqueous phase was extracted with two additional portions of ether before washing the combined extracts with 5% sodium hydroxide (1 L) and saturated salt solution. After drying the extracts over sodium sulfate, solvent removal left an oil which was distilled under reduced pressure to afford 276 g (60%) of **2** [bp 50 °C (0.3 mm)]. Anal. Calcd for C_6H_7ClO: Cl, 27.15. Found: Cl, 27.30.

3-(2-Diethylmalonyl)cyclohex-2-en-1-one (3a). To 5.4 g (0.126 mol) of sodium hydride in 100 mL of 1,2-dimethoxyethane in an atmosphere of nitrogen was added 20 g (0.128 mol) of diethyl malonate dropwise, and the reaction mixture was refluxed for 20 min. To the still warm reaction mixture was then added 10.0 g (0.077 mol) of **2** and it was refluxed for 3 h. After cooling the reaction mixture to ca. 0 °C, 350 mL of ice–water was added, and the solution was then acidified with concentrated hydrochloric acid and extracted with three portions of chloroform. The combined extracts were washed with water and dried over sodium sulfate prior to solvent removal in vacuo which afforded an oil. Distillation in vacuo gave **3a**: bp 148 °C (0.6 mm); UV (MeOH) 232 nm (ϵ 13 500); NMR ($CDCl_3$) δ 1.30 (6 H, t, J = 7 Hz, $-CH_3$), 4.25 (1 H, s, malonyl H), 4.27 (4 H, q, J = 7 Hz, CH_2 of ester), 6.04 (1 H, br s, vinyl proton). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.09; H, 7.24.

Methyl α-Cyano-3-oxo-1-cyclohexene-1-acetate (3b). To 2.4 g (0.1 mol) of sodium hydride in 75 mL of 1,2-dimethoxyethane in an atmosphere of nitrogen was added 9.94 g (0.105 mol) of methyl cyanoacetate, and the reaction mixture was refluxed for 1 h and then cooled to room temperature. To the heterogeneous reaction mixture was then added 6.5 g (0.05 mol) of **2** dropwise and stirring was continued for an additional 3 h. The reaction mixture was diluted with 300 mL of ice–water and acidified with concentrated hydrochloric acid, and the insoluble product present was collected by filtration. The filtrate was extracted with three portions of chloroform, and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave a solid residue. This was combined with solid collected by filtration above, and these were washed with Skelly B to provide 8.6 g (9) of **3b.** Recrystallization from ethyl acetate gave the pure compound as the enol: mp 188–189 °C; UV (MeOH) 338 nm (ϵ 27 000); NMR ($CDCl_3$) δ 1.78 (2 H, br quintet, J = 6 Hz, $-CH_2-$), 2.50 (2 H, br t, J = 6 Hz, $-CH_2-$), 2.87 (2 H, br t, J = 6 Hz, $-CH_2-$), 3.67 (3 H, s, $-OCH_3$). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.37; H, 5.95; N, 7.25.

α-Cyano-3-oxo-1-cyclohexene-1-acetamide (3c). To 58 g (2.42 mol) of sodium hydride in 1.8 L of 1,2-dimethoxyethane (DME) under an atmosphere of nitrogen at room temperature was added portionwise over a 30-min period 198 g (2.35 mol) of cyanoacetamide. The reaction mixture was then refluxed for 30 min before cooling to room temperature, whereupon 145.2 g (1.12 mol) of 3-chlorocyclohex-2-en-1-one (**2**) in 100 mL of benzene was added over a 15-min period. The reaction mixture was refluxed for 1 h before cooling in an ice bath, followed by the dropwise addition of a solution of 10 mL of water in 20 mL of methanol. An additional 500 mL of water was then added before removal of most of the organic solvents in vacuo. Acidification of the remaining aqueous solution to pH 1 with dilute hydrochloric acid caused formation of a precipitate which was collected and washed with several portions of water. Recrystallization from ethanol–water–ethyl acetate (4:1:2) gave in two crops 147.7 g of **3c**: mp 181–183 °C; UV (MeOH) 370 nm (ϵ 21 900); NMR (C_5D_5N) δ 1.73 (2 H, m), 2.41 (2 H, m), 2.93 (2 H, m). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.94; H, 5.88; N, 15.55.

Treatment of 3a with Dimethylformamide Diethyl Acetal. To 1.0 g (0.0039 mol) of **3a** in 5 mL of dimethylformamide was added 0.5 g (0.0034 mol) of dimethylformamide diethyl acetal, and the solution was stirred at room temperature for 16 h. After addition of water the solution was extracted with ether, and the extracts were washed with a saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave an oil whose NMR and UV spectra indicated a preponderance (>80%) of starting material. When **3a** was treated with excess acetal reagent at 70–75 °C for 30 h, the usual workup gave a residue whose NMR spectrum gave little indication of the desired adduct but rather the ethyl enol ether of the starting material. Further characterization was not pursued.

Treatment of 3b with Dimethylformamide Diethyl Acetal. To 1.0 g (0.0052 mol) of **3b** in 8 mL of dimethylformamide was added 1.0 g (0.0068 mol) of dimethylformamide diethyl acetal, and the reaction mixture was stirred at room temperature for 19 h. A small amount of water was added to destroy the excess reagent, and the solvent was removed in vacuo to give an oil whose NMR spectrum indicated a mixture of starting material and the ethyl enol ether of the starting material. Further characterization was not pursued.

(a) 2,3,5,6,7,8-Hexahydro-3,8-dioxo-4-isoquinolinecarbonitrile (5, X = CN) via Dimethylformamide Diethyl Acetal. To 40 g (0.225 mol) of **3c** in 125 mL of dimethylformamide under an atmosphere of nitrogen at room temperature was added 40 g (0.27 mol) of dimethylformamide diethyl acetal dropwise over a 10-min period. After stirring the reaction mixture overnight at room temperature, 10 mL of water was added and the solvent was removed in vacuo. The oily residue was taken up into 450 mL of 2.5% sodium hydroxide solution and then washed eight times with chloroform. Neutralization of the basic solution with dilute hydrochloric acid solution afforded 33.6 g (80%) of **5.** Recrystallization from aqueous acetone gave the pure material: mp >290 °C; UV (MeOH) 227 nm (ϵ 17 900), 232 sh (16 000), 279 (13 000), 324 (6800); NMR (C_5D_5N) δ 1.92 (2 H, m), 2.58 (2 H, m), 2.97 (2 H, m), 8.72 (1 H, s, 1-H). Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.60; H, 4.45; N, 15.02.

(b) 5 (X = CN) via Triethyl Orthoformate. To 75 g (0.42 mol) of **3c** in 400 mL of dimethylformamide was added 75 g (0.505 mol) of triethyl orthoformate, and the reaction mixture was heated at steam bath temperature for 3 h. The solvent was then removed in vacuo to afford an oil which was taken up into hot ethyl acetate. Upon cooling 60 g (75%) of **5** resulted, identical in all respects with that produced as in (a) above. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.94; H, 4.53; N, 15.02.

2,3,5,6,7,8-Hexahydro-3,8-dioxoisoquinoline (6). A solution of 89.5 g (0.476 mol) of **5** in 4 L of 48% hydrobromic acid solution was refluxed for 16 h. The acid was removed in vacuo and the residue was taken up into 200 mL of water. After cooling the solution in an ice bath, sufficient 50% sodium hydroxide solution was cautiously added until the solution assumed a slightly basic pH. The solid which formed was collected and washed with several portions of water and, after drying, afforded 63.5 g (82%) of **6.** Recrystallization from aqueous acetone provided the pure material: mp 246–248 °C dec; UV (MeOH) 279 nm (ϵ 16 700), 221 (13 500); NMR (C_5D_5N) δ 1.96 (2 H, m), 2.57 (2 H, m), 2.92 (2 H, t), 5.50 (1 H, s, 4-H), 8.70 (1 H, s, 1-H). Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.93; H, 5.63; N, 8.59.

3-Methoxy-8-oxo-5,6,7,8-tetrahydroisoquinoline (7). To 63.5 g (0.5 mol) of **6** in 4 L of benzene was added 56.0 g (0.2 mol) of silver carbonate and 110.0 g (0.775 mol) of methyl iodide, and the heterogeneous reaction mixture was refluxed in the dark in an atmosphere of nitrogen for 5 h. The cooled reaction mixture was then filtered through a cake of diatomaceous earth which was washed with an additional portion of benzene. The filtrate was then extracted three times with 4 N hydrochloric acid solution, and the combined aqueous extracts were washed three times with chloroform. The acidic extracts were cooled before neutralization with 50% sodium hydroxide solution and the neutralized aqueous solution was extracted four times with ether. The combined extracts were washed with saturated salt solution and dried over sodium sulfate, and upon solvent removal an oil remained which crystallized upon standing at room temperature. Recrystallization from Skelly B gave 46.4 g (68%) of product. An additional recrystallization from Skelly B gave the analytical sample: mp 55.5–57 °C; UV (MeOH) 268 nm (ϵ 13 100); IR ($CDCl_3$) 5.92, 6.23, 7.80 μm; NMR ($CDCl_3$) δ 2.14 (2 H, m, 6-H's), 2.64 (2 H, br t, 7-H's), 2.91 (2 H, br t, 5-H's), 3.97 (3 H, s, $-OCH_3$), 6.56 (1 H, br s, 4-H), 8.83 (1 H, br s, 1-H). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 68.17; H, 6.48; N, 7.68.

3-Methoxy-5,6,7,8-tetrahydro-8-[(2-methyl-1,3-dioxocyclopent-2-yl)ethylidene]isoquinoline (9). To 10.0 g of **7** (0.057 mol) in 140 mL of xylene cooled to −20 °C in an atmosphere of nitrogen was added 45 mL of 2.85 M vinylmagnesium chloride in tetrahydrofuran (0.126 mol), diluted with 60 mL of xylene dropwise over a 45-min period. The reaction mixture was stirred at ca. −15 °C for an additional 90 min before addition of 100 mL of saturated ammonium chloride solution. After warming to room temperature the layers were separated, and the aqueous phase was extracted with an additional portion of ether. The combined extracts were washed with saturated ammonium chloride solution and then saturated salt solution and dried over sodium sulfate. To this solution was added 6.9 g (0.058 mol) of 2-methylcyclopenta-1,3-dione and 5.8 g (0.058 mol) of triethylamine, and it was then heated so as to remove the ether and tetrahy-

drofuran present. After removal of these lower boiling solvents, the reaction mixture was refluxed over a Dean-Stark trap for 16 h under an atmosphere of nitrogen. After cooling, 75 mL of 5% sodium hydroxide solution was added and after shaking the layers were separated. The aqueous phase was extracted with an additional portion of benzene and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. The dried solution was treated with activated charcoal and filtered before solvent removal in vacuo. The residual oil was taken up into ether and upon cooling 7.5 g (4) of product resulted: mp 79–80.5 °C; UV (MeOH) 262 nm (ε 18 000); IR ($CHCl_3$) 5.78, 6.20, 6.73 μm; NMR ($CDCl_3$) δ 1.17 (3 H, s, $-CH_3$), 2.73 (4 H, s, cyclopentyl CH_2's), 3.92 (3 H, s, $-OCH_3$), 5.72 (1 H, br t, vinyl H), 6.44 (1 H, br s, aromatic H), 8.25 (1 H, br s, aromatic H). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.25; H, 7.11; N, 4.74.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8,14-pentaen-17-one (10). To 15 g (0.079 mol) of tosyl acid monohydrate in 750 mL of dioxane was added 8.75 g (0.029 mol) of **9** in 1.5 L of xylene, and the reaction mixture was refluxed in an atmosphere of nitrogen for 3 h. To the cooled solution was added 200 mL of 5% sodium bicarbonate solution and the two layers were separated. The organic phase was washed three times with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave a deep red oil which upon trituration with acetone afforded 3.95 g (48%) of product. Recrystallization from acetone gave the pure compound: mp 167–169 °C dec; UV (MeOH) 298 nm (ε 28 000); NMR ($CDCl_3$) δ 1.14 (3 H, s, 18-CH_3), 3.93 (3 H, s, $-OCH_3$), 5.89 (1 H, t, J = 3 Hz, 15-H), 6.55 (1 H, br s, 4-H), 8.08 (1 H, br s, 1-H). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.14; H, 6.93; N, 5.04.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8,14-pentaen-17-ol (11). To 3.75 g (0.013 mol) of **10** in 125 mL of methanol was added 1.4 g of sodium borohydride in portions at room temperature. The reaction mixture was then stirred for 10 min before acetone was added to destroy the excess reducing agent. The volume of the solution was reduced to ca. 50 mL before addition of a small amount of water, and cooling afforded 3.9 g (97%) of yellow crystalline product (hydrate) in two crops. Recrystallization from aqueous acetone gave **11**: mp 130–136 °C; UV (MeOH) 300 nm (ε 28 000); NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-CH_3), 3.93 (3 H, s, $-OCH_3$), 5.56 (1 H, br t, 15-H), 6.57 (1 H, br s, 4-H), 8.10 (1 H, br s, 4-H). Anal. Calcd for $C_{18}H_{21}NO_2 \cdot H_2O$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.56; H, 7.51; N, 4.51.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8-tetraen-17-one (12). A solution of 0.678 g (0.0024 mol) of **10** in 100 mL of benzene was hydrogenated over a 70-mg portion of 5% Pd/$CaCO_2$ at room temperature and atmospheric pressure. After 1 equiv of hydrogen had been consumed, the catalyst was removed by filtration and the solvent removed from the filtrate. Recrystallization of the residue from methanol gave 0.519 g (77%) of product in two crops: mp 145–149.5 °C; UV (MeOH) 267 nm (ε 18 000); NMR ($CDCl_3$) δ 0.90 (3 H, s, 18-CH_3), 3.92 (3 H, s, $-OCH_3$), 6.57 (1 H, br s, 4-H), 7.97 (1 H, br s, 4-H). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.62; H, 7.59; N, 4.96.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8-tetraen-17-ol (13). A solution of 3.85 g (0.0135 mol) of **11** in 150 mL of benzene was hydrogenated over 1.5 g of 5% Pd–$CaCO_3$ at atmospheric pressure. After the theoretical amount of hydrogen had been consumed, the catalyst was removed by filtration and the filtrate was reduced in volume. Upon cooling, 2.35 g of analytically pure product resulted: mp 155–157.5 °C; UV (MeOH) 267 nm (ε 18 200); NMR ($CDCl_3$) δ 0.79 (3 H, s, 18-CH_3), 3.93 (3 H, s, $-OCH_3$), 6.52 (1 H, br s, 4-H), 7.97 (1 H, br s, 1-H). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.81; H, 8.31; N, 4.87.

The catalyst was then washed with chloroform and from these washes 1.1 g of additional product (90% total yield) was obtained whose purity was suitable for the subsequent reduction and whose NMR spectrum indicated only the presence of the 14α isomer. The mother liquors of the crystallized material indicated a preponderance of the 14β isomer by the presence of an 18-methyl resonance at 1.02 ppm.

(±)-3-Methoxy-2-azaestra-1,3,5(10),8-tetraen-17-ol (13) from 12. To 0.50 g (0.0017 mol) of **12** in 25 mL of methanol and 5 mL of water was added 0.25 g of sodium borohydride in portions. After addition the reaction mixture was stirred at room temperature for 15 min. Acetone was added to destroy the excess reducing agent and the volume of the solution was reduced to ca. 10 mL. Water was then added which caused formation of an oil which solidified upon continued stirring and was collected, providing 0.436 g (87%) of product. Recrystallization from acetone gave material identical with that obtained by hydrogenation of **11**: mp 155.5–158 °C. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.96; H, 8.19; N, 5.00.

(±)-2-Azaestradiol 3-Methyl Ether (15). To 40 mL of distilled ammonia cooled to ca. −70 °C under an atmosphere of nitrogen was added 0.40 g (0.0014 mol) of **13** in 25 mL of tetrahydrofuran, followed by 0.40 g of sodium metal previously cut into small pieces. After 90 min an additional 0.15-g portion of sodium metal was added and stirring continued for 45 min at the above temperature before addition of 4 g of ammonium chloride portionwise. The reaction mixture was allowed to warm to room temperature, ether was added to the heterogeneous mixture, the organic phase was decanted from the inorganic salts present, and the solvent was removed in vacuo. The resultant oily residue (containing a preponderance of **14**) was taken up into 20 mL of benzene and 10 mL of acetone, and the solution was cooled to ca. −10 °C before addition of 0.32 g (0.0014 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in portions. After addition, the temperature was allowed to rise to 10 °C where it was maintained for 40 min. To the reaction mixture was then added 50 mL of 10% sodium bisulfate solution. After shaking, the layers were separated and the aqueous phase was extracted with two additional portions of ether. The combined extracts were washed three times with 5% sodium hydroxide solution and three times with saturated salt solution and dried over sodium sulfate. After decanting the solution from the drying agent a portion of Skelly B was added and the solution was filtered through a cake of diatomaceous earth. Solvent removal in vacuo gave an oil which upon trituration with methanol gave 120 mg of crude product (30%). Recrystallization from methanol gave **15**: mp 153–156 °C; UV (MeOH) 276 nm (ε 3700); NMR ($CDCl_3$) δ 0.78 (3 H, s, 18-CH_3), 3.90 (3 H, s, $-OCH_3$), 6.44 (1 H, br s, 4-H), 8.03 (1 H, br s, 1-H). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.07; H, 8.66; N, 4.72.

***N,N*-Dimethyl-*N*-[2-(5,6,7,8-tetrahydro-8-hydroxy-3-methoxyisoquinol-9-yl)prop-2-en-1-yl]amine (18).** To 179.4 g (1.10 mol) of 2-bromo-3-dimethylamino-1-propene in 2 L of toluene cooled to ca. −40 °C under an atmosphere of nitrogen was added dropwise 1.0 mol of *n*-butyllithium in hexane over a 20-min period. After 30 min of stirring, a solution of 62.0 g (0.35 mol) of **7** in 300 mL of toluene was added to the reaction mixture at a rate so as to maintain a temperature below −30 °C during the addition. After stirring the reaction mixture between −20 and −30 °C for 30 min, saturated ammonium chloride solution was added, and the layers were separated. The organic phase was washed with an additional portion of saturated ammonium chloride solution and then water before extracting five times with 5% aqueous formic acid solution. The combined acidic extracts were washed with benzene–ether (1:1) and then cooled in an ice bath before basifying the solution with concentrated ammonium hydroxide solution. The heterogeneous solution was then extracted five times with ether–benzene (1:1), and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave 61.2 g (67%) of a brown oil which was suitable for utilization in the subsequent step. An analytical sample was prepared by dissolving a portion of the oil into ether, adding Skelly B until the solution became turbid, and filtering through a cake of diatomaceous earth. After concentrating the filtrate, additional Skelly B was added until the solution again became turbid and was filtered as above. Concentrating the filtrate and cooling provided the pure material: mp 66–68 °C; UV (MeOH) 276 nm (ε 3900); NMR ($CDCl_3$) δ 2.35 (6 H, s, NCH_3's), 3.92 (3 H, s, $-OCH_3$), 4.38 (1 H, d, J = 1 Hz, vinyl H), 5.02 (1 H, br s, vinyl H), 6.43 (1 H, br s, 4-H), 8.25 (1 H, br s, 1-H). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.70; H, 8.51; N, 10.84.

***N,N*-Dimethyl-*N*-[2-(5,6-dihydro-3-methoxyisoquinol-8-yl)prop-2-en-1-yl]amine (19).** To 7.1 g (0.027 mol) of **18** in 35 mL of benzene containing 35 mL of pyridine was added dropwise at room temperature 4.5 g (0.029 mol) of phosphorus oxychloride. After stirring at ambient temperature for 4 h, the reaction mixture was cooled in an ice bath before the cautious addition of 25 mL of water. Sufficient 5% sodium hydroxide solution was then added to raise the pH of the aqueous solution to 10, and after addition of ether the layers were separated. The aqueous phase was extracted with two additional portions of ether, and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. An equivalent volume of Skelly B was added to the solution before treating it with activated charcoal and filtering the solution through a cake of diatomaceous earth. Solvent removal in vacuo gave a yellow oil which crystallized upon standing to provide 4.3 g (65%) of product suitable for quaternization. An analytical sample was prepared by subliming a small portion of the oily solid and recrystallizing the sublimate from aqueous methanol: mp 42–45 °C; UV (MeOH) 262 nm (ε 12 900); NMR ($CDCl_3$) δ 2.23 (6 H, s, NCH_3's), 3.10 (2 H, br s, NCH_2), 3.83 (3

H, s, $-OCH_3$), 5.30 (2 H, br m, $=CH_2$), 5.95 (1 H, t, =CH), 6.56 (1 H, br s, 4-H), 7.96 (1 H, br s, 1-H). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.66; H, 8.31; N, 11.64.

***N,N,N*-Trimethyl-*N*-[2-(5,6-dihydro-3-methoxyisoquinol-8-yl)prop-2-en-1-yl]ammonium Iodide (20a).** To 4.3 g (0.018 mol) of crude **19** in 100 mL of benzene was added 10 mL of methyl iodide, and the solution was let stand at room temperature for 3.5 h. The precipitate which formed was collected, washed with additional benzene, and dried, providing 5.9 g (87%) of **20a**. Recrystallization from acetone–ethyl acetate provided the analytical sample: mp 165–169 °C dec; UV (MeOH) 263 nm (12 900); NMR ($CDCl_3$) δ 3.47 (9 H, s, NCH_3's), 3.93 (3 H, s, $-OCH_3$), 4.67 (2 H, br s, NCH_2), 5.88 (1 H, br s, $=CH_2$), 6.22 (1 H, br s, $=CH_2$), 6.35 (1 H, t, =CH), 6.62 (1 H, br s, 4-H), 7.87 (1 H, br s, 1-H). Anal. Calcd for $C_{16}H_{23}N_2OI$: C, 49.75; H, 6.00; N, 7.25. Found: C, 49.81; H, 6.04; N, 6.97.

5,6-Dihydro-3-methoxy-8-[3-(2-methyl-1,3-dioxocyclopent-2-yl)prop-1-en-2-yl]isoquinoline (21) via the Ammonium Hydroxide 20b. To 5.8 g (0.015 mol) of **20a** in 80 mL of methanol and 20 mL of water was added 1.9 g (0.0082 mol) of silver oxide, and the reaction mixture was stirred for 1 h at room temperature in the dark. The solution was filtered through diatomaceous earth before addition of 2.0 g (0.018 mol) of 2-methylcyclopenta-1,3-dione and solvent removal in vacuo with a bath temperature of ca. 50 °C. The resultant oily residue was taken up into 25 mL of dioxane and 150 mL of xylene, and 4 mL of triethylamine was added. The reaction mixture was heated until the solution reached a temperature of ca. 125 °C before addition of a condenser to the reaction flask. After refluxing overnight under an atmosphere of nitrogen, 5% sodium hydroxide solution was added to the cooled reaction mixture, and the layers were separated. The organic phase was washed with saturated salt solution before extracting three times with 2.5% aqueous formic acid solution. The aqueous extracts were washed with three portions of benzene, these were combined with the earlier organic phase, and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo afforded an oil which crystallized upon standing to provide 3.55 g (75%) of **21** which was recrystallized from acetone; mp 102–106 °C; UV (MeOH) 261 nm (ϵ 12 200); NMR ($CDCl_3$) δ 1.08 (3 H, s, 18-CH_3), 2.68 (4 H, s, cyclopentyl CH_2's), 2.75 (2 H, s, 12-CH_2), 3.95 (3 H, s, $-OCH_3$), 5.13 (2 H, m, $=CH_2$), 5.74 (1 H, t, =CH), 6.59 (1 H, br s, 4-H), 7.84 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.06; H, 6.61; N, 4.40.

21 via the Ammonium Iodide 20a. To 0.75 g (0.00625 mol) of 2-methylcyclopenta-1,3-dione in 20 mL of dimethylformamide was added 1.0 g (0.010 mol) of triethylamine, and the reaction mixture was heated to ca. 50 °C in an atmosphere of nitrogen before addition of 1.9 g (0.0005 mol) of **20a**. After heating the homogeneous solution at ca. 135 °C for 5 h, it was allowed to cool and the solvent was removed in vacuo. The residual oil was taken up into water–ether, the pH of the aqueous phase was adjusted to pH 10 with 5% sodium hydroxide solution, and the layers were separated. The aqueous phase was extracted with two additional portions of ether, and the combined extracts were then extracted three times with 2.5% aqueous formic acid solution and once with saturated salt solution and dried over sodium sulfate. Solvent removal gave an oil which was taken up into a small amount of ether and Skelly B was added until the solution became turbid. After treating with activated charcoal and filtering through a cake of diatomaceous earth, solvent removal gave 0.3 g (<20%) of an oil which crystallized upon standing. Recrystallization from aqueous acetone afforded **21** identical in all respects with the product obtained in the previous reaction.

(±)-3-Methoxy-11-methyl-2-azaestra-1,3,5(10),8(14),9(11),-15-hexaen-17-one (23). To 40 mL of concentrated sulfuric acid cooled to 0–5 °C was added 2.4 g (0.0077 mol) of **21** in portions with the reaction temperature kept below 10 °C during the addition. After addition, the cooling bath was removed and the reaction mixture was allowed to assume room temperature over a 20-min period. The solution was then cautiously added to ca. 100 mL of water cooled in an ice bath and the aqueous solution was basified with concentrated ammonium hydroxide to afford 2.1 g (93%) of solid collected by filtration. Recrystallization from acetone gave **23**: mp 197–198.5 °C; UV (MeOH) 244 nm (ϵ 19 000), 280 (15 500), 372 (8200); NMR ($CDCl_3$) δ 1.12 (3 H, s, 18-CH_3), 2.17 (3 H, br s, 11-CH_3), 3.97 (3 H, s, $-OCH_3$), 6.20 (1 H, d, J = 5.5 Hz, 16-H), 6.62 (1 H, br s, 4-H), 7.97 (1 H, d, J = 5.5 Hz, 15-H), 8.18 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.78. Found: C, 77.98; H, 6.66; N, 4.73.

(±)-3-Methoxy-11-methyl-2-azaestra-1,3,5(10),8(14),9(11),-15-hexaen-17-ol (24). To 2.1 g (0.0072 mol) of **23** suspended in 75 mL of benzene and 50 mL of ether cooled to ca. 0 °C under an atmosphere of nitrogen was added 12 g (0.017 mol) of a 20% solution of diisobutylaluminum hydride in toluene over a 10-min period. The reaction mixture was stirred at the above temperature for 15 min before destroying the excess reducing agent with a small amount of 2-propanol. Water was then added, followed by sufficient 1 N hydrochloric acid solution so that the pH of the aqueous solution was adjusted to 6.5–7. The two phases were separated and the aqueous phase was extracted three times with ether–benzene (1:1) and once with chloroform. The combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal gave an oil which upon trituration with alcohol afforded 2.0 g (95%) of solid product. Recrystallization from ethanol gave **24** as the solvate: mp 95–100 °C; UV (MeOH) 257 nm (ϵ 30 700), 263 (29 700); NMR ($CDCl_3$ δ 0.80 (3 H, s, 18-CH_3), 2.15 (3 H, br s, 11-CH_3), 3.97 (3 H, s, $-OCH_3$), 4.40 (1 H, m, 17-H), 6.07 (1 H, m, 16-H), 6.48 (1 H, d, 15-H), 6.60 (1 H, br s, 4-H), 8.18 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{21}NO_2 \cdot C_2H_5OH$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.82; H, 8.08; N, 4.12.

(±)-3-Methoxy-11-methyl-2-azaestra-1,3,5(10),8(14),9(11)-pentaen-17-ol (25). A solution of 1.0 g (0.0034 mol) of **24** in 200 mL of benzene was hydrogenated over a 0.5-g portion of 5% $Pd/CaCO_3$ at room temperature and atmospheric pressure. After two-thirds of an equivalent of hydrogen had been consumed uptake ceased. An NMR spectrum of an aliquot taken from the reaction mixture after this time indicated an absence of vinyl protons. The catalyst was removed by filtration and the solvent removed from the filtrate. Recrystallization of the residue from ethanol gave 0.62 g (62%) of **25** in two crops as the solvate: mp 93–100 °C; UV (MeOH) 242 nm (ϵ 21 900), 247 (20 900), 291 (6700); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 2.03 (3 H, br s, 11-CH_3), 2.25 (2 H, br s, 12-CH_2), 3.93 (3 H, s, $-OCH_3$), 6.54 (1 H, br s, 4-H), 8.13 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{23}NO_2 \cdot C_2H_5OH$: C, 73,43; H, 8.51; N, 4.08. Found: C, 73.54; H, 8.64; N, 4.10.

(±)-3-Methoxy-11β-methyl-2-azaestra-1,3,5(10),8-tetraen-17-ol (26). A solution of 3.7 g (0.017 mol) of **25** in 100 mL of ethanol was hydrogenated over a 1.8-g portion of 5% Pd/Al_2O_3 at room temperature and atmospheric pressure. After an equivalent of hydrogen had been consumed, the catalyst was removed by filtration and the solvent removed from the filtrate. The residual oil was taken up into methanol and gave 2.65 g (72%) of product in two crops: mp (after drying) 164–167.5 °C; UV (MeOH) 267 nm (ϵ 16 400); NMR ($CDCl_3$) δ 0.93 (3 H, s, 18-CH_3), 1.25 (3 H, d, J = 7.5 Hz, 11-CH_3), 3.93 (3 H, s, $-OCH_3$), 6.55 (1 H, br s, 4-H), 7.95 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{25}NO_2 \cdot CH_3OH$: C, 72.47; H. 8.82; N, 4.47. Found: C, 72.64; H, 8.75; N, 4.17.

(±)-3-Methoxy-11-methyl-2-azaestra-2,5(10)-dien-17-ol (27). To ca. 225 mL of freshly distilled liquid ammonia cooled to −70 °C under an atmosphere of nitrogen was added in portions 1.5 g (0.065 mol) of sodium metal previously cut into small pieces. After stirring the blue solution for 20 min, 2.3 g (0.0077 mol) of **26** in 100 mL of tetrahydrofuran was added dropwise over a 15-min period. The reaction mixture was stirred at the above temperature for 30 min after addition before 10 g of ammonium chloride was added portionwise, and the reaction mixture was allowed to reach ca. −33 °C, at which temperature the ammonia evaporated out of the solution. Ether was then added to the residual solution, followed by saturated sodium chloride solution, and the layers were separated. The organic phase was washed with additional saturated salt solution and dried over sodium sulfate. Solvent removal gave ca. 2.3 g of yellow oil whose NMR spectrum indicated a large amount of resonance centered around 3.8 ppm, attributed to the presence of the C-1 and C-4 methylene groups of **27**. In addition, the oil exhibited no aromatic protons and possessed no UV absorption at 267 (**26**) or 278 nm (**28**). This material was used for the subsequent reaction without purification.

(±)-3-Methoxy-11β-methyl-2-azaestra-1,3,5(10)-trien-17-ol (28) and (±)-9-Hydroxy-3-methoxy-11-methyl-2-azaestra-1,3,5(10)-trien-17-ol (29). To the crude oil **27** in 25 mL of acetone and 25 mL of benzene at room temperature was added dropwise over a 5-min period 2.3 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.01 mol) in 10 mL of acetone and 10 mL of benzene. The reaction mixture was stirred at the above temperature for 15 min before 25 mL of saturated sodium bisulfite solution was added, followed by sufficient ether so as to form two layers. After separating, the aqueous phase was extracted with an additional portion of ether, and the combined extracts were washed once with saturated sodium bisulfite solution, three times with 5% sodium hydroxide solution, and three times with saturated sodium chloride solution. The solution was then dried over sodium sulfate and filtered through a cake of diatomaceous earth. Solvent removal in vacuo gave ca. 1.5 g of an oil which upon trituration with ether–methanol gave 0.5 g of **28**. Recrystallization from methanol–water gave the pure material: mp 168–169 °C; UV

(MeOH) 278 nm (ε 3760); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 0.93 (3 H, d, J = 7 Hz, 11-CH_3), 3.90 (3 H, s, -OCH_3), 6.42 (14, br s, 4-H), 7.95 (1 H, s, 1-H). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.95; H, 9.09; N, 4.51.

The mother liquors from the trituration above were chromatographed over silica gel using benzene–ethyl acetate solution as the eluent. Additional **28** was obtained, eluting with 2% ethyl acetate–benzene solution, and provided another 0.14 g after recrystallization from aqueous alcohol. Upon eluting with ethyl acetate (neat) 0.15 g of **29** was obtained. Recrystallization from ethyl acetate provided the pure compound: mp 181–185 °C; UV (MeOH) 275 nm (ε 3650); NMR ($CDCl_3$) δ 0.89 (3 H, s, 18-CH_3), 0.94 (3 H, d, J = 7 Hz, 11-CH_3), 3.90 (3 H, s, -OCH_3), 6.48 (1 H, br s, 4-H), 8.25 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.75; H, 8.52; N, 4.39.

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Registry No.—**1**, 30182-67-3; **2**, 5682-75-7; **3a**, 64761-52-0; **3b**, 64761-53-1; **3c**, 64761-55-3; **5** (X = CN), 56053-56-6; **6**, 56053-57-7; **7**, 65053-58-8; **9**, 56053-60-2; **10**, 56053-61-3; **11**, 64761-51-9; **12**, 56053-64-6; **13** (14α isomer), 64811-74-1; **13** (14β isomer), 64811-75-2; **14**, 64761-54-2; **15**, 64811-76-3; **18**, 58653-16-0; **19**, 58653-17-1; **20a**, 58653-18-2; **20b**, 64761-56-4; **21**, 58653-19-3; **23**, 58653-20-6; **24**, 64761-57-5; **25**, 64761-58-6; **26**, 64811-77-4; **27**, 64811-78-5; **28**, 64811-79-6; **29**, 64761-59-7; diethyl malonate, 105-53-3; methyl cyanoacetate, 105-34-0; cyanoacetimide, 107-91-5; dimethylformamide diethyl acetal, 1188-33-6; triethyl orthoformate, 122-51-0; methyl iodide, 74-88-4; benzyl chloride, 75-01-4; 2-methyl-cyclopenta-1,3-dione, 765-69-5; 2-bromo-3-dimethylamino-1-propene, 14326-14-8.

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(21) The chemical shift of the 11-methyl group of **26** was identical with that of its analogue in the carbocyclic series (cf. ref 17), where the stereochemistry had been unequivocally established.
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cis-4,4′-Stilbenediols. Synthesis from Dienestrol, Structure, and Photocyclization to Dihydrophenanthrenes

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Diels–Alder cycloaddition reactions between dienestrol or its diacetate and dienophiles maleic anhydride, 4-phenyl-1,2,4-triazoline-3,5-dione, dimethyl maleate, 1,4-naphthoquinone, and tetracyanoethylene yielded adducts representing 4,4′-stilbenediols with obligate cis configuration. These compounds are ideally suited for studying the photochemical conversion of stilbene-like molecules to dihydrophenanthrenes without intereference from the *trans*-stilbene isomers. The structures and stereochemistry of the Diels–Alder adducts were established by detailed interpretation of their NMR and mass spectra. UV irradiation of the synthesized *cis*-stilbenes caused photocyclization to the respective 4a,4b-dihydrophenanthrenes without interfering side reactions and with quantum yields in excess of 0.85.

The photooxidative ring closure of stilbenes to phenanthrenes proceeds through nonoxidized 4a,4b-dihydrophenanthrene (DHP) intermediates.[1] Most previous studies of the mechanism of the photocyclization step have been complicated by simultaneous cis–trans isomerization of starting stilbene, by rapid subsequent oxidation of DHP to phenanthrene, or by reverse ring opening of DHP to *cis*-stilbene. Naef and Fischer[2a] circumvented the cis–trans complication by use of precursor stilbenes[2b,c] constrained to cis conformation by their cyclic structures. These authors also eliminated subsequent oxidation to phenanthrenes by rigorous degassing or by substitution of methyl for hydrogen at the appropriate sites. However, thermal and photochemical ring opening of the DHP's remained a complication; the intermediates could not be isolated, but were observed only in situ in photoequilibrium with precursor stilbenes.

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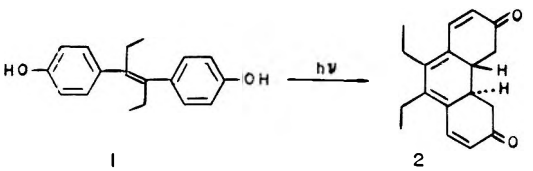
Scheme I



1 2

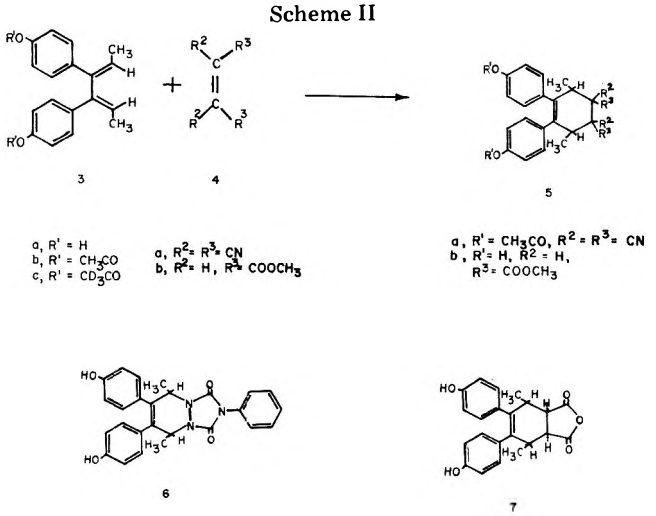
We have previously reported[3] that stilbenes with hydroxy substituents in the para positions of both aromatic rings, such as the estrogenic hormone diethylstilbestrol, undergo photocyclization to DHP's (Scheme I) that can isolated; these are stabilized by double enol–keto tautomerism, are generated quantitatively, are markedly resistant to oxidation, and are only minimally susceptible to ring opening. However, our previous studies of this class were complicated by cis–trans isomerization of the precursor stilbenes, a necessary reaction in the case of diethylstilbestrol.

We now report the synthesis of stilbene-like molecules by Diels–Alder reaction of the estrogenic hormone dienestrol with various dienophiles (Scheme II). The structural features of the resulting adducts are such that photolysis proceeds with complete sequestration of the *cis*-stilbene to DHP reaction, since not only are the adducts constrained to cis conformation, as in the work of Naef and Fischer,[2a] but also stability of the product DHP's is conferred by enol–keto tautomerism, as in our previous studies.[3] The detailed determinations of the structures of the adducts and their photolysis in alcoholic solution are described.

Results and Discussion

The Diels–Alder cycloaddition reactions with **3a** or **3b** readily yielded adducts **5–7.** Since the configuration of **3a** has been determined with accuracy,[4,5] its participation in (4 + 2) multicenter addition reactions is readily understood. The stereospecificity of the concerted Diels–Alder reaction requires that the two methyl groups of **3a** or **3b** be cis in all adducts. Although the phenyl rings in **3a** are twisted out-of-plane with respect to the olefinic bonds, the cis diene moiety is planar and retains the symmetry required for Diels–Alder reactions.[6] Whenever R^2 and R^3 of dienophile **4** are identical, only one adduct can be formed. Thus, single products **6** and **5a** were obtained from the addition of 4-phenyl-1,2,4-triazoline-3,5-dione to **3a** and that of tetracyanoethylene to dienestrol diacetate (**3b**), respectively. Adduct **6** exists in only one form due to inversion of the nitrogen. When substituents R^2 and R^3 are different, however, both endo and exo conformations are possible. Although the reaction of **3a** with maleic anhydride gave only one of the possible conformers, namely, the trans,trans adduct (**7**), the addition of dimethyl maleate yielded both stereoisomers (**5b**), one of which was isolated in a pure state by recrystallization and had a melting point 40 °C above that of the mixture. The reaction of **3a** with 1,4-naphthoquinone also yielded a mixture which, however, could not be resolved.

Scheme II



3 4 5

a, R′ = H
b, R′ = CH_3CO
c, R′ = CD_3CO

a, R^2 = R^3 = CN
b, R^2 = H, R^3 = $COOCH_3$

a, R′ = CH_3CO, R^2 = R^3 = CN
b, R′ = H, R^2 = H, R^3 = $COOCH_3$

6 7

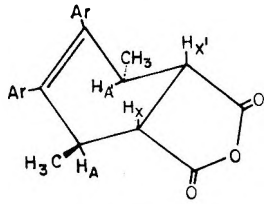
NMR Analysis. In general, the NMR spectra of the adducts followed first-order patterns and showed good agreement with the proposed structures. However, the methine protons in the adducts of **3a** with maleic anhydride, dimethyl maleate, and naphthoquinone and those of **3b** with tetracyanoethylene formed complex spin systems. Therefore, we examined the splitting pattern associated with the methine protons adjacent to the carbonyl groups in **7** as representative of the group.

At 60 MHz, these protons generated an apparent quartet in the δ 2–4 spectral region. At 220 MHz, however, two additional weaker lines were observed, one on each side of the quartet. This complex multiplet was analyzed as the XX′ portion of an AA′XX′ system;[7] the other half of the four-spin complex consisted of the two adjacent methine protons which were part of **3a** before cycloaddition. The calculated values of the respective coupling constants were $^3J_{AA'} = 0$, $^3J_{AX} = 6$, $^3J_{AX'} = 0$, and $J_{XX'} = 9$ Hz. A simulated spectrum computed[8] with these values and chemical shifts of δ 2.29 and 3.68 for the A and X hydrogens, respectively, matched the experimentally recorded NMR spectrum.

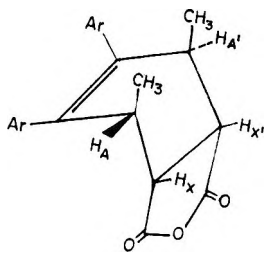
There is little doubt that the cyclohexene ring of **7** formed in the Diels–Alder reaction is in a boat conformation. The alternate chair conformer has so much strain in the bicyclic moiety that we could not build the molecule with Dreiding molecular models. However, there are two possible boat configurations as the methyl groups can be either both axial (**7b**) or both equatorial (**7a**) (Scheme III). Furthermore, each of the two boat molecules may have the methine hydrogen atoms oriented cis,cis or trans,trans.

In view of the values of the coupling constants computed for the possible conformers, it is most likely that **7** exists in the trans,trans configuration and undergoes rapid ring inversion between the two boat conformers. In fact, a dynamic distribution with predominance of the conformer with axial methyl groups would generate an average $^3J_{AX}$ of 6 Hz, the value used to reproduce the experimental spectrum as described above.

Scheme III



7a



7b

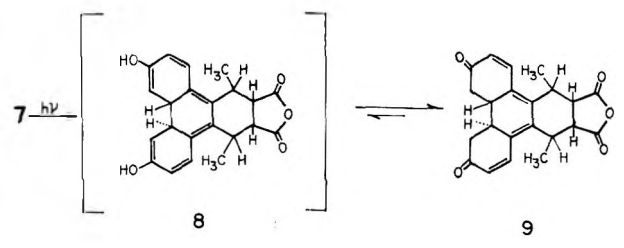
Mass Spectra. Adducts 5–7 showed molecular ions at the expected *m/e* values. With a few exceptions, the ions observed were readily attributable to the expected fragmentation. Three of them, *cis*-stilbenediols **5b**, **6**, and **7**, displayed prominent peaks at *m/e* 107, 121, and 145, whereas diacetate **5a** did not. Conceivably, the three diols could undergo a retro-Diels–Alder reaction[9] to produce **3a**, which, in turn, may fragment to give ions at *m/e* 145 and 121. However, since **3a** itself gives an intense molecular ion peak at *m/e* 266 and since such a peak was observed only in the mass spectrum of **6**, the retro-Diels–Alder reaction does not appear to be a major fragmentation pathway in these adducts. Competing processes appear to be more important. High-resolution studies, undertaken to identify the ions, showed that the peak at *m/e* 145 had a composition of $C_{10}H_9O$ and the peaks at *m/e* 121 and 107 corresponded to C_8H_9O and C_7H_7O, respectively. In corresponding ions of **3c**, deuterium replaced a hydrogen. Metastable studies using the direct analyses of daughter ions (DADI) technique indicated that all these ions were formed from the base-peak fragments. Similarly, the ions at *m/e* 159 and 160 also arose from the base peaks of **3b** and **3c**, respectively. Metastable measurements of **5b** and **6** also showed that the ions at *m/e* 159, 145, 121, and 107 arose from the ion at *m/e* 266. Further work is in progress to determine the structures of these ions.

Photolysis. Dilute methanolic solutions of the synthesized *cis*-stilbenediols were irradiated with 254-nm light. The reactions were readily followed by monitoring the changes in the UV absorption spectra after short, consecutive exposures. The observed UV spectral changes demonstrated that the stilbenediol reactants underwent a clean and efficient photocyclization to diketo-DHP's. The reaction sequence is shown for the maleic anhydride adduct **7** in Scheme IV. Formation of DHP's was demonstrated by the appearance of highly characteristic absorbance maxima around 290 and 410 nm, which were virtually identical with maxima recorded for the isolated,[3] stable DHP **2**. The location of the peak at 410 nm agrees well with empirical calculations for the unusual tetraenedione system, but it is lower than that predicted for the transient hexadienediol tautomer **8** and lower also than those observed for various unstable DHP's.[1] A distinct isosbestic point at 253 nm is formed by the family of scans, thus demonstrating the absence of side reactions. By contrast, time-lapse spectrometry diagrams of stilbenes capable of cis–trans isomerization show an initial lack of isosbesticity during the period required to establish the cis–trans equilibrium.[3b] Furthermore, consecutive spectra show that oxidation to phenanthrene is essentially negligible in buffered neutral solutions, as evidenced by both the isosbestic point and the nonappearance of fine structure characteristic of polynuclear aromatic compounds. Phenanthrenes were produced, however, on irradiation of the adducts in acidic solutions. This behavior in acid is analogous[3b] to that of DHP **2**.

As shown in Scheme IV, the geometry of the inner 4a,4b hydrogens of DHP **9** is trans; this has previously been demonstrated[3b,d] and is a result of orbital symmetry requirements.

Solutions of the DHP's were stable indefinitely when stored in the dark. Neither phenanthrene formation nor ring opening to form the starting stilbenes was observed. This, together with the absence of cis–trans isomerization, makes these adducts ideal for study of the uncomplicated photocyclization of *cis*-stilbene to DHP. Preliminary quantum yield determinations for formation of DHP **9** from *cis*-stilbenediol **7** gave consistent values in excess of 0.85. The remarkable efficiency of this phototransformation is in accord with its observed generality and emphasizes its usefulness in both biochemical and chemical systems.

Scheme IV



Experimental Section

NMR spectra were obtained with a Varian Model A-60 spectrometer, using acetone-d_6 as the solvent and tetramethylsilane as the internal standard. A Varian HR-220 spectrometer was also used to obtain the NMR spectrum of **7** at 220 MHz. Mass spectra were obtained on a Varian MAT 311 instrument interfaced to a Varian MAT SS100MS data system. Some of the spectra were plotted by using a Varian Statos 21 electrostatic printer/plotter. The following conditions were used to obtain mass spectra: ionization energy, 70 eV; ionizing electron current, 300 μA; accelerating voltage, 3 kV; source temperature, 200 °C; and multiplier voltage, 2 kV. The samples were introduced by a direct insertion probe that was heated at a rate sufficient to provide usable spectra. The 10 most abundant ions are reported for each spectrum. The UV spectra were recorded on a Cary 15 spectrophotometer.

Dienestrol (3a). NMR δ 1.50 (d, $CHCH_3$, J = 6.5 Hz), 5.37 (q, $CHCH_3$, J = 6.5 Hz), 6.65–7.3 (m, aromatic protons), 8.45 (s, OH); mass spectrum, *m/e* (relative intensity) 266 (100), 251 (50), 237 (36), 121 (31), 145 (25), 267 (22), 107 (22), 210 (14), 236 (13), 252 (11), 173 (11).

Dienestrol Diacetate (3b). Mass spectrum, *m/e* (relative intensity) 266 (100), 308 (84), 350 (56), 251 (47), 237 (35), 267 (21), 249 (21), 265 (20), 121 (20), 351 (15), 145 (15), 43 (15).

Dienestrol Diacetate-d_6 (3c). Mass spectrum, *m/e* (relative intensity) 268 (100), 253 (96), 312 (94), 46 (93), 122 (55), 239 (42), 108 (37), 238 (36), 146 (34), 250 (30).

Dienestrol–Maleic Anhydride Adduct (7). A solution of 2 g of **3a** and 10 g of maleic anhydride in 150 mL of xylene was refluxed for 3 h and then cooled. Heptane was added, and the solution was refrigerated. Crystallization from $CHCl_3$–hexane and vacuum drying yielded 1.8 g of product (66%), mp 190–191 °C; NMR δ 1.12 (d, $CHCH_3$, J = 7 Hz), 2.70–3.20 (m, $CHCH_3$), 3.58–3.81 (m, O=CCH), 6.20–7.10 (m, aromatic), 8.20 (s, OH); mass spectrum, *m/e* (relative intensity) 364 (100), 277 (52), 121 (43), 365 (28), 292 (21), 107 (21), 251 (19), 278 (13), 237 (13), 131 (13).

Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.65; H, 5.46.

Dienestrol-4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (6). The dienophile was first synthesized following the procedure of Stickler and Pirkle[10] and used without actual isolation. A solution of 3 g of phenylurazole in 150 mL of CH_2Cl_2 and 30 g of Na_2SO_4 was stirred at 0 °C while N_2O_4 was introduced. The resulting red solution was concentrated in vacuo to approximately one-third of its original volume, the concentrate was added to a solution of 2.5 g of **3a** in 100 mL of benzene over a period of 45 min with stirring, and the solvent was removed in vacuo. Several crystallizations from MeOH gave 0.4 g of white crystals (10%), mp 253–254 °C; NMR δ 1.55 (d, $CHCH_3$, J = 7 Hz), 3.08 (s, OH), 4.66 (q, $CHCH_3$, J = 7 Hz), 6.55–7.22 (m, aromatic), 7.3–7.7 (m, *N*-phenyl); mass spectrum, *m/e* (relative intensity) 441 (100), 119 (97), 265 (85), 237 (77), 91 (69), 426 (68), 280 (57), 107 (56), 264 (48), 249 (47).

Anal. Calcd for $C_{26}H_{23}N_3O_4$: C, 70.73; H, 5.25; N, 9.52. Found: C, 70.90; H, 5.36; N, 9.26.

Dienestrol Diacetate–Tetracyanoethylene Adduct (5a). A solution of 0.67 g of **3b** and 0.3 g of tetracyanoethylene in 20 mL of benzene was held at room temperature for 12 h and then evaporated. The yield was 0.6 g of **5a** (60%), which was crystallized from MeOH and dried at 100 °C, mp 164–165 °C; NMR δ 1.51 (d, $CHCH_3$, J = 7 Hz), 2.16 (s, O_2CCH_3), 3.85 (brd q, $CHCH_3$, J = 7 Hz), 7.18 (m, aromatic); mass spectrum, *m/e* (relative intensity) 394 (100), 436 (30), 395 (27), 266 (12), 437 (10), 340 (9), 251 (9), 43 (9), 478 (8), 237 (6).

Anal. Calcd for $C_{28}H_{22}N_4O_4$: C, 70.28; H, 4.64; N, 11.71. Found: C, 70.29; H, 4.49; N, 11.42.

Dienestrol–Dimethyl Maleate Adduct (5b). A solution of 5 g of **3a** and 50 mL of dimethyl maleate was refluxed in 200 mL of xylene for 21 h. The solution was cooled and extracted with dilute NaOH. The extract was acidified with dilute H_2SO_4 and extracted with ethyl

ether. The ether extract was washed with water, dried, and evaporated to an oil. When 100 mL of benzene was added, the crystals that formed were collected and washed with 20 mL of benzene. These crystals, weighing 2.7 g (46%), mp 234–237 °C, after crystallization from C_6H_6–MeCH, gave the pure stereoisomer **5b**, mp 240–243 °C; NMR δ 0.98 (d, $CHCH_3$, J = 7 Hz), 2.67 (m, $CHCH_3$), 2.84 (m, O=CCH), 3.68 (two s, CO_2CH_3), 6.50–7.05 (m, aromatic), 7.92 (s, OH); mass spectrum, *m/e* (relative intensity) 291 (100), 350 (55), 410 (37), 107 (31), 292 (25), 59 (25), 121 (23), 145 (18), 351 (17), 290 (17).

Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39. Found: C, 70.06; H, 6.33.

The original benzene filtrate was evaporated, and crystallization of the residue from MeOH–H_2O gave 3.1 g of a mixture which, by both NMR and elemental analysis, appeared to be about 60% product, a mixture of two stereoisomers, and 40% unreacted **3a**. Most of the starting material was removed from the crude product by sublimation at 160 °C, and the residue was crystallized from MeOH–H_2O to give an isomeric mixture, mp 203–204 °C; NMR δ 1.16 (d, $CHCH_3$, J = 7 Hz), 3.00 (m, $CHCH_3$), 3.42 (m, O=CCH), 3.70 (s, CO_2CH_3), 6.50–7.00 (m, aromatic), 7.85 (s, OH); mass spectrum, *m/e* (relative intensity) 350 (100), 121 (49), 291 (41), 351 (39), 410 (32), 107 (23), 244 (17), 59 (16), 292 (10), 276 (10).

Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39. Found: C, 70.18; H, 6.41.

Dienestrol–1,4-Naphthoquinone Adduct. A solution of 3 g of **3a** and 3 g of naphthoquinone in 50 mL of xylene was heated at 150 °C for 4 h. The reaction mixture was cooled to give crystals of unreacted **3a**. The filtrate was diluted with hexane to yield a product which, after several crystallizations from dilute EtOH, gave a small amount of yellow crystals which melted with decomposition at 250 °C. No elemental analysis was obtained. The NMR spectrum indicated that the product was a mixture of two stereoisomers and that no residual **3a** was present. NMR δ 0.89 (d, $CHCH_3$, J = 7 Hz), 1.13 (d, $CHCH_3$, J = 7 Hz), 3.15 (s, OH), 3.30–3.58 (m, $CHCH_3$), 3.76–3.90 (m, $CHCH_3$), 6.44–7.05 (m, aromatic on phenolic rings), 7.90 (m, o-phenylene).

Photolysis of Adducts. Typically, starting materials were at or near a concentration of 3×10^{-5} M. A Mineralight Model SL (254 nm) 9-W hand lamp was used as the source of UV radiation. Solutions were placed in a 1-cm Teflon-stoppered quartz cuvette (4-mL capacity), irradiated with the lamp flush against the cuvette for intervals timed with a stopwatch, and then scanned directly in the spectrophotometer. No spectral changes were noted during storage in the dark in the absence of irradiation.

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Registry No.—**3a**, 13029-44-2; **3a**–naphthoquinone (isomer I), 64490-43-3; **3a**–naphthoquinone (isomer II), 64521-02-4; **3b**, 24705-62-2; **3c**, 64490-47-7; **5a**, 64490-48-8; **5b** (isomer I), 64490-49-9; **5b** (isomer II), 64550-40-9; **6**, 64490-50-2; **7**, 64490-51-3; **8**, 64490-52-4; **9**, 64490-53-5; maleic anhydride, 108-31-6; phenylurazole, 15988-11-1; dimethyl maleate, 624-48-6; naphthoquinone, 130-15-4; tetracyanoethylene, 670-54-2.

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Facile Synthesis of Hexahydroapoerysopine via Intramolecular Photoarylation of β-Enamino Ketones

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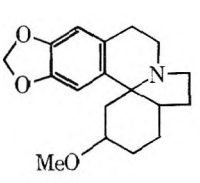
A novel synthesis of hexahydroapoerysopine dimethyl ether (**26**) has been achieved by using photochemical cyclization of β-enamino ketones as a key reaction. The reaction of 3,3a,4,5-tetrahydro-6-methoxy-2*H*-indole (**15**) with 3,4-dimethoxyphenethyl- (**9**) or 2-iodo-4,5-dimethoxyphenethyl iodide (**13**) afforded the corresponding *N*-phenethyl derivatives of 1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one, **17** and **18**, respectively; compound **17** was further brominated to give 7-bromo-1,2,3,3a,4,5-hexahydro-1-(3,4-dimethoxyphenethyl)-6*H*-indol-6-one (**22**). Upon irradiation, the halogenated β-enamino ketones **18** and **22** underwent intramolecular photoarylation and photoreduction, yielding 3,3a-dihydro-2*H*-apoerysopin-1-one dimethyl ether (**21**) and **17**, respectively. Reduction of **21** with $LiAlH_4$ gave the dimethyl ether derivatives of 3,3a,12b,12c-tetrahydro-2*H*-apoerysopin-1-one (**24**) and 2,3,3a,12c-tetrahydroapoerysopine (**25**); the latter was catalytically hydrogenated to 1,2,3,3a,12c,12b-hexahydroapoerysopine dimethyl ether (**26**).

Treatment of tetrahydroerythraline (**1**) under acidic conditions followed by methylation with diazomethane has been reported to yield an optically active base formulated as hexahydroapoerysopine dimethyl ether.[1,2] This reaction has been referred to as the "apo rearrangement".[3] Synthetic routes to such "apo derivatives" possessing the dearomatized ring D are very few in number.[4] We have now devised a new synthesis



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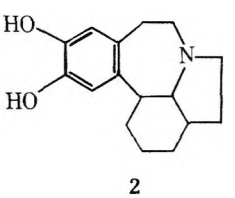

2

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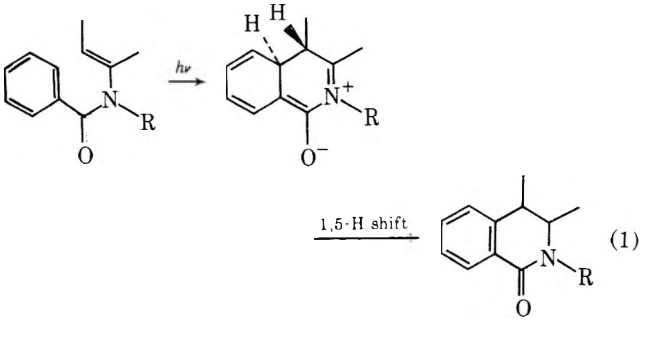
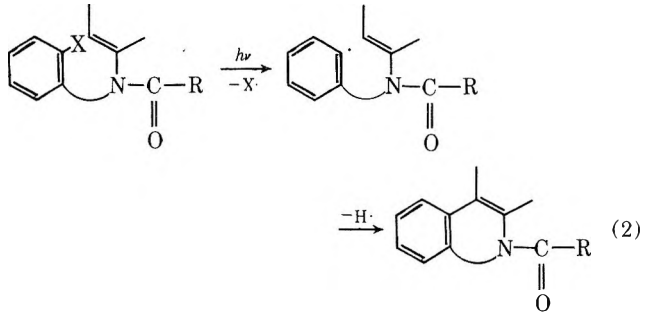
of the title compound from the key intermediate **21** obtained by photolysis of halogen-containing enamino ketones. Our results represent a convenient one-step preparation of β-enamino ketones from the iminoenol ether **15** and new variants of intramolecular arylation.

Intramolecular photoarylations of enamides to heterocyclic ring system have been extensively studied,[5-8] particularly in the field of alkaloid synthesis. The majority of these reactions are regarded as an electrocyclic reaction schematically illustrated by eq 1.[5a,6] Alternatively, a cyclization which takes places via photolysis of halogenoenamides according to eq 2 has been reported in a few cases.[8] Our initial goal was the synthesis of an efficient precursor required for photolysis to form the indolo[7,1-*ab*][3]benzazepine ring system. For this purpose we first attempted to obtain the bromoenamide **5** which, on the basis of eq 2, was expected to undergo photocyclization to the azepine **6**. Thus condensation of the keto acid **3** with the bromophenethylamine **4** was carried out.



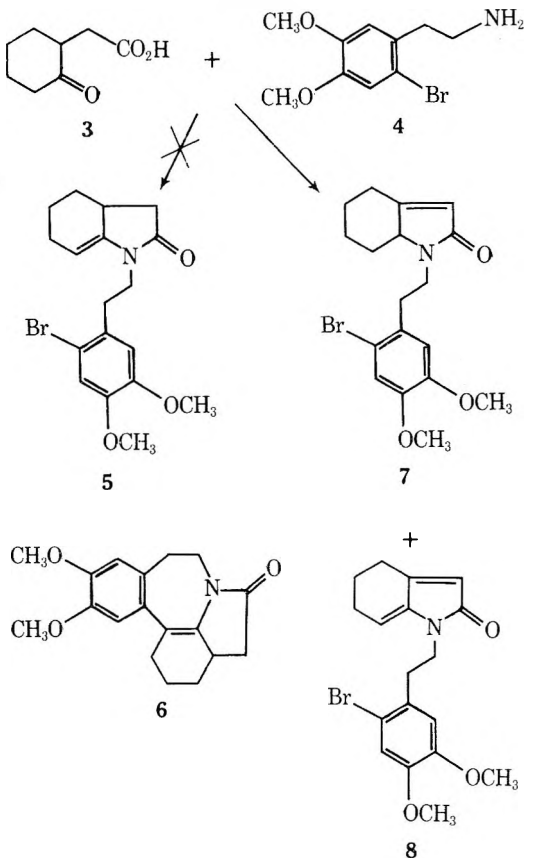


However, the main product was not the desired enamide **5**, but rather the enamide **7** with the enamine double bond in the endo position to the five-membered ring, along with a minor amount of the more stable oxindole **8** which might arise by oxidation during work-up (Scheme I). Upon irradiation of the latter product **8**, an intractable mixture of unidentified products was obtained.

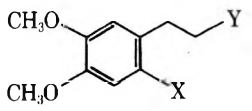
We therefore turned our attention to an alternate suitable substrate needed for photochemical reaction; we planned to fix the enamine double bond in the exo position to five-membered ring by the introduction of a carbonyl group as in the β-enamino ketone **17**. For synthesis of this, we initially explored the use of 1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (**16**) as a starting material, readily prepared from 6-methoxyindoline (**14**) by the method previously reported (Scheme II),[7] since **16** has already the desired fixed exocyclic enamine double bond to the five-membered ring. Accordingly, reaction of **16** with 3,4-dimethoxyphenethyl iodide (**9**) in the presence of sodium hydride in dimethyl sulfoxide gave the *N*-substituted enamino ketone **17** in 35% yield. Alternatively, when the iodide **9** was heated with the iminoenol ether **15** in benzene, *N*-alkylation and C–O bond cleavage proceeded in situ providing the enamino ketone **17** in 49% yield, which, in very small yield, was further *C*-alkylated to give **19**.

From these results the latter route was conveniently chosen for preparing the required precursor **18** to the indolobenza-

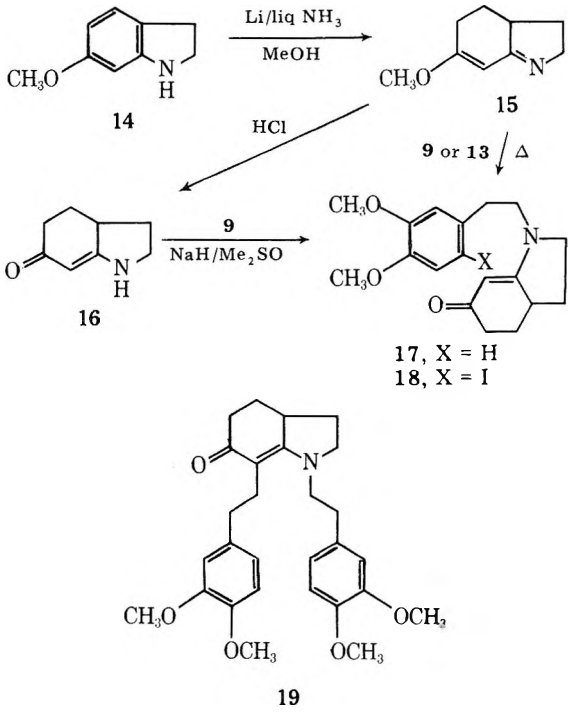
Scheme I



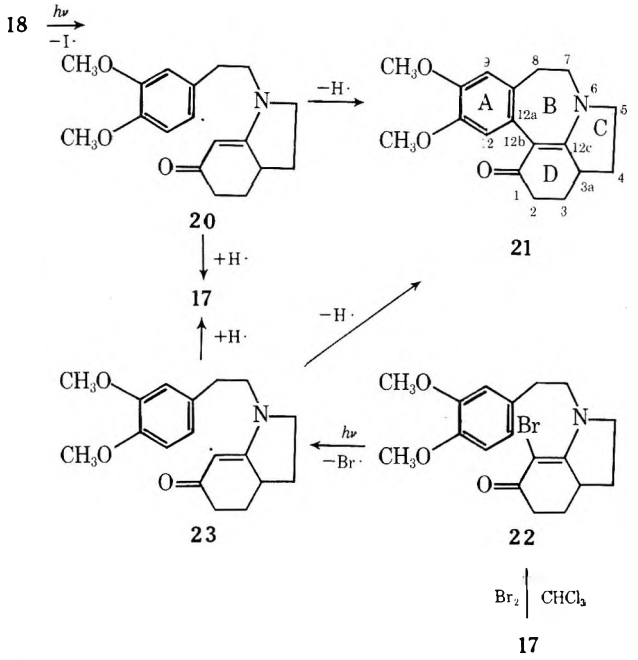
Scheme II



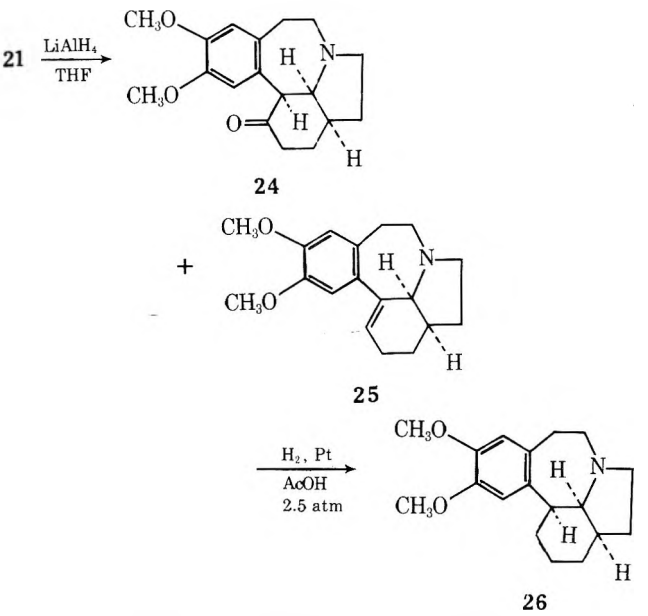
9, X = H; Y = I
10, X = H; Y = OH
11, X = I; Y = OH
12, X = I; Y = Cl
13, X = I; Y = I



Scheme III



Scheme IV



zepine ring system. The synthesis of **18** started with iodination of 3,4-dimethoxyphenethyl alcohol (**10**) in the presence of silver trifluoroacetate in chloroform to afford **11** in 88% yield. Chlorination of **11** with thionyl chloride in the presence of *N*,*N*-diethylaniline in benzene gave the phenethyl chloride **12**, which was then converted to the corresponding iodide **13** by treatment with sodium iodide–methyl ethyl ketone complex. The diiodide **13** was heated with the iminoenol ether **15** in refluxing toluene to give the requisite iodoenamino ketone **18** in 55% yield.

Pyrex-filtered irradiation of **18** in degassed dioxane containing triethylamine using a 100-W high-pressure mercury lamp produced the tetracyclic azepine **21** in 50% yield. As shown in Scheme III, the ring closure to **21** was accompanied by competitive hydrogen transfer to provide the photoreduction product **17** (30% yield), identical with the above synthesized material, likely through initial generating of a common phenyl radical **20**. The azepine ring formation in **21** was confirmed by its NMR spectrum which showed the disappearance of the vinylic proton. In addition, one of two aromatic proton singlets (δ 6.50 and 7.21) was markedly shifted downfield, indicating that the C-12 proton lies in close proximity to the C-1 carbonyl group.

We were next interested in using an enamino ketone bearing a halogen atom at the α position as an alternative precursor to the azepine ring system. Thus **17**, conveniently prepared from the iminoenol ether **15** as described above, was allowed to react with 1 molecular equiv of bromine in chloroform to give the bromoenamino ketone **22** in 75% yield. Irradiation of **22** in acetonitrile in a manner similar to that described for the iodoenamino ketone **18** led to photocyclization to provide **21** and photoreduction to give **17**, in yields of 38 and 13%, respectively. These products may have arisen from radical **23** (Scheme III).

Intermediate **21** was converted into hexahydroapoerysopine as outlined in Scheme IV. Reduction of **21** with $LiAlH_4$ in tetrahydrofurane afforded the apoerysopinone **24** and the tetrahydroapoerysopine **25** in yields of 10 and 63%, respectively. The stereochemical assignment for **25** was based on its NMR analysis involving decoupling experiments in the following way: saturation of the vinylic resonance at δ 6.50 collapsed a doublet at δ 2.73 with fine splitting to a clear-splitting doublet with coupling constant of 6.5 Hz which indicates that the C/D ring junction is cis. It is known[9] that $LiAlH_4$ reduction of β-enamino ketones usually involves Michael addition of hydride and formation of an enolate which can resist further reduction and thus produce β-amino ketones. In that case, the reduction with $LiAlH_4$ leading to the major product **25** may involve the initial formation of **24**, and therefore **24** likely possesses the cis C/D ring junction in relation to the structure of **25**.[10] Cis stereochemistry was tentatively assigned to the B/C ring system of **24** since even if the C-12b epimer of **24** were formed initially, the serious nonbonded interaction between the C-12 aromatic hydrogen and the C-1 carbonyl oxygen would easily cause epimerization to **24** under alkaline conditions in analogy with previous finding.[11] The C-12b stereochemical assignment above in **24** was most strongly suggested by comparing the chemical shift of the C-12 proton in **24** with those of the C-12 protons in **21** and **25**. The value in **24** (δ 6.64) is close to that in **25** (δ 6.78), where the C-12 proton is free from the deshielding effect due to the C-1 carbonyl group, and is strikingly different from that in **21** (δ 7.21, vide supra). These facts indicate that the C-12b proton in **24** should be α oriented so that the C-12 proton in **24** does not suffer a downfield shift by the C-1 carbonyl group.

Hydrogenation of **25** in acetic acid over Adams catalyst at 2.5 atm yielded what is presumed to be hexahydroapoerysopine dimethyl ether (**26**) in 43% yield by delivery of hydrogen to the less hindered α face thus resulting in a B/D cis fusion, in analogy with our previous work.[7] The pyrrolo[1,2-*a*]azepine ring systems (ring B/C) of these products **24**, **25**, and **26** derived from the photoproduct **21** were all presumably trans fused, based on the strong Bohlmann bands observed in the 2700–2800-cm^{-1} region of their IR spectra.

The IR spectrum ($CHCl_3$) of the picrate of our synthetic hexahydroapoerysopine (**26**) was similar to that of the picrate[12] of the compound obtained on rearrangement of natural tetrahydroerythraline (**1**). The UV spectrum of our free base was almost superimposable on that recorded in the literature[1] for the apo rearranged product but differed significantly from that recorded for unrearranged product[1] which has been formulated as hexahydroerysotrine.[2] Although these observations could not exclude the possibility that the compound obtained on rearrangement of **1** is a stereoisomer of **26**, they show unambigously that **1** is subject to an unusual apo rearrangement on acid treatment to form the azepine ring system.

Experimental Section

Melting points are uncorrected and were determined on a Yanagimoto micro apparatus. IR spectra were recorded on a Hitachi 215

grating spectrophotometer. NMR spectra were taken as $CDCl_3$ solutions on a JOEL JNM-PS-100 spectrometer using $(CH_3)_4Si$ as an internal standard. UV spectra were recorded on a Hitachi 124 spectrometer. Mass spectra were obtained on a Hitachi RMU-7L double-focusing spectrometer at 70 eV. GLC analyses were performed on a Shimadzu GC-6A (flame ionization detector) instrument. Merck precoated silica gel F-254 plates (200 × 200 × 0.5 mm) were used for preparative TLC.

Condensation of Cyclohexanone-2-acetic Acid (3) with 2-Bromo-4,5-dimethoxyphenethylamine (4). A mixture of 1.6 g (0.010 mol) of the keto acid **3**[13] and 2.6 g (0.010 mol) of the bromophenethylamine **4** was heated under stirring at 160–170 °C for 7 h under an atmosphere of nitrogen. After cooling, the solidified reaction mixture was dissolved in chloroform, washed in turn with saturated aqueous $NaHCO_3$, 5% HCl, and water, and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on a silica gel column. Benzene–chloroform (10:1) eluted an oily mixture which was further chromatographed on preparative TLC plates with ether as developing solvent to give two major components. The faster moving band gave 0.2 g (5%) of 1-(2-bromo-4,5-dimethoxyphenethyl)-5,6-dihydro-4*H*-oxindole (**8**) as an oil: IR ($CHCl_3$) 1670, 1650, 1640 cm^{-1}; NMR δ 3.83 (s, 6 H, 2 OCH_3), 5.60 (t, J = 4 Hz, 1 H, C-7 vinyl H), 5.75 (s, 1 H, C-3 vinyl H), 6.68 (s, 1 H, C-6′ aromatic H), 6.98 (s, 1 H, C-3′ aromatic H); mass spectrum *m/e* (rel intensity) 379 (3.8, M^+), 377 (4.4, M^+), 298 (68, $M^+ - Br$), 244 (71), 242 (72), 229 (10), 148 (100). The slower moving component was recrystallized from benzene–hexane to give 0.8 g (21%) of 1-(2-bromo-4,5-dimethoxyphenethyl)-5,6,7,7a-tetrahydro-4*H*-oxindole (**7**) as pale yellow prisms: mp 126–128 °C; IR ($CHCl_3$) 1675, 1660; NMR δ 3.84 (s, 6 H, 2 OCH_3), 5.75 (s, 1 H, vinyl H), 6.80 (s, 1 H, C-6′ aromatic H), 7.00 (s, 1 H, C-3′ aromatic H); mass spectrum *m/e* (rel intensity) 381 (3.4, M^+), 379 (3.7, M^+), 300 (40, $M^+ - Br$), 244 (26), 242 (27), 150 (100). Anal. Calcd for $C_{18}H_{22}BrNO_3$: C, 56.85; H, 5.83; N, 3.18. Found: C, 56.97; H, 5.83; N, 3.30.

1,2,3,3a,4,5-Hexahydro-1-(3,4-dimethoxyphenethyl)-6*H*-indol-6-one (17). Method A. To 5 mL of dimethyl sulfoxide (Me_2SO), 0.2 g of NaH was added and the mixture was stirred at room temperature for 30 min under an atmosphere of nitrogen. To this stirred slurry was added a solution of 0.45 g (3.3 mmol) of **16**, prepared by the method previously reported,[7] in 5 mL of Me_2SO followed by a solution of 0.95 g (3.3 mmol) of 3,4-dimethoxyphenethyl iodide (**9**)[14] in 5 mL of Me_2SO. The stirred mixture was heated at 50 °C for 3.5 h and the solvent was evaporated under reduced pressure. The residue was treated with water and extracted with chloroform. After drying ($MgSO_4$), the solvent was evaporated and the residue was recrystallized from benzene–hexane to give 0.35 g (35%) of **17** as colorless prisms: mp 45 °C; IR ($CHCl_3$) 1610, 1565; NMR δ 2.79 (t, 2 H, J = 7 Hz, CH_2Ph), 3.39 (t, 2 H, J = 7 Hz, NCH_2CH_2Ph), 3.83 (s, 6 H, 2 OCH_3), 5.05 (s, 1 H, vinyl H), 6.61 (s, 1 H, C-2′ aromatic H), 6.64 (d, 1 H, J = 11 Hz, C-5′ aromatic H), 6.73 (dd, 1 H, J = 11 and 0.5 Hz, C-6′ aromatic H); mass spectrum (rel intensity) 301 (13, M^+), 164 (62), 150 (100). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.75; H, 7.64; N, 4.57.

Method B. A solution of 1.0 g (6.6 mmol) of the iminoenol ether **15** and 1.9 g (6.5 mmol) of the phenethyl iodide **9** in 20 mL of dry benzene was heated under reflux for 2 h. The solvent was evaporated and the residue was chromatographed on a silica gel column. Initial elution with chloroform afforded 0.03 g (1%) of 1,2,3,3a,4,5-hexahydro-1,7-di(3,4-dimethoxyphenethyl)-6*H*-indol-6-one (**19**), which was recrystallized from ethyl acetate to give colorless prisms: mp 122–124 °C; IR ($CHCl_3$) 1600, 1560, 1555 cm^{-1}; NMR δ 3.75, 3.80, 3.84, and 3.86 (each s, 3 H, OCH_3), 6.60–6.83 (m, 6 H, aromatic H); mass spectrum *m/e* (rel intensity) 465 (3.0, M^+), 315 (100), 165 (25), 150 (38). Further elution with the same solvent yielded 0.95 g (49%) of **17**, identical with the authentic sample prepared by method A above.

2-Iodo-4,5-dimethoxyphenethyl Alcohol (11). A solution of 6.9 g (0.027 mol) of iodine in an adequent amount of chloroform (ca. 90 mL) was added with stirring to a slurry of 6.0 g (0.027 mol) of silver trifluoroacetate[15] and 7.8 g (0.027 mol) of 3,4-dimethoxyphenethyl alcohol (**10**)[14] in 30 mL of chloroform at room temperature. After addition was complete (1 h), the mixture was stirred for an additional 30 min and insoluble substances were removed by filtration. The filtrate was evaporated to yield a residue which was recrystallized from benzene–hexane to give 7.3 g (88%) of **11** as colorless needles: mp 52–54 °C; IR ($CHCl_3$) 3580 cm^{-1}; NMR δ 2.53 (s, 1 H, OH), 2.95 (t, 2 H, J = 7 Hz, CH_2Ph), 3.89 (s, 6 H, 2 OCH_3), 6.82 (s, 1 H, C-6 aromatic H), 7.24 (s, 1 H, C-3 aromatic H); mass spectrum *m/e* (rel intensity) 308 (50, M^+), 277 (100), 181 (5.6), 150 (56). Anal. Calcd for $C_{10}H_{13}IO_3$: C, 38.98; H, 4.25. Found: C, 39.21; H, 4.32.

2-Iodo-4,5-dimethoxyphenethyl Chloride (12). To a solution of 6.0 g (0.019 mol) of the phenethyl alcohol **11** in 20 mL of dry benzene containing 2.6 mL of *N,N*-diethylaniline was added 3.5 g (0.035 mol) of thionyl chloride at room temperature during 15 min under stirring. After heating the mixture on a steam bath for 1.5 h, the solvent and the volatile material were removed under reduced pressure. The residue was extracted with benzene, washed with water then 5% Na_2CO_3, and dried ($CaCl_2$). The solvent was evaporated to give a pale yellow oil which upon column chromatography (silica gel, benzene) gave 5.4 g (85%) of **12**, as colorless needles recrystallized from methanol: mp 76–78 °C; NMR δ 3.13 (t, 2 H, J = 8 Hz, CH_2Ph), 3.70 (t, 2 H, J = 8 Hz, CH_2Cl), 3.86 and 3.88 (each s, 3 H, OCH_3), 6.80 (s, 1 H, C-6 aromatic H), 7.24 (s, 1 H, C-3 aromatic H); mass spectrum *m/e* (rel intensity) 328 (16, M^+), 326 (49, M^+), 277 (100), 164 (12), 150 (12).

2-Iodo-4,5-dimethoxyphenethyl Iodide (13). A suspension of 11.1 g (0.074 mol) of NaI in 84 mL of dry methyl ethyl ketone was heated under reflux for 1.5 h. To this was added a solution of 16 g (0.049 mol) of the phenethyl chloride **12** in 6 mL of dry methyl ethyl ketone and the mixture was heated at reflux for 2 h. After the mixture was cooled, the inorganic substances were removed by filtration and the filtrate was evaporated. The residue was extracted with ether, washed with water, and dried ($CaCl_2$). Removal of the solvent left 15 g of crude material of **13** as a colorless solid which can be used as such for the following reaction. GLC analysis (1.5% SE-30/Chromosorb W, 200 °C) showed that this material contained about 5% unreacted phenethyl chloride. Pure **13** was obtained by several recrystallizations from methanol: mp 55–57 °C; mass spectrum *m/e* (rel intensity) 418 (37, M^+), 291 (14), 277 (20), 164 (100).

1,2,3,3a,4,5-Hexahydro-1-(2-iodo-4,5-dimethoxyphenethyl)-6*H*-indol-6-one (18). A solution of 0.9 g (6.0 mmol) of the iminoenol ether **15** and 2.5 g (6.0 mmol) of the diiodide **13** in 20 mL of dry toluene was heated at reflux for 2 h. The solvent was evaporated and the residue was chromatographed on a silica gel column. Initial elution with benzene gave 0.9 g (36%) of the unreacted diiodide **13**. Further elution with ethyl acetate gave 1.4 g (55%) of **18** as crystalline material (mp 127–130 °C) which was recrystallized from benzene–hexane to give pure **18** as colorless prisms: mp 129–130 °C; IR ($CHCl_3$) 1600, 1565 cm^{-1}; NMR δ 3.82 (s, 6 H, 2 OCH_3), 5.14 (s, 1 H, vinyl H), 6.64 (s, 1 H, C-6′ aromatic H), 7.18 (s, 1 H, C-3′ aromatic H); mass spectrum *m/e* (rel intensity) 427 (0.7, M^+), 300 (83, $M^+ - I$), 290 (16), 244 (5.0), 164 (7.5), 150 (100). Anal. Calcd for $C_{18}H_{22}INO_3$: C, 50.60; H, 5.19; N, 3.28. Found: C, 50.81; H, 5.12; N, 3.48.

7-Bromo-1,2,3,3a,4,5-hexahydro-1-(3,4-dimethoxyphenethyl)-6*H*-indol-6-one (22). To a stirred solution of 570 mg (1.9 mmol) of **17** in 20 mL of chloroform was added a solution of 310 mg (1.9 mmol) of bromine in 20 mL of chloroform at room temperature in the period of 30 min and stirring was continued for an additional 30 min. The mixture was washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography on silica gel using chloroform as eluent and recrystallization from ethyl acetate to yield 540 mg (75%) of **22** as colorless leaves: mp 127–129 °C; IR (Nujol) 1590, 1575, 1555 cm^{-1}; NMR δ 2.94 (t, 2 H, J = 8 Hz, CH_2Ph), 3.86 (s, 6 H, 2 OCH_3), 6.78 (s, 3 H, aromatic H); mass spectrum *m/e* (rel intensity) 377 (2.4, $M^+ - 2H_2$), 375 (2.5 M^+, $-2H_2$), 301 (29), 277 (28), 164 (100), 150 (94). Anal. Calcd for $C_{18}H_{22}BrNO_3$: C, 56.85; H, 5.83; N, 3.68. Found: C, 57.03; H, 5.87; N, 3.63.

Irradiation of 1,2,3,3a,4,5-Hexahydro-1-(2-iodo-4,5-dimethoxyphenethyl)-6*H*-indol-6-one (18). A solution of 1.90 g (4.45 mmol) of **18** in 75 mL of dioxane containing 4.5 mL of triethylamine was purged with nitrogen for 1 h and irradiated under nitrogen atmosphere through Pyrex with a 100-W high-pressure mercury lamp. After 18 h, when TLC examination indicated consumption of most of the starting material, the mixture was washed with water and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed on a silica gel column using chloroform as eluent. The first fraction contained 0.70 g (50%) of 3,3a-dihydro-2*H*-apoerysopin-1-one dimethyl ether (**21**) as a pale yellow syrup: IR (neat) 1610, 1580 cm^{-1}; NMR δ 3.85 (s, 6 H, 2 OCH_3), 6.50 (s, 1 H, C-9 aromatic H), 7.21 (s, 1 H, C-12 aromatic H); mass spectrum *m/e* (rel intensity) 299 (100, M^+), 284 (48), 195 (43), 134 (43); mass spectrum (high resolution) calcd for $C_{18}H_{21}NO_3$, 299.1521, and found, 299.1549.

The second fraction contained 0.40 g (30%) of the deiodinated product **17** identical with the material prepared by the above method.

Irradiation of 7-Bromo-1,2,3,3a,4,5-hexahydro-1-(3,4-dimethoxyphenethyl)-6*H*-indol-6-one (22). A solution of 200 mg (0.53 mmol) of **22** in 75 mL of acetonitrile containing 0.5 mL of triethylamine was purged with nitrogen for 1 h then irradiated as described above for 18. After 20 h of irradiation, the solution was washed

with water and evaporated. The residue was chromatographed in the same manner for 18 to give 60 mg (38%) of **21** and 20 mg (13%) of **17**. Each product was identical with the respective authentic specimen described above.

Reduction of 3,3a-Dihydro-2*H*-apoerysopin-1-one Dimethyl Ether (21) with Lithium Aluminum Hydride. A solution of 200 mg (0.67 mmol) of **21** in 10 mL of dry THF was added slowly to a stirred slurry of 80 mg (2.1 mmol) of $LiAlH_4$ and 20 mL of dry THF with ice–water cooling. The mixture was stirred at room temperature for 1 h, excess hydride was destroyed by addition of 1 mL of ethyl acetate, and the complex was destroyed by addition of 1 mL of water. The mixture was filtered through Celite and the filtrate was evaporated. The residue was extracted with chloroform, washed with water, and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on a silica gel column using chloroform as eluent. The first fraction contained 20 mg (9.9%) of 3,3a,12b,12c-tetrahydro-2*H*-apoerysopin-1-one dimethyl ether (**24**) as colorless prisms (mp 143–145 °C): IR (Nujol) 2775 and 2720 (Bohlmann bands), 1710 cm^{-1} (ketone C=O); NMR δ 3.81 and 3.84 (each s, 3 H, OCH_3), 6.54 (s, 1 H, C-9 aromatic H), 6.64 (s, 1 H, C-12 aromatic H); mass spectrum (high resolution) calcd for $C_{18}H_{12}NO_3$, 301.1708, and found, 301.1678. The second fraction yielded 120 mg (63%) of 2,3,3a,12c-tetrahydroapoerysopine dimethyl ether (**25**) as colorless crystals (mp 80–82°C): IR (KBr) 2770 and 2725 cm^{-1} (Bohlmann bands); NMR δ 2.73 (d, 1 H, J = 6.5 Hz, 12c-H), 3.90 (s, 6 H, 2 OCH_3), 6.05 (dd, 1 H, J = 4.5 and 3 Hz, vinyl H), 6.66 (s, 1 H, C-9 aromatic H), 6.78 (s, 1 H, C-12 aromatic H); mass spectrum *m/e* (rel intensity) 285 (60, M^+), 270 (75), 277 (22), 143 (100); mass spectrum (high resolution) calcd for $C_{18}H_{23}NO_2$, 285.1729, and found, 285.1699.

1,2,3,3a,12b,12c-Hexahydroapoerysopine Dimethyl Ether (26). To a solution of 55 mg (0.19 mmol) of the tetrahydroapoerysopine **25** in 20 mL of acetic acid, 5 mg of PtO_2 was added, and the mixture was hydrogenated at room temperature in a Parr hydrogenator at a starting pressure of 2.5 atm for 12 h. After removal of catalyst by filtration, the filtrate was evaporated under reduced pressure. The residue was extracted with chloroform, washed with 10% Na_2CO_3, and dried ($MgSO_4$). The solvent was evaporated and the residual oil was purified by preparative TLC on silica gel using chloroform–methanol (10:1) as developing solvent to give 24 mg (43%) of **26** as pale yellow liquid: IR (neat) 2775 and 2735 cm^{-1} (Bohlmann bands); UV (EtOH) λ_{max} (log ϵ) 228 (3.86), 283 (3.47) nm; NMR δ 3.84 and 3.87 (each s, 3 H, OCH_3), 6.58 (s, 1 H, C-9 aromatic H), 6.65 (s, 1 H, C-12 aromatic H); mass spectrum *m/e* (rel intensity) 287 (100, M^+), 272 (51), 259 (20), 244 (28), 165 (88); mass spectrum (high resolution) calcd for $C_{18}H_{25}NO_2$, 287.1885, and found, 287.1859. This material was dissolved in a small amount of methanol and converted to the picrate with an ethereal solution of picric acid. The crystalline product precipitated by standing over night in a refrigerator was collected by filtration and recrystallized from methanol, yielding the pure picrate as yellow needles, mp 233–234 °C. Anal. Calcd for $C_{18}H_{25}NO_2 \cdot C_6H_3N_3O_7$: C, 55.81; H, 5.46; N, 10.85. Found: C, 55.83; H, 5.51; N, 10.87.

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Registry No.—**3**, 1438-96-6; **4**, 63375-81-5; **7**, 64705-35-7; **8**, 64705-36-8; **9**, 64728-23-0; **10**, 7417-21-2; **11**, 64705-37-9; **12**, 64728-24-1; **13**, 64705-38-0; **15**, 59601-27-3; **16**, 64705-39-1; **17**, 64705-40-4; **18**, 64705-41-5; **19**, 64705-42-6; **21**, 64705-43-7; **22**, 64705-44-8; **24**, 64705-45-9; **25**, 64705-46-0; **26**, 64705-47-1; **26** picrate, 64705-48-2.

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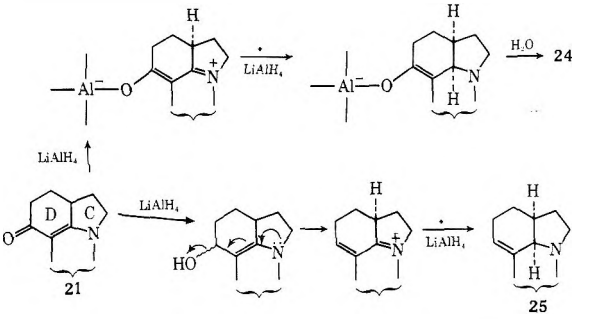
(10) In $LiAlH_4$ reduction of **21**, the pathway that **25** arises from **24** is not secure since the mechanism of $LiAlH_4$ reduction of β-enamino ketones is not well established. Reduction by the following mechanism could also explain the stereochemical results:



In both processes marked by asterisks the hydride ion could transferred to the least hindered α side of the >C=N$^+$< function to give the product with C/D cis ring junction in each case.
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Photocyclizations of α-(1-Cyclohexenyl)cinnamic Esters

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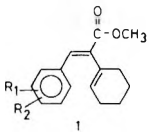
The photocyclizations of some α-(1-cyclohexenyl)cinnamic acid esters are described. Under oxidative conditions 5,6,7,8-tetrahydrophenanthrenes are formed in good yield. Under anaerobic conditions hexahydrophenanthrenes are formed. Their structure and the mechanisms of formation are discussed.

The photochemical cyclization of stilbenes into 9,10-dihydrophenanthrene derivatives under nonoxidative conditions has been examined by several authors.[1] In a previous paper[2] some of us clarified the mechanism for the cyclization of methyl α-phenylcinnamate (a) to 9-carbomethoxy-9,10-dihydrophenanthrene (f) (Scheme I). Kinetic studies revealed that the reaction occurs via the 4a,4b-dihydrophenanthrene derivative b, and it was established that the rearrangement b → f does not involve a photochemical 1,3-suprafacial shift. In a polar solvent a protonation–deprotonation reaction gives rise to c, which is in a tautomeric equilibrium with 4a,9-dihydrophenanthrene d. These reaction steps are decisive for the formation of the 9,10-dihydrophenanthrene. A necessary condition for this reaction is not only the presence of an enolizable group at C-9 of b but also a suitable source of hydrogen atoms in the medium (e.g., an alcohol as solvent) because the final conversion of d into 9,10-dihydrophenanthrene (f) proceeds via a radical reaction, which is probably photochemically induced.

In a parallel study an effort was made to extend the synthetic utility of this type of reaction to the photocyclizations of various methyl α-(1-cyclohexenyl)cinnamates (**1a–c**).

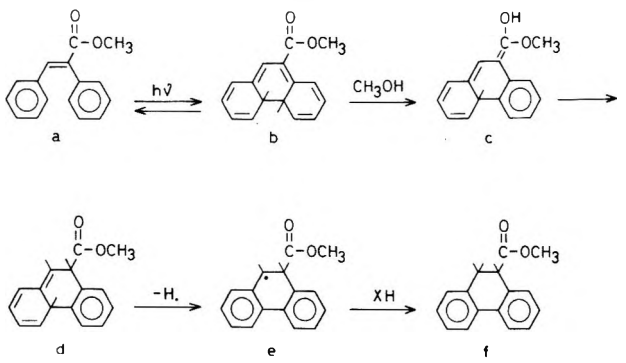


1

a) $R_1 = H, R_2 = CF_3$ (4)
b) $R_1 = R_2 = Cl$ (2,4)
c) $R_1 = R_2 = OCH_3$ (3,5)

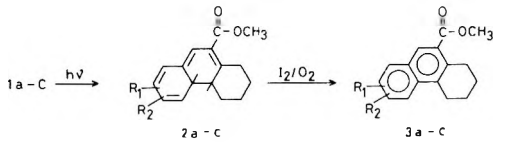
Hayward and Leznoff,[3] in an investigation of the photoreactivity of 1,4-diarylbutadienes, have shown that these compounds undergo photodehydrocyclizations which correspond to the reaction of stilbenes on irradiation in the presence of an oxidant, but the 4-aryl residue seems to be unnecessary for this type of reaction.[4] Recently, the intermediacy of a previously proposed[4] dihydro intermediate in this reaction was further substantiated.[5] Therefore, it could be expected

Scheme I



that the photolysis of compounds **1a–c** under oxidative conditions should proceed according to a scheme (Scheme II) which is formally analogous to the stilbene–phenanthrene photodehydrocyclization.

Scheme II



The fate of the intermediate **2a–c** under nonoxidative conditions had not been studied previously, and it seemed worthwhile to compare its reactivity with that of the corresponding α-carbomethoxy-4a,4b-dihydrophenanthrene intermediate in the photocyclization of methyl α-phenylcinnamates.[2]

Synthesis

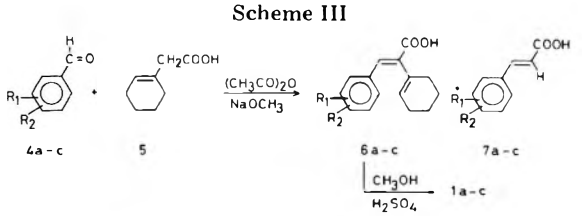
The cinnamates **1a–c** were readily prepared by the condensation of the benzaldehydes **4a–c** with 1-cyclohexenylacetic acid (**5**) and subsequent esterification of the resulting acid (**6**). The yields of the desired condensation products varied from 20 to 84%, depending upon the amount of acetic anhydride and the nature of the benzaldehyde used; with a large molar excess of the anhydride a competitive condensation between the aldehyde and the solvent led to substantial amounts of cinnamic acids (**7**) (Scheme III).

Oxidative Photocyclizations

Irradiation of the cinnamates **1a–c** in methanol through quartz and in the presence of iodine and air gave the expected 5,6,7,8-tetrahydrophenanthrenes **3a–c** in good yields (62–88%) and as the only products (Scheme II). The structures were established by elemental analyses and spectral evidence. NMR spectra indicated in all cases the proper ratio of aromatic, allylic, and aliphatic protons (see Experimental Section). The infrared spectra were also clearly indicative of α,β-unsaturated carboxylic esters.

Irradiations under similar conditions using a Pyrex filter gave no reaction. It is remarkable that the yields are high compared with those in the diphenylbutadiene cyclizations.[3]

Scheme III



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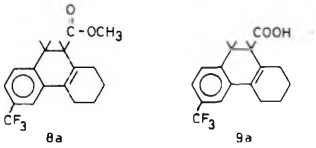
Nonoxidative Photocyclizations

Irradiations of **1a–c** in methanol through quartz and under nitrogen gave different results, depending on the aromatic substitution of the parent compound. In every case, the photochemical nature of the reactions was established by control irradiations in which Pyrex filters were used. In these latter instances only starting materials were recovered in quantitative yields. The results with each compound will be discussed separately.

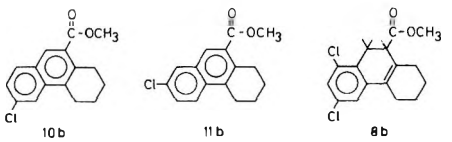
A. Methyl α-(1-Cyclohexenyl)-4′-trifluoromethylcinnamate (1a). The nonoxidative irradiation of **1a** gave, after workup, three compounds in 57, 24, and 5% yield, respectively. The main product showed an unconjugated ester carbonyl band (1745 cm^{-1}) in its IR spectrum. The NMR spectrum indicated the absence of vinyl protons. The occurrence of an ABC pattern in the NMR spectrum at δ 2.95 (dd, J_{AB} = 13.5, J_{AC} = 6 Hz), 3.18 (dd, J_{AB} = 13.5, J_{BC} = 3.5 Hz), and 3.02 (dd, J_{AC} = 6, J_{BC} = 3.5 Hz) is completely consistent with structure **8a**. The second product appeared to be an acid:



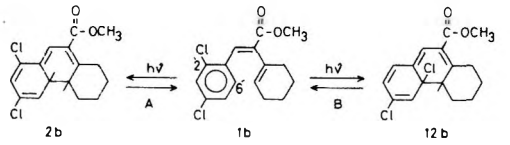
IR ν_{max} 1710 cm^{-1}; UV λ_{max} 275, 225 nm. The ABC pattern in its NMR spectrum was badly resolved, even at 220 MHz; δ 2.99 (s ?), 3.19 and 2.98 (possible dd). The compound must be **9a**, however, since the same product was obtained by basic hydrolysis of **8a**. It is supposed that **8a** is hydrolyzed during column chromatography. The third product appeared to be **3a**, which arises from **1a** under oxidative conditions. This might be due to the residual oxygen present in the solvent.

The structure of the main product suggests that it arises from an initially formed photocyclization product **2a** via similar rearrangements as those leading from 9-carbomethoxy-4a,4b-dihydrophenanthrenes to 9-carbomethoxy-9,10-dihydrophenanthrenes in the nonoxidative photocyclization of stilbene derivatives.[2] The similarity was further substantiated by irradiation of **1a** in CD_3OD. The principal product had an NMR spectrum which showed the disappearance of the signal at δ 3.02 (H_c) and the loss of one proton intensity in the combined positions H_A and H_B. The signals for H_A and H_B also collapse to doublets with $J_{AB} \sim 2$ Hz (deuterium coupling). Apparently the rearrangements proceed through the intermediacy of the solvent, leading to a mixture of *cis*- and *trans*-deuterio compounds.

B. Methyl α-(1-Cyclohexenyl)-2′,4′-dichlorocinnamate (1b). Irradiation of **1b** in degassed methanol solution gave one major product, a small amount of the oxidative product **3b**, and a considerable amount of tar. The IR spectrum of the major product indicated a conjugated ester carbonyl (1720 cm^{-1}). Both mass spectrum and elemental analysis showed only one chlorine and fit the formula $C_{16}H_{15}ClO_2$. The NMR spectrum (220 MHz) showed four aromatic (and/or vinyl) protons, two of which occurred as an AB quartet, indicative of two adjacent aromatic protons. One of these was coupled to another proton; δ 7.98 (s), 7.57 (d, J = 9 Hz), 7.26 (dd, J = 9, J' = 1.5 Hz), 7.76 (d, J' = 1.5 Hz). Of two possible structures **10b** and **11b**, the former must be the correct one as no reasonable precursor for **11b** exists.



The formation of **10b** can be ascribed to initial photocyclization at C-2′ (reaction B) instead of C-6′ (reaction A, see eq 1). Subsequent elimination of hydrogen chloride, possibly



(1)

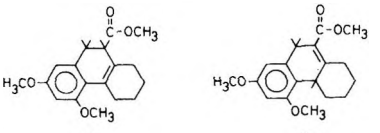
in the same way as reported for the comparable elimination of methanol in the photocyclization of 2-methoxystilbene, should then give **10b**.[6]

It is remarkable that **10b** is not found as a product in the oxidative photocyclization of **1b**. An explanation might be that the ratio **2b**/**12b** is high and the oxidation of **2b** more rapid. Under nonoxidative conditions the formation of hydrogen chloride (from **12b**) might interfere with the continuation of the process, promoting the formation of **10b** and considerable amounts of polymeric products.

To prevent any possible influence of the acid formed, the irradiation of **1b** was repeated under identical conditions, except for the presence of some powdered anhydrous potassium carbonate in the reaction medium. Three products were isolated in yields of 32, 16 and 2%, respectively. The mass spectrum of the major product gave a parent ion *m/e* 310, indicating a structure isomeric with the starting material. The IR spectrum showed an unconjugated ester carbonyl (1740 cm^{-1}). The NMR spectrum (220 MHz) contained a similar ABC pattern at slightly different δ values as found for **8a**; 3 doublets of doublets at δ 3.30 (J_{AC} = 6.6, J_{BC} = 4.7 Hz), 2.73 (J_{AB} = 14.6, J_{AC} = 6.6 Hz), and 3.33 (J_{AB} = 14.6 J_{BC} = 4.7 Hz). In the UV spectrum λ_{max} 274 nm (ε 7740) is comparable to values found for several 5,6,7,8,9,10-hexahydrophenanthrenes[6] (maxima around 268–275 and/or 277–280 nm, extinction coefficients from 10 000 to 19 000). The structure must, therefore, be **8b**, corresponding to the main product of the nonoxidative irradiation of **1a**. Apparently the main routes for the photocyclizations of **1a** and **1b** under nitrogen are equal when potassium carbonate is added in the irradiation of **1b**.

The second and third photoproducts from **1b** were, respectively, the monochlorotetrahydrophenanthrene **10b**, also formed in the absence of the base, and **3b**, formed under oxidative conditions.

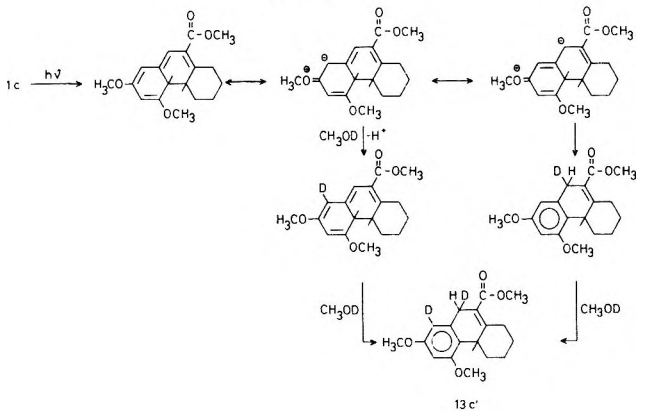
C. Methyl α-(1-cyclohexenyl)-3′,5′-dimethoxycinnamate (1c). On irradiation of **1c** in methanol under nitrogen, pure crystalline needles (mp 105–106 °C) precipitated from the ice–acetone-chilled reaction solution in 86.5% yield. The mass spectrum had the same parent peak as the starting material. The IR spectrum indicated a conjugated ester carbonyl (1710–1720 cm^{-1}), contrary to the expected structure **8c**.



Moreover, the UV spectrum showed λ_{max} 275 nm (ε 2080) and 283 (1910), the extinctions of which are considerably lower than that expected for a styrene chromophore. **13c** was the only reasonable structure that could be corroborated by the NMR spectrum (220 MHz), which showed the absence of vinyl protons, a broad two-proton singlet (δ 3.52) due to the methylene protons at C-10, a multiplet at δ 1.97 coupled to two other protons (J = 12, J' = 3.5 Hz) which can be ascribed to C-4b–H and a one-proton signal at δ 1.17 coupled to three adjacent protons (J = 24, J' = 12, J'' = 4 Hz) which can be ascribed to one of the protons at C-8, which is deshielded by the neighboring carbomethoxy group.

When the irradiation of **1c** was performed in perdeuter-

Scheme IV



iomethanol, **13c'**, containing two deuterium atoms, was isolated (Scheme IV). The integrated NMR spectrum of the deuterated product showed that the broad singlet (δ 3.52) had been reduced to a one-proton signal and that, in addition, one aromatic proton had been replaced. The same result was obtained on irradiation of **1c** in CH_3OD, indicating that the deuterium was introduced in an ionic process. It was established that deuterium exchange on the aromatic ring also occurred after the initial formation of **13c**. On irradiation of **13c** in $CDCl_3$ (or CH_3OD), the solution turned dark green (only in chloroform) and deuterium appeared in the aromatic ring, as shown by NMR (the same dark green solution occurred when **1c** was irradiated in chloroform). The exchange appears to be solely in one position, postulated to be the 1 position.

The incorporation of deuterium during the nonoxidative photocyclization of **1c** can be caused by the high electron density in the initially formed cyclization product **2c** as a consequence of the strongly electron-donating methoxy substituents. Subsequent reactions may be as shown in Scheme IV. It is not clear why the proton at C-3 does not exchange in a similar way.

It is remarkable that the shift of the second double bond in the central ring of the primary electrocyclization product (**2c**), which takes place in the photocyclization of **1a** and **1b**, fails to come about in the photolysis of **1c** under similar conditions.

Conclusion

In summary, it appears that on irradiation under oxidative conditions the α-(1-cyclohexenyl)cinnamic esters **1a–c** behave similarly as methyl α-phenylcinnamate; they are converted into the 5,6,7,8-tetrahydrophenanthrenes **3a–c** in high yields (Scheme II).

Under nonoxidative conditions, however, the primarily formed photoproducts (**2a–c**) undergo secondary reactions which strongly depend on the substituents present in the aromatic ring of the parent compound. With **1a** having a *p*-trifluoromethyl substituent, the process proceeds analogously to the photoconversion of the α-phenylcinnamic ester, as shown in Scheme I. In the photolysis of the dimethoxy compound (**1c**), however, the enolization step in Scheme I is surpassed by a very rapid ionic reaction as described in Scheme IV. The 2,4-dichloro derivative **1b** behaves differently as two isomeric primary photoproducts (**2b** and **12b**) arise. One of them, **12b**, spontaneously eliminates hydrochloric acid, which interferes with the formation of the "normal" product **8b**. Addition of potassium carbonate restores the formation of the latter product.

Experimental Section

All melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were carried out either by Galbraith Laboratories, Inc., Knoxville, Tenn., or by the Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

The infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrophotometer. The ultraviolet (UV) spectra were taken with a Cary Model 14M recording spectrometer. All extinction coefficients are molar, the units being $cm^2\ mol^{-1}$. Nuclear magnetic resonance (NMR) spectra were recorded with either a (a) JEOL (Japan Electron Optics Laboratory Co.) Model JNM-MN-60, or (b) by Union Carbide Corp., Eastview, N.Y., on a Bruker 90-MHz instrument, or (c) by Rockefeller University's Nuclear Magnetic Resonance Laboratory on a Varian 220-MHz machine. In all proton magnetic resonance (NMR) spectra, tetramethylsilane was the internal reference. In the carbon-13 magnetic resonance (^{13}C NMR) spectra, perfluorobenzene was the reference. Mass spectra were determined on a Hitachi Perkin-Elmer RMS-4 mass spectrometer.

All chemical solvents were of reagent quality and were used as obtained from the manufacturers.

Irradiation solutions were placed in cylindrical quartz tubes (unless otherwise noted) of varying capacities. All tubes were approximately 30 cm long, but the diameters varied from 0.7 cm (6–7-mL capacity) to 2.3 cm (100-mL). The tubes were sealed by means of rubber serum caps and were then suspended in the center of a Rayonet–Srinivasan–Griffin photochemical reactor equipped with 16 300-nm lamps (21 W). The solution temperatures were typically 35–40 °C inside the reactor due to the heat generated by the lamps.

α-(1-Cyclohexenyl)-2',4'-dichlorocinnamic Acid (6b). To 15 mL of acetic anhydride in a 500-mL three-neck flask equipped with a mechanically driven stirring blade (Teflon), an addition funnel with a gas inlet adapter, and a condenser with a calcium chloride drying tube was added with stirring 2.5 g of dry sodium methoxide powder. The solution was externally heated to approximately 50 °C for 15 min. To this warm solution was added 6.0 g of melted 1-cyclohexenylacetic acid. The solution was heated at 50 °C for an additional 30 min, during which time "swelling and coagulation" occurred, which necessitated efficient stirring and heating to maintain a homogeneous liquid phase. To the still warm solution 5.0 g of 2,4-dichlorobenzaldehyde without any additional washing was added. The solution was heated to 110 °C overnight.

The solution, still warm, was treated with 5-mL portions of water over a 2-h period while stirring and heating was continued. Approximately 60–75 mL of water was used altogether. Precipitation occurred more efficiently and faster recovery of the acid was achieved by taking up the entire oily solid directly into diethyl ether in a separatory funnel and washing with water until the washings were neutral. The ethereal layer was washed twice with sodium bicarbonate solution and then with water again (the smaller molecular weight 2,4-dichlorocinnamic acid, mp 232–233 °C, a byproduct of the condensation of the aldehyde with acetic anhydride, appeared to be removed in the bicarbonate wash. Excessive base washings could cause loss of the desired acid). The ether layer was then washed with saturated sodium bisulfite solution to remove any unreacted aldehyde and then with water. After drying over magnesium sulfate and filtering, the solvent was evaporated on a rotary evaporator. Recrystallization of the crude solid in boiling carbon tetrachloride removed the remaining cinnamic acid, 0.4 g, mp 230–232 °C. Further recrystallization from hexane gave 4.3 g of the desired acid (50.5%), mp 141–150 °C (probably a mixture of the cis and trans isomers), as cream-colored needles. The IR spectrum (KBr pellet) gave ν_{max} 2900, 2600, 1680, 1580, 1470, 1415, 1280, 1100, 1050, 925, 870, 825, 815, and 783 cm^{-1}. The NMR spectrum (CD_3OD) showed peaks at δ 7.3–7.7 (4 H, m), 5.5 (1 H, brd s), and 2.1 and 1.7 (8 H, converging m). The mass spectrum gave parent ion *m/e* 296 and indicated the presence of two chlorines.

Anal. Calcd for $C_{15}H_{14}Cl_2O_2$: C, 60.60; H, 4.75; Cl, 23.90. Found: C, 60.06; H, 4.72; Cl, 25.15.

α-(1-Cyclohexenyl)-4'-trifluoromethylcinnamic Acid (6a). The same general method was used as in the preparation of **6b.** Recrystallization from a minimum amount of boiling CCl_4 removed 0.2 g of the cinnamic acid byproduct, mp 229–230 °C. Chilling of the mother liquor in dry ice/acetone gave 4.4 g of the desired acid, mp 122–129 °C. The IR spectrum (KBr pellet) gave ν_{max} 2900, 1685, 1620, 1416, 1322, 1280, 1165, 1132, 1070, and 1017 cm^{-1} (the cinnamic acid byproduct gave ν_{max} 2300–3300, 1685, 1640, 1430, 1320, 1290, 1225, 1180, 1140, 1075, 1020, 990, 840, and 700 cm^{-1}). The NMR spectrum ($CDCl_3$) showed signals at δ 1.57–2.45 (8 H, m), 6.01 (1 H, brd s), and 8.13 (5 H, s). The mass spectrum gave parent ion *m/e* 296.

Anal. Calcd for $C_{16}H_{15}F_3O_2$: C, 64.86; H, 5.10; F, 19.24. Found: C, 65.07; H, 4.95; F, 17.89. Anal. Calcd for the cinnamic acid byproduct $C_{10}H_7F_3O_2$: C, 55.56; H, 3.27; F, 26.37. Found: C, 55.92; H, 3.46; F, 24.94.

α-(1-Cyclohexenyl)-3′,5′-dimethoxycinnamic Acid (6c). The same method was used as in the preparation of 2,4-dichloro- and 4-trifluoromethyl derivatives. Quantities of reagents used were acetic anhydride, 20 mL (total), sodium methoxide, 3.2 g (total), cyclohexenylacetic acid, 7.0 g, and 3,5-dimethoxybenzaldehyde, 8.3 g. Workup was simplified since the acid could be filtered from the aqueous acidified solution. Total yield was 10.5 g (73%), mp 121.5–133.5 °C. The IR spectrum (KBr pellet) gave ν_{max} 2900, 1675, 1590, 1457, 1422, 1341, 1280, 1208, 1160, 1072, and 1060 (doublet), 925, 873, and 831 cm^{-1}. The NMR spectrum (CCl_4) showed δ 1.85 and 2.25 (8 H, brd m) and singlets at δ 4.08 (6 H), 6.17 (1 H, brd), 6.81 (1 H, brd), 7.26 (1 H), 732 (1 H), and 8.17 (1 H). The mass spectrum gave parent *m/e* 288.

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.81, 70.62; H, 6.96, 7.11.

Methyl α-(1-Cyclohexenyl)-2′,4′-dichlorocinnamate (1b). A solution of 0.4 g of the acid in 15 mL of absolute methanol containing 0.75 mL of concentrated H_2SO_4 was refluxed for 2 h, after which it was cooled to room temperature and allowed to stand over the weekend. The solution was poured onto crushed ice and extracted with diethyl ether. The ether extracts were washed with a saturated $NaHCO_3$ solution until the rinsings were basic and then with water. After drying over Na_2SO_4 and filtering, evaporation of the solvent gave 0.5 g (100%) of the crude ester as an oil.

The IR spectrum (liquid film) gave ν_{max} 2900, 2820, 1710, 1580, 1455, and 1430 (doublet), 1380, 1245, 1145, 1100, 1050, 1025, 930, 870, 818, 790, 767, and 748 cm^{-1}. The NMR spectrum (CCl_4) showed two converging multiplets centered at δ 1.6 and 2.0 (8 H) and signals at δ 3.75 (3 H, s), 5.47 (1 H, brd s), and 7.0–7.6 (4 H, m). The mass spectrum showed parent ion *m/e* 310 and indicated the presence of two chlorines.

Anal. Calcd for $C_{16}H_{16}Cl_2O_2$: C, 61.73; H, 5.18; Cl, 22.81. Found: C, 61.85; H, 5.12; Cl, 23.20.

Methyl α-(1-Cyclophexenyl)-4′-trifluoromethylcinnamate (1a). Mp 66–70 °C. The IR spectrum (KBr pellet) gave ν_{max} 3400, 2930, 1720, 1620, 1440, 1330, 1243, 1212, 1170, 1133, 1073, 1022, 946, 926, 854, 839, 744, and 722 cm^{-1}. The NMR spectrum (CCl_4) gave δ 1.4–2.4 (8 H, m), 3.95 (3 H, s), 5.88 (1 H, brd s), 7.90 (1 H, s), and 8.10 (4 H). The mass spectrum showed a parent ion at *m/e* 310.

Anal. Calcd for $C_{17}H_{17}F_3O_2$: C, 65.80; H, 5.52; F, 18.69. Found: C, 65.47; H, 5.37; F, 21.08.

Methyl α-(1-Cyclohexenyl)-3′,5′-dimethoxycinnamate (1c). The IR spectrum (smear) gave ν_{max} 2900, 1710, 1585, 1452 and 1425 (doublet), 1230, 1156, 1069, 1020, 922, and 837 cm^{-1}. The NMR spectrum (CCl_4) gave δ 1.85 and 2.34 (8 H, brd m), 4.08 (9 H, s), 6.08 (1 H, brd s), 6.88 (1 H, t, J = 2.3 Hz), 7.30 (2 H, d, J = 2.3 Hz), and 8.04 (1 H, s). The mass spectrum gave parent ion *m/e* 302.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.44; H, 7.34. Found: C, 71.38; H, 7.29.

Methyl 1,3-Dichloro-5,6,7,8-tetrahydrophenanthrene-9-carboxylate (3b) from the Oxidative Irradiation of Methyl α-(1-Cyclohexenyl)-2′,4′-dichlorocinnamate (1b). A solution of 1.0 g of the methyl cinnamate in 100 mL of absolute methanol containing 0.5 g of iodine was irradiated for 15 h. The product crystallized out of the cooled solution. Filtration and washing with hexane gave 0.4 g of the tetrahydrophenanthrene **3b**, mp 127–128 °C, as colorless needles. (This product can also be recrystallized from hexane/ether or sublimed below its melting point at 80–100 mm.) More product, 0.2 g, was recovered from the mother liquor by chromatographing the concentrated oil on silica gel and eluting with 1:1 hexane/benzene. Total yield was 0.6 g (61.7%). The IR spectrum (KBr pellet) gave ν_{max} 2900, 1710, 1602 and 1575 (doublet), 1425, 1260, 1180, 1153, 1090, 1030, 1008, 900, 861, 802, and 779 cm^{-1}. The NMR spectrum (CCl_4) gave peaks at δ 1.75 and 2.95 (8 H, m), 3.80 (3 H, s), and three one-proton singlets at δ 7.3, 7.6, and 8.25. The mass spectrum showed parent ion *m/e* 308. The UV spectrum (MeOH) showed λ_{max} 344 nm (ε 2650), λ_{sh} 332 (2720), and λ_{max} 292–300 flat (11 370).

Anal. Calcd for $C_{16}H_{14}Cl_2O_2$: C, 62.13; H, 4.56; Cl, 23.28. Found: C, 61.66; H, 4.61; Cl, 25.32.

Methyl 3-Trifluoromethyl-5,6,7,8-tetrahydrophenanthrene-9-carboxylate (3a) from the Oxidative Irradiation of Methyl α-(1-Cyclohexenyl)-4′-trifluoromethylcinnamate (1a). Yield 71%, mp 64–64.5 °C. The IR spectrum (KBr pellet) showed ν_{max} 2900, 1735, 1437, 1380, 1323, 1300, 1178, 1155, 1140, 1075, 999, and 905 cm^{-1}. The NMR spectrum ($CDCl_3$) showed signals at δ 2.06 (4 H, m), 3.39 (4 H, m), 4.28 (3 H, s), 8.29 (1 H, d J = 9 Hz), 8.59 (1 H, d, J = 9 Hz), 8.88 (1 H, s), and 9.00 (1 H, s). The mass spectrum gave parent ion *m/e* 308.

Anal. Calcd for $C_{17}H_{15}F_3O_2$: C, 66.23; H, 4.90; F, 18.49. Found: C, 66.57; H, 4.95; F, 17.94.

Methyl 2,4-Dimethoxy-5,6,7,8-tetrahydrophenanthrene-9-carboxylate (3c) from the Oxidative Irradiation of Methyl α-(1-Cyclohexenyl)-3′,5′-dimethoxycinnamate (1c). Yield 65.0%, mp 89–91 °C. The IR spectrum (CCl_4) showed ν_{max} 2900, 1730, 1625, 1452, 1390, 1310, 1260, 1203, 1153, 1067, 1020, and 950 cm^{-1}. The NMR spectrum ($CDCl_3$) showed broad multiplets at δ 1.6–2.1 (4 H) and 3.0–3.9 (4 H). Two poorly separated singlets appeared at δ 3.96 (6 H) and 4.00 (3 H) and other peaks at δ 4.1 (3 H, s), 6.79 (1 H, d, J = 2.5 Hz), 6.99 (1 H, d, J = 2.5 Hz), and 8.35 (1 H, s). The mass spectrum gave a parent ion *m/e* 300.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.88; H, 6.79.

Methyl 3-Chloro-5,6,7,8-tetrahydrophenanthrene-9-carboxylate (10b) from the Nonoxidative Irradiation of Methyl α-(1-Cyclohexenyl)-2′,4′-dichlorocinnamate (1b). A solution of 2.5 g of the acrylate in 1000 mL of absolute methanol was placed in a large quartz vessel and purged for 30 min with a stream of dry nitrogen. The solution was irradiated for a total of 102 h and checked at 71, 96, and 102 h, respectively, by thin-layer chromatography (silica gel sheets developed in 9:2 hexane/diethyl ether) until little or no starting material was observed (starting material had an R_f 0.43 and absorbed 2537-Å light, while the product had R_f 0.36 and fluoresced in 2537-Å light). An NMR sampling of the final reaction solution showed less than 10% starting ester remaining.

The entire solution was evaporated to a semisolid residue, which was taken up in diethyl ether and dried over Na_2SO_4. After filtration and evaporation, 2.8 g of an oily brownish yellow residue was obtained. This oil was chromatographed on silica gel, eluting with 25% diethyl ether in hexane, to give 0.5 g of solid, mp 78–98 °C, and 0.1 g of solid, mp 82–94 °C. Recrystallization from methanol/hexane removed starting material and left a fairly pure product in the mother liquor. The recovery of product (mp 96–104 °C) of reasonable purity was 34.1%, 0.6 g. The IR spectrum (liquid film) gave ν_{max} 2900, 2820, 1720, 1620, 1585, 1440, 1365, 1280, 1237, 1205, 1150, 1080, 1025, 997, 902, 874, and 805 cm^{-1}. The mass spectrum showed parent ion *m/e* 274, with major fragments at 242, 214, 195, and 197. Only one chlorine was indicated. The NMR spectrum (CCl_4, 220 MHz) showed signals at δ 7.26 (1 H, dd, J = 9, J' = 1.5 Hz), 7.57 (1 H, d, J = 9 Hz), 7.76 (1 H, d, J = 1.5 Hz), 7.98 (1 H, s), 3.85 (3 H, s), 3.05 (2 H, t, J = 6 Hz). 2.95 (2 H, t, J = 6 Hz), and 1.73 (4 H, m). The 60-MHz spectrum (CCl_4) showed δ 1.93 (6 H, m), 3.25 (4 H, m), 3.95 (3 H, s), and 7.45–8.40 (4 H, m). The UV spectrum (MeOH) showed λ_{sh} 340 nm (ε 3330) and λ_{max} 301 (4420), 280–290 flat (6750), and 241 (48 000).

Anal. Calcd for $C_{16}H_{15}ClO_2$: C, 69.94; H, 5.50; Cl, 12.91. Found: C, 69.88; H, 5.51; Cl, 12.42.

Methyl 1,3-Dichloro-5,6,7,8,9,10-hexahydrophenanthrene-9-carboxylate (8b) from the Nonoxidative Irradiation of Methyl α-(1-Cyclohexenyl)-2′,4′-dichlorocinnamate (1b) in the Presence of Potassium Carbonate. A solution of 1.0 g (3.2×10^{-3} M) of cinnamate **1b** dissolved in 75 mL of absolute methanol containing 0.4 g (3.2×10^{-3} M) of potassium carbonate was purged with a gentle stream of nitrogen for 30 min and then irradiated for 15 h. The solution was poured into 50 mL of diethyl ether and extracted with 25-mL portions of aqueous saturated salt solution until the washings were neutral. After drying over $MgSO_4$ and filtering, evaporation of the ether gave 0.9 g of a yellowish oily residue. The residue was chromatographed on a 12 × 0.44 in. o.d. column of silica gel, eluting with increasing amounts of chloroform in pentane (10–100%). Based on NMR integrations of the eluted fractions, 0.18 g of starting material was recovered. The three products were methyl 1,3-dichloro-5,6,7,8,9,10-hexahydrophenanthrene-9-carboxylate (**8b**), 0.27 g (32.4%), methyl 3-chloro-5,6,7,8-tetrahydrophenanthrene-9-carboxylate (**10b**), 0.12 g (15.7%), and methyl 1,3-dichloro-5,6,7,8-tetrahydrophenanthrene-9-carboxylate (**3b**), 0.02 g (1.8%). The structures of the two tetrahydrophenanthrenes were established by comparison with authentic materials.

Repetitive column chromatography gave 0.09 g of pure hexahydro product **8b** as an oil. The IR spectrum (CCl_4) gave ν_{max} 2905, 1740, 1580–1540, 1455 and 1440 (doublet), 1170–1160, 1098, 1090, 1028, and 860 cm^{-1}. The NMR spectrum (CCl_4, 220 MHz) gave δ 1.74 (4 H, m), 2.31 (4 H, m), 2.73 (1 H, dd, J_{AB} = 14.6, J_{AC}, 6.6 Hz), 3.30 (1 H, dd, J_{AC} = 6.6, J_{BC} = 4.7 Hz), 3.33 (1 H, dd, J_{AB} = 14.6, J_{BC} = 4.7 Hz), 3.56 (3 H, s), and an AB quartet at δ 6.93 and 7.04 (2 H, J = 2.00 Hz). The mass spectrum showed parent ion *m/e* 310, with a base peak of 251. Other major fragments were 211, 209, 191, and 189. Two chlorines were indicated. The UV spectrum (MeOH) had λ_{max} 274 nm (ε 7740), 249 (10 760), 237 (18 410), 230 (21 360), and 224 (20 590).

Anal. Calcd for $C_{16}H_{16}Cl_2O_2$: C, 61.75; H, 5.18; Cl, 22.79. Found: C, 61.73; H, 5.09.

Attempts to oxidize the hexahydrophenanthrene system to either

the tetrahydrophenanthrene or the phenanthrene using Pd- or Pt-on-carbon or *N*-bromosuccinimide and dibenzoyl peroxide gave no reaction.

Methyl 3-Trifluoromethyl-5,6,7,8,9,10-hexahydrophenanthrene-9-carboxylate (8a) from the Nonoxidative Irradiation of Methyl α-(1-Cyclohexenyl)-4'-trifluoromethylcinnamate (1a). A solution of 0.50 g of cinnamate **1a** in 50 mL of absolute methanol containing 0.122 g of K_2CO_3 was purged with nitrogen and irradiated for 15 h. The solution was taken up in diethyl ether, washed with water, dried over $MgSO_4$, filtered, and evaporated to give 0.54 g of a yellow oil. The oil was taken up in chloroform and chromatographed on a 12 × 0.5 in. column of silica gel, eluting with increasing amounts of chloroform in hexane (10–100%). The products were methyl 3-trifluoromethyl-5,6,7,8-tetrahydrophenanthrene-9-carboxylate (**3a**), 0.02 g (4.6%), methyl 3-trifluoromethyl-5,6,7,8,9,10-hexahydrophenanthrene-9-carboxylate (**8a**), 0.29 g (57.0%), and 4-trifluoromethyl-5,6,7,8,9,10-hexahydrophenanthrene-9-carboxylic acid (**9a**), mp 154–161 °C dec, 0.11 g (23.9%). The IR spectrum (smear) of **8a** showed ν_{max} 2900, 1745, 1432, 1330, 1278, 1243, 1165, 1120, 1098, 1080, 990, 895, and 841 cm^{-1}. The NMR spectrum (CCl_4, 60 MHz) showed signals at δ 1.99 (4 H, m), 2.6 (4 H, brd m), 3.4 (3 H, m) 3.95 (3 H, s), and 8.12 (3 H, m). A 220-MHz (CCl_4) scan showed δ 0.88 (1 H, q, J = 6 Hz), 1.27 (1 H, s), 1.78 (2 H, m), 1.90 (1 H, m), 2.16 (1 H, m), 2.39 (1 H, m), 2.60 (1 H, m), 2.95 (1 H, dd, J = 6, J' = 13–13.5 Hz), 3.57 (3 H, s), 7.17 (1 H, d, J = 6.8–7 Hz), 7.34 (1 H, d, J = 6.8–7 Hz), and 7.37 (1 H, s). UV and analytical data were obtained on the solid acid derivative **9a** (see below).

3-Trifluoromethyl-5,6,7,8,9,10-hexahydrophenanthrene-9-carboxylic Acid (9a) from the Hydrolysis of Methyl 3-Trifluoromethyl-5,6,7,8,9,10-hexahydrophenanthrene-9-carboxylate (8a). A solution of 0.20 g of the hexahydrophenanthrene methyl ester (**8a**) in 10 mL of absolute methanol containing 20 mL of 25% aqueous sodium hydroxide was refluxed overnight. The basic solution was cooled and extracted with diethyl ether. The aqueous layer was acidified with HCl and extracted with ether. After drying over $MgSO_4$, the solution was filtered and evaporated to give 0.16 g (81.4%) of a white powder, mp 162.5–163.5 °C dec [sublimes ~150 °C (760 mm)].

This material was identical with that obtained in the irradiation above. The IR spectrum (KBr pellet) showed ν_{max} 3350, 3050, 2900, 2700–2500, 1710, 1415, 1333, 1273, 1236, 1167, 1120, and 840 cm^{-1}. The NMR spectrum (CCl_4, 220 MHz) gave δ 1.59–2.05 (4 H, m), 2.05–2.73 (4 H, m), 2.98 (1 H, dd, J = 20, J' = 6.5–7 Hz), 2.99 (1 H, s), 3.17 (1 H, dd, J = 20, J' = 8 Hz), 7.14 (1 H, d, J = 8 Hz), 7.30 (1 H, d, J = 8 Hz), 7.35 (1 H, s), and 11.23 (1 H, brd s). The mass spectrum gave parent ion m/e 296. The UV spectrum (MeOH) gave λ_{max} 275 nm (ε 5760) and 225 (12 660).

Anal. Calcd for $C_{16}H_{15}F_3O_2$: C, 64.86; H, 5.10; F, 19.24. Found: C, 64.57; H, 4.88; F, 18.75.

Irradiation of Methyl α-(1-Cyclohexenyl)-4'-trifluoromethylcinnamate (1a) using a Pyrex Filter. A solution containing 0.9 g of **1a** in 90 mL of absolute methanol was purged for 1 h with a stream of dry nitrogen and placed in a Pyrex tube. After irradiating for 15 h, the solvent was removed on a rotary evaporator to give 0.9 g of a yellow oil. The NMR of this oil indicated only starting ester.

The recovered **1a** from the above irradiation was dissolved in 90 mL of absolute methanol containing 0.4 g of K_2CO_3. After purging for 1 h with nitrogen and irradiating for 15 h, the solvent was removed to give 0.9 g of unreacted **1a**.

Nonoxidative Irradiation of Methyl α-(1-Cyclohexenyl)-4'-trifluoromethylcinnamate (1a) in Perdeuteriomethanol. A solution of 0.3 g of the ester in 15 mL of CD_3OD was purged with nitrogen and irradiated (quartz) for 25 h. An NMR spectrum of the crude reaction residue, after solvent removal, showed mostly unreacted ester. The residue was redissolved in 15 mL of CD_3OD with 0.05 g of K_2CO_3 in it, repurged, and irradiated for an additional 20 h. Workup, followed by drying over $MgSO_4$ and filtering, gave 0.3 g of a yellow oil (NMR showed little or no starting material remaining). This was chromatographed over silica gel, eluting with hexane followed by 10% $CHCl_3$ in hexane. Of 50–75-mL fractions, fractions 33–38 contained 0.1 g of impure **3a**. Fractions 39–41 gave 0.14 g of partially deuterated **8a** (see text for discussion of NMR spectrum).

Methyl Dimethoxy-5,5α,6,7,8,10-hexahydrophenanthrene-9-carboxylate (13c) from the Nonoxidative Irradiation of Methyl α-(1-Cyclohexenyl)-3',5'-dimethoxycinnamate (1c). A solution of 1.0 g of cinnamate **1c** in 100 mL of absolute methanol was purged for 1 h with nitrogen. After irradiating for 15 h, the reaction was cooled in an ice/acetone bath to induce crystallization of the product. Filtering, washing sparingly with chilled 1:1 MeOH/H_2O, and air-drying gave 0.87 g of colorless needles (86.5%), mp 105–106.5 °C. The IR spectrum (CCl_4) showed ν_{max} 2900, 1720, 1600, 1492, 1460, 1428, 1380, 1343, 1270, 1240, 1200, 1155, 1120, 1099, and 1060 cm^{-1}. The NMR spectrum showed a marked solvent effect; therefore, results obtained with both CCl_4 and C_6D_6 (220 MHz) are reported here. NMR (C_6D_6) δ 1.32 (1 H, octet, J_1 = 23.5, J_2 = 12, J_3 = 5 Hz), 1.48–1.70 (3 H, m), 1.73–1.93 (2 H, m), 2.55 (1 H, multiplet of doublets, J = 12–12.5 Hz), 3.27 (3 H, s), 3.39 (3 H, s), 3.47 (3 H, s), 3.58 (1 H, q of d, J_1 = 10.5–11, J_2 = 7, J_3 = 3.75 Hz), 3.74 (2 H, d, J = 3 Hz), 4.02 (1 H, m of d, J = 10.5–11 Hz), 6.17 (1 H, d, J = 2.3 Hz), and 6.31 (1 H, d, J = 2.3 Hz). NMR (CCl_4) δ 1.17 (1 H, octet, J_1 ~ 24, J_2 ~ 11.5–12, J_3 ~ 4 Hz), 1.36–1.6 (1 H, m), 1.6–1.9 (3 H, m), 1.97 (1 H, brd d with fine structure, J ~ 12 Hz), 2.30 (1 H, ibid.), 3.35 (1 H, m), 3.52 (2 H, brd s), 3.6–3.7 (1 H, m), 3.67 (6 H, s), 3.76 (3 H, s), and 6.12 (2 H, AB q, J = 2.5). A carbon-13 NMR spectrum (CCl_4, 22.63 MHz) was obtained in a effort to verify the presence of the tetrasubstituted internal double bond, and it was found to be entirely consistent with the proposed structure. Bands are reported in ppm (from Me_4Si) (one carbon unless noted otherwise): 28.2, 31.2, 32.8, 33.8, 38.1, 42.2, 51.8, 55.9 (2 C), 103.1, ~132.4 (buried under C_6F_6 internal standard), 118.4 (2 C), 135.0, 153.3, 158.4, 160.0, and 168.3 ppm. The UV spectrum (MeOH) gave λ_{max} 283 nm (ε 1910), 275 (2080), and strong end absorption. The mass spectrum showed parent ion m/e 302. The molecular weight by the Rast method was found to be 300.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.29; H, 7.48.

Attempted Rearrangement of Methyl 2,4-Dimethoxy-5,5α,6,7,8,10-hexahydrophenanthrene-9-carboxylate (13c) to Methyl 2,4-Dimethoxy-5,6,7,8,9,10-hexahydrophenanthrene-9-carboxylate (8c). A solution of 0.1 g of hexahydrophenanthrene **13c** dissolved in 15 mL of benzene containing 0.05 g of *p*-toluenesulfonic acid (monobasic) was refluxed overnight. The reaction solution was washed with saturated aqueous sodium bicarbonate solution and water, dried over Na_2SO_4, filtered, and evaporated to give 0.1 g of unreacted starting material (IR, NMR).

Attempted Oxidation of Methyl 2,4-Dimethoxy-5,5α,6,7,8,10-hexahydrophenanthrene-9-carboxylate (13c) to Methyl 2,4-Dimethoxy-5,6,7,8-tetrahydrophenanthrene-9-carboxylate (3c) or Its Phenanthrene Derivative. Method A. Powdered 10% palladium-on-carbon, 0.15–0.20 g, was added to 0.25 g of the hexahydro compound **13c** in 10 mL of xylene. The solution was refluxed for 70 h. After cooling, filtering, and removing the xylene by distillation, the residue was shown to be only starting material (IR, TLC).

Method B. A mixture of 0.15 g of the hexahydrophenanthrene **13c**, 0.16 g of *N*-bromosuccinimide, 0.03 g of dibenzoyl peroxide, 0.7 g of potassium acetate, and 0.87 mL of glacial acetic acid in 6.5 mL of carbon tetrachloride was maintained at reflux for 16 h, during which time additional quantities of dibenzoyl peroxide were added. (The presence of an orange solution indicated that additional peroxide was necessary.) The cooled solution was poured into cold 5% aqueous HCl, and the precipitate was collected and washed well with water and a small amount of benzene. The IR spectrum indicated only unreacted starting material.

Method C. A solution of 0.11 g of **13c** and 0.03 g of the biacetyl in 20 mL of benzene was irradiated over the weekend with 3500-Å light. After solvent removal, the residue was extracted with benzene and washed with water. The solution was passed through 2 g of alumina, eluting with light petroleum ether/benzene (1:1). A complete recovery or unreacted starting material was obtained.

Methyl 2,4-Dimethoxy-5,5α,6,7,8,10-hexahydro-1,10-dideuteriophenanthrene-9-carboxylate (13c') from the Nonoxidative Irradiation of Methyl α-(1-Cyclohexenyl)-3',5'-dimethoxycinnamate (1c) in Deuteriomethanol. A solution containing 0.6 g of cinnamate **1c** and 0.28 g of K_2CO_3 in 25 mL of CD_3OD was purged for 1 h with nitrogen and irradiated for 30 h (after 15 h, 20% of the starting cinnamate was still present). The solvent was removed, and the yellow oily residue was taken up in diethyl ether and washed with D_2O. After drying over $MgSO_4$ and filtering, the ether was removed to give 0.6 g of yellow oil (crude NMR indicated little or no starting material or tetrahydrophenanthrene **3c**), which was chromatographed on silica gel, eluting with increasing amounts of chloroform in hexane. The first fractions gave a yellow-brown crystalline product, 0.28 g (46%), mp 99.5–102 °C, which could be further purified to a colorless powder by recrystallization from CCl_4, mp 101–103 °C (the spectral data were obtained on this sample). Further elutions gave 0.34 g (55%) of a yellow viscous oil, the NMR and IR of which indicate that the material is essentially the same structure as above, except that it may be a mixture of differently deuterated materials. The IR spectrum (KBr pellet) gave weak CD bands at ν_{max} 2075 and 2220 cm^{-1}. The relative intensity of the CH bands (relative to C=O) was

considerably lower than in the undeuterated material. The carbonyl band was unchanged (1710 cm^{-1}) while other significant bands fell at 1600, 1460, 1425, 1363, 1340, 1222, 1122, and 837 cm^{-1}. (See text for a discussion of the NMR spectrum.) The mass spectrum gave parent ion *m/e* 304 and indicated the absence of any oxidative product or material that was deuterated additionally.

Irradiation of **1c** under identical conditions in monodeuteriomethanol (CH_3OD) yielded **13c'** also.

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Registry No.—**1a,** 64490-61-5; **1b,** 64490-62-6; **1c,** 64490-63-7; **3a,** 64490-64-8; **3b,** 64490-65-9; **3c,** 64490-66-0; **4a,** 455-19-6; **4b,** 874-42-0; **4c,** 7311-34-4; **5,** 18294-87-6; **6a,** 64490-67-1; *E*-**6b,** 64490-68-2; *Z*-**6b** , 64490-69-3; **6c,** 64490-70-6; **7a,** 2062-26-2; **7b,** 1201-99-6; **8a,** 64490-71-7; **8b,** 64490-72-8; **9a,** 64490-73-9; **10b,** 64490-74-0; **13c,** 64490-75-1; **13c',** 64490-76-2.

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Synthetic Studies on Lignan Lactones: Aryl Dithiane Route to (±)-Podorhizol[1] and (±)-Isopodophyllotoxone and Approaches to the Stegane Skeleton

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The details of the conjugate addition of aryl dithiane anions to 2-butenolide are discussed. The results of the trapping of the resultant lactone enolates with an aryl halide and aryl aldehyde are detailed. The transformation of these intermediates into podorhizol (**4a**) and isopodophyllotoxone (**12a**) is also explored. The structures of products from attempted intramolecular Ullmann couplings in the stegnane series are established.

The antileukemic lignan lactones steganacin (**1a**) and steganangin (**1b**)[4] are but only two members of a growing class of naturally occurring bis(benzyl)[*a,c*]cyclooctadienes which include among their members schizandrin,[5] kadsurin, kadsuranin,[6] and gomisins A, B (**2a**), C (**2b**),[7] and D (**2c**).[8] The unusual ring system present in these substances and the close biogenetic relationship between the structures **1** and the antitumor lactone podophyllotoxin[9] **3** and its derivatives[10] have both initiated and renewed interest in the development of new methodology for the synthesis of these substances. To date the syntheses of steganacin,[11] steganone,[11,12] isostegane,[13] and deoxyschizandrin[14] have been realized.

Our concern in this area lay in the development of an efficient synthetic method which would be amenable to the construction of members of the stegane, podophyllane, and secopodophyllane (e.g., podorhizol (**4a**)) families. It appeared attractive to employ an acyl anion equivalent of piperonal which could undergo conjugate addition to 2-butenolide and whose resultant lactone anion could effect subsequent alkylation or aldol condensation with the appropriate benzylic halide or aromatic aldehyde (Scheme I).

Although the anions **5a–d** failed to give clean addition products, the thioethyl acetal anion provided the Michael adduct **7a** in 50% yield when exposed to 2-butenolide in THF at −78 °C[15] followed by low-temperature protonation. This yield was measurably improved (88%) by employing the dithiane **5f,** thereby providing the congener **7b.** Anion **5f** and the dithiane anion of benzaldehyde both added in a conjugate fashion to methyl cinnamate and methyl crotonate in 70–85% yield. The lactone enolate of **7b** could be generated successfully with lithium diisopropylamide (LDA) in THF at −78 °C followed by alkylation (−78 → 25 °C) with 3,4,5 trimethoxybenzyl chloride in the presence of 1 equiv of hexamethylphosphoramide (HMPA) in 56% yield. A more efficient route involved the direct alkylation[17] of the lactone enolate generated by Michael addition, thereby providing all of the required carbon atoms present in these lactones in a one-pot reaction. It was assumed at this point that the stereochemistry of **6a** was trans since it would be expected that alkylation would occur trans to the bulky aryl dithiane moiety. The assignment was confirmed when the dithiane was cleaved with HgO–BF_3 in aqueous THF to provide the ketone **6d,** prepared by Drake[18] some 20 years earlier. Moreover, the dithiane **6a** was transformed as described by Schlessinger[13] (Ni(R); VOF_3) to isostegane (**8**), whose unnatural biphenyl twist and trans-fused lactone have been defined by x-ray analysis. Any conversion of isostegane (**8**) to steganone (**1c**) would be dependent upon a selective benzylic oxidation to introduce oxygen and relieve the unnatural biphenyl twist.[19]

The intramolecular oxidative coupling of electron-rich aromatic rings appears to be unsuccessful only in instances where the benzylic position is capable of forming a cation, is deactivated (i.e., carbonyl), or is capable of oxidation.[11,13,20] Thus, oxidation of dithiane **6a** with either VOF_3 or $Mn(acac)_3$ or by anodic oxidation efficiently provided dihydronaphthalene **9,** without any indication of biaryl coupling. Although the biaryl couplings require a strong acid medium [e.g., trifluoroacetic acid (TFA)], the dithiane underwent cyclization even in the absence of TFA. Dihydronaphthalene **9** could be further oxidized to the naphthalene by either overexposure

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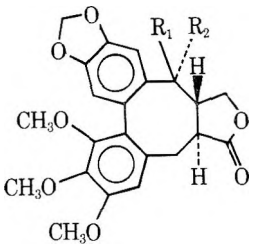
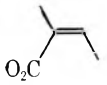
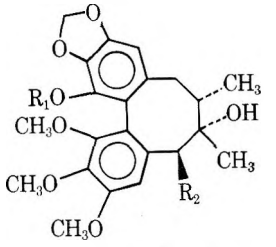
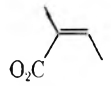


1a, R_1 = OAc; R_2 = H

b, R_1 =  ; R_2 = H

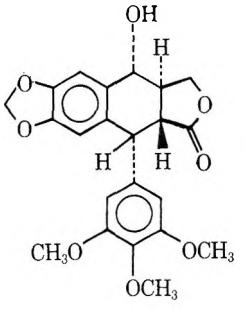
c, R_1, R_2 = O



2a, R_1 = CH_3; R_2 = 

b, R_1 = CH_3; R_2 = $CO_2C_6H_5$

c, $R_1 \rightarrow R_2$ = $CH_2CHCH_3CHCH_3(OH)CO_2$



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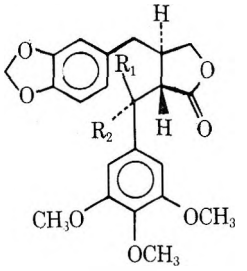


4a, R_1 = OH; R_2 = H

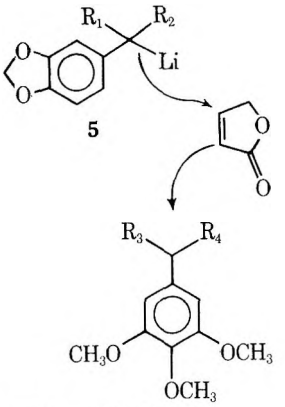
b, R_1 = H; R_2 = OH

to $Mn(acac)_3$ or treatment with manganese dioxide and was found to be identical with the naphthalene prepared by a different route.[21]

The keto lactone **6d** gave a complex mixture of products with VOF_3 and provided, upon oxidation with $Mn(acac)_3$, the cinnamate **10**, whose structure was assigned in part on the appearance of a vinylic one-proton doublet at δ 7.72 (J = 2 Hz) in accord with established values.[22,24] Attempts to oxidatively cyclize the alcohols **6e** or their acetates **6f** led to the tetrahydronaphthalene **11**. The appearance of a one-proton C–H at δ 3.95 (J = 15 Hz) served to establish the trans relationship between the protons at C-1 and C-2. This cyclization is not effected by the oxidants but rather by the solvent, trifluoroacetic acid.

The anion of lactone **7b** in THF at −78 °C was efficiently trapped with 3,4,5-trimethoxybenzaldehyde to provide the erythro and threo aldol products **6b** and **6c** in ratio of 52:48, respectively. House[23] has shown that the aldol condensation kinetically provides more of the threo isomer in solvents of low polarity. Accordingly, when the aldol condensation was conducted in 1:1 ether–1,2-dimethoxyethane, the isomer **6c** (threo) predominated over isomer **6b** (erythro) in a 3:1 ratio. Since it has been established[23] that J_{threo} (6–9 Hz) > $J_{erythro}$ (2–4 Hz) due to hydrogen bonding in the aldol products, the stereochemical assignments could be readily made since isomer **6b** displayed a doublet (R_4 = H) at δ 5.16 (J = 2.0 Hz) and

Scheme I



a, R_1 = R_2 = CO_2CH_3

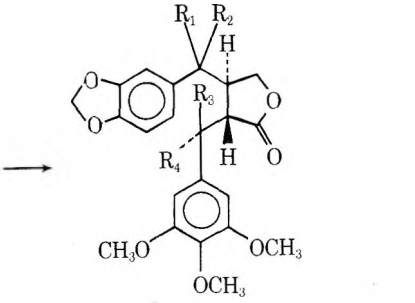
b, R_1 = CN; R_2 = $OCH(OC_2H_5)CH_3$

c, R_1 = CN; R_2 = $N(CH_2CH_2)_2$

d, R_1 = H; R_2 = SOC_6H_5

e, R_1 = R_2 = SC_2H_5

f, R_1, R_2 = $SCH_2CH_2CH_2S$



6a, R_1, R_2 = $SCH_2CH_2CH_2S$; R_3 = R_4 = H

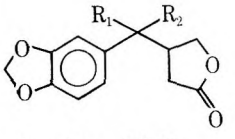
b, R_1, R_2 = $SCH_2CH_2CH_2S$; R_3 = OH; R_4 = H

c, R_1, R_2 = $SCH_2CH_2CH_2S$; R_3 = H; R_4 = OH

d, R_1, R_2 = O; R_3 = R_4 = H

e, R_1 = OH; R_2 = R_3 = R_4 = H

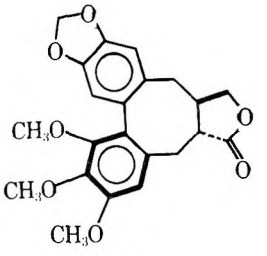
f, R_1 = OAc; R_2 = R_3 = R_4 = H



7a, R_1 = R_2 = SC_2H_5

b, R_1, R_2 = $SCH_2CH_2CH_2S$

c, R_1, R_2 = O



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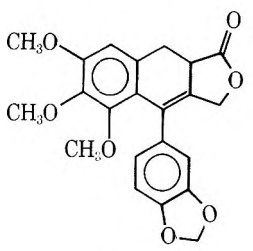
isomer **6c** revealed a doublet (R_3 = H) at δ 4.77 (J = 6.8 Hz).

Desulfurization of erythro dithiane **6b** with Raney nickel W-2 in refluxing ethanol gave rise to (±)-podorhizol (**4a**), identical (solution IR, HPLC, TLC, 270-MHz NMR) with a sample of natural (−)-podorhizol.[24] In a similar manner, the threo isomer gave rise to (±)-epipodorhizol (**4b**), whose spectral properties were in accord with reported[24] values.

Acid hydrolysis of the naturally occurring glycoside of (−)-podorhizol effects cyclization to deoxyisopodophyllotoxin (**12a**) as the major component and deoxypodophyllotoxin (**12b**) as the minor product, without prior dehydration to the anhydro derivative prior to cyclization.[24] Treatment of erythro dithiane **6b** with stannic chloride in methylene chloride produced a homogeneous solution which cleanly afforded a single product of cyclization. The 270-MHz NMR spectrum clearly revealed this compound to be the dithiane of isopodophyllotoxone (**12c**) since the C-1 proton appeared as a doublet at δ 4.01 ($J_{1,2}$ = 11 Hz) and the C-2 proton appeared as a doublet of doublets at δ 3.42 ($J_{1,2}$ = 11, $J_{2,3}$ = 15 Hz). Under the mild cyclization conditions, only a single stereoisomer is produced



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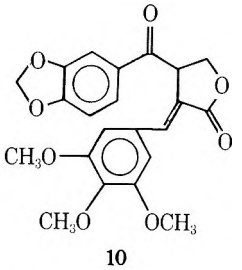

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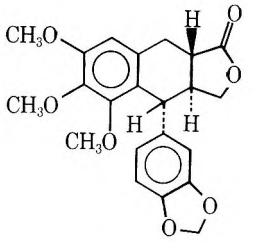
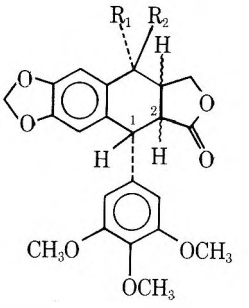


11



12a, 2α-H; 3β-H; $R_1 = R_2 = H$
b, 2β-H; 3α-H; $R_1 = R_2 = H$
c, 2α-H; 3β-H; $R_1 = R_2 = O$ (isopodo)
d, 2β-H; 3α-H; $R_1 = R_2 = O$ (podo)
e, 2α-H; 3α-H; $R_1 = R_2 = O$ (picro)
f, 2β-H; 3β-H; $R_1 = R_2 = O$ (isopicro)
g, 2α-H; 3β-H; $R_1 = H$; $R_2 = OH$
h, 2β-H; 3α-H; $R_1 = OH$; $R_2 = H$
i, 2α-H; 3β-H; $R_1, R_2 = SCH_2CH_2CH_2S$

with the trans-fused lactone remaining intact. On the other hand, the threo isomer **6c** formed an insoluble precipitate from which the starting material could be isolated. However, prolonged refluxing of the solution eventually effected cyclization to the same material. This discrepancy in solubility and reactivity can be considered due to the threo isomer being more prone to forming a stable cyclic tin salt, having the trimethoxybenzene ring equatorially oriented. The erythro isomer would have the same substituent in the less stable axial arrangement, thereby allowing more facile decomposition to the benzylic cation. This minor inconvenience was circumvented by accomplishing the ring closure with trifluoroacetic acid in methylene chloride. Moreover, podorhizol and epipodorhizol were readily cyclized under both of these sets of conditions to deoxyisopodophyllotoxin (**12a**).

Oxidative removal of the dithiane function in the cyclization product produced (±)-isopodophyllotoxone (**12c**), based upon the appearance of the C-1 proton at δ 4.28 ($J_{1,2}$ = 11 Hz) and the C-2 proton at δ 3.06 ($J_{1,2}$ = 11, $J_{2,3}$ = 15 Hz) in the 270-MHz NMR spectrum. The physical and spectral properties of our racemic **12c** were not in accord with those of the same material prepared by Gensler[25] by the oxidation of (±)-isopodophyllotoxin (**12g**) with MnO_2. The structure of (±)-**12g** was on firm ground since hydrogenolysis of its *O*-acetate provided the known (±)-deoxyisopodophyllotoxin (**12a**).

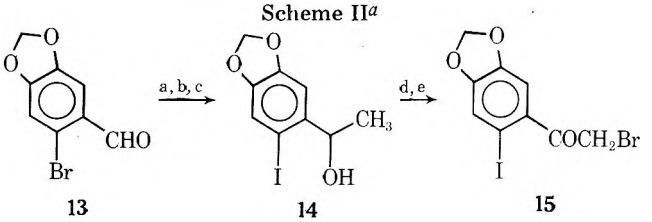
The 270-MHz NMR spectrum of Gensler's racemic ketone[26,27] was found to be identical with a sample of picropodophyllone[27] (**12e**) prepared from (−)-podophyllotoxin (**12h**) by C-2 epimerization[28] and room temperature MnO_2 oxidation.[29] This epimerization may have arisen in refluxing dioxane from traces of base present in the MnO_2. The 270-MHz NMR spectra of the remaining two ketones, podophyllotoxone (**12d**) (from (−)-**12h** by oxidation) and (−)-isopicropodophyllone (**12f**),[30] were recorded and found to be distinctly different from **12c** and **12d**. In particular, the trans-fused lactones podophyllotoxone (**12d**) and isopodophyllotoxone (**12c**) are highly resolved spectra relative to their cis counterparts.

The inability to form the dibenzocyclooctadiene skeleton by oxidative means prompted consideration of an intramolecular Ullmann coupling of the two aromatic rings. Although it was possible to achieve bromination of the trimethoxybenzene ring of **6d** under various conditions, it was not possible to brominate the 6 position of the deactivated methylenedioxybenzene ring. In fact, dibromination of the trimethoxybenzene ring occurred preferentially. An attempt to circumvent this difficulty by preparing the lithiodithiane of 6-bromopiperonal was unsuccessful since *n*-butyllithium effected metal–halogen exchange followed by proton exchange to give the lithiodithiane **5f**.

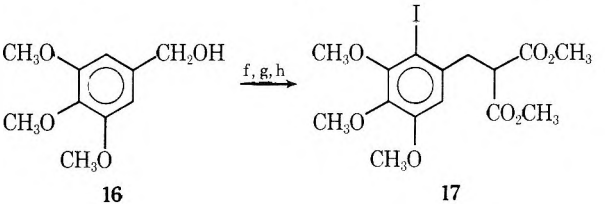
The requisite aryl halides **18a** and **18b** were synthesized by modification of Drake's method[18] (Scheme II). Attempted intramolecular coupling with copper bronze in refluxing DMF afforded as the major product the monodehalogenated iodide **18c**, in accord with the observations of Semmelhack[31] in a related system employing tetrakis(triphenylphosphine)-nickel(0) in DMF. On occasion a product of longer retention time (HPLC) could be detected, but never produced in sufficient quantity. Variations in reaction temperatures, concentration, sources of copper powder, or activation of the copper[32] powder gave approximately the same yield of the reduced iodide **18c**.

Cuprous triflate[33] in DMF at reflux (150–160 °C) also reduced the diiodide **18a** to the monoiodide **18c** along with

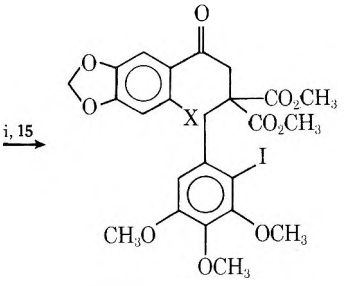
Scheme II[a]



13 14 15



16 17



18a, X = I
b, X = Br
c, X = H
d, X = symmetrical dimer
e, X = $PO(OC_2H_5)_2$

[a] a, CH_3MgBr; b, 2 equiv of *n*-BuLi; c, I_2; d, Jones reagent; e, Br_2/HBr; f, $Hg(OAc)_2/I_2$; g, $SOCl_2$; h, $NaCH(CO_2COCH_3)_2$/THF; i, NaH/THF

minor amounts of the longer retention-time material. When the reaction temperature was reduced to 100 °C, the starting material was completely consumed with reproducible formation of the longer retention-time product and the absence of the monoiodide **18c**. Lower temperatures resulted in the recovery of starting material. This new product was assigned the symmetrical dimeric structure **18d** on the basis of spectral data and combustion analysis. Since bromine exchnges slower than iodine in the Ullmann reaction,[34] it was considered that iodobromide **18b** at higher dilution would favor intramolecular over intermolecular coupling. This did not prove to be the case since dimer **18d** was obtained in approximately the same yield as was previously obtained. This indicates that the bromide with its ortho carbonyl is still a more reactive moiety than the doubly ortho-flanked iodide.

The halogen of the trimethoxybenzene ring, which is flanked by two ortho substitutents (methoxy and alkyl chain), is reduced in reactivity by not only steric factors, but probably electronic factors as well. The Ullmann cyclization of 2-iodo-3-ethylbenzoic anhydride (7-membered ring) has been realized in 90% yield by employing copper powder in refluxing DMF. Although the electron-withdrawing carbonyl group ortho to the halogen plays a role in activating the halogen, the ring size and intramolecular nature of the coupling play a significant role since methyl 2-iodo-3-ethylbenzoate coupled in only 41% yield.[35]

When the diiodide **18a** was heated in the presence of the copper(I) iodide–triethyl phosphite complex in DMF at 100 °C, a crystalline product was isolated in 89% yield. The elemental combustion analysis (C, H, I) was in accord with structure **18e**. The site of the phosphorus residue was revealed by the large coupling of the ortho (J = 12 Hz) and meta (J = 4 Hz) protons in the methylenedioxybenzene ring. This aromatic Michaelis–Arbuzov reaction has been observed by Tavs[36] when aromatic halides and triethyl phosphite are heated in the presence of copper powder, albeit in low yield.

It can be concluded from these results and efforts in this area on a related system[31] [**18b**, bis(decarbomethoxy)] that the enhanced reactivity of the halogen ortho to an electron-withdrawing group permits either reduction or intermolecular reactions faster than intramolecular coupling with doubly ortho-flanked aryl halides. When one of the two groups is electron withdrawing, intramolecular couplings may occur. This intramolecular reaction can be applied in systems where steric hindrance, halide activation, ring size, and reagents are optimized.[37]

Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are corrected. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Infrared spectra were determined on a Perkin-Elmer Model 700A or 421 spectrometer. Nuclear magnetic resonance spectra were obtained on either a Varian Model A-60A, JEOL minimar 100, Perkin-Elmer Model R-32, or Bruker HX-270. Chemical shifts are reported in δ units using tetramethylsilane as an internal reference.

Solvents are reagent grade and were used as received. Chloroform and methylene chloride, when used as reaction solvents, were distilled from phosphorus pentoxide under a nitrogen atmosphere. Tetrahydrofuran, ether, and glyme were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Dimethylformamide (DMF) was distilled from calcium hydride at atmospheric pressure under a nitrogen atmosphere. Butyllithium was purchased from Alfa–Ventron and titrated according to the method of Gilman or Kofron.[38] Low temperatures were maintained with CO_2–acetone baths. In all workup procedures the drying process involved treatment with anhydrous magnesium sulfate and filtering in vacuo prior to concentration in vacuo.

In reactions requiring anhydrous conditions the apparatus and transfer equipment were dried at 100–110 °C for at least 2 h and cooled to 25 °C under a nitrogen atmosphere before use.

Analytical high-pressure chromatograms were obtained using a 50 × 2 mm Porasil T column eluted with 30% THF–hexane with a 0.5 mL/min flow rate in conjunction with an Isco UV-type 6 detector and electronic integrator system.

3-(3′,4′-Methylenedioxybenzoyl)butyrolactone Dithiane (7b). To a stirred solution of 1.20 g (5.0 mmol) of piperonal dithiane dissolved in 10 mL of dry THF maintained under a nitrogen atmosphere at −78 °C was added a solution of 2.18 mL (5.10 mmol, 2.34 M) of n-butyllithium in hexane.[39] The resultant orange solution was stirred for 0.5 h and then treated with a solution of 0.42 g (5.0 mmol) of 2-butenolide in 1 mL of THF. The reaction mixture was stirred for 0.5 h and then quenched with 10% aqueous acetic acid (5 mL) and allowed to warm to 25 °C. The solution was extracted thoroughly with ethyl acetate, and the extracts were combined, washed with water, and dried. Evaporation of the solvent afforded a yellow solid. Recrystallization from benzene–ether gave the lactone **7b** (88%) as fine white crystals: mp 154–155 °C; IR ($CHCl_3$) 2930, 1780, 1249 cm^{-1}; NMR ($CDCl_3$) δ 1.97 (2, H, m), 2.68 (6 H, m), 4.28 (2 H, m), 6.02 (2 H, s), 6.78 (1 H, d, J = 10 Hz), 7.48 (3 H, m).

Anal. Calcd for $C_{15}H_{16}O_4S_2$: C, 55.53; H, 4.97; S, 19.76. Found: C, 55.50; H, 4.98; S, 19.76.

3-(3′,4′-Methylenedioxybenzoyl)butyrolactone (7c). To a stirred solution of 10 mL of 15% aqueous THF maintained under a nitrogen atmosphere was added 0.91 g (4.2 mmol) of red mercuric oxide and 0.52 mL (4.2 mmol) of freshly distilled boron trifluoride etherate.[40] A solution of 0.47 g (1.5 mmol) of butyrolactone dithiane **7b** dissolved in 10 mL of THF was added, and the reaction mixture was allowed to stir at 25 °C for 12 h. The reaction mixture was diluted with 20 mL of ether followed by filtration to remove the precipitated salts. The ether solution was successively washed to pH 10 with saturated sodium carbonate and to neutrality with saturated sodium chloride and dried. Removal of the solvent left a white powder. Crystallization from ether–pentane afforded the keto lactone **7c** (85%) as long white needles: mp 118–119 °C (lit.[16] 118–119 °C); IR ($CHCl_3$) 1780, 1675, 1250 cm^{-1}; NMR ($CDCl_3$) δ 2.88 (2 H, m), 4.45 (3 H, m), 6.10 (2 H, s), 6.94 (1 H, d, J = 9 Hz), 7.45 (1 H, s), 7.55 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.43; H, 4.31.

***trans*-2-(3″,4″,5″-Trimethoxybenzyl)-3-(3′,4′-methylenedioxybenzoyl)butyrolactone Dithiane (6a) (Michael-Alkylation Procedure).** To a stirred solution of 2.40 g (10.0 mmol) of piperonal dithiane in 20 mL of dry THF maintained under a nitrogen atmosphere at −78 °C was added a solution of 4.35 mL (10.0 mmol, 2.3 M) of n-butyllithium in hexane. The resulting orange solution was stirred for 0.5 h before addition of 0.84 g (10.0 mmol) of 2-butenolide dissolved in 2 mL of THF. The reaction mixture was stirred for 0.5 h and then treated dropwise with a solution of 2.61 g (10.0 mmol) of 3,4,5-trimethoxybenzyl bromide and 1.80 mL (10.0 mmol) of HMPA dissolved in 5 mL of THF. The reaction mixture was slowly warmed to room temperature overnight followed by the addition of water. The reaction mixture was thoroughly extracted with ethyl acetate, and the extracts were combined, washed with water, and dried. Evaporation of the solvent left an orange gum. Crystallization from benzene afforded the lactone dithiane **6a** (86%) as fine white crystals: mp 146–146.5 °C; IR ($CHCl_3$) 1765, 1595, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.84 (2 H, m), 2.76 (8 H, m), 3.83 (9 H, s), 4.03 (1 H, d, J = 10 Hz), 4.64 (1 H, dd, J = 6, 10 Hz), 6.03 (2, H, s), 6.25 (2 H, s), 6.78 (1 H, d, J = 9 Hz), 7.35 (1 H, s), 7.46 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{25}H_{28}O_7S_2$: C, 59.50; H, 5.59; S, 12.71. Found: C, 59.32; H, 5.63; S, 12.75.

2-(3″,4″,5″-Trimethoxybenzyl)-3-(3′,4′-methylenedioxybenzoyl)butyrolactone (6d). To a stirred solution of 2 mL of 15% aqueous THF maintained under a nitrogen atmosphere was added 87 mg (0.40 mmol) of red mercuric oxide and 56 mg (0.40 mmol) of freshly distilled boron trifluoride etherate. A solution of 100 mg (0.20 mmol) of butyrolactone dithiane **6a** dissolved in 10 mL of THF was added, and the reaction mixture was allowed to stir for 2 h at room temperature. Methylene chloride (20 mL) was added followed by filtration of the precipitated salts. The methylene chloride solution was successively washed to pH 10 with saturated sodium carbonate and to neutrality with saturated sodium chloride and dried. Evaporation of the solvent left a white solid. Recrystallization from methylene chloride–ether gave the keto lactone **6d** (95%) as flat white plates: mp 142–143.5 °C (lit.[18] 140–143 °C); IR ($CHCl_3$) 1785, 1680 cm^{-1}; NMR ($CDCl_3$) δ 3.07 (2 H, m), 3.56 (2 H, m), 3.73 (6 H, s), 3.78 (3 H, s), 4.31 (2 H, m), 6.05 (2 H, s), 6.32 (2 H, s), 6.83 (1 H, d, J = 10 Hz), 7.31 (3 H, m).

5-Oxopodorhizol Dithiane (6b) and 5-Oxoepipodorhizol Dithiane (6c). To a stirred solution of 2.40 g (10.0 mmol) of piperonal

dithiane dissolved in 20 mL of dry THF maintained under a nitrogen atmosphere at −78 °C was added a solution of 4.6 mL (10.2 mmol, 2.1 M) of *n*-butyllithium in hexane. The resulting orange solution was stirred for 0.5 h followed by the addition of 0.84 g (10.0 mmol) of 2-butenolide in 2 mL of dry THF. The reaction mixture was stirred for 0.5 h and then treated with 1.96 g (10.0 mmol) of 3,4,5-trimethoxybenzaldehyde[41] in 5 mL of THF. After an additional 2 h the reaction mixture was quenched with 10% acetic acid and allowed to warm to ambient temperature. Ethyl acetate was added, and the resulting organic phase was washed with water and dried. The solution was concentrated on a steam bath and, upon cooling, crystallization occurred yielding fine white needles (93%) consisting of a 52:48 diastereomeric mixture of **6b** and **6c** as shown by analytical HPLC. Fractional crystallization from ethyl acetate gave 2.47 g (47%) of hydroxylactone **6b**: mp 205–206 °C; IR ($CHCl_3$) 1755, 1590, 1490 cm^{-1}; NMR ($CDCl_3$) δ 1.82 (2 H, m), 2.82 (6 H, m), 3.86 (9 H, s), 4.03 (1 H, m), 4.47 (1 H, m), 4.97 (1 H, d, J = 9.2 Hz), 5.16 (1 H, d, J = 2.0 Hz), 6.08 (2 H, d, J = 3.6 Hz), 6.37 (2 H, s), 6.66 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{25}H_{28}O_8S_2$: C, 57.67; H, 5.42; S, 12.32. Found: C, 57.61; H, 5.43; S, 12.26.

The mother liquors provided 1.85 g (36%) of the hydroxylactone **6c** (from ethyl acetate): mp 180–181 °C; IR ($CHCl_3$) 3500, 1760, 1590, 1480 cm^{-1}; NMR ($CDCl_3$) δ 1.85 (2 H, m), 2.91 (7 H, m), 3.88 (9 H, s), 4.05 (1 H, m), 4.69 (1 H, d, J = 9.9 Hz), 4.77 (1 H, d, J = 6.8 Hz), 6.09 (2 H, d, J = 13.5 Hz), 6.52 (2 H, s), 6.84 (1 H, d, J = 7.9 Hz), 7.35 (1 H, s), 7.48 (1 H, d, J = 7.9 Hz).

Anal. Calcd for $C_{25}H_{28}O_8S_2$: C, 57.67; H, 5.42; S, 12.32. Found: C, 57.51; H, 5.44; S, 12.18.

(±)-Podorhizol (4a). A suspension of 8 mL of W-2 Raney nickel and 1.04 g (2.0 mmol) of 5-oxopodorhizol dithiane (**6b**) in 60 mL of absolute ethanol was refluxed for 2 h under a nitrogen atmosphere. The cooled reaction mixture was filtered through Celite and evaporated. The residue was passed through a short silica gel column employing ether as the eluent. Evaporation of the solvent and trituration of the residue from diisopropyl ether afforded an amorphous white solid. Recrystallization from ether provided lactone **4a** (72%) as fine white crystals, identical in all respects (IR, NMR, TLC, HPLC) with a natural sample of (−)-podorhizol:[42] mp 125–126 °C: IR ($CHCl_3$) 3500, 1760, 1595, 1490 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (1 H, m), 2.48 (1 H, m), 2.61 (1 H, m), 2.81 (1 H, m), 3.83 (9 H, s), 3.97 (1 H, m), 4.39 (1 H, m), 5.27 (1 H, d, J = 2.2 Hz), 5.92 (2 H, d, J = 9.2 Hz), 6.23 (1 H, s), 6.31 (1 H, d, J = 7.7 Hz), 6.47 (2 H, s), 6.59 (1 H, d, J = 7.7 Hz).

Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.46; H, 5.81.

(±)-Epipodorhizol (4b). In the manner described (vide supra), 0.40 g (0.80 mmol) of dithiane **6c** gave, upon crystallization from ethanol, lactone **4b** (74%) as white plates: mp 133.5–134.5 °C; IR ($CHCl_3$) 3500, 1750, 1590, 1490 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (3 H, m), 2.45 (1, H, m), 2.60 (1 H, m), 3.83 (3 H, s), 3.89 (6 H, s), 4.06 (2 H, m), 4.81 (1 H, d, J = 6.6 Hz). 5.92 (2 H, s), 6.34 (2 H, m), 6.65 (3 H, m).

Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.48; H, 5.84.

(±)-Isodeoxypodophyllotoxone (12a). To a stirred solution of 42 mg (0.10 mmol) of (±)-podorhizol (**4a**) dissolved in 10 mL of methylene chloride maintained under a nitrogen atmosphere at 25 °C was added 0.12 mL (1.0 mmol) of stannic chloride. The clear solution was stirred for 1 h, poured into saturated sodium bicarbonate solution, and extracted with methylene chloride. The combined extracts were dried and evaporated, affording a white powder which was homogeneous by high-resolution NMR and HPLC. Crystallization from chloroform–ether provided the lactone **12a** (78%) as fine white crystals: mp 256.5–257 °C (lit.[25] 255–256 °C); IR ($CHCl_3$) 2925, 1785, 1485 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (2 H, m), 2.94 (2 H, m), 3.82 (6 H, s), 3.85 (3 H, s), 4.01 (3 H, m), 4.52 (1 H, m), 5.89 (2 H, d, J = 2.9 Hz), 6.35 (1 H, s), 6.41 (2 H, s), 6.60 (1 H, s).

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.30; H, 5.59.

(±)-Isopodophyllotoxone Dithiane (12i). To a stirred solution of 0.52 g (1.0 mmol) of 5-oxopodorhizol dithiane (**6b**) dissolved in 25 mL of methylene chloride maintained under a nitrogen atmosphere at 25 °C was added 0.12 mL (1.0 mmol) of stannic chloride. The clear solution was stirred for 1 h, poured into saturated sodium bicarbonate solution, and extracted with methylene chloride. The combined extracts were dried and evaporated, providing a white solid which was diastereomerically pure as determined by high-resolution NMR and HPLC. Recrystallization from chloroform–ether afforded the dithiane **12i** (90%) as fine white crystals: mp 290–300 °C dec; IR ($CHCl_3$) 2930, 1785, 1505 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (1 H, m), 2.24 (1 H, m), 2.87 (2 H, m), 3.01 (2 H, m), 3.23 (1 H, m), 3.42 (1 H, dd, J = 11, 13.9 Hz), 3.82 (6 H, s), 3.84 (3 H, s), 4.01 (1 H, d, J = 11 Hz), 4.54 (1 H, dd, J = 8, 11 Hz), 4.72 (1 H, t), 5.93 (2 H, s), 6.27 (1 H, s), 6.43 (2 H, s).

Anal. Calcd for $C_{25}H_{26}O_7S_2$: C, 59.74; H, 5.21; S, 12.76. Found: C, 59.49; H, 5.31; S, 12.63.

(±)-Isopodophyllotoxone (12c). To a stirred solution of 1.14 g (5.0 mmol) of *N*-iodosuccinimide in 10 mL of 10% aqueous acetone cooled in an ice–water bath (0–5 °C) was added 602 mg (1.2 mmol) of isopodophyllotoxone dithiane **12i** dissolved in 50 mL of acetone. The deep red reaction mixture was slowly warmed to 25 °C over 2 h, followed by the addition of 10 mL of aqueous sodium sulfite solution. The acetone was evaporated in vacuo, and the aqueous residue was extracted with ethyl acetate. The combined extracts were washed with water and dried. Evaporation of the solvent and crystallization from chloroform–ether provided the keto lactone **12c** (68%) as fine white crystals: mp 223–225 °C; IR ($CHCl_3$) 2950, 1780, 1695, 1480 cm^{-1}; NMR ($CDCl_3$) δ 3.06 (1 H, dd, J = 11, 15.3 Hz), 3.41 (1 H, m), 3.82 (6 H, s), 3.87 (3 H, s), 4.23 (1 H, d, J = 11 Hz), 4.44 (1 H, t, J = 9.9 Hz), 4.64 (1 H, dd, J = 9.2, 9.9 Hz), 6.02 (2 H, s), 6.39 (3 H, brd s), 7.46 (1 H, s).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 63.87; H, 4.93.

1,2-Dihydro-3-hydroxymethyl-4-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxy-2-naphthoic Acid γ-Lactone (9). A stirred solution of 504 mg (1.0 mmol) of lactone dithiane **6a** dissolved in 50 mL of 10% trifluoroacetic acid–methylene chloride maintained under a nitrogen atmosphere was cooled to −20 °C. The temperature was not allowed to drop below −25 °C as the trifluoroacetic acid froze and precipitated from solution. A solution of 1.05 g (3.0 mmol) of manganese(III) tris(acetylacetonate) (MTA[43]) dissolved in 15 mL of methylene chloride was added rapidly to the dithiane solution. Upon addition of the MTA the reaction mixture became a brilliant blue which slowly changed to dark green as excess MTA was added. The solution was stirred for 1 h, zinc dust was added, and the reaction mixture was warmed to room temperature. The solvent was removed under reduced pressure. The residue was triturated with methylene chloride and filtered. The filtrate was washed with saturated sodium bicarbonate solution and water, and dried. Evaporation of the solvent and acetylacetone left a white foam. Crystallization from ether–chloroform afforded the dihydronaphthalene lactone **9** (50%) as needles: mp 180–182 °C; IR ($CHCl_3$) 1770, 1220 cm^{-1}; NMR ($CDCl)_3$ δ 2.97 (2 H, m), 3.35 (3 H, s), 3.79 (3 H, s), 3.82 (3 H, s), 4.71 (1 H, dd, J = 3.5, 16 Hz), 5.12 (1 H, dd, J = 3.5, 16 Hz), 6.00 (2 H, s), 6.65 (3 H, m), 6.83 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.62; H, 5.09.

(*E*)-2-(3″,4″,5″-Trimethoxybenzylidene)-3-(3′-4′-methylenedioxybenzoyl)butyrolactone (10). To a stirred solution of 352 mg (1.0 mmol) of manganese(III) tris(acetylacetonate) dissolved in 40 mL of 30% trifluoroacetic acid–methylene chloride was added dropwise a solution of 103 mg (0.25 mmol) of keto lactone **6d** dissolved in 1 mL of methylene chloride. The reaction mixture was stirred for 12 h, zinc dust was added, and the solvent was evaporated. The residue was dissolved in methylene chloride, filtered, washed with water, and dried. Evaporation of the solvent and acetylacetone left a dark brown foam which was preabsorbed on silica gel (1 g) and chromatographed. Elution with 1:1 ether–hexane gave a yellow powder. Crystallization from ethanol afforded 30% of the benzylidene lactone (**10**) as fine yellow crystals: mp 177–178 °C; IR ($CHCl_3$) 2960, 1750, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.59 (6 H, s), 3.82 (3 H, s), 4.39 (1 H, dd, J = 3, 9 Hz), 4.73 (1 H, t, J = 9.5 Hz), 5.13 (1 H, d, J = 9.5 Hz), 6.10 (2 H, s), 6.51 (2 H, s), 6.91 (1 H, d, J = 8 Hz) 7.42 (1 H, s), 7.54 (1 H, d, J = 8 Hz), 7.72 (1 H, d, J = 2.2 Hz).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 63.84; H, 4.86.

1,2β,3α,4β-Tetrahydro-3-hydroxymethyl-4-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxy-2-naphthoic Acid γ-Lactone (11). To a stirred suspension of 828 mg (2.0 mmol) of keto lactone **6d** in 40 mL of absolute methanol cooled in an ice–water bath (0–5 °C) was added 150 mg (4.0 mmol) of sodium borohydride. The reaction mixture was stirred for 3 h, during which time the solution became homogeneous. Dilute hydrochloric acid (1%) was added until the reaction mixture was acidic, and the solvent was evaporated at room temperature. The aqueous solution was extracted with methylene chloride. The organic extracts were combined, washed with water, and dried. Removal of the solvent afforded lactone alcohol **6e** as a foam (99%). This product was used without further purification: IR ($CHCl_3$) 3500, 1770 cm^{-1}; NMR ($CDCl_3$) δ 2.69 (4 H, m), 3.82 (9 H, s), 3.93 (2 H, d, J = 8 Hz), 4.61 (1 H, d, J = 6 Hz), 6.00 (2 H, s), 6.43 (2 H, s), 6.80 (3 H, s).

A solution of 832 mg (2.0 mmol) of lactone alcohol **6e** dissolved in 5 mL of methylene chloride was added dropwise to 40 mL of 10%

trifluoroacetic acid–methylene chloride solution at 25 °C maintained under a nitrogen atmosphere. After stirring for 3 h the solvent was evaporated, and the residue was dissolved in chloroform and filtered, providing the tetrahydronaphthalene lactone (**11**, 90%) upon recrystallization from benzene–ether: mp 218.5–219.5 °C; IR ($CHCl_3$) 2960, 1780, 1495, 1125 cm^{-1}; NMR ($CDCl_3$) δ 2.41 (2 H, m), 3.07 (1 H, m), 3.20 (3 H, s), 3.74 (3 H, s), 3.87 (3 H, s), 3.95 (1 H, d, J = 15.4 Hz), 4.07 (1 H, d, J = 15.4 Hz), 4.19 (1 H, m), 5.93 (2 H, s), 6.58 (3 H, m), 6.73 (1 H, d, J = 7.7 Hz).

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.32; H, 5.60.

α-Methyl-6-bromopiperonyl Alcohol. Methylmagnesium bromide was prepared from 6.08 g (0.25 mol) of magnesium turnings and 28.50 g (17 mL, 0.30 mol) of methyl bromide in 200 mL of ether maintained under a nitrogen atmosphere. To this solution was added 45.80 g (0.20 mol) of 6-bromopiperonal (**13**) in small portions. After completion of the addition the reaction mixture was refluxed for 2 h, cooled, and then carefully poured into 75 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was extracted well with ether. The combined organic extracts were washed once with water, dried, and evaporated, affording a white solid. Crystallization from ether–hexane gave the alcohol as fluffy white crystals (93%): mp 53.5–54 °C; IR ($CHCl_3$) 3440, 3075, 2900, 1470, 1220, 1035 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (3 H, d, J = 6 Hz), 5.14 (1 H, q, J = 6 Hz), 5.95 (2 H, s), 6.92 (1 H, s), 7.06 (1 H, s).

Anal. Calcd for $C_9H_9O_3Br$: C, 44.11; H, 3.70; Br, 32.60. Found: C, 44.05; H, 3.72; Br, 32.53.

α-Methyl-6-iodopiperonyl Alcohol (14). To a stirred solution of 2.45 g (10.0 mmol) of the above bromo alcohol in 50 mL of dry THF under a nitrogen atmosphere and cooled to −78 °C was added a solution of 9 mL (21.0 mmol, 2.34 M) of n-butyllithium in hexane. The faint yellow solution was stirred for 0.5 h and then treated dropwise with a solution of 5.59 g (22.0 mmol) of iodine dissolved in 15 mL of THF. The iodine color was discharged immediately upon contact with the solution. At no time during the reaction was the temperature allowed to rise above −65 °C. After the addition was completed the cooling bath was removed, and the reaction mixture was quenched at 0 °C by the addition of 20 mL of saturated aqueous sodium sulfite solution. Ether and water were then added, the layers were separated, and the aqueous phase was extracted well with ether. The combined extracts were washed once with water, dried, and evaporated. The residue was crystallized from ether–hexane affording alcohol **14** (71%) as white crystals: mp 72–73 °C; IR ($CHCl_3$) 3440, 3075, 2900 1470, 1035 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (3 H, d, J = 6 Hz), 4.96 (1 H, q, J = 6 Hz), 5.94 (2 H, s), 7.06 (1 H, s), 7.17 (1 H, s).

Anal. Calcd for $C_9H_9O_3I$: C, 37.01; H, 3.11; I, 43.45. Found: C, 36.89; H, 3.15; I, 43.50.

3,4-Methylenedioxy-6-iodoacetophenone. To a well-stirred solution of 6.28 g (21.5 mmol) of iodo alcohol **14** dissolved in 50 mL of reagent grade acetone and cooled in an ice–water bath to 5 °C was added 6 mL (48 mequiv) of 8 N Jones reagent. After stirring for 0.5 h 3 mL of isopropyl alcohol was added, and the dark solution was warmed to 25 °C. Water was added and the acetone was evaporated. The aqueous phase was then extracted well with ether. The combined organic extracts were washed once with water and once with saturated sodium bicarbonate solution and dried. Removal of the solvent gave a brown residue. Two crystallizations from ether–hexane afforded the acetophenone (72%) as white crystals: mp 84.5–85 °C; IR ($CHCl_3$) 3025, 2910, 1690, 1475, 1380 cm^{-1}; NMR ($CDCl_3$) δ 2.85 (3 H, s), 6.05 (2 H, s), 7.06 (1 H, s), 7.38 (1 H, s).

Anal. Calcd for $C_9H_7O_3I$: C, 37.27; H, 2.43; I, 43.75. Found: C, 37.23; H, 2.45; I, 43.72.

α-Bromo-3,4-methylenedioxy-6-iodoacetophenone (15). To a solution of 2.90 g (10.0 mmol) of 3,4-methylenedioxy-6-iodoacetophenone in 50 mL of chloroform was added 1.76 g (11.0 mmol) of bromine followed by 1 drop of 48% hydrobromic acid. After a short induction period a vigorous reaction ensued as hydrogen bromide was evolved. The reaction mixture was stirred for 12 h at 25 °C with protection from moisture. Saturated aqueous sodium sulfite solution (10 mL) was added, the layers were separated, and the aqueous phase was extracted thoroughly with chloroform. The extracts were combined, washed once with water, and dried. Evaporation of the solvent afforded a dark oil which slowly solidified. Recrystallization from ether–pentane afforded the phenacyl bromide **15** (71%) as sparkling yellow crystals: mp 74.5–75 °C; IR ($CHCl_3$) 2910, 1690, 1475 1235 cm^{-1}; NMR ($CDCl_3$) δ 4.40 (2 H, s), 6.07 (2 H, s), 7.05 (1 H, s), 7.35 (1 H, s).

Anal. Calcd for $C_9H_6O_3BrI$: C, 29.30; H, 1.64; Br, 21.66; I, 34.40. Found: C, 29.31; H, 1.67; Br, 21.55; I, 34.26.

2-Iodo-3,4,5-trimethoxybenzyl Alcohol. To a stirred suspension of 14.34 g (45.0 mmol) of mercuric acetate and 8.92 g (45.0 mmol) of 3,4,5-trimethoxybenzyl alcohol (**16**) in 100 mL of methylene chloride was added dropwise 11.43 g (45.0 mmol) of iodine in 100 mL of the same solvent. The iodine color was discharged immediately upon contact with the solution. The reaction mixture was stirred for 3 h and filtered, and the precipitated salts were washed well with methylene chloride. The filtrate was washed with water and dried. Evaporation of the solvent left an oil contaminated with red mercuric iodide. The oil was taken up in boiling ether and filtered. Hexane was added to the filtrate, and the cloudy solution was allowed to cool slowly, affording the iodo alcohol as a white fluffy powder (76%). Recrystallization from hexane gave the iodo alcohol (70%) as long white crystals: mp 56.5–57.5 °C; IR ($CHCl_3$) 3450, 2950, 1105 cm^{-1}; NMR ($CDCl_3$) δ 3.88 (3 H, s), 3.90 (6 H, s), 4.66 (2 H, s), 6.97 (1 H, s).

Anal. Calcd for $C_{10}H_{13}O_4I$: C, 37.06; H, 4.04; I, 39.15. Found: C, 36.98; H, 4.02; I, 39.05.

2-Iodo-3,4,5-trimethoxybenzyl Chloride. To a mixture of 4.57 g (14.1 mmol) of 2-iodo-3,4,5-trimethoxybenzyl alcohol and 1.82 g (15.0 mmol) of *N,N*-dimethylaniline in 50 mL of dry benzene cooled in an ice-water bath to 5 °C was added dropwise 1.79 g (15.0 mmol) of thionyl chloride in 10 mL of benzene. The cooling bath was removed, and the dark solution was refluxed for 1 h. The reaction mixture was cooled, washed successively with water, 10% hydrochloric acid, saturated aqueous sodium bicarbonate, and water and dried. Evaporation of the solvent left an oil which solidified upon standing. Recrystallization from ether–hexane afforded the benzyl chloride (92%) as white prisms: mp 69–69.5 °C; IR ($CHCl_3$) 2950, 1330, 1105 cm^{-1}; NMR ($CDCl_3$) δ 3.92 (9 H, s), 4.74 (2 H, s), 6.96 (1 H, s).

Anal. Calcd for $C_{10}H_{12}O_3ClI$: C, 35.06; H, 3.53; Cl, 10.35; I, 37.05. Found: C, 35.15; H, 3.54; Cl, 10.29; I, 36.94.

Dimethyl 2-Iodo-3,4,5-trimethoxybenzylmalonate (17). To a suspension of 0.58 g (12.0 mmol) of sodium hydride (Alfa–Ventron, 50% dispersion in mineral oil) in 80 mL of THF under a nitrogen atmosphere was added 13.21 g (100 mmol) of distilled dimethyl malonate in 20 mL of THF. After the initial gas evolution had subsided the solution was refluxed for 0.5 h and then treated dropwise with a solution of 3.42 g (10 mmol) of 2-iodo-3,4,5-trimethoxybenzyl chloride in 20 mL of THF over a 2-h period. The reaction mixture was refluxed for 24 h and then cooled and acidified with 10% aqueous acetic acid. Ether and water were added, and the layers were separated. The organic phase was washed twice with water, once with brine, and dried. Evaporation of the solvent and excess dimethyl malonate (~5 mm with a heat gun) left a residual oil which solidified upon cooling. Recrystallization from ether–hexane afforded the benzyl malonate **17** (93%) as fine white needles: mp 49.5–51.5 °C; IR ($CHCl_3$) 2950, 1735, 1095 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (2 H, d, J = 4.5 Hz), 3.69 (6 H, s), 3.80 (3 H, s), 3.82 (3 H, s), 3.84 (3 H, s), 6.60 (1 H, s).

Anal. Calcd for $C_{15}H_{19}O_7I$: C, 41.11; H, 4.37; I, 28.96. Found: C, 41.08; H, 4.39; I, 28.87.

Dimethyl 2-Iodo-3,4,5-trimethoxybenzyl-3′,4′-methylenedioxy-6′-iodophenacylmalonate (18a). To a stirred solution of 3.16 g (7.2 mmol) of dimethyl 2-iodo-3,4,5-trimethoxybenzyl malonate (**17**) dissolved in 20 mL of dry THF under a nitrogen atmosphere was added 0.35 g (7.3 mmol) of sodium hydride (Alfa–Ventron, 50% dispersion in mineral oil). After the vigorous reaction had subsided the solution was refluxed for 0.5 h, cooled in an ice–water bath to 5 °C, and treated dropwise with a solution of 2.73 g (7.4 mmol) of α-bromo-3,4-methylenedioxy-6-iodoacetophenone (**15**) dissolved in 8 mL of THF. A white precipitate formed immediately upon addition of the phenacyl bromide. The reaction mixture was slowly warmed to 25 °C overnight. Water and ethyl acetate were added, and during extraction a heavy emulsion formed which was filtered through Celite. The organic phase was dried, and removal of the solvent left a yellow solid. Two recrystallizations from methylene chloride–ether gave the malonic ester **18a** (59%) as fine light yellow needles: mp 141–142 °C; IR ($CHCl_3$) 3020, 2960, 1735, 1695, 1220 cm^{-1}; NMR ($CDCl_3$) δ 3.56 (2 H, s), 3.62 (2 H, s), 3.78 (6 H, s), 3.83 (3 H, s), 3.85 (6 H, s), 6.02 (2 H, s), 6.57 (1 H, s), 7.03 (1 H, s), 7.35 (1 H, s).

Anal. Calcd for $C_{24}H_{24}O_{10}I_2$: C, 39.69; H, 3.33; I, 34.95. Found: C, 39.69; H, 3.35; I, 35.01.

Dimer 18d. A mixture of 0.20 g (0.28 mmol) of dimethyl 2-iodo-3,4,5-trimethoxybenzyl-3′,4′-methylenedioxy-6′-iodophenacylmalonate (**18a**) and 0.58 g (2.0 mmol) of cuprous(I) triflate[33] in 10 mL of dry DMF was stirred and heated at 100 °C under a nitrogen atmosphere for 16 h. The reaction mixture was then cooled, and the solvent was evaporated at 5 mm with the aid of a heat gun. The residue was preabsorbed on silica gel, and elution from a silica gel column (10/1) with ether afforded a solid (70 mg). The solid was further purified using (GLC (64 × 10 cm Merck 60H silica gel column eluted with 30% ethyl acetate–benzene, flow rate 1 mL/min). Crystallization of

the solid from ether–chloroform afforded dimer **18d** (48%) as white prisms: mp 179–180 °C; IR ($CHCl_3$) 2950, 1735, 1685, 1475 cm^{-1}; NMR ($CDCl_3$) δ 3.23 (4, h, s), 3.56 (4 H, s), 3.63 (12 H, s), 3.71 (6 H, s), 3.85 (12 H, s), 6.02 (4 H, s), 6.47 (2 H, s), 6.50 (2 H, s), 7.19 (2 H, s).

Anal. Calcd for $C_{48}H_{48}O_{20}I_2$: C, 48.06; H, 4.04. Found: C, 47.99; H, 4.19.

Phosphonate 18e. A mixture of 0.363 g (0.50 mmol) of dimethyl 2-iodo-3,4,5-trimethoxybenzyl-3′,4′-methylenedioxy-6′-iodophenacylmalonate (**18a**) and 0.893 g (2.50 mmol) of cuprous iodide–triethyl phosphite complex[44] in 15 mL of dry DMF was heated at 100 °C for 16 h with stirring under a nitrogen atmosphere. The reaction mixture was cooled, and the solvent was evaporated at 5 mm with the aid of a heat gun. The residue was chromatographed on silica gel (20/1), and elution with 30% ether–hexane gave the unreacted cuprous iodide–triethyl phosphite complex. Elution with ether afforded an oil which slowly crystallized. Recrystallization from ether afforded the analytically pure phosphonate **18e** (89%) as fine white needles: mp 128.5–129.5 °C; IR ($CHCl_3$) 2975, 1730, 1245, 1030 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (6 H, t, J = 7.5 Hz), 3.62 (2 H, s), 3.71 (2 H, s), 3.76 (9 H, s), 3.84 (6 H, s), 4.14 (4 H, qt, J = 7.5 Hz), 6.07 (2 H, s), 6.77 (1 H, s), 6.95 (1 H, d, J = 4.5 Hz), 7.37 (1 H, d, J = 12 Hz).

Anal. Calcd for $C_{28}H_{34}IO_{13}P$: C, 45.66; H, 4.65; I, 17.23. Found: C, 45.69; H, 4.68; I, 17.20.

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Registry No.—**4a,** 59366-91-5; **4b,** 59366-92-6; **6a,** 59311-34-1; **6b,** 59311-35-2; **6c,** 59366-93-7; **6d,** 59311-31-8; **6e,** 6267-80-7; **7b,** 59311-29-4; **7c,** 59311-30-7; **9,** 59311-33-0; **10,** 64490-54-6; **11,** 64490-55-7; **12a,** 64550-41-0; **12c,** 64550-42-1; **12i,** 64490-56-8; **13,** 15930-53-7; **14,** 64490-57-9; **15,** 64490-58-0; **16,** 3840-31-1; **17,** 64490-59-1; **18a,** 64490-60-4; **18d,** 64521-00-2; **18e,** 64521-01-3; piperonal dithiane, 56579-86-3; 2-butenolide, 497-23-4; 3,4,5-trimethoxybenzyl bromide, 21852-50-6; 3,4,5-trimethoxybenzaldehyde, 86-81-7; MTA, 14284-89-0; α-methyl-6-bromopipenonyl alcohol, 64490-44-4; 3,4-methylenedioxy-6-iodoacetophenone, 61599-79-9; isopropyl alcohol, 67-63-0; 2-iodo-3,4,5-trimethoxybenzyl alcohol, 64490-45-5; 2-iodo-3,4,5-trimethoxybenzyl chloride, 64490-46-6; thionyl chloride, 7719-09-7; dimethyl malonate, 108-59-8; cuprous iodide–triethyl phosphite complex, 4221-63-7.

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Chemistry of Phosphorous Acid: New Routes to Phosphonic Acids and Phosphate Esters

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Imines derived from aryl aldehydes, when heated with phosphorous acid in the absence of solvent, yield α-amino phosphonic acids (**6**). Imines from aliphatic aldehydes give only moderate yields of phosphonic acids together with amines from reduction of the imines. Phosphorous acid can give exclusively phosphonic acids, by addition of strong acid, or exclusively reduction, by addition of base (Et_3N) when reacted with imines. Enamines are readily reduced with phosphorous acid and, in the presence of an alcohol phosphoric acid monoesters are produced. Aqueous formaldehyde and phosphorous acid methylate amines in a procedure analogous to the Eshweiler–Clark method.

Although many phosphorus compounds are recognized as important reagents in organic chemistry, phosphorous acid itself has been almost neglected. Probably the most significant use is in the preparation of phosphonic acid chelating agents.[1,2] Acylation of phosphorous acid[3] to hydroxyethylidenediphosphonic acid and the Mannich-type reaction involving phosphorous acid, amine, and formaldehyde[2] are examples. The Mannich-type procedure is applicable to a wide range of primary and secondary aliphatic amines.

$$>NH + HCHO + HP(=O)(OH)_2 \xrightarrow{HCl} >NCH_2P(=O)(OH)_2 \quad (1)$$

This reaction only proceeds efficiently when performed under strongly acidic conditions which, in practice, is provided by an excess of hydrochloric acid. Another drawback to this procedure, in addition to the requirement for low pH, is that only formaldehyde can be used as the carbonyl reactant.[4] The present study was undertaken in an attempt to find conditions which would allow the use of a variety of carbonyl compounds. As discussed below, conditions were discovered which extended the scope of the α-amino phosphonic acid synthesis and which also uncovered high-yield reduction processes.

Results

Phosphonic Acids. As indicated above, the Mannich-type procedure of Moedritzer and Irani[2] is only applicable to the synthesis of aminomethylenephosphonic acids. A recent report[5] that the *N*-benzyl-α-aminophosphonic acids **2b–d** could be prepared by this procedure appears to be in error. A careful examination of the reaction mixture failed to reveal even trace amounts of these phosphonic acids.[4b] Furthermore, authentic samples of the acids **2b–d** exhibited properties (^1H and ^{13}C NMR spectra, dissociation constants) consistent with expectation but significantly different from those reported by Szczepaniak and Siepak.[5]

$$PhCH_2NH_2 + \underset{\mathbf{1}}{\overset{R_1}{\underset{R_2}{>}}C=O} + HP(OH)_2 \longrightarrow \underset{\mathbf{2}}{PhCH_2NHC(R_1)(R_2)P(=O)(OH)_2}$$

a, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = H$; $R_2 = CH_2CH_3$
d, $R_1 = CH_3$; $R_2 = CH_2CH_3$

The addition of hypophosphorous acid (H_3PO_2) to a variety of amines in solvents such as ethanol (eq 2) has been known for a number of years.[6] Attempts to carry out the addition of phosphorous acid to imines under similar conditions were unsuccessful, but nevertheless it seemed reasonable to assume that conditions could be found which would allow such an addition. In fact, this was realized by simply heating equimolar amounts of imine and phosphorous acid in the absence of solvent. For example, *N*-benzylidenebenzylamine (**3**) when heated with phosphorous acid gave an almost quantitative yield of *N*-benzyl-α-aminobenzylphosphonic acid (**4**). Solid phosphorous acid was added to the imine and as the temperature was raised to 70–80 °C a homogeneous liquid was obtained. Further heating to 100–115 °C induced a vigorous exothermic reaction which was complete in a few minutes. Table I lists a number of phosphonic acids obtained by this procedure. Previous preparations of structures such as **4** had been effected by adding dialkyl phosphonates to imines, such as **3**, followed by hydrolysis.[7] The addition of phosphorous acid to 3,4-dihydroisoquinoline (**7**) to yield 1,2,3,4-tetrahydroisoquinoline-1-phosphonic acid (**8**) is a further example.

$$R_1N=C(R_2)(R_3) + H_3PO_2 \longrightarrow R_1NC(R_2)(H)(R_3)P(=O)(OH) \quad (2)$$

$$PhCH_2N=CHPh + HP(=O)(OH)_2 \longrightarrow \underset{\mathbf{4}}{PhCH_2NHCHPh(P(=O)(OH)_2)}$$
(**3**)

Imines derived from aliphatic aldehydes or dialkyl ketones give much lower yields of phosphonic acids than those derived from aryl aldehydes. In these cases it was found that reduction of the imine to the corresponding amine was a competing reaction.

Reduction Reactions of Phosphorous Acid. The reducing properties of phosphorous acid are quite well known, for

Table I. α-Aminophosphonic Acids

$$\underset{\mathbf{5}}{R_1N=C(R_2)(R_3)} + HP(OH)_2 \longrightarrow \underset{\mathbf{6}}{R_1NC(R_2)(H)P(=O)(OH)_2}$$

Compd	R_1	R_2	R_3	Yield, %
a	$PhCH_2$	Ph	H	98
b	CH_3	Ph	H	61
c	CH_3CH_2	Ph	H	68
d	t-C_4H_9	Ph	H	40
e	$PhCH_2$	p-ClC_6H_4	H	87
f	$PhCH_2$	$-CH(CH_3)_2$	H	40
g	$PhCH_2$	o-HOC_6H_4	H	10

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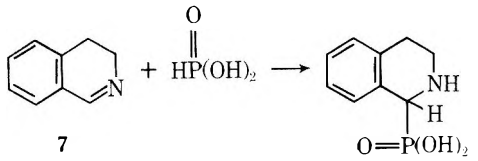
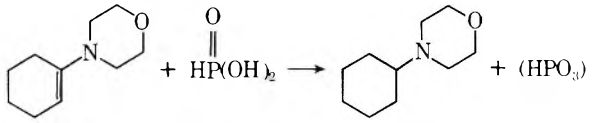


7 8

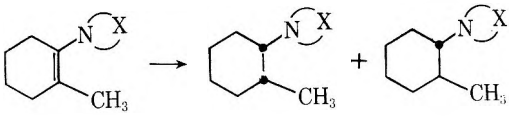
example, in the reduction of halogens to halide ions.[8] However, as far as can be ascertained, there are no reports in the literature of the use of phosphorous acid as a reducing reagent in organic chemistry. The reaction of the imine **5f** with phosphorous acid, in which the competing pathways of addition and reduction were observed, suggested that under appropriate conditions reduction could become predominant. In fact, when equimolar amounts of 1-morpholinocyclohexene (**9**) and phosphorous acid were heated to 100 °C a vigorous reaction ensued which gave the reduction product **10** in 91%



9 10

yield. Similar results were obtained with morpholinocyclopentene. Enamines derived from aldehydes such as isobutyraldehyde were also reduced, although in lower yield. An examination of the ^{31}P NMR spectra of the reaction mixtures from the enamine reductions provides convincing evidence for the fate of the phosphorous acid. The major absorption occurs at +22 ppm (relative to 85% H_3PO_4) assigned to trimetaphosphate (minor absorption at 0 ppm). By carrying out the reduction in the presence of an alcohol, such as butanol, butyl phosphate is obtained, but no ^{31}P NMR absorption is observed at +22 ppm. On the basis of these results, it can be claimed that the combination of enamine and phosphorous acid is a new phosphorylating reagent. Phosphorylation of alcohols using phosphorous acid and an oxidizing agent, e.g., iodine[9] or mercuric ion,[10] has been reported by other workers.

In light of the similarity in reducing properties of phosphorous acid and formic acid noted by Van Wazer,[8] it was of interest to compare these reagents in the reduction of the enamines **11a** and **11b**, derived from 2-methylcyclohexanone.



11 12 13

a, X = $-(CH_2)_4-$
b, X = $-(CH_2)_2O(CH_2)_2-$

Madsen and Iversen have recently reported that formic acid reduces these or related enamines with a high degree of stereoselectivity.[11] The results in Table II show that phosphorous acid is slightly less stereoselective than formic acid, a somewhat surprising result in view of the apparent larger size of the phosphorous acid.

In an investigation of the effect of reaction conditions on the reduction process, it was found that heating imine **3** with phosphorous acid in the presence of triethylamine dramatically altered the course of the reaction. Under these conditions no phosphonic acid **4** was formed, but instead an efficient reduction reaction yielding dibenzylamine (>95%) took place. The course of the reaction of imine **5f** with phosphorous acid was similarly influenced by added acid or amine as summarized in Table III.

Table II. Reduction of Enamines 11a and 11b

Enamine	Reducing agent	Yield, %	Ratio of cis/trans[12] (12/13)
11a	Phosphorous acid	85	75:25
11a	Formic acid	87	85:15[11]
11b	Phosphorous acid	64	81:19
11b	Formic acid	50	87:13

Table III. Effect of Added Amine or Acid on Imine/HP(O)(OH)$_2$ Reactions

Imine (equiv)	H_3PO_3, equiv	Additive (equiv)	Products (equiv)
3 (1)	1	None	Phosphonic acid **4** (0.95)
3 (1)	1	Et_3N (1)	Dibenzylamine (0.95)
5f (1)	1	None	Phosphonic acid (0.41), amine (0.5)
5f (1)	1	Et_3N (1)	Amine (0.72)
5f (1)	1	TsOH (1)	Phosphonic acid (0.9)

Table IV. *N*-Methylated Amines via Reductive Methylation

	Yield, %	
Amine	HP(O)(OH)$_2$/formaldehyde	Eshweiler–Clark[13]
Piperidine	40	80
Morpholine	54	
Cyclohexylamine	55	
Benzylamine	72	80

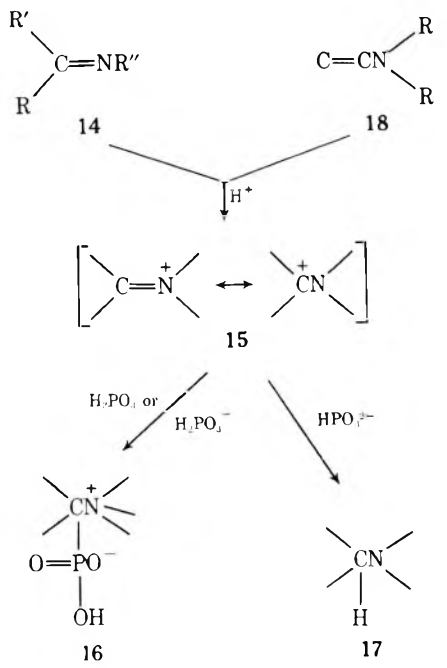
Attempts to carry out reductions with phosphorous acid in the presence of water were moderately successful. A number of amines were readily methylated in good yield upon heating with aqueous formaldehyde and phosphorous acid. Examples are presented in Table IV which also provide a comparison with the familiar Eshweiler–Clark method. A somewhat less efficient reductive alkylation was achieved by heating morpholine with benzaldehyde and aqueous phosphorous acid from which benzylmorpholine (18%) was obtained.

Discussion

On the basis of the results described in the preceding sections, it does not seem possible to provide a detailed mechanism for the phosphorous acid reactions. The addition of diesters of phosphorous acid (dialkyl phosphonates) to imines is generally considered to involve the phosphorus specie acting as a nucleophile.[14] Phosphorous acid may therefore be acting in a similar manner.

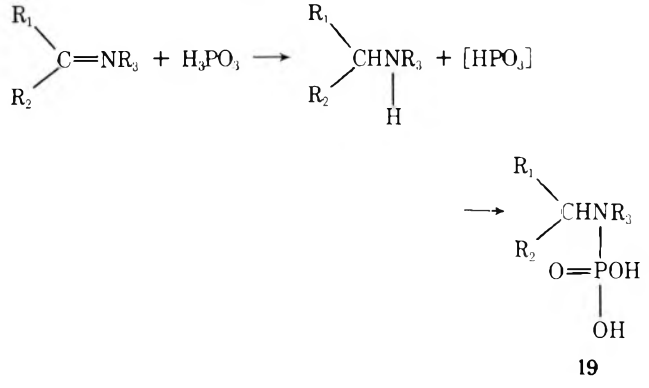
The initial step in the interaction between imines and phosphorous acid is postulated to be protonation of the imine[15] by the acid to yield **15** (Scheme I). In imines from aryl aldehydes (**14**, R = Ar), efficient addition of the phosphite monoanion to iminium cation **15** occurs to produce α-aminophosphonic acid **16**. When these same imines **14** (R = Ar) are heated with phosphorous acid and an equivalent of basic amine, the product is amine **17**. The phosphorous acid must be present as the dianion in this case. Reduction is not surprising in view of the oxidation potential of HPO_3^{2-}, 1.12 V,[8] comparable to that of formate ion, 1.01 V. An imine from an aliphatic aldehyde **14** (R^1 = alkyl) or an enamine **18** is considerably more basic than **14** (R = Ar),[16] so that some phosphite dianion could be formed from **14** (R = alkyl) and phosphorous acid. Although the concentration of dianion should be quite low, the results (see Table III) indicate that reduction is faster than addition. The formation of phosphonic acids **16** by reaction of imines and phosphorous acid in the presence

Scheme I



of strong acid (TsOH), which presumably protonates the imine, suggests that neutral phosphorous acid is sufficiently nucleophilic to add to **15**. This conclusion is supported by the results of Moedritzer and Irani,[2] which show that very low pH is *required* for the formaldehyde/amine/H_3PO_3 reaction (eq 1) to be efficient.

Under basic conditions where reduction of enamine or imine takes place it is postulated that metaphosphate (HPO_3) is formed. As mentioned above ^{31}P NMR evidence for the formation of trimetaphosphate and the phosphorylation of alcohols lead to this conclusion. When an imine is reduced, a secondary amine and metaphosphate are formed as primary products which can then interact to form the phosphoramidate **19**. Although isolation and characterization of **19** have



not been achieved, indirect evidence for its formation has been obtained. First a significant improvement in the isolated yield of secondary amines is obtained if the reaction mixture from reduction is heated with aqueous acid prior to basification and extraction and, secondly, ^{31}P NMR spectra suggest the presence of **19**.

Scheme I summarizes the chemistry involved in the reactions between phosphorous acid and imines or enamines. From a synthetic standpoint the important results are: (a) α-aminophosphonic acids are formed in high yield from imines and phosphorous acid under anhydrous acidic conditions; (b) imines and enamines are reduced by phosphorous acid under anhydrous basic conditions; and (c) phosphorous acid can also be used for phosphorylation or reductive methylation.

Experimental Section

Melting points are uncorrected. The elemental analyses were performed by Clark Microanalytical Laboratories and Petrolite Corporation, Analytical Section. ^1H NMR spectra were obtained with a Varian A-60 spectrometer, and ^{31}P and ^{13}C spectra with a Jeol FX-60 spectrometer operating at 24.15 and 15.04 MHz, respectively.

General Procedure for the Preparation of Phosphonic Acids. A mixture of imine (0.2 mol) and phosphorous acid (0.2 mol) was stirred with a mechanical stirrer and slowly heated to 75–80 °C, whereupon the reactants gave a homogeneous liquid. Further heating to 100–120 °C brought about a vigorous reaction resulting in a significant viscosity increase and an internal temperature of 140–160 °C. The source of heat was removed and water (100 mL) was added as the temperature reached 95–100 °C. The crude α-aminophosphonic acid is purified by crystallization or by ion exchange chromatography.

***N*-Benzyl-α-aminobenzylphosphonic Acid (6a).** The crude acid separated from water, mp 230–234 °C, in 98% yield. Recrystallization from acetic acid/water gave pure **6a**: mp 233–234 °C (lit.[7b] 233–236 °C); NMR (D_2O + NaOH) δ 3.67 (s, 2, CH_3N), 3.8 (d, 1, J = 16 Hz, CHP), 7.33 (s, 5, PhH), 7.45 (s, 5, PhH).

***N*-Methyl-α-aminobenzylphosphonic Acid (6b).** Upon cooling the aqueous solution of the crude reaction mixture the acid was obtained in 61% yield. Recrystallization from water gave pure acid **6b**: mp 242–245 °C (lit.[17] 255 °C dec); NMR (D_2O) δ 2.63 (s, 3, NCH_3), 4.05 (d, 1, J = 14 Hz, CHP), 7.50 (s, 5, PhH); ^{13}C NMR (D_2O) δ 33.7 (NCH_3), 65.1 (d, J = 125 Hz, CP).

Anal. Calcd for $C_8H_{12}NO_3P$: N, 6.97; P, 15.42. Found: N, 6.90; P, 15.52.

***N*-Ethyl-α-aminobenzylphosphonic Acid (6c).** The crude acid, mp 223–226 °C, was obtained in 68% yield. Recrystallization from water/ethanol gave pure phosphonic acid: mp 225–226 °C; NMR (D_2O) δ 1.25 (t, 3, J = 7 Hz, CH_3CH_2), 3.06 (q, 2, J = 7 Hz, CH_2CH_3), 4.35 (d, 1, J = 16 Hz, CHP), 7.50 (s, 5, PhH).

Anal. Calcd for $C_9H_{14}NO_3P$: C, 50.23; H, 6.51; N, 6.51; P, 14.42. Found: C, 50.68; H, 6.84; N, 6.60; P, 14.47.

***N*-*tert*-Butyl-α-aminobenzylphosphonic Acid (6d).** The crude acid was obtained in 80% yield. Recrystallization from aqueous ethanol gave pure acid **6d** (40%): mp 228–230 °C dec; NMR (D_2O) δ 1.33 (s, 9, CH_3), 4.63 (d, 1, J = 18 Hz, CHP), 7.60 (s, 5, PhH); ^{31}P NMR δ −10.1.

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.84; H, 7.68; N, 6.06; P, 12.60.

***N*-Benzyl-α-amino-(4-chlorobenzyl)phosphonic Acid (6e).** The crude acid, mp 226–230 °C, was obtained in 87% yield. Recrystallization from acetic acid/water gave pure acid **6e**, mp 227–230 °C.

Anal. Calcd for $C_{14}H_{15}ClNO_3PH_2O$: C, 50.98; H, 5.16; N, 4.35; P, 9.41. Found: C, 51.46; H, 5.39; N, 4.50; P, 9.53.

***N*-Benzyl-α-amino(2-hydroxybenzyl)phosphonic Acid (6g).**[18] The crude acid was purified by the procedure of Zon and Mastalerz[18] to yield the pure phosphonic acid in 10% yield, mp 277–280 °C. The identity of the acid was verified by comparison with an authentic sample prepared as described by Zon and Mastalerz:[18] NMR (D_2O + NaOH) δ 3.70 (s, 2, CH_2N), 4.30 (d, 1, J = 17 Hz, CHP), 6.7–7.5 (m, 9, ArH); ^{13}C NMR δ 52.9, 59.7 (d, J = 135 Hz), 117.6, 119.1, 128.4, 128.8, 129.0, 129.9, 131.2, 131.6; ^{31}P NMR δ −16.9.

1,2,3,4-Tetrahydroisoquinolyl-1-phosphonic Acid (8). The crude acid separated as pale yellow needles from water (60%). Recrystallization gave analytically pure acid: mp 256–258 °C; NMR (D_2O) δ 1.5–3.2 (m, 4, CH_2), 4.11 (d, 1, J = 17 Hz CHP), 7.2–7.3 (m, 4, ArH); ^{31}P NMR δ −15.9 (J_{PCH} = 17 Hz); ^{13}C NMR (D_2O) δ 28.8 (C_4), 40.7 (C_3), 57.0 (d, J = 126 Hz, C_1) 126.6–130.0.

Anal. Calcd for $C_9H_{12}NO_3P$: C, 50.70; H, 5.63; N, 6.57; P, 14.55. Found: C, 51.05; H, 5.99; N, 6.30; P, 14.74.

***N*-Benzyl-1-amino-2-methylpropylphosphonic Acid.** The imine (18.9 g, 0.12 mol) derived from isobutyraldehyde and benzylamine was reacted with phosphorous acid (9.6 g, 0.12 mol) by the general method described above, but a modified workup procedure was applied as follows. The reaction mass was cooled to 85 °C and dissolved in water (40 mL). Concentrated HCl (20 mL) was added and the solution heated at reflux for 30 min. After cooling, the solution was basified and extracted with ether to yield benzyl isobutylamine: 10.3 g (54%); NMR ($CDCl_3$) δ 0.89 (d, 6, J = 6 Hz, CH_3), 1.4–2.2 (m, 1, CH), 2.43 (d, 2, J = 7 Hz, CH_2CH), 3.75 (s, 2, CH_2Ph), 7.28 (s, 5, ArH); ^{13}C NMR ($CDCl_3$) δ 20.7, 28.4, 54.2, 57.6, 126.7, 128.0, 128.2, 140.9. The hydrochloride from ethanol had mp 183–184 °C (lit.[19] 175–176 °C).

The basic aqueous solution was reacidified, evaporated to dryness, and extracted with anhydrous ethanol. The ethanol extract yielded

N-benzyl-1-amino-2-methylpropylphosphonic acid: 13.4 g (41%); mp 100–103 °C; NMR (D_2O) δ 1.05 (d, 6, J = 6 Hz, CH_3), 2.0–2.5 (m, 1, $CH(CH_3)_2$), 2.48 (d of d, 1, J = 15, 5 Hz, PCH), 3.97 (s, 2, CH_2Ph), 7.50 (s, 5, ArH); ^{31}P NMR (D_2O) δ −10.7; ^{13}C NMR (D_2O) δ 22.1, 23.0, 30.6, 53.8, 65.5 (d, J = 132 Hz, CP), 132.7, 133.1, 133.5, 134.5.

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.54; H, 7.86; N, 5.42; P, 12.71.

Modification of the General Phosphonic Acid Procedure. (a) Effect of Added Acid. A mixture of the imine (**5f**) from isobutyraldehyde and benzylamine (0.1 mol), phosphorous acid (0.1 mol), and *p*-toluenesulfonic acid (0.1 mol) was heated with gentle stirring at 120–130 °C for 45 min. After cooling to 85 °C, water (35 mL) was added. ^{31}P NMR analysis of this solution showed one major peak at −12.9 ppm (phosphonic acid) and a minor peak at −4.7 ppm (phosphorous acid), but no evidence of phosphate. Ion exchange on Dowex 50-W and elution with water yielded *p*-toluenesulfonic acid. Elution with 5 N HCl yielded *N*-benzyl-1-amino-2-methylpropylphosphonic acid (**6f**) (90%), identical with that from the previous experiment.

(b) Effect of Added Base. A mixture of imine **5f** (0.13 mol), triethylamine (0.13 mol), and phosphorous acid (0.13 mol) was heated at 115–120 °C for 6 h. After cooling to 75 °C, water (45 mL) and HCl (40 mL) were added and the solution was heated at reflux before extraction of neutral and acidic components. Basification and extraction yielded *N*-benzylisobutylamine (15.9 g, 72%), bp 205–208 °C, identical with the sample above.

General Procedure for Reductive Methylations Using Formaldehyde/Phosphorous Acid. A solution of phosphorous acid (1 equiv) in 40% aqueous formaldehyde (1 equiv) was added dropwise to the amine (1 NH equiv) during 20–30 min with vigorous stirring and ice bath cooling to maintain a temperature of 15–25 °C. Following the addition, the reaction mixture was heated at reflux for 2 h. After cooling, the reaction mixture was basified and the amine recovered by ether extraction in the normal manner.

Benzyldimethylamine. Benzylamine was converted into benzyldimethylamine in 72% yield: bp 179–180 °C (lit.[20] 181 °C); picrate mp 88–89 °C (lit.[20] 93 °C); NMR ($CDCl_3$) δ 1.92 (s, 6, NCH_3), 3.12 (s, 2, CH_2Ph), 7.03 (s, 5, ArH).

Cyclohexyldimethylamine. Cyclohexyldimethylamine was obtained from cyclohexylamine in 55% yield: bp 156 °C (lit.[21] 159 °C); picrate mp 178–180 °C (lit.[21] 176–177 °C).

***N*-Methylmorpholine.** *N*-Methylmorpholine was obtained in 54% yield: bp 116 °C (lit.[20] 116–117 °C); picrate mp 224–226 °C (lit.[20] 225 °C); NMR ($CDCl_3$) δ 1.77 (s, 3, NCH_3), 2.07 (m, 4, NCH_2), 3.35 (m, 4, OCH_2).

***N*-Methylpiperidine.** Piperidine was converted into *N*-methylpiperidine in 40% yield: bp 106 °C (lit.[20] 107 °C); picrate mp 225–227 °C (lit.[20] 223–224 °C); NMR ($CDCl_3$) δ 1.52 (m, 6, CH_2), 2.26 (s, 3, NCH_3), 2.38 (m, 4, NCH_2).

Enamine Reductions. Preparation of *N*-Cyclohexylmorpholine (10). A mixture of morpholinocyclohexene (32.3 g, 0.19 mol) and phosphorous acid (15.9 g, 0.19 mol) was stirred and heated. As the temperature reached 90–100 °C, an exothermic reaction took place. The reaction mass was maintained at 95–100 °C for 30 min, cooled, diluted with water, basified, and extracted with ether. Evaporation of the ether extract yielded *N*-cyclohexylmorpholine (29.7 g, 91%): picrate mp 177–178 °C (lit.[22] 176–177 °C); NMR ($CDCl_3$) δ 1.0–2.2 (m, 11, CH_2, CH), 2.50 (m, 2, NCH_2), 3.66 (m, 2, OCH_2); ^{13}C NMR ($CDCl_3$) δ 25.7, 26.4, 29.0, 49.8, 63.6, 67.4.

***N*-Cyclopentylmorpholine.** A mixture of cyclopentenylmorpholine (30 g, 0.2 mol) and phosphorous acid (16.4 g, 0.2 mol) was stirred and heated. As the mixture reached 70–75 °C, an exothermic reaction ensued with a resulting viscosity increase. After heating at 100–105 °C for 30 min, the reaction mixture was dissolved in water, basified, and extracted with ether. Evaporation yielded *N*-cyclopentylmorpholine: 24 g (80%); picrate mp 163–164 °C (lit.[22] 159–162 °C); ^{13}C NMR ($CDCl_3$) δ 24.6, 30.0, 53.9, 68.0, 68.6.

1-Methyl-2-morpholinocyclohexane (12b and 13b). By the procedure described above the morpholine enamine of 2-methylcyclohexanone was reduced in 65% yield to a mixture of *cis*- and *trans*-1-methyl-2-morpholinocyclohexane (**12b** and **13b**): bp 105–106 °C (5.2 mm). GLC gives a cis/trans ratio of 81:19. Utilizing formic acid, a ratio of cis/trans of 87:13 was obtained.

1-Methyl-2-pyrrolidinocyclohexane (12a and 13a). The pyrrolidine enamine of 2-methylcyclohexanone was reduced with phosphorous acid as above to a cis/trans mixture of 1-methyl-1-pyrrolidinocyclohexane (**12a** and **13a**) in 85% yield: bp 85–87 °C (5.1 mm). GLC gave a cis/trans ratio of 75:25.

1-Isobutylpiperidine. The enamine from isobutyraldehyde and piperidine was reduced by the above method to yield 1-isobutylpiperidine (68%): bp 159–160 °C (lit.[23] 160–162 °C); NMR ($CDCl_3$) δ 1.07 (d, 6, J = 6 Hz, CH_3), 1.4–1.8 (m, 7, CH_2, CH), 2.0–2.5 (m, 6, NCH_2). The amine yielded a picrate, mp 145–146 °C (lit.[23] 144–145 °C).

Phosphorylation Using Phosphorous Acid. Phosphorylation of 1-Butanol. Phosphorous acid (8.2, 0.1 mol) was added to morpholinocyclohexene (16.6 g, 0.1 mol) in butanol (16 g, 0.216 mol), and the mixture was heated at 110 °C for 30 min. After the reaction, the mixture was dissolved in ethanol (30 mL) and ether (100 mL) was added. The ether phase was discarded and the ether-insoluble portion dissolved in water (50 mL). Passage of the aqueous solution through Dowex 50-W ion-exchange resin and elution with water yielded butyl phosphate (13.3 g, 86%). The monoanilinium salt from ethanol gave mp 133–135 °C (lit.[10a] 138–140 °C); NMR (D_2O) δ 0.93 (t, 3, J = 7 Hz, CH_3), 1.1–1.7 (m, 4, CH_2), 3.82 (q, 2, OCH_2), 7.47 (m, 5, PhH); ^{31}P NMR (D_2O) δ 0.5; ^{13}C NMR (D_2O) δ 14.2, 19.5, 33.2 (d, J = 7 Hz), 67.0 (d, J = 5, 5 Hz), 124.0, 130.2, 131.3. Elution with 4 N HCl yielded *N*-cyclohexylmorpholine as its hydrochloride (11 g, 66%).

Phosphorylation of Benzyl Alcohol. Following the above procedure, benzyl phosphate was obtained in 90% yield (based on phosphorous acid) upon elution from Dowex 50-W ion-exchange resin. The phosphate was characterized as its anilinium salt: mp 150–153 °C (from ethanol) (lit.[10a] mp 150–153 °C); ^{31}P NMR (D_2O) δ 0.3; ^{13}C NMR (D_2O) δ 68.3, 122.3, 127.6, 128.8, 129.3, 129.9, 131.2, 132.0.

***N*-Benzylmorpholine.** A mixture of benzaldehyde (24 g, 0.22 mol), morpholine (19.1 g, 0.22 mol), phosphorous acid (18.0 g, 0.22 mol), and water (75 mL) was heated under reflux for 8 h. The basic fraction was separated to yield *N*-benzylmorpholine (7.2 g, 18%): hydrochloride, from ethanol, mp 245–246 °C (lit.[20] 243 °C).

Anal. Calcd for $C_{11}H_{15}NOHCl$: N, 6.56; Cl^-, 16.63. Found: N, 6.30; Cl^-, 16.16.

***N*-Benzylcyclohexylamine.** Under the general conditions for phosphonic acid formation, the imine from cyclohexanone and benzylamine underwent mainly reduction. Distillation of the basic extract gave benzylamine (15%) and *N*-benzylcyclohexylamine (65%): bp 120–125 °C (3 mm); NMR ($CDCl_3$) δ 1.0–1.6 (m, 10, CH_2), 2.4 (m, 1, CHN), 3.67 (s, 2, CH_2Ph), 7.03 (s, 5, PhH); hydrochloride mp 252–254 °C (lit.[24] 252–253 °C).

Registry No.—**5a,** 780-25-6; **5b,** 622-29-7; **5c,** 6852-54-6; **5c,** 6852-58-0; **5e,** 13540-93-7; **5f,** 22483-21-2; **5g,** 886-08-8; **6a,** 25881-35-0; **6b,** 36032-68-5; **6c,** 64760-70-9; **6d,** 64760-69-6; **6e,** 64760-71-0; **6f,** 64760-72-1; **6g,** 61146-25-6; **7,** 3230-65-7; **8,** 64760-73-2; **9,** 670-80-4; **10,** 6425-41-8; **11a,** 5049-40-1; **11b,** 6127-98-6; **12a,** 36949-94-7; **12b,** 64760-74-3; **13a,** 36949-95-8; **13b,** 64760-75-4; isobutyraldehyde, 78-84-2; benzylamine, 100-46-9; benzylisobutylamine, 42882-36-0; cyclopentenylmorpholine, 936-52-7; benzyldimethylamine, 103-83-3; *N*-methylmorpholine, 109-02-4; morpholine, 110-91-8; piperidine, 110-89-4; *N*-methylpiperidine, 626-67-5; *N*-cyclopentylmorpholine, 39198-78-2; 1-piperido-2-methyl-prop-1-ene, 673-33-6; 1-isobutylpiperidine, 10315-89-6; butanol, 71-36-3; butylphosphonate aniline salt, 64760-76-5; benzyl alcohol, 100-51-6; benzylphosphonate aniline salt, 64760-77-6; benzaldehyde, 100-52-7; *N*-benzylmorpholine HCl, 64760-78-7; cyclohexanone, 108-94-1; *N*-benzylcyclohexylamine, 4383-25-9; phosphorous acid, 13598-36-2; cyclohexyldimethylamine, 98-94-2; cyclohexylamine, 108-91-8; butyl phosphonate, 16456-56-7; benzyl phosphonate, 10542-07-1.

Supplementary Material Available. Calculated ^{13}C spectra of 1-methyl-2-morpholinocyclohexane are presented in Table V (1 page). Ordering information is given on any current masthead page.

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Notes

N-Benzyl-α-amino Phosphonic Acids

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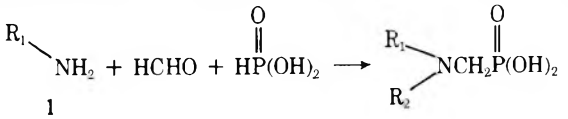
The Mannich-type reaction of amines with formaldehyde and phosphorous acid is a very useful procedure for the preparation of aminomethylenephosphonic acids.[1] One of the limitations of this procedure is that primary amines (**1**) treated with 1 equiv of formaldehyde and phosphorous acid yield a mixture of mono- and bis(methylenephosphonic) acids (**2a** and **2b**).[2] A further limitation appears to be in the choice of

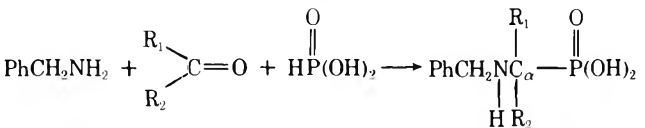


1 **2**

a, R_2 = H
b, R_2 = $CH_2P(=O)(OH)_2$

carbonyl component; all examples reported use formaldehyde with one exception in a patent.[3]

In light of the above, the recent report[4] that benzylamine reacts with a series of carbonyl compounds (**3a–d**) to yield



3 **4**

a, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_2CH_3$; $R_2 = H$
d, $R_1 = CH_2CH_3$; $R_2 = CH_3$

monophosphonic acids **4a–d** and, in particular, that best yields are obtained upon reacting 2 equiv of **3** and phosphorous acid for each equivalent of benzylamine is unexpected. Furthermore, the dissociation constants reported for these phosphonic acids are significantly different from those of other α-amino phosphonic acids.[2b] The present work was, therefore, undertaken in an attempt to resolve these discrepancies.

In our hands benzylamine heated with acetone, propionaldehyde or methyl ethyl ketone, and phosphorous acid by the procedure of Szczepaniak[4] yielded white crystalline products. The ^1H NMR spectra of these products showed only two peaks, at δ 4.2 and 7.5, in the ratio 2:5. Basification of these solids liberated benzylamine, showing that the solids were benzylamine salts. Careful examination of the mother liquors from the crystallization by ^{31}P NMR yielded no evidence for the presence of even traces of phosphonic acids. In the case of formaldehyde the only product isolated was the bis(methylenephosphonic) acid **2b** (R_1 = $PhCH_2$–).

Authentic samples of the phosphonic acids **4a–d** were obtained by hydrolysis of the corresponding ethyl or isopropyl esters **5a–d** prepared by the method of Fields.[5] In the hydrolysis of the esters **5b** and **5d**, some degradation was observed resulting in the recovery of benzylamine. The ^{13}C and ^{31}P NMR spectra of the acids **4a–d**, as shown in Table I, provided proof of structure together with other analytical data.

The dissociation constants of the acids **4a–d** were measured by potentiometric titration. Table II summarizes the results of our measurements and includes for comparison the results of Szczepaniak[4] and some other data from the literature for α-amino phosphonic acids.[6] It can be seen that the results from the present study are consonant with results from other workers.[6]

We conclude that the phosphonic acids **4a–d** cannot be prepared by the direct route from phosphorous acid and that the acids, when obtained by an authentic process, yield the expected acid dissociation constants.

Experimental Section

Melting points are uncorrected. The elemental analyses were performed by Clark Microanalytical Laboratories and Petrolite Corpo-

Table I. ^{31}P and ^{13}C NMR Data for α-Amino Phosphonic Acids

Registry no.	Compd	R_1	R_2	δ $^{31}P^a$	δ $^{13}C^b$ (J_{C-P}, Hz) C_α	R_1	R_2
49622-09-5	**4a**	H	H	−16.6	53.1 (138)		
49622-10-8	**4b**	CH_3	CH_3	−15.4	59.8 (136)	25.1	25.1
26067-66-3	**4c**	CH_2CH_3	H	−17.3	65.2 (135)	29.9, 18.5	
49622-12-0	**4d**	CH_2CH_3	CH_3	−14.8	62.9 (143)	26.9, 8.4 (6)	19.7

[a] Relative to 85% H_3PO_4 internal reference. [b] Relative to Me_4Si internal reference.

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Table II. Dissociation Constants of α-Amino Phosphonic Acids

Compd	pK_{a_1}	pK_{a_2}	Ref
4a	3.22	6.16	4
4a	5.40	10.10	This work
4b	3.66	6.29	4
4b	6.02	9.75	This work
4c	3.55	6.33	4
4c	6.00	10.70	This work
4d	3.65	6.23	4
4d	5.53	10.68	This work
$NH_2C(CH_3)_2P(=O)(OH)_2$	6.05	10.43	6
$NH_2CH(Ph)P(=O)(OH)_2$	5.60	9.50	6

ration, Analytical Section. ^1H NMR spectra were obtained with a Varian A-60 spectrometer, ^{31}P and ^{13}C spectra with a Jeol FX-60 spectrometer operating at 24.15 and 15.04 MHz, respectively.

***N*-Benzyliminobis(methylenephosphonic) Acid (2b, R_1 = $PhCH_2$–).** In precisely the manner described[4] benzylamine (0.1 mol) was reacted with phosphorous acid (0.2 mol) and formaldehyde (0.2 mol). The yield of white crystals, virtually insoluble in ethanol, was 14 g. Recrystallization from water yielded pure **2b** (R_1 = $PhCH_2$);[1] mp 257–258 °C; NMR (D_2O) (as sodium salt) δ 3.50 (d, 4, J = 12 Hz, NCH_2P), 4.85 (s, 2, $PhCH_2$), 7.62 (s, 5, PhH).

Anal. Calcd for $C_9H_{15}NO_6P_2$: N, 4.75; P, 21.02. Found: N, 4.64; P, 20.88.

***N*-Benzyl-α-aminomethylphosphonic Acid (4a).** Diethyl *N*-benzyl-α-aminomethylphosphonate (25.7 g, 0.1 mol) was heated under reflux in 18% hydrochloric acid (200 mL) for 2 h. Evaporation of the aqueous acid yielded a gum. Crystallization from ethanol/ether yielded **4a** as its hydrochloride: mp 272–274 °C; NMR (D_2O) δ 3.28 (d, 2, J = 13 Hz, NCH_2P), 4.37 (s, 2, $PhCH_2N$), 7.50 (s, 5, PhH).

Anal. Calcd for $C_8H_{12}NO_3PHCl$: C, 40.42; H, 5.47; N, 5.89; P, 13.05. Found: C, 40.64; H, 5.66; N, 5.63; P, 13.44.

***N*-Benzyl-2-amino-2-propylphosphonic Acid (4b).** Hydrolysis of the corresponding ethyl ester as described above yielded after crystallization the acid **4b**: mp 177–180 °C from ethanol; NMR (D_2O) δ 1.68 (d, 6, J = 12 Hz, CH_3CP), 4.44 (s, 2, $PhCH_2$), 7.55 (s, 5, PhH).

Anal. Calcd for $C_{10}H_{16}NO_3P$: C, 52.40; H, 6.99; N, 6.11; P, 13.54. Found: C, 52.69; H, 7.12; N, 5.78; P, 13.35.

***N*-Benzyl-1-amino-1-propylphosphonic Acid (4c).** As in the case of **4a**, the acid crystallized from ethanol/ether as its hydrochloride: mp 182–184 °C; NMR (D_2O) δ 1.10 (t, 3, J = 7 Hz, CH_3CH_2), 2.0 (m, 2, CH_2CH_3), 3.1–3.6 (m, 1, CHP), 4.43 (s, 2, CH_2Ph), 7.55 (s, 5, PhH).

Anal. Calcd. for $C_{10}H_{16}NO_3P$·HCl: N, 5.27; P, 11.68; Cl^-, 13.37. Found: N. 4.90; P, 11.76; Cl^-, 13.37.

Dissolution of the hydrochloride in ethanol and treatment with propylene oxide gave the free acid **4c**, mp 227–228 °C (lit.[7] mp 222–224 °C).

***N*-Benzyl-2-amino-2-butylphosphonic Acid (4d).** The acid was obtained from the corresponding ethyl ester as described above and crystallized from ethanol/ether: mp 125–128 °C; NMR (D_2O) δ 1.13 (t, 3, J = 7 Hz, CH_2CH_3), 1.60 (d, 3, J = 14 Hz, CH_3CP), 1.9–2.3 (m, 2, CH_2), 4.47 (s, 2, CH_2Ph), 7.57 (s, 5, PhH).

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.29; H, 7.40; N, 5.58; P, 12.25.

Registry No.—**2b**, 6056-53-7; 4a HCl, 64715-31-7; **4a** diethyl ester, 50917-70-9; **4b** diethyl ester, 64715-32-8; **4c** HCl, 64715-33-9; **4c** diethyl ester, 42274-96-4; 4d diethyl ester, 64740-22-3; benzylamine, 100-46-9; formaldehyde, 50-00-0; phosphorous acid, 13598-36-2.

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N-Iodosuccinimide for the Synthesis of Rose Oxide

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The use of *N*-iodosuccinimide (NIS) in the synthetic field is less explored than that of *N*-bromosuccinimide (NBS). Djerassi et al.[1,2] have found that NIS is incapable of performing certain free-radical chain iodinations typical of the radical chain brominations brought about by NBS. NIS has been shown to react with enol acetates derived from ketones to give iodo ketones.[2] The mechanism of the reaction seems to be ionic in nature. In another unusual free-radical iodination reaction characteristic of NIS, a vinylic proton is replaced by iodine.[3]

In the present note, we report the use of NIS in the synthesis of rose oxide (III) from citronellol (I) in one step. The synthesis of the same compound from citronellol or citronellyl acetate using NBS is reported to be a multistep process in which allylic bromination is followed by dehydrobromination with a base and finally hydrolysis and cyclization with an acid.[4] With the use of NIS, all these steps are combined into one, giving rose oxide in yields up to 36%. The probable mechanism of the reaction may be represented as shown in Scheme I.

From the above sequence of reactions, it appears that the mechanism involved is similar to that of allylic bromination by NBS. However, in the case of NIS, allylic iodination is immediately followed by dehydroiodination, resulting in the formation of dehydrocitronellols IIa and IIb.[5] The cyclization of dehydrocitronellol to rose oxide is facilitated by iodine, which itself is generated during the course of the reaction.

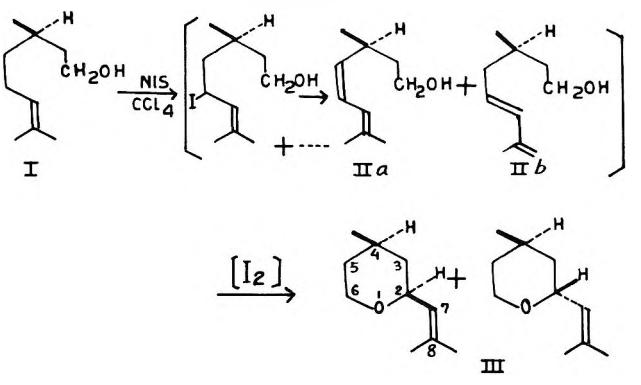
In summary, while the reaction of citronellol with NBS (in CCl_4) gives a bromo derivative of citronellol, the reaction with NIS (in CCl_4) gives rose oxide as the major product. Changing the reaction medium to dioxane and acetic acid gave only a trace amount of rose oxide.

Experimental Section

NIS was prepared by the method of Djerassi and Lenk.[6] A 10-g amount of the citronellol[7] and 22 g of *N*-iodosuccinimide were taken up in 80 mL of CCl_4, and the mixture was refluxed in a water bath for 45 min. The dark violet solution obtained was shaken several times with an aqueous solution of sodium thiosulfate until the iodine was completely removed. It was then washed with distilled water and dried over anhydrous sodium sulfate. The solution was concentrated and subjected to column chromatography on silica gel. Elution with petroleum ether–benzene (10:1) afforded pure rose oxide: 3.6 g (cis/trans, 81:19);[8] bp 48 °C (1.5 mm); $[\alpha]^{20}_D$ +27.5°; ^1H NMR (60 MHz) δ 0.90 (d, J = 8 Hz, 3 H, C-4), 1.52 (d, J = 1.2 Hz, 3 H, C-8), 1.66 (d, J = 1.2 Hz, 3 H, C-8), 3.0–4.0 (m, 3 H, C**H**–O–CH_2), 5.10 (m, 1 H, =CH).

Acknowledgment. We wish to thank Dr. Y. V. Subbarao of the Regional Research Laboratory, Hyderabad, for the ^1H

Scheme I



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NMR data, and S.C.T. wishes to thank the Council of Scientific and Industrial Research, New Delhi, for the Postdoctoral fellowship award.

Registry No.—**I**, 106-22-9; *cis*-**III**, 876-17-5; *trans*-**III**, 876-18-6; *N*-iodosuccinimide, 516-12-1.

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(8) The ratio of the *cis*- and *trans*-(rose oxide) was calculated from GLC only.

Reinvestigation of the Synthesis of 2′-Deoxyadenosylhomocysteine[1]

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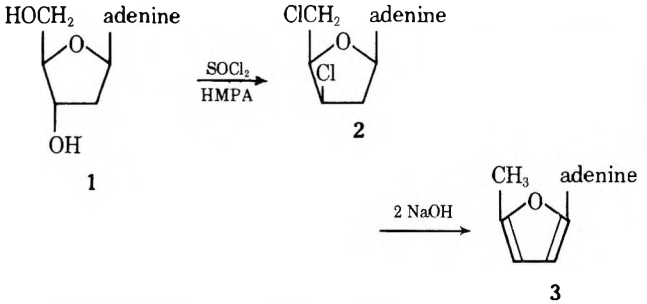
Recently two laboratories described convenient methods for the preparation of *S*-adenosylhomocysteine and some of its analogues.[2,3] Both methods employ the hexamethylphosphoramide–thionyl chloride reagent of Kikugawa and Ichino[4] to prepare the 5′-chloro-5′-deoxynucleosides, which upon condensation with either DL-homocysteine thiolactone in 2 N alkali[2] or DL-homocystine in sodium and liquid ammonia[3] yield the desired products. Borchardt and co-workers[3] reported the syntheses of *S*-adenosylhomocysteine and its analogues containing N^6-methyladenine, N^6-methyl-3-deazaadenine, and 7-deazzaadenine, as well as 2′- and 3′-deoxyadenosine. The purported synthesis of the last two analogues is surprising in light of our earlier observations that chlorination of 2′-deoxyadenosine by the method of Kikugawa and Ichino[4] does not yield 5′-chloro-2′,5′-dideoxyadenosine but rather the dichlorinated nucleoside, 9-(3,5-dichloro-2,3,5,-trideoxy-β-D-*threo*-pentofuranosyl)adenine (**2**).[5] Condensation of this dichloronucleoside with L-homocysteine could lead to the disubstituted analogue, 9-(3,5-dihomocysteinyl-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl)adenine, or the two monosubstituted analogues, 9-(3-chloro-5-*S*-homocysteinyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine and 9-(5-chloro-3-*S*-homocysteinyl-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl)adenine.



These compounds would be expected to undergo elimination reactions under the basic conditions of the condensation reactions. Indeed, McCarthy and co-workers[6] have demonstrated that a similar compound, 2′,5′-dideoxy-5′-*S*-ethyl-3′-*O*-*p*-toluenesulfonyl-5′-thioadenosine, is converted to 9-(5-methyl-2-furyl)adenine (**3**) via two base-catalyzed elimination reactions when treated with potassium *tert*-butoxide in dimethyl sulfoxide.

In order to resolve this inconsistency, we have reinvestigated the synthesis of the analogue of *S*-adenosylhomocysteine involving 2′-deoxyadenosine under reaction conditions used in both laboratories.[2,3] Our results demonstrate that chlorination of 2′-deoxyadenosine with thionyl chloride in hexamethylphosphoramide yields exclusively 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (**2**). Paper chromatography of the crude reaction mixture in three solvent systems showed only **2** and adenine. Under the conditions of the condensation reactions, **2** undergoes two eliminations and an isomerization to 9-(5-methyl-2-furyl)adenine (**3**). The NMR spectra of **3** readily confirm its structure; the 270-MHz ^{1}H NMR spectrum shows the C-5′ protons as a three-proton singlet while the ^{13}C NMR spectrum shows a prominent resonance in the methyl region. Further evidence for the isomerization was obtained by conducting the reaction in a mixture of sodium deuterioxide and deuterioethanol. The ^{13}C NMR spectrum of the crystalline product demonstrates that one atom of deuterium is incorporated at carbon-5′, which now appears as a triplet, while the ^{1}H NMR spectrum indicates the presence of only two C-5′ protons. The ^{1}H NMR and ^{13}C NMR spectra also show that substitution of deuterium has occurred at C-8. The 80-MHz ^{1}H NMR spectra of **3** and its 5′-monodeuterio derivative are also in accordance with the assigned structures. The C-3′ proton of **3** appears as a set of quartets due to the long-range coupling of the three C-5′ protons, while for the deuterio derivative the C-3′ proton appears as a set of triplets.

This two-step reaction sequence provides a most convenient synthetic route to these unsaturated purine derivatives.

Experimental Section

Melting points were measured on a hot stage equipped with a microscope and are not corrected. Pulse proton and carbon-13 nuclear magnetic resonance spectra were recorded with a Bruker 270-MHz, a Varian CFT-20, and a Varian XL-100-15 spectrometer; chemical shifts are recorded in parts per million downfield from tetramethylsilane. Ultraviolet spectra were recorded with a Cary Model 15 spectrophotometer. Descending chromatography on Whatman No. 1 paper was conducted with the following solvent systems: 1-butanol–ethanol–water (50:15:35), *sec*-butyl alcohol–ammonium hydroxide–water (50:14:36), 1-butanol–acetic acid–water (40:10:50). Nucleosides on paper chromatograms were detected by their absorption of ultraviolet light; homocysteine derivatives were located with ninhydrin.

5′-Chloro-5′-deoxyadenosine and 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine were prepared as described before.[5]

***S*-Adenosylhomocysteine. Method 1.** To a solution of L-homocysteine thiolactone hydrochloride (1.15 g, 7.49 mmol) in 12 mL of 2 N sodium hydroxide was added 1.0 g (3.5 mmol) of 5′-chloro-5′-deoxyadenosine. The reaction mixture was stirred vigorously at 80 °C for 1.5 h and then acidified to pH 6 with dilute acetic acid. The solution was applied to an ion-exchange column (2 × 60 cm of Dowex 50-X2, 200–400 mesh, NH_4^+ form) and eluted with water. The fractions containing the desired product were pooled and evaporated to dryness, and the residue was crystallized from water–methanol to yield 520 mg (39%) of *S*-adenosyl-L-homocysteine: mp 195–199 °C (lit.[3] 212 °C).

Method 2. To a solution of L-homocystine (400 mg, 1.5 mmol) in 50 mL of liquid ammonia was added sufficient sodium to give a blue solution. Solid ammonium chloride was then added to just discharge the color. 5′-Chloro-5′-deoxyadenosine (600 mg, 2.1 mmol) was added and the reaction mixture was stirred at −33 °C for 12 h. The reaction mixture was evaporated to dryness, the residue was dissolved in water, and the desired product was purified as described above: yield 393 mg (49%); mp 198–202 °C; UV λ_{max} (pH 1) 257 nm (ϵ 12.8 × 10^3); UV λ_{max} (pH 7) 259 nm (ϵ 14.3 × 10^3); UV λ_{max} (pH 11) 259 nm (ϵ 14.1 × 10^3); ^{1}H NMR (Me_2SO-d_6) 1.84, 1.99 (2 m, 2, $C_\beta H$), 2.64 (t, 1, $J_{\alpha,\beta}$ = 7.5 Hz, $C_\alpha H$), 2.79, 2.95 (2 m, 2, $C_\gamma H$), 3.31 (q, 2, $J_{5'a,5'b}$ = −15.0 Hz,

$C_{5'}H$), 4.03 (q, 1, $J_{2',3'}$ = 10.0 Hz, $J_{3',4'}$ = 6.0 Hz, $C_{3'}H$), 4.17 (q, 1, $C_{2'}H$), 4.73 (t, 1, $J_{4',5'}$ = 6.0 Hz, $C_{4'}H$), 5.90 (d, 1, $J_{1',2'}$ = 5.2 Hz, $C_{1'}H$), 7.30 (s, 2, NH_2), 8.16 (s, 1, C_2), and 8.37 ppm (s, 1, C_8); ^{13}C NMR (D_2O) 28.78 (C-5′), 31.44 (C-γ), 34.56 (C-β), 54.76 (C-α), 73.24 (C-3′), 74.52 (C-2′), 84.0 (C-4′), 88.37 (C-1′), 119.18 (C-5), 140.55 (C-8), 149.25 (C-4), 153.38 (C-2), 155.88 (C-6), and 174.83 ppm (COO^-).

Reaction of **2** with L-homocysteine thiolactone hydrochloride in 2 N sodium hydroxide or with L-homocystine in sodium and liquid ammonia was described above for 5′-chloro-5′-deoxyadenosine and examination of the reaction mixtures by paper chromatography showed only **3** and no condensation products. From these reaction mixtures **3** could be isolated in approximately 50% yield.

9-(5-Methyl-2-furyl)adenine (3). 9-(3,5-Dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (**2**, 500 mg, 1.64 mmol) was suspended in a mixture of 6 N sodium hydroxide (2.7 mL) and ethanol (5.3 mL) and stirred at 70 °C for 10 min. During this time the reactant dissolved and a new precipitate formed. The reaction mixture was stored at 4 °C overnight to yield 204 mg (58%) of **3**. Recrystallization from ethanol provided **3** as colorless needles: mp 235–236 °C (mp 205–215 °C dec when heated slowly) (lit.[6] 236–237 °C); $[\alpha]^{22}_D$ 0°; UV λ_{max} (pH 1) 252 nm (ϵ 21.3 × 10^3); UV λ_{max} (pH 7) 252 nm (ϵ 19.3 × 10^3); UV λ_{max} (pH 11) 251 nm (ϵ 18.8 × 10^3); ^1H NMR (270 MHz) (Me_2SO-d_6) 2.34 (s, 3, $C_{5'}H$), 6.32 (s, 1, $C_{3'}H$), 6.60 (d, 1, $J_{2',3'}$ = 3.0 Hz, $C_{2'}H$), 7.47 (s, 2, NH_2), 8.21 (s, 1, C_2H), and 8.40 ppm (s, 1, C_8H); ^1H NMR (80 MHz) (Me_2SO-d_6) 2.34 (q, 3, $J_{2',5'}$ = 0.30 Hz, $J_{3',5'}$ = 1.1 Hz, $C_{5'}H$), 6.30 (oct, 1, $J_{2',3'}$ = 3.1 Hz, $C_{3'}H$), 6.59 (q, 1, $C_{2'}H$, 7.40 (s, 2, NH_2), 8.21 (s, 1, C_2H), and 8.38 ppm (s, 1, C_8H); ^{13}C NMR (Me_2SO-d_6) 17.00 (C-5′). 105.90 and 111.33 (C-2′ and C-3′), 121.90 (C-5), 142.66 (C-8 and C-4′), 152.81 (C-1′), 152.98 (C-4), 157.19 (C-2), and 159.81 ppm (C-6).

[5′-^{2}H,8-^{2}H]-9-(5-Methyl-2-furyl)adenine (4). **2** (500 mg, 1.64 mmol) was suspended in a mixture of 7.5 N sodium deuterioxide (2.1 mL) and deuterioethanol (5.9 mL) and heated at 70 °C for 10 min. The reaction mixture was worked up as described above to yield 185 mg (52%) of crystalline **4**: mp 235–236 °C; ^1H NMR (80 MHz) (Me_2SO-d_6) 2.34 (m, 2, $C_{5'}H$), 6.30 (sx, 1, $J_{2',3'}$ = 3.1 Hz, $J_{3',5'}$ = 1.1 Hz, $C_{3'}H$), 6.59 (d, 1, $C_{2'}H$), 7.40 (s, 2, NH_2), 8.21 (s, 1, C_2H); ^{13}C NMR (Me_2SO-d_6) 16.61 (t, $J_{C,^2H}$ = 20.0 Hz, C-5′), 105.94 and 111.43 (C-2′ and C-3′), 122.06 (C-5), 142.90 (C-4′), 153.08 (C-1′), 153.18 (C-4), 157.40 (C-2), and 160.08 ppm (C-6).

Acknowledgments. The authors thank Drs. J. M. Wood and R. L. Thrift of the Freshwater Biological Institute for the 270-MHz ^1H NMR spectra and Dr. N. A. Matwiyoff of the Los Alamos Scientific Laboratory for the use of the Varian XL-100 spectrometer.

Registry No.—**2**, 63162-55-0; **3**, 6979-90-4; **4**, 64784-77-6; L-homocysteine thiolactone hydrochloride, 31828-68-9; 5′-chloro-5′-deoxyadenosine, 892-48-8; *S*-adenosyl-L-homocysteine, 979-92-0; L-homocystine, 626-72-2.

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Synthesis of Methyl Arylmethyl 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropylphosphonates as Potential Insecticides

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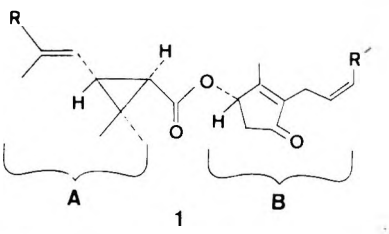
The interest generated by the insecticidal properties and low mammalian toxicity of the extracts of pyrethrum flowers has prompted many detailed investigations into the chemical nature of the chrysanthemate esters.[1-3] The esters **1** have been isolated and synthesized along with numerous synthetic analogues. Many of the previous investigations have dealt with a modification of the 2-methyl-1-propenyl group attached to the acid functionality A[5,6] or the replacement of the cyclopentenone alcohol moiety B by other suitable alcohols.[4] Many of these synthetic analogues exhibit enhanced insecticidal activity and a lowered rate of degradation when compared to the natural materials.[7] A heteroatom modification of the carboxylic function has not been reported. We now report the successful synthesis of compounds related to the chrysanthemate esters **1** in which the carboxylic function has been replaced by a phosphonic function.



1

R=Me, $COOCH_3$
R=Me, Et, $CH{=}CH_2$

The synthesis of ethyl chrysanthemate by Staudinger[9] was accomplished by the reaction of ethyl diazoacetate and 2,5-dimethyl-2,4-hexadiene. The availability of dimethyl diazomethylphosphonate[8] prompted us to attempt the synthesis of the phosphonochrysanthemates using a similar procedure.

Dimethyl diazomethylphosphonate (**2**) was treated with an excess of 2,5-dimethyl-2,4-hexadiene in methylene chloride in the presence of copper powder to give dimethyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropylphosphonate (**3**). Although the cis/trans structural isomers could be separated by gas chromatography, no attempt was made to use the individual structural or optical isomers for our initial investigations. The esters which we chose to prepare were the phosphorus analogues of the chrysanthemate esters reported to have high insecticidal properties.

The diester **3** was selectively saponified to yield monomethyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropylphosphonic acid (**4**). This acid was converted into its silver salt, silver methyl 2,2-dimethyl-3-(2-methyl-1-propenyl)-

Scheme I

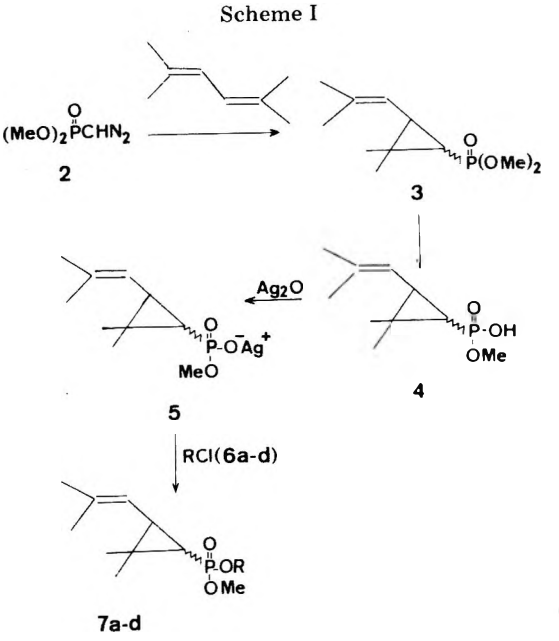
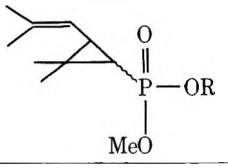
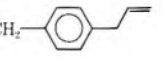
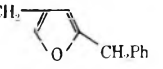


Table I



Compd	Registry no.	R	Yield, %	Bp, °C (mm)
7a	64771-44-4	$-CH_2-C_6H_4$-3-OPh	22	170–190 (0.05)
7b	64771-45-5	$-CH_2-C_6H_2$-2,4,6-Me_3	27	110–125 (0.05)
7c	64771-46-6		14	140–141 (0.01)
7d	64771-47-7		2	196–200 (0.001)

cyclopropylphosphonate (**5**), by reacting it with freshly prepared silver oxide in subdued light. The silver salt **5** was a white semicrystalline solid which rapidly turned brown upon exposure to light. Reaction of the appropriate arylmethyl alcohols with the sodium and potassium salts of this acid, or with the corresponding pyrophosphate made by reaction with dicyclohexylcarbodiimide,[10] all failed. The desired esters **7** were successfully prepared by the reaction of the silver salt **5** with the desired arylmethyl chlorides, **6**, which were prepared from the reaction of the alcohol with thionyl chloride in pyridine.[11] These alcohols were prepared by literature methods.[12–14] The entire sequence is shown in Scheme I. Chromatographic workup followed by a vacuum distillation afforded the desired phosphonic esters **7**.

The yields in the reaction of the silver salt **5** with the corresponding arylmethyl chloride **6** along with the boiling points of the diester products **7** are listed in Table I.

Preliminary tests of esters **7a–d** for their toxicity to houseflies (*Musca domestica*) and cigarette beetles (*Lasioderma serricorne*) by the general method of Bull and Ridgeway[16] have indicated greatly decreased insecticidal activity compared to their carboxylic ester counterparts. It is not known whether this initially observed low activity is a result of metabolism and transport differences from the carboxylic ester systems or the loss of the specific spatial orientation required for maximum insecticidal activities.

Experimental Section

All melting points and boiling points are uncorrected. Solvents and commercial reagents were purified by conventional methods. ^1H NMR spectra were recorded at 60 MHz with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded using a Perkin-Elmer Model 621 infrared spectrophotometer. Mass spectra were obtained from a CEC type 21-104 mass spectrometer at a 70-eV ionizing voltage.

Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All compounds analyzed within ±0.40% of the calculated values for carbon, hydrogen, and phosphorus except compound **7d**. This compound was extremely sensitive to light and air and was too unstable for an accurate combustion analysis. The stability was somewhat improved by dissolving the compound in acetone.

The IR, ^1H NMR, and mass spectra of all compounds agree with those expected for the proposed structures.

Dimethyl Diazomethylphosphonate (2). Dimethyl diazomethylphosphonate (**2**) was prepared in 44% yield by the method of Seyferth and Marmor.[8] *Caution:* the product is potentially carcinogenic and explosive!

Dimethyl 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropylphosphonate (3). A solution of 150 mL of freshly distilled 2,5-dimethyl-2,4-hexadiene and 50 mL of methylene chloride was stirred under nitrogen with 7.60 g (120 mg-atoms) of copper powder. To this was added 7.50 g (50 mmol) of dimethyl diazomethylphosphonate (**2**) dissolved in 25 mL of methylene chloride. The suspension was stirred vigorously for a total of 8 days. Solvent and excess 2,5-dimethyl-2,4-hexadiene were removed by bulb-to-bulb vacuum distillation at room temperature. The residue was taken up in 100 mL of benzene,[17] filtered from the copper powder and concentrated on the rotary evaporator. Upon distillation 6.45 g (56%) of product **3** was recovered as a clear colorless oil: bp 76–77°C (0.15 mm); mass spectrum M^+ *m/e* 232 (6), 123 (100); ^1H NMR ($CHCl_3$-*d*) δ 0.52 (1 H, d of d, *J* = 7, 2 Hz), 1.1–1.6 (7 H, m), 1.73 (6 H, s), 3.72 (6 H, d, *p*-OCH_3, *J* = 11 Hz), 4.92 (1 H, d, C=CH, *J* = 7 Hz); IR (NaCl–neat liquid) 2960, 2860, 1360, 1250, 1070–1030, 820, 790 cm^{-1}. Anal. Calcd for $C_{11}H_{21}O_3P$: C, 56.88; H, 9.11; P, 13.34. Found: C, 57.22; H, 9.24; P, 12.96.

Silver Methyl 2,2-Dimethyl-3-(2-methylpropenyl)cyclopropylphosphonate (5). A mixture of 1.20 g (5 mmol) of **3**, 220 mg (5 mmol) of sodium hydroxide, 10 mL of methanol, and 25 mL of water was refluxed vigorously for 24 h. The clear solution was treated with 2.0 g of Baker 50W-X12 ion-exchange resin (H^+ form) and diluted with water, and the oil formed was dissolved in methanol and filtered. The mono acid **4** was deposited as a clear colorless oil upon evaporation of the water and methanol. It was characterized by the preparation of the anilinium salt in 70% yield, mp 89.5–93 °C, as white microfine needles (hexane). Anal. Calcd for $C_{16}H_{26}NO_3P$: C, 61.72; H, 8.42; N, 4.50. Found: C, 61.36; H, 8.60; N, 4.33.

A solution of 1.09 g of **5** (5 mmol) in 200 mL of acetronitrile and 50 mL of water was mixed with 2.40 g (10 mmol) of silver oxide, which was freshly prepared by the general method of Willstätter and Pfannenstiel.[15] The mixture was refluxed in darkness 30 min, filtered hot, and evaporated to dryness in a foil-covered flask. The product amounted to 1.52 g (93%) of white solid **5**, which rapidly turned brown upon exposure to light and air. It was used immediately without further purification.

Arylmethyl Chlorides 6a–d. The 2,4,6-trimethylbenzyl chloride was purchased from the Aldrich Chemical Company, Inc. The remaining arylmethyl chlorides were prepared by the general procedure of Frazer,[11] from the corresponding alcohols. *p*-Allylbenzyl alcohol, *m*-phenoxybenzyl alcohol, and 2-benzyl-4-furfuryl alcohol were prepared by literature methods.[12–14]

General Procedure for the Preparation of Methyl Arylmethyl 2,2-Dimethyl-3-(2-methylpropenyl)cyclopropylphosphonates (7). To 1.52 g (4.7 mmol) of the silver salt **5** in 250.0 mL of dry acetonitrile was added 6.0 mmol of the appropriate arylmethyl chloride **6**. The suspension was refluxed with stirring in a foil-covered flask under nitrogen for at least 2 h. The silver chloride was filtered from the cooled solution and the solvent was evaporated to yield an oily residue.

The residue was chromatographed on a silica gel column, using benzene,[17] until the excess chloride was completely eluted. The silica gel was extracted with hot ethyl acetate and filtered. The extract was evaporated and the residue fractionally vacuum distilled to afford the pure esters **7**. A listing of boiling points and yields can be found in Table I.

Acknowledgments. The authors are grateful to Mrs. Margie Scott and Mrs. Rebecca Wright for their technical assistance.

Registry No.—**2**, 27491-70-9; **3**, 64771-48-8; 4 aniline salt, 64771-50-2; **5**, 64771-51-3; 2,5-dimethyl-2,4-hexadiene, 764-13-6; *p*-allylbenzyl chloride, 36875-10-2; *m*-phenoxybenzyl chloride, 53874-66-1; 2-benzyl-4-furfuryl chloride, 33486-19-0; 2,4,6-trimethylbenzyl chloride, 1585-16-6.

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(17) *Caution:* suspected carcinogen.

New Synthesis of 3,7-Dimethylpentadec-2-yl Acetate Sex Pheromone of the Pine Sawfly *Neodiprion lecontei*

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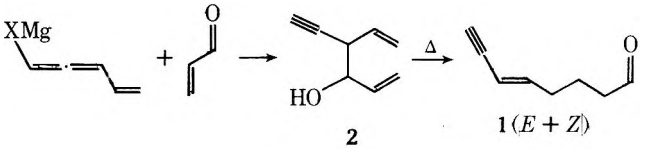
Recently,[1] we published a two-step synthetic sequence for aldehydes **1** by (i) the reaction of vinylallenic Grignard reagents with $\alpha\beta$-ethylenic ketones and (ii) the oxy-Cope transposition in refluxing diglyme of the resulting 4-ethynyl hexa-1,5-dien-3-ols **2** (Scheme I).

We report here an application of this sequence in the synthesis of the title pheromone **3** (*dl*), the structure of which was demonstrated by Coppel and co-workers in 1976.[2] A seven-step synthesis of **3** from 2,6-dimethylcyclohexanone was proposed very recently.[3]

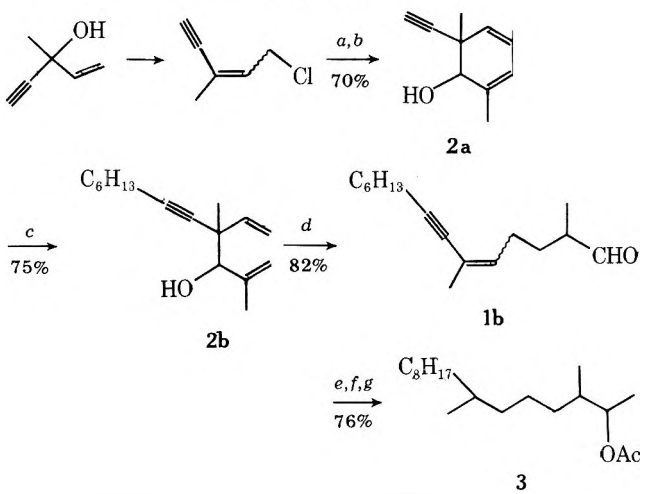
5-Chloro-3-methylpent-3-en-1-yne is readily prepared from 3-methylpent-4-en-1-yn-3-ol.[4] Its vinylallenic Grignard reagent reacts with methacrolein leading to alcohol **2a** which is easily alkylated by *n*-hexyl bromide using lithium amide in liquid ammonia. Heating of **2b** for 2 h in refluxing diglyme gives the fairly unstable aldehyde **1b**. After hydrogenation of **1b** the synthesis of **3** is terminated as outlined in Scheme II by reaction of methylmagnesium iodide with the corresponding saturated aldehyde. The overall yield from alcohol **2a** to the pheromone (identified by comparison of its spectra with those previously described) is 47%.

Scheme I



2 **1** (*E* + *Z*)

Scheme II



[a] Mg/Et_2O, 0 °C. [b] methacrolein. [c] $LiNH_2$/liq NH_3, $C_6H_{13}Br$. [d] diglyme reflux. [e] H_2, Pd/C 5%/AcOEt. [f] CH_3MgI/Et_2O. [g] Ac_2O.

Experimental Section[5]

The starting 3-methylpent-4-en-1-yn-3-ol was kindly provided by Dr. Pesnelle from Sté Roure-Bertrand.

2,4-Dimethyl-4-ethynylhexa-1,5-dien-3-ol (2a). The Grignard reagent of 11.5 g (0.1 mol) of 5-chloropent-3-en-1-yne is prepared and condensed with 7 g (0.1 mol) of methacrolein following published procedure;[1] 10.5 g (70%) of **2a** ($E_{0.2}$ = 47–48°) are obtained: IR (neat liq) 3550, 3450, 3300, 3080, 3060, 3010, 2100, and 1640 cm^{-1}; NMR (CCl_4) δ 1.20 and 1.28 (3 H, 2 s corresponding to threo and erythro isomers 1/1), 1.74 and 1.77 (3 H, 2t, J = 1.5 Hz), 2.30 (1 H, s), 2.52 (1 H, s, exchange with D_2O), 3.81 (1 H, s), 4.7–6.1 (5 H, M); mass spectrum 150 $M^{+\cdot}$ (1), 79 (100). Anal. Calcd: C, 79.95; H, 9.39. Found: C, 79.75; H, 9.71.

2,4-Dimethyl-4-vinyldodec-1-en-5-yn-3-ol (2b). Alcohol **2a** (10.5 g, 0.07 mol) is added after 5 min to a solution cooled to −45 °C of 0.15 mol of lithiumamide in 150 mL of liquid ammonia (freshly prepared from 1.0 g of lithium). *n*-Hexyl bromide (12.5 g, 0.075 mol) is then added after 10 min and the reaction mixture is stirred for 5 h at −45 °C. After addition of 200 mL of ether, ammonia is slowly evaporated. The residue is hydrolyzed by 200 mL of crushed ice and the solution was extracted with ether. The organic layer is washed until neutral and dried over $MgSO_4$. Evaporation of solvent leaves 15 g of crude material which by chromatography over silica gel (eluant petroleum ether–ether 4:1) gives 11.5 g (75%) of **2b** contaminated with about 10% aldehyde **1b**. This aldehyde seems to be formed during purification and complicates isolation of pure **2b** on a large scale: IR (neat liq) 3550, 3450, 3080, 3010, and 1640 cm^{-1}; NMR (CCl_4) δ 0.87 (3 H, t), 1.0–1.6 (11 H, M), 1.75 (3 H, M), 2.0 (1 H, M exchange with D_2O), 2.20 (2 H, M), 3.8 (1 H, broad s), 4.7–6.1 (5 H, M).

2,6-Dimethyltetradec-5-en-7-ynal (1b). A solution of 4.4 g (0.019 mol) of alcohol **2b** (contamined with ~10% of **1b**) in 100 mL of diglyme is refluxed for 2.25 h. After cooling, 400 mL of ether is added; the resulting solution is washed 15 times with 30 mL of water in order to eliminate diglyme and dried over $CaCl_2$. The unstable aldehyde (3.6 g 82%) is purified by chromatography over silica gel (eluent petroleum ether–ether 9:1) after removal of the solvent: IR (neat liq) 3010, 2700, 2220, 1730, 1670, and 1630 cm^{-1}; NMR (CCl_4) δ 0.89 (3 H, t), 1.05 (3 H, d, J = 7 Hz), 1.15–1.70 (13 H, M), 1.80–2.40 (5 H, M), 5.5 (1 H, M), 9.70 (1 H, d, J = 1 Hz); mass spectrum m/e 234 $M^{+\cdot}$ (20), 164 (99), 93 (100).

2,6-Dimethyltetradecanal. Aldehyde **1b** (2 g, 0.085 mol) in 30 mL of ethyl acetate is hydrogenated at ordinary pressure using 5% Pd/C as catalyst. After filtration and evaporation of solvent, 1.88 g (94%) of saturated aldehyde are obtained, pure enough (TLC) to be used without further purification: IR (neat liq) 2700, 1725 cm^{-1}; NMR (CCl_4) δ 0.9 (6 H, M), 1.05 (3 H, D, J = 7 Hz), 1.1–2.4 (20 H, M), 9.62 (1 H, d, J = 1 Hz); mass spectrum m/e 240 $M^{+\cdot}$ (0.5), 57 (100).

3,7-Dimethylpentadec-2-yl acetate (3). The Grignard reagent is prepared from 1.42 g (0.01 mol) of methyl iodide, 0.36 g (0.015 g-atom) of magnesium, and 10 mL of anhydrous ether. To the magnetically stirred solution is added at 0 °C 1.34 g (0.006 mol) of the saturated aldehyde dissolved in 5 mL of ether. After 20 min of stirring at 0 °C, 2 g (0.02 mol) of acetic anhydride in 2 mL of ether is dropped into the mixture which is hydrolyzed by 20 mL of a saturated solution of NH_4Cl 20 min after the end of the addition. The organic layer is separated, washed with 3 × 20 mL of H_2O, and dried over $CaCl_2$. The pheromone is, after removal of the solvent, purified by chromatography over silica gel (eluent: petroleum ether–ether 9:1) and 1.35 g (81%) of **3** is obtained: IR (neat liq) 1735, 1240 (identical to one described (**3**)) cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (9 H, M), 1.0–1.7 (25 H, M), 1.97 (3 H, s), 4.80 (1 H, M); ^{13}C NMR ($CDCl_3$) δ 170.5)s), 74.24 (d), 74.03 (d), 73.95 (d), 24 peaks between 37.6 and 14.1; mass spectrum m/e 298 $M^{+\cdot}$ (0), 255 (5), 254 (11), 238 (33), 116 (14), 87 (45), 44 (55), 43 (100). Anal. Calcd: C, 76.45; H, 12.83. Found: C, 76.03; H, 12.66. All the prominent peaks were also described by Coppel et al.[2]

Registry No.—**1b**, 64682-96-8; *erythro*-**2a**, 64682-97-9; *threo*-**2a**, 64682-98-0; **2b**, 64728-32-1; **3**, 59056-74-5; hexyl bromide, 111-25-1; 2,6-dimethyltetradecanal, 64682-99-1.

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Harringtonolide, a Plant Growth Inhibitory Tropone from *Cephalotaxus harringtonia* (Forbes) K. Koch

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As part of a program involving a search for new naturally occurring plant regulants, we examined an ethanolic extract of the seeds of *Cephalotaxus harringtonia* (Taxaceae).[2] The growth of several species of plants was inhibited by applications of this extract. A group of tumor-inhibiting alkaloids, the harringtonines, had been isolated from this yew and characterized.[3] We tested isoharringtonine and the mixed alkaloids obtained from *C. harringtonia* in several plant bioassays but found no significant activity. Work was then begun to isolate and characterize the principal plant growth inhibitor present in the C. *harringtonia* seeds, and we now report on the isolation and the physical and chemical properties of the inhibitor.

The 2-propanol extract of the *C. harringtonia* seeds was first partitioned between hexane and aqueous methanol. The methanol-soluble portion was then chromatographed on Bio-Beads S-X2 in THF. The growth inhibitor was isolated by chromatography on silica gel with chloroform–acetonitrile, followed by high-performance liquid chromatography (HPLC) using a similar system. The successive steps in the purification sequence were monitored by a bean second-internode assay.[4] The active compound, harringtonolide, was isolated as a pale yellow solid for which no satisfactory elemental analysis was obtained. An empirical formula, $C_{19}H_{18}O_4$, was determined for the molecular ion by high-resolution mass spectrometry. The base peak in the spectrum was 282 indicating a facile elimination of CO.

The ultraviolet spectrum [λ_{max} 242, 310 nm (ϵ 20 000, 7000)] suggested the presence of a tropone moiety [cf. 4-isopropyltropone (nezukone), λ_{max} 230, 310 nm (ϵ 30 000, 15 000)].[5] The infrared spectrum contained bands assignable to lactone (1758 cm^{-1}), unsaturated ketone (1624 cm^{-1}), and olefin (1560 cm^{-1}); the latter two were similar to the 1635- and 1580-cm^{-1} bands of nezukone. The NMR spectrum contained signals among which these assignments could be made: methyl at δ 0.90 (doublet), methyl at δ 2.36 (singlet), one proton at δ 1.76 (quartet), and two protons at δ 6.92 and 6.98 (singlets).

Hydrogenation of harringtonolide over Pd/C resulted in a hexahydro product as determined by low-resolution mass spectrometry. The ultraviolet spectrum contained only end absorption. The infrared contained a lactone band (1750 cm^{-1}) and a carbonyl band at 1730 cm^{-1} with a shoulder at 1700 cm^{-1}. No band assignable to the olefinic moiety was found.

To determine the structure of harringtonolide an x-ray crystallographic analysis was undertaken. The compound crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 8.38 Å, b = 22.34 Å, and c = 7.68 Å. There is one molecule per asymmetric unit corresponding to a calculated crystal density of 1.43 g/cm^3. A partial structure was obtained by application of the symbolic addition procedure for noncentrosymmetric crystals.[6] The fragment was then developed into the full structure by the tangent formula refinement and expansion method.[7] Hydrogen atoms were located in a difference map and the structure was then refined by full-matrix least-squares methods to a final R factor, agreement between observed and calculated structure factors, of 0.078. The drawing in Figure 1 which was constructed with the experimentally determined atomic positions displays the results of the x-ray analysis. Full crystallographic details will be published.[8]

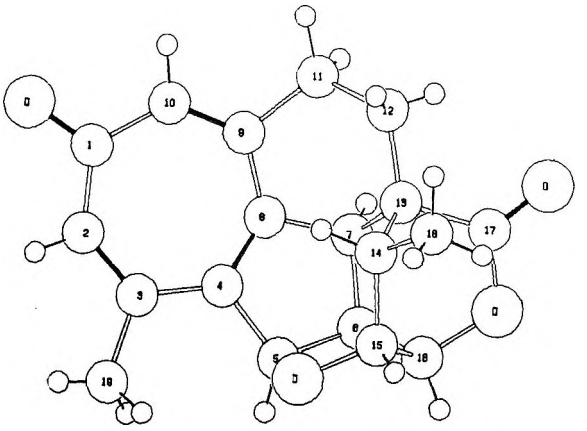

Figure 1. Molecular structure of harringtonolide as found in the crystal.

Further study of the NMR spectrum after the structure determination by x-ray crystallography permitted other assignments to be made (Table I). Confirmation of the assignment of the methyl doublet on C-18 and the adjacent proton quartet on C-14 was made by a double resonance experiment. A similar experiment indicated that irradiation of the δ 4.0 proton diminished the multiplicity of the δ 5.32 signal so the C-15 proton was assigned to δ 5.32 and C-16 to δ 4.0. The multiplets at δ 1.25 and 2.70 could be assigned to methine protons on C-6 and C-7 based on a double resonance experiment; however, only a slight collapse of the complex multiplets was obtained on irradiation of either signal. The δ 2.70 multiplet appeared to be composed of the overlap of C-12 methylene signals with those of the C-7 proton. The δ 6.92 and 6.98 signals were assigned to the protons at C-2 and C-10, consistent with data for protons α to the tropone carbonyl.[9] The ^{13}C NMR spectra of harringtonolide were obtained and assignments for the various positions were made with the aid of data obtained from an off-resonance decoupling experiment and similarities to model compounds (Table I).[10,11] The δ 186.393 for C-1 ($CDCl_3$) was near the value reported for the same carbon in tropone, δ 187.5 (CCl_4).[12]

Harringtonolide was found to be an inhibitor of plant

Table I. NMR Spectra of Harringtonolide

Carbon	^1H	^{13}C
1		186.393[a] s
2	6.92[b] s (1 H)	139.143[c] d
3		143.582[d] s
4		145.015[d] s
5	5.47 m (1 H)	79.951[e] d
6	1.25 m (1 H)	41.733 d
7	2.70 m (1 H)	49.881 d
8		145.645[d] s
9		145.855[d] s
10	6.98[b] s (1 H)	141.494[c] d
11	3.51 m (2 H)	32.281 t
12	2.70 m (2 H)	22.326 t
13		43.746 s
14	1.75 q (1 H)	39.951 d
15	5.32 m (1 H)	79.946[e] d
16	4.0 m (1 H)	85.492 d
17		173.456 s
18	0.90 d (3 H)	14.704 q
19	2.36 s (3 H)	23.839 q

[a] Multiplicity: d, doublet; m, multiplet; s, singlet; t, triplet; q, quartet. Multiplicity in ^{13}C spectra obtained through off-resonance decoupling. Values are in δ units relative to Me_4Si. [b–e] Assignments with the same superscript may be interchanged.

growth on two test species, tobacco and beans. The emulsified compound (10^{-3} M) when applied to the axils of decapitated tobacco plants effected a complete inhibition of bud growth for at least 14 days.[13] Necrosis of the meristematic tissue usually occurred and was also observed in the application of the tropone lactone to the second internode of 7-day-old bean plants. Concentrations of 1, 5, or 10 μg of the compound suspended in lanolin were sufficient to cause necrosis above the point of application within 4 days. Inhibition of growth (46%) with no indication of necrosis was observed with an application of 0.1 μg of harringtonolide to the second internode. No translocation of the harringtonolide below the point of application was seen.

Very few tropones have been found in higher plants, although the number of tropolones (2-hydroxytropones) identified in the Cupressaceae and Liliaceae is somewhat greater.[14] The latter compounds, derived from terpenes, are thought to function as fungicidal compounds in the heartwood of a number of species of trees.[15] Many terpenic lactones have been isolated from higher plants and exhibit growth regulatory activity.[16] Harringtonolide appears to be the first complex tropone containing a lactone function to be characterized. No effort has been made thus far to determine the portion(s) of the molecule responsible for the observed biological activity. We do not know whether similar compounds remain to be discovered in other *Cephalotaxus* species.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and were uncorrected. UV spectra were obtained with a Beckman 25 spectrophotometer. IR spectra were taken as KBr pellets on a Perkin-Elmer 621 spectrophotometer. ^{1}H NMR spectra were obtained at 100.1 MHz and the ^{13}C spectra at 25.2 MHz with a Varian XL-100 spectrometer. $CDCl_3$ was the solvent with Me_4Si as the internal standard. HPLC was performed on a Spectra-Physics 3500B instrument equipped with a Schoeffel 700 spectrophotometric detector. Low-resolution mass spectra were obtained with a Du Pont 21-491B spectrometer using the direct-probe method with a 70-eV ionizing voltage. High-resolution mass spectral analyses were made on an AEI MS-9 mass spectrometer by the direct-probe method using an electron-impact ionization at 70 eV. The ion source temperature was 180 °C and perfluorkerosene was the internal standard.

Isolation of Harringtonolide. Seeds of *Cephalotaxus harringtonia*[17] (2.5 kg) were ground and extracted exhaustively with *i*-PrOH at 80 °C. The resulting extract was partitioned between hexane–MeOH–H_2O (10:9:1). The MeOH-soluble portion was partioned by countercurrent distribution in four separatory funnels with the two-phase system, CCl_4–$CHCl_3$–MeOH–H_2O (280:120:320:80). The inhibitor was located in the upper phases of the four funnels by use of the bean second-internode assay. The active fraction was then applied to a gel permeation column packed with Bio-Beads S-X2 in THF. The further purified fraction was then chromatographed on a silica gel column with $CHCl_3$–CH_3CN (9:1). A R_f of 0.50 was obtained for harringtonolide on silica with $CHCl_3$–CH_3CN (4:1). The active compound was recrystallized from CH_2Cl_2 by addition of MeOH (30 mg). The final purification was done by HPLC with the detector set at 319 nm with 640 psi and a flow rate of 0.8 mL/min. The column used was 0.25 m × 4 mm with Spherisorb 5 μm silica. The solvent was $CHCl_3$–CH_3CN (9:1).

Harringtonolide. The compound was obtained as pale yellow crystals: mp 285–288 °C dec; $[\alpha]^{30}_D$ 83.0° (c 1.5, $CHCl_3$); UV (EtOH) λ_{max} 242 nm (ε 20 000), 310 (7000); IR (KBr) 3400, 2960, 2925, 1758, 1730 (sh), 1624, 1560, 1430, 1370, 1235, 1075, 960, 870, 750 cm^{-1}; MS *m/e* 310.1241, 310 (M^+, 21), 283 (18), 282 ($M^+ - CO$, 100), 225 (13), 209 (15), 207 (11), 199 (61), 197 (11), 195 (18), 181 (30), 179 (22), 169 (30), 168 (28), 167 (40), 165 (40), 153 (35), 144 (40), 143 (67), 142 (30).

Reduction of Harringtonolide. Compound (4 mg) was dissolved in EtOAc and then reduced at 45 psi of H_2 over 5% Pd/C: low-resolution MS 316 (M^+, 89), 314 (71), 312 (32), 298 (36), 282 (17), 258 (74), 55 (100).

Plant Bioassays. Harringtonolide was applied to plants in a lanolin carrier or as an emulsified suspension prepared by dissolving the compound in THF and adding Tween 20 surfactant to give a final concentration of 1% solvent and surfactant on addition of H_2O. Xanthi tobacco was used in the assay. Beans (*Phaseolus vulgaris* cv. Pinto) were used for the second internode assay. Treatments were replicated at least twice.

Acknowledgments. The authors thank D. W. Spaulding for conducting the bean second internode assay and M. S. Greenbaum for technical assistance. The NMR analyses were performed by M. O. Mattingly of the Department of Chemistry, University of Maryland. The high-resolution analysis was performed at the Mass Spectrometry Laboratory of the Florida State University. The samples of isoharringtonine and mixed alkaloids from *Cephalotaxus* were furnished by R. G. Powell, Horticultural and Special Crops Laboratory, Northern Regional Research Center, ARS, Peoria, Ill.

Registry No.—Harringtonolide, 64761-48-4; hexahydroharringtonolide, 64761-49-5.

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(17) The plant material was obtained from Dr. R. E. Perdue, Jr., Medicinal Plant Resources Laboratory, BARC, Beltsville, Md. Initial samples were collected as part of the USDA program developed with the Cancer Chemotherapy National Service Center, NIH.
(18) Figure 1 was drawn using the computer program ORTEP: J. K. Johnson, "Report ORNL-3794", Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(19) Mention of a trademark or proprietary product does not constitute a guarantee or warranty of the product by the U.S. Department of Agriculture and does not imply its approval to the exclusion of other products that may also be suitable.

A Correction on the Reduction of Dihydrocodeinone with Formamidinesulfinic Acid. Stereoselective Reduction of Dihydropseudocodeinone

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We have shown in earlier papers[2,3] that formamidinesulfinic acid (FSA, aminoiminomethanesulfinic acid) reduces the carbonyl group of a number of 6-ketones of the morphine series with complete stereoselectivity to the corresponding secondary alcohols with β configuration of the hydroxyl. This stereoselectivity stands in marked contrast to the one observed on hydride reduction, where such ketones tend to

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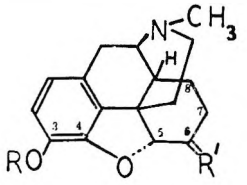
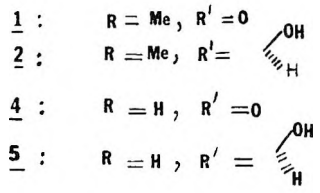
produce both epimers, with strong preponderance of the compound with α-OH.[4,5]

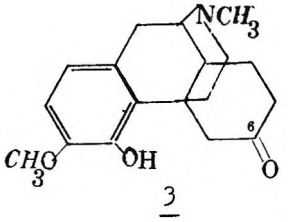
With one exception (see below), all compounds of the morphine series which have been reduced with FSA so far contained a free phenolic hydroxyl in position 3.

The reduction product of the one nonphenolic compound, dihydrocodeinone (1), was assumed[3] to be dihydroisocodeine, **2**, by analogy with the results obtained with the phenolic ketones; this assignment seemed further supported by the mass spectrometric molecular weight and by comparison of the ^{1}H NMR spectrum with one of authentic dihydroisocodeine shown in a paper by Okuda et al.[7]

It has recently been brought to our attention by Dr. F. I. Carroll[8] that repetition of our reduction of 1 yielded not 2 but an isomer, the phenolic ketone dihydrothebainone,[9] **3**. We





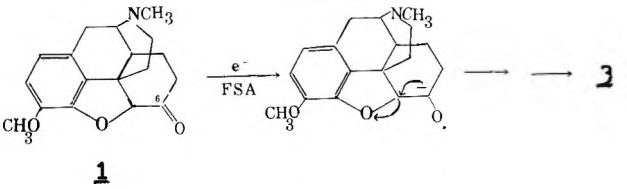


have now reinvestigated this reaction and wish to report that it does indeed yield 3 rather than 2; the product, obtained in 63% yield, was identified by melting point, mixture melting point, and comparison of its IR and ^{1}H NMR spectra with those of an authentic sample.[10] In marked contrast to the other reductions with FSA studied so far, the reduction of 1 proceeds thus with opening of the oxygen bridge and, surprisingly, with retention of the carbonyl. Scission of the oxygen bridge has been observed repeatedly during reduction of 1 and related ketones by various methods[11] and is not unexpected in such α-keto ethers. It is of interest, however, that it should take place in 1 and not in any of the closely related 6-ketones with free phenolic hydroxyl which had been examined earlier;[2,3] in particular, dihydromorphinone, 4 (compound 9 of ref 2), the free phenol of which 1 is the methyl ether, is smoothly reduced to dihydro-α-isomorphine, **5**, with intact oxygen bridge; compound 5 was unequivocally identified by comparison (decomposition point, IR, ^{1}H NMR) with an authentic sample.[10a] This discrepancy in the behavior of 1 and 4 will be discussed below.

Much more surprising is the failure of the ketone 3 to be reduced further by the FSA used in its preparation. Nakagawa and Minami[12a] have shown that FSA in aqueous ethanolic alkali smoothly reduces a wide variety of ketones to the secondary alcohol in high yield; the survival of the carbonyl of 3 is thus puzzling.[12b]

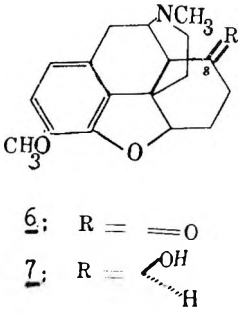
The unexpected finding that FSA merely cleaves the oxygen bridge of 1 while leaving its carbonyl intact nullifies the claim made earlier[3] that 6β-OH derivatives of the *codeine* series are accessible directly by FSA reduction of the corresponding

Scheme I



ketones. However, the preparation of these alcohols by reduction of 6-ketones with free phenolic hydroxyl (e.g., 4) with FSA and methylation of the resulting secondary alcohol (e.g., 5) should still be much superior to other methods reported in the literature.[13]

Our observations during the reduction of 1 illustrate the need for a thorough study of the scope and limitations of the FSA reduction of ketones. As a contribution to this study we have examined the behavior of dihydropseudocodeinone,[14] **6**, on reduction with FSA. As expected, this 8-ketone of the codeine series gave nonphenolic dihydropseudocodeine,[15] **7**,



the corresponding secondary alcohol with β orientation of the hydroxyl; the reaction in this case conforms entirely to the FSA reduction of the phenolic 6-ketones.[2,3] Compound 7 (mp 152–155 °C), obtained in 52% yield, was identified by comparison with an authentic sample[10a] (mixture melting point, IR, ^{1}H NMR).

We further attempted the reduction of two ketones completely unrelated to the morphine series. The carbonyl of camphor did not undergo reduction under a variety of conditions; (+)-3-bromocamphor was debrominated to (+)-camphor having the same optical activity as that of an authentic sample.

The fact that the oxygen bridge is cleaved in the phenol ether 1 but not in the corresponding free phenol 4 calls for some further comment. Such cleavage reactions have been observed frequently enough in free 3-phenols of the morphine series; the long-known conversion of morphine itself into apomorphine[16] on treatment with acid, its isomerization into *O*-demethylthebainone[17] under the influence of Pd/C, and instances of hydrogenolysis[18] of morphine derivatives with a double bond in position 6 may be quoted. However, all those reactions take place in *acidic* or *neutral* medium. In contrast, the reductions with FSA are carried out in the presence of alkali, i.e., on the phenolate ion, and it is understandable that formation of another such ion in ortho position to the existing one (in the morphine series) should be suppressed. Nakagawa and Minami[12a] have formulated the reduction of fluorenone by FSA as a free-radical process on the basis of ESR studies and the formation of the pinacol, (9,9′-bifluorenyl)-9,9′-diol, under certain conditions. Assuming general validity of this interpretation, the reduction of 1 can be written as shown in Scheme I. Admittedly, this formulation fails to explain the resistance of 3 to further reduction. We are at present examing the reduction of 3 and other related compounds lacking the oxygen bridge.

Experimental Section

Experimental procedures were as reported earlier.[2] Formamidinesulfinic acid was obtained from Eastman Organic Chemicals, Rochester, N.Y. Optical rotations were measured on a high-precision polarimeter No. 80 (O.C. Rudolph and Sons). The (+)-3-bromocamphor was obtained from Aldrich Chemicals Co., Inc., Milwaukee, Wis.

Reduction of Dihydropseudocodeinone (6) to Dihydropseudocodeine (7). A solution of 114 mg (0.38 mmol) of the free base **6** was dissolved in EtOH (20 mL). This solution was stirred under a current of nitrogen. A solution of FSA (164 mg, 1.52 mmol) and NaOH (121.6 mg, 3.04 mmol) in H_2O (15 mL) was added, and the reaction mixture was heated on a water bath at 80–85 °C for 2 h. It was next cooled and EtOH was carefully removed by evaporation. The white precipitate formed on chilling was collected by suction filtration and washed with ice cold water. The product, **7**, mp 152–155 °C (lit.[15] mp 155 °C), weighed 60 mg (52%): IR (KBr disk) 3380, 3170, 2940, 1605, 1625, 1500 cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$, Me_4Si 6.7 (q, 2 H, aromatic), 4.54 (m, 1 H, 8α-H), 3.86 (s, 3 H, OCH_3), 3.49 (broad s, 1 H, 5β-H), 2.42 (s, 3 H, NCH_3); mass spectrum (70 eV) *m/e* 301 (M^+).

Reduction of (+)-3-Bromocamphor. To a solution of (+)-3-bromocamphor (11.55 g, 0.05 mol) in 95% EtOH (50 mL) was added NaOH (16 g, 0.4 mol) in H_2O (16 mL) and FSA (21.6 g, 0.2 mol). The reaction mixture was stirred under a current of nitrogen at 80–85 °C, as in the previous experiment, for 2 h; it was cooled and then concentrated tc half its volume and extracted with $CHCl_3$ (50 mL), the organic layer was washed with water, dried (Na_2SO_4), and evaporated in vacuo to give 5 g of (+)-camphor (66%): mp 179.5 °C; $[\alpha]^{20}_D$ +44.2° (c 10, $CHCl_3$).

Acknowledgment. We thank Mr. Charles H. Strom for obtaining NMR and mass spectra. One of us (N.C.) is thankful to Dr. Ralph A. Stephani for his helpful discussions and encouragement. Supported in part by Grants No. DA-00297. We are thankful to Mr. Henry Reha for his assistance in preparing illustrations.

Registry No. —**6**, 5056-91-7; **7**, 3883-12-3; (+)-3-bromocamphor, 55057-87-9; (+)-camphor, 46449-3; FSA, 1758-73-2; dihydrocodeinone, 125-29-1; dihydrothebainone, 847-86-9.

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(10) (a) This sample, from the collection of the late L. F. Small, was kindly furnished by Dr. E. L. May. (b) Our product **3** in the form of its free base has a mp 134–136 °C (lit.[9] mp 139–143 °C); IR ($CHCl_3$) 3525, 3025, 2950, 1710, 1480, 1440, and 1280 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.44 (s, 3 H, NCH_3), 3.85 (s, 3 H. OCH_3), 4.28 (distorted d, J = 14 Hz, 1 H).
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N,N-Dialkyl-2-oxocycloalkanonecarboxamide Photochemistry. Possible δ-Hydrogen Abstraction in 2-Substituted Cycloalkanones

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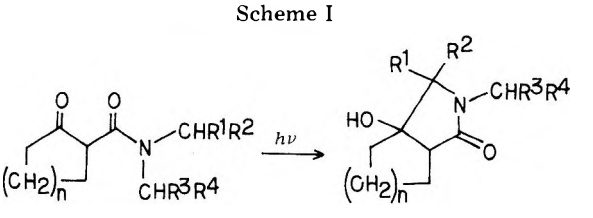
The Norrish types I and II reactions of ketones are the most widely studied of photochemical processes.[1] Cyclic ketones bearing γ hydrogens can undergo both reactions.[2] The rate of the type I reaction (α cleavage) is enhanced by a substituent on the α carbon, and reducing the size of the ring increases the rate of α cleavage.[2a,b] Consequently, little hydrogen abstraction is observed from 2-substituted cyclopentanones because the rate constant for γ-hydrogen abstraction is not fast enough to compete with the rate of α cleavage.[2a,b] It is well-known that the rate of δ-hydrogen abstraction is much slower than that of γ-hydrogen abstraction.[3] Therefore, there is no example of δ-hydrogen abstraction of 2-substituted cyclopentanones or cyclohexanones. We previously reported the photocyclization of acyclic β-oxo amides to pyrrolidin-2-ones[4] and now wish to report that of *N,N*-dialkyl-2-oxocycloalkanonecarboxamides to bicyclic lactams via an unprecedented δ-hydrogen abstraction in simple 2-substituted cycloalkanones.

Irradiation of a benzene solution of *N,N*-dibenzyl-2-oxocyclopentanecarboxamide (**1a**) in a Pyrex vessel under nitrogen with a high-pressure mercury lamp gave the bicyclic lactam **2a**, mp 116–117 °C, in 64% yield (see Scheme I). The structure of the lactam **2a** was elucidated by spectral data and elemental analysis. The IR spectrum of **2a** showed characteristic hydroxy (3400 cm^{-1}) and five-membered lactam carbonyl (1670 cm^{-1}) absorptions. The NMR spectrum showed a singlet at δ 4.17, attributable to the C-4 methine proton. These results indicate that only one stereoisomer was produced exclusively from the oxo amide **1a**. The C-4 phenyl group seems to be trans to the C-6 methylene group by analogy to pyrrolidin-2-ones.[4b] This configuration would be expected to be the more thermally stable. Similarly, irradiation of *N,N*-diisopropyl-2-oxocyclopentanecarboxamide (**1b**) and 2-oxocyclohexanecarboxamide (**1c**) under the same conditions also afforded the corresponding bicyclic lactams **2b** and **2c**, respectively. The structures of the lactams were determined by IR and NMR spectra and by elemental analyses. The ring-fusion stereochemistry of **2a**, **2b**, and **2c** was presumed

Scheme I



	1					2					
	n	R^1	R^2	R^3	R^4	*n*	R^1	R^2	R^3	R^4	yield, %
a,	1	H	Ph	H	Ph	1	H	Ph	H	Ph	64
b,	1	Me	Me	Me	Me	1	Me	Me	Me	Me	41
c,	2	Me	Me	Me	Me	2	Me	Me	Me	Me	46
d,	1	H	H	H	H	1	H	H	H	H	0
e,	2	H	H	H	H	2	H	H	H	H	0
f,	1	H	Ph	H	H	1	H	Ph	H	H	18

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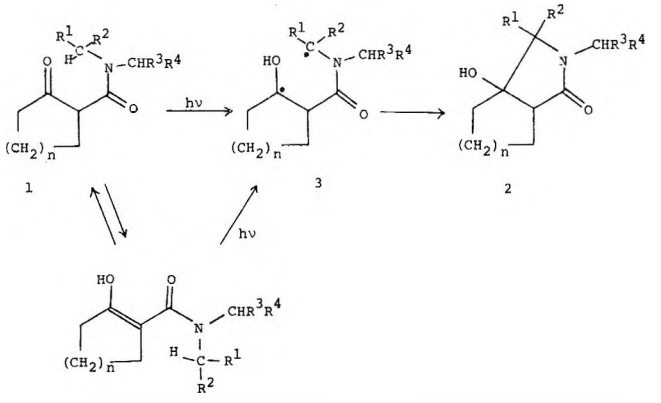

Figure 1. The process of δ-hydrogen abstraction through a seven-membered transition state.

to be cis because the alternative trans ring juncture would be energetically unfavorable.[5] The α-cleavage products could not be detected in photolysis of **1a**, while ca. 25% of the products (unsaturated aldehydes) were produced in the case of **1b**[6] and **1c**. But they were not completely purified. On the other hand, photolyses of *N,N*-dimethylcarboxamides **1d** and **1e** did not give lactams but only polymeric intractable material.

Formation of the bicyclic lactams can be explained in terms of photocyclization involving δ-hydrogen abstraction by the ketone carbonyl through a seven-membered transition state (see Figure 1). Another route which involves hydrogen abstraction by the olefinic carbon (C-2) of the enol form of **1** through a five-membered transition state seems to be improbable because (a) *N,N*-dibenzyl-2,2-dimethylbenzoylacetamide, which carries no enolizable hydrogens, also undergoes the cyclization[4b] and (b) hydrogen abstraction by an olefinic carbon through a five-membered transition state is a rarely observed process.[7]

The process of hydrogen abstraction through a seven-membered transition state is a surprisingly rare event in the photochemistry of cycloalkanones. The hydrogen abstraction in 2-oxocycloalkanonecarboxamides seems to be remarkably affected by substituents on the nitrogen atom. Substituents which stabilize the 1,5 biradical (**3**) apparently enhance the abstraction. This fact is further supported by the regioselectivity in the photoreaction of *N*-benzyl-*N*-methyl-2-oxocyclopentanecarboxamide (**1f**).

Irradiation of the oxo amide **1f** under the same conditions gave an *N*-methyl bicyclic lactam in 18% yield, which was produced through benzylic hydrogen abstraction by the ketone carbonyl. No *N*-benzyl bicyclic lactam, which would be formed through methyl hydrogen abstraction, was isolated. These results are consistent with the regioselectivity usually observed in the photochemistry of ketones[8] and seems to indicate that 2-oxocycloalkanonecarboxamides undergo photocyclization through the typical biradical intermediate.

Effective quenching of the photocyclization of the oxo amide **1a** by 0.1 M piperylene was not observed. This result indicates that the cyclization of the 2-oxocycloalkanonecarboxamide, like most cycloalkanones,[9] mainly proceeds from the n,π* singlet state of the oxxo amide, although a rapid triplet-state reaction is not necessarily eliminated from the available data.

A mechanism involving initial electron transfer from the amide nitrogen to the ketone carbonyl and subsequent δ-proton transfer[10] is also conceivable because intramolecular photoreactions via electron transfer are usually unquenchable[10] (see Figure 2). However, it is known that photoreduction of ketones by amines via electron or charge-transfer interaction does not show such regioselectivity as described above.[11] Davidson and Lambeth reported that the benzylic

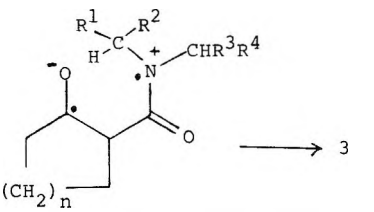

Figure 2. A mechanism involving an initial electron transfer from the amide nitrogen to the ketone carbonyl and subsequent δ-proton transfer.

C–H bond was less reactive than the methyl C–H bond in the photoreduction of benzophenone by N-alkylated diphenylamines.[12] Therefore, the mechanism involving electron transfer seems to be less probable, although the possibility can not be excluded.

In conclusion, the photocyclization of the *N,N*-dialkyl-2-oxocycloalkanonecarboxamides can be most reasonably explained in terms of δ-hydrogen abstraction from the n,π* singlet (or triplet) state. This indicates that δ-hydrogen abstraction is unusually fast. Such a rapid rate, however, is not unreasonable for the structure. The enhancement by a nitrogen atom is expected since atoms with lone pairs of electrons stabilize radicals.[8] Furthermore, **1a–c** have to rotate only two bonds to achieve the favored geometry for hydrogen abstraction because the α bond and the CO–N bond are fixed during the photoprocess. The frozen rotation in these cyclic oxo amides should further enhance the rate of the intramolecular hydrogen abstraction. Lewis et al. reported the remarkable rate enhancement in type II cyclization of conformationally restricted molecules.[13] Finally, these results indicate that δ-hydrogen abstraction in 2-substituted cyclopentanones or cyclohexanones occurs only when the δ hydrogens are strongly activated by substituents, and the abstraction is further enhanced by conformational factors.

Experimental Section

IR spectra were recorded with a Hitachi EPI-2 spectrometer and NMR spectra with a Hitachi R-20 spectrometer (tetramethylsilane as an internal standard). An Ushio 450-W high-pressure mercury lamp was used as the irradiation source.

The 2-oxocycloalkanonecarboxamides were prepared according to previously described methods.[14]

General Procedure for Photoreactions of 2-Oxocycloalkanonecarboxamides. A solution of the 2-oxocycloalkanonecarboxamide (**1**, 500 mg) in 80 mL of benzene was irradiated in a Pyrex vessel under nitrogen with a high-pressure mercury lamp. The solvent was removed in vacuo, and the residue was chromatographed on silica gel. Elution with benzene–ethyl acetate afforded the bicyclic lactams **2**.

(i) 3-Benzyl-5-hydroxy-4-phenyl-3-azabicyclo[3.3.0]octan-2-one (2a). Mp 116–117 °C; IR (KBr) 3400, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.4–1.2 (m, 6 H, CH_2), 2.7 (m, 1 H, 1-CH), 2.8 (brd s, 1 H, OH), 3.39 and 5.18 (AB q, 2 H, J = 15.0 Hz, CH_2Ph), 4.17 (s, 1 H, 4-CH), 6.0–7.45 (m, 10 H, aromatic).

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.18; H, 6.84; N, 4.46.

(ii) 5-Hydroxy-3-isopropyl-4,4-dimethyl-3-azabicyclo[3.3.0]octan-2-one (2b). Mp 114–115 °C; IR (KBr) 3350, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 6 H, 4-CH_3), 1.40 (d, 6 H, J = 6.0 Hz, $CH(CH_3)_2$), 1.5–2.1 (m, 6 H, CH_2), 2.6 (m, 1 H, 1-CH), 2.95 (s, 1 H, D_2O exchangeable), 3.30 (sep, 1 H, J = 6.0 Hz, $CH(CH_3)_2$).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.38; H, 9.85; N, 6.59.

(iii) 5-Hydroxy-3-isopropyl-4,4-dimethyl-3-azabicyclo[4.3.0]nonan-2-one (2c). Mp 147–148 °C; IR (KBr) 3400, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (s, 6 H, 4-CH_3), 1.3–1.7 (m, 8 H, CH_2), 1.42 (d, 6 H, J = 6.5 Hz, $CH(CH_3)_2$), 2.55 (m, 1 H, 1-CH), 2.60 (s, 1 H, OH, D_2O exchangeable), 3.37 (sep, 1 H, $CH(CH_3)_2$).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.10; H, 10.16; N, 6.05.

(iv) 5-Hydroxy-3-methyl-4-phenyl-3-azabicyclo[3.3.0]octan-2-one (2f). Mp 149–150 °C; IR (KBr) 3350, 1670 cm^{-1};

NMR ($CDCl_3$) δ 1.5–2.2 (m, 6 H, CH_2), 2.67 (s, 3 H, CH_3), 4.47 (s, 1 H, 1-CH), 7.0–7.4 (m, 5 H, aromatic).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.40. Found: C, 72.72; H, 7.31.

Registry No.—**1a**, 64425-71-4; **1b**, 64425 72-5; **1c**, 64425-73-6; **1f**, 64425-74-7; **2a**, 64425-75-8; **2b**, 64425-76-9; **2c**, 64425-77-0; **2f**, 64425-78-1.

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Reduction of Aromatic Amides by Sodium in Liquid Ammonia

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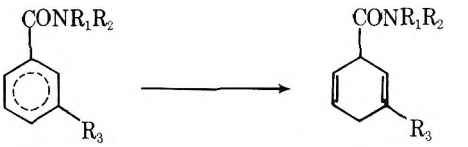
Because of reported variations for Birch reduction[1] of aromatic amides, we undertook a study of the reduction of benzamide (**1**), *m*-methoxybenzamide (**2**), *N*-methylbenzamide (**3**), and *N,N*-dimethylbenzamide (**4**).

We have found that some ring reduction of **1** to 1,4-dihydrobenzamide (**5**) occurs with sodium and either ethanol or *tert*-butyl alcohol while Kuehne and Lambert[2] report ring reduction with *tert*-butyl alcohol but not with ethanol. However we found *tert*-butyl alcohol more effective than ethanol with reduction proceeding well with 3.42 equiv of sodium regardless of whether the sodium or the *tert*-butyl alcohol was added last.[3]

In contrast ethanol gave poor and erratic results with the amount of **5** varying from reduction to reduction but never exceeding 50% when the procedure of adding sodium last was used. The crude product contained unreduced **1**, tetrahydro products, as well as **5** but not benzaldehyde or toluene. These latter two compounds were sought using GLC and were not found. Nor was any hydrobenzamide (**11**) found. Progressively increasing the sodium from 3.3 equiv to 5.0, 7.0, or 9.0 equiv progressively decreased the amount of unreduced **1**, increased the amount of tetrahydro products, but did not substantially increase **5**. This strongly suggests that **5** is an intermediate in the formation of the tetrahydroproducts. One experiment using 5.0 equiv of sodium plus an equimolar mixture of ethanol and *tert*-butyl alcohol gave no improvement over use of ethanol alone.

Also with *tert*-butyl alcohol, its addition last or sodium addition last made little or no difference. But in the case of ethanol, its addition last gave even less **5** than when sodium was added last.



1, R_1, R_2, R_3 = H
2, R_1, R_2 = H; R_3 = OCH_3
3, R_1, R_3 = H; R_2 = CH_3
4, R_3 = H; R_1, R_2 = CH_3

5, R_1, R_2, R_3 = H
6, R_1, R_2 = H; R_3 = OCH_3
7, R_1, R_3 = H; R_2 = CH_3

If no ammonium chloride was added to neutralize the alkoxide before work-up, then air oxidation of **5** to reform **1** occurred. A control experiment started with a solution of **5** in ammonia containing sodium ethoxide which was similarly exposed to air resulted in reformed **1**. Kuehne and Lambert[2] also report similar base-catalyzed air oxidations.

m-Methoxybenzamide (**2**) was reduced to 1,4-dihydro-3-methoxybenzamide (**6**) with 3.3 equiv of sodium and ethanol at −75 °C. At −33 °C more extensive reduction occurred yielding a mixture which was not separated. When 8.0 equiv of sodium at −33 °C was used, more extensive reduction resulted[4] in formation of 1,4,5,6-tetrahydro-3-methoxybenzyl alcohol (**8**). Kuehne and Lambert[2] report no reduction of **2** with 3.3 equiv of sodium and formation of **6** with 7.6 equiv of sodium.

While we can offer no firm explanation as to why our results[5] with **1** and **2** differ from those of Kuehne and Lambert,[2] it can be noted that the effects of many experimental variables on the Birch reduction are incompletely understood.[6]

Possibly more of their sodium was consumed in a side reaction. Thus reduction of **1** may have been too incomplete to be detected and reduction of **2** would have required more sodium. Such a side reaction might be sodium with alcohol and/or ammonia to produce hydrogen. Since their work, small amounts of colloidal iron, which commonly occur in commercial ammonia, have been reported to catalyze this reaction and affect Birch reductions.[6b-d]

An additional factor must be involved in the reduction of **1** with ethanol as more extensive reduction to tetrahydro products occurs. This consumes additional sodium but also requires formation of a conjugated diene as isolated double bonds are not reduced under these conditions. The conjugated diene could form if the more acidic ethanol is less specific in protonation of the anion intermediate than *tert*-butyl alcohol or by rapid rearrangement of initially formed unconjugated diene. The alkoxide produced in the reduction could catalyze this rearrangement and, as ethanol is reported[6b] to react faster than *tert*-butyl alcohol under these conditions, the more rapidly formed ethoxide could catalyze rearrangement faster than the more slowly formed *tert*-butoxide.

The following two experiments indicate the latter explanation is insufficient to explain the different results with ethanol and *tert*-butyl alcohol. Based on the report of Dryden[6b] that the presence of 0.5 or 1.0 ppm of iron increased the rate of the reaction of *tert*-butyl alcohol and sodium to that comparable to ethanol and sodium, we did a reduction using *tert*-butyl alcohol, adding 3.42 equiv of sodium last and having 1 ppm of iron present. There was a definite increase in the rate of disappearance of the sodium but **5** was still obtained in good yield and without any appreciable tetrahydro product. Another experiment using *tert*-butyl alcohol with 3.42 equiv of *tert*-butoxide initially present with 3.42 equiv of sodium

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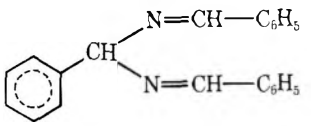
added last also yielded **5** in good yield without appreciable tetrahydro product. Possibly ethoxide catalyzes the double bond isomerization more rapidly than does *tert*-butoxide. Formation of more further reduced products with ethanol than with *tert*-butyl alcohol also occurs[6e] for reduction of anisoles and aromatic amines.

That ring reduction of **2** is easier than **1** is understandable as the methoxy group would stabilize the radical anion intermediate.[7] Anisole undergoes reduction more than three times faster than benzene.[8]

Reduction of *N*-methylbenzamide (**3**) resembled that of benzamide with ring reduction occurring with either ethanol or *tert*-butyl alcohol. With 5.0 equiv of sodium added last, ethanol gave some dihydro product (presumably 1,4-dihydro-*N*-methylbenzamide (**7**)), which was not successfully isolated, but mostly 1,4,5,6-tetrahydro-*N*-methylbenzamide (**9**), which was isolated and characterized. Use of *tert*-butyl alcohol added last and 3.42 equiv of sodium or use of ethanol and either 4.0 or 3.42 equiv of sodium added last yielded product which was largely the dihydro product and small amounts of starting material and tetrahydro product. Attempts to isolate the dihydro product by recrystallization were unsuccessful as the material underwent air oxidation back to **3** and some polymerization during these attempts. No presence of toluene or benzaldehyde was detected. No addition of NH_4Cl after reduction and before work-up resulted in increased **3** apparently reformed by air oxidation and little or no dihydro product.

The structure of **9** was assigned as NMR showed two vinyl hydrogens and the only other possibility with two vinyl hydrogens, 1,2,5,6-tetrahydro-*N*-methylbenzamide, was prepared and found not to be identical.

Unlike the other aromatic amides, *N,N*-dimethylbenzamide (**4**) underwent reduction of the amide group to form benzaldehyde (**10**) which was isolated as was hydrobenzamide (**11**), the condensation product of benzaldehyde and ammonia. The path for such a reduction has been proposed by Benkeser[9] for the related electrochemical reduction of amides and consists of stepwise addition of electrons and protons to the carbonyl group.



11

Although we found no toluene in the reduction of **4**, in principle it could form. Reduction of benzaldehyde to benzyl alcohol is to be expected[10] and benzyl alcohols are reduced to aromatic hydrocarbons under similar conditions.[6a,10]

Thus aromatic amides under Birch conditions follow a pattern of ring reduction if there is an amide hydrogen present and amide reduction if there is not. Presence of an amide hydrogen allows formation of an amide anion which protects the amide group from reduction.[2] When ring reduction occurs, it is in the 1,4 positions as with aromatic acids rather than in the 2,5 positions observed with most substituents. Thus aromatic amides with an amide hydrogen resemble aromatic acids and not aromatic amidines,[11] sulfonamides,[12] and sulfinic acids[13] which are reduced in the functional group and not in the ring.

Experimental Section[14]

Reduction of Benzamide (1). To a stirred, refluxing (−33 °C) mixture of 800 mL of NH_3, 200 mL of anhydrous *tert*-butyl alcohol, and 10.0 g (0.0826 mol) of **1** was added 6.3 g (0.274 g-atom, 3.32 equiv) of sodium in small pieces over a period of 10 min. After the deep blue color faded (15 min), 30 g of NH_4Cl was cautiously added and the ammonia was allowed to evaporate. The solid residue was dissolved in water and the organic material was extracted with four 250-mL portions of methylene chloride. The combined extracts were dried over $MgSO_4$. Evaporation of the solvent left 5.09 g (0.0413 mol, 50.0%) of solid, mp 137–143 °C, which NMR indicated was more than 90% 1,4-dihydrobenzamide (**5**) with possible small amounts of tetrahydro material and less than 10% of **1**. After two recrystallizations from benzene the mp was 152–153 °C [lit.[2] mp 154–155 °C]. Additional extracts could yield 3 to 4.5 g of less pure **5**.

After one reduction, 200 mL of ether was added and the ammonia was allowed to evaporate through two traps cooled in ice. GLC of the trapped liquid indicated no toluene. GLC of the ether layer indicated no toluene or benzaldehyde.

Reduction of 10.0 g (0.066 mol) of *m*-methoxybenzamide (**2**) was done as for **1** above but with 135 mL of absolute ethanol and a temperature (−75 °C) near dry ice. Seven extractions yielded 9.7 g (0.064 mol, 97%) of solid, mp 135–144 °C. Two recrystallizations from benzene and petroleum ether gave 3.25 g (32%) of 1,4-dihydro-3-methoxybenzamide (**6**), mp 161–163 °C [lit.[2] 158–160 °C].

Reduction of 10.0 g (0.074 mol) of *N*-methylbenzamide (**3**) was done as for **1** above but with 12 mL of absolute ethanol added last over 30 min. NMR of the 7.42 g of semisolid product, mp 72–74 °C, indicated small amounts of **3**, some 1,4,5,6-tetrahydro-*N*-methylbenzamide (**9**), but mostly material believed to be the expected 1,4-dihydro-*N*-methylbenzamide (**7**) (strong absorption at δ 5.8). Increasing the sodium to 5.0 equiv (8.51 g) yielded 9.23 g of viscous, brown liquid which NMR indicated was mostly **9**. GLC on 10 ft, 10% carbowax on 80/100 mesh firebrick treated with HMDS yielded sufficient **9**, mp 49–50 °C, for characterization: NMR ($CDCl_3$) δ 1.5–2.4 (complex m, 7 H, ring CH_2 and CH groups), 2.8 (d, 3 H, $NHCH_3$, J = 4.5 Hz), 2.7–3.2 (complex m, 1 H, –NH–), 5.5–6.2 (m, 2 H, vinyl H). Anal. Calcd for $C_8H_{13}ON$: C, 69.06; H, 9.35; N, 10.07; O, 11.51. Found: C, 69.07; H, 9.51; N, 10.07; O, 11.66.

Reduction of *N,N*-Dimethylbenzamide (4). From a procedure similar to that for **1** above, 10.0 g (0.0673 mol) of **4**, 5.11 g of sodium (0.222 g-atom, 3.3 equiv), and 9.0 mL of ethanol added last yielded 8.11 g of a viscous liquid which NMR indicated contained benzaldehyde, hydrobenzamide (**11**), and starting material. GLC confirmed the presence of benzaldehyde. From a similar reduction using 3.09 g (0.135 g-atom, 2.0 equiv) of sodium 0.42 g (0.0040 mol, 5.9% yield) of benzaldehyde was separated by means of sodium bisulite extractions and converted to 2,4-dinitrophenylhydrazone, mp 237–240 °C [lit.[15] 237 °C].

The **11** was identical to the authentic sample prepared from ammonia and benzaldehyde; after recrystallization four times from ethanol the mp was 103–104 °C [lit.[16] 102 °C]. Heating **11** produced 2,4,5-triphenylimidazole, mp 253–260 °C; after three recrystallizations from ethanol the mp was 274–275 °C [lit.[17] 276.5–277 °C]; picrate mp was 235–236 °C [lit.[18] mp 234 °C].

Whether ethanol or *tert*-butyl alcohol was used or whether the alcohol or the sodium was added last, the product was the same. Increasing the sodium to 5.0 or 10.0 equiv resulted in an uncharacterized, complicated mixture.

Acknowledgments. Appreciation is expressed to the Research Corp. for their support of the early stages of this investigation by a Frederick Gardner Cottrell grant, and to Dr. G. E. Pollard and the Shell Development Co., Modesto, Calif. for many of the NMR spectra.

Registry No.—**1**, 55-21-0; **2**, 5813-86-5; **3**, 613-93-4; **4**, 611-74-5; **5**, 64739-70-4; **6**, 64739-71-5; **7**, 64739-72-6; **9**, 64739-73-7; **10**, 100-52-7; **11**, 92-29-5; ammonia, 7664-41-7; sodium, 7440-23-5; 2,4,5-triphenylimidazole, 484-47-9.

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Stereochemistry of Grignard Additions to α-Keto Esters

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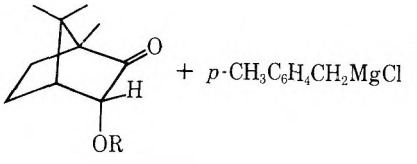
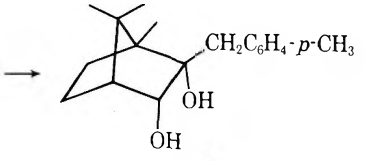
We have previously reported[1] unexpected stereospecificity in Grignard additions to α-keto esters in the bornane series and now wish to describe unexpected results obtained with a series of α-keto esters in the 2,2,5,5-tetramethyltetrahydrofuran series. In the earlier work, *cis*-2,3-dihydroxy-2- (or 3-) (*p*-methylbenzyl)bornanes were obtained from the four possible α-ketol *p*-chlorobenzoates even when this required the unusual exo attack of *p*-methylbenzylmagnesium chloride on the bornane system. For example, reaction of the *p*-chlorobenzoate **1a** of 3-*endo*-hydroxy-2-bornanone (**1b**) with the reagent afforded only 2,3-*cis*,*endo*-dihydroxy-2-*exo*-(*p*-methylbenzyl)bornane (**2**) and bis(*p*-methylbenzyl)-*p*-chlorophenylcarbinol (**3**).



1a, R = *p*-ClC$_6$H$_4$CO
b, R = H

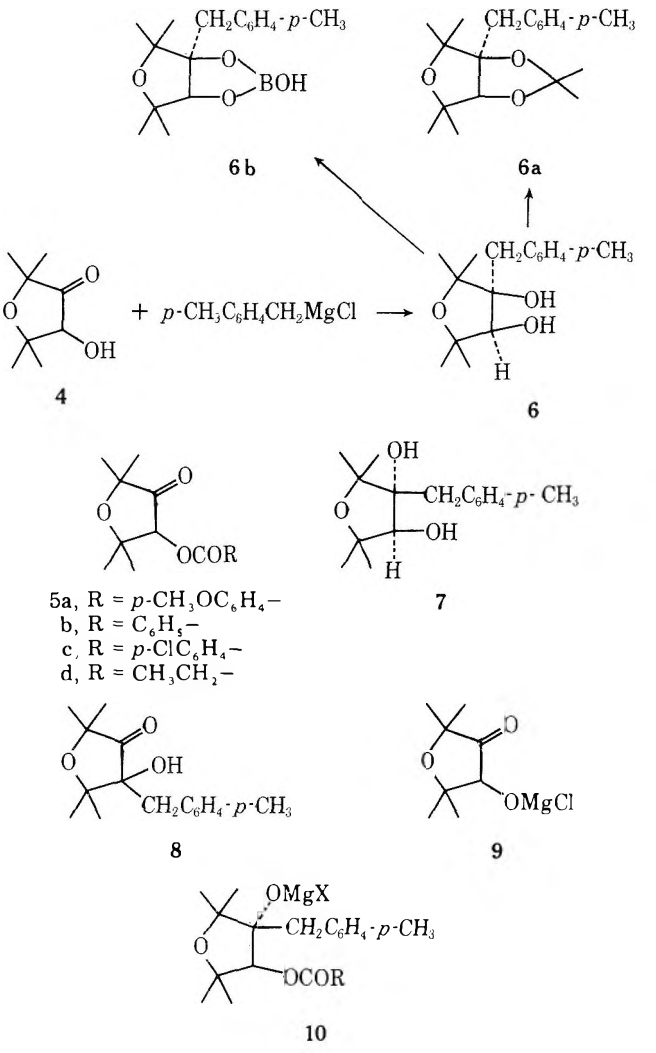


2

+ $(p\text{-}CH_3C_6H_4CH_2)_2CC_6H_4\text{-}p\text{-}Cl$ (OH)

3

In the course of an investigation of photochemical reactions of the unusual α-diketone, 2,2,5,5-tetramethyltetrahydrofuran-3,4-dione,[2] with aldehydes, the corresponding α-ketol **4** and a number of its esters (**5a–d**) became available. In view of the earlier results, it appeared of interest to investigate their reactions with the Grignard reagent. Reaction of **4** with *p*-methylbenzylmagnesium chloride afforded the *cis*-diol **6** in nearly quantitative yield. The cis configuration was assigned on the basis of rapid cleavage with sodium periodate and formation of an acetonide (**6a**) and a borate ester (**6b**), both of which regenerated **6** upon hydrolysis. The *trans*-diol **7** was obtained together with **6** and **6b** upon sodium borohydride reduction of 3-hydroxy-3-(*p*-methylbenzyl)-2,2,5,5-tetramethyltetrahydrofuran-4-one[2] (**8**) or together with **6** from Grignard reactions of the esters **5a–d**. Pure **7** was isolated from its mixture with **6** by reaction of the mixture with acetone and anhydrous cupric sulfate, followed by chromatographic separation of **7** from **6a**. In addition to this failure to form an acetonide, the trans configuration of **7** was confirmed by its complete failure to form a borate ester or to react with sodium periodate under conditions comparable to those used successfully with **6**. Both **6** and **7** were oxidized to **8** under mild conditions.



Gas chromatographic retention times of **6** and **7** differed markedly. It was thus readily possible to establish the stereochemistry of reaction of the esters **5a–d** with *p*-methylbenzylmagnesium chloride and to compare the results with the complete specificity observed in the bornane series and with **4**. Results of a series of experiments using a 3.5-fold excess of Grignard reagent are summarized in Table I. It is interesting

Table I. Reactions of Esters of 3-Hydroxy-2,2,5,5-tetramethyltetrahydrofuran-4-one (4) with *p*-Methylbenzylmagnesium Chloride[a]

Ester	Registry no.	*cis*-Diol **6**,[b] %	*trans*-Diol **7**,[b] %
p-Methoxybenzoate **5a**	64314-66-5	20	80
Benzoate **5b**	64314-67-6	25	75
p-Chlorobenzoate **5c**	64314-68-7	50	50
Propionate **5d**	64314-69-8	68	32

[a] Addition of ca. 0.08 M ester in ether to a 3.5-fold excess of ca. 0.34 M Grignard reagent in ether. [b] Determined by gas chromatographic analysis.

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to note the considerable variation in product composition; the least stabilized ester group, the propionate **5d**, afforded 68% of *cis*-diol **6** while the most stabilized ester, the *p*-methoxybenzoate **5a**, yielded only 20% of **6**. The only other compounds present in significant amounts were the appropriate tertiary alcohol and 1,2-bis(*p*-tolyl)ethane.[3]

These surprising results appear to reflect a competition between initial attack of Grignard reagent at the ester or at the ketone carbonyl groups,[4] in contrast to α-keto esters in the bornane series where it was shown that the initial attack occurred at the ester group to give an α-ketol (e.g., **1b**). In the case of initial attack at the ester group, which would be most preferred with **5d** and least so with **5a**, the initial product would be the same solvated magnesium salt **9** which is formed by reaction of **4** with the reagent. This species is attacked from the side of the molecule trans to the original ester or hydroxyl group either because of the considerable steric bulk of the solvated OMgCl group or due to stabilization of the transition state for *cis*-diol formation by coordination with magnesium or due to a combination of both factors.[5,6]

It then follows that the initial attack of reagent at the keto group of the intact keto ester involves considerable stereoselectivity in the opposite sense, with attack occurring preferentially from the same side as the ester group. The resulting intermediate, **10**, would then react further at the ester function to give *trans*-diol **7**. The factors responsible for this selectivity are unclear; possibly coordination of Grignard reagent with the ester carbonyl group plays a role. It might be noted that both benzoin and its methyl ether reacted stereospecifically with Grignard reagents;[7] both reactions followed the same stereochemical course.

Experimental Section

Melting points are uncorrected. Infrared spectra were determined in potassium bromide pellets and NMR spectra in deuteriochloroform solution at 60 MHz using tetramethylsilane as the internal standard.

Gas Chromatographic Analysis. A 10 ft × ⅛ in. glass column packed with 1% XE-60 on 100–120 mesh Gaschrom Q was used at 160 °C and 30 mL of N_2/min. Retention times were 1,2-bis(*p*-tolyl)ethane, 1.7; acetonide **6a**, 2.5; *cis*-diol **6**, 6.0; *trans*-diol **7**, 10.0; and tertiary alcohol **3**, 14.5 min.

***cis*-3-(*p*-Methylbenzyl)-2,2,5,5-tetramethyltetrahydrofuran-3,4-diol (6).** The Grignard reagent prepared from freshly distilled *p*-methylbenzyl chloride (0.56 g) and magnesium (0.12 g) in ether (5 mL) was treated with a solution of hydroxy ketone **4** (0.16 g) in ether (5 mL). After stirring at room temperature for 1.5 h, 1 drop of water was added, and the solution was poured into cold, dilute sulfuric acid. The layers were separated, the aqueous layer was washed twice with ether, and the combined ether extracts were washed with sodium bicarbonate solution, dried over sodium sulfate, and concentrated. The crude product was crystallized twice from hexane to give analytically pure **6** (0.25 g, 94%): mp 132.5–133 °C; IR max 3460, 3200 cm^{-1}; IR (CH_2Cl_2) 3560 cm^{-1}; NMR δ 1.16 (6 H), 1.33 (6 H), 1.66 (d, J = 7 Hz, 1 H) superimposed on a broad absorption centered at about 1.7 (1 H, both 1.66 and 1.7 disappeared on addition of deuterium oxide), 2.35 (3 H), 2.83 (2 H), 4.10 (d, J = 7 Hz, 1 H; converted to a singlet upon addition of deuterium oxide), 7.23 (4 H). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.79; H, 9.20.

A sample (5 mg) of **6** in a few drops of acetone was treated with a few drops of 8 N chromic acid solution, followed after 1 min by a few drops of methanol. Extraction with ethyl acetate, drying, and concentration to a small volume was followed by GC analysis. A peak identical in retention time with that of 3-(*p*-methylbenzyl)-3-hydroxy-2,2,5,5-tetramethyltetrahydrofuran-4-one[2] (**8**) was observed.

A solution of **6** (11 mg) in methanol (2 mL) was treated with an aqueous solution (0.75 mL) of sodium metaperiodate (0.5 g/3 mL). After 20 min at room temperature, crystals of sodium iodate began to separate; GC analysis after 10 h showed that all **6** had been consumed.

A solution of **6** (17 mg) in methanol (2 mL) was treated with an aqueous solution (7 mL) of boric acid (110 mg/20 mL). White crystals began to separate after 0.5 h. After 3 h at room temperature, the crystals of the borate ester **6b** were filtered: mp 184–187 °C; identical by comparison of the IR spectra with **6b** obtained from reduction of **8** with sodium borohydride.

Separation of Cis and Trans Diols. The mixture (1.05 g) of diols **6** and **7** from the reaction of **5c** with *p*-methylbenzylmagnesium chloride was dissolved in dry acetone (10 mL) and anhydrous cupric sulfate (1.0 g) added. The resulting slurry was stirred magnetically at room temperature and portions (1.0 g) of cupric sulfate were added after 24 and 48 h. Progress of the reaction was followed by GC. After 7 days, the peak for *cis*-diol **6** had almost completely disappeared with concomitant formation of the peak corresponding to acetonide **6a**; the peak for the trans-isomer **7** was unchanged. The solution was filtered, the cupric sulfate was washed with acetone, and the combined acetone solutions were evaporated under reduced pressure to give a colorless oil (1.04 g) which was chromatographed on Florisil (14 g). Elution with hexane afforded **6a** (0.27 g). A sample was evaporatively distilled at 150 °C (0.05 mm pressure) to give **6a** as a colorless oil: IR max (film) 1380, 1080 cm^{-1}; NMR δ 0.6 (3 H), 1.30 (9 H), 1.38 (3 H), 1.45 (3 H), 2.28 (3 H), 2.98 (2 H), 4.24 (1 H), 7.10 (4 H). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.46; H, 9.08.

Heating a sample of **6a** (8 mg) in 1 mL of 50% aqueous acetic acid for 4 h resulted in complete conversion to **6** as shown by GC monitoring of the reaction.

Further elution of the column with 50–80% benzene–hexane afforded crystalline *trans*-diol **7** (0.48 g), mp 108–115 °C. Crystallization from hexane gave the analytical sample of **7**: mp 120–120.5 °C; IR max 3560, 3345 cm^{-1}; IR (CH_2Cl_2) 3620, 3570 cm^{-1}; NMR δ 1.20 (3 H), 1.28 (6 H), 1.37 (3 H), 1.60 (br, 1 H, disappeared upon addition of deuterium oxide), 2.25 (d, J = 4 Hz, 1 H, converted to a singlet upon addition of deuterium oxide), 7.10 (d, J = 8 Hz, 2 H), 7.21 (d, J = 8 Hz, 2 H). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.67; H, 9.14.

7 was recovered unchanged after 24 h of treatment with sodium periodate or boric acid under conditions described above for **6**.

Reduction of 3-(*p*-Methylbenzyl)-3-hydroxy-2,2,5,5-tetramethyltetrahydrofuran-4-one (8) with Sodium Borohydride. A solution of **8**[2] (1.00 g) and sodium borohydride (0.60 g) in methanol (20 mL) was allowed to stand overnight at room temperature. Water (10 mL) and acetic acid (5 mL) were added and, after 10 min, the solution was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated salt solution, dried, and concentrated to give a clear oil (1.18 g) which was shown by GC analysis to contain **6** and **7** in a ratio of about 1:4.

The mixture was chromatographed on silica gel (35 g). Elution with 20% benzene–hexane afforded the borate ester **6b** (0.50 g). A sample was recrystallized from aqueous methanol to give **6b** as white crystals: mp 183–185 °C; IR max 3450 cm^{-1} (br). Elution with 10–40% ethyl acetate–benzene gave a mixture (0.74 g) of **6** and **7**.

The crude product from another reduction of **8** (0.25 g) was refluxed for 3 h in a solution prepared from sodium hydroxide (2 g), methanol (8 mL), and water (3 mL). After the usual workup the crude product (0.22 g) was shown by GC analysis to contain 43% of **6** and 57% of **7**.

Reactions of Keto Esters 5a–d with *p*-Methylbenzylmagnesium Chloride. Solutions of esters in anhydrous ether (1 g of ester/50 mL of ether) were added to a 3.5-fold excess of Grignard reagent prepared from magnesium and *p*-methylbenzyl chloride in ether (1 g of chloride/25 mL of ether). Reaction times and workup were as described above for the reaction of **4**. The crude reaction products were analyzed by gas chromatography. No significant peaks were observed except those due to 1,2-bis(*p*-tolyl)ethane, **6**, **7**, and the tertiary alcohol derived from the ester.

Acknowledgment. Technical assistance was provided by Mr. K. Jenni.

Registry No.—**4**, 14744-19-5; **6**, 64314-70-1; **6a**, 64314-71-2; **6b**, 64314-72-3; **7**, 64314-73-4; **8**, 64314-74-5; *p*-methylbenzylmagnesium chloride, 29875-07-8.

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Synthesis of α,β-Unsaturated Carbonyl Compounds by Palladium(II)-Catalyzed Dehydrosilylation of Silyl Enol Ethers

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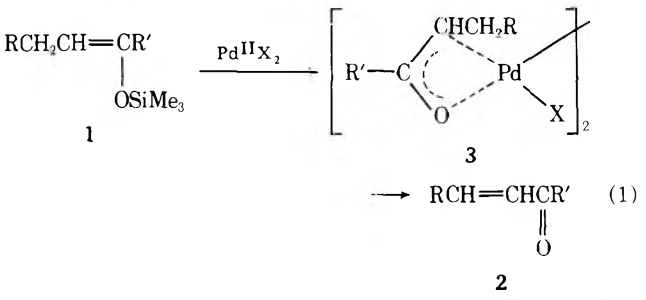
α,β-Unsaturated carbonyl compounds are very versatile in organic syntheses, especially in the synthesis of steroidal natural products, and various methods for the introduction of the α,β carbon–carbon double bond to ketones and aldehydes have been explored.[1] One of the general approaches to α,β-unsaturated carbonyl compounds involves direct dehydrogenation of the corresponding saturated carbonyl compounds with strong oxidizing agents.[2] It has been reported that $Pd^{II}Cl_2$ catalyzes the dehydrogenation of saturated ketones to give the corresponding α,β-unsaturated ketones,[2d-f] but the conversion in this direct dehydrogenation using $Pd^{II}Cl_2$ catalyst is generally low, and the products are complicated because of the lack of regiospecificity in the case of unsymmetrical ketones.

We have already reported a new synthesis of 1,4-diketones by the reaction of silyl enol ethers with Ag_2O, in which Ag(I) enolate intermediates are assumed.[3] Herein, we wish to report a new and versatile method for the preparation of α,β-unsaturated carbonyl compounds (**2**) by the reaction of silyl enol ethers (**1**) with $Pd^{II}(OAc)_2$ in acetonitrile, in which an intermediate of the oxo-π-allylpalladium(II) complex (**3**)[4] may be involved. An interesting feature of this reaction is the regiospecific introduction of an α,β carbon–carbon double bond to unsymmetrical ketones via the corresponding silyl enol ethers as shown in eq 1.



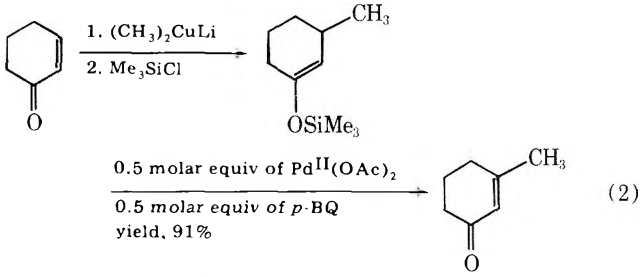
1 → 3 → RCH=CHCR' (1), O; 2

A general experimental procedure is illustrated as follows. To a stirring solution of $Pd^{II}(OAc)_2$ (0.5 mmol) and *p*-benzoquinone (0.5 mmol) in acetonitrile (4 mL), silyl enol ether (1.0 mmol) was added under nitrogen at room temperature, and then the resultant mixture was stirred for 2–30 h. Gas chromatography of the reaction mixture indicated that the desired α,β-unsaturated carbonyl compound **2** was produced in an excellent yield together with a few percent of the corresponding saturated carbonyl compound. The product of **2** was isolated by column chromatography on silica gel eluting with benzene and identified by comparison of its IR and NMR spectra with those of an authentic sample. Some results are summarized in Table I.

Use of a stoichiometric amount of $Pd^{II}(OAc)_2$ in the above reaction afforded a quantitative yield of the desired α,β-unsaturated carbonyl compound even in the absence of *p*-benzoquinone. Therefore, *p*-benzoquinone in the present reaction appears to function to regenerate an active Pd(II) species.[2d] In fact, 1,4-bis(trimethylsilyloxy)benzene and *p*-trimethylsilyloxyphenol were isolated from the reaction mixture. When $Pd^{II}(OAc)_2$ was decreased to 0.25 molar equiv in the presence of 1.0 molar equiv of *p*-benzoquinone, however, the dehydrosilylation was decelerated remarkably, resulting in a considerable decrease in the yield of α,β-unsaturated carbonyl compound **2** and an increase in the yield of the corresponding saturated carbonyl compound (run no. 3). Use of $Pd^{II}Cl_2$ instead of $Pd^{II}(OAc)_2$ produced a moderate yield of α,β-unsaturated carbonyl compound, being contaminated with a substantial amount of the saturated carbonyl compound (run no. 4). The less effectiveness of $Pd^{II}Cl_2$ may be due to the poor solubility of $Pd^{II}Cl_2$ in acetonitrile. The $Pd^{II}Cl_2$–$(C_6H_5CN)_2$ complex, which is soluble in benzene, furnished an improved result (run no. 5).

Regiospecificity of this reaction is illustrated by the dehydrosilylations with 2- (**1d**)[5] and 6-methyl-1-trimethylsilyloxy-1-cyclohexene (**1e**) producing a 94% yield of 2-methyl-2-cyclohexenone (**2d**) and an 85% yield of 6-methyl-2-cyclohexenone (**2e**), respectively, without being contaminated with any isomeric cycloolefinic ketones (runs no. 7 and 8).

Furthermore, the combination of this dehydrosilylation with the preparation[6] of silyl enol ethers from enolates, which were generated regiospecifically by the conjugate addition of lithium dialkylcopper to α,β-unsaturated carbonyl compounds, makes the present synthesis of α,β-unsaturated carbonyl compounds more useful, as exemplified in eq 2.



(2)

Another important feature of the present reaction is the stereoselectivity of the olefin geometry of the α,β-unsaturated carbonyl compounds produced. The $Pd^{II}(OAc)_2$-induced dehydrosilylation of an *E* and *Z* mixture of 1-trimethylsilyloxy-1-cyclododecene (**1g**) produced selectively (*E*)-2-cyclododecenone (**2g**) in a 94% yield. Similarly, (*E*)-3-nonen-5-one (**2h**) and (*E*)-2-hexenal (**2i**) were produced selectively by the dehydrosilylations of an *E* and *Z* mixture of 5-trimethylsilyloxy-4-nonene (**1h**) and 1-trimethylsilyloxy-1-hexene (**1i**), respectively. No *Z* products have been observed.

The Pd(II)-catalyzed dehydrosilylation in this study, which may be regarded as a reverse reaction of the transition-metal-induced 1,4-addition of hydrosilanes to α,β-unsaturated carbonyl compounds,[7] is considered to involve the oxo-π-allylpalladium(II) complex (**3**)[4] as a key intermediate. Actually, in the reaction of the silyl enol ether of acetophenone with $Pd^{II}Cl_2$ a stable oxo-π-allylpalladium(II) complex corresponding to **3** was isolated. Work is in progress to investigate a full scope of the synthesis of α,β-unsaturated carbonyl compounds and the chemistry of oxo-π-allylpalladium(II) complexes.

Experimental Section

Materials. Silyl enol ethers (**1**) were prepared from the corresponding ketones, aldehydes, and trimethylchlorosilane according to the reported procedure.[8] 3-Methyl-1-trimethylsilyloxy-1-cyclohexene was prepared by the conjugate addition of lithium dimethylcopper to 2-cyclohexenone followed by treating with trimethylchlorosilane according to the reported procedure.[6] $Pd^{II}(OAc)_2$ and $Pd^{II}Cl_2$ were commercial reagents. $Pd^{II}Cl_2$–$(C_6H_5CN)_2$ was prepared according to the reported procedure.[9]

Preparation of 2-Cyclohexenone by $Pd^{II}(OAc)_2$-Catalyzed Dehydrosilylation of 1-Trimethylsilyloxy-1-cyclohexene (1b). To a clear solution of 112 mg (0.5 mmol) of $Pd^{II}(OAc)_2$ and 54 mg (0.5 mmol) of *p*-benzoquinone in 4 mL of acetonitrile, 170 mg (1.0 mmol) of 1-trimethylsilyloxy-1-cyclohexene (**1b**) was added with stirring under nitrogen at room temperature, and then the mixture was stirred for 3 h. Gas chromatography of the reaction mixture indicated 2-

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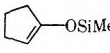
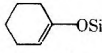
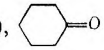
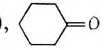
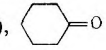
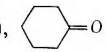
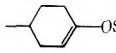
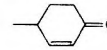
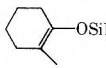
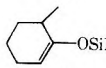
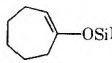
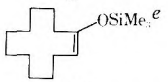
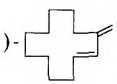
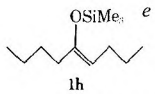
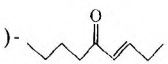
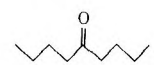
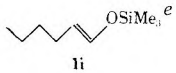
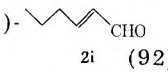
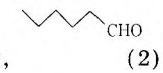
Table I. Preparation of α,β-Unsaturated Carbonyl Compounds by Pd(II)-Catalyzed Dehydrosilylation of Silyl Enol Ethers[a]

Run no.	Silyl enol ether 1	Registry no.	Pd(II) salt (equiv)	Registry no.	Reaction, h	Registry no.	Products (%)[b]	Registry no.
1	 1a	19980-43-9	$Pd(OAc)_2$ (0.5)	3375-31-3	2	930-30-3	 2a (98),  (1)	120-92-3
2	 1b	6651-36-1	$Pd(OAc)_2$ (0.5)		3	930-68-7	 2b (95),  (3)	108-94-1
3	1b		$Pd(OAc)_2$[c] (0.25)		26		2b (61),  (20)	
4	1b		$PdCl_2$[c] (0.5)	7647-10-1	26		2b (50),  (42)	
5	1b		$PdCl_2(PhCN)_2$[c,d] (0.5)	14220-64-5	3		2b (76),  (15)	
6	 1c	38671-78-2	$Pd(OAc)_2$ (0.5)		5	5515-76-4	 2c (91),  (8)	589-92-4
7	 1d	19980-35-9	$Pd(OAc)_2$ (0.5)		30	1121-18-2	 2d (94),  (5)	583-60-8
8	 1e	19980-33-7	$Pd(OAc)_2$ (0.5)		5	6610-21-5	 2e (85),  (8)	
9	 1f	22081-48-7	$Pd(OAc)_2$ (0.5)		2	1121-66-0	 2f (91),  (8)	502-42-1
10	 1g[e]		$Pd(OAc)_2$ (0.5)		4	6221-50-7	(E)-  2g (94),  (4)	830-13-7
11	 1h[e]		$Pd(OAc)_2$ (0.5)		3	52688-00-3	(E)-  2h (97),  (2)	502-56-7
12	 1i[e]		$Pd(OAc)_2$ (0.5)		3	6728-26-3	(E)-  2i (92),  (2)	66-25-1

[a] Dehydrosilylation was carried out by mixing 1.0 mmol of silyl enol ether and 0.5 mmol of $Pd(OAc)_2$ in 4 mL of acetonitrile in the presence of 0.5 mmol of *p*-benzoquinone at room temperature, unless otherwise stated. [b] Yields based on the starting silyl enol ether are determined by GLC. [c] 1.0 mmol of *p*-benzoquinone was used. [d] Benzene (4 mL) was used instead of acetonitrile solvent. [e] An *E* and *Z* mixture.

cyclohexenone was produced in a 95% yield together with a 3% yield of cyclohexanone. 2-Cyclohexenone was isolated in about 85% yield by column chromatography on silica gel eluting with benzene.

$Pd^{II}(OAc)_2$-catalyzed dehydrosilylation of other silyl enol ethers (1) was similarly carried out. The reaction time is indicated in the Table I. Products of α,β-unsaturated carbonyl compounds were identified by comparison of their IR and NMR spectra with those of authentic samples. The stereochemistry of (*E*)-2-cyclododecenone (**2g**) and (*E*)-2-hexenal (**2i**) was convincingly confirmed by comparison of their IR and NMR spectra with those of authentic samples.[10] The stereochemistry of (*E*)-3-nonen-5-one (**2h**) was determined by the NMR coupling constant (J_{H-H} = 15.6 Hz) of the olefinic protons.

Preparation of 2-Cyclohexenone by $Pd^{II}Cl_2$-$(C_6H_5CN)_2$-Catalyzed Dehydrosilylation of 1-Trimethylsilyloxy-1-cyclohexene (1b). A mixture of 54 mg (0.5 mmol) of *p*-benzoquinone and 192 mg (0.5 mmol) of $Pd^{II}Cl_2$-$(C_6H_5CN)_2$ was dissolved in 4 mL of benzene with stirring. To the homogeneous solution, 170 mg (1.0 mmol) of 1-trimethylsilyloxy-1-cyclohexene (**1b**) was added, and then the reaction mixture was stirred at room temperature for 3 h. The product of 2-cyclohexenone was isolated by column chromatography on silica gel eluting with benzene.

Registry No.—(*Z*)-**1g**, 55314-46-0; (*E*)-**1g**, 55314-44-8; (*Z*)-**1h**, 64682-31-1; (*E*)-**1h**, 64682-32-2; (*Z*)-**1i**, 64728-30-9; (*E*)-**1i**, 64682-33-3.

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(5) The $Pd^{II}(OAc)_2$-catalyzed dehydrosilylation of **1d** proceeded very slowly but gave a good yield of 2-methyl-2-cyclohexenone (**2d**) without loss of regiospecificity.

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Structure and Reactivity.[1] 2. 2-*tert*-Butyl-3-cyano-7-oxabicyclo[4.1.0]heptane Stereoisomers: Pseudoaxial *tert*-Butyl Conformer and Epoxidation Reaction Path

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The stereoselectivities of alkene epoxidations are sometimes rather difficult to rationalize;[2] for the two examples given in Figure 1, the inhibited syn attact is obviously related to steric hindrance, the cyano group being also rather bulky in syn-1,3 situations; the electrostatic interaction of this group may also play a part in this stereoselectivity.

When the cyano group is equatorial, no stereoselectivity occurs: 50% of anti attack on *trans*-4-cyano-5-phenylcyclohexene in 1,2-dichloroethane as a solvent.[4]

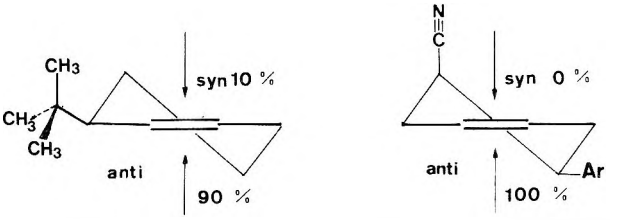

Figure 1. Induced stereoselectivities in the epoxidation of 3-*tert*-butylcyclohexene[3] and 4-cyano-5-arylcyclohexene.[4]

Taking into account these results and the observed stereoselectivity for 4-cyanocyclohexene, 82 to 90% of anti attack,[5] and also the conformational populations for this compound ($\Delta G° \simeq 0$),[6] one can predict the ratio of the rates of anti attack (k(a)) on each conformer (a and e)

$$3{,}5 < (k_a(a)/k_e(a)) < 8$$

This result lacks in precision, but it shows a faster attack on the conformer with an axial cyano group. This analysis is based on the reasonable assumption, first made by Rickborn and Lwo,[7] that the transition state conformation must be very similar to that of the starting alkene; the use of the ground state populations is then possible without violating the Curtin–Hammet principle.[8]

The problem of the epoxidation of *cis*- and *trans*-3-*tert*-butyl-4-cyanocyclohexenes must be also related to their conformational behavior:

(a) For the cis isomer, there is only one conformer at room temperature, the one with a pseudoequatorial *tert*-butyl group and an axial cyano substituent; the ring is in a half-chair conformation; this information has been established by NMR study[9] and an x-ray crystal structure analysis.[10]

(b) For the trans isomer, NMR[9] and vibrational[11] studies agree with two equally populated conformers.

(c) The "pseudoequatorial *tert*-butyl" conformer of this trans isomer has a *sofa* conformation similar to the one which has been determined in the crystallographic study of *trans*-1-acetoxy-3-*tert*-butyl-4-cyanocyclohexene;[12] the ring dihedral angles are $\phi_{12} = -4.3°$, $\phi_{23} = -1.1°$, $\phi_{34} = +29.4°$, $\phi_{45} = -58.6°$, $\phi_{56} = +53.3°$, $\phi_{61} = -23.5$; the dihedral angle of the *tert*-butyl and the cyano C–C bonds is 86.5°.

(d) For the second conformer of the trans isomer ("pseudoaxial *tert*-butyl") we can reasonably expect another *sofa* conformation in which the axial character of the *tert*-butyl group would be less pronounced than in a half-chair conformation.

These conformational data are sufficiently uncommon to justify a study of the reactivity of these compounds; the epoxidation reaction is especially interesting owing to the relative simplicity of the reaction path (one-step reaction).

Results and Discussion

The epoxidation of *cis*-3,6,6-trideuterio-3-*tert*-butyl-4-cyanocyclohexene by *p*-nitroperbenzoic acid in chloroform gives only one compound **1**, which is proved by gas chromatography and NMR spectroscopy. Except small differences in chemical shifts and in coupling constants, the NMR spectra of **1** and of its parent cyclohexene are quite identical.

The corresponding set of NMR parameters is reported in Table I. Long-range coupling constants (^4J) are observed between each of the two bridgehead protons (H_1 and H_6) and a proton located near the cyano group (H_3 and H_4, respectively); the difference between these two coupling constants is small but sufficient to allow the identification of transitions of protons H_1 and H_6. The coupling between H_6 and one of the

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Table I. NMR Parameters [a] of Deuteriated 2-*tert*-Butyl-3-cyano-7-oxabicyclo[4.1.0]heptanes

		1			2			3		
		b	*c*	*d*	*b*	*c*	*d*	*b*	*c*	*d*
$(CH_3)_3C$		1.14	1.13	1.10	1.08	1.08	1.08	1.08	1.08	1.08
H_{3c}		2.86	2.97	2.68				2.66	2.71	2.59
H_{3t}					2.14	2.43	2.11			
H_{4c}		1.57	1.50	1.48	1.85	1.86	1.84	1.81	1.89	1.80
H_{4t}		1.78	1.71	1.66	1.68	1.78	1.65	1.54	1.64	1.52
H_1		3.16	3.10	2.93	2.95	3.04	2.89	3.10	3.13	3.04
H_6		3.31	3.19	3.08	3.05	3.12	2.99	3.16	3.22	3.20
^3J	1–6	3.9	4.0	3.9	4.0	4.0	4.2	4.2	4.2	4.0
	3_c–4_c	2.6	2.9	2.9				4.2	4.0	4.1
	3_c–4_t	4.2	4.1	4.2				4.6	4.9	4.9
	3_t–4_c				12.9	12.8	12.7			
	3_t–4_t				3.9	3.8	4.0			
	3_t–D						1.4			
^2J	4_c–4_t	−13.4	−13.6	−13.6	−13.2	−13.3	−13.2	−13.6	−13.2	−13.8
^4J	6–4_t	0.8	0.8	0.9						
	1–3_c	1.0	1.0	1.0						

[a] Me_4Si as a reference for the chemical shifts δ; T = 303 K. [b] Solvent $CDCl_3$. [c] Solvent $(CD_3)_2CO$. [d] Solvent CS_2.

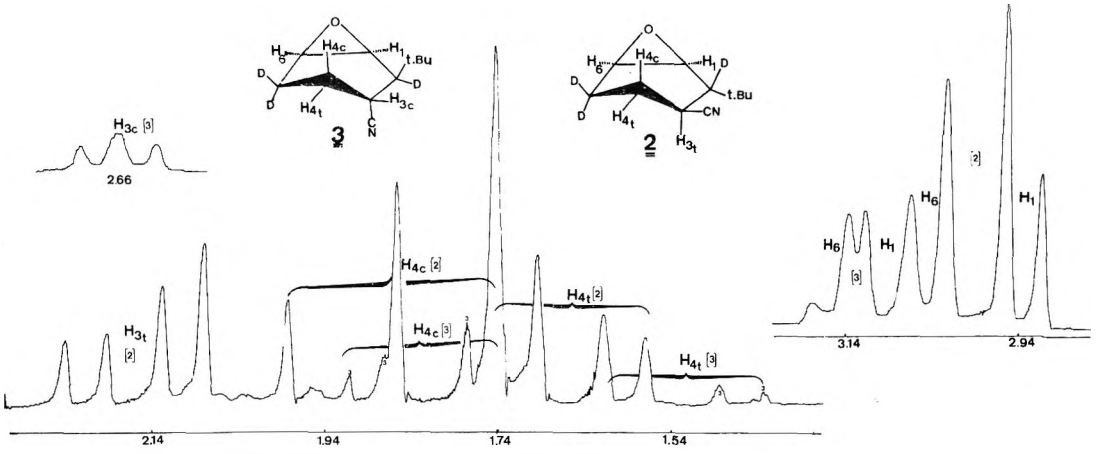

Figure 2. Deuterium decoupled 100-MHz NMR spectrum of a mixture of isomer epoxides **2** and **3**.

H_4 protons involves an equatorial situation of the latter; the vicinal coupling constants (^3J) between H_3 and H_4 protons (2.9 and 4.2 Hz) require an equatorial H_3 proton.

Our assumption that the epoxy bridge of **1** is trans with respect to the two other substituents is supported by the stereoselectivity of the reaction (Figure 1), the syn approach of the peroxy acid being hindered by the two substituents.

The epoxidation of *trans*-3,6,6-trideuterio-3-*tert*-butyl-4-cyanocyclohexene gives a mixture of isomers, where **2** is the major one (87% estimated by GC). In the NMR spectrum of this mixture (Figure 2), the identification of the lines corresponding to **2** is straightforward; thus, when the deuterium decoupling is stopped, the four lines at δ 2.14 give four triplets ($^3J_{HD}$ = 1.4 Hz); therefore, we have a proof that this proton is coupled to only one deuterium, and the value $^3J_{HD}$ (equivalent to $^3J_{HH} \simeq 9$ Hz) agrees with an anti relationship of the two nuclei; then, these lines are those of proton H_3, this one being preferentially axial. The splitting at $\delta \simeq 1.85$ results from two large couplings and the three lines are attributed to the axial H_4 proton. The attribution of protons H_1 and H_6 is allowed by the observation of a difference between the half-height line widths (^4J coupling between H_6 and H_{4t}) and by the examination of the spectrum without deuterium decoupling (triplets for H_1 lines).

The NMR spectrum (Figure 2) of the minor isomer **3** is clear enough to obtain all its parameters, the overlap of the spectra being limited. The low-field lines (δ 2.66) are attributed to the H_{3c} proton, the equatorial situation of which is strongly suggested by the high chemical shift and by the narrowness of the signal (8.8 Hz). Once again, the axial and equatorial positions of H_{4c} and H_{4t} respectively are proved by examination of the spectrum without deuterium decoupling (H_{4c} lines being broader than H_{4t} ones); further, the effect of $Eu(fod)_3$ is 1.6 times stronger for H_{4c} than for H_{4t}.

The NMR parameters obtained after LAOCOON analysis of the spectra of **2** and **3** are reported in Table I; the vicinal coupling constants of **3** are small ($^3J_{34} \simeq 4.2$ Hz), which is a proof of the larger stability of the conformer with an axial cyano group (equatorial H_3); this conformer must have a pseudoaxial *tert*-butyl group.

Our assumption about the relative positions of the epoxide ring (Figure 3) can be justified: (a) by the stereoselectivity of the epoxidation which is mainly governed by the hindrance of the *tert*-butyl group (no effect of the equatorial cyano group in the starting cyclohexene); and (b) by the conformational equilibrium of **3**, only possible with a trans relationship between the epoxide ring and the axial cyano group. For the opposite assumption the two dipoles of these groups would be roughly parallel and would display a repulsive electrostatic interaction, the importance of which can be estimated to 0.9 kcal mol^{-1}.[13]

For compound **1**, the 4.2 Hz value of the ^3J coupling constant between the trans protons H_{3c} and H_{4t} is consistent with a large proportion of the conformer with the *tert*-butyl and

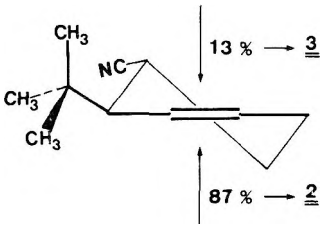

Figure 3. Stereoselectivity in the epoxidation of *trans*-3-*tert*-butyl-4-cyanocyclohexene.

cyano groups pseudoequatorial and axial, respectively, just as in the parent cyclohexene.[9]

For compound **2**, the trans coupling constant (between H_{3t} and H_{4c}) has the same magnitude (12.8 Hz) as the specific coupling constant of a diequatorial conformer. Thus, we observe an important difference with the parent cyclohexene in which the two conformers are equally populated; this difference can be ascribed to the unfavorable electrostatic interaction between the epoxy and cyano groups in the diaxial conformer of **2**.

The most striking result is obtained with epoxide **3** for which the diequatorial conformer is much less populated than the diaxial one, in spite of the steric interaction between the *tert*-butyl and epoxide groups in this latter conformer. To explain this fact, we cannot argue that there is a balancing between this *tert*-butyl epoxide interaction and a stronger *tert*-butylcyano gauche interaction (in the diequatorial conformer) because this latter interaction, acting alone in the parent cyclohexene, only leads to a 1:1 conformational equilibrium.

To explain the conformational equilibrium of **3**, we must investigate the possibilities of minimization of the different steric interactions by ring distortions. In the diequatorial conformer, the evolution from a *half-chair* to a *sofa* conformation relieves the *tert*-butylcyano gauche interaction, but the *tert*-butyl group is taking an isoclinal position[14] which increases its interaction with the oxygen atom.[15] Thus, the diequatorial conformer presents conflicting interactions which are not operative in the diaxial conformer; in that one, the evolution to a *sofa* conformation decreases the axiality of the *tert*-butyl group, relieving the *tert*-butyl epoxide interaction which is not outweighed by any other steric interaction.

In this coherent interpretation, the terms pseudoequatorial and pseudoaxial are meaningless in describing the conformational positions of the *tert*-butyl group. These terms are still useful as we initially make reference to half-chair conformers.

Reaction Paths

For the epoxidation of *trans*-3-*tert*-butyl-4-cyanocyclohexene, an energy profile is proposed (Figure 4) which points out the equal stabilities of the ee′ and aa′ cyclohexene conformers and, for the minor product **3**, the energy difference between the two conformers.

The two reaction paths leading to this product proceed through transition states whose relative energies reflect more or less those of the conformers of **3** according to the nature of these transition states, $\Delta G^{\ddagger}$ being zero for a reactant-like transition state or being equal to $\Delta G°$ (**3**) for a product-like transition state. At least, the reaction path which takes off from the aa′ cyclohexene is responsible for 50% in the formation of **3**, but that extreme situation corresponds to the unlikely assumption of a reactant-like transition state; moreover, this reaction path is favored by the axial position of the cyano group (see the introductory section).

Therefore, the epoxide **3** is mainly obtained from the aa′ cyclohexene conformer; this conclusion elucidates why the

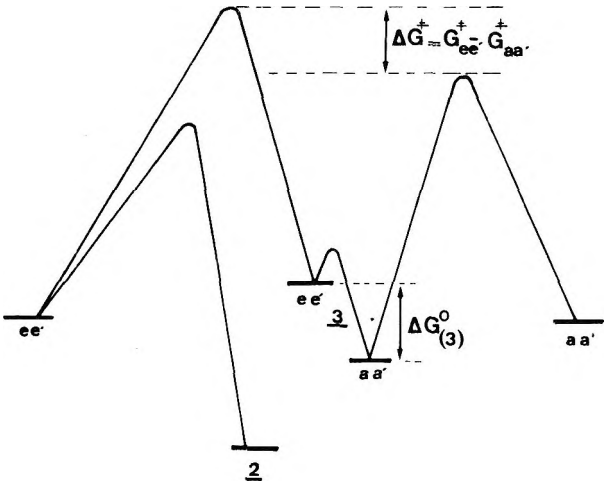

Figure 4. Energy profile of the epoxidation of *trans*-3-*tert*-butyl-4-cyanocyclohexene (product-like transition state hypothesis).

stereoselectivity is only 74% which is lower than that of the 3-*tert*-butylcyclohexene epoxidation (80%). A higher stereoselectivity (>80%) was effectively expected for the epoxidation of the ee′ conformer of *trans*-3-*tert*-butyl-4-cyanocyclohexene; with respect to a syn attack, the *tert*-butyl group of its *sofa* conformation causes greater hindrance to syn attack than the same group in the half-chair conformation of 3-*tert*-butylcyclohexene.

Conclusion

This study of the epoxidation of strongly strained molecules shows that a good knowledge of energetical and geometrical data on the reactants and on the products is a prerequisite to any interpretation of the stereoselectivity.

Experimental Section

NMR spectra were recorded on a Varian XL 100 spectrometer equiped with an heteronuclear spin decoupler.

Epoxidations were achieved according to ref 16. The ratios of epoxides **2** (retention time: 50 min) and **3** (retention time: 22 min) were determined by gas chromatography with a digital integrator (LTT 4200) operating at the output of a Girdel 300 chromatograph (column Reoplex 10% on Chromosorb W 60/80 non-Acid Washed, at 120 °C).

For epoxide **1** (retention time: 23 min) mp 50–51 °C (uncorrected).

Registry No.—**1**, 64683-03-0; **2**, 64726-48-3; **3**, 64726-49-4; *cis*-3,6,6-trideuterio-3-*tert*-butyl-4-cyanocyclohexene, 63125-70-2; *trans*-3,6,6-trideuterio-3-*tert*-butyl-4-cyanocyclohexene, 63125-66-6.

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(15) In a *sofa* conformation, one of the methyls of the *tert*-butyl group would be 2.6 Å away from the oxygen atom, the sum of the van der Waals radii being 3.4 Å; the first distance has been calculated by using the geometry of the corresponding cyclohexene,[10] the oxygen being located on this structure at 1.42 Å from the C_1 carbon and in a plane having a 104° dihedral angle with the C=C—C plane.
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Decomposition Kinetics of Isopropyl *tert*-Butyl Peroxide[1]

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In general, thermal decompositions of di-*tert*-alkyl peroxides occur by the unimolecular homolytic cleavage of the oxygen–oxygen linkage of the peroxide functionality.[2] Similarly, radical induced decompositions of di-*tert*-alkyl peroxides generally involve attack by the radical at the peroxide functionality.[3] In contrast, the chemistry of primary and secondary alkyl peroxides suggests extensive involvement of the α hydrogens of the alkyl groups in their decompositions as evidenced by the formation of molecular hydrogen in intramolecular, nonradical forming, decomposition reactions.[4] Hydrogen formation via an intramolecular decomposition is not possible for dialkyl peroxides having one tertiary alkyl group and, therefore, only one primary or secondary alkyl group. Hiatt and his co-workers[5] found, for example, that *tert*-butyl diphenylmethyl peroxide yielded no molecular hydrogen on decomposition. They also reported that the thermolysis was a first-order reaction with kinetic parameters that suggested that decomposition proceeded by unimolecular cleavage of the oxygen–oxygen linkage of the peroxide functionality. These observations suggest that the decomposition of *tert*-butyl diphenylmethyl peroxide, at least, does not involve reaction of the α hydrogen of the diphenylmethyl moiety in the rate-determining process.

Our investigation of the thermal decompositions of isopropyl *tert*-butyl perioxide (1) indicate that induced decompositions of this peroxide do occur. Both the kinetics of the decompositions in different solvents as well as the distributions of the reaction products suggest that the induced decomposition involves attack of an α hydrogen on the isopropyl moiety of 1 by a peroxide-derived *tert*-butoxyl radical.

Results and Discussion

Decomposition of isopropyl *tert*-butyl peroxide in both *tert*-butylbenzene and cumene at 135 °C yielded isopropyl alcohol, acetone, and *tert*-butyl alcohol as the major reaction products (eq 1–4) (see Table I). The observed reaction products could be explained in terms of the reactions with the solvent of the isopropoxyl and *tert*-butoxyl radicals formed by the unimolecular thermolysis of 1. The sum of the amounts of acetone, isopropyl alcohol, and *tert*-butyl alcohol is, in both solvents, equal to twice the amount of peroxide that has decomposed. However, the more rapid rate of decomposition of the peroxide in *tert*-butylbenzene relative to its decomposition rate in cumene and the higher acetone/isopropyl alcohol ratio found in the decompositions in *tert*-butylbenzene indicate that decomposition mechanism(s) other than the unimolecular homolysis shown in eq 1 likely are operative.

$$\underset{\mathbf{1}}{(CH_3)_3COOCH(CH_3)_2} \longrightarrow (CH_3)_3CO\cdot + \cdot OCH(CH_3)_2 \quad (1)$$

$$(CH_3)_3CO\cdot \longrightarrow (CH_3)_2C{=}O + CH_3\cdot \xrightarrow{RH} CH_4 + R\cdot \quad (2)$$

$$(CH_3)_3CO\cdot + RH \rightarrow (CH_3)_3COH + R\cdot \quad (3)$$

$$(CH_3)_2CHO\cdot + RH \rightarrow (CH_3)_2CHOH + R\cdot \quad (4)$$

The good agreement between the amounts of decomposition products formed and the peroxide that has decomposed, as well as the absence of any detectable amounts of acetaldehyde among the reaction products, indicate that the isopropoxyl radical does not fragment (eq 5) to any significant extent, but likely participates only in hydrogen abstraction reactions to yield isopropyl alcohol. The amount of isopropyl alcohol formed, therefore, serves as a measure of the extent of unimolecular decomposition of the peroxide (27% in *tert*-butylbenzene and 59% in cumene at 135 °C). Consequently, about 73% of the peroxide decomposes in *tert*-butylbenzene by some route that does not involve formation of the isopropoxyl radical, whereas only about 40% of the peroxide follows a similar path of decomposition in cumene.

$$(CH_3)_2CHO\cdot \rightarrow CH_3CHO + CH_3\cdot \quad (5)$$

The induced decomposition of the peroxide via the chain sequence shown in eq 6 and 7 accounts for the formation of acetone from the isopropoxyl moiety of the peroxide. The extent of the induced decomposition is dependent on the partitioning of the hydrogen abstraction reactions of the *tert*-butoxyl radical between the peroxide and the solvent. The extent of induced decomposition would be expected, as observed, to be less in cumene, which has a benzylic hydrogen atom that is comparatively more reactive toward reaction with the *tert*-butoxyl radical, than in *tert*-butylbenzene which has only the less reactive primary alkyl hydrogens.

$$(CH_3)_3CO\cdot \text{ (or } CH_3\cdot) + (CH_3)_2CHOOC(CH_3)_3 \xrightarrow{k_6} (CH_3)_3COH \text{ (or } CH_4) + \underset{\mathbf{2}}{(CH_3)_2\dot{C}OOC(CH_3)_3} \quad (6)$$

$$(CH_3)_2\dot{C}OOC(CH_3)_3 \xrightarrow{k_7} (CH_3)_2C{=}O + (CH_3)_3CO\cdot \quad (7)$$

$$((CH_3)_3CO\cdot \rightarrow (CH_3)_2C{=}O + CH_3\cdot) \quad (8)$$

The rate laws for the decompositions of 1 in these solvents are the combined rates for the unimolecular decomposition and the induced decomposition.

$$-d[Per]/dt = k_1[Per] + k_6[(CH_3)_3CO\cdot][Per] \quad (9)$$

Table I. Decompositions of 1 in Cumene and *tert*-Butylbenzene

Time, min	Peroxide remaining, mmol	Products, mmol: Acetone	Isopropyl alcohol	*tert*-Butyl alcohol
		Cumene[a]		
0	1.22			
40	1.11	0.07	0.05	0.11
80	1.00	0.13	0.12	0.19
120	0.91	0.18	0.17	0.26
160	0.82	0.22	0.23	0.33
200	0.75	0.28	0.28	0.41
243	0.67	0.33	0.34	0.46
280	0.62	0.35	0.37	0.49
320	0.56	0.41	0.39	0.56
		tert-Butylbenzene[a]		
0	1.11			
40	0.92	0.26	0.03	0.10
80	0.78	0.45	0.08	0.22
120	0.65	0.57	0.09	0.27
160	0.55	0.67	0.13	0.33
200	0.49	0.74	0.14	0.37
243	0.42	0.82	0.18	0.39
280	0.37	0.88	0.18	0.42
320	0.34	0.89	0.21	0.46

[a] Solvent/peroxide = 5:1.

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The observed kinetic order of the peroxide in these decomposition reactions would depend both on the extent of the contribution of the induced decomposition to the overall rate *and* on the rate-limiting step (or steps) in the chain sequence (eq 6 and 7) for the induced decomposition. Thus, if the unimolecular fragmentation of the radical **2** in reaction 7 is the rate-limiting step of the chain sequence, the steady-state concentration of **2** would be greater than that of the *tert*-butoxyl radical and termination of the chain would be a bimolecular interaction of **2**.

$$2 \xrightarrow{k_{10}} \text{termination products} \qquad (10)$$

The rate law for peroxide decomposition would be that shown in the equation

$$-\mathrm{d[Per]}/dt = k_1[\mathrm{Per}] + k_7(k_1/2k_{12})^{1/2}[\mathrm{Per}]^{1/2} \qquad (11)$$

Likewise, if both steps of the chain sequence proceed with equal facility, the steady-state concentration of the two chain-carrying radicals would be comparable and the cross-termination process would be operative.

$$2 + (CH_3)_3CO\cdot \xrightarrow{k_{12}} \text{termination products} \qquad (12)$$

The rate law for the peroxide decomposition would be that shown in the equation

$$-\mathrm{d[Per]}/dt = k_1[\mathrm{Per}] + (k_1k_6k_7/k_{12})^{1/2}[\mathrm{Per}] \qquad (13)$$

Finally, if the hydrogen abstraction from **1** by the *tert*-butoxyl radical (eq 6) is rate limiting, termination would involve a bimolecular interaction of two *tert*-butoxyl radicals,

$$2\,(CH_3)_3CO\cdot \xrightarrow{k_{14}} \text{termination products} \qquad (14)$$

and the rate law is

$$-\mathrm{d[Per]}/dt = k_1[\mathrm{Per}] + k_6(k_1/2k_{14})^{1/2}[\mathrm{Per}]^{3/2} \qquad (15)$$

Interestingly, the rate data for the decomposition of **1** in neither cumene nor *tert*-butylbenzene show strictly first-order dependency for the peroxide. The deviation observed in a first-order plot of the rate data for the decomposition of peroxide in cumene is less pronounced than it is in *tert*-butylbenzene.

Subjecting the rate data in Table I to a curve-fitting procedure[6] that indicates the kinetic order of a component shows a "best-fit" for the rate law (eq 16) for the reaction in cumene ($k_{obsd} = 2.32 \times 10^{-3}$; stand dev = 0.10×10^{-4}).

$$-\mathrm{d[Per]}/dt = k_{obsd}[\mathrm{Per}]^{1.1} \qquad (16)$$

Similar treatment of the rate data for the decomposition of **1** in *tert*-butylbenzene indicates the rate law (eq 17) for the decomposition reaction ($k_{obsd} = 4.65 \times 10^{-3}$; stand dev = 0.10×10^{-3}).

$$-\mathrm{d[Per]}/dt = k_{obsd}[\mathrm{Per}]^{1.4} \qquad (17)$$

Finding kinetic orders for the peroxide greater than unity indicate that the rate law (eq 15) is operative for the decomposition of the peroxides. Further, the observed kinetic orders for the peroxide reflect the contributions of the induced decomposition to the overall decomposition rates and the observed rate laws support the conclusion based on the product analysis, namely that the induced decomposition is more extensive in *tert*-butylbenzene than in cumene.

Experimental Section

Isopropyl *tert*-Butyl Peroxide. This material was prepared in the following manner using the general method described by Dickey and Bell.[7] A mixture of potassium *tert*-butyl peroxide (128 g, 1 mol) and isopropyl bromide (160 g, 1.3 mol) in 120 mL of isopropyl alcohol was stirred at room temperature for 1 week. The reaction mixture was poured into 4 L of water and the resulting organic layer was separated, washed several times with water, dried over anhydrous Na_2SO_4, and distilled. The isopropyl *tert*-butyl peroxide (26.4 g, 20% of theory) distilled at 36 °C at 70 mm. The NMR spectrum of the material showed a doublet centered at 1.19 ppm and singlet at 1.25 ppm (total, 15 H) and a heptet centered at 4.10 ppm (1 H).

Peroxide Decomposition Products Analysis. Solutions of isopropyl *tert*-butyl peroxide in *tert*-butylbenzene and in cumene (1:5 molar ratio of peroxide to solute) were placed in sealed glass tubes and heated at 135 °C in an oil bath. Tubes were removed at the time intervals designated in Table I and cooled to room temperature, and an accurately weighed portion of the reaction mixture was mixed with an accurately weighed amount of isoamyl acetate. The latter served as an internal standard for the gas chromatographic (10 ft × ¼ in. column packed with dodecyl phthalate on Chromosorb W) analysis of the unreacted peroxide and the reaction products acetone, isopropyl alcohol, and *tert*-butyl alcohol.

Registry No.—**1**, 15879-99-9; potassium *tert*-butyl peroxide, 14970-33-3; isopropyl bromide, 75-26-3; cumene, 98-82-8; *tert*-butylbenzene, 98-06-6; acetone, 67-64-1; isopropyl alcohol, 67-63-0; *tert*-butyl alcohol, 75-65-0.

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Reaction of Alkali Metal Cyanides with Alkyl Halides in HMPA or HMPA Containing Crown Ether

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Recently it was shown that potassium cyanide reacted with alkyl halides in benzene or acetonitrile containing crown ether to give high yields of alkyl cyanides.[1] We now wish to report the results of studies dealing with the reaction of sodium or potassium cyanide with alkyl halides in hexamethylphosphoramide (HMPA) in the presence or absence of 18-crown-6. The results show that sodium cyanide reacts rapidly with alkyl halides in HMPA even at room temperature with no crown ether present, that sodium cyanide reacts much faster with alkyl halides than potassium cyanide when no crown ether is present, and that even in a very polar aprotic solvent such as HMPA crown ether can increase the rate of reaction.

Reaction of sodium cyanide with alkyl halides in HMPA at room temperature with no crown ether present gave high yields of alkyl cyanides as shown in Table I. Isocyanides were not observed. Although the reactions shown in Table I were allowed to proceed for 24 h, the time required for complete reaction of the alkyl halide was usually much less. For example, 1-bromohexane completely reacted with sodium cyanide (1.5 mol equiv) in less than 1 h at room temperature. Also both 1-chlorohexane and 2-bromooctane reacted with sodium cy-

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Table I. Reaction of Alkyl Halides with Sodium Cyanide[f] in HMPA[a,g]

Halide	Registry no.	Products	% yield[b]
1-Bromohexane	111-25-1	1-Cyanohexane	98
1-Chlorohexane	544-10-5	1-Cyanohexane	96
1-Bromodecane	112-29-8	1-Cyanodecane	96
2-Chlorooctane	628-61-5	2-Cyanooctane	87[c]
		1- and 2-octenes	8
2-Bromooctane	557-35-7	2-Cyanooctane	84
		1- and 2-octenes	11
2-Iodooctane	557-36-8	2-Cyanooctane	59
		1- and 2-octenes	27
Cyclopentyl bromide	137-43-9	Cyclopentyl cyanide	65
		cyclopentene	*d*
Cyclohexyl bromide	108-85-0	Cyclohexyl cyanide	3
		cyclohexene	*d*
o-Dichlorobenzene		No reaction[e]	

[a] All reaction mixtures were stirred for 24 h at room temperature except in the cases of 2-chlorooctane and o-dichlorobenzene. [b] Yields were determined by GLC. [c] The reaction mixture was heated at 80 °C for 30 h. [d] Yield of alkene was not determined; no starting material remained. [e] There was no reaction even after 72 h at 120 °C with 18-crown-6 present. [f] Registry no. 143-33-9. [g] Registry no. 680-31-9.

Table II. Reaction of Alkyl Halides with Sodium or Potassium Cyanide[d] in HMPA or HMPA Containing 18-Crown-6[a,e]

Reaction	Alkyl halide	Type of cyanide	18-Crown-6[b]	% yield of alkyl cyanide[c]
1	1-Bromohexane	NaCN	No	98
2	1-Chlorohexane	NaCN	No	70
3	1-Chlorohexane	NaCN	Yes	79
4	1-Chlorohexane	KCN	No	10
5	1-Chlorohexane	KCN	Yes	81
6	1-Bromohexane	KCN	Yes	65

[a] All reactions were stirred for 5.7 h at room temperature. In all reactions except for the first, this reaction time was insufficient for complete reaction of the alkyl halide. [b] In some reactions as indicated, 5 mmol of 18-crown-6 was also present. [c] Yields were determined by GLC. [d] Registry no. 151-50-8. [e] Registry no. 17455-13-9.

anide in less than 8 h. An exception was 2-chlorooctane which required a reaction time of 30 h at a higher temperature (80 °C). In contrast, Liotta and co-workers[1] found that reaction of 1-bromohexane and 2-chlorooctane with potassium cyanide (2 mol equiv) in acetonitrile at 83 °C with 18-crown-6 present required reaction times of 40 and 244 h, respectively.

High yields of alkyl cyanides were obtained even from some secondary alkyl halides. The 84% yield of 2-cyanooctane obtained from 2-bromooctane was higher than that reported by Liotta and co-workers.[1] The higher yield is most likely due to the lower reaction temperature which disfavors the competing elimination reaction. The 87% yield of 2-cyanooctane from 2-chlorooctane is equal to that reported by Starks[2] using a phase-transfer catalyst system and is the highest yield of alkyl cyanide obtained from a secondary halide by any procedure. The aryl halide, *o*-dichlorobenzene, failed to react with sodium cyanide even when heated at 120 °C for 72 h. Addition of 18-crown-6 had no effect. This result is in contrast to our previous report[3] where sodium methoxide reacted readily with *o*-dichlorobenzene under similar conditions to give a 78% yield of o-chloroanisole.

Reaction of alkyl halides with alkali metal cyanides under the same conditions except for changes in the type of metal cyanide used and the presence or absence of 18-crown-6 gave the results shown in Table II. The reaction time was the same in all runs and was insufficent for complete reaction except in the case of 1-bromohexane with sodium cyanide. Reaction of sodium cyanide with 1-chlorohexane was much faster than that of potassium cyanide when no crown ether was present (reactions 2 and 4). This is probably due to the fact that sodium cyanide is more soluble in HMPA than potassium cyanide. When crown ether was added to improve the solubility of the potassium cyanide, it reacted with 1-chlorohexane at about the same rate as sodium cyanide (reactions 3 and 5). Addition of crown ether also improved the reactivity of sodium cyanide (reactions 2 and 3) although not as dramatically as in the case of potassium cyanide. We have observed similar effects of crown ethers in the reactions of potassium salts of carboxylic acids with alkyl halides in HMPA.[4] Although sodium cyanide reacted much more rapidly with 1-bromohexane than 1-chlorohexane, potassium cyanide reacted with 1-bromohexane in the presence of crown ether more slowly than 1-chlorohexane (reactions 5 and 6). Although this observation is contrary to the normally accepted leaving group order, it does agree with the observations of Liotta and co-workers[1] for similar reactions in acetonitrile.

Experimental Section

General Procedure (Table I). A mixture of alkyl halide (20 mmol), ground sodium cyanide (1.47 g, 30 mmol), and 40 mL of HMPA in a flask equipped with a drying tube was magnetically stirred for 24 h at room temperature (~21 °C). The reaction mixture was then poured into 80 mL of water which was extracted with two 80-mL portions of ether. The combined ether extract was washed with three 20-mL portions of water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure. The yield of alkyl cyanide was determined by analysis of the residual liquid by GLC (6 ft × 0.25 in. 10% SE-30 on 60–80 mesh Chromosorb W). Product purified by GLC gave an infrared spectrum and refractive index identical to that observed or reported for an authentic sample. In the case of 2-chlorooctane the reaction was performed as above except the reaction mixture was heated at 80 °C for 30 h in a flask equipped with a condenser and drying tube. In the case of *o*-dichlorobenzene the reaction mixture which included 1.32 g (5 mmol) of 18-crown-6 was heated at 120 °C for 72 h.

General Procedure (Table II). A mixture of alkyl halide (10 mmol), ground metal cyanide (16.6 mmol), 20 mL of HMPA, and in some cases 1.32 g (5 mmol) of 18-crown-6 was magnetically stirred in a flask equipped with a drying tube for 5.7 h at room temperature (~21 °C). The reaction mixture was then poured into 40 mL of water which is extracted with two 40-mL portions of ether. The combined ether extract was washed with three 10-mL portions of water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure. The yield of alkyl cyanide was determined by analysis of the residual liquid by GLC (6 ft × 0.25 in. 10% SE-30, 100 °C). Product purified by GLC gave an infrared spectrum and refractive index identical to that of an authentic sample.

References and Notes

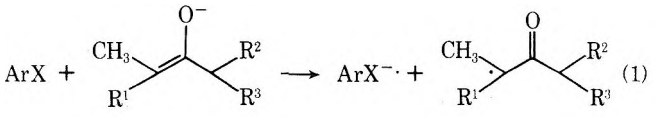
(1) F. L. Cook, C. W. Bowers, and C. L. Liotta, *J. Org. Chem.*, **39**, 3416 (1974).
(2) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).
(3) J. E. Shaw, D. C. Kunerth, and S. B. Swanson, *J. Org. Chem.*, **41**, 732 (1976).
(4) Reaction of potassium pivalate with *sec*-butyl bromide in HMPA at room temperature for 24 h gave an 83% yield of *sec*-butyl pivalate when no 18-crown-6 was present and a 90% yield when 18-crown-6 present. Reaction between potassium butyrate and cyclopentyl bromide gave a 58% yield of cyclopentyl butyrate with no 18-crown-6 present and an 85% yield with 18-crown-6 present. Neither potassium pivalate or butyrate were completely soluble in HMPA although potassium pivalate was more soluble than potassium butyrate.

Communications

Evidence for Intermolecular Hydrogen Atom Transfer in Photostimulated $S_{RN}1$ Reactions Involving Ketone Enolates

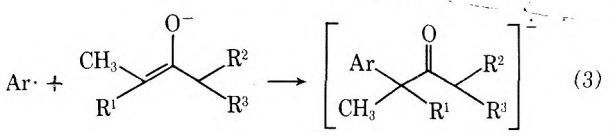
Summary. Photostimulated $S_{RN}1$ reaction of potassio-2,4-dimethyl-3-pentanone with iodobenzene is accompanied by a competing reaction in which 2,4,4,6,8-pentamethylnonane-3,7-dione is formed by a mechanism originating with β-hydrogen abstraction from the enolate by phenyl radical.

Sir: Photostimulated reactions of ketone enolates with carboaromatic and heteroaromatic halides have been shown to afford products resulting from introduction of an aryl or heteroaryl residue at the α carbon of the ketone.[1-4] Considerable evidence[1-5] has been gathered to show that these nucleophilic substitutions occur via a radical chain mechanism designated as $S_{RN}1$[6] and generalized in eq 1–4. Initiation (eq 1) is prob-

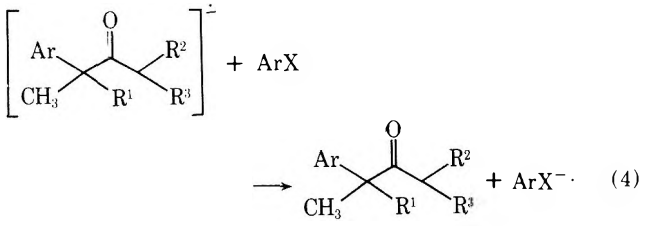


(1)

$$ArX^{-}\cdot \longrightarrow Ar\cdot + X^{-} \qquad (2)$$



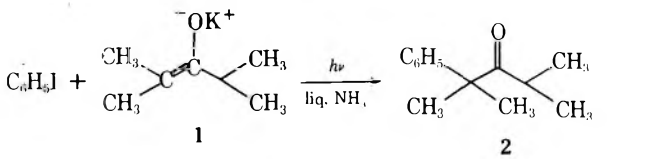
(3)



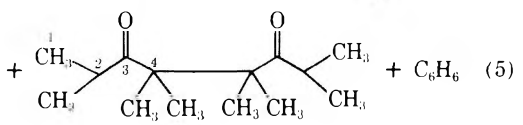
(4)

ably provided by electron transfer from the enolate to the aromatic substrate, perhaps through formation of a charge-transfer complex.[6] Subsequent propagating steps involve fragmentation of the aryl radical anion to form an aryl radical and halide ion (eq 2), combination of the aryl radical with the enolate (eq 3), and then electron transfer from the resulting radical anion to another substrate molecule (eq 4).

Although such reactions have been found to be rather general, the potassio salts of acetophenone and propiophenone react poorly with halobenzenes, while reactions of tertiary enolates are accompanied by a competing ketone dimerization.[1] For example, under illumination potassio-2,4-dimethyl-3-pentanone (**1**) reacts sluggishly with iodobenzene



1 **2**

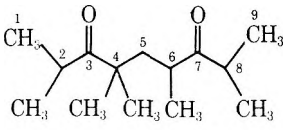


(5)

3

to form phenylated ketone **2** (32%) accompanied by benzene (20%) and 20% of a dimeric product which has been assigned structure **3**[1,3] (eq 5). In contrast to this, **1** reacts with 2-bromopyridine[2] and 2-chloroquinoline[3] to give the expected α-heteroaryl ketones unaccompanied by significant amounts of dimer.

When we repeated the reaction of **1** with iodobenzene as described previously,[1] we found that ketone **2** and benzene were formed in essentially the yields reported.[7] However, the dimeric product isolated (preparative GLC) from this reaction, as well as from the reaction of **1** with 2-bromopyridine, *is not* **3.** Instead, the ^1H NMR and ^{13}C NMR spectra[8] require assignment of structure **4**[9] to this compound. Thus, the ^1H

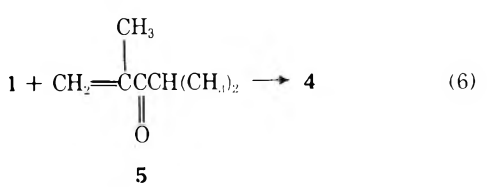


4

NMR spectrum contains an ABX pattern of δ_A 1.42, δ_B 2.15, and δ_X 2.56, with J_{AB} = 14, J_{AX} = 3, and J_{BX} = 7 Hz. This pattern is inconsistent with structure **3**, but in accord with **4**, since the diastereotopic protons at C-5 of the latter compound would be expected to give rise to an ABX spin system through coupling with the methine hydrogen at C-6. Besides the ABX pattern, two septets arising from the methine protons at C-2 and C-8 are distinguishable at δ 2.67 (J = 6 Hz) and 3.07 (J = 7 Hz), as well as a methyl multiplet (21 H) at δ 1.10.

The proton-decoupled ^{13}C NMR spectrum of **4** contains two carbonyl resonances at 217.4 and 219.3 ppm, along with 12 peaks attributable to saturated carbon atoms.[10] The ^1H NMR spectrum of an authentic sample of **3**, prepared from 2,4-dibromo-2,4-dimethyl-3-pentanone by means of zinc–copper couple[11] or by the action of acetyl peroxide on 2,4-dimethyl-3-pentanone,[1] consists of a doublet at δ 1.04 (J = 7 Hz), a singlet at δ 1.24, and a septet at δ 3.14 (J = 7 Hz) in a ratio of 12:12:2. The ^{13}C NMR spectrum of **3** is characterized by resonances for one carbonyl carbon at 219.4 ppm and four saturated carbons at 20.1, 22.3, 35.6, and 53.3 ppm for C-1, C-5, C-2, and C-4, respectively. The IR spectrum of **3**, which contained a carbonyl band at 1700 cm^{-1}, is nearly identical with that of **4.**

Assignment of structure **4** is substantiated by our obtaining the same substance, with identical spectra, from Michael addition of **1** to **5** (eq 6). From **5**[13] (20 mmol) and **1** (21 mmol)



(6)

5

in 100 mL of liquid ammonia, allowed to react 60 min in the dark, **4** was isolated in 65% yield.

Interpretation of the formation of **4** is suggested by a recent report of Semmelhack and Bargar.[12] They showed by a series of deuterium labeling experiments that aryl radicals produced during intramolecular photo-$S_{RN}1$ reactions can abstract a hydrogen atom from the β position of the side-chain enolate to effect reductive dehalogenation of the aromatic ring with

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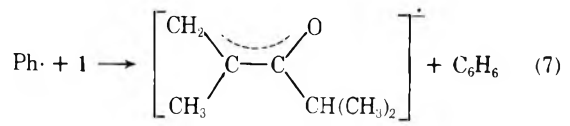
concomitant generation of an α,β-unsaturated ketone function in the side chain. Similarly, ester enolates containing β hydrogens effect reduction of aryl halides by intermolecular hydrogen atom transfer.[12]

Accordingly, we postulate that phenyl radical, besides adding to 1 (eq 3), abstracts a β hydrogen as shown in eq 7. Thereby formed are benzene and **6**, which is the radical anion of **5**.



(7)

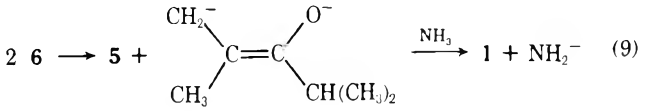
6

Being the radical anion of an α,β-unsaturated ketone, **6** is probably too stable to transfer an electron rapidly to iodobenzene, as in eq 8. Were that to happen a propagation cycle

$$\mathbf{6} + \mathrm{PhI} \not\rightarrow \mathbf{5} + [\mathrm{PhI}]^{-\cdot} \qquad (8)$$

comprising steps 2, 7, and 8 would coexist with the normal $S_{RN}1$ cycle of steps 2, 3, and 4, and no interpretation of the sluggishness of the overall reaction of PhI with 1 would be offered. (The very low $S_{RN}1$ reactivity of acetophenone enolate ions with aryl and heteroaryl halides is probably of similar origin, the radical anion $[ArCH_2COPh]^{-\cdot}$ being unable to transfer an electron rapidly enough to ArX, as in step 4, to maintain the propagation cycle.)

The sluggishness of the overall reaction of PhI with 1 suggests that termination steps accompany or follow the formation of benzene and **4**. We suggest that disproportionation of **6**, as in eq 9, is the termination step. Dianion **7** is rapidly protonated to form **1**, as shown, and 1 adds to **5** to form **4** (eq 6).



(9)

7

The present results demonstrate for the first time that intermolecular hydrogen atom transfer can be a significant competing process in photostimulated reactions involving ketone enolates and carboaromatic substrates. With halogenated aromatic azines, however, this mode of reductive dehalogenation plays a less important role.[2]

Acknowledgment. We are pleased to acknowledge financial support of the National Science Foundation under Grant No. CHE 74-20520 at Virginia Polytechnic Institute and State University and Grant No. CHE 76-11364 at the University of California, Santa Cruz.

References and Notes

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(2) A. P. Komin and J. F. Wolfe, *J. Org. Chem.*, **42**, 2481 (1977).
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(5) S. Hoz and J. F. Bunnett, *J. Am. Chem. Soc.*, **99**, 4690 (1977).
(6) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, 92, 7463 (1970).
(7) We observed that negligible reaction occurred in the dark (2% in 3 h).
(8) NMR spectra were obtained at 100 MHz for ^{1}H NMR and at 25.15 MHz for ^{13}C NMR from $CDCl_3$ solutions using Me_4Si as an internal standard.
(9) This compound [bp 80–83 °C (0.6 Torr); IR (neat) 1705 cm^{-1} (C=O)] gave a satisfactory combustion analysis.
(10) The saturated carbon absorbances and their tentative assignments are as follows: δ 18.7 and 18.9 (C-2 and/or C-8 CH_3), 19.9 (C-6 CH_3), 20.1 and 20.3 (C-2 and/or C-8 CH_3), 23.7 and 25.3 (C-4 CH_3), 34.1 (C-5), 39.8 (C-6), 41.2 and 41.4 (C-2 and C-8), and 41.3 ppm (C-4).
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(12) M. F. Semmelhack and T. M. Bargar, *J. Org. Chem.*, **42**, 1481 (1977).
(13) Enone **5** was prepared from 2-bromo-2,4-dimethylpentan-3-one according to the procedure of A. Bienvenue and B. Duchatellier, *Tetrahedron*, **28**, 833 (1972).

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Reactions in Dry Media. Ferric Chloride Adsorbed on Silica Gel. A Multipurpose, Easily Controllable Reagent[1]

Summary: $FeCl_3$ adsorbed on a chromatographic type silica gel was found to be effective for rapid, high yield and selective dehydration of alcohols, as well as for pinacol and acyloin type rearrangements. The same reagent containing ca. 2% water epimerizes tertiary alcohols and converts epoxides into diols.

Sir: One of the advantages of reactions on solid adsorbents is their use as support for selective reagents which are inefficient or inactive in solution.[1,2] We report on the use of such a reagent, consisting of ferric chloride adsorbed on chromatographic grade silica gel for rapid, high yield, selective dehydration and epimerization of alcohols, epoxide openings, and rearrangements involving carbonium or oxonium ion intermediates.[3]

When silica gel (Merck Kiesegel 60, particle size 0.063–0.200 mm, 70–230 mesh) is mixed with ~10% its weight of hydrated ferric chloride ($FeCl_3 \cdot 6H_2O$) dissolved in a polar volatile solvent (such as methanol, acetone, ether, etc.), followed by evaporation at ~50–60 °C under high vacuum (0.1 Torr) for ~3 h, a dry yellowish-brown powder is obtained.[4,5] This powder is an effective reagent for dehydration of allylic, tertiary, and sterically strained secondary alcohols, as exemplified in Table I.

The dehydrations are performed either by dissolving the substrate in a volatile solvent, mixing it with ~100 times its weight of reagent, and evaporating to dryness under high vacuum or when the substrate is volatile, by mixing it directly with the reagent. After being left for a short time at room temperature, the products are eluted from the silica gel with an organic solvent. The dehydrations are very fast, generally taking place immediately on contact of the substrate with the adsorbed reagent, and resulting in high yields of pure products.

Addition of ~2% water by weight to the dry $FeCl_3$–SiO_2 reagent results in a bright yellow powder (wet $FeCl_3$–SiO_2 reagent) which is still capable of dehydrating allylic alcohols, and to a lesser extent, tertiary alcohols. However, high water concentration (>10%) may completely deactivate this reagent.

We have observed that the wet $FeCl_3$–SiO_2 reagent in some cases efficiently epimerizes tertiary carbinols. Thus both *cis*- and *trans*-1,4-dimethylcyclohexanols were converted quantitatively to an equilibrium mixture of the two epimers, consisting of 56% of the trans epimer.[6] When these cyclohexanols were labeled with ^{18}O, the ensuing mixture of epimers was devoid of the label. On the other hand, by using wet $FeCl_3$–SiO_2 reagent prepared by adding $H_2{}^{18}O$ to the dry $FeCl_3$–SiO_2

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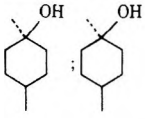
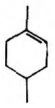
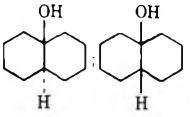
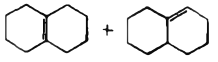
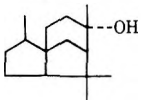
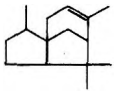
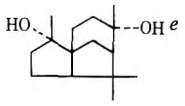
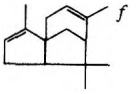
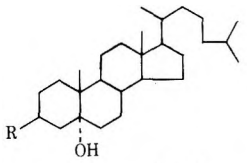
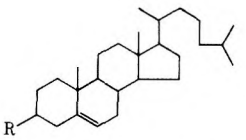
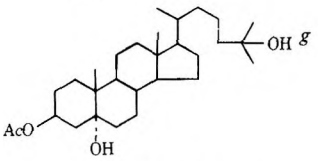
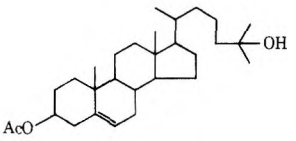
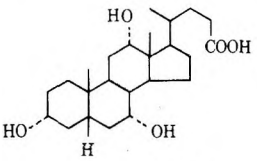
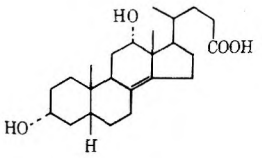
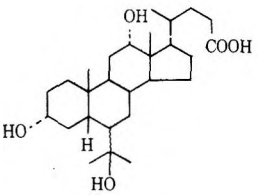
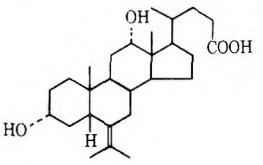
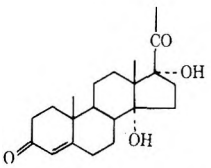
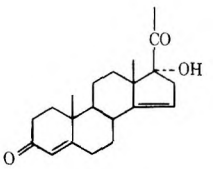
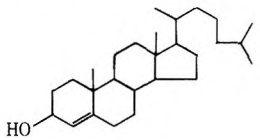
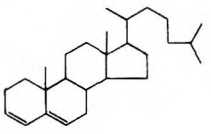
Table I. Selective Dehydrations Carried out with $FeCl_3$ on Silica Gel

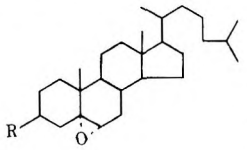
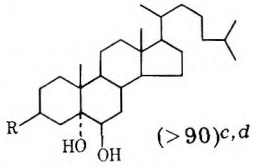
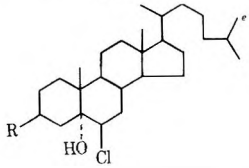
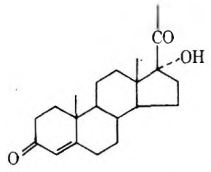
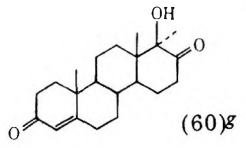
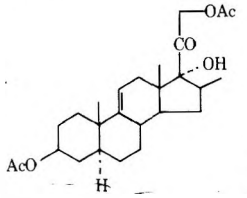
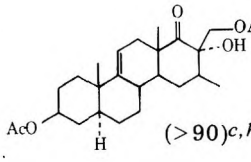
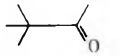
Entry	Substrate	Product (% yield)[a,b]	
1			(>90)[c]
2			(>90)[c,d]
3			(>90)[c]
4			(>90)[c]
5 R = H 6 R = OH			(80)
7			(72)
8			(75)
9 6α 10 6β			(85)[h]
11			(>90)[c,i]
12			(>90)

[a] The yields were not optimized. [b] All the known compounds were identified by a comparison with the authentic samples. [c] These conversions were almost quantitative and no other products were isolated. [d] The ratio of 9,10-octalin and 1,9-octalin was 1.4:1. [e] Prepared from cedrol with O_3 on SiO_2: E. Keinan, Ph.D. Thesis, Feinberg Graduate School, the Weizmann Institute of Science, Rehovot, Israel (1977). See also: E. Trifilieff, L. Bang, and G. Ourisson, *Tetrahedron Lett.*, 2991 (1977). [f] $[\alpha]_D$ + 10°; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3 H), 1.06 (s, 3 H), and 5.3 (m, 2 H). [g] Reference 9. [h] M. Lahav, L. Leiserovitz, R. Popovitz, and Ch.P. Tang, *J. Am. Chem. Soc.*, in press. [i] B. M. Bloom, E. J. Agnello, and G. D. Laubach, *Experientia*, 12, 27 (1956).

reagent, an incorporation of ^{18}O into both epimers was observed. Impregnation of *cis*-9-decalol into the wet $FeCl_3$–SiO_2 reagent resulted in ~85% conversion to a 1:4 mixture of alcohols and olefins consisting of *trans*- and *cis*-decalols and 9,10- and 1,9-octalines in a 4:1 and 1.4:1 ratio, respectively. An identical mixture was obtained from *trans*-9-decalol.[7]

To simplify the experimental procedure, and at the same time to control the formation of the desired products, the substrate was impregnated into the inactive $FeCl_3$–SiO_2 reagent (containing ~10% water by weight). This powder was

Table II. Epoxide Opening and Rearrangements Carried Out with $FeCl_3$ on Silica Gel

Entry	Substrate	Product (% yield)[a,b]
1 R = H 2 R = OH		 (>90)[c,d]  R = H (65)[e] R = OH (55)[f,e]
3		 (60)[g]
4		 (>90)[c,h]
5		 (70)

[a] The yields were not optimized. [b] All the known compounds were identified by a comparison with the authentic samples. [c] These conversions were almost quantitative and no other products were isolated. [d] With wet $FeCl_3$–SiO_2 reagent. [e] With dry $FeCl_3$–SiO_2 reagent. [f] Accompanied by cholestan-6-one (15%) and a rearranged product. [g] D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling, and G. Roberts, *J. Am. Chem. Soc.*, **77**, 6585 (1955). [h] D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **82**, 4012 (1960).

connected either to a high vacuum pump or left in a desiccator over P_2O_5. The slow water removal at room temperature gradually transformed the reagent into its active form. The concurrent reaction progress is easily followed by sampling or by the change in color from bright to brownish yellow. This reaction may be stopped at the desired stage by adding a polar solvent which dissolves $FeCl_3$, and may be resumed after removing the solvent under vacuum. Thus, *cis*- and *trans*-1,4-dimethylcyclohexanols impregnated into the inactive $FeCl_3$–SiO_2 reagent were epimerized after being left for a short time in a dessicator over P_2O_5, and were dehydrated to 1,4-dimethylcyclohexene after a longer time. The dehydration of the other alcohols listed in Table I was also performed by mixing with the inactive reagent, and then by evaporating at high vacuum, or leaving in a desiccator over P_2O_5.

The $FeCl_3$–SiO_2 reagent was found in some instances to be a highly effective Lewis-acid type reagent, converting epoxides into 1,2-diols or chlorohydrins, rearranging ketols, 1,2-diols, and epoxides as exemplified in Table II. The hydrolytic opening of the epoxides was performed with wet $FeCl_3$–SiO_2 reagent (Table II, entries 1 and 2, footnote *d*). On the other hand, the dry reagent converted the epoxides to mixtures consisting mainly of chlorohydrins[8] (Table II, entries 1 and 2, footnote *e*).

The examples in Table I show a selectivity of the $FeCl_3$–SiO_2 reagent in dehydration of polyhydroxy compounds which is normally difficult to attain in solution. These regioselective dehydrations are synthetically useful since they do not necessitate special protection of the additional hydroxyl functions present in the molecule (Table I, entries 5, 6, 7, 8, 9, 10) or specifically designed reagents (Table I, entry 8).[10]

It is also noteworthy that the rearrangement of the ketol, 17α-hydroxyprogesterone (Table II, entry 3), leads to a different product than the one obtained with Lewis acids in solution.[11] This and the previous examples suggest that the definite geometrical requirements necessary for the interaction between the adsorbed $FeCl_3$ and the oxygen function of the substrate are responsible for the specificity of this reagent.

References and Notes

(1) For previous paper in this series, see E. Keinan and Y. Mazur, *J. Am. Chem. Soc.*, **99**, 3861 (1977).

(2) F. J. Kakis, M. Fetizon, N. Douchkine, M. Golfier, P. Mourgues, and T. Prange, *J. Org. Chem.*, **39**, 523 (1974); G. H. Posner, A. W. Runquist, and M. Chapdelaine, *ibid.*, **42**, 1202 (1977); G. H. Posner, R. B. Perfetti, and A. W. Runquist, *Tetrahedron Lett.*, 3499 (1976); H. B. Kagan, *Pure Appl. Chem.*, **46**, 177 (1976); J. M. Lalancette, M. J. Fournier-Breault, and R. Thiffault, *Can. J. Chem.*, **52**, 589 (1974); S. L. Regen and Ch. Koteel, *J. Am. Chem. Soc.*, **99**, 3837 (1977); E. C. Taylor, C. S. Chiang, A. McKillop, and J. F. White, *ibid.*, **98**, 6750 (1976); H. Selig, M. Rabinovitz, I. Agranat, C. H. Lin, and L. Ebert, *ibid.*, **98**, 1601 (1976); G. Cainelli, G. Cardillo, M. Orena, and S. Sandri, *ibid.*, **98**, 6737 (1976).

(3) $FeCl_3$ in solution is used mainly as a mild oxidizing reagent (cf. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1–5, Wiley, New York, N.Y., 1967–1975). Recently, anhydrous $FeCl_3$ in anhydrous ether was utilized for conversion of epoxides to chlorohydrins [J. Kagan, B. E. Firth, N. Y. Smith, and Ch. G. Boyajian, *J. Org. Chem.*, **42**, 343 (1977)] and anhydrous $FeCl_3$ in acetic anhydride for the cleavage of ethers [B. Ganem and V. R. Small, *ibid.*, **39**, 3728 (1974)].

(4) In this form $FeCl_3$ is physically adsorbed on the silica gel, since it may be eluted from it with polar solvents. Excessive heating transforms this reagent into dark brown powder in which $FeCl_3$ is partly decomposed and cannot be eluted either with organic solvents or with water.

(5) The reagent may also be prepared using aqueous $FeCl_3$ solution. In order to achieve a homogeneous adsorption, it is advisable to mix an equal volume of hydrated $FeCl_3$ in an organic solvent such as acetone with silica gel followed by evaporation of the solvent. Identical results were obtained using silica gel containing $FeCl_3 \cdot 6H_2O$ in concentrations between 4 and 10%.

(6) Cf. N. L. Allinger and C. D. Liang, *J. Org. Chem.*, **33**, 3319 (1968).

(7) The ratio of the decalols is in favor of the cis epimer as compared to the equilibrium ratio (P. D. Bartlett, R. E. Pincock, J. H. Rolston, W. G. Schindel, and L. A. Singer, *J. Am. Chem. Soc.*, **87**, 2590 (1965). This may be due to the more rapid dehydration of the *trans*-9-decalol.

(8) Quantitative conversion of the epoxides into chlorohydrins was achieved using more active $FeCl_3$–SiO_2 reagent prepared by heating the silica gel impregnated with $FeCl_3$ to higher temperature (>80 °C), see ref 4. To be published later.

(9) A. Rotman and Y. Mazur, *J. Chem. Soc., Chem. Commun.*, 15 (1974); Cholestane-3β,5α,25-triol 3-acetate (Table I, entry 9) is an intermediate in the synthesis of the biologically active 25-hydroxyvitamin D_3 and the direct conversion of the former to 25-hydroxycholesteryl 3-acetate simplifies the synthesis of that vitamin D.

(10) A. W. Devor and H. W. Marlow, *J. Am. Chem. Soc.*, **68**, 2101 (1946).

(11) The major products in the rearrangement of 17α-hydroxypregnan-20-ones with boron trifluoride etherate or aluminum alkoxides are the 17α-hydroxy-17β-methyl 17a-ketones (and not the 17aβ-hydroxy-17aα-methyl 17-ketones formed with $FeCl_3$–SiO_2). See: N. L. Wendler in "Molecular Rearrangement", Vol. 2, P. de Mayo, Ed., Interscience, New York, N.Y., 1964, pp 1099–1113; D. N. Kirk, and M. P. Hartshorn "Steroid Reaction Mechanisms", Elsevier, Amsterdam, 1968, p 294; D. W. Kirk and A. Mudd, *J. Chem. Soc., Perkin Trans. 1*, 1450 (1975).

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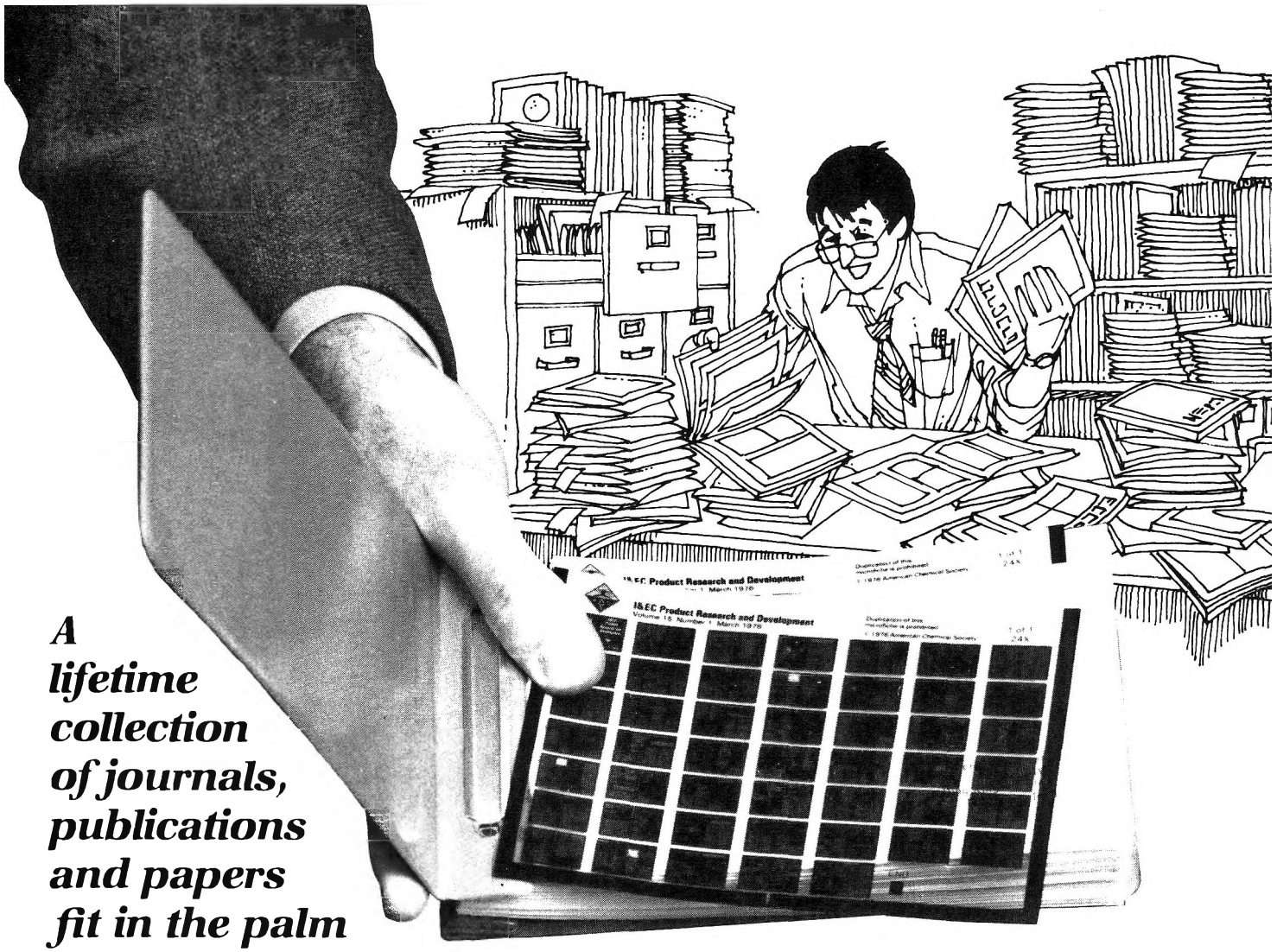

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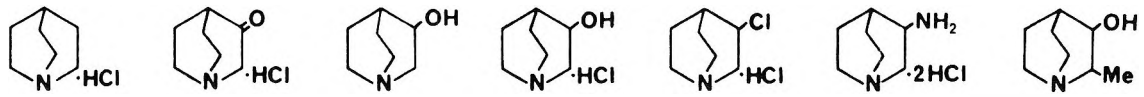
The Quinuclidines



The main interest in **quinuclidines**[1] is two-fold.

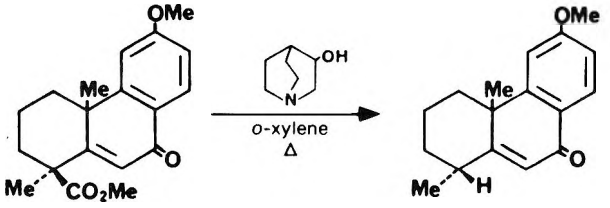
Firstly, **quinuclidine** itself promises to become an important polymerization catalyst,[2] particularly as this base can now be supplied in bulk and is no longer just a laboratory curiosity.

Secondly, several esters of **3-quinuclidinol** are important hypotensives,[3] antispasmodics,[4] agents for the treatment of glaucoma,[5] and tranquilizers.[6]

Quinuclidine also forms complexes with organometallic compounds.[7,8]

2-Methoxytropone is demethylated by a four-fold excess of **quinuclidine** in refluxing benzene in 60% yield.[9]

Parish, Huang and Miles[10] reported that β-keto esters and vinylogous β-keto esters are cleaved in high yield (~95%) when heated under reflux for 6 hours with 5 equivalents of **3-quinuclidinol** in *o*-xylene. They concluded that this reaction may represent a model for a corresponding enzymatic reaction.



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